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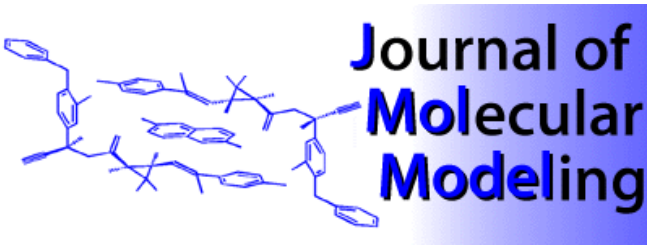

FULL PAPER

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Molecular Modeling of Calixarenes with Group I Metal Ions

Steven E.J. Bell[1], M. Anthony M[c]Kervey[1], Darren Fayne[2], Patrick Kane[2], and Dermot Diamond[2]

[1] School of Chemistry, The Queen's University of Belfast, Belfast BT9 5AG, N. Ireland. Tel. +44-232-274470; Fax +44-232 382117. E-mail S.Bell@qub.ac.uk

[2] Department of Chemistry, Dublin City University, Glasnevin, Dublin 9, Ireland.

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Abstract Molecular mechanics calculations have been used to model the geometries of the complexes of Group I metal ions with calix[n]arenes (n = 4,5). A simple procedure in which the calixarene atoms are assigned partial charges on the basis of AM1 calculations and the metal ions are allowed to bind electrostatically to the calixarenes produces surprising good results when the resulting structures are compared to known crystallographic data on the complexes. Encapsulated solvent molecules and/or counterions can be included in the calculations and, indeed, are necessary to reproduce the X-ray data.

Keywords Calixarenes, Metallocalixarenes, Host-guest interactions, Inclusion complexes, Molecular mechanics

Introduction

Molecular mechanics calculations are already well established in the field of calixarene chemistry. Up to this point their primary use has been in exploring the conformations of the metal-free calix[n]arenes (n=4-6) [1-4] , although the results of very detailed molecular dynamics calculations on metallo-calix[4]arenes which also included solvent molecules have been published [5,6]. Numerous studies have shown that most of the widely available molecular mechanics force-fields can be used to give very reasonable molecular structures for the various conformations available to calix[n]arenes (n=4-6) but the methods are rather less successful in predicting the energy ordering of the conformations which can be adopted by any given molecule [7].

Correspondence to: S. E. J. Bell

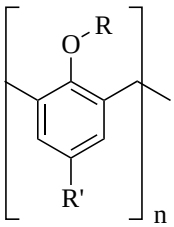
Since one of the main driving forces for studies of this class of compounds is their ability to coordinate metal ions, in some cases with a high degree of selectivity, it is important to understand the structure, not only of the metal-free compounds, but also of the metal complexes which they form. The complexes typically have contain more than 30 heavy atoms so that *ab-initio* methods with large basis sets are prohibitively expensive for routine studies. While it is possible to carry out semi-empirical studies the need for large concerted motions of the aryl rings during geometry optimisation makes these calculations rather lengthy. Moreover, it is not established that semi-empirical methods are significantly better than molecular mechanics methods, even for studies of the metal-free calixarenes [7]. For these reasons we have attempted to model the structures of metallocalixarenes using a simple molecular mechanics force field (MM+), testing the optimised geometries against known crystal structures. Ultimately, it would be extremely useful to develop a method which gives reliable predictions of the strength and selectivity of binding to metal ions but as a

first step in this process it is necessary to demonstrate that molecular mechanics methods can at least reproduce metallo-calixarene geometries. Any force field unable to generate correct geometries would not be expected to provide a basis for a calculating binding energies *etc*, although the converse is, of course, not necessarily true. This geometrical information should be useful not only in guiding the synthesis of new calixarenes but also should provide a method of generating reasonable input geometries for more sophisticated modelling techniques.

Unfortunately, although there is a very extensive database of metal-free calixarene single-crystal X-ray structures, the data set for metallo-calixarenes is much more limited. However, crystal structures of calixarenes with encapsulated Na^+, K^+, Rb^+ and Cs^+ ions are known. This gives a reasonable range of Group I metal ions with which to test the modelling procedure. Moreover, the compounds span calix[4]-arenes and calix[5]arenes which bind through the oxygen atoms of alcohols, ethers, esters or amides. A method which successfully reproduces the geometries of all the above, such as one we describe below, could be regarded as of general utility.

Method

All calculations were carried out using the HyperChem [8] molecular modelling package (Release 4) running on a 75 MHz Pentium PC. Metal-free calixarenes were geometry optimised using the default MM+ force field within HyperChem, which is a modified version of the MM2 force field developed by Allinger *et al* [9]. For the metal-free calixarenes dipole/dipole interactions were used without any artificial distance cut-off. These calculated structures for the metal-free calixarenes, rather than the X-ray data for the complexes (with or without a central metal ion), were then used as the starting point for the calculations on the metal complexes. This was done specifically because we wanted to develop a method for generating model structures of metal complexes for which no X-ray crystallographic data are available.



1 R=$CH_2CON(Et)_2$, R'=^{t}Bu, n=4
2 R=CH_2CO^tBu, R'=^{t}Bu, n=5
3 R=CH_3, R'=^{t}Bu, n=4
4 R=H, R'=^{t}Bu, n=4

Scheme 1

Partial charges were calculated for each of the ligands using AM1 [10-12] calculations on a fragment of the parent compound (normally one full aryl ring and its substituents plus ethyl groups at the bridging methylene positions). These charges were then transferred, with some averaging and rounding off, to the entire parent compound, which meant that the equivalent atoms in each aryl ring in the calixarene were assigned the same charge. It is more straightforward to calculate partial charges on the full complex by modelling its structure (with no encapsulated metal ion), carrying out a single point calculation on this structure and then using this charge distribution directly in calculations on the metal complexes but this gives unsymmetrical charge distributions (i.e. chemically non-equivalent binding sites) unless the structure used has a suitably high symmetry axis (a C_4 axis in the calix[4]arenes, for example), which is not normally the case. In cases where the crystal structure of the metal complex is known it would be possible to carry out such a single point AM1 calculation on the known calixarene structure, which might well give a better representation of the charge distribution in the complex, but again this is only possible for complexes whose structure has already been determined.

Since the default force field only contains parameters for neutral Group 1 metal atoms the metal ions were replaced, for the purposes of the calculation, with atoms of the closest-lying noble gases which are isoelectronic with them. The default parameters for properties such as the van der Waals

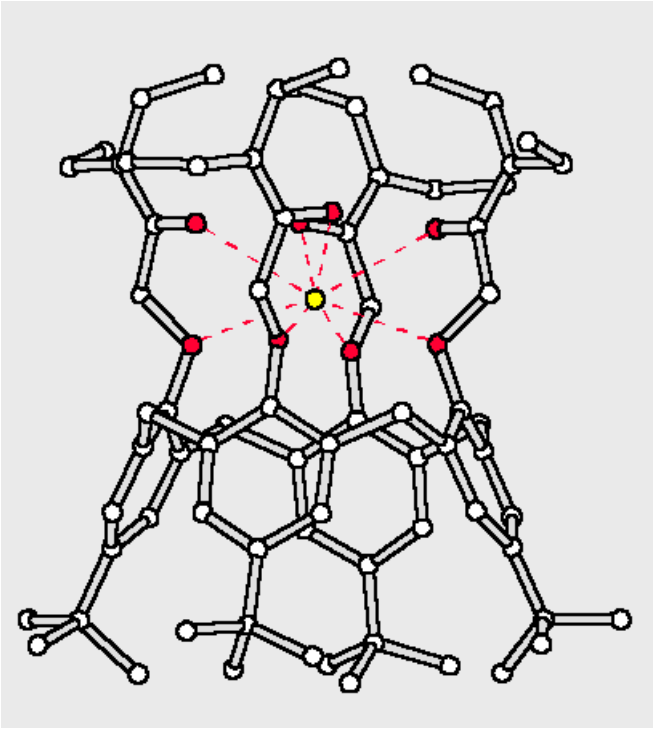


Figure 1 *The model structure of the K^+ complex of* ***1***

radii of the noble gases are very close to those recommended for Group 1 ions. The noble gas atoms were then assigned a formal +1 charge. To simulate encapsulation of the metal ions the model ions were placed at an arbitrary position within the calixarene, normally in the vicinity of the expected binding sites, and the calixarene structure was then allowed to relax around the ion by geometry optimisation using the assigned partial charges and the electrostatic option. No attempt was made to place the metal ions at the positions where they are found in the X-ray structure, indeed since the structures of the metal-free calixarenes used to give the starting geometries for the metal complexes can be quite different from those of the full metallo-calixarene complex it is not possible to determine what the position of the metal ion before optimisation should actually be. In cases where the potentially-ligating carbonyl groups in the free calixarene were pointing directly out of the cavity their torsion angles were manually adjusted so that pointed into the cavity, if this was not done either the optimisation to the final encapsulating structure took excessively large numbers of cycles or local minima with incomplete coordination around the metal centre were encountered. These local minima had significantly higher energies (typically by 5-10 kcal mol^{-1}) than the fully coordinated complexes. The geometries and partial charges on solvent molecules were calculated using the AM1 parameter set. In calculations of calixarene structure with solvent molecules, the solvent molecules were inserted directly into the calixarene as described below with no scaling of the AM1 partial charges.

Published crystal structures were taken from the Cambridge Structural Database [13]. RMS diferences between calculated and x-ray structures are given in Table 1 of the Supplementary Material.

Results and Discussion

The ability of molecular mechanics to reproduce the geometry of a given conformation of metal-free calixarene has already been widely demonstrated in the literature [2-7] so, for the sake of brevity, the calculated geometries of the metal-free compounds, which were used as the starting points for the structures, are not discussed here. All the metal-free calix[4]arenes discussed here (except the alcohol, which is strongly intramolecularly hydrogen bonded) have an approximately C_{2v} (rectangular) symmetry, while their metal complexes are approximately C_{4v} (square). The calix[5]arenes have no regular geometry. Several of the metallo-calixarenes whose crystal structures have been determined crystallise with solvent molecules in their cavities and/or have closely-associated counterions. For this reason we felt it necessary to include appropriate solvent molecules and/or counterions in the calculations of the structures of the complexes if these were known to lie within either the upper or lower cavities of

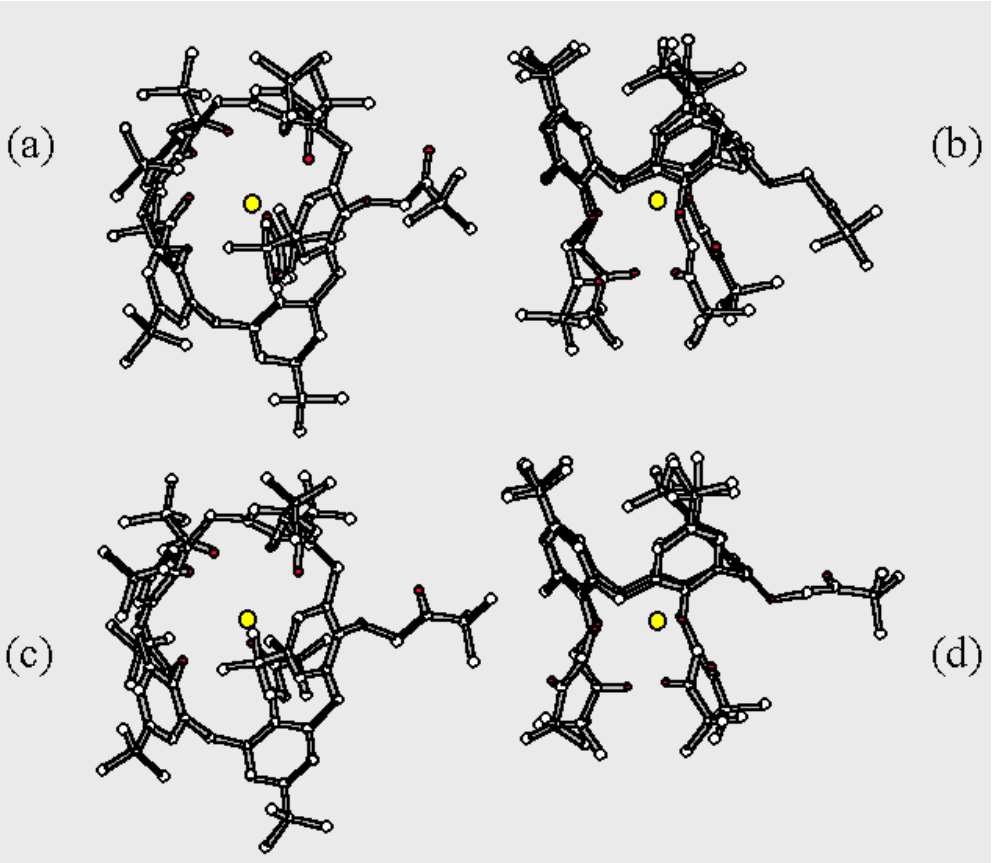


Figure 2 *Orthogonal views of* (**a**),(**b**) *the modelled structure and* (**c**),(**d**) *the X-ray structure of the* Rb^+ *complex of* ***2***

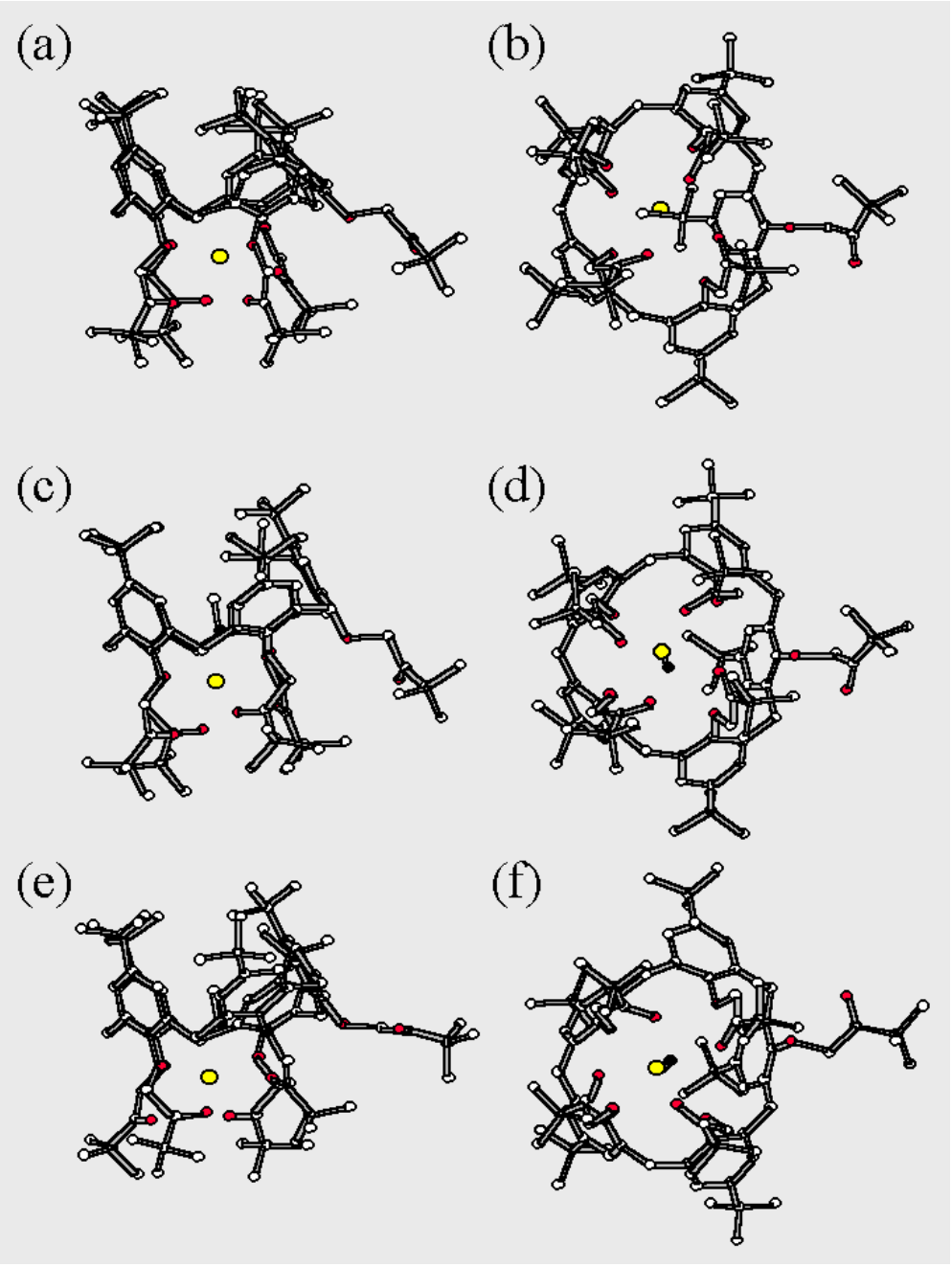


Figure 3 *Orthogonal views of : (***a***),(***b***) the model structure of the Na^+ complex of* ***2*** *with no solvent included in the model; (***c***),(***d***) the model structure of the Na^+ complex of* ***2*** *with a methanol solvate; (***e***),(***f***) the X-ray structure of the Na^+ complex of* ***2***

the calixarenes, solvent molecules or counterions lying outside the cavities were not included in the calculations. This is a reasonable step since the purpose of the calculations we report here is not to predict whether solvent/counterions will associate with the calixarenes in the solid state but rather is to determine if a simple force field can predict the structure of such an assembly. Excluding encapsulated solvent molecules when it is known they are present results in calculated structures which would need to be compared to hypothetical solvent-free complexes rather than actual data available. The most straightforward examples are, of course, those complexes with no included solvent molecules and where the counterions are sufficiently distant from the encapsulated metal ions that they can be safely excluded from the calculations (in the examples below this

Figure 1 shows the calculated structure of the K^+ complex of the calix[4]arene tetraethyl amide **1**, whose crystal structure is reported in Reference 14. The calculated structure has the correct 4-fold symmetry axis, i.e. the structure has 'squared up' on introduction of the metal ion, and the metal lies between the planes defined by the ether and carbonyl oxygen atoms. The distances between opposite ether oxygens and opposite amide oxygens, which define the size of the coordination cavity, are 5.0 Å and 4.7 Å, respectively. The corre-

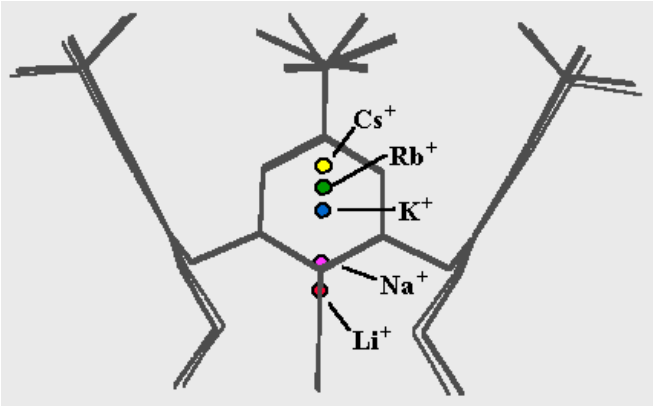


Figure 4 *Overlayed model structures of the complexes of* ***3*** *with Li^+, Na^+ , K^+, Rb^+ and Cs^+*

sponding distances in the X-ray structure are 4.7 Å and 5.1 Å. The X-ray structure also shows that the upper cavity is filled by a methanol molecule that has no strong intermolecular interactions with the host. We have found that inclusion of this solvent molecule in the model has a negligible effect on the calculated structure of the complex. Calculations on this complex by Wipf *et al* [5] using a similar electrostatic binding approach in the Amber force field gave a similar result.

The metal-free calix[5]arene **2**, which is an ester, has a non- regular cone geometry in that one of the aryl rings tilts into the central cavity. The same general conformation is also observed in its Rb^+ complex, whose crystal structure is shown in Fig. 2 [15]. The Rb^+ ion lies approximately in the mean plane defined by the four ether oxygen atoms which it lies closest to (i.e. well above the mean carbonyl oxygen plane) and is not coordinated by the oxygen atoms of the inward-tilting ring. The crystallographic and calculated structures for this complex, both shown in Fig. 2, are very similar. The most significant inter-atomic distances are given in Table 2 of the Supplementary Material. The main features of the geometry (calixarene ring tilting angles and position of the encapsulated metal ion within the calixarene) are well reproduced by the calculated geometry. This is rather more impressive than the successful prediction of the highly symmetrical calix[4]arene structure shown above, since any force field with reasonable ion size parameters for the metal ion and coordinating atoms could well minimise to a symmetrical structure for the calix[4]arene, even if the metal-oxygen interactions were significantly overestimated in the calculation. It is much less likely that a force field with excessively strong attractive interactions could lead to the very irregular structure shown in Fig. 2.

The single crystal X-ray structure of the Na^+ complex of **2** (Fig. 3(e)) shows that it rather different from the Rb^+ complex, the inward tilting aryl ring is much more upright and the metal ion lies farther below the average plane of the four coordinating ether oxygens [15]. However, the complex crystallises with one methanol solvent molecule in the cavity so that these differences could be due either to the change in the central metal ion or to the encapsulated solvent. In the calculated structure of the Na^+ complex with no solvent included, shown in Fig. 3(a), the conformation of the calixarene is similar to that of the Rb^+ complex. Inclusion of the methanol solvent molecule brings the calculated structure (Fig. 3(c) and Table 3 of Supplementary Material) much closer to that obtained crystallographically, with a more upright displacement of the inward tilting aryl ring and the Na^+ ion lying between the carbonyl and ether oxygen planes. The position of the solvent is also reasonably well reproduced in the calculated structure.

The tetraether **3** and tetraalcohol **4** complexes of calix[4]arenes are structurally the simplest of all the complexes investigated and we might expect that there would be pronounced similarities between them. Figure 4 shows the calculated structures for a series of metal complexes of the tetramethylether **3**. There is clear trend in these structures with increasing ion size driving the metal higher above the ether oxygen plane and into the upper cavity. The position of the Cs^+ ion in this simple model agrees rather well with the crystal structure [16] of the Cs^+ complex of the tetraalcohol **4** and in both cases the complex has an approximate C_4 axis. However, the model Na^+ complex is very different from the known structure [17], the position of the Na^+ ion is well above the ether oxygen plane in the model while it is below it in the crystal structure. Indeed, the position of the Na^+ in the crystal structure is considerably lower even than the position of the Li^+ in the series of models. In order to determine if it was a systematic error in the modelling method which caused this discrepancy we carried out more careful modelling studies on the Cs^+ complex of **4**, the Na^+ complex of **3** and, since no crystallographic data were available for the Li^+ complex, compared the MM+-derived model Li^+ complex of **4** with a model of the same complex derived from semi-empirical calculations.

The most difficult complex to model is the simplest of all the structures attempted, the Cs^+ complex of **4**. The main difficulty is that in its metal-free form the complex contains strong intramolecular hydrogen bonds between the phenolic residues on the lower rim [16]. We have found that the simple MM+ forcefield does not accurately reproduce the structure of this molecule, which should not be too surprising since it does not contain any explicit hydrogen-bonding interaction terms. Moreover, the Cs^+ complex of **4** forms only in alkaline solution where it is believed one of the phenolic residues is deprotonated. In order to try to simulate the effect of deprotonating a single phenolic alcohol we have calculated partial charges on both deprotonated and protonated phenolic residues and averaged the resulting charges in a 3:1 ratio. These charges were then set on all of the four phenolic residues. The structure of the model Cs^+ complex generated through this procedure, which also has an acetonitrile solvent molecule included in the normal way, is shown in Fig. 5, along with the X-ray data. The position of the Cs^+ ion within the cavity is close to that found in the crystal structure. The encapsulated solvent molecule is tilted away from the central symmetry axis by 50^0 in the model, which is in poor agreement with the crystallographic data, but the N atom

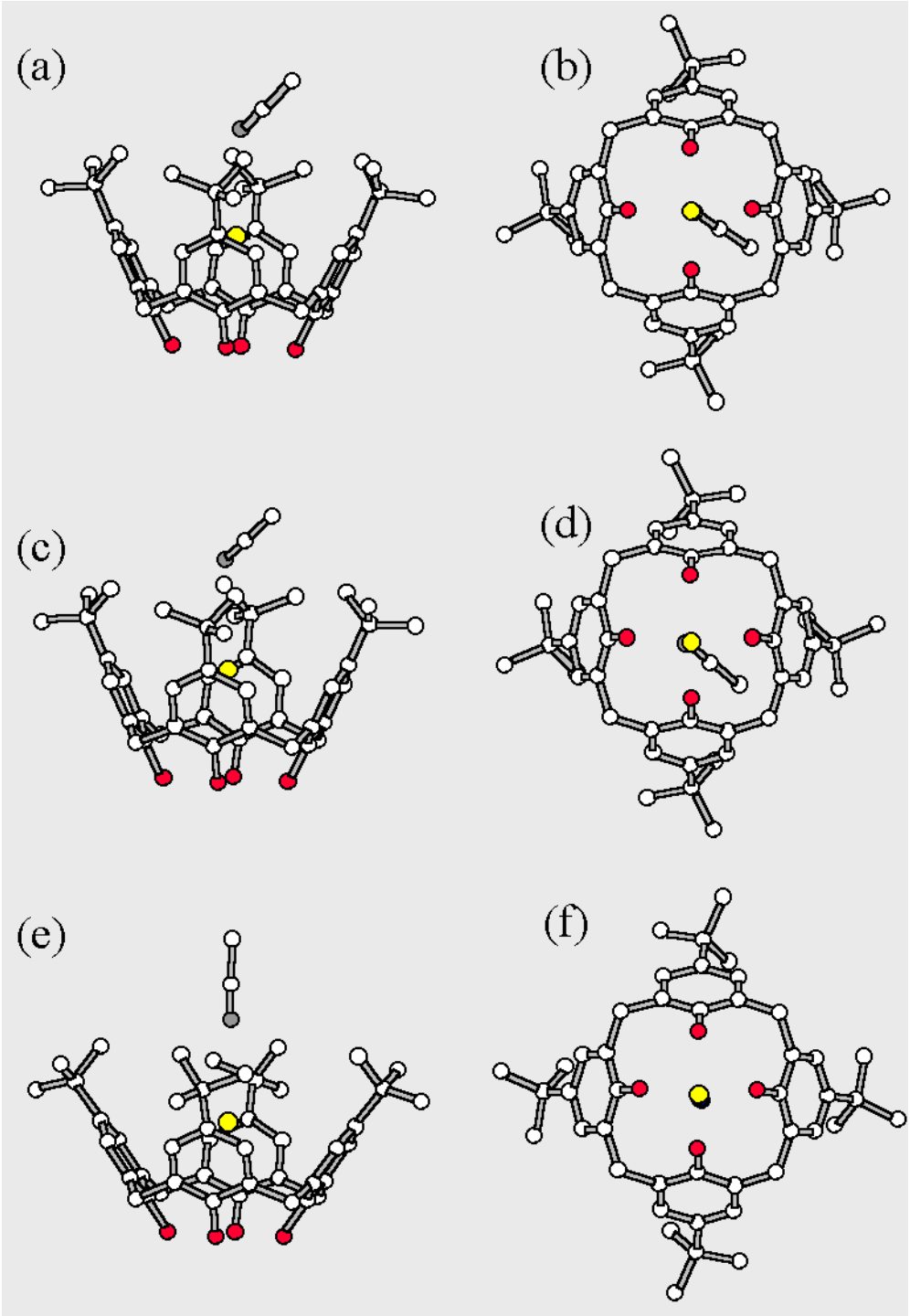


Figure 5 *Orthogonal views of : (***a***), (***b***) the model structure of the Cs^+ complex of* ***4*** *using partial charges for a singly-ionised complex; (***c***), (***d***) a similar model structure obtained using partial charges for a neural calixarene; (***e***), (***f***) the X-ray structure of the complex. An acetonitrile solvate is shown in each of the structures*

of the solvent in the model structure lies 3.54 Å from the metal centre, which compares reasonably well with the 3.29 Å value in the known structure so that there is no gross discrepancy in the model. In addition, we found that the simpler procedure of treating the calixarene as a simple neutral species and calculating the partial charges on that basis also led to a structure (shown as Fig. 5(c)) which is acceptably close to the crystallographic data. The only difference in interatomic distance between the two models which was greater than 0.1 Å was that the second model structure had a metal -solvent distance of 3.54 Å, almost half the error found for the alternative procedure (see Table 4 of Supplementary Material).

There is no crystallographic data on the Li^+ complex of **4** with which to judge the accuracy of the model of this complex (shown in Fig. 6(a)), but it is possible to model this complex completely independently from the molecular mechan-

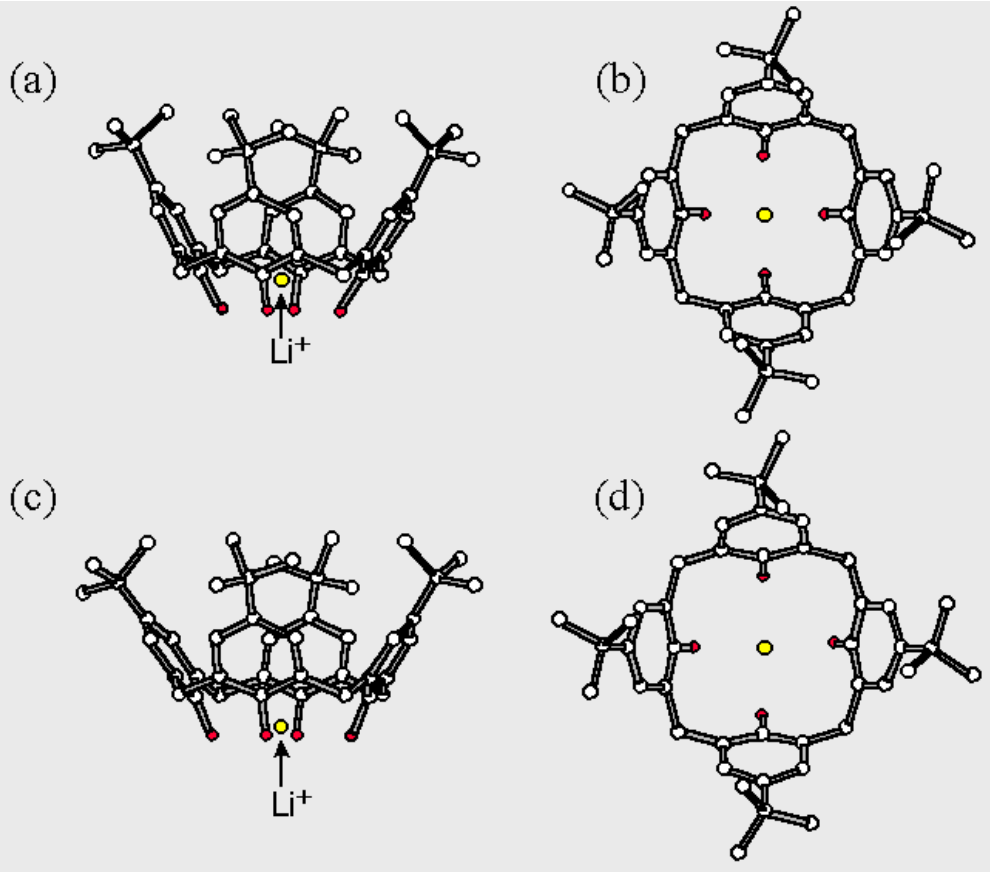


Figure 6 *Orthogonal views of model structures of the Li^+ complex of **4**: (**a**), (**b**) modelled using molecular mechanics; (**c**), (**d**) modelled using PM3*

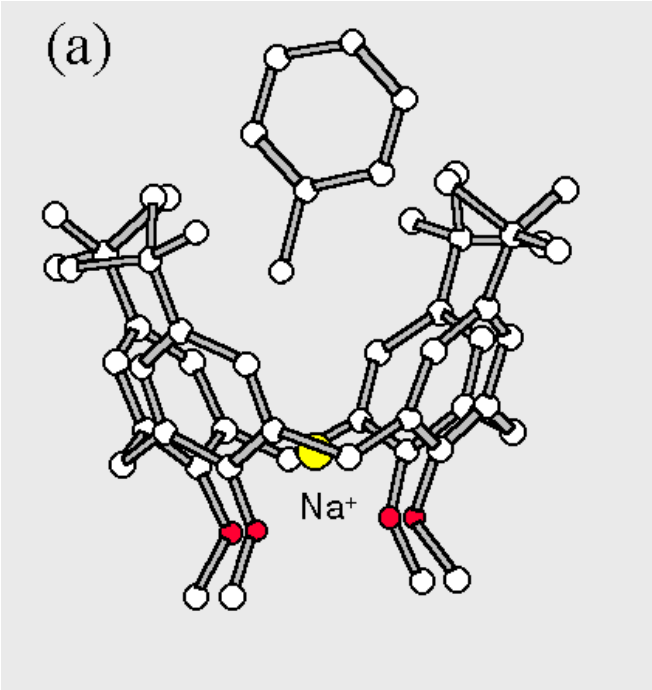


Figure 7a *The model structure of the Na^+ complex of **3** with a toluene solvate*

ics calculation using semi-empirical PM3 methods [18]. The result of this calculation is also shown in Fig. 6. where it is compared to the MM+ -derived structure. The main difference between these Li^+ complexes and the Cs^+ complex of the same calixarene is that both the modelling methods give Li^+ structures where the Li^+ ion lies between the mean planes defined by the phenolic oxygens and by the bridging methylene carbons, while in the Cs^+ complex the metal lies deep within the cavity on the upper rim. The PM3 calculation does, however, place the Li^+ ion 0.7 Å lower in the cavity.

Since the trend in metal ion positions in the simple tetraalcohols predicted by the MM+ procedure seems to agree reasonably well with other independent data the disparity between the model and crystal structure [17] of the Na^+ complex of **3** described above is surprising and merits further investigation. Figure 4 showed the calculated structure of the Na^+ complex of **3** with no solvent or counterion included in the calculation, inclusion of a toluene molecule at the upper rim produces the structure shown in Fig.7(a). This structure also reproduces the calixarene aryl ring tilt angles found in the crystal structure but again the Na^+ ion lies above the mean plane of the ether oxygens in the calculated structure while it is below the mean plane in the crystal structure. Closer inspection of the crystallographic data reveals that, in contrast to the structures discussed thus far, the counterion lies only 2.83 Å from the Na^+ ion i.e. little more than the sum of the Van der Waals radii of Na^+ and closest carbon atom of the

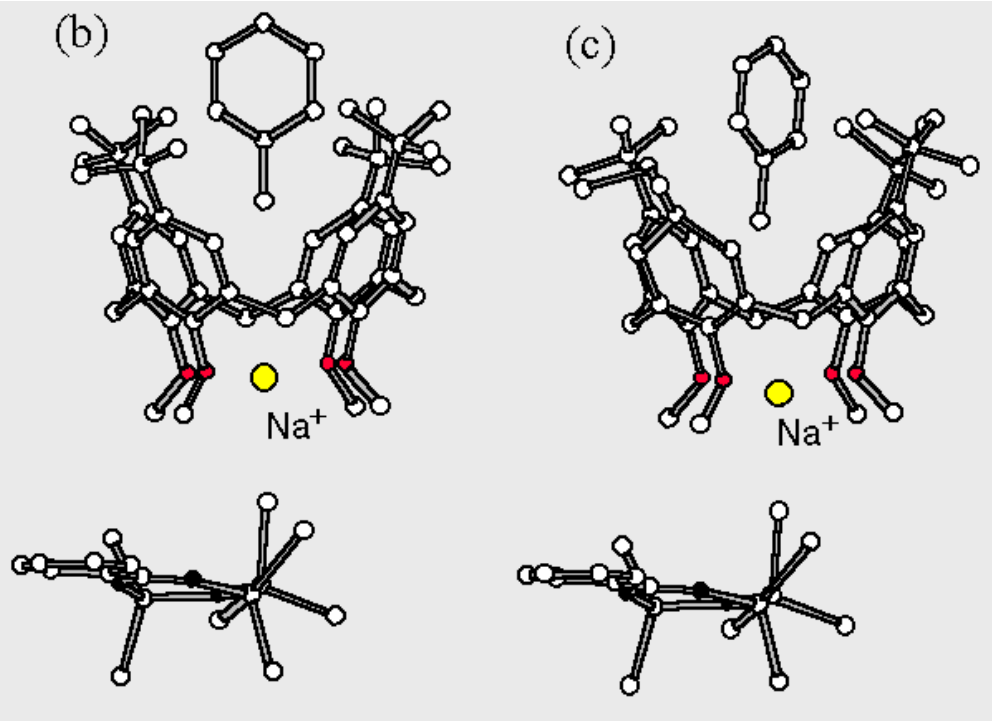


Figure 7 *(***b***) The model structure of the* Na^+ *complex of* ***3*** *with a toluene solvate shown in (a) after inclusion of a fixed counterion, (***c***) the X-ray structure of the complex*

counterion. A counterion in such close proximity to the metal centre might well be expected to have a significant effect on the structure of the complex. For the purposes of these calculations the model of the complex was modified by placing a counterion at the position where it is known to lie from the crystallographic data. After the counterion was fixed in position the geometry of the calixarene, solvent and Na^+ ion was allowed to relax. Figure 7(b) shows the structure of the complex which resulted. Inclusion of the close lying counterion has caused the Na^+ ion to move 1.53 Å lower in the cavity than it was in the first model (Fig. 7(a)), it now lies below the ether oxygen plane and very close to its position in the crystal structure. In effect, the carbon atom of the counterion, which carries a net positive charge has provided an additional electrostatic driving force which pulls the metal ion below the mean ether oxygen plane. The toluene solvate also moves down into the cavity on addition of the counterion and again this movement brings its position much closer to that found in the actual complex.

In summary, this straightforward and computationally undemanding method is surprisingly good at reproducing the structures of a range of metallo-calixarenes. This implies that the force field employed is at least reasonably good at balancing the conflicting demands of the electrostatic interactions between the ligating oxygen atoms and the encapsulated metal ions with the stretching/bending forces induced in the calixarene by the metal ion inclusion. The method is not, nor is it intended to be, in any way rigorous or highly accurate. It gives predictions of metal ion positions within calix[n]arenes in the solid state which, in the worst cases, are up to 0.5 Å in error, although the average error is considerably less. There is clearly potential for refining the method as more crystallographic data become available, indeed we found that we could adjust the metal ion parameters to make near-perfect fits to the crystallographic data but felt that we could have little confidence in the transferability of these arbitrary parameters to other complexes. However, the method as it stands already provides a simple and inexpensive visualisation tool which should be useful for the design of new calixarene derivatives.

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Supplementary Material Available Tabulated RMS values for modelled and X-ray structures of the metal complexes of calixarenes **2, 3** and **4** (Table 1), structures of the modelled complexes as *.mol files and tabulated comparisons of the most significant inter-atomic distances for modelled and X-ray structures of these complexes (Tables 2- 5).

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