Supramolecular Interactions

DOI: 10.1002/anie.201106018

Selective Host–Guest Binding of Anions without Auxiliary Hydrogen Bonds: Entropy as an Aid to Design**

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As the major goal in host–guest binding, selectivity aims at maximizing the free-energy difference $\Delta\Delta G$ between competing guests upon complexation by a molecular host. Based on the fundamental Gibbs–Helmholtz relationship ($\Delta G = \Delta H - T\Delta S$), this goal can be approached from the enthalpic (ΔH) as well as from the entropic (ΔS) side. However, the conventional route primarily addresses the former alternative, targeting a host compound capable of optimal attractive enthalpic interactions with the guest species. The complexes then possess a defined mutual disposition of the moieties of host and guest that translates into a structural fit resembling a lock-and-key relationship.[1–4] In fact, some examples taken from biological or abiotic recognition adhere to such a simple enthalpy-dominated scenario and thus adequately reflect the real situation. In most cases however, supramolecular interactions generally involve substantial entropy contributions to the free-energy outcome[5] that arise, among other sources, from a wider distribution of populated energy minima. The corresponding increase in configurational entropy mirrors structural diversity and might even overwhelm an unfavorable endothermic result of a singular structural fit. To this end, entropy rather than enthalpy governs guest binding, rendering the intentional use of the entropy component in molecular design an attractive option.

A prerequisite to harnessing entropy in guest recognition is a strategy to uncouple the structural uniqueness in direct host–guest binding mandated by selectivity from the global enhancement in the number of thermally accessible microstates, the experimental entropy $\Delta S°$.[6,7] Herein we embark on an attempt to outmatch the intrinsic uncertainty endemic to high entropy in supramolecular interactions. The trick relies on the subdivision into partial systems segregating the mutual host–guest interaction from all other molecular rearrangements primarily involving the solvent.[8] Whilst the former partial process should be accompanied by negative entropy owing to the loss of many inter- and intramolecular degrees of freedom, the latter is presumed to contribute a positive entropy share owing to the solvation change experienced on guest inclusion into the host cavity.[9] If one can design the host in such a way as to minimize the entropy loss in the direct host-guest interaction while maximizing entropy generation in all other partial processes beneficial entropy production can be gained without sacrificing structural integrity and thus selectivity.

Hosting of anions generally involves a huge change in solvation, thus presenting an attractive and demanding test case.[4,10] To lure a negatively charged guest into a unique position within the host compound, the solvation shell must be largely stripped. The enthalpy required in this process must be provided by the newly established host–guest attraction. Comparability among various guests requires that the overall structure of the complexes is essentially unaffected.

A promising candidate to meet these criteria is the quaternized adamanzane derivative **3** (Scheme 1), which builds upon a variety of congeners[11–14] of proven utility in anion complexation.[15–19] Common to all members in this family is the mechanism of anion encapsulation, which rests on the strong Coulombic force resulting from the overlay of four positive charges. Their disposition, enforced by the high connectivity of the cage, creates an attractive potential gradient to drag the anionic guest into the cavity, thereby surpassing a substantial barrier on immigration.[20,21] An X-ray crystal analysis indicated that the cavity is large enough, yet snuggly filled, when occupied by iodide anion.[22] Owing to the high charge, these compounds are only weakly soluble in organic solvents and on top bring in counteranions as potential competitors in the envisaged encapsulation process. Such problems are solved on attaching anionic moieties covalently to the nitrogen atoms, thus rendering the entire molecule electroneutral but zwitterionic.[23,24] Provided the anionic substructures are weakly coordinating[25–27] and positioned at the molecular periphery, the fundamental driving force for anion entrapment should remain unaffected while the flaws of the original host design are suppressed. The dioxanato COSAN compound **2**[28] can be attacked by tertiary amines, furnishing quaternary ammonium salts with opening of the oxonium ring.[29] When attempted with the macrotricyclic tertiary tetraamine **1**,[30] the initial alkylation steps proceeded smoothly, yet success in the final quaternization depended on the high purity of the oxonium salt to avoid adventitious protonation of the basic nitrogen atom as well as on quite harsh conditions to overcome the unfavorable inwards-directed disposition of the lone electron pair at the last nitrogen center.[31–33] Extensive optimization of the reaction conditions and product purification gave the desired tetrahedral zwitterion **3** in 57% yield.[34]

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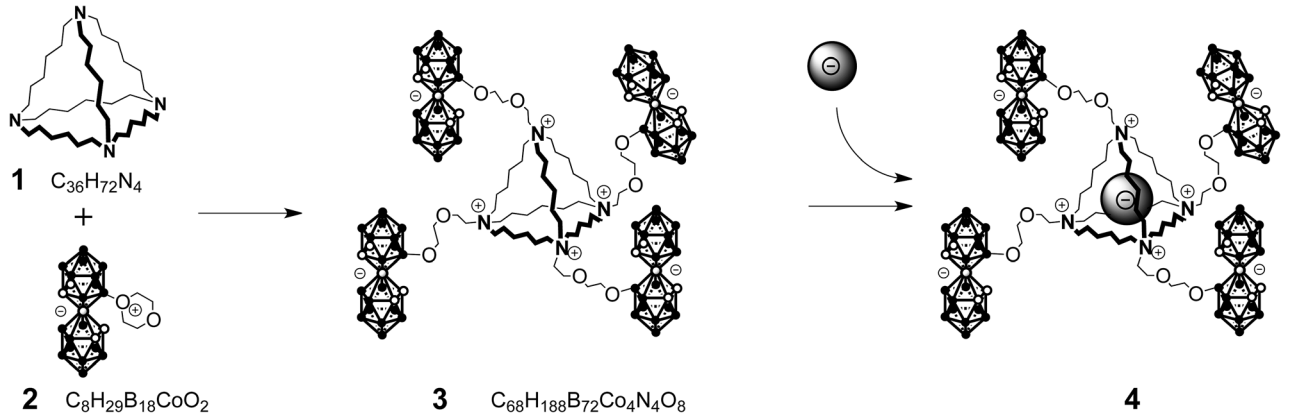
[**] We gratefully acknowledge the generous financial support of this research by the Hans-Fischer-Gesellschaft München. We are also indebted to Prof. H. Mayr and Dr. A. Ofial, LMU München, for their collegial help and permission to use their ITC instrument. We also thank Prof. Vladimir Král, Technical University of Prague, for directing our attention to the unique properties of COSAN dioxanate.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201106018.



Scheme 1. Synthesis of adamanzane derivative **3** from tetrahedral amine **1** and dioxanato COSAN compound **2** and proposed complexation of anions.

The anion-binding capacity of the electroneutral zwitterionic receptor **3** was tested initially using negative-mode MALDI mass spectrometry.[34] The plain isotope pattern shown by the uncomplexed receptor **3** was completely exchanged for the respective isotope pattern of the anionic 1:1 host–guest complexes once the respective tetraalkylammonium salts had been added to the probe. No complexes of higher stoichiometry, which are quite abundant in the mass spectra of simple quaternary ammonium salts, were observed. Contrary to our expectation, very large anions such as BF_4^-, ClO_4^-, and PF_6^-, which certainly cannot penetrate the interior cage of host **3** for steric reasons, also formed 1:1 stoichiometric adducts under the conditions of MALDI-MS analysis. Undoubtedly, the high positive charge density of the tetrahedral faces is insufficiently screened by the independently mobile and weakly-coordinating anionic COSAN appendices, opening a door to the nonspecific association of another bulky anion. In polar solutions, such interactions are diminished by the dielectric shielding of the solvent, rendering only the strongest interactions observable at the moderate (millimolar) concentrations. As a corollary, host **3** shows the expected time-averaged tetrahedral symmetry by NMR spectroscopy, giving rise to just nine signals in the ^{1}H- and ^{13}C-spectra, though the former are considerably broadened, which is apparently due to slow conformational equilibration.

The presumption that anion binding by **3** results from guest encapsulation is not only predicted by the design concept and on computational grounds,[35,36] but is also corroborated by experimental evidence. For instance, the binding of bromide by **3** in acetone produces the ^{13}C NMR spectra depicted in Figure 1. Addition of about half an equivalent of the guest salt generates two sets of signals for the cage positions, confirming the formation of a complex of identical symmetry in slow exchange with the parent unoccupied host. Obviously, the interconversion between the free host and its bromide complex involves a considerable activation barrier, as is conceivable from guest penetration into the host cavity through a window in the tetrahedral face possessing a smaller opening than the interior of the cage. Furthermore, the quasi ion-pairing of guest anions with the zwitterion produced from tripropylamine and **2** representing one corner of host **3**, yet being devoid of the cavity structure,

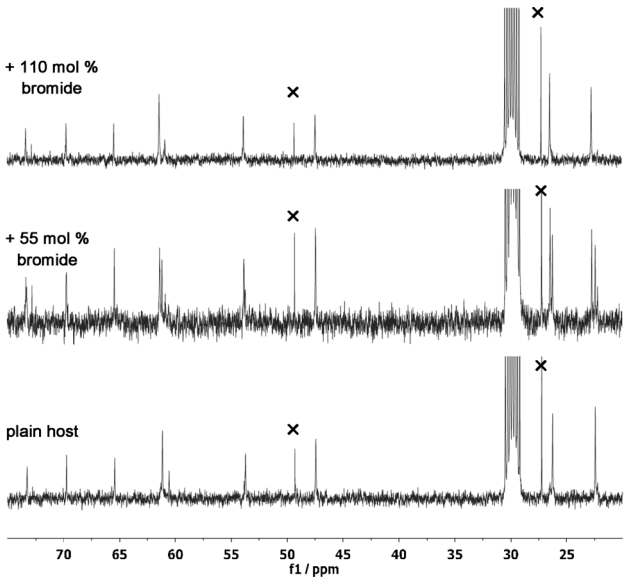


Figure 1. ^{13}C NMR spectra of host **3** upon addition of $Ph_4P^+Br^-$ in [D_6]acetone. The marked signals arise from methyl *tert*-butyl ether, which co-precipitates in a stoichiometric 3:1 ratio on purification; see the Supporting Information, Figure S3.

shows neither an appreciable affinity nor a noticeable barrier of association. As a corollary, the host–guest binding seen with the receptor **3** must emerge from the invasion of the guest into the interior of the host.

When inspected by ^{1}H NMR spectroscopy, the interaction of certain tetraalkylammonium salts with host **3** in a variety of solvents (DMSO, acetonitrile, acetone) showed concentration-dependent shifts of the cage signals only, indicative of an encapsulation process of the anion. In highly polar DMSO-solution the halides and anions of similar size (Supporting Information, Table A) induce a saturation behavior of the chemical shift change, which is largest for the α-CH_2 signals and generally feature a downfield migration. Owing to the broad and overlapping resonances, the quantitative analysis required a 2D-NMR evaluation of the peak shifts. On the other hand, the anions of larger size which had shown 1:1 association with host **3** in the gas phase (BF_4^-, ClO_4^-, PF_6^-,

AcO^-) did not cause any significant shifts of the host signals in DMSO. In general, there is a crude correlation of the observed maximum chemical shift change with anion size, although more subtle features relating to the geometry and/or the hydrogen bonding capacity of the guest cannot be overlooked.

A peculiar case is represented by the flat and aromatic tetrazolate anion (pK_a 8.2 in DMSO) that opened the possibility to monitor the association event by ^1H NMR spectroscopy, following the host as well as the guest protons. Both modes of monitoring agree to within a factor of two in the affinity constant ($\Delta G° \approx 0.4$ kcal mol^{-1}). Based on the equilibrium constants (see the Supporting Information, Table A), host **3** qualifies as an outstanding electroneutral receptor for common anions in highly competitive media, such as DMSO, which outmatches other non-charged anion hosts by several orders of magnitude.[37–39] Moreover, its mechanism of binding does not rely on metal coordination nor on conventional hydrogen bonding that forms the basis for binding of negatively charged species in almost any other anion receptor. Thus, anions that are hardly susceptible to complexation[40] by hydrogen-bond-donating hosts like BH_4^-, tetrazolate, or NO_3^- are readily bound with exceptional affinity.

The energetic signature of this encapsulation process was probed by isothermal calorimetric titration (ITC). For all anionic species, we invariably found strong endothermic binding (Figure 2, Table 1), indicating that the exclusive cause for complexation is the overwhelmingly positive entropy of association. Unlike other ionic associations in polar solvents, which are also characterized by high positive entropies,[41] we observe good preservation of a 1:1 binding stoichiometry irrespective of the individual chemical nature, the absolute charge, or the charge density of the guest. Quite a number of common anions (HSO_4^-, $H_2PO_4^-$, $H_2PO_2^-$, SCN^-, ClO_4^-, BF_4^-), however, did not show any sign of complexation in DMSO solvent. This clear-cut distinction in guest complexation indicates rather rigid restrictions for binding. An obvious criterion is guest size. If the guest dimensions are larger than the portal open for penetration into the cavity, the guest will be rejected. SCN^-, ClO_4^-, and BF_4^- supposedly belong to this category, as their ionic sizes are greater than the largest ion effectively bound, namely iodide. The size correlation is another strong argument in favor of the encapsulation process. However, size restriction cannot rationalize the rejection of HSO_4^- or $H_2PO_4^-$, as these anions are nominally smaller than iodide.[42] We attribute their reluctance to enter the host cavity to their hydrogen-bond donating capacity, which distinguishes them from the other anions and leads to strong solvates with DMSO, itself being one of the best hydrogen bond acceptors known.[43]

Regarding the origin of binding, an inspection of the enthalpy and entropy components is revealing. The compensation plot depicted in Figure 3 encompassing all anions bound is linear with good regression ($R = 0.93$) and has a slope somewhat lower than 1 (0.84). When I^- and HCO_3^-, which appear as outliers to the regression line and probably represent special cases owing to their large size (I^-) or hydrogen-bonding capacity (HCO_3^-), are excluded, the linear fit is substantially improved (slope = 0.92; intercept +27.9; $R = 0.97$). Obviously, the principal mechanism for anion binding derives from an offset towards a positive and general entropy contribution that is intrinsic to all guest species and thus represents a non-specific share.

In view of the encapsulation process, the burst in entropy may just reflect the general desolvation phenomenon in the first place of the negatively charged species on invasion of the guest into the molecular cage (the entropy change is

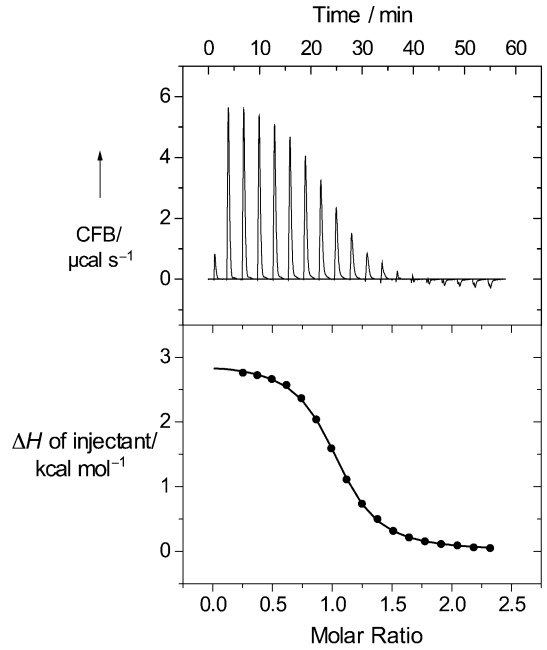


Figure 2. Isothermal titration calorimetric determination of cyanide binding to host **3** in DMSO at 303 K. The upper panel shows the heat pulses experimentally observed in each titration step (CFB = cell feedback current). The lower panel reports the respective time integrals translating as the heat evolved for each aliquot and its coherence to a 1:1 binding model. Model: OneSites, $\zeta^2/DoF = 223.6$, $N = 1.01 \pm 0.003$, $K = 8.8 \times 10^4 \pm 2.6 \times 10^3$ M^{-1}, $\Delta H° = +12.22 \pm 0.05$ kJ mol^{-1}, $\Delta S° = +135.1$ J K^{-1} mol^{-1}.

Table 1: Energetics of host–guest binding of **3** with tetraalkylammonium salts in DMSO at 303 K as determined by isothermal microcalorimetry (ITC).

	Salt	K_{ass} [M^{-1}]	$\Delta G°$ [kJ mol^{-1}]	$\Delta H°$ [kJ mol^{-1}]	$T\Delta S°$ [kJ mol^{-1}]
1	TEA^+Cl^-	1.2×10^5	−29.38	+15.05	+44.45
2	TEA^+Br^-	9.3×10^4	−28.81	+12.31	+41.13
3	TEA^+I^-	3.3×10^3	−20.4	+17.64	+38.03
4	$TEA^+N_3^-$	6.4×10^4	−27.87	+15.43	+43.36
5	$TEA^+NO_2^-$	5.0×10^4	−27.24	+9.62	+36.89
6	$TEA^+NO_3^-$	1.8×10^4	−24.63	+4.71	+29.29
7	TBA^+CN^-	8.8×10^4	−28.67	+12.24	+40.95
8	TEA^+OCN^-	2.4×10^4	−25.40	+9.64	+34.99
9	$TBA^+F^- \cdot 3\,H_2O$	1.8×10^4	−24.66	+13.25	+37.90
10	$TEA^+HF_2^-$	2.4×10^4	−25.39	+28.99	+54.39
11	$TEA^+HCO_3^-$	1.4×10^3	−18.22	+27.14	+45.38
12	$TEA^+BH_4^-$	7.8×10^4	−28.36	+14.15	+42.47
13	TEA^+ tetrazolate$^-$	2.4×10^4	−25.43	+18.66	+44.12
14	TEA^+_2 oxalate^{2-}	1.7×10^4	−24.53	+35.90	+60.34

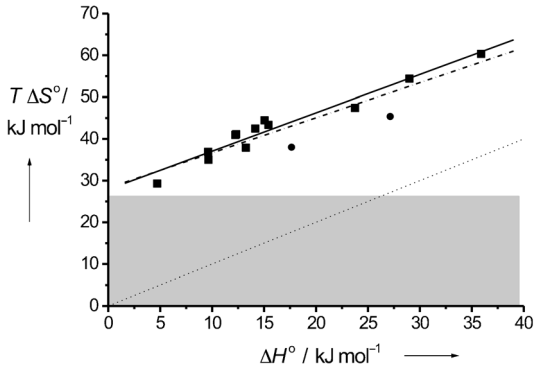


Figure 3. Compensation plot of the enthalpic versus the entropic components of anion binding to host **3**. ••••• ideal compensation as a guide to the eye; –•–• linear regression fit to all data; —— best fit omitting the two outliers (●). The shaded area represents the unspecific share of the total entropy change.

represented by the shaded area in Figure 3). The release of bound solvent molecules into the bulk phase, however, involves both interaction partners, as the change in charge density of the host on guest penetration must also alter its solvation. Furthermore, each guest adds a supplementary pack of interaction energy defined by the individual molecular properties of the guest, thus characterizing the specific balance of that species in the interactions with DMSO versus the interior of the host.

Considering the entropic component $T\Delta S°$ (Figure 3) the span attributable to the unspecific fraction ($+28$ kJ mol^{-1}) is unusually large and of the same order of magnitude as the maximum specific contribution (oxalate: $+32$ kJ mol^{-1}). Most anions, however, add a smaller specific share, suggesting the dominance of the unspecific contribution that indicates a common fundamental binding mechanism.

The stringent enthalpy–entropy compensation renders the range in binding free energy $\Delta G°$ rather small (Table 1).[44–46] Host **3**, thus, emerges as an agent that is very capable of discrimination of anions into binding and non-binding guests according to a threshold in favorable entropy gained on encapsulation, yet its capacity for differentiation among the binders is limited and does not exceed a factor of about 80.

The respective surplus in terms of entropy can make up for quite large deficits in enthalpy that result from the corresponding trade of the endothermic change in solvation of both host and guest and the exothermic transfer of the guest into the positively charged interior of the host. The experimental observation confirms that this balance is largely ruled by solvation outmatching the specific host–guest interaction. The binding process in the case at hand is very weakly sensitive to the geometry, basicity, hydrogen-bond donor/acceptor capacity, or electron pair donor capability of the guest, and is thus distinct from all other artificial anion hosts in addressing the most fundamental property that defines an anion: the negative charge.

The electroneutral yet zwitterionic host **3** qualifies as a rare and conceptionally rather unique example for binding negatively charged guests in polar organic solvents such as DMSO. The small and structurally enforced molecular cavity serves as an unspecific microsolvent that is capable of replacing the entire solvation shell from the guest by virtue of a strong electrostatic potential. Although the enthalpic balance is quite unfavorable in this encapsulation process, highly stable complexes are formed owing to a dramatic gain in entropy as a consequence of releasing the solvent molecules from the solvation sphere primarily of the guest. In contrast to the mainstream concepts of anion complexation, which rely on dedicated enthalpic interactions between host and guest, such as hydrogen- or halogen-bonding, electron-pair donor–acceptor interactions, or the exploitation of general van-der-Waals binding following shape complementarity, host **3** just defines an initially unoccupied space having an electropositive potential suitable for anion inclusion with minimal impact on its molecular structure. The success of this idea feeds our hope that entropy tailoring can be added to the toolbox routinely used in the design of specific receptors without compromising their structural integrity.

Received: August 25, 2011
Published online: November 18, 2011

Keywords: anions · cage compounds · calorimetry · enthalpy–entropy compensation · host–guest systems

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