

FULL PAPER

Modelling of the Sodium Complex of a Calixarene Tetraester in the 1,3-Alternate Conformation

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Abstract This paper describes the use of molecular mechanics to model the geometry of the sodium complex of a calix[4]arene tetraester, in the 1,3-alternate conformation **1**. Partial charges were assigned to the calixarene on the basis of semi-empirical (AM1, PM3, MNDO, INDO, CNDO and ZINDO) calculations and the binding of the sodium ion to the calixarene was modelled using molecular mechanics. Agreement between the optimised and X-ray structures of the complex was very good. The effect of placing the cation in different starting positions on the energy-minimised geometry of the complex is described.

Keywords Calixarene tetraester, Sodium complex, Molecular mechanics, Semi-empirical, Partial charge, Geometry optimisation, Atom type

Introduction

The principal use of molecular mechanics in calixarene chemistry to date has been to explore the conformations of the metal-free calix[4]arenes [1], although the results of very detailed molecular dynamics calculations on calixarene metal complexes which included solvent molecules, have also been published [2]. However, the crystal structures of a number of calixarenes with encapsulated Group 1 ions are now available and the molecular modelling of these complexes was the subject of a recent paper [3]. The calixarenes studied in that investigation were in the so-called 'cone' conformation, an example is given in Figure 2. However,

calixarenes with other conformations are known and one of these, the tetraester, **1**, in the '1,3-alternate' conformation, is the subject of this study. This latter conformation is illustrated in Figure 1. In **1**, there is the possibility that complexation of the metal cation can take place at several sites within the calixarene. Therefore, it is of interest to determine what effect varying the initial position of the cation has on the optimised geometry of the complex.

Method

Optimisations were carried out using the HyperChem [4] molecular modelling package (version 4) running on a 180 MHz Pentium Pro PC with 32 MB RAM.

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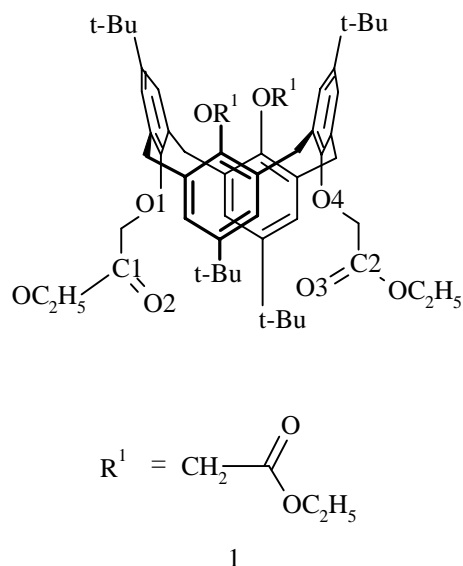


Figure 1 Line rendering of the compound modelled, **1**. The atom labels O1, O2, O3, O4, C1 and C2 are used again in Figure 10 to Figure 13, inclusive. The pendant groups with atoms with the labels O1, O2 and C1 are part of the pendant group in the '1' position while the pendant group in the '3' position contain the atoms with labels O3, O4, and C2. The 'R¹' groups are in the '2' and '4' positions

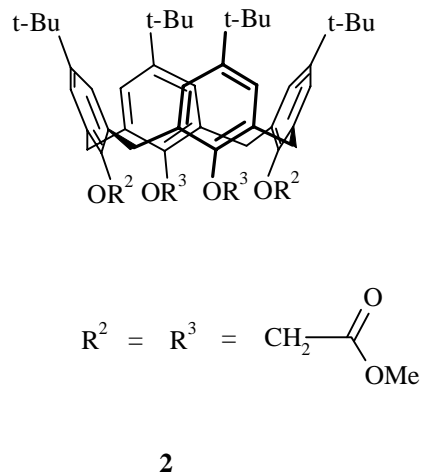


Figure 2 Line rendering of **2**, which is discussed in the text to highlight the difference in the distribution of electron density between **1** and **2**. The R² pendant groups indicate the location of the '1' and '3' positions, while the R³ groups are in the '2' and '4' positions

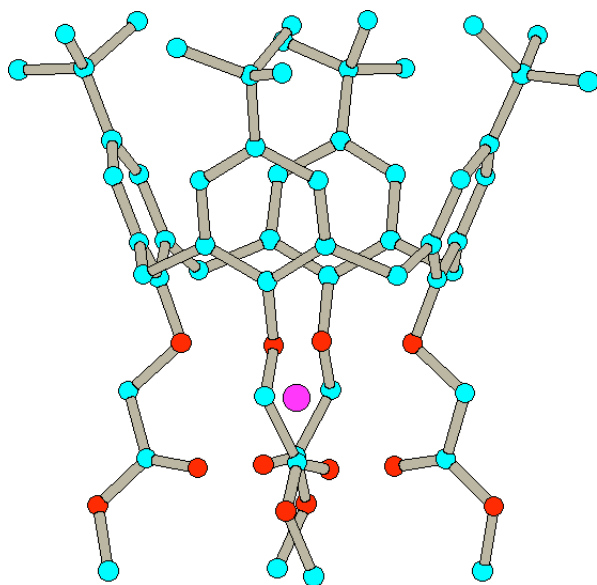
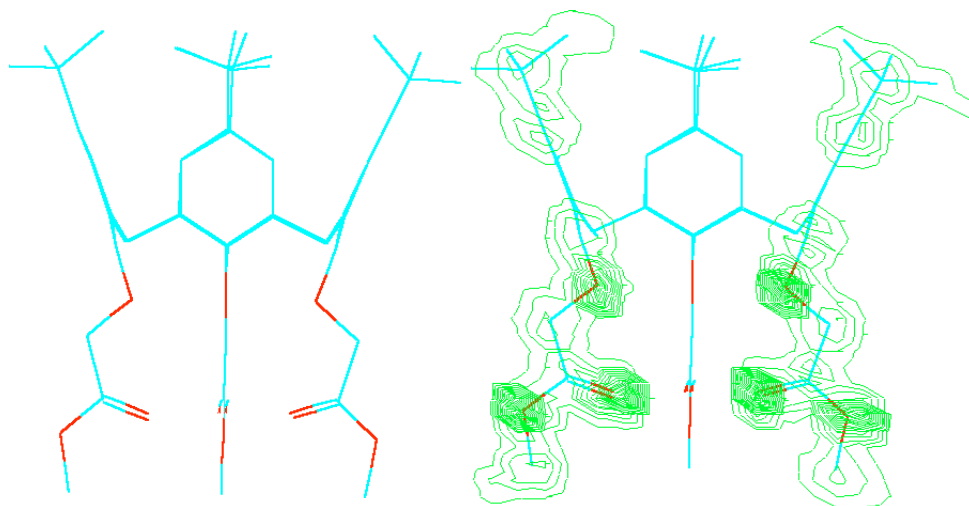


Figure 3 Ball and tube rendering of the side-on view of the optimised structure of **2:Na⁺**. PM3 partial charges were placed on the ligand with Method 2 and by initially placing the ion close to the optimised position. The initial geometry used for the ligand was that of the optimised structure of the free ligand. Colour code: cyan - carbon, red - oxygen, magenta - sodium

Tetraester calix[4]arenes, in the cone conformation, such as **2**, are well established as ionophores for the Na⁺ ion [5]. There is very strong evidence, from NMR spectroscopy, that **2**, upon complexation with Na⁺, remains in a 'cone' conformation but (unlike the free ligand) has a four-fold symmetry and that the ion is coordinated by the four phenoxy oxygen atoms and the four carbonyl oxygen atoms [6]. This eight-fold coordination is found in the energy-minimised model of the complex (see Figure 3) and in the X-ray structure of the complex formed between the tetraamide analogue of **2** and K⁺ [7]. Thus, it is clear that Na⁺ ion can be complexed by **2** and other, similar calixarenes in one region only. (In the cone conformation, the carboxylate oxygen atoms of **2** do not have the correct orientation to interact with the Na⁺ ion collectively, either on their own or with the other types of oxygen atoms in **2**).

Examination of the total charge density contour plot for **2**, given in Figure 4b, identifies the phenoxy, carbonyl and carboxylate oxygen atoms as giving regions of high electron density (a very similar plot would be obtained if the contour plot were taken in a plane approximately containing the '2' and '4' pendant groups). The contour plot for **1**, shown in Figure 5b, indicates that although the same types of atoms give regions with high electron density, these atoms are dispersed over the entire molecule, rather than clustered in a single obvious binding site. Thus, the 1,3-alternate conformation of **1** creates several possible complexation sites and this is in contrast to the number of sites available in the case of **2**. (It is important to note that the model in Figure 4a and Figure 4b was obtained by rearranging, for illustration pur-

Figure 4 Stick rendering of the structure of **2**, without, (left) and with, (right) the total charge density contour plot superimposed. The contour plots were determined after carrying out a single-point PM3 calculation on **2**. They apply to a plane which is parallel to the plane of the page and which contains the centre of mass of the molecule



poses, the ligand geometry in the optimised structure of **2**:Na⁺, so that the phenoxy and carbonyl oxygen atoms of the two pendant groups on opposite sides of the cavity were approximately in the same plane. However, for Figure 5a and Figure 5b, no such rearrangement of the geometry of **1** structure was carried out.)

The X-ray structure of the **1**:Na⁺ complex is given in Figure 6a and Figure 7a [8], (the Cambridge Crystallographic Data Centre [9] reference is YERFIK). This complex was chosen for further modelling studies because its structure suggests that there is the possibility of migration of the cation. Furthermore, the apparent multiple binding sites allow us to test the extent to which the modelling procedure can find the global minimum (in terms of energy) of an optimised structure more rigorously than is possible in the case of the 'cone' calix[4]arenes. In this work, it is assumed that the global minimum corresponds to the X-ray structure.

The modelling procedure uses electrostatic interactions to bind the metal ion within the calixarene, which means that partial charges must be calculated for the ligand. In this work

three methods were used to calculate these charges. The first method was to use a single point, semi-empirical calculation (AM1 [10]) on a compound similar to **1** (one full aryl ring and its substituents plus ethyl groups substituted at the bridging positions on the ring, see Figure 8). These charges (Method 1) were then transferred, with averaging and rounding off, to the entire molecule of **1**, meaning that chemically equivalent atoms were assigned the same charge. The transferring of charges is a labour-intensive process and consequently, partial charges were also calculated on the full ligand with the AM1, MNDO [11, 12] and PM3 [13, 14] semi-empirical methods (Method 2), which was a less laborious process. Another advantage of the latter method is that we can see the effect that assigning slightly different partial charges to atoms that are chemically equivalent but conformationally different has on the optimised geometry of the complex. This is relevant to the modelling of **1**:Na⁺, as the geometry of the pendant groups in the '2' and '4' positions of **1** is different to that of the pendant groups in the '1' and '3' positions. However, Methods 1 and 2 both suffer from the

Figure 5 As for Figure 4 except that **1** is shown

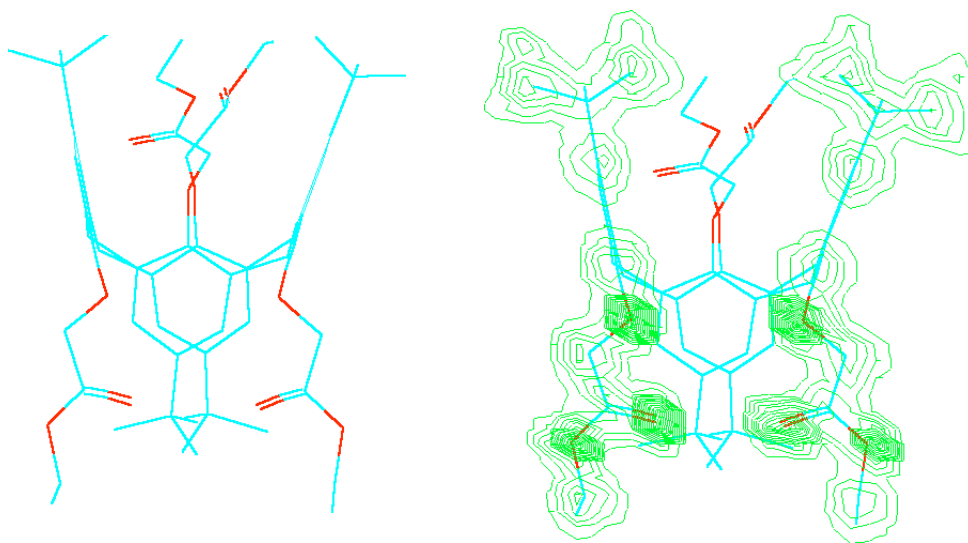


Table 1 RMS Overlay Errors and distance of the optimised Na⁺ position from its X-ray position, following the superimposition of optimised structures upon the X-ray structure of 1:Na⁺ [a]

Determination of Partial Charges	RMS Overlay Error / Å	Optimised Na ⁺ - X-ray Na ⁺ / Å [b]
AM1 / Method 1	0.733	0.45
AM1 / Method 2	0.734 [c]	0.46 [c]
MNDO / Method 2	0.731 [c]	0.33 [c]
PM3 / Method 2	0.731 [c]	0.32 [c]
INDO / Method 3	0.951	0.34
CNDO / Method 3	0.942	0.32
ZINDO/1 / Method 3	0.981	0.54

[a] All the values quoted refer to optimised structures after the Na⁺ ion was initially placed in Position 2 (see Figure 9)

[b] The distances between the optimised and X-ray positions of the Na⁺ ion were measured after superimposing three

of the methylene bridging carbons of the optimised structure on those of the X-ray structure

[c] In these cases, virtually identical results (the values differ in the third decimal place only) were obtained when the Na⁺ ion was placed in different starting positions

disadvantage that because the calculations are carried out on the free ligand, they do not take into account withdrawal of electron density from the ligand when it binds with a cation. Accordingly, partial charges were also determined by carrying semi-empirical calculations on the full metal complex using those methods which have parameters for sodium - INDO [15], CNDO [16] and ZINDO/1 [17] (Method 3).

The molecular mechanics MM+ force field available with the HyperChem software (and indeed, the other force fields available in HyperChem) contain no parameters for Group 1 metal ions and therefore, as in previous studies [3], the atom type for neon was used for the sodium ion since neutral neon is isoelectronic with Na⁺. The ion was assigned a formal charge of +1 in the case of Methods 1 and 2.

The starting geometry used for the ligand for both the molecular mechanics and semi-empirical calculations was

that of the ligand as in the X-ray structure of 1:Na⁺. Hydrogen atoms needed to be added, as the X-ray structure did not contain them. With Methods 1 and 3, the ion was initially placed in Position 2 only - the position it occupies in the X-ray structure (see Figure 5a and 8). When partial charges were assigned with Method 2 the initial position of the Na⁺ ion was varied as shown in Figure 8. The geometry of the structure was subsequently optimised using the MM+ force field within HyperChem, which is a modified version of the MM2 force field developed by Allinger *et al.* [18]. A combination of three algorithms were used: steepest descent initially, then Polak-Ribiere and finally, Newton-Raphson. The atomic charges electrostatic interaction option was used without any artificial distance cut-off. The terminating gradient was 0.001 kcal·mol⁻¹·Å⁻¹.

Figure 6 Ball and tube rendering of the side-on views of the X-ray (left) and optimised (right) structures of 1:Na⁺. The optimised structure was obtained by placing PM3 partial charges with Method 2 and by initially placing the ion in Position 2. The atom labels in (a) are used to define the region of the cation and are also used in Tables 2 and 3 and Figure 9 to 12, inclusive

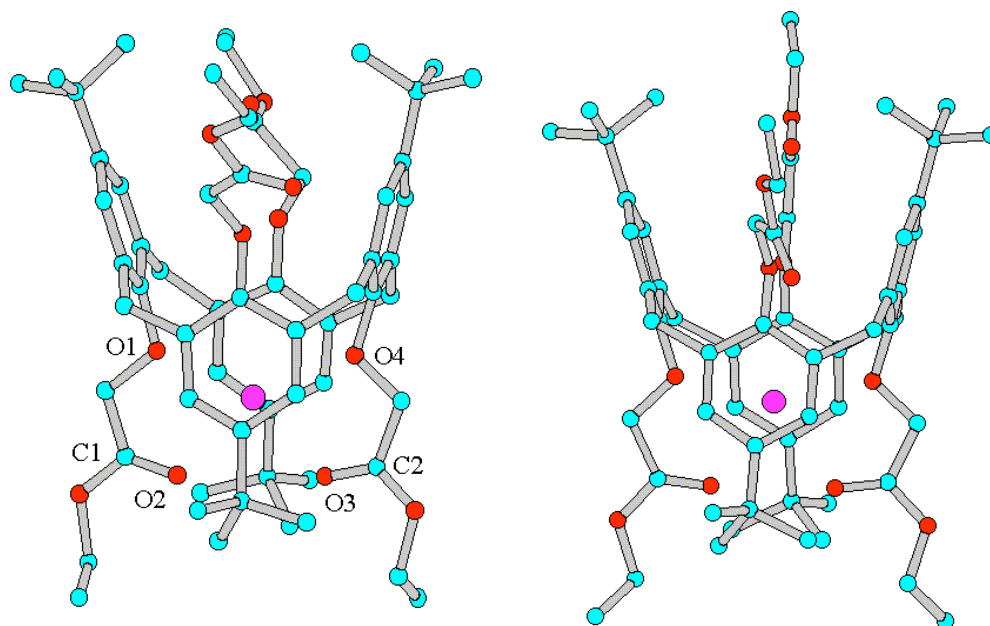


Table 2 Critical distances and torsional angle for the X-ray and optimised structures of 1:Na⁺ in the region of the Na⁺ ion

Determination of Partial Charges	O2-O3 / Å	O1-O4 / Å	Mean of O2-Na ⁺ -O3-Na ⁺ / Å	Mean of O1-Na ⁺ -O4-Na ⁺ / Å	ϕ / ° [a]
X-ray	3.29 [b]	4.39 [b]	2.33 [b]	2.39 [b]	-6.14 [b]
AM1 / Method 1	2.98 [c]	4.57 [c]	2.55 [c]	2.32 [c]	-7.94 [c]
AM1 / Method 2	2.96	4.56	2.54	2.32	-8.22
MNDO / Method 2	2.99	4.51	2.46	2.32	-8.02
PM3 / Method 2	3.06 [d]	4.61 [d]	2.42 [d]	2.38 [d]	-7.83 [d]
INDO / Method 3	4.36 [e]	4.81 [e]	2.59 [e]	2.74 [e]	-11.04 [e]
CNDO / Method 3	4.30	4.80	2.60	2.70	-10.94
ZINDO/1 / Method 3	4.91	5.06	3.00	2.75	-9.41

[a] This is the improper torsional angle made by the lines joining atoms O1 and C1 and C2 and O4

[b] These values are also given in Figure 10

[c] These values are also given in Figure 11

[d] These values are also given in Figure 12

[e] These values are also given in Figure 13

[f] The values quoted for Method 2 are almost identical for each of the five starting positions for the Na⁺ ion. For the distances quoted, variation occurs in third decimal place, while the range over which the improper torsional angle varies is ca. 0.1°

The quality of fit of the structure to the X-ray structure was assessed by superimposing each optimised structure upon it and calculating the Root Mean Square (RMS) Overlay Error.

Results and discussion

MM optimisations of 1:Na⁺ (partial charges assigned with Methods 1 and 2), produced structures (see Figure 6b and 7b) that closely match the X-ray structure (shown in Figure 6a and 7a), as judged by the smallness of the RMS Overlay

Errors, given in Table 1. Of these structures, that produced using the combination of the PM3 semi-empirical method and Method 2 of assigning partial charges gave the best results, as judged by the error in the cation positions in the X-ray and optimised structures (see Table 1) and by examination of the geometry of the complex in the region of the cation (compare Figure 10 with Figure 11 and 12).

It is worth noting that virtually identical structures were obtained when the AM1, MNDO and PM3 semi-empirical methods were used to determine partial charges with Method 2 and also when the AM1 method was used to assign charges with Method 1 (see Figure 11 and 12, where partial charges were assigned with AM1/Method 1 and PM3/Method 2 re-

Figure 7 As for Figure 6, except that the view through the cavities are shown

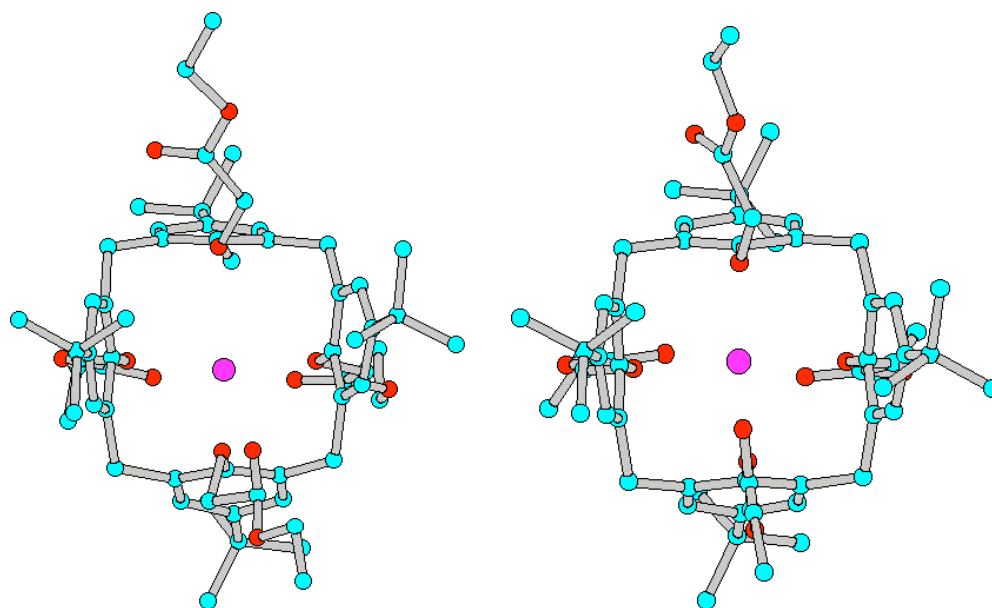
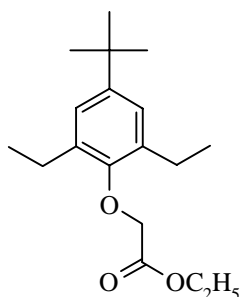


Figure 8 Line rendering of compound **1** used to assign partial charges by Method 1



spectively). The former result would suggest that the optimised structure of this complex is independent of the semi-empirical method used to assign partial charges to the ligand, while the latter result indicates that (albeit slightly) different initial conformations of the pendant groups in the ligand and any resultant differences in partial charge between chemically equivalent atoms in the pendant groups with different conformations, have a small effect on the optimised structure of the ligand in the complex.

A very encouraging result is the fact that, when Method 2 was used to assign partial charges, the geometries of the optimised structures of the complex (both in terms of the conformation of the ligand and the position of the ion) are

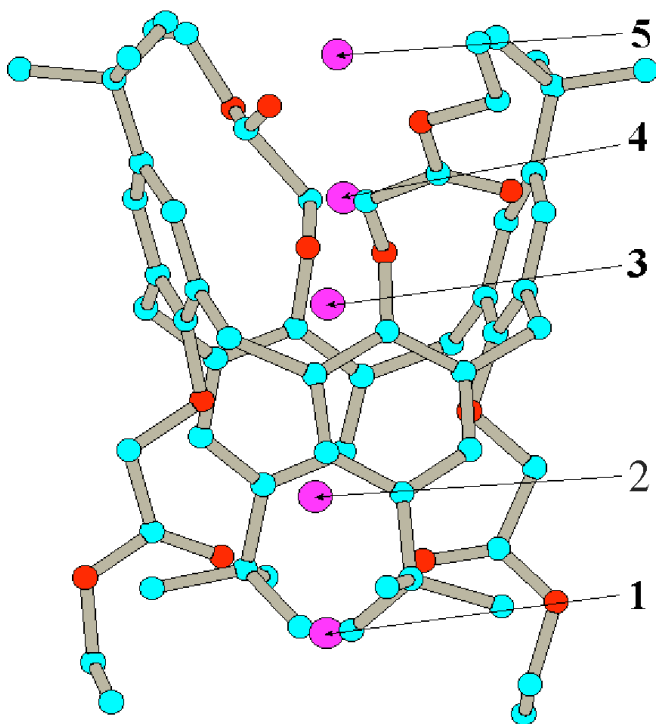


Figure 9 Ball and tube rendering of the side-on view of the X-ray structure of **1:Na⁺**, showing the different positions in which the **Na⁺** ion was initially placed when carrying out the optimisations. In the X-ray structure, the **Na⁺** ion is in Position 2

almost identical, regardless of the initial position of the ion, for each of the three semi-empirical methods used (see Tables 1 and 2).

It is very interesting to note that though the conformation of the ligand initially used was that of the X-ray structure, the two pendant groups most involved in the binding of the ion as indicated by the X-ray structure (the '1' and '3' pendant groups), are the least involved according to the optimised structures, regardless of the initial position of the ion, i.e., when, for example, the ion was placed initially placed in Position 2 - its position in the X-ray structure - its optimised position was that of Position 3 with the corresponding rearrangement of the both pairs of pendant groups. It is important to realise that in the X-ray structure, the '1' and '3' pendant groups of the ligand have a geometry that is very well suited to complexation with the **Na⁺** ion as the ion is approximately equidistant from the carbonyl and phenoxy oxygen atoms of these pendant groups, and the two carbonyl groups and the **Na⁺** ion are approximately in the same plane. This movement of the ion from Position 2 to Position 3 suggests that the energy barrier to the migration is relatively small. This is supported by evidence, obtained from dynamic ¹H NMR measurements [19], that the **Na⁺** ion oscillates rapidly (163 s⁻¹) across the hydrophobic arene cavity in an intramolecular fashion.

A very noticeable difference between the optimised structures (when partial charges were assigned with Methods 1 and 2) and the X-ray structure of **1:Na⁺** concerns the final position of the **Na⁺** ion. In those optimised structures where partial charges were assigned with Methods 1 and 2, it is nearer to the phenoxy oxygen atoms than the carbonyl oxy-

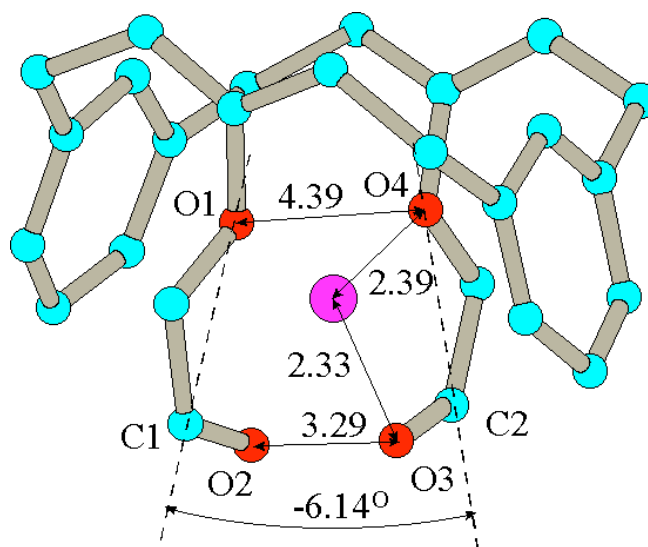


Figure 10 Ball and tube rendering of the side-on view of the X-ray Structure of **1:Na⁺**, showing the geometry of the complex in the region of the cation. The metal to ligand distances shown, given in Angstroms, are mean distances, for oxygen atoms of a given type. The measurements shown are also given in Table 2

gen atoms, whereas in the X-ray structure, the Na^+ ion is positioned lower in the cavity, by 0.32 to 0.46 Å, as is shown in Table 1. Furthermore, as illustrated in Figure 11 and 12, the optimised structures produced using Methods 1 and 2 give the impression that the Na^+ ion is bound mainly by the two phenoxy oxygen atoms of the pendant groups in the '1' and '3' positions, whereas the X-ray structure (see Figure 10) indicates that the carbonyl oxygen atoms in these pendant groups are involved in the complexation to a very similar degree as the phenoxy oxygen atoms. However, as might be expected for a complex containing 154 atoms, the difference in position of the ion in the X-ray and optimised structures has little effect on the RMS overlay error; when the ligand from the optimised and X-ray structures (i.e., *without* the ion) are superimposed on each other, the RMS overlay error changes little from that obtained with the ion present, typically by ca. 0.03 Å.

In molecular modelling, differences in the ion position between X-ray and optimised structures can arise because a counterion and/or solvent molecule(s) were not included in the modelling. Preliminary work (results not shown) in which a perchlorate ion (sodium perchlorate was used to prepare the $1:\text{Na}^+$ complex [8]) was initially placed just below the '1' and '3' pendant groups of the ligand resulted in an optimised position of the perchlorate ion which was in the cavity created by the '1' and '3' pendant groups, with an distance of 3.65 Å between the Na^+ ion and the nearest chlorine atom. This result is clearly at variance with the X-ray structure because the latter structure indicates that the perchlorate counterion is outside both cavities of the calixarene. We feel justified in excluding solvent molecules from these modelling studies because they are not part of the X-ray structure.

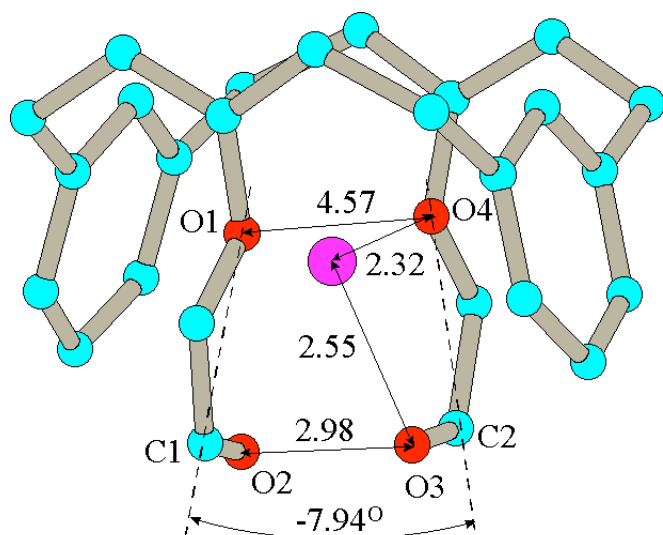


Figure 11 As for Figure 10, except that the optimised structure of $1:\text{Na}^+$ is shown, in the region of the cation. The ion was initially placed in Position 2 and AM1 partial charges were assigned to the ligand with Method 1

The part of the complex where the X-ray and optimised structures match least, and therefore, presumably the main reason for the magnitude of the RMS Overlay Error, is in the conformation of the pendant groups not involved in the complexation of the sodium (compare Figure 6a with 6b and Figure 7a with 7b). For example, Figure 7a clearly shows that the orientation of the one of the carbonyl groups of the pendant group in 3-position of the X-ray structure is very different to that in the optimised structure, shown in Figure 7b. The same feature was also present in the optimised structures obtained for the AM1 and MNDO semi-empirical methods and also when Method 1 was used to assign AM1 partial charges.

When Method 3 was used to assign partial charges, the quality of fit was poorer than when Methods 1 and 2 were used (see the RMS Overlay Errors in Table 1 and compare Figure 10 with 13). A possible reason for this is the fact that the use of Method 3 resulted in partial charges on the sodium of typically +0.3, which is in contrast to the charge of +1 which was formally assigned to the sodium ion with Methods 1 and 2. Thus, it is possible that the greater magnitude of the partial charges on the ligand atoms generated by Method 3 caused intra-ligand attractive and repulsive forces to be greater than with Methods 1 and 2, leading to a poorer quality fit with the X-ray structure. The Na^+ ion in these optimised structures is approximately equidistant from the phenoxy and carbonyl oxygen atoms, as in the X-ray structure, but the ligand geometry in the region of the cation is noticeably different to that shown by the X-ray structure. This leads to a RMS Overlay Error which is significantly larger than that found when partial charges were assigned with Methods 1 and 2. In particular, the distances between the phenoxy oxy-

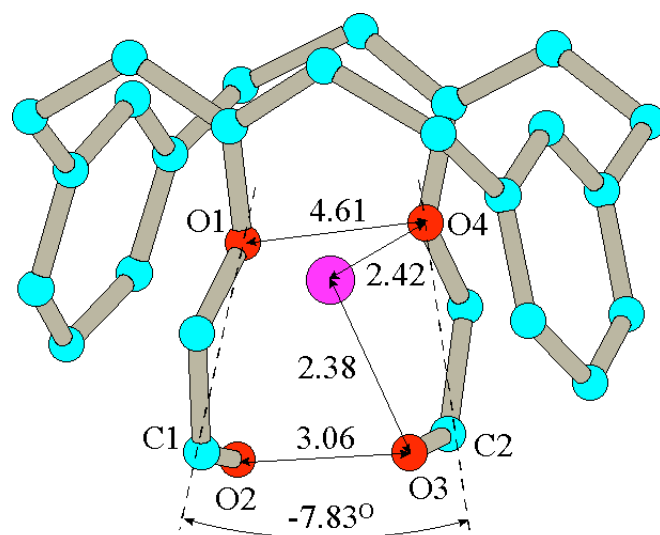


Figure 12 As for Figure 10, except that the optimised structure shown has PM3 partial charges assigned with Method 2

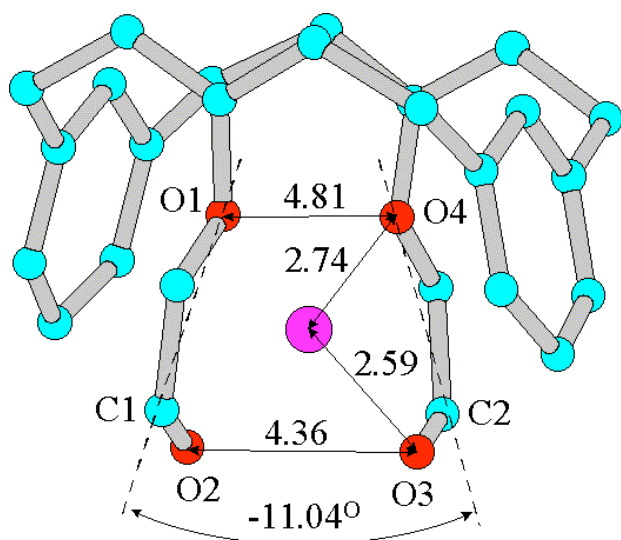


Figure 13 As for Figure 11, except that the optimised structure shown has INDO partial charges assigned with Method 3

gen atoms and between the carbonyl oxygen atoms diagonally across the cavity differ from the corresponding distances in the X-ray structure to a much greater extent than when Methods 1 and 2 were used to assign partial charges (compare Figure 10 with 13). Also, the carbonyl and phenoxy oxygen atoms of one pendant group which bind with the Na^+ ion are not in the same plane as those atoms of the pendant group on the opposite side of the cavity. This feature is also present in the X-ray structure and those optimised structures where partial charges were assigned with Methods 1 and 2 but to a lesser extent (see Table 2).

A possible source of inaccuracy in the modelled structures is the use of the neon atom type for the sodium ion. In HyperChem, the atom type for an element that does not form covalent bonds, consists of just two parameters r^* and ϵ . For neon, $r^* = 1.60 \text{ \AA}$ and $\epsilon = 0.09 \text{ kcal mol}^{-1}$. For example, the parameters used by Grootenhuis and Kollmann [20] in studies of Na^+ binding to crown ethers ($r^* = 1.60 \text{ \AA}$ and $\epsilon = 0.01 \text{ kcal mol}^{-1}$) were also applied by us, resulting in slightly poorer RMS overlay errors, differing typically by 0.05 \AA , i.e., the use of an ϵ value whose magnitude was nine times smaller than that used to define the atom type for neon in HyperChem, made little difference to the result. It should be possible to adjust these parameters to give better agreement between the modelled and X-ray structures and work in this area is ongoing.

While it is likely that the atom type that they developed was suited to crown ethers more than to calixarenes, it is also possible that the different result obtained was due to the use of a different force field (that found in AMBER [21] which was the software package used by Grootenhuis and Kollmann). In general, good results are not expected when an atom type, developed for use with one force field, is used with another one [22]. We also wish to explore the extent to which the initial conformation of the ligand affects the geometry of the optimised structure of the complex.

Conclusion

This paper demonstrates that in some calixarenes at least, the optimised geometry of the ligand in the complex and the final position of the ion is independent of the initial position of the ion and this is a very encouraging result. We have also demonstrated that improved results are obtained when metal cations (of Group 1 and Group 2, at least) are assigned formal charges than when partial charges are calculated for both the ligand and the metal ion. There is scope for refining the proposed method, as more crystallographic data becomes available and where it is possible to take into account the polarizability of the ion. However, the method described in this paper, when combined with the previously described method [3], does provide a very useful visualisation tool for calixarene cation complexes.

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