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SYNTHESIS AND STUDIES OF BINDING PROPERTIES OF CALIX[4]ARENES FUNCTIONALISED WITH AMIDE AND HYDROXAMATE MOIETIES AND THEIR THIOCARBONYL ANALOGUES

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THESE

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« SYNTHESIS AND STUDIES OF BINDING PROPERTIES OF CALIX[4]ARENES FUNCTIONALISED WITH AMIDE AND HYDROXAMATE MOIETIES AND THEIR THIOCARBONYL ANALOGUES »

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Résumé de la thèse

«Synthèse et étude des propriétés complexantes de dérivés amides et hydroxamiques des calix[4]arènes et de leurs analogues thiocarbonylés»

Cette thèse a été réalisée en cotutelle entre l'Université de Strasbourg (Directrice de Thèse: Dr Véronique HUBSCHER-BRUDER) et l'Université de Technologie de Gdansk (Directrice de Thèse: Prof. Maria BOCHEŃSKA).

Depuis leur découverte en 1872, les calixarènes présentent un intérêt croissant en raison de leurs remarquables propriétés de complexation vis-à-vis des cations métalliques. L'introduction de divers groupements fonctionnels sur la structure des calixarènes conduit à une grande variété de dérivés présentant des propriétés différentes et pouvant être utilisés comme récepteurs moléculaires. De nombreuses études ont été consacrées à optimiser la sélectivité. Actuellement, des efforts considérables sont entrepris pour protéger l'environnement. Il est bien connu que les cations des métaux lourds sont toxiques et font courir des risques important à la santé humaine et à l'environnement. En vue de la protection de l'environnement, il est important de détecter et de mesurer les niveaux de métaux lourds tels que le plomb, le cadmium et l'argent et de métaux de transition (cuivre, zinc...) dans les eaux naturelles et l'eau potable.

Le but principal de ce travail était la synthèse de calix[4]arènes modifiés par des substituants thiocarbonylés. La présence d'atomes de soufre sur ces molécules devrait induire une bonne sélectivité vis-à-vis de cations tels que Pb^{2+}, Cu^{2+}, Cd^{2+} et Ag^{+} par rapport aux cations des métaux alcalins et alcalino-terreux.

Quatre familles de dérivés ont été synthétisées: des dérivés amides et thioamides, des dérivés hydroxamates et acides hydroxamiques. Des essais ont été réalisés pour préparer les analogues thiocarbonylés des dérivés hydroxamates et acides hydroxamiques qui n'étaient pas encore décrits dans la littérature.

L'objectif était ensuite d'étudier les propriétés de reconnaissance ionique de ces composés et d'établir des relations entre ces propriétés et la structure de ces composés. Les méthodes suivantes ont été utilisées: la spectrophotométrie d'absorption dans l'UV et la potentiométrie dans deux solvants aux propriétés différentes, le méthanol et l'acétonitrile, la

microcalorimétrie dans l'acétonitrile, la spectroscopie RMN du proton dans le mélange chloroforme - méthanol et le transfert biphasique des sels métalliques (picrates, nitrates) d'une phase aqueuse vers une phase organique de dichlorométhane contenant les ligands. Dans certains cas, l'étude cristallographique par rayon X des ligands libres et de leurs complexes avec Pb^{2+} a été effectuée. La sélectivité des dérivés thioamides et hydroxamates a été évaluée en utilisant ces composés comme éléments sensibles dans des électrodes à membranes sélectives (ISE).

Cette thèse comporte quatre chapitres.

Le premier présente une revue bibliographique décrivant l'état de l'art concernant les méthodes de synthèse des différents types de dérivés étudiés et l'étude de leurs interactions avec les cations métalliques.

Le deuxième chapitre est consacré à la synthèse et la caractérisation des nouveaux dérivés faisant l'objet de ce travail.

Le troisième chapitre présente les bases théoriques des différentes méthodes utilisées dans ce travail pour étudier les interactions entre les dérivés obtenus et certains cations métalliques ainsi que les résultats expérimentaux et leur discussion.

Le dernier chapitre rapporte l'application des dérivés thioamides et hydroxamates dans des électrodes sélectives à membranes (ISE).

Une conclusion générale clôture ce travail.

Calix[4]arènes amides et thioamides

Synthèse. Neuf calix[4]arènes substitués par des groupements thioamides (six dérivés thioamides tertiaires (composés **1T**-**6T**) et trois dérivés thioamides secondaires (composés **7T**-**9T**)) ont été synthétisés à partir des dérivés amides correspondants (composés **1A**-**9A**). Ces derniers ont été obtenus par la méthode dite « mixed anhydrides method » qui consiste en une première étape à faire réagir le dérivé acide carboxylique du calix[4]arène avec du chloroformiate d'éthyle en présence de triéthylamine. Dans une deuxième étape, l'intermédiaire réactionnel est directement traité par des amines appropriées. Les produits finaux, les dérivés amides **1A**-**9A**, ont été obtenus avec des rendements modérés à très bons (24 - 98%). Dans la plupart des cas, les rendements sont meilleurs que ceux rapportés dans la littérature. Les amides **5A** et **6A** ont également été préparés par une autre méthode utilisant l'α-chloroacétamide appropriée. Les deux voies de synthèse ont ainsi pu être comparées. Le produit **6A** a été obtenu avec un rendement de 78%, meilleur que celui rapporté dans la

littérature (57%) et que celui obtenu par la « mixed anhydrides method » (44%). Le produit **5A** est obtenu avec un rendement de 27% (accompagné de son complexe de Na^+ avec un rendement de 55%), meilleur que celui de la méthode «mixed anhydrides method» (44%). On constate dans les deux cas, que la seconde méthode est plus efficace.

Les structures radiocristallographiques des deux amides **1A** et **3A** ont été résolues. La structure de **1A** était déjà connue dans la littérature, et celle de **3A** est présentée ici pour la première fois. Les deux structures montrent la conformation cône de ces composés. Dans les deux cas, deux des substituants en position distale pointent en direction des cycles aromatiques du calixarène.

Les dérivés thioamides ont été préparés par thionation des amides en utilisant le réactif de Lawesson dans du toluène sec à 90°C sous atmosphère d'argon pendant 24h.

Les produits **7T**-**9T** ont été obtenus purs directement après recristallisation dans le mélange CH_2Cl_2/MeOH avec des rendements compris entre 64 et 72 %, tandis que pour les autres dérivés (**1T-6T**) une étape supplémentaire de purification par chromatographie sur colonne s'est avérée nécessaire. Dans ce cas, les rendements varient entre 12 et 68%. Les ligands porteurs de groupements alkyles (**2T-4T)**, cristallisant avec difficulté, ont été obtenus avec les rendements les plus faibles (12-30%).

Tous ces composés ont été caractérisés par microanalyse, par ^{1}H RMN et, dans certains cas (**5T, 6T, 7T, 9T**), par diffraction des rayons X. Ces deux dernières techniques ont permis de confirmer leur conformation en cône. En particulier, les structures radiocristallographiques des ligands **7T** et **9T** mettent en évidence leurs conformations en cône pincé et l'existence de liaisons hydrogène intramoléculaires N-H…S.

Interactions ligand-cation. Les propriétés d'extraction des dérivés thioamides ont été testées vis-à-vis de représentants des séries des cations alcalins (Na^+), alcalino-terreux (Ca^{2+}), lanthanides (Gd^{3+}) et des cations des métaux lourds (Ag^+, Cd^{2+} et Pb^{2+}) et de transition (Zn^{2+} et Cu^{2+}). Elles ont été comparées à celles obtenues pour les deux dérivés thioamides connus dans la littérature: le ligand **1T**, re-synthétisé dans ce travail, et le ligand **III**, porteur de substituants pyrrolidinyles, de structure apparentée à celle du ligand **5T**.

Les résultats montrent que tous les dérivés thioamides extraient quantitativement Ag^+ mais qu'ils sont de mauvais extractants des cations alcalins, alcalino-terreux, de Gd^{3+}, Cd^{2+} et Zn^{2+}. Les pourcentages d'extraction de Pb^{2+} et Cu^{2+} dépendent fortement de la nature des fonctions thioamides sur ces composés. La présence de thioamides secondaires réduit très fortement le pouvoir extractant. Par exemple Pb^{2+} est extrait à 56% par le dérivé diéthyl

thioamide **1T** alors qu'il ne l'est pas le dérivé éthylthioamide **7T**. Pb^{2+} est le cation le mieux extrait par le ligand **5T** porteur de substituants cycliques. Le niveau d'extraction de ce cation, plus élevé avec **5T** qu'avec **1T**, est cependant plus faible qu'avec le ligand **III**, pour lequel l'extraction de Pb^{2+} est presque quantitative.

Les dérivés amides tertiaires correspondants s'avèrent très efficaces aussi bien pour les cations à caractère « dur » comme Na^+ et Ca^{2+} que pour les cations « mous » comme Ag^+, Cd^{2+} et Pb^{2+}. Avec les cations Cu^{2+} et surtout Zn^{2+} et Gd^{3+} les pourcentages d'extraction observés sont nettement plus faibles. Par contre, les dérivés amides secondaires ne montrent aucune affinité pour tous les cations étudiés, y compris Ag^+. Le faible pouvoir extractant des dérivés amides et thioamides secondaires pourrait être lié à l'existence de liaisons hydrogène intramoléculaires entre les groupements NH et les atomes d'oxygène ou de soufre. Les résultats d'extraction confirment donc que le remplacement des atomes d'oxygène des amides tertiaires par des atomes de soufre conduit à des composés hautement sélectifs pour Ag^+ et Pb^{2+} par rapport aux cations des métaux alcalins et alcalino-terreux.

Les études de complexation par spectrophotométrie UV dans l'acétonitrile ont confirmé la forte affinité des dérivés thioamides tertiaires pour les cations des métaux lourds (Ag^+, Cd^{2+} et Pb^{2+}) et pour Cu^{2+}. L'addition des sels de ces cations entraine de fortes variations du spectre du ligand, contrairement à l'ajout de sels de sodium. Dans le cas des thioamides secondaires, des modifications spectrales importantes ont été observées lors des ajouts de sels d'argent. L'interprétation des spectres montre la formation d'espèces dont la stoechiométrie et la stabilité dépendent du cation. Des complexes ML et M_2L ont été trouvés avec Ag^+ avec tous les ligands (et avec Pb^{2+} dans le cas du ligand **2T**), alors que des espèces ML_2 ont été mises en évidence avec Pb^{2+}, Cu^{2+} et Cd^{2+}, parfois accompagnées de complexes ML dans le cas de Pb^{2+}. Les complexes les plus stables sont ceux de Ag^+ ce qui peut s'expliquer facilement par la forte affinité des atomes de soufre pour les cations Ag^+ de caractère « mou ». En ce qui concerne les complexes de Pb^{2+}, les constantes de stabilité les plus élevées ont été trouvées avec les ligands **5T** et **6T** (log β_{ML2} = 11,5 et 11,2, respectivement). Celles-ci sont beaucoup plus élevées qu'avec les thioamides **1T-4T** porteurs de substituants linéaires. Les constantes de stabilité des complexes de Cu^{2+} sont de 1 à 2 ordres de grandeur inférieures à celles des complexes de Pb^{2+}. Par contre, le complexe de Cu^{2+} avec le ligand **1T** est le plus stable.

La stabilité des complexes de Cd^{2+} varie peu avec les ligands (log β_{ML2} compris entre 8,6 à 9,3). Avec le ligand **6T**, cependant, aucune modification spectrale n'est observée lors de l'addition d'ions Cd^{2+}, suggérant une faible complexation.

La stoechiométrie et la stabilité des complexes de Ag^+ a été confirmée par potentiométrie et dans certains cas par microcalorimétrie. Cette deuxième technique a permis de déterminer les paramètres thermodynamiques (enthalpies et entropies de complexation) et les constantes de stabilité des complexes de Ag^+, Cd^{2+} et Cu^{2+} avec le ligand **5T**. Les résultats mettent en évidence la nature fortement enthalpique de la stabilisation du complexe M_2L de Cu^{2+}. Ce terme enthalpique particulièrement élevé et favorable est partiellement compensé par un terme entropique négatif et défavorable, suggérant des modifications conformationnelles et une ré-organisation importantes du ligand lors de la complexation. Cette situation est différente de celle des complexes correspondants de Cd^{2+} et Ag^+, pourtant globalement plus stables, et pour lesquels les termes enthalpiques et entropiques sont nettement plus faibles.

Les structures cristallographiques des complexes du plomb avec les ligands **5T** et **9T** fournissent des informations sur les changements conformationnels du ligand lors de la complexation de Pb^{2+}. Dans le complexe de stoechiométrie 1:1, le cation est en interaction avec les quatre atomes d'oxygène phénoliques et respectivement avec deux et quatre atomes de soufre des thiocarbonyles. La conformation des ligands complexés est plus régulière (moins pincée) que celle des ligands libres.

Les interactions entre les thioamides **5T**, **7T** et **9T** et les cations Pb^{2+} et Ag^+ ont été confirmées également par la ^1H RMN qui a permis la localisation du cation métallique dans le complexe. Les déplacements chimiques importants des protons des ligands, en particulier ceux situés à proximité des groupes OCH_2CS, suggèrent une contribution des atomes d'oxygène phénoliques et des atomes de soufre des thiocarbonyles dans la complexation des cations Pb^{2+} et Ag^+. Aucune variation spectrale n'a été observée lors de l'addition de Pb^{2+} avec les thioamides secondaires, ce qui n'exclut pas, cependant, la possibilité de formation du complexe. En effet celle-ci a été prouvée, par ailleurs, par radiocristallographie et par ^1H RMN.

En ce qui concerne les dérivés amides, les études de la complexation par spectrophotométrie UV dans le méthanol et dans l'acétonitrile ont confirmé leur forte affinité pour les cations de métaux alcalins tels que Na^+, mais aussi pour Ag^+, Cd^{2+} et Pb^{2+}. Les constantes de stabilité les plus élevées sont obtenues pour les complexes des amides tertiaires. On constate les mêmes tendances que celles observées en extraction. Dans le cas de Ag^+ il n'a pas été possible de chiffrer avec précision la valeur de ces constantes. C'est pourquoi, la complexation du cation Ag^+ a également été suivie par potentiométrie à l'aide d'une électrode d'argent. Les résultats ont montré que les constantes de stabilité des complexes ML de Ag^+ sont nettement plus faibles que celles des thioamides correspondants ($\Delta \log \beta \sim 5 - 6$ unités

log), contrairement aux autres cations, qui forment des complexes généralement plus stables avec les amides qu'avec les thioamides. Les constantes de stabilité sont généralement plus élevées dans l'acétonitrile que dans le méthanol, en accord avec les propriétés de solvatation des deux solvants. Seules les constantes de stabilité des complexes de Ag^+ dans l'acétonitrile sont inférieures à celles obtenues dans le méthanol, vraisemblablement en raison de la tendance qu'ont les ions Ag^+ à former des complexes avec ce solvant.

Electrodes sélectives. *L*es dérivés thioamides obtenus ont été incorporés comme éléments sensibles dans la membrane d'électrodes sélectives (ISEs) et testés pour leur sélectivité vis-à-vis de Pb^{2+}. Les études ont permis de déterminer les caractéristiques de ces électrodes et leurs coefficients de sélectivité. Les electrodes basées sur les thioamides tertiaires **1T-6T** sont stables jusqu'à 2 à 3 mois d'utilisation, tandis que la durée de vie des électrodes contenant les thioamides secondaires **7T-9T** est beaucoup plus courte, d'environ 2 semaines. L'influence de la structure du ligand sur les propriétés ionophoriques a été examinée pour **1T-7T** ainsi que l'effet des deux plastifiants (BBPA et NPOE) utilisés pour réaliser les membranes de PVC. La meilleure réponse a été obtenue pour le thioamide tertiaire **5T** avec une pente proche de la valeur de Nernst, soit 27,5 mV/dec et 29,2 mV/dec, respectivement pour les deux types de membranes, et un domaine de linéarité étendu (de 6 à 1 ou 2 unités log). Avec ce ligand, les électrodes répondent également à Cu^{2+}, avec des valeurs de pentes typiques des ions monovalents, 57,6 mV/dec (BBPA) et 57,7 mV/dec (NPOE). Ces valeurs élevées suggèrent que le cation Cu^{2+} est certainement associé avec des anions dans la membrane. Parmi les thioamides secondaires (**7T**-**9T**), les électrodes contenant l'ionophore **7T** ont un comportement quasi-Nernstien pour Pb^{2+} avec les deux plastifiants. Des électrodes incorporant les ionophores **8T** et **9T** conduisent à une réponse sub-Nerstienne (S = 25,1 et 24,4, respectivement).

Les coefficients de sélectivité ont été déterminés par la méthode dite des solutions séparées (« separate solution method »). On constate en général que les coefficients de sélectivité sont meilleurs pour des électrodes avec une membrane PVC/NPOE, avec cependant une exception pour Cd^{2+}. L'affinité de ce cation pour les plastifiants a été démontrée sur la base des coefficients de sélectivité déterminés avec une membrane ne contenant pas de ligand.

Les dérivés thioamides possèdent de très bonnes propriétés ionophoriques avec une sélectivité pour Pb^{2+} vis-à-vis d'un grand nombre des cations.

Les dérivés porteurs de substituants cycliques, tels que **5T** et **6T**, sont plus sélectifs que ceux porteurs de substituants linéaires. Les coefficients de sélectivité déterminés pour l'ionophore **5T** sont certainement les meilleurs. Ce composé pourrait être utilisé pour élaborer un capteur potentiométrique hautement sélectif pour les ions Pb^{2+} ou pour la détermination de Cu^{2+} sans la présence de Pb^{2+}.

Les sélectivité observées dans les électrodes à membrane dopées avec du BBPA comme plastifiant sont comparables avec celles observées en extraction et en complexation, soit $Pb^{2+} > Cu^{2+} > Cd^{2+}$.

Calix[4]arènes hydroxamates et acides hydroxamiques

Synthèse. Cinq calix[4]arènes substitués par des groupements hydroxamates (un dérivé tris-substitué (composé **10**) et quatre dérivés tétra-substitués (composés **11-14**)) et par des groupements acide hydroxamique (deux dérivés tris-substitués (composés **15** et **16)** et deux dérivés tétra-substitués (composés **17** et **18**)) ont été synthétisés par la méthode dite « mixed anhydrides method ». Ils ont été obtenus avec de bons rendements compris entre 48 et 82%.

Ces composés ont été caractérisés par ^{1}H RMN et par microanalyse dans les cas des ligands **14-18**. La ^{1}H RMN et dans certains cas (composés **11** et **13**) la diffraction des rayons X ont montré leur conformation en cône. En particulier, les structures cristallographiques des ligands **11** et **13** mettent en évidence l'existence de liaisons hydrogène intramoléculaires N-H…O.

Des essais réalisés pour préparer les analogues thiocarbonylés des dérivés hydroxamates et acide hydroxamique obtenus sont restés infructueux. La thionation directe des dérivés hydroxamates en utilisant le réactif de Lawesson conduit à un produit dont la structure cristallographique montre la présence de deux ponts di-sulfures. Ce composé incorporé dans la membrane d'électrodes sélectives n'a montré aucune propriété ionophorique intéressante. La réaction de thioacylation s'est révélée également inefficace, le produit isolé étant l'amide secondaire du calix[4]arène, résultant de la réduction de l'acide hydroxamique.

***Interactions ligand-cation*.** Comme les dérivés amides secondaires, les dérivés hydroxamates porteurs de groupements NH (**10-13**) sont de faibles extractants. De même il a

été difficile de déterminer les constantes de stabilité des complexes formés par spectrophotométrie en raison des très faibles modifications spectrales du ligand lors de la complexation.

En revanche, le dérivé hydroxamate substitué sur les atomes O et N (**14**), montre des pourcentages d'extraction significatifs, en particulier pour Na^+, Pb^{2+} et Ag^+. Il est cependant moins efficace que les amides tertiaires. Pour ce ligand, les constantes de stabilité des complexes de Na^+, Pb^{2+} et Cd^{2+} ont été déterminées par spectrophotométrie UV dans le méthanol. L'interprétation a montré la formation d'espèces ML_2 accompagnées de complexes ML avec Na^+ et Pb^{2+}, et d'espèces ML_2 avec Cd^{2+}. Des complexes ML et ML_2 avec Ag^+ ont été mis en évidence par potentiométrie. Aucun changement spectral significatif n'a été remarqué lors de l'ajout de Cu^{2+}, indiquant l'absence ou de très faibles interactions entre ce ligand et ce cation.

La fonction acide hydroxamique est bien connue pour sa grande affinité vis-à-vis du fer. Les calixarènes hydroxamiques obtenus dans ce travail (**15-18**) ont été étudiés en extraction vis-à-vis des métaux lourds (Cd^{2+}, Pb^{2+}) et de transition (Co^{2+}, Ni^{2+}, Zn^{2+}, Fe^{3+}, Cu^{2+}) et dans des conditions de compétition ce qui a permis d'évaluer la possibilité d'une séparation effective. Les résultats d'extraction ont montré que tous ces ligands extraient très efficacement Fe^{3+} (%E > 60) et presque quantitativement Cu^{2+}. Avec les ligands **15** et **17**, les pourcentages d'extraction de Pb^{2+} sont de 85 et 62%, respectivement. Dans l'extraction compétitive, les pourcentages d'extraction diminuent généralement en présence d'un autre cation en solution. Des résultats particulièrement intéressants ont été obtenus avec le ligand **17** pour l'extraction de Pb^{2+} en présence de Cd^{2+}. Dans ces conditions, Pb^{2+} est presque quantitativement extrait et le pourcentage d'extraction est plus élevé que pour les expériences individuelles. Au contraire, le pourcentage d'extraction de Cd^{2+} est abaissé par rapport à l'extraction individuelle. Ces résultats sont très importants dans le contexte de l'élimination et de séparation du plomb d'autres métaux toxiques comme Cd^{2+} et pourraient s'expliquer par des effets cinétiques. De plus, l'utilisation de ces ligands pourrait permettre de séparer Cu^{2+} et Zn^{2+} qui sont souvent présents simultanément.

Electrodes sélectives. Incorporés comme éléments sensibles dans la membrane d'électrodes sélectives (ISEs), les dérivés hydroxamates possèdent une sélectivité pour Pb^{2+} dans le cas des hydroxamates O-substitués (**10-13**) et pour Na^+ dans le cas du ligand O- et N-substitué (**14**). Les électrodes basées sur les ionophores **10, 11** et **13** donnent une réponse quasi-Nernstienne pour Pb^{2+} avec un large domaine de linéarité (6 ou 5 à 2 unités log). Il est

intéressant de noter que les électrodes basées sur l'ionophore **12** présentent une pente de calibration de 51,2 mV / dec, typique d'espèces monovalentes. Ceci suggère que le cation Pb^{2+} est associé avec les anions NO_3^- dans la membrane. Probablement, les chaînes butyle présentes dans la structure de **12** sont suffisamment flexibles pour élargir la cavité et ainsi favoriser l'extraction de l'anion dans la membrane. Dans les autres cas, les substituants peu volumineux comme les groupes méthyles ou rigides comme les groupes iso-propyles ne permettent probablement pas l'extraction de l'anion vers la membrane.

Les coefficients de sélectivité ont été déterminés par la méthode dite « separate solution method ». Les dérivés hydroxamates **11-13** pourraient être utilisés pour déterminer la concentration des ions Pb^{2+}, mais en l'absence de cations Na^+ et K^+, qui sont les ions les plus interférents. Cependant, leur sélectivité est meilleure que celle des ionophores amides secondaires, mais le manque de sites donneurs mous comme les atomes de soufre, fait qu'ils sont beaucoup moins sélectifs que les calix[4]arène-thioamides. Par contre, leur sélectivité pour Pb^{2+} par rapport aux cations des métaux lourds et de transition (par exemple, Cd^{2+} et Cu^{2+}) est très satisfaisante.

L'ordre de sélectivité pour Na^+ par rapport aux métaux lourds tels que Pb^{2+}, Cd^{2+} et Cu^{2+} avec l'ionophore **14** est en d'accord avec les données d'extraction (E% Na^+ > E% Pb^{2+} >> E% Cd^{2+} > E% Cu^{2+}). En outre, la constante de stabilité la plus élevée déterminée par spectrophotométrie UV a été trouvée pour le complexe de Na^+, bien que des constantes de stabilité similaires soient observés pour les complexes des cations Pb^{2+} et Cd^{2+}.

Les électrodes incorporant dans leurs membranes des dérivés thioamides des calixarènes devraient constituer des outils analytiques prometteurs pour le contrôle des niveaux de pollution en plomb des eaux naturelles et des eaux potables

Streszczenie

«Synteza oraz badanie właściwości kompleksujących kaliks[4]arenów modyfikowanych podstawnikami amidowymi i hydroksamowymi oraz ich tiokarbonylowymi analogami»

Praca została zrealizowana we współpracy pomiędzy Uniwersytetem w Strasburgu (Promotor: Dr Véronique HUBSCHER-BRUDER) oraz Politechniką Gdańską (Promotor: Prof. Maria BOCHEŃSKA).

Szybki rozwój przemysłu obserwowany w ostatnich latach niesie ze sobą potrzebę kontrolowania jego negatywnego wpływu na środowisko naturalne. Szczególnie ważnym aspektem jest potrzeba monitorowania i kontrolowania stężenia jonów metali ciężkich, jak np. ołowiu czy kadmu, metali mających toksyczne działanie na wszystkie organizmy żywe. Wykrycie stężenia jonu metalu na niskim poziomie wymaga konstrukcji czujnika wysoce selektywnego oraz czułego na dany jon. Fakt ten inspiruje chemików-syntetyków poszukujących metod syntezy coraz to bardziej selektywnych związków.

Modyfikowany kaliks[4]aren stanowi doskonały materiał badawczy ze względu na swoje niezwykłe właściwości kompleksujące. Głównym celem mojej pracy doktorskiej była synteza pochodnych kaliks[4]arenu modyfikowanych podstawnikami tiokarbonylowymi. Wprowadzając do struktury kaliks[4]arenu atomy siarki, można liczyć na wzrost powinnowactwa takich ligandów do niektórych jonów metali ciężkich, np. ołowiu, miedzi czy kadmu, a jednocześnie uzyskanie wysokiej selektywności w stosunku do jonów metali I i II grupy. Celem było również porównanie właściwości kaliks[4]aren-tioamidów z ich odpowiednimi kaliks[4]aren-amidami, które również syntezowano w niniejszej pracy. Podjęto również próbę otrzymania pochodnych kaliks[4]arenu z podstawnikami tiohydroksamowymi z chronioną grupą hydroksylową oraz/lub podstawioną na atomie azotu. Takie zwiąki nie były dotąd opisane w literaturze. W celach porównawczych zsyntezowano i zbadano również pochodne hydroksamowe kaliks[4]arenu. Kolejnym celem było badanie oddziaływań ligandów z kationami metali przy pomocy różnych metod badawczych takich jak: spektroskopia ^{1}H NMR, analiza rentgenograficzna kryształów kompleksów, ekstrakcja, spektrofotometria UV, potencjometria z zastosowaniem elektrody srebrowej oraz mikrokalorymetria. Selektywność kompleksowania przez związki kaliks[4]aren-tioamidowe

oraz pochodne hydroksamowe oceniono wstępnie stosując te związki jako materiały sensorowe w membranowych elektrodach jonoselektywnych.

Praca została przedstawiona w formie czterech rozdziałów, każdy poprzedzony krótkim wstępem literaturowym.

Rozdział pierwszy stanowi przegląd literaturowy dotyczący metod syntezy omawianych klas pochodnych kaliksarenu oraz obrazuje dotychczasowe prace w zakresie badań oddziaływań tych pochodnych z kationami metali.

W rozdziale drugim zaprezentowano szczegóły dotyczące syntezy związków. Otrzymano dziewięć pochodnych tioamidowych *p-tert*-butylokaliks[4]arenu (związki **1T-6T**, będące trzeciorzędowymi amidami oraz drugorzędowe amidy, związki **7T-9T**), z których tylko związek **1T** znany był z wcześniejszych doniesień literaturowych.

Otrzymano też dziewięć pochodnych amidowych, oznaczonych jako **1A-9A** (związek **4A** otrzymano w tej pracy po raz pierwszy), które były substratami do otrzymania związków tioamidowych. Wśród pochodnych hydroksamowych syntezowano związki z grupą –NH, podstawione na atomie tlenu (**10-13**) oraz związek **14** podstawiony grupą metylową zarówno na atomie tlenu, jak i azotu. Otrzymano również cztery kaliks[4]aren-kwasy hydroksamowe z wolną grupą OH (**15-18**). Syntezowane związki były charakteryzowane za pomocą widm ^{1}H NMR (potwierdzając otrzymanie ligandów w pożądanej konformacji stożkowej), widm IR, a w niektórych przypadkach analizą elementarną. Otrzymano w sumie osiem struktur krystalograficznych ligandów (**5T, 6T, 7T, 9T, 1A, 3A, 11, 13**), wśród nich tylko jedna struktura (związku **1A**) znana jest z literatury, pozostałe prezentowane są tu po raz pierwszy. Badania rentgenostrukturalne potwierdzają konformację stożkową tych ligandów, a w przypadku związków **7T, 9T, 11** oraz **13** również obecność wiązań wodorowych stabilizujących konformację cząsteczki.

Rozdział trzeci przedstawia metody badań oddziaływań ligandów z jonami metali wykorzystane w tej pracy i jest podzielony na trzy podrozdziały. Krótki wstęp poprzedza podstawy teoretyczne metod badań oraz opis przeprowadzonych doświadczeń. Następnie omówione są wyniki badań oraz dyskusja wniosków.

Dyskusję otwiera przedstawienie widm ^{1}H NMR zsyntezowanych kompleksów ligandów **5T, 7T** oraz **9T** z jonami Pb^{2+}, a w przypadku liganda **5T** również z jonami Ag^{+}. Stwierdzono znaczne przesunięcia chemiczne protonów w widmach kompleksów w stosunku do wolnego liganda, szczególnie protonów aromatycznych, a także tych, znajdujących się w sąsiedztwie grup OCH_2CS, co sugeruje udział eterowych atomów tlenu oraz atomów siarki w kompleksowaniu kationów Pb^{2+} i Ag^{+}.

Otrzymano dwie struktury krystalograficzne kompleksów z jonami Pb^{2+} ligandów **5T** oraz **9T**. Stwierdzono, iż kation Pb^{2+} jest wiązany z czteroma eterowymi atomami tlenu oraz dwoma bądź czteroma atomami siarki.

Właściwości ekstrakcyjne pochodnych tioamidowych kaliks[4]arenu zostały zbadane z wybranymi kationami metali z grupy I (Na^{+}), grupy II (Ca^{2+}), lantanowców (Gd^{3+}), metali ciężkich (Ag^{+}, Cd^{2+}, Pb^{2+}) oraz przejściowych (Zn^{2+} i Cu^{2+}). Wyniki pokazują, iż ligandy te są słabymi ekstrahentami jonów Na^{+}, Ca^{2+}, Gd^{3+}, Cd^{2+} oraz Zn^{2+}. Prawie ilościowo ekstrahują Ag^{+}, a procent ekstrakcji Pb^{2+} oraz Cu^{2+} zależy od rzędowości tioamidu. Drugorzędowe kaliks-tioamidy są słabymi ekstrahentami, prawdopodobnie ze względu na obecność wiązań wodorowych w cząsteczce, utrudniających dostęp kationów do wnęki liganda oraz/lub ze względu na wysoką hydrofilowość powstałego kompleksu pozostającego w fazie wodnej. Jednakże prawie ilościowo ekstrahują Ag^{+}. Odpowiadające im drugorzędowe kaliks-amidy (**7A-9A**) wykazują również słabe właściwości ekstrakcyjne badanych jonów, włączając w to kation Ag^{+}. Ligandy **1A-6A** będące trzeciorzędowymi kaliks-amidami, ekstrahują prawie ilościowo zarówno kationy o charakterze twardych kwasów, takich jak Na^{+} i Ca^{2+}, jak również te, o charakterze bardziej miękkich kwasów (Ag^{+}, Cd^{2+}, Pb^{2+}). Wyniki ekstrakcyjne potwierdzają, iż zastąpienie twardych centrów koordynacji (atomów tlenu) bardziej miękkimi atomami siarki, powoduje wzrost powinowactwa do bardziej miękkich kationów jak Ag^{+} i Pb^{2+} oraz wzrost selektywności w stosunku do kationow I i II grupy.

Badania kompleksowania metodą spektrofotometrii UV w acetonitrylu potwierdzają wysokie powinowactwo trzeciorzędowych tioamidów do metali ciężkich (Ag^{+}, Cd^{2+}, Pb^{2+}) oraz Cu^{2+}, dla których wyznaczono stałe trwałości kompleksów. Pod wpływem dodatku soli Na^{+}, nie zarejestrowano znaczących zmian w widmie liganda, co świadczy o braku, bądź bardzo niewielkim oddziaływaniu tioamidów z jonami Na^{+}. Najwyższe stałe trwałości uzyskano dla kompleksów z jonami Ag^{+}, a model kompleksu (ML + M_2L) potwierdzono metodą potencjometryczną i mikrokalorymetryczną. Miareczkowanie mikrokalorymetryczne zastosowano również w celu wyznaczenia parametrów termodynamicznych oraz stałych trwałości kompleksów z jonami Cd^{2+} oraz Cu^{2+} dla liganda **5T**. Podczas gdy tworzenie kompleksu z jonami Ag^{+} i Cd^{2+} jest termodynamicznie korzystne, formowanie się kompleksu z jonami Cu^{2+} „kosztuje” ligand znaczną reorganizację struktury w celu przyjęcia kationu Cu^{2+}, co uwidacznia bardzo niska i niekorzystna wartość czynnika entropii.

Badania kompleksowania metodą spektrofotometrii UV w metanolu i acetonitrylu potwierdzają wysokie powinowactwo trzeciorzędowych amidów do takich metali jak Na^{+}, ale również do Ag^{+}, Cd^{2+}, Pb^{2+} oraz Cu^{2+}. Wyznaczone stałe trwałości kompleksów z jonami

Na^+, Ag^+, Cd^{2+} oraz Pb^{2+} dla trzeciorzędowych kaliks-amidów, a także w niektórych przypadkach dla drugorzędowych kaliks-amidów są wysokie. Badania kompleksowania jonów Ag^+ śledzono metodą potencjometryczną z zastosowaniem elektrody srebrowej. Stałe trwałości uzyskane w acetonitrylu były wyższe od tych wyznaczonych w metanolu, co ma związek z odmiennymi właściwościami solwatującymi obu rozpuszczalników. Odmiennie sytuacja wygląda tylko dla kompleksów z jonami Ag^+, dla których stałe trwałości w acetonitrylu były niższe niż te uzyskane w metanolu ze względu na tendencję jonów Ag^+ do tworzenia kompleksów z acetonitrylem. Wyniki badań spektrofotometrycznych są zgodne z tendencję zauważoną w badaniach ekstrakcyjnych.

Pochodne hydroksamowe z grupami NH (związki **10-13**), podobnie jak drugorzędowe kaliksaren-amidy, charakteryzują się słabymi właściwościami ekstrakcyjnymi. Brak znaczących zmian w widmie UV pod wpływem dodatków soli Pb^{2+} oraz Ag^+ nie pozwolił na wyznaczenie stałych trwałości kompleksów. Wśród tej grupy pochodnych kaliksarenowych, jedynie związek **14**, podstawiony grupą metylową na atomie azotu oraz tlenu, znacznie ekstrahuje Na^+, Pb^{2+} i Ag^+ (%E ≥ 41), a stałe trwałości kompleksów z jonami Na^+, Pb^{2+} i Cd^{2+} wyznaczono metodą spektrofotometryczną. Stałą trwałości kompleksu z jonami Ag^+ wyznaczono potencjometrycznie. Ligand **14** swoimi właściwościami kompleksującymi przypomina trzeciorzędowe kaliksaren-amidy.

Kwasy hydroksamowe kaliks[4]arenu (związki **15-18**) zostały zbadane w ekstrakcji z zastosowaniem poszczególnych kationów metali Cd^{2+}, Pb^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cu^{2+} i Fe^{3+} oraz w ekstrakcji konkurencyjnej z dwoma lub trzema kationami w mieszaninie. Ligandy te są dobrymi ekstrahentami Fe^{3+} oraz Cu^{2+} (w przypadku Cu^{2+} ekstrakcja praktycznie ilościowa). Ligandy niepodstawione na atomie azotu (**15** i **17**) wykazują się znacznymi zdolnościami ekstrakcyjnymi Pb^{2+}. W warunkach ekstrakcji konkurencyjnej, procent ekstrakcji obniża się w obecności innego kationu w roztworze. Szczególnie ciekawe wyniki uzyskano dla liganda **17**, gdzie procent ekstrakcji Pb^{2+} w obecności Cd^{2+} jest wyższy niż w przypadku ekstrakcji indywidualnej kationów. Pozwala to na bardzo efektywne usunięcie i oddzielenie jonów Pb^{2+} od jonów Cd^{2+}. Ponadto wyniki ekstrakcyjne z zastosowaniem tych ligandów są ciekawe także z punktu widzenia możliwości separacji Cu^{2+} od Zn^{2+}, które często występują razem.

Rozdział czwarty dotyczy membranowych elektrod jonoselektywnych. Po wstępie teoretycznym, przedstawiono wyniki zastosowania pochodnych tioamidowych (**1T-9T**) oraz hydroksamowych (**10-13**) jako potencjalne materiały czujnikowe w membranowych elektrodach jonoselektywnych i zbadano ich selektywność w stosunku do jonów Pb^{2+}. Elektrody oparte na jonoforach **1T-6T**, bedące trzeciorzędowymi tioamidami są stabilne

nawet do 2-3 miesięcy będąc w użyciu, podczas gdy czas życia elektrod z jonoforami **7T-9T** jest dużo krótszy (około 2 tygodni).

Jonofory **1T-7T** zbadano w dwóch różnych membranach (PVC/BBPA oraz PVC/NPOE) zawierających różne plastyfikatory. Stwierdzono, że lepsze współczynniki selektywności uzyskano w elektrodach z membraną PCV/NPOE, niż w PCV/BBPA. Wyjątek stanowi Cd^{2+}, dla którego lepszą selektywność uzyskano w elektrodach z membraną PVC/BBPA. Powinnowactwo kationów do plastyfikatora wykazano na podstawie wyznaczonych współczynników selektywności z pustą membraną, niezawierającą liganda. Wykazano, iż jonofory oparte na tioamidach z cyklicznymi podstawnikami, takimi jak w związkach **5T** oraz **6T**, charakteryzują się lepszą selektywnością, niż te oparte na liniowych podstawnikach. Współczynniki selektywności wyznaczone dla jonoforu **5T** są zdecydowanie najlepsze, niezależnie od użytego plastyfikatora. Z powodzeniem związek ten mógłby być wykorzystany do budowy wysoce selektywnego na jony Pb^{2+} czujnika potencjometrycznego.

Porównując współczynniki selektywności wyznaczone w elektrodach jonoselektywnych z membraną PVC/BBPA dla Pb^{2+} w stosunku do innych metali ciężkich takich jak Cu^{2+} i Cd^{2+} z wynikami ekstrakcyjnymi, można zauważyć podobną tendencję (E% Pb^{2+} >> E% Cu^{2+} >> E% Cd^{2+}). Stałe trwałości kompleksów wyznaczone spektrofotometrycznie maleją w kolejności: Pb^{2+} > Cu^{2+}> Cd^{2+}, co w pewien sposób również potwierdza selektywność uzyskaną w badaniach elektrodowych.

Pochodne hydroksamowe (**11-13**) mogłyby być wykorzystane w celu oznaczenia stężenia jonow Pb^{2+}, lecz w nieobecności kationów Na^{+} i K^{+}, które są najbardziej przeszkadzającymi jonami. Ich selektywność jest jednak lepsza od kaliksarenowych jonoforów opartych na amidach drugorzędowych, lecz brak miękkich centrów koordynacji, jak atomy siarki, powoduje, iż w porównaniu z przedstawionymi tu niektórymi kaliks[4]aren-tioamidami, są zdecydowanie mniej selektywne.

W przeciwieństwie do II-rzędowych pochodnych hydroksamowych **10-13**, jonofor **14** podstawiony zarówno na atomie tlenu jak i azotu, wykazuje się selektywnością na jony Na^{+}. Współczynniki selektywności wyznaczone względem Na^{+} dla metali ciężkich, takich jak Pb^{2+}, Cd^{2+} i Cu^{2+} są zgodne z wynikami ekstrakcyjnymi (E% Na^{+} > E% Pb^{2+} >> E% Cd^{2+} > E% Cu^{2+}). Ponadto, stała trwałości kompleksu z jonami Na^{+} wyznaczona metodą spektrofotometryczną jest najwyższa, chociaż podobne stałe trwałości wyznaczono też dla kompleksów z jonami Pb^{2+} oraz Cd^{2+}.

Abbreviations

A complete list of abbreviations used in text:

BBPA - bis(1-butylpentyl) adipate
CHEMFET – chemically modified field effect transistor
DBP – dibutyl phthalate
DBS – dibutyl sebacate
DEHA – bis(2-ethylhexyl) adipate
DL – detection limit
DMF – dimethyl formamide
DMSO – dimethyl sulfoxide
DOP – di(n-octyl) phthalate
DOS – bis(n-octyl) sebacate
EA – elemental analysis
EMF – electromotive force
ESI – Electrospray ionisation
FIM – fixed interference method
HSAB – Hard and Soft Acids and Bases
IR – infra red
ISE – ion-selective electrode
IUPAC – International Union of Pure and Applied Chemistry
KT*p*ClPB – potassium tetrakis(*p*-chlorophenyl) borate
LR –Lawesson Reagent or linear range (only in Chapter IV)
MPM – matched potential method
Na_2EDTA – disodium ethylenediamine tetraacetic acid
NMR – nuclear magnetic resonance
o-NPOE – *o*-nitrophenyl octyl ether
PIM – polymer inclusion membrane
PVC – poly(vinyl chloride)
SSM – separate solution method
THF – tetrahydrofuran
TLC – thin layer chromatography
UV – ultra violet

In this work, compounds were named as follows:

- intermediates as **S_1-S_{11}**
- final products as **1T-9T** (calix[4]arene-thioamides); **1A-9A** (calix[4]arene-amides); **10-14** (calix[4]arene-hydroxamates); **15-18** (calix[4]arene-hydroxamic acids)
- literature compounds as **I-LXI**; if the same compound is studied in this work and in the literature, its number is specified in brackets, e. g. **I** (**1A**).

INDEX

INTRODUCTION

Supramolecular chemistry is nowadays a fast growing field of chemistry, combining organic chemistry (synthesis of ligands), coordination chemistry (complexes of metal ions with the ligands), physical chemistry (studies of ligand interaction with metal ions using different techniques), biochemistry and biology (recognition and substrate binding according to the "lock and key" principle). Among a variety of macrocyclic compounds, with which supramolecular chemistry deals, are calixarenes. Since their discovery, calixarenes have received great interest and much research effort has been made to modify their structure.

The basic principle which helps in designing new host molecules is the theory of Hard and Soft Acids and Bases (Pearson HSAB theory). According to this theory, hard bases like oxygen atoms show preferences to hard acids like alkali or alkaline earth cations (Na^+, Li^+, Ca^{2+} …). In contrast, softer sulphur atoms present an affinity for softer cations, such as Ag^+, Cd^{2+} or Pb^{2+}.

Particularly noteworthy are heavy metals which accumulate in the human body and cause numerous neurological diseases. At present, the importance of detecting and controlling the toxic heavy metals (such as Cd^{2+} or Pb^{2+}) in waters, is extremely important and give a challenge for chemists who design and synthesise selective ligands for those cations.

The objective of this thesis is to design and synthesise functionalised calix[4]arenes as potential sensing material for transition and heavy metal cations. The attention is focused mainly on calix[4]arene-thioamides. Although some examples of calixarene-thioamides applications are known from the literature, it is worth to say that only few publications deal with, for instance, stability constants determination which is important in studying new ligands properties.

The relationship between the ligand structure and its properties, i. e. to find out how even small structural changes can affect the properties of new ionophores, is of great interest.

The properties of calix[4]arene-thioamides were compared with their corresponding calix[4]arene-amides which were synthesised as substrates for thioamides synthesis.

Another group of calix[4]arene derivatives synthesised in this work is O- or/and N-substituted hydroxamides. It was planned to compare their binding properties with the properties of thiocarbonyl analogues. Calix[4]arene-thiohydroxamic acids and calix[4]arene-thiohydroxamates would be interesting as complexing ligands. The presence of significantly different atoms: N, O and S makes these compounds poly-dentate able to complex different metals. So far, such ligands were not reported in the literature. By introduction of soft sulphur

atoms into the structures of calix[4]arene-hydroxamic acids and calix[4]arene-hydroxamates, the improvement of ionophoric properties of such compounds was expected.

Nine calix[4]arene-thioamides **1T-9T** (**Figure 1**) were synthesised together with their corresponding amides **1A-9A** (**Figure 2**).

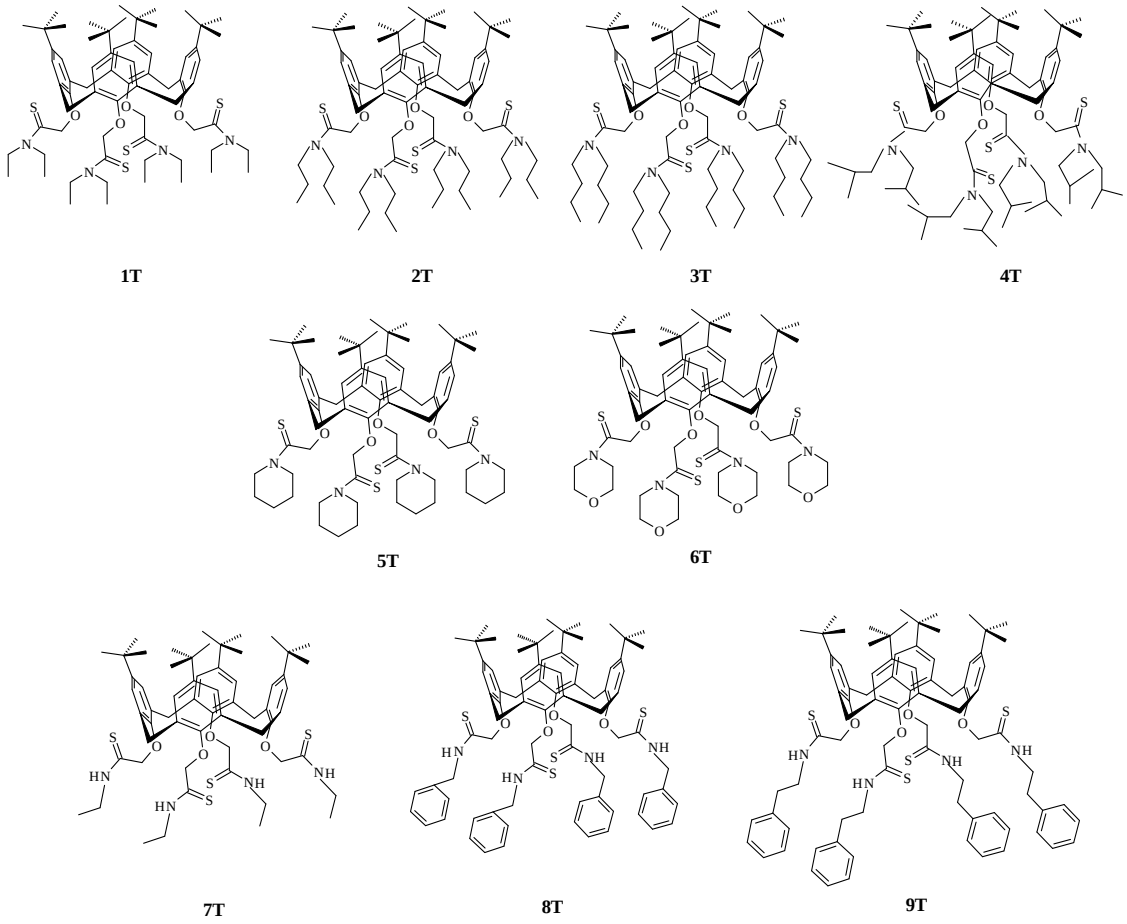


Figure 1. Calix[4]arene-thioamides (**1T-9T**) synthesised and studied in this work

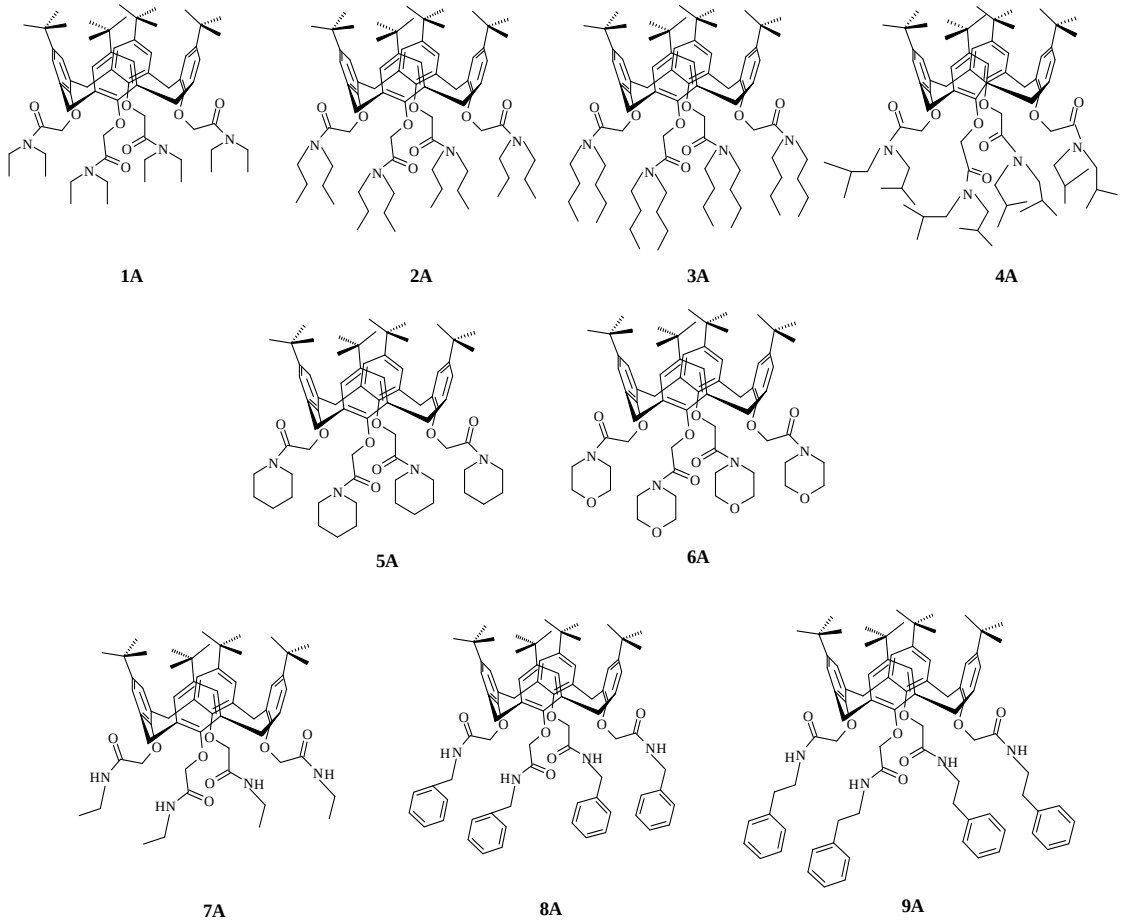


Figure 2. Calix[4]arene-amides (**1A-9A**) synthesised and studied in this work

Moreover five O- and O- and N-substituted hydroxamate derivatives **10-14** (**Figure 3**) as well as four N-substituted or N- free hydroxamic acids **15-18** were prepared (**Figure 4**).

The interactions between those ligands and metal ions were studied using different methods: X-ray crystal structure analysis, ^{1}H NMR, liquid-liquid extraction, UV absorption spectrophotometry, microcalorimetry and potentiometry with the use of an Ag^{+}/Ag electrode. Calix[4]arene-thioamides **1T-9T** and calix[4]arene-hydroxamates **10-14** were applied as sensing materials in ion-selective membrane electrodes (ISEs).

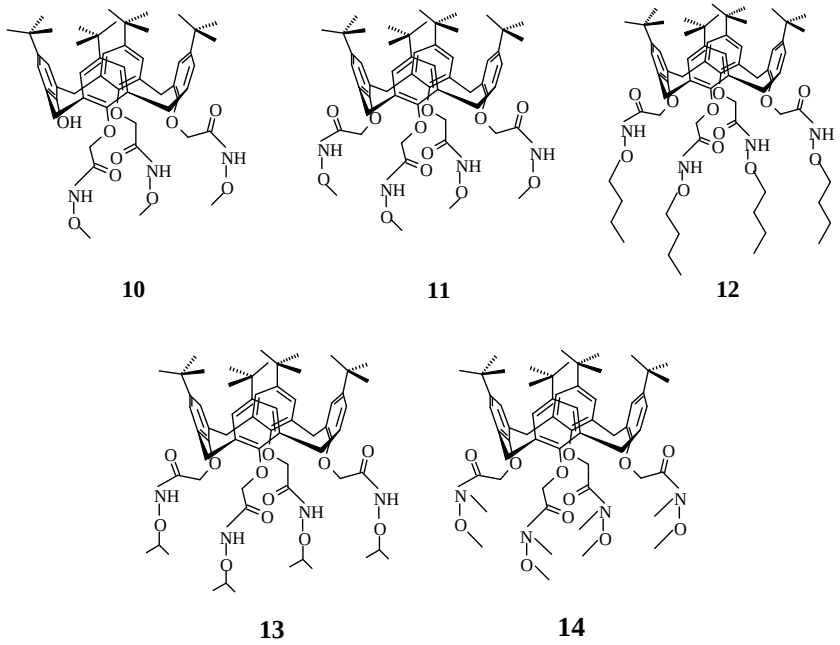


Figure 3. Calix[4]arene-hydroxamates (**10-14**) synthesised and studied in this work

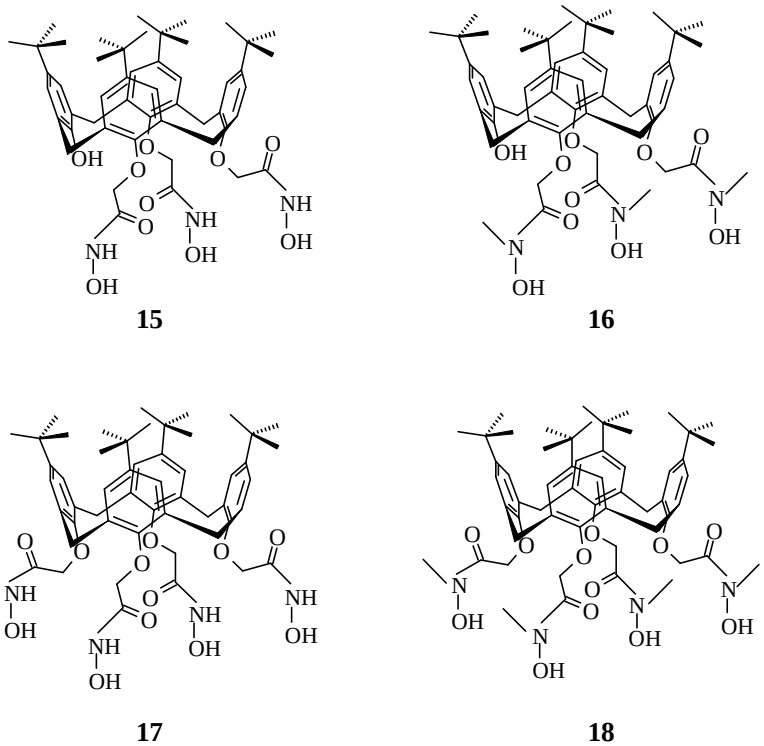


Figure 4. Calix[4]arene-hydroxamic acids (**15-18**) synthesised and studied in this work

My work is presented in four chapters.

In the first Chapter, a literature review on the synthetic methods and binding properties of calix[4]arene derivatives studied here, is given.

Chapter II presents the synthesis and characterisation of the studied ligands.

Chapter III is devoted to the ligand-cation interaction studies. The theorethical bases of the methods used are described and followed by the results and discussion, which is subdivided into four parts corresponding to each ligand family: calix[4]arene-thioamides, calix[4]arene-amides, calix[4]arene-hydroxamates and calix[4]arene-hydroxamic acids.

Chapter IV is ascribed to the study of ionophoric properties of calix[4]arene-thioamides and calix[4]arene-hydroxamates in ion-selective membrane electrodes. The results follow a short theorethical introduction to ion-selective electrodes.

A general conclusion closes this work.

CHAPTER I:

BIBLIOGRAPHIC SURVEY

1. Calixarene-thioamides

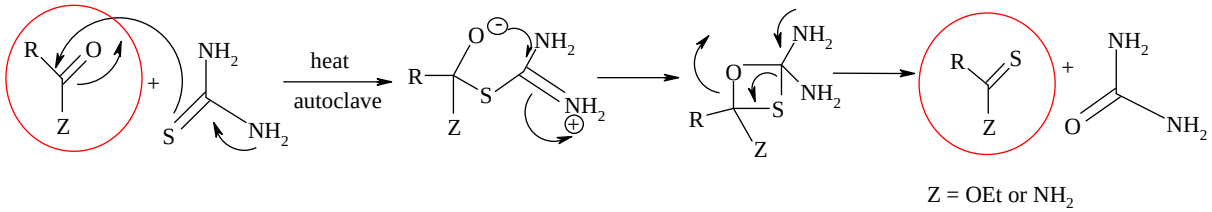
1.1. Presentation of thionating reagents

Thionation, the conversion of carbonyl into thiocarbonyl groups, is widely applied in organic syntheses. In the past, thiophosgene and analogous compounds were used for thiocarbonyl transfer [1]. Nevertheless this method is often ineffective and nowadays other different reagents are used. Here, I present various thionating agents used in converting carbonyls into thiocarbonyls.

The use of hydrogen sulfide gas (H_2S) in the presence of an acid catalyst provides clean products with good yields. Therefore, the method is still employed, despite some difficulties with the use of hydrogen sulfide gas [2]. The acid used as catalyst is usually hydrogen chloride, which reversibly protonates the carbonyl group. H_2S is then used for substitution at carbon atom and subsequent elimination gives the thiocarbonyl.

Other reagents have been also successfully applied in such transformation, namely bis-(tricyclohexyltin) sulfide with boron trifluoride [3], bis(trimethylsilyl)sulfide and $CoCl_2 \times 6H_2O$ [4], thionation of *gem*dichlorides with sodium hydrogen sulfide [5], thioacetic acid [6] or potassium xanthate [7]. These reactions are usually taking more time, require an excess of reagents and provide products with moderate yields.

A simple, rapid, high-yielding (yield >80%) and environmentally safe method for the conversion of esters and amides to the corresponding thio-compounds was carried out using thiourea as thionating agent under solvothermal reaction [8]. The probable mechanism of this reaction is presented in **Scheme I-1**.



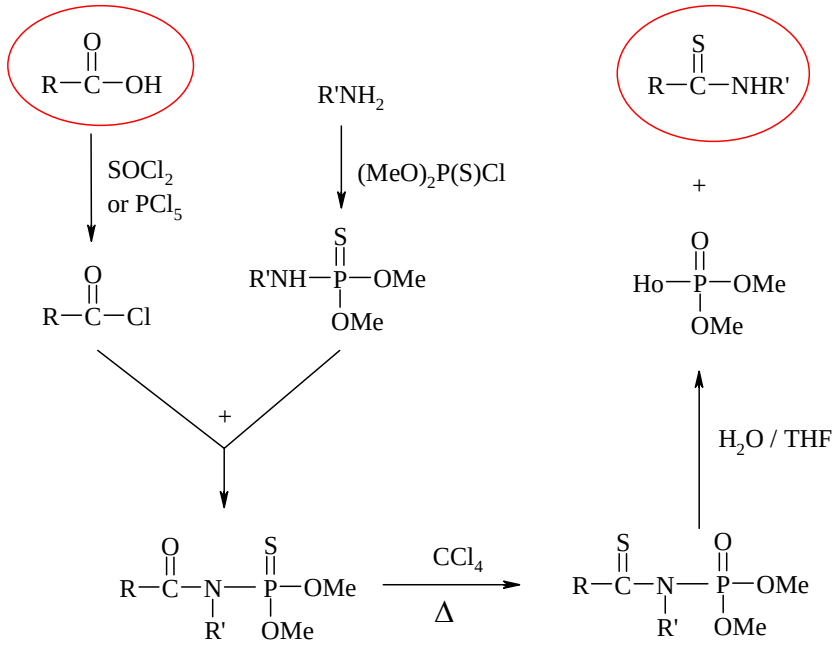
Scheme I-1. Synthesis of thioesters and thioamides using thiourea under solvothermal reaction [8]

It involves the initial attack of the thiourea sulphur atom assisted by the lone electron pair on the nitrogen at the carbonyl carbon atom of the ester/amide giving oxathietane as an intermediate. These intermediates undergo a ring-opening reaction leading to the formation of

the desired thioester or thioamide and urea as the side product. Although this method is efficient, the reaction needs to be carried out in autoclave. This raises the costs of such method.

Commonly used are inorganic reagents containing phosphorus and sulphur atoms, such as: PCl_5/Na_2SO_4, P_2S_5/NEt_3, $RPS(OR')_2$, $PSCl_n(NMe_2)_{3-n}$.

K. E. DeBruin and E. E. Boros have used a commercially available and inexpensive organophosphorus reagent (dimethyl chlorothiophosphate) in thioamides preparation starting from carboxylic acids (via acid chlorides) and amines (**Scheme I-2**) [9].



Scheme I-2. Thioamides preparation using dimethyl chlorothiophosphate [9]

Despite some advantages, it is a multistep reaction and can be applied only for N-monosubstituted thioamides preparation [9].

The most universal reagent is a diphosphorus pentasulfide P_4S_{10} (**Figure I-1.)** [10, 11]. Since its first use in 1886 in the synthesis of Michler's thioketone, it has gained much attention and has found wide application in thiocarbonyl compounds preparation.

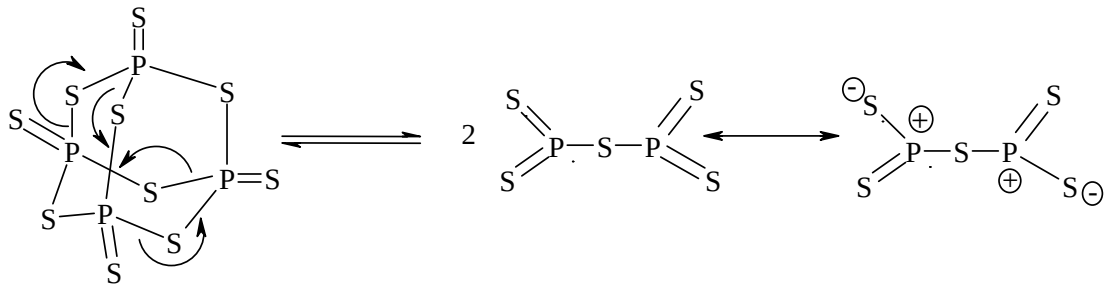
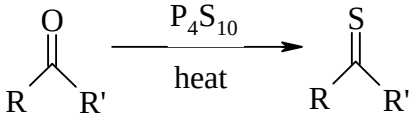


Figure I-1. Diphosphorus pentasulfide (P_4S_{10}) and its dissociation mechanism



Scheme I-3. Thionation with diphosphorus pentasulfide (P_4S_{10})

The main problem is the insolubility of this reagent in most of the organic solvents and the need of a large excess of reagent. These reactions are mainly performed in boiling toluene, xylene or pyridine. The main advantage of this method is the good yield of reaction, no organic by-products and easy purification of the product.

A very successful phosphorus based reagent, which is considered to be an organic analogue of P_4S_{10}, is the 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-phosphetane-2,4-disulfide known as Lawesson's Reagent (LR) (**Figure I-2)** [12].

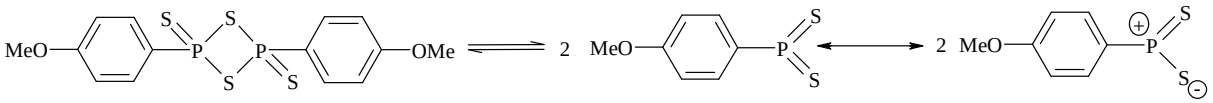


Figure I-2. 2,4-bis 4-methoxyphenyl)-1,3-dithia-2,4-phosphetane-2,4-disulfide; Lawesson's Reagent (LR) and its dissociation mechanism

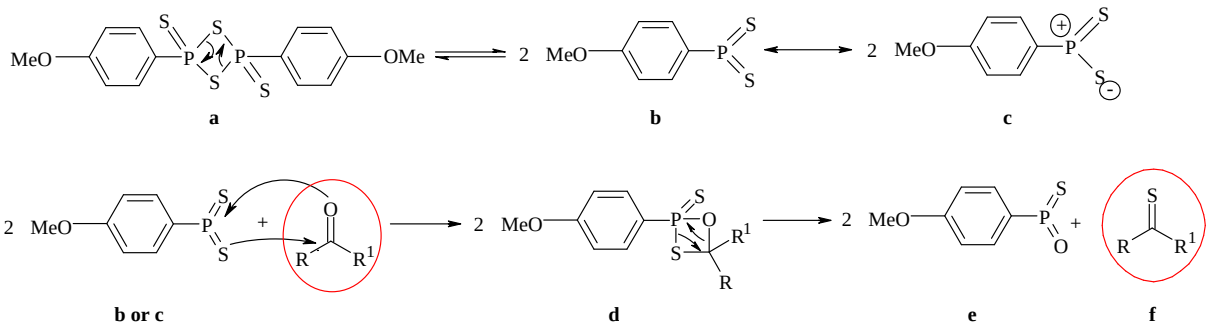
The first synthesis of LR was investigated in 1956 [12]. This compound can be easily obtained in the reaction of diphosphorus pentasulfide with anisole (150°C, 6h, 70%) [12-14]. The reaction of red phosphorus, elemental sulphur and anisole (150-155 °C, 6 h, 76%) also allows to obtain LR [15].

LR was used for the first time in 1967 by H. Hoffman and G. Schuhmacher in the transformation of benzophenone to thiobenzophenone [16].

In 1978, S.-O. Lawesson and co-workers reported investigations of that reagent in the conversion of carbonyl into thiocarbonyl compounds [12, 17-19]. It was indicated that LR is not stable in solution at temperatures over 110°C, and decomposes or polymerizes slowly [20].

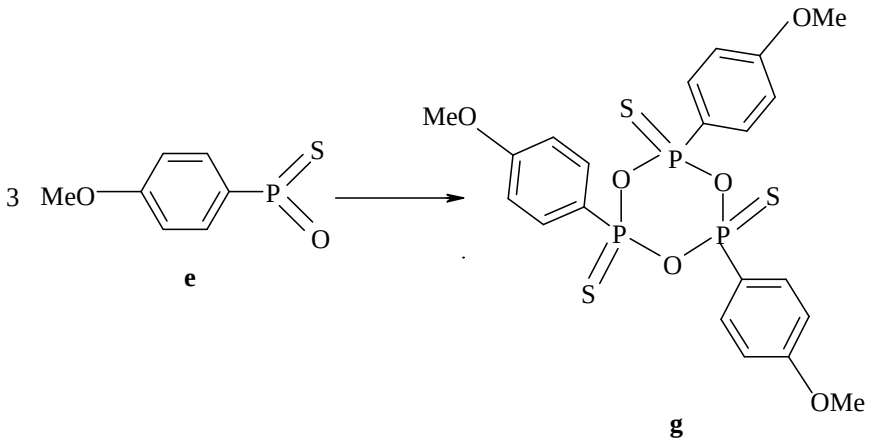
Nowadays, LR is commercially available. This reagent is soluble in benzene, toluene, xylene and is regarded as an excellent reagent for converting carbonyl into thiocarbonyl compounds. LR remains the most important reagent in thionation chemistry. Several reviews concerning the use of LR in thionation chemistry have appeared (three of them, among the most recent: [21-23]).

The mechanism of thionation reaction using LR is described in the literature [13, 14]. LR (**a**) is in equilibrium with a highly reactive dithiophosphate ylide (**b**). Both mesomeric structures (**b** or **c**) can react with carbonyl compounds to form thiaoxaphosphetane (**d**) (which decomposes in a Witting-type reaction to the thioketone (**e**)) and the corresponding thiocarbonyl compound (**f**) can be formed (**Scheme I-4**).



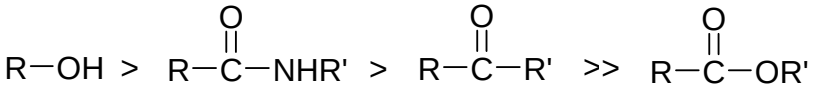
Scheme I-4. Mechanism of the thionation reaction using the Lawesson's Reagent [13]

S.-O. Lawesson and co-workers also had found that the trimer *p*-methoxyphenylmetathiophosphonate (**g**) is formed as a side product of (**e**) (**Scheme I-5**) [17]. The P-O bond is much stronger than the P-S bond, which results in the thermodynamically more stable product (**e**) formation.



Scheme I-5. Formation of *p*-methoxyphenylmetathiophosphonate (**g**) [17]

M. Ori and T. Nishio reported the reactivity order of LR towards hydroxyl and carboxyl groups [24]. The authors indicated that hydroxyl group is the most reactive and ester is the least reactive among hydroxyl, amide, ketone, and esters functional groups. In between are the amides and ketones. The reactivity order is as follows:



R. S. Varma and D. Kumar have developed an efficient method of the synthesis of thio-analogues of ketones, flavones, isoflavones, lactones, amides and esters under solvent-free conditions [25]. By mixing the substrates with the Lawesson's Reagent followed by exposure to microwave irradiation, the corresponding thio-analogues were obtained with very good yields (i. e. ≥ 93% for thioamides synthesis). That method possesses many advantages, like shorter reaction time, no need to use dried hydrocarbon solvents and an excess of the Lawesson's Reagent and no side products generation.

Thionation of hydroxamic acids

The synthesis of thiocarbonyl analogues of hydroxamic acids is much more difficult and the accessibility of a successful thionating reagent is limited. Most of the thioacylating agents are unstable and their synthesis is complicated or expensive.

Unsubstituted thiohydroxamic acids can be obtained in very low yields mainly due to their instability and tendency to decompose during isolation into nitriles, elemental sulphur and water [26].

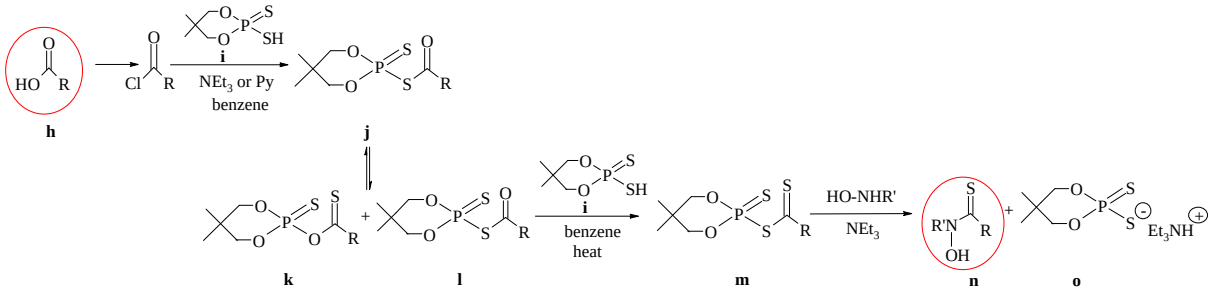
In general organic chemistry, we can find two different ways of N-substituted thiohydroxamic acids synthesis [27].

a. Thioacylation of the respective hydroxylamines or its N- and O-derivatives

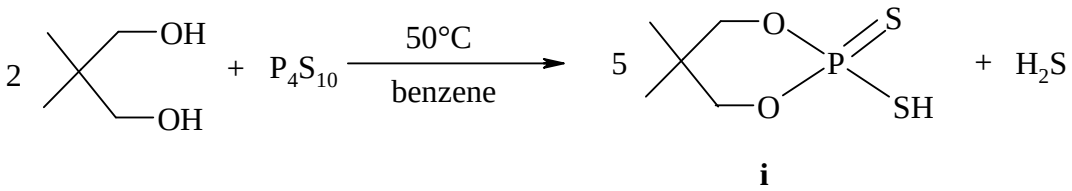
The method is limited by finding a stable thioacylating agent. The methods proposed are based on the reaction of a magnesium salt of a dithiocarboxylic acid (or their esters, thionocarboxylic acid esters or acid chlorides) with hydroxylamine. That reaction is the oldest for thiohydroxamic acids synthesis [28].

More recently, a very efficient thioacylating agent S-thioacyldithiophosphate (**m**) was prepared and used [29-31].

Scheme I-6 presents the way of carboxylic acids conversion into thioacyl dithiophosphates (**m)**, which is a promising thioacylating agent. This method is based on isomerisation of acyl dithiophosphates (**j)** to O-thioacyl monothiophosphates (**k)**. The dithiophosphoric acid (**i**) used in the reaction can be obtained as presented in **Scheme I-7**.



Scheme I-6. Conversion of carboxylic acids into thioacylating reagent (**m**) and its reaction with nucleophile – hydroxylamine



Scheme I-7. Synthesis of 5,5-dimetyl-2-sulfanyl-2-thioxo-1,3,2-dioxaphosphinan (**i**)

The mixture of (**k)** and (**l)** treated with dithiophosphoric acid **(i**) yields S-thioacyl dithiophosphate (**m)** exclusively [31].

Resulting thioacyl dithiophosphate is added to the solution or suspension of a nucleophile (hydroxylamine) with one equivalent of a base (triethylamine). Subsequent washing with water, drying and solvent evaporation yields crude product with moderate to very good yields (57-94 %).

The authors demonstrated that this method allows using even unprotected hydroxylamine, i.e. without necessity of hydroxyl group protection. However, in the case of higher steric hindrance or N,N-disubstituted hydroxylamines, O-thioacyl hydroxylamines are formed instead of the desired thiohydroxamic acids [31].

b. Direct thionation of hydroxamic acids

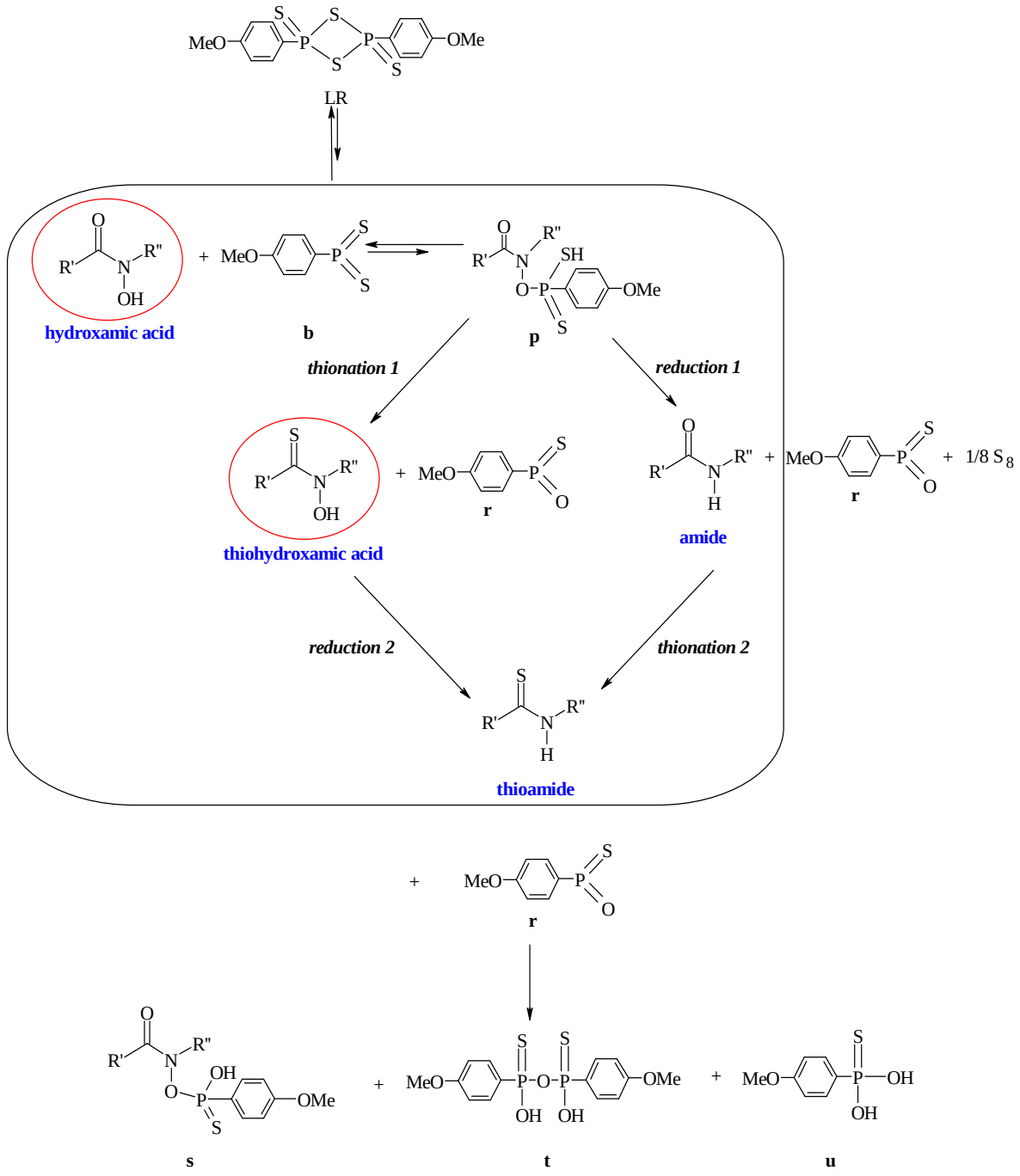
Some of the thionating agents were tested in direct thionation of hydroxamic acids. Some of them, like P_4S_{10} provides only small quantity of thiohydroxamic acids in a complex mixture [32-33].

A three-step procedure was presented by H. Rzepa and co-workers [34].

The first step is the O-acylation of the hydroxamic acid, followed by thionation with the use of Lawesson's Reagent. The last step is the deprotection of the hydroxyl group. Nevertheless, this synthetic method provides low to moderate reaction yields (10-50%) and due to the multistep procedure was not considered to be the best one.

Some of the N-alkyl benzothiohydroxamic acids were obtained with moderate yields (40-60%) using Lawesson's Reagent [35].

The authors have also proved the formation of the corresponding benzamides and thiobenzamides as by-products. They have explained that four reactions are taking place in that synthesis: two parallel reactions (the benzohydroxamic acid thionation and deoxygenation providing the corresponding amide) and two subsequent steps (reduction of benzothiohydroxamic acid and thionation of benzamide, both leading to the thioamide formation) [35]. W. Przychodzeń has proposed the reaction mechanism of Lawesson's Reagent (LR) with hydroxamic acids shown in **Scheme I-8** [36].



Scheme I-8. Thionation of hydroxamic acids using Lawesson's Reagent [36]

According to the suggested mechanism, metadithiophosphonate (**b**) generated from LR attacks the hydroxyl group of hydroxamic acid yielding adduct **p** (O-dithiophosphonylated hydroxamic acid). Its stability depends on the N-O bond energy. Breakdown of **p** gives amide (***reduction 1***), metathiophosphonate (**r**) and a sulphur atom. As the formation of adduct **p** is a reversible process, a further reaction on the carbonyl oxygen atom of metadithiophosphonate (**b**) occurs, which leads to the thiohydroxamic acid

(***thionation 1***) and metathiophosphonate (**r**). It has been proved that monomeric metathiophosphonate (**r**) does not form trimer, which is typical for amides reaction with LR. Subsequent reduction of thiohydroxamic acid (***reduction 2***) and thionation of amide (***thionation 2***) gives thioamide. Next metathiophosphonate molecule (**r**) is transformed into a dimer pyrothiophosphonate (**t**) together with O-thiophosphonylhydroxamic acid (**s**) which is formed in the reaction of metathiophosphonate (**r**) with unreacted hydroxamic acid. The hydrolysed product of compound (**r)** - anisylthiophosphonic acid (**u**) was also isolated.

In 2006, W. Przychodzeń reported on the effects of substituents on LR reactivity in direct thionation of hydroxamic acids [37].

More than 30 selected N-substituted hydroxamic acids were subjected to LR reaction in THF at room temperature. It has been concluded that this direct thionation method is useful for N-alkyl aceto- and benzohydroxamic acids lacking electron-donating groups in the aromatic rings. In such cases, thiohydroxamic acids were isolated with up to 60% yield. Some hydroxamic acids were shown to fail to undergo thionation due to the steric hindrance around the carbonyl as well as around the N-OH group. In that case only the corresponding amides were obtained.

As it was presented, direct thionation of hydroxamic acids leads to a complex mixture of compounds, consisting of thiohydroxamic acid, amide, thioamide and unreacted hydroxamic acid. Compounds **(s), (t), (u)** were also present in the mixture as a result of subsequent thionation and reduction. Thioacylation method showed here, seems to be a very effective and an easy way for thiohydroxamic acids synthesis. However, the authors indicated that in the case of higher steric hindrance or N,N-disubstituted hydroxylamines, O-thioacyl hydroxylamines are formed instead of the desired thiohydroxamic acids.

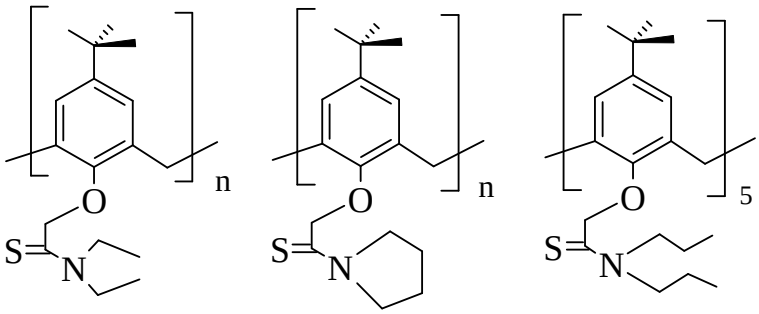
Such reactions have never been reported with calixarenes.

Lawesson’s Reagent, the most convenient thionating agent, was used in my work for calix[4]arene-thioamides synthesis. Attempts were made to obtain calix[4]arene-thiohydroxamates using Lawesson’s Reagent in direct thionation of calix[4]arene-hydroxamates. Thioacylation method presented here was also tested in order to obtain calix[4]arene-thiohydroxamates.

1.2. Binding properties of calixarene-thioamides

There are several papers which describe calixarene-thioamides binding properties. These were mostly studied in liquid-liquid extraction experiments and were applied as active materials in the membranes of ion-selective electrodes or in chemically modified ion-sensitive field-effect transistors (CHEMFETs).

In 1992, results of liquid-liquid extraction studies carried out according to the Pedersen procedure with *p-tert*-butylcalix[4]-, [5]- and [6]-arenes functionalised with thioamide moieties were reported [38] (**Figure I-3**).



I (1T) n = 4 **III** n = 4 **V**

II n = 6 **IV** n = 5

Figure I-3. *p-tert*-Butylcalix[4]-, [5]- and [6]-arenes functionalised with thioamide moieties (**I-V**) studied in extraction experiments [38]

It was shown that the thioamides **I-V** did not extract alkali, alkaline earth or lanthanide cations. As expected, a strong affinity for Ag^+ and Pb^{2+} was observed (%E ≥ 80 and ≥ 32, respectively). Extraction of Cu^{2+} cations was less efficient (%E ≥ 15) and that of Cd^{2+} with ligands **IV** and **V** was quite satisfying (%E = 42 and 38, respectively). The data were compared to those obtained for the corresponding amides [39] which are good extractants for Na^+ and K^+ ions, but also show a strong affinity for softer cations such as Pb^{2+}, Cd^{2+} and Ag^+. It has been concluded that thioamides having softer sulphur instead of oxygen atoms show a preference for heavy metal cations and a limited binding ability towards alkali and alkaline earth ions [38].

In 1997, the first X-ray crystal structure of the lead complex of *p-tert*-butylcalix[4]arene diethylthioamide **I (1T)** was reported (**Figure I-4**) [40].

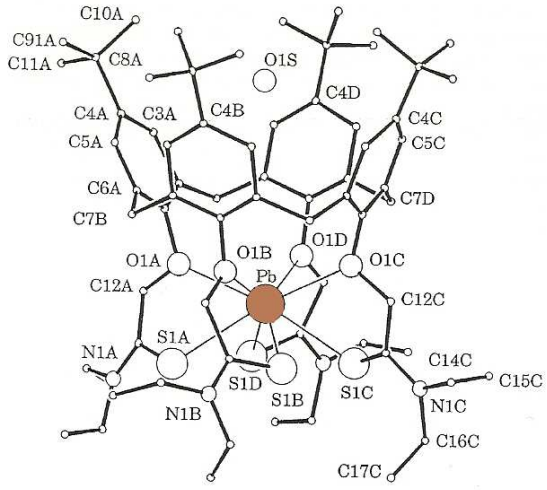
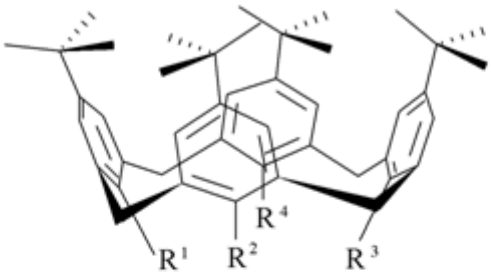


Figure I-4. X-ray crystal structure of the Pb^{2+} complex with calix-diethylthioamide [40]

It was observed that the thioamide derivative adopts an open distorted *cone* conformation, in which all thiocarbonyl sulphur atoms are oriented towards the Pb^{2+} cation which is bound to four ethereal oxygen atoms and four thiocarbonyl sulphur atoms. In this complex, one molecule of solvent was found inside the cavity [40].

K. M. O'Connor et al. tested tetra-diethylthioamide **I (1T)** as ionophore for Ag(I) in ion-selective PVC/NPOE (*o*-nitrophenyl-octyl ether) membrane electrode and obtained a linear response with a slope of 45.67 mV/dec. Hg^{2+} and Na^{+} were the most interfering ions. The selectivity coefficient for Ag^{+} versus Pb^{2+} was $\log K^{pot}_{Ag,Pb} = -1.7$. After being in contact during 24 hours with a Pb^{2+} solution, the electrode did not respond to Ag^{+} any longer, as a result of the membrane poisoning by Pb^{2+} ions [41].

P. L. H. M. Cobben et al. in 1992 presented the selective recognition of heavy metal cations by chemically modified ion sensitive field effect transistors (CHEMFETs) using calix[4]arene-thiocarbamates **VI-VII** and calix[4]arene-thioamides **VIII-XIII** in *cone* conformation as active materials in the membrane (**Figure I-5**) [42].



VI $R^1 - R^4 = OCH_2CH_2SC(S)N(C_2H_5)_2$

VII $R^1 = R^3 = OCH_2CH_2SC(S)N(C_2H_5)_2$, $R^2 = R^4 = O\textit{n}Pr$

VIII $R^1 = R^3 = OCH_2C(S)N(CH_3)_2$, $R^2 = R^4 = OH$

IX $R^1 = R^2 = OCH_2C(S)N(CH_3)_2$, $R^3 = R^4 = OH$

X $R^1 - R^4 = OCH_2CH_2OCH_2C(S)N(CH_3)_2$

XI $R^1 = R^3 = OCH_2CH_2OCH_2C(S)N(CH_3)_2$, $R^2 = R^4 = O\textit{n}Pr$

XII $R^1 = R^3 = OCH_2C(S)N(CH_3)_2$, $R^2 = R^4 = O\textit{n}Pr$

XIII $R^1 - R^4 = OCH_2C(S)N(CH_3)_2$

Figure I-5. Calix[4]arene-thiocarbamates (**VI-VII)** and calix[4]arene-thioamides (**VIII-XIII**) studied in chemically modified ion sensitive field effect transistors (CHEMFETs) [42]

The ionophore **VI**, having four thiocarbamoyl groups, when incorporated into PVC/DOP (dioctyl phthalate) CHEMFETs membrane gave a Nernstian response to Cu^{2+} with a slope of 31 mV/dec in the presence of Ca^{2+} (log $K^{pot}_{Cu/Ca}$ = -1.7), Cd^{2+} (log $K^{pot}_{Cu/Cd}$ = -2.0) and Pb^{2+} (log $K^{pot}_{Cu/Pb}$ = -1.6). Potassium cations acted in this case as the most interfering ion, probably due to the higher partition coefficient for K^+ compared to Cu^{2+} for the membrane plasticised with dioctyl phthalate (PVC/DOP). The same compound **VI** incorporated in the PVC/NPOE membrane showed better selectivity versus K^+ [42]. Nevertheless, the electrode with that plasticizer did not have a reproducible response to Cu^{2+} ions.

The response of electrodes with ionophore **VII,** possessing only two thiocarbamoyl groups, to Cu^{2+} ions in the PVC/DOP membrane, was not reproducible. By changing the plasticizer to NPOE and by increasing the amount of the ionophore in the membrane, better results were obtained. Despite the selective response towards Cu^{2+} ions a slope of 54-59 mV/dec was obtained. That was explained by the formation of monovalent ion-pair species (CuA^+) within the membrane [42].

The nernstian response to Cd^{2+} ions was observed for two disubstitued ionophores **VIII** (substituted on two opposite aromatic rings) and **IX** (substituted on two adjacent aromatic rings). Ionophore **VIII** was more selective than **IX** in the presence of Ca^{2+}. Further investigations with compounds **X** and **XI** possessing an extended cavity proved that those ionophores provide better selectivity for Cd^{2+} versus K^+ and Ca^{2+} in comparison to the ionophores **VIII** and **IX**. Generally, the tetra-substituted compound **X,** showed better selectivity than the di-substituted **XI**. No selectivity was found in the case of the ionophore **X** in the presence of Pb^{2+} and Cu^{2+}.

Two electrodes with ionophores **XII** and **XIII** in a PVC/NPOE membrane showed selectivity for Pb^{2+}. The selectivity coefficients given as logK for **XIII** and (in parentheses) for **XII** were: $\log K^{pot}_{Pb/K}$ = -5.2 (-2.8), $\log K^{pot}_{Pb/Ca}$ = -4.3 (-4.2), $\log K^{pot}_{Pb/Cd}$ = -4.2 (-1.7), $\log K^{pot}_{Pb/Cu}$ = -3.4 (-2.7). It was confirmed that the electrode with **XIII**, having four thioamide groups, was more selective and also gave a better Nernstian response than the electrode with **XII** bearing two thioamide moities [42].

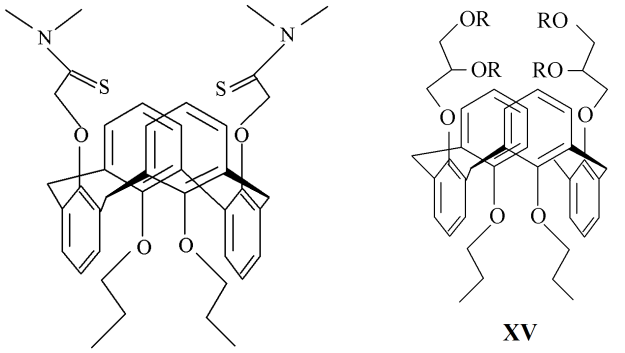
The same ionophores (**XII** and **XIII)** were later applied in Pb-selective electrodes by E. Malinowska et al [43]. The electrode membranes with both ionophores plasticised with NPOE gave an almost theorethical Nernstian response for Pb^{2+} when using 5×10^{-3} mol L^{-1} $PbCl_2$ as internal electrolyte. The same conclusion was formulated with the tetra-substituted thioamide **XIII**, which is more selective for Pb^{2+} ions than its di-substituted counterpart**,** over the great variety of cations studied: Li^+, K^+, Na^+, NH_4^+, Ca^{2+}, Mg^{2+}, Ba^{2+}, Cu^{2+}, Cd^{2+}, Co^{2+}, Zn^{2+}, Ni^{2+} ($\log K^{pot}_{Pb/M} < -3$). Ligand **XIII** was also studied in a membrane plasticised with BBPA (bis-(butylpentyl)-adipate), but in that case Na^+ strongly interfered, because generally BBPA plasticizer favors complexation of Na^+. Ligand **XIII** is now a commercially available Pb-selective ionophore.

T. Sokalski et al. described the influence of the composition of the internal filling solution on the response of Pb(II)-selective membrane electrodes [44]. The results obtained with ionophore **XIII** were compared with those obtained earlier by E. Malinowska et al. [43]. The internal filling solution contained: 10^{-2} mol $L^{-1}Na_2EDTA$, 10^{-3}mol L^{-1} $PbCl_2$ and 10^{-2} mol L^{-1} or 2 mol L^{-1} NaCl. It was concluded that inner electrolyte should contain higher concentration of the interfering ion and lower concentration of the primary ion. Very low detection limits were thus obtained, below 10^{-10} mol L^{-1}[44].

A. Ceresa and E. Pretsch determined the stability constant of the Pb^{2+} complex with the compound **XIII** in a DOS/PVC membrane. The value of $\log \beta_{\mathbf{XIII}\text{-}Pb}$ = 15.9 indicated that a

rather strong 1:1 complex with Pb^{2+} was formed. The stability constants of the complex with other cations were also relatively high: log $\beta_{\mathbf{XIII}\text{-}Cu}$ =12.1 and log $\beta_{\mathbf{XIII}\text{-}Cd}$ =10.0 for Cu^{2+} and Cd^{2+}, respectively [45].

R. J. W. Lugtenberg et al. studied novel calix[4]arene thioamides in the *1,3-alternate* conformation and their selectivities for Pb^{2+} and Cd^{2+} in chemically modified field effect transistors (**Figure I-6**) [46]. CHEMFETs with ionophore **XIV** in PVC/NPOE membranes gave a Nernstian response with a slope of 30 mV/dec for $Pb^{2+}$and was selective in the presence of interfering cations such as Cd^{2+}, Ca^{2+}, Cu^{2+}, K^{+} [46]. The results were compared with the data obtained by P. L. H. M. Cobben et al. with the corresponding *cone* – conformer (**XII**) [42].



XIV **XV**

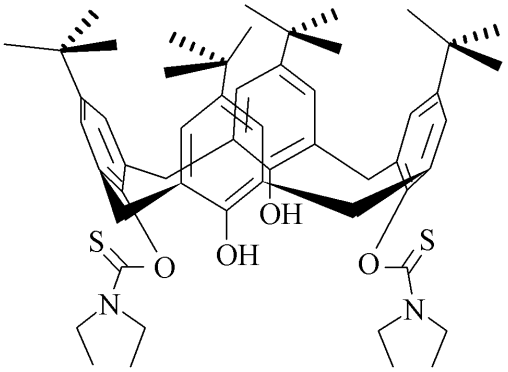
R = $CH_2C(S)N(Me)_2$

Figure I-6. Calix[4]arene-thioamides (**XIX** and **XV**) studied in chemically modified ion sensitive field effect transistors (CHEMFETs) [46]

It was clearly pointed out that the *1,3-alternate* conformer is more selective towards Pb^{2+} than its *cone* counterpart in the presence of other cations. It was explained that in the *1,3-alternate* conformation, there is no interaction with hard oxygen atoms of the two propoxy moieties and cation-π interactions favour the complexation with the more polarizable Pb^{2+}. A Nernstian response towards Cd^{2+} in the presence of Ca^{2+} and K^{+} was observed for ionophore **XV** in CHEMFETs with PVC membranes plasticised by DOP. Moreover, the authors have reported that those CHEMFETs are also selective for Cd^{2+} in the presence of Cu^{2+} which was not observed for CHEMFETs with incorporated *cone*-conformer of ionophore **X,** having four $CH_2CH_2OCH_2C(S)N(CH_3)_2$ groups attached to the phenolic oxygen atoms [42]. It is worth to

point out that ionophore **XV** is the first calix[4]arene derivative which is selective for Cd^{2+} in the presence of Pb^{2+}. However, the selectivity is only log $K^{pot}_{Cd/Pb}$ = -0.7 [46].

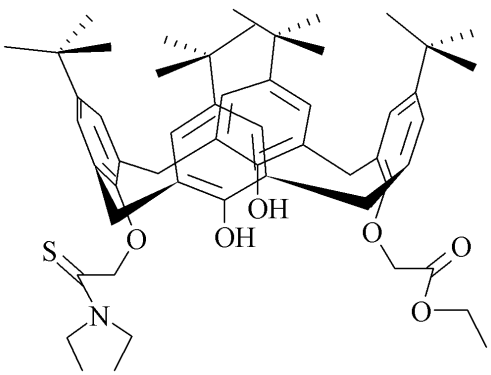
M. G. Drew et al. reported the first X-ray crystal structure of calix[4]arene-diethylthioamide substituted only in two opposite rings, compound **XVI (Figure I-7)**. The calix[4]arene was shown to have a pinched *cone* conformation [47].



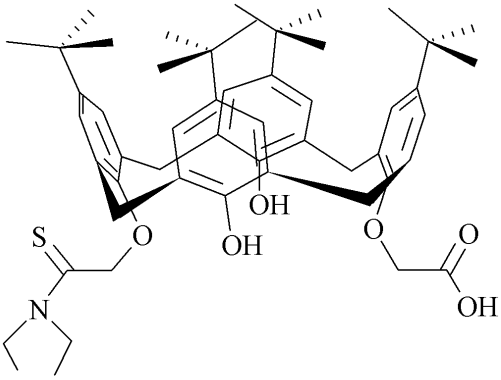
XVI

Figure I-7. Calix[4]arene-thioamide (**XVI**)

In 2001 G. P. Nicholson et al. patented the method of preparation of some novel calixarenes, among them **XVII,** having one ester and one thioamide group and **XVIII** being the analogous mono-acid and mono-thioamide and their use for the sequestration of metal ions (**Figure I-8**) [48]. Lawesson's Reagent as a thionating agent was used in those synthetic procedures. Both sulphur containing calix[4]arenes presented here were able to extract Cd^{2+} from a solution at pH = 9.4.



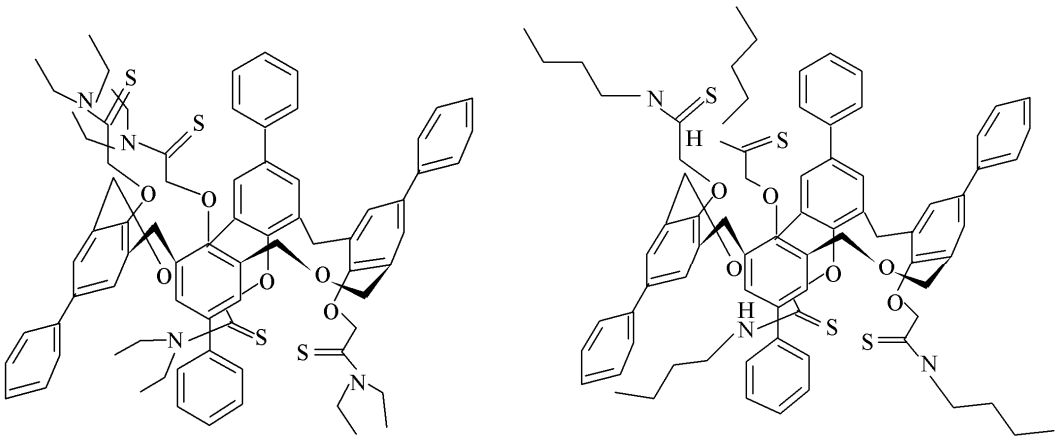
XVII



XVIII

Figure I-8. Calix[4]arene-monothioamides **XVII** and **XVIII** used to complex metal ions [48]

In 2002, K. No et al., presented two tetra-homodioxacalix[4]arene thioamides in *1,2-alternate* conformation (compounds **XIX** and **XX**) (**Figure I-9**) [49].

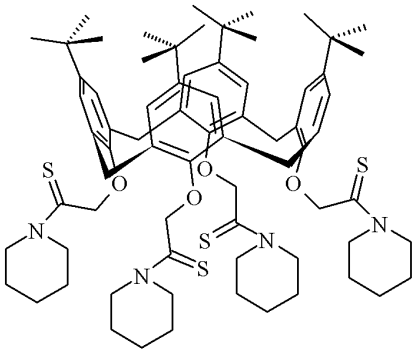


XIX **XX**

Figure I-9. Tetra-homodioxacalix[4]arene thioamides in *1,2-alternate* conformation (**XIX** and **XX**) studied in extraction experiments [49]

The metal picrate extraction with compounds **XIX** and **XX** was investigated and their strong affinity towards Ag^+ was reported. The mass spectra analysis showed that M_2L complex was formed with Ag^+ [49].

In 2009 F. Torma et al., published results on the adsorptive stripping voltammetric determination of Pb^{2+} using calix[4]arene-thioamide **XXI** as ionophore (**Figure I-10**) [50].



XXI (5T)

Figure I-10. Calix[4]arene thioamide **XXI (5T)** used in the adsorptive stripping voltammetric determination of Pb^{2+} [50]

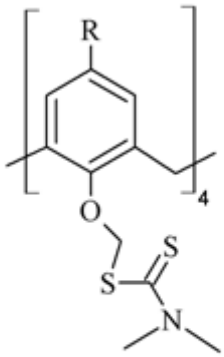
This method is based on the accumulation of lead ions from the solution phase onto the surface of a chemically modified bismuth-film electrode by complexation with the ionophore in open circuit. The cyclic voltammetry curves showed reduction and oxidation peaks corresponding to the electrochemical reaction of lead which proved the Pb^{2+} - ligand complexation [50].

The application of calix-thioamide-based chemically modified carbon paste electrodes in voltammetric stripping analysis was proposed by D. W. M. Arrigan et al. and used for accumulation of Pb^{2+}, Cu^{2+} and Hg^{2+} [51].

Calix[4]arenes appended with thiocarbamoyl moieties were tested in CHEMFETs by P. L. H. M. Cobben [42] and found to be selective for Cu^{2+} cations.

Those compounds were widely studied also in extraction experiments by A. T. Yordanov et al. [52, 53].

For instance, they tested the extraction of some cations using compound **XXII** and **XXIII** with four thiocarbamoyl groups (**Figure I-11**) [52-56].



XXII R = *t*Bu
XXIII R = H

Figure I-11. Calix[4]arene-thiocarbamoyl derivatives **XXII** and **XXIII** studied in extraction experiments [52-56]

Later, compound **XXIII**, similar to **XXII,** but without *tert*-butyl groups was synthesised [54, 55].

Extraction of Hg^{2+}, Hg_2^{2+}, $MeHg^{+}$, Ag^{+}, Pd^{2+}, Au^{3+}, Pt^{2+}, Ni^{2+}, Pb^{2+} and Cd^{2+} was performed with these compounds from aqueous solution (10^{-3} mol L^{-1} in 0.1 mol L^{-1} HNO_3) into $CHCl_3$. Both ligands extracted quantitatively Pd^{2+} and Au^{3+}, (%E = 100% with **XXII** and 100% and

97%, respectively with **XXIII**) whereas for the rest of the cations, the percentages of extraction were much lower. The lowest extraction was shown in the case of Hg_2^{2+} and $MeHg^+$ cations with compound **XXIII**. There was no extraction of Pb^{2+}, Cd^{2+}, Ni^{2+} and Pt^{2+} with the ligand **XXII**. Although, Pd^{2+} and Pt^{2+} have similar ionic radius, they were extracted differently [53]. Moreover, soft sulphur atoms should bind more strongly the softer platinum cation. The authors explained this fact by different lability of the two complexes. The crystal structures of the free ligands **XXII** and **XXIII** were obtained and the X-ray diffraction data were discussed [52, 55].

Also, A. T. Yordanov et al. investigated the extraction of some metal ions with the compounds **XXIV** and **XXV**, in which the same sulphur containing moiety as in compound **XXII** were attached to the upper rim of a calix[4]arene. Two derivatives were synthesised: with the free OH groups (compound **XXIV**) and OMe (compound **XXV**) at the lower rim [57]. The extraction procedure was applied to Ag^+, Hg^{2+}, Ni^{2+}, Pd^{2+}, Pt^{2+} and Au^{3+} ions [57]. With compound **XXIV**, the extraction of these cations led to gelatinous precipitates formation, therefore, the extraction percentage was not determined. The derivative **XXV** showed very good selectivity for Au^{3+} (%E = 99) over Ag^+ (%E = 14) and for Pd^{2+} (%E = 100) and Hg^{2+} (%E = 73) over Ni^{2+} (%E<1). The extraction selectivity was found to be similar to that of the derivatives substituted at the lower rim [54].

The binding properties of gold, palladium, mercury and silver salts with compound **XXIII** by electronic absorption spectroscopy were studied in order to better understand the possible sites of metal coordination [58]. The authors indicated that the ligand is complexed to the metal ion by a metal-sulphur interaction.

Conclusion

It can be concluded that calixarenes functionalised with various thioamide moieties are working as receptors for heavy metal cations. In particular, sulphur containing calixarenes appended with SC=S groups in the molecule are good extractants for metal ions such as Au^{3+}, Pd^{2+} and Hg^{2+} while tested in CHEMFETs, those compound showed selectivity for Cu^{2+} cations. Calix-thioamides with C=S moieties are promising ionophores for selective complexation of transition and heavy metal cations like Pb^{2+}, Ag^+, Cd^{2+} and Cu^{2+}.

Collected examples of calixarene-thioamides proved that those compounds are of particular value and they require special attention as they can work as Pb-selective ionophores. They can be used not only in controlling the level of toxic heavy metals, but also

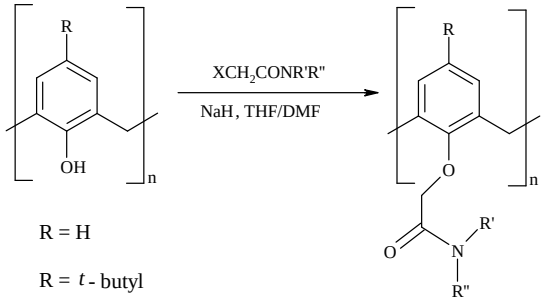
for their removal. It is worth to stress that very few publications deal with stability constants determination of the complexes with calix-thioamides, these data being extremely important in studies of new ligands binding properties.

2. Calixarene-amides

2.1. Methods of synthesis

Calixarene-amide derivatives can be obtained by several following methods:

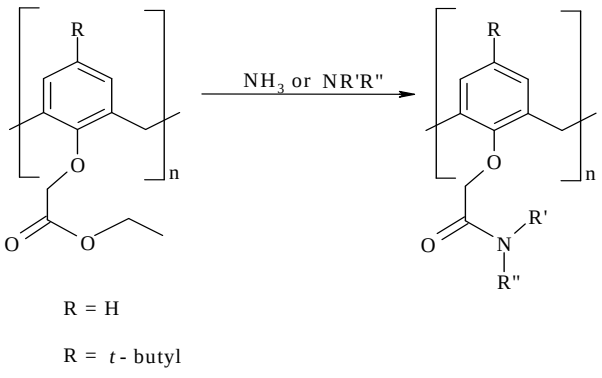
1) Using appropriate amides of α-chloroacetic acid chloride.



Scheme I-9. Calixarene-amides synthesis using amides of α-chloroacetic acid chloride

In this method, used for the first time by G. Calestani et al. [59], a calixarene suspended in THF/DMF solvents mixture is reacted with an appropriate α-chloroacetamide in the presence of a base. That method although widely used in calix-amide synthesis, carries the risk of Na^+ complex formation with the final calix-amide product as a result of using the required NaH as a strong base. Such cases have already been reported [60].

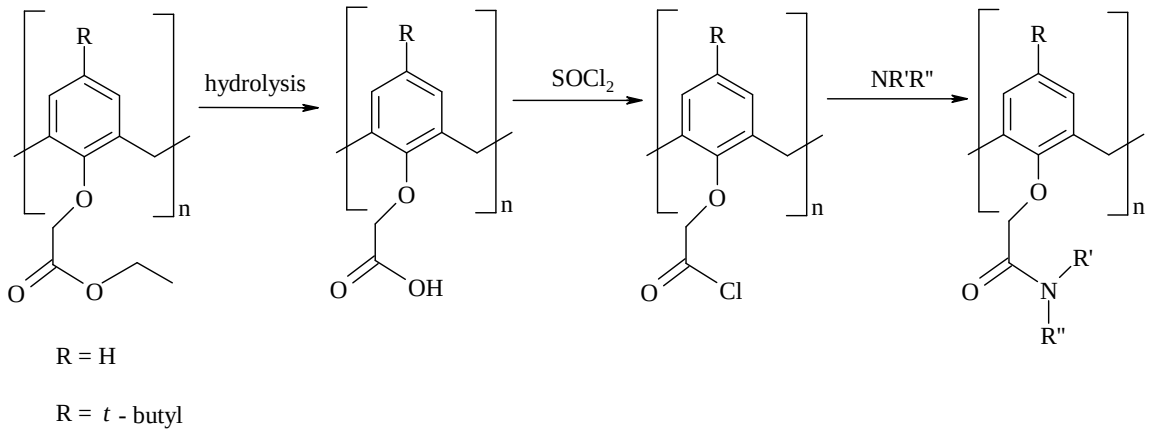
2) Amonolysis or aminolysis of calixarene-esters [61, 62]



Scheme I-10. Calixarene-amides synthesis by amonolysis or aminolysis of calixarene-esters

In this method, depending on the substrates used (ammonia or primary or secondary amines) we can obtain unsubstituted, mono or di-substituted calixarene-amides, respectively. The big disadvantage of this method is a long time of reaction (8-10 days).

3) Activation of calixarene-acids by acid chloride formation [39].



R = H

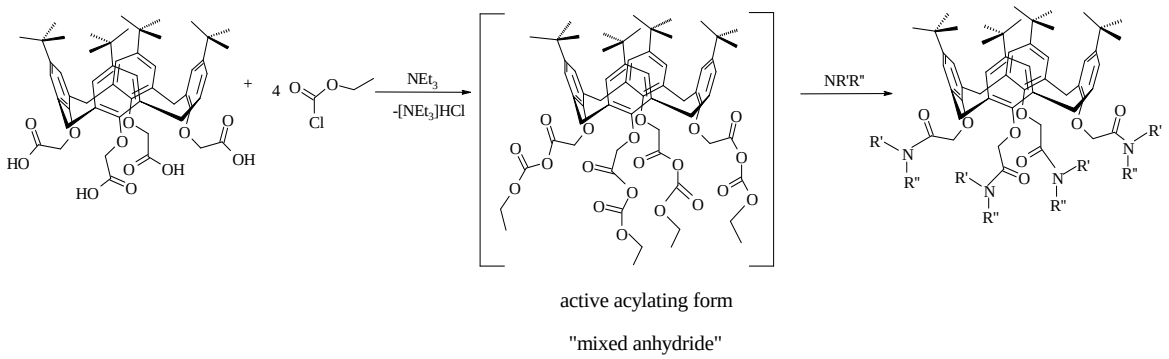
R = *t* - butyl

Scheme I-11. Calixarene-amides synthesis via calix-acid chloride formation

In this few-step synthesis, proposed by M. A. McKervey, calix-ester is hydrolysed to calixarene-acid then by using, for example, thionyl chloride, the calixarene-acid chloride is obtained. Subsequent reaction with an appropriate amine leads to calixarene-amides.

4) Activation of calixarene-acids using mixed anhydrides method [63]

The mixed anhydrides method is widely used in the peptides chemistry in order to create a peptide bond, usually using coupling reagents, such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) or dicyclohexylcarbodiimide (DCC). In calixarene chemistry, the method was firstly introduced by U. Lesińska, who used ethyl chloroformate as a coupling reagent. Due to the low steric barrier such activation enables the tetra-substitution with very good yields. Moreover, the products are obtained in the desired *cone* conformation.



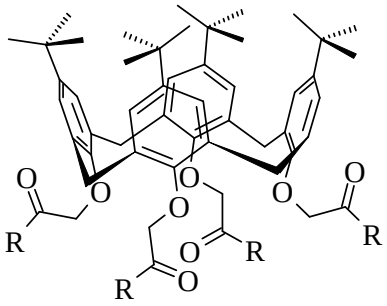
Scheme I-12. Synthetic route of calixarene-amides synthesis via mixed anhydrides method

In that method, calixarene-acid dissolved in dichloromethane is reacted with ethyl chloroformate in the presence of triethylamine. The active acylating intermediate formed is used without isolation in a subsequent substitution of an appropriate amine. The reaction is carried out at low temperature (-5°C). This method possesses several advantages such as: short time of reaction (about 1-2 h), high yield (better than in the methods described earlier), preparation of pure products without necessity to purify by column chromatography. Moreover, this method does not require the use of irritant reagent such as thionyl chloride and leads to pure *cone* conformation.

In my work, all studied calix[4]arene-amides were prepared by the mixed anhydrides method. Two of the calix[4]arene-amides were prepared by both ways: mixed anhydrides method and using an appropriate α-chloroacetamide, in order to be able to compare both methods.

2.2. Binding properties of calix[4]arene-amides

Calix[4]arene-amides have been widely studied since almost three decades. Tetra-substituted *p-tert*-butylcalix[4]arene-amides already reported are presented in **Figure I-12**. The first calix[4]arene tertiary amide, the diethylamide **XXVI (1A**) was synthesised in 1987 and studied by X-ray crystallography [59].



XXVI (1A) R = N(CH2CH3)2

XXVII (2A) R = N(CH2CH2CH3)2

XXVIII (3A) R = N(CH2CH2CH2CH3)2

XXIX R = N(CH2CH2CH2CH2CH3)2

XXX R = N(CH2CH2CH2CH2CH2CH3)2

XXXI R = N(CH2CH2CH2CH2CH2CH2CH3)2

XXXII R = N(CH3)(CH2CH2CH2CH2CH2CH2CH3)

XXXIII R = N(CH2CH2CH2CH2)

XXXIV (5A) R = N(CH2CH2CH2CH2CH2)

XXXV (6A) R = N(CH2CH2)2O

XXXVI R = N-CH=CH2

XXXVII R = N-C≡CH

XXXVIII R = N(CH2C6H5)2

XXXIX R = N(CH3)(CH2C6H5)

XL (7A) R = HN(CH2CH3)

XLI R = HN(CH2CH2CH2CH3)

XLII (8A) R = HN(CH2C6H5)

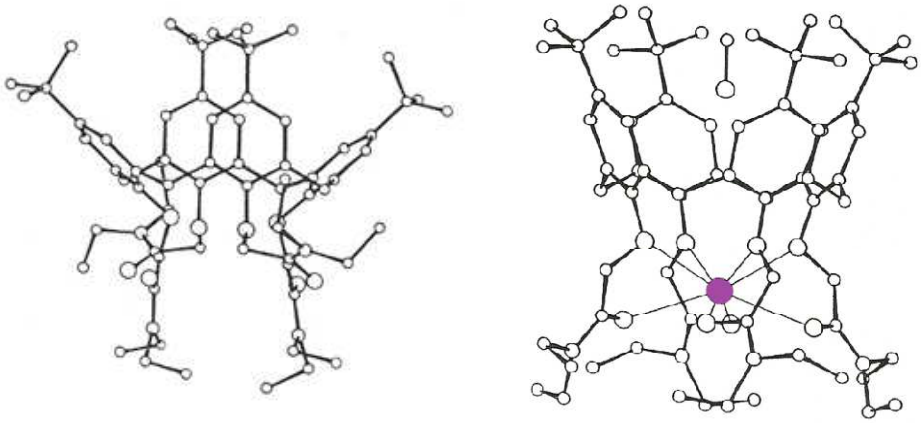
XLIII (9A) R = HN(CH2CH2C6H5)

XLIV R = HN(CH2CH2C5H4N)

Figure I-12. Tetra-substituted *p-tert*-butylcalix[4]arene-amides already studied at the beginning of this work

Binding of I and II group metal cations

The preorganisation of hard basic donor sites towards alkali and alkaline earth metal cations was proved by the first X-ray crystal structure of the potassium complex with the ligand **XXVIII (1A)** presented in **Figure I-13**.



1A **1A-K^+**

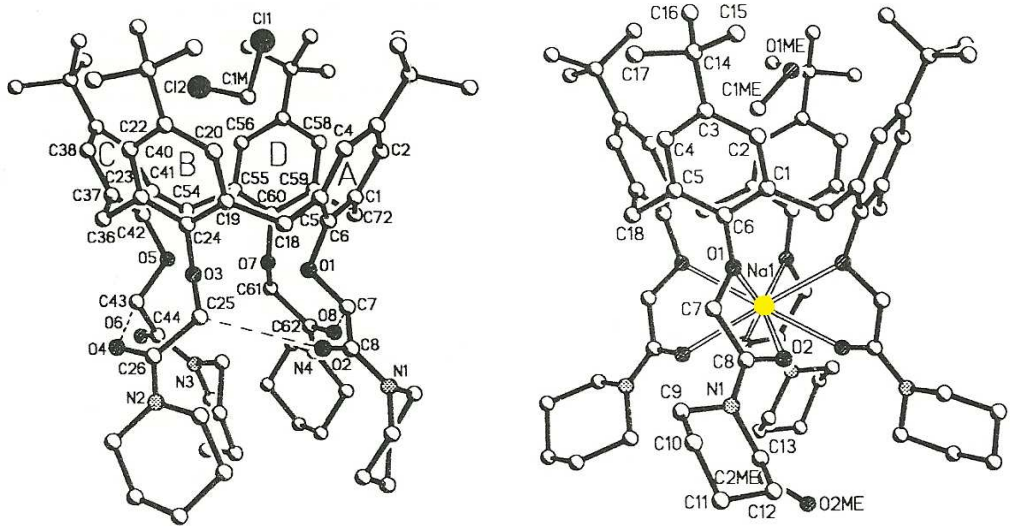
Figure I-13. X-ray crystal structure of the free ligand **XXVI (1A)** and of its complex with potassium cation (**1A-K^+**) [59]

The crystal structure analysis proved that ligand **1A** adopts a slightly distorted *cone* conformation. In the free ligand, aromatic rings A and C are almost parallel and B and D are nearly perpendicular. The four carbonyl groups are not all directed towards the centre of the cavity, which makes that it has not a definite size. It seems like the ligand is not completely preorganised to bind a certain cation, nevertheless in the presence of a metal ion, the four chelating arms can converge as shown in the X-ray crystal structure of **1A-K^+** complex (**Figure I-13**). The conformation of the amide in the complex is more symmetrical and the potassium cation is encapsulated in the environment of four ethereal oxygen atoms and four carbonyl oxygen atoms.

Additional confirmation of the binding sites involved in complexation was given by ^{1}H NMR spectra of the ligand alone and its complexes with K^+ and Na^+ cations. They indicated that the most affected protons were the methylene protons of the (-O-$\underline{CH_2}$-CO-N-(CH_2-CH_3)$_2$) which were shifted upfield by 0.37 ppm (K^+) and 0.49 ppm (Na^+) [64].

Since that publication, numerous tetra-substituted calix[4]arene-amides have been widely studied and their binding abilities were mostly tested towards alkali and alkaline earth cations.

The X-ray crystal structure of amide **XXXIV (5A)** and of its complex with Na^+ cation has been reported (**Figure I-14**) [65].



5A **5A-Na$^+$**

Figure I-14. X-ray crystal structure of the free ligand **XXXVI (5A)** and of its complex with sodium cation (**5A-Na$^+$**) [65]

The structure showed that the ligand is in *cone* conformation preorganised for complexation of the cation. The *cone* conformation in the complex is more regular and all carbonyl oxygen atoms converge to the position which enables the sodium cation encapsulation.

Extractive properties of some cited calix[4]arene-amides are presented in **Table I-1**. It has been shown, that the extraction levels depend on the nature of the amide substituents. All the tertiary calix-amides **XXVI-XXXI** and **XXXIII** showed a high extraction level for the first group of cations, especially for Na^+ (>87.6%) whose size is the most suitable for encapsulation. The general extraction trend with alkali metal cations for tertiary amides is as follows:

$$Na^+ > K^+ > Li^+ > Rb^+ > Cs^+$$

Among ligands **XXVI-XXXI**, possessing alkyl moieties, the size of the substituents did not play an important role and there was no regular change of %E with the carbon chain elongation. For ligands with substituents having multiple bonds, such as allyl or with cyclic structures such as pyrrolidinyl (**XXXIII, XXXVI-XXXIX**), a decrease of the extraction level can be observed, especially for K^+. It is evident, that the presence of such substituents increases the rigidity of all the molecules and only cations with the appropriate size can suit

the cavity. The electronic withdrawing character of substituents with multiple bonds reduces the basicity of the carbonyl groups which can explain the drop of extraction observed. The dependence of the %E values on the size of cation for some examples of amide derivatives can be well observed in **Figure I-15**. Ligand **XXXVII** showed the best selectivity for Na^+ over K^+ ($S = \%E(Na^+)/\%E(K^+) = 6.67$).

Table I-1. Literature data (%E and selectivity S) for the extraction of alkali and alkaline earth metal cations by tetra-substituted calix[4]arene-amides

ligand	Li^+	Na^+	K^+	Rb^+	Cs^+	S (Na^+/K^+)	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
XXVI [a]	62.5	95.5	73.7	24	11.8	1.29	9	98	86.3	74
XXVII [b]	71.6	95	79.6	33.3	9.7	1.19	-	-	78.5	-
XXVIII [b]	67.7	92.0	87.4	37.8	14.8	1.17	-	-	74.0	-
XXIX [b]	69.9	93.0	80.9	37.3	14.4	1.15	-	-	76.6	-
XXX [b]	71.2	87.6	77.2	36.9	26.2	1.13	-	-	68.4	-
XXXI [b]	74.6	94.8	84.6	48.3	28.4	1.12	-	-	65.0	-
XXXIII [a]	47.8	91.1	57.5	16.1	11.2	1.58	88	-	72.1	67
XXXVI [b]	40.1	91.5	63.7	16.0	6.4	1.44	-	-	53.4	-
XXXVII [b]	8.6	76.0	11.4	3.9	2.8	**6.67**	-	-	2.4	-
XXXVIII [b]	36.5	79.8	56.1	14.4	11.5	1.42	-	-	27.9	-
XXXIX [b]	50.2	95.0	68.7	24.1	15.1	1.38	-	-	27.9	-
XL [c]	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1		≤ 1	≤ 1	-	≤ 1
XLII [d]	< 1	2.7	< 1	5.2	3.1		< 1	5.8	4.6	4.8
XLIV [e]	10	15	7	5	2		3	9	< 1	-

[a] from ref [39], [b] from ref [66], [c] from ref [67], [d] from ref [68], [e] from ref [61]

Among alkaline earth metal cations, mostly Sr^{2+} was studied and the results showed significant percentages of extraction, which decreased significantly with ligands **XXXVI-XXXVII.** With ligand **XXVI (1A)**, for which all the II group metal cations was tested, the highest percentage of extraction was noted for Ca^{2+}, similar in size to Na^+.

Ligands **XL, XLII, XLIV** appended with secondary amide moieties occurred to be inefficient extractants. The possibility of forming intra- and intermolecular hydrogen bonds might afftect the cation binding.

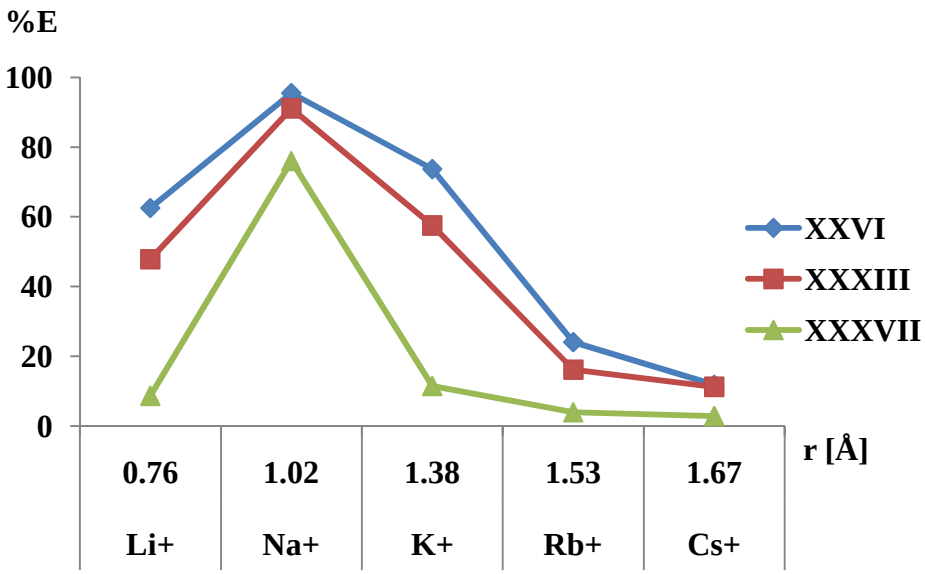


Figure I-15. Percentages of alkali cation extracted (%E) by ligands **XXVI**, **XXXIII** and **XXXVII** as a function of their ionic radius

For some calix[4]arene-amide derivatives cited here, the stability constants of the complexes formed in methanol (MeOH) and in acetonitrile (ACN) were determined (**Table I-2**).

Table I-2. Stability constants (log β) of alkali and alkaline earth metal cations complexes with some calix[4]arene-amides

ligand	Li^+	Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
XXVI (MeOH) [a]	4.1 [s]	7.9 [p]	5.8 [p]	3.8 [s]	2.5 [s]	≤ 1 [s]	≥ 9 [p]	≥ 9 [p]	7.2 [p]
XXVI (ACN) [b]	≥ 8.5 [p]	≥ 8.5 [p]	≥ 8.5 [p]	5.7 [p]	3.5 [s]	nd	nd	nd	nd
XXXIII (MeOH) [a]	3.0 [s]	7.2 [p]	5.4 [p]	3.1 [s]	≤ 1 [s]	nd	nd	nd	nd
XXXVII (MeOH) [b]	3.8 [s]	6.6 [p]	3.5 [s]	2.8 [s]	1.4 [s]	nd	nd	nd	nd
XL (MeOH) [c]	≤ 1 [s]	3.3 [s]	≤ 1 [s]	≤ 1 [s]	≤ 1 [s]	≤ 1 [s]	5.1 [s]	4.6 [s]	3.2 [s]
XLIV (ACN) [e]	5.5 [s]	5.5 [s]	nd	nd	nd	5.6 [s]	5.5 [s]	4.7 [s]	5.9 [s]
[s] spectrophotometry, [p] potentiometry, "nd" – not determined [a] from ref [39], [b] from ref [66], [c] from ref [67], [e] from ref [61]									

With ligand **XXVI**, the stability constants of the alkali metal cations complexes are higher in acetonitrile than in methanol, as a result of different solvating properties of both solvents. The stability constants determined in MeOH with this ligand are higher than those obtained with ligand **XXXIII** appended with cyclic moieties. With ligand **XL** having secondary amide moieties, significant stability constants could be determined only for Na^+, Ca^{2+}, Sr^{2+} and Ba^{2+}. The possible formation of hydrogen bonds might affect the complexing ability of such a

ligand. Ligand **XLIV** with aromatic amine substituents formed stable complexes in acetonitrile with the majority of the tested cations but the stability constants were much lower that those obtained with the ligand **XXVI** appended with linear diethyl substituents.

Binding of transition and heavy metal cations

Relatively little information can be found about binding abilities of transition and heavy metal cations with calixarene-amides.

In 1995, P. D. Beer et al. obtained crystals of the complexes of Fe^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+} and Pb^{2+} with ligand **XXVI (1A)** with suitable for X-ray analysis [69]. It was proved that in those complexes, the calixarene scaffold adopted a distorted *cone* conformation. In Fe^{2+}, Zn^{2+} and Pb^{2+} complexes, all 8 oxygen atoms are involved in complexation and the cation-oxygen bond distances are similar. In the case of Cu^{2+} complex, the four Cu-O (carbonyl) distances are much shorter than those of the four Cu-O (ether). In the Ni^{2+} complex, the cation has its six nearest neighbours in a distorted – octahedral environment. The example of the Pb^{2+} complex is given in **Figure I-16**.

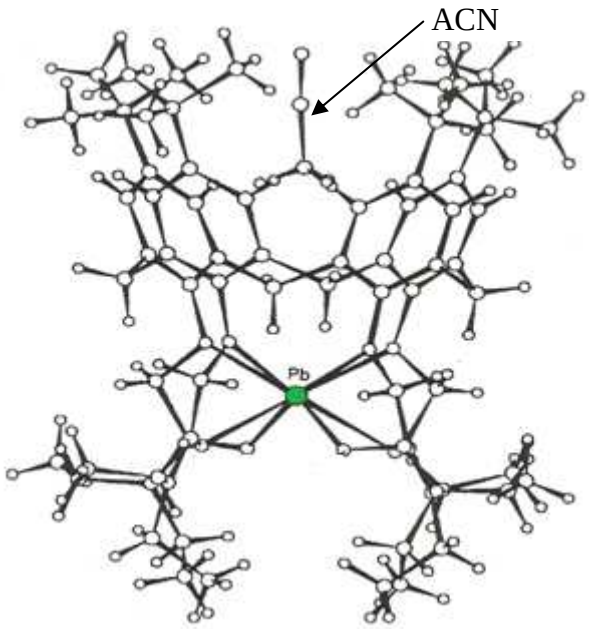


Figure I-16. X-ray crystal structure of **1A**-Pb^{2+} complex showing the included ACN [69]

These authors were the first to provide an evidence that calixarene-amides can successfully bind not only I and II group cations, but also the transition and heavy metals as well.

Another example of X-ray crystal structure of calixarene-amide complex with transition metal cation has also been reported by F. Arnaud-Neu et al. [40] (**Figure I-17**).

In that complex, the metal is bound to four carbonyl oxygen atoms and four ethereal oxygen atoms. Likewise in already mentioned crystal structure of **1A**-Cu^{2+} complex, the distances between copper and the ethereal oxygen atoms are much longer than the distances between copper and the carbonyl oxygen atoms. This might be explained by the different coordination requirements of Cu^{2+} as compared to those of the other metal ions, such as Pb^{2+}.

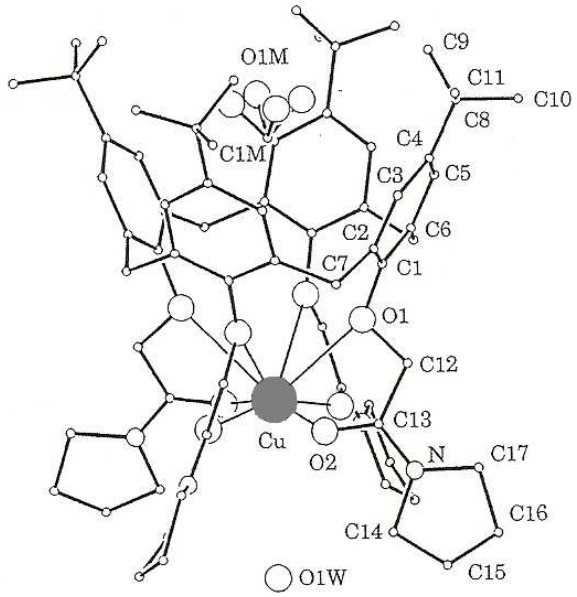


Figure I-17. X-ray crystal structure of **XXXIII**-Cu^{2+} complex [40]

The results of the extraction of some heavy and transition metal cations with ligands **XXVI (1A)** and **XXXIII** are presented in **Figure I-18.**

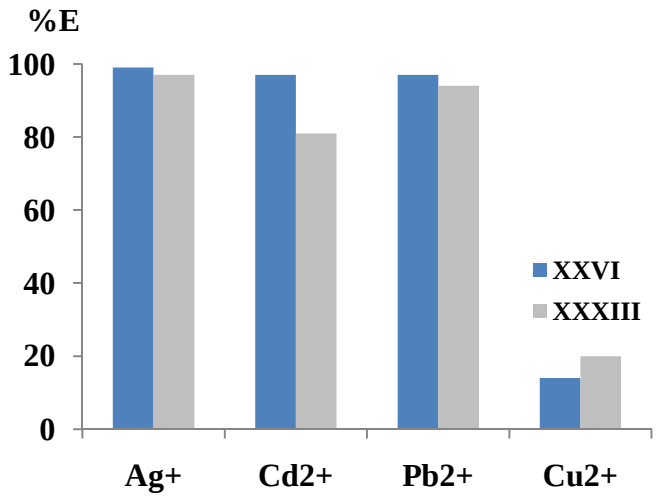


Figure I-18. Extraction of Ag^{+}, Cd^{2+}, Pb^{2+} and Cu^{2+} with ligands **XXVI (1A)** and **XXXIII**

This graph clearly shows that the amides cited here extract Ag^+, Cd^{2+}, Pb^{2+} almost quantitatively and Cu^{2+} up to 20% [39]. The extraction efficiency for Ag^+, Cd^{2+} and Pb^{2+} is as high as for Na^+ and K^+.

The stability constants in MeOH of **1A** complexes of Ag^+ (log β_{ML} = 7.2 [39]) , Cd^{2+} (log β_{ML} = 8.50), Pb^{2+} (log β_{ML} = 8.40) and Cu^{2+} (log β_{ML} = 6.50) were determined by competitive potentiometry with an Ag^+/Ag electrode [70] (see **Table I-3**). Their high values confirmed the strong affinity of tertiary calixarene-amides, at least as far as ligand **1A** is concerned, for transition and heavy metal cations.

Ligand **XLIV** appended with pyridine moieties was also studied in complexation of transition metal cations by UV-spectrophotometry. The results of experiments in acetonitrile are presented in **Table I-4**.

Table I-3. Stability constants in MeOH of Ag^+, Cd^{2+}, Pb^{2+} and Cd^{2+} complexes with ligand **XXXVI (1A)** determined by potentiometry [39, 70]

cation	Model (M:L)	logβ
Ag^+	1:1	7.20
Cd^{2+}	1:1	8.50
Pb^{2+}	1:1	8.40
Cu^{2+}	1:1	6.50

Table I-4. Stability constants in ACN of Cr^{2+}, Co^{2+}, Ni^{2+} and Cu^{2+} and Zn^{2+} complexes with ligand **XLIV** [61]

cation	Model (M:L)	logβ
Cr^{2+}	2:1	8.14
Co^{2+}	1:2	8.90
Ni^{2+}	1:2	8.54
Cu^{2+}	2:1	9.27
Zn^{2+}	1:1	4.44

With ligand **XXVI**, the highest stability constants were determined for Cd^{2+} and Pb^{2+} complexes. This proved that calixarene-amides possess an affinity not only for hard metal cations, like Ca^{2+} and Na^+, but also for softer cations such as Cd^{2+}, Pb^{2+} and Ag^+, what is in agreement with the extraction results. The stoichiometry of complexes of transition metal cations with ligand **XLIV** depended on the cation tested. The highest stability constants were obtained with Cu^{2+}.

Application in ion-selective electrodes (ISEs)

Calix[4]arenes with tertiary amide functions are well known as Na^+- selective ionophores. The first calix[4]arene-amide – **XXVI (1A)** applied in liquid DBS membranes of ISE showed a selectivity for Na^+ over the other alkali metal cations ($\log K_{Na,M} \leq -2.5$) and over the alkaline earth cations ($\log K_{Na,M} \leq -3.5$) [71].

Since the extraction studies showed significant percentages of Pb^{2+} and Cd^{2+} extraction, it has been also reasonable to check the selectivity for Na^+ over those and other transition and heavy metal cations.

The ionophore **XXVI (1A)** incorporated in DEHA membrane ISE electrodes showed a lower selectivity for Na^+ over Pb^{2+} and Cd^{2+} than over K^+ ions ($\log K_{Na,Pb} \leq -2.9$ and $\log K_{Na,Cd} \leq -3.2$ compared to $\log K_{Na,K} \leq -3.6$) [72], which proved the higher affinity for Pb^{2+} and Cd^{2+} than for K^+.

DEHA has a structure similar to BBPA which in many cases is a good plasticizer for Na^+ - selective electrodes, whereas the Pb^{2+} cation usually prefers a more polar plasticizer such as NPOE. The *o*-phenyloctyl ether (*o*-NPOE) gave only a poor response of 45 [mV]/dec to Na^+. This might be due to the specific interaction of the phenyl ether with the amide carrier, possibly with the amide linkage in the membranes.

Elongation of the chain of the amide substituents (ionophore **XXVIII (3A**)) slightly influenced the selectivity coefficients for Na^+ over the other alkali and alkaline earth cations which were generally better with shorter-chain substituents [60, 73]. It can be suggested that ligands with more bulky flexible substituents can adjust to the cation size more easily than those bearing short-chain moieties, which results in lower selectivity.

Ligands **XXXIV (5A)** and **XXXV (6A)** were incorporated in DOS membranes of ISE and showed ionophoric properties similar to those of **XXVI (1A)**. They showed good selectivity for Na^+ over other metal ions from I and II group [60], comparable with the results obtained for **1A**. Moreover, the ionophore **XXXV (6A)** was tested in the same conditions as **1A** in DEHA membranes towards heavy and transition metal cations. Slightly better selectivity for Na^+ over Pb^{2+} was achieved, which $\log K_{Na,Pb} = -3.2$ [74]. It has been shown that the influence of the tertiary amide substituent attached to the calix[4]arene does not play an important role. Ionophores with flexible or more rigid substituents like diethylamide or piperidinyl act similarly in ion-selective electrodes. They all show similar selectivity for Na^+ over the other metal cations, including for instance Pb^{2+} and Cd^{2+}.

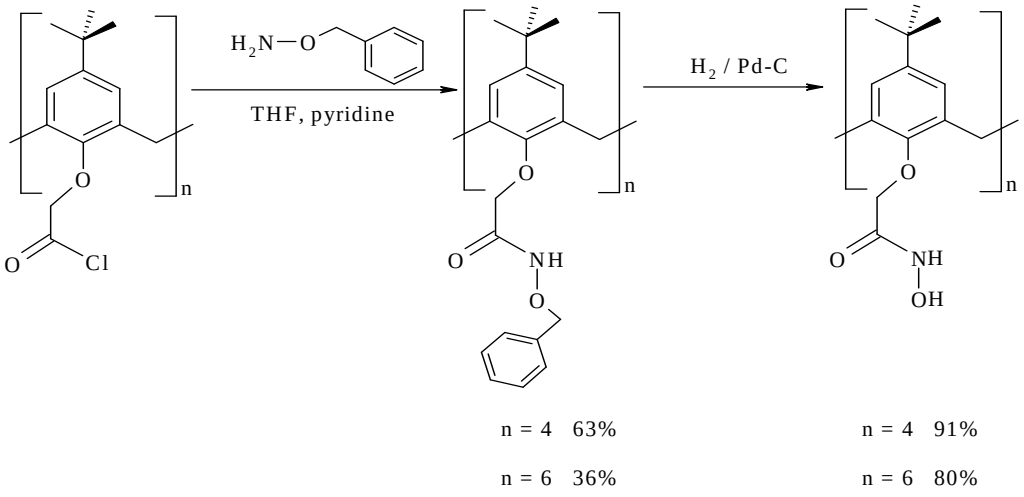
In the contrary, the electrodes based on secondary calix[4]arenes amides like **XL (7A), XLII (8A), XLIII (9A)** are selective for Pb^{2+}, with a wide linearity range (-log a = 7.3-1.9) and an almost theorethical Nernstian calibration slope (S = 30.8-31.5 mV/dec) [75].
Whereas the selectivity coefficients for Pb^{2+} over the other heavy and transition metal cations (i. e. $\log K_{Pb,Cu} \leq -2.5$ and $K_{Pb,Cd} \leq -3.0$) are quite good, the selectivity over Na^+ is only about -1.

3. O- or/and N- substituted calixarene-hydroxamates

3.1. Methods of synthesis

There are only few reports about the synthesis of calixarene-hydroxamates, which are briefly recalled in the following sections.

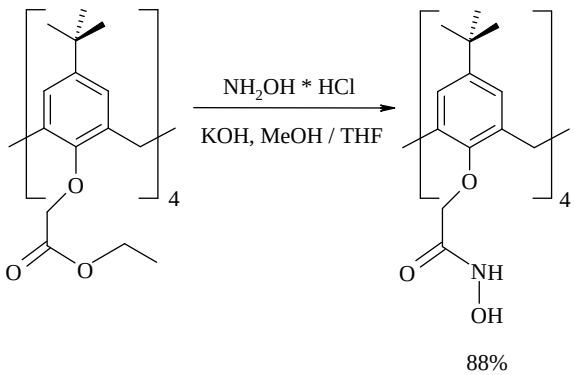
1) O-acylation of calixarene-acid chlorides



Scheme I-13. Calixarene-hydroxamates synthesis via O-acylation of calixarene-acid chloride

The first example was reported by S. Shinkai and co-workers in 1990 [76, 77]. The authors used acylated O-benzylhydroxylamine as substrate and calixarene-acid chloride to obtain O-substituted hydroxamate derivative. Subsequent catalytic hydrogenation led to calixarene-hydroxamic acid [76, 77].

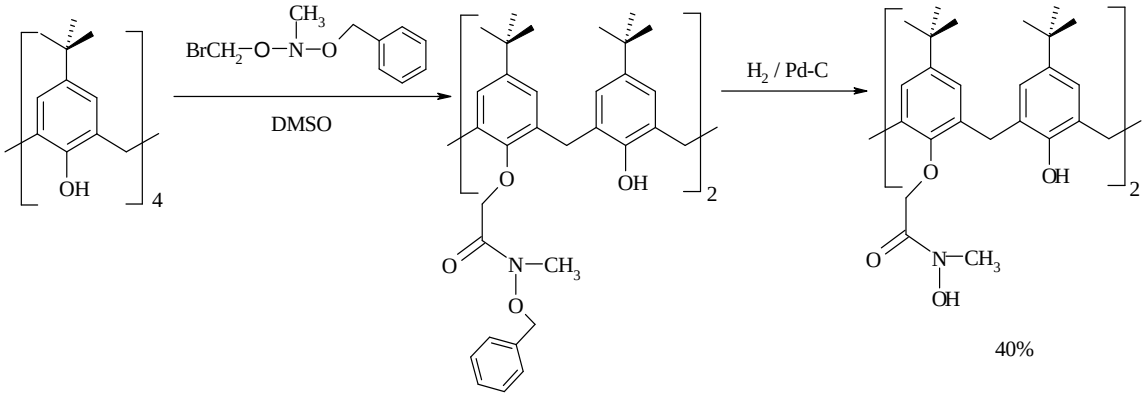
2) Aminolysis of calixarene-esters with hydroxylamines [62]



Scheme I-14. Calixarene-hydroxamates synthesis by aminolysis of calixarene-esters

This method, proposed by McKervey, was also applied for calixarene-amides preparation [61].

3) Use of bromoacetate derivatives of protected hydroxylamine [78]

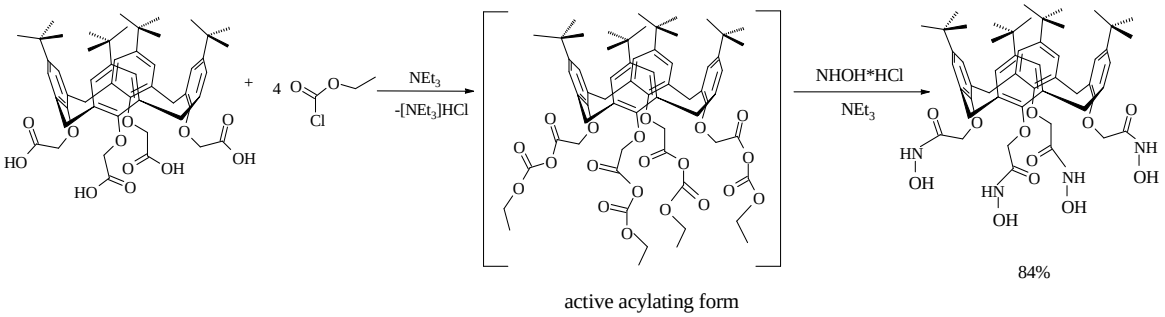


Scheme I-15. Calixarene-hydroxamates synthesis using bromoacetate derivatives of protected hydroxylamine

In this method, proposed by A. Shanzer and co-workers calix[4]arene is reacted with bromoacetate derivative of protected hydroxylamine and subsequent hydrogenation leads to calixarene-hydroxamic acid.

4) Mixed anhydrides method [63]

This method can be used for calixarene-amides, calixarene-hydroxamates and calixarene-hydroxamic acids synthesis.



Scheme I-16. Example of calix[4]arene-hydroxamic acid obtained via mixed anhydrides method [63]

In this work, all calix[4]arene-hydroxamates with protected and unprotected hydroxylamine groups were prepared by mixed anhydrides method which is a very effective and universal synthetic route. This method does not require purification by column

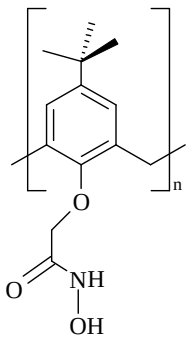
chromatography and the pure products can be obtained in high yields, higher than those achieved by methods 1-3 presented before.

3.2. Binding properties of O- or/and N- substituted calixarene-hydroxamates

Naturally occurring compounds with hydroxamic acid moieties, known as siderophores are produced by fungi and bacteria and act as sequestering agents for Fe^{3+} incorporation into the microorganisms [79]. Their excellent binding properties found biomedical application in removal of Fe^{3+} and Al^{3+} from the body. It has been reported that siderophores show affinity also for other metal cations such as: Pb^{2+}, Cu^{2+} or Ni^{2+} as well as UO_2^{2+} [79].

Calixarenes appended with hydroxamate groups can be regarded as synthetic siderophores and were mainly tested in extraction experiments of uranyl and transition metal cations. As acidic ligands they can liberate protons, providing anions, which then complex with the metal cations to form an ion pair.

S. Shinkai and co-workers investigated hydroxamate derivatives of calixarenes **XLV (17)** and **XLVI** (**Figure I-19**) and found, on the basis of extraction experiments, that those compounds were excellent uranophiles [76, 77]. The quantitative extraction of UO_2^{2+} at pH = 5 was demonstrated, but also they well extracted UO_2^{2+} even at low pH, which indicates that the dissociation of the hydroxamic groups is facilitated by binding to UO_2^{2+}.

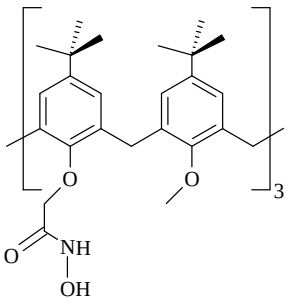


XLV (17) **n = 4**
XLVI **n = 6**

Figure I-19. Calixarene-hydroxamate derivatives **XLV (17)** and **XLVI** tested in extraction of UO_2^{2+} [76, 77]

They have also studied those compounds in extraction of transition and precious metal cations from water into chloroform [80]. They performed an individual extraction at pH = 2.2 and pH = 5.4. It was shown that at pH = 5.4, the tetramer extracted more than 50% of Co^{2+}, Zn^{2+} and Fe^{3+} and almost quantitatively Cu^{2+} and Pd^{2+}. At that pH, the hexamer extracted more than 50% of Ni^{2+}, Zn^{2+} and Pd^{2+} and almost quantitatively Fe^{3+} and Cu^{2+}. The percentage of cation extracted at pH = 2.2 was much decreased, except for Fe^{3+} cation which is well extracted even at low pH.

The same hexamer **XLVI** and calix[6]arene tris-hydroxamic acid **XLVII** (**Figure I-20**) were studied for transition and precious metal nitrate extraction from water into 1,2-dichloroethane [81].



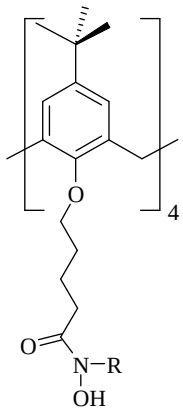
XLVII

Figure I-20. Calix[6]arene-tris-hydroxamic acid (**XLVII**) tested in extraction of transition and precious metal cations [81]

In individual extraction experiments at pH = 5.3, the ligand **XLVII** extracted more than 50% of Fe^{3+}, Cu^{2+}, Pb^{2+}, Zn^{2+} and Pd^{2+}. Acetate, sodium and potassium ions present in the aqueous solution, were not co-extracted. Competitive experiments were also carried out and showed that **XLVII** was able to separate Pb^{2+} from Cd^{2+} (%E = 65 and 1%, respectively).

The affinity of **XLVII** for Pu^{4+} and U^{6+} has been studied recently by B. Boulet et al. [82], who showed that Pu^{4+} can be separated from U^{6+} by choosing the appropriate pH value.

L. Dasaradhi et al. studied calix[4]arenes with secondary and tertiary hydroxamic functions (**Figure I-21**) and found that these compounds extract almost quantitatively UO_2^{2+} at pH $\geq$ 5 [83].

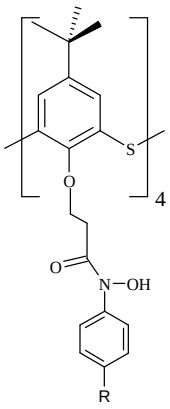


XLVIII R = H
XLIX R = CH_3

Figure I-21. Calix[4]arene-hydroxamic acids **XLVIII** and **XLIX** studied in extraction experiments

They indicated that the secondary hydroxamic acid **XLVIII** is a better extractant of Cu^{2+} compared to the tertiary hydroxamic acid **XLIX**.

Recently, it has been reported that the 1, 3 – alternate thiacalix[4]arene with hydroxamic acid substituents (**Figure I-22**) shows a high affinity towards vanadate ions [84].



L R = H
LI R = CH_3
LII R = OCH_3
LIII R = Br
LIV R = COOH
LV R = NO_2

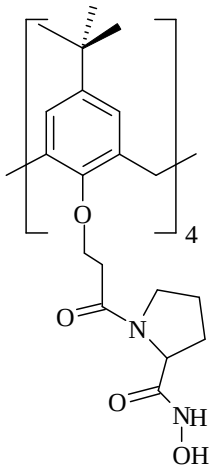
Figure I-22. Various thiacalix[4]arene-hydroxamic acids **L-LV** studied in extraction of vanadate ions [84]

The deep-purple color of the organic phase indicated the complex formation. The extraction of vanadate ions using those ligands was almost quantitative (%E > 99). The authors found the formation of 1 : 2 (L : M) vanadate complexes with the above ligands.

The solid phase extraction has gained much attention due to the availability of a wide variety of sorbent phases.

S. Hutchinson et al. synthesised and supported on octadecylsilica and XAD-4 resin a tetra-hydroxamate derivative of calixarene (**XLV**). They studied the extractive properties of various cations at different pH [62]. Fe^{3+}, Pb^{2+} and Cu^{2+} were quantitatively extracted below pH = 5 while for the other metal cations such as Co^{2+}, Cd^{2+}, Mn^{2+}, Ni^{2+} and Zn^{2+}, pH = 8 was required for quantitative extraction.

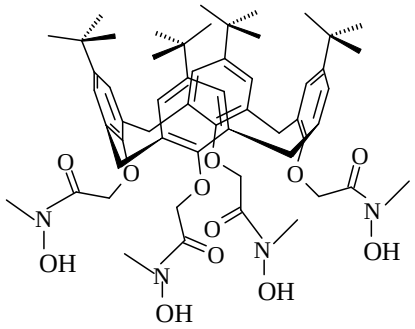
Metal ion extraction by calixarene tetra-proline hydroxamic acid (**LVI**) (**Figure I-23**) supported on octadecylsilica was investigated by J. D. Glennon et al [85]. At pH = 5, Pb^{2+}, Cu^{2+} and Fe^{3+} were extracted quantitatively and Co^{2+}, Ni^{2+} and Cd^{2+} in more than 50%.



LVI

Figure I-23. Calix[4]arene-tetra-proline hydroxamic acid **LVI** used in extraction of transition and heavy metal cations [85]

Recently, the tetra-substituted calix[4]arene-hydroxamate **LVII** (**18**) (**Figure I-24**) was applied in the transport of Pb^{2+} across a Polymer Inclusion Membrane (PIM) [86].

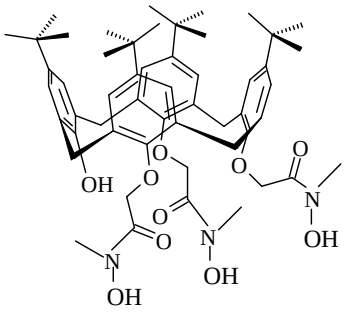


LVII (18)

Figure I-24. Calix[4]arene-hydroxamate derivative **LVII (18)** investigated in the transport of Pb^{2+} across Polymer Inclusion Membrane [86]

A competitive heavy and transition metal cations transport was performed. Two different solutions: one containing Zn^{2+}, Cd^{2+} and Pb^{2+} cations mixture and the second consisting of Co^{2+}, Ni^{2+} and Pb^{2+} cations at equimolar concentration were prepared. It occurred that only Pb^{2+} was transported across the membrane, whereas transport for Zn^{2+} was less than 3% and the rest of the cations stayed in the source phase.

The assessment of selectivity of this compound was investigated in ion-selective membrane electrodes [87]. The electrodes responded to Pb^{2+} and to Fe^{3+} ions within the similar linear range but no Pb^{2+} / Fe^{3+} selectivity was found. Tris-substituted analogue of **LVII (18),** compound **LVIII (16)** presented in **Figure I-25**, occurred to be more selective for Pb^{2+} over Fe^{3+} (log $K_{Pb,Fe}$ = -3.1), nevertheless the electrode with incorporated ionophore **LVIII (16)** in NPOE membrane, showed a typical monovalent cations slope in lead solution (S_{Pb} =58.9 mV/dec) and typical divalent cations slope in iron solution (S_{Fe} = 29 mV/dec) [87]. This suggests the formation of monovalent and divalent species such as $Pb(A)^{+}$ and $Fe(A)^{2+}$ in the membrane.

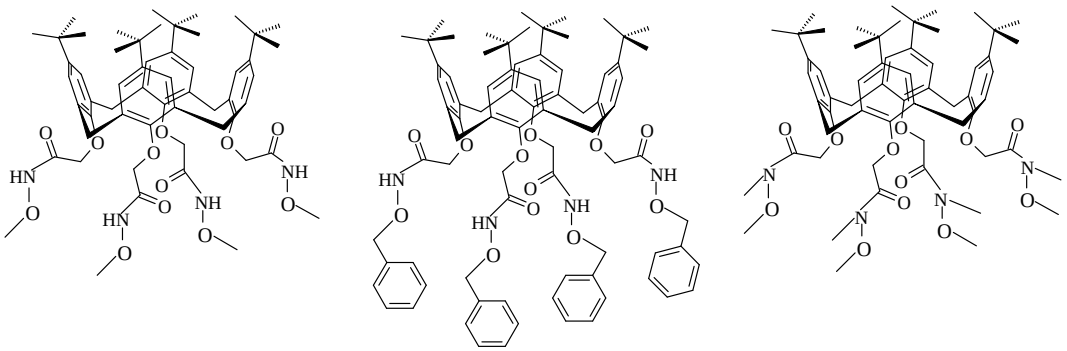


LVIII (16)

Figure I-25. Calix[4]arene-tris-hydroxamic acid **LVII (16)** studied in ISEs [87]

Preliminary studies of ionophoric properties of derivative **XLV (17)** showed that likewise ligand **LVII (18),** no selectivity was found for Pb^{2+} over Fe^{3+} which proved a similar affinity of calixarene-hydroxamic acids for Fe^{3+} and Pb^{2+} [88].

It occurred that O-hydroxamates of calix[4]arenes act as Pb-selective ionophores. Preliminary studies in ion-selective electrodes, using, among others, ligands **LIX (11), LX, LXI (14)** were carried out in our team earlier (**Figure I-26**) [88].



LIX (11) **LX** **LXI (14)**

Figure I-26. Calix[4]arene-hydroxamates derivatives **LIX (11), LX** and **LXI (14)** studied in ISEs [88]

The electrodes with incorporated ligands **LIX (11)** and **LX** responded to Pb^{2+} cations in a wide concentrations range. Nevertheless, the selectivity for Pb^{2+} over Na^{+} was not satisfactory and did not allow to determine the concentration of Pb^{2+} in real samples in the presence of Na^{+}. In the contrary, ligand **LXI (14)**, substituted on O and N atoms, showed selectivity for Na^{+} cations and thus possesses a binding affinity similar to that of calixarene-amides.

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CHAPTER II:

SYNTHESIS AND CHARACTERISATION OF THE LIGANDS

1. Introduction

In my work, nine tetra-substituted calix[4]arene-thioamides (compounds **1T-9T**) were synthesised and they are presented in **Figure II-1**.

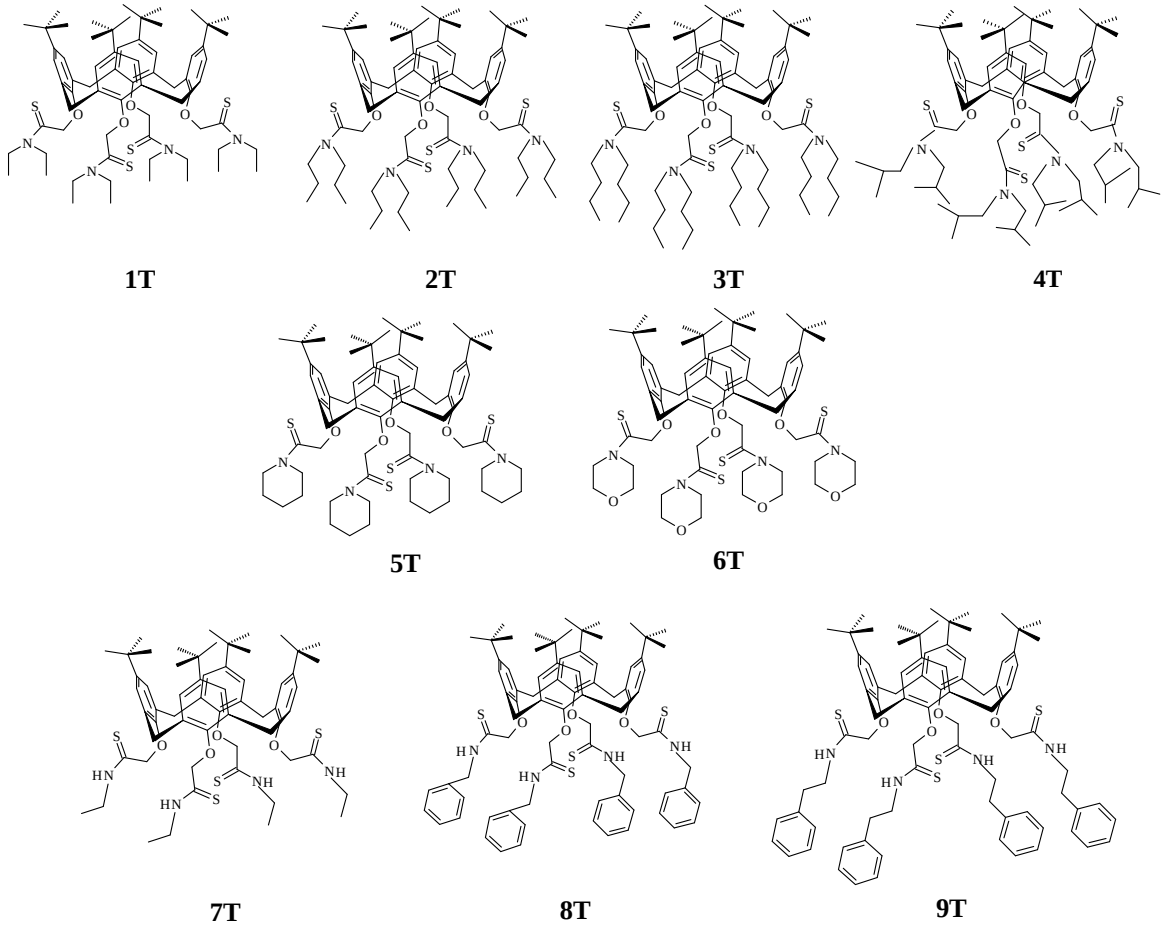


Figure II-1. Calix[4]arene-thioamides (**1T-9T**) synthesised and studied in this work

Ligand **1T** has been already known and preliminary studies have been published [1-3]. The influence of the substituents attached to the calixarene on their binding properties was studied in this work. Ligands **1T-3T** possesses flexible substituents which can adjust to the cation size by forming an appropriate entrance to the cavity. The isomer of **3T** (*n*-butyl), the ligand **4T** (*iso*-butyl) was synthesised to compare the binding properties of both isomers. Ligands **5T** and **6T** possess more rigid bulky cyclic thioamide moieties. Three ligands bearing secondary thioamide functions (**7T-9T**) were also prepared.

The properties of calix[4]arene-thioamides (**1T-9T**) were compared with their corresponding calix[4]arene-amides (**1A-9A**) (**Figure II-2**) which were synthesised for this work as substrates for thioamides synthesis.

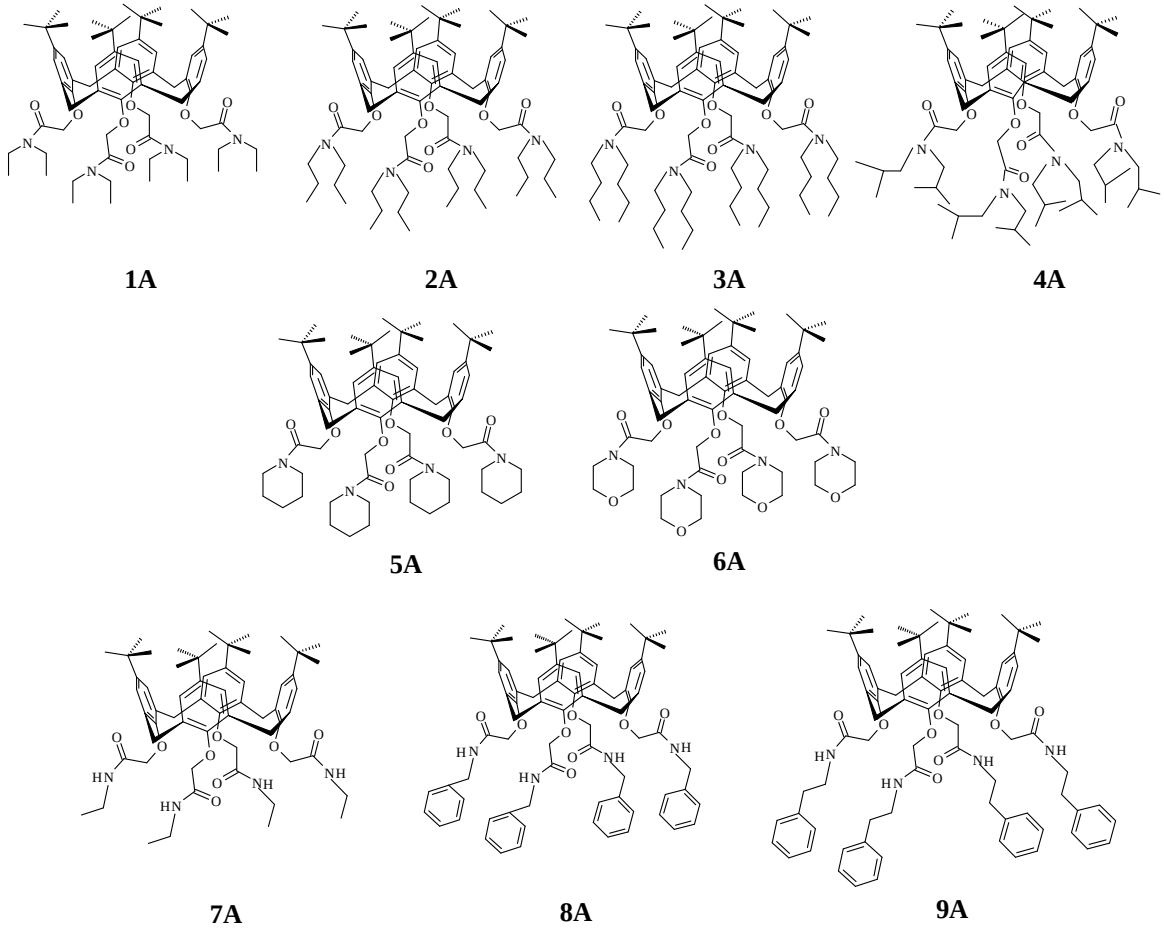


Figure II-2. Calix[4]arene-amides (**1A-9A**) synthesised and studied in this work

The amide derivatives of calix[4]arenes have been studied earlier, but we found interesting to compare the properties of amides **1A-9A** with the thiocarbonyl analogues **1T-9T**. According to our best knowledge, ligand **4A** was synthesised for the first time.

The third group of calix[4]arene derivatives synthesised in this work are O-substituted hydroxamides. Five different ligands (**10-14**) were synthesised (**Figure II-3)** which were earlier studied in our group as ionophores for ISEs [4, 5].

Ligands **11-13** are tetrakis-O-alkylated hydroxamate derivatives of calix[4]arene, whereas ligand **10** is tris-O-methylsubstituted analogue of **11**. The last one, ligand **14** is an O- and N- substituted hydroxamate derivative.

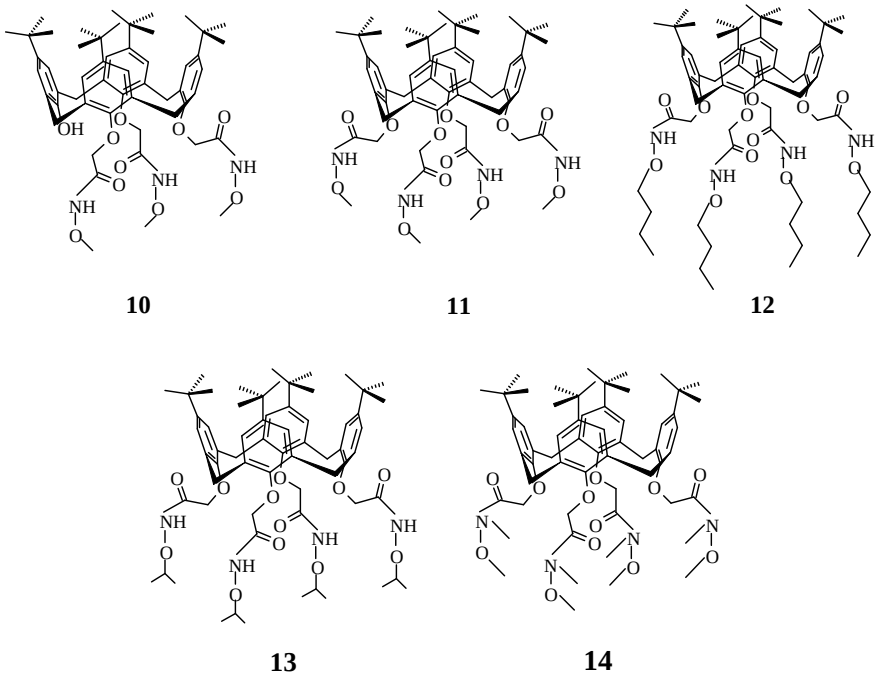


Figure II-3. Calix[4]arene-hydroxamates (**10-14**) synthesised and studied in this work

The fourth family of calix[4]arene-derivatives studied here possesses hydroxamic acid moieties as substituents. They are presented in **Figure II-4** as compounds **15-18**. Some of them were also previously studied by our group as ionophores in ISEs [5, 6]. Two tris-substituted ligands (**15** and **16**) and two tetrakis-substituted ligands (**17** and **18**) were synthesised.

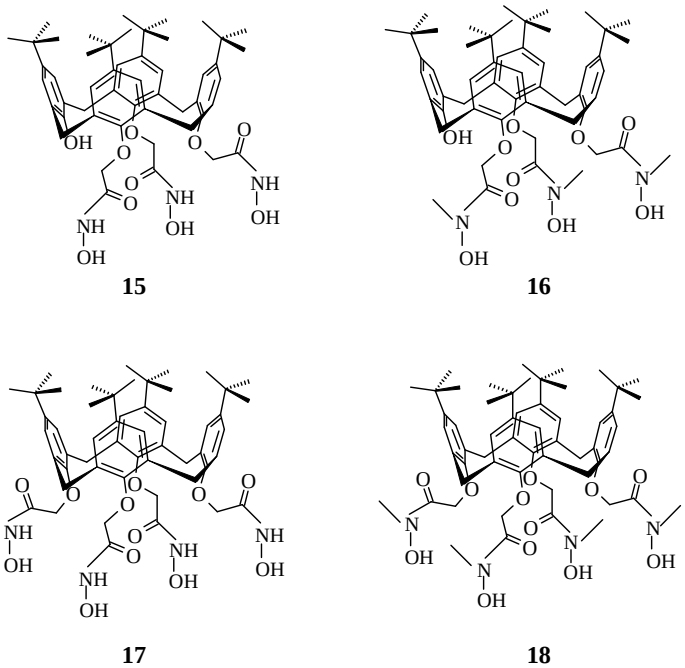
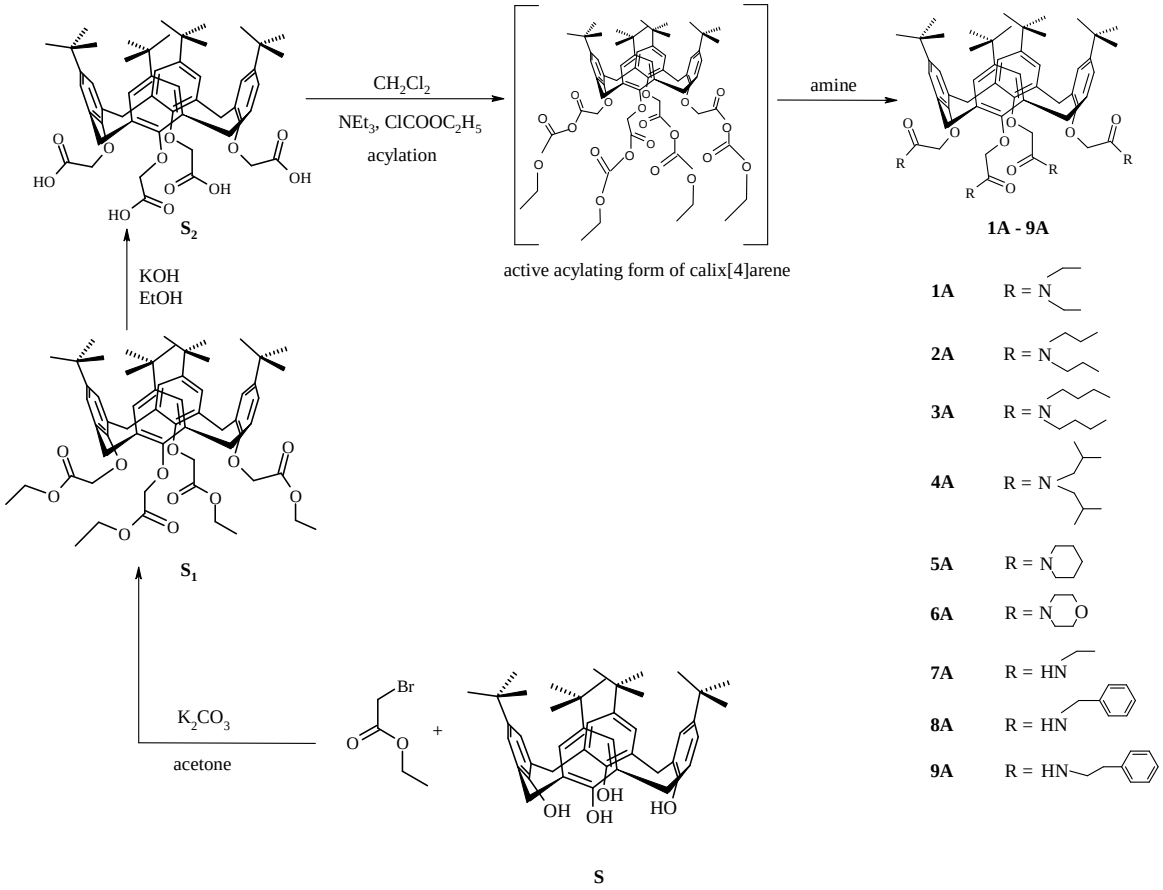


Figure II-4. Calix[4]arene-hydroxamic acids (**15-18**) synthesised and studied in this work

2. Synthesis of calix[4]arene-amides (1A-9A)

All amide derivatives were prepared as substrates for calix[4]arene-thioamides synthesis in 3 steps as presented in **Scheme II-1**.



Scheme II-1. Synthesis of calix[4]arene-amide derivatives **1A-9A**

In the first step, the parent *p-tert*-butyl-calix[4]arene (**S**) was transformed into "calix[4]arene-tetra-ester" (**S_1**). Subsequent hydrolysis of calix[4]arene-ester **S_1** (step 2) led to "calix[4]arene-tetra-acid" (**S_2**) which was the starting material in the final synthesis of amides (**1A-9A**) via mixed anhydrides method (step 3).

In the first step, *p-tert*-butyl-calix[4]arene (**S**) suspended in acetone, was treated with 20 equivalents of ethyl bromoacetate in the presence of 20 equivalents of K_2CO_3. The reaction was refluxed for 6 days to give after crystallisation from a CH_2Cl_2/MeOH mixture, the 25,26,27,28-tetrakis(ethoxycarbonylmethoxy)-*p-tert*-butylcalix[4]arene (**S_1**) with 79% yield. This procedure was adapted from literature [7]. The *cone* conformation of **S_1** was proved by ^{1}H NMR spectroscopy.

In the second step, the intermediate **S_1** was reacted with 4.2 equivalents of KOH dissolved in a small amount of H_2O. The reaction was heated under reflux in ethanol for 24h until the substrate disappeared completely (procedure from [8]).

The product of the reaction was acidified and isolated to give the 25,26,27,28-tetrakis(hydroxycarbonylmethoxy)-*p*-*tert*-butylcalix[4]arene (**S_2**) with 90% yield. The structure of **S_2** was confirmed by ^{1}H NMR spectroscopy. A broad peak at about 12.2 ppm corresponding to the 4 protons of the carboxylic groups appeared. That signal shifted to lower field suggests strong hydrogen bond formation between four acidic CO<u>OH</u> groups.

In the last step (procedure from [9]), the acylation of the intermediate **S_2** with 4.2 equivalents of ethyl chloroformate in the presence of 4.2 equivalents of triethyl amine led to the active anhydride form, which reacted with an appropriate amine in large excess (10-24 equivalents) gave the final products – amides (**1A-9A**) with moderate to very good yields: 24 - 98%. In most cases the reaction yields were better than those reported in the literature. In the preparation of the amide **9A**, the amine hydrochloride was used. Before introducing the amine hydrochloride into the reaction mixture, it was released from its hydrochloride form by adding triethyl amine which formed triethyl amine hydrochloride.

X-ray crystal structures of two (**1A** and **3A**) amides were obtained. The **1A** crystal structure is already known from the literature [10, 11] and is presented in **Figure II-5**. Its packing in the molecular cell is shown in **Figure II-6**.

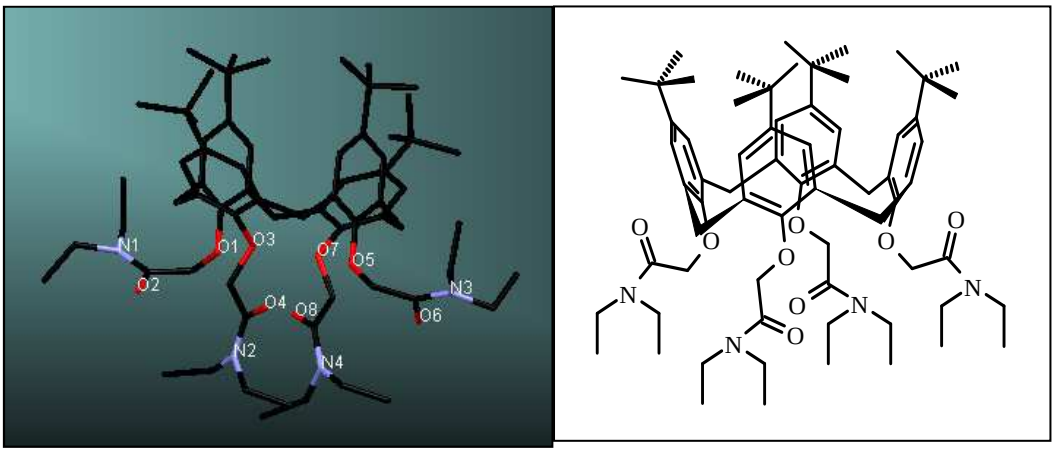


Figure II-5. X-ray crystal structure of **1A**

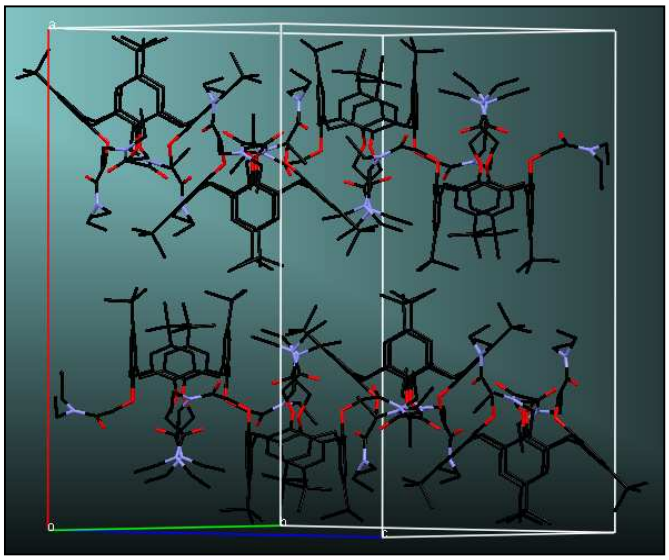


Figure II-6. Packing of **1A** in the molecular cell

The second X-ray structure, presented here for the first time, corresponds to the ligand **3A** and is depicted in **Figure II-7**.

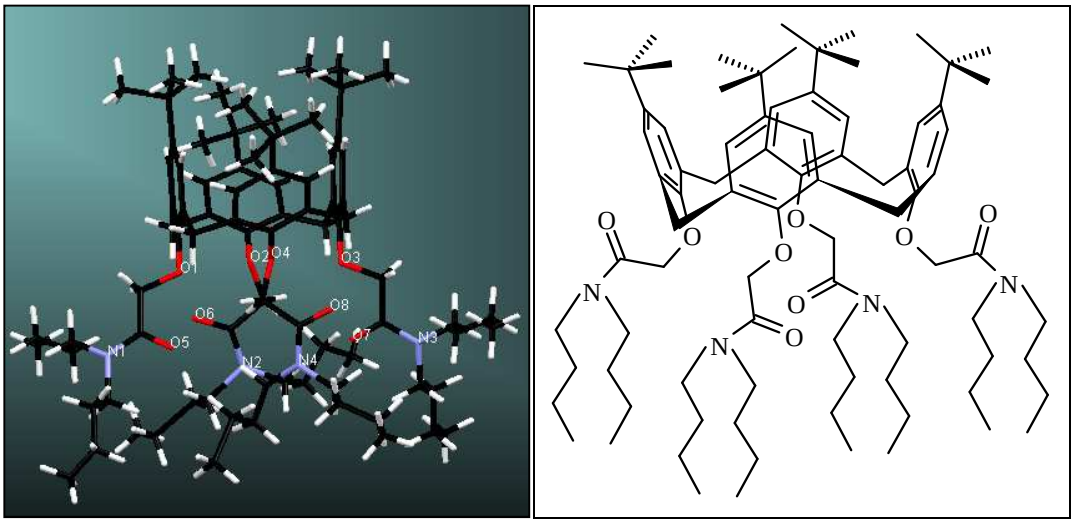


Figure II-7. X-ray crystal structure of **3A**

We can see that two distal amides substituents are bent to the up position, likewise the ligand **1A**.

The “head-to-tail” packing in the molecular cell typical for calixarenes is presented in **Figure II-8**.

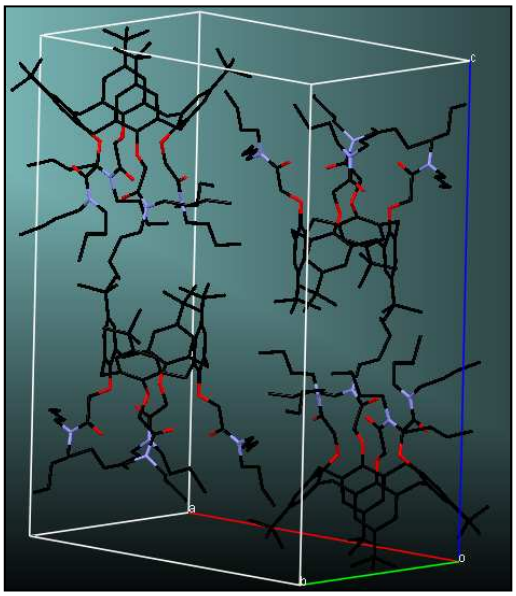
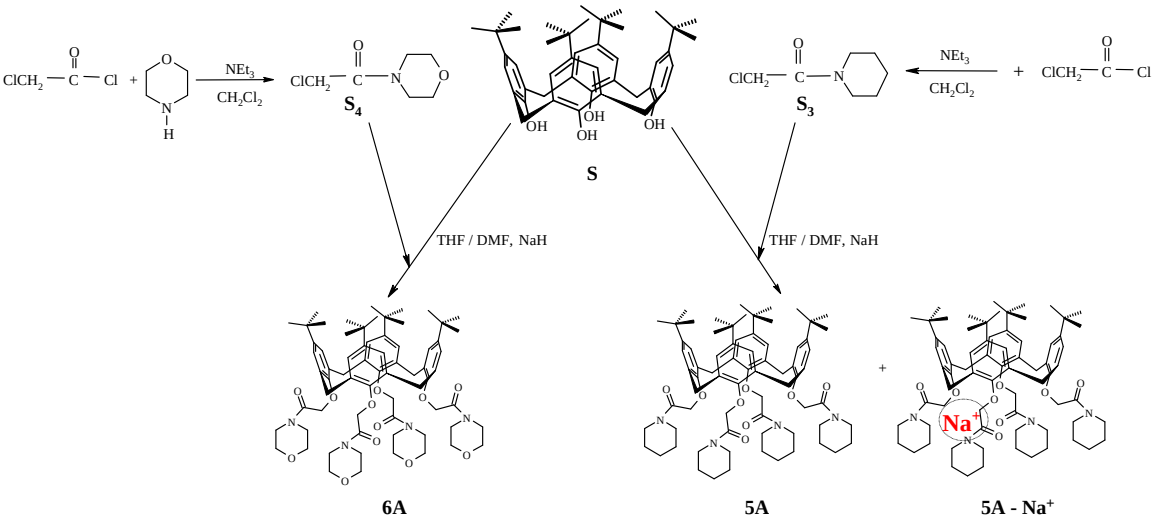


Figure II-8. Packing of **3A** in the molecular cell

The amides **5A** and **6A** were prepared by two different methods. The second method, using an appropriate α-chloroacetamide (**S_3** and **S_4** respectively) [12] is presented in **Scheme II-2**.



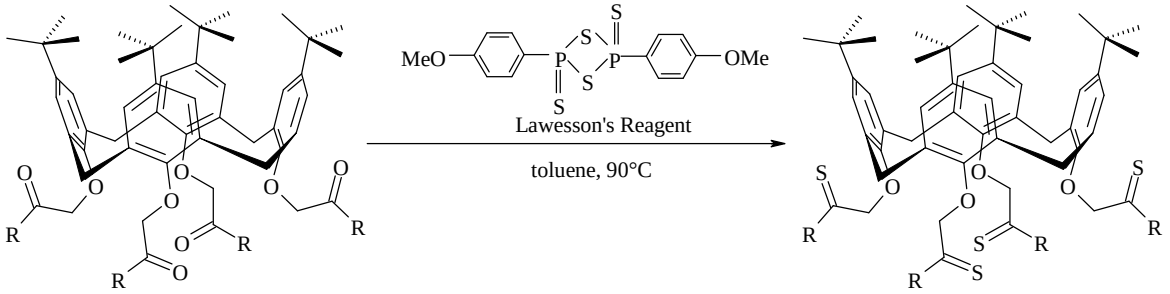
Scheme II-2. An alternative method of amides synthesis used for the ligands **5A** and **6A** preparation

The intermediates **S_3** and **S_4** were prepared according to the procedure described in [12, 13] by reacting the α-chloroacetyl chloride in CH_2Cl_2 with 1.2 equivalent of an appropriate amine in the presence of 1.2 equivalent of NEt_3. The oily products **S_3** and **S_4** were used without further purification.

The parent calix[4]arene dissolved in 30 mL of the solvent mixture (5/1) THF/DMF was treated with 10 equivalents of 50% NaH. Subsequently, 16 equivalents of the appropriate α-chloroacetamide (**S_3** or **S_4**) were added and the reaction was carried out for 15h at 60°C. Ligand **6A** was obtained as a pure product with 78% yield, better than that reported in the literature (57%) and that obtained by the "mixed anhydrides method" (44%). Product **5A** was obtained with 27% yield (together with its Na^+ complex with 55% yield), better than the method of "mixed anhydrides method" (44%). In both cases, the second method is more efficient.

3. Synthesis of calix[4]arene-thioamides (1T-9T)

Thioamide derivatives of *p-tert*-butylcalix[4]arene were prepared using Lawesson's Reagent as thionating agent (**Scheme II-3**) according to the procedure described in [14]. Nine calix[4]arene-thioamides (**1T-9T**) were obtained [15, 16].



1A-9A **1T-9T**

1A, 1T R = N

2A, 2T R = N

3A, 3T R = N

4A, 4T R = N

5A, 5T R = N

6A, 6T R = N O

7A, 7T R = HN

8A, 8T R = HN

9A, 9T R = HN

Scheme II-3. Synthesis of calix[4]arene-thioamide derivatives (**1T-9T**)

The amides (all in *cone* conformation) were reacted with 2.2 equivalents of Lawesson's Reagent in dry toluene at 90°C under argon for about 24h. The corresponding thioamides were tetra-substituted derivatives, also in *cone* conformation. In most cases they were purified by means of silica gel chromatography before crystallisation from

CH_2Cl_2/MeOH mixture. Ligands **7T-9T** which did not require further purification were obtained in good yields (64-72%), whereas for the rest of thioamides (**1T**-**6T**) purification by column chromatography was necessary and the pure products were prepared with 12-68% yields. Ligands appended with alkyl substituents (**2T**-**4T**) crystallised with difficulty and therefore, were obtained with low or moderate yields 12-30% after further purification.

The *cone* conformation of thiocarbonyl compounds was confirmed by ^{1}H NMR spectroscopy of the ligands and in the case of thioamides **5T, 6T, 7T** and **9T** also by X-ray crystal structure analysis.

Figure II-9 presents the ^{1}H NMR spectrum of the thioamide **6T** ((a) upper spectrum) and its corresponding amide **6A** ((b) lower spectrum).

The *cone* conformation of **6T** can be confirmed by the presence of characteristic peaks in the ^{1}H NMR spectrum: one singlet corresponding to the *tert*-butyl protons at 1.10 ppm, an AB system of the methylene protons at 3.18 and 4.89 ppm, one singlet for the 8 protons of -O-CH_2-C=S at 5.21 ppm and one singlet of the aromatic protons at 6.83 ppm. The larger size of the sulphur atom (1.04 Å of ionic radius) as compared to the oxygen atom (0.66 Å of ionic radius) is the reason for slight shifts of the signals in thioamides spectra in comparison to the spectra of the corresponding amides, used as starting materials.

However, the biggest chemical shifts are noticed for the protons located close to the sulphur atoms. The signals corresponding to the NCH_2 protons are significantly shifted downfield. Futhermore, it can be seen that they are splitted into four separate singlets, whereas in the corresponding amide spectrum, the singlets are much closer to each other. That can be explained by the rotation barrier caused by the bigger sulphur atom.

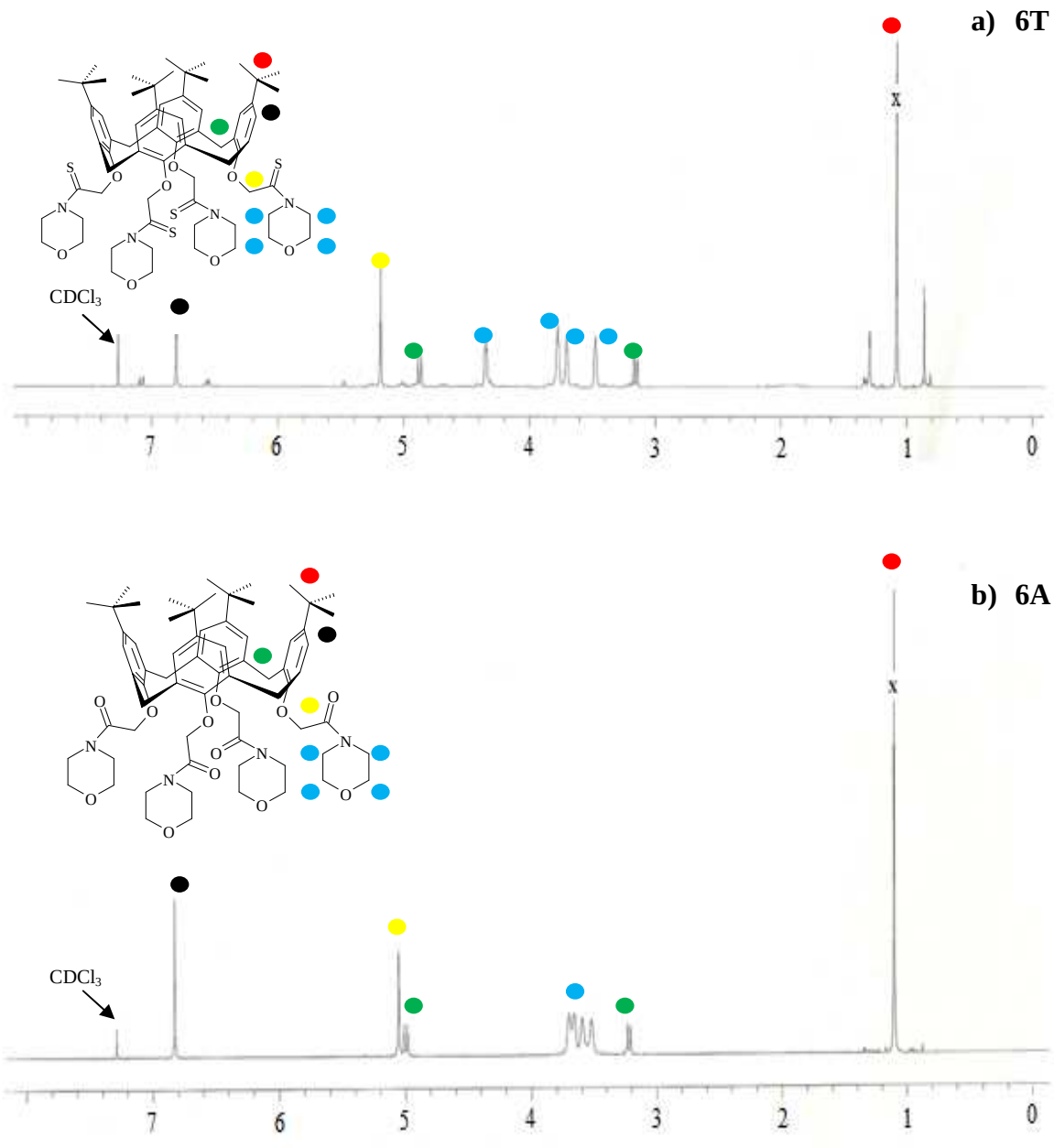


Figure II-9. ^{1}H NMR spectrum in $CDCl_3$ of the thioamide **6T** ((a) upper spectrum) and its carbonyl analogue **6A** ((b) lower spectrum)

X-ray structure analysis of the single crystals of several calix[4]arene-thioamides (**5T-7T, 9T**) confirmed that the compounds adopt a pinched *cone* conformation, in which two rings A – C are almost parallel, whereas the two other (rings B and D) are almost perpendicular [15, 16]. The dihedral angles between the aromatic rings A – C and B – D of calix[4]arene-thioamides **5T**, **6T, 7T** and **9T** are presented in **Table II-1**.

Table II-1. Dihedral angles of the calix fragments for calix[4]arene-thioamides **5T, 6T, 7T, 9T**

ligand	5T	6T	7T	9T
Defining rings	**Dihedral angles between rings [°]**			
A - C	8.92	9.76	3.77	1.24
B - D	75.16	74.62	83.55	89.47

The X-ray crystal structure of the compound **5T** is presented in **Figure II -10** [16].

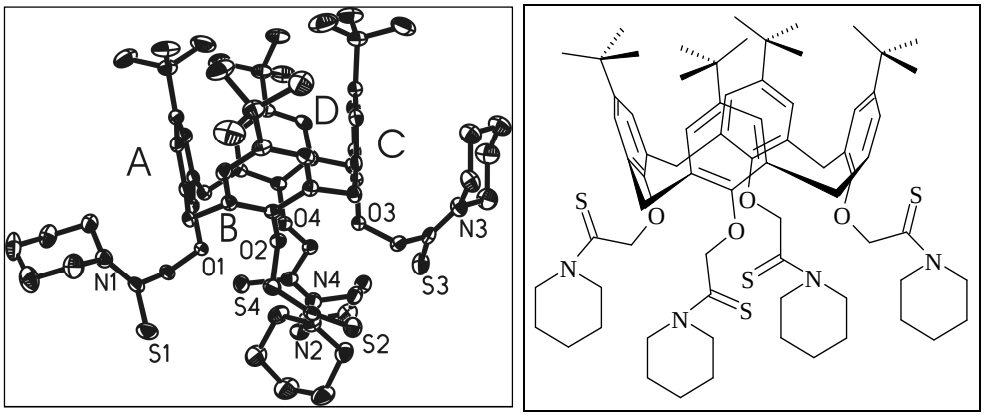


Figure II-10. X-ray crystal structure of the compound **5T** [16]

In that structure, thiocarbonyl groups are oriented outside the center in position optimal for weak dispersion intermolecular interactions such as C–H…S contacts as it is shown in **Figure II-11** (interactions marked in white dots). The characteristic “head to tail” packing for calix[4]arenes in the molecular cell, can be observed.

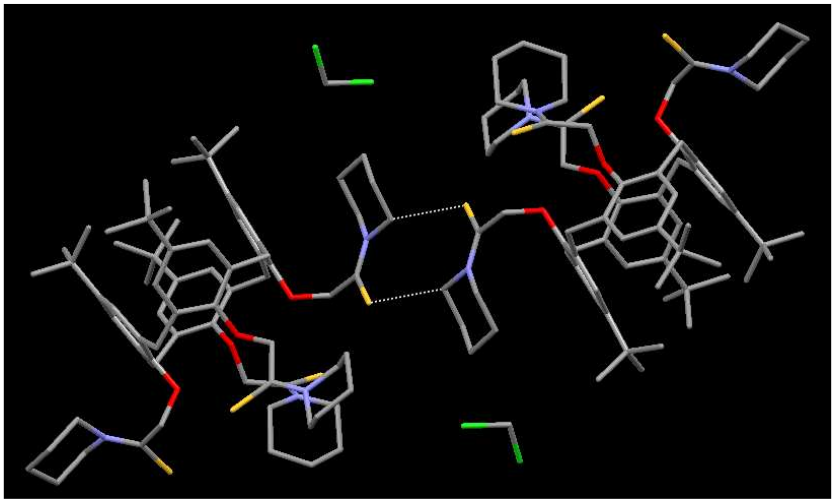


Figure II-11. Presentation of the intermolecular interactions of the C–H…S type between two units of the compound **5T** in a molecular cell

One molecule of the solvent, dichloromethane, was found outside the cone for a single molecule of calixarene (in green).

It is worth to compare the X-ray crystal structure of calix[4]arene-thioamide **5T** with its carbonyl analogue-amide **5A** (**Figure II-12**).

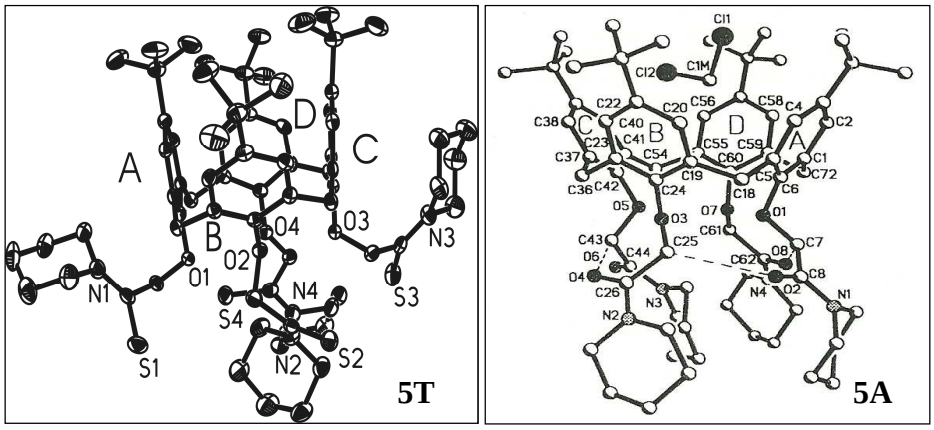


Figure II-12. Comparison of X-ray crystal structure of calix[4]arene-thioamide **5T** and its carbonyl analogue – amide **5A** [16, 17]

Some conformational differences are due to the presence of larger sulphur atoms in the thioamide **5T** structure in comparison to oxygen in amide **5A**. As it was already mentioned, thioamide **5T** adopts a distorted *cone* conformation with two rings almost parallel and two others almost perpendicular, whereas in the corresponding amide **5A** structure, the angles are quite similar (the average dihedral angle is 64.03°) [17].

As we could see in **Figure II-11**, in thioamide structure, the thiocarbonyl groups are oriented to the position optimal for intermolecular interactions, which causes that the two distal thiopiperidine moieties are bent up, which we do not see in the structure of the corresponding amide **5A**.

Another X-ray crystal structure obtained corresponding to the compound **6T** is presented in **Figure II-13** [15]. Likewise in the structure of **5T**, thiocarbonyl groups are oriented outside the cavity. In the molecular cell, two molecules of **6T** are oriented upside down to each other (**Figure II-14**).

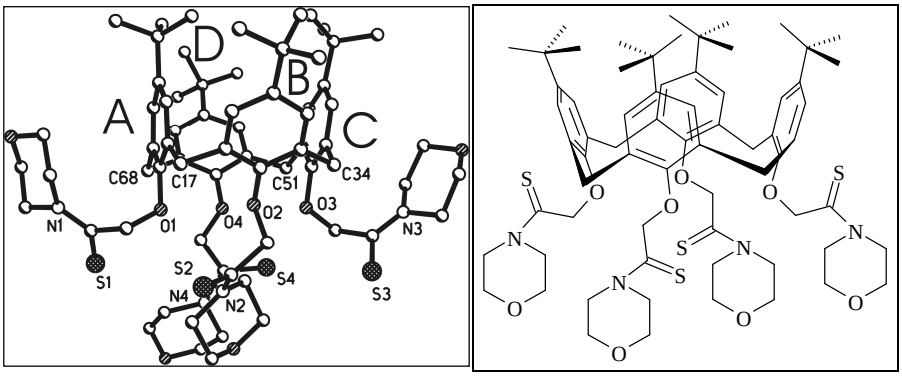


Figure II-13. X-ray crystal structure of the compound **6T** [15]

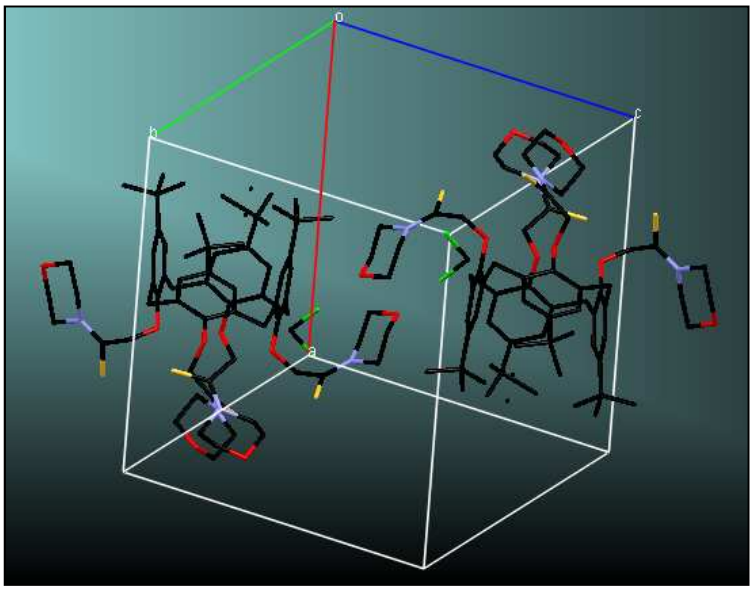


Figure II-14. Two units of the compound **6T** in the molecular cell

Also, a dichloromethane molecule was present in the structure, outside the cone (in green).

It was also possible to obtain crystals suitable for X-ray analysis in the case of the secondary thioamides **7T** and **9T** which are depicted in **Figures II-15** and **II-16**, respectively [15]. In the structure of **7T** no specific strong intermolecular interactions were found in the crystal, however, the conformation is stabilised by a net of intramolecular hydrogen bonds which are shown in **Figure II-15**.

The characteristics of those interactions are listed in **Table II-2**.

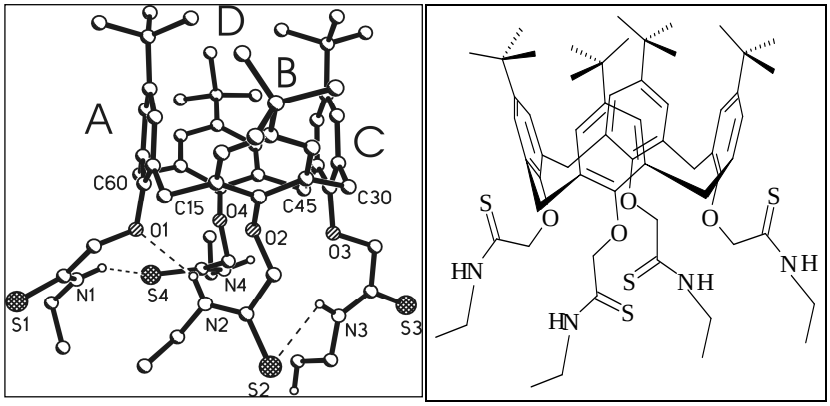


Figure II-15. X-ray crystal structure of the compound **7T** [15]

The crystal structure of the other secondary thioamide **9T** is presented below.

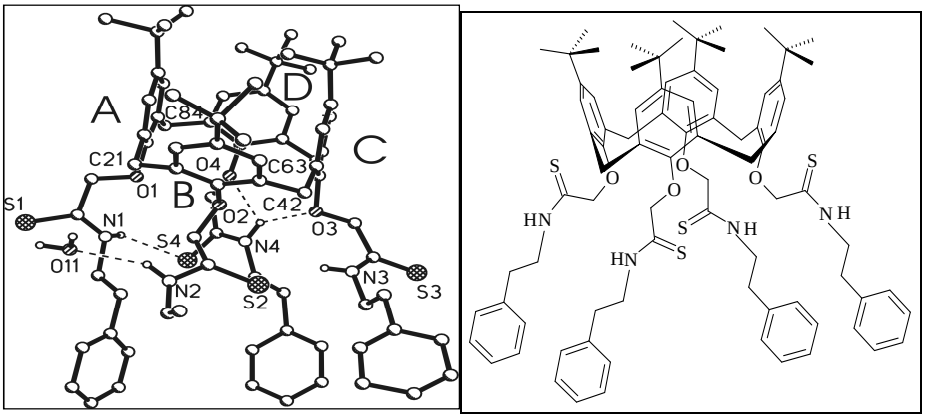


Figure II-16. X-ray crystal structure of the compound **9T** (one arm is omitted for the sake of clarity) [15]

Here, thiocarbonyl groups are located in position optimal for forming intermolecular interactions. A molecule of water was found in a position that generates a hydrogen bond of the N-H…O type. All hydrogen bonds found in the structure are specified in **Table II-2**.

Table II-2. Hydrogen bonds (Å, °) in the structures of **7T** and **9T** (D – donor, A – acceptor) [15]

Compound	Atom label	D-H	H···A	D···A	Angle (DHA)
7T	N2-H2…O1	0.89(3)	2.19(4)	3.006(6)	152(6)
	N1-H1…S4	0.85(3)	2.72(5)	3.368(6)	134(5)
	N3-H3…S2	0.87(3)	3.22(6)	3.726(7)	120(5)
9T	N1-H1…S4	0.86(4)	2.81(4)	3.568(13)	147(4)
	N2-H2…O11	0.88(4)	2.30(7)	3.11(2)	151(11)
	N4-H4…O3	0.89(4)	2.27(6)	2.967(9)	134(6)
	N4-H4…O4	0.89(4)	2.18(6)	2.684(9)	115(5)

4. Synthesis of calix[4]arene-hydroxamates (10-14)

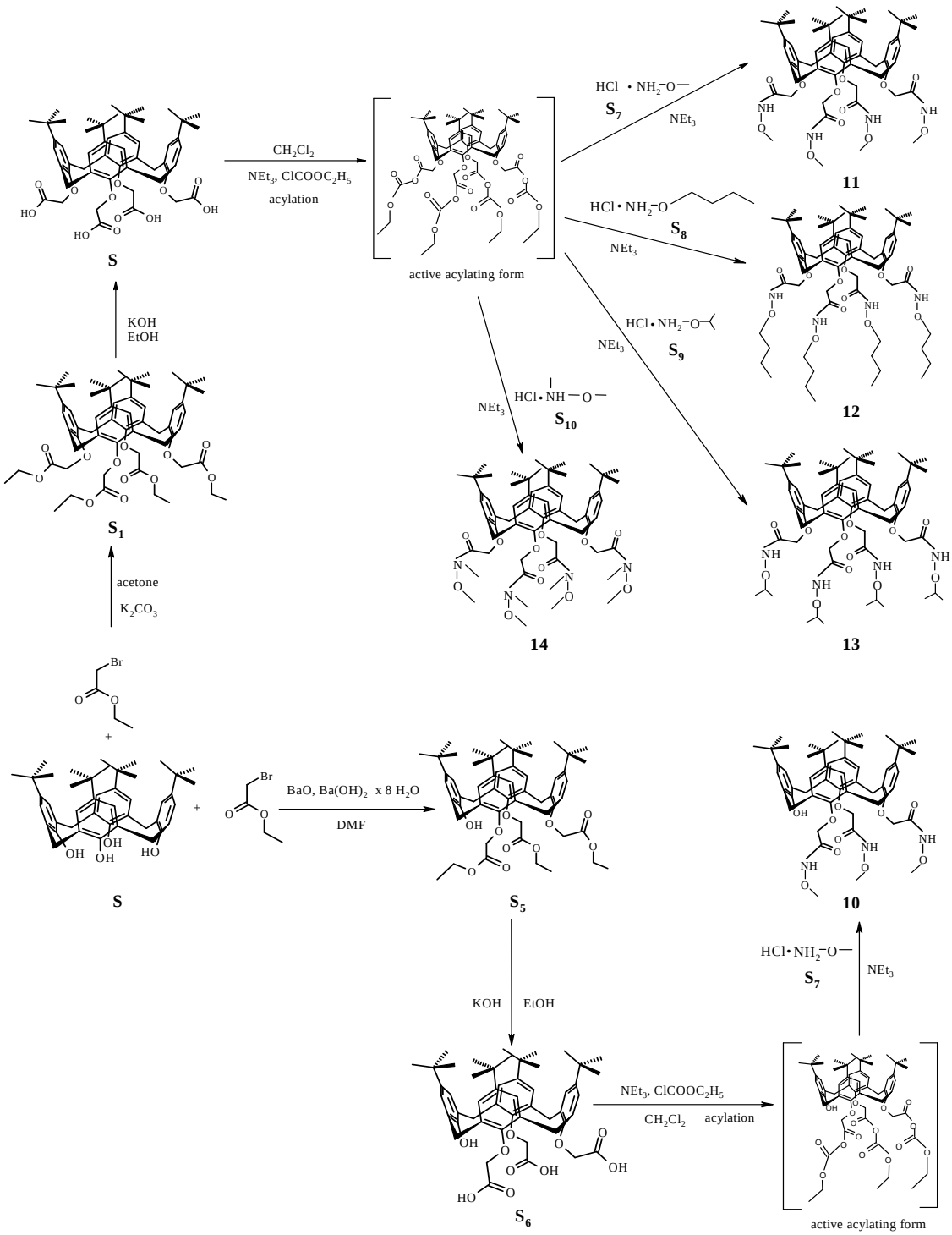
Hydroxamate derivatives of calix[4]arene were synthesised in few steps. For the tetra-substituted derivatives, the first two steps are the same as for amides and consist of the calix[4]arene-ester preparation (**S_1**) and subsequently the calix[4]arene-carboxylic acid synthesis (**S_2**). The final products (**11-14**) were prepared via mixed anhydrides method [9] as it is shown in **Scheme II-4**.

The intermediates **S_7-S_9** were synthesised, whereas **S_{10}** was purchased from Aldrich company. In order to prepare the intermediates **S_7-S_9**, N-hydroxyphthalimide in DMF was reacted with 0.8 equivalent of Na_2CO_3 and 2 equivalents of an appropriate alkyl iodide (**Scheme II-5**). The reaction was carried out for 15h until the reaction mixture colour changed from dark red to yellow. Crystallisation from water gave the intermediates **S_7a – S_9a**. The procedure was adapted from [18].

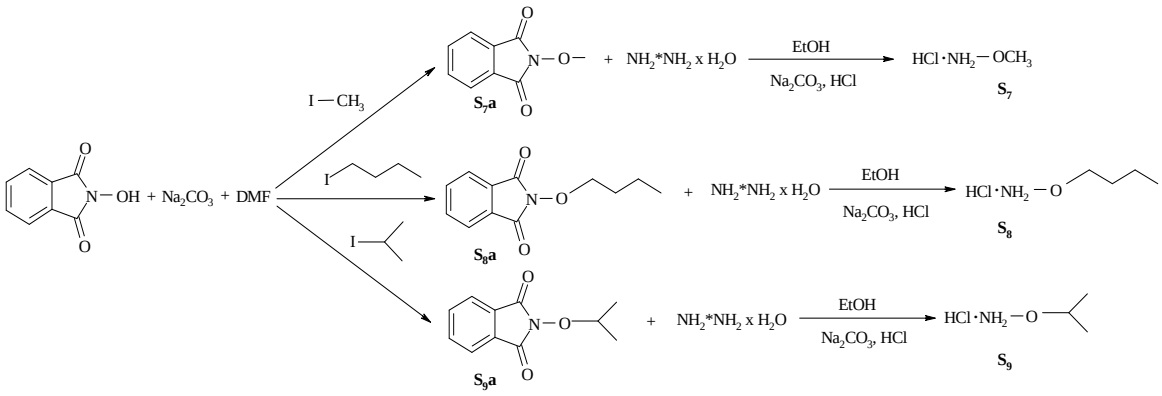
Next, the reaction with 5 equivalents of 40% hydrazine monohydrate at 60°C in EtOH was performed in order to obtain the intermediates **S_7-S_9**.

Similarly to the amides synthesis, the acylation of the calix[4]arene-acid (**S_2**) with 4.2 equivalents of ethyl chloroformate in the presence of 4.2 equivalents of triethyl amine led to the active acylating form. Subsequently, 24 equivalents of an appropriate hydroxylamine hydrochloride (**S_7-S_{10}**) were added.

Before introducing the hydroxylamine hydrochloride to the reaction mixture, it was released from its hydrochloride form by adding the same equivalent of NEt_3. The four tetra-substituted hydroxamate derivatives (**10-14**) were prepared.



Scheme II-4. Synthesis of calix[4]arene-hydroxamate derivatives **10-14**



Scheme II-5. Synthesis of intermediates S_7-S_9

X-ray crystal structure of the compound **11** is presented in **Figure II-17**.

The ligand adopts a pinched *cone* conformation with two aromatic rings almost perpendicular and two others almost parallel. Below, in **Figure II-18** we can see a packing of the molecular cell of compound **11**. Also well visible is a net of intra- and intermolecular hydrogen bonds of the N-H…O type.

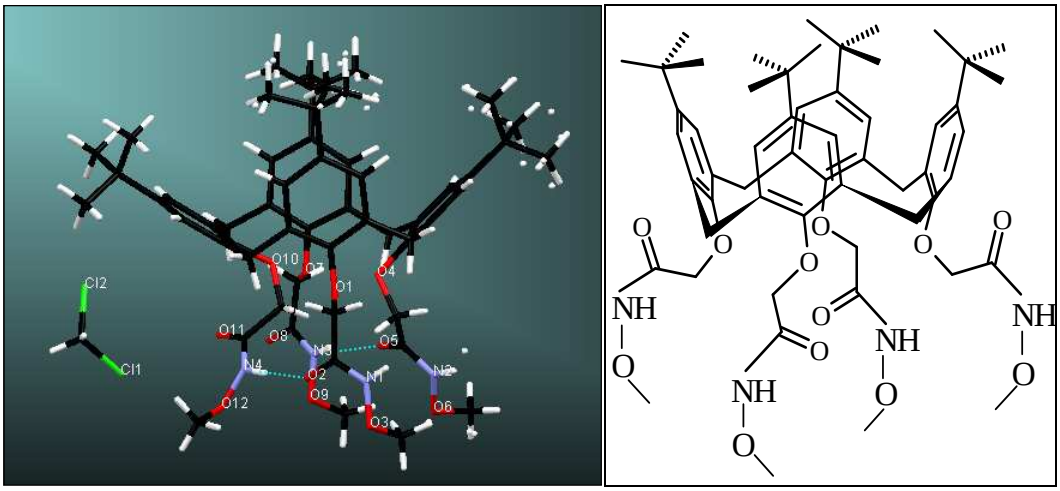


Figure II-17. X-ray crystal structure of the compound **11**

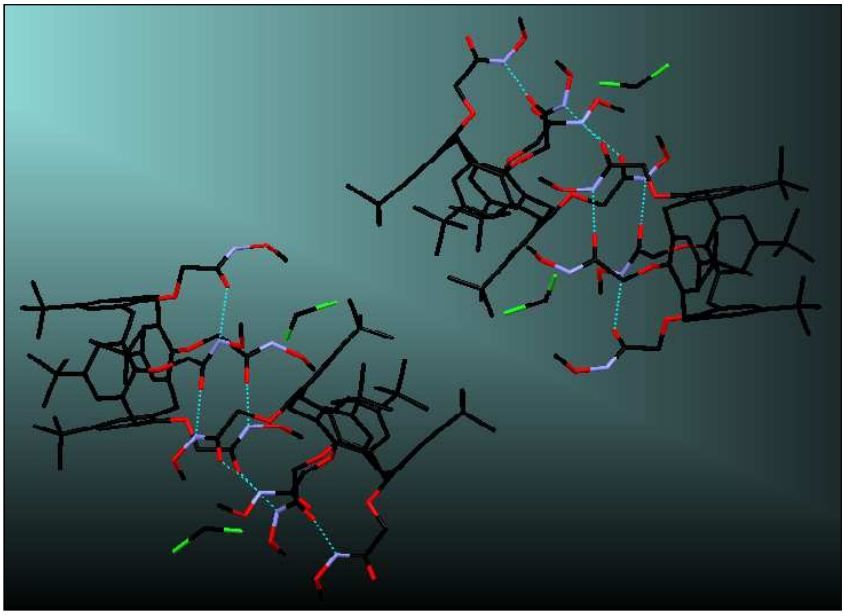


Figure II-18. Packing of the compound **11** in the molecular cell

One dichloromethane solvent molecule outside the cone was found (in green).

The X-ray structure of a hydroxamate derivative, ligand **13** is presented in **Figure II-19**.

Similarly, the ligand **13** crystallised in distorted *cone* conformation with no molecule of solvent trapped in the crystal. The possible formation of hydrogen bonds was confirmed and some intra- and intermolecular interactions are visible in **Figure II-20**.

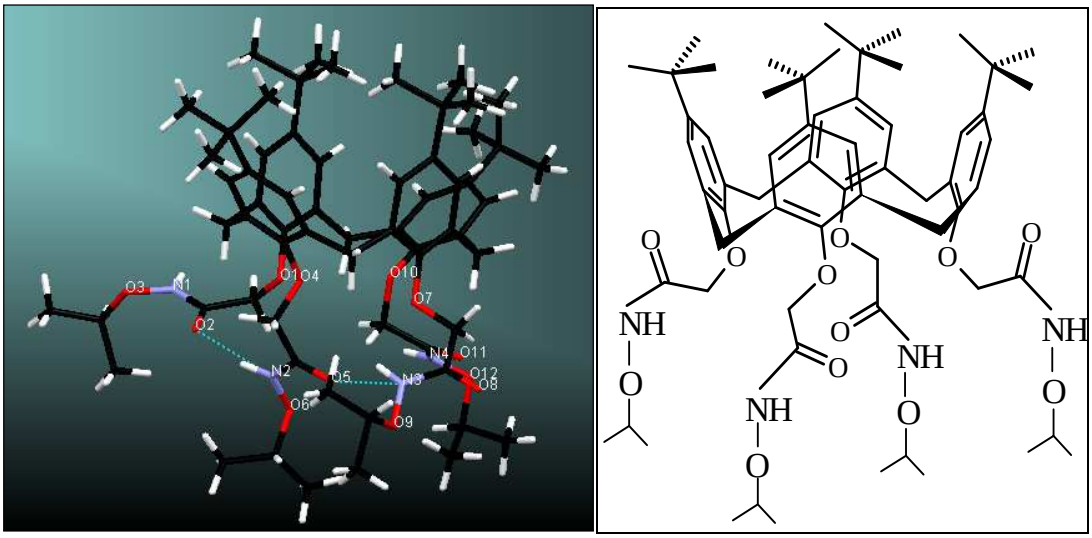


Figure II-19. X-ray crystal structure of the compound **13**

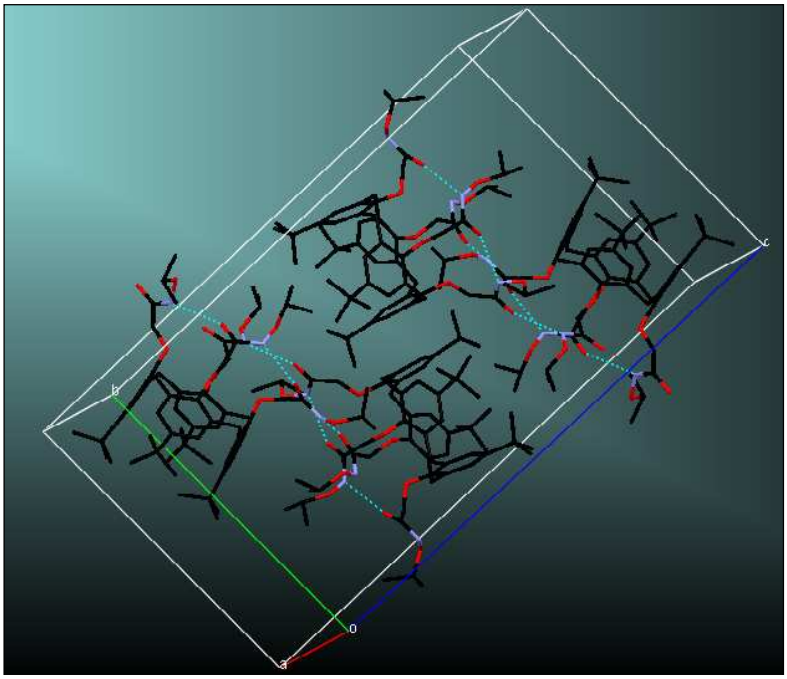


Figure II-20. Packing of the compound **13** in the molecular cell

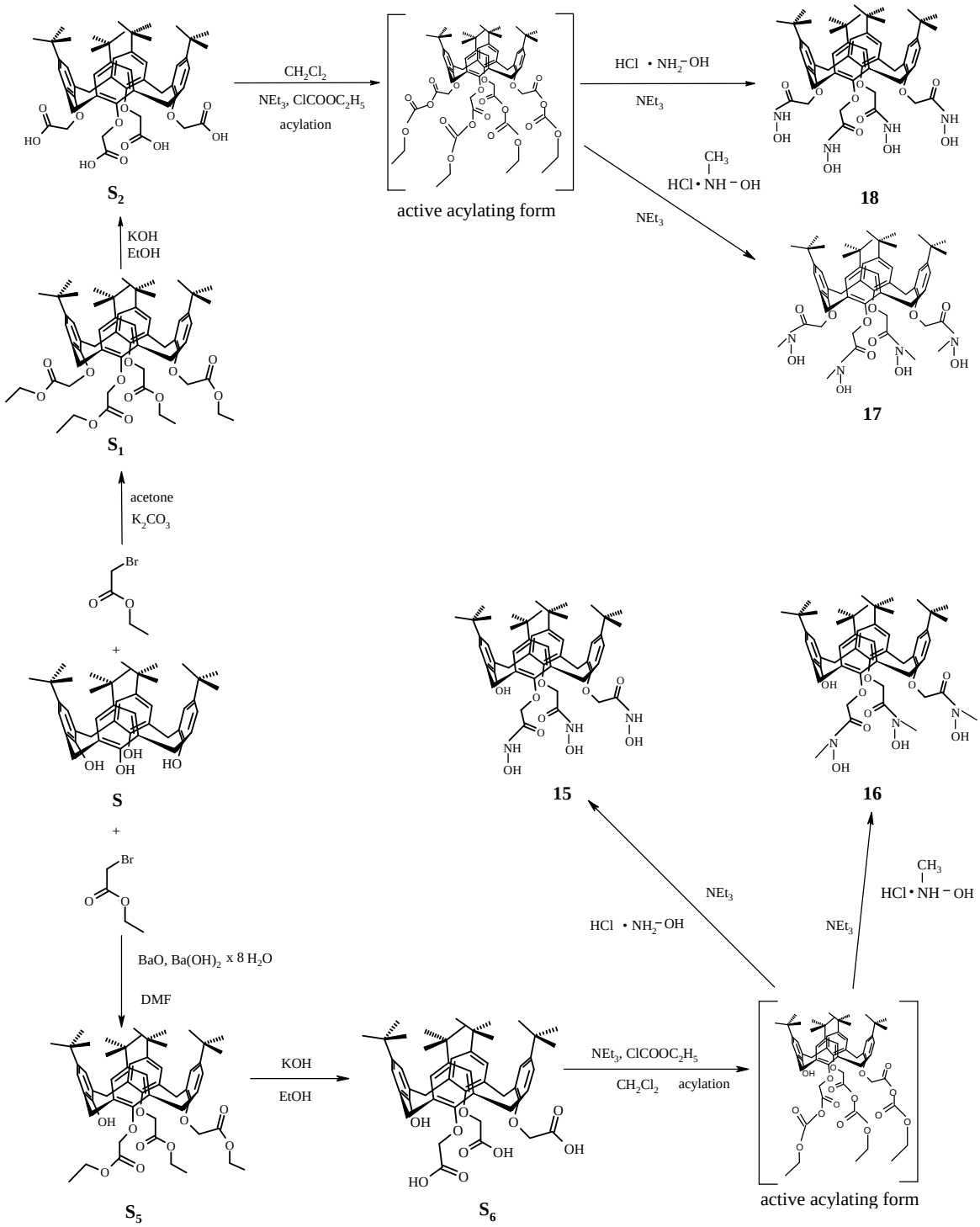
The tris-substituted hydroxamate derivative **10** was also synthesised. The synthesis procedure for intermediate $\mathbf{S_5}$ was adapted from literature [19]. $\mathbf{S_5}$ was prepared starting from the parent calix[4]arene **S** which was reacted with 3.5 equivalents of BaO and 1.5 equivalent of $Ba(OH)_2 \times 8H_2O$ in DMF. Subsequent addition of 10 equivalents of ethyl bromoacetate, gave a crude product which was purified by column chromatography to give the pure product $\mathbf{S_5}$ with 62% yield.

In the second step, the intermediate $\mathbf{S_5}$ was reacted according to the literature [8] with 3.2 equivalents of KOH dissolved in a small quantity of H_2O and the reaction was carried out in EtOH to give calix[4]arene-acid $\mathbf{S_6}$ with 90% yield.

The final product, tris-substituted hydroxamate derivative **10** was obtained according to the procedure applied for the tetra-substituted derivatives, nevertheless, 3.2 equivalents of ethyl chloroformate and triethyl amine were used to obtain an active acylation form. Then, 18 equivalents of the hydroxylamine hydrochloride $\mathbf{S_7}$ were added to give the final product **10** with 76% yield.

5. Synthesis of calix[4]arene-hydroxamic acids (15-18)

The final products - calix[4]arene-hydroxamic acid derivatives **15-18** were obtained using mixed anhydrides method [9] and the synthetic route is presented in **Scheme II-6**.



Scheme II-6. Synthesis of the four calix[4]arene-hydroxamic acid derivatives **15-18**

Tetra-substituted products (**17** and **18**) were obtained by reacting calix[4]arene-carboxylic acid (**S_2**) with 4.2 equivalents of ethyl chloroformate in the presence of 4.2 equivalents of triethyl amine and subsequent addition of 24 equivalents of an appropriate hydroxylamine hydrochloride. Crystallisation from a CH_2Cl_2/Et_2O mixture gave pure products **17** and **18** with 82% and 60% yields, respectively.

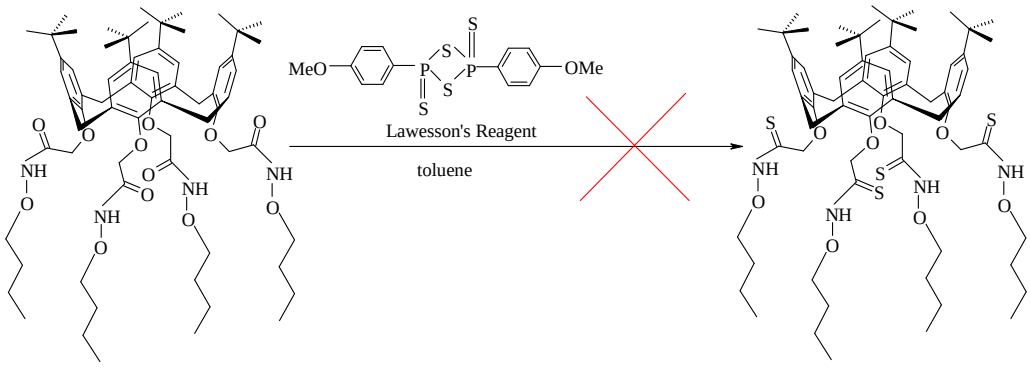
Tris-substituted compounds (**15** and **16**) were prepared similarly. Starting from calix[4]arene-carboxylic acid (**S_6**) by reacting 3.2 equivalents of ethyl chloroformate and 3.2 equivalents of triethyl amine, the active acylating form was obtained. Then, 18 equivalents of an appropriate hydroxylamine hydrochloride were added. Subsequent crystallisation from a CH_2Cl_2/Et_2O mixture gave pure products **15** and **16** with 76% and 79% yields.

Before hydroxylamine hydrochloride was introduced to the reaction mixture, it was released from its hydrochloride form by adding the same equivalent of NEt_3.

6. Thiocarbonyl analogues of calix[4]arene-hydroxamates and calix[4]arene-hydroxamic acids

Some attempts were made to obtain thiocarbonyl analogues of the synthesised hydroxamates and hydroxamic acid derivatives of calix[4]arenes, which has not been reported so far.

Using Lawesson's Reagent and O-substituted hydroxamate derivative (**12**) in toluene, instead of the desired product presented in **Scheme II-7**, the compound (**19**) presented in **Figure II-21** was obtained.



Scheme II-7. The attempted way of thiohydroxamate derivative (**12T**) preparation

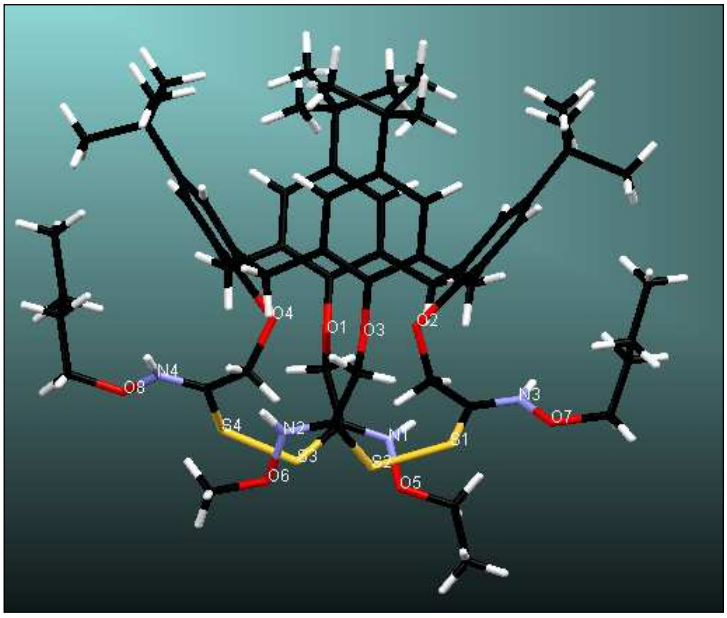
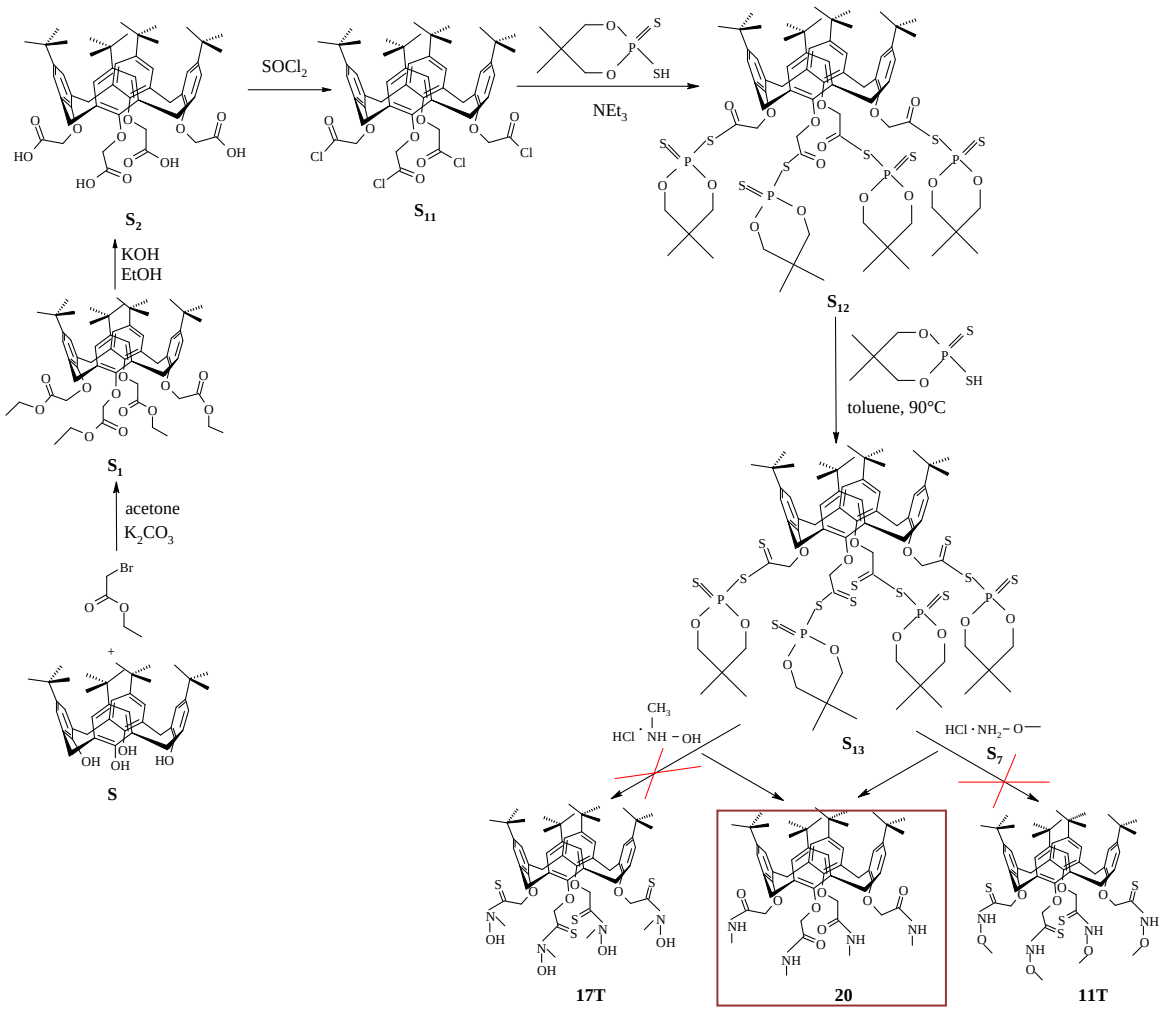


Figure II-21. X-ray crystal structure of the product **19** obtained in the reaction of calix[4]arene-hydroxamate **12** with Lawesson Reagent

X-ray crystal structure analysis of **19** showed that instead of expected thiocarbonyl compound, two sulphur-sulphur bridges were formed. Moreover, only two butyl chains are present in this structure, probably due to transesterification. The compound **19** was applied in ion-selective electrodes but did not have interesting ionophoric properties.

It has been reported that in a complex mixture of products, thiohydroxamic acids may be isolated in the highest yield in a reaction of Lawesson's Reagent with hydroxamic acids in tetrahydrofuran at room temperature [20]. However, the attempts to repeat that reaction in the case of *p-tert*-butylcalix[4]arene-hydroxamic acids failed and only unreacted substrates were present in the reaction mixture. The reaction progress was controlled by spraying the TLC plate with methanolic solution of $FeCl_3$ which results in purple colour stains indicating the presence of only hydroxamic acids. In the case of thiohydroxamic acids existence, the black stains would appear on the silica gel plates [21].

A very convenient method of thiohydroxamic acids preparation was proposed more recently by L. Doszczak and J. Rachoń [22] using an efficient thioacylating agent: S-thioacyldithiophosphate. The synthesis route and expected products (**17T** and **11T**) are shown in **Scheme II-8**.



Scheme II-8. Synthetic route of calix[4]arene-thiohydroxamic acids **17T** and **11T** preparation

In the first step, 25,26,27,28-tetrakis(chloroformylmethoxy)calix[4]arene (**S_{11}**) was prepared. For this purpose, the intermediate **S_2** was reacted with thionyl chloride ($SOCl_2$) for 3h under reflux. The IR spectrum of the obtained intermediate **S_{11}** showed a characteristic for acid chloride absorption band at ν_{max} = 1800 cm^{-1}. Subsequently, the intermediate **S_{11}** was treated with 4.2 equivalents of S-thioacyldithiophosphate and then 4.2 equivalents of triethyl amine were added into the cooled solution. The ^1H NMR spectrum of the intermediate **S_{12}** confirmed that this step was successful. Next step involved heating in dry toluene (instead of carcinogenic benzene) the intermediate **S_{12}** with 8 equivalents of S-thioacyldithiophosphate. The reaction was controlled by thin layer chromatography (TLC). The obtained product **S_{13}** was used without further purification. In the last step, the cooled solution of **S_{13}** was reacted with 20 equivalents of hydroxylamine hydrochloride and 24 equivalents of NEt_3. Unfortunately, instead of the desired products **17T** and **11T**, the compound **20** presented in **Figure II-22** was obtained.

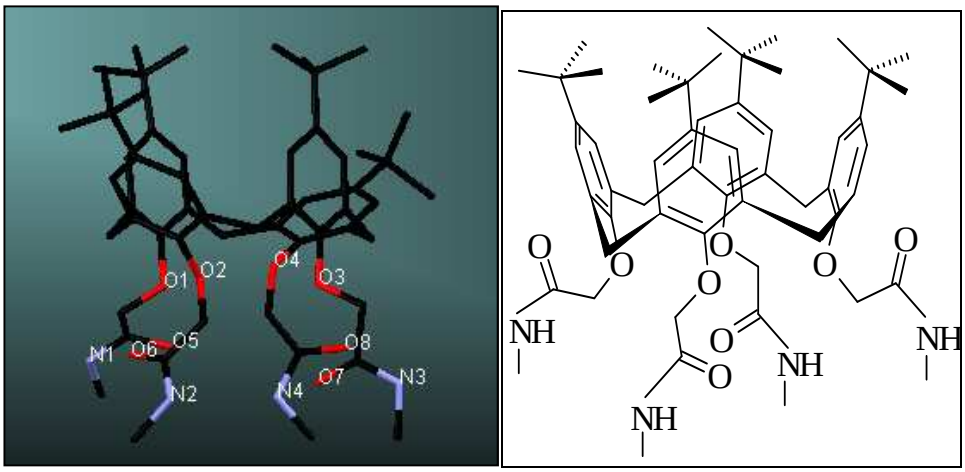


Figure II-22. X-ray crystal structure of the isolated compound **20**

The isolated product was a secondary methylamide of calix[4]arene. It is evident that the reaction goes towards reduction of hydroxamic acid, rather than thioacylation. It has been reported that in the case of high steric hindrance the reaction cannot be successful. So far no examples of calixarene-thiohydroxamic acids preparation were reported.

7. Characterisation of the ligands

7.1. General information: methods of characterisation and materials

TLC was performed on silica gel plates Merck 60 F_{254}. Chromatography columns were prepared with Kieselgel Merck. The melting points were uncorrected.

^{1}H NMR spectra were recorded in $CDCl_3$ or in few cases in DMSO on a Varian instrument (200 MHz or 500 MHz) at Gdansk University of Technology (GUT). IR spectra were obtained on a Perkin-Elmer 580 Spectrophotometer at GUT. ESI mass spectra were done on a Mariner instrument in Institute of Organic Chemistry PAN in Warsaw. Elemental analyses were performed on Carlo Erba Instrument CHNS EA 1108-Elemental Analyzer at Gdansk University.

Experimental diffraction data were collected on a KM4CCD kappa-geometry diffractometer, equipped with a Sapphire2 CCD detector. Enhanced X-ray MoKa radiation source with a graphite monochromator was used. The X-ray crystal structures were solved at GUT in the Department of Inorganic Chemistry by Dr J. Chojnacki.

Data reduction, absorption correction, space group determination, solution and refinement were made using CrysAlis software package (Oxford Diffraction, 2008) [23]. Determination of the unit cells and data collection were carried out at 120 K.

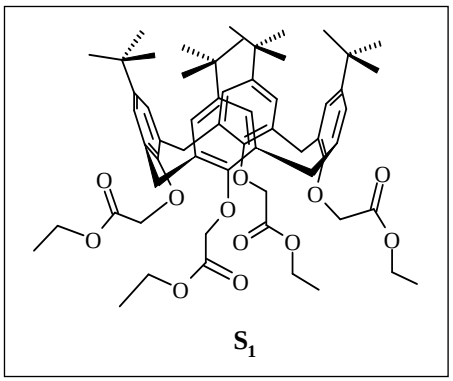
An initial structure model was obtained by charge flipping (SUPERFLIP, Palatinaus [24]) and all of the non-hydrogen atoms were refined with anisotropic thermal parameters by full matrix least-squares procedure based on F^2. Calculations were carried out using the SHELX system [25] run under WINGX environment [26].

Reagents used for syntheses: *p-tert*-butylcalix[4]arene (**S**), ethyl bromoacetate, triethyl amine, ethyl chloroformate, NaH, chloroacetyl chloride, Lawesson's Reagent, N-methyl, N-methoxyhydroxylamine hydrochloride (**S_{10}**), are commercially available and were purchased from Aldrich. N-hydroxyphtalimide and N-butoxyhydroxylamine hydrochloride (**S_8**) were synthesised before [5].

The organic solvents: tetrahydrofuran (THF), dimethylformamide (DMF), dichloromethane (CH_2Cl_2), methanol (MeOH), diethyl ether (Et_2O), acetone, ethyl alcohol (EtOH), were reagent grade.

7.2. Syntheses of intermediates (**S_1-S_{11}**)

Synthesis of calix[4]arene-esters



S_1

25,26,27,28-tetrakis(ethoxycarbonylmethoxy)-*p-tert*-butylcalix[4]arene (S_1)

Into a 250 mL round bottom flask containing 5.0 g (7.7 mmol) of *p-tert*-butylcalix[4]arene **S**, 21.25 g (154 mmol) of K_2CO_3 were added and the mixture was dissolved in 100 mL of acetone and refluxed for 6h. Then the solution of ethyl bromoacetate 17.1 mL (154 mmol) in 15 mL of acetone was added dropwise. After 6 days, the reaction mixture was cooled and the solvent was removed. The crude product was dissolved in CH_2Cl_2 and extracted twice with water (30 mL) and with 0.1 mol L^{-1} HCl (30 mL). The combined organic layers were dried over $MgSO_4$, then filtered and the solvent was removed. The

crude product was obtained after crystallisation from CH_2Cl_2/MeOH mixture giving 6 g (6.05 mmol) of the pure compound **S_1** as transparent crystals.

Yield: 79%, lit. 88% [7]

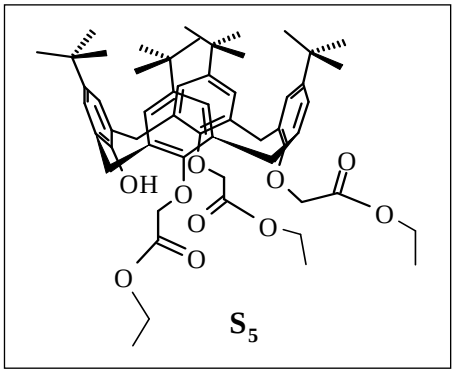
$C_{60}H_{80}O_{12}$; M.W. = 992.2 g/mol; m.p. = 148-150°C, lit. 154-155°C [7];

IR ν_{max} (C=O) 1758 cm^{-1};

R_f = 0.4 (petroleum ether / ethyl acetate, 4/1)

^{1}H NMR (500 MHz, $CDCl_3$): *cone* conformation δ [ppm]: 1.10 (s, 36H, C-($\underline{CH_3}$)$_3$); 1.32 (t, 12H, -O-CH_2-$\underline{CH_3}$); 3.22 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 13.18 Hz); 4.24 (q, 8H, -O-$\underline{CH_2}$-CH_3); 4.83 (s, 8H, -O-$\underline{CH_2}$-CO); 4.88 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 13.18 Hz); 6.80 (s, 8H, Ar-$\underline{H}$).

25-hydroxy-26,27,28-tris(ethoxycarbonylmethoxy)-*p*-*tert*-butylcalix[4]arene (S_5)



S_5

Into a 250 mL flask containing 2.592 g (4 mmol) of *p*-*tert*-butylcalix[4]arene **S**, 2.142 g (14 mmol) of BaO and 1.934 g (6.13 mmol) of $Ba(OH)_2 \times 8H_2O$ dissolved in 100 mL of DMF were stirred at room temperature for 1h. After that time, the solution of ethyl bromoacetate 4.44 mL (40 mmol) in 15 mL of DMF was added dropwise and the mixture was stirred for another hour. Subsequently, 100 mL of 1 mol L^{-1} HCl and 30 ml of CH_2Cl_2 were added. After the phase separation, the aqueous layer was extracted three times with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed. The crude product was purified by column chromatography using as an eluent the mixture of petroleum ether/ethyl acetate (8/1). The following crystallisation from CH_2Cl_2/MeOH mixture was used to give 2.259 g (2.49 mmol) of the pure product **S_5**.

Yield: 62%, lit. 78% [19]

$C_{56}H_{74}O_{10}$; M.W. = 906.2 g/mol; m.p. = 160-166°C, lit. 168-169 [19];

IR ν_{max} (C=O) 1757 cm^{-1};

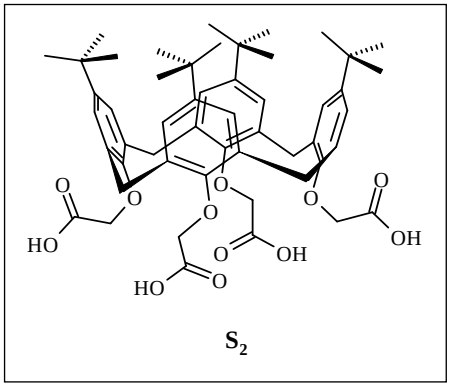
R_f = 0.5 (petroleum ether / ethyl acetate, 4/1)

^{1}H NMR (200 MHz, $CDCl_3$): *cone* conformation δ [ppm]: 0.87 (s, 18H, C-($\underline{CH_3}$)$_3$); 1.28 (s, 9H, C-($\underline{CH_3}$)$_3$); 1.29 (s, 9H, C-($\underline{CH_3}$)$_3$); 1.22 (t, 3H, -O-CH_2-$\underline{CH_3}$); 1.35 (t, 6H, -O-CH_2-$\underline{CH_3}$); 3.26 (d, 2H, Ar-$\underline{CH_2}$-Ar, *J* = 13.11 Hz); 3.32 (d, 2H, Ar-$\underline{CH_2}$-Ar, *J* = 13.11 Hz); 4.15 (q, 2H, -O-$\underline{CH_2}$-CH_3); 4.28 (m, 4H, -O-$\underline{CH_2}$-CH_3); 4.34 (d, 2H, Ar-$\underline{CH_2}$-Ar, *J* = 13.11 Hz); 4.95 (d, 2H, Ar-$\underline{CH_2}$-Ar, *J* = 13.11 Hz); 4.54 (s, 2H, O-$\underline{CH_2}$-CO); 4.65 (s, 1H, O-$\underline{CH_2}$-CO);

4.73 (s, 1H, O-$\underline{CH_2}$-CO); 5.08 (s, 2H, O-$\underline{CH_2}$-CO); 6.60 (s, 2H, Ar-$\underline{H}$); 6.82 (s, 1H, Ar-$\underline{H}$); 7.01 (s, 2H, Ar-$\underline{H}$); 7.03 (s, 1H, Ar-$\underline{H}$); 7.07 (s, 2H, Ar-$\underline{H}$)

Synthesis of calix[4]arene-acids

25,26,27,28-tetrakis(hydroxycarbonylmethoxy)-*p-tert*-butylcalix[4]arene (S_2)



S_2

Into a 250 mL flask containing 3 g (3.02 mmol) of calix[4]arene-ester **S_1** and 4.06 g (72.5 mmol) of KOH dissolved in a small quantity of H_2O, 40 mL of EtOH was added and the mixture was stirred under reflux until the substrate disappeared completely (about 24h). Then the reaction mixture was cooled, 30 mL of water was added and acidified with 2 mol L^{-1} HCl to pH = 2. The solution was extracted three times with CH_2Cl_2 (3 × 60 mL). Organic layers were collected and dried over $MgSO_4$, filtered and the solvent was removed. 2.4 g (2.73 mmol) of the product **S_2** were thus obtained as a white powder.

Yield: 90%, lit. 89% [8]

$C_{52}H_{64}O_{12}$; M.W. = 880.2 g/mol; m.p. 272-274°C, lit. 278-281°C [8];

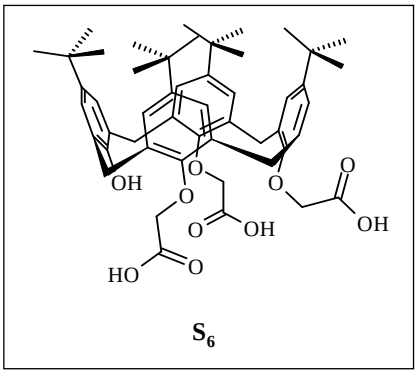
IR (C=O) ν_{max} = 1729 cm^{-1};

R_f = 0.2 (chloroform / methanol, 6/1)

^{1}H NMR (500 MHz, DMSO): *cone* conformation δ [ppm]:

1.07 (s, 36H, C-($\underline{CH_3}$)$_3$); 3.23 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 12.21 Hz); 4.78 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 12.21 Hz); 4.60 (s, 8H, O-$\underline{CH_2}$-CO); 6.94 (s, 8H, Ar-$\underline{H}$); 12.2 (bs, 4H, $\underline{OH}$)

25-hydroxy-26,27,28-tris(hydroxycarbonylmethoxy)-*p-tert*-butylcalix[4]arene (S_6)



S_6

The compound **S_6** was prepared following the procedure applied for calix[4]arene-carboxylic acid **S_2**. The difference was, that instead of 4.2 equivalents of KOH, 3.2 equivalents were added to hydrolise 3 ester arms. The product **S_6** was obtained as white powder.

Yield: 90%

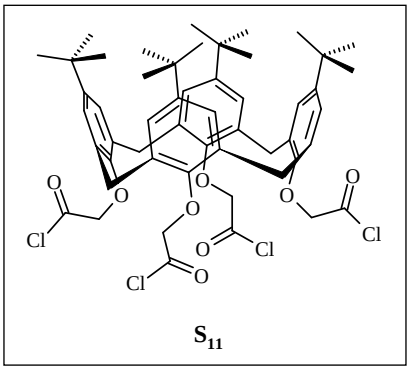
$C_{50}H_{62}O_{10}$; M.W. = 822.2 g/mol; m.p. 271-274°C;

IR (C=O) ν_{max} = 1736 $cm^{-}1$; Rf = 0.8 (methanol / chloroform 4/1)

^{1}H NMR (200 MHz, $CDCl_3$): *cone* conformation δ [ppm]: 0.92 (s, 18H, C-($\underline{CH_3}$)$_3$); 1.22 (s, 9H, C-($\underline{CH_3}$)$_3$); 1.26 (s, 9H, C-($\underline{CH_3}$)$_3$); 3.30 (d, 2H, Ar-$\underline{CH_2}$-Ar, *J* = 13.27 Hz); 3.35 (d, 2H, Ar-$\underline{CH_2}$-Ar, *J* = 13.27 Hz); 4.30 (d, 2H, Ar-$\underline{CH_2}$-Ar, *J* = 13.27 Hz); 4.42 (d, 2H, Ar-$\underline{CH_2}$-Ar, *J* = 13.27 Hz); 4.58 (s, 4H, O-$\underline{CH_2}$-CO); 4.67 (s, 2H, O-$\underline{CH_2}$-CO); 6.72 (s, 3H, O$\underline{H}$); 6.73 (s, 1H, O$\underline{H}$); 6.80 (s, 4H, Ar$\underline{H}$); 7.04 (s, 2H, Ar-$\underline{H}$); 7.13 (s, 2H, Ar-$\underline{H}$)

Synthesis of calix[4]arene-acid chloride

25,26,27,28-tetrakis(chloroformylmethoxy)calix[4]arene (S_{11})



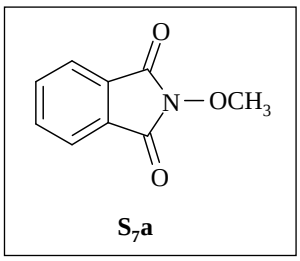
S_{11}

In a 100 mL flask, 0.31 g (0.35 mmol) of calix[4]arene-acid **S_2** was dissolved in 5 mL (68 mmol) of thionyl chloride and the solution was heated under reflux for 3 h. After that time, the solution was cooled and evaporated to dryness. The residue was washed six times with CH_2Cl_2 and subsequently the solvent was evaporated in order to remove the excess of $SOCl_2$. 0.33 g (0.35 mmol) of the product **S_{11}** were obtained quantitatively. The acid chloride was used without further purification.

$C_{52}H_{60}O_8Cl_4$; M.W. = 954.2 g/mol; IR (C=O) ν_{max} = 1800 cm^{-1}

Synthesis of hydroxylamine hydrochlorides

N-methoxyphthalamide (S_7a)



S_7a

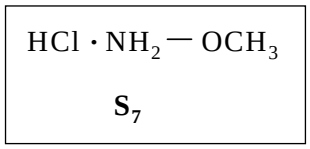
Into a 250 mL flask containing 8 g (50 mmol) of N-hydroxyphthalamide and 4.25 g (40 mmol) of Na_2CO_3, 100 mL of DMF was added. The mixture was stirred at room temperature for 2h and subsequently, 6 mL (100 mmol) of methyl iodide was added dropwise and the reaction was continued for the next 15 h. The characteristic colour change of the reaction mixture from dark red to yellow proved that the reaction was finished. The product **S_7a** was obtained after crystallisation from water.

Yield: 86%

$C_9H_7O_3N$; M.W. = 177.1 g/mol; m.p. = 125-127°C, lit. 132-133 [18]

R_f = 0.6 (hexan / ethyl acetate 4/1)

Methoxyhydroxylamine hydrochloride (S_7)



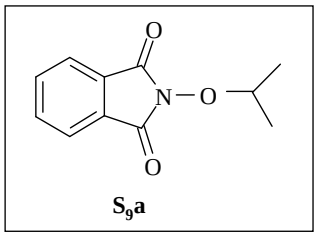
S_7

In a 250 mL flask, 7.4 g (41.81 mmol) of N-methoxyphthalamide **S_7a** was dissolved in 90 mL of EtOH and subsequently, 10.6 g (212 mmol) of 40% hydrazine monohydrate was added dropwise. The reagents were stirred and heated at 60°C until a white, thick precipitate appeared. After cooling down, the precipitate was dissolved in 10% Na_2CO_3 solution in water. The reaction mixture was distilled and the fraction of the crude product was collected at the temperature range 86-87°C. The solution was acidified with 20 mL of 2 mol L^{-1} HCl to pH = 2 and water was removed under vacuum to give 3.32 g (39.72 mmol) of the pure product **S_7**.

Yield: 95%, lit. 80% [18]

CH_6ONCl; M.W. = 83.5 g/mol; m.p. = 148-153°C, lit. 150°C [18]

N-isopropoxyphthalamide (S_9a)



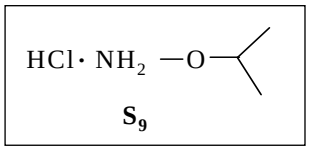
S_9a

The intermediate **S_9a** was prepared similarly to **S_7a**, using isopropyl iodide.

Yield: 49%, lit. 88% [18]

$C_{11}H_{11}O_3N$; M.W. = 205.2 g/mol; m.p. = 49-50°C, lit. 53-54°C [18]; R_f = 0.3 (hexan / ethyl acetate 4/1)

Isopropoxyhydroxylamine hydrochloride (S_9)



S_9

The intermediate **S_9** was prepared as **S_7**. The fraction of the crude product was collected at the temperature range 81-85°C.

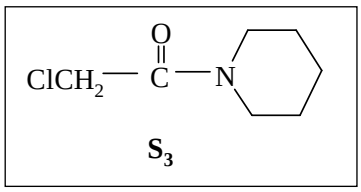
Yield: 83%, lit. 85% [18]

$C_3H_{10}ONCl$; M.W. = 111.5 g/mol; m.p. = 88-90°C, lit. 94-95°C [18]

^{1}H NMR (200 Hz, D_2O) δ [ppm]: 1.23 (s, 3H, -CH-($\underline{CH_3}$)$_2$); 1.26 (s, 3H, -CH-($\underline{CH_3}$)$_2$); 4.32 (m, 1H, -$\underline{CH}$-(CH_3)$_2$)

Synthesis of α-chloroacetamides

α-chloroacetpiperidide (S_3)



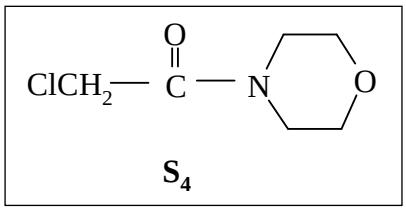
S_3

To the cooled mixture consisting of 10 mL (100 mmol) of piperidine, 13.9 mL (100 mmol) of NEt_3 and 60 mL of CH_2Cl_2, 6.7 mL (84 mmol) of chloroacetyl chloride in 20 mL of CH_2Cl_2 was added dropwise. The reaction mixture was stirred overnight at room temperature and then washed with H_2O, then with 1 mol L^{-1} HCl and sodium carbonate solution. The aqueous layer was extracted three times with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed. The oily product **S_3** was used without further purification.

$C_7H_{12}ONCl$; M.W. = 161.5 g/mol; IR ν_{max} (C=O) 1659 cm^{-1};

^{1}H NMR (500 Hz, $CDCl_3$) δ [ppm]: 1.56-1.64 (m, 6H, $(\underline{CH_2})_3$); 3.44 (t, 2H, -N-$\underline{CH_2}$); 3.55 (t, 2H, -N-$\underline{CH_2}$); 4.06 (s, 2H, Cl-$\underline{CH_2}$ -CO-)

α-chloroacetmorpholide (S_4)



S_4

The compound **S_4** was prepared similarly to **S_3** using morpholine.

$C_6H_{10}O_2NCl$; M.W. = 163.5 g/mol;

IR ν_{max} (C=O) 1646 cm^{-1};

^{1}H NMR (500 Hz, $CDCl_3$) δ [ppm]: 3.46-3.70 (m, 8H, $(\underline{CH_2})_4$); 4.03 (s, 2H, Cl-$\underline{CH_2}$ -CO-)

7.3. Synthesis of calix[4]arene-amide derivatives (**1A-9A**)

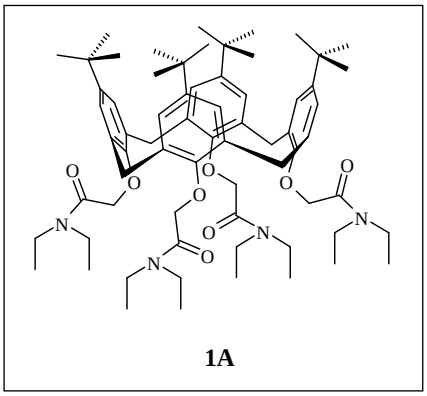
Calix[4]arene-amides **1A-9A** were synthesised according to the mixed anhydrides method [9] starting from the calix[4]arene-carboxylic acid **S_2** and using an appropriate amine.

General procedure for calix[4]arene-amides preparation:

In a 100 mL flask, calix[4]arene-carboxylic acid **S_2** was dissolved in dry CH_2Cl_2 (10 mL) and the solution was stirred and cooled to -5°C. Subsequently, 4.2 equivalents of NEt_3 and then 4.2 equivalents of ethyl chloroformate were added. The solution was stirred at -

5°C for 0.5h and then an appropriate amine in 5 mL of CH_2Cl_2 was added. After 2h, the mixture was diluted with CH_2Cl_2 (15 mL), washed with water (15 mL), then with 0.1 mol L^{-1} HCl (15 mL) and again with water (15 mL). The water phase was extracted twice with CH_2Cl_2 (30 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was crystallised from CH_2Cl_2/MeOH mixture to give the pure products **1A-9A**.

25, 26, 27, 28-tetrakis(N,N-diethylcarbonylmethylene)-*p-tert*-butylcalix[4]arene (1A)



1A

20 equivalents of diethylamine were used and the product **1A** was obtained as transparent crystals.

Yield: 91%; lit. 95% [10], 86% [9];

$C_{68}H_{100}O_8N_4$; M.W. = 1101.5 g/mol;

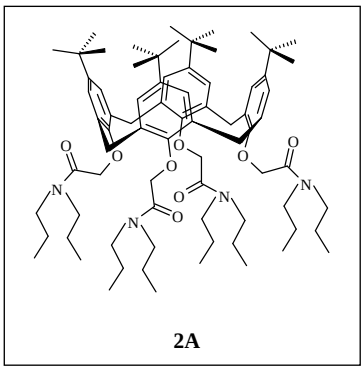
m.p. = 223-225ºC, lit. 228-229°C [10], 220-224°C [9];

IR ν_{max} (C=O) 1658 cm^{-1};

R_f = 0.7 (chloroform / methanol, 8/1)

^{1}H NMR (200 MHz, $CDCl_3$): *cone* conformation δ[ppm]: 1.08 (s, 36H, C-($\underline{CH_3}$)$_3$); 1.16 (t, 24H, -N-(CH_2-$\underline{CH_3}$)$_2$); 3.20 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 13.1 Hz); 3.35 (q, 16H, -N-($\underline{CH_2}$-CH_3)$_2$); 5.02 (s, 8H, -O-$\underline{CH_2}$-CO); 5.23 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 13.1 Hz); 6.80 (s, 8H, Ar-$\underline{H}$).

25, 26, 27, 28-tetrakis(N,N-di-*n*-propylcarbonylmethylene)-*p-tert*-butylcalix[4]arene (2A)



2A

24 equivalents of di-*n*-propylamine were used and the product **2A** was obtained as transparent crystals.

Yield: 44%, lit. 72% [27]

$C_{76}H_{116}O_8N_4$; M.W. = 1212.46 g/mol;

m.p. = 193-196°C, lit. 187-189°C [27]

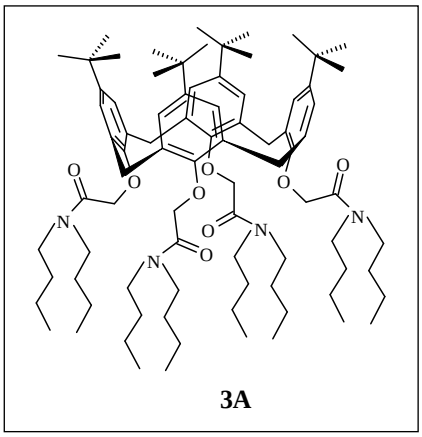
IR ν_{max} (C=O) 1658 cm^{-1};

R_f = 0.4 (chloroform / methanol, 8/1)

^{1}H NMR (500 MHz, $CDCl_3$): *cone* conformation δ [ppm]: 0.9 (tt, 24H, -N-(CH_2-CH_2-$\underline{CH_3}$)$_2$); 1.10 (s, 36H, C-($\underline{CH_3}$)$_3$); 1.56 (m, 16H, -N-(CH_2-$\underline{CH_2}$-CH_3)$_2$); 3.20 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 12.7 Hz); 3.19 (t, 8H, -N-($\underline{CH_2}$-CH_2-CH_2-CH_3)$_2$); 3.27 (t, 8H, -N-($\underline{CH_2}$-CH_2-

CH_2-$CH_3)_2$); 5.04 (s, 8H, -O-$\underline{CH_2}$-CO); 5.21 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 12.7 Hz); 6.81 (s, 8H, Ar-$\underline{H}$)

25, 26, 27, 28-tetrakis(N,N-di-*n*-butylcarbonylmethylene)-*p*-*tert*-butylcalix[4]arene (3A)



3A

18 equivalents of di-*n*-butylamine were used and the product **3A** was obtained as transparent crystals.

Yield: 92%, lit. 75% [27]

$C_{84}H_{132}O_8N_4$; M.W. = 1324.46 g/mol;

m.p. = 210-211°C, lit. 193-194 °C [27];

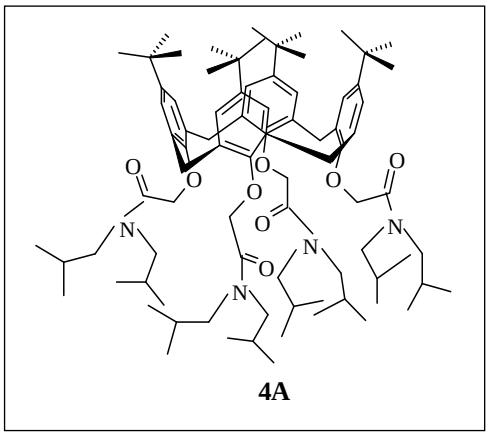
IR ν_{max} (C=O) 1659 cm^{-1};

R_f = 0.8 (chloroform / methanol, 6/1)

^{1}H NMR (500 MHz, $CDCl_3$): *cone* conformation

δ [ppm]: 0.94 (m, 24H, -N-(CH_2-CH_2-CH_2-$\underline{CH_3}$)$_2$); 1.10 (s, 36H, C-($\underline{CH_3}$)$_3$); 1.32 (m, 16H, -N-(CH_2-CH_2-$\underline{CH_2}$-CH_3)$_2$); 1.52 (m, 16H, -N-(CH_2-$\underline{CH_2}$-CH_2-CH_3)$_2$); 3.19 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 13.18 Hz); 3.20 (t, 8H, -N-($\underline{CH_2}$-CH_2-CH_2-CH_3)$_2$); 3.31 (t, 8H, -N-($\underline{CH_2}$-CH_2-CH_2-CH_3)$_2$); 5.01 (s, 8H, -O-$\underline{CH_2}$-CO); 5.14 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 13.18 Hz); 6.81 (s, 8H, Ar-$\underline{H}$)

25, 26, 27, 28-tetrakis(N,N-di-*iso*-butylcarbonylmethylene)-*p*-*tert*-butylcalix[4]arene (4A)



4A

24 equivalents of di-*iso*-butylamine were used and the product **4A** was obtained as transparent crystals.

Yield: 24%

$C_{84}H_{132}O_8N_4$; M.W. = 1324.46 g/mol;

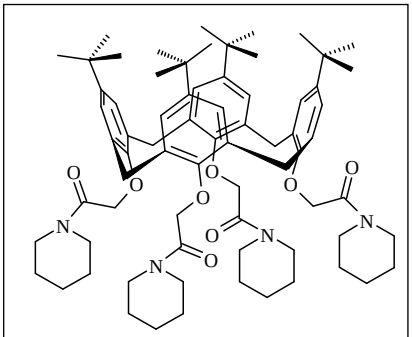
m.p. = 165-167°C; IR ν_{max} (C=O) 1657 cm^{-1};

R_f = 0.7 (chloroform / methanol, 6/1)

^{1}H NMR (500 MHz, $CDCl_3$): *cone* conformation

δ [ppm]: 0.84 (d, 24H, -N-((CH_2-CH-$\underline{CH_3}$)$_2$)$_2$); 0.90 (d, 24H, -N-((CH_2-CH-$\underline{CH_3}$)$_2$)$_2$); 1.07 (s, 36H, C-($\underline{CH_3}$)$_3$); 1.87 (m, 4H, -N-((CH_2-$\underline{CH}$-CH_3)$_2$)$_2$); 2.0 (m, 4H, -N-((CH_2-$\underline{CH}$-CH_3)$_2$)$_2$); 3.13 (d, 8H, -N-(($\underline{CH_2}$-CH-CH_3)$_2$)$_2$); 3.16 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 12.7 Hz); 3.20 (d, 8H, -N-(($\underline{CH_2}$-CH-CH_3)$_2$)$_2$); 4.97 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 12.7 Hz); 4.99 (s, 8H, -O-$\underline{CH_2}$-CO); 6.80 (s, 8H, Ar-$\underline{H}$)

25, 26, 27, 28-tetrakis(piperidinylcarbonylmethylene)-*p-tert*-butylcalix[4]arene (5A)



5A

Compound **5A** was prepared by two methods: mixed anhydrides method (see **Scheme II-1**) and using α-chloroacetpiperidide (see **Scheme II-2**).

In procedure 1 (via mixed anhydrides method), 16 equivalents of piperidine were used and the pure compound **5A** was obtained as white crystals.

Yield: 47%, lit. 84% [9];

$C_{72}H_{100}O_8N_4$, M.W. = 1148.6 g/mol;

m.p. = 274-277°C, lit. 261-265°C [9]; IR ν_{max} (C=O) 1661 cm^{-1};

R_f = 0.5 (chloroform / methanol, 6/1)

^{1}H NMR (200 MHz, $CDCl_3$): *cone* conformation δ[ppm]: 1.08 (s, 36H, C-($\underline{CH_3}$)$_3$); 1.45-1.64 (m, 24H, -N-CH_2-($\underline{CH_2}$)$_3$-); 3.19 (d, 4H, Ar-CH_2-Ar, *J* = 12.74 Hz); 3.43-3.52 (m, 16H, -N-($\underline{CH_2}$)$_2$-); 5.01 (s, 8H, -O-$\underline{CH_2}$-CO); 5.09 (d, 4H, Ar-CH_2-Ar, *J* = 12.74 Hz); 6.79 (s, 8H, Ar-$\underline{H}$)

Procedure 2:

In a 250 mL flask,1 mmol of calix[4]arene **S** was dissolved in 30 mL of the mixture (5/1) of dried and freshly distilled THF and DMF. The mixture was stirred and heated at 50°C for about 30 minutes. After addition of 10 mmol of NaH (50% in oil), the mixture was stirred for another 1h. Then, 16 mmol of α-chloroacetpiperidide was added dropwise and the reaction mixture was left stirring for another 15h at 60°C. Then the solution was evaporated to dryness, the residue was treated with 10 mL of water, acidified with 1 mol L^{-1} HCl and the crude product was extracted three times with CH_2Cl_2. The collected organic layers were washed with water, dried over $MgSO_4$, filtered and then the solvent was removed. Crystallisation of the oily product from ethyl ether gave the pure product **5A** and the fraction of its complex with Na^+ (**5A-Na$^+$**).

Product **5A**:

Yield: 27%, lit. 27% [12]; $C_{72}H_{100}O_8N_4$, M.W. = 1148.6 g/mol; m.p. 279-281°C, lit. 267-270°C [12];

IR ν_{max} (C=O) 1661 cm^{-1}; R_f = 0.5 (chloroform / methanol, 6/1)

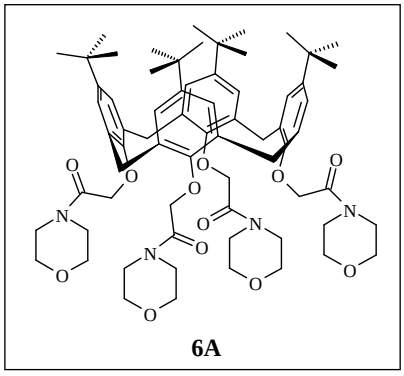
^{1}H NMR (200 MHz, $CDCl_3$): *cone* conformation δ[ppm]: 1.08 (s, 36H, C-($\underline{CH_3}$)$_3$); 1.58-1.56 (m, 24H, -N-CH_2-($\underline{CH_2}$)$_3$-); 3.21 (d, 4H, Ar-CH_2-Ar, *J* = 12.53 Hz); 3.44-3.54 (m, 16H, -N-($\underline{CH_2}$)$_2$-); 5.05 (s, 8H, -O-$\underline{CH_2}$-CO); 5.05 (d, 4H, Ar-CH_2-Ar, *J* = 12.53 Hz); 6.82 (s, 8H, Ar-$\underline{H}$)

Na^+ complex **5A-Na$^+$**:

Yield: 55%, lit. 82% [12]; $C_{72}H_{100}O_8N_4$-Na, M.W. = 1171.6 g/mol; m.p. = 257-259°C, lit. 245-250°C [12]; IR ν_{max} (C=O) 1659 cm^{-1}; R_f = 0.7 (chloroform/methanol, 6:1)

^{1}H NMR (500 MHz, $CDCl_3$): *cone* conformation δ [ppm]: 1.17 (s, 36H, C-($\underline{CH_3}$)$_3$); 1.66-1.72 (m, 24H, -N-CH_2-($\underline{CH_2}$)$_3$-); 3.24 (bs, 8H, -N-($\underline{CH_2}$)$_2$-); 3.34 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 11.72 Hz); 3.64 (bs, 8H, -N-($\underline{CH_2}$)$_2$-); 4.49 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 11.72 Hz); 4.60 (s, 8H, -O-$\underline{CH_2}$-CO); 7.13 (s, 8H, Ar-$\underline{H}$)

25, 26, 27, 28-tetrakis(morpholidinylcarbonylmethylene)-*p*-*tert*-butylcalix[4]arene (6A)



6A

Compound **6A** was obtained similarly to **5A** by two methods (see Scheme **I-1** and **I-2**).

In procedure 1, 20 equivalents of morpholine were used and the pure compound **6A** was obtained as white powder.

Yield: 44%

$C_{68}H_{92}O_{12}N_4$; M.W. = 1156 g/mol; m.p. = 276-281°C;

IR ν_{max} (C=O) 1661 cm^{-1};

R_f = 0.9 (chloroform / methanol, 3/1)

^{1}H NMR (200 MHz, $CDCl_3$): *cone* conformation δ [ppm]: 1.09 (s, 36H, C-($\underline{CH_3}$)$_3$); 3.21 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 13.0 Hz); 3.55-3.67 (m, 32H, -N-($\underline{CH_2}$)$_4$); 4.98 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 13.0 Hz); 5.07 (s, 8H, -O-$\underline{CH_2}$-CO); 6.82 (s, 8H, Ar-$\underline{H}$).

Procedure 2:

Compound **6A** was obtained using α-chloroacetmorpholine and the same procedure as for **5A** was applied. Crystallisation of the oily product from ethyl ether gave the pure product **6A** as white powder.

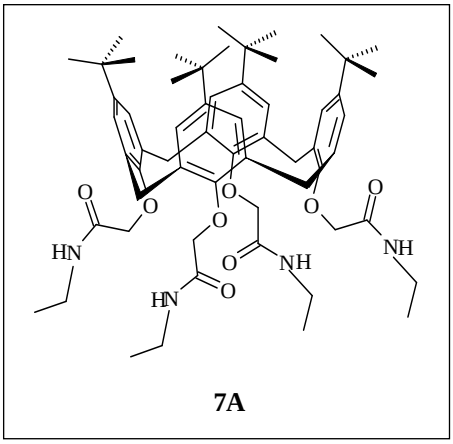
Yield: 78%, lit. 57% [12];

$C_{68}H_{92}O_{12}N_4$; M.W. = 1156 g/mol; m.p. = 294-296°C, lit. 302-305°C [12];

IR ν_{max} (C=O) 1661 cm^{-1}; R_f = 0.9 (chloroform / methanol, 3/1)

^{1}H NMR (200 MHz, $CDCl_3$): *cone* conformation δ [ppm]: 1.10 (s, 36H, C-($\underline{CH_3}$)$_3$); 3.22 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 12.7 Hz); 3.52, 3.60, 3.66 and 3.70 (s, 32H, -N-($\underline{CH_2}$)$_4$); 5.00 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 12.7 Hz); 5.05 (s, 8H, -O-$\underline{CH_2}$-CO); 6.83 (s, 8H, Ar-$\underline{H}$).

25, 26, 27, 28-tetrakis(N-ethylcarbonylmethylene)-*p*-*tert*-butylcalix[4]arene (7A)



7A

20 equivalents of N-ethylamine were used and the product **7A** was obtained as transparent crystals.

Yield: 85%, lit. 51% [28]

$C_{60}H_{84}O_8N_4$; M.W. = 998.6 g/mol;

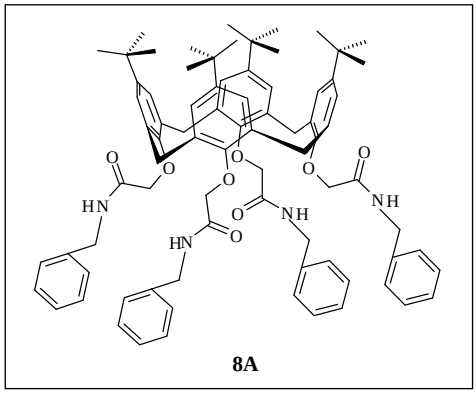
m.p. = 303-305ºC, lit. 316-318°C [28];

IR ν_{max} (C=O) 1658 cm^{-1};

R_f = 0.7 (chloroform / methanol, 6/1)

^{1}H NMR (200 MHz, $CDCl_3$): *cone* conformation δ [ppm]: 1.10 (s, 36H, C-($\underline{CH_3}$)$_3$); 1.21-1.24 (m, 12H, -NH-CH_2-$\underline{CH_3}$); 3.33 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 12.64 Hz); 3.44-3.47 (m, 8H, -NH-$\underline{CH_2}$-CH_3); 4.50 (bs, 12H, -O-$\underline{CH_2}$-CO + Ar-$\underline{CH_2}$-Ar); 6.81 (s, 8H, Ar-$\underline{H}$); 7.28 (s, 4H, -N-$\underline{H}$).

25, 26, 27, 28-tetrakis(N-benzylcarbonylmethylene)-*p*-*tert*-butylcalix[4]arene (8A)



8A

24 equivalents of N-benzylamine were used and the product **8A** was obtained as transparent crystals.

Yield: 75%, lit. 71% [29]

$C_{80}H_{92}O_8N_4$; M.W. = 1236.9 g/mol;

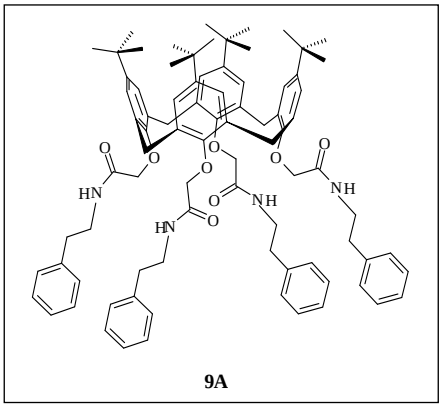
m.p. = 274-276ºC, lit. > 270°C [29];

IR ν_{max} (C=O) 1645 cm^{-1};

R_f = 0.6 (chloroform / methanol, 6/1)

^{1}H NMR (200 MHz, $CDCl_3$): *cone* conformation δ [ppm]: 1.07 (s, 36H, C-($\underline{CH_3}$)$_3$); 3.15 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 13.19 Hz); 4.40 (bs, 12H, -O-$\underline{CH_2}$-CO + Ar-$\underline{CH_2}$-Ar); 4.46 (m, 8H, -NH-$\underline{CH_2}$-Ar); 6.75 (s, 8H, Ar-$\underline{H}$); 7.23 (m, 20H, Ar-$\underline{H}_{BENZYL}$); 7.78 (s, 4H, -N-$\underline{H}$).

25, 26, 27, 28-tetrakis(N-phenythylcarbonylmethylene)-*p-tert*-butylcalix[4]arene (9A)



9A

10 equivalents of N-ethylbenzylamine hydrochloride were used and the product **9A** was obtained as transparent crystals. Before introducing hydrochloride to the reaction mixture, 10 equivalents of NEt_3 were added to release N-ethylbenzylamine from its hydrochloride form.

Yield: 98%, lit. 59% [30]

$C_{84}H_{100}O_8N_4$; M.W. = 1292.5 g/mol;

m.p. = 216-220ºC, lit. 223-225°C [30]; IR ν_{max} (C=O) 1647 cm^{-1};

R_f = 0.4 (chloroform / methanol, 6/1)

^{1}H NMR (200 MHz, $CDCl_3$): *cone* conformation δ [ppm]: 1.08 (s, 36H, C-($\underline{CH_3}$)$_3$); 2.87 (t, 8H, -NH-CH_2-$\underline{CH_2}$-Ar); 3.16 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 13.11 Hz); 3.57 (m, 8H, -NH-$\underline{CH_2}$-CH_2-Ar); 4.39 (bs, 12H, -O-$\underline{CH_2}$-CO + Ar-$\underline{CH_2}$-Ar); 6.77 (s, 8H, Ar-$\underline{H}$); 7.18-7.26 (m, 20H, Ar-$\underline{H}_{BENZYL}$); 7.57 (bs, 4H, -N-$\underline{H}$)**.**

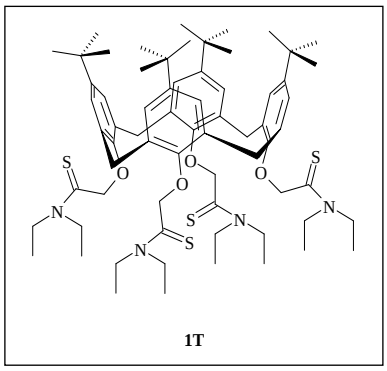
7.4. Synthesis of calix[4]arene-thioamide derivatives (**1T-9T**)

All calix[4]arene-thioamides (compounds **1T-9T**) were synthesised according to the procedure described in [14] starting from the corresponding calix[4]arene-amides using Lawesson's Reagent as a thionating agent.

General procedure for calix[4]arene-thioamides preparation:

In a 100 mL flask, a mixture consisting of an appropriate calix[4]arene-amide and 2.2 equivalents of Lawesson's Reagent was dissolved in 20 mL of dry toluene and was stirred for 24h at 90°C under argon. After that time, the solvent was removed under vacuum and the resulting residue was diluted with CH_2Cl_2 and washed with water. The organic phase was dried over $MgSO_4$, filtered and then the solvent was removed. The products **1T-9T** were obtained as pale brown powders or yellowish crystals after crystallisation from the CH_2Cl_2/MeOH mixture, or if necessary were purified by column chromatography.

25, 26, 27, 28-tetrakis(N,N-diethylthiocarbonylmethylene)-*p-tert*-butylcalix[4]arene (1T) [15]



1T

The pure product **1T** was obtained after crystallisation from CH_2Cl_2/MeOH mixture as pale brown powder.

Yield: 68%, lit. 69% [3]

$C_{68}H_{100}O_4N_4S_4$; M.W. = 1165.8 g/mol;

m.p. = 212-218°C, lit. 92-94°C [3];

IR ν_{max} (C=S) 1642 cm^{-1};

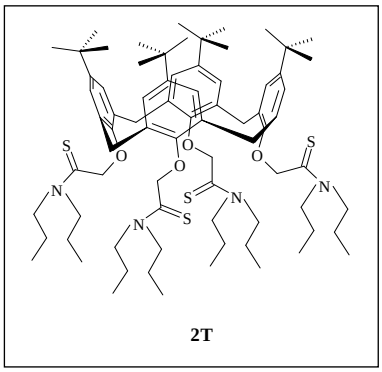
R_f = 0.6 (chloroform / methanol, 6/1)

^{1}H NMR (200 MHz, $CDCl_3$): *cone* conformation δ [ppm]: 1.08 (s, 36H, C-($\underline{CH_3}$)$_3$); 1.24 (t, 12H, -(N-CH_2-$\underline{CH_3}$)$_2$); 1.32 (t, 12H, -(N-CH_2-$\underline{CH_3}$)$_2$); 3.17 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 12.69 Hz); 3.61 (q, 8H, -(N-$\underline{CH_2}$-CH_3)$_2$); 3.98 (q, 8H, -(N-$\underline{CH_2}$-CH_3)$_2$); 4.76 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 12.69 Hz); 5.09 (s, 8H, -O-$\underline{CH_2}$-CS); 6.79 (s, 8H, Ar-$\underline{H}$).

EA calc. for $C_{68}H_{100}O_4N_4S_4$: C 70.06, H 8.65, N 4.81, S 11.0%;

Found: C 69.67, H 8.57, N 4.38, S 11.18%.

25, 26, 27, 28-tetrakis(N,N-di-*n*-propylthiocarbonylmethylene)-*p-tert*-butylcalix[4]arene (2T)



2T

The crude product was purified by column chromatography using $CHCl_3$/MeOH, (30/1) as an eluent and then crystallisation from CH_2Cl_2/MeOH mixture gave pure product **2T** as pale brown powder.

Yield: 30%

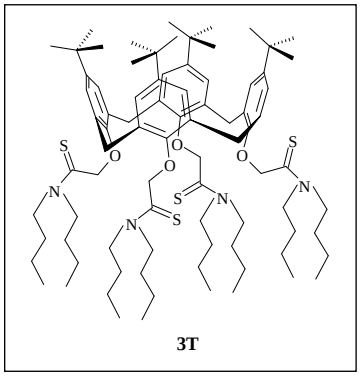
$C_{80}H_{116}O_4N_4S_4$; M.W. = 1277.8 g/mol;

m.p. = 202-203°C; IR ν_{max} (C=S) 1643cm^{-1};

R_f = 0.7 (chloroform / methanol, 12/1)

^{1}H NMR (200 MHz, $CDCl_3$): *cone* conformation δ [ppm]: 0.9 (t, 24H, -(N-CH_2-CH_2-$\underline{CH_3}$)$_2$); 1.06 (s, 36H, C-($\underline{CH_3}$)$_3$); 1.66 (m, 16H, -(N-CH_2-$\underline{CH_2}$-CH_3)$_2$); 3.10 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 12.9 Hz); 3.45 (t, 8H, -(N-$\underline{CH_2}$-CH_2-CH_3)$_2$); 3.80 (t, 8H, -(N-$\underline{CH_2}$-CH_2-CH_3)$_2$); 4.65 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 12.9 Hz); 5.15 (s, 8H, -O-$\underline{CH_2}$-CS); 6.71 (s, 8H, Ar-$\underline{H}$).

25, 26, 27, 28-tetrakis(N,N-di-*n*-butylthiocarbonylmethylene)-*p*-*tert*-butylcalix[4]arene (3T)



The crude product was purified by column chromatography using $CHCl_3$/MeOH, (15/1) as an eluent and then crystallisation from CH_2Cl_2/MeOH mixture gave the pure product **3T** as yellowish crystals.

Yield: 17%;

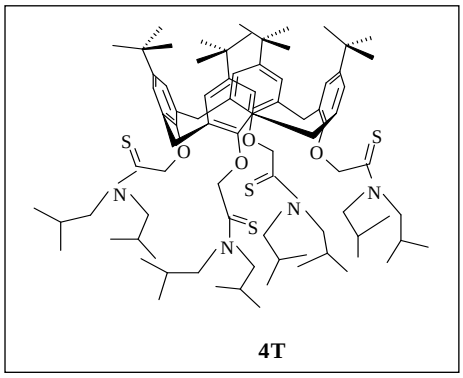
$C_{84}H_{132}O_4N_4S_4$; M.W. = 1388.46 g/mol;

m.p. = 194-196°C; IR ν_{max} (C=S) 1645cm^{-1};

R_f = 0.8 (chloroform / methanol, 12/1)

^{1}H NMR (200 MHz, $CDCl_3$): *cone* conformation δ [ppm]: 0.92 (m, 40H, -(N-CH_2-CH_2-CH_2-CH_3)$_2$); 1.23 (m, 16H, -(N-CH_2-CH_2-CH_2-CH_3)$_2$); 1.26 (s, 36H, C-(CH_3)$_3$); 3.10 (d, 4H, Ar-CH_2-Ar, *J* = 12.9 Hz); 3.15 (t, 8H, -(N-CH_2-CH_2-CH_2-CH_3)$_2$); 3.85 (t, 8H, -(N-CH_2-CH_2-CH_2-CH_3)$_2$); 4.65 (d, 4H, Ar-CH_2-Ar, *J* = 12.9 Hz); 5.15 (s, 8H, -O-CH_2-CS); 6.55 (s, 8H, Ar-H).

25, 26, 27, 28-tetrakis(N,N-di-*iso*-butylthiocarbonylmethylene)-*p*-*tert*-butylcalix[4]arene (4T)



The crude product was purified by column chromatography using $CHCl_3$/MeOH, (15/1) as an eluent and then crystallisation from CH_2Cl_2/MeOH mixture gave the pure product **4T** as pale brown powder.

Yield: 12%;

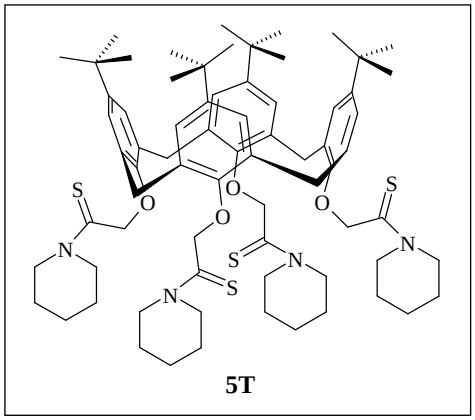
$C_{84}H_{132}O_4N_4S_4$; M.W. = 1388.46 g/mol;

m.p. = 182-184°C; IR ν_{max} (C=S) 1650 cm^{-1};

R_f = 0.6 (chloroform / methanol, 12/1)

^{1}H NMR (200 MHz, $CDCl_3$): *cone* conformation δ [ppm]: 1.07 (m, 56H, -(N-CH_2-CH-(CH_3)$_2$)$_2$; 1.30 (s, 36H, C-(CH_3)$_3$); 3.20 (d, 4H, Ar-CH_2-Ar, *J* = 12.7 Hz); 3.65 (m, 16H, -(N-CH_2-CH-(CH_3)$_2$)$_2$; 4.75 (d, 4H, Ar-CH_2-Ar, *J* = 12.7 Hz); 5.25 (s, 8H, -O-CH_2-CS); 6.70 (s, 8H, Ar-H).

25, 26, 27, 28-tetrakis(piperidinylthiocarbonylmethylene)-*p-tert*-butylcalix[4]arene (5T) [16]



5T

The crude product was purified by column chromatography (SiO_2, $CHCl_3$, next mixture of $CHCl_3$/MeOH, 6/1) and then crystallisation from CH_2Cl_2/MeOH mixture gave the pure product **5T** as yellowish crystals.

Yield: 49%

$C_{72}H_{100}O_4N_4S_4$; M.W. = 1212.6 g/mol;

m.p. = 246-250°C; IR ν_{max} (C=S) 1653 cm^{-1};

R_f = 0.7 (chloroform / methanol, 6/1)

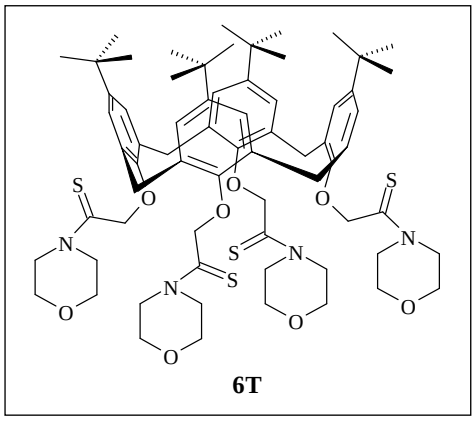
^{1}H NMR (500 MHz, $CDCl_3$): *cone* conformation δ [ppm]: 1.09 (s, 36H, C-($\underline{CH_3}$)$_3$); 1.7 (bs, 24H, ($\underline{CH_2}$)$_3$); 3.17 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 12.70 Hz); 3.76 (bs, 8H, -N-$\underline{CH_2}$-); 4.28 (bs, 8H, -N-$\underline{CH_2}$-); 4.79 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 12.70 Hz); 5.18 (s, 8H, -O-$\underline{CH_2}$-CS); 6.79 (s, 8H, Ar-$\underline{H}$).

EA calc. for $C_{72}H_{100}O_4N_4S_4$: C 71.26, H 8.31, N 4.62, S 10.57%;

Found: C 71.16, H 8.31, N 4.48, S 10.14%;

MS (ESI): $[M/z+Na]^+$ = 1235.7, calc. for $[M/z+Na]^+$ = 1235.6.

25, 26, 27, 28-tetrakis(morpholidinylthiocarbonylmethylene)-*p-tert*-butylcalix[4]arene (6T) [15]



6T

The crude product was purified by column chromatography using $CHCl_3$/MeOH, (20/1) as an eluent and then crystallisation from CH_2Cl_2/MeOH mixture gave the pure product **6T** as pale brown crystals.

Yield: 59%;

$C_{68}H_{92}O_8N_4S_4$; M.W. = 1221.7 g/mol;

m.p. = 240-245°C; IR ν_{max} (C=S) 1649 cm^{-1};

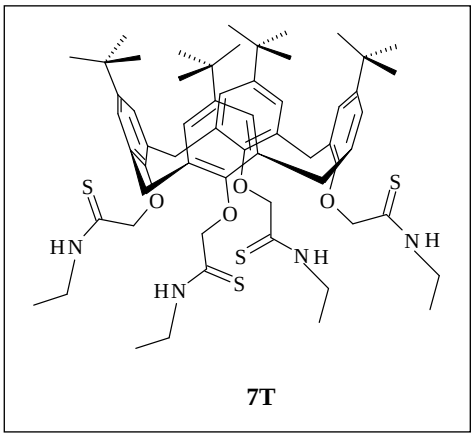
R_f = 0.7 (chloroform / methanol, 16/1)

^{1}H NMR (500 MHz, $CDCl_3$): *cone* conformation δ [ppm]: 1.10 (s, 36H, C-($\underline{CH_3}$)$_3$); 3.18 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 12.69 Hz); 3.50 (s, 8H, -N-CH_2-$\underline{CH_2}$-O); 3.73 (s, 8H, -N-CH_2-$\underline{CH_2}$-O); 3.79 (s, 8H, -N-$\underline{CH_2}$-CH_2-O-); 4.37 (s, 8H, -N-$\underline{CH_2}$-CH_2-O-); 4.89 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 12.69 Hz); 5.21 (s, 8H, -O-$\underline{CH_2}$-CS); 6.83 (s, 8H, Ar-$\underline{H}$).

EA calc. for $C_{68}H_{92}O_8N_4S_4$: C 66.79, H 7.58, N 4.58, S 10.47%;

Found: C 66.91, H 7.70, N 3.56, S 9.79%.

25, 26, 27, 28-tetrakis(N-ethylthiocarbonylmethylene)-*p-tert*-butylcalix[4]arene (7T) [15]



7T

The pure product **7T** was obtained after crystallisation from CH_2Cl_2/MeOH mixture as yellow crystals.

Yield: 72%;

$C_{60}H_{84}O_4N_4S_4$; M.W. = 1053.6 g/mol;

m.p. = 263-264°C; IR ν_{max} (C=S) 1643 cm^{-1};

R_f = 0.3 in chloroform

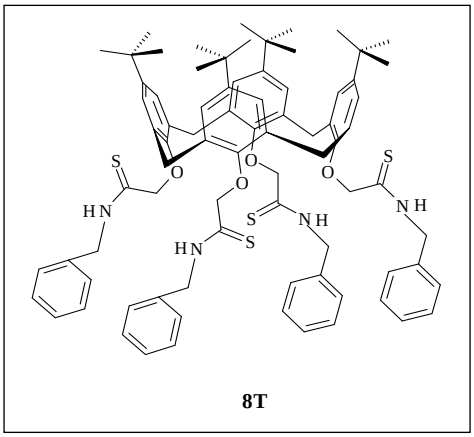
^{1}H NMR (200 MHz, $CDCl_3$): *cone* conformation

δ [ppm]: 1.09 (s, 36H, C-($\underline{CH_3}$)$_3$); 1.24-1.33 (m, 12H, -NH-CH_2-$\underline{CH_3}$); 3.35 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 12.9 Hz); 3.83-3.89 (m, 8H, -NH-$\underline{CH_2}$-CH_3); 4.35 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 12.9 Hz); 4.91 (s, 8H, -O-$\underline{CH_2}$-CS); 6.82 (s, 8H, Ar-$\underline{H}$); 8.60 (bs, 4H, N-$\underline{H}$)

EA calc. for $C_{60}H_{84}O_4N_4S_4$: C 68.40, H 8.04, N 5.32, S 12.15%;

Found: C 68.39, H 7.99, N 4.24, S 10.39%.

25, 26, 27, 28-tetrakis(N-benzylthiocarbonylmethylene)-*p-tert*-butylcalix[4]arene (8T) [15]



8T

Crystallisation from CH_2Cl_2/MeOH mixture gave the pure product **8T** as yellow powder.

Yield: 69%

$C_{80}H_{92}O_4N_4S_4$; M.W. = 1301.9 g/mol;

m.p. = 191-194°C;

IR ν_{max} (C=S) 1644cm^{-1};

R_f = 0.3 in chloroform

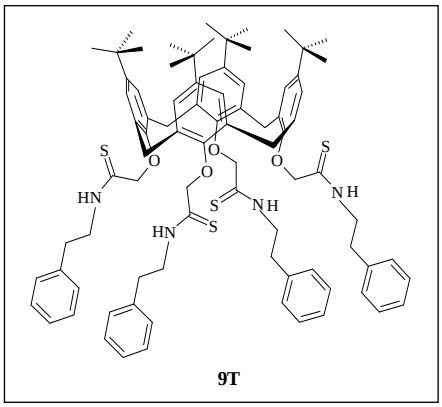
^{1}H NMR (200 MHz, $CDCl_3$): *cone* conformation

δ [ppm]: 1.06 (s, 36H, C-($\underline{CH_3}$)$_3$); 3.0 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 13.18 Hz); 4.17 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 13.18 Hz); 4.81 (s, 8H, -O-$\underline{CH_2}$-CS); 4.97 (d, 8H, -NH-$\underline{CH_2}$-Ar-H); 6.66 (s, 8H, Ar-$\underline{H}$); 7.26-7.35 (m, 20H, -NH-CH_2-Ar-$\underline{H}$);

EA calc. for $C_{80}H_{92}O_4N_4S_4$: C 73.81, H 7.12, N 4.30, S 9.85%;

Found: C 72.1, H 7.03, N 4.08, S 9.61%.

25, 26, 27, 28-tetrakis(N-phenythylthiocarbonylmethylene)-*p-tert*-butylcalix[4]arene (9T) [15]



9T

Crystallisation from CH_2Cl_2/MeOH mixture gave the pure product **9T** as yellow crystals.

Yield: 64%

$C_{84}H_{100}O_4N_4S_4$; M.W. = 1356.9 g/mol;

m.p. = 233-235°C;

IR ν_{max} (C=S) 1643cm^{-1};

R_f = 0.6 in chloroform

^{1}H NMR (200 MHz, $CDCl_3$): *cone* conformation

δ [ppm]: 1.08 (s, 36H, C-($\underline{CH_3}$)$_3$); 2.99 (t, 8H, -NH-CH_2-$\underline{CH_2}$-Ar-H); 3.11 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 13.35 Hz); 4.06 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 13.35 Hz); 4.06 (m, 8H, -NH-$\underline{CH_2}$-CH_2-Ar-H); 4.81 (s, 8H, -O-$\underline{CH_2}$-CS); 6.73 (s, 8H, Ar-$\underline{H}$); 7.22-7.26 (m, 20H, -NH-CH_2-CH_2-Ar-$\underline{H}$);

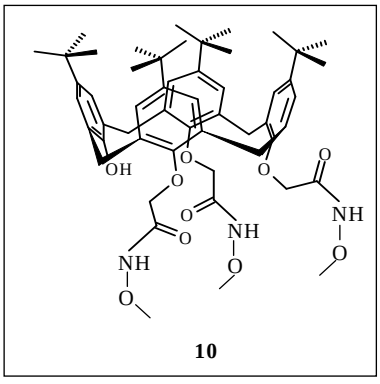
EA calc. for $C_{84}H_{100}O_4N_4S_4$: C 74.29, H 7.42, N 4.13, S 9.43%;

Found: C 73.85, H 7.41, N 3.99, S 9.32%.

7.5. Synthesis of hydroxamate derivatives (**10-14**)

Hydroxamate derivatives of calix[4]arene (compounds **10-14**) were prepared via mixed anhydrides method and the general procedure is the same as given for calix[4]arene-amides. All amines used in the reactions were in hydrochloride form. It was thus necessary to release them from its hydrochloride form by adding the same equivalent of NEt_3 to the solution. Compounds **10-14** were obtained after crystallisation from the CH_2Cl_2/hexan/Et_2O mixture.

25-hydroxy, 26, 27, 28-tris(N-methoxycarbonylmethylene)-*p-tert*-butylcalix[4]arene (10)



10

To obtain ligand **10**, 3.2 equivalents of NEt_3, 3.2 equivalents of ethyl chloroformate and 18 equivalents O-methoxyhydroxylamine hydrochloride **S_7** were used.

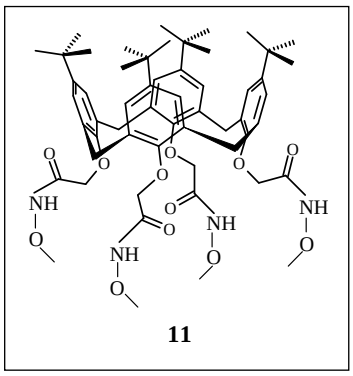
Yield: 48%

$C_{53}H_{71}O_{10}N_3$; M.W. = 910.2 g/mol; m.p. = 236-237°C; IR ν_{max} (C=O) 1670 cm^{-1};

R_f = 0.7 (chloroform / methanol, 12/1)

^{1}H NMR (500 MHz, $CDCl_3$): *cone* conformation δ [ppm]: 0.84 (s, 18H, C-($\underline{CH_3}$)$_3$); 1.36 (s, 9H, C-($\underline{CH_3}$)$_3$); 1.38 (s, 9H, C-($\underline{CH_3}$)$_3$); 3.35 (d, 2H, Ar-$\underline{CH_2}$-Ar, *J* = 12.7 Hz); 3.39 (d, 2H, Ar-$\underline{CH_2}$-Ar, *J* = 12.7 Hz); 3.91 (s, 3H, -O-$\underline{CH_3}$); 4.06 (s, 6H, -O-$\underline{CH_3}$); 4.18 (d, 2H, Ar-$\underline{CH_2}$-Ar, *J* = 12.7 Hz); 4.24 (d, 2H, Ar-$\underline{CH_2}$-Ar, *J* = 12.7 Hz); 4.40 (s, 2H, -O-$\underline{CH_2}$-CO); 4.54 (s, 4H, -O-$\underline{CH_2}$-CO); 6.53 (s, 2H, Ar-$\underline{H}$); 6.59 (s, 2H, Ar-$\underline{H}$); 7.15 (s, 2H, Ar-$\underline{H}$); 7.24 (s, 2H, Ar-$\underline{H}$).

25, 26, 27, 28-tetrakis(N-methoxycarbonylmethylene)-*p-tert*-butylcalix[4]arene (11)



11

24 equivalents of O-methoxyhydroxylamine hydrochloride **S_7** were used and the compound **11** was obtained after re-crystallisation from CH_2Cl_2/MeOH mixture as white crystals.

Yield: 76%, lit. 98% [9]

$C_{56}H_{76}O_{12}N_4$; M.W. = 996.2 g/mol;

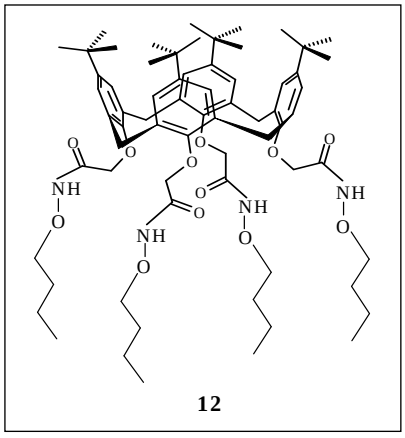
m.p. = 222-223°C, lit. 195-197°C [9];

IR ν_{max} (C=O) 1666 cm^{-1};

R_f = 0.5 (chloroform / methanol, 10/1)

^{1}H NMR (500 MHz, $CDCl_3$): *cone* conformation δ [ppm]: 1.09 (s, 36H, C-($\underline{CH_3}$)$_3$); 3.22 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 12.2 Hz); 3.84 (s, 12H, -O-$\underline{CH_3}$); 4.38 (d, 4H, -Ar-$\underline{CH_2}$-Ar, *J* = 12.2 Hz); 4.43 (s, 8H, -O-$\underline{CH_2}$-CO-); 6.81 (s, 8H, Ar-$\underline{H}$); 11.1 (s, 4H, -N-$\underline{H}$)

25, 26, 27, 28-tetrakis(N-butoxycarbonylmethylene)-*p-tert*-butylcalix[4]arene (12)



12

24 equivalents of O-butoxyhydroxylamine hydrochloride **S_8** were used and the compound **12** was obtained as white powder.

Yield: 57%, lit. 80% [5]

$C_{68}H_{100}O_{12}N_4$; M.W. = 1164.2 g/mol;

m.p. = 215-217°C, lit. 204.5-206°C [5];

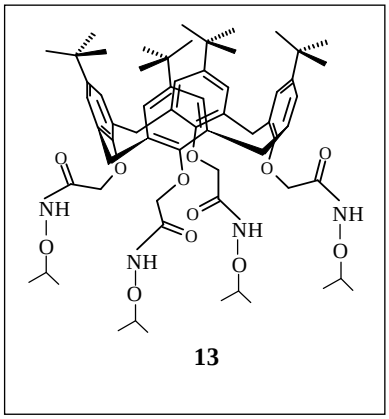
IR ν_{max} (C=O) 1661 cm^{-1}

R_f = 0.9 (chloroform / methanol, 12/1)

^{1}H NMR (200 MHz, $CDCl_3$): *cone* conformation δ [ppm]: 0.95 (t, 12H, -O-CH_2-CH_2-CH_2-CH_2-$\underline{CH_3}$); 1.06 (s, 36H, C-($\underline{CH_3}$)$_3$); 1.42 (m, 8H, -O-CH_2-CH_2-CH_2-$\underline{CH_2}$-CH_3); 1.68 (m, 8H, -O-CH_2-CH_2-$\underline{CH_2}$-CH_2-CH_3); 3.20 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 13.0 Hz); 4.03 (t, 8H, -O-

$\underline{CH_2}$-CH_2-CH_2-CH_2-CH_3); 4.37 (bs, 12H, -O-$\underline{CH_2}$-CO + Ar-$\underline{CH_2}$-Ar, *J* = 13.0 Hz); 6.79 (s, 8H, Ar-$\underline{H}$); 10.74 (s, 4H, -N-$\underline{H}$)

25, 26, 27, 28-tetrakis(N-isopropoxycarbonylmethylene)-*p*-*tert*-butylcalix[4]arene (13)



13

24 equivalents of O-*iso*-propoxyhydroxylamine hydrochloride **S_9** were used and the compound **13** was obtained after recrystallisation from CH_2Cl_2/MeOH mixture as white crystals.

Yield: 68%, lit. 97% [5]

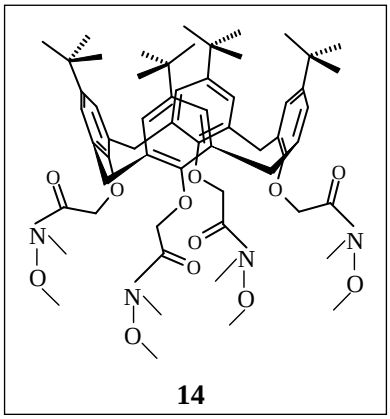
$C_{64}H_{92}O_{12}N_4$; M.W. = 1108.2 g/mol;

m.p. = 232-233°C, lit. 226-228.5°C [5];

IR ν_{max} (C=O) 1670 cm^{-1}; R_f = 0.7 (chloroform / methanol, 12/1)

^{1}H NMR (200 MHz, $CDCl_3$): *cone* conformation δ [ppm]: 1.06 (s, 36H, C-($\underline{CH_3}$)$_3$); 1.39 (d, 24H, -O-CH-($\underline{CH_3}$)$_2$); 3.19 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 12.5 Hz); 4.35 (bs, 12H, -O-$\underline{CH_2}$-CO + Ar-$\underline{CH_2}$-Ar, *J* = 12.5 Hz); 4.45 (m, 4H, -O-$\underline{CH}$-(CH_3)$_2$); 6.79 (s, 8H, Ar-$\underline{H}$); 10.78 (s, 4H, -N-$\underline{H}$)

25, 26, 27, 28-tetrakis(N-methyl, N-methoxycarbonylmethylene)-*p*-*tert*-butylcalix[4]arene (14)



14

24 equivalents of N-methyl, N-methoxyhydroxylamine hydrochloride were used and the compound **14** was obtained as white powder.

Yield: 67%, lit. 77% [5]

$C_{60}H_{84}O_{12}N_4$; M.W. = 1052.3 g/mol;

m.p. = 230°C, lit. 242-245.5°C [5];

IR ν_{max} (C=O) 1665 cm^{-1};

R_f = 0.7 (chloroform / methanol, 4/1)

^{1}H NMR (200 MHz, DMSO): *cone* conformation δ [ppm]: 0.91-1.21 (bs, 36H, C-($\underline{CH_3}$)$_3$); 3.11 (m, 16H, -N-$\underline{CH_3}$ + Ar-$\underline{CH_2}$-Ar, *J* = 12.5 Hz); 3.66 (s, 12H, -N-O-$\underline{CH_3}$); 4.56-4.96 (m, 12H, -O-$\underline{CH_2}$-CO + Ar-$\underline{CH_2}$-Ar, *J* = 12.5 Hz); 6.75-7.27 (m, 8H, Ar-$\underline{H}$)

EA calc. for $C_{60}H_{84}O_{12}N_4 \cdot CH_3OH$: C 67.56, H 8.18, N 5.17%;

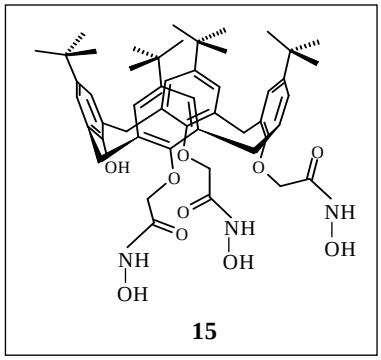
Found: C 67.41, H 7.86, N 4.41%

7.6. Synthesis of calix[4]arene-hydroxamic acid derivatives (**15-18**)

Calix[4]arene-hydroxamic acids were prepared via mixed anhydrides method according to the general procedure:

In a 100 mL flask, calix[4]arene-carboxylic acid **S_2** was dissolved in dry CH_2Cl_2 (10 mL) and the solution was stirred and cooled to -10°C. Subsequently, 4.2 equivalents of NEt_3 (or 3.2 equivalents in the case of tris-substituted derivatives) and then, 4.2 equivalents of ethyl chloroformate (or 3.2 equivalents) were added. The solution was stirred at -10°C for 0.5h and then 24 equivalents (or 18 in case of tris-substitution) of an appropriate amine hydrochloride in 5 mL of CH_2Cl_2 were added. Before introducing amine hydrochloride to the reaction mixture, it was release from its hydrochloride form by adding the same equivalent of NEt_3. After about 1h, the mixture was diluted with CH_2Cl_2 (15 mL), washed with water (15 mL), then with 0.1 mol L^{-1} HCl (15 mL) and again with water (15 mL). The water phase was extracted twice with CH_2Cl_2 (30 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was crystallised from CH_2Cl_2/Et_2O mixture to give the pure products **15-18**.

25-hydroxy-26, 27, 28-tris(N-hydroxycarbonylmethylene)-*p-tert*-butylcalix[4]arene (15)



15

To obtain compound **15**, 18 equivalents of N-hydroxylamine hydrochloride were used.

Yield: 76%;

$C_{50}H_{65}O_{10}N_3$; M.W. = 868.2 g/mol;

m.p. = 190°C;

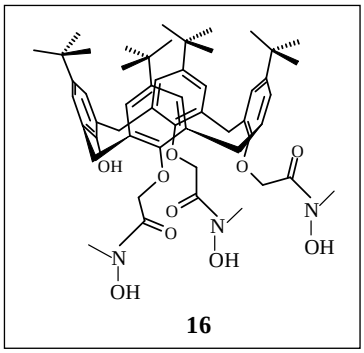
IR ν_{max} (C=O) 1645 cm^{-1};

R_f = 0.7 (chloroform / methanol, 6/1)

^{1}H NMR (500 MHz, DMSO): *cone* conformation δ[ppm]: 0.96 (s, 18H, C-($\underline{CH_3}$)$_3$); 1.20 (s, 9H, C-($\underline{CH_3}$)$_3$); 1.22 (s, 9H, ; C-($\underline{CH_3}$)$_3$); 3.30 (d, 2H, Ar-$\underline{CH_2}$-Ar, *J* = 13.67 Hz); 4.26 (d, 2H, Ar-$\underline{CH_2}$-Ar, *J* = 13.67 Hz); 4.40 (d, 2H, Ar-$\underline{CH_2}$-Ar, *J* = 13.19 Hz); 4.45 (d, 2H, Ar-$\underline{CH_2}$-Ar, *J* = 13.19 Hz); 4.22 (s, 2H, -O-$\underline{CH_2}$-CO); 4.41 (s, 4H, -O-$\underline{CH_2}$-CO); 6.78 (s, 2H, Ar-$\underline{H}$); 6.91 (s, 2H, Ar-$\underline{H}$); 7.07 (s, 2H, Ar-$\underline{H}$); 7.20 (s, 2H, Ar-$\underline{H}$); 7.10 (s, 1H, N-$\underline{H}$); 7.24 (s, 2H, N-$\underline{H}$); 9.09 (s, 1H, O-$\underline{H}$); 10.53 (s, 1H, O-$\underline{H}$); 10.83 (s, 2H, O-$\underline{H}$)

EA calc. for $C_{50}H_{65}O_{10}N_3 \cdot 0.5\ HCl \cdot NH_2OH$: C 66.52, H 7.48, N 5.43%; Found: C 66.81, H 7.45, N 3.34%.

25-hydroxy- 26, 27, 28-tris(N-methyl, N-hydroxycarbonylmethylene)-*p-tert*-butylcalix[4]arene (16)



16

18 equivalents of N-methylhydroxylamine hydrochloride were used to prepare ligand **16**.

Yield: 79%, lit. 55% [5]

$C_{53}H_{71}O_{10}N_3$; M.W. = 910.2 g/mol;

m.p. = 217-221°C, lit. 214°C [5]

IR ν_{max} (C=O) 1650 cm^{-1};

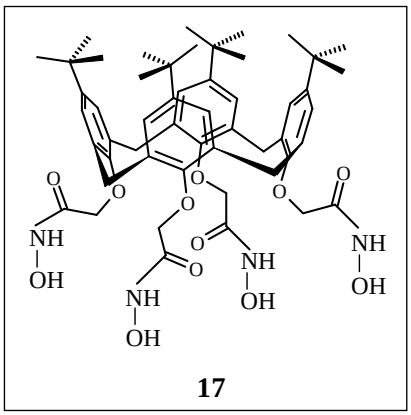
R_f = 0.7 (chloroform / methanol, 6/1)

^{1}H NMR (500 MHz, DMSO): *cone* conformation δ[ppm]: 0.94 (s, 18H, C-($\underline{CH_3}$)$_3$); 1.17 (s, 18H, C-($\underline{CH_3}$)$_3$); 3.14 (s, 9H, -N-$\underline{CH_3}$); 3.18 (d, 2H, Ar-$\underline{CH_2}$-Ar, *J* = 12.7 Hz); 3.22 (d, 2H, Ar-$\underline{CH_2}$-Ar, *J* = 12.7 Hz); 4.37 (d, 2H, Ar-$\underline{CH_2}$-Ar, *J* = 12.7 Hz); 4.54 (d, 2H, Ar-$\underline{CH_2}$-Ar, *J* = 12.7 Hz); 4.95 (s, 6H, -O-$\underline{CH_2}$-CO); 6.70 (s, 2H, Ar-$\underline{H}$); 6.81 (s, 2H, Ar-$\underline{H}$); 6.94 (s, 2H, Ar-$\underline{H}$); 7.02 (s, 2H, Ar-$\underline{H}$); 9.70 (s, 1H, O-$\underline{H}$); 9.84 (s, 3H, O-$\underline{H}$)

EA calc. for $C_{53}H_{71}O_{10}N_3 \cdot 0.5\ CH_3OH \cdot 0.5\ HCl \cdot NH(OH)CH_3$: C 67.01, H 7.91, N 5.06%;

Found: C 67.72, H 7.70, N 4.48%.

25, 26, 27, 28-tetrakis(N-hydroxycarbonylmethylene)-*p-tert*-butylcalix[4]arene (17)



17

24 equivalents of N-hydroxylamine hydrochloride were used to obtain compound **17**.

Yield: 82%, lit. 84% [9], 91% [31]

$C_{52}H_{68}O_{12}N_4$; M.W. = 941.1 g/mol;

m.p. = 220°C, lit. 214-217°C [9], 214°C [31];

IR ν_{max} (C=O) 1640 cm^{-1};

R_f = 0.7 (chloroform / methanol, 6/1)

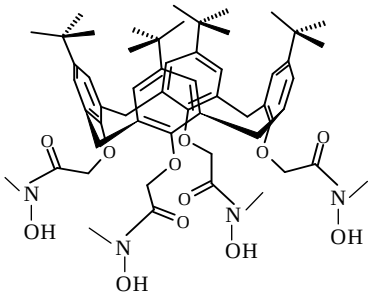
^{1}H NMR (500 MHz, DMSO): *cone* conformation

δ [ppm]: 0.91-1.24 (bs, 36H, C-($\underline{CH_3}$)$_3$); 3.23 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 13.18 Hz); 4.11-4.87 (m, 16H, -O-$\underline{CH_2}$-CO + Ar-$\underline{CH_2}$-Ar, *J* = 13.18 Hz); 6.68-7.13 (m, 8H, Ar-$\underline{H}$)

EA calc. for $C_{52}H_{68}O_{12}N_4 \cdot 0.5\ HCl \cdot NH_2OH$: C 64.00, H 7.23, N 6.46%;

Found: C 64.18, H 7.41, N 3.79%.

25, 26, 27, 28-tetrakis(N-methyl, N-hydroxycarbonylmethylene)-*p-tert*-butylcalix[4]arene (18)



18

24 equivalents of N-methylhydroxylamine hydrochloride were used to obtain compound **18**.

Yield: 60%, lit. 95% [9];

$C_{56}H_{76}O_{12}N_4$; M.W. = 996.2 g/mol;

m.p. = 214-215°C, lit. 214-215°C [9];

IR ν_{max} (C=O) 1646 cm^{-1};

R_f = 0.5 (chloroform / methanol, 6/1)

^{1}H NMR (500 MHz, DMSO): *cone* conformation δ [ppm]: 1.04 (bs, 36H, C-($\underline{CH_3}$)$_3$); 3.14 (m, 16H, -N-$\underline{CH_3}$ + Ar-$\underline{CH_2}$-Ar, *J* = 12.7 Hz); 4.76 (d, 4H, Ar-$\underline{CH_2}$-Ar, *J* = 12.7 Hz); 4.88 (s, 8H, -O-$\underline{CH_2}$-CO); 6.78 (s, 4H, Ar-$\underline{H}$); 9.72 (s, 4H, -O-$\underline{H}$)

EA calc. for $C_{56}H_{76}O_{12}N_4$: C 67.45, H 7.68, N 5.62%;

Found: C 67.24, H 7.61, N 5.62%.

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CHAPTER III:

LIGAND – CATION INTERACTION STUDIES

1. Introduction

There are several methods to study ligand-cation interactions which allow to determine the complex stability constants [1]. These methods can be classified in three groups: spectroscopic, electrochemical and thermodynamic methods (**Table III - 1**).

Table III - 1. Methods used for ligand-cation interaction studies

Spectroscopic	Electrochemical	Thermodynamic
NMR UV/VIS Spectrophotometry Fluorescence Mass spectroscopy	Polarography Conductometry Potentiometry: • use of Ag^+/Ag electrode • use of Ion Selective Electrodes (ISE)	Microcalorimetry Extraction

The techniques used in this thesis are underlined and will be discussed in details in this chapter. The part concerning ion selective electrodes will be described in Chapter IV.

2. Methods of investigation

2.1. Biphasic transfer: liquid – liquid extraction

2.1.1. Principle

Liquid-liquid extraction is a method of separation of solutes based on their solubilities in two different immiscible phases, an aqueous phase and an organic phase, containing the diluent and the extractant. When these two phases are in contact, the solute M is distributed between them and the following equilibrium is reached [2, 3]:

$$M_{aq} \rightleftharpoons M_{org} \qquad \text{(III – 1)}$$

where the subscripts $_{aq}$ and $_{org}$ correspond to the aqueous and the organic phase, respectively.

During the extraction process, according to the Berthelot-Nernst law [4], the distribution ratio $K_{d,M}$ of the solute M depends on its activity (a_M) and is constant at given temperature and ionic strength *I*. $K_{d,M}$ is described by the following equation:

$$K_{d,M} = \frac{a_{M,org}}{a_{M,aq}} \quad \text{(III – 2)}$$

Knowing also the relation:

$$a_M = [M] \times f_M \quad \text{(III – 3)}$$

$K_{d,M}$ can be expressed as:

$$K_{d,M} = \frac{[M]_{org} \times f_{M,org}}{[M]_{aq} \times f_{M,aq}} \quad \text{(III – 4)}$$

where:

$[M]_{org}$ - is the concentration of M in the organic phase

$[M]_{aq}$ - is the concentration of M in the aqueous phase

When the activity coefficients f are equal to 1, the distribution constant of the solute M depends on the ratio of concentration in both phases:

$$K_{d,M} = \frac{[M]_{org}}{[M]_{aq}} \quad \text{(III – 5)}$$

It should be specified that a solute M can often change its chemical form due to dissociation, association, or solvation processes, etc. Thus, in practice, the distribution coefficient (D_M) is used, which is defined as the ratio of the sum of the concentrations of all forms of the solute (ionised plus un-ionised) in each of the two phases:

$$D_M = \frac{\sum[M]_{org}}{\sum[M]_{aq}} \quad \text{(III – 6)}$$

The distribution coefficient may be pH dependent. Thus, the pH of the aqueous phase may be, if necessary, buffered to a specific value such that it cannot be significantly perturbed by the introduction of the solute.

The extraction results may also be expressed as the percentage %E of M extracted. D_M and %E are related by the following equation:

$$\%E = \frac{100 \times D_M}{D_M + \frac{V_{org}}{V_{aq}}} \quad \text{(III – 7)}$$

where:

V_{org} and V_{aq} are the volumes of the organic phase and the aqueous phase, respectively.

2.1.2. Different types of extractants

Solvating extractants

This extraction of metal ions proceeds by replacement of water molecules by basic donor atoms such as O, S or N of the neutral extractant L. The basic role of a solvating molecule is to increase the solubility of the inorganic species in the organic phase. This extraction process can be expressed by the following equilibrium:

$$M_{aq}^{m+} + mA_{aq}^{-} + nL_{org} \rightleftharpoons MA_mL_{n,org} \quad \text{(III – 8)}$$

The distribution coefficient can be derived from the expression:

$$D_M = \frac{[MA_mL_n]_{org}}{[M^{m+}]_{aq}} \quad \text{(III – 9)}$$

Solvating extractants are widely used in the nuclear fuel cycle. A well known example of such extractants is tri-*n*-butyl phosphate (TBP) used in the Pu^{4+} and UO_2^{2+} extraction from nitric acid medium. This process called “PUREX” (Plutonium Uranium Reduction EXtraction) [5] can be described by the following equilibria:

$$Pu_{aq}^{4+} + 4NO_{3\,aq}^{-} + 2\,TBP_{org} \rightleftharpoons Pu(NO_3)_4 \cdot 2TBP_{org} \quad \text{(III – 10)}$$

$$UO_{2\,aq}^{2+} + 2\,NO_{3\,aq}^{-} + 2\,TBP_{org} \rightleftharpoons UO_2(NO_3)_2 \cdot 2TBP_{org} \quad \text{(III – 11)}$$

According to equilibria, the metal ion extraction increases with the concentration of either the extractant or nitrate ions.

Chelating extractants

In these compounds, metal ion combines with a polyfunctional base, capable of occupying two or more positions of the coordination sphere of the metal ion, to form a cyclic compound. Chelating extractants such as beta-diketones or 8-hydroxyquinolines have been widely used for the separation of actinide ions [5].

Ion-pair extractants

This type of extraction proceeds through the formation of ion-pair species between the metal-bearing ions and counterions provided by the ligand.
Acidic ligands by liberating protons, provide anions, which then complex with the metal cations to form an ion-pair what can be presented as the following equilibrium:

$$M_{aq}^{m^+} + LH_{n,org} \rightleftharpoons MLH_{(n-m)org} + mH_{aq}^{+} \qquad \text{(III – 12)}$$

The distribution coefficient is then described as follows:

$$D_M = \frac{\left[MLH_{(n-m)}\right]_{org}}{\left[M^{m^+}\right]_{aq}} \qquad \text{(III – 13)}$$

Basic ligands, provide cations that complex with aqueous anionic metal complexes to form ion pairs. An example of basic extractants are amines and quaternary ammonium salts. The extraction process can be expressed by the following equilibrium scheme:

$$A_{aq}^{n^-} + n(R^+X^-)_{org} \longrightarrow (R_n^+A^{n^-})_{org} + nX_{aq}^- \qquad \text{(III – 14)}$$

where:
R^+ – is a basic extractant
X^- - is the counterion of R^+
A^{n^-} - is the anion

The distribution coefficient is expressed as:

$$D_A = \frac{[R^+X^-]^n_{org}}{[X^-]^n_{aq}} \qquad \text{(III – 15)}$$

Synergistic extraction

The word “synergism” means working together. This word in solvent extraction was introduced by Blake *et al* in 1958. Generally, it refers to the situation where the extraction of metal ions in the presence of two or more extractants is more efficient than that expected from the total sum of the individual extractants [5].

Nowadays, synergistic extraction is widely used and a well known example is the extraction of UO_2^{2+} and Pu^{4+} from nitric acid medium by a mixture of a beta-diketone and neutral oxo donors such as TOPO (trioctyl phosphine oxide) [6].

2.1.3. Experimental protocols used in this work

The amide, thioamide and hydroxamate derivatives of calixarene synthesised in this work were tested using the picrate extraction method. The hydroxamic derivatives, being acidic ligands, were studied in extraction by the nitrate extraction method.

Picrate extraction method

The general scheme of a picrate extraction process can be presented as follows:

$$M^{m+}_{aq} + mPic^-_{aq} + nL_{org} \rightleftharpoons \left(ML^{m+}_n Pic^-_m\right)_{org} \qquad \text{(III-16)}$$

If complexation occurs, the metal ion is transferred to the organic phase together with the yellow coloured picrate counterion as depicted in **Figure III-1**.

Picrate anion, due to the presence of nitrate groups conjugated with the aromatic ring, possesses a characteristic absorption spectrum between 300 and 400 nm [7]. Thus, the absorbance of the picrate anion remaining in the aqueous phase after extraction can be followed by spectrophotometry.

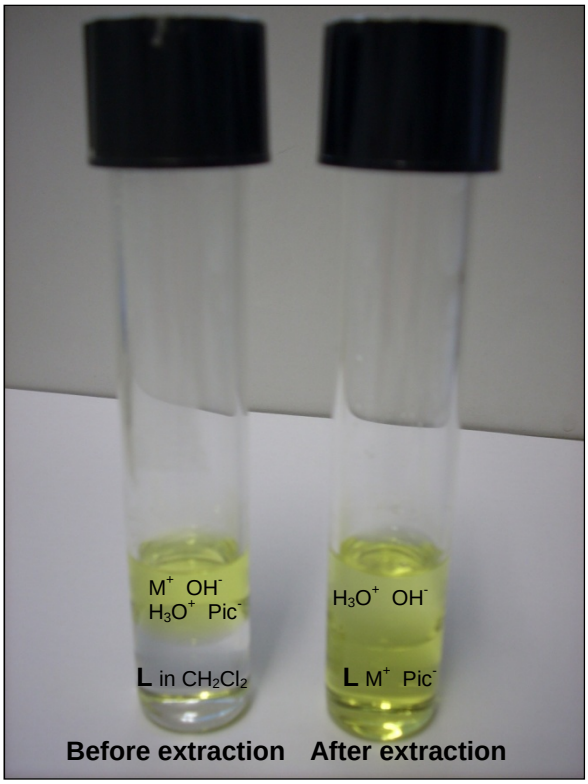


Figure III-1. Illustrative representation of picrate extraction process

The extraction of picrate metal salts was carried out according to the Pedersen procedure [8]: 5 mL of a 2.5×10^{-4} mol L^{-1} aqueous metal picrate solution and 5 mL of a 2.5×10^{-4} mol L^{-1} calix[4]arene solution in CH_2Cl_2 were mechanically shaken for 10 min, then magnetically stirred in a thermostated water bath at 20.0 ± 0.1 ºC for 30 min. After that time, the tubes were left standing for at least 30 min without stirring, in order to obtain complete phase separation. The absorbance A of the picrate anion remaining in the aqueous phase after extraction was determined spectrophotometrically at λ_{max} = 355 nm. The percentage of cation extracted (%E) from water into dichloromethane was then calculated from the equation:

$$\%E = \frac{(A_0 - A)}{A_0} \times 100 \qquad \text{(III – 17)}$$

where A_0 is the absorbance of a blank experiment without ligand.

Nitrate extraction method

The extraction procedure was adapted from the literature to study the extractive properties of acidic ligands [9, 10]:

25 mL of an aqueous phase containing metal nitrate at the concentration of 1.06×10^{-4} mol L^{-1} and 5 mL of the organic phase containing the ligand dissolved in dichloromethane at the concentration equal to 5.3×10^{-4} mol L^{-1} were placed together in a 50 mL flask and shaken in a thermostated water bath at 30°C for about 12h. After that time the two phases were separated and the aqueous layer was analysed by atomic absorption spectrometry (Varian 55) with an air-acetylene flame.

The aqueous solution was buffered to pH = 5.4 with 0.01 mol L^{-1} acetate buffer (8.2×10^{-3} mol L^{-1} CH_3COONa and 1.8×10^{-3} mol L^{-1} CH_3COOH). The ionic strength was kept constant at $I = 0.1$ mol L^{-1} using KCl.

It is evident that above the pH = 4 iron precipitates from the aqueous solution, thus the extraction process could not be studied at pH = 5.4. In this case, the pH was lowered to 2.2 with HNO_3.

The percentages of cation extracted from water into dichloromethane were calculated according to the following equation:

$$\%E = \frac{([Metal]_{blank} - [Metal]_{water})}{[Metal]_{blank}} \times 100 \qquad \text{(III – 18)}$$

where:

$[Metal]_{blank}$ corresponds to the blank experiment (metal concentration in the aqueous phase extracted with pure dichloromethane)

$[Metal]_{water}$ corresponds to the metal concentration in the aqueous phase after extraction

Competitive metal ion extraction experiments were performed to determine the potential of the synthesised acidic ligands as selective extractive agents of Pb^{2+} in the presence of Cd^{2+} and of Cu^{2+} in the presence of Zn^{2+} and Ni^{2+} cations which are usually present together.

Two kinds of metal salts mixture were prepared: mixtures of the heavy metal ions: Pb^{2+} and Cd^{2+}, and mixtures of the transition metal ions Cu^{2+}, Zn^{2+} and Ni^{2+}. The concentration of each

metal ion was 1.06×10^{-4} mol L^{-1}. The experimental conditions were the same as for the individual extraction experiments.

2.2. Complexation in homogeneous medium

Complex formation with a neutral ligand can be described according to the general equation:

$$mM^{n+} + nL \rightleftharpoons M_m L_n^{n+} \qquad \text{(III – 19)}$$

The corresponding thermodynamic stability constant β^0 is expressed as :

$$\beta^0 = \frac{a_{M_m L_n^{n+}}}{a_{M^{n+}}^m a_L^n} \qquad \text{(III – 20)}$$

$$\beta^0 = \frac{\left[M_m L_n^{n+}\right]}{\left[M^{n+}\right]^m [L]^n} \times \frac{f_{M_m L_n^{n+}}}{f_{M^{n+}}^m \times f_L^n} \qquad \text{(III – 21)}$$

According to the Debye-Hückel theory, activity coefficients depend on the ionic strength *I* of the solution:

$$I = 0.5 \sum C_i z_i^2 \qquad \text{(III – 22)}$$

where C_i and z_i are the concentration and the charge of the species i, respectively.

In diluted solutions (molar concentrations below 0.001 mol L^{-1}) it can be assumed that the value of the activity coefficient is equal to 1. In other cases, the activity coefficients are calculated according to the equation:

$$-\log f_{\pm} = Az^2 \left[\frac{\sqrt{I}}{I + aB\sqrt{I}}\right] - CI \qquad \text{(III – 23)}$$

where A, B and C are experimental constants depending on the solvent and the temperature and “a” a parameter related to the size of ions.

The value of the activity coefficient can be considered as constant if the ionic strength is constant. Addition of a supporting electrolyte allows to fix the ionic strength and hence the activity coefficients and to determine in these experimental conditions, an apparent stability constant β:

$$\beta = \frac{\left[M_m L_n^{n+}\right]}{\left[M^{n+}\right]^m [L]^n} \quad \text{(III – 24)}$$

which depends on the solvent, the temperature, the ionic strength and the nature of the supporting electrolyte [4].

Stepwise and cumulative stability constants

A cumulative or in other words, overall constant is the stability constant for the complex formation from the reagents.

For example, the overall constant β_{21} for the formation of a M_2L^{n+} complex can be derived from the equation:

$$2M^{n+} + L \rightleftharpoons M_2L^{n+} \quad \text{(III – 25)}$$

$$\beta_{21} = \frac{[M_2L^{n+}]}{\left[M^{n+}\right]^2 [L]} \quad \text{(III – 26)}$$

The stepwise constants, K_1 and K_2 refer to the successive formation of the complexes:

$$M^{n+} + L \rightleftharpoons ML^{n+} \qquad K_1 = \frac{\left[ML^{n+}\right]}{\left[M^{n+}\right][L]} \quad \text{(III – 27)}$$

$$ML^{n+} + M^{n+} = M_2L^{n+} \qquad K_2 = \frac{[M_2L^{n+}]}{\left[ML^{n+}\right]\left[M^{n+}\right]} \quad \text{(III – 28)}$$

$$\beta_{21} = K_1K_2 = \frac{[M_2L^{n+}]}{[M^{n+}]^2[L]} \quad \text{(III – 29)}$$

$$\log \beta_{21} = \log K_1 + logK_2 \quad \text{(III – 30)}$$

2.2.1. Nuclear Magnetic Resonance spectroscopy (NMR)

Principle

Nuclear Magnetic Resonance (NMR) is considered to be one of the most important method which provides detailed information about the structure, dynamics, reaction state, and chemical environment of molecules. This technique is based on the fact that most of the organic compounds, whose nuclei have nonzero nuclear spin, have magnetic properties. When

placed in a magnetic field, nuclei such as ^{1}H or ^{13}C absorb electromagnetic radiation at a frequency characteristic of the isotope.

Depending on the local chemical environment, different protons in a molecule resonate at slightly different frequencies.

The resonance frequency is given as a difference between the resonance frequency of the signal (υ_s) and a reference resonance frequency (υ_{ref}). For the nuclei ^{1}H, ^{13}C, and ^{29}Si, TMS (tetramethylsilane) is commonly used as a reference. This difference divided by the fundamental NMR frequency (υ_0) gives the chemical shift (δ).

$$\delta = \frac{\vartheta_s - \vartheta_{ref}}{\vartheta_0} \times 10^6 \qquad \text{(III-31)}$$

The frequency shifts are extremely small and are generally expressed in parts per million (ppm) [11].

^{1}H NMR spectroscopy was used in this work to investigate the ligands structure but also to study ligand-cation interactions upon addition of certain metal salts. It gives the possibility to establish the binding sites involved in the complexation process.

Experimental protocol

Direct complexation reaction was performed in order to obtain complexes as a powder and to characterise them by ^{1}H NMR technique. For this purpose, 15 mg of the thioamide derivative were dissolved in chloroform and then an appropriate salt (Pb^{2+} or Ag^{+} perchlorates) in excess was added. After about 24h of stirring, the resulting precipitate was filtered off, dried and analysed by ^{1}H NMR technique in a $CDCl_3$/MeOD (1/1) mixture.

2.2.2. UV absorption spectrophotometry

Principle

The light beam crossing the sample, can be partially absorbed when the following condition is fulfilled [12]:

$$h\vartheta = E'' - E' \qquad \text{(III – 32)}$$

where:

h - is the Planck constant equal to 6.62 x 10^{-34} J·s

ϑ – is the radiation frequency in Hz or 1/s

E'', E' – is the molecule energy in the excited and the initial states, respectively

The energy changes can be expressed as the absorption spectrum of the sample.

A part of the light can be reflected at the interface or scattered. To eliminate losses caused by the reflected and scattered lights, reference measurement should be performed. For this purpose, the light is transmitted through the reference cell containing the supporting electrolyte in pure solvent. Thus, the losses in both cells are supposed to be the same.

Actually, spectrophotometers measure the transmittance and not the absorbance. Transmittance T is defined as the ratio of the intensity of the monochromatic light emerging from the sample (I) to the intensity of this light entering the sample (I_0) [13]:

$$T = \frac{I}{I_0} \qquad \text{(III - 33)}$$

Absorbance A is commonly used in quantitative analysis, where it is required to obtain the concentration of the substance:

$$A = log\frac{I_0}{I} \qquad \text{(III – 34)}$$

The relation between these two parameters is given by the following equation:

$$A = log\frac{1}{T} \qquad \text{(III – 35)}$$

A is related to the concentration c of the absorbing species according to the expression known as the Lambert-Beer law [11]:

$$A = \varepsilon \cdot c \cdot l \qquad \text{(III – 36)}$$

where:

ε - is the molar absorption coefficient, a fundamental molecular property in a given solvent, at a particular temperature and pressure

c - is the concentration of the light - absorbing substance (mol L^{-1})

l - is the length of the light - path in the spectrophotometer cell (cm)

If the Lambert – Beer law is fulfilled, the absorbance is linearly proportional to the sample concentration in solution.

The absorbance is an additive property, what means that the absorbance of the multicomponent solution is equal to the sum of the absorbances of the individual species present in this solution.

Ion complexation involves energy changes of the electrons in the ligand molecule, which result in spectrum changes of the ligand. Spectrophotometric titration allows to follow the complexation as a function of spectral changes.

Experimental protocol

The spectrophotometric titrations were performed in methanol or/and acetonitrile on a Shimadzu UV-2101-PC spectrophotometer, at 25ºC and at the ionic strength 0.01mol L^{-1} using Et_4NNO_3, Et_4NCl or Et_4NClO_4. Titrations were carried out according to the procedure described in the literature [14].

A solution containing metal nitrates, chlorides or perchlorates of known concentration (C_M) was added directly in the spectrophotometric cell (1 cm of pathlength) containing 2 mL of the ligand solution in the presence of tetraethylammonium nitrate, chloride or perchlorate as supporting electrolyte. The ligand concentration ranged between 10^{-5} mol L^{-1} and 4×10^{-4} mol L^{-1}. The spectral changes of the ligand solution upon additions of the metal solution were recorded between 250 and 350 nm. The metal solution was added until no spectral changes were observed. The ratio $R = C_M / C_L$ reached at the end of the titration varied between 1.5 and 5. Before each experiment, the baseline was recorded with the two cells containing the adequate supporting electrolyte solution. The data obtained were treated using the program SPECFIT [15, 16] in order to obtain the stability constants.

Data treatment

The program SPECFIT is commonly used for the determination of stability constants from spectrophotometric experiments [15, 16]. The program uses a Marquardt algorithm [17] for the least – squares determination of non – linear parameters. The calculations involve the

decomposition of the M × W matrix of absorbances Y into two smaller matrices of the concentrations C (M × S) and of the molar absorptivities A (S × W), where M, S and W are the numbers of measured spectra, absorbing species and wavelength, respectively. The matrix R defined by the equation III-37 must be minimised by adjustment procedures based on the mass action law in order to allow an optimum determination of the matrices C and A.

$$R = C \times A - Y \qquad (III - 37)$$

The matrix Y is subjected to factor analysis to find a number of lineary independent absorbing species and is used to determine the stability constants.

While dealing with the program, the spectra of the known components (ligand and metal) together with their initial concentrations and volumes used are introduced into the program and the model type is simulated. The equilibrium constants are then calculated together with the molar absorption coefficients of each complex.

2.2.3. Potentiometry with the use of an Ag^+/Ag electrode

Principle

When the spectrophotometric method did not allow to determine the stability constants, or when the stability constants were too high ($\log \beta > 6$), the potentiometric method was used. During a potentiometric titration, the potential of an electrode specific to an ion involved in the complexation is followed [18].

The electrode response in the cell is described by the Nernst equation:

$$E = E^0 + \frac{2.3 \cdot RT}{z_M F} log(a_M) \qquad (III - 38)$$

where: $\frac{2.3 \cdot RT}{z_M F} = S$

S – is the slope of the calibration linear plot (~ 59 mV for monovalent cations),

E^0 – is the standard potential of the electrode,

a_M – is the activity of the cation M in the aqueous phase,

z_M – is the charge number of the cation M,

R - is the gas constant (8.31 J/kmol),

T - is the temperature (298 K),

F - is the Faraday constant (96500 C)

In our case, we used a silver electrode in order to follow the concentration of the free Ag^+ cations during the complexation of this cation with the studied ligands.

The potentiometric cells used for measurements consist of a reference and a sample compartment as presented in **Figure III-2**.

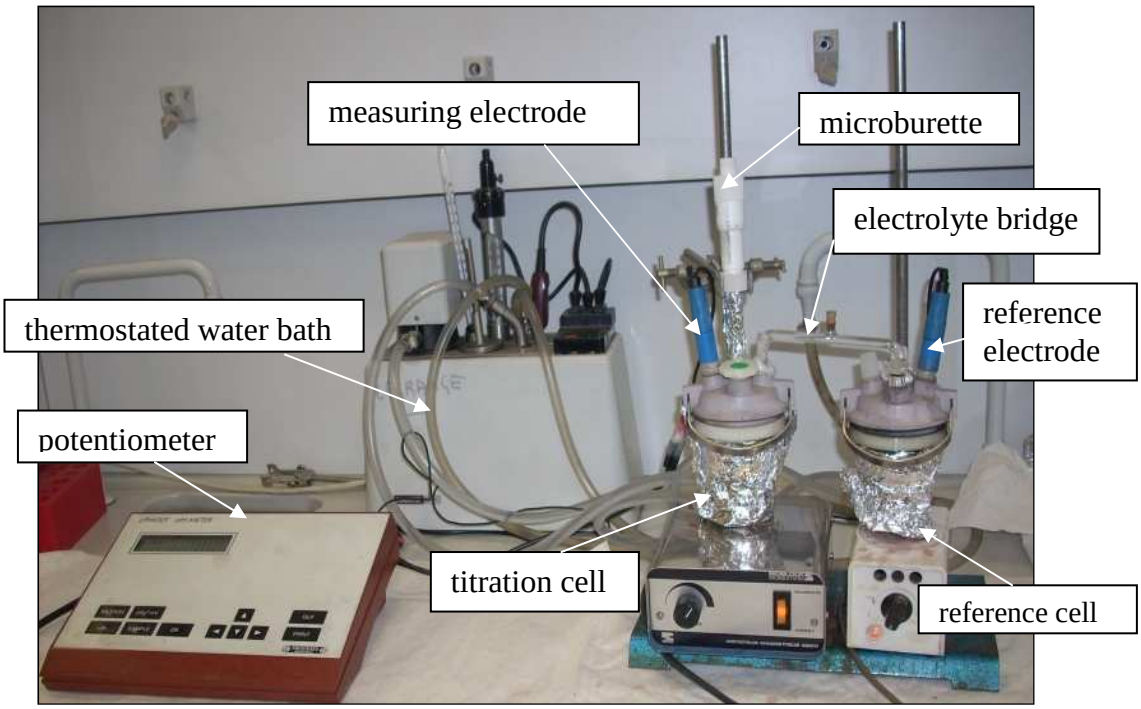


Figure III-2. Scheme of the potentiometric device used in this work

Experimental protocol

10^{-2} mol L^{-1} silver nitrate stock solutions were used. Silver solutions were protected from the light by an aluminium foil and kept in darkness. Their concentration was determined by titration with sodium chloride in water. The amide derivatives solutions were prepared in methanol or/and in acetonitrile at a concentration ~ 2.5×10^{-4} mol L^{-1} in the presence of 10^{-2} mol L^{-1} Et_4NNO_3 solution. Because of their low solubility in methanol, the thioamides derivatives were studied in acetonitrile at a concentration ~ 2.5×10^{-4} mol L^{-1}.

The concentration of free silver ions was measured with a metallic silver electrode (M 291 Ag-9, Radiometer, Copenhagen) and potentials were measured with a potentiometer (LPH 430T pH-meter). The reference electrode (Ag^+/Ag electrode) was dipped in a concentrated silver nitrate solution in methanol or acetonitrile (10^{-2} mol L^{-1}) which was in electrical contact with the sample solution by an electrolyte bridge containing 10^{-2} mol L^{-1}

Et_4NNO_3 in the adequate solvent. All potentiometric measurements were performed in a jacketed titration cell thermostated at (25.0 ± 0.1)°C and protected from the light by an aluminium foil. All titrations were carried out using a microburette with a precision of ± 0.0001 mL. The ionic strength was kept constant at $I = 10^{-2}$ mol L^{-1} using Et_4NNO_3 as supporting electrolyte.

To determine the stability constants of the Ag^+ - ligand complex, the following procedure was applied [14]. Before each experiment the silver electrode was calibrated. For this purpose, the silver electrode was placed in the reaction vessel containing 10 mL of the supporting electrolyte Et_4NNO_3 solution in methanol or acetonitrile (10^{-2} mol L^{-1}). The solution was titrated with 1 mL of an $AgNO_3$ solution of known concentration in methanol or acetonitrile and the cell potential was measured. The potential values were plotted against the logarithm of the silver nitrate concentration. Then the measuring cell was washed and 10 mL of the ligand solution in acetonitrile or methanol was placed in the reaction vessel and titrated with 1.5 mL of silver nitrate solution of known concentration and the potential was measured until $R = [Ag^+] / [L] \sim 2.5$.

The potential values obtained were treated using the program SIRKO [19] to compute the stability constants log β.

Data treatment

The program SIRKO is based on an "universal" response function and allows to calculate the stability constants by processing the data from different physico-chemical methods (spectrophotometry, potentiometry, calorimetry etc.). It is based on the general function:

$$F = Y_0 + Y_e \times \sum_{k=1}^{S} E_k \times [C_k] \times V - V_1 \times log(\sum_{k=1}^{S} EH_k \times [C_k]) \qquad \text{(III - 39)}$$

Here, the program SIRKO was used to compute the equilibrium constants from potentiometric sets of data. In that case, having defined $Y_e = 0$, $E_k = 0$, Y_0 is a constant value, and we obtain the ordinary Nernst equation.

The mathematical model of the equilibrium chemical system is defined by the number of reagents and complexes, the complexes stoichiometry and the number of mass-balance equations.

2.2.4. Microcalorimetry

Principle

Microcalorimetric titrations allow to measure the temperature changes as a function of the titrant added and to determine the values of the enthalpies of complexation (ΔH) and stability constants (β).

The quantity of heat evolved or absorbed in a microcalorimetric experiment (Q) is equal to the multiplication of the temperature change ΔT by the heat capacity of the microcalorimetric vessel (C_S):

$$Q = C_S \times \Delta T \qquad \text{(III – 40)}$$

The total amount of the heat exchanged (Q) during the titration consists of the thermal effects corresponding to the complexation ($Q_{complex}$) and to other effects which can be chemical (Q_c) or non-chemical (Q_{nc}). Non-chemical effects correspond to the heat associated with the mixing of solvents at different temperatures or solution stirring. Chemical effect correspond to the heat of dilution of the titrant, the heat of solvation, etc.

The thermal effect of the complexation is given, therefore, by the equation:

$$Q_{complex} = Q - (Q_{nc} + Q_c) \qquad \text{(III – 41)}$$

Knowing the value of the enthalpy of complexation and of the stability constant β, we can calculate the entropy of the complexation ΔS_c from the following equation:

$$\Delta G_c = \Delta H_c - T\Delta S_c \qquad \text{(III – 42)}$$

where $\Delta G_c = - RT \ln \beta$

Thermal Activity Monitor (TAM)

Calorimetric titrations were performed with a 2277 TAM thermal activity monitor under isothermal conditions. The Thermal Activity Monitor is a free-standing multichannel microcalorimeter (**Figure III-3**). The sensitivity and high level of precision of the TAM is due largely to the stability of the heat sink which surrounds the measuring cylinders. This heat sink is formed by a closed 25L thermostated water bath, maintained to $\pm 2 \times 10^{-4}$ ºC within the working range of 5-80 ºC.

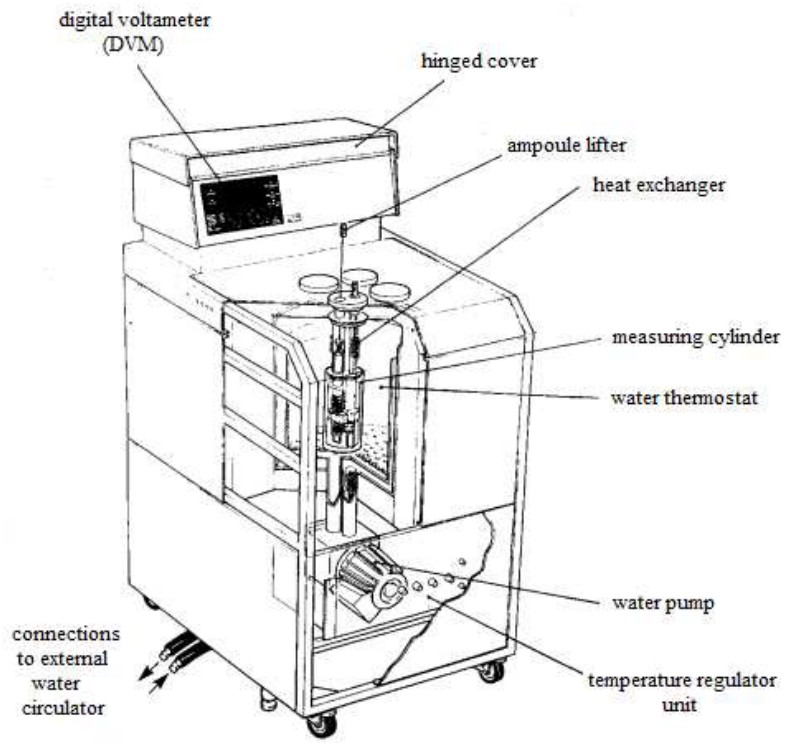


Figure III-3. Schematic representation of the Thermal Activity Monitor (TAM)

Samples are introduced in a measuring cylinder which, together with its individual signal amplifier, forms a complete measuring channel. In a cylinder, measurement takes place in a measuring cup situated between a pair of Peltier thermophile heat sensors which are in contact with a metal heat sink. The heat flow to or from the measuring cup goes through the Peltier elements which convert the heat energy into the voltage signal. As a result, the thermogram obtained represents thermal energy changes per unit of time.

Experimental protocol

Before a titration experiment, two electrical calibrations (static and dynamic) of the microcalorimeter are performed.

The static calibration is done with empty lifters and the goal is to ensure that the heat generated by the calibration resistor is equal to the heat measured by the instrument. The dynamic calibration corrects the heat flow monitored by the heat detector, for the thermal inertia of the system to increase the accuracy and shorten the time. The dynamic calibration is included in the method used for titration and is automatically performed before each experiment.

The experiments were carried out in acetonitrile with thioamides **1T, 5T-9T** against Ag^{+} cations and also with representative thioamide **5T** against Cu^{2+}, Cd^{2+} and Pb^{2+}. The titrations were carried out at 25°C on 2.5 mL of $2.5 \times 10^{-4} - 1 \times 10^{-3}$ mol L^{-1} of the ligands solution in acetonitrile using a 4 mL glass cell. The heats of complexes formation were measured after addition of 17 × 15 mL aliquots of $7 \times 10^{-4} - 3 \times 10^{-2}$ mol L^{-1} of silver, cadmium and copper nitrates in the same solvent. In the case of the titrations against Pb^{2+}, because of the low solubility of $Pb(NO_3)_2$ salt in acetonitrile above a concentration of 5×10^{-4} mol L^{-1}, the ligand concentration had to be lowered adequately to about 2×10^{-5} mol L^{-1}.

As recommended, the microcalorimeter response was controlled by the determination of the complexation enthalpy of Cs^{+} in water with 18C6 in methanol [20]. The enthalpies of complexation (ΔH) and the stability constants were derived from these data using the ligand binding analysis program DIGITAM version 4.1 [21] and after correction for the heat of dilution of the metal salts determined in separate titrations without the ligands.

Data treatment

The data obtained were treated with the DIGITAM program. In a ligand binding function, the concentrations and the volume used of both, the ligand and metal are introduced in the software. The thermal effect of the dilution process is substracted from the Q values. The suitable model can be thus defined and the equilibrium constants (β) as well as the reaction enthalpies for the overall reaction can be determined.

3. Results and discussion

3.1. Calix[4]arene-thioamide derivatives

3.1.1. Characterisation of the complexes

^{1}H NMR characterisation

The interactions with Pb^{2+} and Ag^{+} were studied by ^{1}H NMR technique with the ligand **5T**. Additionally, to prove that ligands based on secondary thioamides interact with Pb^{2+} cations, complexes of Pb^{2+} with **7T** and **9T** were prepared and characterised by ^{1}H NMR. All spectra were recorded in the mixture: $CDCl_3$/MeOD, 1/1.

The results obtained for ligand **5T** are illustrated in **Figure III-4** and presented in **Table III-2**.

The *cone* conformation of the ligand **5T** was confirmed by the presence of one singlet at 1.07 ppm corresponding to the *tert*-butyl protons, an AB system for the methylene protons at 3.18 and 4.75 ppm, one singlet at 5.15 ppm ascribed to the 8 protons of O-CH_2-C=S and one singlet at 6.84 ppm for the aromatic protons. Significant peaks shifts were observed upon addition of Pb^{2+} and Ag^{+} cations. Changes observed are due to rearrangement of the ligand upon complexation. As we can notice, the spectra of the two complexes are very different from each other.

The *tert*-butyl protons were among the least affected by the complexation and slightly shifted downfield by 0.13 and 0.07 ppm in the Pb^{2+} and Ag^{+} complexes, respectively. This can be easily explained as those protons are located far away from the cavity. Hence, they should not be as much affected as the other protons. The 8 aromatic hydrogen atoms are shifted downfield by 0.48 ppm in the Pb^{2+} complex and 0.26 ppm in the Ag^{+} complex. The AB system corresponding to the methylene protons in the Pb^{2+} complex are located at 3.62 and 4.64 ppm, whereas in the Ag^{+} complex they are placed at 3.49 and 4.46 ppm. It can be seen that in the complexes these peaks are moved closer together than in the free ligand. The singlet corresponding to the 8 protons of O-CH_2-C=S also affected by the complexation moves downfield from 5.15 for the free ligand to 5.16 and 5.34 ppm in the presence of Pb^{2+} and Ag^{+}, respectively. All signals of the thioamide NCH_2 protons are significantly shifted as well. In the free ligand, the two singlets corresponding to 24 protons at 1.47 (8 protons) and 1.68 ppm (16 protons) give two singlets in the spectrum of the complexes situated at 1.93

ppm (8 protons) and 1.92 (16 protons) for Pb^{2+} and at 1.70 (16 protons) and 1.92 ppm (8 protons) for Ag^{+} .

In the case of Ag^{+} complex, the main signals affected by the complexation were those of the $OCH_2C{=}S$ groups suggesting that sulphur atoms and ethereal oxygen atoms are involved in complexation. Those peaks are not strongly affected by the complexation in the case of Pb^{2+} complex ($\Delta\delta$ = -0.01). One should take into account, that the chemical shift observed is an average value obtained for the protons of the OCH_2CS groups. The unsymmetric nature of the complex may explain the different chemical shifts observed in the Pb^{2+} complex spectrum and in the Ag^{+} complex spectrum, where all thiocarbonyl groups are probably involved in complexation. Significant shifts were also observed for peaks corresponding to the AB system of the methylene bridge protons and to the aromatic protons of the calixarene scaffold due to the conformational changes in the ligand structure upon metal bonding. Thiocarbonyl sulphur atoms converge to the centre of the cavity, leading to the electron density reduction of the aromatic protons. As a consequence, protons are deshielded and shifted downfield.

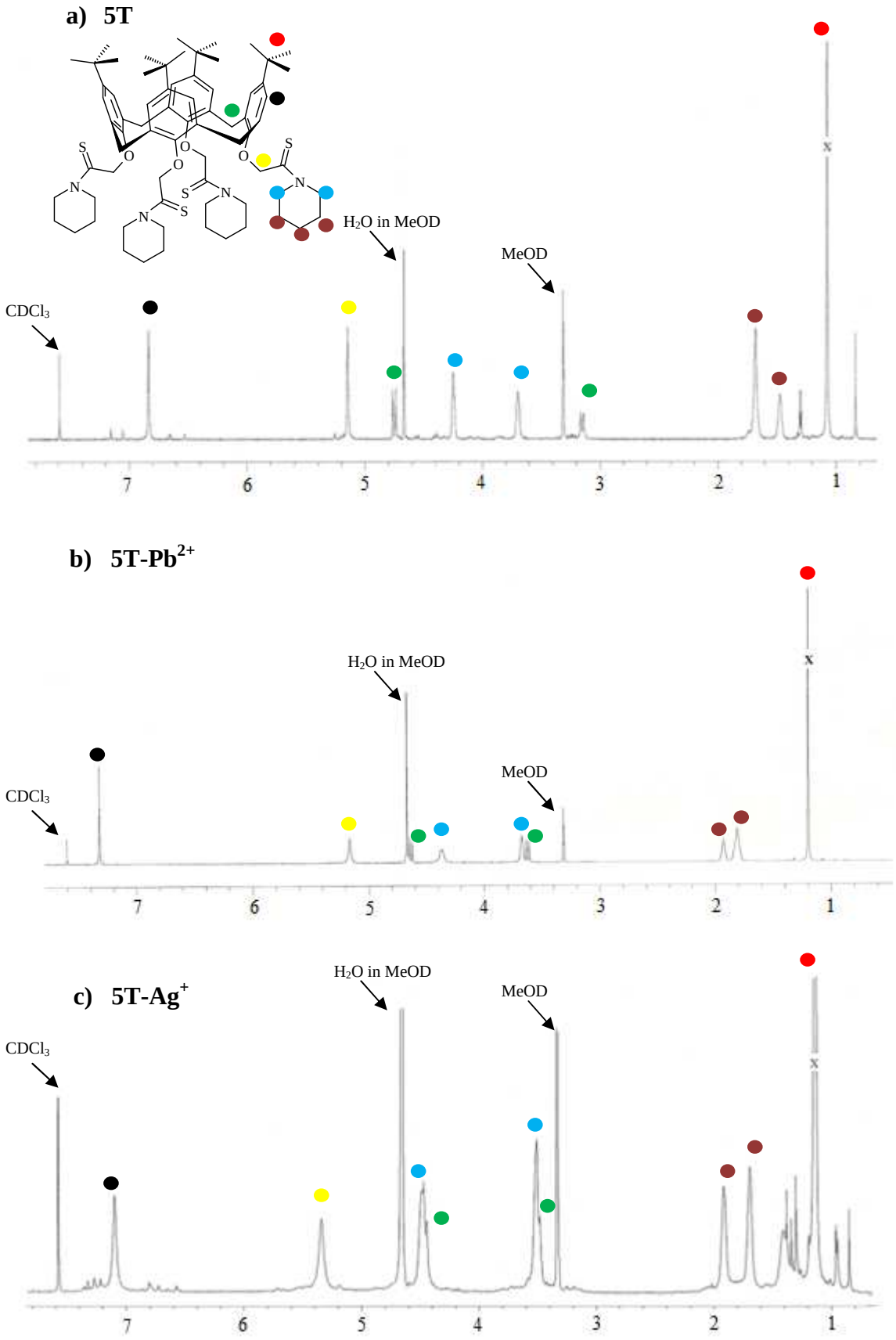


Figure III-4. ^{1}H NMR spectra ($CDCl_3$/MeOD, 1/1) of the free ligand **5T** (a) and of **5T** in the presence of Pb^{2+} (b) and Ag^{+} (c)

Table III-2. Changes (Δδ) of proton chemical shifts (δ) [ppm] in the spectrum of ligand **5T** upon addition of Pb^{2+} and Ag^{+} ($CDCl_3$/MeOD, 1/1)

	***tert*-butyl** **36H**	**$(CH_2)_3$** **24H**	**$N(CH_2)_2$**		**$ArCH_2Ar$**		**$OCH_2C{=}S$** **8H**	**ArH** **8H**
			8H	**8H**	**$4H_{eq}$**	**$4H_{ax}$**		
δ (**5T**)	1.07 (s)	1.47 8H (bs) and 1.68 16H (bs)	3.70 (bs)	4.25 (bs)	3.18 (d)	4.75 (d)	5.15 (s)	6.84 (s)
δ (**5T-Pb^{2+}**)	1.20 (s)	1.92 16H (bs) and 1.93 8H (bs)	3.67 (bs)	4.37 (bs)	3.62 (d)	4.64 (d)	5.16 (s)	7.32 (s)
Δδ	-0.13	-0.46 (8H) and -0.24 (16H)	+0.03	-0.12	-0.44	+0.11	-0.01	-0.48
δ (**5T-Ag^{+}**)	1.14 (s)	1.70 16H (bs) and 1.92 8H (bs)	3.51 (bs)	4.49 (bs)	3.49 (d)	4.46 (d)	5.34 (s)	7.10 (s)
Δδ	-0.07	-0.24 (8H) and -0.02 (16H)	+0.19	-0.24	-0.31	+0.29	-0.19	-0.26
s – singlet, bs – broad singlet, d - doublet								

Pb^{2+} complexes with **7T** and **9T** were prepared and analysed by ^{1}H NMR spectroscopy.

Figure III-5 and **Table III-3** presents the changes observed upon addition of Pb^{2+} to the ligand **7T**. Peaks characteristic for a *cone* conformation can be found, although they are significantly shifted compared to the free ligand. The singlet of the *tert*-butyl protons was slightly shifted downfield ($\Delta\delta$ = 0.12 ppm). The singlet corresponding to the 8 aromatic hydrogen atoms are shifted downfield from 6.82 to 7.29 ppm. Interestingly, only the signal of the equatorial protons corresponding to an AB system of the methylene atoms were shifted downfield ($\Delta\delta$ = 0.26 ppm), whereas no shifts of axial protons were observed. Moreover, 8 protons of $N\underline{CH_2}CH_3$ groups were also not disturbed upon complexation. In contrary, 12 protons in the same $NCH_2\underline{CH_3}$ groups were slightly affected and the signal is shifted downfield ($\Delta\delta$ = 0.12-0.14 ppm). The singlet of the 8 protons of O-CH_2-C=S was moved downfield from 4.86 to 5.14 ppm.

Changes observed upon complexation of Pb^{2+} with ligand **9T** are illustrated in **Figure III-6** and the chemical shifts are presented in **Table III-4.** The singlets corresponding to the *tert*-butyl protons and to the 8 aromatic hydrogen atoms were slightly shifted downfield ($\Delta\delta$ = 0.11 ppm and 0.47 ppm, respectively). The 8 protons of O-CH_2-C=S are also affected by the complexation and the corresponding singlet was moved downfield from 4.60 to 5.10 ppm. The AB system corresponding to the methylene protons in the Pb^{2+} complex are shifted downfield and they are located at 3.43 and 4.39 ppm. The signals of the 8 protons of $N\underline{CH_2}CH_2ArH$ and of the 8 protons of $NCH_2\underline{CH_2}ArH$ were moved downfield ($\Delta\delta$ = 0.14 and 0.05 ppm, respectively). The least affected peaks were those of the 20 aromatic protons from $NCH_2CH_2Ar\underline{H}$ groups, as expected from their position far away from the cavity site.

In both cases, the main signals affected by the complexation were those of the OCH_2C=S groups what suggests that sulphur and ethereal oxygen atoms are involved in the complexation. A significant shift is also observed for the aromatic protons of the calixarene scaffold due to the conformational changes in the ligand structure upon metal bonding.

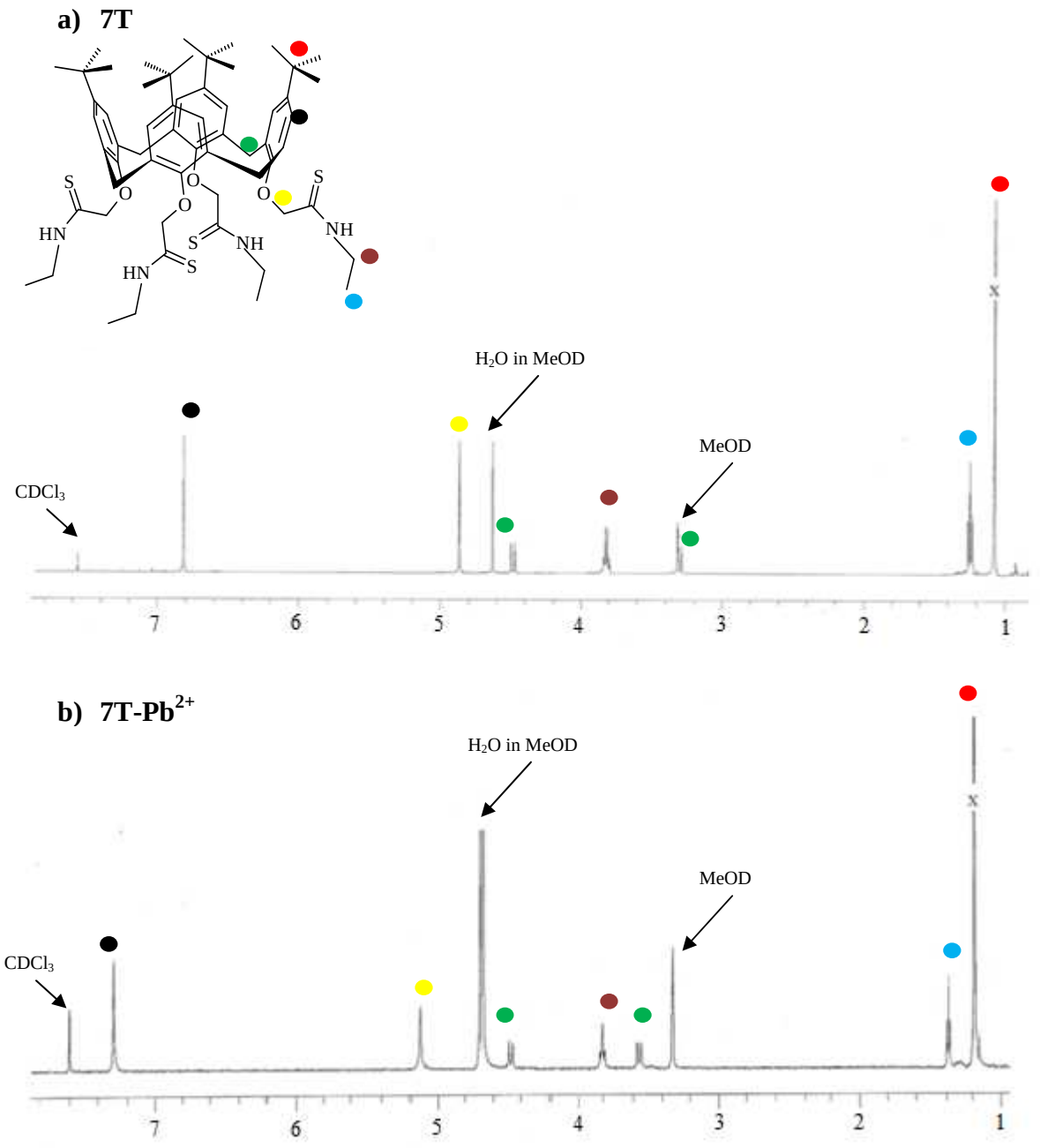


Figure III-5. ^{1}H NMR spectra ($CDCl_3$/MeOD, 1/1) of the free ligand **7T** (a) and of **7T** in the presence of Pb^{2+} (b)

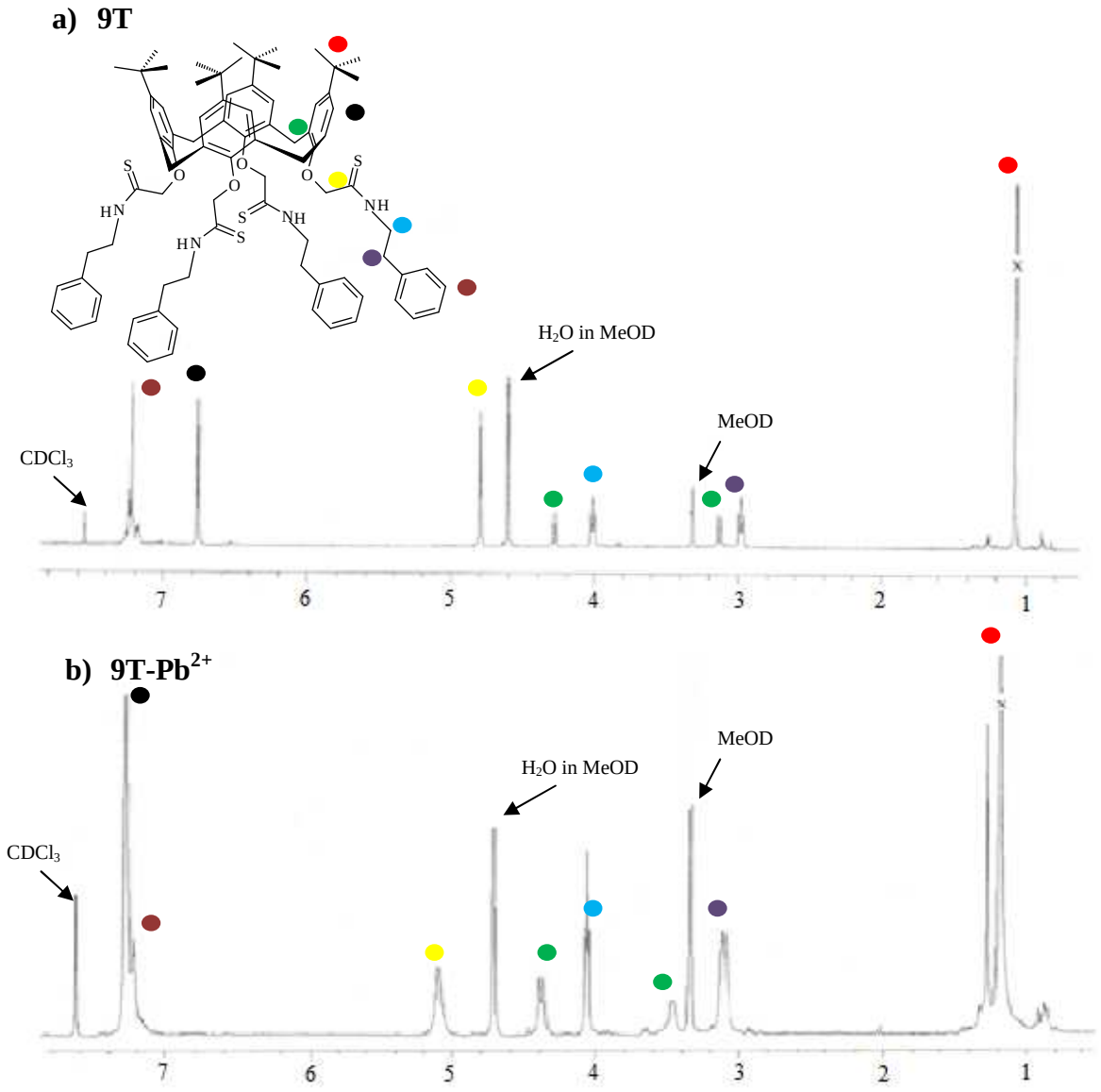


Figure III-6. ^{1}H NMR spectra ($CDCl_3$/MeOD, 1/1) of the free ligand **9T** (a) and of **9T** in the presence of Pb^{2+} (b)

Table III-3. Changes (Δδ) of proton chemical shifts (δ) [ppm] in the spectrum of ligand **7T** upon addition of Pb^{2+} ($CDCl_3$/MeOD, 1/1)

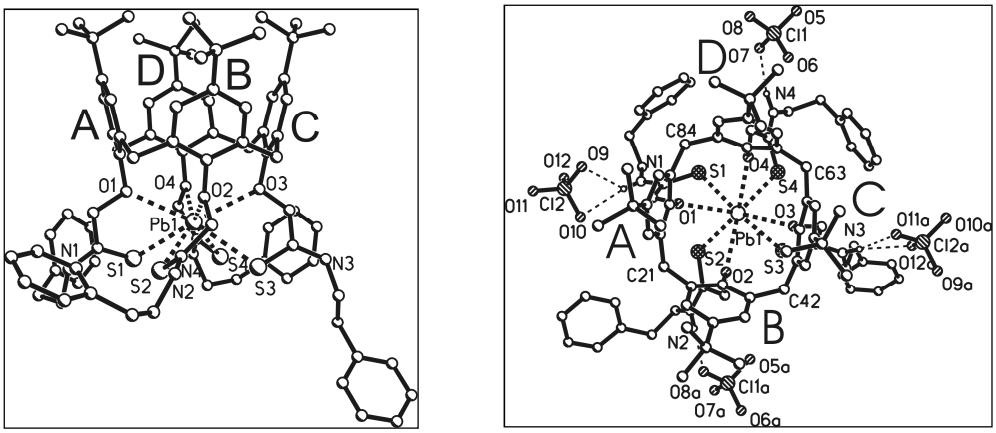
	***tert*-butyl** **36H**	**-NH-CH_2-$\underline{CH_2}$-CH_3** **12H**	**-NH-$\underline{CH_2}$-CH_3** **8H**	**$ArCH_2Ar$**		**$OCH_2C{=}S$** **8H**	**ArH** **8H**
				$4H_{eq}$	**$4H_{ax}$**		
δ (**7T**)	1.07 (s)	1.23-1.26 (m)	3.80-3.84 (m)	3.30 (d)	4.48 (d)	4.86 (s)	6.82 (s)
δ (**7T-Pb^{2+}**)	1.19 (s)	1.35-1.40 (m)	3.80-3.84 (m)	3.56 (d)	4.48 (d)	5.14 (s)	7.29 (s)
Δδ	-0.12	-0.12 to -0.14	0	-0.26	0	-0.28	-0.47
s – singlet, d – doublet, m - multiplet							

Table III-4. Changes (Δδ) of proton chemical shifts (δ) [ppm] in the spectrum of ligand **9T** upon addition of Pb^{2+} ($CDCl_3$/MeOD, 1/1)

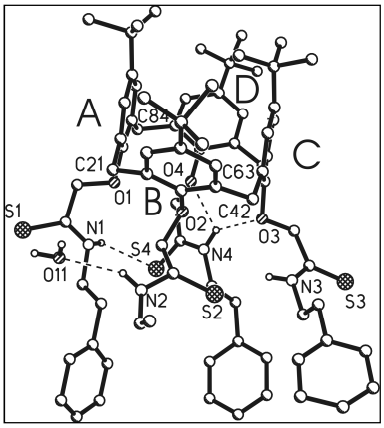
	***tert*-butyl** **36H**	**-NH-CH_2-$\underline{CH_2}$-ArH** **8H**	**-NH-$\underline{CH_2}$-CH_2-ArH** **8H**	**-NH-CH_2-CH_2-Ar$\underline{H}$** **20H**	**$ArCH_2Ar$**		**$OCH_2C{=}S$** **8H**	**ArH** **8H**
					$4H_{eq}$	**$4H_{ax}$**		
δ (**9T**)	1.07 (s)	2.98 (t)	4.01 (t)	7.21-7.25 (m)	3.13 (d)	4.28 (d)	4.60 (s)	6.76 (s)
δ (**9T-Pb^{2+}**)	1.18 (s)	3.12 (bs)	4.06 (t)	7.18-7.23 (m)	3.43 (d)	4.39 (d)	5.10 (s)	7.23 (s)
Δδ	-0.11	-0.14	-0.05	0.03-0.02	-0.3	-0.11	-0.5	-0.47
s – singlet, bs – broad singlet, d – doublet, t – triplet, m - multiplet								

X-ray crystal structures analysis

In order to obtain solid complexes of Pb^{2+}, Ag^{+}, Cd^{2+} and Cu^{2+} with some thioamides derivatives synthesised, crystallisation was performed. With this aim, the thioamide was dissolved in a minimum amount of CH_2Cl_2. Subsequently, a methanol solution of an appropriate salt was added. The mixture was kept at room temperature for several weeks. It was possible to obtain two X-ray crystal structures of Pb^{2+} complexes with calix[4]arene-thioamides **5T** and **9T** [22, 23]. To our best knowledge, these structures were obtained for the first time. The X-ray crystal structures of the free ligand **9T** and of the **9T-Pb^{2+}** complex are shown in **Figure III-7**.



a) **9T-Pb^{2+}** b) **9T-Pb^{2+}**

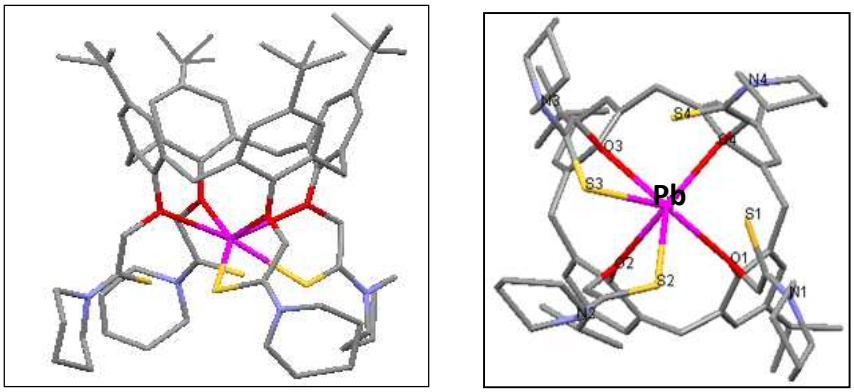


c) **9T**

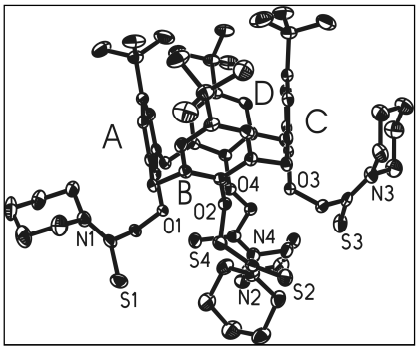
Figure III-7. X-ray crystal structures of: a) the Pb^{2+} complex with **9T** (a side view); b) an upper rim view of **9T-Pb^{2+}**; c) the free ligand **9T** (a side view); in order to show hydrogen bonding network two neighbour symmetry equivalents of perchlorate anions are drawn [22]

This is the second example of a X-ray structure of a lead perchlorate complex with a calix[4]arene thioamide derivative. The Pb-complex of calixarene-diethyl thioamide (**1T-Pb^{2+}**) described in [24] contained (in average) half of water molecule trapped in the cone void. Both structures show some similarities. The Pb^{2+} cation in **9T-Pb^{2+}** is bound to four ethereal oxygen atoms and four thiocarbonyl sulphur atoms. The *cone* conformation of **9T-Pb^{2+}** is more regular (less pinched) than of the free ligand **9T** (**Figure III-7**). Notable difference in the conformation between the complex **9T-Pb^{2+}** and the ligand **9T** is the orientation of aromatic rings **B** and **D** which in the **9T-Pb^{2+}** are not perpendicular anymore (dihedral angle of 52.7(9)^{o}). The dihedral angles between rings **A**–**D** are quite uniform and are in the range of 62.9–77.4^{o}. The N–H groups, being hydrogen bond donors, are oriented outside. The perchlorate anions are located in positions optimal for intermolecular hydrogen bonding of the N–H...O type.

Some attempts were done to determine the parameters of the structure of the Pb^{2+} complex with ligand **5T.**



a) **5T-Pb^{2+}** b) **5T-Pb^{2+}**

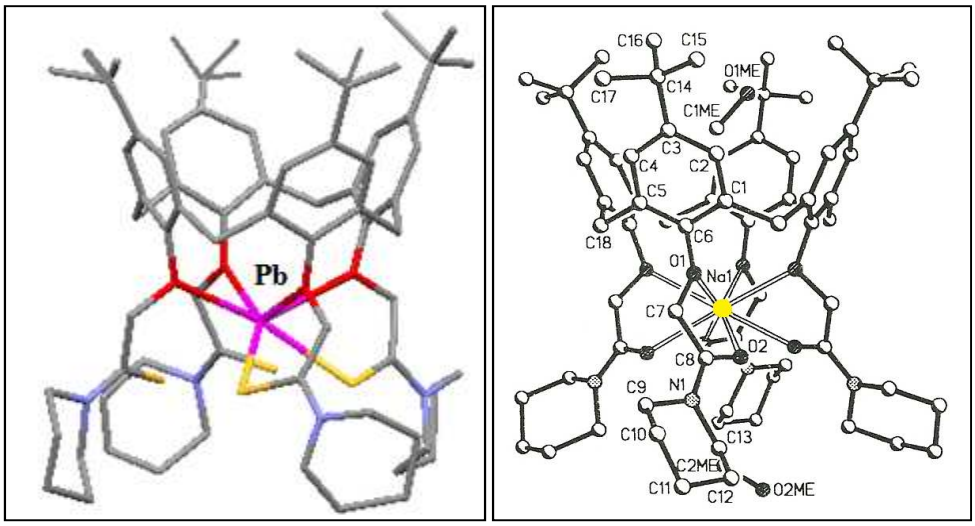


c) **5T**

Figure III-8. X-ray crystal structures of: a) the Pb^{2+} complex with **5T** (a side view); b) an upper rim view of **5T-Pb^{2+}** complex; c) the free ligand **5T** (a side view) [23]

However, due to the low quality of the crystals, it was impossible to solve the structure completely. Nevertheless, it appears that the *cone* conformation of the complex is more uniform than that of the free ligand (**Figure III-8**), the dihedral angles being ca. 37-44°. It seems that in this structure the lead atom is 6-coordinated and strongly bound to two sulphur and four oxygen atoms. The two distal thiopiperidine moieties are no more bent up in the complex structure. The Pb-S and Pb-O distances are not uniform making the complex rather unsymmetric.

Figure III-9 allows the comparison of the X-ray crystal structure obtained for the Pb^{2+} complex with ligand **5T** and the Na^{+}complex with the analogous amide derivative **5A**.



a) **5T-Pb^{2+}** b) **5A-Na^{+}**

Figure III-9. Comparison of the X-ray crystal structures of: a) **5T-Pb^{2+}** and b) **5A-Na^{+}** [25]

The notable difference is that the Pb^{2+} cation in the complex with **5T** is bound to four ethereal oxygen atoms and two sulphur atoms, whereas in the complex with **5A**, Na^{+} is eight coordinated and bound to four ethereal oxygen atoms and four carbonyl oxygen atoms. However, one can notice, that in both structures, the arrangement of piperidinyl substituents is quite similar with all four groups forming a pseudo-cavity suitable for cation encapsulation.

3.1.2. Liquid – liquid extraction studies

The extractive properties of new calix[4]arene-thioamides (**2T-9T**) were studied towards heavy metal cations (Pb^{2+}, Ag^{+}, Cd^{2+}), transition metal cations (Cu^{2+} and Zn^{2+}) and Na^{+}, Ca^{2+}, Gd^{3+}, chosen as representatives for alkali, alkaline earth and lanthanide cations. Results are given in **Table III-5**. Data were compared with those obtained for ligand **1T**, (resynthesised in this work) and ligand **III** which are also discussed in Chapter I.

Table III-5. Percentage extraction (%E)* of metal picrates ($C_M = 2.5 \times 10^{-4}$ mol L^{-1}) with ligands **1T-9T** ($C_L = 2.5 \times 10^{-4}$ mol L^{-1}) from water into dichloromethane (organic to aqueous ratio o/a = 1, T = 20°C)

ligand/cation	Na^{+}	Ca^{2+}	Cu^{2+}	Zn^{2+}	Cd^{2+}	Ag^{+}	Pb^{2+}	Gd^{3+}
III[a]	4	nd	47	nd	9	98	96	nd
1T[a,b]	7	≤ 1	19.0	≤ 1	8	80.0	56.0	≤ 1
2T	2.8	nd	28.1	nd	nd	84.9	36.1	nd
3T	1.8	nd	nd	nd	nd	87.5	42.1	nd
5T[c]	8.5	3.2	29.4	3.6	2.2	86.8	66.4	2.6
6T[b]	6.3	4.6	14.5	1.6	≤ 1	99.2	50.9	4.8
7T[b]	≤ 1	≤ 1	1.9	≤ 1	≤ 1	92.1	≤ 1	≤ 1
8T[b]	2.0	2.8	2.9	≤ 1	1.3	85.5	≤ 1	1.6
9T[b]	≤ 1	1.6	2.3	≤ 1	1.4	98.0	≤ 1	≤ 1

*values with uncertainties less than 5%
[a] data from ref. [24], [b] data from ref. [22], [c] data from ref. [23]
"nd" - not determined

It can be clearly seen that the thioamides presented here are weak extractants for alkali, alkaline earth and lanthanide cations (at least for Gd^{3+}). This can be explained by the presence in the structure of soft sulphur atoms having a preference for soft cations according to the Pearson's HSAB theory [26]. They all extract almost quantitatively Ag^{+} (%E ≥ 80), however, no specific relationship between the extraction efficiency and the thioamide structure could be noticed for this cation. The extraction level of Pb^{2+} depends strongly on the thioamide function (secondary or tertiary). Ligands **1T-6T**, bearing tertiary thioamide moieties are good extractants of Pb^{2+} (%E > 36), whereas the secondary thioamide derivatives (**7T-9T**) are totally ineffcetive (%E ≤ 1). The highest extraction level is obtained with ligand

5T bearing cyclic thiopiperidine moieties. It is, however, not as good as the structurally similar ligand **III**, which extracts Pb^{2+} almost quantitatively (96%) [24]. We can see that the increase of the carbon chain length on the thioamide substituents (ligands **2T** and **3T**) results in poorer Pb^{2+} extraction compared to **1T**. Among the transition metal ions, only Cu^{2+} is fairly extracted by the tertiary thioamide derivatives (**2T-6T**). The secondary thioamide derivatives (**7T-9T**) were inefficient with this cation.

The extraction sequence of transition and heavy metal cations with tertiary thioamides is as follows:

$$\%E\ (Ag^{+}) > \%E\ (Pb^{2+}) > \%E\ (Cu^{2+}) > \%E\ (Cd^{2+})$$

As it was demonstrated in Chapter I, calixarenes appended with secondary amide moieties, are weak extractants, mainly due to intra- and intermolecular hydrogen bonding combined with the high hydrophicility of the extracted complexes [27]. It has also been reported that intramolecular hydrogen bonding in calix[4]arenes bearing amino acid moieties affected the extractability towards metal ions [28]. Thioamides are weak hydrogen bond acceptors but strong hydrogen bond donors in comparison to amides due to the electronegativity of the sulphur atom [29]. Therefore, secondary thioamides should have a strong ability to form hydrogen bonds. This is supported by the observation in the crystal structures of ligands **7T** and **9T** of several intramolecular hydrogen bonds (see Chapter II, **Table II-2**). This fact may explain very low extraction efficiency of ligands **7T-9T** for Pb^{2+} and other transition and heavy metal cations.

It is worth to point out, that tertiary thioamides like **5T** and **6T** may have potential application in separation process of Pb^{2+} in the presence of Na^{+} or Cd^{2+} cations, which are inefficiently extracted.

3.1.3. Spectrophotometric studies in acetonitrile

UV spectrophotometric titrations were carried out only in acetonitrile for Na^{+}, Cs^{+}, Ag^{+}, Cd^{2+}, Pb^{2+} and Cu^{2+} with thioamides **1T-3T, 5T-9T** because these ligands are not soluble enough in methanol.

Upon addition of cesium and sodium salts, ligands spectra remained practically unchanged, what indicated no or very little complexation of these cations with these tested ligands. On the contrary, significant spectral changes were observed upon addition of silver, cadmium, lead and copper salts.

Complexation of Ag^+

An example of spectral changes of ligand **6T** upon addition of Ag^+ is shown in **Figure III-10**. They are characterised by an increase of the absorbance until a ratio close to 1 confirming the formation of a ML complex. Very little changes can be noticed above R=1. They are characterised by the decrease of absorbance until a ratio about 2. It was calculated that those changes did not correspond to the dilution effect of the ligand sample. They rather suggest the M_2L complex formation in solution simultaneously.

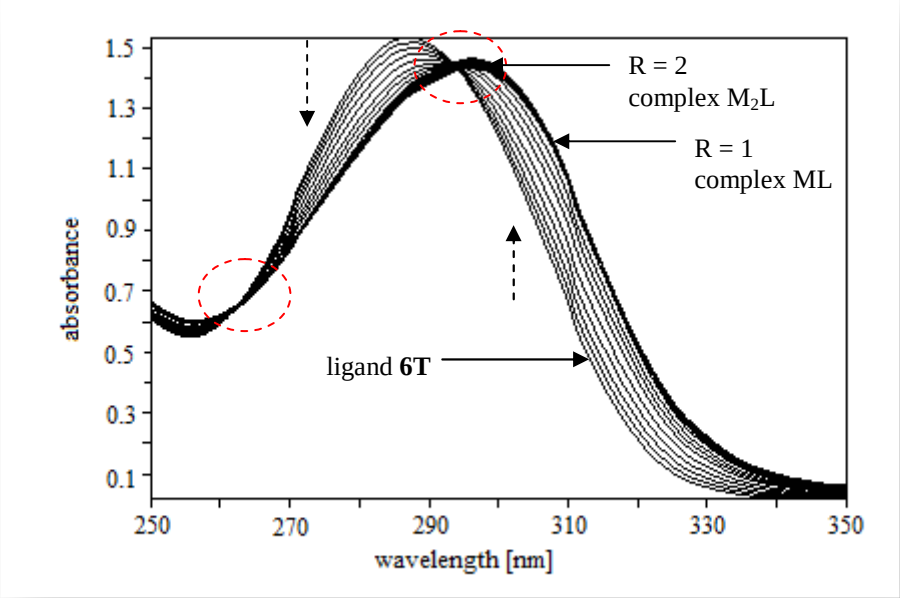
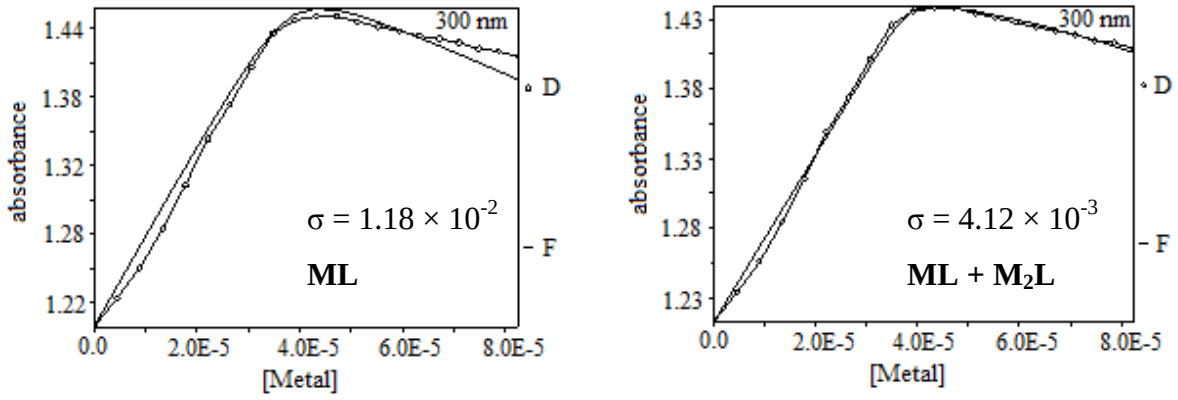


Figure III-10. Changes in the UV spectrum of **6T** upon addition of $AgNO_3$ in acetonitrile, I = 10^{-2}mol L^{-1} Et_4NNO_3 ($C_L = 4 \times 10^{-5}$mol L^{-1}, $0 \leq R \leq 2.26$)

The interpretation of these spectra using the program SPECFIT confirmed that the ML complex is accompanied with a small quantity of M_2L complex. The standard deviation on the absorbances (σ) presented in **Figure III-11** is smaller and the fit is improved when taking into account two ML and M_2L complexes existing simultaneously in solution instead of assuming a unique ML complex. This situation was found for all the thioamides studied.



a) **b)**

Figure III-11. Experimental and calculated absorbances (at 300 nm) *vs.* the metal cation concentration for the complexation of Ag^{+} with **6T** assuming the formation of a ML complex a) or ML + M_2L species b)

Complexation of Pb^{2+}

Notable spectral changes upon addition of Pb^{2+} were observed in the case of the tertiary thioamides (**1T-3T, 5T-6T**), whereas spectra of ligands based on secondary thioamide moieties (**7T-9T)** remained practically unchanged. That could indicate no complexation of Pb^{2+} with those ligands what is in accordance with the extraction results. However, once should remember that significant proton peaks shifts were noticed in those ligands ^{1}H NMR spectra upon addition of Pb^{2+} which is an evidence of ligands-Pb^{2+} interactions. Confirmation of these interactions is obviously the X-ray crystal structure of a Pb^{2+} complex with the ligand **9T**. It should be taken into account that no extraction, or no UV spectral changes does not always lead to exclude complex formation (e. g. in the solid state). Such interactions in these cases were expected as the presence of soft sulphur atoms enhances the possibility of complex formation with soft cations such as Pb^{2+} or Ag^{+}.

The examples of ligands **5T** and **6T** spectral changes upon addition of Pb^{2+} are depicted in **Figures III-12** and **III-13**, respectively. From **Figure III-12** we can see that the spectral changes increase until a ratio close to 0.5, indicating the formation of a ML_2 complex. No changes were observed upon further Pb^{2+} additions.

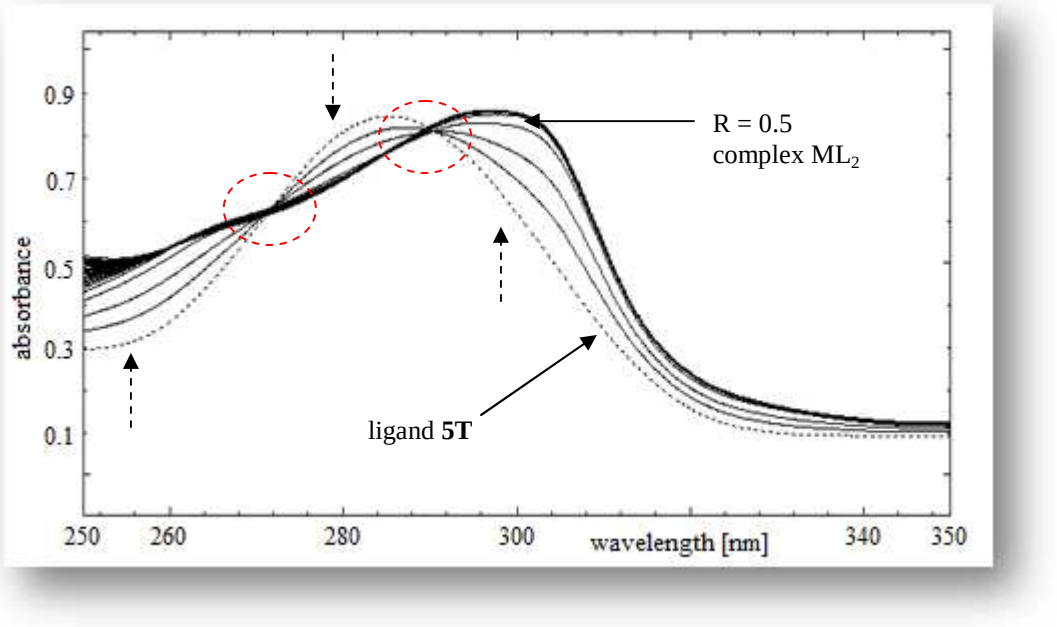


Figure III-12. Changes in the UV spectrum of **5T** upon addition of $Pb(NO_3)_2$ in acetonitrile, $I = 10^{-2}$mol L^{-1} Et_4NNO_3 ($C_L = 2 \times 10^{-5}$mol L^{-1}, $0 \leq R \leq 3.15$)

Such spectral changes were also observed for ligands **1T** and **3T**. A ML_2 complex of Pb^{2+} was found for the majority of tertiary thioamides, except for ligand **2T** for which ML and M_2L complexes are formed. In the case of ligands **3T** and **6T**, the ML_2 complex is accompanied with a ML species.

As we can notice in **Figure III-13** the isosbestic point until the ratio R = 0.5 suggests the formation of a ML_2 complex. However, the spectral changes end at a ratio close to 1 indicating the existence of a second ML species in solution. Program SPECFIT confirmed those assumptions. **Figure III-14** allows the comparison of the fits obtained with the two models ($ML+ML_2$) and ML_2 alone (found for the majority of thioamides). The experimental curve perfectly overlies the theoretical calculations for the ML + ML_2 model, whereas the fit for the ML_2 model alone is by far less good.

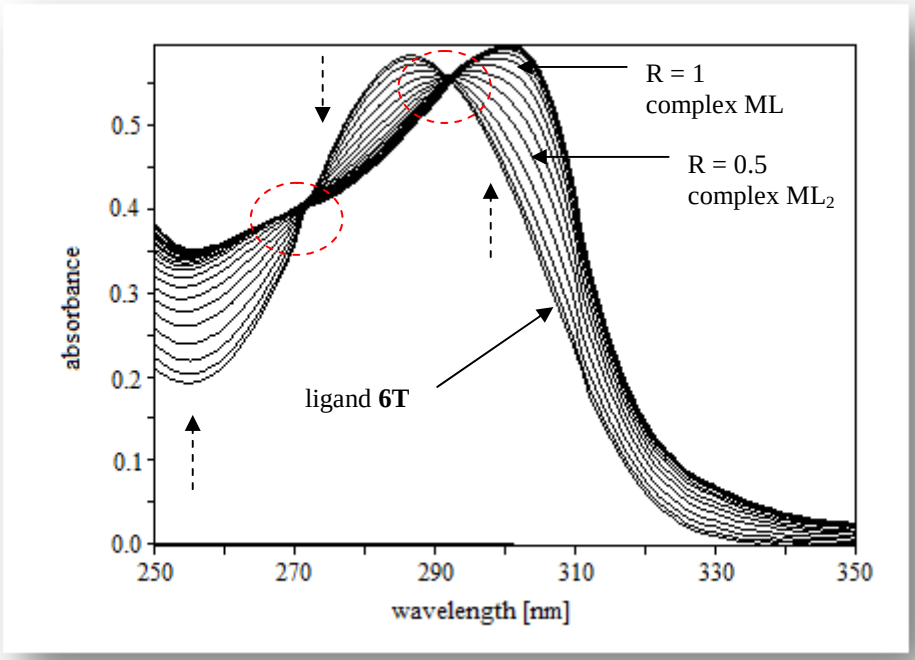
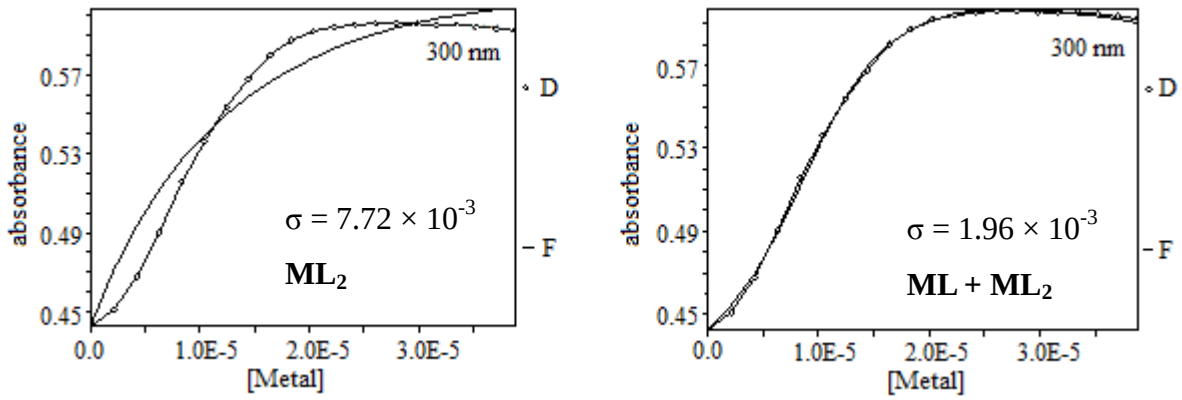


Figure III-13. Changes in the UV spectrum of **6T** upon addition of $Pb(NO_3)_2$ in acetonitrile, $I = 10^{-2}$mol L^{-1} Et_4NNO_3 ($C_L = 1.5 \times 10^{-5}$mol L^{-1}, $0 \leq R \leq 2.84$)



a) **b)**

Figure III-14. Experimental and calculated absorbances (at 300 nm) *vs.* the metal cation concentration for the complexation of Pb^{2+} with **6T** assuming the formation of a ML complex a) or ML + ML_2 species b)

Complexation of Cu^{2+}

Only the spectra of the ligands based on tertiary thioamides changed upon addition of Cu^{2+}. Practically no changes were observed in the spectra of ligands **7T-9T** appended with secondary thioamides moieties. This confirms, in a way, extraction results and indicate no or very little complexation of Cu^{2+} cations with these ligands. The example of the spectral changes undergone by the ligand **5T** upon addition of Cu^{2+} is presented in **Figure III-15**. They are characterised by a decrease of the absorbance until a ratio close to 0.5 suggesting ML_2 complex formation. Similar spectral changes were observed for other tertiary thioamides and ML_2 complexes were found.

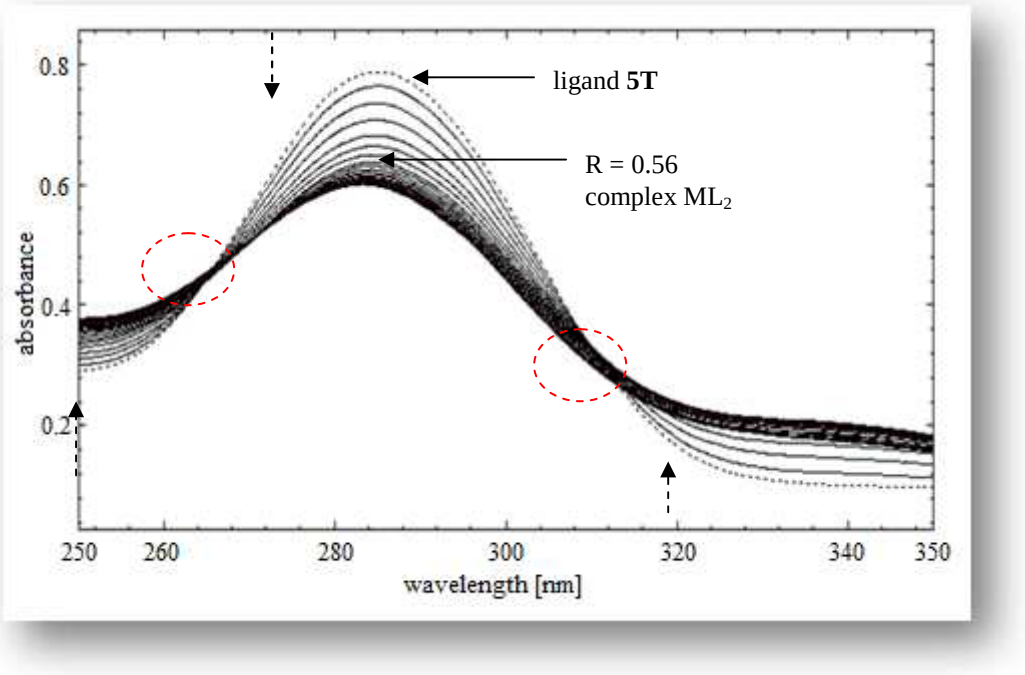


Figure III-15. Changes in the UV spectrum of **5T** upon addition of $Cu(NO_3)_2$ in acetonitrile, $I = 10^{-2}$mol L^{-1} Et_4NNO_3 ($C_L = 2 \times 10^{-5}$mol L^{-1}, $0 \leq R \leq 1.61$)

Complexation of Cd^{2+}

Similarly, small though significant changes in the ligand spectrum upon additions of Cd^{2+} were noted only in the case of the tertiary thioamides. The spectral changes of ligand **1T** upon addition of Cd^{2+} are shown in **Figure III-16** as an example. They are characterised by an increase of the absorbance until a ratio close to 0.5 suggesting ML_2 complex formation. It is worth to add that these changes appeared only when working with an excess of Cd^{2+}, ($R = [Cd^{2+}]/[L]$ at least 3). Interestingly, the spectral changes during complexation are strongly

shifted appearing only below 280 nm in comparison to the typical spectra obtained upon Ag^+, Pb^{2+} and Cu^{2+} additions, where the spectra change in the whole range of wavelength. This fact may suggest that Cd^{2+} occupies another place in the complex structure. Similar spectral changes were observed with the other tertiary thioamides and ML_2 complexes were found.

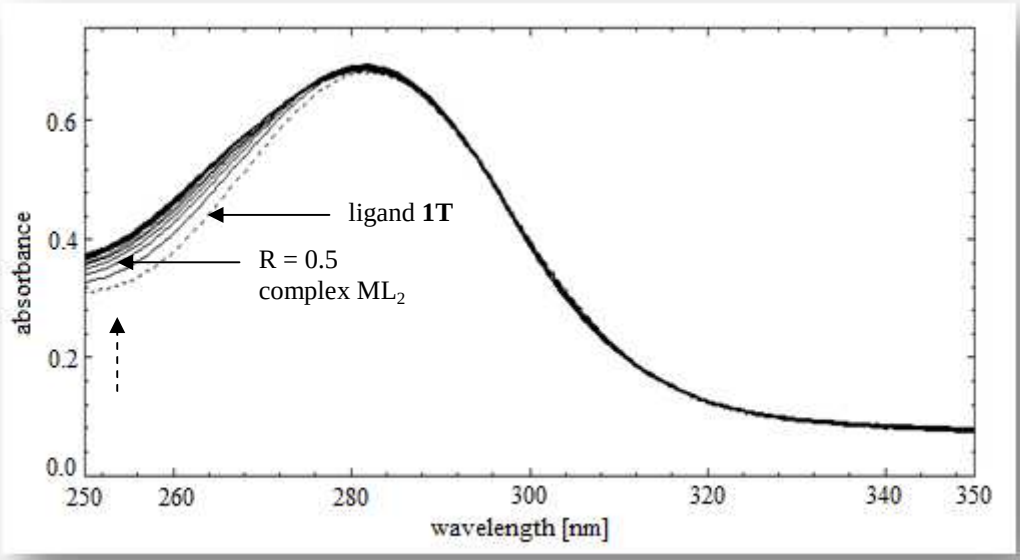


Figure III-16. Changes in the UV spectrum of **1T** upon addition of $Cd(NO_3)_2$ in acetonitrile, $I = 10^{-2}$mol L^{-1} Et_4NNO_3 ($C_L = 2 \times 10^{-5}$mol L^{-1}, $0 \leq R \leq 3.11$)

The overall stability constants of Ag^+, Pb^{2+}, Cd^{2+} and Cu^{2+} complexes with calix[4]arene-thioamides **1T-3T, 5T-9T,** determined by UV absorption spectrophotometry are given in **Table III-6**.

The most stable complexes are formed with Ag^+ cations ($\log \beta_{ML} > 6$). This can be easily explained by the strong affinity of soft sulphur atoms for soft Ag^+ cations (according to the Pearson's HSAB theory [26]). Tertiary thioamides form the most stable complexes with Ag^+ ($\log \beta = 7.1$ with ligands **1T, 5T** and **6T**, $\log \beta = 7.8$ with ligand **2T** and $\log \beta = 6.39$ with **3T**). Among the secondary thioamides (**7T-9T**), the structurally simplest ligand **7T**, forms the strongest complex with high stability constants, comparable with those obtained with tertiary thioamides. Still strong complexes, but with about one log unit lower stability constants, are formed with ligands **8T** and **9T** possessing bulky, secondary thioamide moieties.

Table III-6. Overall stability constants (log $\beta \pm \sigma$*) of Ag^+, Pb^{2+}, Cu^{2+} and Cd^{2+} complexes with ligands **1T-3T, 5T-9T** (acetonitrile, T = 25°C, $I = 10^{-2}$ mol L^{-1} Et_4NNO_3)

ligand	complexes	Ag^+	Pb^{2+}	Cu^{2+}	Cd^{2+}
1T	ML	7.1 ± 0.5			
	ML_2		10.6 ± 0.4	11.3 ± 0.4	8.9 ± 0.4
	M_2L	11.41 ± 0.08			
2T	ML	7.8 ± 0.8	3.95 ± 0.05		
	ML_2			10.0 ± 0.2	9.325 ± 0.007
	M_2L	12.1 ± 0.9	9.1 ± 0.1		
3T	ML	6.39 ± 0.09	5.5 ± 0.3		
	ML_2		10.5 ± 0.3	9.0 ± 0.2	9.2 ± 0.3
	M_2L	9 ± 1			
5T [a]	ML	7.1 ± 0.3			
	ML_2		11.5 ± 0.2	10.4 ± 0.1	8.6 ± 0.2
	M_2L	11.9 ± 0.8			
6T	ML	7.1 ± 0.5	6.4 ± 0.1		
	ML_2		11.2 ± 0.4	8.9 ± 0.2	-
	M_2L	11.7 ± 0.5			
7T	ML	7.1 ± 0.5	-		
	M_2L	11.3 ± 0.5			
8T	ML	6.4 ± 0.8	-		
	M_2L	10.6 ± 0.2			
9T	ML	6.1 ± 0.2	-		
	M_2L	10.3 ± 0.4			

* standard deviation of at least two independent experiments
"-" no significant spectral changes
[a] data published in [23]

Figure III-17 allows the comparison of the stability constants of the ML_2 complexes of Pb^{2+}, Cu^{2+} and Cd^{2+}. With ligands **3T, 5T** and **6T**, the most stable complexed are formed with Pb^{2+} cations what is in agreement with the extraction data. The highest stability constants of Pb^{2+} complexes are ascribed to ligands **5T** and **6T** with quite similar values (log β_{ML2} = 11.5 and 11.2, respectively). The structurally different ligands **1T** and **3T** form Pb^{2+} complexes whose stability constants are about one order of log unit lower than those determined with **5T** and **6T** and are quite similar (log β_{ML2} = 10.6 and 10.5, respectively). With ligand **2T**, the value of log β for the ML complex is about two orders of magnitude lower than with the ligand **6T**. It can lead to the assumption that thioamides appended with cyclic moieties form more stable complexes with Pb^{2+} than those bearing linear substituents. It can be clearly seen from **Figure III-17** that with **1T** the highest stability constant was found for Cu^{2+} complex (not for Pb^{2+}) which is almost as strong as the Pb^{2+} complexes with ligands **5T** and **6T**. The elongation of the carbon chain in the structures of ligands **2T** and **3T** results

in lower stability constants of the Cu^{2+} complexes compared to **1T**. The stability constants of Cd^{2+} complexes are more or less the same and vary between 8.6 and 9.3 log units. The exception is the ligand **6T**, for which the absence of significant spectral changes upon addition of Cd^{2+} solution prevented the determination of any stability constant. These results show, in a way, the high selectivity for Pb^{2+} and Cu^{2+} over Cd^{2+} cations previously observed in liquid-liquid extraction.

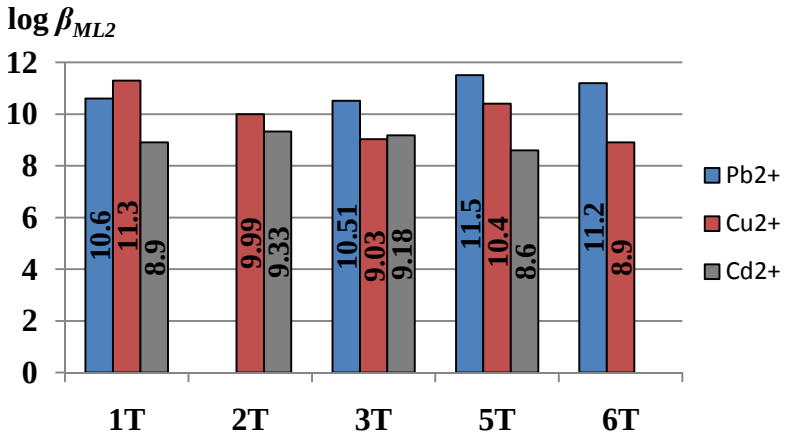


Figure III-17. Stability constants of ML_2 complexes of Pb^{2+}, Cu^{2+} and Cd^{2+} with ligands **1T-3T**, **5T** and **6T** in acetonitrile

3.1.4. Potentiometric studies in acetonitrile

The potentiometry is a particularly accurate method for the determination of Ag^+ complex stability constants. Potentiometric titrations using an Ag^+/Ag electrode were therefore performed to confirm the stoichiometry and the stability constants of Ag^+ complexes with the studied thioamides firstly determined by spectrophotometry. This latter technique showed the formation of strong ML complexes accompanied by M_2L complexes.

Different models were tested and the best fit between the experimental and calculated data for all the thioamides investigated was found for ML and M_2L complexes existing simultaneously in solution. This is in full agreement with the spectrophotometric results. Two examples of the potential variations versus molar ratio ([M]/[L]) plots for the complexation of $AgNO_3$ with ligands **1T** and **9T** are presented in **Figures III-18** and **III-19**, respectively.

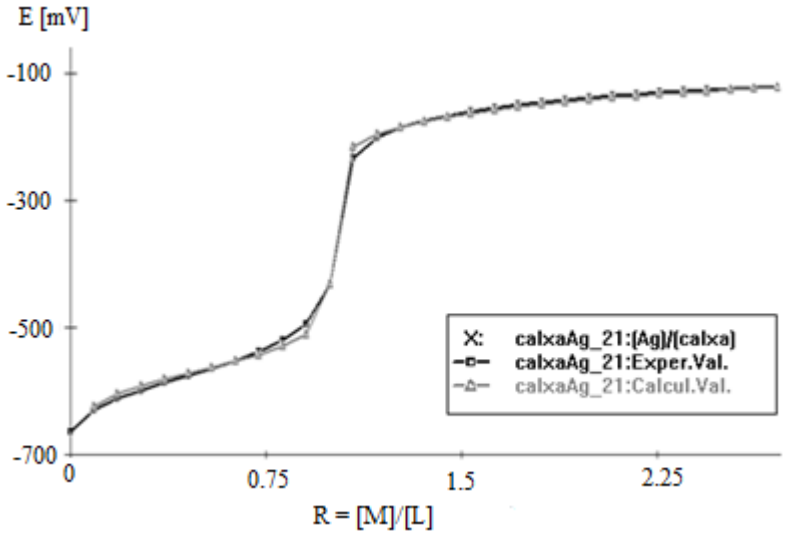


Figure III-18. Experimental and calculated (assuming ML and M_2L complexes) potentiometric curves for the complexation of Ag^+ with ligand **1T**

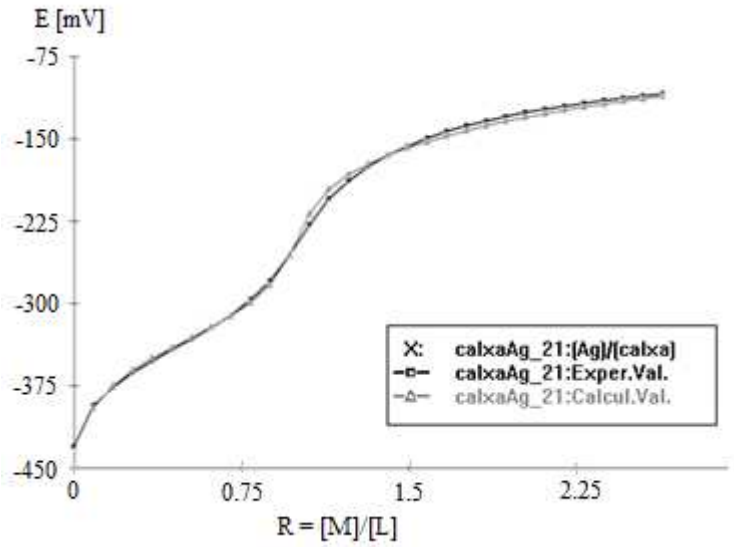


Figure III-19. Experimental and calculated (assuming ML and M_2L complexes) potentiometric curves for the complexation of Ag^+ with ligand **9T**

The potentiometric curves depicted in **Figures III-18** and **III-19** are well S-shaped and clearly show the formation of ML complex. The interpretation was also improved by considering additional M_2L complexes.

The results of the two independent experiments performed with each ligand are presented in **Table III-7**.

The stability constants determined by this method are very high, especially for the ligands bearing tertiary thioamide moieties (**1T-3T, 5T-6T**), up to log β_{ML} = 11.32 with **1T**. Among the secondary thioamides, **7T** forms the most stable complexes with the highest stability constants comparable to those of the complexes with the tertiary thioamide **6T**.

Regarding the stepwise constants it can be seen that M_2L complexes have much lower stability constants than ML complexes (i.e. for ligand **1T** values are: log β_{ML} = 11.32 and log β_{M2L} = 15.34). The potentiometric method using an Ag^+/Ag electrode is a very sensitive method for the determination of the stability constants of silver complexes. Thus, the second less stable M_2L complexes were found with a quite good accuracy.

Figure III-20 enables the comparison of the Ag^+ complexes stability constants determined by the two methods. As we can observe, the values determined by potentiometry are always higher than those obtained by spectrophotometry. Despite these differences, the stoichiometries and the general trends are the same. In details, considering the potentiometric results, tertiary thioamides (**1T-3T, 5T-6T**) form more stable Ag^+ complexes than secondary thioamides. Both methods revealed that the secondary thioamide **7T** forms an Ag^+ complex almost as strong as those obtained with the tertiary thioamide **6T**.

Table III-7. Overall stability constants (log $\beta \pm \sigma$*) for Ag^+ complexes with ligands **1T-3T, 5T-9T** determined by the potentiometric method using an Ag^+/Ag electrode (acetonitrile, T=25°C)

ligand		**1T**	**2T**	**3T**	**5T**[a]	**6T**	**7T**	**8T**	**9T**
Complexes	**ML**	11.32 ± 0.07	10.25 ± 0.04	10.14 ± 0.04	10.41 ± 0.07	8.9 ± 0.1	8.10 ± 0.06	7.83 ± 0.01	7.51 ± 0.01
	M_2L	15.34 ± 0.09	13.50 ± 0.05	13.7 ± 0.1	15.18 ± 0.07	12.67 ± 0.07	13.01 ± 0.05	11.45 ± 0.09	11.86 ± 0.01

*standard deviation of two experiments
[a] data published in [23]

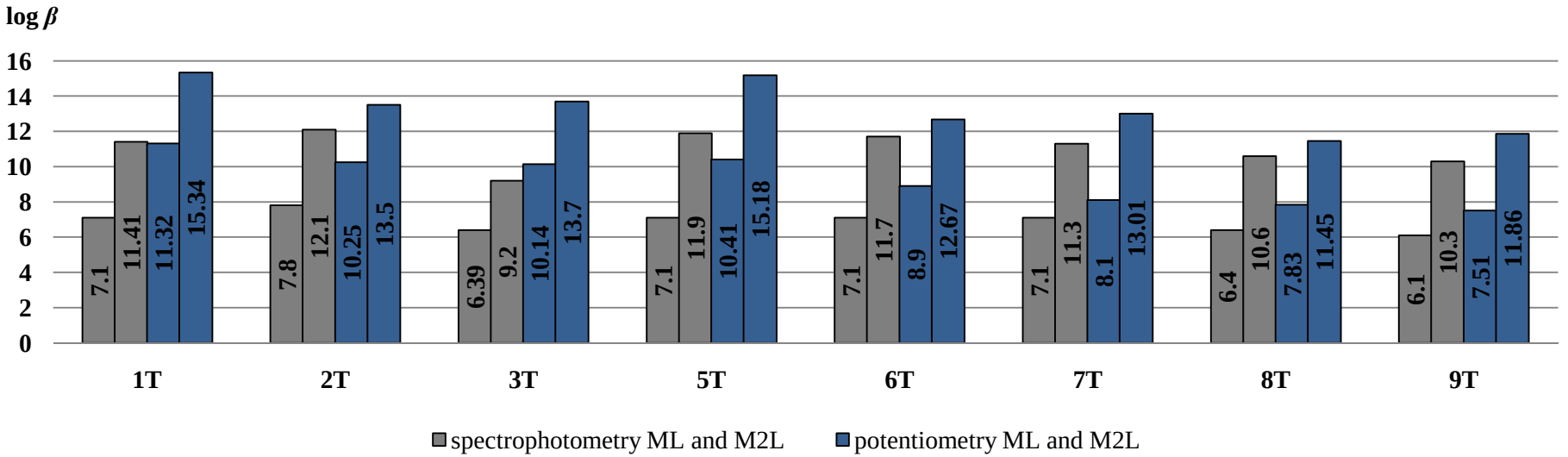


Figure III-20. Stability constants of Ag^+ (ML and M_2L) complexes with ligands **1T-3T, 5T** and **6T** determined in acetonitrile by potentiometry and spectrophotometry

3.1.5. Microcalorimetric studies in acetonitrile

Microcalorimetric titrations were carried out with ligands **1T, 5T-9T** in the presence of Ag^{+} in acetonitrile. Additionally, with the ligand **5T**, titrations were performed against Cd^{2+}, Cu^{2+} and Pb^{2+} cations in the same solvent. **Figure III-21** presents the thermograms recorded during the titrations of **5T** with Ag^{+}, Cd^{2+} and Cu^{2+} and the corresponding dilution.

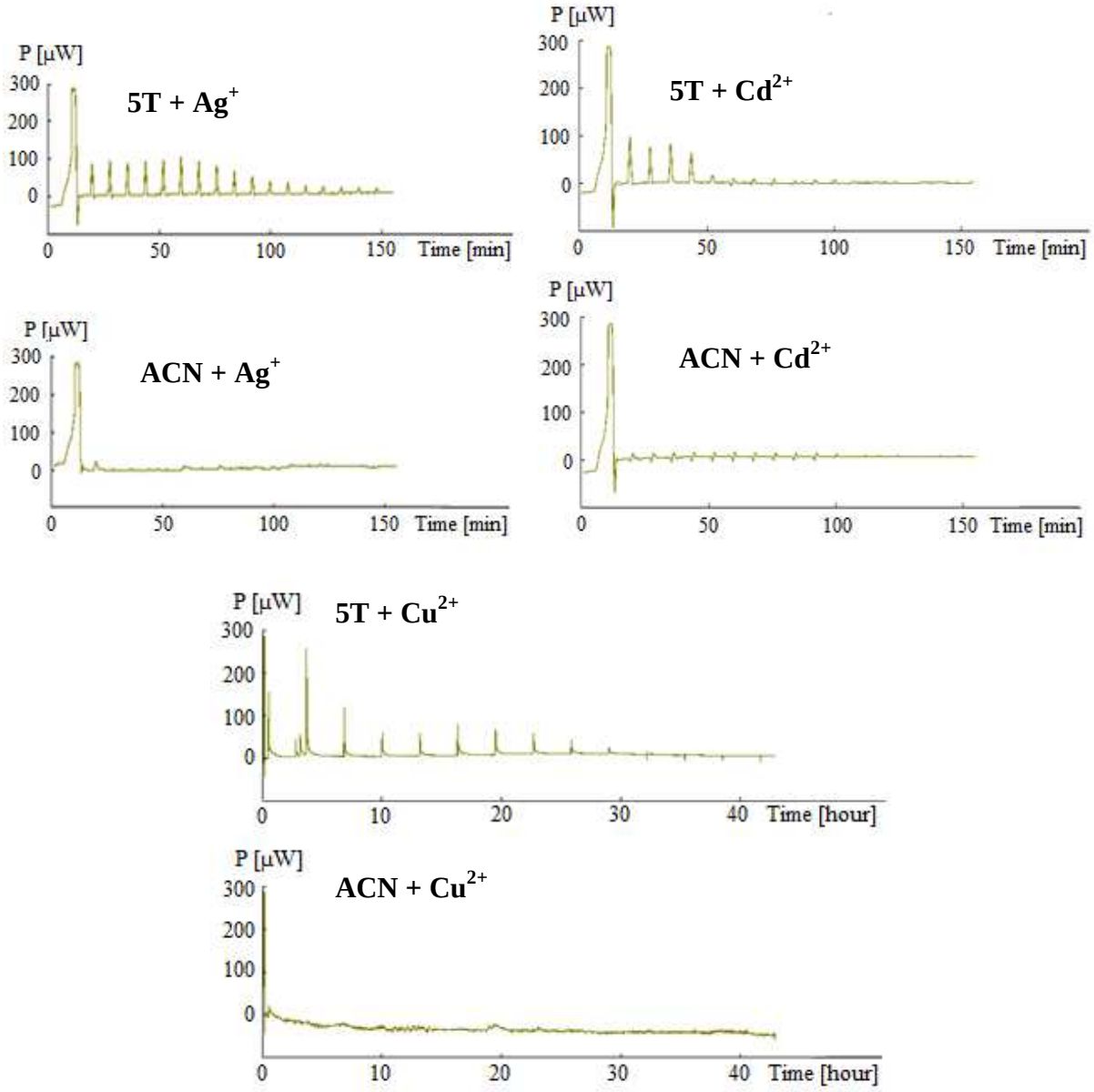


Figure III-21. Microcalorimetric titrations of 2.5 mL of **5T** (2.6×10^{-4} mol L^{-1}) by addition of 17 × 15 µL of 7.3×10^{-3} mol L^{-1} Ag^{+}, 1.1×10^{-2} mol L^{-1} Cd^{2+} and 14 × 15 µL of 1.4×10^{-2} mol L^{-1} Cu^{2+} in acetonitrile, at 25 °C, Δt = 6 min between two injections (in the case of Ag^{+} and Cd^{2+}) and Δt = 3h in the case of Cu^{2+}. The lower graph corresponds to the dilution of the salt in pure acetonitrile.

They represent the dependence of the heat Q as a function of time upon complexation. For each experiment, the heat of dilution was determined, and then subtracted from the total heat. For each system, the lower graph corresponds to the dilution of the salt in pure acetonitrile. The exothermic effect due to the complexation is very important compared to that of the dilution in the case of Ag^{+}, Cd^{2+} and Cu^{2+}, whereas practically no heat effect was observed upon addition of Pb^{2+}. However, it should be taken into account that, because of the solubility limits of both, the ligand and $Pb(NO_3)_2$ in acetonitrile, the titrations were performed at much lower metal and ligand concentrations, compared to titrations with the other metal ions. Therefore the experimental conditions are not the same in the case of Pb^{2+}. This fact does not exclude that the complexation of Pb^{2+} occurs. As it was presented before, extraction and UV spectrophotometric experiments showed that the Pb^{2+} complex is indeed formed.

It is worth to note, that titrations with Ag^{+} and Cd^{2+} were accomplished within relatively short time as observed in thermograms. The case of Cu^{2+} titrations was different, as it was necessary to increase the time between each injection, even up to 1-3h, to have the peaks returned to the baseline level.

The thermograms were treated using the program DIGITAM and the best fit for Ag^{+} complexation was found for the ML + M_2L model in all cases, what is in agreement with spectrophotometric and potentiometric results. The corresponding fits with the ligand **5T** are presented in **Figure III-22**.

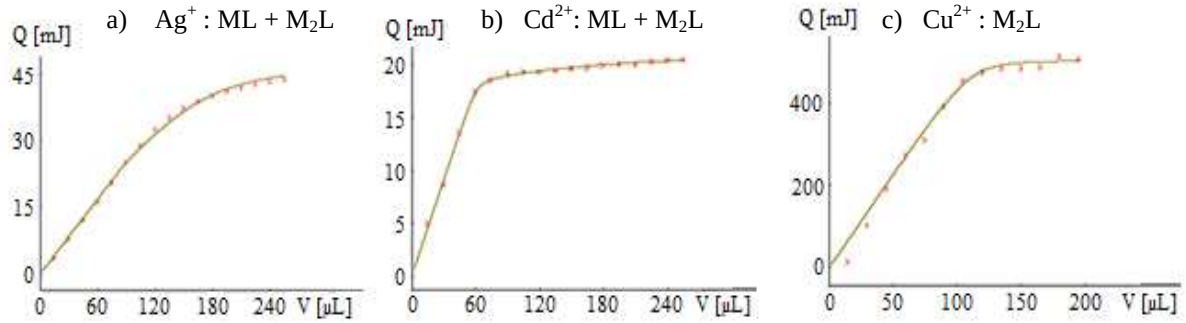


Figure III-22. Experimental (x) and calculated (line) corrected heat vs. the volume of titrant added assuming the formation of a) and b) ML + M_2L species and c) M_2L species for the microcalorimetric titration of **5T** with Ag^{+} , Cd^{2+} and Cu^{2+}, respectively

To interpret these experimental documents, the values of log β for the ML complexes of Ag^+ were settled to the values found by spectrophotometry and the value of log β_{M2L} for M_2L complexes were refined. They were found to be in good agreement with the spectrophotometric data. ML + M_2L complex were as well found with ligand **5T** in the case of Cd^{2+}, whereas for Cu^{2+}, the best fit was obtained assuming only the M_2L species.

The corresponding overall thermodynamic complexation parameters obtained for Ag^+ are given in **Table III-8.**

Table III-8. Overall thermodynamic complexation parameters of Ag^+ with ligands **1T, 5T-9T** in acetonitrile. Stepwise parameters for M_2L complexes are presented in blue

ligand	complexes	logβ	-ΔG [kJ mol^{-1}]	-ΔH [kJ mol^{-1}]	$T\Delta S$ [kJ mol^{-1}]
1T	ML M_2L	7.1* 11.1 ± 0.1 (11.41)*	40.1 63.3 ± 0.7 23.2	44.6 ± 0.5 69 ± 3 24.4	-4.1 ± 0.5 -6 ± 4 -1.9
5T	ML M_2L	7.1* 11.9 ± 0.1 (11.9)*	40.1 67.9 ± 0.8 27.8	34 ± 3 60 ± 2 26	6 ± 3 8 ± 1 2
6T	ML M_2L	7.1* 11.2 ± 0.1 (11.7)*	40.1 63.7 ± 0.6 23.6	24 ± 4 45 ± 8 21	16 ± 4 19 ± 9 3
7T	ML M_2L	7.1* 10.9 ± 0.3 (11.3)*	40.1 63 ± 2 22.9	23.7 ± 0.7 58 ± 4 34.3	16.4 ± 0.7 5 ± 5 -11.4
8T	ML M_2L	6.4* 9.8 ± 0.3 (10.6)*	36.5 56 ± 2 19.5	27 ± 3 51 ± 11 24	10 ± 3 5 ± 9 -5
9T	ML M_2L	6.1* 10.1 ± 0.3 (10.3)*	34.8 58 ± 2 23.2	23 ± 1 56 ± 5 33	12 ± 1 2 ± 7 -10
*spectrophotometric data					

We can see that the thermodynamic stability of both ML and M_2L complexes is enthalpy controlled, as ΔH values are very favourable. **Figure III-23** presents energy diagrams of Ag^+ complexation with ligands **1T, 5T-9T** for the ML complexes. The most favourable enthalpy contribution of Ag^+ complex stability is observed with ligand **1T** and only for this ligand the entropy term is unfavourable. This suggests that the coordination of Ag^+ cation with ligand **1T** is compensated by a loss of degree of freedom resulting in the negative entropy observed.

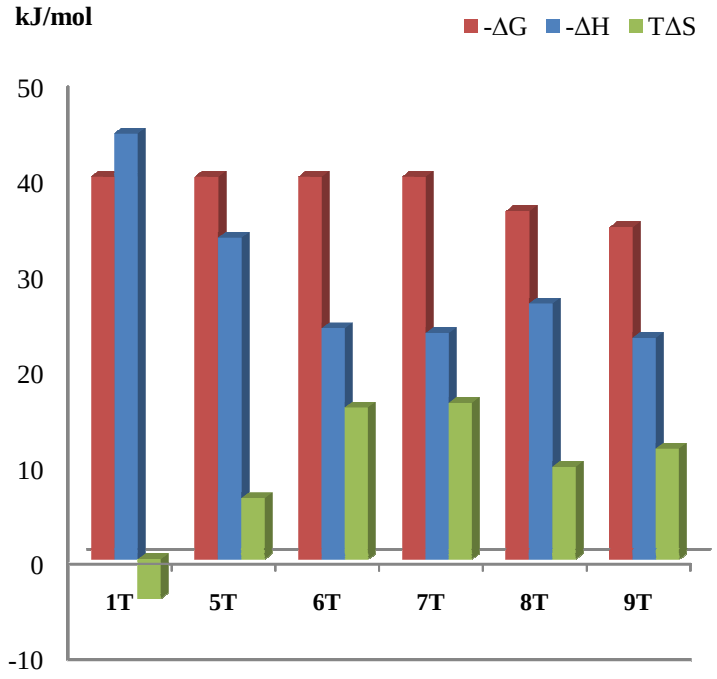


Figure III-23. Energy diagrams of Ag^+ complexation with ligands **1T, 5T-9T** (ML complexes)

In fact, stepwise parameters Δ*H*, Δ*G* and *T*ΔS for M_2L complexes are equal to the differences between overall values for these complexes and those corresponding to ML complexes. Taking this into account, the formation of M_2L complexes is characterised by a stronger negative enthalpy term with all the ligands suggesting strong interactions with the binding groups. The entropy contribution is near zero except for ligands **7T-9T** for which it is negative and unfavourable.

Table III-9 presents the thermodynamic parameters for Ag^+, Cd^{2+} and Cu^{2+} complexes with the ligand **5T**. It can be seen that for Cd^{2+}, these results are not in agreement with the spectrophotometric data, because of the different model found (only ML_2 in spectrophotometry). The enthalpy and entropy contributions are both favourable, but the global stability is enthalpy controlled, as for the Ag^+ complex, the Δ*H* values being smaller. With Cd^{2+}, the stability constant of ML complex is almost one log unit lower and of M_2L complex is more than two log units lower compared to Ag^+ complexes. These results can be explained by the fact that both cations are soft acids, for which the soft sulphur atoms present in thioamides possess a high affinity.

Table III-9. Thermodynamic complexation parameters of Ag^{+}, Cd^{2+} and Cu^{2+} with ligand **5T** in acetonitrile (T=25°C)

cation	complexes	log *β*	-Δ*G* [kJ mol^{-1}]	-Δ*H* [kJ mol^{-1}]	*T*Δ*S* [kJ mol^{-1}]
Ag^{+}	ML	7.1*	40.1	34 ± 3	7 ± 3
	M_2L	11.9 ± 0.1	67.9 ± 0.8	60 ± 2	8 ± 1
		(11.9)*			
Cd^{2+}	ML	6.30 ± 0.08	35.9 ± 0.4	29 ± 2	7 ± 1
	M_2L	9.5	54.3	35 ± 3	19 ± 4
	ML_2	(8.6)*			
Cu^{2+}	M_2L	7.2 [a]	41.1 [a]	637.9 [a]	-596.8 [a]
	ML_2	(10.4)*			
*spectrophotometric data					

Figure III-24 allows the comparison of the thermodynamic parameters for M_2L complexes of Ag^{+}, Cd^{2+} and Cu^{2+} with **5T**. It is obvious that Cu^{2+} behaves differently from the other two cations. It is characterised by a very high favourable enthalpy contribution and a strongly negative and unfavourable entropy. This situation suggests very strong interactions between Cu^{2+} and the ligand, leading to a huge loss of degree of freedom. A similar energetic pattern was observed for the complexation of Cu^{2+} with the *p-tert*-butyldihomooxacalix[4]arene tetra(2-pyridylmethoxy) derivative [30].

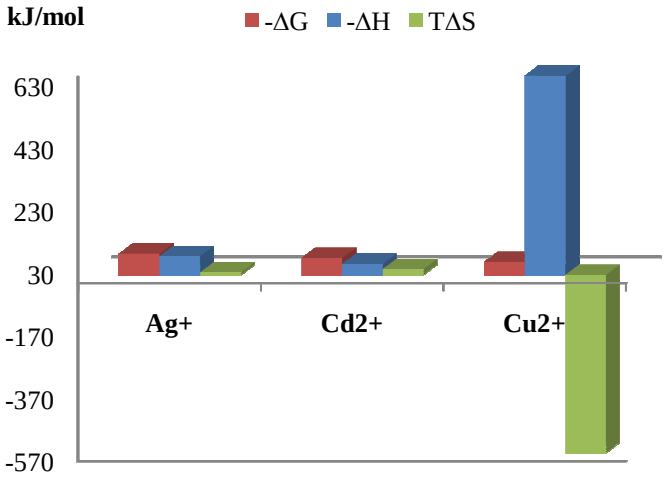


Figure III-24. Energy diagrams for the complexation of Ag^{+}, Cd^{2+} and Cu^{2+} with ligand **5T** (M_2L complexes)

3.2. Calix[4]arene-amide derivatives

3.2.1. Liquid – liquid extraction studies

We were interested to compare the extractive properties of calix[4]arene-thioamides discussed previously with their carbonyl analogues – calix[4]arene-amides. For this purpose, the same cations were studied in extraction experiments as with thioamides (Na^+, Ca^{2+}, Pb^{2+}, Ag^+, Cd^{2+}, Cu^{2+}, Zn^{2+} and Gd^{3+}). The extractive properties of some calix[4]arene-amides studied in this work were already known, like for **1A, 2A** and **3A** (with only Na^+) and **7A** (with Na^+, Ca^{2+} and Cd^{2+}) [14, 31, 32].

The extraction results with calix[4]arene-amides are presented in **Table III-10**.

Table III-10. Percentage extraction (%E)* of metal picrates (C_M = 2.5 × 10^{-4} mol L^{-1}) with ligands **1A-9A** and in parentheses for the corresponding thioamides (**1T-9T**) (C_L = 2.5 × 10^{-4} mol L^{-1}) from water into dichloromethane (organic to aqueous ratio o/a = 1, T = 20°C)

ligand/ cation	Na^+	Ca^{2+}	Cu^{2+}	Zn^{2+}	Cd^{2+}	Ag^+	Pb^{2+}	Gd^{3+}
1A[a]	95.5 (7)	98 (≤ 1)	14 (19)	10.3 (≤ 1)	97 (8)	99 (80)	97 (56)	5.4 (≤ 1)
2A	95[b] (2.8)	97 nd	14.2 (28.1)	11.8 nd	90.6 nd	98.3 (84.9)	93.7 (36.1)	13.7 nd
3A	92[b] (1.8)	92.5 nd	10.0 nd	8.5 nd	80.0 nd	93.9 (87.5)	89.8 (42.1)	7.4 nd
4A	80.8	63.2	19.4	14.8	61.5	92.6	73.6	13.7
5A	95.2 (8.5)	95.2 (3.2)	23.5 (29.4)	10.4 (3.6)	86.9 (2.2)	95.2 (86.8)	94.6 (66.4)	4.1 (2.6)
6A	73.7 (6.3)	52.9 (4.6)	14.8 (14.5)	5.0 (1.6)	22.6 (≤ 1)	72.9 (99.2)	65.6 (50.9)	1.2 (≤ 1)
7A	≤ 1[c] (≤ 1)	≤ 1[c] (≤ 1)	≤ 1 (1.9)	≤ 1 (≤ 1)	≤ 1[c] (≤ 1)	≤ 1 (92.1)	≤ 1 (≤ 1)	≤ 1 (≤ 1)
8A	≤ 1 (2.0)	≤ 1 (2.8)	≤ 1 (2.9)	≤ 1 (≤ 1)	≤ 1 (1.3)	≤ 1 (85.5)	≤ 1 (≤ 1)	≤ 1 (1.6)
9A	≤ 1 (≤ 1)	≤ 1 (1.6)	≤ 1 (2.3)	≤ 1 (≤ 1)	≤ 1 (1.4)	≤ 1 (98)	≤ 1 (≤ 1)	≤ 1 (≤ 1)

*values with uncertainties less than 5%
"nd" not determined
[a] data from ref. [14], [b] data from ref. [31], [c] data from ref. [32]

As already mentioned in Chapter I, the extractive properties of calixarene-amide derivatives depend strongly on the nature (primary or secondary) of the functional groups attached. **Table III-10** confirms this pattern. The strong affinity of tertiary amide derivatives

2A-6A towards hard acids, such as Na^+ and Ca^{2+} cations but also towards the softer Pb^{2+}, Cd^{2+} and Ag^+ cations can be seen. These results are consistent with those observed with already known calixarene-amides (e. g. **1A**). On the contrary, ligands **8A** and **9A** bearing secondary amide functional groups are ineffective extractants (%E ≤ 1) (what was proved before for ligand **7A**, also having secondary amide moieties). Such an affinity for the different cations results in the small selectivity of calixarene-amides.

As we established before, a different extraction pattern is observed with the corresponding thioamide derivatives. **Figure III-25** illustrates the extractive affinity of the representative calix[4]arene-thioamide **5T** and its corresponding amide **5A**.

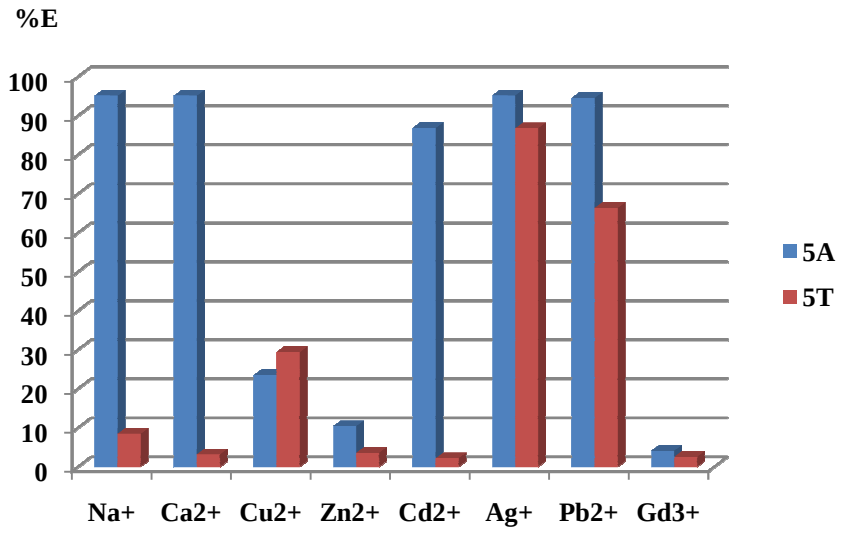


Figure III-25. Comparison between the extraction profiles of calix[4]arene-thioamide **5T** and its carbonyl analogue, calix[4]arene-amide **5A**

It can be clearly seen, that the introduction of softer sulphur atoms into the calixarene frame promoted their ability to bind heavy metal cations with a very good selectivity over a great variety of cations, such as Na^+, Ca^{2+} and Cd^{2+}, which were almost quantitatively extracted by amides, but hardly extracted by thioamides. A similar profile may be observed for other amide-thioamides pairs (i. e. **2A – 2T**), except for those with secondary functional groups which are, as stated before, weak extractants. It is worth to mention, that the case of Ag^+ is different, as this cation is very well extracted by secondary thioamides, but not at all by the corresponding amides. This may be due to the different hydrophicility of Ag^+ complexes with the two kinds of ligands: those with amides prefer to stay in the aqueous phase, while those with the thioamides are more easily transferred to the organic phase.

3.2.2. Spectrophotometric and potentiometric studies in methanol and acetonitrile

UV absorption spectrophotometric titrations were carried out in methanol for Na^+, Pb^{2+}, Cu^{2+}, Cd^{2+} and Ag^+ with calix[4]arene-amides **1A-9A**, except **6A** which was not soluble in methanol. Studies in acetonitrile were performed for Pb^{2+}, Cu^{2+}, Cd^{2+} and Ag^+ with **1A, 2A** and **4A**. Because of the low solubility of ligands **5A-9A** in acetonitrile, the titrations could not be performed in this medium with these ligands.

Studies in methanol

Significant spectral changes were observed upon addition of all the cations tested in the case of tertiary amides **1A-5A**, whereas spectra of ligands **7A-9A** based on secondary amides significantly changed only upon addition of Pb^{2+}, and also of Na^+ and Cd^{2+} in the case of **7A**. The examples of the spectral changes undergone by ligands **1A** and **7A** upon addition of Pb^{2+} are depicted in **Figure III-26** and **III-27**, respectively.

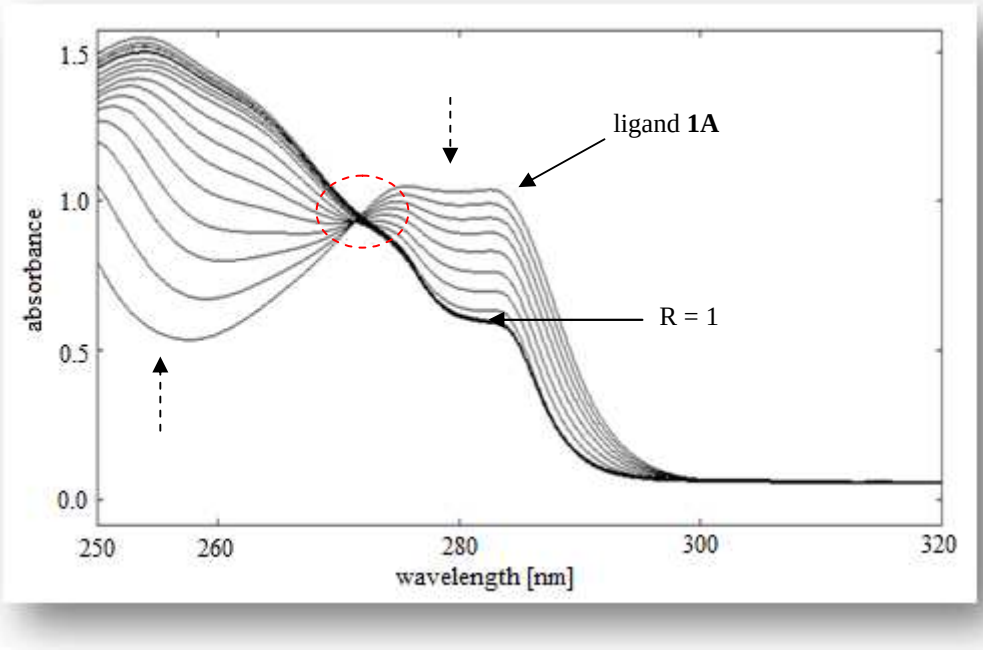


Figure III-26. Changes in the UV spectrum of **1A** upon addition of $Pb(NO_3)_2$ in methanol, I = 10^{-2}mol L^{-1} Et_4NNO_3 ($C_L = 4 \times 10^{-4}$mol L^{-1}, $0 \leq R \leq 2.0$)

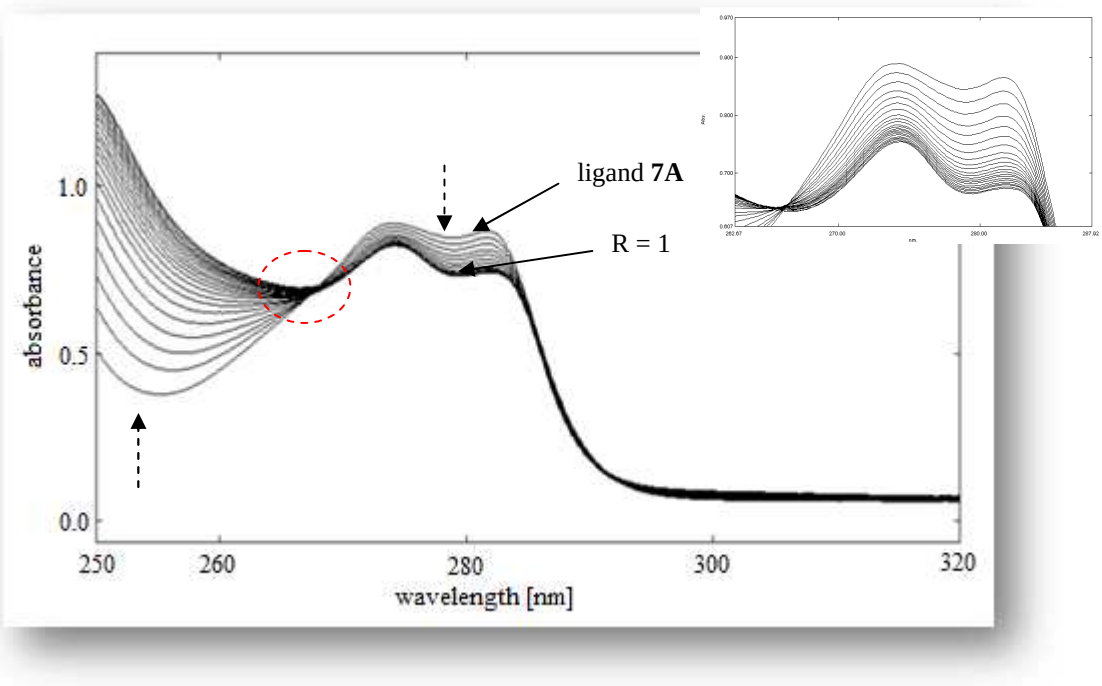


Figure III-27. Changes in the UV spectrum of **7A** upon addition of $Pb(NO_3)_2$ in methanol, I = 10^{-2}mol L^{-1} Et_4NNO_3 ($C_L = 4 \times 10^{-4}$mol L^{-1}, $0 \leq R \leq 2.5$)

The spectral changes observed upon addition of Pb^{2+} were more important with tertiary amides than with secondary amides, what can be seen by comparing both Figures **(III-26** and **III-27)**. In each case, the changes were characterised by a decrease of the absorbance until a ratio close to 1 suggesting ML complex formation. However, an isosbestic point is visible until a ratio R close to 0.5 indicating ML_2 complex formation in solution simultaneously. Program SPECFIT confirmed those assumptions. A model involving the two ML + ML_2 complexes was found for all the amides tested, except **4A**, for which only the presence of ML_2 complex was found.

Titrations with Na^+ showed complexes with various stoichiometries depending on the ligand. A ML complex was found with **1A** (tertiary amide) and **7A** (secondary amide), both ligands having ethyl substituents. The two ML and ML_2 species were confirmed with tertiary amides **4A** and **5A**, whereas for ligands **2A** and **3A** only a ML_2 complex was found.

In the case of Cu^{2+} complexation, ML_2 complexes were found with ligands **1A-5A**, whereas for **2A**, the ML_2 complex was accompanied by a ML complex. For ligand **1A**, literature data based on potentiometric determination correspond to the formation of a ML complex [14] whereas the ML_2 complex of Cu^{2+} was found in our studies by UV absorption spectrophotometry. No significant spectral changes were observed upon addition of Cu^{2+} in the case of secondary calix[4]arene-amides (**7A-9A**) indicating no or very little complexation.

ML and ML_2 complexes were also found for Cd^{2+} complexes with amides **1A-7A**, except **2A**, for which only a ML_2 complex was confirmed.

The overall stability constants of Na^+, Pb^{2+}, Cu^{2+} and Cd^{2+} complexes with calix[4]-arene-amides **1A-5A, 7A-9A** determined in methanol by spectrophotometry are given in **Table III-11**.

Interpretation of UV spectra upon addition of Ag^+ in methanol was very troublesome. Despite significant changes in the ligands spectra, it was not possible to derive the stoichiometry of the complexes and their stability constants. For that reason, potentiometric titrations with the use of an Ag^+/Ag electrode were performed and results are given in **Table III-11**.

Table III-11. Overall stability constants (log $\beta \pm \sigma$*) of Na^+, Pb^{2+}, Cu^{2+}, Cd^{2+} and Ag^+ complexes with ligands **1A-5A, 7A-9A** (methanol, T = 25ºC, $I = 10^{-2}$ mol L^{-1} Et_4NNO_3 or Et_4NCl)

ligand	complexes	Na^+	Pb^{2+}	Cu^{2+}	Cd^{2+}	Ag^+
1A	ML	$7.9^{p,a}$	5.8 ± 0.1	$6.5^{p,a}$	7.4 ± 0.3	$7.2^{p,a}$
	ML_2		9.5 ± 0.2	8.4 ± 0.2	11.6 ± 0.2	
2A	ML		5.12 ± 0.05	4.6 ± 0.3		6.71 ± 0.04^p
	ML_2	8.8 ± 0.5	8.4 ± 0.3	8.60 ± 0.08	9.0 ± 0.4	11.28 ± 0.06^p
3A	ML		6.3 ± 0.3		7.5 ± 0.4	6.6 ± 0.1^p
	ML_2	11.4 ± 0.4	11.4 ± 0.4	5.6 ± 0.2	12.7 ± 0.9	10.92 ± 0.06^p
4A	ML	5.8 ± 0.5			6.5 ± 0.4	6.71 ± 0.04^p
	ML_2	10.5 ± 0.7	11.34 ± 0.05	6.2 ± 0.3	11.10 ± 0.09	11.29 ± 0.08^p
5A	ML	7.1 ± 0.8	6.235 ± 0.007		7.6 ± 0.2	5.92 ± 0.06^p
	ML_2	12 ± 1	10.7 ± 0.3	6.34 ± 0.09	11.1 ± 0.2	10.62 ± 0.04^p
7A	ML	3.3^b	4.50 ± 0.06	-	3.72 ± 0.06	-
8A	ML	-	4.16 ± 0.01	-	-	-
9A	ML	-	4.55 ± 0.2	-	-	-

* standard deviation of at least two independent experiments
"-" no significant spectral changes
^{p} determined by potentiometric method
^{a} data from [14]
^{b} data from [32]

The stability constants of Pb^{2+} complexes for ligands **7A-9A** appended with secondary amide moieties are comparable to each other but are much lower than those obtained with the tertiary amides (by about 1-2 log units). With ligand **7A**, log β values of 3.3 and 3.72, were found for Na^+ and Cd^{2+} complexes, respectively. However they are lower than those obtained for the Pb^{2+} complex. To recall, calix[4]arene-amide based on the secondary amide moieties

were working as Pb(II) selective ionophores. Here, we observed that the stability constants of Pb^{2+} complexes are indeed the highest.

The stability constants obtained with ligands **1A-5A** depend on both the ligand and the cation. However, it is difficult to find a clear dependence between the ligand structure and the value of the stability constants. **Figure III-28** presents the overall stability constants of ML_2 complexes with ligands **1A-5A**.

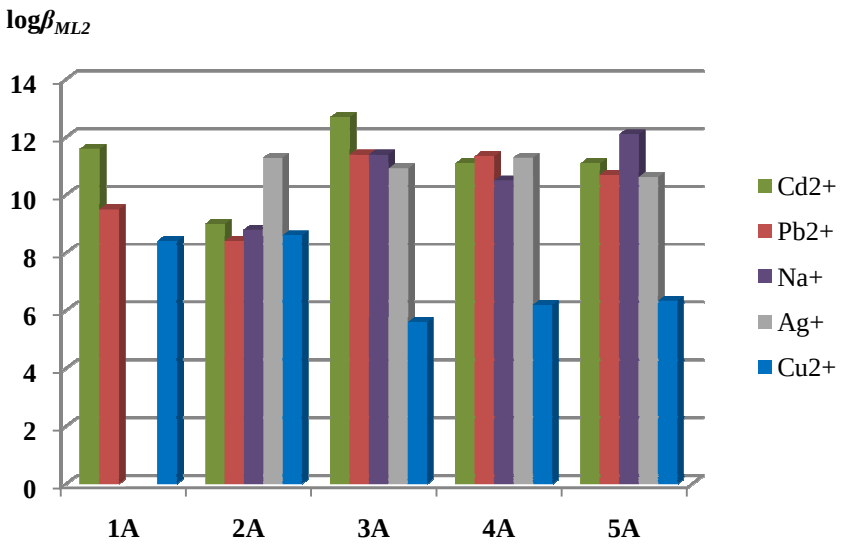


Figure III-28. Stability constants of ML_2 complexes of Cd^{2+}, Pb^{2+},Cu^{2+}, Ag^{+} and Na^{+} with ligands **1T-5T** in methanol

It can be seen that with all ligands, the Cu^{2+} complexes are the weakest and with **2A**, the value of log β is of the same order of magnitude as those of the Na^{+} and Pb^{2+} complexes. This is in accordance with extraction data, where the %E of Cu^{2+} was the lowest among all the cations studied. The extraction of Cd^{2+}, Pb^{2+}, Ag^{+} and Na^{+} was almost quantitative, (%E > 90%) and it was therefore difficult to distinguish the affinity of these ligands as the cations were all very well extracted. The UV spectrophotometric studies confirm, in a way, the extraction results.

Studies in acetonitrile

Studies in acetonitrile were limited due to the solubility limits with most of the amides in the studied conditions. Hence, UV spectrophotometric titrations were performed with ligands **1A, 2A** and **4A** and the results were compared with those obtained in methanol. These studies also allow us to compare the stability constants of amides **1A** and **2A** with their

corresponding thioamides **1T** and **2T**, for which UV spectrophotometric titrations were done in acetonitrile as well.

Significant spectral changes were observed upon addition of Pb^{2+}, Cu^{2+}, Cd^{2+} and Ag^{+}. However, the spectral changes upon addition of Ag^{+} were interpretable only in the case of ligand **1A**. Despite significant changes in the **2A** and **4A** ligands spectra, it was not possible to determine the stoichiometry of the complexes and their stability constants. In these cases, the stability constants of Ag^{+} complexes are derived from potentiometric experiments.

The example of the ligand **1A** spectral changes upon addition of Pb^{2+} in acetonitrile is depicted in **Figure III-29**.

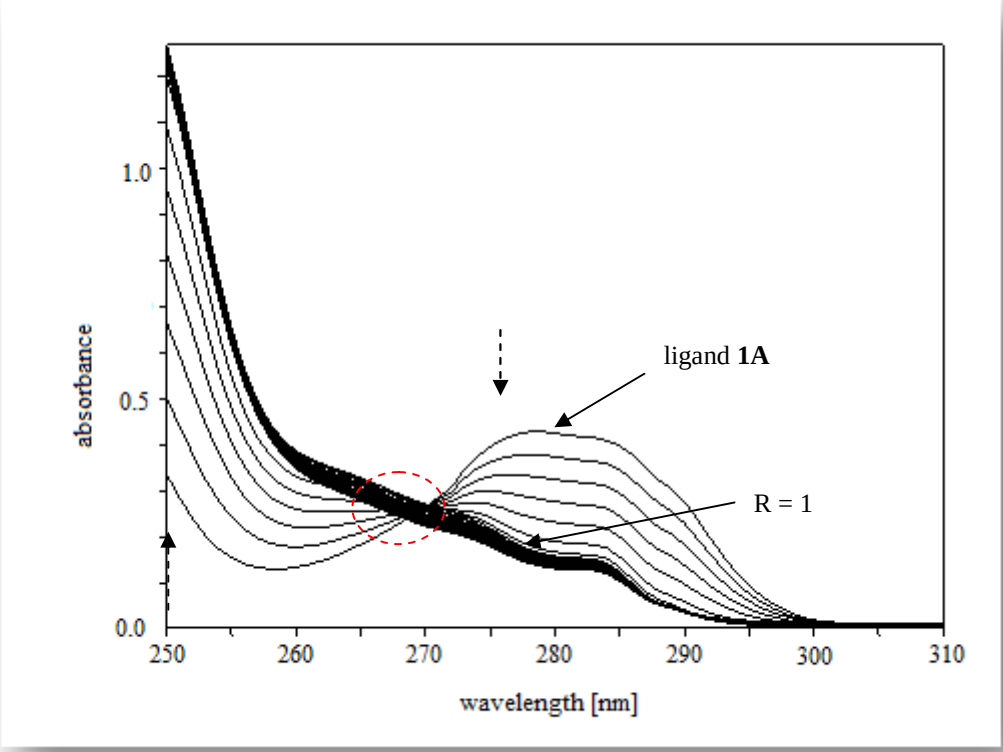


Figure III-29. Changes in the UV spectrum of **1A** upon addition of $Pb(NO_3)_2$ in acetonitrile, $I = 10^{-2}$mol L^{-1} Et_4NNO_3 ($C_L = 5 \times 10^{-4}$mol L^{-1}, $0 \leq R \leq 2.4$)

The specta are characterised by the decrease of the absorbance until a ratio close to 1 indicating ML complex formation. An isosbestic point occurred until a ratio R close to 0.5 suggesting ML_2 complex formation in solution simultaneously. Those assumptions were confirmed using the Program SPECFIT . Similar spectral changes upon addition of Pb^{2+} were obtained with ligands **2A** and **4A**, for which the presence of two ML and ML_2 species was

found as well. The same model was defined for Cd^{2+} and Cu^{2+} complexes (with the exception of ligand **1A**, for which only a ML_2 complex was found with Cu^{2+}). For ligand **1A**, where spectrophotometric method was successful in determining the stoichiometry and the stability constants of Ag^+ complexes, the model ML + ML_2 was also found. It seems that in acetonitrile, the stoichiometry of complexes is more evident, compared to methanol, and the interpretation of the results is easier.

The overall stability constants log β of Na^+, Pb^{2+}, Cu^{2+}, Cd^{2+} and Ag^+ complexes with calix[4]arene-amides **1A, 2A** and **4A** determined in acetonitrile and in methanol (in red) are given in **Table III-12**.

Table III-12. Overall stability constants (log β ± σ*) of Na^+, Pb^{2+}, Cu^{2+}, Cd^{2+} and Ag^+ complexes with ligands **1A, 2A** and **4A** (acetonitrile, T = 25ºC, $I = 10^{-2}$ mol L^{-1} Et_4NNO_3); in red values of log β in methanol

ligand	complexes	Na^+	Pb^{2+}	Cu^{2+}	Cd^{2+}	Ag^+
1A	ML	≥ 8.5 [p,b]	7.80 ± 0.07 5.8 ± 0.1		8.005 ± 0.007 7.4 ± 0.3	7.7 ± 0.3 (5.44 ± 0.02)[p] 7.2[p,a]
	ML_2		12.6 ± 0.1 9.5 ± 0.2	8.9 ± 0.4 8.4 ± 0.2	12.2 ± 0.2 11.6 ± 0.2	12.7 ± 0.2 (9.54 ± 0.04)[p]
2A	ML	nd	7.49 ± 0.07 5.12 ± 0.05	6.7 ± 0.6 (4.6 ± 0.3)	8.015 ± 0.007	5.84 ± 0.01[p] 6.71 ± 0.04[p]
	ML_2		12.4 ± 0.5 8.4 ± 0.3	11.6 ± 0.3 8.60 ± 0.08	13.8 ± 0.5 9.0 ± 0.4	9.54 ± 0.03[p] 11.28 ± 0.06[p]
4A	ML	nd	7.63 ± 0.07	4.99 ± 0.06	7.4 ± 0.3 6.5 ± 0.4	5.73 ± 0.04[p] 6.71 ± 0.04[p]
	ML_2		13.0 ± 0.2 11.34 ± 0.05	8.8 ± 0.1 6.2 ± 0.3	12.4 ± 0.4 11.10 ± 0.09	8.72 ± 0.05[p] 11.29 ± 0.08[p]

* standard deviation of at least two independent experiments
"nd" – not determined
[p] determined by potentiometric method
[a] data from [14]
[b] data from [31]

Both methanol and acetonitrile have big dielectric constants (ε = 32.6 and 36.2, respectively) making them good dissociating solvents. However, their ions solvation ability is different in agreement with their respective donor numbers (DN = 19 and 14, respectively) [33]. Methanol tends to solvate cations and the ligand must compete with the solvent molecule to bind with a cation. For this reason, the stability constants determined in methanol and acetonitrile are different as an effect of different solvation properties.

It can be seen that the stability constants determined in acetonitrile are generally higher than those obtained in methanol. This is not the case with Ag^+, for which the opposite trend is observed. The low stability of the complexes of Ag^+ in acetonitrile is possibly due to a competition between the ligand and the solvent molecules.

It is worth to compare the stability constants for the pair of ligands amide - thioamide in the same conditions. This comparison was made between **1A** and **1T** and between **2A** and **2T**. The results are put together in **Table III-13**. Values corresponding to thioamides are marked in blue.

Table III-13. Overall stability constants (log $\beta \pm \sigma$*) of Pb^{2+}, Cu^{2+}, Cd^{2+} and Ag^+ complexes with ligands **1A** and **2A** and their thioamide analogues in blue **1T** and **2T** (acetonitrile, T = 25ºC, $I = 10^{-2}$ mol L^{-1} Et_4NNO_3)

ligand	complexes	Pb^{2+}	Cu^{2+}	Cd^{2+}	Ag^+
1A/**1T**	ML	7.80 ± 0.07		8.005 ± 0.007	$(5.44 \pm 0.02)^p$ 11.32 ± 0.07^p
	ML_2	12.6 ± 0.1 10.6 ± 0.4	8.9 ± 0.4 11.3 ± 0.4	12.2 ± 0.2 8.9 ± 0.4	$(9.54 \pm 0.04)^p$
	M_2L				15.34 ± 0.09^p
2A/**2T**	ML	7.49 ± 0.07 3.95 ± 0.05	6.7 ± 0.6	8.015 ± 0.007	5.84 ± 0.01^p 10.25 ± 0.04^p
	ML_2	12.4 ± 0.5	11.6 ± 0.3 10 ± 0.3	13.8 ± 0.5 9.3 ± 0.07	9.54 ± 0.03^p
	M_2L	9.1 ± 0.1			13.50 ± 0.05^p

* standard deviation of at least two independent experiments
^{p} determined by potentiometric method

It was possible to compare the overall stability constants of Pb^{2+}, Cu^{2+} and Cd^{2+} complexes of ML_2 stoichiometry and of ML complex of Ag^+ for the **1A-1T** pair. Moreover, the stability constants of Cu^{2+} and Cd^{2+} as well as of Ag^+ and Pb^{2+} for the **2A-2T** pair can be compared as well. Those stability constants are generally lower for the corresponding thioamides, except for the Cu^{2+} complex with **1T**, for which log β is more than two units higher than with its carbonyl analogue **1A**. The ML complex of Pb^{2+} with **2T** is characterised also by a lower stability constant as compared to the corresponding complex with **2A**. The stability constants of the ML complexes of Ag^+ determined by the potentiomeric method were found almost two times higher (in log units) with thioamides than with amides derivatives.

3.3. O- and O- or N-substituted calix[4]arene-hydroxamate derivatives (**10-14**)

3.3.1. Liquid – liquid extraction studies

The cation-binding properties of hydroxamate derivatives (ligands **10-14**) have been assessed by liquid–liquid extraction of the metal picrates from water into dichloromethane. O-substituted hydroxamate derivatives **10-13** did not show interesting extractive properties (%E < 7, **Table III-14**).

Table III-14. Percentage extraction (%E)* of metal picrates ($C_M = 2.5 \times 10^{-4}$ mol L^{-1}) with ligands **10-14** ($C_L = 2.5 \times 10^{-4}$ mol L^{-1}) from water into dichloromethane (organic to aqueous ratio o/a = 1, T = 20°C)

ligand/cation	Na^+	Ca^{2+}	Cu^{2+}	Zn^{2+}	Cd^{2+}	Ag^+	Pb^{2+}	Gd^{3+}
10	≤ 1	≤ 1	1.5	1.2	≤ 1	3.8	3.5	≤ 1
11	1.9	≤ 1	1.7	1.7	1.7	3.5	1.9	≤ 1
12	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1	4.4	1.6	≤ 1
13	3.2	1.2	2.0	2.6	≤ 1	6.3	3.2	1.3
14	46.0	27.6	16.6	17.6	23.1	42.8	41.4	12.4
*values with uncertainties less than 5%								

In the case of ligand **11**, the extraction of lead nitrate at pH = 5.4 was tested according to the procedure used for calix[4]arene-hydroxamic acids derivatives (ligands **15-18**). The result (5.5%) confirmed that this ligand is a weak extractant, independently of the method used. As in the calix[4]arene-amides series presented in this work and also reported in the literature [32], the weak extractive properties of hydroxamates derivatives can be explained by the presence of hydrogen bonds, confirmed by the X-ray crystal structures of ligands **11** and **13**.

In ligand **14,** the substitution of O and N avoids the formation of such hydrogen bonds. The extraction percentage is much higher in comparison to ligands **10-13**. This ligand extracted in more than 40% hard cations such as Na^+, but also softer cations like Pb^{2+} and Ag^+. Ca^{2+} and Cd^{2+} were also fairly extracted (27.6 and 23.1 %, respectively). The ligand **14** possesses extractive properties similar to tertiary calixarene-amides (the extraction sequence is also the same) although it is a less efficient extractant than the calixarene-amides studied in this work.

3.3.2. Spectrophotometric and potentiometric studies in methanol

The spectral variations upon addition of Pb^{2+} and Ag^{+} for ligands **10-13** were too small to be interpreted. This confirms, in a way, the extraction results and suggests the weak affinity of those compounds for these two studied cations.

For ligand **14**, possessing the best extractive properties among calix[4]arene-hydroxamates presented here, significant spectral changes were observed upon addition of Na^{+}, Pb^{2+}, Cd^{2+} and Ag^{+} salt solutions. They are characterised by a decrease of the absorbance until a ratio close to 1. The example of the spectrophotometric titration of the ligand **14** by Pb^{2+} is presented in **Figure III-30**. One isosbestic point can be noticed, confirming the formation of at least one complex.

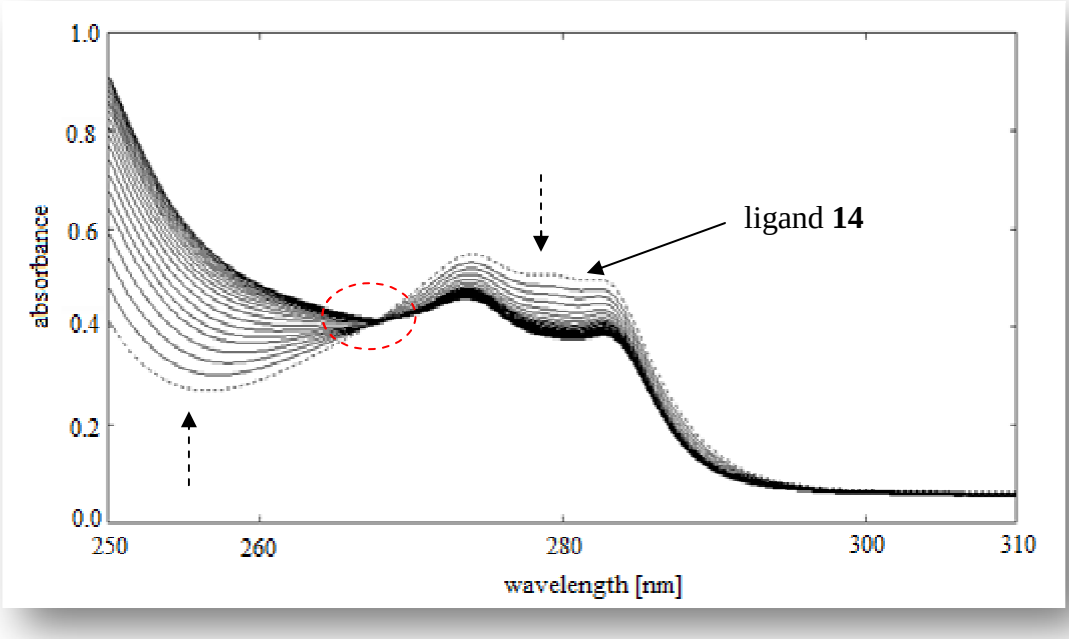


Figure III-30. Changes in the UV spectrum of **14** upon addition of $Pb(NO_3)_2$ in methanol, I = 10^{-2}mol L^{-1} Et_4NNO_3 ($C_L = 2 \times 10^{-4}$mol L^{-1}, $0 \leq R \leq 1.5$)

No siginificant spectral changes were noticed upon addition of Cu^{2+}, indicating no or little complexation of Cu^{2+} by this ligand. The ligand spectral changes upon addition of Ag^{+} were irregular and difficult to interpret. Thus potentiometric titrations using an Ag^{+}/Ag electrode were performed and the data were treated using the program SIRKO. **Figure III-31** presents the fit between experimental and calculated data corresponding to ML and ML_2

complex formation. Significant potential changes can be noticed until R close to 1. Above that ratio the potential is quite stable suggesting that the complexation is completed.

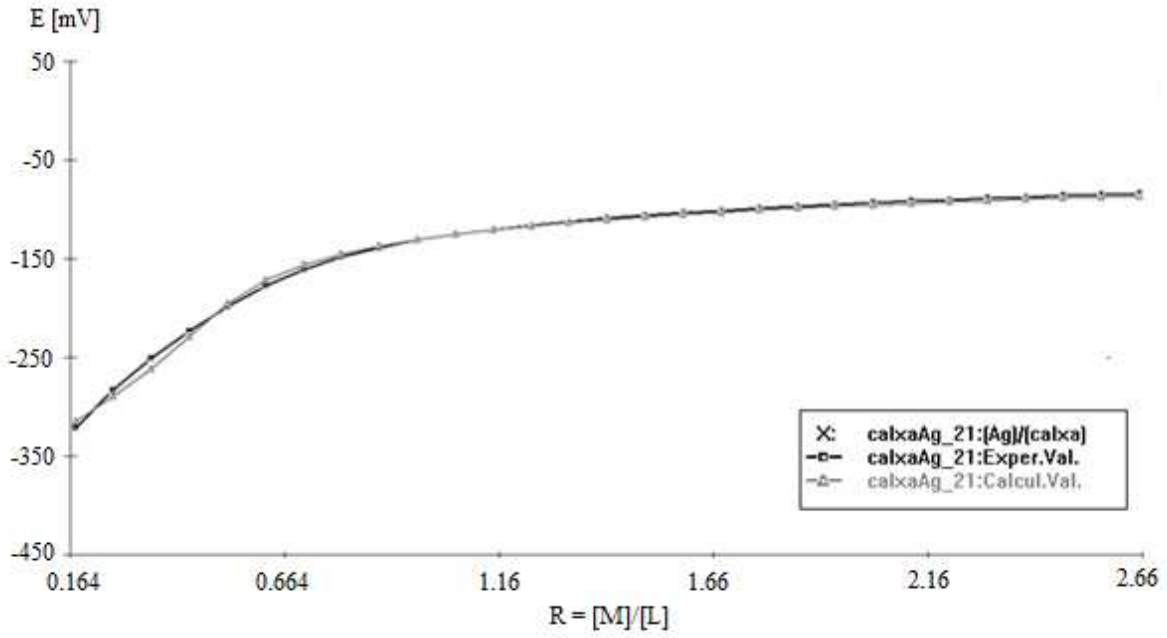


Figure III-31. Potentiometric changes upon addition of $AgNO_3$ in methanol; fit between experimental (×) and calculated (line) data assuming the formation of ML and ML_2 complexes formation with ligand **14**, $I = 10^{-2}$mol L^{-1} Et_4NNO_3 ($C_L = 2.6 \times 10^{-4}$ mol L^{-1}, $0 \leq R \leq 2.66$)

The interpretation of these spectra led to the results given in **Table III-15**.

Table III-15. Overall stability constants ($\log \beta \pm \sigma^*$) of Na^+, Pb^{2+}, Cd^{2+} and Ag^+ complexes with **14** (methanol, T = 25°C, I = 10^{-2}mol L^{-1} Et_4NNO_3 or Et_4NCl)

complexes	Na^+	Pb^{2+}	Cd^{2+}	$Ag^{+\,p}$
ML	5.19 ± 0.05	4.34 ± 0.02		5.26 ± 0.05
ML_2	9.0 ± 0.5	8.4 ± 0.3	8.9 ± 0.2	10.41 ± 0.02
*standard deviation of at least two independent experiments *p* determined by potentiometry with an Ag^+/Ag electrode				

The formation of two ML and ML_2 complexes simultaneously was found in the case of Na^+, Pb^{2+} and Ag^+ and only a ML_2 species is formed with Cd^{2+}. It can be seen that the strongest complexes are formed with Ag^+ and Na^+ cations.

Although this ligand showed similar complexing properties to calixarene-amides, the stability constants of its complexes are lower.

3.4. Calix[4]arene-hydroxamic acid derivatives

3.4.1. Individual liquid – liquid extraction studies

The calix[4]arene-hydroxamic acids, being acidic ligands, were studied using the nitrate extraction method at pH = 5.4. In the case of Fe^{3+} extraction, the pH was lowered to 2.2 with HNO_3.

The extraction data are presented in **Table III-16** and in **Figure III-32**.

Table III-16. Percentage extraction (%E)* of metal nitrates ($C_M = 1.06 \times 10^{-4}$ mol L^{-1}) with ligands **15-18** ($C_L = 5.3 \times 10^{-4}$ mol L^{-1}) from water into dichloromethane (T = 30°C)

ligand/cation	Co^{2+}	Ni^{2+}	Zn^{2+}	Pb^{2+}	Fe^{3+}	Cu^{2+}	Cd^{2+}
15	48.1	52.1	62.4	85.4	70.7	97.7	32.1
16	2.1	15.4	≤ 1	2.6	63.1	88.5	5.5
17	45.8	54.2	60	61.6	59.8	89.0	32.7
17[a]	54	17	63	nd	54	88	nd
18	6.2	41.9	1.6	8.5	89.3	98.0	5.5

*values with uncertainties less than 5%
[a] extraction H_2O-$CHCl_3$, data from ref. [9]
"nd" - not determined

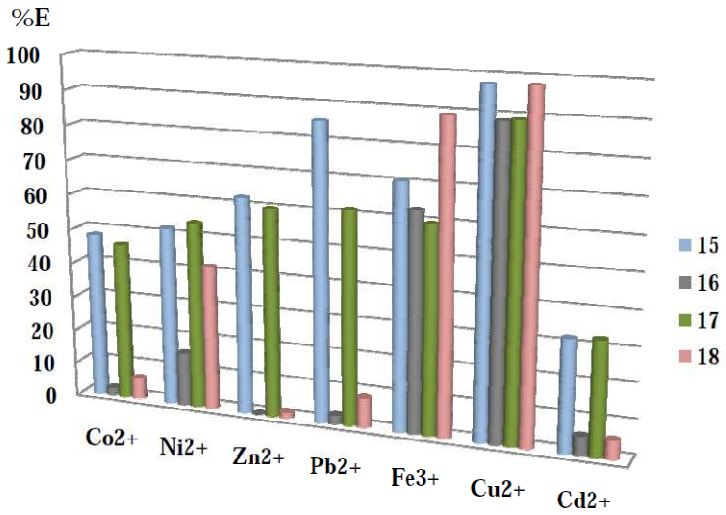


Figure III-32. Percentage extraction (%E) of metal nitrates with ligands **15-18**

It can be seen that ligands **15** and **17** unsubstituted on nitrogen atoms are better extractants for Co^{2+}, Ni^{2+}, Zn^{2+}, Pb^{2+} and Cd^{2+} ions than those having methyl groups on nitrogen atoms (ligands **16** and **18**). It was observed before by Dasaradhi et al. [34] that generally compounds bearing secondary hydroxamate functions are more efficient extractants than those with tertiary hydroxamate substituents. As suggested, the steric strain of the methyl groups eclipsing the chain can destabilise the conformation, in which the tertiary hydroxamate binds the metal ion making the secondary hydroxamic acid a superior extractant.

Almost quantitative extraction of Cu^{2+} was obtained for all ligands **15-18**.
It is commonly known that at pH = 5.4 the precipitation of iron takes place. In this case, the pH was lowered to 2.2 with HNO_3 and all the ligands (**15-18**) extracted Fe^{3+} efficiently.

The characteristic orange colour of the organic phase suggests the presence of iron complex with hydroxamate-compounds (**Figure III-33**).

Figure III-33. Characteristic orange colour of hydroxamate **15-18** complexes with Fe^{3+}, samples 1-4 and 0 correspond to the ligands **15-18** and to the blank experiment without the ligand, respectively

Extraction results with the ligand **17** were compared with the literature data [9] where chloroform was used instead of dichloromethane as the organic phase. It can be seen from **Table III-16** that the difference in percentage extraction of Co^{2+}, Zn^{2+}, Fe^{3+} and Cu^{2+} is no more than 8%, except for Ni^{2+} which was extracted significantly from water into dichloromethane (54.2%) and much less (17%) from water into chloroform [9].

3.4.2. Competitive liquid-liquid extraction studies

- *Competitive extraction of metal ions with ligand **15***
-

Pb^{2+} - Cd^{2+} mixture (**Figure III-34**)

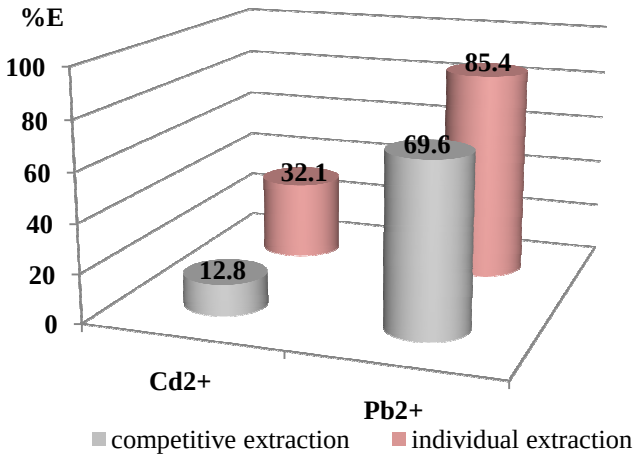


Figure III-34. Percentage extraction of Pb^{2+} and Cd^{2+} in individual and competitive extraction experiments with ligand **15**

It is a classical situation, when the percentage of the extraction decreases in the presence of the other cation in solution. Nevertheless, Pb^{2+} is extracted in almost 70% and quite good selectivity over Cd^{2+} can be seen.

Cu^{2+} - Zn^{2+} - Ni^{2+} mixture (**Figure III-35**)

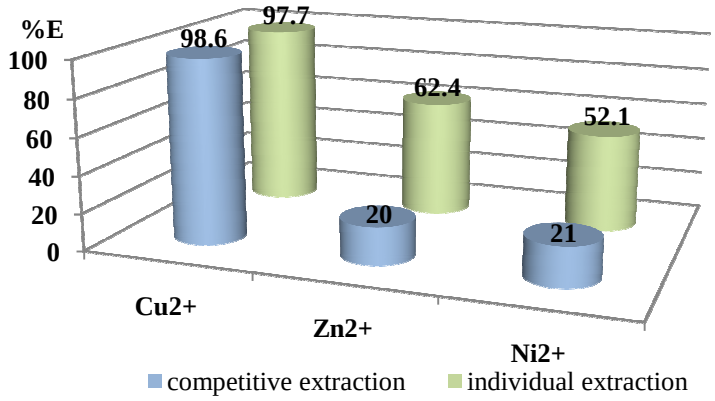


Figure III-35. Percentage extraction of Cu^{2+}, Zn^{2+} and Ni^{2+} in individual and competitive extraction experiments with ligand **15**

It can be seen that Cu^{2+} is still almost quantitatively extracted in the presence of Zn^{2+} and Ni^{2+} cations in solution. Significant decrease of extraction percentages of Zn^{2+} and Ni^{2+} can be noticed what gives the possibility to separate Cu^{2+} from the two other cations.

- *Competitive extraction of metal ions with ligand **16***

Pb^{2+} - Cd^{2+} mixture (**Figure III-36**)

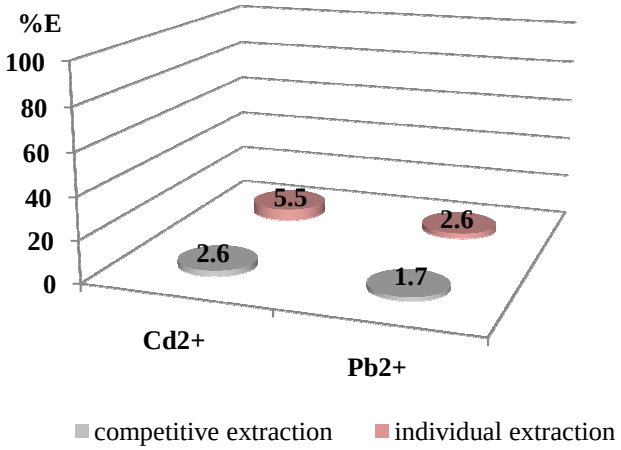


Figure III-36. Percentage extraction of Pb^{2+} and Cd^{2+} in individual and competitive extraction experiments with ligand **16**

The percentages of Pb^{2+} and Cd^{2+} extraction slightly decrease in the case of the two cations present together in solution. The competitive extraction confirmed weak extraction of Cd^{2+} and Pb^{2+} by ligand **16**.

Cu^{2+} - Zn^{2+} - Ni^{2+} mixture (**Figure III-37**)

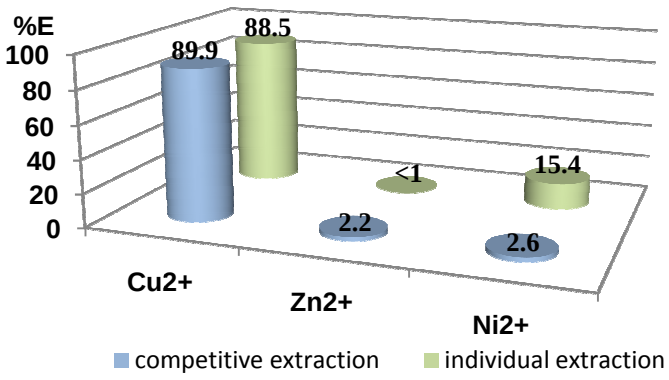


Figure III-37. Percentage extraction of Cu^{2+}, Zn^{2+} and Ni^{2+} in individual and competitive extraction experiments with ligand **16**

In the presence of Zn^{2+} and Ni^{2+}, Cu^{2+} is almost quantitatively extracted. This confirms the results of individual extraction experiments. Moreover, the percentage extraction of Ni^{2+} decreases. Therefore, ligand **16** could be successfully used in separation processes of Cu^{2+} from Zn^{2+} and Ni^{2+}, often present together.

- *Competitive extraction of metal ions with ligand **17***

Pb^{2+} - Cd^{2+} mixture (**Figure III-38**)

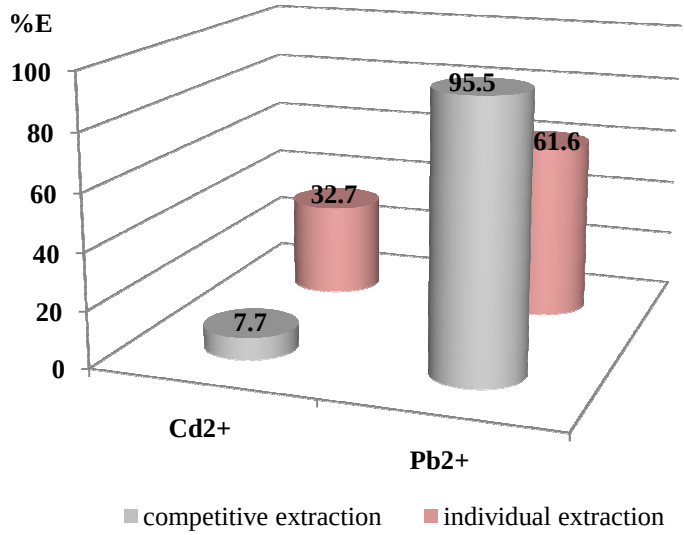


Figure III-38. Percentage extraction of Pb^{2+} and Cd^{2+} in individual and competitive extraction experiments with ligand **17**

Interesting results were obtained for Pb^{2+} extraction in the presence of Cd^{2+} in solution with ligand **17**. Pb^{2+} is almost quantitatively extracted when present with Cd^{2+} and showed higher percentage extraction than for individual experiments. In contrary, the percentage of Cd^{2+} extraction decreases compared to the individual extraction. These results are very important for the removal of Pb^{2+} and its separation from other toxic metals like Cd^{2+}.

Although a synergistic effect is more ascribed to the situation where two extractants are present together, it can be assumed, in a way, that synergistic effect occurred in this case. It is evident that the presence of Cd^{2+} tends to increase the percentage extraction of Pb^{2+}. This may be explained by a "salting effect" due the presence of an excess of nitrates anions in competitive experiments compared to individual ones, which "pushes" the transfert of Pb^{2+} from the aqueous to the organic phase. Nevertheless, this situation was not observed with the other ligands. Another explanation could be that the complexation kinetics is faster for Pb^{2+}

than for Cd^{2+}. In this case all the molecules of ligand **17** would be occupied by the complex formation with Pb^{2+}.

Cu^{2+} - Zn^{2+} - Ni^{2+} mixture (**Figure III-39**)

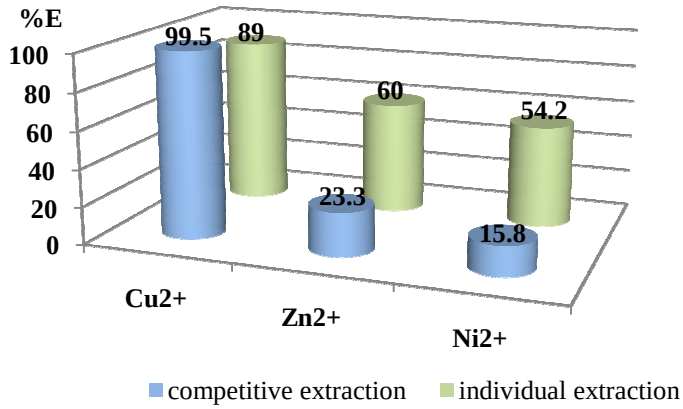


Figure III-39. Percentage extraction of Cu^{2+}, Zn^{2+} and Ni^{2+} in individual and competitive extraction experiments with ligand **17**

An increase of Cu^{2+} extraction (about 10%) was observed in the case of mixed solutions containing Cu^{2+}, Zn^{2+} and Ni^{2+} together. Moreover, the percentages of Zn^{2+} and Ni^{2+} decrease 3 times compared to the individual extraction.

- *Competitive extraction of metal ions with ligand **18***

Pb^{2+} - Cd^{2+} mixture (**Figure III-40**)

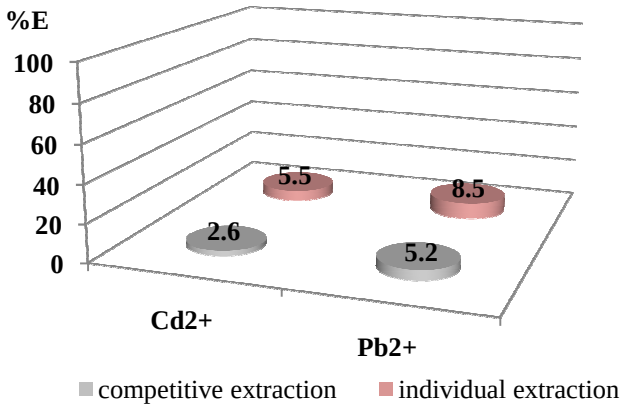


Figure III-40. Percentage extraction of Pb^{2+} and Cd^{2+} in individual and competitive extraction experiments with ligand **18**

An extraction profile similar to that of ligand **16** was observed for **18**. The percentages of Pb^{2+} and Cd^{2+} extraction slightly decrease in the case of the two cations present together in solution and the weak extraction of Cd^{2+} and Pb^{2+} by the ligand **18** was confirmed.

Cu^{2+} - Zn^{2+} - Ni^{2+} mixture (**Figure III-41**)

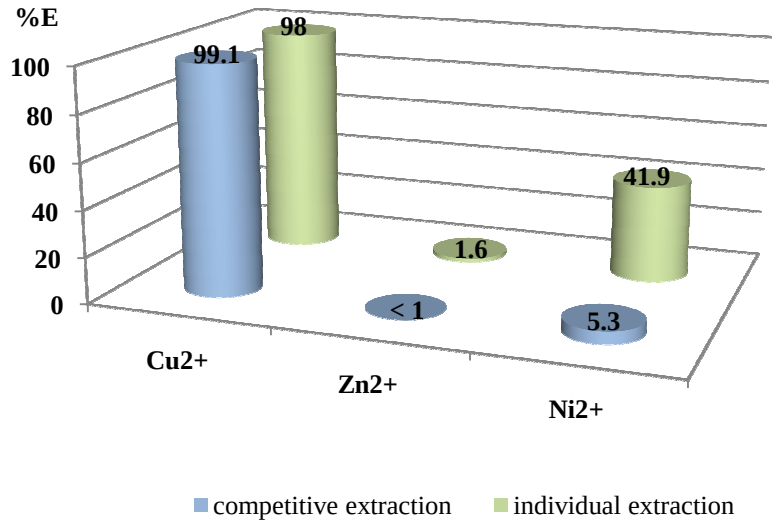


Figure III-41. Percentage extraction of Cu^{2+}, Zn^{2+} and Ni^{2+} in individual and competitive extraction experiments with ligand **18**

Likewise ligand **16**, ligand **18** shows very good selectivity for Cu^{2+} over Zn^{2+} and Ni^{2+} when they are present together. Cu^{2+} still remains extracted almost quantitatively, whereas the percentage of Ni^{2+} extraction decreases significantly.

4. Conclusions

In this chapter, the binding properties of the four groups of calix[4]arene derivatives synthesised (thioamides, amides, hydroxamates and hydroxamic acids) are presented. Eight thioamides (**1T-3T, 5T-9T**) were studied and their binding properties were compared to those obtained with the corresponding amides (**1A-3A, 5A-9A**).

The extraction properties of thioamide derivatives were studied towards representatives of the series of alkali (Na^{+}), alkaline earth (Ca^{2+}) lanthanides (Gd^{3+}), heavy metal (Ag^{+}, Cd^{2+} and Pb^{2+}) and transition (Zn^{2+} and Cu^{2+}) cations. Compounds **1A** and **1T**,

partly studied before, were also synthesised and tested with all cations studied in our experimental conditions. The results showed that all these ligands quantitatively extract Ag^+ but they are poor extractants of alkali, alkaline earth and lanthanide cations. The percentages of extraction of Pb^{2+} and Cu^{2+} strongly depend on the nature of the thioamide functions in these compounds. The presence of secondary thioamides strongly reduces the extraction efficiency.

The corresponding tertiary amide derivatives are very effective for "hard" cations as Na^+ and Ca^{2+} but also for "softer" cations such as Ag^+, Cd^{2+} and Pb^{2+}. The secondary amide derivatives show no affinity for all cations studied, including Ag^+. The low extraction efficiency of secondary amide and thioamide derivatives could be related to the existence of intramolecular hydrogen bonds between NH groups and oxygen atoms or sulphur. The extraction results confirmed that the replacement of the oxygen atoms of the tertiary amides by sulphur atoms leads to compounds highly selective for Ag^+ and Pb^{2+} towards the alkali and alkaline earth metal cations.

Studies of complexation by UV spectrophotometry in acetonitrile confirmed the high affinity of tertiary thioamides derivatives for heavy metal cations (Ag^+, Cd^{2+} and Pb^{2+}) and Cu^{2+}. Upon addition of these cations, strong variations of the ligand spectrum were observed, whereas they remained practically unchanged upon addition of sodium salts. Their interpretation showed the formation of species whose stoichiometry and stability depended on the cation. The formation of ML + M_2L complexes was confirmed by potentiometry and microcalorimetry in the case of Ag^+, which formed with all ligands the most stable complexes. Additional microcalorimetric titrations were performed with the ligand **5T** against Cd^{2+}, Pb^{2+} and Cu^{2+} cations. Exothermic heat effect was observed in the case of Cd^{2+} and Cu^{2+}, whereas in our conditions, very little heat effect was detected with Pb^{2+} cations.
The system **5T**/Cu^{2+} showed a particularly high favourable enthalpy stabilisation and strongly negative, unfavourable entropy term of the complex formed.

We were able to obtain two X-ray crystal structures of Pb^{2+} complexes with ligands **5T** and **9T**, presented for the first time. It was shown that the metal cation is bound to four phenolic oxygen atoms and to two and four sulphur thiocarbonyl atoms, respectively.

The interactions with Pb^{2+} and Ag^+ were studied by ^{1}H NMR technique with the ligand **5T**. Significant chemical shifts in ligands spectra were noted indicating complex formation. Additionally, complexes of Pb^{2+} with secondary thioamides **7T** and **9T** were prepared and characterised by ^{1}H NMR. Notable spectral changes were shown what proved

the interactions of secondary thioamides with Pb^{2+} cations, which could not be achieved by other techniques (extraction, UV spectrophotometry).

Studies of complexation by UV spectrophotometry in methanol and acetonitrile confirmed the strong affinity of amide derivatives for alkali metal cations such as Na^{+}, but also for the softer Ag^{+}, Cd^{2+} and Pb^{2+} cations. Very high stability constants were obtained for complexes of those cations and lower for Cu^{2+}, what is in the accordance with extraction results. The secondary amides showed quite stable complexes with Pb^{2+}, although not as stable as for the tertiary amides. The complexation of Ag^{+} cation was also followed by potentiometry with a silver electrode.

Hydroxamate derivatives bearing NH groups (**10-13**) likewise the secondary amides are weak extractants. It was also difficult to determine the stability constants of complexes formed by spectrophotometry because of very small spectral changes of the ligand spectrum upon metal ions additions. In contrast, the hydroxamate derivative substituted on the N and O atoms (**14**) showed significant percentage of extraction, especially for Na^{+}, Pb^{2+} and Ag^{+}, although lower than with the tertiary amides. For this ligand, stability constants of Na^{+}, Pb^{2+}, Cd^{2+} and Cu^{2+} complexes were determined by UV absorption spectrophotometry in methanol. The complexation of Ag^{+} cation was followed by potentiometry with a silver electrode.

Calixarene-hydroxamic acids (**15-18**) were tested in individual extraction experiments of heavy (Cd^{2+}, Pb^{2+}) and transition (Co^{2+}, Ni^{2+}, Zn^{2+}, Fe^{3+}, Cu^{2+}) metal ions and in competitive experiments which were used to evaluate the possibility of selective separation. The individual extraction results showed that all these ligands extracted Fe^{3+} and Cu^{2+} very efficiently (almost quantitatively in the case of Cu^{2+}). With ligands **15** and **18**, the percentage of Pb^{2+} extraction was 85 and 62%, respectively. In the competitive extraction, the extraction percentage generally decreased in the presence of another cation in solution. Particularly interesting results were obtained with ligand **18** for the extraction of Pb^{2+} in the presence of Cd^{2+}. Under these conditions, Pb^{2+} is almost quantitatively extracted and the extraction percentage is higher than for individual experiments. In contrast, the percentage extraction of Cd^{2+} is lowered compared to the individual extraction data. These results are very important in the context of separation and removal of Pb^{2+} from other toxic metals such as Cd^{2+}. In addition, the use of these ligands allows to separate Cu^{2+} and Zn^{2+} which are often present together.

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CHAPTER IV:

STUDIES OF CATION-IONOPHORE INTERACTION IN ION-SELECTIVE MEMBRANE ELECTRODES

1. Ion-selective electrodes, potentiometric sensors

Ion Selective Electrodes (ISEs) become increasingly important in the field of chemical sensors. The IUPAC Commission on General Aspects of Analytical Chemistry has defined chemical sensors as follows:

"A chemical sensor is a device that transforms chemical information, ranging from the concentration of a specific sample component to total compostition analysis, into a useful analytical signal" [1].

The first ion selective electrode constructed in 1909 by Z. Klemensiewicz and F. Haber was the glass electrode, used for pH measurements (concentration of hydrogen ions) [2]. Since that time, the progress in ion selective electrodes development was enormous. In 1967, W. Simon and Z. Stefanac proposed an electrode specific for potassium ions, in which the ion carrier, named ionophore in 1965 by B. C. Pressman [3], was the natural macrocyclic antibiotic valinomycin [4] (**Figure IV-1**).

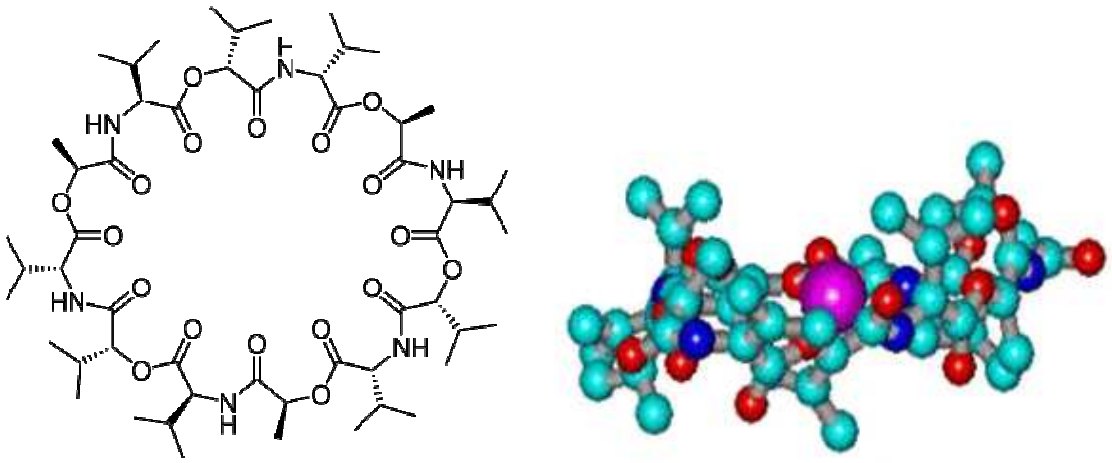


Figure IV-1. Chemical structure of valinomycin and its complex with potassium cation

It was the beginning of the electrodes based on polyvinyl chloride (PCV) membranes containing an ionophore and a plasticizer. Nowadays, ion selective electrodes play an important role as an analytical tool especially in biomedical analysis but there is also a new trend to use them in monitoring of toxic heavy metal ions in the environment.

The number of suitable ionophores is growing each year. Functionalised calix[4]arenes find an important place among them [5-7].

1.1. Measuring cell

The potentiometric cell consists of an ion selective electrode and a reference electrode as presented in **Figure IV-2**. Both electrodes are immersed in the sample solution.

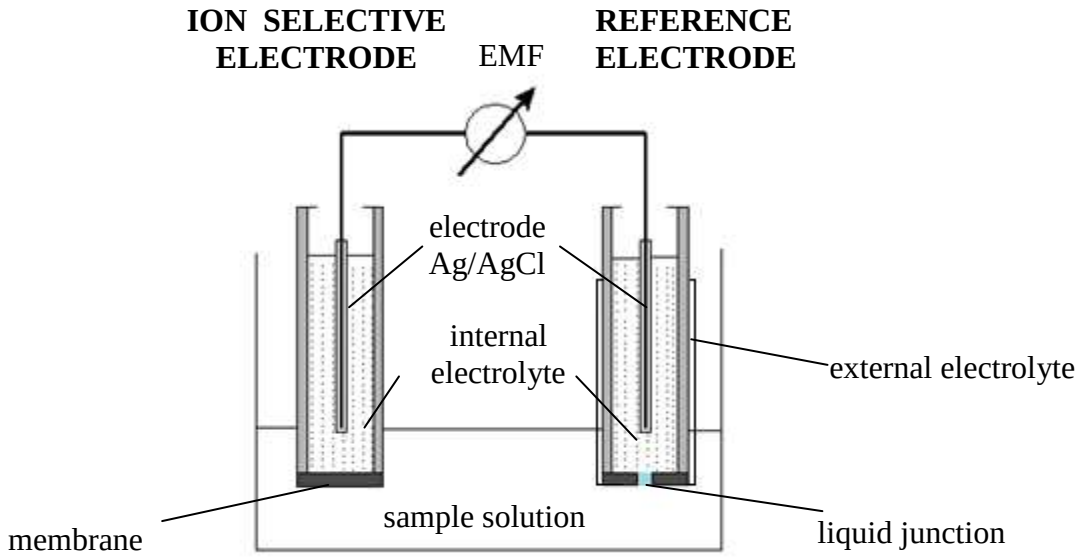
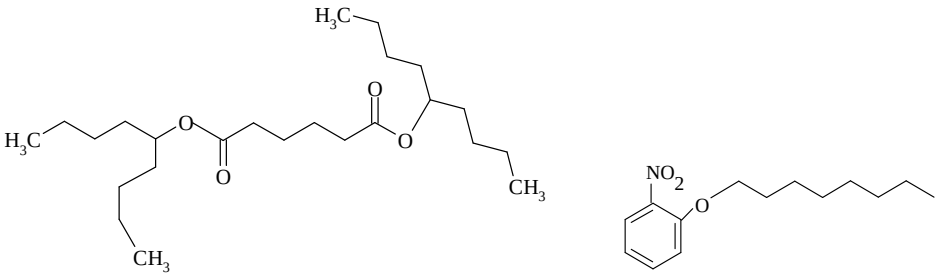


Figure IV-2. Scheme of the potentiometric cell

The reference electrode has an external jacket which plays a role of electrolyte bridge containing electrolyte solution which does not interfer in the analysis.

1.2. Electrode membrane

The electrode membrane based on a polymer (usually polyvinyl chloride (PCV)) and a plasticizer is a non-polar phase acting as a barrier between the internal electrolyte and the measured sample solution. The most important component of the membrane is an ion carrier, called ionophore. The essential parameter characterising a good ionophore, is its lipophicility, expressed as log P, determining the ionophore stability in the membrane. A plasticizer provides the elasticity of the membrane as well as the ionophore mobility within the membrane. In this work, two different plasticizers were used: the ester type – bis(1-butylpentyl) adipate (BBPA) and the more polar *o*-nitrophenyl-octyl ether (NPOE). Their chemical structures are depicted in **Figure IV-3**.



a) **b)**

Figure IV-3. Chemical structures of the plasticizers used: **a)** - bis(1-butylpentyl) adipate (BBPA); **b)** - *o*-nitrophenyl-octyl ether (NPOE)

Another additive, a lipophilic salt, is usually added in very small quantity. Its role is to prevent anions extraction from the sample solution to the membrane and thus avoid the lost of the membrane selectivity and its working as an ion – exchanger. The lipophilic salt used in this work was potassium tetrakis-(*p*-chlorophenyl)borate (KT*p*ClPB) presented in **Figure IV-4**.

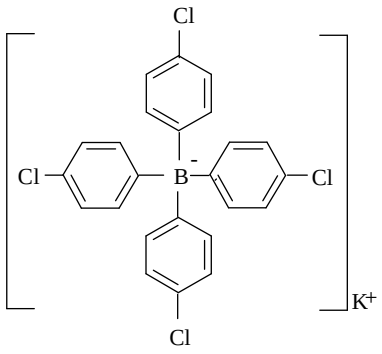


Figure IV-4. Chemical structure of potassium tetrakis-(*p*-chlorophenyl)borate (KT*p*ClPB)

1.3. Electrode response

The scheme of the potentiometric cell can be also presented as follows:

ION SELECTIVE ELECTRODE REFERENCE ELECTRODE

Ag / AgCl | internal electrolyte | membrane | sample | internal electrolyte | KCl | AgCl / Ag

E_1 E_2 E_M E_D E_3 E_4

where:

E_D, E_M are the diffusion and the membrane potential, respectively

$E_1 – E_4$ are interfacial potentials

For each electrode $E_1 – E_4$ are constants and do not depend on the ions type or their concentration in the sample solution. The diffusion potential E_D is constant in defined conditions or is so small that it can be neglected.

Electrode response is based on the ion transfer from the sample solution into the membrane, which provides the potential difference on both sides of the membrane, what is called membrane potential E_M.

We can describe the membrane electrode response as:

$$E = E' + E_M \qquad \text{(IV-1)}$$

With $$E' = E_1 + E_2 + E_3 + E_4 + E_D$$

The measured cell EMF (electromotive force) depends on the type of the ions and their concentration in the sample and it can be described by the Nikolsky-Eisenman equation:

$$EMF = E^0 + \frac{2.3 \cdot RT}{z_A \cdot F} log\left[a_A + \sum K_{A,B}^{pot} \cdot a_B^{z_A/z_B}\right] \qquad \text{(IV-2)}$$

where:

E^0 [mV] is the standard potential of the electrode,

R is the gas constant (8.31 $J \cdot K^{-1} \cdot mol^{-1}$),

T is the temperature [K],

F is the Faraday constant (96485 $C \cdot mol^{-1}$),

a_A is the activity of the primary ion (A) and z_A its charge,

$\sum K_{A,B}^{pot}$ is the selectivity coefficient,

a_B is the activity of the interfering ion (B) and z_B its charge.

1.4. Characteristics and parameters of the electrodes

There are several parameters describing the electrode characteristic. The definitions were given by IUPAC in 1975 [8] and later in 1994 [9].

The electrode characteristic is defined as “a plot of the cell EMF (electromotive force measured as ion-selective electrode potential minus external reference electrode potential) of

a given ion-selective electrode cell assembly *vs.* the logarithm of the single ionic activity (concentration) of a given species" [8, 9]. It is presented in **Figure IV-5**.

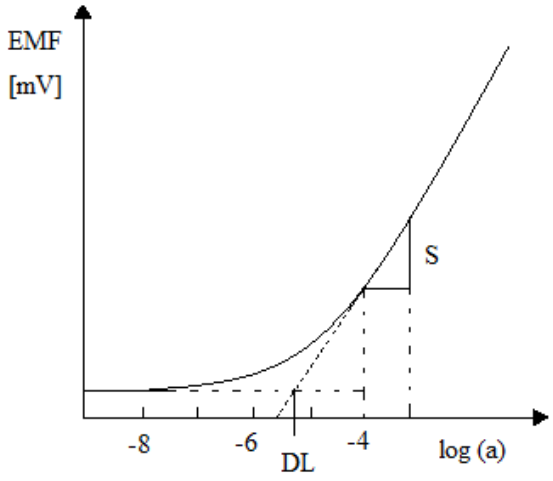


Figure IV-5. Cation-selective electrode characteristic

1.4.1. Slope

The potentiometric signal has a linear dependence of the ion activity logarithm in a certain range of concentration. It can be described by the Nernst equation:

$$EMF = E^0 + \frac{2.3 \cdot RT}{z_A \cdot F} \log(a_A) = E^0 + Slog(a_A) \qquad \text{(IV-3)}$$

Nernstian response occurs when the slope S of the linear part is equal to 59.16 mV for monovalent cations and to 29.58 mV for divalent cations.

1.4.2. Detection Limit (DL)

Detection limit is determined from the cross point of the lines fitted to the linear segments of the EMF *vs.* log (a) curve, where (a) denotes the single ion activity of the primary ion [8, 9]. The determination of the detection limit is depicted in **Figure IV-5**.

1.4.3. Potentiometric Selectivity Coefficient $K_{A,B}^{pot}$

Potentiometric selectivity coefficient defines the ability of an ion-selective electrode to distinguish a particular ion from the others [8, 9]. The value of $K_{A,B}^{pot}$ is defined by the Nicolsky-Eisenman equation (IV-2). The smaller selectivity coefficient, the greater the electrode preference for the primary ion. For example, $K_{A,B}^{pot} = 10^{-3}$ means, that the primary ion (A) of 1000 times lower activity than the interfering ion (B) can generate the same measured cell voltage.

There are several methods for determining the selectivity coefficients recommended by IUPAC.

- *Fixed interference method (FIM)[8-11]*

The EMF of a cell comprising an ion-selective electrode and a reference electrode (ISE cell) is measured with solutions of constant activity of interfering ion, a_B, and varying activity of the primary ion, a_A. The EMF values obtained are plotted *vs*. the logarithm of a_A. The intersection of the extrapolation of the linear portions of this plot indicates the value of a_A which is to be used to calculate $K_{A,B}^{pot}$ from the Nicolsky-Eisenman equation:

$$logK_{A,B}^{pot} = loga_A - \frac{z_A}{z_B} loga_B \qquad \text{(IV-4)}$$

- *Separate solution method (SSM) ($a_A = a_B$)[9]*

The EMF of a cell comprising an ion-selective electrode and a reference electrode (ISE cell) is measured with each of two separate solutions, one containing only the ion A of the activity a_A, the other containing only the ion B at the same activity $a_B = a_A$. If the measured values are E_A and E_B, respectively, the value of $K_{A,B}^{pot}$ may be calculated from the equation:

$$logK_{A,B}^{pot} = \frac{(E_B - E_A) \cdot z_A \cdot F}{2.303 \cdot RT} + \left(1 - \frac{z_A}{z_B}\right) \cdot loga_A \qquad \text{(IV-5)}$$

Actually, IUPAC recommends using SSM method to calculate the selectivity coefficients by extrapolation of the linear segment of the electrode characteristics in the

primary ion until log(a_A) = 0 [10, 11]. The values of potentials E_A and E_B can be compared and the selectivity coefficients determined:

$$logK_{A,B}^{pot} = \frac{(E_B^0 - E_A^0)}{S} \quad \text{(IV-6)}$$

- *Separate solution method (SSM) II ($E_A = E_B$)[10]*

The concentrations of a cell comprising an ion-selective electrode and a reference electrode (ISE cell) are adjusted with each of two separate solutions, one containing only the ion A of the activity a_A, the other containing only the ion B of the activity as high as required to achieve the same measured cell voltage. From any pair of activities a_A and a_B giving the same cell voltage, the value of $K_{A,B}^{pot}$ may be calculated from the equation:

$$logK_{A,B}^{pot} = loga_A - \frac{z_A}{z_B} loga_B \quad \text{(IV-7)}$$

- *Matched potential method (MPM)[12]*

In this method, the potentiometric selectivity coefficient is defined as the activity ratio of primary and interfering ions that give the same potential change under identical conditions. At first, a known activity (a'_A) of the primary ion solution is added into a reference solution that contains fixed activity (a_A) of primary ions, and the corresponding potential change (ΔE) is recorded. Next, a solution of an interfering ion is added to the reference solution until the same potential change (ΔE) is recorded. The change in potential produced at the constant background of the primary ion must be the same in both cases.

$$logK_{A,B}^{pot} = log\frac{(a'_A - a_A)}{a_B} \quad \text{(IV-8)}$$

This method does not depend on the Nicolsky-Eisenman equation and was introduced by V. P. Y. Gadzekpo and G. D. Christian [13].

2. Experimental part

2.1. Chemicals and materials

Poly(vinylchloride) (PVC, high molecular fraction), *o*-nitrophenyl octyl ether (NPOE), bis(1-butylpentyl)adipate (BBPA) and lipophilic salt, potassium tetrakis(*p*-chlorophenyl)borate (KT*p*ClPB), were purchased from Fluka (Selectophore). Tetrahydrofuran (THF) p.a. (from POCh) was dried and freshly distilled before use. All aqueous salts solutions: LiCl, NaCl, KCl, CsCl, $MgCl_2$, $CaCl_2$, $SrCl_2$, $BaCl_2$, $MnCl_2$, $CoCl_2$, $NiCl_2$, $Cu(NO_3)_2$, $ZnCl_2$, $Pb(NO_3)_2$, $CdCl_2$, (POCh) (all p.a. grade) were prepared using ultra-pure water from Hydro-lab (RO) Station (conductivity below 0.1 μS cm^{-1}). Ionophores used were *p-tert*-butylcalix[4]arene-thioamides **1T-9T** and *p-tert*-butylcalix[4]arene-hydroxamates **10-13**.

2.2. Membrane and electrode preparation and EMF measurements

The membrane composition was the same for each electrode and consisted of 1.64 wt % of ionophore (about 3 mg), 32.7 wt % PVC (60 mg), 65.4 wt % NPOE) or BBPA (120 mg) and 0.22 wt % KT*p*ClPB (about 0.4 mg). All these components of total weight of about 184 mg were dissolved in 1.5 ml of dried and freshly distilled THF. The solution was poured into a glass ring of 24 mm in diameter. After overnight of slow solvent evaporation, several small membranes of 7 mm in diameter were cut from the mother membranes and incorporated into Ag/AgCl electrodes bodies of IS 561 type (Moeller S. A. Zurich, Switzerland). These were filled up with an internal electrolyte : $Pb(NO_3)_2$ 10^{-3} mol L^{-1}, Na_2EDTA 5×10^{-2} mol L^{-1}. Three electrodes of the same kind were made. As a reference, a double-junction electrode Eurosensor EAgClK – 312 was used with 1mol L^{-1} NH_4NO_3 solution in the bridge cell. The measurements were carried out at 20°C using a 16-channel LAWSON LAB potentiometer (16 EMF, USA) and the cell of the following type:

Ag/AgCl|internal electrolyte|membrane|sample solution|1mol L^{-1} NH_4NO_3|1mol L^{-1} KCl|AgCl /Ag

2.3. Electrode characteristics and selectivity coefficients

The potentiometric measurements of heavy and transition metal ions were performed at pH = 4, adjusted with 10^{-4} mol L^{-1} HNO_3. Activity coefficients were estimated using the semi empirical Pitzer's model which describes the non ideal behavior of the electrolytes up to high concentrations [14-17]. The single ion acitivities were calculated taking into account the complexation with Cl^-, NO_3^- and OH^- (hydrolysis) [18]. The selectivity coefficients were determined by the Separate Solution Method (SSM) according to the latest recommendation of IUPAC [10, 11]. The linear range of the characteristics were extrapolated to the activity of 1. In order to obtain unbiased values of selectivity coefficients, the calibration of the electrodes was performed for various cations, starting from the most discriminating. The selectivity coefficients were calculated according to the equation:

$$logK_{Pb,B}^{pot} = \frac{(E_B^0 - E_{Pb}^0)}{S_{Pb}} \quad \text{(IV-6)}$$

where: S_{Pb} corresponds to the experimental slope of electrodes in primary Pb^{2+} cation solution

B is ascribed to the interfering ion

3. Results and discussion

3.1. Calix[4]arene-thioamides

p-tert-Butylcalix[4]arene-thioamides synthesised in this work (**1T-9T**) were used as ionophores in the membranes of ion selective electrodes.

The ionophores based on tertiary thioamides **1T-6T** and a representative of the secondary thioamides-based ionophore **7T** were tested in membranes containing two different plasticizers: BBPA (log P = 10.2) and NPOE (log P = 5.6). The properties of the studied electrodes, their characteristics and linear range are given in **Table IV-1**.

The results show that the studied calix[4]arene-thioamides act as Pb(II)-selective ionophores. The best linear response for Pb^{2+} is obtained with the tertiary thioamide **5T** in both membranes, PVC/NPOE and PVC/BBPA. The electrode slope was close to Nernstian value: 29.2 mV/dec and 27.5 mV/dec in BBPA and in NPOE, respectively within a wide linear range (6-1 and 6-2). The electrodes responded also to Cu^{2+}, Cd^{2+} and Na^+ ions within a wide range of activity.

Table IV-1. Characteristics of the studied ion-selective electrodes with calix[4]arene-thioamides (**1T-9T**)

Ionophore number	Primary cation	Slope S ± σ* [mV/dec]	Linear range LR - log a	Plasticizer
1T[a]	**Pb^{2+}**	32.6 ± 2.0	6-1	BBPA
	Cu^{2+}	32.0 ± 0.9	4-1	
	Pb^{2+}	36.7 ± 1.4	6-1	NPOE
	Cu^{2+}	28.2 ± 1.2	4-1	
2T	**Pb^{2+}**	36.4 ± 0.8	6-3	BBPA
	Pb^{2+}	38.9 ± 0.3	7-2	NPOE
3T	**Pb^{2+}**	40.9 ± 0.7	6-3	BBPA
	Pb^{2+}	30.9 ± 0.7	6-2	NPOE
4T	**Pb^{2+}**	30.8 ± 0.9	6-3	BBPA
	Pb^{2+}	30.1 ± 0.6	6-3	NPOE
5T[b]	**Pb^{2+}**	29.2 ± 1.7	6-1	BBPA
	Cu^{2+}	57.6 ± 1.8	6-2	
	Cd^{2+}	23.4 ± 1.8	6-2.5	
	Na^{+}	53.3 ± 0.77	5-1	
	Pb^{2+}	27.5 ± 1.7	6-2	NPOE
	Cu^{2+}	57.7 ± 2.5	6-1	
	Cd^{2+}	31.2 ± 1.2	6-2	
	Na^{+}	49.9 ± 0.82	5-1	
6T[a]	**Pb^{2+}**	36.5 ± 1.1	5-1	BBPA
	Cu^{2+}	33.2 ± 1.8	5-1	
	Pb^{2+}	29.4 ± 2.1	5-1	NPOE
	Cu^{2+}	32.2 ± 1.9	6-3	
7T	**Pb^{2+}**	31.2 ± 0.7	5-3	BBPA
	Pb^{2+}	27.5 ± 0.2	6-2	NPOE
8T[a]	**Pb^{2+}**	25.1 ± 1.1	5-1	NPOE
	Cu^{2+}	36.6 ± 2.2	6-1	
9T[a]	**Pb^{2+}**	24.4 ± 1.2	4-1	NPOE
	Cu^{2+}	32.5 ± 1.9	6-1	

Composition of the internal electrolyte: $Pb(NO_3)_2$ 10^{-3} mol L^{-1}, Na_2EDTA $5x10^{-2}$ mol L^{-1};
* Standard deviation of at least three independent measurements
[a] data published in [19]
[b] data published in [20]

Figure IV-6 presents the potentiometric response to Pb^{2+}, Na^{+}, Cu^{2+} and Cd^{2+} of the electrodes with ionophore **5T** in PVC/NPOE membrane. These electrodes showed close to Nernstian response with all these cations excepted with Cu^{2+} for which a typical value for monovalent ion was found in both membranes (BBPA and NPOE): 57.6 mV/dec and 57.7 mV/dec, respectively. This behavior has already been reported for other calixarene-thioamide

ionophore and suggests that anions in the sample may be associated in the membrane with the Cu^{2+}- ionophore complex leading to an increased slope [21]. However, after 2-3 weeks, the electrode slope for Cu^{2+} cations decreased to about 45 mV/dec, probably as a result of Pb^{2+} uptaking within the membrane.

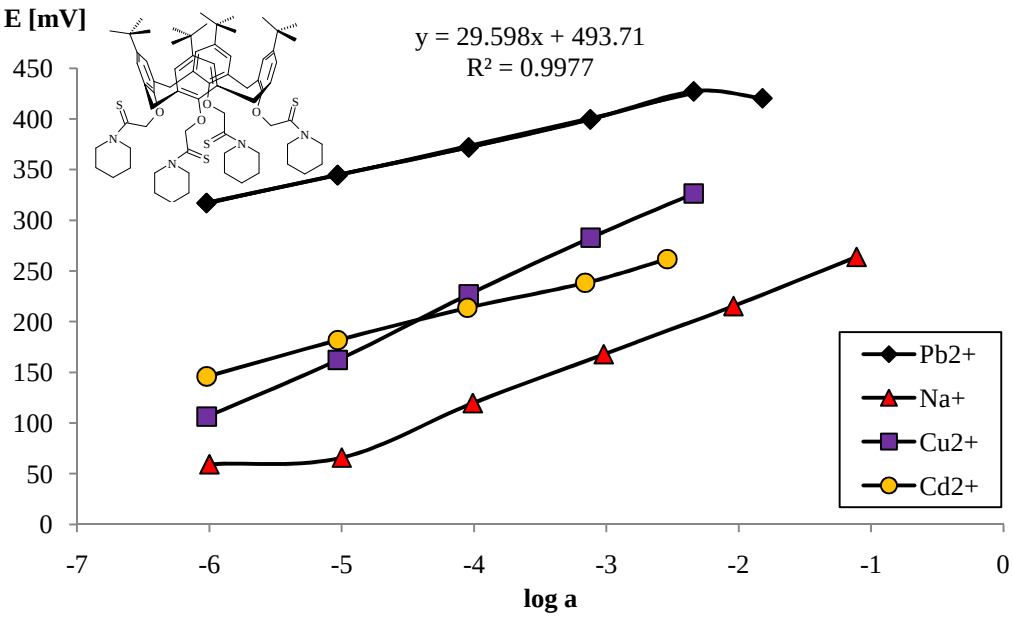


Figure IV-6. Responses of the electrodes containing ionophore **5T** in Pb^{2+}, Na^{+}, Cu^{2+} and Cd^{2+} solutions (PVC/NPOE membrane) [20]

The electrodes with the structurally similar ionophore **6T** showed almost theoretical Nernstian slope for Pb^{2+} ions in PVC/NPOE membranes, whereas in PVC/BBPA membranes a slightly over Nernstian slope was obtained. Slightly over Nernstian response for Cu^{2+} cations in a wide range of activity was also observed in both plasticizers.

It is interesting to compare the characteristics of the electrodes containing ionophores **5T** and **6T** appended with tertiary cyclic thioamides to those obtained with ionophores **1T-4T** having linear substituents. The electrodes with ionophore **1T** responded to Pb^{2+} ions in a wide range of activity (6-1), similarly to electrodes with ionophore **5T** and **6T** but with slightly over Nernstian slope. The example of the electrode characteristics for Pb^{2+} with ionophores **1T** and **6T** are presented in **Figure IV-7**.

The electrodes with ionophores **2T-4T** responded to Pb^{2+} within shorter linear range.

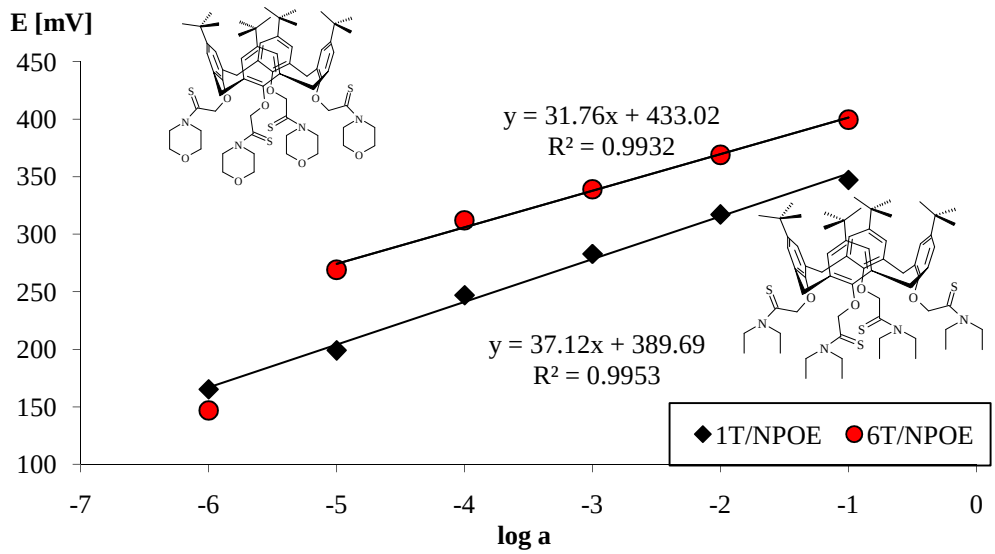


Figure IV-7. Responses of the electrodes containing ionophores **1T** and **6T** in Pb^{2+} solution (PVC/NPOE membrane) [19]

Among secondary thioamides (**7T-9T**), the electrodes with ionophore **7T** showed near-Nernstian behavior for Pb^{2+} in both plasticizers. However, the linear range was larger for PVC/NPOE membrane electrodes than for PVC/BBPA plasticized membranes. Electrodes with incorporated ionophores **8T** and **9T** gave slightly under-Nernstian response (S = 25.1 and 24.4, respectively). These two electrodes responded also to Cu^{2+} cations in a wide range of activity (6-1).

The lifetime of the electrodes based on secondary thioamides is much shorter (only about 2-3 weeks) than that of electrodes based on the tertiary thioamides which were stable after at least 2-3 months. The electrode characteristic with ionophore **9T** in Pb^{2+} solution in the first 3 days and after 10 days is shown in **Figure IV-8**.

Generally, better characteristics for Pb^{2+} electrodes were observed for PVC/NPOE membranes in agreement with the results reported earlier showing that NPOE is preferred for Pb-sensors, whereas BBPA seems to be the best plasticizer for Na^+ or Li^+ sensors [22].

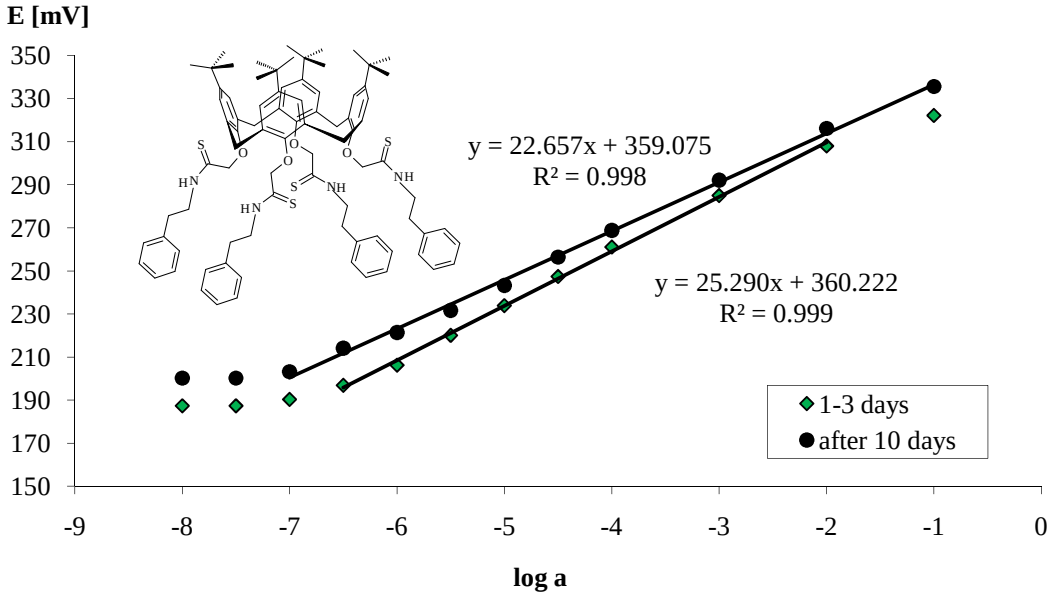


Figure IV-8. Responses of the electrodes containing ionophore **9T** in Pb^{2+} solution in the first 3 days and after 10 days (PVC/NPOE membrane) [19].

The potentiometric selectivity coefficients are shown in **Table IV-2** and illustrated in the diagrams presented in **Figure IV-9** (PVC/NPOE membrane) and in **Figure IV-10** (PVC/BBPA membrane). The selectivity coefficients were also determined for PVC/BBPA and PVC/NPOE electrodes membranes without ionophore in the same experimental conditions to reveal cations affinity to the tested plasticizers.

Analysing the diagram of selectivity coefficients determined for PVC/NPOE membrane (**Figure IV-9**), it can be seen that ionophores **5T** and **6T** appended with tertiary cyclic thioamide moieties are much more selective for Pb^{2+} than those possessing tertiary linear substituents, ionophores **1T-4T**. The best selectivity coefficients were obtained with ionophore **5T**. The results show that the first and second groups of cations are very well discriminated ($logK_{Pb,B}^{pot} \leq -6.25$) in PVC/NPOE membrane.

Although Cu^{2+} interfered the most, one should take into account the fact that the electrode response to Cu^{2+} cations was unusually "monovalent" which results in bad selectivity coefficient. However, **Figure IV-6** shows quite good Pb^{2+}/Cu^{2+} selectivity estimated by the gap between the electrode responses to Pb^{2+} and Cu^{2+} ions.

Good selectivity coefficients were also obtained with incorporated ionophore **6T**, structurally similar to ionophore **5T**. Here, the most interfering ions were Na^{+} and Cu^{2+}, but they were, nevertheless, quite well discriminated ($logK_{Pb,B}^{pot} \leq -3.3$).

The ionophore **1T** shows the least good selectivity coefficients for Pb^{2+} over all cations studied. With such a low selectivity, this compound cannot be selected as potential ionophore for the detection of Pb^{2+} in real samples.

The selectivity of the other ionophores appended with linear substituents **2T-4T**, the selectivity coefficients for Pb^{2+} over the other cations were slightly better than those obtained for ionophore **1T**. Nevertheless, no particular dependence between the ligand structure **2T-4T** and their ionophoric properties can be noticed. There is no doubt, however, that ionophores with cyclic thioamide substituents **5T** and **6T** are more selective than ionophores **1T-4T** (except **5T**, when dealing with the selectivity over Cu^{2}).

The electrodes containing ionophores **7T-9T** showed better selectivity than those containing **1T-4T** (apart from the selectivity over Cs^{+} and Cu^{2+}, which are the most interfering ions). Quite satisfying Pb^{2+} over Na^{+} selectivity was obtained with those electrodes ($logK_{Pb,Na}^{pot} \leq -3.19$).

As in PVC/NPOE membranes, the selectivity coefficients obtained in PVC/BBPA membranes based on ionophores **5T** and **6T** are smaller than those determined with electrodes containing ionophores **1T-4T** (**Figure IV-10**). Those results show that the role of plasticizer should not be negleted, but the behavior of the electrode depends mainly on the properties of the ionophore.

This might be explained by the good flexibility of linear substituents which can adjust to the cation size which is not the case for the rigid cyclic moieties.

It can be seen that generally better selectivity coefficients were obtained with PVC/NPOE membranes than with a PVC/BBPA membranes. However, better Pb^{2+}/Cd^{2+} selectivity coefficients were obtained in PVC/BBPA membrane with tertiary thioamides as ionophores. That suggests stronger affinity of cadmium for NPOE than for BBPA plasticizer, which is confirmed by the Pb^{2+}/Cd^{2+} selectivity coefficient obtained for the PCV/BBPA electrode without ionophore. This behavior is not observed for the electrode containing the ionophore **7T** bearing secondary thioamide functions. It can be also seen that NPOE plasticizer improves K^{+} and Cs^{+} cations uptaking to the membrane, whereas BBPA promotes Na^{+} selectivity.

Table IV-2. Potentiometric selectivity coefficients $logK_{Pb,M}^{pot}$ of the electrodes based on ionophores **1T-9T** and of electrodes without ionophores

cation	**1T**/BBPA[a]	**1T**/NPOE[a]	**2T**/BBPA	**2T**/NPOE	**3T**/BBPA	**3T**/NPOE	**4T**/BBPA	**4T**/NPOE	**5T**/BBPA[b]	**5T**/NPOE[b]	**6T**/BBPA[a]	**6T**/NPOE[a]	**7T**/BBPA	**7T**/NPOE	**8T**/NPOE[a]	**9T**/NPOE[a]	BBPA	NPOE
Pb^{2+}	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Na^{+}	-0.9	-1.8	-0.95	-2.47	-0.92	-0.63	0.73	0.11	-4.3	-6.25	-3.3	-3.3	-0.96	-3.19	-4.5	-4	7.23	2.54
K^{+}	-0.9	-1.2	-1.15	-3.63	-0.94	-3.43	0.46	-1.83	-5.4	-7.3	-3.9	-4.3	-1.96	-5.6	-5.00	-4.7	7.81	7.07
Li^{+}	-2.2	-3.5	-3.21	-5.07	-2.77	-4.15	-2,00	-3.52	-7.21	-8.9	-5.6	-5.8	-1.88	-5.78	-6.8	-7.3	6.97	0.23
Cs^{+}	-1,00	0.3	-3.68	-4.91	-2.99	-5.46	-2.13	-4.11	-8.98	-10.2	-4.8	-6.2	-2.3	-2.82	-0.15	-0.5	8.34	10.79
Mg^{2+}	-5.04	-5.02	-5.55	-8.08	-6.22	-6.55	-4.48	-7.31	-11.00	-12.2	-7.8	-9.35	-4.5	-5.46	-9.3	-8.9	-4.67	-1.77
Ca^{2+}	-3.7	-3.6	-5.14	-6.5	-5.32	-5.18	-4.77	-5.67	-11.5	-13.1	-6.7	-7.54	-4.39	-5.69	-7.5	-7	-0.33	0.37
Sr^{2+}	-3.7	-3.5	-4.95	-6.97	-5.24	-5.65	-4.42	-5.52	-10.5	-11.1	-6.00	-6.4	-4.5	-6.79	-6.8	-6.9	-1.48	-0.97
Ba^{2+}	-3.7	-3.5	-5.97	-7.47	-5.17	-6.12	-4.97	-6.63	-11.5	-11.7	-6.4	-7.5	-5.52	-6.65	-7.1	-7	-3.91	0.56
Mn^{2+}	-4.6	-4.52	-3.82	-6.33	-5.24	-4.06	-2.68	-4.88	-11.1	-11.6	-7.08	-8.07	-4.74	-5.39	-8.6	-8.3	0.5	-1.6
Co^{2+}	-4.3	-3.8	-6.72	-8.24	-6.87	-8.29	-6.22	-7.57	-13.3	-13.8	-7.4	-9.2	-6.8	-8.31	-8.1	-7.9	-2.74	-2.04
Ni^{2+}	-3.85	-3.8	-4.12	-5.17	-4.35	-5.62	-3.3	-5.55	-10.2	-12.2	-7.4	-8.5	-4.02	-6.47	-9.3	-9.4	-2.51	-0.93
Cu^{2+}	-1.6	-2.2	-1.92	-3.49	-3.12	-3.39	-3.19	-2.55	-0.83	-0.54	-3.1	-3.8	0.81	-0.98	-0.8	-1.5	-2.51	-0.02
Zn^{2+}	-4.25	-4.3	-4.7	-7.4	-5.59	-5.38	-4.69	-5.17	-11.7	-11.1	-7.08	-9.28	-5.87	-4.4	-8.4	-8.1	-0.23	-1.67
Cd^{2+}	-4.06	-3.7	-4.99	-2.92	-4.59	-2.88	-4.31	-2.54	-7.96	-5.41	-5.32	-4.4	-2.53	-4.37	-4.2	-4.5	-3.48	-2.61

[a] data published in [19]; [b] data published in [20]

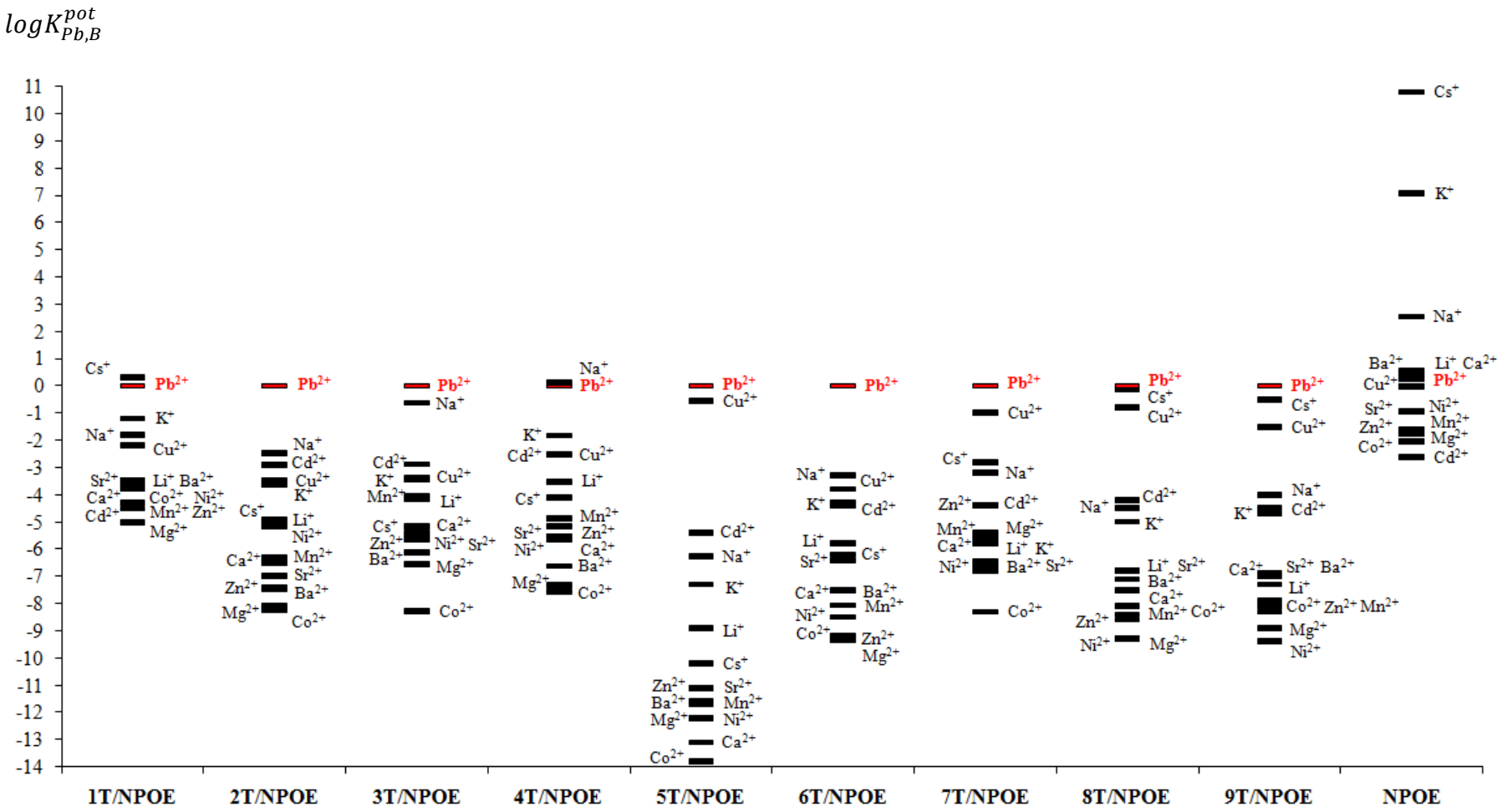


Figure IV-9. Selectivity coefficients ($logK^{pot}_{Pb,B}$) determined by the Separate Solution Method (SSM) for electrodes containing **1T-9T** and for electrodes without ionophore (PVC/NPOE membrane).

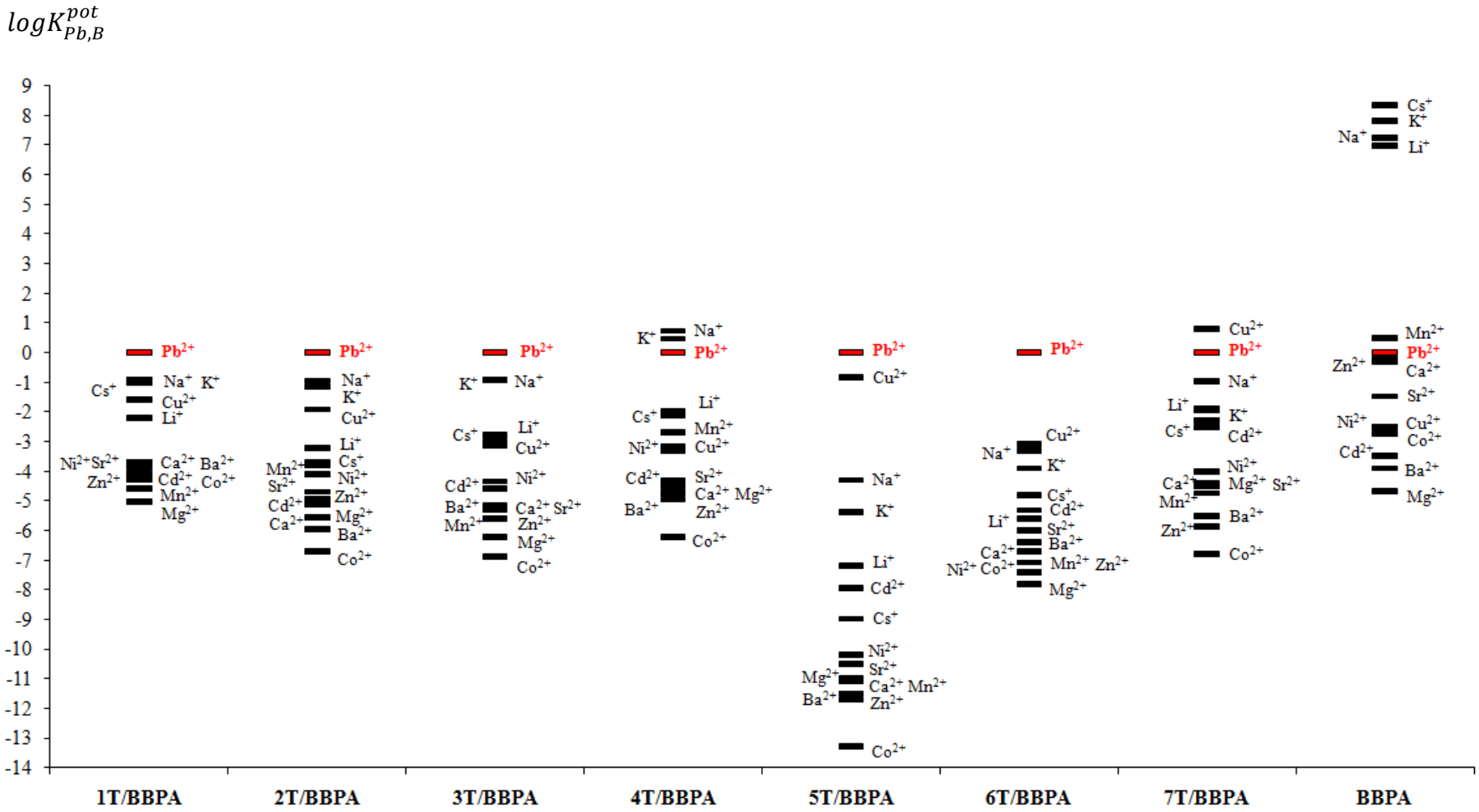


Figure IV-10. Selectivity coefficients ($logK^{pot}_{Pb,B}$) determined by the Separate Solution Method (SSM) for electrodes containing **1T-9T** and for electrodes without ionophore (PVC/BBPA electrode membrane).

3.2. Calix[4]arene-hydroxamates

Four O-alkyl substituted-calix[4]arene-hydroxamates synthesised (**10-13**) were tested as active materials in ion selective membrane electrodes plasticised by NPOE for Pb^{2+} - selectivity. The literature data of potentiometric measurements carried out before in our group with ionophore **14** are given as well.

The electrodes characteristics are given in **Table IV-3**. Those based on ionophores **10**, **11** and **13** showed near-Nernstian response in Pb^{2+} solution within a wide linear range (6-2 or 5-2).

Table IV-3. Characteristics of the studied ion-selective electrodes with calix[4]arene-hydroxamates **10-14** (PVC/NPOE membrane).

Ionophore number	Primary cation	Internal electrolyte	Slope S ± σ* [mV/dec]	Linear range LR - log a
10	**Pb^{2+}**	KNO_3 10^{-2} mol L^{-1}, Na_2EDTA 10^{-2} mol L^{-1}	29.2 ± 0.8	6-2
11	**Pb^{2+}** Na^+ K^+	KNO_3 10^{-2} mol L^{-1}, Na_2EDTA 10^{-2} mol L^{-1}	29.0 ± 0.5 44.9 ± 0.2 44.5 ± 0.5	6-2 4-1 4-1
11[a]	**Pb^{2+}** Na^+ K^+	$Pb(NO_3)_2$ 10^{-3} mol L^{-1}, Na_2EDTA 5×10^{-2} mol L^{-1}	32.6 ± 2.4 44.2 ± 2.3 40.5 ± 1.2	6-2 4-1 4-1
12	**Pb^{2+}**	KNO_3 10^{-2} mol L^{-1}, Na_2EDTA 10^{-2} mol L^{-1}	51.2 ± 1.6	6-2
13	**Pb^{2+}**	KNO_3 10^{-2} mol L^{-1}, Na_2EDTA 10^{-2} mol L^{-1}	32.6 ± 0.7	5-2
14[b]	**Na^+**	$Mg(NO_3)_2$ 5×10^{-3} mol L^{-1}	60.6	5.8-1.9

*standard deviation of at least two or three independent measurements
[a] data published in [23]
[b] data from [24]

For electrodes with ionophore **11**, two inner electrolytes were tested: a mixture of KNO_3 10^{-2} mol L^{-1} and Na_2EDTA 10^{-2} mol L^{-1} and a mixture of ($Pb(NO_3)_2$ 10^{-3} mol L^{-1} and Na_2EDTA 5×10^{-2} mol L^{-1}, i. e. the same as that used for thioamides. We can see that the electrodes responded also to Na^+ and K^+ cations within linear range 4-1, but not as good as to Pb^{2+}. The electrode characteristics are presented in **Figure IV-11**.

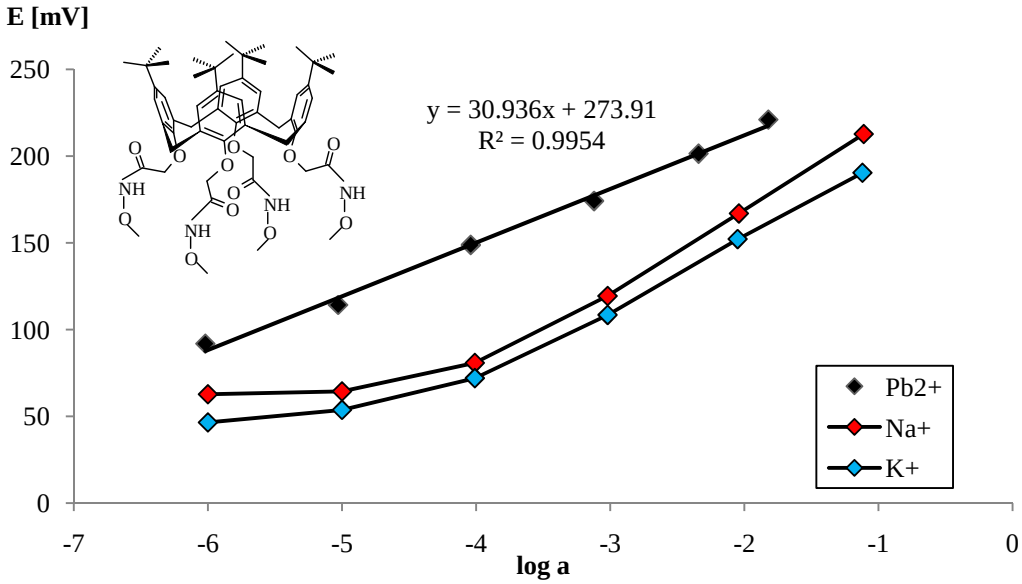


Figure IV-11. Responses of the electrodes containing ionophore **11** in Pb^{2+}, Na^{+} and K^{+} solution (inner electrolyte: $Pb(NO_3)_2$ 10^{-3} mol L^{-1}, Na_2EDTA 5×10^{-2} mol L^{-1}) (PVC/NPOE membrane).

The electrodes based on ionophore **12** showed over Nernstian behavior with a slope of 51.2 mV/dec, rather typical for monovalent species. It suggests that the Pb^{2+} cation is associated with NO_3^- anion in the membrane. Such cases have already been reported for other Pb-selective ionophores [25]. The flexible butyl chains in the ionophore **12** structure expand the cavity so that it may help anion extraction to the membrane.

In other cases, the small methyl substituents or more rigid iso-propyl moieties might not allow uptaking bulky anions to the membrane.

The ionophore **14**, which is substituted on both N- and O- heteroatoms behaved differently. The results showed, that the electrode based on this ionophore responded to Na^{+} cations with a slope typical for monovalent ions (60.6 mV) [24]. It gives an idea, that this compound possesses a binding affinity similar to that of tertiary calix[4]arene-amides which are good Na^{+}- selective ionophores. It has already been noticed and mentioned in CHAPTER I, that changing calix[4]arene-tertiary amides to secondary amides modifies the ionophoric and complexing behavior, shifting the preference from Na^{+} to Pb^{2+}. In calix[4]arene-hydroxamate, we can observe similar trend. O-substituted secondary hydroxamates are Pb-selective ionophores, but those substituted on both atoms (N- and O-) respond to Na^{+} cations. The selectivity coefficients are presented in **Table IV-4** and in **Figure IV-12**.

Table IV-4. Potentiometric selectivity coefficients ($logK^{pot}_{Pb,M}$) or ($logK^{pot}_{Na,M}$) of studied electrodes containing ionophores **10-14**.

cation	10	11	12	13	14
Pb^{2+}	0.00	0.00	0.00	0.00	-2.8
Na^{+}	-2.7	-0.8	-1.91	-2.2	0.00
K^{+}	-1.3	-0.2	-3.10	-2.03	-1.9
Cu^{2+}	-1.6	-3.8	-4.3	-4.55	-3.6
Zn^{2+}	-1.7	-3.7	-4.08	-4.1	-4.1
Cd^{2+}	-0.9	-4.2	-3.4	-2.8	-3.7

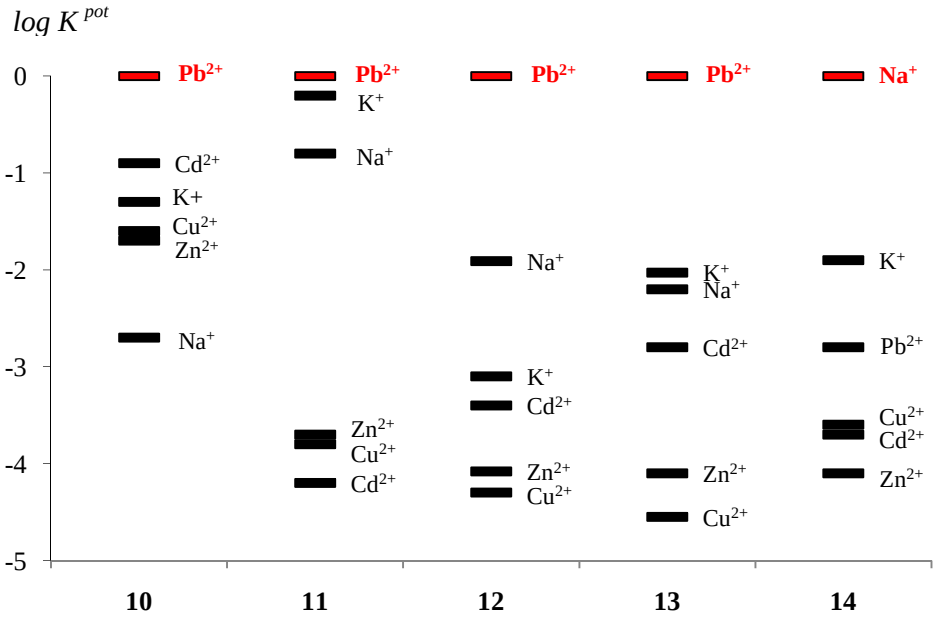


Figure IV-12. Selectivity coefficients ($logK^{pot}_{Pb,B}$) or ($logK^{pot}_{Na,B}$) determined by the separate solution method (SSM) for calix[4]arene-hydroxamates **10-14**.

Among Pb-selective hydroxamates (**10-13**), the ionophore **11** possesses good selectivity coefficients for Pb^{2+} over the other heavy and transition metal cations such as Cd^{2+}, Cu^{2+} and Zn^{2+} ($logK^{pot}_{Pb,B} \leq -3.7$). However, the strong affinity for Na^{+} and K^{+} cations ($logK^{pot}_{Pb,B} > -1$) was revealed. For electrodes with ionophores **12** and **13** having more bulky substituents, the selectivity for Pb^{2+} over Na^{+} and K^{+} is improved and the selectivity coefficients are better than those obtained with ionophores based on secondary amides [7]. It is worth to point out that the slope obtained for Pb^{2+} cation in the case of ionophore **12**, was

over Nernstian (51.2 mV/dec) which results in bad determination of the selectivity coefficients.

It can be clearly seen that the tris-substituted ionophore **10** is characterised by the worst selectivity coefficients among the studied calix[4]arene-hydroxamates for most of the cations studied which can be explained by the lack of coordination centres compared to tetra-substituted calix[4]arene-hydroxamates.

The selectivity coefficients obtained for electrodes with ionophore **14** are similar to those reported for tertiary amides. For example the selectivity coefficients found ($logK^{pot}_{Na,K} \leq -1.9$ and $logK^{pot}_{NaPb} \leq -2.8$) are comparable to those obtained with calix[4]arene-morpholide (**6A**) ($logK^{pot}_{Na,K} \leq -2.3$ and $logK^{pot}_{NaPb} \leq -3.2$).

4. Conclusions

This chapter reports the studies of the ionophoric properties of nine *p-tert*-butylcalix[4]arene-thioamides (**1T-9T**) and four *p-tert*-butylcalix[4]arene-hydroxamates (**10-13**). These compounds were used as sensing materials and tested towards Pb^{2+}- selectivity. The tertiary thioamides (**1T-6T**) formed stable, long lasting electrodes, whereas the electrodes based on the secondary thioamides (**7T-9T**) were not so stable in the membrane and their lifetime was much shorter.

The electrodes containing calix[4]arene-thioamides appended with cyclic moieties like ionophores **5T** or **6T** possess better selectivity for Pb^{2+} than those with acyclic substituents (**1T-4T** and **7T-9T**). Special attention should be focused on ionophore **5T**, having cyclic thiopiperidinyl moieties, for which the selectivity coefficients were remarkable, except those over Cu^{2+} cations. However, the electrode slope for Cu^{2+} cations had a value typical for monovalent ions, which resulted in bad selectivity coefficient for Pb^{2+} over Cu^{2+}.

Ionophores **1T-7T** were tested in membranes with two different plasticizers (NPOE and BBPA). The data obtained showed, that generally the selectivity coefficients were better in NPOE plasticised membranes than in BBPA membranes. However, the selectivity coefficients for Pb^{2+} over Cd^{2+} were better in BBPA containing membranes, which is caused by the preference of Cd^{2+} cations to NPOE plasticizer. Those assumptions were confirmed by the results obtained with the electrodes without ionophore, where only the type of plasticizer used affected the selectivity. The electrodes based on ionophores **8T** and **9T** might be applied successfully in the detection of Pb^{2+} in real samples in the absence of Cu^{2+} and Cs^{+}. But the

measurements in so called flow-system will not be possible due to the low durability of the electrodes.

Tetra-substituted calix[4]arene-hydroxamates (**11-13**) could be successfully applied as Pb^{2+}- selective ionophores and used in the determination of Pb^{2+} concentration but in the absence of Na^{+} and K^{+} cations, which were the most interfering ions. Nevertheless, the selectivity coefficients for Pb^{2+} over Na^{+} and K^{+} are better than those reported for the secondary calix[4]arene-amides. Data were compared with those reported before for ionophore **14**, which occurred to be Na^{+}- selective ionophore, with selectivity coefficients similar to those revealed for tertiary calix[4]arene-amides.

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GENERAL CONCLUSION

The aim of this thesis was to design and synthesise *p-tert*-butylcalix[4]arene derivatives functionalised with amide and hydroxamate groups as well as their respective thiocarbonyl analogues, thioamides and thiohydroxamates. By introducing soft sulphur atoms into the structure of the calix[4]arene, the preference for binding heavy and transition metal cations, toxic for human beings, was expected. The interactions of these ligands with several representative cations (Na^+, Ca^{2+}, Gd^{3+}, Ag^+, Cd^{2+}, Pb^{2+}, Zn^{2+} and Cu^{2+}) were studied using different techniques: liquid-liquid extraction, ^1H NMR, X-ray diffractometry, UV spectrophotometry, potentiometry and microcalorimetry. Some of these thioamides and hydroxamates derivatives were used as active materials in ion-selective membrane electrodes (ISEs).

p-tert-Butylcalix[4]arene - amides and thioamides derivatives

Nine calix[4]arenes substituted with thioamide groups (six tertiary thioamide derivatives **1T-6T** and three secondary thioamide derivatives **7T-9T**) were prepared in a one-step synthesis starting from the corresponding amides (compounds **1A-9A**) using Lawesson's reagent as thionating agent. The starting materials were all obtained by the mixed anhydrides method and in the case of compounds **5A** and **6A** also by using the appropriate α-chloroacetamides. According to our best knowledge, ligand **4A** was obtained by us for the first time. Compounds **1A** and **1T**, partly studied before, were also synthesised. The amides and thioamides derivatives were obtained in the desired *cone* conformation confirmed by the presence in all ^1H NMR spectra its characteristic peaks.

Moreover, calix[4]arene-thioamides were characterised by microanalysis and in some cases (**5T, 6T, 7T, 9T**), by X-ray diffraction, presented by us for the first time. The latter technique also confirmed the *cone* conformation of these compounds and in particular, showed the pinched *cone* conformation and the existence of intramolecular hydrogen bonds of the NH ... S type in the structures of ligands **7T** and **9T**. The X-ray crystal structures of the calix[4]amides **1A** and **3A** were resolved, the former being already known in the literature and the latter obtained for the first time.

The extraction properties of thioamide derivatives showed almost quantitative extraction of Ag^+ whereas these compounds are very weak extractants of Na^+, Ca^{2+}, Gd^{3+}, Cd^{2+} and Zn^{2+} cations.

The percentages extraction of Pb^{2+} and Cu^{2+} depend strongly on the nature of the thioamide function (secondary or tertiary). The presence of secondary thioamides strongly reduces the extraction efficiency.

The corresponding tertiary amide derivatives **1A-5A** were very good extractants for both "hard" cations such as Na^+ and Ca^{2+} (%E > 63) and for "soft" cations such as Ag^+, Cd^{2+} and Pb^{2+} (%E ≥ 61.5). In the contrary, the secondary amide derivatives showed no affinity for all the cations studied, including Ag^+. The low extraction efficiency of secondary amide and thioamide derivatives might be related to the existence of intra- and intermolecular hydrogen bonds which restrained the accessibility of the cations to the calixarene cavity and the high hydrophicility of the extracted complexes. The extraction results thus showed that the replacement of the oxygen atoms of tertiary amides by sulphur atoms leads to compounds highly selective for Ag^+ and Pb^{2+} over Na^+, Ca^{2+} and Cd^{2+}.

Studies of complexation by UV absorption spectrophotometry in acetonitrile confirmed the high affinity of tertiary thioamide derivatives for heavy metal cations (Ag^+, Cd^{2+} and Pb^{2+}) and Cu^{2+}. The absence of significant spectral changes upon addition of Na^+ salt indicated no or very little interactions of these ligands towards Na^+ and in this way, showed the good selectivity of the studied calix[4]arene-thioamides for Ag^+, Cd^{2+}, Pb^{2+} and Cu^{2+}. The interpretation of the spectra obtained for thioamide derivatives has shown the formation of species with different stoichiometry and stability depending on the cation and the ligand. For Ag^+, two ML and M_2L species are formed with all the ligands. These stoichiometries were also confirmed by potentiometry and microcalorimetry. For Cu^{2+} and Cd^{2+}, the formation of only one ML_2 complex is observed, whereas for Pb^{2+}, different models were found according to the ligand (ML_2, ML and M_2L or ML and ML_2). The most stable complexes were formed with Ag^+ cations. Microcalorimetric titrations also allowed the determination of the thermodynamic parameters and the stability constants of Cd^{2+} and Cu^{2+} complexes with the ligand **5T**. In the case of Cu^{2+} a particularly high enthalpic stabilisation of the complex formed is observed. This high and favourable enthalpic term is partly compensated by a strongly negative and unfavorable entropic contribution, probably due to the strong conformational changes of the ligand upon complexation.

The crystal structures of Pb^{2+} complexes with **5T** and **9T** showed a more regular cone conformation as compared to the free ligand. However, the coordination of the cation in both complexes is not the same. In the two **9T**-$\mathbf{Pb^{2+}}$ and **5T**-$\mathbf{Pb^{2+}}$ complexes the cation is bound to the four ethereal oxygen atoms and to four and two sulphur atoms of the thiocarbonyl groups,

respectively. The Interactions between thioamides **5T, 7T** and **9T** and heavy metal cations (Pb^{2+} and Ag^{+}) were also confirmed by ^{1}H NMR which allowed the location of the metal cation in the complex. The most affected protons were those situated near the OCH_2CS groups, suggesting a contribution of the oxygen and sulphur atoms in the complexation of Pb^{2+} and Ag^{+} cations.

Concerning the amide derivatives, studies of complexation by UV absorption spectrophotometry in methanol and in acetonitrile confirmed their strong affinity for alkali metal cations such as Na^{+}, but also for Ag^{+}, Cd^{2+} and Pb^{2+}, which form highly stable complexes. The stoichiometry of the complexes formed depends on the cation and the ligand but is different from that observed for the corresponding thioamide derivatives. The spectrophotometric results showed the same trend observed in the extraction. The stability constants were higher in acetonitrile than in methanol, which is in agreement with the different solvating properties of the two solvents. In contrast, the stability constants of the Ag^{+} complexes were lower than those obtained in methanol due to the tendency of Ag^{+} ions to form complexes with acetonitrile.

The nine thioamides were incorporated in the PVC-membrane of ion-selective electrodes (ISEs) and tested as sensing materials for Pb-selectivity. Electrodes based on ionophores **1T-6T**, which are tertiary thioamides were stable up to 2-3 months, while the lifetime of the electrodes with ionophores **7T-9T** based on the secondary thioamides, was much shorter (about 2 weeks). Ionophores **1T-7T** were tested in two different PVC membranes containing BBPA and NPOE as plasticizers. The selectivity coefficients were found to be better for electrodes with the latter membranes except for the Pb^{2+} over Cd^{2+} selectivity which was better with PVC/BBPA membranes. This can be explained by the the stronger affinity of Cd^{2+} for NPOE**.** It has been shown that thioamide derivatives possess very good ionophoric properties and are selective for Pb^{2+} over a large number of cations. It was established that the ionophores bearing cyclic, rigid thioamide substituents, such as **5T** and **6T**, are more selective than those having more flexible linear substituents. Remarkable selectivity coefficients have been determined for ionophore **5T**, which could be successfully used to design Pb(II) sensors. The selectivity pattern (Pb^{2+} over Cu^{2+} and Cd^{2+}) obtained in ion selective electrodes doped with BBPA plasticizer can be related to the extraction trend which was as follows: %E Pb^{2+} >> %E Cu^{2+} >> %E Cd^{2+}. This pattern is also in agreement with the values of the stability constants of metal complexes determined by UV spectrophotometry which were observed to decrease in the order: $Pb^{2+} > Cu^{2+} > Cd^{2+}$.

***p-tert*-Butylcalix[4]arene-hydroxamates and hydroxamic acids**

Five calix[4]arenes substituted with hydroxamate groups (the tris-substituted derivative **10** and the four tetra-substituted derivatives **11-14**) and with hydroxamic acid groups (the two tris-substituted derivatives **15** and **16** and the two tetra-substituted derivatives **17** and **18**) were synthesised by the "mixed anhydrides method." These compounds were characterised by ^{1}H NMR and in the case of **14-18** also by microanalysis. The ^{1}H NMR spectroscopy and in the case of **11** and **13**, the X-ray crystal analysis showed the *cone* conformation of all these compounds. In particular, the crystal structure of ligands **11** and **13**, presented in this work for the first time, indicated the existence of intramolecular hydrogen bonds of the NH ... O type.

Some trials were performed to prepare calix[4]arene-thiohydroxamates and thiohydroxamic acid, compounds which have never been reported before. Unfortunately, those attempts were unsuccessful. The direct thionation of hydroxamate derivatives using Lawesson's Reagent led to a product whose crystal structure confirmed the presence of two disulphide bridges. Such compound when used as active material in the membrane of ion-selective electrode did not show interesting ionophoric properties. The thioacylation reaction led to the reduction of the hydroxamic acid and the isolated product was the secondary calix[4]arene-amide.

As the secondary amide derivatives, hydroxamate derivatives bearing NH groups (**10-13**) showed weak extracting properties. It was also difficult to determine the stability constants of the complexes formed using absorption spectrophotometry because of the very small spectral changes of the ligand upon addition of metal salts. In contrary, the hydroxamate derivative substituted on O and N atoms (**14**), showed important percentages extraction, especially for Na^{+}, Pb^{2+} and Ag^{+} (%E > 41). The interactions between **14** and these cations were also studied by UV absorption spectrophotometry in methanol. The stoichiometry of the complexes formed and their stability could be derived from the significant spectral variations observed upon addition of cations. The complexation of Ag^{+} was also followed by potentiometry.

The extraction ability of calix[4]arene-hydroxamic acids synthetised in this work (**15-18**) was studied towards heavy metal cations (Cd^{2+}, Pb^{2+}) and transition metal cations (Co^{2+}, Ni^{2+}, Zn^{2+}, Fe^{3+}, Cu^{2+}). The results showed that all these ligands extracted Fe^{3+} and Cu^{2+} very

efficiently (in the case of Cu^{2+} almost quantitatively). With ligands **15** and **17**, the extraction percentages of Pb^{2+} were high (85 and 62% respectively).

Competitive extraction experiments were also performed and showed a decrease of the extraction percentages when several cations are present together in solution. Particularly interesting results were obtained with ligand **17** for which the extraction of Pb^{2+} in the presence of Cd^{2+} was almost quantitative and higher than for individual experiments. In contrary, the percentage of Cd^{2+} extraction was lower than in the individual extraction. These results are very important in the context of the removal and separation of Pb^{2+} from other toxic metals such as Cd^{2+}. In addition, ligands **15-18** could be used to separate Cu^{2+} and Zn^{2+}, which are often found together.

The use of hydroxamate derivatives **10-13** as active materials in the membrane of ion-selective electrodes (ISEs), showed selectivity for Pb^{2+}, whereas ligand O-and N-substituted (**14**) responded to Na^{+} cations. Hydroxamate derivatives (**11-13**) could be used to determine the concentration of Pb^{2+} ions in the absence of Na^{+} and K^{+}, cations which were the most interfering ions.

Although the selectivity of hydroxamate derivatives is better than that of secondary amides calixarenes, it is lower that the selectivity determined with the calix[4]arene-thioamides presented in this work. The selectivity order for Na^{+} over heavy metals such as Pb^{2+}, Cd^{2+} and Cu^{2+} with ionophore **14** is in agreement with the trend found in the extraction (%E Na^{+} > %E Pb^{2+} >> %E Cd^{2+} > %E Cu^{2+}).

Electrodes based on calix[4]arene-thioamides, particularly on compounds **5T** and **6T** are promising analytical tools for monitoring Pb^{2+} concentration in natural and drinking waters.

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1.“Calix-thioamides as ionophores for transition and heavy metal cations”
J. Kulesza, M. Bocheńska
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2.“Lower Rim Substituted *p-tert*-Butyl-Calix[4]arene. Part 16. Synthesis of 25, 26, 27, 28-tetrakis(piperidinethiocarbonylmethylene)-*p-tert*-butylcalix[4]arene and its interaction with metal ions”
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1.“Comparison of all-solid-state lead(II) selective electrodes based on electronically conducting polymer and derivatives of calixarenes as ionophores”
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Opis rozprawy

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Data obrony	
Tytuł rozprawy	*„Synthesis and studies of binding properties of calix[4]arenes functionalised with amide and hydroxamate moieties and their thiocarbonyl analogues"*
Język rozprawy	angielski
Słowa kluczowe	calix[4]arene, thioamides, amides, hydroxamates, hydroxamic acids, heavy metals, extraction, ^{1}H NMR, X-ray crystal structures, UV spectrophotometry, potentiometry, microcalorimetry, ion-selective electrodes
Streszczenie rozprawy w jęz. polskim (max. 1400 znaków)	Potrzeba monitorowania i kontrolowania stężenia jonów metali ciężkich, jak np. Pb^{2+} czy Cd^{2+}, mających toksyczne działanie na wszystkie organizmy żywe inspiruje chemików-syntetyków poszukujących metod syntezy coraz to bardziej selektywnych związków. Celem tej pracy była synteza pochodnych amidowych i hydroksamowych kaliks[4]arenu oraz ich tiokarbonylowych odpowiedników. Otrzymano dziewięć pochodnych tioamidowych oraz ich odpowiednich pochodnych amidowych, pięć pochodnych hydroksamowych, a także cztery kaliks[4]aren-kwasy hydroksamowe z wolną grupą OH. Badanie oddziaływań ligandów z kationami metali badano przy pomocy różnych technik: spektroskopia ^{1}H NMR, analiza rentgenograficzna kryształów, ekstrakcja, spektrofotometria UV, potencjometria oraz mikrokalorymetria. Selektywność pochodnych tioamidowych oraz hydroksamowych oceniono wstępnie stosując te ligandy jako materiały sensorowe w membranowych elektrodach jonoselektywnych. Wprowadzając do struktury kaliks[4]arenu atomy siarki, uzyskano wzrost powinnowactwa pochodnych tioamidowych do niektórych jonów metali ciężkich, np. Pb^{2+}, Cu^{2+} czy Cd^{2+} a jednocześnie uzyskano wysoką selektywność w stosunku do jonów metali I i II grupy. Na szczególną uwagę zasługują trzeciorzędowe tioamidy z cyklicznymi ugrupowaniami, które z powodzeniem mogłyby być zastosowane do budowy wysoce selektywnego na jony Pb^{2+} czujnika chemicznego.
Tytuł i streszczenie rozprawy w jęz. angielskim (max. 1400 znaków	The need of monitoring and controlling the concentration of heavy metal ions such as Pb^{2+} or Cd^{2+}, which have toxic effects on all living organisms inspires chemists to synthesise more and more selective compounds. The aim of this work was the synthesis of amide and hydroxamate derivatives of calix[4]arenes and their thiocarbonyl analogues. Nine thioamide derivatives as well as their respective amide derivatives, five hydroxamate derivatives and four calix[4]arene-hydroxamic acids with free OH groups were obtained. Studies of ligands interactions with metal cations were investigated using different techniques: ^{1}H NMR spectroscopy, X-ray crystal structure analysis, extraction, UV spectrophotometry, potentiometry and microcalorimetry. Selectivity of thioamide and hydroxamate derivatives was assessed using these ligands as sensor materials in ion-selective membrane electrodes. The replacement of the oxygen atoms by sulphur atoms led to compounds highly selective for some heavy metal ions such as Pb^{2+}, Cu^{2+} or Cd^{2+} over the I and II group of metal cations. Particularly noteworthy are the cyclic tertiary thioamides which can be successfully applied in Pb^{2+} - sensors.