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Alkali Metal Cation Binding of Tetraethyl Resorcarene: An *Ab Initio* and Mass Spectrometry Study

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The complex formation between alkali metal cations (Li^+, Na^+, K^+, Rb^+, Cs^+) and the most stable conformation of tetraethyl resorcarene, the C_4 crown, was studied by *ab initio* methods. The conformational change of the host resorcarene, the most favourable binding locations and the relative binding energies of the cations are reported. In addition, mass spectrometric H/D exchange reactions were carried out; the divergent results obtained for the lithium complex are well explained by the results obtained in the *ab initio* calculations.

Keywords: Supramolecular complexes; Resorcarenes; H/D exchange; ESI mass spectrometry

INTRODUCTION

The one-pot synthesizable resorcarenes are a relatively new class of artificial host compounds [1–2], that have found use as hosts for quaternary methylammonium compounds [3], especially acetylcholine [4–7], for alcohols and diols [8–12], and alkali metal cations [13,14]. The C_4 crown conformation, with its circular homodirectional array of intramolecular hydrogen bonds between the OH-groups, is the most stable conformational form [15]. This arrangement provides a total of four H-bonds, one for each pair of OH-groups. The bonds appear to be 'flip-flop' in nature, with the directions of the H-bonds continually changing. The tetraethyl resorcarene[†] under investigation is depicted in Fig. 1.

In this figure the directions of the H-bonds are marked with arrows. The crown conformation of resorcarene provides a π-basic cavity for cationic guests to dock in and form a supramolecular complex with the host. The upper rim of the cavity is formed by the OH-groups and the resorcinol hydrogens pointing 'up', while the lower rim is at the level of the resorcinol hydrogens pointing 'down'. The cavity is approximately coniform in shape, tapering towards the lower rim. In this study the formation of supramolecular complexes between tetraethyl resorcarene and five alkali metal cations (Li^+, Na^+, K^+, Rb^+, Cs^+) was investigated by *ab initio* methods. The reason for choosing this particular resorcarene was its use in our earlier mass spectrometry and molecular modelling studies. In addition, mass spectrometric gas-phase H/D exchange experiments were carried out for all the alkali metal cation complexes. The mass spectrometric experiments and theoretical calculations both refer to species in the gas phase.

RESULTS AND DISCUSSION

Ab Initio Calculations

The results from the calculations include: (a) the conformational change of the host resorcarene, (b) the most favourable docking location for each alkali metal cation, and (c) the relative energies of the binding interactions of the cations. The complexation of the alkali cations affected the structure of the resorcarene host: conformational change was observed with all alkali cations. The most stable and highly symmetrical C_4 crown, with a homodirectional intramolecular H-bonding system, adopted a boat-like C_2 pinched-crown structure

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[†] IUPAC name: 2,8,14,20-tetraethyl-5,11,17,23-tetramethylpentacyclo-[19.3.1.$1^{13,7}$.$1^{9,13}$.$1^{15,9}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol.

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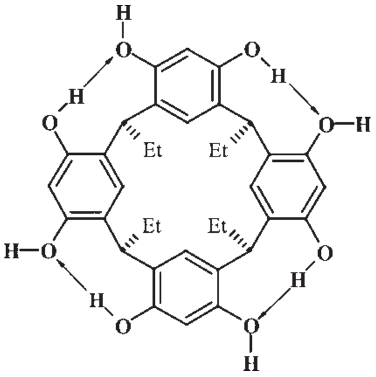

FIGURE 1 Tetraethyl resorcarene with homodirectional array of intramolecular H-bonds.

when the alkali cation was present in the cavity. The affect of the alkali cation is as follows: the cation interferes with the vulnerable electrostatic system of the resorcarene host leading to conformational change and, simultaneously, the formation of the host–guest complex. Two of the facing resorcinols of the C_4 crown approach the cationic guest causing the cavity to become elliptical. The degree to which the resorcinols, or 'broadsides', approach depends on the volume of the guest cation (Li$^+$ is an exception). The approach of the broadsides simultaneously creates 'stern' and 'bow' resorcinols, giving rise to the C_2 pinched crown. The dimensions of the complexes are reported in Table I.

The volume of the resorcarene cavity is mainly determined by the van der Waals radii of the resorcinol carbons. Because of the negative charge of the cavity, the alkali cations would be expected to be located as deep in the cavity as possible. According to the calculations, the energetically most favourable position of all cations except Li$^+$ was deep inside the cavity, as predicted. The energetically most favourable position of Li$^+$ was towards one pair of OH-groups in the upper rim of the cavity, as shown in Fig. 2a. This is in accordance with the molecular modelling (MMFF94) results reported by Letzel *et al.*, [16] who proposed that the most favourable binding site for small alkali cations (Li$^+$ and Na$^+$) is close to the resorcinol/pyrogallol OH-groups at the upper rim.

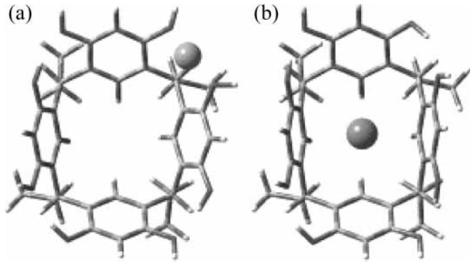

FIGURE 2 Optimized (a) Li$^+$ complex and (b) Na$^+$ complex of tetraethyl resorcarene.

As expected, the vertical location of the cationic guests inside the cavity was dependent on the volume of the cation. Na$^+$ preferred to be more or less in the middle of the cavity, while Cs$^+$ preferred to be close to the upper rim. The vertical locations of the cationic guests are given in Table II. The vertical height of the 'empty' cavity of the C_4 crown from the lower to the upper rim is *ca* 3.81 Å.

Examination of the relative binding energies of the alkali cations revealed a clear relationship between cationic volume and strength of binding: the smaller the cationic volume, the stronger the binding. The same tendency has been reported earlier for small alkali cations with benzene [17,18]. Induction and electrostatic interactions are the major sources of the attraction, and the induction interaction becomes more significant as the cation size decreases [17]. It can be assumed, therefore, that the induction interaction between Li$^+$ and the oxygens of two OH-groups determines the most favourable binding location of Li$^+$. The binding energies are presented in Table II.

The order of binding energies is the opposite to what would be expected from the experimental results for competitive complex formation in the solution state, where the Cs$^+$ complex, not the Li$^+$ complex, was the most abundant [13,14]. The complexation in solution is affected by various

TABLE I Effect of alkali cation complexation on the resorcarene skeleton. The distances shown are internuclear between the opposite upper-rim resorcinol hydrogens

Complex	Length (Å)	Width (Å)
C_4 crown	9.89	9.89
Li^{+*}	10.98	8.93
Li$^{+\dagger}$	11.07	7.72
Na$^+$	11.21	7.28
K$^+$	10.97	8.02
Rb$^+$	10.79	8.44
Cs$^+$	10.60	8.83

*Upper rim complex.
†Cavity complex.

TABLE II Positions of the cationic guests. The distance is the vertical distance from the nucleus of the cation to the base of the lower rim (at the level of the 'broadside' resorcinol hydrogens pointing down). The energy is the relative binding energy of the cation. BSSE corrections are included

Complex	Distance (Å)	Energy (kJ/mol)
Li^{+*}	3.78	− 376
Li$^{+\dagger}$	2.22	− 244
Na$^+$	2.39	− 210
K$^+$	3.01	− 160
Rb$^+$	3.30	− 145
Cs$^+$	3.62	− 125

*Upper rim complex.
†Cavity complex.

factors, including solvation and ion-pair formation. In addition, the solution- and gas-phase binding energies are not necessarily directly comparable, because the electrostatic interaction energies are increasing in the gas phase because of the absence of the solvent [19].

It is noteworthy that the calculations also yielded a relatively stable Li^+ complex where the cation was located in the middle of the cavity. Although the binding energy is much weaker than that of the upper rim complex, it is still stronger than the binding energies of the complexes with the other alkali cations located in the middle. In this case the vertical location of Li^+ inside the cavity was volume-dependent.

These calculated results are valid for supramolecular complexes having a homodirectional array of intramolecular H-bonds. It is unlikely that significantly more stable structures occur when the H-bonded system is altered because of the considerable energy required to change the resorcarene skeleton structure [15].

Mass Spectrometric H/D Exchange Reactions

The monomeric alkali cation complexes were also investigated experimentally by mass spectrometric means: gas-phase H/D exchange reactions were carried out for all five complexes of tetraethyl resorcarene. It can be assumed that all eight resorcinol OH hydrogens of the resorcarene are available for deuterium exchange. In our earlier study [14] we found that the monomeric sodium complex was inert; that is no exchange was observed between resorcinol hydrogens and deuterium.

In this study, the same trend as that observed earlier for sodium was found for the larger alkali cations (K^+, Rb^+, Cs^+): no H/D exchange occurred. The result was the opposite for the Li^+ complex; all of its hydroxyl hydrogens were exchanged with deuterium. The H/D exchange spectra of Na^+ and Li^+ resorcarene complexes with a reaction time of 120 s are depicted in Fig. 3.

These different results are well explained in terms of the binding site of the cations and the intramolecular flip-flop H-bonding between the OH-groups of the resorcarene. Our earlier results suggested the presence of an intramolecular flip-flop H-bonding system in this resorcarene. The same system has also been proposed for the closely related calixarenes [20]. Flip-flopping also hinders the H/D exchange reaction [21–23].

According to our calculations, Li^+ locates preferably near the upper rim of the cavity towards a pair of OH-groups. This location causes interference with the flip-flop H-bond system between these two OHs. Because the whole flip-flop system is interconnected, with each OH dependent on the others, the remaining three OH pairs suffer interference as well. As a result, all of the hydrogens are available for deuterium exchange.

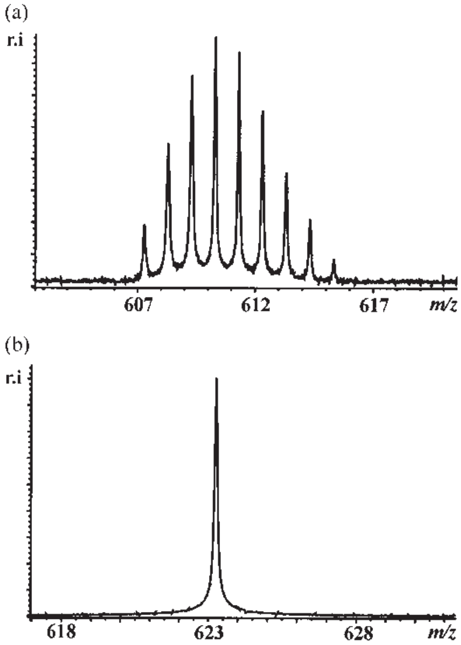

FIGURE 3 H/D exchange mass spectrum of (a) Li^+ complex (M: 607 u) and (b) Na^+ complex (M: 623 u) with 120 s reaction time.

The H/D exchange experiments were carried out with the monomeric Li^+ complex (molecular mass m/z 607 u) with reaction times up to 120 s. The main peak of the spectrum with reaction time 120 s is m/z 611 u, representing the exchange of four hydrogens, but the exchange of all eight hydrogens is also clearly observed (Fig. 3a). The whole exchange reaction showed an excellent linear correlation as a function of time as seen in Fig. 4, where the sum of the exchange products is presented as a function of time. The abundance of the parent ion steadily decreases as the number of exchanges increases. The calculated efficiency of the H/D exchange reaction is 0.0011.

The overall exchange process could proceed as follows: the docking of Li^+ between two OHs causes interference to the flip-flop H-bond system.

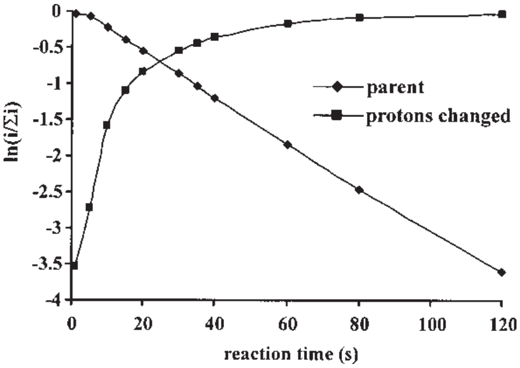

FIGURE 4 Amount of ions in the H/D exchange reaction of Li^+ complex as a function of time.

As a result, the first two exchanges occur via the 'salt bridge'-like mechanism [24]. However, the whole flip-flop system is interconnected, with each OH dependent on the others, thus the remaining three OH-pairs suffer interference as well. This interference probably slows or even prevents the flip-flopping movement thus enabling the presence of more stationary intramolecular H-bonds. The nature of these H-bonds enables the formation of a stable collision intermediate for the exchange to take place [25,26] and, furthermore, the exchange of the remaining six hydrogens. The enfeebled flip-flop movement is still retarding these exchanges.

The results for the H/D exchange with the Na^+ complex are totally different. The Na^+ preferably locates in the middle of the cavity, and the distances to the OH-hydrogens is so great that the flip-flop system remains undisturbed, that is the flip-flopping occurs despite the presence of Na^+. Thus no exchange occurs even at longer reaction times (Fig. 3b). This same behaviour holds for the resorcarene complexes with larger alkali cations. No H/D exchange was observed for any of them. Even though the volume of the cation is greater, the distance remains too great for interference with the flip-flopping and no exchange occurs. In addition, the high vacuum of the Fourier transform ion cyclotron resonance (FTICR) cell would decrease the stability of any collision complex, although it does not hinder the exchange process, as was seen in the case of the Li^+ complex.

CONCLUSIONS

Molecular modelling results suggest that all five alkali metal cations are located inside the resorcarene cavity. Four of the alkali cations (Na^+, K^+, Rb^+, Cs^+) locate approximately in the middle of the cavity, with the vertical location determined by the volume of the cation. The most favourable location for the Li^+, by contrast, is near to the upper-rim OH-groups, and this affects the behaviour of the monomeric Li^+ complex in the H/D exchange experiments. A relationship was also observed between the cationic volume and binding interaction: the smaller the volume the stronger the interaction. The formation of the supramolecular complex induces a conformational change in the molecular skeleton of the host tetraethyl resorcarene from C_4 crown to C_2 pinched crown. In mass spectrometric H/D exchange experiments the Li^+ complex exchanged all its hydrogens with deuterium, whereas no reaction occurred with the other alkali cation complexes. This result is explained by the interference caused to the intramolecular flip-flop H-bonding system by the binding location of Li^+. Our results clearly show the congruence between the gas-phase mass spectrometric experiments and theoretical calculations, whereas, as expected, the solution-state complexation experiments yielded divergent results. Further calculations aimed at investigating the complexation with resorcarenes are in progress.

EXPERIMENTAL

Ab Initio Calculations

The starting geometry of the host resorcarene was the most stable conformation, the C_4 crown, observed in our earlier study [15]. The alkali metal cations were located in the interior of the resorcarene cavity and the supramolecular complexes formed were fully optimized with Gaussian 98 [27]. The Hartree–Fock (HF) method was used. The basis sets used were 3-21G for the resorcarene skeleton, 6-31G++(d,p) for the eight OH-groups, and 3-21G for the alkali metal cations. The latter set was acquired via the internet from the Extensible Computational Chemistry Environment Basis Set Database.[‡] The larger basis set for the OH-groups was used to improve the description of the lone electron pairs, which affect the ability to form intramolecular H-bonds. Despite the limitations of the relatively small basis set 3-21G, it is expected to reasonably account for the structures [28]. BSSE corrections were made to the relative binding energies using the counterpoise method [29]. The interaction energies should be considered as approximate owing to the limited size of the basis set and the lack of electron correlation effects.

Mass Spectrometry

Samples

The X-ray structure and characterization of tetraethyl resorcarene have been reported earlier [30]. All commercial solvents and reagents were used as received. The stock solution of tetraethyl resorcarene was made by dissolving it in acetonitrile. The final sample solution was made by dilution with methanol, leading to a final sample concentration

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[‡] Basis sets were obtained from the Extensible Computational Chemistry Environment Basis Set Database, Version 7/30/02, as developed and distributed by the Molecular Science Computing Facility, Environmental and Molecular Sciences Laboratory, which is part of the Pacific Northwest Laboratory, PO Box 999, Richland, WA 99352, USA, and funded by the US Department of Energy. The Pacific Northwest Laboratory is a multiprogram laboratory operated by Battelle Memorial Institute for the US Department of Energy under contract DE-AC06-76RLO 1830. Contact David Feller or Karen Schuchardt for further information.

of 10 pmol/μl or lower. The alkali metal cations were introduced into the sample solution as chlorides dissolved in water. All sample solutions contained a 1:1 ratio of host to guest.

Equipment

The mass spectrometry experiments were performed on the Bruker BioApex II 47e FTICR mass spectrometer (Bruker Daltonics, Billerica, USA) equipped with an Infinity™ cell, a 4.7-Tesla 160-mm bore superconducting magnet and an external electrospray ion source. In H/D exchange reactions, deuterated ammonia (ND_3) was introduced into the cell via a variable leak inlet valve and the pressure was allowed to rise to 8×10^{-8} torr. Ions generated in the external ESI source and transferred to the cell were collisionally cooled in the ICR cell, isolated using the CHEF technique [31] and then allowed to react with neutral reagent with delay times from 1 s up to 120 s. The measurements were controlled using Bruker XMASS software version 5.0.6. The efficiency of the H/D exchange reaction was calculated with a literature procedure [32] (ADO program).

Acknowledgements

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