Published in final edited form as:

Org Chem Front. 2019 April 21; 6(8): 1236–1243. doi:10.1039/C9QO00182D.

Binding Properties and Supramolecular Polymerization of a Water-Soluble Resorcin[4]arene

Jacobs H. Jordan, Anthony Wishard, Joel T. Mague, Bruce C. Gibb

Department of Chemistry, Tulane University, New Orleans, LA 70118, USA, bgibb@tulane.edu

Abstract

Controlling the self-assembly of molecules in water is difficult because the small size, polarity, and hydrogen bond donating and accepting properties of water attenuate most non-covalent interactions. Here we describe how resorcinarene **1**, with pyridinium pendent groups, assembles in water to form head-to-tail assemblies. These small supramolecular polymers form because they offer greater stabilization than any latent head-to-head assembly of resorcinarenes to form dimeric (or hexameric) containers. Instead, the resorcinarene bowl – particularly if negatively charged – is a good host for the pyridinium pendent groups of a second resorcinarene. Alternatively, resorcinarene **1** is also a good host for complexing anions and cations of any added salt. In combination therefore, host **1** possesses a rich repertoire of supramolecular properties that is dependent on the ionic strength and the nature of salts, pH, and the concentration of the host. These findings provide new information about controlling the self-assembly of resorcinarenes in water.

Graphical Abstract

Introduction

For nearly four decades resorcinarenes have revealed a rich repertoire of supramolecular properties.^[1] The history of solution-based studies of these fascinating hosts dates to the 1980's,^[2] when sugar-binding was (very reasonably) mistaken to occur in a 1:1 manner. A hint of this mis-characterization came in 1997 when MacGillivray and Atwood reported the solid-state structure of a hexameric resorcin[4]arene assembly held together in part by 8 water molecules and 60 hydrogen bonds;^[3] an assembly also subsequently demonstrated with pyrogallolarenes.^[4] Pioneering work by Shivanyuk and Rebek revealed that in the presence of suitable guests (including sugars) resorcinarenes formed similar assemblies in

solution,^[5] and it is now well accepted that where there are solid-state hexameric assemblies of resorcinarenes and pyrogallolarenes there are stable, solution equivalents.^[6]

To date, the solid-state and solution assembly of these hexamers have been studied using, among other techniques, NMR spectroscopy,^[7] mass spectrometry,^[8] fluorescence,^[9] and electrochemistry.^[10] A key general conclusion is that resorcinarenes need trace water to self-assemble in organic solvents, whereas pyrogallolarenes can assemble in dry conditions.^[11] However, too much of a hydrogen bonding solvent inhibits solubility and assembly; the current “record” being the pyrogallolarene hexamer which is stable in 1:1 acetone–water.^[4b]

Building on this understanding, resorcinarene hexamers have been used as catalysts^[12] and nano-reactors.^[13] Examples of catalysis include: gold-mediated reactions,^[12a] the conversion of isonitriles to N-formylamides,^[12b] Diels–Alder reactions in a fluorous biphasic system,^[12c] acetal hydrolysis,^[12d] terpene cyclizations,^[13a, b, 14] iminium catalyzed reduction of α,β -unsaturated aldehydes with high enantiomeric ratio,^[15] cycloadditions of nitrones,^[13c] epoxide isomerizations,^[16] cyclodehydration-rearrangements of unsaturated alcohols,^[17] and Friedel–Crafts reactions.^[18]

We are interested in the formation of water-soluble containers as nano-reactors and were intrigued by the point that the aforementioned “record” for a hexameric assembly in polar solvent actually reflected a solubility limit and may not reflect an intrinsic stability limit of the hexamer. There are relatively few fully water-soluble resorcinarenes reported in the literature,^[19] and so to investigate resorcinarene assembly further we report here a new host that whilst not forming hexameric assemblies in water, does demonstrate anion and cation complexation properties, and undergoes supramolecular polymerization by head-to tail self-assembly.

Results and Discussion

Synthesis and characterization of host **1**

For rapid access to water-soluble resorcinarenes we chose to place ammonium centers at the pendent groups (feet). Specifically, we chose pyridinium groups and targeted resorcinarene **1** (Scheme 1), which we envisioned was readily available from known **2**.^[20]

In initially targeting **2** we identified improved conditions for its synthesis utilizing a condensation between resorcinol and 4-chlorobutanal dimethyl acetal in a 10:3 mixture of MeOH and 36% HCl_{aq} at 55 °C for 3–5 days. The use of the acetal resulted in slightly longer reaction times, but a simplified work-up gave yields of **2** as high as 95% on the multi-gram scale. Resorcinarene host **1** was subsequently synthesized on the gram scale by treating **2** with excess pyridine. Attempts to synthesize the analogous trimethylammonium derivative by alkylation with trimethylamine were unsuccessful, instead generating an insoluble polymer.

Resorcinarene **1** was found to be water soluble to at least ~50 mM in unbuffered solutions, and soluble across a broad pH range (<1 to ~11). However, ¹H NMR spectroscopy revealed signal-shifting and broadening in a range of buffered solutions above pH 7 suggestive of

aggregation. Indeed, upon titration of the unbuffered host with small aliquots of NaOD, at pH 12.5 there were no discernable signals observed in the ^1H NMR spectrum and visual evidence of a precipitate. To a first approximation this process was shown to be reversible by the addition of DCl (see Figure S17). Additionally, the ^1H NMR spectrum of **1** was also shown to be concentration dependent. Figure 1 shows a stack of ^1H NMR spectra using the PGSE sequence for water-signal suppression. Upon serial dilutions of **1** most resonances underwent shifts between $\delta = 0.1\text{--}0.7$ ppm. Upfield shifts of 0.7 and 0.3 ppm were noted for H_j and H_i respectively (see Scheme 1 for proton designations), whilst downfield shifts of between 0.1–0.4 ppm were noted for H_2 , H_3 , and H_4 of the pyridinium groups, and the H_n methylene and H_e aromatic resonances. Two-dimensional diffusion-ordered ^1H NMR spectroscopy (DOSY) measurements revealed that whereas the host is essentially monomeric at concentrations of ~ 1.6 mM ($D = 2.32 \times 10^{-10} \text{ m}^2\cdot\text{s}^{-1}$), at 25 mM a higher order aggregate formed ($D = 1.14 \times 10^{-10} \text{ m}^2\cdot\text{s}^{-1}$, see Figure S15 – Figure S16).

Taken together, the effects of salts/acid and bases and concentration suggests that resorcinarene **1** has intertwined ion-binding and self-assembly properties; a conclusion suggested by the binding properties of previously reported cavitands. For example, the study of cavitands possessing phosphonate esters in their pendent groups have revealed how they can be used as ion-pair receptors,^[21] whilst cavitands with ammonium pendant groups have been shown to bind anions.^[22] These points suggest that the four pyridinium groups of host **1** might function as an anion binding site. Furthermore, the bowls of resorcinarenes are known to complex cationic guests.^[1a, 23] This suggests that the eight free phenolic hydroxyl groups at the upper-rim of **1** could function as a cation binding site whilst leaving the “crown” free to complex anions (Figure 2). To investigate this possibility, we carried out a series of titrations between **1** and a variety of different salts.

NMR titrations of host **1** with salt guests

Host **1** is comprised of a resorcinarene bowl of four aromatic rings and eight ionizable phenolic oxygens, and a “crown” of four pendent pyridinium groups. As we will discuss, the four aromatic protons (designated H_e , Figure 2) at the rim of the bowl experience induced chemical shifts upon cation complexation, whereas anion complexation to the pyridinium crown results in chemical induced shifts for H_j and H_i (Figure 2). In this regard, we define binding as occurring when the chemical induced signal shifts were greater than $\delta = 0.05$ ppm.

We first titrated **1** with NaCl and NaI. These studies revealed no evidence of Na^+ binding to the bowl. In contrast, there were significant shifts (Figure S19 to Figure S22) in the H_i and H_j resonances, coupled with minor signal shifts in H_2 , H_3 , and H_4 , indicative of anion complexation to the crown of pyridiniums. Anion affinities for Cl^- and I^- were determined to be $K_a = 14 \pm 3 \text{ M}^{-1}$ and $200 \pm 20 \text{ M}^{-1}$ respectively. Within error the same values were obtained irrespective of whether shifts in H_j or H_i were fitted individually or globally.

We also examined a range of ammonium halides as guests. Screening the ^1H NMR spectrum of **1** (1 mM) in the presence of a large excess (>10 equiv.) of different salts (Figure S18) revealed little or no binding of *n*-hexyl-, *n*-decyl-, and phenethyl-trimethylammonium cations. In contrast, the addition of ethyl pyridinium iodide revealed both anion and cation

complexation. Correspondingly, the Cl^- and I^- salts of methyl and butyl pyridinium were selected for ^1H NMR spectroscopic titration experiments to quantify the extent of anion and cation association to host **1**. By way of example, Figure 3 shows the titration between **1** and butyl pyridinium iodide. Fitting the shift in the H_e signal to a 1:1 model gave a butyl pyridinium K_a value of $560 \pm 34 \text{ M}^{-1}$. In contrast, the titration with methyl pyridinium iodide gave a methyl pyridinium affinity of $K_\text{a} = 300 \pm 9 \text{ M}^{-1}$. The same experiments with chloride salts revealed weaker pyridinium binding: $K_\text{a} = 53 \pm 2 \text{ M}^{-1}$ and $89 \pm 15 \text{ M}^{-1}$ for the methyl and n-butyl pyridinium cation respectively.

Figure 4 summarizes the cation and anion affinities obtained from the titration data (See Supporting Information, Table S1 for complete details). Evidently the larger and more polarizable the anion and cation are, the stronger they associate with host **1**. The stronger binding of the pyridinium cations, and in particular the butyl pyridinium cation, may suggest that the hydrophobic effect also plays a role in the binding of these ions. Irrespective of the different contributions to binding, the data also reveals a degree of positive cooperativity between the two binding sites of host **1**; whilst a line linking the iodide salts and a line linking the chloride salts are roughly parallel, the spread of cation affinities along the chloride line is much smaller than the spread of cation affinities for the iodide series. Hence, iodide (pyridinium) binding to the crown (resorcinarene bowl) site induces a conformational change in the resorcinarene bowl (crown) that is more suited to cation (iodide) complexation.

It is interesting to note that considering literature precedent these anion and cation affinities are somewhat weaker than expected. For example, complexation free energies for anions to a related cavitand receptor bearing a crown of four trimethylammonium groups ranged from -11.7 to $-20.1 \text{ kJ mol}^{-1}$.^[22] Similarly, chloride salts of aromatic trimethylammonium guests binding to a (rim) sulfonated resorcinarene host have been found to be -13.1 to $-15.4 \text{ kJ mol}^{-1}$.^[23d] Here, the observed values host **1** are roughly $3\text{--}7 \text{ kJ mol}^{-1}$ less favorable. This is attributed to two factors: 1) The larger degree of conformational flexibility in resorcinarene **1** may result in reduced affinities for anion binding relative to the related (but more rigid) cavitand receptor;^[22] 2) the unfavorable electrostatic interactions between cationic guests and the pyridinium crown in host **1** likely weaken binding relative to analogous hosts without positively charged groups.^[23d]

Overall, these results confirm **1** is a ditopic receptor forming a ternary complex in the presence of certain organic halide salts.

Nature and extent of self-assembly of host **1**

Our initial studies with ^1H and DOSY NMR spectroscopy revealed a significant degree of aggregation of host **1** at high pH and at high concentrations. This data, and the measured affinities for cationic and anionic guests, strongly suggest a head-to-tail type polymerization. If this is the case, it is constructive to note that the binding of a pyridinium group into the anionic resorcinarene bowl of a second host is itself in competition with the counter chloride ions inherent to each host molecule. Thus, based on the determined association constant for (sodium) chloride to host **1** ($K_\text{a} = 14 \text{ M}^{-1}$), a 50 mM solution of host (i.e. one that is 200 mM chloride) can be calculated to be 70% complexed with chloride. Under these conditions

the corresponding chemical shifts (δ) in the host signals for H₂, H₃, and H₄ of the pyridinium moieties are shifted $\delta \approx 0.3$ ppm relative to a 1 mM solution of the host. In contrast, titration of a 1 mM host **1** solution with sodium chloride up to 200 mM salt (i.e., to 73% complexation), leads to very small signal shifts for resonances other than H₃ ($\delta = 0.16$ ppm). This demonstrates that, whilst real, chloride competition with resorcinarene head-to-tail aggregation is small. In other words, the observed ¹H NMR signal broadening and shift as a function of concentration (Figure 1) arises from self-assembly of the resorcinarene.

Continuous linear aggregation of an assumed, homogenous (one-component) system with a known monomer initial concentration can be described by the following model:

which, in general refers to the isodesmic model for K_E .^[24] This can be used to derive N (the number average of polymer aggregates) in terms of the total concentration (C_T) and C_N (Equation 1):

$$N = \frac{C_T}{C_N} = \frac{C_T}{C_1 + C_2 + \dots C_n} = \frac{2KC_T}{-1 + \sqrt{4KC_T + 1}} \quad (\text{Eq. 1})$$

Equation 1 assumes no cooperativity. A plot of δ vs the total host concentration fit to a linear aggregation model gave a value for $K_E \approx 800 \text{ M}^{-1} \pm 5\%$. This is greater than that observed for the pyridinium guests, suggesting that additional interactions between the hosts play a role. This association constant corresponds to $N \approx 5$ at a host concentration of 25 mM. At higher concentrations larger assemblies undoubtedly ensue, but there are solubility issues. For example, under neutral conditions and at concentrations of 30–50 mM the calculated assembly is $N \approx 6$ –7. However, although initially stable such solutions precipitate after 1–2 days.

Figure 5a shows the concentration dependence of the diffusion coefficient D upon increasing concentration of **1**. At a concentration when the presumed pseudo-spherical host **1** is monomeric (0.78 mM), using the Stokes-Einstein equation, DOSY NMR spectroscopy revealed an average hydrodynamic diameter of ~ 1.7 nm. In contrast, at 25 mM where the host is assumed to assemble into a “rod”, DOSY data and a model for rod-like nanoparticles coupled with the Stokes-Einstein equation^[25] provides a hydrodynamic diameter of ~ 3.8 nm. Assuming a linear aggregate, changes in average diameter can be attributed to increases along the linear axis of the rod such that the length L is equal to the diameter times the aspect ratio.^[25b] Thus, a hydrodynamic diameter of 3.8 nm corresponds to a “rod” of $N = 5$, i.e., matching the size found from the isodesmic model. At this concentration, strong correlations were observed between aromatic H_e and the methylenes H_n and H_m of the “feet” (boxed region, Figure 5b), confirming the head to tail aggregation in solution.

The assembly of **1** was also examined by Dynamic Light Scattering (DLS). DLS requires a solution of sizable ionic strength for accurate determinations,^[26] and with this in mind,

phosphate buffer was selected to assess the behavior of **1** under four different conditions: Cases 1–4 (Table 1 and Figure S32). In all cases, the largest error resided with the lowest concentration of host tested due to two contributing factors: 1) count rates were significantly lower at concentrations of **1** <1 mM resulting in poor residuals and autocorrelation curves, and; 2) at this concentration in some experiments partial aggregates were observed and inconsistent sizes/bimodal distributions (pertaining to monomer to dimer transitions) were obtained.

In the neutral conditions of Case 1, at concentrations below 1 mM **1** was essentially monomeric (hydrodynamic diameter of 1.8 nm). Above this concentration the system was better behaved, with apparent hydrodynamic diameters corresponding to a dimer irrespective of the precise concentration. Under all tested conditions, the host is 51–58% complexed with chloride; thus, Cl[−] can bind to the crown and compete with the host for complex formation, reducing the propensity to form larger aggregates and thereby reducing the overall observed aggregate size.

In Case 2, at the lowest concentration tested the host appeared on average slightly larger than in the presence of sodium chloride: hydrodynamic diameter of 2.2 nm corresponding to an aggregate of $N = 1.8$. At concentrations of 3 mM and above DLS indicated an aggregate of $N = 3–5$, whilst at the higher concentrations similar aggregates were observed along with trace amounts of larger aggregates. This small amount of aggregation is attributed to the slightly basic conditions bringing about limited deprotonation of the phenolic rim hydroxyls and increasing favorable cation-anion interactions.

Case 3 and Case 4 examined assembly under acidic conditions. In both cases, the expected increase in particle size was evident with increasing concentration. However, in Case 3 the apparent hydrodynamic diameter was always smaller than that observed under Case 1 and Case 2. This was also so with the lowest concentrations of Case 4. Previous work has identified how anionic solutes are screened at lower salt concentrations than cationic ones.^[26a] Thus we believe that the larger apparent sizes in Case 4 arise because these two sets of conditions are near the limit for screening cationic species, with the higher ionic strengths of Case 4 increasing screening to an effective level. Interestingly, comparing Case 2 and Case 4 reveals differences in apparent hydrodynamic volumes that must arise because the extent of phenol ionization at pH = 3 is less than that under basic conditions. As a result, assembly is attenuated.

Solid-state analysis

Additional support for head-to-tail polymerization was obtained from a crystal structure of host **1**, obtained from EtOH-H₂O, which showed the head-to-tail assembly of **1** into anti-parallel chains. Two offset anti-parallel resorcinarenes are evident in the unit cell (Figure 6), one of which (left in Figure 6) was partially disordered at the pendant feet positions containing multiple partial occupancy of the pyridinium moieties. The unit cell also contained multiple disordered water molecules, with several hydrogen bonded waters between the resorcinarene pairs as well four kinds of hydrated chloride ions (*vide infra*).

The distance between opposing aromatic protons of a bowl was 7.3 Å across the short span and 12.0 Å across the long one, whilst the longest cross-sectional distance was 20.0 Å down the long axis of a chain of resorcinarenes from one terminal pyridinium group to the next, and approximately 7 Å from the top of the bowl to the base of the host. These values are in good agreement with DLS and DOSY measurements.

The chloride atoms either lie between adjacent anti-parallel repeating chains of subunits (Cl1 & Cl4, left, Figure 7), or within a single chain of hosts (Cl2 & Cl3, right, Figure 7). All chlorides are coordinated to multiple (disordered) waters, but beyond this solvation, three (Cl1, Cl2, and Cl4) are hydrogen bonded to a combination of phenolic OH groups and pyridinium groups, whilst Cl3 has only pyridinium groups in its vicinity. Specifically, chloride Cl1 is hydrogen bonded to a phenol, face-coordinated to a pyridinium of one host, and C(2)–H hydrogen bonded to a different pyridinium group from the separate anti-parallel chain of hosts. Cl2 is C(2)–H coordinated to two pyridiniums from the same host molecule and hydrogen bonded to a rim phenol of an adjoining host in the same chain. Cl3 is unique in that it is edge coordinated to two pyridiniums and is further surrounded by (although not within close contact of) two pyridinium faces. These four pyridiniums belong to two host molecules of the same chain. Finally, Cl4 lies between host chains, hydrogen bonded to a phenol from one chain and a pyridinium pendent group from the adjacent chain.

Overall, two of the pyridinium moieties from each host are engaged in host-host interactions, and the disorder in the pyridinium pendent groups is tied to the exact occupancy of chloride ions or water molecules in the crystal. In combination these results suggest that in the crystal, the host is trapped half-way between being a host for salts and being a supramolecular polymer.

Resorcinarenes and pyrogallolarenes usually adopt head-to-head hydrogen bonded dimers, tail-to-tail bilayers, or hexameric assemblies in the solid state.^[3-4, 6c, 23c, 27] Host **1**, however, adopts a head-to-tail aggregation (Figure 8) in the asymmetric unit. The extended cell of host **1** indicates the two subunits interdigitate with a boat-conformer resorcinarene bowl as one host binding the pendent pyridinium guest of the adjoining subunit. Further, between hosts, the average phenol (O) to pyridinium (N) distance is 3.9 ± 0.3 Å accounting for multiple close contacts between each cleft.

An important observation is that whereas the estimated *N* value obtained by DOSY or DLS assumes no interdigitation of subunits, the crystal structure reveals that because of interdigitation the host dimer is only ~6 Å (+30%) longer than the monomer. Thus, estimates of *N* from DLS and DOSY are probably at best a minimal estimate of the assembly in solution, and the multimer may in fact be considerably longer.

The binding-geometry and self-assembly observed in the solid-state provides clear support for the nature of the assembly of **1** in solutions. The fact that a number of solvent molecules (3–4) are co-located with the anion at the crown in the solid-state suggests that in solution anion binding at this crown site is not accompanied by complete desolvation of the guest. Thus, one should not rely too much on hydration free energies or hydration enthalpies to

estimate the ease of ion complexation in water; partial desolvation is more than sufficient to attain recognition.

Conclusions

We have synthesized a water-soluble ditopic resorcinarene host that displays selective binding of pyridinium cations in its resorcinarene bowl, and iodide anions in its crown of pyridinium pendent groups. We have also shown that this same preference for binding anions and cations leads to head-to-tail self-assembly in both the solid and the solution state. We surmise that this type of assembly is observed because head-to-head type pairing such as those seen in dimeric or hexameric assemblies is relatively weak, such that the presence of cationic pendent groups overwhelms any such interaction and instead promotes supramolecular polymer formation. Future work will explore other molecular architectures to further explore self-assembly in water.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors gratefully acknowledge the support of the National Institutes of Health (GM125690). A.W. also acknowledges the Louisiana Board of Regents for a graduate student fellowship (LEQSF(2013–18)-GF-13).

References

- [1] a). Schneider HJ and Schneider U, Journal of inclusion phenomena and molecular recognition in chemistry 1994, 19, 67–83;b)Timmerman P, Verboom W and Reinhoudt DN, Tetrahedron 1996, 52, 2663–2704.
- [2]. Aoyama Y, Tanaka Y and Sugahara S, J. Am. Chem. Soc 1989, 111, 5397–5404.
- [3]. MacGillivray LR and Atwood JL, Nature 1997, 389, 469–472.
- [4] a). Gerkenmeier T, Iwanek W, Agena C, Frohlich R, Kotila S, Nather C and Mattay J, Eur. J. Org. Chem 1999, 2257–2262;b)Atwood JL, Barbour LJ and Jerga A, Chem. Commun. (Cambridge, U. K.) 2001, 2376–2377;c)Atwood JL, Barbour LJ and Jerga A, J. Supramol. Chem 2002, 1, 131–134;d)Atwood JL, Barbour LJ and Jerga A, Proc. Natl. Acad. Sci. U. S. A 2002, 99, 4837–4841. [PubMed: 11943875]
- [5] a). Shivanyuk A and Rebek J Jr., Proc Natl Acad Sci U S A 2001, 98, 7662–7665; [PubMed: 11427733] b)Shivanyuk A and Rebek J Jr., Chem. Commun. (Cambridge, U. K.) 2001, 2424–2425.
- [6] a). Avram L and Cohen Y, J. Am. Chem. Soc 2002, 124, 15148–15149; [PubMed: 12487570] b)Avram L and Cohen Y, J. Am. Chem. Soc 2003, 125, 16180–16181; [PubMed: 14692746] c)Evan-Salem T, Baruch I, Avram L, Cohen Y, Palmer LC and Rebek J Jr., Proc. Natl. Acad. Sci. U. S. A 2006, 103, 12296–12300; [PubMed: 16894154] d)Cohen Y, Evan-Salem T and Avram L, Supramol. Chem 2008, 20, 71–79.
- [7]. Avram L and Cohen Y, Chemical Society Reviews 2015, 44, 586–602. [PubMed: 25110858]
- [8]. Beyeh NK, Kogej M, Aahman A, Rissanen K and Schalley CA, Angew. Chem., Int. Ed 2006, 45, 5214–5218.
- [9] a). Barrett ES, Dale TJ and Rebek J, Chem. Commun. (Cambridge, U. K.) 2007, 4224–4226;b)Salgarno SJ, Bassil DB, Tucker SA and Atwood JL, Angew. Chem., Int. Ed 2006, 45, 7019–7022;c)Barrett ES, Dale TJ and Rebek J Jr., J. Am. Chem. Soc 2008, 130, 2344–2350. [PubMed: 18220396]

- [10]. Philip I and Kaifer AE, *J. Org. Chem* 2005, 70, 1558–1564. [PubMed: 15730274]
- [11]. Avram L and Cohen Y, *Org. Lett* 2003, 5, 3329–3332. [PubMed: 12943419]
- [12] a). Adriaenssens L, Escribano-Cuesta A, Homs A, Echavarren AM and Ballester P, *Eur. J. Org. Chem* 2013, 2013, 1494–1500; b) Bianchini G, Sorella GL, Canevar N, Scarso A and Strukul G, *Chemical Communications* 2013, 49, 5322–5324; [PubMed: 23649107] c) Shimizu S, Usui A, Sugai M, Suematsu Y, Shirakawa S and Ichikawa H, *Eur. J. Org. Chem* 2013, 2013, 4734–4737; d) Zhang Q and Tiefenbacher K, *J. Am. Chem. Soc* 2013, 135, 16213–16219; [PubMed: 24131349] e) Catti L, Zhang Q and Tiefenbacher K, *Synthesis* 2016, 48, 313–328; f) Zhang Q, Catti L and Tiefenbacher K, *Acc. Chem. Res* 2018, 51, 2107–2114. [PubMed: 30153000]
- [13] a). Zhang Q and Tiefenbacher K, *Nat. Chem* 2015, 7, 197–202; [PubMed: 25698327] b) Zhang Q, Catti L, Pleiss J and Tiefenbacher K, *J. Am. Chem. Soc* 2017, 139, 11482–11492; [PubMed: 28590723] c) La Manna P, De Rosa M, Talotta C, Gaeta C, Soriente A, Floresta G, Rescifina A and Neri P, *Org. Chem. Front* 2018, 5, 827–837.
- [14]. Zhang Q, Catti L, Kaila VRI and Tiefenbacher K, *Chem. Sci* 2017, 8, 1653–1657. [PubMed: 28451294]
- [15] a). Bräuer TM, Zhang Q and Tiefenbacher K, *Angewandte Chemie International Edition* 2016, 55, 7698–7701; [PubMed: 27259076] b) Brauer TM, Zhang Q and Tiefenbacher K, *J. Am. Chem. Soc* 2017, 139, 17500–17507. [PubMed: 29090917]
- [16]. Caneva T, Sporni L, Strukul G and Scarso A, *RSC Adv.* 2016, 6, 83505–83509.
- [17]. Catti L, Poethig A and Tiefenbacher K, *Adv. Synth. Catal* 2017, 359, 1331–1338.
- [18]. La Manna P, Talotta C, Floresta G, De Rosa M, Soriente A, Rescifina A, Gaeta C and Neri P, *Angew. Chem., Int. Ed* 2018, 57, 5423–5428.
- [19] a). Sanabria E, Vargas E, Estesio MA, Perez-Redondo A and Maldonado M, *Molecules* 2015, 20, 9915–9928; [PubMed: 26029860] b) Hong M, Zhang Y-M and Liu Y, *J Org Chem* 2015, 80, 1849–1855; [PubMed: 25584396] c) Zhou Y, Jie K and Yao Y, *New J. Chem* 2017, 41, 916–919; d) Avram L, Cohen Y and Rebek J Jr., *Chem. Commun. (Cambridge, U. K.)* 2011, 47, 5368–5375; e) Nicod L, Chitry F, Gaubert E, Lemaire M and Barnier H, *Journal of inclusion phenomena and macrocyclic chemistry* 1999, 34, 143–154.
- [20]. Fujimaki M, Kawahara S, Matsuzawa Y, Kurita E, Hayashi Y and Ichimura K, *Langmuir* 1998, 14, 4495–4502.
- [21]. Tancini F, Gottschalk T, Schweizer WB, Diederich F and Dalcanale E, *Chem. - Eur. J* 2010, 16, 7813–7819, S7813/7811–S7813/7815. [PubMed: 20540049]
- [22]. Jordan JH, Gibb CLD, Wishard A, Pham T and Gibb BC, *J Am Chem Soc* 2018, 140, 4092–4099. [PubMed: 29533064]
- [23] a). Schneider H-J, Güttles D and Schneider U, *Angewandte Chemie International Edition in English* 1986, 25, 647–649; b) Mansikkamaeki H, Nissinen M, Schalley CA and Rissanen K, *New J. Chem* 2003, 27, 88–97; c) Atwood JL and Szumna A, *Journal of Supramolecular Chemistry* 2002, 2, 479–482; d) Arena G, Contino A, Fujimoto T, Sciutto D and Aoyama Y, *Supramol. Chem* 2000, 11, 279–288; e) Mustafina AR, Skripacheva VV, Gubaidullin AT and Konovalov AI, *Journal of Structural Chemistry* 2005, 46, S76–S83; f) Morikawa O, Yamaguchi H, Katsube Y, Abe K, Kobayashi K and Konishi H, *Phosphorus, Sulfur Silicon Relat. Elem* 2006, 181, 2877–2886; g) Brown PO, Enright GD and Ripmeester JA, *Journal of Supramolecular Chemistry* 2002, 2, 497–500; h) Rissanen K, Nissinen M and Mansikkamaeki H, *Chem. Commun. (Cambridge, U. K.)* 2002, 0, 1902–1903; i) Morozova JE, Syakaev VV, Shalaeva YV, Ermakova AM, Nizameev IR, Kadirov MK, Voloshina AD, Zobov VV, Antipin IS and Konovalov AI, *Soft Matter* 2017, 13, 2004–2013. [PubMed: 28197613]
- [24] a). Ji X, Wang H, Li Y, Xia D, Li H, Tang G, Sessler JL and Huang F, *Chem. Sci* 2016, 7, 6006–6014; [PubMed: 27617079] b) Park JS, Yoon KY, Kim DS, Lynch VM, Bielawski CW, Johnston KP and Sessler JL, *Proc. Natl. Acad. Sci. U. S. A* 2011, 108, 20913–20917, S20913/20911–S20913/20934; [PubMed: 22160675] c) Chen Z, Lohr A, Saha-Möller CR and Würthner F, *Chemical Society Reviews* 2009, 38, 564–584. [PubMed: 19169466]
- [25] a). Ortega A and Torre J. G. a. d. l., *The Journal of Chemical Physics* 2003, 119, 9914–9919; b) Wang J, Yang Y, Yu M, Hu G, Gan Y, Gao H and Shi X, *Journal of the Mechanics and Physics of Solids* 2018, 112, 431–457.

- [26] a). Wishard A and Gibb BC, Beilstein J Org Chem 2018, 14, 2212–2219; [PubMed: 30202474]
b)Smith AM, Lee AA and Perkin S, J Phys Chem Lett 2016, 7, 2157–2163. [PubMed: 27216986]
- [27] a). Dalgarno SJ, Power NP, Antesberger J, McKinlay RM and Atwood JL, Chem. Commun. (Cambridge, U. K.) 2006, 3803–3805;b)Heaven MW, Cave GWV, McKinlay RM, Antesberger J, Dalgarno SJ, Thallapally PK and Atwood JL, Angew. Chem., Int. Ed 2006, 45, 6221–6224.

Figure 1:
¹H NMR (500 MHz, D₂O) showing concentration dependence of **1** from 50 to 0.78 mM by serial ½ dilution. The PGSE pulse sequence was used for water suppression to visualize the shift in H_n.

Figure 2:

Host **1** as a ditopic receptor binding an anion at the “crown” of pyridinium groups, and cation at the upper rim in the aromatic bowl. Proton assignments for H_j, H_l, and H_e highlighted.

Figure 3:

^1H NMR titration for host **1** (1.0 mM) with butyl pyridinium iodide up to 100 equivalents. The δ values for H_e and H_l were fit to a 1:1 binding model for cation and anion affinity respectively.

Figure 4:

Selected guests and “salt” affinities for host **1** (origin offset for clarity). Titrations of host and guest were performed on 1.0 mM solutions of **1** in unbuffered D₂O and monitored either H_I or H_J (for anion affinity) and H_e (for cation affinity). The colored ellipses represent the error in the measurements of cation (X-axis) and anion (Y-axis) affinity respectively.

Figure 5:

a) Concentration dependence of diffusion coefficient D (from DOSY NMR, 500 MHz, D_2O , 298 K) of **1** and calculated and experimentally determined values for N based on $K = 800 \text{ M}^{-1}$, Eq. 1 and DOSY data. Error bars (standard deviation) are from the error in the DOSY measurements from different host signals; b) Partial NOESY NMR (500 MHz, D_2O , 298 K) spectrum of **1** at 25 mM. The boxed region shows correlations between the aromatic H_e proton and the methylenes H_n and H_m .

Figure 6.

a) thermal ellipsoid model of unit cell of **1** (view down b axis). The resorcinarene with three disordered pendent groups is on the left. Hydrogens and solvent removed for clarity.

Figure 7. Packing orientation of four distinct chloride ions in crystal structure. Chloride shown as green space-filling spheres. Host **1** as wire-frame models. Solvent and some noncontact atoms removed for clarity. Clockwise from top left: Cl1, Cl2, Cl3, and Cl4.

Figure 8.

Partial packed slice from the crystal cell of **1**. Alternating host **1** molecules are shown in blue and red. Dark blue and light red indicate the pyridinium pendent groups of blue and red hosts respectively. The chloride ions are shown in light green.

Scheme 1:

Synthesis of tetra-pyridinium octol (**1**, counterion Cl⁻). Reagents and conditions are: i) 4-chlorobutyl dimethyl acetal, MeOH-HCl, 55 °C, 5 d; ii) Pyr, 88 °C, 72 h. The proton assignments of **1** highlighted.

Table 1.

Average DLS determined, apparent hydrodynamic diameters (nm) for host **1** under various buffered conditions.^a

Concentration (mM)	25.00	12.50	6.250	3.125	1.563	0.7813
Case 1) ^b	2.6(4) ± 0%	2.7(5) ± 2% ^c	2.6(3) ± 7% ^c	2.7(5) ± 3%	2.9(5) ± 13% ^c	1.8(3) ± 71% ^c
Case 2) ^b	3.2(7) ± 7% ^c	3.5(6) ± 3% ^c	3.7(4) ± 0%	3.8(7) ± 6%	3.6(5) ± 2%	2.2(4) ± 38% ^c
Case 3) ^b	1.7(3) ± 4%	1.6(3) ± 0%	1.5(2) ± 0%	1.6(3) ± 4%	1.5(2) ± 5%	1.1(2) ± 25% ^c
Case 4) ^b	2.3(5) ± 3%	2.2(3) ± 0%	2.0(4) ± 4%	1.9(4) ± 4%	1.6(2) ± 14% ^c	1.2(1) ± 24% ^c

^a) Averages of two determinations.

^b) All solutions prepared in 18.2 MΩ·cm H₂O.

^c) the value represents the weighted average of one or more bimodal distributions. Case 1) 100 mM NaCl (*I* = 100 mM); Case 2) 40 mM pH 7.3 phosphate buffer (*I* = 85 mM); Case 3) 40 mM pH 3.0 phosphate buffer (*I* = 35 mM); Case 4) 97 mM pH 3.0 phosphate buffer (*I* = 85 mM). All values for ionic strength ignore contributions from the host. The number in parantheses represents the average size distribution for the two determinations (e.g., 2.6 nm ± 0.3 nm and 2.6 nm ± 0.5 nm gives 2.6 nm ± 0.4 nm), whilst the error between two measurements under a given set of conditions is given as the standard deviation over the mean (as a percentage).