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ARTICLE

Development of calix[4]arenes modified at their narrow- and wide-rims as potential metal ions sensor layers for microcantilever sensors: further studies

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Abstract: The development of a microcantilever (MCL) sensing device capable of simultaneously detecting several metal ionic species in aqueous media with low limits of detection requires a variety of sensing layers that are ion specific. Calix[4]arenes are robust molecules that can be easily modified and have been extensively studied for their ion binding properties. They are also capable of forming self-assembled monolayers (SAMs) on the gold layers of MCLs and are capable of detecting various metal ions with different anionic counterions in aqueous solutions. In this paper, we report on the effect of the alkoxy group in the narrow rim [*O*-(*alkoxy*carbonyl)methoxy] substituents of bimodal calix[4]arenes, which have been used as metal ion MCL sensing layers, using classical solution state experimental studies. A DFT computational study to compare the experimental results with several metal ions is also reported herein.

Key words: calix[4]arenes, microcantilever sensors, host–guest complexation, supramolecular, DFT.

Résumé : La mise au point d'un dispositif de détection à base de micropoutres capable de détecter simultanément plusieurs espèces d'ions métalliques dans des milieux aqueux avec de faibles limites de détection nécessite diverses couches sensibles à chaque ion. Les calix[4]arènes sont des molécules robustes qui peuvent être facilement modifiées et qui ont été largement étudiées pour leurs propriétés de liaison à des ions. Ils sont également capables de former des monocouches autoassemblées (ou SAM pour *self-assembled monolayers*) sur les couches d'or recouvrant les micropoutres et de détecter divers ions métalliques associés à différents contre-ions anioniques dans des solutions aqueuses. Dans le présent article, nous décrivons, au moyen d'études expérimentales classiques en solution, l'effet du groupe alcoxy dans les substituants [*O*(*alcoxy*carbonyl) méthoxy] du bord étroit de calix[4]arènes bimodaux utilisés comme couches de détection d'ions métalliques sur des micropoutres. Nous présentons également une étude théorique de calculs DFT à laquelle nous comparons les résultats expérimentaux obtenus avec plusieurs ions métalliques. [Traduit par la Rédaction]

Mots-clés : calix[4]arènes, capteurs à base de micropoutres, complexation hôte-invité, supramoléculaire, DFT.

Introduction

We have been interested in the development of sensing devices that could detect metal ions in situ in aqueous solutions and could be coupled to a transmitting device. Such a device would be of particular interest in not only continuously monitoring water effluent from mining or other industrial processing operations in the environment, but also monitoring potable water supplies.[1,2] Among the questions posed in pursing this objective is how to establish and distinguish the stoichiometries and stabilities of the different ionic species, in particular for transition metal ions that can exist in the aqueous medium to be analyzed. Such information can be crucial for determining their concentrations, as well as their so-called speciation curves (species distribution vs. pH). In addition, these data may allow, up to a certain extent, the modeling of the composition, in particular experimental conditions of complex systems involving a variety of ligands and metal ions present in environmental and biological systems while keeping in mind chemical consistency.[3] For this purpose, a variety of analytical techniques such as atomic absorption spectrometry (AAS), inductively coupled plasma-optical emission spectrometry (ICP-OES), ICP-mass spectrometry (ICP-MS), atomic fluorescence spectrometry (AFS), nuclear magnetic resonance spectroscopy (NMR), and potentiometry have been used.[4] These techniques are all suitable due to their sensitivity, ability to detect many different elements, and low limits of detection. NMR spectroscopy is a powerful method for speciation, which can be investigated through either metal nuclei or ligand nuclei, and it can therefore be used to determine the strength of metal binding and the kinetics, besides providing useful information related to the structure of molecules in solution.[5] One of the approaches that we have investigated in recent years has been to develop sensitive microcantilevers (MCLs)[6] as sensing devices with suitably functionalized calix[4]arenes[7–11] as

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the actual metal sensing layers on the MCLs. In these studies, we found that calix[4]arenes-functionalized MCLs were capable of sensitively detecting selected metal ions in solution. Three different types of bimodal calix[4]arenes were used as sensing layers, and our results demonstrated that each type of sensing layer showed a definite preference towards different metal ions and their counterions. Our studies were also extended to investigate the role of the counterions in the interaction between calix[4]arene-modified MCLs and metal ions, where we concluded that both the cation and their counterions significantly contributed to the MCL signal. Employing such differently functionalized MCLs onto a suitably modified detecting system can be used to selectively monitor the individual components within a mixture of metal ions.[11] We now report some additional studies that we have conducted with this objective in mind.

The chemistry and applications of calixarenes in diverse fields in chemistry including synthesis, nanotechnology, supramolecular chemistry, and coordination chemistry have seen a tremendous growth in recent decades. The calixarene that has seen the greatest number of applications as a basic synthetic building block is *tetrakis-tert*-butylcalix[4]arene **1**. The molecule is relatively easily accessible due to the pioneering efforts of Gutsche and his coworkers[12] and is a robust molecule consisting of four *p tert*-butyl-substituted phenols that are linked in a cyclic array by four $-CH_2-$ groups. Due to the hydrogen bonding of the four hydroxyl groups and the steric repulsion of the four *tert*-butyl groups at the opposite end, the molecule can adopt a distinct "basket"-like structure, with a "narrow" and a "wide" rim (Fig. 1).

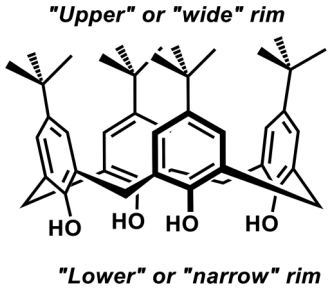
Controlled functionalization has mostly been conducted at the narrow end of **1** by *O*-alkylation of the phenolic hydroxyls[13] and in fewer cases by direct substitution via a Sonogashira reaction.[14] *O*-Alkylated derivatives have been widely studied for their solution phase ionophoric and other supramolecular properties.[15] The wide rim can also be functionalized by first removing the *tert*-butyl groups via *retro*-Friedel-Crafts *de-tert*-butylation reactions to form the de-*tert*-butylated calix[4]arene **2** (which will be referred to here simply as "calix[4]arene" to distinguish it from **1**) followed by subsequent reaction(s).[16] Calix[4]arene thereby can be modified at both its narrow- and wide-rim thereby expanding the potential utility of the molecule. We have used such an approach to generate calix[4]arenes that are capable of forming self-assembled monolayers (SAMs) onto the gold layers of MCLs and detecting calcium, potassium, rubidium, and cesium ions with various anion counterions in aqueous solutions. In this paper, we report on the effect of the alkoxy group in the narrow rim [*O*-(*alkoxy*carbonyl)methoxy] substituents of bimodal calix[4]arenes, which have been used as metal ion MCL sensing layers, with classical solution state experimental studies. A DFT computational study to compare the experimental results with several metal ions is also reported herein.

Materials and methods

Synthesis

The synthesis of the bimodal calixarenes, which were used to form the SAMs on the gold-coated MCLs, is outlined in Scheme 1. The precursor **1** can either be synthesized by Gutsche's detailed methodology[12] or can be purchased from commercial sources. De-*tert*-butylation of **1** produces **2** efficiently in 80% yields. In turn, **2** can be easily functionalized using NaH with allylbromide in THF at reflux to form **3** in 80% yields. Heating **3** in *N*,*N*-dimethylaniline at 210 °C for 24 h effects a smooth Claisen rearrangement to form the *tetrakis p*-substituted wide-rim product **4** in 70% yields. Thioacetylation of the terminal alkene groups, using thioacetic acid in dioxane at reflux with AIBN-catalysis, forms **5**. Finally, the narrow-rim hydroxyls of **5** were alkylated with either methoxy- or ethoxy-bromoacetate to form **6** or **7**, respectively, in >75% yields.[17]

Fig. 1. Structural representation of *tetrakis-tert*-butylcalix[4]arene (**1**) showing its "upper" or "wide" rim and the opposite "lower" or "narrow" rim.



Microcantilever measurements

Detailed procedures for the generation of the SAMs of **6** and **7** and for the methodologies employed with our MCL setup are given in our previous reports[7–11] and in the studies by Alodhayb[18] and Braim.[19] It was found that different simultaneous surface stress changes were observed with MCLs coated with [*O*-(methoxycarbonyl)methoxy]calix[4]arene **6** and *O*-(ethoxycarbonyl)methoxy]calix[4]arene **7** in a 16 MCL array sensing system in response to 10^{-6} M aqueous solutions of $CaCl_2$, $SrCl_2$, and CsCl.

Complexation studies

Stock solutions (~1.50×10^{-3} M) of **6** and **7** were prepared in a 4:1 CD_3OD:$CDCl_3$ solvent mixture. From concentrated (~1.00–2.00×10^{-1} M) stock solutions of the following salts: $CaCl_2$, $CaBr_2$, CaI_2, $Ca(ClO_4)_2$, $Ca(NO_3)_2$, $Ca(TFA)_2$, LiI, NaI, KI, and AgTFA (TFA = trifluoroacetate), small aliquots (~5.0 μL) of the salt solutions were added to 0.60 mL of the respective calixarene solution in a NMR tube. After shaking manually for 5 min following each addition, the resulting ^{1}H NMR (300 MHz, Varian) spectra were recorded at 24 ± 1 °C. Each titration experiment was conducted in duplicate. From the resulting chemical shift changes measured, the apparent binding or association constants (K_{assoc}) were calculated using Thordarson's global binding curve fitting program.[20]

Results and discussion

To the best of our knowledge, the first reported study using a calixarene-based sensing layer on a MCL was that by Ji et al. who showed this to be a sensitive and selective detector for cesium ions.[21] Their calixarene, which was in a 1,3-alternate conformation, was functionalized with a benzocrown-6-ether linking a pair of distal phenol groups, and on the opposite face, each of the remaining pairs were functionalized with 11-mercapto-1-undecanoxy ether groups. The thiol groups were used to "anchor" their modified calix[4]arene to the gold surface on the MCL as a SAM. In our case, with compounds **6** and **7**, we found that it was not necessary to reduce the thioesters to the corresponding thiols to bind to the gold surfaces of the MCLs. Also, in our case, our molecules were clearly in cone (or crown) conformations and also formed more robust SAMs. To shed light on the differential responses seen with the initial MCL studies and to extend those studies to a larger group of analytes, solution complexation studies with **6** and **7** were designed. Although fluorescence titrations would have been more sensitive and thus be more comparable with the lower limits of detection seen with the MCL studies, these could not be used in this present study because the two calixarenes of interest were neither water soluble nor fluorogenic. We therefore limited our analytical approach to using ^{1}H NMR titrations instead. Figure 2 shows the results of the ^{1}H NMR titration with **6** with successive additions of aliquots of a $CaCl_2$ solution. With

Scheme 1. Synthesis of methoxy and ethoxy calix[4]arenes **6** and **7**.

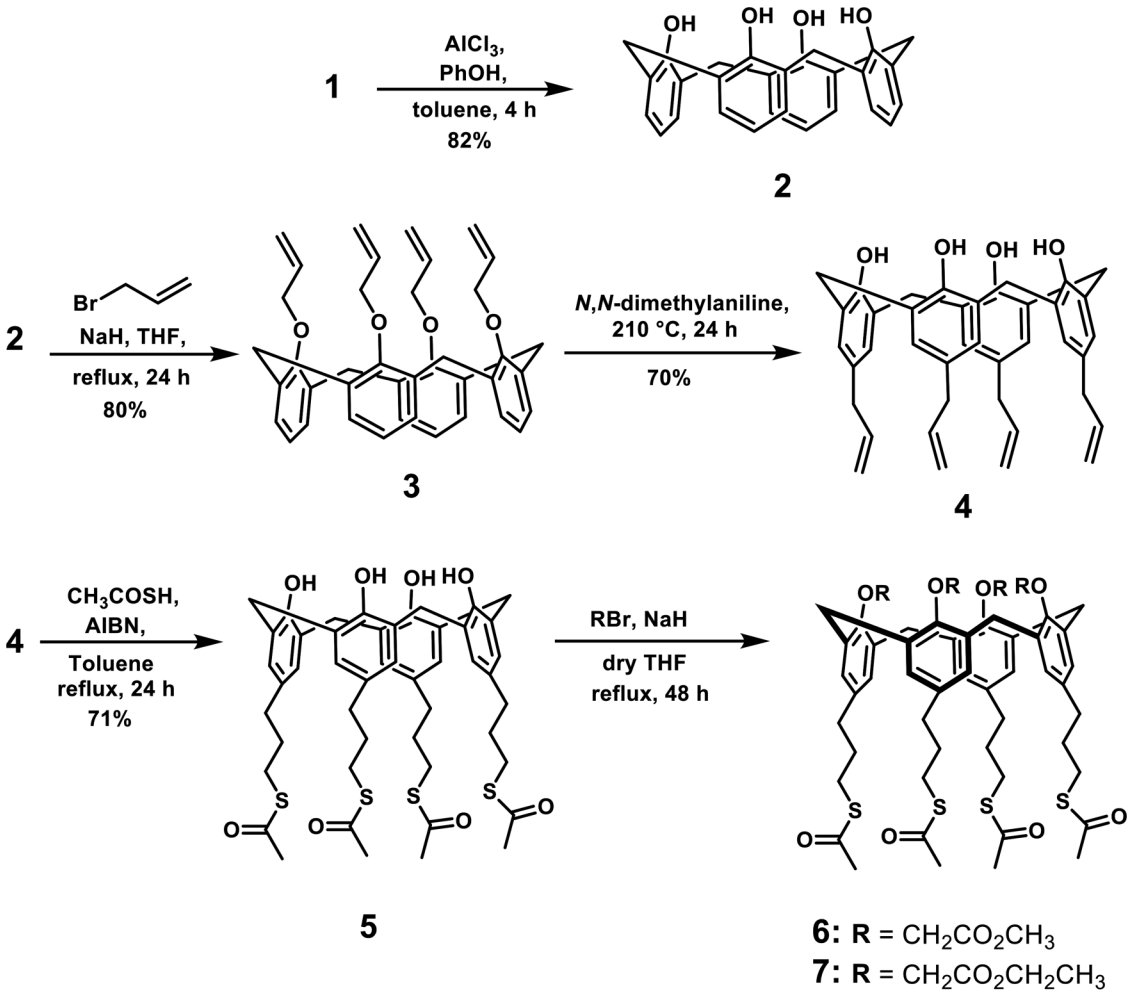
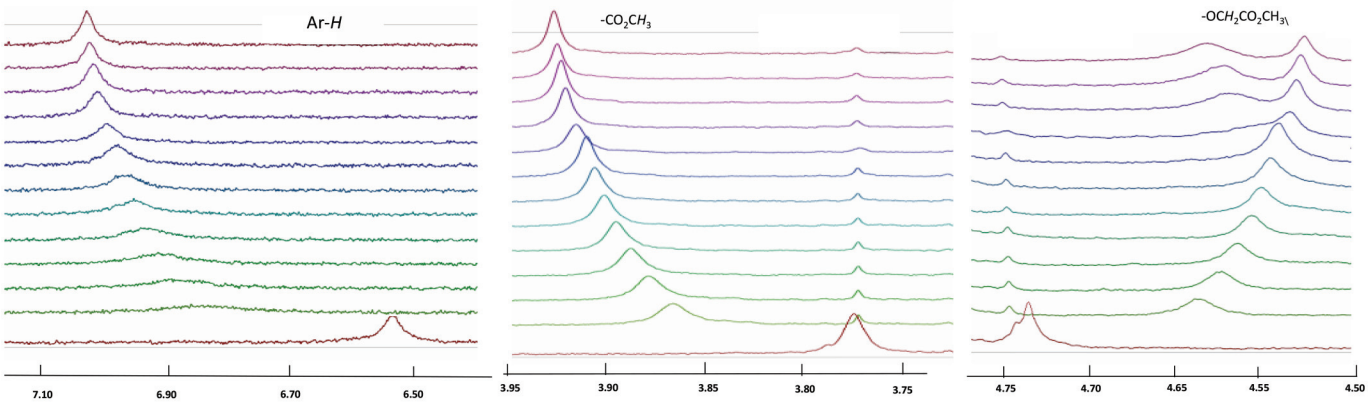
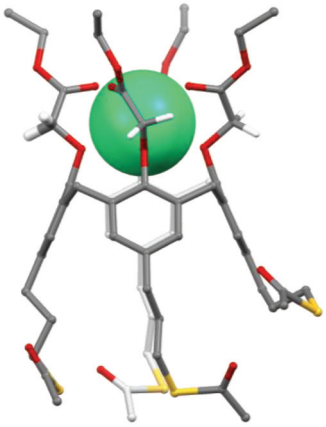


Fig. 2. Partial ^{1}H NMR (300 MHz, 4:1 CD_3OD:$CDCl_3$) titration curves showing the chemical shift changes of (left) –COO*CH*$_3$, (middle) –O*CH*$_2$COOCH$_3$, and (right) the aromatic ring protons of **6** (1.50×10^{-3} M) with successive additions of $CaCl_2$. Note: an unidentified minor impurity in the host molecule shows up at 3.77 and 4.75 ppm.[22] [Colour online.]



increasing amounts of $CaCl_2$, downfield chemical shift changes from δ = 3.776 to 3.925 ppm for the singlet signals due to the –CO_2CH_3 protons can be seen, whereas the singlet signals of the –O*CH*$_2$CO$_2$CH$_3$ methylene group protons are shifted upfield from δ = 4.737 to 4.580 ppm. Similar chemical shift changes could also be discerned for the calixarene aromatic (Ar-*H*) singlet signals, which were shifted downfield from δ = 6.840 to 7.026 ppm, but upfield chemical shift changes from δ = 2.324 to 2.188 ppm could be seen for the singlet of the –SCO*CH*$_3$ group methyl protons signals. Global analysis using all four major discernable signal changes yielded a K_{assoc} = 235 ± 15% M^{-1} (Supplementary Table S1 and Fig. S1). The largest chemical shift changes were seen for the aromatic

Fig. 3. DFT optimized molecular structure of the Ca^{2+} complex with [*O*-(ethoxycarbonyl)methyl]calix[4]arene **7**. The location of the –O*CH*$_2$O– methylene protons within the shielding cone of the aromatic rigs can be seen. [Colour online.]



proton signal, suggesting that the site of complexation between the Ca^{2+} is closer to the aromatic rings rather than being at the thioacetate functionalities on the wide rim. The de-shielding of these protons is due to the electron-withdrawing effect of the metal ion binding to the oxygen atoms on the narrow rim. The DFT calculations, as follows, support this model (Fig. 3) and also reveal that the –O*CH*$_2$CO$_2$CH$_3$ protons are bent outwards and fall into the shielding cone of the aromatic rings. Notably, at the higher relative amounts of the guest, broadening of the –O*CH*$_2$CO$_2$CH$_3$ methylene group protons signals start to show up, suggesting that the conformational flexibility of the group is being reduced relative to the NMR time scale.

Analogous observations were made from the ^{1}H NMR titrations of all of the salts tested. The corresponding chemical shifts seen with the titration of the ethyl ester analogue **7** with $CaCl_2$ revealed that the calixarene aromatic (Ar-*H*) protons singlet signals were shifted downfield from $\delta = 6.523$ to 7.059 ppm and the –CO$_2$CH$_2$*CH*$_3$ methyl group protons triplet signals were shifted from $\delta = 1.31$ to 1.411 ppm, respectively. However, upfield changes in the chemical shifts can also be seen for the –SCO*CH*$_3$ group methyl protons singlet signals from $\delta = 2.325$ to 2.177 ppm and the –ArO*CH*$_2$CO$_2$CH$_2$CH$_3$ methylene group protons singlet signals from $\delta = 4.732$ to 4.532 ppm. From the 1:1 binding isotherm, the global analysis using the major discernable signal changes yielded a K_{assoc} = 444 ± 10% M^{-1}. As can be discerned from the chemical shift data, in this case, the largest chemical shift changes are again seen for the aromatic signals, suggesting that the guest is bound in a similar manner to the methoxy analogue **6**. Table 1 summarizes all of the K_{assoc} data that could be determined from the NMR titrations and were based upon the chemical shift changes for the proton signals, which showed the greatest changes in the titration experiments. With the exception of $CaCl_2$, $CaBr_2$, and CaI_2, the other calcium salts examined revealed no discernable chemical shift changes in the titration experiments. With $CaBr_2$ and CaI_2, only very small chemical shift changes were observed, but it should be noted that these salts had only very limited solubility in the solvent system used for the NMR titrations and no reliable binding constants could be determined.

The data for the calcium salts suggest that a possible mode of complexation with the calixarene hosts could involve the salt binding to the host in the solvent system used, as tight contact ion pairs or triplets,[23,24] although this was not proven in the current study, in which case, the larger ions would not be as easily accommodated by the host calixarene molecules. In the titration

Table 1. K_{assoc} values for **6** and **7** with representative salts.

	K_{assoc}	
Salt	**6**	**7**
$CaCl_2$	235±15%	444±10%
NaI	1680±10%	6890±17%
KI	19.7±1%	47.6±1%
AgTFA	283±6%	1700±7%

Note: The ± error here is not a measure of precision of replicates but represents the percent error resulting from the global-fit calculations, because only single titration experiments in each case were conducted.

Table 2. Computed interaction energies ΔE (kcal mol^{-1}) for **6** and **7** in gas and with solvent corrections.

	ΔE (kcal mol^{-1})		
Complex	Gas phase	Methanol solvent	Acetonitrile solvent
6:Mg^{2+}	–369.7	–71.55	–70.75
6:Ca^{2+}	–315.8	–51.27	–48.87
6:Sr^{2+}	–278.6	–40.65	–40.01
6:Ag^{+}	–118.1	–35.98	–35.74
6:Na^{+}	–109.1	–22.97	–22.72
6:K^{+}	–91.5	–22.86	–22.44
6:Cs^{+}	–57.4	–17.78	–17.82
7:Mg^{2+}	–381.7	–74.42	–73.59
7:Ca^{2+}	–321.7	–54.44	–53.73
7:Sr^{2+}	–284.4	–42.41	–41.76
7:Ag^{+}	–121.2	–37.11	–36.87
7:Na^{+}	–112.2	–24.12	–23.87
7:K^{+}	–94.7	–23.51	–23.42
7:Cs^{+}	–60.7	–18.87	–18.89

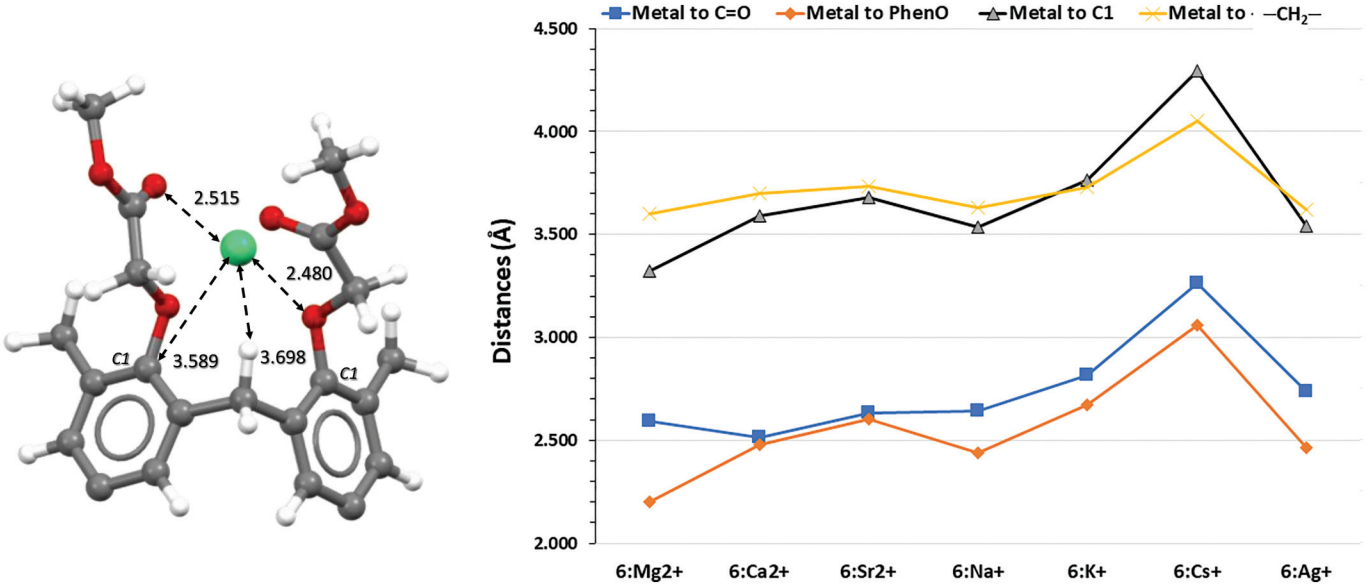
experiments with NaI using similar concentrations of the host and guest molecules, the first addition of the NaI afforded a large chemical shift change (140 and 155 Hz, respectively, with **6** and **7**) for the aromatic proton, indicating that equimolar binding occurred and afforded binding constants of 1680 ± 10% and 6900 ± 10% M^{-1}, respectively. However, with KI (Supplementary Figs. S5 and S6), more gradual chemical shifts could be discerned from the titration experiments and K_{assoc} values of 19 ± 2% and 48 ± 4% could be obtained from the global analyses with **6** and **7**. For further comparison purposes, ^{1}H NMR titration experiments were attempted with NaCl, KCl, KBr, and KNO_3, but these salts were not sufficiently soluble in the solvent mixture used in the experiments. Table 1 summarizes the apparent binding constants measured.

To determine where the site of binding likely occurs in these calixarenes, AgTFA was used as a probe, because it contains the soft-metal ion Ag^+ that could be expected to bind to the thioacetate moieties. As with the other salts tested, AgTFA showed the higher binding constant with the ethyl ester calix **7** (1700 ± 7% vs. 283 ± 10%). Again, the largest chemical shift changes were seen with the aromatic protons and not, as was anticipated, with the thioacetate methyl group (Supplementary Figs. S7 and S8). With $Ca(TFA)_2$ in the same solvent system, however, by way of contrast, no chemical shift changes could be observed. This suggests that the primary site for the Ag^+ complexation could still be either at the same site as the other cations tested or possibly deeper within the cavity of the four electron-rich aromatic rings.

Computational studies

To better understand the binding properties of receptors **6** and **7** with the ions studied, a limited preliminary DFT computational

Fig. 4. Left: DFT computed structure of the Ca^{2+}:**6** complex (all other atoms are hidden from view) showing the distances computed. Right: the graph with all of the other metal ions. [Colour online.]



investigation was carried out.[25] The individual structures were fully geometry-optimized using Gaussian 09[26] at the PBE1PBE level of DFT and the LANL2DZ basis set.[27] The calculated interaction or apparent binding energies (ΔIE kJ/mole) for receptors **6** and **7** complexes are shown in Table 2 and were determined in the gas phase and with solvent continuum corrections for methanol and acetonitrile, using the following equation: $\Delta IE = \{E(\text{Calix:Metal}^{n+})\text{complex} - [E(\text{Calix}_{\text{free}}) - E(\text{Metal}^{n+})]\}$.

For the selected distances that are shown in Table 2, the average values were determined for the four equivalent locations in each of **6** and **7**, measured to the respective metals. Figure 4 shows a representative example of the measurements. Subsequently, the corresponding ΔIE values were determined using solvent corrections and the continuum solvent modes for both methanol and acetonitrile.

The data in Table 3 (shown only for gas phase distances) indicate that there are insignificant differences between the four computed distances in both calixarenes despite the fact that the experimentally derived binding constants showed higher values for the ethoxycalix **7**. Nevertheless, there are clear correlations between the larger chemical shifts seen with the aromatic hydrogen atoms in both calixarenes with the salts tested, i.e., the deeper the metal ion is within the upper or narrow rim, the larger is the effect on the aromatic protons.

A similar study was reported by Marcos and coworkers[28] using tetrasubstituted diethylamide and morpholide *p-tert*-butyl-calix[4]arenes using several different metal salts including $Ca(ClO_4)_2$, NaSCN, KSCN, and $AgCF_3SO_3$. In their ^{1}H NMR studies, their host molecules were in CD_3OD solutions to which $CDCl_3$ solutions of the metal salts were added. In their examples, the largest chemical shift change value with 1:1 binding studies of each of the four cations (Ca^{2+}, Na^+, K^+, and Ag^+), which we report in this study, was reported for the Ca^{2+}. The axial methylene bridge protons of their tetrasubstituted diethylamide compound shifted upfield by 515 Hz and the aromatic protons shifted downfield by 210 Hz. However, a larger upfield chemical shift of 245 Hz was observed for the methylene protons of the $-OCH_2O-$ group of the same tetrasubstituted diethylamide with the 1:1 binding with Na^+ (245 Hz vs. 90 Hz with Ca^{2+}). In our case, the maximum upfield chemical shift changes noted with **7** and **6** were for the aromatic hydrogen protons, which were 162 and 56 Hz, respectively, with Ca^{2+}. With Na^+, the corresponding downfield shifts were 170 and 199 Hz, respectively, and 161 and 154 Hz, respectively with Ag^+ (Supplementary Tables S1–S8).

Table 3. Computed metal to selected atoms distances in **6** and **7**.

Complex	Metal to PhenO (Å)	Metal to C=O (Å)	Metal to C1 (Å)	Metal to bridge CH_{axial} (Å)
6:Mg^{2+}	2.200±0.012	2.594±0.553	3.325±0.036	3.601±0.026
6:Ca^{2+}	2.480±0.005	2.515±0.004	3.589±0.006	3.698±0.007
6:Sr^{2+}	2.601±0.004	2.632±0.002	3.678±0.007	3.735±0.007
6:Na^+	2.437±0.008	2.642±0.093	3.534±0.011	3.629±0.024
6:K^+	2.673±0.007	2.816±0.008	3.763±0.013	3.732±0.014
6:Cs^+	3.059±0.013	3.263±0.018	4.294±0.078	4.051±0.022
6:Ag^+	2.465±0.002	2.739±0.011	3.540±0.009	3.618±0.011
7:Mg^{2+}	2.201±0.010	2.590±0.555	3.328±0.041	3.609±0.029
7:Ca^{2+}	2.484±0.004	2.508±0.005	3.596±0.009	3.694±0.021
7:Sr^{2+}	2.603±0.003	2.628±0.004	3.683±0.011	3.735±0.009
7:Na^+	2.439±0.008	2.636±0.096	3.537±0.012	3.630±0.026
7:K^+	2.675±0.007	2.815± 0.008	3.768±0.014	3.734±0.013
7:Cs^+	3.059±0.013	3.256±0.018	4.251±0.014	4.052±0.023
7:Ag^+	2.468±0.003	2.709±0.015	3.546±0.010	3.619±0.014

Conclusions

The study reported herein was able to show that the complexation behaviour in which both host and guests were in solution and the MCL responses reported in our earlier MCL studies were similar, in that higher apparent binding constants and MCL responses could be observed with the *O*-ethoxycarbonyl calix **7**. From the DFT investigation, the computed interaction energy data from Marcos' study and ours are highly correlated ($r^2 = 0.98$) despite the structural differences of the host molecules (Supplementary Fig. S9). We were unable to compare the experimental NMR data binding constants because the experimental conditions were quite different. Namely, in the Marcos study, counterions that were non-coordinating were used, whereas we used halide counterions, with the exception of Ag^+ in the present study, so solubility and tighter ion pairs or ion triplets may have had a greater impact on our NMR data. However, overall, our conclusions are that in our examples, the cations are also bound by the metal ion – oxygen

interactions within the cavities defined by the phenoxy and the carbonyl oxygen atoms. Furthermore, the effect upon the de-shielding of the aromatic rings is due to the relative sizes of the metal ions and their counterions.

Supplementary data

Supplementary data are available with the article at https://doi.org/10.1139/cjc-2021-0119.

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