Zwitterionic Guanidinium Compounds Serve as Electroneutral Anion Hosts

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Abstract: The complexation of anions in solvating phases by artificial receptors requires the total or at least partial replacement of their solvation shells by the mutual supramolecular interactions. Supplementing well-known approaches that rely on net electrostatic charges or extensive hydrogen bonding for guest complexation the present work focuses on the alternative concept of charge separation in the host to create a cationic site suitable for strong interaction with negatively charged guests. An anionic moiety balancing the overall host charge to zero is incorporated in a way to prevent collapsing into an ion pair. Using bicyclic guanidinium anchor groups for direct guest binding and a *closo*-borane cluster as an anionic countercharge the ditopic zwitterionic host **17** was designed and prepared in a convergent synthetic scheme. Despite its electroneutrality **17** binds inorganic and organic oxoanions such as sulfate, oxalate, squarate and *p*-nitrophenyl phosphate with affinity constants reaching $3.1 \times 10^4\ M^{-1}$ in DMSO (squarate^{2-}) or $1.1 \times 10^5\ M^{-1}$ in acetonitrile (*p*-nitrophenyl phosphate^{2-}). Clean 1:1 host−guest stoichiometry is found in dilute solutions, whereas at higher concentrations different complex compositions and host dimerization are observed. Titration calorimetry reveals the major role of entropy in host−guest association. In essence, anion binding by **17** and its congeners in strongly solvating solvents such as DMSO is favored by massive positive association entropies that in the case of sulfate complexation to **17** override an unfavorable positive binding enthalpy constituting an exclusively entropy-driven process.

Host−guest binding of anions in condensed phases is successful only if the host can provide sufficient favorable interaction modes to outmatch the solvation free energies of both binding partners. A straightforward option to meet this requirement is to rely on strong and far-reaching attractive Coulombic forces, that is, to employ highly charged cationic host species. Following this guideline a vast variety of structures have been examined[1] which, in general, will associate a guest species of opposite charge rather readily even under competitive solvation conditions. This ion pairing process thus is unavoidable and ultimately limits the guest selectivity. Intuitively, one may expect that the difference in the interaction free energies $\Delta\Delta G$ of two competing guests causing the discrimination between them should rise the more negative the free energy of binding ΔG_{ass} becomes. As a corollary, high selectivity should be seen with molecular hosts that bind their anionic guests rather strongly. Although this is observed experimentally, for example, in the series of polyaza macrocycles forming multiply charged cations on protonation, this approach offers no general solution to the problem of binding specific anionic guests. The construction of the corresponding hosts calls for the prudent implementation of structural moieties addressing the *differences* between competing guests in order to support their discrimination. Frequently, these differences are rather subtle and require delicate balancing of the barriers for discrimination built into the host structure. In the presence of overwhelmingly dominant electrostatic interactions the tuning of low-energy contributions in host−guest interactions may be hard to achieve. Hosts of high charge also suffer from the obligatory presence of counteranions which unspecifically bind to the host compound and furthermore contribute to the ionic strength. For these reasons the desired complexation of the targeted guests is diminished. Multiply charged hosts are also notoriously poorly soluble in nonaqueous solvents restricting their use to the aqueous environment. Specific anion hosts, however, may find their use also as extractants in anion separation or membrane transport[4] as well as in ion-selective electrodes (ISE).[5] The

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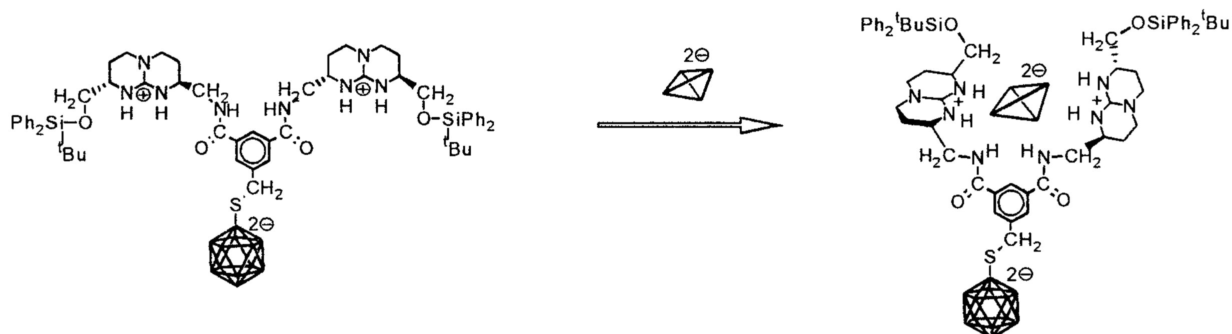
Scheme 1



specific recognition event then must happen in an organic phase and also has to avoid extremely strong guest binding for kinetic reasons.

All of these arguments may be taken to support an alternative host design: Molecular recognition of anions ought to be brought about by electroneutral host compounds relying on ion–dipol forces as in the plethora of hydrogen bonding hosts[6] or specifically designed cage compounds.[7] While this concept succeeds in solvents of low polarity, it is generally not applicable in the more polar organic solvents (DMSO, methanol, etc.) which also solvate host and guest species by strong dipolar interactions. The inspection of biological molecular hosts reveals still another principle to selectively complex anions even under the most competitive conditions. They manage to desolvate and transfer negatively charged guests to peculiar sites in the interior of their protein skeleton by virtue of unbalanced positive charges and an array of preorganized hydrogen bond donor groups. In many cases, exemplified for example by phosphate binding protein (PBP),[8] a guanidinium moiety in the side chain of an arginine residue plays the role of a primary anchor function which is supplemented by an ensemble of H-bond donors furnishing a binding site of unique complementarity and preorganization. As a result sulfate ion having the same charge as phosphate at physiological pH is discriminated by a factor of 10^5 in water.[9] Despite their polyionic nature the net charge of proteins is rather small so that most single charged groups are counterbalanced by some function of opposite sign leading overall to almost electroneutrality. The trick played by proteins to make them successful anion hosts is the segregation of charges enforced by a particular folding of the covalently connected backbone. The prevention of collapse into ion pairing of unlike charged functions opens the possibility of using the strong Coulombic attraction of cationic guanidinium groups toward oxoanions[10] while minimizing the adverse effects of the counterions. The same concept has been realized in an abiotic host before by attachment of carboxylate moieties to an anion-binding macrotricyclic cage compound.[11]

These zwitterionic compounds **1** have good water solubility and are fully functional anion hosts over a broad pH-regime but require a laborious preparation and do not lend themselves to nonaqueous applications. Here we report on an alternative approach resting on the same basic concept of charge separation, however, in a synthetically more accessible open-chain receptor design.

Results and Discussion

Receptor Design. The strategic idea underlying host construction has been reported in a previous paper[12] and consists of exploiting the inherent difference in binding affinity of the bicyclic guanidinium moiety **2**[13−15] to hydrogen-bond accepting oxoanions on one hand versus the so-called noncoordinating anions[16,17] on the other. The latter do not contain lone electron pairs and their charge is well delocalized to avoid any hydrogen-bonding properties. This is in contrast to most oxoanions which typically are quite basic (phosphate, carboxylate, sulfate, etc.) and interact strongly with guanidinium groups such as **2**. The binding motif **3** forms the basis in the design of a number of polytopic receptors for a variety of biologically important anions,[18−20] where A and B represent additional anchor groups. Within this frame we embarked on the preparation of ditopic

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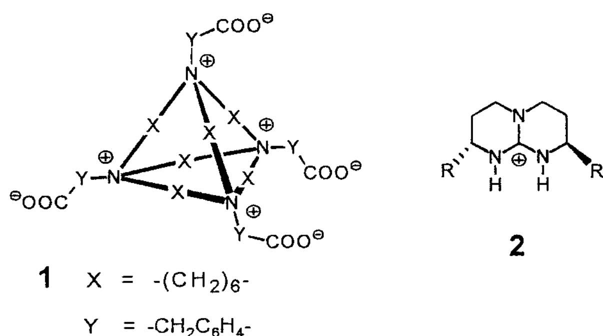
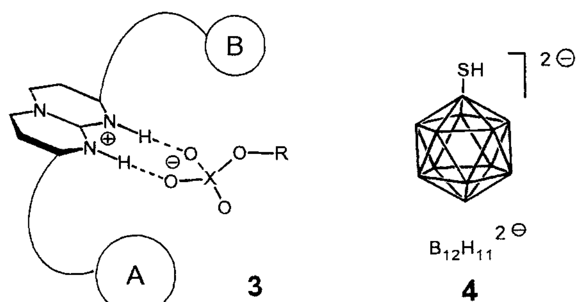
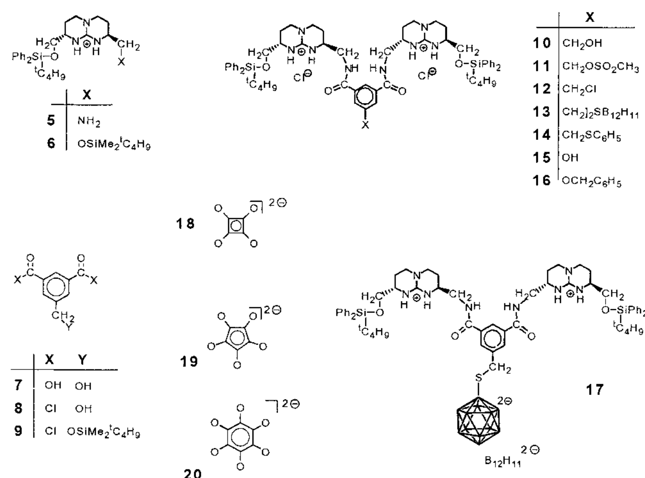
receptors containing two bicyclic guanidinium moieties linked by an aromatic spacer unit (Scheme 1). This design was directed toward binding of doubly charged oxoanions mandating cooperative action of both anchor functions.





The prime virtues of this design reside in the building-block approach that enables a convergent strategy and allows ready modification. The open-chain branched layout of the receptor ensures adaptability of the host structure comforting the needs of guest solvation shell displacement. Even though a price in terms of the entropically demanding folding of the host must be paid, experience tells that this path is preferable to attempting total preorganization of the host. The incorporation of two cationic guanidinium units required the attachment of a substructure containing two negative charges to arive at an electroneutral receptor. Among the various candidates the dianionic icosahedral boron cluster compound **4** appeared optimal with respect to its proven chemical stability and marked lipophilicity[22] and its well worked out chemistry of attachment to organic structures[23] which results from its use in the field of boron neutron capture therapy BNCT.[24] Being a strong nucleophile the thiolate of **4** required an electrophilic point of attachment to the spacer unit. Thus, our concept contained a benzyclic halide moiety in the spacer in addition to two carboxylic acid functions for anchor group attachment. To maximize the mutual distance between the charged groups and to simplify the analysis of host−guest-binding by NMR the symmetrical arrangement of substituents at the spacer hub was chosen.

Host Synthesis. Earlier host−guest-binding studies involving the guanidinium building-block **2** had established that connecting the anchor group to the spacer unit via *sec*-amide junctions is profitable for anion binding.[21] In addition to the aminomethyl guanidinium module **5**[25] the isophthalic acid derivative **10** was required and obtained by lithium aluminum hydride reduction of methyl trimesitoate and subsequent hydrolysis.[26] After initial attempts to couple both modules using Schotten−Baumann conditions on the acid chlorides **8** or **9** had failed because of undesired side reactions the attachment proceeded smoothly employing HBTU/TEA at ambient temperature. This peptide coupling reagent proved superior to DCC or some other standard amidation reagents but required RP-chromatographic purification of the product **10** to furnish a 72% yield. For connecting the dianionic borocaptate cluster **4**, the benzyl alcohol **10** was converted to the mesylate **11** at low temperature as prolonged reaction times or higher temperatures gave the corresponding benzyl chloride **12**. The subsequent substitution reaction with the boron cluster **4** in the presence of strong base has some analogy in the literature.[23,27] Using a variety of conditions two products were obtained in various ratios. While the reaction in acetonitrile with triaza-bicyclodecene (TBD) as a base almost exclusively furnished the undesired sulfonium salt **13** (cf. ref 23) switching the solvent to DMF gave preferentially the target compound **17**. The yield of **17** was decreased when **12** was used as the alkylating agent of **4**. In many reactions an intense blue coloration appeared which, however, had no bearing on the yield and may be attributed to a stable sulfur radical.[28] For comparison the thioether **14** was prepared by the same procedure as for **17** to give a ditopic host containing the same primary interaction site for the guest anion as in **17** but possessing a 2-fold cationic net charge. Irrespective of the charge difference borocaptate **4** and thiophenol have very similar sizes.[22] Though the spectral data of **14** and **17** are fully consistent with the assigned structures we notice a marked difference in the ^{1}H NMR signal of the methylene group bearing the thio substituent: Compound **14** displays a singlet at 4.15 ppm in accord with a freely rotating CH_2 group. In contrast **17** shows 2 mutually coupled doublets indicating conformational locking and a well-defined folded structure. Experiments discussed below provide arguments in favor of intermolecular association to cause this observation.



Molecular Modeling. The target structure **17** is zwitterionic and though efforts were taken to minimize the specific interactions of the substructures carrying unlike charges the Coulombic

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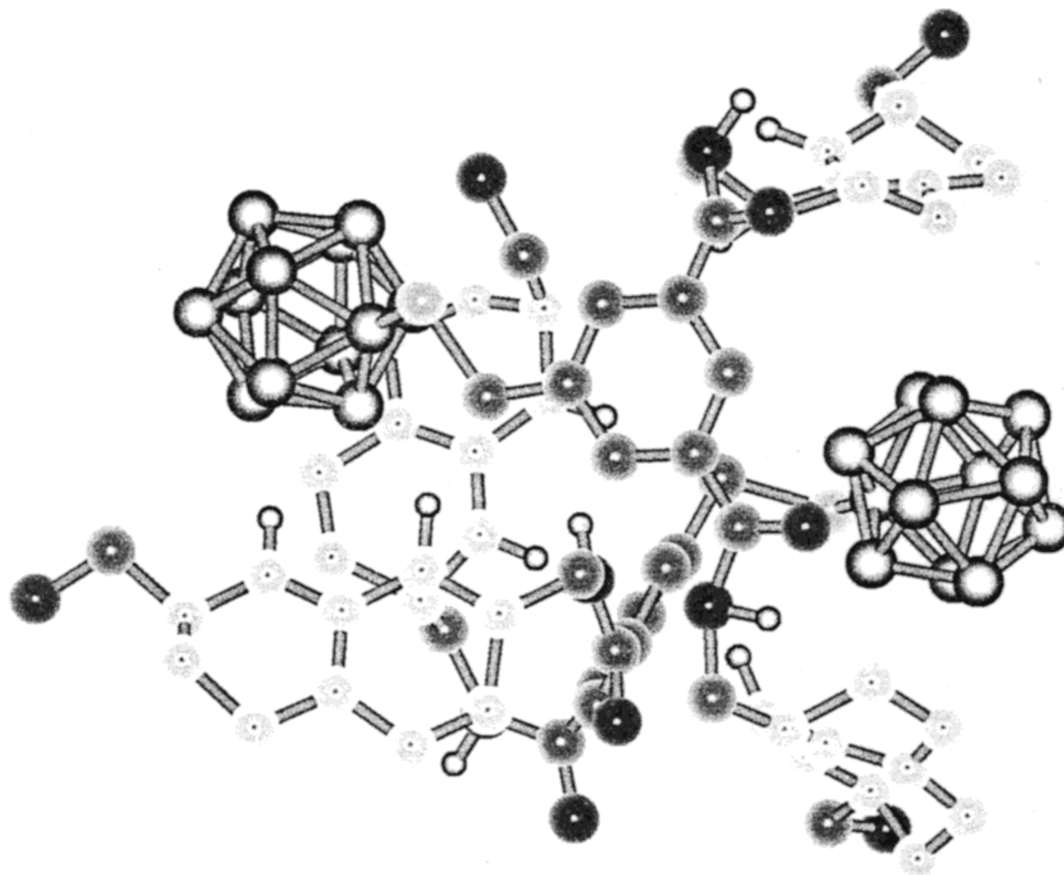

Figure 1. Energy-minimized structure of the dimer of **17** obtained by molecular modeling i.vac. using the MM+ force field. H-atoms and the silyl-protecting groups were omitted for clarity.

attraction between them cannot be annihilated due to its universal character. To learn about the preferred modes in this interaction we undertook molecular modeling calculations in vacuo without adjustment of the dielectric constant. First the distribution of partial charges in **17** was obtained from semiempirical AM1 calculations. In a second step molecular dynamics used the MM+ force field on an ensemble of two separated molecules followed by optimization of the ensemble geometry by energy minimization at intervals. The low-energy structure depicted in Figure 1 shows a dimer in which the substructures of complementary charge of both monomers associate mutually to form what we call a yin–yang dimer. The guanidinium units approach the boron cluster anions side-on, indicating the total absence of hydrogen bonds between them. Although this picture may not reflect the true structure of **17** in solution, it is taken as a good suggestion that the intermolecular association of two molecules of **17** satisfying its unspecific electrostatic needs is more favorable than the intramolecular folding to reach the same goal.

NMR and UV studies. The ^{1}H NMR spectrum of **17** in DMSO is concentration-dependent. This is particularly obvious in the shift of the guanidinium NH signals which only moderately move to lower field ($\Delta\delta_{max} = 0.35$ ppm) on increasing the concentration, indicating that these functions are not primarily involved in supramolecular interactions. The shifts can be cleanly modeled by a 1:1 dimerization process. The Hostest 5.0 fitting program[29] gives an apparent dimerization constant of 250 M^{-1}. The self-association is diminished on addition of 50 mM tetrabutylammonium perchlorate (K_{dim} = 100 M^{-1}) as an inert electrolyte. Increasing the ionic strength weakens electrostatic interactions in general, and this testifies to the origin of the dimerization process.

The addition of bromide or nitrate salts to solutions of **17** in DMSO did not cause any change in the NMR spectra. When oxalate dianion, hydrogenphosphate, or adenosine monophosphate was added, dramatic shifts of all N–H signals were observed initially in support of strong host–guest associations. However, these interactions could not be quantified because rapid deuterium exchange rendered these signals soon invisible, and we were unable to resolve the shifts of other signals due to severe overlap. Feeling that the high basicity of the guest anions in DMSO were responsible we added up to 10 vol % of water but without improving the analytical problem. Less basic anions such as sulfate or the quasi-aromatic dianion squarate **18**, however, under the same conditions gave titration curves that were readily analysable by curve fitting employing a mixed model of 1:1 host–guest association and host dimerization.[29] In this way $K_{ass}(SO_4^{2-}$, DMSO) = 356 M^{-1} was obtained (see Table 1) with a correlation coefficient of $R^2 = 99.94$. A small but systematic deviation from the fit curve might indicate that complexes of different stoichiometry might be present in solution as well. If this assumption holds the 1:1 association constant K_{ass} would be diminished, but the data at hand do not allow the meaningful and reliable interpretation in this sense. The considerably larger squarate dianion **18** caused intense shifts

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Table 1. 1:1 Host−Guest Association of Zwitterionic Host **17** with Anionic Guests in DMSO at 25 °C

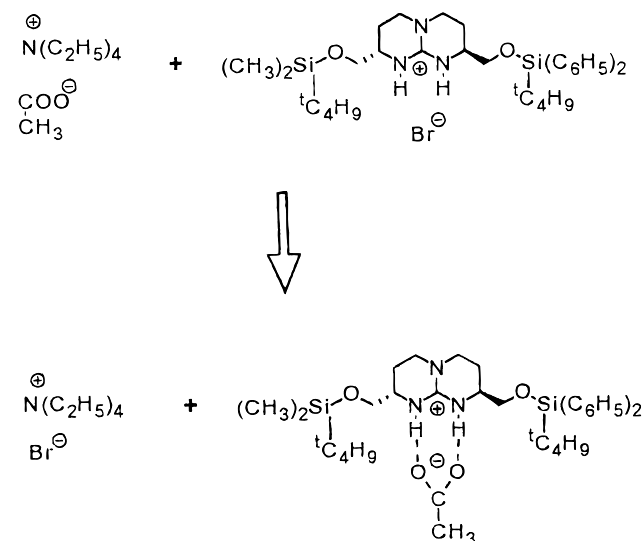
anion	K_{ass} (M^{-1})	*p*-range[31]	titration method
NO_3^-, Br^-	no effect		NMR
SO_4^{2-}	350	0.43 − 0.89	NMR
p-nitrophenyl phosphate^{2-}	7×10^3	0.33 − 0.61	UV
squarate^{2-} **18**	3.1×10^4	0.22 − 0.83	UV
croconate^{2-} **19**	2.5×10^4	0.41 − 0.76	UV
rhodizonate^{2-} **20**	1.8×10^4	0.35 − 0.73	UV

in the ^{1}H NMR spectrum in DMSO, but the complex was too stable to reliably derive an association constant. Instead, we observed that this guest experienced an intensity enhancement of its $\lambda = 313$ nm UV-absorption band on complexation. Employing Benesi-Hildebrand conditions ([**17**] $\geq$ 10 $\times$ [**18**]) or curve-fitting procedures both revealed the formation of a strong 1:1 complex giving $K_{ass} = 3.1 \times 10^4$ M^{-1}. In a similar manner the homologous oxoanions croconate **19** and rhodizonate **20** were evaluated and showed binding constants somewhat smaller but within a factor of 2 from the one found for squarate. Applying UV titration to the binding of *p*-nitrophenyl phosphate which particularly lends itself to this method owing to the long wavelength n $\rightarrow$ π* transition at $\lambda = 436$ nm[30] required solubilization of this guest in DMSO. Adding cryptand[2.2.2] to a slurry of the sodium salt formed the stable alkaline cation cryptand encapsulation complex and weakened the ion pairing with the guest anion. Using this auxiliary, a 1:1 association constant of 7×10^3 M^{-1} was deduced from the titration data. All of these UV titrations were performed with 10−100 μM concentrations of the host **17**. Host dimerization in this regime is negligible and need not be accounted for in the K_{ass}-calculation.

On comparison to zwitterionic **17** the biscationic pendant host **14** shows very little change in its N−H NMR signals on dilution ($\Delta\delta \leq 0.05$ ppm, 0 $\rightarrow$ 12 mM). It thus appears safe to assume that there is no aggregation in this concentration range which is also plausible, viewing the net charge of this host. The NMR-titration of **14** taking sulfate as a guest yields $K_{ass} = 175$ M^{-1} in DMSO. Contrary to the naive expectation, the host having precisely the same primary guest binding site but a +2 net charge exhibits a weaker affinity by 2-fold than its counterpart with a formal charge of zero. We conclude there is apparently no screening of the guest binding affinity from the anionic portion in the zwitterionic host **17**. The weaker binding power of cationic **14** may be due to the ionic strength of this receptor, which cuts down on the unspecific component of electrostatic guest binding.

Isothermal Titration Calorimetry. Although NMR titrations are indispensable tools in the wide-range collection of information on supramolecular associations and can provide clues on the structural mode of host−guest relationships, the elucidation of the thermodynamic parameters $\Delta G°$, $\Delta H°$, and $\Delta S°$ by this instrumental method is laborious, insensitive, and error-prone. A more direct access to those important data is offered by modern isothermal titration calorimetry (ITC),[32] allowing the ready dissection of association free energies into its enthalpic and entropic components. Since both are mutually compensating in weak supramolecular interactions,[33] the knowledge of the individual enthalpy and entropy parts rather than their composite, the free energy $\Delta G°$, which is readily recalculated from K_{ass}, is required to gain insight into the intimacies of host−guest binding. Because calorimetric measurements are truly integral reflections of all processes occurring in solution, it is of utmost importance to design very simple host−guest reactions to arrive at interpretable results. A good example is given by the host−guest binding of the prototypical oxoanion acetate to the bicyclic guanidinium anchor group **6** (Scheme 2). In the concentration range used for collecting the caloric data the salts on the left-hand side of the equation in Scheme 2 as well as tetraethylammonium bromide are strong electrolytes and almost completely dissociated in polar solvents like methanol, DMSO, or acetonitrile. The only process to happen along with all changes in the solvation of the species involved is the host−guest complex formation of the guanidinium cation and acetate anion. The corresponding ITC measurements and the titration curves produced therefrom are shown in Figure 2. As is immediately apparent from the sign of the heat pulses, host−guest binding of these partners is exothermic in acetonitrile and DMSO solvents, whereas the heat effects in methanol are minute and do not allow us to decide whether there is no interaction at all in this solvent or the reaction enthalpy adventitiously is near zero. From the slope of the titration curves, itself being obtained by plotting the integrals of the heat pulses, the standard free energy $\Delta G°$ can be obtained. With $\Delta G°$ and $\Delta H°$ (the step height of the titration curve) the entropy $\Delta S°$ can be calculated from the Gibbs−Helmholtz equation (see Table 2). It comes as a surprising result that in the former two cases the stability of host−guest binding is not only due to the strong enthalpic attraction but also to a favorable positive entropic component. This association process combines two molecular species to form one complex, yet the overall entropy of the system increases, owing to the release of bound solvent molecules. Similar entropic effects are widespread in aqueous systems[34] but have also been observed with supramolecular associations in organic

Scheme 2



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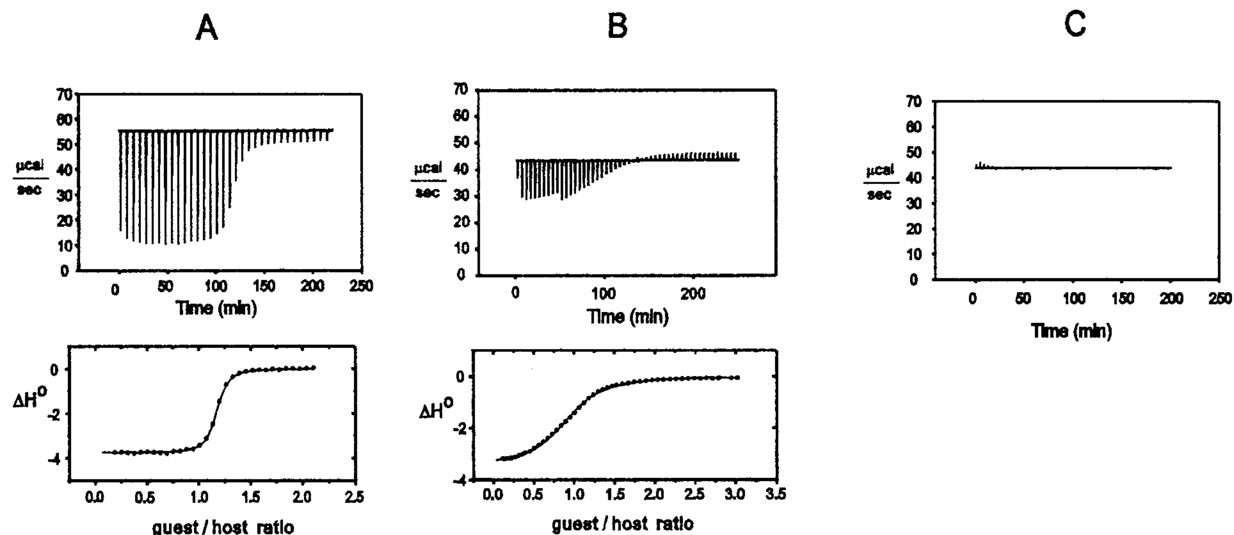

Figure 2. ITC analysis of the guanidinium-acetate host−guest binding at 30 °C according to Scheme 2. (a) In acetonitrile, [**6**] = 1.92 mM; (b) in DMSO, [**6**] = 2.5 mM; the step in the plot of heat pulses is due to a change in the titrand volume added and is accounted for by the evaluation software; (c) in methanol.

Table 2. Thermodynamic Parameters Evaluated by ITC of Tetraethylammonium Acetate Binding to **6** at 30 °C

	CH_3CN	DMSO
K_{ass} (M^{-1})	2.0×10^5	6.5×10^3
$\Delta G°$ (kJ mol^{-1})	−30.7	−22.1
$\Delta H°$ (kJ mol^{-1})	−15.5	−14.2
$\Delta S°$ (J mol^{-1} K^{-1})	+50.2	+26.1

Table 3. Host−Guest Complexation of {Na^+cryptand[2.2.2]}$_2$ *p*-Nitrophenyl Phosphate by Compounds **17**, **15**, and **16** in Acetonitrile at 30 °C

	K_{ass} (M^{-1})	$\Delta G°$ (kJ mol^{-1})	$\Delta H°$ (kJ mol^{-1})	$\Delta S°$ (J K^{-1} mol^{-1})
17	1.1×10^5	−29.2	−33.5	−14.1
15	1.6×10^5	−30.2	−37.7	−24.7
16	1.1×10^5	−29.2	−28.4	+2.4

solvents.[35] The difference in stability of the guanidinium acetate complex (Scheme 2) in CH_3CN or DMSO is primarily attributable to the less positive $\Delta S°$ value in the latter case, probably reflecting a smaller number of the bigger DMSO molecules set free on host−guest binding.

Caloric data may also provide structural information if a collection of hosts of similar structure is compared. For instance, the binding of *p*-nitrophenyl phosphate in acetonitrile to the zwitterionic host **17** and two analogues **15** and **16** having exactly the same primary anion binding site but differing at a remote location having none or a neutral substituent at this position all produce the same binding constant within experimental error (Table 3). However, the immediately obvious conclusion denying any influence of the remote substituent on the guest binding process is false, because the unfolding of the binding enthalpies and entropies clearly demonstrate its participation.

ITC measurements also offer an explanation for the surprisingly weak binding of sulfate dianion to the zwitterionic host **17** in DMSO. While analogous dicationic guanidinium hosts bind this guest very tightly ($K_{ass} > 10^6$ M^{-1} [36]) the ITC analysis gives K_{ass} (SO_4^{2-}, DMSO) = 200 M^{-1} which is in reasonable agreement with the value obtained by NMR-titration. The close inspection, however, reveals an exclusively entropy-driven endothermic process having $\Delta H° = +10.5$ kJ mol^{-1} and $\Delta S° = +78$ J K^{-1} mol^{-1}. Most surprisingly the nonlinear regression gives $n = 0.5$ as an independent fit parameter meaning that there are two binding sites of equal affinity on each host **17**. Obviously, there is no cooperative binding of both guanidinium anchor groups to sulfate when the anionic boron cluster resides in the molecule translating into a 10 000-fold reduction in guest affinity.

Taking squarate as a guest anion the calorimetric technique unravelled a more complicated host−guest binding process with **17** than anticipated on the basis of the UV titration. Unlike the clear 1:1 stoichiometric complexation observed in the micromolar concentration range (see above) the ITC-measurements at 100-fold higher concentration showed a stepwise binding event first forming a complex of 2:1 host: guest stoichiometry (inflection an $n = 0.5$) which on further addition of the guest solution gives rise to a step having 1:1 (or maybe 2:2) stoichiometry. With the software at hand the second step was evaluated giving $K_{ass} = 8.9 \times 10^5$ M^{-1} in an exothermic and entropically driven process. The observation of stepwise binding indicates that squarate **18** does not bind with full complementarity to host **17** and satisfies all of its coordination needs in DMSO. It is also not possible to decide from these data on the sequence of binding events, that is, whether squarate binds to the host dimer or rather a 1:1 host−guest complex is formed that associates another host molecule in a subsequent step. Viewing the simple structures we tend to speculate that there is a random binding order. The boron cluster, however, is not innocent in this binding since the analogous host compound **14** on binding squarate **18** shows very similar thermodynamic parameters (Table 4) but lacks the stepwise binding feature.

Conclusions

The contradicting goals of high affinity for anionic guests under competitive solvation conditions, yet good lipophilicity were addressed in a new receptor design. A zwitterionic host **17** was constructed in a building-block approach and proved active in oxoanion binding in DMSO. The binding studies in comparison to those of charged hosts of very similar structure showed a minor influence of the net charge only. Instead the

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Table 4. ITC Evaluation of Host−Guest Binding in DMSO at 30 °C[a]

		14	17
squarate **18**	K_{ass} (M^{-1})	6.2×10^5	8.9×10^5
	$\Delta G°$ (kJ mol^{-1})	−33.6	−34.5
	$\Delta H°$ (kJ mol^{-1})	−7.4	−5.4
	$\Delta S°$ (J K^{-1} mol^{-1})	+86.6	+96.0
	n	0.85	1.10
sulfate	K_{ass} (M^{-1})	not determined	200
	$\Delta G°$ (kJ mol^{-1})		−13.3
	$\Delta H°$ (kJ mol^{-1})		+10.5
	$\Delta S°$ (J K^{-1} mol^{-1})		+78
	n		0.5

[a] The data given for the **18** to **17** interaction refer to the step giving the 1:1 complex.

role of the solvent in host−guest binding was apparent from calorimetric measurements and materializes in positive reaction entropies of respectable size. One is led to conclude that solvation design is a profitable way to supplement host−guest complementarity in the construction of selective artificial hosts.

Experimental Section

General methods. Proton-, ^{11}B-, and ^{13}C NMR spectra were recorded on a Bruker AM 360 (360 MHz) instrument and are calibrated to tetramethylsilane as internal standard (^{11}B to BF_3OEt_2 as external standard). Mass spectra were obtained on Varian MAT CH5 (FAB) or Finnigan LQC (ESI) instruments at the TU-München. MALDI-TOF spectra were measured on a Micromass TofSpec at the University of Bonn. IR spectra were measured on a Perkin-Elmer FTIR 1600 instrument. HPLC-analyses were performed on Merck−Hitachi instruments (L6200A or L7100 pump connected to L4250 or L7400 UV-detectors or to a Eurosep DDL-31 light-scattering detector). As columns, Prontosil C_8 SH (125 × 4 mm) or Nucleosil C_{18} (250 × 4 mm) were used with mixtures of acetonitrile/water containing 30 mM of H_3PO_4 and 30 mM $NaClO_4$ or 0.1% trifluoroacetic acid (for detection with light scattering detector). Column chromatography (HPLC) was performed in Michel−Miller columns packed with RP-modified silica (Nucleoprep 100−30 C8) connected to a Knauer 364 HPLC pump, a Phillips PU 8620 photometer and a LKB fraction collector.

Solvents were distilled before use except for DMF which was purchased in anhydrous quality from Aldrich and acetonitrile which was purchased in HPLC-quality from Zefa). All other chemicals were purchased in reagent quality and used as received. Aqueous solutions were prepared from deionized, glass-distilled water. All reactions were carried out in an atmosphere of nitrogen and solvents (CH_2Cl_2, CH_3CN) were passed through a small column of activated alumina directly into the reaction vessel. Sodium borocaptate **4** (^{10}B-enriched) was purchased from Boron Biological Inc. Aminomethylguanidinium chloride **5**[13f] and 5-hydroxymethylisophthalic acid[26] were prepared as previously described.

Synthesis. Guanidinium-benzyl Alcohol 10. Aminomethyl guanidinium chloride **5** (500 mg, 0.982 mmol, HCl salt) was dissolved in 3 mL of DMF and added to a suspension of 5-hydroxymethylisophthalic acid **7** (91.7 mg, 0.468 mmol) in 2 mL of acetonitrile. The minimum amount of DMF was then added with stirring to furnish a clear solution followed by *N*-methylmorpholine (0.5 mL, 5 mmol). To the resulting suspension a solution of *O*-(benzotriazol-1-yl)-tetramethyluronium hexafluorophosphate (HBTU, 426 mg) in a mixture of acetonitrile/DMF (1:1 vol) was added dropwise with stirring. After 1 h, another 20 mg of solid **5** and 30 mg of solid HBTU were added, followed by another 30 mg of **5** (solid) and 40 mg of HBTU (solid). After the final addition, the HPLC analysis showed complete conversion to one main product. The mixture was diluted with 30 mL of CH_2Cl_2, washed with 0.1 M HCl, 1 M Na_2CO_3 (2×), 0.1 M HCl and water (20 mL portions each) and dried over Na_2SO_4. The residue obtained on filtration and removal of the solvent under reduced pressure was purified by flash chromatography (Nucleoprep 100−30 μm, C_8, 35 × 4 cm, CH_3OH/H_2O (85/15 vol) containing 30 mM H_3PO_4 and 30 mM $NaClO_4$). The fractions containing **10** were pooled, concentrated under reduced pressure, and extracted with CH_2Cl_2 (3×). The combined extracts were washed with brine (2×) and dried over Na_2SO_4. After removal of the solvent in vacuo, **10** was obtained as the chloride salt (366 mg, 72%). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.46 (s), 8.38 (s), 8.07 (s), 7.93 (s), 7.73 (s), 7.70 (s), 7.56−7.59 (m), 7.31−7.40 (m), 4.46 (s), 3.84 (s), 3.21−3.84 (m), 2.01 (m), 1.87−1.89 (m), 1.03 (s). ^{13}C NMR ($CDCl_3$, 90 MHz), δ 167.3 (CO), 151,1 (C^+), 142 (ArCH), 135.5 (silyl), 134.8 (ArC), 132.9 (ArCH), 132.6 (silyl), 129.8 (silyl), 127.6 (silyl), 124.0 (ArCH), 65.6 (CH_2O), 64.0 (CH_2O), 49.7 (CHN), 48.0 (CHN), 45.2 (CH_2N), 45.0 (CH_2N), 43.8 (CH_2N), 26.7 (CH_3), 23.7 (CH_2), 22.6 (CH_2), 19.1 (C). MS (FAB) *m/e* 1070 ($M{\cdot}Cl^+$, 40%), 1034 (100%), 186 (95%).

Guanidinium-mesylate 11. The benzyl alcohol **10** (291 mg, 0.263 mmol) was dissolved in 5 mL of dry CH_2Cl_2, 110 μl of triethylamine (TEA, 3 equiv) were added, and the resulting mixture was cooled to −10 °C. Then 0.5 mL of a freshly prepared 1 M solution of methanesulfonyl chloride in CH_2Cl_2 was added dropwise via syringe, and stirring was continued at −10 °C for 30 min after which HPLC analysis indicated complete conversion to a single product. The reaction mixture was washed with 0.1 M HCl and 1 M $NaClO_4$ and dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, **11** (perchlorate salt) was obtained as a colorless, viscous residue and used directly for further conversion. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.98 (s), 7.92 (s), 7.75 (d), 7.70 (s), 7.56−7.59 (m), 7.31−7.42 (m), 7.17 (s), 6.82 (s), 5.27 (dd), 3.84 (s), 3.21−3.67 (m), 1.88−2.04 (m), 1.02 (s). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 160.3 (CO), 150.9 (C^+), 135.5 (silyl), 134.9 (ArC), 133.4 (ArC), 132.6 (silyl), 130.5 (ArCH), 129.8 (silyl), 127.6 (silyl), 125.5 (ArCH), 70.7 (CH_2O), 65.7 (CH_2O), 50.0 (CHN), 47.8 (CHN), 45.2 (CH_2N), 44.8 (CH_2N), 43.9 (CH_2N), 37.6 (CH_3, mesyl), 26.6 (CH_3), 23.7 (CH_2), 22.6 (CH_2), 19.0 (C).

Borocaptate-receptor 17. The residue of the mesylate **11** obtained above was dissolved in dry DMF, and a stream of nitrogen was passed through the solution for 10 min. Likewise, 169 mg of sodium borocaptate **4** (0.8 mmol) was dissolved in 2 mL of DMF and was degassed. Both solutions were combined to give a pale green solution to which a solution of 1,5,7-triazabicyclo[4.4.0]dec-5-en (TBD) (21 mg, 0.14 mmol in 0.25 mL of DMF) was added slowly via syringe pump over 90 min. HPLC analysis showed the disappearance of the starting material, and the reaction mixture was diluted with 20 mL of CH_2Cl_2 and washed with 0.1 M HCl (2×) and brine. After drying over Na_2SO_4 and filtration and removal of the solvent under reduced pressure, the residue was purified by column chromatography (Nucleoprep 100, 30 μm, C_8, 30 × 2.1 cm, CH_3CN/H_2O (86/14 vol) containing 30 mM H_3PO_4 and 30 mM $NaClO_4$). The fractions containing **17** were pooled, carefully neutralized with 0.2 M NaOH, concentrated under reduced pressure and extracted with CH_2Cl_2 (3×). The combined extracts were dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, **17** was obtained as a slightly yellow solid (161 mg, 52% from **10**). ^{1}H NMR (DMSO-d_6, 360 MHz) δ 8.81 (s, NH), 8.23 (s, 1H, ArH), 7.86 (s, 2H, ArH), 7.81 (s, NH), 7.49−7.62 (m, 8H, ArH), 7.40−7.45 (m, 12H, ArH), 4.41 (dd, 2H, $ArCH_2$), 3.20−3.63 (m, 20H); 1.70−2.05 (m, 8H, CH_2), 1.00 (s, 18H, CH_3). ^{13}C NMR ($CD_3CN/CDCl_3$, 90 MHz) δ 165.4 (7, CO), 150.2 (C^+), 134.5 (silyl), 132.7 (ArCH), 132.1 (ArC), 131.8 (silyl), 130.7 (ArCH), 129.1 (silyl), 128.1 (silyl), 124.5 (ArCH), 65.2 (CH_2O), 49.3 (CHN), 47.8 (CHN), 45.2 (CH_2S), 44.4 (CH_2N), 44.1 (CH_2N), 43.0 (CH_2N), 25.5 (CH_3), 23.0 (CH_2), 21.5 (CH_2), 18.9 (C). ^{11}B NMR (CD_3CN, 115,5 MHz) δ −12 (−16) (m). IR (KBr, cm^{-1}) 3431 (s), 2506 (w), 1624 (s), 1540 (w). MS (MALDI-TOF, negative-mode, 2,5-dihydroxybenzoic acid as matrix) *m/e* 1180 (M^-).

Guanidinium-benzyl Chloride 12. 5-^{t}Butyldimethylsilyloxymethylisophthalic acid (0.6 g, 2 mmol) were suspended in 20 mL of toluene, 1 mL of oxalic acid chloride was added, and the mixture was stirred overnight. After the solvent was stripped off, CH_2Cl_2 (100 mL) was added to the residue, and the resulting slurry was filtered. The filtrate was concentrated to dryness to yield 530 mg of the acid chloride **9** (1.52 mmol). The residue of **9** was dissolved in 10 mL of CH_2Cl_2, the amino compound **5** (1.58 g, 3.3 mmol, HCl salt) was added, and the solution was cooled to 0 °C. TEA (1.7 mL, 12 mmol) was added dropwise over a period of 60 min with stirring. The reaction mixture

was diluted with 40 mL of CH_2Cl_2, washed with 1 M HCl (3×), and dried over Na_2SO_4. The residue obtained after filtration and removal of the solvent under reduced pressure was purified by column chromatography (Nucleoprep 100, 30 μm, C_8, CH_3OH/H_2O, step gradient first 75/25, then 80/20 vol, containing 30 mM H_3PO_4 and 30 mM $NaClO_4$). Employing the same workup as described for **11**, 360 mg of **12** (0.32 mmol, 21% from **8**), 250 mg of **10,** and 250 mg of a mixture of **10** and **12** were obtained. ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.86 (s, 1H, ArCH), 8.68 (m, 2H, NH), 8.29 (s, 2H, NH), 8.09 (s, 2H, ArCH), 8.02 (s, 2H, NH), 7.60−7.63 (m, 8H, silyl), 7.31−7.41 (m, 12H, silyl), 4.60 (s, 2H, CH_2Cl), 3.90 (m, 2H, CH_2O), 3.50−3.77 (m, 8H, CHN, CH_2N), 3.11−3.47 (m, 10H, CHN, CH_2N), 1.95−2.10 (m, 4H, CH_2), 1.75−1.90 (m, 4H, CH_2), 1.03 (s, 18H, CH_3). ^{13}C NMR (90 MHz, $CDCl_3$) δ 167.0 (CO), 151.1 (C^+), 138.2 (ArC), 135.5 (silyl), 134.3 (ArC), 132.7 (silyl), 131.4 (ArCH), 129.9 (silyl), 127.8 (silyl), 126.1 (ArCH), 65.4 (CH_2O), 49.3 (CHN), 47.7 (CHN), 45.4 (CH_2Cl), 45.0 (CH_2N), 44.7 (CH_2N), 43.5 (CH_2N), 26.9 (CH_3), 23.6 (CH_2), 22.5 (CH_2), 19.1 (C). MS (ESI) *m/e* 1165.2 ([M · TFA]$^+$, 100%), 1087.2 ([M · Cl]$^+$, 7%), 526.8 (M^{2+}, 22%).

Thioether 14. The mixture of **10** and **12** obtained above (250 mg, combined ∼0.18 mmol) was dissolved in 10 mL of CH_2Cl_2 and subjected to standard mesylation: 0.4 mL of a freshly prepared 1 M solution of TEA in CH_2Cl_2 was added, and the mixture was cooled to 0 °C. Then 0.4 mL of a freshly prepared 1 M solution of methanesulfonyl chloride in CH_2Cl_2 was added dropwise with stirring followed by 0.4 mL of the TEA solution. After stirring at 0 °C for 60 min the reaction mixture was washed with 0.1 M HCl (3×), 1 M $NaClO_4$ and dried over Na_2SO_4. The residue obtained after filtration and removal of the solvent was divided into two aliquots, one-half was dissolved in 3 mL of CH_2Cl_2, 25 mg TBD was added, and the resulting mixture was cooled to 0 °C. Thiophenol (18 μl, 0.18 mmol) was added dropwise, and stirring was continued for 60 min. The reaction mixture was washed with 0.1 M HCl (2×) and 1 M Na_2CO_3 (2×) and dried over Na_2SO_4. After filtration and concentration of the solution to a volume of ∼0.5 mL, the crude product was precipitated by addition of diethyl ether. The product was collected by centrifugation, separated from the supernatant, and dissolved again in 0.5 mL of CH_2Cl_2. Precipitation and redissolving was repeated 3 times. The crude product obtained in this manner was distributed in a two-phase system (prepared from $HCCl_3$/heptanes/CH_3OH/0.1 M NaCl in a volumetric ratio of 2/2/2/1), the lower phase was separated and washed 3 times with fresh upper phase. After drying of the lower phase over Na_2SO_4, filtration and removal of the solvent under reduced pressure, gave **14** as a slightly yellow solid (42 mg, 41%). ^{1}H NMR ($CDCl_3$; 360 MHz) δ 8.71 (s, 1H, ArCH), 8.47 (s, 2H, NH), 8.13 (s, 2H, NH), 8.03 (s, 2H, ArCH), 7.84 (s, 2H, NH), 7.49−7.62 (m, 8H, silyl), 7.40−7.45 (m, 12H, silyl), 7.14−7.29 (m, 5H, Bn), 4.15 (s, 2H, CH_2S), 3.86 (m, 2H, CH_2O), 3.17−3.73 (m, 18H, CHN, CH_2N), 2.03 (m; 4H, CH_2), 1.85 (m, 4H, CH_2), 1.03 (s; 18H, CH_3). ^{13}C NMR ($CDCl_3$; 90 MHz) δ 167.2 (CO), 151.2 (C^+), 138.6 (Bn), 135.8 (ArC); 135.5 (silyl), 133.9 (ArC), 132.7 (silyl), 131.7 (ArCH), 130.0 (silyl, Bn), 128.9 (Bn), 127.8 (silyl), 126.5 (Bn), 124.8 (ArCH), 65.4 (CH_2O), 49.3 (CHN), 47.9 (CHN), 45.2 (CH_2N), 44.8 (CH_2N), 43.4 (CH_2N), 38.7 (CH_2S), 26.9 (CH_3), 23.7 (CH_2), 22.5 (CH_2), 19.1 (C). MS (ESI) *m/e* 1239.2 (40%, [M · TFA]$^+$), 1125.7 (100%, M^+), 563.8 (40%, M^{2+}).

Benzyl ether 16. 5-Benzyloxyisophthalic acid[37] (184 mg, 0.68 mmol) was suspended in 3 mL of thionyl chloride, triphenylphosphine (2 mg) was added, and the mixture was heated under reflux for 60 min.[38] Excess thionyl chloride was removed in a stream of nitrogen, and the residue was dissolved in 5 mL of CH_2Cl_2 containing 707 mg aminomethylguanidine **5** (chloride salt). The solution was cooled to 0 °C, and TEA (840 μl, 6 mmol) was added dropwise with stirring. Stirring was continued for 30 min followed by washings with 0.1 M HCl (3×) and brine. After drying over Na_2SO_4 and filtration, the solution was concentrated under reduced pressure, and the product was precipitated by addition of diethyl ether. After separation and drying in vacuo **16** was obtained as a white solid (chloride salt, 723 mg, 91%). ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.85 (NH), 8.59 (s, 1H, ArCH), 8.53 (s, 1H, NH), 8.47 (s, 1H, NH), 7.72 (s, 2H, ArCH), 7.59−7.63 (m, 8H, silyl), 7.3−7.45 (m, 12H, silyl), 5.11 (s, 5H, Bn), 3.1−3.9 (m, 20H, CHN, CH_2N), 1.95−2.10 (m, 4H, CH_2), 1.75−1.95 (m, 4H, CH_2), 1.00 (s, 18H, CH_3). ^{13}C NMR (90 MHz; $CDCl_3$) δ 167.0 (CO), 151.0 (C^+), 136.6 (Bn), 135.5 (silyl), 135.1 (ArC), 132.7 (silyl), 129.9 (silyl), 128.4 (Bn), 127.7 (silyl), 127.5 (Bn), 119.0 (ArCH), 117.6 (ArCH), 70.1 (Bn), 65.2 (CH_2O), 49.1 (CHN), 47.6 (CHN), 45.0 (CH_2N), 44.5 (CH_2N), 43.5 (CH_2N), 26.8 (CH_3), 23.6 (CH_2), 22.5 (CH_2), 19.1 (C). MS (ESI) *m/e* 1224 (100%, [M · TFA]$^+$), 1145 (90%, [M · Cl]$^+$), 555.7 (85%, M^{2+}).

Phenol 15. The benzyl ether **16** (646 mg, 0.546 mmol) was dissolved in a mixture of 5 mL of ethanol and 2.5 mL of cyclohexene, 100 mg $Pd(OH)_2$/C (20%) was added, and the mixture was heated under reflux for 4 h, after which another 100 mg of the catalyst were added. Heating was continued for another 4 h, and then the suspension was filtered through Celite. The residue was rinsed with CH_3OH, and the filtrates were combined and the solvents stripped off. Reprecipitation of the residue from CH_2Cl_2 (1 mL) + diethyl ether was repeated twice. Finally, the solid was separated and dried in vacuo, yielding **15** as a white solid (chloride salt, 565 mg, 95%). ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.43 (s, NH), 8.66 (s, 1H, ArCH), 8.28 (s, NH), 8.07 (s, 2H, ArCH). 7.59−7.63 (m, 8H, silyl), 7.3−7.45 (m, 12H, silyl), 3.1−3.9 (m, 24H, CH_2O, CHN, CH_2N), 1.95−2.10 (m, 4H, CH_2), 1.75−1.95 (m, 4H, CH_2), 1.00 (s, 18H, CH_3). ^{13}C NMR (90 MHz; $CDCl_3$) δ 167.5 (CO), 157.1 (ArC), 151.0 (C^+), 135.3 (silyl), 134.6 (ArC), 132.5 (silyl), 129.6 (silyl), 127.6 (silyl), 117.8 (ArCH), 117.3 (ArCH), 65.3 (CH_2O), 49.2 (CHN), 47.9 (CHN), 45.0 (CH_2N), 44.5 (CH_2N), 43.0 (CH_2N), 26.6 (CH_3), 23.4 (CH_2), 22.4 (CH_2), 18.9 (C). MS (ESI) *m/e* 1133.2 (100%, [M · TFA]$^+$), 1055.4 (55%, [M · Cl]$^+$), 510.7 (60%, M^{2+}).

Binding Studies. ITC titrations were performed using a MCS-ITC instrument (MicroCal Inc., Northampton, MA). All measurements were performed at 303 K. Stock solutions were prepared by weighing the substances directly in volumetric flasks. In general, the host solution was filled into the cell of the ITC instrument and guest solutions were added with the syringe. In each case control experiments with dilution of guest solution in neat solvent were performed. The dilution of the host was found to be negligible. Analysis and curve fitting was done using the software Origin 2.9.

NMR titrations were performed on a Bruker AM 360 instrument at 298 K in DMSO-d_6. The concentrations of guest and host were varied, and the shift of the NH-protons was followed in the ^{1}H NMR spectra and analyzed with Wilcox's HOSTEST program.[29]

UV titrations were performed using a Eppendorf 1101M photometer equipped with a thermostated cuvette holder in 1 cm cuvettes at 298 K in DMSO. The change in adsorption at $\lambda = 436$ nm (for *p*-nitrophenyl phosphate) or 313 nm (for the cyclic oxoanions) was followed and analyzed by standard Benesi-Hildebrand plots[39] (for [host] > 10 × [guest]) or curve fitting using the HOSTEST routines. Solutions of *p*-nitrophenyl phosphate, croconate **19** and rhodizonate **20** in DMSO were prepared by stirring the bis-alkaline salts with 2 equiv of cryptand-[2.2.2] in volumetric flasks until a clear solution was obtained.

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