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Surprises in the Design of Anion Receptors: Calorimetry Prevents False Reasoning

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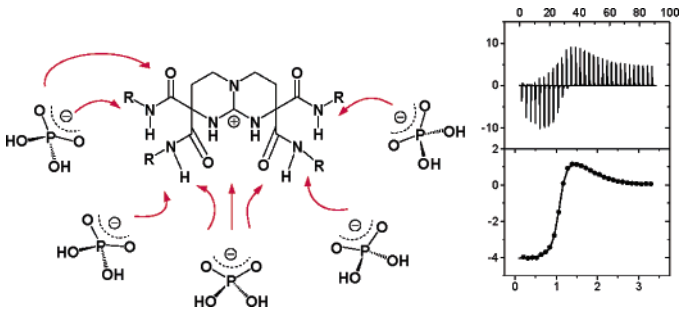
ABSTRACT



Supplementing bicyclic guanidinium anion receptors with four *sec*-carboxamido groups leads to enhanced affinity for oxoanions, however, for a different reason than originally planned. Calorimetric analysis reveals that better binding is due to higher association entropies rather than more negative enthalpies. Thus, molecular design following geometric and functional complementarity principles may misguide supramolecular constructions aimed at a unique host–guest binding mode, as required, e.g., by self-assembly or catalysis.

In supramolecular design, the optimization of host−guest binding relies primarily on the tuning of the noncovalently interacting interfaces in particular with respect to geometric and functional group complementarity. The goal is to maximize the mutual fit of the binding partners, which then is presumed to result in utmost affinity as a consequence of a unique individual interaction motif, the structure of the host−guest complex. Using the guanidinium−oxoanion host−guest pair (cf. Figure 1) as a prominent example, we show with the help of a calorimetric analysis that the outcome in an effort in tailoring this interaction furnishes an improved affinity as expected, however, for a different energetic reason. Rather than boosting reciprocal enthalpic attraction, the better binding emerges from more positive association entropies. This result bears on the molecular design of artificial receptors since those applications relying on precise structuring of the host−guest complex, e.g., in enthalpy (ΔH)-dominated processes such as self-assembly or catalysis, may be differentiated from others that primarily address Gibb's enthalpy (ΔG) differences as, e.g., in extractions.

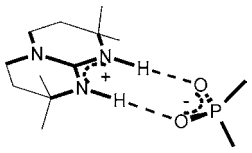


Figure 1. Sketch of the guanidinium oxoanion binding motif as it occurs in many biological and abiotic receptors.

The guanidinium group has a rich history both in biological[1] and artificial receptors.[2] Especially successful examples of the latter class employed the bicyclic version (Figure 1), which limits the variety of low-energy guest-binding modes

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and may additionally be readily incorporated into polytopic hosts following peripheral substitution.[3−5] The tetracarboxamide **1** was selected as the primary target because it combines a high density of hydrogen donor functions suitable for anion binding[6] with straightforward options for modification and incorporation into polymodular hosts. Ideally, all hydrogen bond donors should converge with their sticky sides onto the bound guest anion, which as a result would be held in a unique position by strong attractive forces. The formation of such an eminent and singular binding mode should surface in an exothermic effect relative to a tetraallyl-substituted host **2** lacking these functions. The congested disposition of the carboxamide anchor groups must hamper their proper solvation, thus adding another favorable enthalpic contribution to guest binding, because of the reduced costs of desolvation. Conversely, the almost isodirectional superposition of the hydrogen bond dipolar vectors is energetically unfavorable[7] and should diminish the observable exothermicity. In addition, intramolecular hydrogen bonding between neighboring amido groups may prevent their optimal orientation toward the guest. However, such an event, for geometric reasons, can extinguish only part of the hydrogen bond donicity and cannot eliminate the entire binding power. In summary, the tetracarboxamido host **1** is expected to show enhanced enthalpic binding in comparison to the tetraallyl congener **2**.

The preparation of the target compound **1** followed a different and considerably shortened strategy than used in the established syntheses of this class.[8] A first indication that the product deviated in the subtle mode of anion binding from the ordinary behavior seen with other bicyclic guanidinium hosts[9] was realized from the NMR titration of **1** with dihydrogenphosphate in acetonitrile (Figure 2).

While the signal of the guanidinium NH protons broadened and eventually vanished in the baseline on addition of the anion, the amide NH resonance experienced the expected downfield shift, reflecting their direct participation in guest complexation. The change in chemical shift, however, at the concentration chosen did not comply with an ordinary 1:1 stoichiometric binding model but showed systematic deviations indicative of additional binding events. The deconvolution of higher order complexation using this limited data set proved to be unsuccessful.

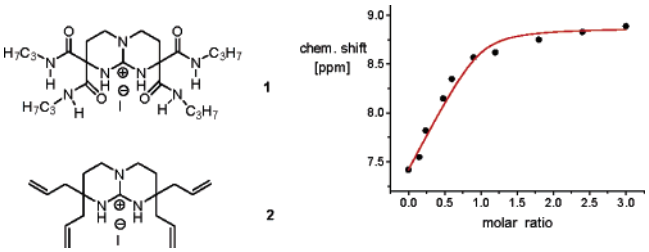

Figure 2. NMR titration of guanidinium host **1** (amide NH signal) with dihydrogenphosphate (as a TBA salt) in acetonitrile at 1.0 mM, ambient temperature. The solid line represents the best fit to a 1:1 binding model.

More telling in this respect were the isothermal calorimetric titrations (ITCs) depicted in Figure 3. The addition of the host **1** into the solution of the dihydrogenphosphate in acetonitrile (panel A) produced a heat response distinguishing various successive phases. Apparently, several processes occurred depending on the actual stoichiometric ratio of the host and guest partners. The initial stages (host:guest ratio $n < 0.3$) featuring a high excess of phosphate anion over the guanidinium host undoubtedly reflect higher order complexation but eluded our quantitative analysis. The stoichiometric regime with $n > 0.5$ was cleanly described by a binding model in which a low-affinity and endothermic 1:2 host−guest binding step is taken over by an exothermic 1:1 complexation as soon as the host−guest ratio allows the latter complex to be formed in substantial amounts. The

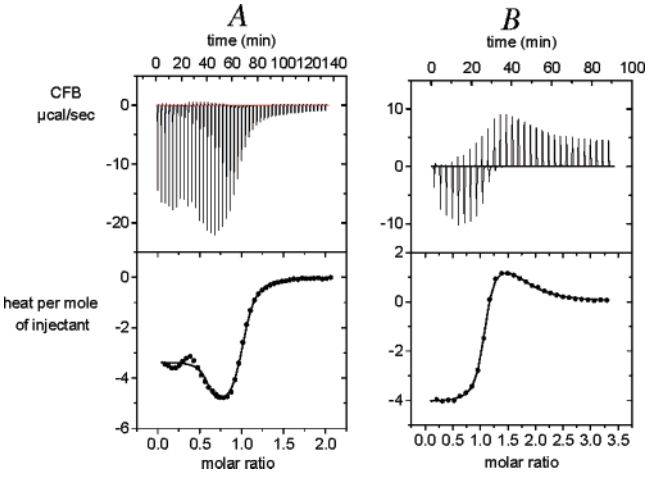

Figure 3. ITC traces of the titration of **1** into dihydrogenphosphate (1.53 mM, as a TBA salt) in acetonitrile at 293 K (panel A) or adding $H_2PO_4^-$ into host **1** solution at 0.69 mM (panel B). The lines represent the best fit to a two-independent-site model. The derived energetic constants for the 1:1 binding step are included in Figure 4.

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validity of this sequence of events was probed by inverting the titration sequence (panel B). Under these conditions, the exothermic formation of the 1:1 complex precedes the endothermic 1:2 process after which the heat evolution ceases because higher complexes are not formed due to their weaker affinity and the moderate excess of guest anion applied.

The energetic parameters for the 1:1 process in both titration modes are almost congruent. The mere fact that higher order complexes were observed with the carboxamido host **1** but not with **2**[3,12] suggests less stringency in the binding configurations of the former. The excellent data fit using a two-independent-site model rather than a sequential-site model would at first sight suggest noncooperativity between the binding steps. As the former model uses more adjustable parameters for fitting, conclusions on the cooperativity of binding on this basis appear to be hasty. The 1:2 step association constant could not be determined with fidelity owing to the small fraction of the saturation isotherm detectable in the 1:2 stoichiometric step. On top, severe cross correlation of the fit parameters originating from a flat error minimum just allowed estimation of the formation constant to be smaller than the 1:1 binding step by at least a power of ten. Structural investigation by NMR did not provide any clue on the various guest binding modes because of the fast guest exchange.

On comparing the binding energetics of **1** and **2**, we noticed a quite unexpected yet seemingly constitutive feature of polytopic guest binding. In the entire series of oxoanions probed (Figure 4), the 1:1 complex formation constants of host **1** versus host **2** are enhanced, putatively corroborating the naïve anticipation that the sheer number of attractive interactions leads to increased binding strength and thereby determines the affinity. The inspection of the calorimetric data discloses this as an error. In all cases, the enthalpic interaction reflecting the net attraction of the binding partners is smaller for the carboxamido host **1** than for the alkylated analogue **2**. The enhanced affinity observed is exclusively due to an overwhelming increase in the entropic component of association, $T\Delta S$.

The rationalization calling for the disruption of putative ion pairs that iodide counterion might preferentially form with the amide **1** rather than with the less hydrogen bonding host **2** is implausible. First, ion pairing with iodide is rather weak under the conditions applied, as was shown in another trend analysis with benzoate as a guest,[12] and on a second count should contribute an invariant share throughout the guest series. Instead, we observe dramatic variations differentiating the individual guest anions. A straightforward explanation to account for this surprising result is the release of the supposedly well-structured solvent shell, solvating the polar amido functions to the bulk solvent.[10] If this were the only reason, one would expect the most massive effect for

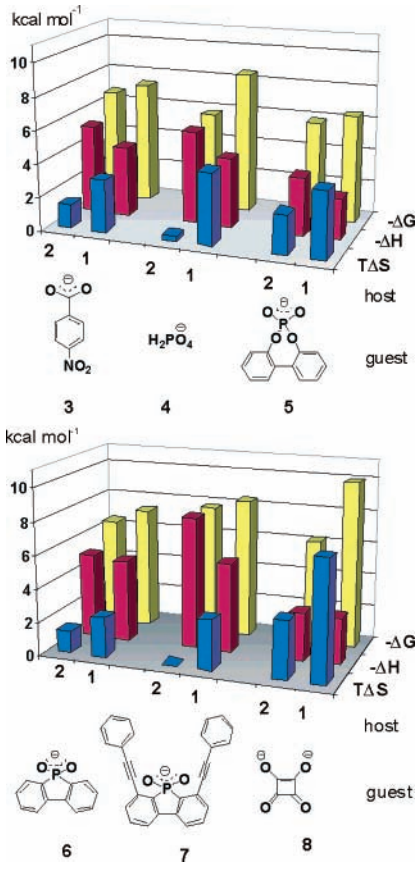

Figure 4. Comparison of the binding energetics of 1:1 stoichiometric complexes of guest species **3**−**8** (as a TBA salt) to guanidinium hosts **1** and **2** in acetonitrile.

phosphinate **7** since this guest undoubtedly features the most extended interface between the binding partners and commonly solvent release correlates with the interface area of host and guest.[11] Whereas the anionic portion of the guests ready for interaction with the guanidinium sites within the series is very similar, indeed, changes could derive from the more hydrophobic scaffolds holding them. The expectation of enhanced desolvation in the case of the larger anions yet does not meet with the experimental observations. The greatest entropic differences between hosts **1** and **2** are found in the associations with the smallest anions, **4** and **8**. Desolvation as a major cause of the association entropy differences must also suffer from the proximity of all polar moieties in **1**, which limits their adequate solvation, leading to a smaller number of solvent molecules set free on guest binding and thus to a less positive gain in entropy. One may expect the absolute contribution of this effect not to be great at all because only the difference in solvent ordering between the solvation shell and the bulk counts. With respect to entropy, both environments should rather resemble each other because, as judged from the standard molar entropy ($\Delta S° = 149.6$ J K^{-1} mol^{-1}), acetonitrile is one of the most structured organic solvents known. Furthermore, if differential desolvation of the two guanidinium hosts were to blame, one

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should see a more uniform absolute difference within the series than is actually observed.

In conclusion, the significant entropy differences found are thus believed to originate from variations in the number and stiffness of the mutual binding modes encompassing the partners rather than from desolvation. The guests capable of creating and populating a larger variety of energetically low-lying host−guest configurations, i.e., the symmetrical anions phosphate and squarate, experience the greatest gains in binding entropy. As a corollary, the binding energetics as well as the presence of higher-order complexes support the view that enhanced affinity in guest binding by host **1** results from *weakened* structural definition of the host−guest associated ensemble. The introduction of several hydrogen bonding functions into the parent host skeleton counteracts rather than promotes the formation of a well-structured host−guest complex. The importance of this entropic contribution for design has been analyzed recently.[12,13]

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Affinity and selectivity in directional supramolecular systems are composite responses of frequently counteracting influences. The analysis of structure as probed, e.g., by NMR methods, in many instances may then be a flawed tool in their study because of the averaging between rapidly interconverting species. Here, an example from abiotic host−guest complexation demonstrates the utility of an energetic analysis to avoid the pitfall of false reasoning that may follow from all too simple design concepts.

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Supporting Information Available: Synthetic scheme of the preparation of compound **1**, characterization of the product and some key intermediates, and a table containing the thermodynamic parameters depicted in Figure 4. This material is available free of charge via the Internet at http://pubs.acs.org.

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