A Conformational Study of the Calixspherand and its Complexes with Alkali-metal Cations

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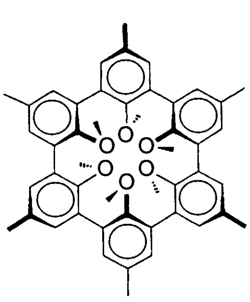
The calixspherand **2** forms kinetically very stable complexes with alkali-metal cations. This molecule is not completely preorganized for binding of a cation, as is evidenced from the results of NOESY spectroscopy and X-ray diffraction measurements. Both in $CDCl_3$ solution and in the solid state the free ligand adopts a cone conformation, whereas the Na^+ complex adopts a 'flattened' partial cone conformation. Molecular-mechanics calculations with different programs give rather biased results. Calculations with QUANTA (the all atom CHARMM-force field) correctly predict the conformation of the free ligand but not of the complexes, whereas with MACROMODEL (the united atom AMBER-force field) the experimentally observed conformation had the lowest energy only for the Na^+ complex. The calculated geometries of the experimentally found conformations of the free ligand and the Na^+ complex agree well with the X-ray structures, especially for the structures that were obtained with QUANTA. A comparison of the calculated structures of the Na^+, K^+ and Rb^+ complexes showed that larger cations force the terphenyl bridge to bend away, thereby opening up the cage of the ligand and making the cation more accessible to solvent molecules. This might explain the considerably lower kinetic and thermodynamic stability of the Rb^+ complex compared with those of the Na^+ and K^+ complexes.



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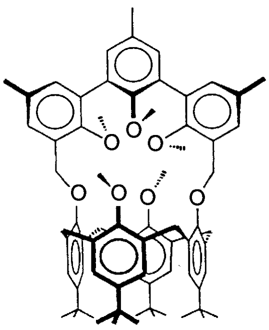

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Following the work of Cram *et al.* on the preorganized spherand molecule **1**,[1] which forms kinetically very stable complexes with Li^+ and Na^+, the synthesis of ligands that form kinetically stable complexes with larger cations, especially Rb^+, has been pursued in our laboratory. The combination of spherand and calix[4]arene chemistry has led to the synthesis of calixspherand **2**.[2] This compound indeed forms very stable complexes with Na^+ and K^+, which have half-life times of decomplexation extrapolated to room temperature of 3.7 and 2.2 years in $CDCl_3$ saturated with D_2O, but less so with Rb^+ (half-life of 2.8 h).[2b] The X-ray structure of the Na^+ complex of calixspherand **2** shows that the cation is completely shielded from the surroundings, so that not even the counter-ion, in this case the picrate ion, can have any direct interaction with the cation (see Fig. 1).[2a] Also remarkable is the conformation of the calix[4]arene moiety, which is between a cone and a partial cone and has been called a 'flattened' partial cone. From the similarity between the solution ($CDCl_3$) ^1H NMR spectra of both the Na^+ complex and the free ligand we have previously concluded that the free ligand exists in a comparable conformation, so that the calixspherand seems to be perfectly preorganized in the right conformation for binding a cation.[2a]

We have previously studied the conformations of calix[4]arenes by means of molecular mechanics calculations with the all atom AMBER-force field in MACROMODEL.[3] In these calculations the 'flattened' partial cone conformation was not once observed as an energy minimum. Kollman *et al.* have studied the complexation of spherand **1** with Li^+, Na^+ and K^+ by means of molecular-mechanics calculations with the united atom AMBER-force field.[4] Very recently, Miyamoto and Kollman have published a molecular dynamics study of the alkali-metal complexation by calixspherand **2**.[5] They were able to reproduce our experimentally found relative free energies of cation complexation and also calculated the absolute binding free energy of Rb^+. However, they considered only the conformation as found in the Na^+ complex and did not discuss the possibility of other conformations of the complexes and of the free ligand.

The objective of the work described in this paper was to investigate the conformational preferences of the calixspherand molecule both as a free ligand and in its complexes with Na^+, K^+ and Rb^+ by means of molecular-mechanics calculations. The results of these calculations are complemented with a detailed investigation of the conformations of the calixspherand and its complexes in $CDCl_3$ solution by two-dimensional ^1H NMR spectroscopy, and the determination of the X-ray structure of the free ligand.

Results

Molecular-mechanics Calculations.—The molecular mechanics calculations were performed with the programs MACROMODEL[6] (the united atom AMBER-force field)[7] and QUANTA[8] (the all atom CHARMM-force field).[9] In the calculations using QUANTA two different sets of atomic charges

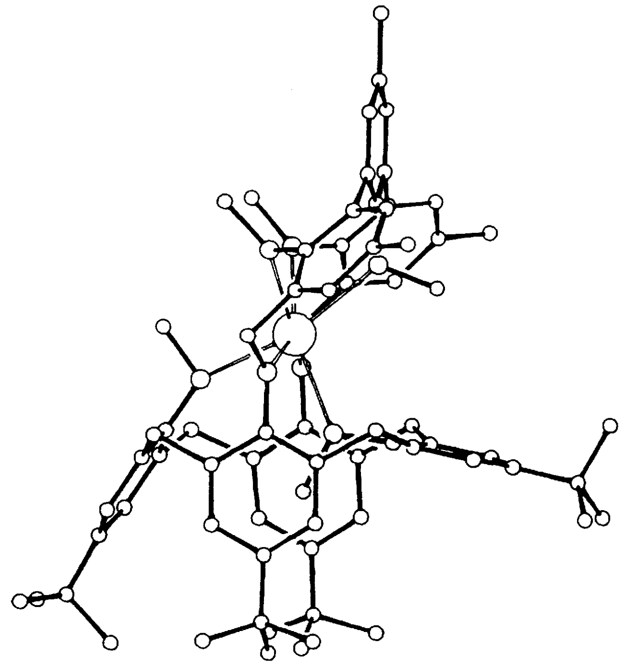

Fig. 1 X-Ray structure of the complex of calixspherand **2** with sodium picrate

Table 1 Calculated total energies of conformations of calixspherand **2**[a]

Conformation[b]	MACROMODEL/AMBER	QUANTA/CHARMM Gasteiger	QUANTA/CHARMM Charge templates
cone1	—[c]	—[c]	+16.6
cone2	—[c]	—[c]	+9.8
cone3	0	0	0
paco1	−10.8	+4.5	+3.7
paco2	−2.1	+0.2	+4.6
alt13	−10.8	+13.6	+11.7

[a] Energies are relative to those of *cone3* in kcal mol^{-1}. [b] See Fig. 2. [c] This conformation is not an energy minimum.

were used, which were calculated either with the Gasteiger method[10] or from template charges provided with the program. For the van der Waals parameters of the cations two different sets were used, those of Åqvist,[11] which are present in the CHARMM-force field in QUANTA, and the parameters published by Grootenhuis and Kollman.[12] In the calculations with MACROMODEL the cation parameters published by Wipff and Kollman were used.[13] The results for the free ligand **2** are summarized in Table 1 and for its Na$^+$, K$^+$ and Rb$^+$ complexes in Table 2. In Fig. 2 the structures of six important conformations are drawn. Because of the asymmetry of the bridge two partial cones can be distinguished, one in which the rotated anisole ring of the calix[4]arene moiety faces one (the inner) methoxy group of the bridge (*paco1*), and one in which the other anisole ring is rotated, which thus faces the two outer methoxy groups of the bridge (*paco2*). *cone1* and *cone2* are the respective 'flattened' partial cones. Other conformations are possible in which one or more of the methoxy groups of the bridge are rotated, but these are generally quite distorted. Some of these do have energies close to that of the starting conformation, but they were not further considered, as their methoxy groups are not well oriented for complexation of a cation.

The results of the calculations with MACROMODEL for the free ligand show that the partial cone (*paco1*, same anisole ring rotated as in the X-ray structure of the Na$^+$ complex) and the

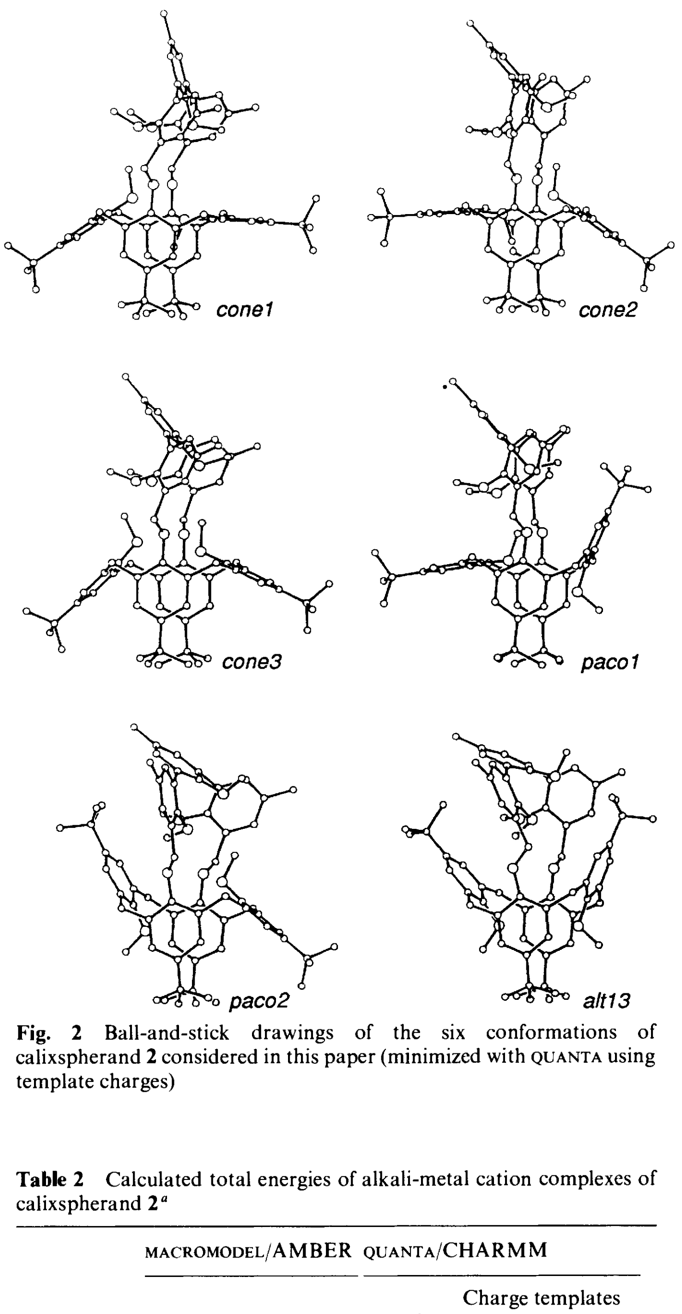

Fig. 2 Ball-and-stick drawings of the six conformations of calixspherand **2** considered in this paper (minimized with QUANTA using template charges)

Table 2 Calculated total energies of alkali-metal cation complexes of calixspherand **2**[a]

Complex[b]		MACROMODEL/AMBER	QUANTA/CHARMM		
				Charge templates	
		Wipff	Gasteiger Åqvist	Åqvist	Grootenhuis
2·Na$^+$	*cone1*	−1.8	+0.7	−2.1	−1.6
	cone2	−1.1	+0.8	−5.6	−7.1
	cone3	0	0	0	0
	paco1	—[c]	+1.0	−3.1	—[c]
	paco2	—[c]	+1.2	−5.0	—[c]
	alt13	+7.3	+1.2	−6.3	+1.4
2·K$^+$	*cone1*	−1.0	—[c]	−3.8	−2.0
	cone2	−3.9	—[c]	−6.2	−5.5
	cone3	0	0	0	0
	paco1	—[c]	−2.7	−7.5	−2.5
	paco2	—[c]	−1.6	−6.2	−4.8
	alt13	+3.4	−4.2	−10.3	−5.8
2·Rb$^+$	*cone1*	−1.5	—[c]	—[c]	−3.1
	cone2	−4.4	—[c]	−6.6	−6.0
	cone3	0	0	0	0
	paco1	—[c]	−4.2	−10.2	−6.0
	paco2	—[c]	−2.7	−6.9	−5.8
	alt13	+1.9	−6.0	−11.6	−9.2

[a] Energies relative to those of *cone3* in kcal mol^{-1}. [b] See Fig. 2. [c] This conformation is not an energy minimum.

Table 3 Assignments of the ^1H NMR spectra of calixspherand **2** and its complexes with Na^+ and K^+ ($CDCl_3$, room temperature)[a,b]

	2	**2**·Na^+	**2**·K^+		**2**	**2**·Na^+	**2**·K^+
ArH, A (s, 2 H)	6.91	6.76	6.75	$OCH_{2.1}$ (d, 2 H)	5.49	5.99	5.80
ArH, B_1 (d, 2 H)	6.54	6.90	6.97	$OCH_{2.2}$ (d, 2 H)	4.16	4.14	4.14
ArH, B_2 (d, 2 H)	6.71	7.17	7.24	OCH_3, A (s, 3 H)	2.94	−0.05	0.07
ArH, C (s, 2 H)	7.20	7.33	7.37	OCH_3, C (s, 3 H)	3.82	4.29	4.04
ArH, D_1 (d, 2 H)	7.02	7.01	7.06	OCH_3, D (s, 6 H)	3.48	3.69	3.57
ArH, D_2 (d, 2 H)	7.05	7.20	7.20	OCH_3, E (s, 3 H)	1.06	1.50	1.53
ArH, E (s, 2 H)	7.29	7.33	7.35	CH_3, D (s, 6 H)	2.32	2.40	2.38
CH_2, AB_{ax} (d, 2 H)	4.11	3.63	3.71	CH_3, E (s, 3 H)	2.46	2.49	2.50
CH_2, AB_{eq} (d, 2 H)	3.12	3.13	3.35	$C(CH_3)_3$, A (s, 9 H)	1.23	1.10	1.08
CH_2, BC_{ax} (d, 2 H)	4.60	4.62	4.53	$C(CH_3)_3$, B (s, 18 H)	0.87	1.04	1.07
CH_2, BC_{eq} (d, 2 H)	3.29	3.66	3.67	$C(CH_3)_3$, C (s, 9 H)	1.36	1.31	1.32

[a] For numbering scheme, see Fig. 3. [b] Resonances are given in ppm relative to Me_4Si.

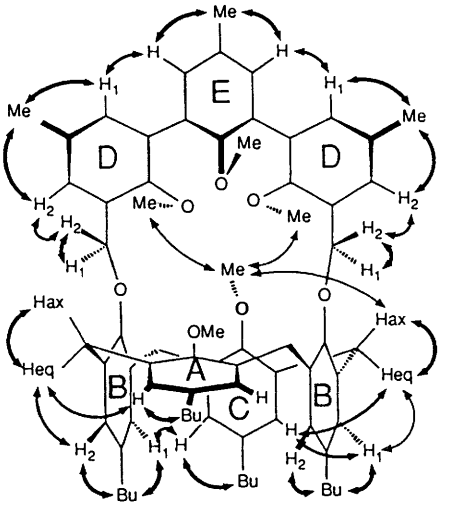

Fig. 3 Observed NOE interactions in the Na^+ and K^+ complexes of **2**. The thickness of the arrows is a measure for the magnitude of the NOE effect. Symmetry-related NOE effects are not always indicated.

1,3-alternate have comparable energies. This seems to indicate that the ligand is preorganized for cation binding (barring other conformations of the terphenyl bridge). In all complexes with a partial cone (*paco1* or *paco2*) the conformation changed to a 'flattened' partial cone (*cone1* or *cone2*) after minimization. For the Na^+ complex the conformation as found in the X-ray structure (*cone1*) has the lowest energy. It is very intriguing that for the complexes with the larger cations K^+ and Rb^+ the other 'flattened' partial cone (*cone2*) has a lower energy than *cone1*.

The calculations with QUANTA give completely different results. For the free ligand the cone (*cone3*) is found as the lowest energy conformation, before both partial cones, independent of the charges on the atoms. For the complexes, the 1,3-alternate conformation, in most cases, has the lowest energy. The conformation as found in the X-ray structure of the Na^+ complex (*cone1*) is a very unfavourable conformation both for the free ligand and for the complex. In a few calculations the starting conformation of the complexes changed from *cone1* to *paco1* or from *cone2* to *paco2* (in the complexes with the larger cations K^+ and Rb^+), or from *paco1* to *cone1* or from *paco2* to *cone2* in the complexes with Na^+.

Two-dimensional ^1H *NMR Spectroscopy.*—In order to obtain further information on the conformations of the calixspherand and its complexes, we examined their solution structures by two-dimensional ^1H NMR spectroscopic methods. A COSY and a NOESY spectrum were recorded of the free ligand and of the complexes with Na^+ (bromide salt) and K^+ (picrate salt) in $CDCl_3$. These spectra made it possible to assign for the first time the complete ^1H NMR spectra of these compounds. The assignments are summarized in Table 3, using the numbering scheme as shown in Fig. 3. The observed NOE peaks for the Na^+ and K^+ complexes are also indicated in Fig. 3.

The assignments of the signals in the spectra of all three compounds are fairly straightforward if one starts from the *tert*-butyl signals of rings B and the methyl signals of rings D (these signals are unique because they have a double intensity). From the weak NOE signals between OCH_3,C and OCH_3,D and CH_2, BC_{ax} it is clear that the anisole ring of the calix[4]arene moiety that faces two methoxy groups of the bridge is not rotated, both in the free ligand and in the complexes. For the free ligand the presence of an additional weak NOE signal between the signals of OCH_3,A and CH_2,AB_{ax} seems to indicate that this molecule adopts the cone conformation. There is no NOE signal observable between OCH_3,A and OCH_3,D. However, if the solution structure looks like *cone3* in Fig. 2, in which OCH_3,A points to the oxygen atom of OCH_3,E, then it seems very unlikely that this NOE signal would be present. There is no direct evidence for the orientation of ring A in the complexes. However, because the spectra of the complexes are very similar but differ considerably from the spectrum of the free ligand, even in parts remote from the complexed cations, it is reasonable to assume that they exist in a different conformation, so that ring A of the calix moiety must be rotated. It seems natural to assume the same conformation as in the X-ray structure, the complexed cation not permitting any great mobility of the ligand.

The fact that the free ligand exists in the cone conformation, which is different from the conformation in the Na^+ complex, implies that the free ligand is flexible, insofar as the anisole rings of the calix[4]arene moiety can rotate. That this is indeed the case is confirmed by the NOESY spectrum of the free ligand, as this shows, in addition to the (negative) cross-peaks indicating NOE interactions, some positive cross-peaks, which indicate that chemical exchange takes place. It is unfortunately not possible to assign the corresponding diagonal peaks to other conformations, for the signals of the other conformation(s) are very weak and constitute 5% or less of the mixture.

X-Ray Structure of Compound [$^2H_6$]-**2**.—In our study of the complexation and decomplexation rates of alkali-metal cations by calixspherand **2**, we made use of a hexadeuteriated compound [$^2H_6$]-**2**, in which the two methoxy groups of the calix[4]arene moiety are replaced by trideuteriomethoxy groups.[2b] Crystallization from methanol by slow evaporation of the solvent afforded small crystals that were suitable for the determination of the structure by X-ray diffraction. As can be seen from Fig. 4 the calixspherand adopts a cone conformation comparable to *cone3* in Fig. 2. The orientation of the methoxy

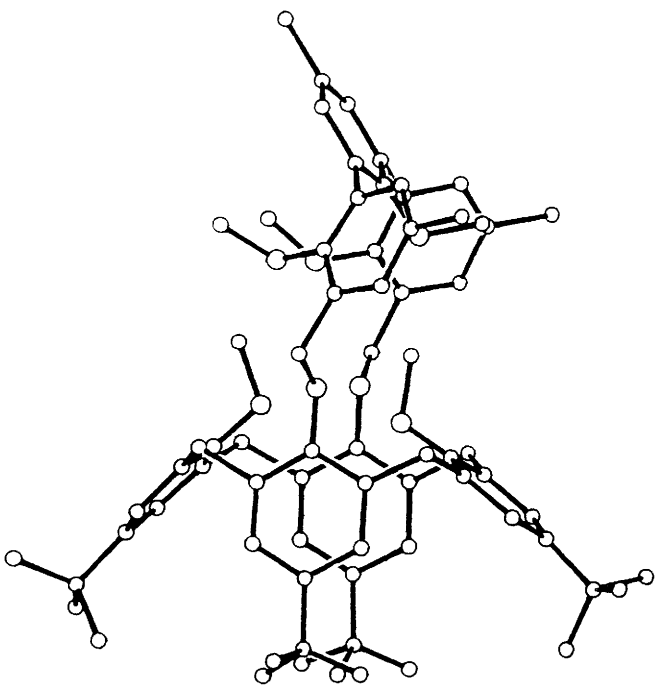

Fig. 4 X-Ray structure of calixspherand **2**

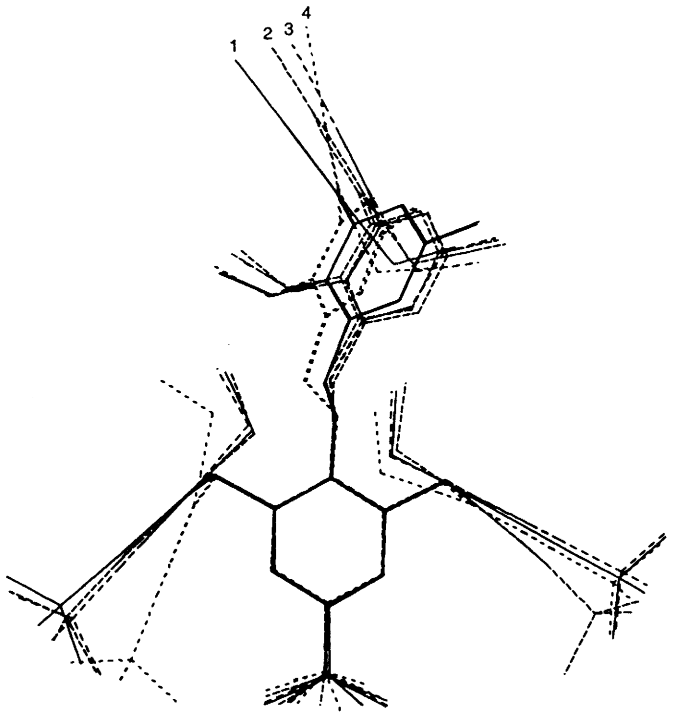

Fig. 5 Calculated structures of the free ligand (*cone3*) in comparison with the X-ray structure. 1, QUANTA (template charges); 2, X-ray structure; 3, QUANTA (Gasteiger charges); 4, MACROMODEL.

groups of the terphenyl bridge is the same as in the Na^+ complex, so that apparently the rotation of these methoxy groups is hindered. Another interesting feature is that the methoxy group (OCH_3,A) of the calix[4]arene moiety at the side of the two outer methoxy groups (OCH_3,D) of the terphenyl bridge, does indeed point towards the oxygen atom of the middle methoxy group (OCH_3,E), as was mentioned in the discussion of the NOESY spectrum of the free ligand in solution.

Discussion

From the experimental data it can be concluded that the calixspherand is not as preorganized for complexation of alkali-metal cations as was originally thought.[2b] The conformation of the calix[4]arene moiety changes from the cone conformation (*cone3*) in the free ligand to a 'flattened' partial cone conformation (*cone1*) in the Na^+ complex, as evidenced by the structures in the solid state and in solution. The X-ray structures further indicate that the terphenyl bridge in the free ligand is already in the conformation suitable for complexation, so that this part of the molecule is preorganized for binding of a cation.

The results of the molecular-mechanics calculations and the experimental results (NOESY, X-ray) do not agree very well. The calculations with MACROMODEL give reasonable results for the complexes but not so for the free ligand, whereas QUANTA gives the lowest energy to the correct conformation of the uncomplexed calixspherand, but not for its cation complexes. Obviously, these calculations can only be expected to give an approximation of the situation in reality, as no provision was made for effects of the solvent or of the crystal environment. However, one would have expected some consistency between the results of different programs. Part of the problems may be caused by the fact that the cation parameters were not optimized together with the other force-field parameters. On the other hand one could expect that parameters would by now have become transferable between the different programs. The results once again illustrate that great care must be taken in choosing the force field when performing molecular-mechanics calculations.

The calculated geometries of the free ligand show relatively small differences with the coordinates of the X-ray structure (see Fig. 5). The root-mean-square average deviations from the X-ray structure are only 0.24 and 0.25 Å for the two QUANTA structures (calculated for 67 heavy atoms, not including the methyl groups of the *tert*-butyl groups). However, the MACROMODEL structure deviates considerably, 0.67 Å. For the Na^+ complex the deviations range from 0.15 to 0.33 Å (also for 67 heavy atoms), the best being the QUANTA structure calculated with template charges and Grootenhuis' cation parameters (Fig. 6).

A number of conclusions might therefore be drawn from the differences between the calculated geometries of the complexes with Na^+, K^+ and Rb^+ (see Fig. 7). It has already been concluded from the changes in the chemical shift of the methoxy group in the cavity (OCH_3,A:δ is -0.05, 0.07 and 0.20 for the complexes with Na^+, K^+ and Rb^+, respectively) that this methoxy group is forced to move out of the cavity by the larger cations.[2b] This is confirmed by the calculations, although it is only a small effect. The larger cations also force the terphenyl bridge to bend away, thereby opening up the complex on one side. A conformational change of the bridge is also apparent from the chemical shift of its central methoxy group (OCH_3,E:δ is 1.50, 1.53 and 1.72 for the complexes with Na^+, K^+ and Rb^+, respectively).[2b] This might explain the considerably reduced (kinetic) stability of the Rb^+ complex, in comparison with the Na^+ and K^+ complexes. The opening of the complex makes the cation more easily accessible to solvent molecules, which are then able to assist in the decomplexation process, whereas this is not possible in the Na^+ and K^+ complexes. This opening effect was observed with all four force fields used in the calculations.

Conclusions

Two-dimensional ^1H NMR experiments (NOESY) have proved that the calixspherand exists in $CDCl_3$ solution in the

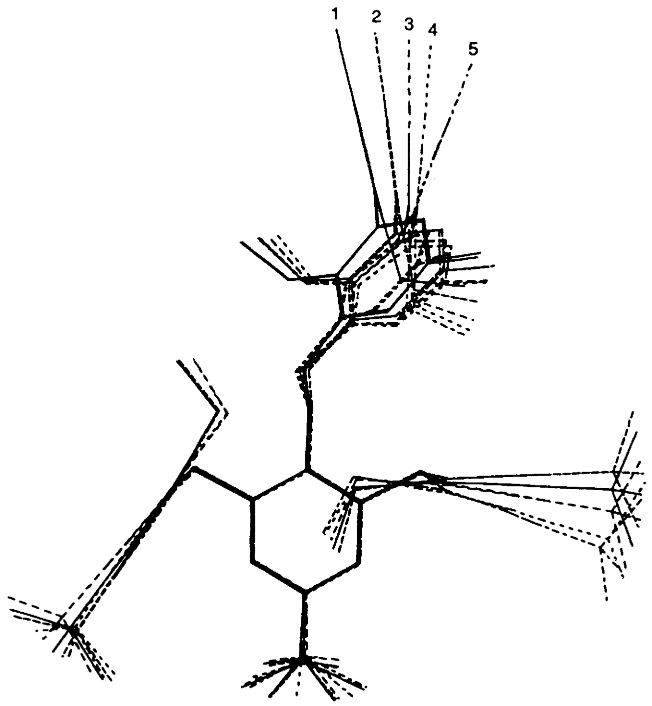

Fig. 6 Comparison of the calculated Na$^+$ complexes of **2** (*cone1*) with the X-ray structure. 1, QUANTA (template charges, Åqvist); 2, QUANTA (Gasteiger charges, Åqvist); 3, QUANTA (template charges, Grootenhuis); 4, X-ray structure; 5, MACROMODEL.

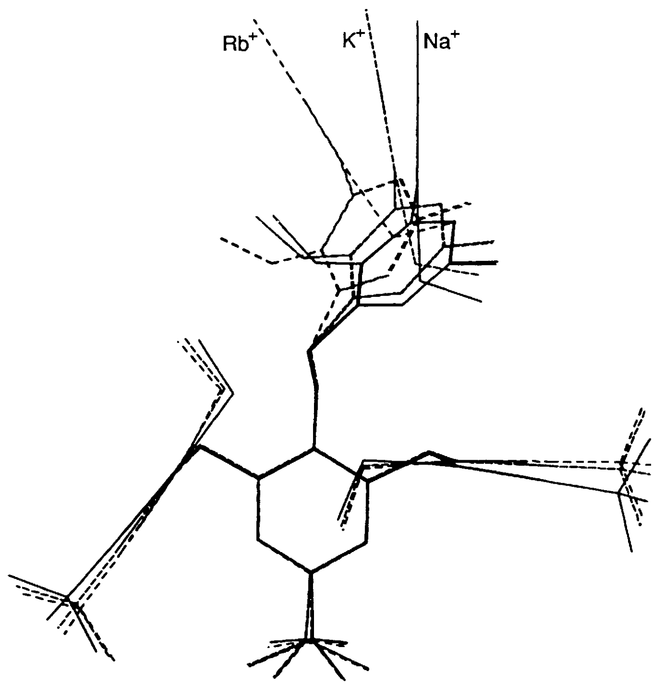

Fig. 7 Comparison of the calculated structures of Na$^+$, K$^+$ and Rb$^+$ complexes of **2** (*cone1*, calculated with QUANTA, template charges and Grootenhuis' cation parameters).

same cone conformation as in the solid state. The Na$^+$ and K$^+$ complexes exist in solution in the same conformation, which is most likely the 'flattened' partial cone, as in the X-ray structure of the Na$^+$ complex. Thus, the calixspherand is not completely preorganized for complexation of alkali-metal cations, and can still change its conformation in solution.

Molecular-mechanics calculations on the calixspherand and its complexes with alkali-metal cations gave completely opposite results with the two programs used. The neglect of the environment in the calculations and the possible non-compatibility of the cation parameters with the other force-field parameters do not fully explain why the two programs perform so differently.

The calculated geometries of the Na$^+$, K$^+$ and Rb$^+$ complexes show that the cation in the Rb$^+$ complex is the more accessible to the solvent than in the Na$^+$ and K$^+$ complexes. This might explain the decreased (kinetic) stability of the Rb$^+$ complex relative to those of the Na$^+$ and K$^+$ complexes.

Experimental

Molecular-mechanics Calculations.—The calculations with the united atom AMBER force field[7] were performed with version 1.5 of MACROMODEL[6] on a VAX 8650 computer. This force field differs from the original AMBER force field[7] in that generalized parameters have been added to allow modelling on many types of molecule, beside the peptides and DNA molecules for which the force field was developed. The force field was used without modification of any of the parameters. This means that electrostatic energies were calculated with point charges derived from bond dipole moments given in the standard AMBER parameter list of MACROMODEL.[6] The partial charges on the atoms of the ligand were doubled in the complexes to imitate the polarization effect of the cations, following earlier calculations with AMBER (united atom force field) on alkali-metal cation complexes of 18-crown-6[14] and cryptand [222].[13] For the cations a charge of +1 was assumed and their van der Waals parameters were taken from the study of the alkali-metal cation complexes of cryptand [222].[13] A relative permittivity $\varepsilon = 1.0$ was used. The 1–4 van der Waals and 1–4 electrostatic energies were scaled down by a factor of two. The cut-off distances for the van der Waals and electrostatic interactions were set to a value of 100 Å to allow all interactions to be taken into account. The charges on the atoms are depicted in the Appendix and a list of all used parameters is given.

Starting geometries were drawn manually in the ORGANIC INPUT mode of the program. From the cone the other conformations were easily derived by adjustment of the dihedral angles around the bonds of the aromatic rings to the methylene carbon atoms. The structures were optimized by minimization of the energy until the root-mean-square of the gradient had reached a value of 0.01 kcal mol^{-1} Å^{-1}.

The QUANTA calculations were carried out with version 3.2 of this program[8] on a Personal Iris of Silicon Graphics. Starting geometries were obtained from the X-ray structure of the Na$^+$ complex of **2** and subsequent adjustment of the relevant dihedral angles. All atoms were taken into account. The calculations were carried out with the standard parameter set of QUANTA 3.2. Charges on the atoms were calculated both from charge templates and by the Gasteiger method.[10] In cases where charge templates were used, the resulting net charge was smoothed over all atoms (excluding the cation) to obtain a total charge of zero on the molecule. For the cations either the parameters available in QUANTA (which were taken from Åqvist)[11] or the parameters used in the AMBER calculations (all atom force field) on the complexes of two dibenzocrown ethers were used.[12] A list of all parameters is given in the Appendix. The energy calculations were performed with the standard cut-off values of 15 Å (with switch functions between 11 and 14 Å), and a relative permittivity $\varepsilon = 1.0$. Every structure was optimized with the adopted-basis Newton–Raphson method to a value of the root-mean-square of the gradient of 0.1 kcal mol^{-1} Å^{-1} and subsequently with Newton–Raphson to 0.001 kcal mol^{-1} Å^{-1}.

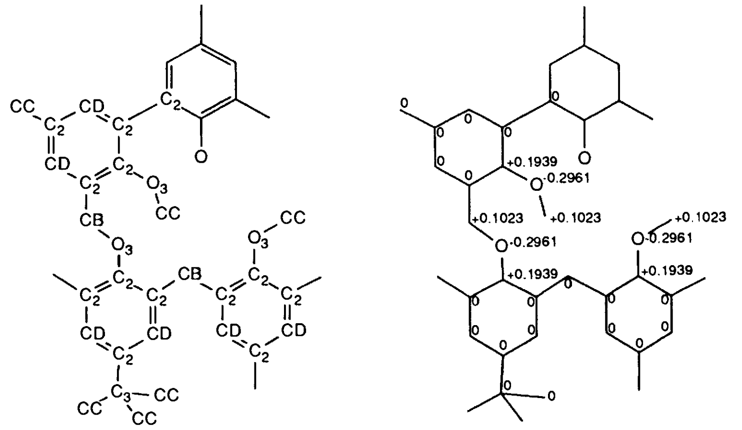

Fig. A.1 Atom types and charges used in the calculations with MACROMODEL (the united atom AMBER-force field)

Table A.1 AMBER-force field parameters in MACROMODEL 1.5

	$E_{\min}$[a]	$r_{\min}$[a]
Atom type	kcal mol^{-1}	Å
C2	−0.12	1.85
CD	−0.12	1.85
C3	−0.06	1.80
CB	−0.12	1.925
CC	−0.15	2.00
O3	−0.15	1.65
NA[b]	−0.05	1.6
K[b]	−0.08	2.0
RB[b]	−0.095	2.2

	k_l	r_0
Bond	kcal mol^{-1} Å^{-2}	Å
C2–C2	325	1.495
C2=C2	469	1.40
C2=CD	469	1.40
C2–C3	317	1.522
C2–CB	317	1.522
C2–CC	317	1.522
C2–O3	450	1.364
C3–CC	310	1.526
CB–O3	386	1.425
CC–O3	386	1.425

	k_θ	θ_0
Bond angle	kcal mol^{-1} deg^{-2}	deg
C2–C2–C2	85	120
C2–C2–CD	85	120
C2–C2–CB	70	120
C2–C2–O3	70	120
CD–C2–CD	85	120
CD–C2–C3	70	120
CD–C2–CB	70	120
CD–C2–CC	70	120
C2–CD–C2	85	120
C2–C3–CC	63	114
CC–C3–CC	63	112.4
C2–CB–C2	63	112.4
C2–CB–O3	63	112.4
C2–O3–CB	100	112
C2–O3–CC	100	112

	$k_n/2$		δ
Dihedral angle	kcal mol^{-1}	n	deg
X–C2–C2–X	0.8	2	0
X–C2=C2–X	1.325	2	0
X–C2=CD–X	1.325	2	0
X–C2–C3–X	0	0	0
X–C2–CB–X	0	0	0
X–C2–O3–X	0.9	2	0
X–CB–O3–X	1.45	3	0

	k_Γ		
Improper dihedral angle	kcal mol^{-1}	n	δ
C2–X–X–X	10.5	2	0

[a] $E_{\min}$ and $r_{\min}$ are related to the van der Waals parameters A and B as follows: $A = -E_{\min}\cdot(r_{\min})^{12}$, $B = -2E_{\min}\cdot(r_{\min})^6$. [b] Cation parameters according to Wipff and Kollman (ref. 12).

Two-dimensional ^{1}H *NMR Experiments.*—The calixspherand **2** and its complexes with NaBr and potassium picrate were synthesized as described in the literature.[2b]

The spectra of the free ligand and its Na$^+$ complex were recorded on a Bruker AM-400, and of the K$^+$ complex on a Bruker AM-600 spectrometer. The proton COSY spectra were recorded with the standard COSYPHDQ pulse sequence and the proton NOESY spectra with the NOESYPH pulse sequence, both of which are supplied with the Bruker software, with time-proportional-phase-incrementation (TPPI) to obtain pure phase lineshapes. A mixing time of 1 s was used in all NOESYPH experiments. In a typical experiment 512 t_1 increments were taken, and each FID of 1024 data points was the accumulation of 16 scans. The acquisition of each FID was preceded by four dummy scans to establish steady state. A $\pi/2$ shifted sine-bell window function was applied to the F_1 and F_2 domains. After zero-filling in the F_1 dimension the final data matrix size was 1024 × 1024 of real data points with digital resolution of 4.8 Hz (sweep width 5000 Hz on AM-400) or 6.9 Hz (sweep width of 7042 Hz on AM-600).

X-Ray Structure Determination.—The details of the data collection and the solving of the X-ray structure of compound **2**, together with tables of atomic positional and thermal

Table A.2 CHARMM-force field parameters in QUANTA 3.2

Atom type	E_{min}[a] kcal mol^{-1}	r_{min}[a] Å
CT	−0.0903	1.80
C6R	−0.05	2.04
C6RP	−0.05	2.04
HA	−0.042	1.33
OE	−0.1591	1.60
MNA[b]	−0.026	2.048
MK[b]	−0.009 05	2.493
MRB[b]	−0.006 53	2.661
MNA[c]	−0.01	1.60
MK[c]	−0.03	2.00
MRB[c]	−0.035	2.20

Bond	k_l kcal mol^{-1} Å^{-2}	r_0 Å
CT–CT	268	1.529
CT–C6R	345	1.50
CT–HA	340	1.09
CT–OE	380	1.407
C6R–C6R	440	1.387
C6R–C6RP	450	1.387
C6R–HA	370	1.08
C6R–OE	330	1.38
C6RP–C6RP	360	1.485

Bond angle	k_θ kcal mol^{-1} deg^{-2}	θ_0 deg
CT–CT–CT	58.35	112.7
CT–CT–C6R	70	111.6
CT–CT–HA	37.5	110.7
C6R–CT–C6R	70	109.47
C6R–CT–HA	40	109.47
C6R–CT–OE	80	109.47
HA–CT–HA	33	107.8
HA–CT–OE	55.5	109.47
CT–C6R–C6R	70	120
C6R–C6R–C6R	70	120
C6R–C6R–C6RP	70	120
C6R–C6R–HA	31	120
C6R–C6R–OE	65	120
C6RP–C6R–C6RP	70	120
C6RP–C6R–HA	31	120
C6RP–C6R–OE	60	120
C6R–C6RP–C6R	70	120
C6R–C6RP–C6RP	70	120
CT–OE–C6R	61	108

Dihedral angle	$k_n/2$ kcal mol^{-1}	n	δ deg
X–CT–CT–X	0.15	3	0
X–CT–C6R–X	0.01	6	0
X–CT–OE–X	0.36	3	0
X–C6R–C6R–X	3.1	2	180
X–C6R–C6RP–X	3.1	2	180
X–C6R–OE–X	1.4	2	180
X–C6RP–C6RP–X	0.8	2	180

Improper dihedral angle	k_Γ kcal mol^{-1} deg^{-2}	Γ deg
C6R–X–X–CT	130	0
C6R–X–X–C6R	30	0
C6R–X–X–C6RP	140	0
C6R–X–X–HA	75	0
C6R–X–X–OE	150	0
C6RP–X–X–C6RP	130	0

[a] E_{min} and r_{min} are related to the van der Waals parameters A and B as follows: $A = -E_{min}\cdot(r_{min})^6$, $B = -2E_{min}\cdot(r_{min})^6$. [b] Cation parameters according to Åqvist (ref. 10). [c] Cation parameters according to Grootenhuis (ref. 11).

parameters, bond distances, and bond angles have been deposited at the Cambridge Crystallographic Data Centre.*

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* For details of the CCDC deposition scheme see 'Instructions for Authors (1992),' *J. Chem. Soc., Perkin Trans. 2*, 1992, issue 1.

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Appendix

AMBER Parameters in MACROMODEL 1.5.—The AMBER-force field in version 1.5 of MACROMODEL has the following form:

$$E_{\text{total}} = \sum_{l} k_l(l - l_0)^2 + \sum_{\theta} k_\theta(\theta - \theta_0)^2 + \sum_{\omega} \tfrac{1}{2}k_n[1 + \cos(n\omega - \delta)] +$$

$$\sum_{\Gamma} \tfrac{1}{2}k_\Gamma[1 + \cos(n\Gamma - \delta)] + \sum_{i<j} \{A_{ij}/r_{ij}^{12} - B_{ij}/r_{ij}^{6} + e_ie_j/4\pi\varepsilon r_{ij}\} +$$

$$\sum_{\text{H-bonds}} \{C_{ij}/r_{ij}^{12} - D_{ij}/r_{ij}^{10}\}$$

where:

l_0 and θ_0 are the reference bond lengths and bond angles
l, θ, and ω are the actual bond lengths, bond angles and torsion angles
Γ is an improper torsion angle
n is the periodicity and δ is the phase angle of the torsional barrier
k_l and k_θ are the force constants for bond stretching and angle bending
k_n is the barrier to free rotation
k_Γ is the barrier to out-of-plane deformation of atoms in planar groups
r_{ij} is the distance between two non-bonded atoms that are three or more bonds apart
A_{ij} and B_{ij} are the van der Waals parameters for each pair of atoms
e_i and e_j are the partial charges on atoms i and j
C_{ij} and D_{ij} are the H-bond parameters for each hydrogen-bonded pair of atoms.

The atom types and the charges on the atoms that were used are depicted in Fig. A.1. All the parameters used are listed in Table A.1.

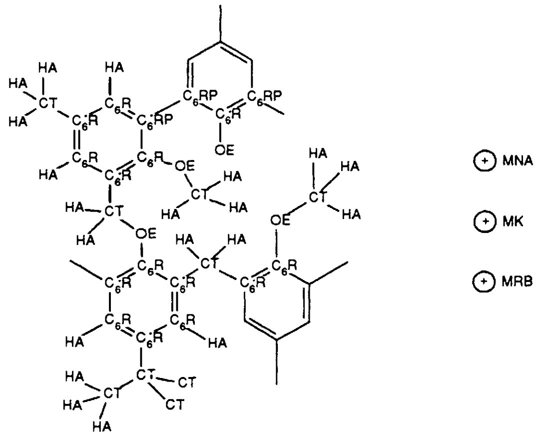


Fig. A.2 Atom types used in the CHARMM calculations with QUANTA

CHARMM Parameters in QUANTA 3.2.—The CHARMM-force field in QUANTA has the following form:

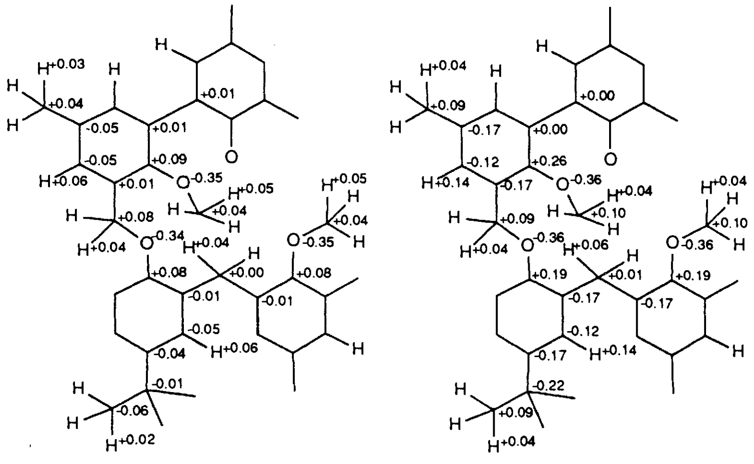
$$E_{\text{total}} = \sum_{l} k_l(l - l_0)^2 + \sum_{\theta} k_\theta(\theta - \theta_0)^2 + \sum_{\omega} k_n[1 + \cos(n\omega - \delta)] +$$

$$\sum_{\Gamma} k_\Gamma(\Gamma - \pi)^2 + \sum_{i<j} \{A_{ij}/r_{ij}^{12} - B_{ij}/r_{ij}^{6} + e_ie_j/4\pi\varepsilon r_{ij}\}$$

where:

l_0 and θ_0 are the reference bond lengths and bond angles
l, θ, and ω are the actual bond lengths, bond angles and torsion angles
Γ is an improper torsion angle
n is the periodicity and δ is the phase angle of the torsional barrier
k_l and k_θ are the force constants of bond stretching and angle bending
k_n is the barrier to free rotation
k_Γ is the barrier to out-of-plane deformation of atoms in planar groups
r_{ij} is the distance between two non-bonded atoms that are three or more bonds apart
A_{ij} and B_{ij} are the van der Waals parameters for each pair of atoms
e_i and e_j are the partial charges on atoms i and j.

The atom types that were used are depicted in Fig. A.2, and the charges on the atoms in Fig. A.3. All parameters used are listed in Table A.2.



(*a*) (*b*)

Fig. A.3 Atom charges calculated (*a*) according to the Gasteiger method (ref. 9) and (*b*) from template charges