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Dual Binding Modes of a Small Cavitand

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ABSTRACT

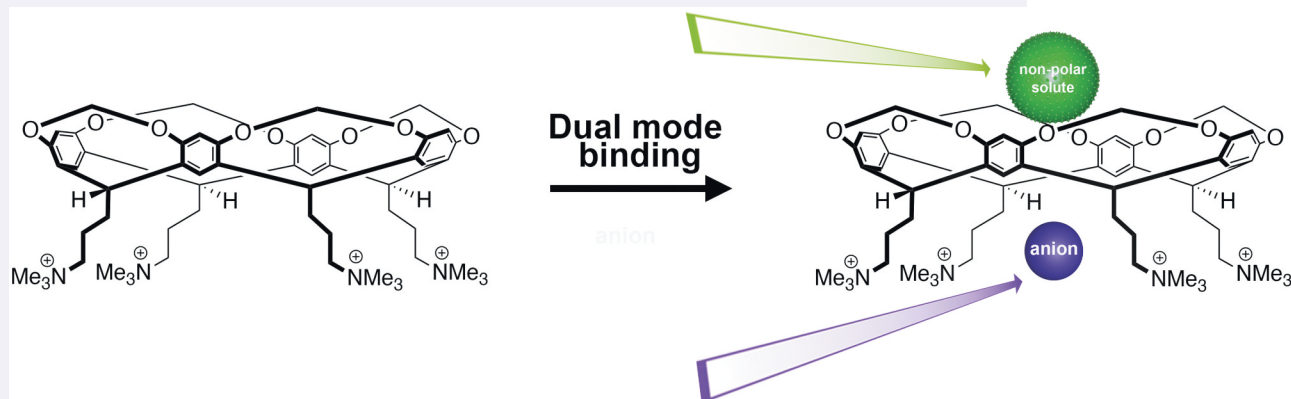
The small size and high cohesiveness of water means that water-mediated interactions are strongly context dependent. As a result, there is still much to learn about how non-polar solutes and ions interact with themselves or each other. To help address this issue, we report here on a cavitand host, TMAX-Cl (2). Possessing two different binding sites, a shallow non-polar dish that binds hydrophobes, and a crown of ammoniums that bind anions, TMAX-Cl (2) provides insight into the hydrophobic and Hofmeister effects. We find that binding to the non-polar site is weak, suggesting that a larger surface area is needed for substantial binding. In contrast, binding to the crown of ammoniums is relatively strong, despite the high dielectric of water. These findings provide a better understanding of water-mediated interactions, and define the supramolecular properties of TMAX-Cl 2 as we continue our studies of this host and related water-soluble cavitands.

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Cavitand; anion; hydrophobic effect; Hofmeister effect; host-guest chemistry



Introduction

Cavitands such as **1** (Figure 1) are well-established hosts that, in the presence of hydrophobic guests, form dimeric capsular complexes assembled via the hydrophobic effect. By internalising guests in their inner-spaces, these capsules can control their physical [2] and photophysical [3–5] properties, as well as their chemical [6,7] and photochemical [4,8,9] reactivity [10]. The range of guests that can bind to the pocket of hosts such as **1** is large; ranging from hydrocarbon gases to steroids, and even 'hydrophobic' anions such as I^- , ClO_4^- and PF_6^- . Host **1** has another trick up its sleeve, namely it can bind anions to its crown of four ammonium groups at its base [11,12]. Although located on the exterior of the host, anion binding to this site can affect the reactivity

of internalised guests by changing the effective charge and electrostatic potential field (EPF) of a cavitand/capsule [6,7].

This much stated, there is still much we do not know about the physico-chemical properties of these hosts. For example, although in the most general of terms we can state that the desolvation of the non-polar surface of the guest and that of the cavity and rim of the host, are key to hydrophobe binding and assembly, the context dependency of the hydrophobic effect makes more specific information difficult to obtain [13–18]. Similarly, although we have some understanding of the differences in anion selectivity displayed by the pocket and the crown, simultaneous binding can make it difficult to separate these two events and gain a detailed picture.

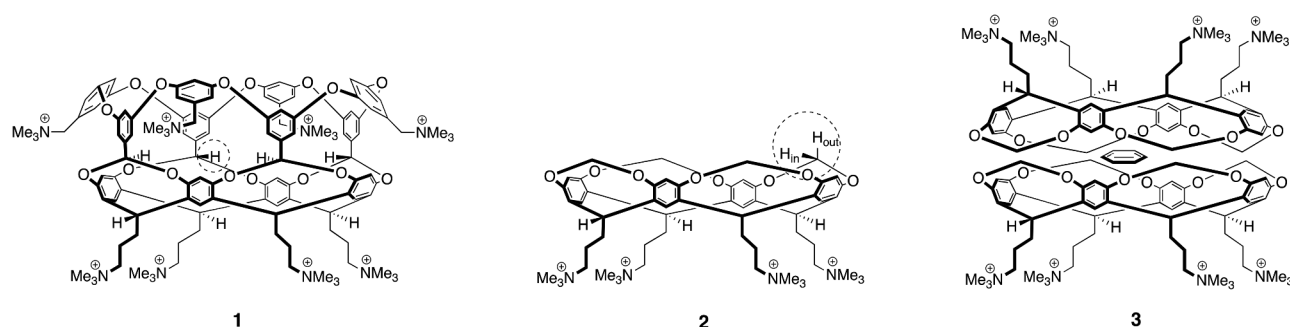


Figure 1. Structures of cavitand hosts **1** and **2**, and theoretical dimeric 2:1 complex of **2** with benzene. Examples of the benzal hydrogens and acetal hydrogens of structures **1** and **2** are circled.

To improve our understanding of the properties of molecules such as **1**, we recently reported on the synthesis of a new water-soluble cavitand, TMAX-Cl, **2** (Figure 1) [19]. With this host in hand, we hypothesised that its shallow pocket may be able to bind non-polar guests, whilst the crown of the host would bind anions in essentially the same way as the crown of **1**. We report on this dual-mode binding here, using a combination of [1]H NMR spectroscopy titrations to examine non-polar guest binding, and Isothermal Titration Calorimetry (ITC) titration experiments to assess anion complexation.

Non-polar guest binding to TMAX-Cl (**2**)

TMAX-Cl **2** was readily synthesised in three steps: namely, formation of the corresponding chloropropyl-footed resorcinarene, bridging this resorcinol with bromochloromethane to add the four acetal groups, and a fourfold Menshutkin reaction with trimethyl amine to replace the pendant halide groups. Ion exchange to remove any bromide counter-ions arising from the bridging of the resorcinol gave the tetra-chloride salt TMAX-Cl, **2**. For reference, the synthesis is shown in Scheme S1 (Supporting Information).

We were interested to determine if the minimal non-polar surface of TMAX-Cl **2** could bind suitable guests, and if so, whether or not such 1:1 complexes could also form 2:1 capsular complexes such as the theoretical benzene complex (**3**) shown in Figure 1. To investigate this we considered a broad range of guests: benzene, toluene, anisole, pyridine, tetrahydrofuran, 1,4-dioxane, cyclopentane, isopropyl alcohol, 1,2-dichloroethane, dichloromethane, chloroform-d, bromochloromethane, dibromomethane, iodomethane, bromoethane, 1-bromopropane and methane. This list was based on two general criteria. First, prior work from the Sherman group revealed that guests such as benzene, pyridine, and 1,4-dioxane, can be entrapped within carceplexes [20,21], and that these carceplexes are themselves

formed from the non-covalent dimerisation of cavitands akin to host **2** around a guest molecule. With this literature noted, it was anticipated that such guests may be close to the ideal size to trigger dimerisation of host **2** and the formation of 2:1 ‘sandwich’ complexes (**3**, Figure 1). Second, we selected a number of small halogenated guests because the four benzal hydrogen atoms of deep-cavity cavitands such as **1** (circled in Figure 1) form strong C–H...X–R hydrogen bonds with halogenated guests [22,23]. Thus, it was assumed that the presence of halogen atoms would help promote the formation of 1:1 and/or 2:1 host-guest complexes of **2**.

Probing for host-guest complex formation relied on [1]H NMR spectroscopic titration experiments, utilising the two distinctive signals from the acetal protons of **2** as the reporter atoms. We anticipated that H_{in} would be particularly responsive to changes in the local electronic environment arising from guest binding, whereas H_{out} would be responsive to host dimerisation. Because of the low solubility of most of the guests, and the corresponding difficulty in controlling the concentration of their aqueous solutions, we opted for titrations using the pure guest. Whilst this strategy adds uncertainty in terms to the binding constants obtained being absolute, we assumed that at least internally the affinity determinations would be consistent.

Preliminary investigations identified select guest binding using a 10 mM solution of **2** in pure D₂O. As there was no pH change between the beginning and end of the titrations (no ionisable groups on the host or guests), buffer was not used. Guest binding was identified by the downfield shifting of the H_{in} [1]H NMR signal with select guests. In no case did we observe significant shifting of other signals. Thus, there was no evidence of host dimerisation from significant movement of the H_{out} signal. Similarly, there were no significant shifts in the signals from the methylene groups of the pendant (trimethyl)ammonium propyl groups that would be expected if the guest bound to the host by nestling

within these chains. For the aforementioned guests, we found no affinity to TMAX-Cl **2** for: benzene, toluene, anisole, pyridine, tetrahydrofuran, 1,4-dioxane, cyclopentane, isopropyl alcohol, and methane. Additionally, 1,2-dichloroethane, dichloromethane, and bromoethane associated with only the weakest of affinities. In contrast, chloroform-d, bromochloromethane, dibromomethane, iodomethane, and 1-bromopropane were observed to associate with sufficient affinity that association constants could be reliably obtained. In each case binding was fast on the $[1]H$ NMR timescale (300 MHz), and as a result we carried out (14 point) titration experiments to obtain binding isotherms revealing the shift in H_{in} as a function of the host-guest ratio. Figure 2 shows a representative example for the complexation of iodomethane to **2**. In this particular case, the growing high-field signal from the methyl of the guest could also be used to track complexation.

We used Bindfit [24,25] to determine the affinity constants of these five most strongly associating guests (Table 1). All isotherms fitted the 1:1 binding model, with residual errors from the non-linear fitting of between 2% and 10% (Supporting Information). Not unexpectedly, the larger residual errors were obtained for the weaker binding guests, and to maximise reliability of the data the weaker affinity constants were determined from five titration experiments, whilst the stronger affinities were obtained using three to four titrations. Full details of these titration experiments are given in the Supporting Information. The obtained average binding constants and their standard deviations are shown in Table 1.

Considering the nature of the binding and non-binding guests suggests that one or more halogen atom is key to complexation. CPK models reveal that the larger the halogen atom of the guest, the greater the number of simultaneous $C-H_{in} \cdots X-R$ hydrogen bonds it can form with the acetal groups of TMAX-Cl **2**. An iodine atom can form four

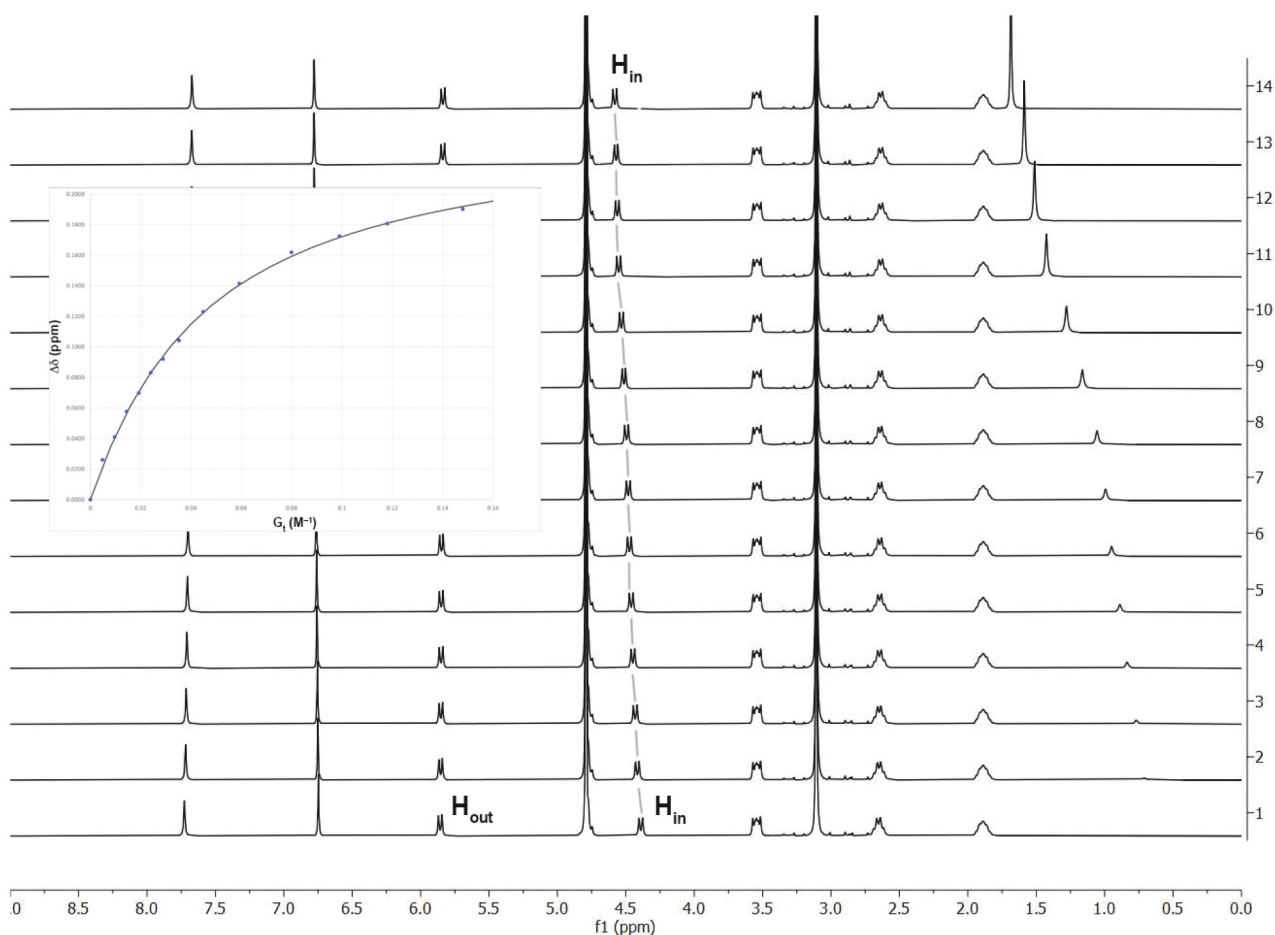


Figure 2. Representative titration data for the binding of iodomethane to TMAX-Cl **2**. The reporter proton H_{in} is indicated. $[Host] = 1$ mM. Spectra 1–14 are for 1) free host; and the following equivalents of guests: 2) 0.48; 3) 0.96; 4) 1.45; 5) 1.93; 6) 2.41; 7) 2.89; 8) 3.53; 9) 4.5; 10) 5.94; 11) 8.03; 12) 9.96; 13) 11.88; 14) 14.94. The growing, high-field signal arises from the methyl group of the guest.

Table 1. Summary of association constants (K_a) for halogenated guests binding to host **2** at 298 K.^a

Guest	K_a (M^{-1})	Std. dev.	ΔG ($kJ\ mol^{-1}$) ^b
Dibromomethane	45	± 10	9.43
1-Bromopropane	31	± 7	8.51
Chloroform-d	20	± 6	7.42
Bromochloromethane	15	± 4	6.71
Iodomethane	25	± 4	7.97

^aReported (average) K_a values and standard deviations are derived from titration experiments ran in at least triplicate.

^bCalculated value based on reported K_a value. Errors in $\Delta G < 10\%$, eg, for dibromomethane, $8.81 < \Delta G < 9.93\ kJ\ mol^{-1}$.

simultaneous hydrogen bonds, a bromine atom three, and a chlorine atom 2 [22]. In the case of deep-cavity cavitands such as **1**, this increase in simultaneous hydrogen bonding leads to an increase in guest affinity: $R-I > R-Br > R-Cl$ [22,23], and with this in mind it is perhaps not surprising that iodomethane and dibromomethane are two of the strongest binding guests. The other strong binder, 1-bromopropane, is more complicated because of its flexibility. Prior work involving a combination of Raman multivariate curve resolution vibrational spectroscopy and X-ray crystallography has revealed that the *gauche-trans* equilibrium of this guest is shifted towards the latter upon binding to α -cyclodextrin [26]. Analogously, we surmise that the guest binds to TMAX-Cl **2** with its bromine atom in the crown of acetal hydrogens, and its propyl group nestled on the side rim of the host. An overall *gauche* conformation of the guest would maximise host-guest interactions and minimise exposure of non-polar surface to the aqueous bulk.

In cases where the residual errors were relatively large, systematic rather than random deviations from the 1:1 model were occasionally observed at low equivalents of guest (e.g., Figure S17 in Supporting Information). We envisioned two possibilities for these deviations: host dimerisation or counter-ion binding. Regarding the former, DOSY [1]H NMR analysis (Supporting Information) revealed that the apparent hydrodynamic volume of the host did not change in the presence of varying equivalents of guest. At all stages of the titration, DOSY [1]H NMR indicated a monomeric host. Counter-ion binding is a second possibility. Certainly, deep-cavity cavitands have measurable affinities for charge diffuse anions [11,27]; however, even the larger cavities of these hosts had no measurable affinity for chloride ions, and we saw no direct evidence of bowl-anion affinity is recent work [19].

The affinity constants of 1:1 complexes with deep-cavity cavitands such as **1** can easily be as high as $1 \times 10^6\ M^{-1}$. Hence, our studies here reveal the precipitous drop-off in affinity when the size of the pocket of a host is reduced. Is this drop-off tied to the hydrophobic effect? Simulations frequently imply

that water-mediated hydrophobic interactions between small non-polar molecules are repulsive [18]; at least for convex surfaces. Perhaps this is true here, and the affinities in Table 1 arise purely because of $C-H_{in} \cdots X-R$ hydrogen bonding. A study of homologues from iodomethane through 1-iodopentane may reveal the degree to which non-polar surfaces lead to attractive water-mediated hydrophobic interactions in TMAX-Cl **2**. Regardless, the data here points to intermediately sized hosts – larger than **2** but not as large as **1** – as possessing the minimum requirements for sufficiently strong guest complexation for utilisation.

Anion binding to TMAX-Cl (**2**)

In studies with host **1**, we had determined the affinity of a range of anions to both the crown and pocket of the host. We had observed some fascinating selectivities of anion affinity to the two different pockets; in the most general of terms, larger, polarisable anions preferentially bound to the pocket of the host, whereas small more hydrated anions bound to its crown. However, simultaneous binding to both pockets limited the depth of analysis.

TMAX-Cl **2** offered the ideal opportunity to gain more information regarding anion binding to the crown of these hosts. Consequently, we turned to Isothermal Titration Calorimetry (ITC) to obtain the thermodynamic data for halide binding to the host. In all complexations studied, the Wiseman parameters c ($c = [Host] \times K_a$) was relatively small, and consequently we utilised standard protocols to ensure high-quality data [28,29]. In preliminary studies, we observed changes in the pH upon titrating salts into solutions of host **2**, and although these were small, we opted to study the affinity of the halides under buffered conditions. Specifically, we examined halide affinity in 10 mM sodium phosphate buffer at pH = 3 and pH = 7.3 [30]. To account for the heating of salt dilution during titration, in each experiment, we subtracted from the raw data the data for the addition of salt to a host-free solution. In repeated attempts, we did not observe any affinity of fluoride for TMAX-Cl **2**. However, excellent data were obtained for the other halides. A representative example, the binding of bromide at pH = 7.3, is shown in Figure 3.

Within each series of halide guests, the order of affinity (weakest to strongest) was as follows: $Cl^- < Br^- < I^-$. We attribute the sizeable range in affinity, e.g., $\Delta G = 9.1\ kJ\ mol^{-1}$ for Cl^- and I^- at pH 7.3, to differences in the hydration free energies of each anion. Iodide has a relatively low hydration free energy of $-283\ kJ\ mol^{-1}$, and as a result, we surmise that its solvation shell can readily adjust or partially move aside to allow the

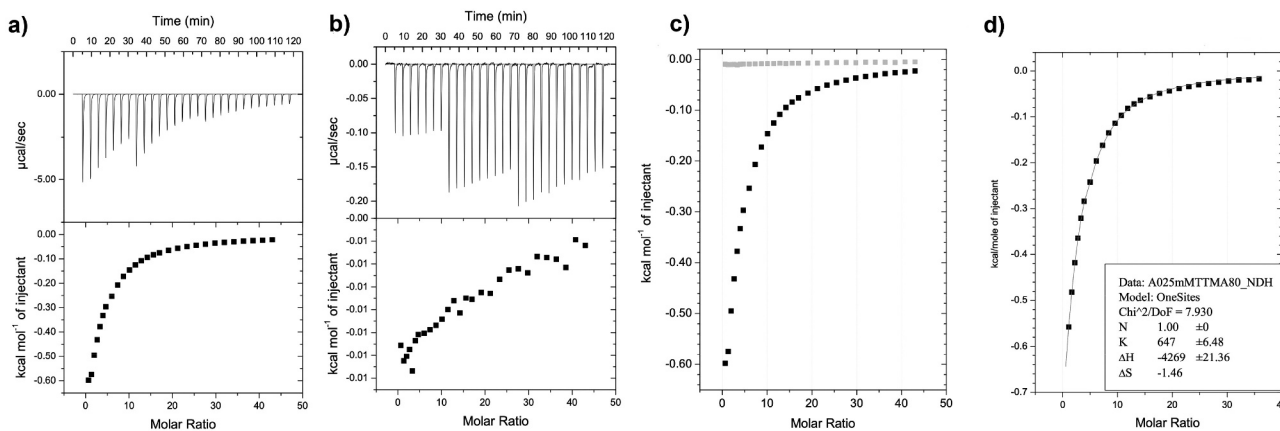


Figure 3. Representative ITC data for anion binding to TMAX-Cl (**2**) ([host] = 0.25 mM, 10 mM sodium phosphate buffer, pH = 7.3). Data are for the complexation of Br[−]: (a) Raw data for the titration of NaBr into a solution of TMAX-Cl (**2**); (b) reference titration of NaBr into the host-free solution; (c) Combined binding isotherms showing raw data (a) in black and reference titration data (b) in grey; (d) ITC titration data after subtraction of reference.

formation of direct I[−]⋯Me₃N⁺R interactions involving Coulombic, C–H⋯I[−] hydrogen bonding, and van der Waals interactions with the pendant groups of the host. In contrast, chloride is too strongly solvated to form direct interactions with the host (−347 kJ mol^{−1}). As a result, we surmise it primarily forms rather long and weak Coulombic interactions with TMAX-Cl **2**.

All complexations were strongly exothermic, and the larger the halide the greater the exothermicity. Thus, at pH = 7.3 iodide binding released 11.5 kJ mol^{−1} more heat than chloride binding. Entropy changes for guest binding were small, but there was a significant difference between the pH solutions: (−TΔS) = 1.3 and −2.1 kJ mol^{−1} at pH 7.3 and 3.0, respectively. In other words, whereas in general complexation is more favourable at lower pH, the enthalpic benefit to anion binding is smaller, but this is compensated for by a favourable change in −TΔS.

We had previously used [1H] NMR spectroscopy to measure halide binding to the crown of host **1** in 10 mM phosphate at pH = 7.3[11]. A comparison of these data (120, 740 and 3,200 M^{−1} for Cl[−], Br[−] and I[−] respectively) with those in Table 2 reveals gratifying similarities, suggesting that despite the complication of the second pocket in host **1**, our earlier K_a determinations were accurate.

Conclusions

We have shown that TMAX-Cl **2** possesses two very different binding sites: the first, a shallow non-polar dish of a pocket that binds hydrophobic guests with the assistance of hydrogen bonding to its acetal groups, the second, a crown of ammonium groups that bind anions. Binding to the non-polar site is weak, suggesting that a larger surface area is needed for substantial

Table 2. ITC-derived binding constants and thermodynamic data for halides binding to TMAX-Cl (**2**).^a

	Guest	K _a (M ^{−1})	ΔG (kJ/mol)	ΔH (kJ/mol)	−TΔS (kJ/mol)
10 mM sodium phosphate buffer, pH = 7.3	I [−]	3,677	−20.3	−22.7	2.4
	Br [−]	652	−16.1	−17.7	1.6
	Cl [−]	92	−11.2	−11.2	0.0
10 mM sodium phosphate buffer, pH = 3.0	I [−]	5,827	−21.5	−18.7	−2.8
	Br [−]	978	−17.2	−17.9	0.7
	Cl [−]	132	−12.1	−8.6	−3.5

^aAt 298 K. Errors in ΔH, K_a and ΔG were obtained by performing at least three titrations and averaging. The obtained average ΔH and ΔG values were then used to calculate the average −TΔS value. All errors were less than 10%.

binding. In contrast, binding to the crown of ammonium groups is relatively strong, despite the high dielectric of water which is often thought of as an effective screen for Coulombic interactions. These findings provide a better understanding of cavitands such as **1** and define the supramolecular properties of TMAX-Cl **2** as we continue our studies of this host and related water-soluble cavitands.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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References

- [1] Ashbaugh HS, Gibb BC, Suating P. Cavitand complexes in aqueous solution: collaborative experimental and computational studies of the wetting, assembly, and function of nanoscopic bowls in water. *J Phys Chem A*. **2021**;125(13):3253–3268.
- [2] Cai X, Kataria R, Gibb BC. Intrinsic and extrinsic control of the pKa of thiol guests inside Yoctoliter containers. *J Am Chem Soc*. **2020**;142(18):8291–8298.
- [3] Kaanumalle LS, Gibb CLD, Gibb BC, et al. Controls the photophysics of aromatic molecules by suppressing their favored solution pathways. *J. Am. Chem. Soc*. **2005**;127(11):3674–3675.
- [4] Natarajan A, Kaanumalle LS, Jockusch S, et al. Controlling photoreactions with restricted spaces and weak intermolecular forces: exquisite selectivity during oxidation of olefins by singlet oxygen. *J Am Chem Soc*. **2007**;129(14):4132–4133. 10.1021/ja070086x.
- [5] Chen JY-C, Jayaraj N, Jockusch S, et al. NMR study of supramolecular effects of paramagnetic interaction between a nitroxide in bulk aqueous media. *J. Am. Chem. Soc*. **2008**;130(23):7206–7207.
- [6] Wang K, Cai X, Yao W, et al. Electrostatic control of macrocyclization reactions within nanospaces. *J. Am. Chem. Soc*. **2019**;141(16):6740–6747.
- [7] Yao W, Wang K, Ismaiel YA, et al. Electrostatic potential field effects on amine macrocyclizations within Yoctoliter spaces: supramolecular electron withdrawing/donating groups. *J Phys Chem B*. **2021**;125(32):9333–9340.
- [8] Kaanumalle LS, Gibb CLD, Gibb BC, et al. Controlling photochemistry with distinct hydrophobic nano-environments. *J. Am. Chem. Soc*. **2004**;126(44):14366–14367.
- [9] Gibb CLD, Sundaresan AK, Ramamurthy V, et al. Templatation of the excited-state chemistry of α -(*n*-Alkyl) Dibenzyl Ketones: how guest Packing within a nanoscale supramolecular capsule influences photochemistry. *J. Am. Chem. Soc*. **2008**;130(12):4069–4080.
- [10] Ismaiel YA, Gibb BC. Water-soluble Yoctoliter reaction flasks. In: Raynal M, Van Leeuwen Peditors, Supramolecular catalysis - New directions and developments. Wiley-VCH; **2021**. p in press.
- [11] Jordan JH, Gibb CLD, Wishard A, et al. Ion-Hydrocarbon and/or Ion-Ion interactions: direct and reverse Hofmeister effects in a synthetic host. *J Am Chem Soc*. **2018**;140(11):4092–4099.
- [12] Wishard A, Gibb BC. Dynamic light scattering studies of the effects of salts on the diffusivity of cationic and anionic cavitands. *Beilstein J Org Chem*. **2018**;14:2212–2219.
- [13] Ernst NE, Gibb BC. Water runs deep. In: Kubik S, editor. Supramolecular chemistry in water. Weinheim: Wiley-VCH; **2019**. p. 1–33.
- [14] Chandler D. Oil in troubled waters. *Nature*. **2007**;445(7130):831–832.
- [15] Patel AJ, Varilly P, Jamadagni SN, et al. Sitting at the edge: how biomolecules use hydrophobicity to tune their interactions and function. *J Phys Chem B*. **2012**;116(8):2498–2503.
- [16] Ben-Amotz D. Water-Mediated hydrophobic interactions. *Annu. Rev. Phys. Chem*. **2016**;67(1):617–638.
- [17] Hillyer MB, Gibb BC. Molecular shape and the hydrophobic effect. *Annu. Rev. Phys. Chem*. **2016**;67(1):307–329.
- [18] Ben-Amotz D. Hydrophobic ambivalence: teetering on the edge of randomness. *The J. Phys. Chem. Lett*. **2015**;6(9):1696–1701.
- [19] Jordan JH, Mague JT, Ashbaugh HS, et al. Buffer effects in aqueous host-guest systems: screening, competitive binding, or both? Submitted. **2021**.
- [20] Chapman RG, Chopra N, Cochien ED, et al. Carceplex formation: scope of a remarkably efficient encapsulation reaction. *J. Am. Chem. Soc*. **1994**;116(1):369–370.
- [21] Chapman RG, Sherman JC. Study of templation and molecular encapsulation using highly stable and guest-selective self-assembling structures. *J. Am. Chem. Soc*. **1995**;117(35):9081–9082.
- [22] Gibb CLD, Stevens ED, Gibb BC. C-H...X-R hydrogen bonds drive the complexation properties of a nanoscale molecular basket. *J. Am. Chem. Soc*. **2001**;123(24):5849–5850.
- [23] Laughrey ZR, Upton T, Gibb BC, et al. Confirms the importance of C-H...X-R hydrogen bonds in guest binding to deep-cavity cavitands. *Chem. Commun*. **2006**;9:970–972. doi: 10.1039/b515187b
- [24] Thordarson, P. Binding Constants and their Measurements. In Gale PA, Steed JW, editor. Supramolecular Chemistry: From Molecules to Nanomaterials. John Wiley & Sons, Ltd; **2012**; Vol. 2, p. 1–20.
- [25] Thordarson P. Bindfit. [cited **2021** May 21]. <http://supramolecular.org>
- [26] Urbina AS, Boulos VM, Zeller M, et al. Unfolding of 1-Bromopropane in alpha-Cyclodextrin. *J Phys Chem B*. **2020**;124(48):11015–11021.
- [27] Sokkalingam P, Shraberg J, Rick SW, et al. Binding hydrated anions with hydrophobic pockets. *J Am Chem Soc*. **2016**;138(1):48–51.
- [28] Turnbull WB, Daranas AH. On the value of *c*: can low affinity systems be studied by isothermal titration calorimetry?. *J Am Chem Soc*. **2003**;125(48):14859–14866.
- [29] Tellinghuisen J. Isothermal titration calorimetry at very low *C* *Anal. Biochem*. **2008**;373:395–397.
- [30] All data fitted the standard 1:1 model well. We did not observe any reasonable fitting to higher stoichiometry models such as 1:2 and 1:3. A 1:1 complexation model is obviously an approximation; at any instant the four intrinsic counter-ions, or the three counter ions and the guest anion, are likely to be distributed within the Stern layer (where they may be considered guests) and outwith the Stern layer (where they can be considered as free counterions)