Synthesis, Characterization, and X-Ray Structure of 1,2-Bis-crown-5-calix[4]arene. Modeling of Metal Complexation*

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Abstract. 1,2-*bis*-crown-5-calix[4]arene (**3**) was prepared by reacting calix[4]arene (**1**) with tetraethylene glycol di-*p*-toluenesulphonate (**2**) in the presence of cesium carbonate in 9% yield. The X-ray structure of (**3**) was determined. Crystal data for $C_{44}H_{52}O_{10}$ are as follows: monoclinic, space group $P_{2/c}$ with $a = 18.006(8)$ Å, $b = 10.680(4)$ Å, $c = 22.359(6)$ Å, $\beta = 112.93(3)°$, $V = 3958(6)$ Å^3, $Z = 4$, $D_{calc} = 1.2$ g cm^{-3}, the final R value is 0.11 for the 1851 observed reflections ($I > 3\sigma(I)$). The single crystal included two similar but slightly different molecules immobilized in a pinched-cone conformation with C_2 symmetry. The two enantiomorphous molecules were analyzed by molecular mechanics using the GenMol program to model the selective alkali-metal complexation.

1. Introduction

The term calixcrown refers to a family of synthetic macrocyclic receptors presenting a hybrid structure [1] combining in their molecular frame calix[4]arene units and crown ether elements. The first member of this family was reported in 1983 by Alfieri *et al.* [2], who reacted *p-tert*-butylcalix[4]arene with pentaethylene glycol ditosylate to produce a *distal* or 1,3-capped or *mono*-crown-6 derivative in a cone conformation. In a subsequent paper the related 1,3-*p-tert*-butylcalix[4]arene-*bis*-crown-5 was isolated as a by-product during the production of the *mono*-crown-5 compound by a similar reaction [3]. The 1,3-*p-tert*-butylcalix[4]arene-*bis*-crown-5 was shown to be in the 1,3-alternate conformation due to the introduction of a second bridging in the calixarene macroring [3]. In order to prepare a new type of metal cation receptor the stepwise synthesis of a *proximal* or 1,2-*p-tert*-butylcalix[4]arene-*bis*-crown-5 in a cone conformation was reported [4]. The syn-

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thesis began by the regioselective 1,2-*bis* demethylation of the tetramethoxy-*p-tert*-butylcalix[4]arene with TiBr$_4$ [4]. This regioselective Ti(IV)-assisted demethylation led to the formation of 1,2-*p-tert*-butylcalix[4]arene-*bis*-crown-5 [4].

As a part of our work on the synthesis of double calixcrown ethers [5], we reacted calix[4]arene with tetraethylene glycol ditosylate in the presence of cesium carbonate instead of potassium carbonate. Surprisingly, we isolated the 1,2-calix[4]arene-*bis*-crown-5 (3). Calixarene (3) was deduced to be in the cone conformation from spectroscopic data. This conformation was ascertained by X-ray diffractometry. Preliminary metal binding properties of ligand (3) were anticipated by modeling with molecular mechanics.

2. Experimental

2.1. MATERIAL FOR SYNTHESIS

Calix[4]arene (1) was prepared as described in the literature [6]. Tetraethylene glycol di-*p*-toluene sulphonate (2), cesium carbonate, and the solvents were commercial reagents and used without further purification.

2.2. ANALYTICAL PROCEDURES

The melting point was taken on a Büchi 500 apparatus in a capillary sealed under nitrogen. The Silica column was prepared with Kieselgel Merck (Art. 9385). The eluent is specified in the experimental procedure. The ^{1}H-NMR spectrum was recorded at 200 MHz on a Bruker SY200 spectrometer. The FAB mass spectrum was obtained on a VG-Analytical ZAB HF apparatus.

2.3. PREPARATION OF 1,2-*bis*-CROWN-5-CALIX[4]ARENE (3)

Into a 500 mL round-bottomed flask were added calix[4]arene (1) (2.00 g, 4.73 mmol) and cesium carbonate (15.42 g, 47.33 mmol) and acetonitrile (230 mL). The mixture was stirred magnetically for 20 min. Then tetraethylene glycol di-*p*-toluenesulphonate (2.37 g, 4.73 mmol) dissolved in acetonitrile (25 mL) was added. After 4 days of refluxing, the same quantities of tetraethylene glycol di-*p*-toluenesulphonate (2) and cesium carbonate were added. The reflux was maintained for 4 additional days. After cooling to room temperature, the mixture was filtered by suction and washed with dichloromethane. The filtrate was concentrated under reduced pressure to yield an oily residue which was dissolved in dichloromethane and washed with 1 N HCl. The organic layer was dried over sodium. After filtration the solvents were evaporated to dryness to give a transparent yellow oil which was chromatographed on silica with 80 : 20 dichloromethane : acetone mixture as eluent. 1,2-*bis*-crown-5-calix[4]arene (3) was eluted first and recrystallized from methanol. M.p. 206–207°. ^{1}H-NMR 6.69–6.57 (m, 12H, Ar*H*, *meta* and *para*), AB system 4.59 and 3.18 (d, 4H, J_{H-H} = 13.3 Hz, Ar—C*H*$_2$—Ar), A′B′ system

4.39 and 3.14 (d, 4H, J_{H-H} = 13.3 Hz, Ar'—CH_2—Ar'), 3.6–3.1 (m, 32H, O—CH_2CH_2O). FAB m/z: 741.3 (for $C_{44}H_{52}O_{10}$). Yield 9%.

2.4. X-RAY CRYSTAL DATA

In order to avoid solvent molecule inclusion no recrystallisation was attempted and a suitable fragment (0.30 $\times$ 0.30 $\times$ 0.40 mm^3) was cut with a razor blade into a crystalline block obtained during the synthesis.

Data collection on an Enraf Nonius CAD-4 diffractometer (7796 measured reflections, T = 298 K, 1851 observed reflections, with $I_{net} > 3.0\sigma(I_{net})$). Program used to solve the structure: MULTAN 80 [7]. Program to refine the structure by full matrix least squares: SHELX [8]. Molecular graphics: ORTEP II [9], GenMol [10].

2.5. MODELING OF CALIXARENE

Modeling of compound (3) with and without cations has been performed with the GenMol Program. GenMol [10] is a molecular mechanics program using an original force field designed to obtain accurate geometries, well adapted to modeling molecules such as calixarenes in order to understand their ability to complex alkaline cations.

3. Results and Discussion

The synthesis of (3) was conducted according to Scheme 1. Calix[4]arene (1) was refluxed for 8 days under nitrogen with 2 equivalents of tetraethylene glycol di-p-toluenesulphonate (2) (added in two equal crops) in acetonitrile in the presence of cesium carbonate in large excess. The reaction mixture was observed to contain numerous products from which (3) could be isolated by chromatography probably because it was eluted first. Analytical data were in agreement with the proposed structure in which two glycolic chains are attached to the calix[4]arene (1) (FAB mass 741.3). The presence of two well-resolved AB systems at 4.59 and 3.18 and 4.39 and 3.14 for the methylene protons in the macroring were indicative that (3) is in the cone conformation with the two crown units linked in a *proximal* manner. This geometry should be compared to the one obtained during the formation of doubly crowned calix[4]arene in the 1,3-alternate conformation in which the glycolic chains are attached in a *distal* fashion [4]. The difference is probably due to the use of cesium carbonate instead of potassium carbonate. A recent publication reports the regioselective synthesis of calixcrowns derived from p-*tert*-butylcalix[5]arene [11]. The authors noticed the formation of a *proximal* derivative in a 20% yield in the presence of cesium fluoride [11]. These observations lead us to conclude that the cesium cation is effective in inducing the *proximal* dialkylation of the glycolic chains. It is assumed that after the first O-substitution had occurred the cesium
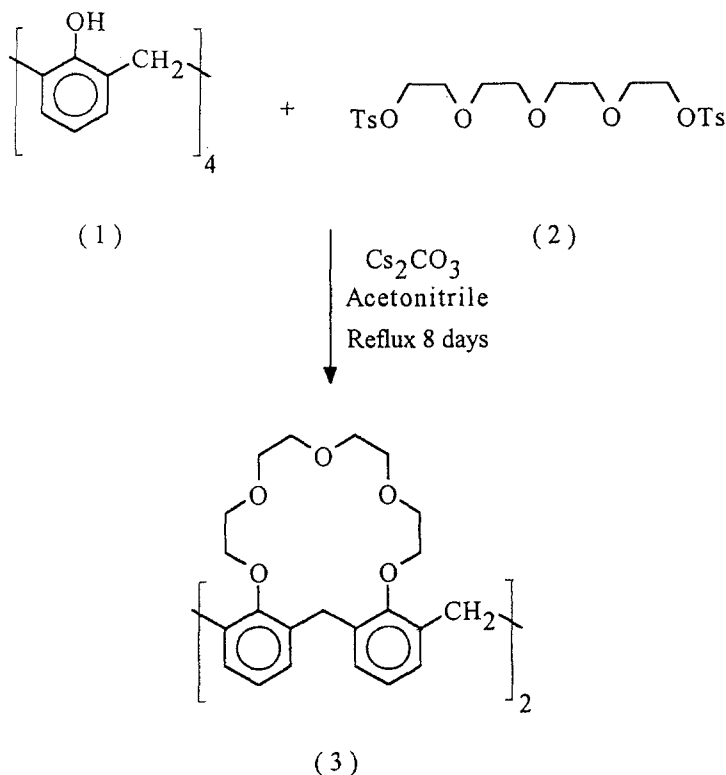
Scheme 1.   Synthesis of 1,2-*bis*-crown-5-calix[4]arene (**3**).
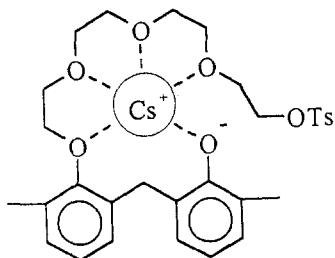
Scheme 2.   Cesium template of the polyether chain.

cation templates the polyether chain to bring the unreacted *p*-toluenesulphonate leaving group in proximity to the adjacent phenolate ion (see Scheme 2).

The molecular arrangement of (**3**) has been ascertained by X-ray crystallographic analysis. Crystal data for $C_{44}H_{52}O_{10}$ (**3**) are: monoclinic space group $P_{2/c}$ with $a = 18.006(8)$ Å, $b = 10.680(4)$ Å, $c = 22.359(6)$ Å, $\beta = 112.03(3)°$, $V = 3958(6)$ Å^3, $Z = 4$, $D_{calc} = 1.24$ g cm^{-3}. The single crystal included two similar but slightly different molecules immobilized in a pinched-cone conformation with C_2 symmetry.
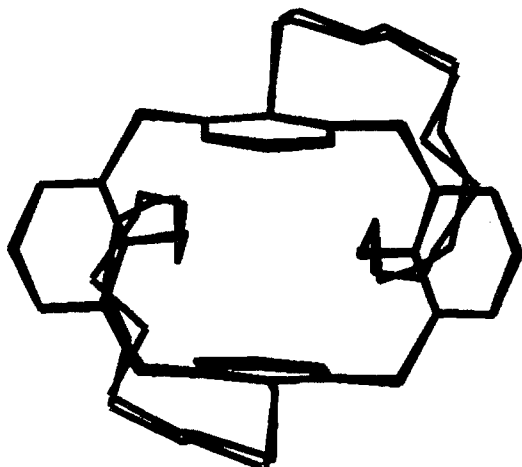
Fig. 1.   The first crystalline molecule superimposed with the mirrored second one. The root mean square value between the two geometries is 0.04 Å.

In Figure 1, the two independent molecules have been superimposed after performing a best molecular fit between one molecule with the mirrored second molecule. Slight differences can be observed. The root mean square value between the two geometries is 0.04 Å.

In Figures 2a and 2b, which are projections of one crystalline molecule (along the binary axis, and orthogonal to this axis) it is seen that the molecular conformation can be characterized by two parameter families. One giving the orientation of the phenyl rings versus the methylene plane, and the other measuring the aperture of the oxygened chains which form an opened 'mouth'. The angles of the phenyl rings with the methylene plane are 140(2)° and 76(2)° for one molecule and 140(2)° and 80(2)° for the second molecule which indicate a great similarity in this part of the molecule. The 'mouth' aperture can be measured by the angle of the mean planes passing through the oxygen atoms, 133(2)° for one molecule and 110(2)° for the other one. The slight geometric differences come from this part of the molecules, which expresses the flexibility of the oxygened chains.

Remark. In solution only one molecular conformation is observed, the cone one, which is the intermediate form between the two enantiomorphous forms observed in the crystal. The two enantiomorphous forms observed in the crystalline state can be exchanged in the solution by a concerted motion of the phenyl rings and the glycolic chains, which can be related to the anisotropic thermal parameters of the corresponding atoms, see Figure 3.

In order to test the program we compared the calculated geometry obtained from GenMol to one geometry observed in the crystalline state. A best molecular fit performed on these molecules gives a root mean square value of 0.04 Å, analogous
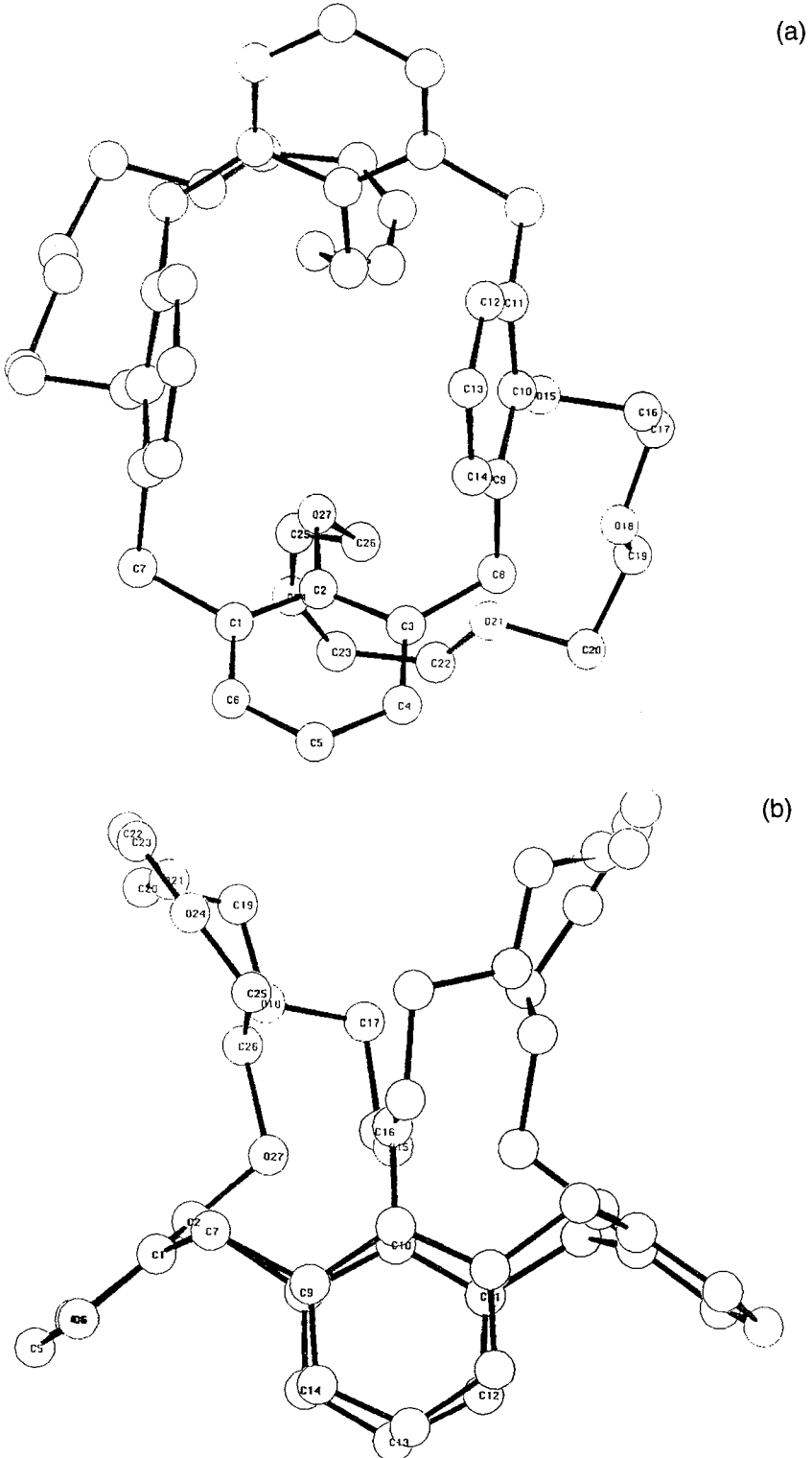
Fig. 2.   Projection along (2a) and perpendicular to (2b) the crystallographic binary axis displaying the pinched-cone conformation of the molecule and the aperture of the glycolic chains.
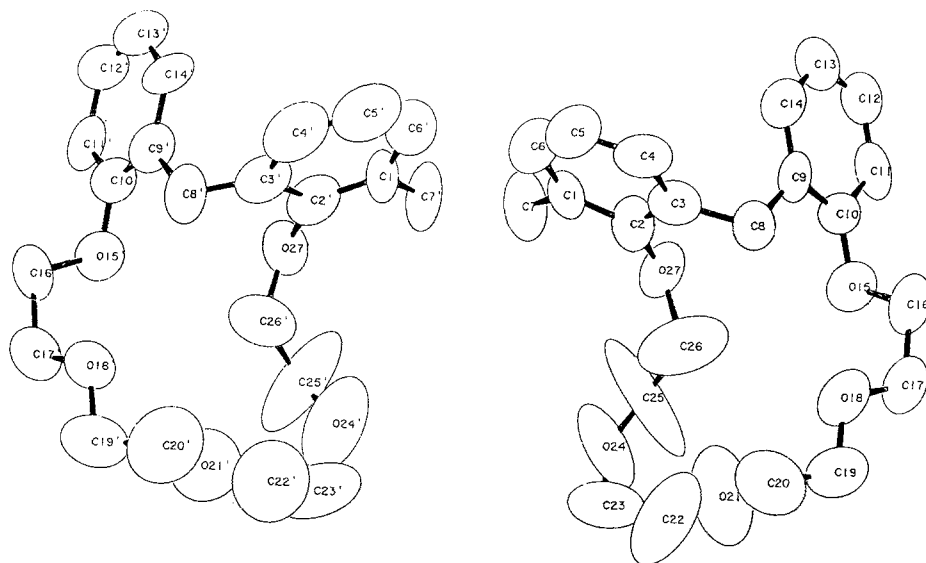
Fig. 3.   ORTEP II drawing of the two crystalline independent parts of the molecules displaying the great thermal ellipsoid of the atoms, expressing exchange ability of one conformation to the other one.

to the value obtained for the fit between the two X-ray molecules, which expresses the quality of the modeled geometry.

The characteristic parameters of the calculated geometry are $143°$ and $79°$ for the angles between the phenyl rings and the methylene plane which correspond to the observed values $(140(2)°, 140(2)°)$ and $(80(2)°, 76(2)°)$ and the angle characteristic of the 'mouth' aperture is $136°$ instead of $133(2)°$ and $110(2)°$ for the experimental values which seems to indicate that *the larger, opened form is the one existing in solution.*

As in solution only the cone conformation occurs, which is the intermediate form, between the two enantiomers observed in the crystal, calculations were performed on the different molecular forms in order to understand the molecular behaviour. The strain energy of the cone form is 128 instead of 125 kcal/mole for both enantiomorphous pinched-cone forms. The pinched-cone forms are the most stable forms, which explains why they are observed in the solid state (the state always corresponding to an energy minimum).

In solution the phenyl rings are agitated, because of the absence of an energy barrier between the different forms. The observed cone form is in fact an average form of the molecule, while the enantiomorphous pinched-cone forms observed in the crystalline state are limit forms of the molecule.

Some alkali-cation extraction results are known on the related molecule to (3) bearing *tert*-butyl groups on the *para* position of the phenyl rings [4]. We decided to model the binding properties of calixarene (3) toward these cations in order to see, first, the geometric modification when adding cations and, second, to know if
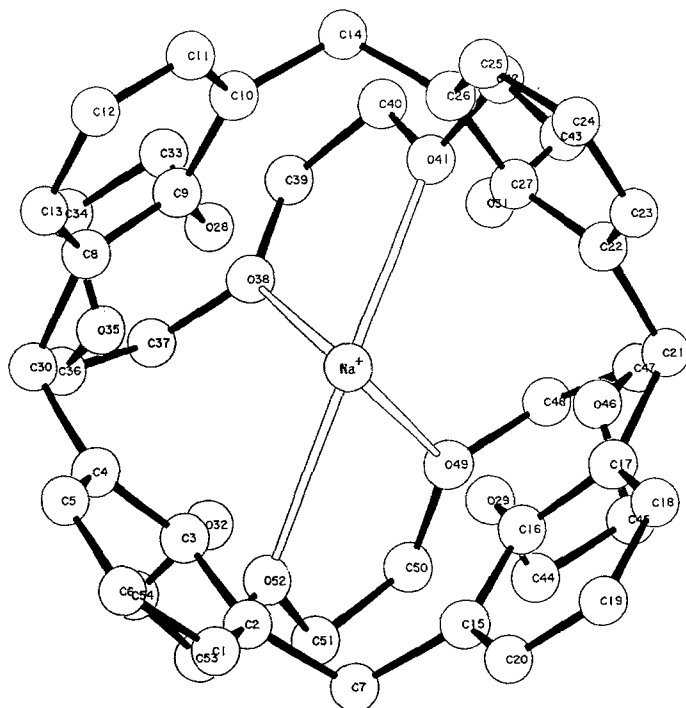
Fig. 4. Complex of calixarene **3** with Na⁺. Only four bonds are formed with this cation.

the program is able to understand the cation extraction properties of ligand (**3**) and related molecules.

Computations of (**3**)-complexations with the different alkaline cations Na⁺, K⁺, Rb⁺, Cs⁺ (with increasing ionic radii values of 0.97, 1.33, 1.47 and 1.67 Å, respectively) were performed. Calculations indicate that the number of bonds between the cation and the oxygen atoms regularly increases from Na⁺ (4 bonds) to Cs⁺ (10 bonds) meaning that (**3**) will selectively extract Cs⁺ cation, as shown from literature data.

Figures 4 and 5 display the geometries of the Na⁺ and Cs⁺ complexes. It is interesting to notice the geometric evolution of the molecule at the phenyl ring level: in both cases the symmetry increases from C_2 in the empty molecule to C_4 when complexed with the cation. The mean angle between the phenyl rings and the methylene plane is 114° in both complexes, which is a mean value between 140° and 80° of the free molecule. The angle between the mean oxygen atom plane, characteristic of the 'mouth' aperture is 82° instead of 133° and 110° in both molecules, which corresponds to the lower value of this parameter.

It is also interesting to remark on the much higher stability of the complexed molecule than of the uncomplexed one. The strain energy changes from 125 kcal/mole to 85 kcal/mole (value obtained without taking account of the counteranion).
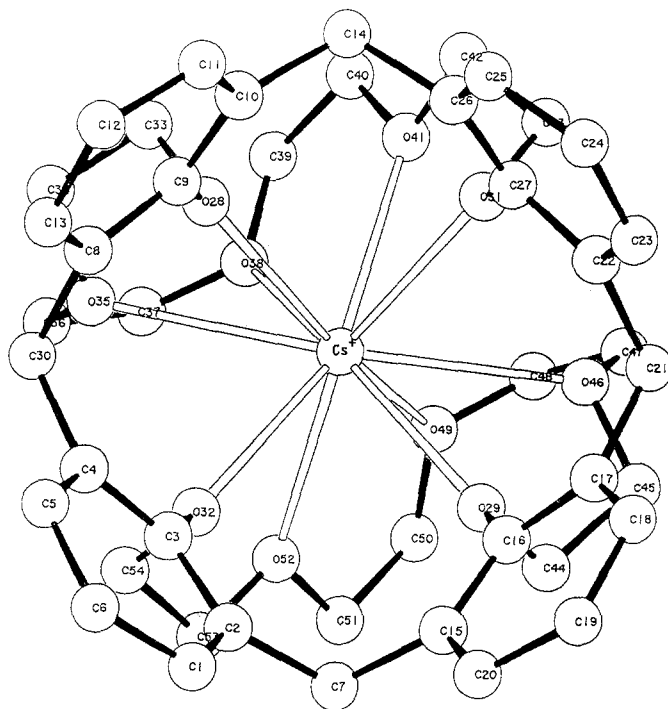
Fig. 5.   Complex of calixarene **3** with Cs⁺. Ten bonds are formed with this cation leading to
a considerably great affinity of this calixarene for Cs⁺.

4. Conclusion

In the present paper we have described an improved synthesis of 1,2-*bis*-crown-
5-calix[4]arene (**3**). The synthesis was achieved by using cesium carbonate. The
X-ray structure of (**3**) indicated the presence of two enantiomorphous molecules
in the crystal. These two enantiomorphous molecules were analyzed by molecular
mechanics using the GenMol program. It was concluded that while the confor-
mation of (**3**) in solution is an average of several forms, in the solid state the
more stable conformations are the pinched-cone forms which are the limit forms
of (**3**). Calculations on supermolecules (**3**) complexed to alkali cations indicated
that ligand (**3**) preferentially binds Cs⁺ compared to the other alkali cations.

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