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Review Article

Bis(crown ether) and Azobenzocrown Derivatives of Calix[4]arene. A Review of Structural Information from Crystallographic and Modelling Studies

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Abstract. The association within one molecule of calix[4]arene and crown ether moieties leads to ligands with new complexing properties. In particular, calix[4]arene *bis*(crown-6) and some of its derivatives have been shown to be highly selective extractants for caesium ions. This review presents the background of the study and the results of crystal structure determinations and molecular modelling calculations performed during the investigation of two molecular families, the *bis*(crown ether) and the azobenzocrown derivatives of calix[4]arene.

Key words: Calixarenes, crown ethers, azobenzene, ditopic receptors, cation complexation, cation extraction, nuclear wastes, crystal structures, molecular modelling, molecular dynamics.

1. Introduction

Several molecular families have been at the origin of the present wide development of macrocyclic and supramolecular chemistry. Following porphyrins, phthalocyanines and saturated polyazamacrocycles, crown ethers, cryptands and spherands have been widely investigated for the last thirty years [1]. Amongst other macrocycles, calixarenes occupy presently a prominent place due to their ready access, easy chemical transformation and complexing properties (or those of their various derivatives) towards cations, anions or neutral molecules, which make them im-

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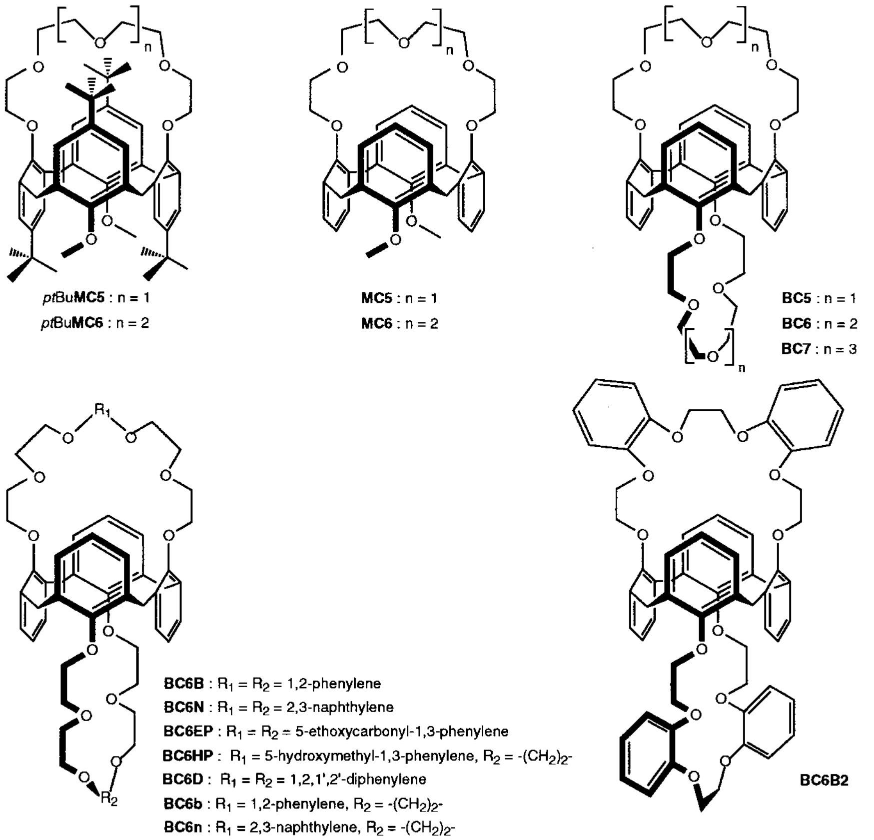
portant hosts [2, 3]. Early on during our extensive studies of calixarene chemistry, we developed an interest in the fusion of the calixarene structure with the critical functional units of other macrocycles [4]. The tetramer calix[4]arene is particularly well suited for such purpose since it forms a rather rigid platform (with four extreme conformations: *cone*, *partial cone*, 1,2-*alternate*, 1,3-*alternate*), suitable for building large assemblies by functionalization of its upper or lower rim.

A domain in which the very specific complexing properties often associated with particular macrocycles are needed is that of nuclear fuel reprocessing. The extraction of α-emitters such as transuranium elements or β/γ-emitters with long or medium half-lives such as ^{135}Cs (2.10^{6} years) and ^{137}Cs (30 years) from high or medium level activity liquid wastes is of utmost importance, in order to reduce the volume of radioactive wastes to be stored in geological formations. On the one hand, the potential of *p*-*tert*-butylcalix[*n*]arenes (n = 4, 6, 8) as liquid membrane carriers for the extraction and transport of caesium ions, at pH values higher than 11, was pointed out more than ten years ago [5]. The key-step in the process is a proton-exchange reaction and the cation is expected to be directly attached to the calixarene so as to form a neutral species. On the other hand, the ability of crown ethers for complexation and extraction of alkali or alkaline-earth cations [6] or actinide ions [see, for example, 7–9] has also been demonstrated. Complexation by crown ethers leads to cationic complexes, with the drawback that, in liquid membrane extraction processes, the counter-ion must accompany the complex through the membrane, which is not the case with neutral calixarene complexes [5]. Synergistic effects in alkali ions extraction by *p*-*tert*-butylcalix[4]arene/crown ether mixtures have been attributed to the formation of complex ion pairs including both ligands, the cation being more closely associated with the crown ether [10]. Accordingly, the potassium/sodium selectivity was shown to be dependent on the crown size, which shows a size complementarity effect between the crown ether and the cation [10]. The association of calixarenes and polyether chains to form a single molecular species was then a promising research way. Following that trend the synthetic group in Strasbourg, in collaboration with the Cadarache group, started its research on extractants based on calixarenes for the removal of caesium ions from waste waters in 1991. The synthetic part of the work has been reviewed several times [11].

Following the synthesis of ‘polypodands’ with open ethylene glycol chains as substituents on the phenolic oxygen atoms of the lower rim [12], the first published calix[4]arene (crown ether) compound, *p*-*tert*-butylcalix[4]arene *mono*(crown-6) (noted *p*tBu**MC6** on Scheme 1) was synthesized by Alfieri *et al.*, from *p*-*tert*-butylcalix[4]arene and pentaethylene glycol ditosylate under basic conditions, and its alkali, alkaline-earth and ammonium extraction properties investigated [13]. These properties were indeed different from those of pure *p*-*tert*-butylcalix[4]arene or 18-crown-6 since *p*tBu**MC6** is able to transport alkali cations from a basic aqueous phase to an acidic phase, which none of the separate constituents can do. Apart from the thermodynamic stability of the complexes, the rate of cation

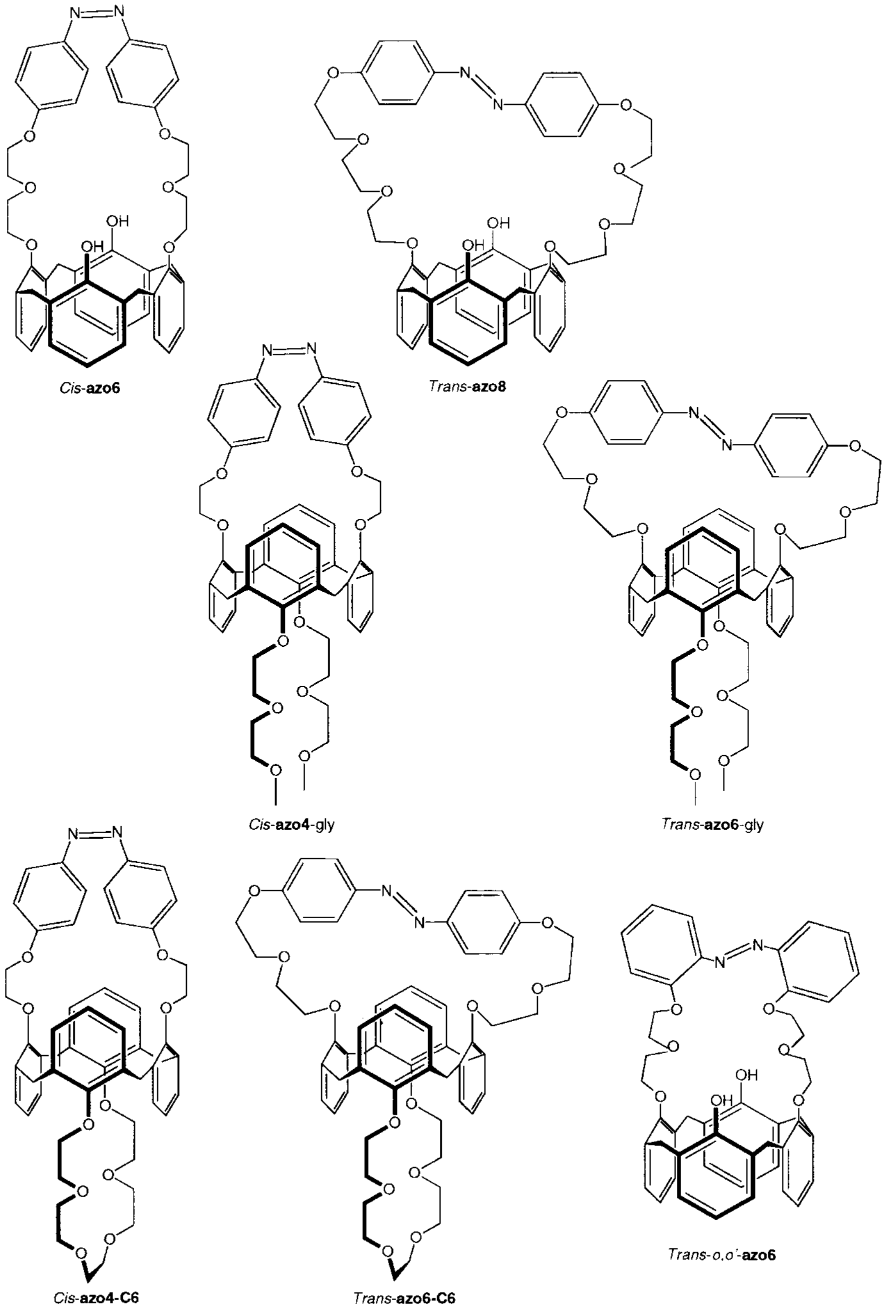


Scheme 1. Mono- and *bis*-crown derivatives of calix[4]arene (the *mono* derivatives are represented in their 1,3-*alternate* conformation).

exchange is reduced when open chains are replaced by crown moieties with similar chemical functions. The subsequent work of the Parma and Twente groups on related compounds has led to important findings. In particular, *p*-*tert*-butyl-1,3-dialkoxycalix[4]arene *mono*(crown-5) (methoxy or ethoxy substituents) (with methoxy: *p*tBu**MC5** on Scheme 1) was shown to be the most selective synthetic receptor for potassium ions known so far [14,15], and to have a better K^+/Na^+ selectivity than the naturally occurring antibiotic valinomycin [16] (however, this natural ionophore has a moderate selectivity, associated with the need to retain reasonably fast exchange kinetics). The preferred conformation for K^+ complexation has been shown to depend on the presence of *para* substituents; the *flattened partial cone* or the 1,3-*alternate* one are the most favorable with or without (**MC5**) *p*-*tert*-butyl groups respectively [16]. Furthermore, cation-π interactions have been found in the potassium complex of 1,3-diisopropoxy-*p*-*tert*-butylcalix[4]arene crown-5 in which the ligand is in the *flattened partial cone* conformation [17]. On the other hand, the crown-4 substituted calix[4]arene was shown to display a Na^+/K^+ selectivity and to be suitable for the design of Na^+ selective electrodes [18].

The selectivity for Cs^+ ions of 1,3-dialkoxycalix[4]arene *mono*(crown-6) appeared as a promising result in the field of nuclear reprocessing technology [19]. It was soon recognised that the 1,3-*alternate* conformation was the best one for caesium complexation due to the possibility of caesium-π interactions [20] and further synthetic work was carried out to fix the molecules in this conformation so as to obtain more selective ligands [21]. Besides the size of the complexing sites, which is of primary importance, other factors appear to govern the selectivity of these ligands; the polarity of the molecule and its solvation state, the steric effects of the *para* substituents and the above-mentioned cation-π interactions have been cited among them [16]. Applications of these ligands (crown-5 and crown-6) in ion extraction, membrane transport, ion sensing by CHEMFETs (chemically modified field effect transistors) or organ imaging (radioactive Rb^+ complexes) have also been widely explored [see, for example, 22–26]. Apart from chains constituted of ether functions only, other bridges have been used, among which one can notice, not exhaustively, azobenzene [27–29], Schiff bases [30–33], spherands [34], bipyridyl [35], diamides [36] or azaethylene [37] containing bridges and also the case of a calix[4]arene-substituted polythiophene [38].

The first calix[4]arene *bis*(crown ether) to be described was a *proximal* 1,2-3,4-substituted compound, in which both crown-5 ether chains were on the same side of the calixarene moiety in the *cone* conformation [39]. The associated K^+ selectivity was reduced with respect to the *mono*(crown)derivative but molecular mechanics calculations indicated that this ligand might however selectively extract Cs^+ ions [40]. The analogous compounds with three and four oxygen atoms in the chains were also obtained and investigated [41]. The first *distal* 1,3-2,4-substituted crown-5 compound, fixed in the 1,3-*alternate* conformation, was obtained as a by-product [42]. In parallel to the studies of the *mono*(crown-6) derivative for caesium recovery from nuclear wastes, an extensive investigation of the 1,3-*alternate* calix[4]arene *bis*(crown-6) family was undertaken (see Scheme 1). The results will be presented hereafter, with a particular emphasis on the structural aspect (crystal structures and molecular modelling). The synthesis of these ligands and the results of solution experiments (complexation, extraction) have been reviewed elsewhere [11,43,44 and references therein]. Calix[4]arene *bis*(crown-6) and some of its derivatives were shown to meet fully the expectations drawn on them for selective ^{137}Cs recovery from solutions highly concentrated in Na^+ ions (about 4M) and either highly acidic (1M) [45–47] or basic [48], with Cs^+/Na^+transport selectivities up to 50000 in liquid membrane processes with NPOE (2-nitrophenyl n-octyl ether) as a solvent. The usefulness of these ligands for the design of caesium-selective PVC electrodes has recently been established, giving the highest selectivity and lowest detection limit to date [49]. Some developments, directed to attain a photocontrol of ion complexation by introducing photoisomerizable azobenzene groups in the crown ether chains, leading to the azobenzocrown derivatives represented on Scheme 2, will also be discussed.



Scheme 2. Azobenzocrown derivatives of calix[4]arene.

Extensive molecular modelling studies, based on molecular dynamics, were performed on calix[4]arene (crown ether)s. Most of the information on structural or energetic properties obtained from modelling of complexes of 1,3-*alternate* dialkoxycalix[4]arene *mono*(crown ether) derivatives in a solvent phase are also useful for the corresponding *bis*(crown ether) derivatives because most of the complexes obtained experimentally from complexation or solvent extraction experiments with these compounds are mononuclear ones [45, 50]. Nevertheless, as it is not our purpose, these simulations will only be reported here but not reviewed in detail.

Related work involving larger calixarenes will not be discussed here. *Mono*-(crown ether) derivatives of calix[5]arene, with possible applications for chiral recognition or catalysis, have been described [51–53], as well as the quaternary ammonium cations receptor calix[6]arene *mono*(crown-6) [54], and the chiral calix[8]arene *bis*(crown-3 and 4), in which the bridge induces a folding of the large calixarene molecule [55, 56]. Worthy of note is also the compound in which an additional polyether loop bridges the two crowns of calix[4]arene *bis*(crown-6) [44, 57], as well as the double calixcrowns, in which two calixarene moieties are bridged by ether chains [58, 59].

2. Crystal Structures

2.1. CALIX[4]ARENE *BIS*(CROWN ETHER)S

The crystal structures of calix[4]arene *bis*(crown ether)s reported up to now are summarized in Table 1, with the numbering adopted in the following, and the molecules are represented in Scheme 1. Compounds with 5, 6 and 7 oxygen atoms in the ether chains, as well as their derivatives and their solvent and cation complexes, are taken into account. Only one compound with *p*tBu groups has been described; extraction experiments of alkali picrates from the solid to a chloroform solution showed that those bulky substituents were blocking the crown ether cavities, hence preventing cation binding [60, 61]. Therefore we focused on compounds without *para* substituents, particularly on crown-6 compounds and their derivatives bearing substituents aimed at increasing their cation complexing strength and selectivity or at modifying the crown ether shape and size.

Structures of the ligands and solvent complexes

Crown ether conformation, effect of the complexed solvent
As a general trend, and as a consequence of the enhanced flexibility of the bridges with increasing length, the ether chains are more bent towards the calixarene mean plane (defined by the four methylene carbon atoms) in the longer chains than in the shorter ones. This is illustrated on Figure 1 in the case of **BC5**, **BC6** and **BC7**. An influence of intermolecular forces in the crystal lattice on the polyether chain shape cannot be ruled out; however, at least in the case of **BC5** and **BC6**, the

Table I. Calix[4]arene *bis*(crown ether)s: crystal data.

Number	Compound	Space Group	*a* (Å) *b* (Å) *c* (Å)	α (°) β (°) γ (°)	*V* (Å^3)	Ref.
1	*pt*Bu**BC5**	$P6_422$	17.092(5)		5097(5)	60
			20.147(7)			
2	**BC5**.0.25$CHCl_3$	$P\bar{1}$	11.151(4)	98.78(3)	4061(3)	61
			16.832(6)	92.02(3)		
			21.929(8)	92.12(3)		
3	**BC6**.4CH_3CN	$C2/c$	18.205(9)		5534(6)	62
			17.669(6)	98.20(2)		
			17.382(15)			
4	**BC6**.3CH_3CN	$P2_1/n$	14.388(3)		5241(5)	63
			26.947(8)	113.19(3)		
			14.707(4)			
5	**BC6**.3CH_3NO_2	$P\bar{1}$	11.085(3)	83.22(3)	2645(3)	64
			11.758(4)	75.50(3)		
			21.203(9)	83.10(2)		
6	Cs**BC6**(NO_3).2CH_3CN	$C2/c$	18.124(6)		5546(4)	62
			17.733(7)	97.39(4)		
			17.401(9)			
7	Cs_2**BC6**$(NO_3)_2$.2CH_3CN	$C2/c$	18.18(1)		5610(12)	62
			17.77(2)	96.79(2)		
			17.48(1)			
8	Cs_2**BC6**I_2.2CH_3CN	$C2/c$	18.150(9)		5623(8)	65
			17.990(9)	97.39(3)		
			17.365(6)			
9	Cs_2**BC6**$(NO_3)_2$	$P\bar{1}$	12.710(5)	100.46(2)	2702(2)	62
			14.107(3)	97.55(3)		
			17.161(5)	113.54(2)		
10	Cs_2**BC6**$(NCS)_2$	$C2$	36.57(2)		5415(6)	66
			11.47(1)	109.03(5)		
			13.65(1)			
11	K**BC6**(NO_3).2CH_3CN	$C2/c$	18.025(8)		5511(6)	67
			17.672(9)	97.55(5)		
			17.454(13)			
12	Na_2**BC6**$(NO_3)_2$.$(H_2O)_2$.CH_3CN	$P2_1/c$	13.487(6)		5220(5)	67
			16.758(9)	101.17(4)		
			23.542(15)			
13	**BC6B**.3CH_3CN	$P2_1/c$	10.391(4)		5440(7)	63
			17.264(11)	94.62(3)		
			30.426(9)			
14	**BC6B**.3CH_3NO_2	$P2_1/n$	10.360(2)		5700(4)	68
			29.164(8)	100.88(3)		
			19.211(11)			
15	Cs_2**BC6B**$(NO_3)_2$.3$CHCl_3$	$Pca2_1$	19.513(10)		7116(5)	66
			15.382(5)			
			23.708(9)			

Table I. Continued.

Number	Compound	Space Group	a (Å) b (Å) c (Å)	α (°) β (°) γ (°)	V (Å^3)	Ref.
16	**BC6N**.$3CH_3CN$	$P2_1/c$	13.876(5)		6298(7)	64
			21.834(9)	104.49(2)		
			21.472(4)			
17	**BC6N**.$C_6H_5CH_3$	$P2_1/n$	20.815(2)		5838(1)	64
			10.697(1)	90.696(8)		
			26.222(3)			
18	Cs_2**BC6N**$(NO_3)_2$.$CHCl_3$.THF.H_2O	Pn	14.602(2)		3758(3)	64
			18.226(6)	113.89(2)		
			15.442(4)			
19	**BC6B2**	$P2_1/a$	26.071(3)		5289(2)	69
			12.948(1)	99.02(2)		
			15.865(5)			
20	**BC6B2**.CH_3NO_2	$P2_1/n$	12.260(3)		5620(4)	70
			16.998(3)	102.50(2)		
			27.624(7)			
21	Cs_2**BC6B2**$(NO_3)_2$.$CHCl_3$.H_2O	$P2_1/n$	13.800(1)		6226(2)	70
			24.636(4)	102.20(1)		
			18.735(1)			
22	**BC6EP**	$P\bar{1}$	20.779(7)	69.85(2)	2782(2)	71
			12.603(4)	78.56(2)		
			11.913(4)	72.81(2)		
23	**BC6HP**.0.57 $CHCl_3$	$P\bar{1}$	18.95(3)	106.93(5)	2557	72
			12.394(9)	101.77(8)		
			11.756(7)	94.63(8)		
24	**BC6D**.$2(CH_3)_2CO$	$P\bar{1}$	10.2616(8)	102.612(10)	3090.2(6)	73
			14.652(2)	99.963(10)		
			21.824(3)	98.882(10)		
25	**BC6b.**$3CH_3CN$	$P2_1/c$	17.4718(8)		5484.9(4)	74
			16.0820(6)	111.117(10)		
			20.9259(10)			
26	Cs**BC6b**(NO_3).$2CH_3CN$	$P2_1/n$	16.0619(5)		5429.0(3)	74
			15.6748(6)	92.594(2)		
			21.5857(6)			
27	**BC6n**.$3CH_3CN$.$CHCl_3$	$P2_1/c$	13.0519(5)		5990.2(6)	74
			20.4239(13)	89.8197(10)		
			22.4713(14)			
28	**BC7**	$P\bar{1}$	11.115(5)	85.12(4)	2458.9	75
			11.710(5)	93.11(5)		
			18.990(7)	91.01(5)		

BC6B: calix[4]arene *bis*(1,2-phenylene-crown-6)
BC6N: calix[4]arene *bis*(2,3-naphthylene-crown-6)
BC6B2: calix[4]arene *bis*[*bis*(1,2-phenylene)-crown-6]
BC6D: calix[4]arene *bis*(1,2,1′,2′-diphenylene-crown-6)
BC6EP: calix[4]arene *bis*[(5-ethoxycarbonyl-1,3-phenylene)-crown-6]
BC6HP: calix[4]arene [(5-hydroxymethyl-1,3-phenylene)-crown-6, crown-6]
BC6b: calix[4]arene (1,2-phenylene-crown-6, crown-6)
BC6n: calix[4]arene (2,3-naphthylene-crown-6, crown-6).

trend illustrated above seems independent of the packing. As a consequence of the flexibility of the chains, numerous different conformations can exist in solution, as will be exemplified from molecular dynamics calculations and also from crystalline structures in the case of an azobenzene containing crown (*vide infra*). ptBu**BC5** and **BC5** have been described in their uncomplexed form, in which some of the oxygen lone pairs are pointing outwards (conversely, the hydrogen atoms of some carbon atoms of the ether chains are pointing inwards). Those ligands cannot be considered to be preorganized for cation complexation, at least in the conformation they assume in the solid state [60, 61]. **BC6** and its derivatives **BC6B**, **BC6N**, **BC6B2**, **BC6b** and **BC6n** form very easily complexes with polar solvents possessing a slightly acidic methyl group, such as acetonitrile and nitromethane (compounds **3**–**5**, **13**, **14**, **16**, **20**, **25**–**27**). In such cases, all the oxygen lone pairs are directed towards the crown centre. Weak C–H$\cdots$O hydrogen bonds involving the oxygen ether atoms, and possibly also dipole-dipole interactions, are likely to account for the position of the solvent molecules, with their methyl group pointing towards the crown centre. In some cases (compounds **17** and **20**), we have obtained uncomplexed crown ethers (one of the crowns only in **20**) in which some of the oxygen lone pairs are directed outwards, as a result of a crown ether conformation different from that of the complexed form (as in the case of **BC5**, some of the hydrogen atoms bonded to carbon atoms of the ether chains are directed inwards). This is illustrated by **BC6N**.3CH_3CN (**16**) and **BC6N**.$C_6H_5CH_3$ (**17**) in Figure 2 (the methyl carbon atoms of the acetonitrile molecules in **16** are located at a mean distance of 3.46(11) Å from the oxygen atoms and at 1.06–1.17 Å from the mean oxygen planes, whereas the toluene molecule in **17** does not interact with the crown ether loops). In compound **20**, a nitromethane molecule is associated with one of the two crowns only, the effect described above being thus illustrated by a single molecule (Figure 3). The torsion angles defined by the crown ether chains provide a simple characterization of the conformation of calixcrowns, as proposed for simple crown ethers [77]. We have reviewed previously the different torsion angle sequences encountered in the compounds under study [64]; the most frequent one, obtained in solvent or cation complexes of **BC6**, corresponds to the regular $g^+g^-g^+g^-g^+$ arrangement of O–C–C–O angles (g designing a *gauche* angle), all the C–O–C–C ones being near 180° (*anti* angle). In the case of the 1,2-phenylene- or 2,3-naphthylene-substituted crowns, the O–C–C–O angle involving the substituent is constrained to 0, giving rise to the sequence $g^+g^-0g^+g^-$ in solvent complexes like **16** (Figure 2), whereas the conformation in the two crowns of **17** is described by ag^+0ag^- and ag^-0ag^- (a designing an *anti* angle), some O–C–C–O angles being transformed from *gauche* to *anti* ones and, conversely, some *anti* C–O–C–C angles becoming *gauche* ones.

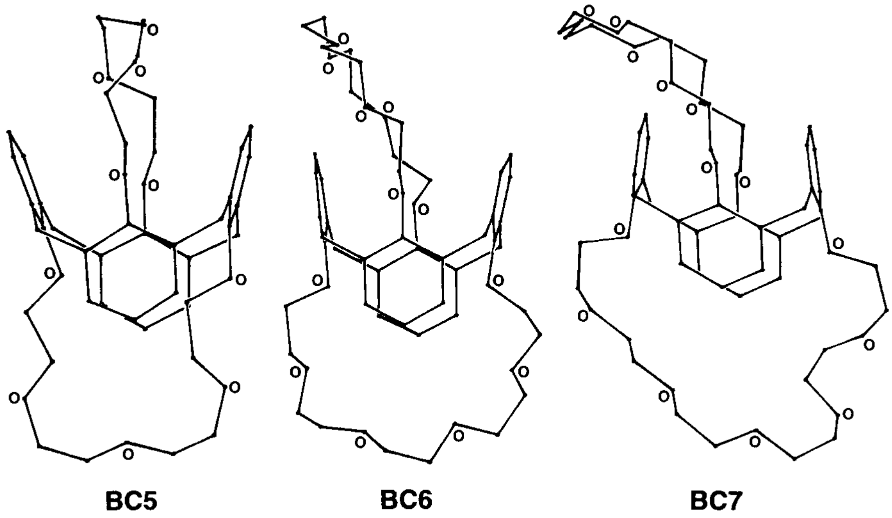


Figure 1. Molecules **BC5** (**2**), **BC6** (**3**) and **BC7** (**28**), illustrating the increasing bridge bending in the series. These molecular drawings and all the following ones have been done with the program ORTEPII [76].

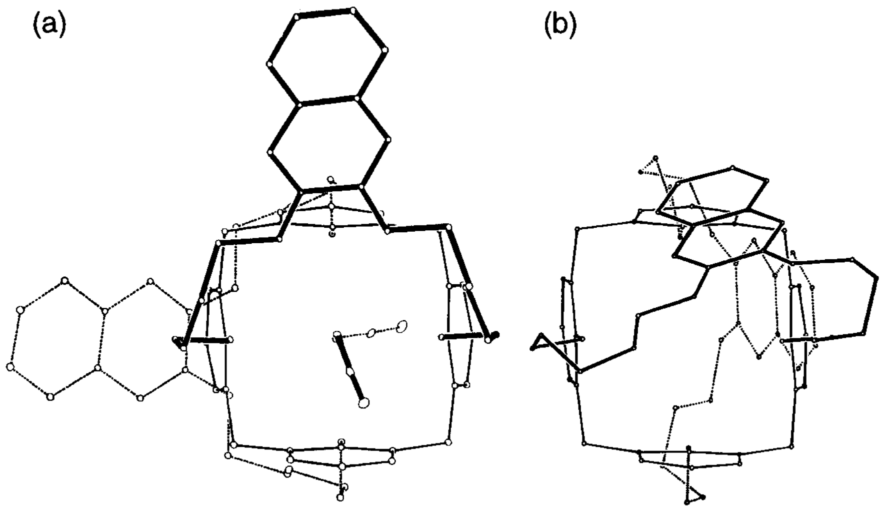


Figure 2. Molecules of **BC6N**.3CH_3CN (**16**) (a) and **BC6N**.$C_6H_5CH_3$ (**17**) (b), viewed perpendicular to the methylene mean plane, illustrating the effect of solvent complexation on the crown conformation. Upper crown and solvent molecule in bold lines, lower ones in dashed lines. Uncomplexed solvent not represented.

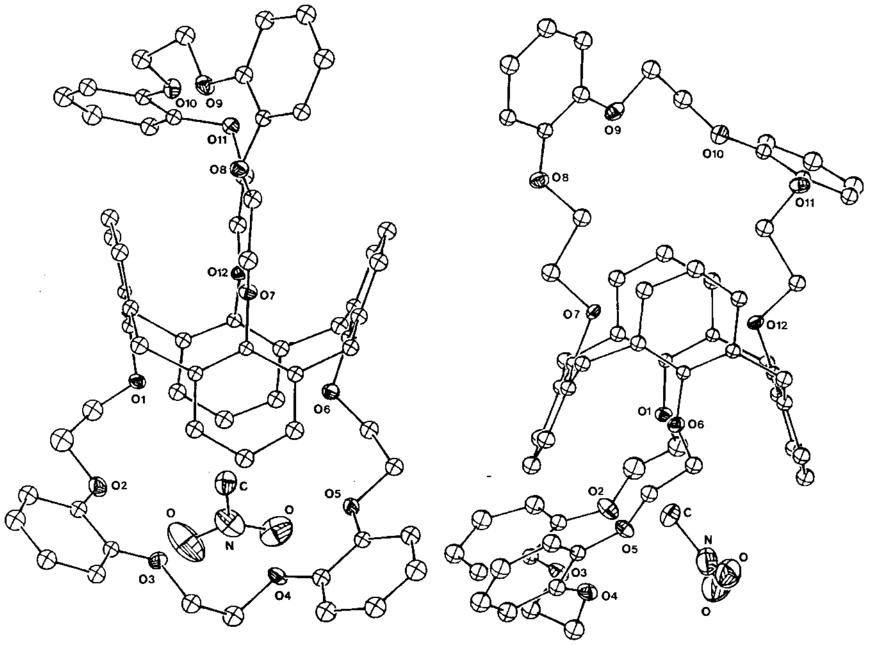


Figure 3. Two views of **BC6B2**.CH_3NO_2 (**20**), illustrating the effect of solvent complexation on the crown conformation.

Dependence of the calixarene geometry upon chain length and substituents

Although all these calixarenes are fixed in the 1,3-*alternate* conformation, some geometrical variations are observed, depending on the strain induced by the bridges. These variations concern the dihedral angles between the phenolic rings and the mean plane defined by the four methylene groups. As shown in Figure 1, **BC5** and **BC6** present a conformation in which all the rings have their phenolic oxygen atoms directed inwards (i.e., the distance between two opposite phenolic oxygen atoms is shorter than the distance between the *para* carbon atoms on the same rings), whereas in **BC7** they are directed outwards, as a consequence of the longer chain length, which may lead to a larger O···O distance in order to minimize the strain. The same phenomenon is observed when a ‘spacer’ is included in the crown ether chain as in **BC6EP** (**22**) and **BC6HP** (**23**), in which cases the phenolic oxygen atoms are also directed outwards. However, the flexibility of the chains makes it impossible to define unambiguous rules concerning the effect of the chain length variation, as exemplified in the case of the diphenyl-containing compound **BC6D** (**24**), in which the chain length is intermediate between those of **BC6EP** and **BC6HP** and that of **BC7**, and in which the phenolic oxygen atoms are nevertheless directed inwards, as a result of a strong distorsion which makes the diphenyl group nearly perpendicular to the base of the bridge (Figure 4).

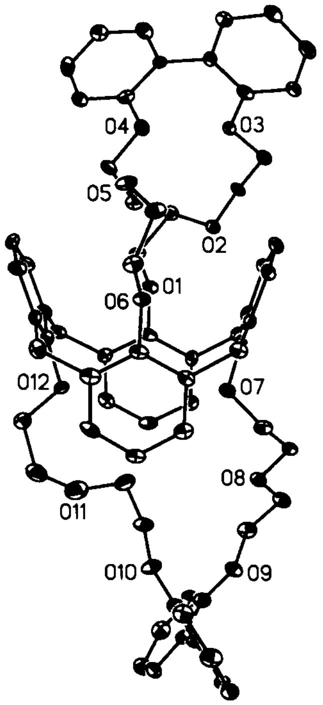


Figure 4. **BC6D** (**24**) (solvent molecules omitted).

Structures of the alkali-metal ion complexes

As already indicated in the introduction, the efficiency of **BC6** (and also of its derivatives **BC6B**, **BC6N** and **BC6B2**) as selective caesium complexants led us to undertake a single crystal structural investigation in order to obtain some information about the origin of this phenomenon. We have thus determined the crystal structures of various caesium complexes of these ligands (with NO_3^-, NCS^- or I^- as counter-ions) as well as those of the sodium and potassium complexes of **BC6**. All these structures are summarized in Table 1. The ligands whose crowns include a 'spacer' (**BC6EP**, **BC6HP**, **BC6D**) do not complex Cs^+, at least inside their ether cavity, since an exocyclic cation binding cannot be ruled out [71, 72] (the presence of a 'spacer' may make it impossible for both donor atoms attached to it to chelate a single metal ion, which may result in exocyclic binding). The radius of the cavity in **BC5** is generally considered as well adapted for K^+ (ionic radius 1.33 Å) or Rb^+ (1.47 Å) but too small for Cs^+ complexation (1.67 Å), whereas the cavity in **BC7** is too large for all these cations. The **BC6** cavity ($\sim$1.7 Å) is well adapted for Cs^+ complexation, but, as will be exemplified hereafter, can also accommodate smaller ions.

Caesium complexes

All the calix[4]arene *bis*(crown ether)s are potential ditopic receptors, with two identical or different cavities in the symmetric or asymmetric species, respectively. Whereas caesium transport phenomena could be rationalized in terms of the formation of 1 : 1 (mononuclear) complexes, X-ray diffraction provided the first proof for the existence of 2 : 1 (binuclear) complexes. Depending on the stoichiometry used during the synthesis, both complexes can be obtained; these ligands can thus be considered as effective ditopic receptors since the bonding of two cations is not prevented by electrostatic repulsions between them [62]. The influence of such electrostatic factors may be minimized by the close association between the cation and its counter-ion which is always observed in the solid state.

More surprisingly, the ligand conformation is so similar in the acetonitrile complex of **BC6** and in its mono- and binuclear caesium complexes that we obtained four compounds with isomorphous structures (compounds **3**, **6**, **7** and **8**). The most frequent crown conformation in the caesium complexes of **BC6** corresponds to the $g^+g^-g^+g^-g^+$ O–C–C–O torsion angles sequence, the same as in the solvent complexes. The same is true for the **BC6B** and **BC6N** caesium complexes since the conformation observed ($g^+g^-0g^+g^-$) is the same as in the solvent complexes. These conformations thus appear to be the more stable when a complexed species (solvent or cation) with an adequate size enforces all the oxygen lone pairs to be directed towards the crown centre. The ideal D_{3d} conformation of 18-crown-6, which is the most common one for complexes in the solid state, with oxygen atoms located alternately above and below the mean plane of the molecule, corresponds also to the sequence $g^+g^-g^+g^-g^+g^-$ [77]. It has been suggested that this conformation is generally a low energy one, the more irregular conformational groups being somewhat higher in energy, and that, although the guest may organize the host in this case, the conformational preferences of the latter are respected [77]. The complexation of caesium ions in the present case does not induce a particularly strained crown conformation. The coordination mode of Cs^+ indicates a good cation/ligand complementarity since, in all the cases reported in Table 1, Cs^+ is bonded to the six oxygen atoms, with distances ranging from 2.995(4) to 3.57(1) (mean value 3.29(14)) Å. The longer and shorter bond distances, in the nine complexes investigated, do not always involve ether oxygen atoms identically located in the bridge, which indicates that the location of Cs^+ can slightly vary near the crown centre. However, the shorter distances are most often with the two oxygen atoms nearer to the calixarene. The cation is located at a distance between 0.3 and 0.8 Å from the mean plane defined by the six oxygen atoms. Cs^+ is also bonded to its counter-ion, either NO_3^- (mono- or bidentate), NCS^- or I^-, which gives 7- or 8-coordination. The distances involving bidentate nitrate ions range from 3.01(3) to 3.17(1) (mean value 3.08(6)) Å in **BC6** complexes, whereas in **BC6B** and **BC6N** complexes, the two Cs–O distances are somewhat different, one (3.10(3) to 3.18(2) (mean value 3.14(3)) Å) being shorter than the other (3.25(3) to 3.32(3) (mean value 3.29(3)) Å). In the case of **BC6B2** (compound **21**, represented on Figure 5), one nitrate ion bridges the Cs^+ ions of two molecules, giving rise to a polymeric structure, while the other one is non-bonding. The Cs–O distances for the ion bonded to two oxygen atoms are comparable to the larger ones in **BC6B** and **BC6N** (3.208(4) and 3.363(4) Å), while for the ion bonded to only one oxygen atom (3.186(4) Å), it is comparable to that observed in the case of a monodentate nitrate ion in a **BC6** complex (compound **9**, 3.15(1) Å). The calixarene itself is involved in the complexation, Cs^+ being bonded in a polyhapto manner to the phenyl rings. The three terminal (i.e., opposite to the phenolic oxygen atom) carbon atoms are nearer to the cation, with distances ranging from 3.09(1) to 3.89(4) (mean value 3.54(16)) Å. This bonding mode has already been observed with calix[4]arene *mono*(crown-6) [19, 21] in the 1,3-*alternate* conformation, however, the existence of π-interactions in such complexes has been questioned [78]. As a result of caesium complexation, the distance between the two facing phenyl rings of **BC6** increases from about 6.25 Å in the uncomplexed form to about 6.5 Å in the complex (mean values), which may indicate some cation/phenyl rings interaction.

Potassium and sodium complexes

Although the cavity size of **BC6** is larger than what is needed for K^+complexation, we obtained single crystals of this complex (**11**), the structure of which is shown in Figure 6, together with the analogous caesium complex **7**. This structure is isomorphous to those of the acetonitrile and Cs^+ complexes **3**, **6**, **7** and **8**. The potassium cation occupies a position near to that of caesium in the preceding complexes, but slightly displaced towards the crown ether extremity (i.e., the part opposite to the calixarene), with K–O distances ranging from 3.068(9) to 3.672(8) (mean values 3.20(9) for the four shorter ones, 3.63(6) for the two longer) Å, and is located at about 0.8 Å from the mean oxygen plane. The crown conformation is the most commonly observed $g^+g^-g^+g^-g^+$.

Such an agreement between host and guest is no longer observed with the sodium ion. We managed to obtain only one complex in the solid state (compound **12**), represented on Figure 6, in which the complexed species is $[Na(H_2O)]^+$. The sodium ion is located in the cavity, on the side of the crown opposite to the calixarene and bonded to three ether oxygen atoms only, with distances in the range 2.44(2)–2.86(2) (mean value 2.6(1)) Å, and is bonded also to a bidentate nitrate ion (2.38(3)–2.55(2) (mean value 2.49(8)) Å). The water molecules coordinated to Na^+ (Na–O 2.18(2) and 2.24(2) Å) are also included in the cavity, on the side of the crown bonded to the calixarene and are hydrogen bonded to the two phenolic oxygen atoms. Hence, the cation/ligand complementarity appears reduced in the case of Na^+ with respect to that of Cs^+ and even K^+, and the co-inclusion of a water molecule is necessary for the complexation to take place. The crown conformations are rather distorted, with the O–C–C–O torsion angles sequences $g^+g^-g^+g^+g^-$ and $g^+g^-g^+g^-g^-$, and some C–O–C–C angles being far from the ideal *anti* value. The crystal structures are on this point in agreement with the extraction experi-

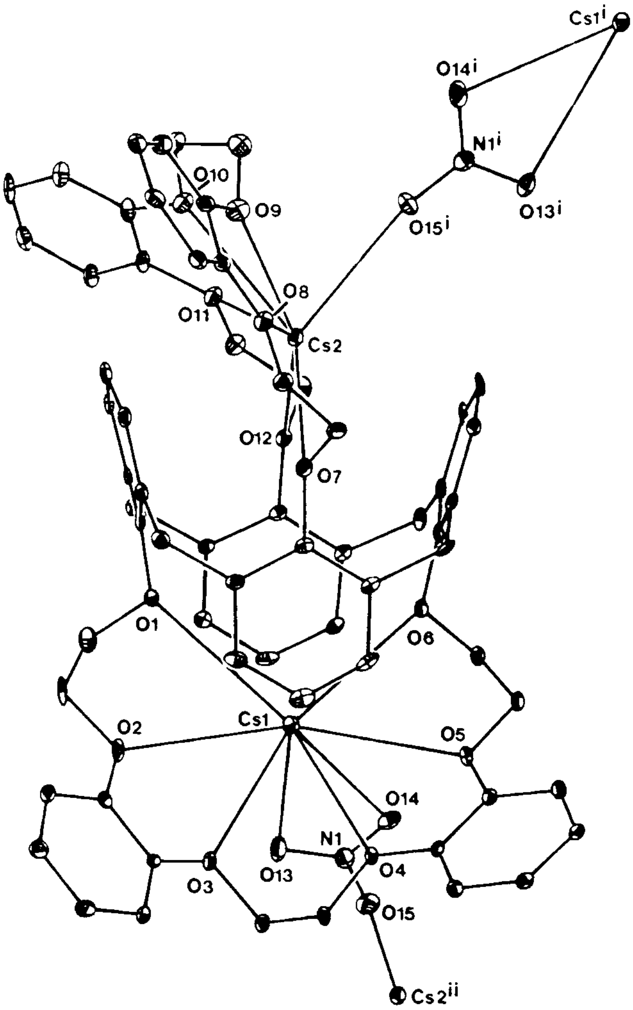


Figure 5. Caesium complex of **BC6B2** (**21**). (Non-bonding nitrate ion and solvent molecules omitted).

ments, which show, as already stated, a high degree of selectivity of these ligands for caesium over sodium ions.

Apart from the crown conformations discussed above, a remark may be made concerning the absolute values of the *gauche* O–C–C–O angles. As already noticed from experimental data, the crown ether building block O–CH_2–CH_2–O forms, when complexed, a five-membered chelate ring with planar preferences decreasing with cation size [79, 80]. It has been shown that, as a consequence, the O–C–C–O torsion angle increases with the cation size towards the preferred value of 75°. This trend observed for simple crown ethers is also true in our case, since the mean value of O–C–C–O angles is 72(3) in the solvent complexes of **BC6**, 67(5) with

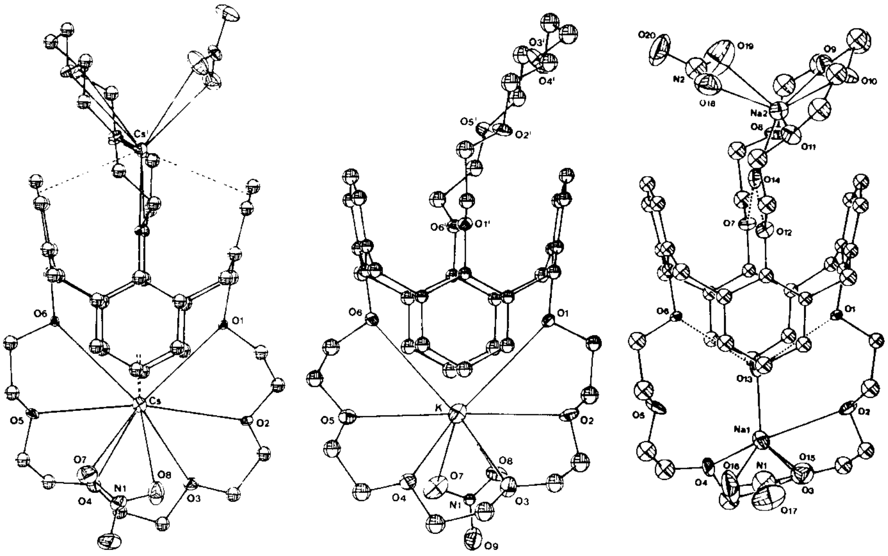


Figure 6. Caesium (**7**), potassium (**11**) and sodium (**12**) complexes of **BC6** (from left to right). Cs^+-π interactions in dashed lines. The sodium complex includes two water molecules, each of them hydrogen bonded to two ether oxygen atoms (dashed lines).

Cs^+, 67(3) with K^+ and 50(14)° for Na^+ (the coordinating O atoms only are taken into account in the last case). Such variations have been considered to provide a measure of structural complementarity [80].

Selectivity of calixcrowns and unsymmetrical calixcrowns

The caesium over sodium selectivity has been shown, from extraction experiments, to increase according to the sequence **BC6** < **BC6B** < **BC6N** < **BC6B2** [46, 70], which could be due to an increasing difficulty to complex Na^+ and/or to an increasing ability to complex Cs^+ (**MC6B2**, the *mono*(crown) derivative analogous to **BC6B2** has also been recently investigated [81] and behaves similarly with respect to **MC6**). We never managed to obtain single crystals of sodium complexes with ligands other than **BC6** in this series, the only crystals isolated in such cases being those of the solvent-complexed ligands, which can be considered as an indication of the first trend. Concerning Cs^+ complexation, the use of an unsymmetrical ligand, with a crown-6 on one side and a 1,2-phenylene-substituted crown-6 on the other (**25**) enabled us to show the preference of this ion for the substituted crown. When reacted with one equivalent of caesium nitrate, this ligand gives complex **26**, in which Cs^+ is bonded by the 1,2-phenylene-substituted crown-6, an acetonitrile molecule being complexed in the other crown. However, due to the competition between cation and solvent, the preferences observed represent relative, and not absolute, affinities. Similar results were obtained from ^{1}H-NMR experiments in chloroform solution (without cation/solvent competition) during the formation of the 1:1 complex of caesium picrate with the related 2,3-naphthylene-substituted ligand **BC6n**, whereas, under the same conditions, Na^+ has been shown to be bonded to the unsubstituted crown [74].

2.2. AZOBENZOCROWN DERIVATIVES OF CALIX[4]ARENE

As indicated in the introduction, azobenzocrown derivatives of calix[4]arene were synthesized with the aim to investigate the possibility of a photocontrol of ion complexation mediated by mechanical allosteric effects. Hamada *et al.* described such a system, based on a calix[4]arene moiety, prior to our work [82]. We determined the crystal structures of the compounds represented in Scheme 2. The crystal data are given in Table 2, in which the azobenzene conformation (*trans* or *cis*) is also indicated. The binding mode of the azobenzene is p,p' apart from compound **37**, for which it is o,o'. The complexing properties of **32** (for which both *trans* and *cis* isomers coexist in solution) have been investigated [83], but no complex was isolated as a single crystal. In this case, Rb^+ and Cs^+ have been shown to drastically increase the percentage of the *cis* isomer, but these ions are complexed by both isomers whereas Na^+ is preferentially extracted by the *trans* one. The presence of alkali cations prevents thermal isomerization, which indicates the strong thermodynamic stability of the complexes. With reference to caesium removal, *trans*-o,o'-**azo6** was used as a photoresponsive extractant, the *cis* isomer transporting the cation while the *trans* one released it simply by warming the receiving phase [83].

Influence of calixarene conformation and chain length on the azobenzene geometry
The most thermodynamically stable conformation for the azobenzene moiety is the *trans* one. The *cis* conformation is only observed in our compounds when the *trans* one would result in too much strain. We have investigated calixcrowns with different numbers of oxygen atoms in the ether chains and a calixarene in *cone* (without substituents in the 2,4 positions, compounds **29**, **30** and **37**) or 1,3-*alternate* (with glycolic chains or ether bridge in the 2,4 positions, compounds **31**–**36**) conformations (the *cone* conformation in the former case may be stabilized by hydrogen bonds between neighbouring phenolic oxygen atoms). For a given calixarene conformation, the strain in the chain is inversely proportional to its length, hence the *trans* isomer will be observed with the longer chains, whereas the *cis* one can be observed with the shorter ones. The *cone* conformation induces a shortening of the distance between the two ends of the bridge, with respect to the 1,3-*alternate* one (the $O1\cdots O6$ distances are 4.976(6)–4.78(1) Å in the former case (compounds **29** and **30**) and 6.02(1)–6.69(1) Å in the latter (compounds **31** and **32**), i.e., a difference of 1.7 Å for a same bridge length). As a consequence, the *cone* conformation induces more strain in the bridge than the 1,3-*alternate* one. As illustrated in Figure 7, this is evidenced by the two compounds with six oxygen atoms: the azobenzene is *trans* when the calixarene conformation is 1,3-*alternate* (**32**) and *cis* when it is a *cone* (**29**), in which case the *trans* form is obtained with

Table II. Azobenzocrown derivatives of calix[4]arene: crystal data.

Number	Compound	Space group	a (Å)	α (°)	V (Å^3)	Ref.
			b (Å)	β (°)		
			c (Å)	γ (°)		
29	*Cis*-**azo6**	$P\bar{1}$	11.129(5)	109.50(3)	2018(3)	84
			13.551(4)	96.12(3)		
			14.921(5)	103.72(3)		
30	*Trans*-**azo8**	$P2_1/a$	15.055(7)		5143(6)	84
			22.257(6)	97.27(3)		
			15.473(6)			
31	*Cis*-**azo4**-gly	$P\bar{1}$	11.207(3)	73.65(2)	2424(2)	84
			13.381(2)	72.25(2)		
			18.150(4)	73.10(2)		
32	*Trans*-**azo6**-gly	$P2_1/n$	15.851(7)		5084(5)	84
			16.272(6)	101.34(3)		
			20.104(3)			
33	*Cis*-**azo4-C6**.$2CH_3NO_2$	$P\bar{1}$	10.958(3)	104.64(1)	2599(9)	85
			11.880(1)	99.23(2)		
			21.317(4)	98.38(1)		
34	Cs*Cis*-**azo4-C6**.$(NO_3).CH_3NO_2$	$P2_1/n$	12.169(4)		5246(7)	85
			29.862(6)	110.57(4)		
			15.420(9)			
35	*Trans*-**azo6-C6**	$P2_1/a$	13.667(4)		5145(4)	86
			18.647(11)	90.72(2)		
			20.188(6)			
	$>$ 268 K	$P2_1/a$	20.341(6)		5258(3)	86
			11.709(3)	112.39(2)		
			23.875(8)			
	$<$ 268 K	$P\bar{1}$	11.608(4)	67.68(3)	5199(3)	86
			20.285(8)	87.78(2)		
			23.894(6)	87.81(3)		
36	*Trans*-**azo6-C6**.$3CH_3NO_2$	$P\bar{1}$	16.639(6)	103.23(3)	6055(3)	87
			19.026(4)	100.13(3)		
			20.055(5)	93.07(2)		
37	*Trans*-*o,o′*-**azo6**.$(CH_3)_2CO$	$P2_1/c$	25.867(2)		8636.4(15)	88
			17.085(2)	106.328(2)		
			20.363(3)			

When not otherwise indicated, the azobenzene is *p,p′*-bonded.
azo4-gly: 25,27-*di*-[2-(2-methoxyethoxy)]-26,28-(*p,p′*-azobenzene)calix[4]arene-crown-4
azo6-gly: 25,27-*di*-[2-(2-methoxyethoxy)]-26,28-(*p,p′*-azobenzene)calix[4]arene-crown-6

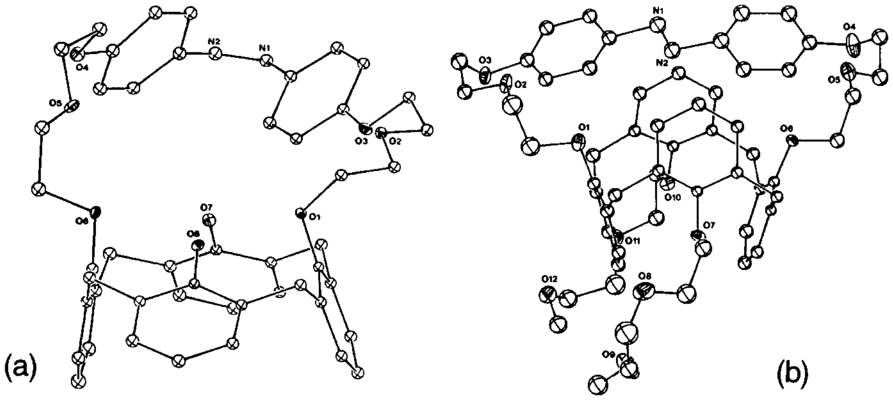


Figure 7. Azobenzene calixcrown derivatives **29** (a) and **32** (b).

eight oxygen atoms (**30**). In all cases, not all the oxygen lone pairs are directed towards the centre. As in the case of the ‘spacers’ reported above, the fit between the ligating sites geometry and the caesium ion requirements is poor and no complex has been isolated in the solid state. We have also determined the structure of compound **37** in which the substituent is an *o,o*′-azobenzene; the conformation of the bridge is different from the previous ones and is likely to induce less strain, for an equivalent number of oxygen atoms, since the isomer observed is the *trans* one, in spite of the *cone* conformation of the calixarene, whereas it is the *cis* one in **29**.

Solvent complexation

Compounds **33** and **36** contain complexed nitromethane solvent molecules. Furthermore, compound **36** contains two solvent molecules, one of them associated with the azobenzene-containing bridge. The solvent complexation by the unsubstituted crown ether bridges shows the features already described. The azobenzene-containing crown is too large for the six oxygen atoms to interact with the methyl group of the solvent: three oxygen atoms only have their lone pair pointing inwards, with O· · ·C(methyl) distances in the range 3.50–3.71 Å for two of them and 4.94–5.18 Å for the other one (two independent molecules in the asymmetric unit), whereas the remaining three oxygen atoms have their lone pair pointing outwards and are at 5.48–6.70 Å from the methyl carbon atom. The solvent can thus be loosely hydrogen bonded to two oxygen atoms only, hence the scarcity of solvent complexation in this family compared to its frequency in the unsubstituted crown ether one.

Calixarene geometry

The calixcrowns in the *cone* conformation do not present any notable features. As already mentioned, this conformation may be stabilized by hydrogen bonds between adjacent phenolic oxygen atoms (O· · ·O distances in the range 2.63–3.00 Å). For the 1,3-*alternate* conformation, compounds **31**, **32**, **35** and **36** display the same trend as the calixarene *bis*(crown ether)s with the longer bridges described above, with the distance between phenolic oxygen atoms on opposite rings longer than the distance between the *para* carbon atoms on the same rings. When the bridge in **35** is replaced by a shorter one with four oxygen atoms (**33**, **34**), the reverse order is observed. If the bridge length gives a general rule concerning the calixarene geometry, some exceptions may exist, as already signalled above, such as the unexpected difference which appears between compounds **31** and **33**. These two compounds possess the same azobenzene-containing bridge (the shorter one, with four oxygen atoms) and differ by the other substituent only (glycolic chains or crown ether), and nevertheless present opposite inclinations of the phenolic rings.

Caesium complexation in the crown-6 site

The relation between the calixarene geometry and that of the azobenzene moiety suggests that the former can be slightly modified if the azobenzene is forced to switch from one form to the other. This could be a way to modify the geometry of a second, unsubstituted, ether bridge and to induce a cation decomplexation by an allosteric effect mediated by the calixarene platform. Conversely, cation complexation in the ether bridge could lead to a switch of the azobenzene geometry. Such a compound (**33**) and its caesium complex (**34**) have been characterized. Unfortunately, the azobenzene-containing bridge in this case is too short and strained (four oxygen atoms only) to undergo a *trans/cis* isomerization. Single crystals of the analogous ligand with six oxygen atoms have not been obtained, but ^{1}H-NMR experiments have shown that both isomers were present in solution and that their ratio was dependent on the cation (K^+, Rb^+, Cs^+, NH_4^+) complexed by the unmodified ether bridge [27]. The calix[4]arene unit can be depicted as transmitting an information from the crown-6 loop to the *trans*/*cis* isomerizable function, acting as a relay-element analogous to a lever.

Conformational polymorphism

In all the compounds described above, as previously indicated for simple calix[4]arene *bis*(crown ether)s, the bridges are generally more bent towards the calixarene mean plane when they are longer and more flexible. However, their important flexibility may be apparent even in solid state investigations. This is illustrated by compound **35**, for which three polymorphs have been structurally characterized. At room temperature, the molecule can crystallize with two highly different conformations for the azobenzene-containing bridge (which arise from different torsion angles in the ether parts, whereas the azobenzene moiety is *trans* in both cases), giving the two conformational polymorphs A and B, represented in Figure 8, both presenting a high degree of disorder. The bridge in A is far more bent towards the calixarene mean plane than in B, and is thus more in agreement with what is observed in other compounds with a similar bridge length. Furthermore, polymorph B undergoes a phase transition at about 268 K, leading to a third polymorphic modification C, more ordered and hence less symmetrical, in which the

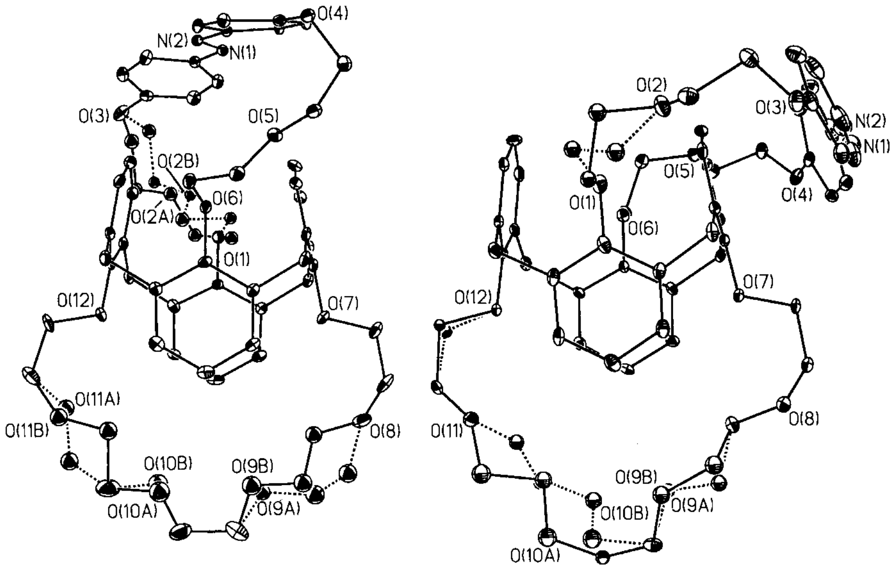


Figure 8. The two room temperature polymorphs (A and B) of compound **35**. Disordered parts in dashed lines.

asymmetric unit comprises two different molecules. Crystal packing interactions are sufficient to induce torsional and conformational changes in the bridges, which is another evidence of the high flexibility of these molecules.

3. Molecular Modelling

To date, two teams (Wipff's in Strasbourg and our group in Cadarache) have undertaken extensive studies based on molecular modelling of crown ether derivatives of calix[4]arene. Both groups used the same software and similar methodologies, but focused on different items. As a first part, we will present the main features of these calculations, then the contribution of each team will be reviewed.

3.1. METHODOLOGY

These ligands and their alkali complexes were studied by molecular dynamics (MD) with a classical force field method [89]. The software used was AMBER 4 [90] with the all-atom parameters PARM91.DAT as a force field and the following representation of the potential energy [91]:

$$E_{\text{pot}} = \sum_{\text{bonds}} K_r(r - r_{\text{eq}})^2 + \sum_{\text{angles}} K_\theta(\theta - \theta_{\text{eq}})^2 + \sum_{\text{dihedrals}} \frac{v_n}{2}(1 + \cos(n\varphi - \eta))$$

$$+ \sum_{i<j}\left[\epsilon_j\left(\left(\frac{R^*}{R_{ij}}\right)^{12} - \left(\frac{R^*}{R_{ij}}\right)^{6}\right)\right] + \sum_{i<j}\left[\frac{q_i q_j}{\epsilon R_{ij}}\right]$$

$$+\sum_{\text{H-bonds}}\left[\epsilon_j\left(\left(\frac{R^*}{R_{ij}}\right)^{12}-\left(\frac{R^*}{R_{ij}}\right)^{10}\right)\right].$$

The cation parameters came from Aqvist [92]. In the gas phase, MD simulations were performed on the alkali complexes at constant temperature (300 K) and energy with a 1.0 fs time step, a dielectric constant set at 1.0 and a residue-based cut-off. In water, the MD simulations used PBC, a time step of 2.0 fs and the SHAKE procedure was used to constrain bonds involving hydrogen atoms. The pressure and temperature were maintained respectively at 1 atm and 300 K through coupling to temperature and pressure baths.

The conformations collected during MD sampling were visualized with the MD/DRAW software [93] and analyzed by the MDS software [94]. Other parameters (water box size, cut-off values, 1–4 scaling for non-bonded interactions, sampling times), as well as atomic charge sets were not common to both research groups.

To evaluate the ligands, structural characterizations and selectivity calculations were performed. In the first case, the concept of host/guest complementarity, which involves assessment of the steric and electrostatic fit of host and guest, was used [95]. A criterion of complementarity is the ability of the macrocycle to provide a coordination environment similar to that of the hydration shell of the cation, which was modelled by $\langle \mathrm{dM}^+\text{–}\mathrm{O}_C \rangle$, the average of the time-averaged dM^+-O distances occurring during the MD runs, to be compared to $\mathrm{dM}^+\text{-}\mathrm{O}_w$, known from experimental and former modelling data [96].

For selectivity calculations, the thermodynamic cycle was considered to be [97]:

$$\begin{tikzcd}
\text{calix} + M^+ \arrow[r, "\Delta \mathrm{G}_1"] \arrow[d, "\Delta G_3"] & \text{calix: } M^+ \arrow[d, "\Delta G_4"] \\
\text{calix} + N^+ \arrow[r, "\Delta G_2"] & \text{calix:} N^+
\end{tikzcd}$$

where, assuming that the system is reversible, the relative binding selectivity is computed by the difference: $\Delta(\Delta \mathrm{G}) = \Delta \mathrm{G}_1 - \Delta \mathrm{G}_2 = \Delta \mathrm{G}_3 - \Delta \mathrm{G}_4$. These $\Delta \mathrm{G}_3$ and $\Delta \mathrm{G}_4$ values are computed by free energy perturbation (FEP) or thermodynamic integration (TI) methods [97] through MD sampling by mutating the Lennard–Jones parameters of the M^+ cation into those of the N^+ one with a coupling factor λ (from $\lambda = 1$ to $\lambda = 0$). This thermodynamic cycle means that the cation selectivity is a compromise between ligand relative affinity towards both cations ($\Delta \mathrm{G}_4$) corrected by the relative desolvation energy ($\Delta \mathrm{G}_3$). Selectivities of complexation or extraction can be computed in that way, depending on the phase where mutations are performed.

3.2. RESULTS

Wipff et al. have worked on calix[4]arene *mono* or *bis*(crown-5) and (crown-6), without any substituent on the crown. They have first focused on the influence on the alkali complexes stability and calixarene selectivity (*in vacuo* or in a water phase) of the calix[4]arene conformation in mobile dimethoxy *mono*(crown) derivatives and of the presence of *p*-*tert*-butyl groups on the upper rim [98]. Much work has been devoted to the influence of the solvent phase, with a particular emphasis on the binding and extraction selectivities, by simulations performed in chloroform or at water/chloroform interfaces [99–100] and in chloroform saturated with water molecules [101]. Solvent effects on the structure and stability of alkali cation complexes (Na^+, K^+ and Cs^+) were extensively studied on **BC6** in the gas phase and in four pure solvents, either involved in solvent extraction or complexation studies, water, methanol, acetonitrile and chloroform [78].

The **BC6**:Cs^+ complex has a similar structure in solution and in the gas phase, with a direct interaction between Cs^+ and solvent molecules (average number of solvent molecules in the first coordination sphere of Cs^+ over the MD runs: 1.4 acetonitrile, 1.3 methanol, 1.8 water and no chloroform). On the contrary, Na^+ can adopt different positions into **BC6**, either highly solvated when the cation is in the crown, or poorly solvated when it lies in the cavity, with the exception of water, small enough to solvate Na^+in both cases. The solvation of the cations is prevented when bulky *p*-*tert*-butyl groups are present.

Assuming that the complex was mononuclear, the selectivity of complexation in these pure solvents appeared to be primarily dependent on the solvent polarity and subsequent interactions with the cation. Indeed, in pure chloroform, like in the gas phase, the four ligands investigated, **BC5**, **BC6** and their *p*-*tert*-butyl analogues, showed a preference for Na^+ with respect to the other alkali cations, due to an intrinsic best affinity for the smallest cations and to a weak desolvation energy (in chloroform, $\Delta G_{3\ Na \rightarrow Cs} = 5.3$ kcal mol^{-1}). In polar solvents, the selectivity is different, due to the ΔG_3 correction ($\Delta G_{3\ Na \rightarrow Cs} = 30.5$ kcal mol^{-1} in methanol, 30.4 kcal mol^{-1} in water and 24.2 kcal mol^{-1} in acetonitrile) with $\Delta G_{4\ Na \rightarrow Cs}$ ranging between 21 and 28 kcal mol^{-1} for **BC6**. Thus, the order of selectivity in methanol is $Cs^+ > Rb^+ > K^+ \gg Na^+$ for **BC6** and *pt*Bu**BC6**, and $Rb^+ \geq K^+ > Cs^+ \gg Na^+$ for **BC5**.

The counter-ion effect was also investigated by modelling **BC6** complexes with the alkali picrates in methanol and chloroform [78]. In methanol, the ion pairs dissociated, but in chloroform, as in the gas phase, the ion pairs remained intimate, with no significant change of position for Cs^+ in **BC6**. This proof of perfect fit contrasted with what was obtained for the smaller K^+ and Na^+ cations, shifted by the picrate towards the top of the crown. The counter-ion appeared also to have a quantitative influence on the selectivity calculated in chloroform, due to an important change of about 10 kcal mol^{-1} of the $\Delta G_{3\ Na \rightarrow Cs}$ value, leading to a sharp decrease of the calculated selectivity for Na^+.

Finally, the stoichiometry of **BC6** complexes was investigated by simulations on binuclear complexes ($2Cs^+$, $2Na^+$ or Cs^+ and Na^+) [78]. In the gas phase and in chloroform, the binuclear complexes were stable but the cation-cation repulsion caused the shift of one of the cations into an *exo* position. In methanol, all the binuclear complexes were unstable, with decomplexation of the cation initially in the *exo* position. Therefore, the possibility of finding binuclear **BC6** complexes appeared dependent on the nature of the complex environment.

BC6 and its alkali cation complexes were also modelled by MD at an explicit water/chloroform interface, in order to get insight into the dynamic behavior and extraction selectivity of such ionophores at a liquid–liquid interface. In a first study [102], free **BC6**, as other macrocyclic extractants (222-cryptand, 18-crown-6, **MC6** . . .), was placed at the interface, equally shared between water and chloroform. During the 550 ps MD run, it slowly diffused to the organic phase and captured two water molecules in interaction with one of the crowns, the other crown pointing towards the chloroform phase. Although mostly lying in the organic phase, it stayed adsorbed at the interface and behave like a surfactant, with its hydrated part comparable to what was simulated in bulk water. This surfactant behavior was common to all the macrocycles tested.

The second study dealt with the **BC6**:Cs^+ complex at a water/chloroform interface [103]. Whatever the starting position of the complex (interface or chloroform phase), after 100 ps of MD run, the situation was the same; the complex was at the interface, with the complexed crown in contact with the aqueous phase and other parts of the calixarene in chloroform. Simulations with the picrate counter-ion were very sensitive to the starting position of the complex, which either dissociated or stayed at the interface with dissociation of the picrate/cation pair.

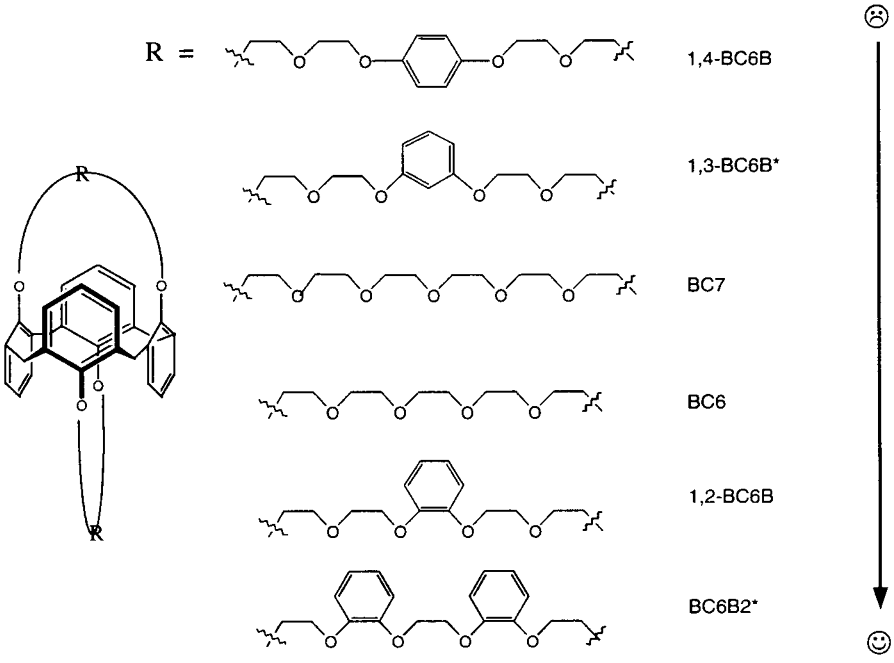
Additional calculations of extraction selectivity were performed by the thermodynamic cycle method, where ΔG_3 was calculated in water, and ΔG_4 either in water or in pure chloroform, representing two extreme cases of water-saturated or water-free organic phase [103]. In both cases, the extraction selectivity was the same, with quantitative differences: $Cs^+ \geq Rb^+ \approx K^+ > Na^+$ when $\Delta G_{4\mathrm{wat}}$ was taken into consideration, or $Cs^+ \gg Rb^+ > K^+ > Na^+$ when the organic phase was modelled by $\Delta G_{4\mathrm{chloroform}}$. From their simulations of solvation of calix[4]arene *mono* and *bis*(crown ether), Wipff *et al.* concluded that, from a quantitative point of view, the selectivity calculated in pure water is closest to the actual extraction selectivity when compared to results from calculations in an organic phase [101].

For our part, we used MD simulations to study a family of calix[4]arene *bis*(crown ether) derivatives with phenylene-substituted crowns, in order to explain their relative affinity towards alkali cations in solvent extraction experiments and, when available, complexation data. The final purpose was to evaluate new compounds by simulation techniques before chemical synthesis. Simple models were used, gas phase and explicit water phase simulations, with a procedure for calculating atomic charge sets consistent with the size and diversity of these compounds [104]. The structural host/guest complementarity was fully investigated as a criterion to discriminate these ligands towards each alkali cation, with a particular emphasis for caesium, which is the most important one in nuclear reprocessing studies. The knowledge of the solvation of these alkali cation complexes in a pure water phase is also of primary interest, keeping in mind that these calixarenes, although insoluble in water, are used as cation carriers between two aqueous phases through a water saturated organic phase.

A preliminary study involved a screening by MD simulations of alkali ion complexes without counter-ion, for the six *bis*(crown ether) derivatives shown in Figure 9, whose extraction properties were known [47]. The discrimination was carried out with respect to host/guest complementarity and MD/FEP simulations in the gas phase, confirmed by simulations in water for the best compounds [105, 106]. For instance, 1,2- and 1,4-phenylene substitution on the top of the crown were compared and it was found that, in agreement with experiment, the 1,2-substituted compound should be better than the parent crown-6 derivative, while the 1,4-substituted compound was a poor complexant. It was also deduced from these calculations that the 1,3-substituted compound was not worth synthesizing for caesium complexation [105]. Later, a dissymmetrical calixarene bearing one crown-6 and one 1,3-phenylene-crown-6 was synthesized with the aim to graft a calix[4]arene *bis*(crown-6) on a solid membrane through the 1,3-phenylene unit [107]. Characterization of the caesium complex showed that the caesium preferred the unsubstituted crown, as expected. The new compound **BC6B2** appeared to be a good complexant for caesium and was further synthesized and experimentally investigated. The efficiency order of the ligands in this series is illustrated in Figure 9.

The stoichiometry of caesium extraction was also investigated since it was found that, in extraction experiments, only mononuclear complexes occurred [45], although X-ray crystal structures showed that binuclear complexes could be formed. The simulations in water showed that the mononuclear complex was intrinsically more stable than the binuclear one, and that its free crown was probably complexed with one water molecule, preventing further caesium complexation unless the experimental conditions (excess of caesium) were favorable [62].

The 1,3-*alternate* conformation is preorganized for Cs^+ complexation, as it delineates a rather cylindrical cavity large enough for the caesium cation. On the contrary, the crown part appeared not to be preorganized. The crown conformation was studied by analysis of the distribution of O–C–C–O dihedral angles in either complexed and uncomplexed crown of **BC6N**, through long samplings (from 1 to 5 ns) in the gas phase at 300 and 500 K [64]. These samplings showed that the free crown is mobile with a clear-cut preference (about 80%) for crown conformations involving one or two non-adjacent *anti* O–C–C–O dihedral angles. Upon caesium complexation, *anti* dihedral angles were no longer sampled but the crown retained some conformational freedom which decreased with the presence of the nitrate counter-ion in front of the crown. These results were fully consistent with X-ray



* : compounds modelled before synthesis

Figure 9. Calix[4]arene *bis*(crown ether)s studied by molecular dynamics in the gas phase, and placed in regard of their structural complementarity towards Cs^+ [105].

diffraction results. It appeared later that **BC6N**, whose crown top is blocked, is the most rigid and preorganized calix[4]arene *bis*(crown-6) of the first series [70].

The simulations described above give rise to some questions. First of all, the lack of complementarity observed for sodium ion questions the representativeness of simulated structures without counter-ion and the possible hydration of sodium structures which is suspected to be of primary importance. Indeed, selectivity calculations performed in an explicit water phase show that the computed Cs^+/Na^+ selectivity is nearest to the experimental selectivity in methanol when the sodium cation is hydrated [106]. The later availability of the crystal structure of the hydrated sodium nitrate complex with **BC6** (compound **12**) confirmed the hypothesis that the sodium complexes should be hydrated. MD simulations were performed from this crystal structure and showed that the location of the water molecule in the complex is dependent on the presence of the nitrate counter-ion in the cation coordination sphere. Furthermore, the visualization of the sodium complexation during a MD run in water shows that this phenomenon is assisted by one of the water molecules belonging to the cation hydration sphere [67], as illustrated in Figure 10.

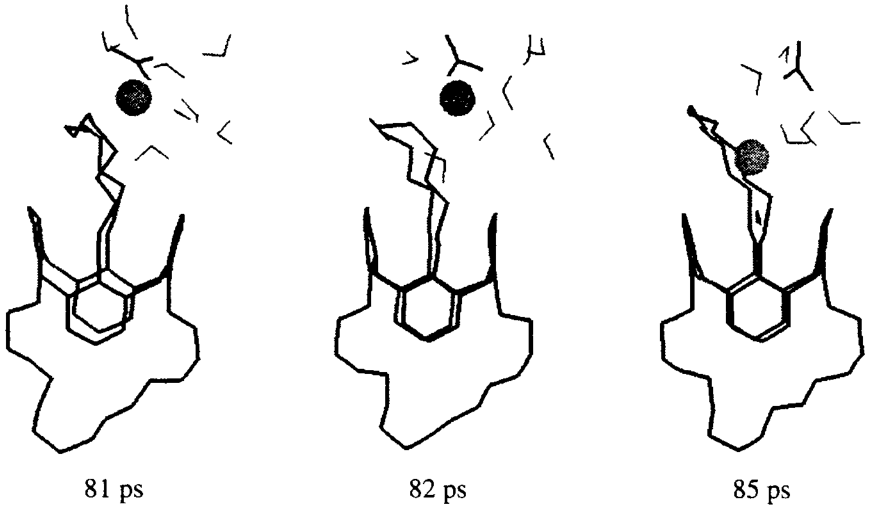
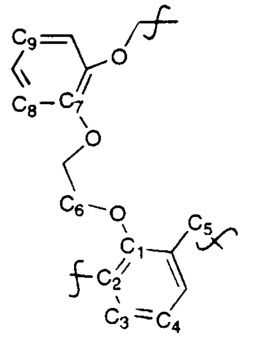


Figure 10. **BC6**:$NaNO_3$ simulated in water. Snapshots of the molecular dynamics run between 81 and 85 ps (hydrogen atoms not represented) [67].

The second question concerns the force field used, mainly the charge sets, because of the predominant electrostatic interactions between the cation and the ligands. The calculation of charge sets on such large molecules is not straightforward. In their simulations, Wipff *et al.* have chosen a known charge set for the crown part, already used for unsubstituted 18-crown-6, and tested four sets of charges for the calixarene cavity (Gasteiger's, *ab initio* ESP, MNDO/ESP and CHARMM force fields) calculated on the *p*-*tert*-butyl-*o*-methyl anisole [78, 98]. These charges are conformation-dependent and we preferred to calculate charge sets by taking into account the calixcrown geometry. MNDO-scaled charges were chosen, which avoid problems of overpolarity for buried atoms when fitting charges to the electrostatic potential [104]. Due to computational limitations, these calculations could not be managed on the whole calixarene in our first studies, and were performed on half the calix[4]arene *bis*(crown ether) [62, 64, 67, 106]. Later, the calculations of these charge sets on the whole molecule showed differences from the charges calculated for the calixarene cavity, which appeared to be less polarized than in the previous calculations [108] (Figure 11).

These differences on charge sets do not change significantly the conclusions drawn on the larger alkali cation complexes (Rb^+ and Cs^+), but could modify the representation of Na^+ and K^+ complexes, more sensitive to the force field used (differences in cation location or hydration in the complex). Taking advantage of the crystal structure of a potassium complex without counter-ion in the cation first coordination sphere, a test was carried out on a *mono*(crown) analogue of **BC6B2**, by comparing MNDO-scaled charges to MNDO/ESP-scaled charges [81]. In agreement with the conclusions of Wipff *et al.*, we found that the less polar-



MNDOx1.26 on the whole calixcrown		**MNDOx1.26 on half the calixcrown**	
C_1 : 0.150	O : -0.346	C_1 : 0.125	O : -0.350
C_2 : -0.119		C_2 : -0.125	
C_3 : -0.020	H_3 : 0.071	C_3 : -0.050	H_3 : 0.071
C_4 : -0.082	H_4 : 0.075	C_4 : -0.087	H_4 : 0.086
C_5 : 0.143	H_5 : 0.001	C_5 : 0.142	H_5 : 0.041
C_6 : 0.220	H_6 : 0.000	C_6 : 0.210	H_6 : 0.000
C_7 : 0.120		C_7 : 0.115	
C_8 : -0.100	H_8 : 0.087	C_8 : -0.103	H_8 : 0.091
C_9 : -0.074	H_9 : 0.080	C_9 : -0.048	H_9 : 0.085

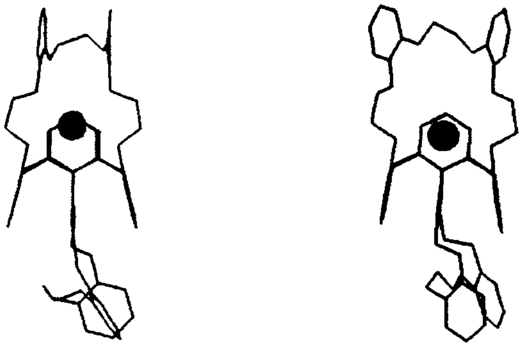
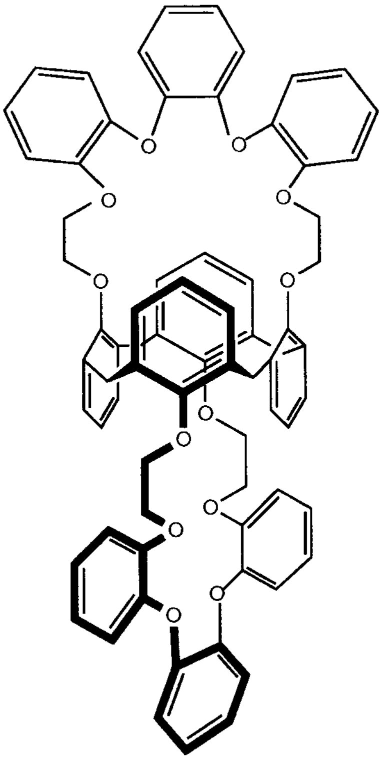


Figure 11. MNDO-scaled charges calculated on **BC6B2** and related sodium structures minimized *in vacuo* (hydrogen atoms not represented) [108].

ized set of charges for the calixarene cavity gave, by far, the best structural and energetic representation of the complexes, which validated our new protocol for charges calculation. A new set of simulations was then undertaken on the *bis*(crown ether) series, including a new compound, **BC6B3**, not yet experimentally evaluated (Scheme 3) [70]. As in the former calculations, observations on host/guest complementarity, and flexibility/rigidification of the crowns fitted well with the known behavior of these calix[4]arene *bis*(crown ether)s towards K^+, Rb^+ and Cs^+ cations. Free energy calculations in a gas phase, compared with ΔG_3 calculations in water, were also in agreement with the solvent extraction into dichloromethane and complexation in acetonitrile for known compounds and suggested a selectivity for Rb^+ for the new **BC6B3** calixarene not yet tested. Although host/guest complementarity shows that Cs^+ fits well into **BC6B3**, the result of free energy calculations compares well with the selectivity change recently observed in the 21-crown-7 series, in which monobenzo and dibenzo derivatives are selective for

Cs^+ but tribenzo-21-crown-7 is selective for Rb^+ in solvent extraction experiments [80].



Scheme 3. Schematic representation of **BC6B3**.

The quantitative evolution of Cs^+/Na^+ selectivity in the series, which experimentally corresponds, at least partially, to a decrease of sodium complexation, could only be explained by solvation considerations since the calculations on $NaNO_3$ complexes showed the same lack of complementarity between Na^+ and the series of calix[4]arene *bis*(crown-6) derivatives. Indeed, simulations in a water phase showed that substitution of the crown by the hydrophobic phenylene group increases the difficulty for the hydrated sodium cation to reach the complexation site [70].

Modelling of calix[4]arene *bis*(crown ether)s is then useful to test new compounds with respect to the needs of experimental investigations, and give insight into some of their properties before chemical synthesis. For example, we have recently checked that a calix[4]arene *bis*(crown-6) in the 1,3-*alternate* conformation, substituted by one nitro group on the upper rim should have complexation properties towards Cs^+ and Na^+ similar to those of **BC6**. This result is of importance in the field of nuclear liquid waste treatment, because this compound is suspected to be generated upon irradiation of the organic phase containing **BC6** contacted with nitric acid, and should be studied in the scope of a future industrial process for caesium recovery [109].

4. Prospects for Other Uses of Calixcrowns

The ligand families whose structural properties have been reviewed herein have been studied in our groups (and also in the Oak Ridge National Laboratories [48]) mainly for their ability to act as selective caesium extractants, a domain in which their potential use for caesium decontamination of liquid waste generated during nuclear fuel reprocessing has led to the deposition of some patents [110]. Furthermore, the possibility of coextracting technetium has recently been demonstrated [111]. Their interest, however, is far more general, as stated in the Introduction in the case of *mono*(crown ether) derivatives. Concerning classical complexing properties, those ligands can be shaped and chemically modified to accommodate other cations, for example transition metal ions of environmental importance. Among other developments worthy of note, one can notice the use of *bis*(crown ether) derivatives in the design of 'molecular machines' [44, 58, 112] or π-basic tubes able to form synthetic ionic channels across membranes. The interest of the latter lies in the investigation of potassium-selective channel proteins (in which a cation-π interaction involving four aromatic residues is proposed [113]) by biomimetic approaches. The *bis*(crown ether) derivatives of calix[4]arene could represent an alternative to one of the systems already described, which consists of tubular receptors made of two facing calix[4]arene bridged by four ethylene links [114]. As a first step towards this goal, the tunneling of cations such as K^+, Rb^+, Cs^+ and NH_4^+ through the π-basic cavity of **BC5**, even at room temperature, has been demonstrated by ^{1}H-NMR spectroscopy [115].

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