Binding Hydrated Anions with Hydrophobic Pockets

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S *Supporting Information*

ABSTRACT: Using a combination of isothermal titration calorimetry and quantum and molecular dynamics calculations, we demonstrate that relatively soft anions have an affinity for hydrophobic concavity. The results are consistent with the anions remaining partially hydrated upon binding, and suggest a novel strategy for anion recognition.

The challenges associated with anion recognition are well known.[1] They have a range of geometries, may be pH sensitive, and are larger than the equivalent isoelectronic cations and have a lower charge to radius ratio. This diffuse nature means that, across all the classes of functional groups utilized to bring about recognition,[1,2] those involving Coulombic attraction and hydrogen bonding have proven to be the most popular. This is particularly true for anion recognition in aqueous solution, where these strategies have been utilized to counter the strong interactions between the anion and its hydration shell.[3] Thus, most of the reported hosts for anions that function in pure/buffered water are cationic.[4] Moving away from this strategy is the idea of utilizing halogen bonds for recognition,[5] an approach that takes advantage of the orthogonality between the requirements for forming halogen bonds and those for forming hydrogen bonds; if the latter is not utilized, competition with water is less important.

An alternative strategy is not to compete with the waters of hydration but to bind the anion with its solvation shell. Although a wide range of ditopic receptors have been synthesized and studied,[6] in general supramolecular chemistry has focused on the recognition of singular species. But why not recognize a hydrated anion rather than a "naked" one? Although this possess many challenges, it sidesteps the energetic requirements of ion desolvation and has the potential to reveal subtleties about ion hydration of import to studies of the Hofmeister effect and how anions interact with biomacromolecules.[7]

One of the key requirements for the recognition of hydrated anions is undoubtedly a large, well-defined binding pocket, the circumambient nature of which allows for multi-point recognition.[8−11] But what are the specifics of such pockets? How many waters of hydration are easily removed from an anion, and is there a preferred hydration geometry for each anion type? Although much has been learned about isolated water clusters[12] and the solvation requirements of ions,[13] what we know of the structural requirements for recognizing hydrated ions is, to our knowledge, limited to the solid state.[14]

We recently showed that perchlorate (ClO_4^-) has an affinity for the hydrophobic pocket of cavitand **1**, and that this association is dependent on the nature of other salts.[15]

1
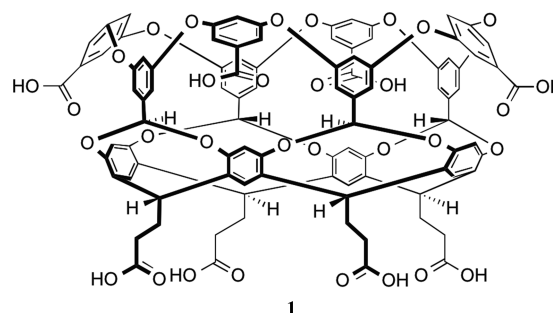
Furthermore, ClO_4^- binding is able to induce Hofmeister effects in the binding of amphiphilic guests to **1**.[16] Here we demonstrate that anion binding to the concavity of **1** is general, use isothermal titration calorimetry (ITC) to identify that these complexation events are strongly exothermic and entropically penalized, and show with a combination of quantum calculations and molecular dynamics simulations that partial solvation of the guest is key to binding.

We examined the affinity of 26 monovalent sodium salts for host **1**. All associations were examined at pH 11.5 to ensure sufficient solubility of the host and avoid protonation-state changes in the guest.[17] Initial screening utilized ^{1}H NMR to qualify and, where possible, quantify each association. This determined 18 anions that bound. Those that did not bind were cyanate (CNO^-), formate (HCO_2^-) acetate ($MeCO_2^-$), ethanesulfonate ($EtSO_3^-$), borohydride (BH_4^-), chloride (Cl^-), fluoride (F^-), and trifluoroacetate ($CF_3CO_2^-$).[18] Of the binding anions, four bound too weakly to give reliable data: bromide (Br^-), azide (N_3^-), bromate (BrO_3^-), and tetrafluoroborate (BF_4^-). Finally, of the remaining 14 guests, two proved problematic: MnO_4^- and $AuCl_4^-$. The former gave a reliable K_a value of 1055 M^{-1} by NMR, but presumably because ITC also detected background reaction of this guest, we could not obtain consistent calorimetric data. Similarly, $AuCl_4^-$ was qualified to bind strongly to the host, but no reliable quantification of this association was possible with either NMR or ITC, even after solutions of the guest were allowed to stand for 48 h to ensure that any decomposition of the guest to form the corresponding tetrahydroxo gold complex (Au-$(OH)_4^-$) was complete.

Table 1 shows the ITC data for the remaining anions. Because the Wiseman parameter for each salt was low ($0.01 \leq c$

Table 1. Thermodynamic Data from NMR and ITC for the Binding of Anions of Sodium Salts to Host 1[a]

anion	K_a (M^{-1})		$\Delta G°$ (cal/mol)	$\Delta H°$ (cal/mol)	$-T\Delta S°$ (cal/mol)
	NMR[b]	ITC[c]			
$Cl_3CCO_2^-$	5383	6337	−5188	−6499	1311
PF_6^-	575	790	−3950	−11610	7658
$MeSO_2S^-$	391	660	−3848	−11983	8136
ReO_4^-	322	371	−3509	−7393	3884
TfO^-	67	314	−3406	−4529	1124
IO_4^-	216	235	−3201	−8029	4828
ClO_4^-	95	160	−3010	−9049	6039
BH_3CN^-	67	152	−2975	−7842	4867
$Cl_2CHCO_2^-$	50	52	−2345	−4129	1787
SCN^-	33	44	−2240	−8508	6268
$N(CN)_2^-$	10	37	−2152	−4219	2067
I^-	11	17	−1680	−5276	3596

[a]The average of two or three individual experiments. [b]25 °C, 10 mM sodium phosphate buffer, pH 11.3. [c]25 °C, 50 mM sodium phosphate buffer, pH 11.5.

$\leq$ 1), each titration required modification, as outlined by Turnbull[19] and Tellinghuisen.[20] Relatedly, the protocols from Turnbull[19] were required because some of the titrations were limited to a maximal 80% complexation. Furthermore, the relatively high salt (titrant) concentrations necessitated reference titrations to account for salt dilution. These provisions gave reliable data, and using the data from non-associating NaCl, we confirmed that the effects of Na$^+$ binding[21] to R−CO$_2^-$ of the host were negligible.

Overall, the K_a values from ITC were higher than those determined by NMR. These differences were attributed to the higher ionic strength of the solutions used in ITC (50 mM versus 10 mM).[15] In general, the binding anions are relatively hydrophobic. In other words they are soft, weakly hydrated, and "weakly coordinating",[22] a term that has a distinct Coulombic force, organic solvent-based etymology contradicting the associations observed here. Although the charge on the octa-anionic host is attenuated by cation condensation to the exterior coat,[23] it is quite surprising that all complexations were enthalpically favored and entropically penalized.

The strongest-binding guest was found to be trichloroacetate ($Cl_3CCO_2^-$), which also had a relatively small entropy penalty of complexation; interestingly, dichloroacetate ($Cl_2CHCO_2^-$) bound >2 orders of magnitude more weakly, with a much smaller enthalpy and a slightly larger entropic penalty. Furthermore, as noted above, acetate demonstrated no affinity for the host.[16a] The strong association of $Cl_3CCO_2^-$ may in part be attributed to the formation of C−H⋯X hydrogen bonds between the inward-pointing benzal protons of the host and the halogen of the guest,[24] a conclusion supported by NMR signal shifts upon complexation (Supporting Information (SI)). However, the much lower affinity of $Cl_2CHCO_2^-$ is unusual. In this case, negligible shifts in the benzal proton NMR signals suggest no C−H⋯X hydrogen bonds, but other shifts do suggest a gross "carboxylate up" binding motif similar to $Cl_3CCO_2^-$ (SI). ITC also revealed that, although it would be expected to have more space to move within the rigid pocket, $Cl_2CHCO_2^-$ actually had a larger entropic penalty for binding

than $Cl_3CCO_2^-$. Hexafluorophosphate (PF_6^-) was also found to bind relatively strongly. Interestingly, this guest bound with the second highest enthalpy, but also the second highest entropic penalty. Thus, although 30% less voluminous than $Cl_3CCO_2^-$, and as an octahedral ion (O_h, symmetry number σ = 24) would be expected to more freely tumble within the pocket of 1, its entropic penalty of complexation was 6 times larger. Similarly, methanethiosulfate ($MeSO_2S^-$) was found to have the strongest enthalpy of complexation but also the highest entropic penalty. Its binding was in sharp contrast to $EtSO_3^-$, which showed no affinity. Presumably, the larger and more polarizable sulfur atom of the thiosulfate is an important electronic factor behind the binding of this anion.

Several tetrahedral anions less reactive than MnO_4^- gave reproducible binding data, specifically ReO_4^-, IO_4^-, and ClO_4^-. As these possess the same geometry, they gave the opportunity to investigate the effects of percentage occupancy (space filling) of the pocket on affinity. However, there was no correlation between their volume (IO_4^- = 65 Å^3, ReO_4^- = 58 Å^3, ClO_4^- = 54 Å^3) and K_a, $\Delta H°$, or $-T\Delta S°$.

The binding of TfO^- was considerably weaker than that of $MeSO_2S^-$, suggesting that the "thiolate" sulfur atom of the latter plays a stronger role in binding than the inductive properties of the F-atoms of TfO^-. However, the fact that $EtSO_3^-$ does not bind indicates that the F-atoms of TfO^- do aid complexation. Triflate was noted to bind to host 1 with the lowest entropic penalty.

Three cyano-containing anions were found to weakly associate: cyanoborohydride (BH_3CN^-), thiocyanate (SCN^-), and dicyanamide ($N(CN)_2^-$. BH_3CN^- and SCN^- bound with relatively strong enthalpies. The fact that SCN^- bound whereas CNO^- did not confirms that charge diffusion is important. One possibility for the strong enthalpy of complexation seen with these anions is an anti-parallel dipole alignment of the cyano dipole with that of the host (∼5 D pointing out of the cavity portal, SI), a hypothesis that would also support the observation that acetonitrile is the best common organic solvent for denaturing capsular complexes formed by 1.[25] Again, however, the binding of these three anions came with an entropic penalty.

Finally, the weakest anion that reliably bound to host 1 was I^-. In this case binding was enthalpically dominated and entropically costly, the latter far more so than for the larger organic anions such as $Cl_3CO_2^-$.

These associations are relatively weak, but that binding does occur is surprising, considering that the host is ostensibly anionic (but see ref 23) and is comprised of electron-rich, not electron-deficient rings.[1,2,26] Moreover, anion complexation is likely in competition with traces of dihydrogen phosphate in the buffer. But why are these complexations entropically penalized?[27] And why is there a poor but defined trend that the smaller the guest, the greater the entropy penalty to binding? It has been shown that the addition or removal of an anion from aqueous solution results in a near-perfect cancellation of the ion−water and water-reorganization contributions to measured hydration entropies.[28] Consequently, it is the solvation state of the bound anion that must be key to the data in Table 1. To test this idea, we performed quantum and molecular dynamics (MD) simulations of complexes between 1 and I^-, ClO_4^-, and Cl^- (SI). The simulations revealed that the larger ions retain about half their solvation shells upon binding (Figure 1). For example, ClO_4^- has 6.4 solvation shell water molecules on average in the bulk and 3.1 when in the host, while much
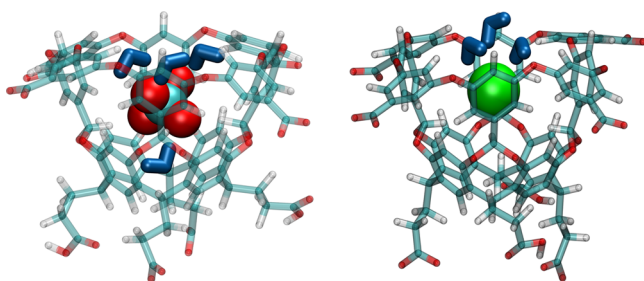
Figure 1. Representative calculated structures of the complexes between **1** and perchlorate (left) and iodide (right).

smaller I⁻ has 7.3 in the bulk but only 3.0 in the host. When restrained within the cavity, Cl⁻ kept most of its solvation shell; it has on average 6.6 in the bulk and 5.3 waters inside the host. These results are consistent with the overall free energy of hydration of these anions.[29]

We subsequently carried out free energy calculations to qualify anion affinity. Specifically, we used thermodynamic integration calculations to find the free energy of binding to both the host and the bulk (SI). These calculations gave negative free energies of complexation for ClO_4^- and I⁻ ($\Delta G°$ = −4.1 versus −8.2 kcal mol⁻¹) and a positive value for Cl⁻. Considering that these calculations involve differences that are a challenge for free energy calculations, and that they were determined under the standard state, it is perhaps not surprising that the empirical and calculated affinities of ClO_4^- and I⁻ are reversed. Our interpretation of these quantum calculations is simply that (1) they conform to which anions can bind and which cannot and (2) binding ions are stabilized by stronger dispersion interactions with the host than they are with water, whereas non-binding ions are stabilized by stronger electrostatic interactions with their hydration shell than with the host (SI).

MD simulations have previously demonstrated that filling the cavity of **1** with water is an exergonic process ($\Delta G_{hyd} \approx -5$ kcal mol⁻¹) dominated by enthalpy ($\Delta H_{hyd} \approx -20$ kcal mol⁻¹) and having a sizable entropic penalty ($-T\Delta S_{hyd} \approx 15$ kcal mol⁻¹).[30] These simulations also revealed that host **1** binds on average four or five waters within its hydrophobic cavity, but can bind up to seven.[30] Considering these points and the data presented here, our working hypothesis is that large anions such as $Cl_3CCO_2^-$ bind with a minimum of (or no) co-complexing waters, but that smaller, "harder" anions are partially solvated by highly organized, entropically costly waters. However, there is no simple relationship between the size of the anion and the entropic cost of binding because the number and arrangement of co-bound waters is intimately tied to the ion-specific thermodynamics of desolvation and how the corresponding stable, partially solvated anions complement the shape of the binding pocket.

These results have manifold implications. The fact that anion binding in water can be affected without complete desolvation—even in the absence of traditionally strong supramolecular motifs for anion recognition—suggests an alternative approach to this difficult task. Moreover, these results dovetail with what is known about anions at the air−water interface[31] and the macromolecule−water interface[32] and, regarding the latter, point to other ways, besides cation−anion or hydrogen bonding, that anions can interact with proteins.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10937.

NMR and ITC titration experiments and details of the quantum and MD simulations (PDF)

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Notes

The authors declare no competing financial interest.

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(17) In free solution, the pK_a values of the conjugate acids of the anions examined range from −20 to + 4.67. However, we have observed that the pK_a of carboxylic acids inside **1** can be shifted as much as 3−4 pK_a units: Wang, K.; Sokkalingam, P.; Gibb, B. C. *Supramol. Chem* **2015**, DOI: 10.1080/10610278.2015.1082563. If this is the case, then at pH 7 species such as acetate, formate, azide, dichloroacetate, and ethyl sulfate would bind primarily in their protonated form.

(18) Of the six anions that did not bind to the host and have reliable thermodynamic data for hydration, all have ΔH_{hyd} values greater than − 373 kcal mol^{-1}. In contrast, for the six binding anions with reliable hydration data, all have ΔH_{hyd} values less than − 338 kcal mol^{-1}. There is, however, no correlation between the hydration and binding thermodynamics discussed here.

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