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Surprises in the Energetics of Host–Guest Anion Binding to Calix[4]pyrrole

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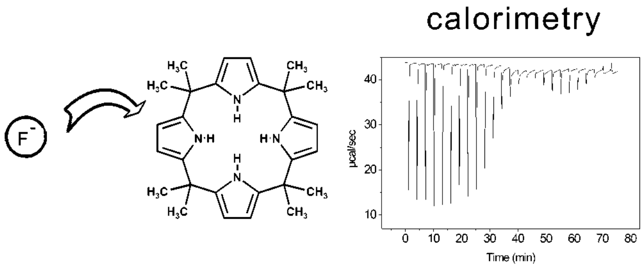
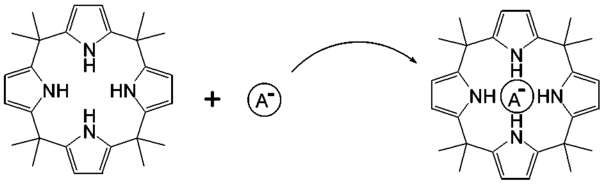
ABSTRACT



Contrary to common expectation, calorimetric measurements do not corroborate the preference of calix[4]pyrrole for fluoride over chloride in acetonitrile solution.

Current concepts of tailoring specific host molecules largely rely on maximizing the mutual interactions with a target guest species (lock-and-key complementarity principle). In this respect the host design can be greatly aided by molecular modeling, but even with this help more often than not the experimental evaluation of host−guest binding reveals selectivity factors way short of the expected discrimination. In many instances structural differences between the modeled and the real complex structures as deduced, e.g., from X-ray crystal structural determinations, can account for the variances. However, in some cases significant deviations from the assumed molecular scenario are manifest despite very close structural similarity. Host−guest binding of anions to the calix[4]pyrrole **1** provides such an example that also appears to be a simple enough system to investigate the origin of the discrepancies. The ultimate goal is to adjust the guidelines for host construction in order to arrive at tools of broader applicability and accuracy.



1 **2**

Calix[4]pyrrole has been known for over a century[1] but has been characterized only recently as an electroneutral host for halide anions with a strong preference for fluoride.[2] Table 1 compiles published binding data (K_{ass}) in several solvents,[3] all of which were determined by NMR-spectroscopic methods. The basic trends in stability in the gas phase and in dichloromethane solution can be reproduced by Monte Carlo simulations or density functional theory calculations.[4] These calculations further draw a detailed picture of conformational

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(1) Baeyer, A. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 2184−2185.
(2) Gale, P. A.; Sessler, J. L.; Král, V. *Chem. Commun.* **1998**, 1−8.

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Table 1. Binding Affinities of Anions as Tetraalkylammonium Salts to Calix[4]pyrrole **1** in Various Solvents

	K_{ass} [M^{-1}]			
	CH_2Cl_2[a]	$CH_3CN/CHCl_3$ 1:9 v/v[b]	CH_3CN/ 0.5% H_2O[c]	DMSO-d_6[d]
fluoride	17 170	23 800	>10 000	1 060
chloride	350	6 800	5 000	1 025
bromide	10	270		
dihydrogen-phosphate	97		1 300	

[a] Reference 3a. [b] Reference 3b. [c] Reference 3c. [d] Reference 3d.

preferences and geometries that resemble closely the host–guest arrangement found in the crystals. However, the selectivity for fluoride over chloride is dramatically overestimated ($\Delta\Delta G_{calc} > 15.1$ kcal mol^{-1}; $\Delta\Delta G_{exp} = 2.3$ kcal mol^{-1}), raising the question whether the plausible but nonproven explanation of interference by water introduced with the fluoride salt[4a] does not adventitiously cover a more fundamental problem in these calculations. The rapid expansion of the field of calixpyrrole receptors[5] has furnished evidence that the predicted preference for fluoride may be annihilated the more polar the solvent becomes.[3d] A damping effect on selectivity by solvent had already been noted in molecular modeling.[4a]

Host–guest associations in polar solvents, however, are prone to enthalpy–entropy compensation[6] rendering the extraction of meaningful energetics of the direct mutual interactions of the binding partners exceedingly difficult. Isothermal titration calorimetry (ITC) could provide a remedy in this situation as this method allows the immediate determination of the enthalpy $\Delta H°$ and the Gibbs enthalpy $\Delta G°$ in supramolecular complexations and the entropy $\Delta S°$ then can easily be calculated from the Gibbs–Helmholtz equation.[7] Here I report on the surprising results of the thermodynamics of anion binding to calix[4]pyrrole in dry acetonitrile.

The choice of solvent was dictated by solubility considerations and by the necessity to minimize ionic aggregation. The high dielectric permittivity of acetonitrile ($\epsilon = 35.6$) in combination with salt concentrations in the low millimolar range or even smaller appeared safe to warrant complete dissociation of the guest salt. In addition, great pains were taken to exclude moisture since even tiny amounts of water may spoil hydrogen bonding interactions in organic solvents.[8] Thus, absolute acetonitrile ($H_2O < 10$ ppm) was employed in all measurements, and all salts as well as the calix[4]-pyrrole host were carefully dried before preparing the titrand solutions.[9] With these precautions clean and reproducible titrations could be performed; an output of typical data illustrating the average quality is depicted in Figure 1 representing the titration of calix[4]pyrrole with $TBA^+H_2PO_4^-$. The directly determined ($\Delta H°$, $\Delta G°$) as well as the derived standard state functions ($\Delta S°$) are given in Table 2.

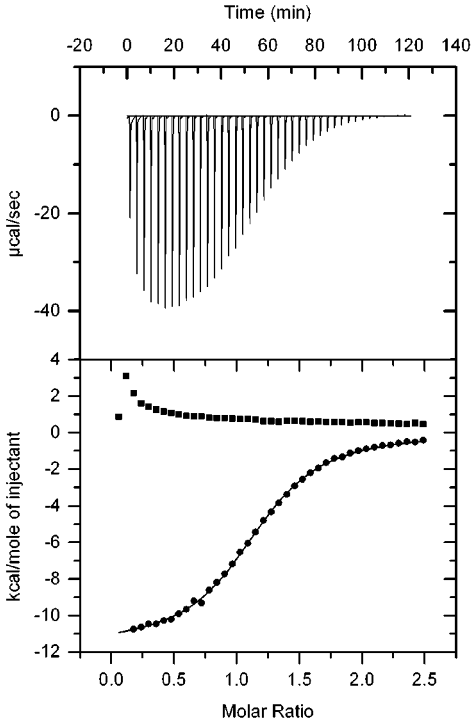

Figure 1. Isothermal calorimetric titration of calix[4]pyrrole **1** (0.914 mM) with $NBu_4H_2PO_4$ (20.5 mM) in dry acetonitrile at 30 °C. The top panel shows the original heat pulses, which were integrated and corrected by a reference titration of the same salt solution into pure acetonitrile. The heats evolved in this reference titration (squares) and the resulting corrected heats (circles) are depicted in the bottom chart along with the fit function (solid line) yielding the thermodynamic values given in Table 2.

A first inspection reveals that the association constants are higher by at least a power of 10 than the published values (Table 1). This result may reflect both the rigorously moisture-free conditions of the calorimetric measurements that boost K_{ass} by suppression of a potential competitor (H_2O) and the fact that the NMR data report just on a *specific*

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(3) (a) Gale, P. A.; Sessler, J. L.; Král, V.; Lynch, V. M. *J. Am. Chem. Soc.* **1996**, *118*, 5140–5141. (b) Turner, B.; Shterenberg, A.; Kapon, M.; Surwinska, K.; Eichen, Y. *Chem. Commun.* **2001**, 13–14. (c) Anzenbacher, P., Jr.; Try, A. C.; Miyaji, H.; Jursikova, K.; Lynch, V. M.; Marquez, M.; Sessler, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 10268–10272. (d) Camiolo, S.; Gale, P. A. *Chem. Commun.* **2000**, 1129–1130.

(4) (a) van Hoorn, W. P.; Jorgensen, W. L. *J. Org. Chem.* **1999**, *64*, 7439–7444. (b) Wu, Y.-D.; Wang, D.-F.; Sessler, J. L. *J. Org. Chem.* **2001**, *66*, 3739–3746.

(5) (a) Anzenbacher, P., Jr.; Jursikova, K.; Sessler, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 9350–9351. (b) Cafeo, G.; Kohnke, F. H.; LaTorre, G. L.; White, A. J. P.; Williams, D. J. *Chem. Commun.* **2000**, 1207–1208. (c) Turner, B.; Botoshansky, M.; Eichen, Y. *Angew. Chem.* **1998**, *110*, 2633–2637. (d) Sato, W.; Miyaji, H.; Sessler, J. L. *Tetrahedron Lett.* **2000**, 6731–6736. (e) Gale, P. A.; Twyman, L. J.; Handlin, C. I.; Sessler, J. L. *Chem. Commun.* **1999**, 1851–1852.

(6) Dunitz, J. D. *Chem. Biol.* **1995**, *2*, 709–712.

(7) (a) Jelesarov, I.; Bosshard, H. R. *J. Mol. Recognit.* **1999**, *12*, 3–18. (b) Cooper, A. *Curr. Opin. Chem. Biol.* **1999**, *3*, 557–563.

(8) Adrian, J. C.; Wilcox, C. S. *J. Am. Chem. Soc.* **1992**, *114*, 1398–1403.

(9) It turned out that calix[4]pyrrole is relatively unstable in solution as judged from the yellow color developing overnight. The calorimetric results reported were always obtained with freshly prepared solutions.

Table 2. Energetics of Binding of Various Anions to Calix[4]pyrrole **1** in Dry Acetonitrile (<10 ppm H_2O) at 30 °C As Determined by Titration Calorimetry[10] ($\Delta H°$, $\Delta G°$ error of fit <0.05 kcal mol^{-1})

		dihydrogenphosphate		fluoride	chloride		bromide
	mode[a]	NBu_4^+	{K⊂cryptand222}$^+$	{K⊂cryptand222}$^+$	NEt_4^+	{K⊂cryptand222}$^+$	NBu_4^+
$\Delta H°$ [kcal mol^{-1}]	A	−11.60	−10.94	−8.25	−8.81	−10.60	−8.34
	B			−10.35	−8.87	−9.80	
$\Delta G°$ [kcal mol^{-1}]	A	−5.79	−5.85	−7.18	−6.90	−7.30	−4.77
	B			−7.08	−6.68	−7.00	
$T\Delta S°$ [kcal mol^{-1}]	A	−5.81	−5.07	−1.05	−1.90	−3.30	−3.56
	B			−3.26	−2.18	−2.80	
K_{ass} [M^{-1}]	A	15 100	16 800	153 000	95 400	185 000	2 770
	B			129 000	66 700	111 000	

[a] A = titration of guest into host solution; B = titration of host into guest solution.

interaction (H-bonding) whereas the calorimetric titrations encompass the more global response. Even more puzzling is the observation that contrary to closely related literature reports[3] there is no preference in affinity for fluoride over, e.g., chloride under these conditions. In fact, the standard enthalpies $\Delta H°$ along with $\Delta G°$ are almost identical within experimental error.

Although there is clear-cut support to the notion that all anion-to-calixpyrrole binding events are enthalpy-driven and entropy-opposed, no special position for fluoride could be assessed. With respect to enthalpy dihydrogen phosphate is a much better guest to calixpyrrole than fluoride. We have to bear in mind at this point that this observation refers to the cummulative enthalpy of all processes happening simultaneously in solution rather than the partial event of the isolated host−guest interaction, e.g., in free space. A much more negative entropic contribution $\Delta S°$ outmatches the enthalpy component $\Delta H°$ finally yielding a composite free enthalpy difference $\Delta\Delta G°$ that favors fluoride versus $H_2PO_4^-$ by an order of magnitude in K_{ass}. Entropy (as $T\Delta S°$) constitutes 20−50% of the total interaction energy even in a non-hydrogen-bonding solvent like acetonitrile and must not be neglected in discussing host−guest affinities.

There are, however, significant deviations from ideal behavior in this putatively simple system. If there were total dissociation of all electrolytes having activity coefficients of 1, the inversion of concentration relations in a 1:1 stoichiometric process should yield the same K_{ass}. The experimental testing of this premise, however, gives small but significant differences testifying to its inappropriateness. Most likely ion pairing equilibria of the salt added but also in the ionic host−guest complex formed may further complicate the analysis. For instance, replacement of the quaternary ammonium by the {potassium⊂cryptand[222]} countercation of the guest anion influences the magnitude of the experimental enthalpy by up to 20%, indicating that even quaternary ammonium cations are less innocent observers to the molecular events happening in solution than commonly believed. In the case of the NR_4^+ fluoride salts, which inadvertently contain some residual water, a concomitant side reaction occurred during the titration that was not observed with the {potassium⊂cryptand[222]} fluoride salt and ultimately spoiled the reliable data evaluation with these salts. The calorimetric trace (Figure 2) shows a progressive change of the shape of the heat pulses along with a shift in the baseline. Continuation of the titration discloses another exothermic process of variable duration having no simple stoichiometric relation to the preceding host−guest binding event. This sequence suggests that some reaction happens in the same time domain as the titration itself (2 h) and definitely proceeds at a slower pace than the supramolecular association. Since water is apparently involved a covalent modification of the host macrocycle could be a reasonable explanation. Reversible ring opening of the macrocycle must involve a covalent hydration step and is known to happen under comparable conditions.[3c]

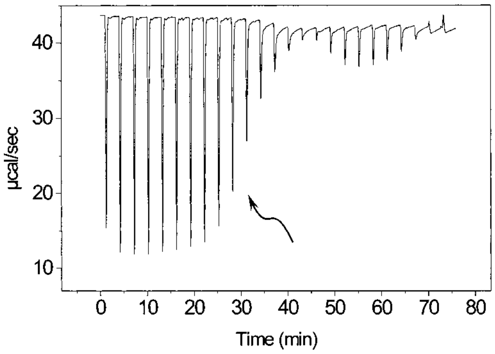

Figure 2. Experimental heat trace in the calorimetric titration of calix[4]pyrrole **1** (0.497 mM) with $NEt_4F{\cdot}2H_2O$ (10.1 mM) in acetonitrile at 30 °C. A 1:1 stoichiometric ratio of host and guest was reached at the position of the arrow.

The calorimetric measurements cannot furnish a detailed mirror image of the molecular events, but they put rigid experimental constraints to explanatory attempts. Here, they clearly reiterate the message that in condensed phases selectivity in its thermodynamic sense (i.e., the ratio of binding constants) with competing guests is not a function of the host structure alone but is heavily dependent on the actual solvent used. Thus, the designation of calixpyrrole as a fluoride receptor at large appears not justified, because the respectable fluoride specificity in dichloromethane or in the gas phase, too, is compromised and eventually vanishes totally in more polar solvents such as acetonitrile (as shown here) or DMSO.[3d] The calixpyrrole case at hand can also open the view upon a general problem in the interpretation of binding data. It is well conceivable that a certain type of binding analysis (e.g., the observation of concentration dependent chemical shifts in NMR) samples a certain binding mode only, rather than relating to the statistical distribution of all bound and unbound host/guest species. In this case guest specificity does not reflect the plain thermodynamic scenario but is subject to the method of measurement. As a corollary, 1:1 complex binding constants will be different depending on the method employed. One can suspect that this potential complication will be more pronounced the more individual and sharp the analytical probe and the weaker the overall host−guest affinity is. Since calorimetry determines the integral heat response of all reactions happening simultaneously in solution the state functions derived on this basis are likely to be closer to the thermodynamic ideal. The extraction of the desired guidelines for host construction then requires the deconvolution of all energetic contributions, which even in the present putatively simple case is more subtle and demanding than initially expected. However, our results clearly point to the dramatic impact of polar solvents on the relative calixpyrrole-anion energetics devaluating the enthalpic arguments based on mutual host−guest interactions that hitherto govern most attempts of host design. Understanding even simple systems seems to require an elevated level of complexity and is somewhat less clear than suggested by high-level calculations.[11]

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(10) A fully computer-operated MCS ITC instrument from Microcal, MA in combination with Origin 5.0 data evaluation software was used.

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