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Supramolecular host-guest complexation of Lash's calix[4]azulene with tetraalkylammonium halides and tetrafluoroborate salts: binding and DFT computational studies

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Calix[4]azulene **1** is shown to be an effective molecular receptor for tetraalkylammonium halide and BF_4^- salts. The respective binding constants were determined using global-fit analyses of the spectral data from UV-vis absorption titration studies. A DFT study of the putative complexes formed with **1**, and the X-ray structure of **1** itself is also reported.

Introduction

In 2002 Colby and Lash[1] reported their remarkably facile synthesis of calix[4]azulene **1** by the Florisil-mediated reaction of azulene **2** (Figure 1) with paraformaldehyde in dichloromethane. Since then, there have been no reports published on any of the potential supramolecular or molecular recognition properties of this intriguing compound.

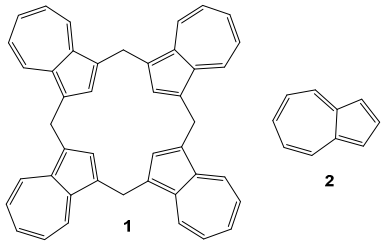

Figure 1. Structures of calix[4]azulene **1** and azulene **2**.

Due to the resemblance of **1** to calix[4]arenes[2] the potential for molecular recognition studies with these compounds is an obvious one and due to our own on-going interest in the supramolecular complexation properties of such deep-cavity containing molecular receptors/[3a-d] We report here our findings with respect to a supramolecular host-guest complexation study of **1** with, in particular, tetraalkylammonium halides and tetrafluroborate salts. A global analytical fitting[4a,b] was used to determine the binding or association constants from UV-vis titration experiments. During the course of our investigations, crystals of calix[4]azulene from benzene solution were obtained which permitted an X-ray structural determination.[5] Concurrently, a DFT (Density Functional Theory)[6] computational study was also conducted on both **1** and its complexes.

Results and discussion

In connection with our on-going studies of the supramolecular complexation properties of macrocyclic compounds, we were interested in evaluating those of **1**. Our own studies have included the supramolecular binding, or complexation, of tetraalkyl-ammonium salts with various macrocyclic cavitands.[3a-d] Calix[4]azulene, on the other hand, is a hydrocarbon compound which among other significant differences, and when compared with other macrocyclic compounds which we have studied, has no heteroatoms in its structure. We were therefore interested in seeing whether this would affect the molecular receptor or binding properties of calix[4]azulene.

The ambient temperature ^{1}H NMR spectrum of **1** shows that the methylene bridge protons appear as a sharp singlet at δ = 4.74 ppm, indicating its conformational flexibility. However, in principle, **1** could potentially adopt *cone*, *partial cone*, *1,3-* or *1,2-alternat*e conformations which are analogous to those that are typically associated with calix[4]arenes.[2] The relatively low solubility of **1** in the usual NMR solvents however, prevented the determination of a coalescence temperature or energy using low-temperature VT-^{1}H NMR spectroscopy.

Since **1** is a hydrocarbon molecule, we hypothesized that its macrocyclic cavity could serve as a site for molecular recognition with, in particular, aromatic hydrocarbon guest molecules, including *e.g.* naphthalene, hexamethylbenzene and C_{60} and C_{70}. However using ^{1}H NMR titration[7] experiments no meaningful chemical shift changes for either the guest molecules or **1** were observed. Hence no evidence could be observed for any supramolecular complexation of these types of guests with **1**.

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† Electronic Supplementary Information (ESI) available: UV-vis titration; X-ray *cif* and *checkcif* files for **1** (CCDC # 1049866) and *.mol* coordinates from DFT computations See DOI: 10.1039/x0xx00000x

Nevertheless, a mole ratio plot from a ^{1}H-NMR titration experiment with tetramethylammonium chloride (TMACl) in $CDCl_3$ as a guest, did reveal that a 1:1 complex of TMACl with **1** formed. The low solubilities however, of both host and guest, precluded accurate determinations of the binding or association constant (K_{assoc}) in subsequent titration experiments. UV-vis spectroscopic titration experiments nevertheless proved more suitable for the studies with TMACl and the other tetraalkylammonium salts reported herein. It should be noted that although fluorescence spectroscopy is more sensitive than UV-vis spectroscopy, and could therefore be used with more dilute (~10^{-5} – 10^{-3} M) solutions than those needed for either ^{1}H-NMR or UV-vis titrations, fluorescence titration experiments could not be used with calix[4]azulene. [8-10]

X-Ray crystallography of 1

During the course of our investigations, green crystals of **1** were obtained from benzene solution which were suitable for a single-crystal X-ray determination. The molecule crystallized in C2/c, with half of one molecule contained in the asymmetric unit (see Figure 2a for the symmetry-expanded full molecule.) Each plane made by C1-C10 and C12-C21 was oriented at 86.27(6)^o to the next plane, with an inversion centre located directly in the middle of the molecule, leading to an anti-arrangement (or C_i-symmetrical conformer) for calix[4]azulene. There was no associated lattice solvent present. However, examination of the packing revealed close associations between the C1-C10 planes of adjacent molecules (plane-to-plane separation of 3.4397(17) Å, off-set by 3.496(3) Å) leading to a staircase arrangement of the molecules parallel to the b-axis, as shown in the space-filling Figure 2b.

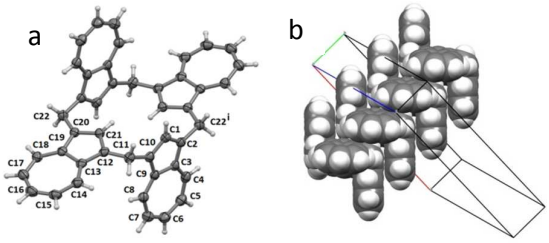


Figure 2: Calix[4]azulene (*a*) represented as 50% displacement ellipsoids. Symmetry operation (i) = ½-x, 1.5-y, 1-z; and (*b*) by a space-filling representation showing the staircase arrangement of molecules parallel to the b-axis.

UV-vis absorption studies

The UV-vis titration behaviour of **1** with tetramethylammonium halides (TMAX, X=Cl^-, Br^- and I^-) could be followed despite the solubility limitations posed by both calixazulene and the TMAX salts. This was achieved using 10-cm pathlength cells in a thermostated dual-beam spectrophotometer. Addition of aliquots of the respective TMAX salts to solutions of **1** (4.8×10^{-5} M) resulted in a quenching of the spectra of **1** in the range of 525-700 nm. Although these quenching changes were small, they were sufficient to allow the resulting K_{assoc} values to be determined. Each of the individual full spectra that were obtained from duplicate titrations were subjected to a non-linear 1:1 global fit analysis.[4b] Average K_{assoc} ± average symptotic "fitting" uncertainty (ASFU) values of 7400 ± 0.44%, 3820 ± 1.3% and 2840 ± 1.2% M^{-1} respectively, for TMACl, TMABr and TMAI were obtained. The trend in K_{assoc} values between these halides is consistent with those seen in other instances.[3a-d] The global analysis approach provides a more accurate description of the equilibria involved since it avoids the manipulation of the actual experimental data to effect linear transformations of non-linear phenomena, and also that quality-of-fit parameters are also generated. The limitations of the classical double-reciprocal Benesi-Hildebrand treatment[11] has been well-documented by others, including ourselves.[4,12]

To evaluate the potential effects of other larger tetraalkylammonium groups, the effects of higher homologues of TMAX, namely those of the corresponding tetraethyl and tetra-*n*-butylammonium salts were examined where possible. Solubility problems encountered with these higher tetraalkylammonium halide homologues, were averted by comparing $TMABF_4$ with tetraethylammonium tetrafluoroborate ($TEABF_4$), and tetra-*n*-butylammonium tetrafluoroborate ($TBABF_4$) since these salts had higher solubilities in the 9:1 (*v/v*) $CHCl_3$:CH_3OH mixed solvent which was the solvent used for all of the UV-vis titrations. The resulting K_{assoc} values are shown in Table 1, Entries 4-6. The trend observed, namely $TMABF_4$>$TEABF_4$ >$TBABF_4$ is consistent with the DFT calculations shown in Table 3.

Table 1. Summary of K_{assoc} values for the tetraalkylammonium salts using the global non-linear fitting program.[4]

Entry		K_{assoc} (M^{-1})
		Average ± ASFU
1	**TMACl**	7400 ± 0.44%
2	**TMABr**	3820 ± 1.3%
3	**TMAI**	2840 ± 1.2%
4	**$TMABF_4$**	5920 ± 1.2%
5	**$TEABF_4$**	5060 ± 1.5%
6	**$TBABF_4$**	3620 ± 1.3%

DFT calculation details

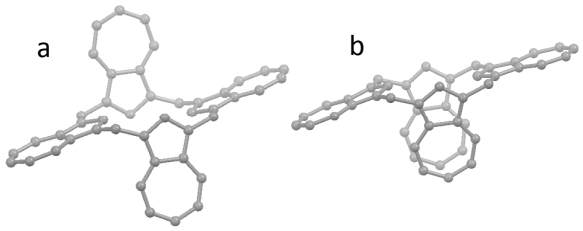
The use of DFT has become increasingly commonplace in organic chemistry[6,13] and among supramolecular chemists in particular. In this work we modeled complexation of the TMA halides and $TMABF_4$ $TEABF_4$, $TBABF_4$ "guests" with the calixazulene host in the gas phase as well as in chloroform solution. All of the DFT calculations were conducted with the *Gaussian-09 rev D.01* code.[14]

B3LYP/6-31G(d)	kJ/mol	B3LYP/6-31G(d)	kJ/mol
Gas phase		*$CHCl_3$*	
C_i	0	C_i	0
C_{2v} *Chair*	+0.34	C_{2v}*-1,3-Alternate*	+0.73
C_{2v}*-1,3-Alternate*	+0.68	C_{2v} *Chair*	+0.33
ωB97xD/6-31G(d)	**kJ/mol**	**ωB97xD/6-31G(d)**	**kJ/mol**
Gas phase		*$CHCl_3$*	
C_s	0	C_s	0
C_{2v}*-1,3-Alternate*	+0.58	C_s*	0
C_i	+10.1	C_i	+8.94

For the work reported herein, Chai and Head-Gordon's ωB97xD[15] functional, which combines the long-range functional ωB97x with the empirical dispersion correction specially parametrized against each other, was used. B3LYP results are provided for comparison purposes only. The popular B3LYP density functional[16] which has often been employed by organic chemists has been shown by many authors, including those cited in References 17-20, to have numerous shortcomings. These shortcomings are related to the lack of dispersion interactions and the deficiencies of DFT with self-interaction errors and long-range behavior. In the last decade, in order to amend the poor performance of standard DFT, the following methods were proposed, and have become widely used: the empirical dispersion corrections by Grimme,[17,21,22] and the long-range hybrid density functionals of Tsuneda and Hirao[20] that, when combined, deliver much improved performance for thermodynamics and structure optimization. The effect is most pronounced for host-guest complexes such as were studied in our work where the interactions are dominated by non-bonded terms.[22]

The standard 6-31G(d) basis set[23] was used for all the atoms. This basis set is small by modern standards but we chose to use it due to the relatively large size of our systems. It was shown that larger basis sets including diffuse functions cause basis set overcompleteness problems for condensed hydrocarbons. In agreement with Fry[24] we found that the 6-31G(d) basis set was not reliable for the energies of complexes containing bromide anion; for iodide, non-relativistic all-electron calculations are not accurate. Therefore, for guests and complexes containing atoms other than first row elements (*i.e.* for TMACl, TMABr, TMAI) we used relativistic ECPs by Hay and Wadt (LANL) along with corresponding LANL2DZ basis set augmented with additional d-,p- polarizational functions.[25,26a-c] Cartesian Gaussian functions (6D, 7F) were used for the halides' LANL2DZ basis set, to make it consistent with the default setting for the 6-31G(d) basis set. For each of the individual components *i.e.* tetraalkylammonium salt, calix[4]azulene and the respective corresponding 1:1 supramolecular complexes, unconstrained geometry optimizations were first conducted in the gas phase. Then, geometries were optimized within the continuum solvation model (PCM)[27a,b] of the chloroform solvent, using default solvent parameters as provided with *Gaussian09 rev D.01*. The results are summarized in Tables 2 and 3.

Free calixazulene



When the coordinates of the free calixazulene from the X-ray structure were subjected to both gas-phase and chloroform-corrected geometry-optimization with either the B3LYP/6-31G(d) or ωB97xD/6-31G(d), the resulting minimized conformer from B3LYP was similar to that of the X-ray structure (Figure 3*a*). However, with ωB97xD the conformer (Figure 3b), is closer to a *C*s-symmetrical "*flattened" 1,3-alternate* conformer.[2b] A C_{2v}*-chair* and a C_{2v}*-1,3-alternate* conformer were also found, but had higher energies 2. The relative energies of the conformers are provided in Table 2.

Table 2. DFT computed relative energy values for the four different conformations of **1**.

Figure 3 Structures and symmetries of the most stable conformers of calix[4]azulene (all hydrogen atoms have been omitted for clarity) from the geometry-optimizations using (*a*) C_i-symmetry from the B3LYP/6-31G(d) geometry-optimization; and (*b*) C_s-symmetry from the ωB97xD/6-31G(d) geometry-optimization.

Inclusion of chloroform solvation does not affect the relative energies of the conformers it can be seen that for B3LYP/6-31G(d) the energy difference between the three studied conformers is negligible, while ωB97xD/6-31G(d) has a marked preference for the *C*s-symmetrical *flattened" 1,3-alternate* conformer, which can be understood by favourable intra-molecular dispersion interaction between the parallel azulene rings in the isolated molecule. These interactions are absent in B3LYP but are included in the ωB97xD functional. The experimentally observed structure shown in Figure 2 (*a*) is probably a result of crystal packing forces. In Table 2, the most stable of the conformers for each of the density functionals were used to compute the "binding" energies of the complexes shown. In one case (shown in Table 2 by the entry marked as C_s*) where the ωB97xD/6-31G(d) geometry-optimized C_{2v}*-1,3-alternate* conformer from the gas phase was subjected to the ωB97xD/6-31G(d) geometry-optimization with the chloroform PCM the resulting conformer was the same as C_s-symmetry.

Calixazulene complexes with trialkylammonium halides and tetrafluoroborates

With all three of the 1:1 calix[4]azulene:TMA halide complexes their geometry-optimized conformers were found to exist with two potential energy surface minima: *1,3-alternate* (shown in Figures 4a-b) and *partial cone* (Figure 4c). The B3LYP/6-31G(d) method initially found only the *1,3-alternate* structures for all three halides; however, according to results from the ωB97xD functionals, this structure is more stable for TMACl and TMABr, while for TMAI, a *partial cone* conformer is preferred by 12.3 kJ/mol. For the tetraalkylammonium tetrafluoroborate salts ($TMABF_4$, $TEABF_4$, $TBABF_4$) geometry optimizations converged to the *partial cone* for

both of the density functionals. Inclusion of the PCM chloroform solvation did not change the energy order of the isomers.

The "binding" or "interaction" (negative) energies ("BE") generally decreased in magnitude (i.e. less energetically favoured) in going from the ωB97xD/6-31G(d) gas-phase to the $CHCl_3$-corrected computed values, to the corresponding B3LYP/6-31G(d)-computed values, as summarized in Table 3. On the other hand, the binding constants observed for the tetramethyl-ammonium halides showed the trend: $Cl^->Br^->I^-$. The BE of the complexes were calculated according to equation (1) where $\mathbf{E_{Calixazulene}}$ is the geometry-optimized energy of calix[4]-azulene **1** and $\mathbf{E_{Tetraalkylammonium\ salt}}$ is that of the respective tetraalkylammonium salt. $\mathbf{E_{Complex}}$ is the geometry-optimized energy of the complex formed from **1** with the respective tetraakylammonium salts.

$$\mathbf{BE = E_{Complex} - \Sigma(E_{Calixazulene} + E_{Tetraalkylammonium\ salt})} \quad (1)$$

Table 3. BE (kJ/mol) of tetralakylammonium salts from geometry-optimized (lowest energy) gas-phase and chloroform-solvated calculations.

	ωB97xD/6-31G(d)		**B3LYP/6-31G(d)**	
	Gas phase	**CH_3Cl**	**Gas phase**	**CH_3Cl**
	kJ/mol	kJ/mol	kJ/mol	kJ/mol
TMACl	-113.9	-77.3	-33.2	-13.1
TMABr	-118.3	-80.8	-34.4	-14.4
TMAI	-133.5 (-121.2)*	-93.0 (-84.0)*	-35.4	-13.9
$TMABF_4$	-144.6	-116.9	-49.93	-20.8
$TEABF_4$	-129.0	-111.9	-29.7	-8.3
$TBABF_4$	-113.5	-115.1	-25.6	-10.1

Note: The values in parentheses are the BEs of the TMAI complexes computed as the corresponding 1,3-alternate conformer of 1.

For the halides and BF_4^-, inclusion of the solvation effects does not change the trends but decreases the BEs uniformly; this is as it should be due to the relative stabilization of the isolated guest which is more polar. The B3LYP density functional predicts significantly weaker binding energies for missing dispersion interactions. Moreover, it does not reveal much difference in binding between the three TMA halide complexes. The more reliable ωB97xD functional predicts increases in the complexes' stability in the order of $Cl^-<Br^-<I^-$ which is in agreement with our experimental findings. As can be seen in Figures 5c (for TMAI) and 6a-c, in order to accommodate both the larger iodide and tetrafluoroborate anion and the larger tetraalkylammonium groups the conformations of the complexes are no longer *1,3-alternate*. For the TMAI, $TMABF_4$ and $TEABF_4$ complexes, *partial-cone* ("*paco*") conformers are adopted and for the $TBABF_4$ complex, a near-*boat*-like conformer as shown in Figure 4 for the calix[4]azulene host, is formed. The binding energy trends for the tetrafluoroborate salts $TMABF_4$> $TEABF_4$> $TBABF_4$ did parallel the trend seen with the corresponding binding constants which were observed (Table 1). To possibly account for the trends in the BEs of the 1:1 complex formation in these salts, there is presumably a greater degree of entropic loss incurred in forming the complexes as the free rotations within the larger alkyl group chains become restricted within the complex.

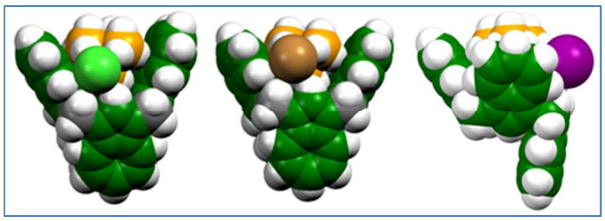


Figure 4. Geometry-optimized (ωB97xD/6-31G(d)) structures computed for: (a) *Left*: TMACl⊂**1** ; (b) *middle*: TMABr⊂**1**; (c) *right:* TMAI⊂**1**.

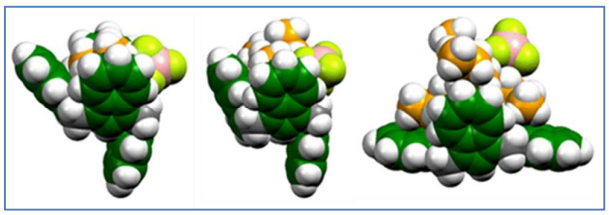


Figure 5. Geometry-optimized (ωB97xD/6-31G(d)) structures computed for: (**a**) *Left*:$TMABF_4$⊂**1**; (b) *middle***:** $TEABF_4$⊂**1**; (**c**) *right*: TBA BF_4⊂**1**.

Conclusions

Calix[4]azulene **1** whose synthesis was reported by Colby and Lash in 2002 has now been shown to be a molecular receptor for tetraalkylammonium halides and thus joins the large group of cavity-containing macrocylic compounds. The binding or association constant values have been determined using the global fittingprogram[4b] with the entire UV-vis spectra derived from the titration experiments. The obtained values show trends similar to those observed by others for tetramethylammonium halides where $Cl^-> Br^- > I^-$. With larger alkyl groups the trend in association constant values is Me>Et>*n*-Bu. DFT calculations with the dispersion-corrected, long range hybrid functional **ω**B97xD support these trends, while the older B3LYP density functional fails due to incorrect description of the weak inter- and intra-molecular interactions.

Acknowledgements

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5 X-ray structure of **1.** Crystal Data for calix[4]azulene: $C_{44}H_{32}$ (*M*=560.69 g/mol): monoclinic, space group C2/c (no. 15), *a*=21.779(11)Å, *b*=4.904(2)Å, *c*=27.269(12)Å, *β* = 97.075(8), *V*= 2891(2) Å^3, *Z* =4, *T*= 153(2) K, μ(MoKα)=0.073 mm^{-1}, *Dcalc* =1.288 g/cm^3, 16217 reflections measured (5.106 ≤ 2Θ ≤ 52.984), 2982 unique (R_{int}=0.0484, R_{sigma}= 0.0321) which were used in all calculations. The final R_1 was 0.0658 (I > 2σ(I)) and wR_2 was 0.1415 (all data). CCDC # 1049866.
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