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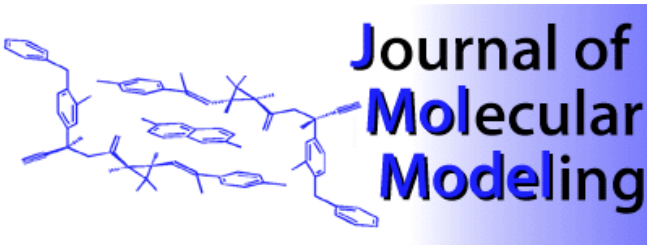

FULL PAPER

Modelling Metal Complexes of Calixarene Esters and Phosphine Oxides Using Molecular Mechanics

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Abstract This paper focuses on the molecular modelling of a number of calixarene ester and phosphine oxide metal ion complexes. Monte Carlo conformational searches, in conjunction with the Merck Molecular Force Field, were carried out using *Spartan* SGI Version 5.0.1. running on *Silicon Graphics O2* workstations. In the case of the calix[4]arene tetraesters, the optimised models strongly suggest that the selectivity of these ligands is strongly related to the eight-fold nature of the coordination with the Na^+ ion, while coordination with the Li^+ ion, for example, is merely three-fold. This feature of eight-fold coordination is also observed in the models of the complexes formed by the calix[4]arene tetraphosphine oxides with calcium. However, whereas the eight-fold coordination is unique to the model of the **TPOL**:Ca^{2+} complex among the ions modelled, this mode of coordination occurs for **TPOS** with sodium and potassium, in addition to calcium. This concurs with the observation that calcium selectivity is obtained with ion selective electrodes based on **TPOL** but not **TPOS**. Though the cavity in the calix[5]arenes **PPOL** and **PPOLx** and the calix[6]arene **HPOL**, in their uncomplexed form, are much larger than that of the corresponding calix[4]arenes, the pattern of selectivity is the same - the ligands are selective for calcium. The models of the complexes of these larger calixarenes, such as **PPOL**:Ca^{2+}, strongly suggest that the reason for this similarity is that four of the available phosphine oxide groups complex with the calcium ion, and the others are forced away from the cavity region for steric reasons. The resulting eight-fold coordination, is therefore, similar to that of the calix[4]arenes studied.

Keywords Calixarene, Molecular mechanics, Monte Carlo simulation, Selectivity, Complexation, Potentiometry, PVC membrane ion-selective electrode, Spartan

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Dedicated to Professor Paul von Ragué Schleyer on the occasion of his 70th birthday

Introduction

The increasing power of computers has meant that in the 1990's it has been possible to model the 3D conformations of calixarenes in spite of the fact that they contain relatively large numbers of heavy atoms (68 for the smallest ligand in this research). Usually, molecular mechanics and dynamics are employed because they are computationally less demanding than semiempirical and *ab initio* methods. In the literature, two types of molecular modelling papers tend to be found, those which concentrate on the calculations and algorithms involved [1] and those in which a greater emphasis has been placed on using modelling to help explain experimental data.[2 ,3]

In the models and X-ray structures of the complexes discussed in this paper the cations are found in the cavities formed at the so called 'lower rim', as the ligands contain a negative polar cavity in this region into which the positive ions fit. This cavity is defined by the phenoxy oxygen atoms (all ligands) and either ester or phosphine oxide groups, depending on the derivative (see Table 1 for structures). A typical example is the X-ray structure of the K^+ complex of *p-t*-butylcalix[4]arene tetraethylamide (**TEAC**, **1**- Table 1), which has four-fold symmetry.[4 ,5] Molecular mechanics, carried out with *HyperChem* software, [6] of the Na^+ complex of *p-t*-butylcalix[4]arene tetramethylacetate **(TME**, **2**- Table 1) leads to very similar results.[7]

Calixarenes containing pendant carbonyl groups have been well established as being selective for alkali cations, with calix[4]arene esters, ketones and amides showing a strong preference for sodium.[8] Calix[6]arene esters have been found to be selective for caesium,[8a,9] which is a reflection of the larger cavity presented by the calix[6]arenes.

Over the years, we have been very successful in constructing potentiometric and optical sensors for a number of common cations using calixarenes as the sensing agent. The use of **TME** in the construction of sodium-selective electrodes was first reported in 1986 [10] and other papers [11 ,12] have established that the related *p-t*-butylcalix[4]arene tetraethylacetate (**TEE**, **3**- Table 1) [13 ,14] and *p-t*-butylcalix-[4]arene tetramethoxyethylacetate (**TMEE**, **4**- Table 1) [15] can also produce excellent sodium-selective electrodes, with the latter exhibiting the best overall sodium selectivity.[16] **TME**-based electrodes have been applied successfully to the analysis of Na^+ in blood [17] and are now being used by several manufacturers of commercial, ISE-based blood electrolyte analysers.

The use of phosphine oxides as extractants for heavy metals, including radioactive materials, has been long established.[18] More recently, it has been shown that calixarene phosphine oxides have superior extracting ability than the acyclic ligands, carbamoylmethylphosphine oxide and trioctyl phosphine oxide for certain lanthanides.[19] However, in routine screening experiments with ISEs, we discovered that *p-t*-butylcalix[4]arene ethyleneoxydiphenylphosphine oxide **TPOL** (**5**- Table 1) produced excellent calcium-selective electrodes.[20] More recently, we have also demonstrated that increasing the cavity size to the equivalent calix[6]arene phosphine oxide derivative **HPOL** (**6**- Table 1) leads to a dramatic change in selectivity in favour of lead.[21] **TME** and **TPOL** have also been shown to produce optrodes with excellent selectivity for sodium and calcium, respectively, by co-immobilising a lipophilic acidochromic dye along with the ligand in the sensor membrane.[22] Figure 1 gives some idea of the changes in selectivity observed when PVC-membrane electrodes are made with some of these calixarene derivatives. Increasing selectivity for the electrode primary (target) ion (i) against interfering ions (j) is given by increasingly positive values for the quantity $-\log K^{pot}_{ij}$ (negative logarithm of the potentiometric selectivity coefficient). For example, for **TMEE**-based electrodes, Na^+ is the primary ion (i), and the value of almost 2.5 for $-\log K^{pot}_{Na,K}$ ($j = K^+$) means that the electrode is around 300 times more responsive to Na^+ ions than K^+ ions. Clearly, the selectivity coefficients show that this electrode is also very selective against Li^+, Ca^{2+} and Mg^{2+} ions. In contrast, electrodes based on **TPOL** are definitely Ca^{2+}-selective, and surprisingly, the calcium selectivity against Li^+, Na^+ and Mg^{2+} improves with the larger calix[5]arenes **PPOLx** and **PPOL** (see **7** and **8**, respectively, Table 1). However, the related compound, *p-t*-butylcalix-[4]arene methyleneoxydiphenylphosphine oxide **TPOS** (**9**- Table 1), which differs from **TPOL** only in the absence of a second methylene 'spacer' between the phosphine oxide groups and the phenoxy oxygen atoms at the lower rim, does not display this Ca^{2+}-selectivity.

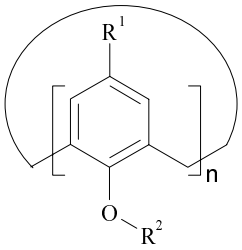
Selectivity is a critical parameter in all sensors, and we were therefore interested in discovering if molecular modelling could offer any insight into the conformational reasons for these results.

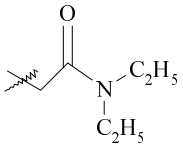
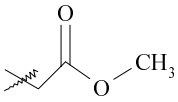
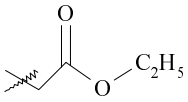
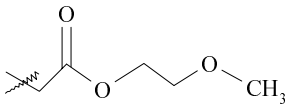
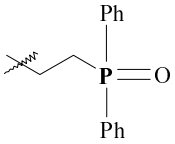
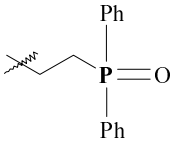
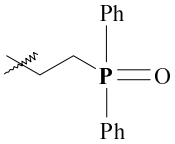
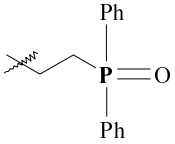
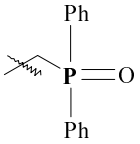
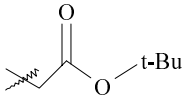
Computational methodology

All molecular modelling calculations were carried out using *Spartan* [23] SGI Version 5.0.1. running on a *Silicon Graphics O2* workstation (MIPS R10000 Rev. 2.7, 195 MHz CPU, 128 MB RAM, IRIX operating system, release 6.3).

The Monte Carlo algorithm was used in conjunction with the Merck Molecular Force Field (MMFF) [24] for the conformational searches followed by molecular mechanics geometry optimisations, carried out *in vacuo*. The conformational searches were carried out using the default conditions in Spartan (simulation temperature: 298 K, terminating gradient for minimisations: 1×10^{-5} kcal mol^{-1} $Å^{-1}$, maximum difference in correlated distances between two conformations that are considered as duplicates: 0.25 Å). A conformational search is a much more comprehensive investigation of the various geometries that can be adopted by the ligand in the complex than a single optimisation process, as it allows the user to generate new conformations by specifying which single bonds to rotate during the search. The method is especially relevant to the modelling of **TPOS** and **TPOL** and their higher oligomer analogues, as the bulkiness of the phenyl groups at the lower rim of these ligands (there are eight

Table 1 Structures of the calixarene derivatives



	acronym	n	R^1	R^2
1	**TEAC**	4	*t*-Bu	
2	**TME**	4	*t*-Bu	
3	**TEE**	4	*t*-Bu	
4	**TMEE**	4	*t*-Bu	
5	**TPOL**	4	*t*-Bu	
6	**HPOL**	6	*t*-Bu	
7	**PPOLx**	5	H	
8	**PPOL**	5	*t*-Bu	
9	**TPOS**	4	*t*-Bu	
10	**PBE**	5	*t*-Bu	

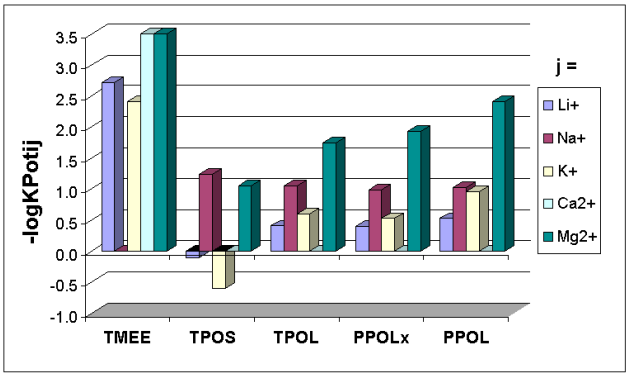


Figure 1 *Potentiometric selectivity coefficients of PVC-membrane sodium-selective electrodes based on **TMEE**, and calcium-selective electrodes based on **TPOS**, **TPOL**, **PPOLx** and **PPOL**. The interfering ions are denoted as j*

such phenyl groups in **TPOS** and **TPOL**) are a greater hindrance to conformational interconversion than the equivalent substituents at the lower rims of the calixarene esters. This means that there is a much greater chance of the optimisation ending in a local minimum than the global minimum if a comprehensive conformational search is not performed as part of the optimisation process.

Studies were carried out on **TMEE**, **TPOS**, **TPOL** and **PPOL** with each of Ca^{2+}, K^+, Na^+, Li^+ and Mg^{2+}.

All torsional angles in each pendant group at the lower rim of each ligand were specified as *torsional angles to be varied* in the conformational searches.

The free ligand of the calixarene was conformationally searched and the global minimum resulting from this search was used as input when carrying out the conformational search of the complex. The searches were repeated with different initial ion positions: above the phenoxy oxygen atoms, below the phosphine oxide groups for **TPOS**, **TPOL** and **PPOL** (or below the carbonyl groups for **TMEE**) and intermediate between these two positions.

All the starting conformations were geometrically optimised, via the *Minimise* module in *Spartan*, which minimises the energy of the structure based on the default force field, TRIPOS,[25] before being submitted for the conformational search.

Results and discussion

For the optimised models of the **TMEE** and **TME** complexes, the Na^+ complex is the most symmetrical, with facing identical aryl rings [26] at virtually equal separation for both complexes (7.93 Å ± 0.00 Å (two values) for **TME:**Na^+ and 7.96 Å ± 0.00 Å (two values) for **TMEE:**Na^+). For example aryl rings on opposite sides of the macrocycle in the **TME:**Na^+ complex are inclined at virtually equal angles (46.72° for one pair of rings on opposite sides of the macrocycle and 46.75° for the other pair of rings). Furthermore, for both ligands, the Na^+ ion sits more or less in the centre of the negatively polar cavity at approximately equal distances from the phenoxy and carbonyl oxygen atoms. In **TME:**Na^+ the metal to phenoxy oxygen distance is 2.55 ± 0.00 Å (four values) and the metal to carbonyl oxygen distance is 2.46 ± 0.00 Å (four values). The corresponding distances in **TMEE:**Na^+ are 2.57 ± 0.01 Å (four values) and 2.41 ± 0.06 Å (four values), respectively (see Figure 2 for views of the **TMEE**:Na^+ complex).

For K^+, the picture is somewhat similar, although the oxygen-ion distances are greater by 0.25 - 0.30 Å. Our results suggest that both **TME** and **TMEE** interact with Na^+ and K^+ ions in an eight-fold manner, involving the four carbonyl and four phenoxy oxygen atoms. Reassuringly, the cation to phenoxy and carbonyl oxygen atom distances obtained for the **TMEE**:K^+ complex are in excellent agreement with those obtained from an X-ray structure of a potassium complex formed by a diethylcarbamoylmethoxy dihydroxycalix-

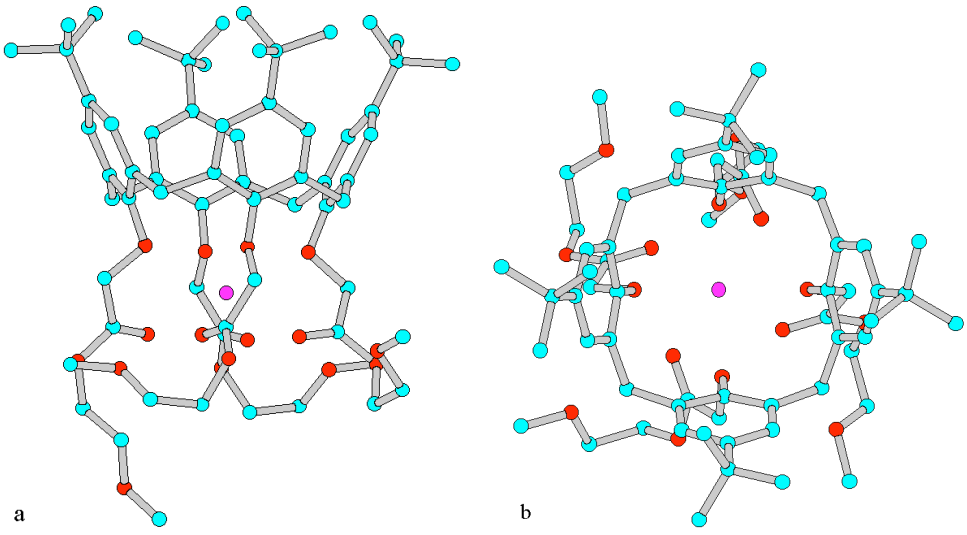


Figure 2 *Ball and tube rendering of the side-on view, (**a**) and the view through the cavity, (**b**) of the model of **TMEE**:Na^+. Hydrogen atoms are not shown for the sake of clarity. Colour scheme: carbon - blue, oxygen - red, sodium - magenta*

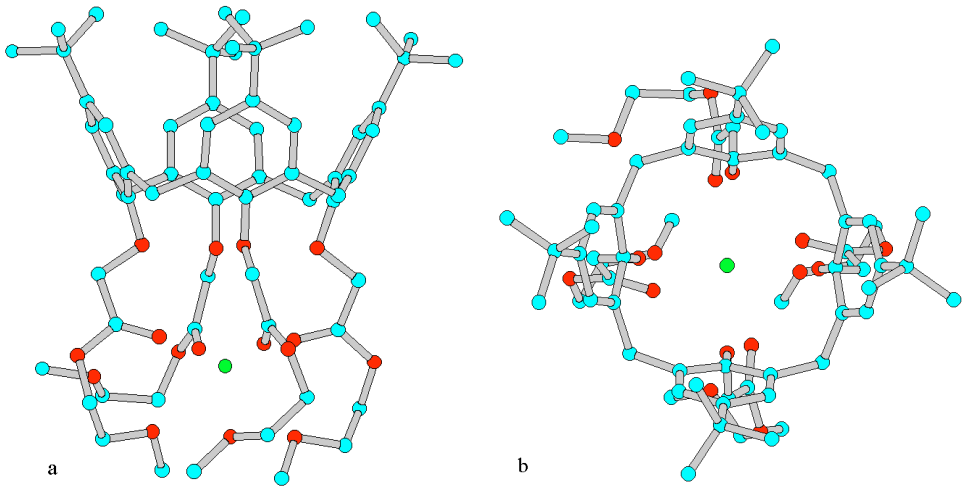


Figure 3 *As for Figure 2, except that the model of the model of* ***TMEE****:Ca^{2+} is shown. Colour scheme: carbon - blue, oxygen - red, calcium - green.*

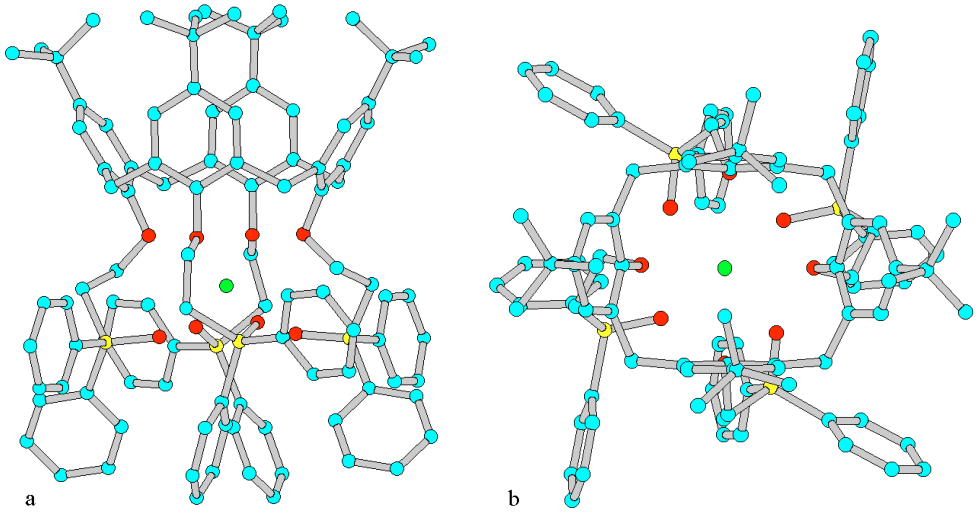


Figure 4 *As for Figure 2, except that the model of the model of* ***TPOL****:Ca^{2+} is shown. Colour scheme: carbon - blue, oxygen - red, calcium - green, phosphorus - yellow*

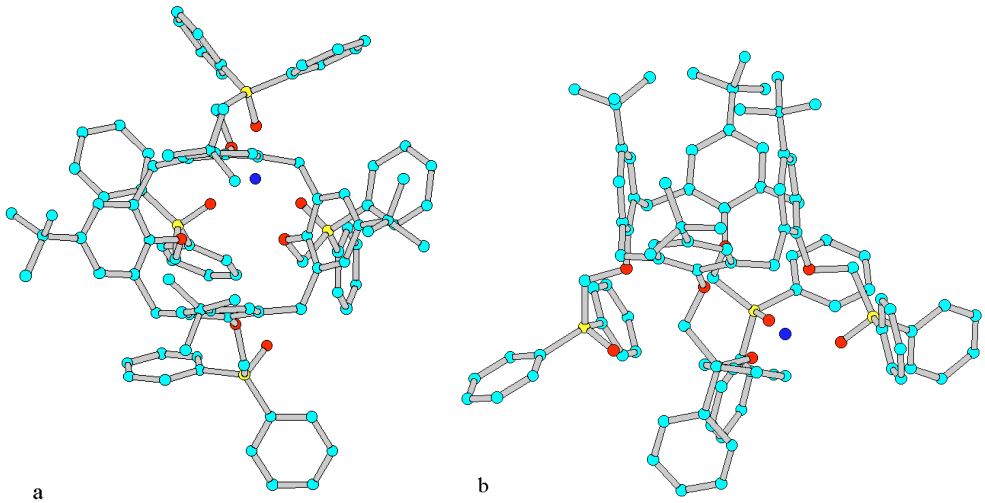


Figure 5 *As for Figure 2, except that the model of the model of* ***TPOS****:Li^{+} is shown. Colour scheme: carbon - blue, oxygen - red, phosphorus - yellow, Lithium - blue*

[4]arene in the 1,3-alternate conformation, that also involves coordination by phenoxy and carbonyl oxygen atoms.[27 ,28]

In contrast, the energy minimised models of the complexes of **TMEE** and **TME** with Li^+, Mg^{2+} and Ca^{2+} have the ion positioned low in the cavity, near the plane of the carbonyl oxygen atoms (the ions are approximately 2.00 Å away from the carbonyl oxygen atoms and 3.5 to 4.05 Å away from the phenoxy oxygen atoms), suggesting that these smaller ions are not capable of interacting with all eight oxygen atoms simultaneously, and therefore tend to position nearer the more strongly polarised carbonyl oxygen atoms. In the case of **TMEE** with Mg^{2+} and Ca^{2+}, there may be some interaction with two of the methoxy oxygen atoms (e.g. distances of 2.68 Å and 2.73 Å, see Figure 3 for views of the **TMEE:**Ca^{2+} complex). Interestingly, the models suggest that these complexes are not as symmetrical as the Na^+ equivalent. For example, distances between facing phenyl rings in the model of the 'free' form of **TMEE** are 9.29 Å and 6.38 Å in the free ligand, and 8.06 Å and 7.83 Å in the Ca^{2+} complex. The corresponding distances exactly the same for the **TMEE:**Na^+ complex at 7.96 Å, as mentioned previously.

Hence, it would seem that the reason why these ligands are so selective for sodium ions in ISEs lies in the formation of a very stable and symmetrical complex due to close interaction of the Na^+ ion with all eight oxygen atoms (4 x phenoxy and 4 x carbonyl) in the cavity.

The remainder of the potentiometric results in Figure 1 involve phosphine oxide calixarene derivatives. The data clearly show that:

- Replacement of the ester substituents at the lower rim with phosphine oxide groups results in a complete loss of the striking sodium selectivity obtained with **TMEE** and **TME** based electrodes.
- The electrodes based on the 'longer' phosphine oxide substituents (**TPOL, PPOLx** and **PPOL**) are calcium-selective, whereas the electrode based on the 'short' phosphine oxide substituent (**TPOS**) exhibits strong interference for potassium and lithium.
- The calcium selectivity is retained, and even slightly improved on moving from the calix[4]arene (**TPOL**) to the larger cavity of the calix[5]arenes (**PPOLx** and **PPOL**)

These results raise several important questions;

1. What is the basis of the calcium selectivity observed in **TPOL**?
2. Why is this selectivity retained in the larger calix[5]arenes (**PPOLx** and **PPOL**)?
3. Why is the calcium selectivity lost in the case of **TPOS**?

TPOL differs from **TPOS** solely in the addition of an extra methylene 'spacer' between the phenoxy and the phosphine oxide oxygen atoms (see structures **5** and **9**, respectively, Table 1). This has the effect of increasing the distance between these groups of oxygen atoms, which would seem to mitigate against efficient complexation of a relatively small cation like Ca^{2+}. Intuitively, one would expect the smaller cavity of **TPOS** to be more predisposed to complex with smaller ions. However, our calculations suggest that a unique rearrangement of the pendant phosphine oxide groups is possible for Ca^{2+} ions that involves them moving upwards to bring the phosphine oxide oxygen atoms into close proximity with the Ca^{2+} ion. The result is that the **TPOL**:Ca^{2+} complex has the cation approximately in the centre of a cavity defined by these four oxygen atoms, and the four phenoxy oxygen atoms at the lower rim (Figure 4). In fact the **TPOL**:Ca^{2+} complex is by far the most symmetrical of the **TPOL** complexes modelled, with distances of 6.31 Å and 8.86 Å between facing phenyl rings of the macrocyclic ring, compared to the 'free' ligand for which the corresponding distances were 6.26 Å and 9.14 Å respectively. In contrast, for the **TPOL**:Na^+ complex, the equivalent distances are 5.55 Å and 9.78 Å, respectively and for the **TPOL:**Li^+ complex the optimised distances were 5.53 Å and 9.85 Å (i.e. the lithium complex is less symmetrical than the free ligand!).

The optimised models of the **TPOL** complexes formed with Li^+, Na^+, K^+ and Mg^{2+} are not shown here but they are very similar in the mode of coordination, location of the cation

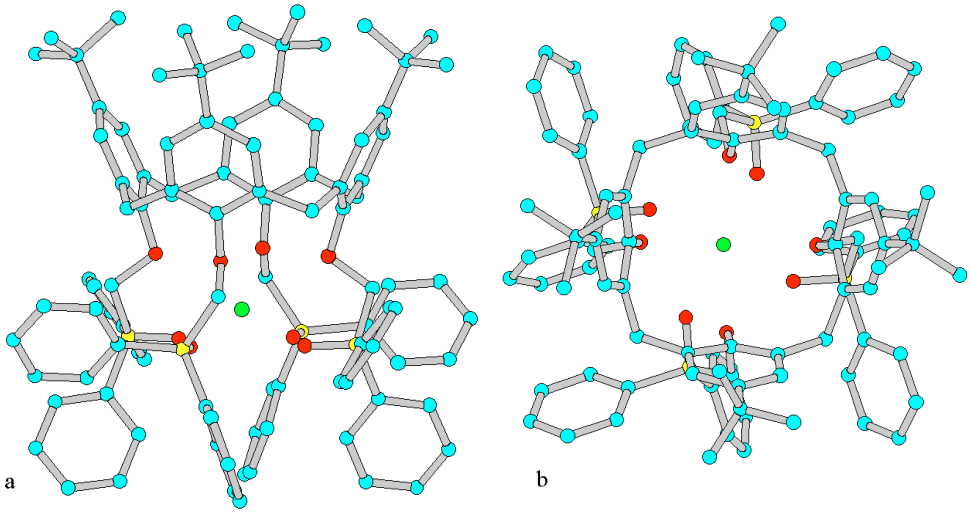


Figure 6 *As for Figure 2, except that the model of* ***TPOS****:*Ca^{2+} *is shown. Colour scheme: carbon - blue, oxygen - red, calcium - green, phosphorus - yellow*

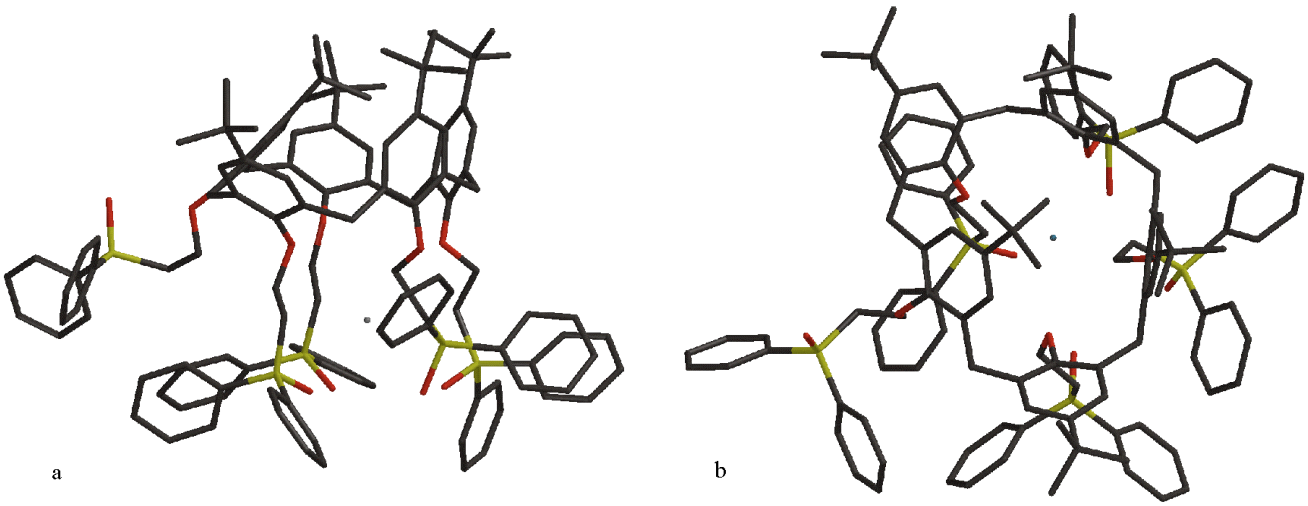


Figure 7 *Tube rendering of the side-on view, (***a***) and the view through the cavity, (***b***) of the model of* ***PPOL****:Ca^{2+}. Hydrogen atoms are not shown for the sake of clarity. Colour scheme: carbon - dark grey -, oxygen - red, phosphorus - yellow, calcium - blue*

and their cation-to-phosphine oxygen distances to that for **TPOS**:Li^+, shown in Figure 5. These models predict that only three of the four available phosphine oxide oxygen atoms are interacting with these ions, and the dramatic rearrangement to a symmetrical cavity seen with Ca^{2+} ions does not occur. Hence, this could be the basis for the observed Ca^{2+}-selectivity of the **TPOL**-based electrode.

In the case of **TPOS**, the results of the conformational searches studies suggest that two different modes of complexation may occur with the cations studied. Firstly, the model of **TPOS**:Li^+ suggests that the cation is positioned near the bottom of the calixarene at a distance of 1.83 Å from the three closest phosphine oxide oxygen atoms. The optimised model of the of **TPOS**:Mg^{2+} (not shown) is very similar to this.

Furthermore, models indicate that neither Li^+ nor Mg^{2+} is coordinated by all four of the phosphine oxide groups in **TPOS**. Instead, a three-fold coordination may be happening with the pendant chain that is least involved in binding the cation being forced outward. That the interaction of **TPOS** with Li^+ and Mg^{2+} is three-fold rather than four-fold is possibly due to steric barriers arising from the relatively large phenyl groups on the pendant chains as they move inwards to coordinate to the very small Li^+ and Mg^{2+} cations.

In contrast, the modelling indicates that for the other cations (Ca^{2+}, Na^+ and K^+) coordination involves both the phenoxy and the phosphine oxide oxygen atoms of **TPOS**, i.e., coordination to the cation is eight-fold in the cases of these ions, with the optimised position of the cation being occupying the cavity created by the two types of oxygen atoms (see **TPOS**:Ca^{2+} model in Figure 6 as an example). Very symmetrical complexes were obtained for these ions, with the distances between pairs of facing phenyl rings being identical to two decimal places in each case at 7.91 Å, 7.87 Å and 7.86 Å, for the Na^+, K^+ and Ca^+ complexes, respectively.

This attainment of a much more symmetrical conformation by calix[4]arenes on complexation is in agreement with previous work [4,5,22,29 ,29] involving molecular modelling, crystallography and NMR spectrometry of calix[4]arene esters such as **TME**, **TMEE** and **TEA** that clearly points to eight-fold coordination occurring with the cation (typically Na^+, see Figure 2, for example). These ligands are similar to **TPOS** in that there is one 'spacer' methylene group between the two types of ligating oxygen atoms defining the negatively polarised cavity. Hence, the conclusion is that the origin of the **TPOL:**Ca^{2+} selectivity may lie in a unique rearrangement of the phosphine oxide groups that results in a strong interaction of **TPOL** with the Ca^{2+} ion but not with the other ions studied. We would further conclude that this rearrangement is not possible with **TPOS**, as the phosphine oxide groups are too close to the phenoxy oxygen atoms. Instead, other ions, and particularly K^+ can fit into the cavity, and the calcium selectivity observed with **TPOL**-based electrodes is lost. This explains the more selective response of TPOS-based electrodes to K^+ ions shown by the negative value of -log $K^{pot}_{Ca,K}$ in Figure 1.

The above discussion provides some basis for the observed selectivity differences within **TPOL**, and between **TPOL** and **TPOS**. But why should the Ca^{2+} selectivity of **TPOL** be retained by the larger calix[5]arenes?

The optimised model of the **PPOL**:Ca^{2+} complex is shown in Figure 7. This suggests that only four of the five available phosphine oxide groups complex with the calcium ion, and the fifth is forced away from the cavity region for steric reasons. The resulting eight-fold coordination, and cavity size, is therefore much more like that of a calix[4]arene than a calix[5]arene, and the strong interaction with the Ca^{2+} ion is once again obtained. This provides a possible explanation of the observed Ca^{2+} selectivity obtained with the **PPOL** and **PPOLx** based electrodes.

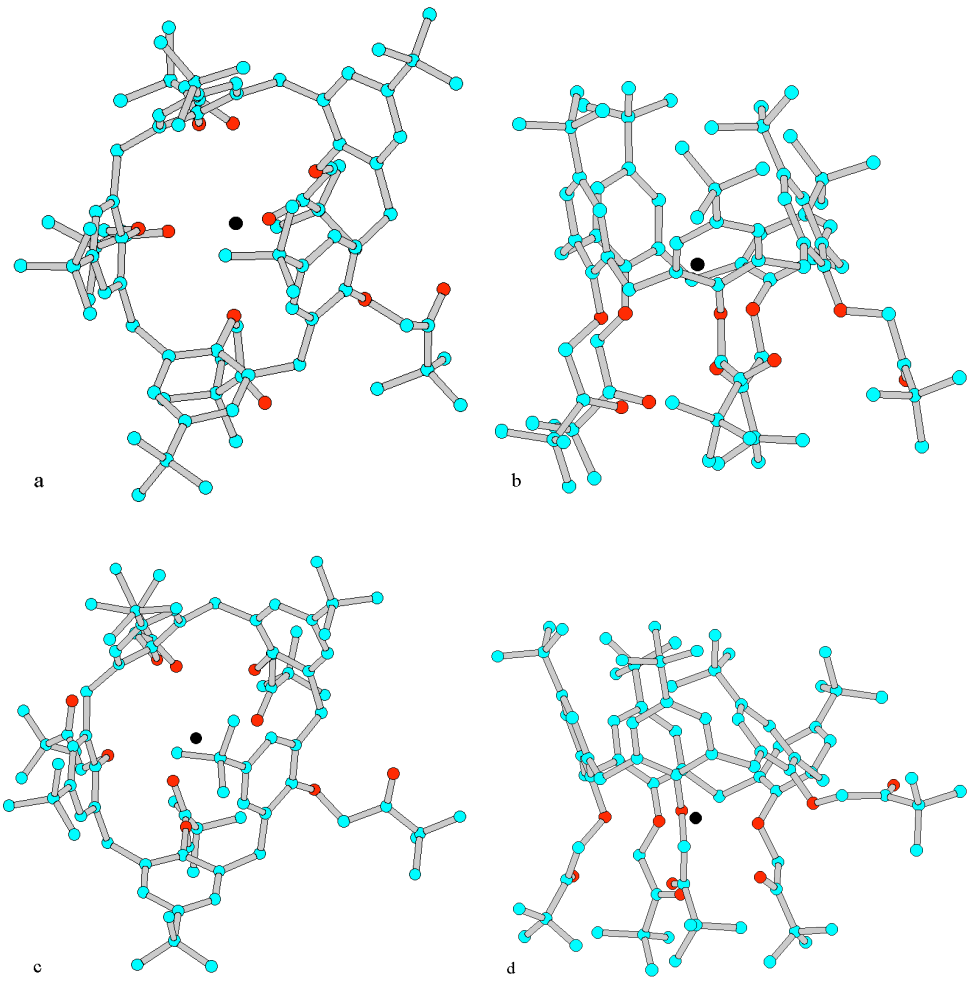


Figure 8 *Orthogonal views of the modelled structure (***a***), (***b***) and the X-ray structure (***c***), (***d***) of* ***PBE****:Rb*$^{+}$

While at first this may seem a strange arrangement of the ligating groups, there is considerable evidence to support these results from previous X-ray structures and molecular modelling of calix[5]arene ion-complexes. For example, the adoption of an eight-fold coordination involving only four of five available ligating groups was reported in the X-ray structure of the Rb^{+} complex of *p-t*-butylcalix[5]arene penta-*t*-butylacetate (**PBE**, **10**, Table 1). Figure 8 shows how closely we were able to reproduce the X-ray structure using molecular mechanics [30] which has the fifth ligating group clearly forced out of the cavity region. This remarkable result provides compelling evidence that a similar binding mechanism is feasible for the **PPOL**:Ca^{2+} complex, and the **PPOLx**:Ca^{2+} complex, and that the optimised model is a realistic representation of the conformation of the **PPOL**:Ca^{2+} complex.

In a related study, we have recently demonstrated that ISEs based on the corresponding calix[6]arene (**HPOL**, **6**, Table 1) are very selective for Pb^{2+} ions (and Hg^{2+} ions at pH < 3) against a wide range of interferents (K^{+}, Na^{+}, Ca^{2+}, Cu^{2+}, Cd^{2+}, Zn^{2+}, Sr^{2+}, Mg^{2+}, Co^{2+} and Ni^{2+}). We have not as yet been able to model the **HPOL**:Pb^{2+} due to the unavailability of atom parameters for lead, and the large size of the ligand precludes the use of *ab initio* approaches. We have modelled the **HPOL**:Ca^{2+} complex, and the optimised geometry suggests that only four of the six phosphine oxide groups are involved in binding the ion, with the two addition groups being forced out of the cavity region in a similar manner to the fifth group in the calix[5]arene discussed above.[21] However, it is possible that this does not occur with larger cations such as Pb^{2+}. We are currently working on a number of approaches to obtain more information about the stereochemistry of the **HPOL**:Pb^{2+} and **HPOL**:Ca^{2+} complexes.

Conclusion

From our molecular modelling studies, it would appear that the selectivity of **TPOL** towards Ca^{2+} lies in a unique eight-fold coordinate complex that involves close interaction of all four phenoxy and four phosphine oxide oxygen atoms with the Ca^{2+} ion. This is not possible with **TPOS** as the closeness of the phenoxy oxygen atoms and the phosphine oxide oxygen atoms enables a number of ions to form stable eight-coordinate complexes. The calcium selectivity of **TPOL** is retained by the larger calix[5]arenes **PPOL** and **PPOLx** prob-

ably because four of the ligating groups bind with the ion, providing a cavity similar to that of the calix[4]arene, with the fifth phosphine oxide group being forced out of the cavity region due to steric interactions.

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Supplementary material available statement All models have been lodged, in PDB format, with the Journal of Molecular Modeling.

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