

Electrostatic control of macrocyclization reactions within nano-spaces

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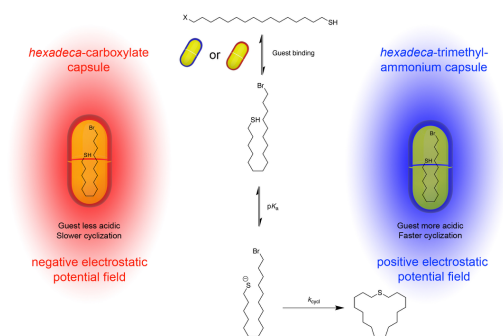
[†] KW performed initial studies into the described system. KW and XC performed the reported rate and guest motif determinations. XC performed the reported pK_a determinations, kinetic confirmation of pK_a of bound guest **2a**, and the Eyring analyses.

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Abstract

The intrinsic structural complexity of proteins makes it hard to identify the contributions of each non-covalent interaction behind the remarkable rate accelerations of enzymes. Coulombic forces are evidently primary, but despite developments in artificial nano-reactor design, a picture of the extent to which these can contribute has not been forthcoming. Here we report on two supramolecular capsules that possess structurally identical inner-spaces that differ in the electrostatic potential field (EPF) that envelops them: one positive, one negative. This architecture means that only changes in the EPF influence the chemical properties of encapsulated species. We quantify these influences via acidity and rates of cyclization measurements for encapsulated guests, and confirm the primary role of Coulombic forces with a simple mathematical model approximating the capsules as Born spheres within a continuum dielectric. These results reveal the reaction rate accelerations possible under Coulombic control and highlight important design criteria for nano-reactors.

Graphical Abstract



Introduction

Although there is still disagreement regarding how all the different non-covalent (and covalent) factors contribute to the remarkable rate accelerations observed in enzymes,^{1,2} it is generally accepted that modulation of the local electrostatic potential (EP, ϕ) around the substrate has a primary role in transition state stabilization.^{3,4}

For some time now, chemists have examined different ways in which reactions can be controlled by EP modulation. For example, by taking advantage of the dissimilar supramolecular properties of Li^+ and ClO_4^- ions, simple rearrangements or elimination reactions in diethyl ether can be greatly accelerated by high concentrations (~5 M) of LiClO_4 .⁵ Building on this type of early work, more recently there has been increasing interest in using oriented external electric fields to exert precise control of non-redox reactions.⁶

Over the last decade supramolecular chemistry has become increasingly proficient at using encapsulation to control stoichiometric as well as catalytic reactions.⁷⁻¹² Regarding the former, covalent hosts,¹³⁻¹⁷ as well as supramolecular containers assembled via the hydrophobic effect,¹⁸⁻²¹ metal coordination,²²⁻²⁵ and hydrogen bonding,²⁶ have all been utilized. Regarding catalysis, supramolecular containers assembled via metal coordination have dominated to date,²⁷⁻³⁶ but hydrogen bonded containers have also proven exceptionally successful.³⁷⁻⁴³

These advancements noted, to our knowledge one area not systematically explored is how the specific control of the EP field within nano-containers can affect reactions. There are two principal factors as to why this is so. First, work in organic solvents has involved uncharged hosts devoid of significant EP fields. Second, although work with water-soluble hosts has involved a diversity of charge-state (–12 to +12) and hence a wide range of EP fields, these different examples have involved a wide variety of structures that make direct comparison difficult. As a step towards understanding how the specific control of the EP field within nano-containers can affect reactions we describe here the reactivity of guests within the dimeric supramolecular capsules formed by octa-carboxylate **1a** and positand **1b** (Figure 1). More specifically, we demonstrate that although the binding sites of capsules **1a**₂ and **1b**₂ are essentially identical, $\text{p}K_{\text{a}}$ values of encapsulated thio-alkanes and the rates of cyclization of α,ω thio-alkane halides are greatly affected by the EP field of the capsule. The results demonstrate the power of Coulombic forces to influence reactions, even when charge groups are remote and fully water solvated within a high dielectric medium. Hence, they shed further light on the contributing factors to enzyme catalysis and reveal new strategies in enzyme mimicry using less complex model systems.

Results and Discussion

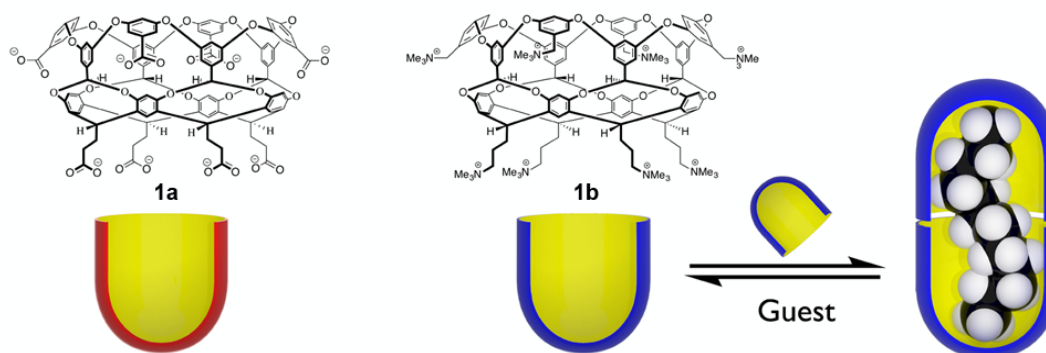


Figure 1: Hosts utilized in this study, octa-carboxylate **1a** and positand **1b**. As illustrated by host **1b**, both hosts dimerize around guests to form supramolecular nano-capsules.

Cavitands **1a** and **1b** assemble via the hydrophobic effect to form dimeric nano-capsules (Figure 1).⁴⁴⁻⁴⁶ The frameworks of these hosts are identical; as are the walls of their inner spaces and the shape and volume they define. Only their exterior coats differ; under basic conditions the external coating of **1a**₂ is nominally hexadeca-anionic, whereas **1b**₂ is hexadeca-cationic. The inner space of either capsule is nominally a dry nano-environment,⁴⁷ however water does solvate empty **1a**,⁴⁸ poorly hydrated anions do bind to **1a** and **1b**,⁴⁹⁻⁵² and small species such as iodide can enter a capsular complex of guest@**1a**₂ via a partial opening, or breathing, mechanism.⁵³ In combination, these results suggest that the inner-space is quite heterogeneous; it is more polar at the equatorial region than the poles. The solubilizing groups of each host are > 1 nm away from the center of their inner spaces. Consequently, the only “direct” influence the charge groups can exert upon encapsulated guests is the Coulombic force intrinsic to the EP field they generate.

It has been previously shown that encapsulation of flexible guests inside containers can force them to adopt high energy U- or J-motifs possessing reverse turns within their main-chain,^{14,54-59} and this phenomenon has been used to enhance cyclizations within 1:1 complexes.^{14,17,60} Thus to demonstrate the role of EP fields, we report here on the encapsulation of α,ω thio-alkane halides, their deprotonation, and their cyclization to the corresponding 13- to 19-membered thio-ethers (Figure 2).

Guest Synthesis and Encapsulation

Of the six guest substrates (Figure 2a), **2a**, **2b**, and **4** were previously reported.⁶¹⁻⁶⁹ These, and the other three novel substrates **3a/b** and **5** were synthesized as described (SI). Non-cyclizing guests **2c**, **3c** and **4b** were commercially available.

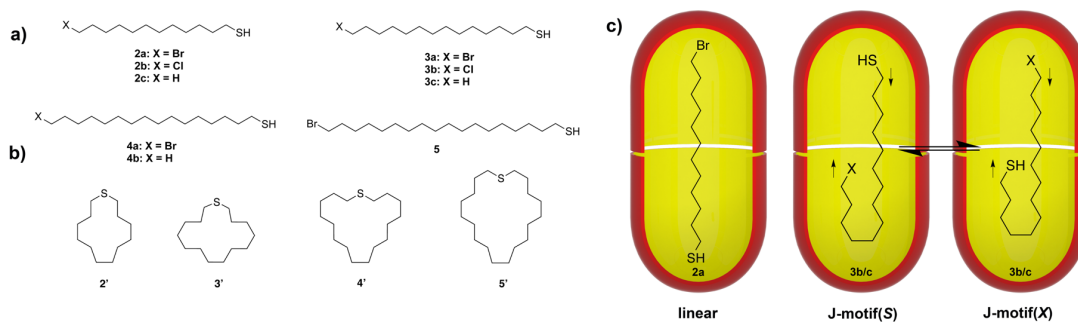


Figure 2: a) Structures of long-chain thiols **2-5** used in this study. b) The cyclic thio-ethers **2'-5'** formed within the containers **1a₂** or **1b₂**. c) Examples of the observed binding motifs of guests using **2a** and **3b/c** as examples: **2a** in a linear motif, and **3b/c** in an equilibrium between J-motif(S) and J-motif(X).

^1H NMR spectroscopy was used to examine guest binding to capsules **1a₂** and **1b₂** in either D_2O or, to observe the bound thiol $-\text{SH}$ signal, H_2O (Figures S8-S40). With the exception of minor changes to the guest binding region the only difference observed between the hosts was that **1b₂** tended to form weaker complexes, such that larger guests were not fully bound.⁷⁰

Binding was confirmed by distinctive, high-field signals in the ^1H NMR spectra of each complex. Prior NMR spectroscopy work¹⁴ and Gauge Invariant Atomic Orbital calculations⁷¹ have confirmed these high-field signals arise because the guest is held close to the diamagnetic, shielding walls of the container, whilst the wide anisotropy arises from the average location of a guest proton within the capsule. Determining this location utilized COSY NMR spectroscopy to assign the signals for free and bound guests and calculating the differences between these ($\Delta\delta$). As a rule-of-thumb, because each pocket is conical, the deeper an atom is located the more upfield shifted is its signal. This protocol revealed that both capsules induced the same motif in each guest, and that overall two, principal motifs were observed (Figure 2c). Shorter guests **2a/b/c** and **3c** were found to bind primarily in a linear motif, whereas longer guests adopted a J-motif(S) with either the thiol terminus bound deeply into a “pole”, or the opposite J-motif(X) with the X group bound deeply. $\Delta\delta$ plots suggest that for both **3a** and **3b** the J-motif(S) predominates, but that the proportion of the J-motif(X) is higher in **3a**. Despite difficulty in assigning all of the signals of bound guests **4** and **5**, based on the much larger signal shifts of the protons at the thiol terminus these too were also assigned as J-motifs(S).

Guest Cyclization and Acidity with Capsules **1a₂** and **1b₂**

The musk fragrance⁷² products **2'-5'** have been reported previously, but yields ranged from low to trace.⁶¹⁻⁶⁴ Unsurprisingly, in a control experiment using a dilute solution of **3a** in

basic aqueous methanol, MALDI-TOF analysis revealed that the majority of the product was random, insoluble polymer (Figure S135).

Table 1: Reaction times and apparent first order rate constants for the cyclization of guests **2a-5a** encapsulated within the capsular hosts **1a₂** and **1b₂**^a

Guest	Host 1a		Host 1b	
	Reaction time	Rate Constant (<i>k</i> , s ⁻¹)	Reaction time	Rate Constant (<i>k</i> , s ⁻¹)
2a	> 27 d.	8.65×10^{-7}	~ 6 min	6.60×10^{-3}
2b	> 60 d	— ^c	24 h	1.80×10^{-5}
3a	~ 8 h	1.28×10^{-4}	< 2 min	— ^b
3b	> 60 d	— ^c	3 h	2.50×10^{-4}
4a	42 h	2.14×10^{-5}	< 2 min ^d	— ^d
5	~ 10 d	3.85×10^{-6}	~2 min ^e	— ^e

^a All experiments were performed with 1.0 mM host **1a** in 8 mM NaOH/D₂O buffer or 1.0 mM host **1b** in D₂O at 25 °C, with the reactions initiated by the addition of excess NaOH to give a 200 mM solution. ^b Reaction too rapid to determine kinetics by ¹H NMR spectroscopy. ^c Apparent first order rate not determined. ^d The product was formed during complex formation (no addition of base necessary). ^e Complex NMR spectra of mixture precluded detailed analysis.

The standard procedure for initiating cyclization was the addition of NaOH to a 2:1 host-guest complex to give a base concentration of 200 mM (versus 1 mM complex). However, one complex with **1b₂** cyclized spontaneously upon mixing of host and guest (*vide infra*). In all cases cyclization was apparent by ¹H NMR spectroscopy (Figures S41-S48), and product formation was confirmed by extraction and analysis by GC-MS and NMR spectroscopy (Figures S57-S61). Yields were quantitative, and analysis revealed that products **2'-5'** adopt a motif in which the S-atom resides in a “polar” region of the capsule (Figures S62-S67).

All substrates cyclized with apparent first-order kinetics. Table 1 presents the reaction time for each host-guest combination, and where it could be readily determined, the rate constant. Inside host **1a₂**, the shortest guests **2a** and **2b** underwent very slow reaction, and within this pair the chloro derivative **2b** reacted the slowest. Guests **3a** and **3b** behaved analogously, with **3a** reacting sufficiently quickly for a rate constant to be readily determined but **3b** reacting very slowly. Interestingly, guest **3a** cyclized 150 times faster than **2a**. We attribute this increase rate for the bigger macrocycle to the fact that **2a** adopts a linear motif in which the reacting termini reside cannot readily react, whereas bound **3a** exists in J-motifs that are preorganized (templated) by the host to undergo cyclization. Guest **4a** and **5a** were respectively found to cyclize six and thirty-three times more slowly than **3a**, suggesting steric hinderance became an issue.

Table 1 also shows that cyclizations within positively charged **1b₂** occur much more quickly (7600 times quicker in the case of **2a**). From the limited data it is evident that guests with linear motifs and chloride leaving groups reacted more slowly than longer brominated guests. For example, based on reaction times **2a** cyclized 370 times faster than chloride **2b**, whilst the rate constant of cyclizing **3b** was found to be 26 times greater than that of **2b**. The cyclization rates of thiols **3a** and **4a** within **1b₂** were both too fast to monitor, with the cyclization of **4a** spontaneous without the addition of base. Because of partial complexation, ¹H NMR spectroscopy could not be used to accurately monitor the formation of **5'** by **1b₂**, however reaction was rapid and spontaneous.

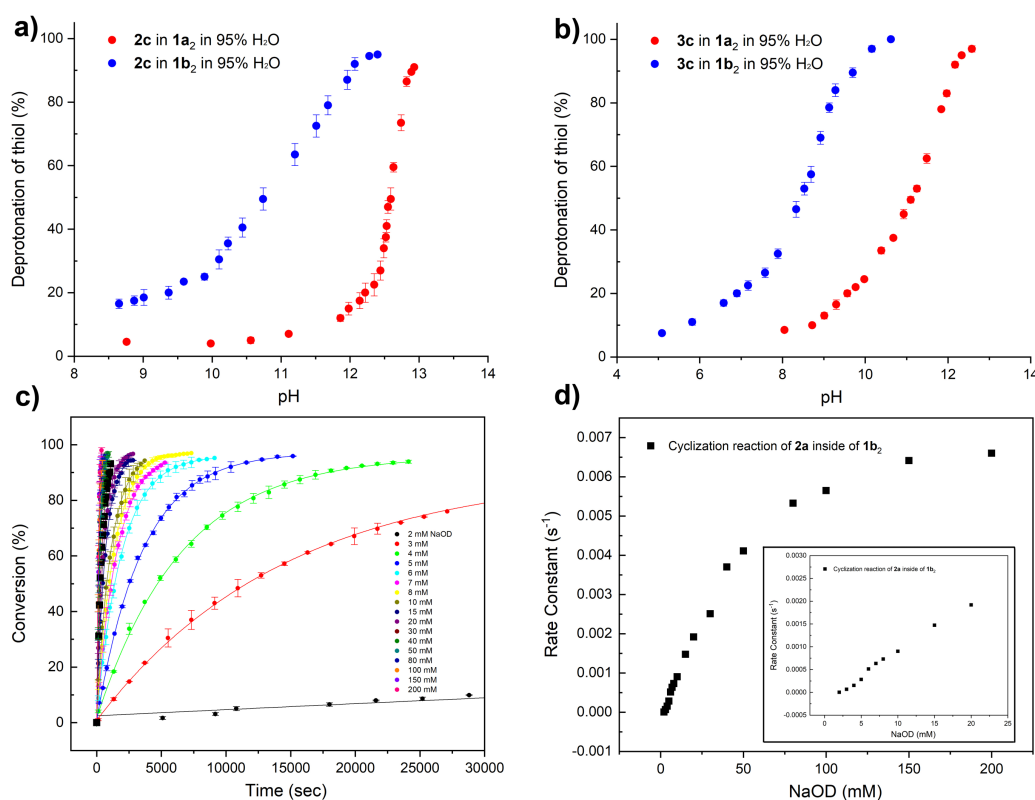


Figure 3: a) pH titration of the complex formed between guest **2c** and hosts **1a₂** and **1b₂**. b) pH titration of the complex formed between guest **3c** and hosts **1a₂** and **1b₂**. c) Graphs of the rate of cyclization of **2a** within the **1b₂** capsule as a function of NaOD concentrations from 2-200 mM. d) Calculated apparent first-order rate constants for the cyclization of **2a** inside **1b₂** as a function of [NaOD] from 2-200 mM. Inset, calculated apparent first-order rate constants as a function of [NaOH] from 2-18 mM.

To probe the effects of encapsulation on acidity, we determined the pK_a values for non-cyclizing guests **2c**, **3c** and **4b** inside the two capsules by titrating the complexes with NaOH and using ¹H NMR spectroscopy to monitor the disappearance of the bound SH signal between −1.9

and -2.8 ppm (95:5 $\text{H}_2\text{O}:\text{D}_2\text{O}$, Figures S103-S113). These experiments revealed that deprotonation did not lead to decomplexation or even to changes in binding motif. The titration curves for **2c** (Figure 3a) reveal pK_a values inside **1a₂** and **1b₂** of 12.6 and 10.7 ± 0.1 respectively. This compares to the typical pK_a of a thiol of ~ 10 - 11 . Thus, a switch from negative to positive capsule increases the acidity two orders of magnitude, but the non-polar inner-space of **1b₂** counters any energetic benefits of placing the thiol in the positive EP field. Guest **3c** inside **1a₂** and **1b₂** was more acidic: $\text{pK}_a = 11.2$ and 8.5 ± 0.1 respectively (Figure 3b). Why this increase? The flatter titration curves of **3c** relative to **2c** when bound to **1a₂** (Figures 3b versus 3a), and the broader signals in the COSY NMR spectra of the **3c** complex (Figures S30 versus S17) suggest that whereas **2c** only adopts a linear motif, longer **3c** adopts this, and to a small extent, a J-motif as well. In such a J-motif, an S-atom at the more solvent-exposed equatorial region of the capsule would be more hydrated and therefore more acidic. For guest **4b** it was not possible to obtain a sufficiently clean NMR spectrum for a titration inside **1b₂**, but within **1a₂** the titration yielded a weak inflection suggestive of the guest adopting multiple motifs with an average pK_a of ~ 9.0 (Figure S113). Overall, these results show that the pK_a of the bound thiol is enhanced by both a positive EP field and increasing guest length. Thus, the spontaneous reactivity of **4a** can in part be attributed to a low pK_a value inside **1b₂**. Importantly, these titrations also reveal two key points: 1) irrespective of the host, 200 mM NaOH is sufficient for full deprotonation of all guests; 2) the average ΔpK_a between the **2c** in **1a₂** and **1b₂** and the corresponding complexes with **3c** is 2.3 units, corresponding to a stabilization within **1b₂** relative to **1a₂** of 13 kJ mol^{-1} ($\Delta\Delta G = 2.3RT\Delta\text{pK}_a$).

Complete deprotonation at 200 mM NaOH was also confirmed kinetically for guest **2a** within **1b₂**. Figure 3c and 3d shows the data for the cyclization as a function of base concentration. At all concentrations data fitted an apparent first order reaction (Figures 3c and S68 – S102), and in totality (Figure 3d) the data showed the rate constant increase saturating at 150 mM NaOD ($\text{pD} \sim 12.7$) commensurate with the full deprotonation of a group of pK_a 10.7 (~ 11.1 corrected for deuterium⁷³). Interestingly, the data also showed an attenuation of the rate constant at low concentration of NaOD (see Figure 3d inset), a phenomenon that we attribute to OD^- binding to the exterior of the capsule⁵² and being unavailable for guest deprotonation.

The combination of the data shown in Table 1 and Figure 3 revealed a rather confined area of chemical-space for Eyring determinations. Nevertheless, it was possible to determine the thermodynamic parameters for three complexes (Table 2) in the presence of 200 mM NaOD: guest **2a** inside **1a₂** (329-349 K, Figure S114 – S120), **2a** inside **1b₂** (278-282 K, Figure S121 – S127), and guest **3a** inside **1a₂** (305 K-322 K, Figure S128 – S134).

The difference between the cyclization inside capsules **1a₂** and **1b₂** is stark; the half-life

for cyclization of **2a** is 3.5×10^3 times shorter in the positive capsule. Alternatively, the free energy of activation ($\Delta G^\ddagger$) for the cyclization of **2a** is over 20 kJ mol^{-1} lower in positive **1b₂** than in **1a₂**. This compares to the 13 kJ mol^{-1} of stabilization for deprotonating guests in **1b₂** versus **1a₂**. Interestingly, this demonstrates that relative to the **1a₂**, positive capsule **1b₂** stabilizes the transition state (TS) more than it does deprotonation. The $\Delta H^\ddagger$ for cyclization in capsule **1b₂** is over $\sim 25 \text{ kJ mol}^{-1}$ lower than in **1a₂**, whereas the $-\Delta S^\ddagger$ from the bound, deprotonated **2a** to its TS is similar for both complexes. This emphasizes that the majority of the rate acceleration seen within **1b₂** arises from enthalpic effects induced by the EP field.

Table 2: Thermodynamic parameters and reaction half-lives determined by Eyring analysis for selected cyclizations inside the capsules **1a₂** and **1b₂** (200 mM NaOH).

Guest	2a in 1a ₂	2a in 1b ₂	3a in 1a ₂
$\Delta G^\ddagger$ (kJ mol ⁻¹)	105.4	84.9	95.4
$\Delta H^\ddagger$ (kJ mol ⁻¹)	82.0	57.7	74.9
$-\Delta S^\ddagger$ (kJ mol ⁻¹)	23.4	27.2	20.5
Half-life (s, 298 K)	3.2×10^5	93	4.8×10^3

The comparison of the cyclization of guests **2a** and **3a** inside **1a₂** is equally as revealing. The $\Delta G^\ddagger$ of cyclization of the **3a** is 10 kJ mol^{-1} lower than **2a**; an effect that is again dominated by enthalpy and aided by a slightly smaller $-\Delta S^\ddagger$ term. We believe the differences between cyclizing **2a** and **3a** stem from the fact that the two termini of linear-bound **2a** must overcome anchoring to the ‘poles’ of the inner-space to approach each other, whereas with J-motif **3a** only one terminus must “detach” from the inner wall of the host to meet the other end of the guest.

Electrostatic Potential and Transition State Stabilization Calculations

To confirm the extent to which Coulombic forces can be expected to influence reactions in **1a₂** and **1b₂**, we turned to calculations and first evaluated the spatial EP (ϕ) of each capsule *in vacuo*. Figure 4a shows the cylindrically averaged ϕ values obtained by rotating each capsule around its C₄ axis. The EP fields about each are very similar, largely differing only in their respective signs; in the interior of the capsules the EPs are comparable in magnitude ($\sim 20 \text{ V}$ or 778 kT/e ($kT/e = 25.7 \text{ mV}$)) and nearly uniform, whilst outside both capsules the magnitude of the EP decays inversely with distance. As expected, the greatest distinction between the two capsules is on their outer surfaces. Encapsulated guests do not contact this boundary region, confirming that the guest to charge-group distances are short enough that guests can be greatly influenced by them, but long enough such that this influence is purely Coulombic.

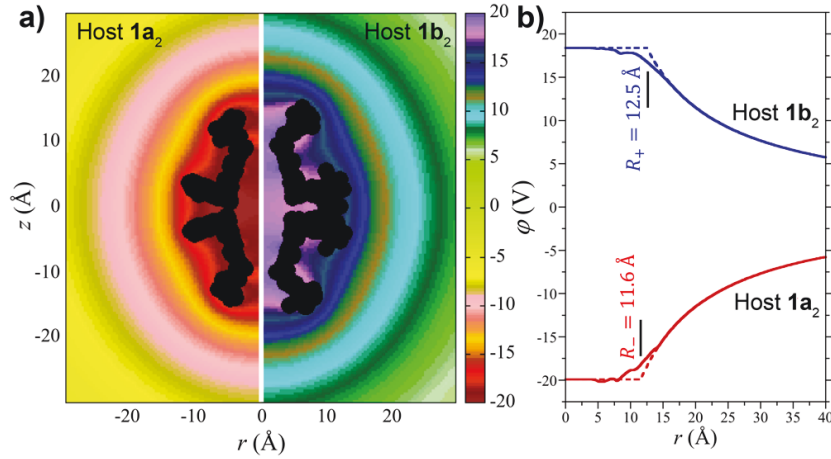


Figure 4: a) Electrostatic potential (EP, ϕ in volts) about (one half of) the empty capsule **1a₂** (left) and **1b₂** (right) *in vacuo*. The perspective is from the equatorial horizontal plane ($z=0$) perpendicular to the principal C_4 axis of the capsules. The EP is cylindrically averaged about the C_4 . The net charge on each capsule is $\pm 16e$. The black shadow indicates the positions of the heavy atoms of each capsule. The EP scale is reported in the legend on the right-hand side of the figure. b) EP about host **1a₂** (red lines) and **1b₂** (blue lines) *in vacuo*, spherically averaged about the central of mass of each capsule. The solid lines indicate the mean EP determined from averaging interactions over the explicit partial charges of each capsule, while the dashed lines indicate the approximate potential distribution determined by spreading the net charge of each capsule on a sphere of radius $R_{+/-}$ (Eq. (1)). The effective Born radii of the capsules are $R_+ = 12.5 \text{ \AA}$ and $R_- = 11.6 \text{ \AA}$, respectively. The mean Born radius of the hosts is $R = 12.0 \text{ \AA}$.

An alternative perspective is to plot the mean potential distribution as a function of distance from the capsules (Figure 4b). This clearly shows the uniformity of the EP inside the hosts, the inverse dependence of the EP on distance outside the capsules, and the subtle differences between the capsules at or close to their surfaces.

Because of the uniformity of ϕ within the capsules, we assumed that the EP fields can be semi-quantitatively described by approximating each dimer to a sphere, whose net charge of $q_{\pm} = \pm 16 e$ is uniformly smeared over its surface at an effective radius $R_{\pm}$, Eq. (1):

$$\phi(r) = \begin{cases} \frac{q_{\pm}}{R_{\pm}} & r \leq R_{\pm} \\ \frac{q_{\pm}}{r} & r > R_{\pm} \end{cases}, \quad (1)$$

where r is the radial distance from the center of the capsule, and $R_{\pm}$ is the Born radius of each capsule (the effective container size that demarks the boundary between the interior and the bulk solvent modeled as a continuum dielectric): $R_- = 11.6 \text{ \AA}$ and $R_+ = 12.5 \text{ \AA}$ for capsules **1a₂** and **1b₂**, respectively. The main difference between the cylindrical averaged potentials and the picture emerging from approximating Eq. (1) is again near $R_{\pm}$ (Figure 4b). Thus, treating the capsules

as spheres is a valid approximation for evaluating the effect of EP on bound charged species.

While this simple model is an excellent approximation, it does not capture the significant role of water. Solvation shell waters on the exterior of the container are polarized by the $\pm 16 e$ charge on the surface. As a result, the charge on the surface of the host is strongly attenuated and there is a corresponding reduction of the inner EP by approximately a factor of 78 (ϵ , the dielectric of water) to ~ 250 mV or $9.7 kT/e$. In addition, any added electrolyte further screens interactions by counterion redistribution in the field of the capsules. To account for these effects in our model we treated water as a dielectric continuum, and approximated the counter-ion effect within the context of Debye-Hückel theory via Eq. (2) to calculate the resulting free energy difference ($\Delta\Delta G_{+-}^*$) to creating a charged species (*) within the anionic and cationic capsules:

$$\Delta\Delta G_{+-}^* = \frac{\delta q(q_- - q_+)}{\epsilon R(1 + \kappa R)} \quad (2)$$

where δq is the charge of the guest ($-1e$), q_- and q_+ is the charge on the capsule, ϵ is the dielectric of the solvent ($= 78$); the dielectric of the inner space of the model ($\epsilon = 1$) is implicit in Eq. (2)), $\kappa^{-1} = 6.8 \text{ \AA}$ is the Debye length for the bulk mixture with 200 mM added monovalent electrolyte (NaOH), and R is the mean Born radius of the positively and negatively charged spherical hosts within the context of the continuum dielectric model ($12.0 \text{ \AA}$). The free energy difference for a species of formal charge minus one in the anionic and cationic capsules determined based on this expression is $\Delta\Delta G_{+-}^* = 17.2 \text{ kJ mol}^{-1}$, differing from that for the cyclization of guest **2a** by 3.2 kJ/mol (Table 2). This free energy difference corresponds to a pK_a shift between the capsules of 3.0, which again is in reasonable agreement with those reported (Figure 3). Overall, these agreements are excellent given the inherent assumptions made in this simple model, not least of which is the neglect of ion-specific binding to the outside of the two capsules.^{52,74} Furthermore, the model confirms the primary role of Coulombic forces in promoting cyclizations within the capsules.

Conclusions

We have reported on the ability of two supramolecular capsules to encapsulate and cyclize guests. These capsules have identical inner-spaces that only differ in the electrostatic potential field that envelops them: one positive, one negative. We find that relative to the negatively charged capsule, the positively charged host increases the acidity of bound guests and increases the rate of cyclization reactions involving a negatively charged transition state. Calculations

confirm that Coulombic forces are the primary reason for this, and that Born spheres are reasonable approximations of these nano-scale hosts. Surprisingly, our findings also show that the TS for cyclization is stabilized more in the positive capsule than simple guest deprotonation, suggesting that the non-polar pocket possesses functionality – beyond the simple EP field – that stabilizes the TS. We are continuing to investigate reactions within these two capsules to identify design criteria for nano-reactors.

Acknowledgements

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