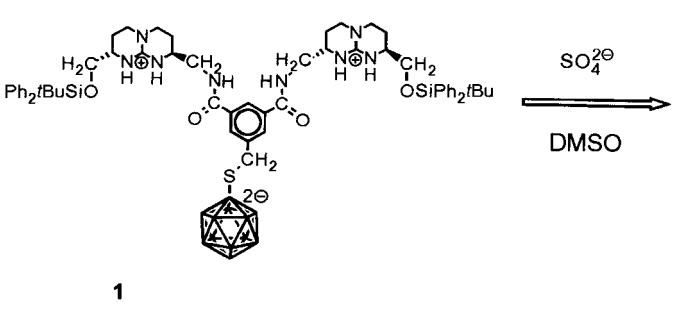
The Binding of Sulfate Anions by Guanidinium Receptors is Entropy-Driven**

Michael Berger and Franz P. Schmidtchen*

There is good reason to attribute the binding of guests by host molecules to functional and geometrical complementarity, and to the preorganization of binding substructures in the artificial receptor.[1] This assumption emphasizes the importance of mutual enthalpic interactions, but disregards entropic contributions that have been found in many cases to govern the host–guest binding event in solution.[2–4] The rational design of abiotic host compounds must therefore address the fundamental contributions to the association free energy separately, and requires in the first place the dissection of its constituent enthalpy and entropy parts by experimentation in order to learn about the options available to avoid total enthalpy–entropy compensation.[5] This phenomenon often disguises and eventually prevents any visible progress in host design.

A study of the binding of the sulfate anion to abiotic guanidinium receptors could provide a good starting point. The ditopic host **1** binds sulfate anions even in DMSO,[6] and congener **2** was able to extract this guest from very dilute (10^{-4} M) aqueous solutions into chloroform with unprecedented efficiency [99.8%; Eq. (1)].[7] An NMR titration study that



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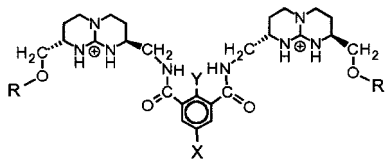
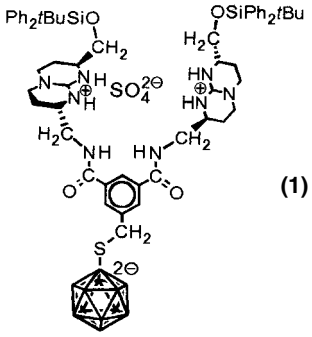
employed the analogous host **2** only gave a lower limit for the association constant (K_a for **2** in $CD_3OD > 10^6\,M^{-1}$), while host **4** in a similar investigation in aqueous DMSO (DMSO/H_2O, 1/1) revealed complexation of sulfate ions with $K_a = 290\,M^{-1}$. In both cases the complexation-induced shifts (CIS) of the aromatic ^1H signals were monitored by NMR spectroscopy, since the more sensitive NH signals experienced sulfate-catalyzed proton exchange that rendered them invisible on the NMR time scale. The splitting of the K_a-related free energies of association $\Delta G_a^\ominus$ into its components $\Delta H_a^\ominus$ and $\Delta S_a^\ominus$ by NMR methods requires rather laborious and imprecise van't Hoff analysis of the binding data. A much more



	X	Y	R	counter-ion
1	$CH_2SB_{12}H_{11}^{2\ominus}$	H	$SitBuPh_2$	—
2	$OC_{16}H_{33}$	H	$SitBuPh_2$	$Cl^\ominus$
3	$OCH_2C_6H_5$	H	$SitBuPh_2$	$Cl^\ominus$
4	CH_2OH	H	H	$Cl^\ominus$
5	OH	H	$SitBuPh_2$	$Cl^\ominus$
6	Br	F	H	$ClO_4^\ominus$

accurate and faster method is isothermal titration calorimetry (ITC),[8] which gives $\Delta H_a^\ominus$ directly as a primary parameter of measurement; $\Delta G_a^\ominus$ and the host–guest stoichiometry n are estimated from titration curve fitting. The reaction entropy $\Delta S_a^\ominus$ may then be readily calculated from the Gibbs–Helmholtz equation.

A typical example of the quality of the data obtained is shown in Figure 1 for the primary heat pulse for the binding of sulfate ions by host **3** in methanol.[9] By integration of each pulse at each titration step the titration curve can be derived and analyzed through curve-fitting methods.[10]



(1)

Guest complexation is strongly endothermic and gives $\Delta H_a^\ominus = +7.7$ kcal mol^{-1}. The fitting process, however, reveals $K_a = 6.8 \times 10^6\,M^{-1}$ and $n = 1.03$ as an independent fit parameter. Thus, at room temperature associa-

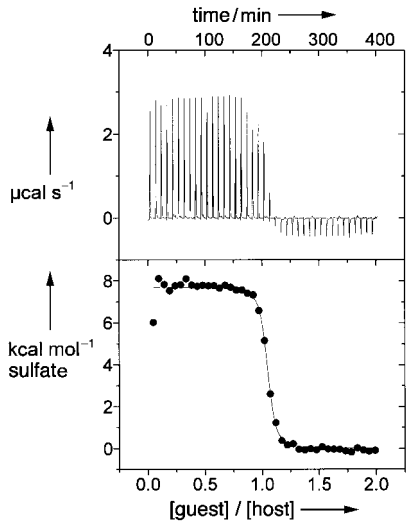


Figure 1. ITC titration of host **3** (0.137 mM) with tetramethylammonium sulfate (2.865 mM) in methanol at 303 K. $\Delta H^\ominus = +7.7$ kcal mol^{-1}; $K_a = 6.8 \cdot 10^6\,M^{-1}$; $n = 1.03$;

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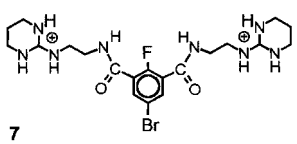
tion is strongly entropy-driven with $T\Delta S^{\circ}_{a}$ by far outweighing the unfavorable ΔH°_{a} value (Table 1). Host **5**, which lacks the benzyl ether functionality of **3**, shows a very similar enthalpy and entropy of association, which indicates that the third aromatic substituent is not involved in guest binding. The

Table 1. Binding of sulfate ions with guanidinium hosts at 303 K.[a]

Host	n	ΔH°_{a} [kcal mol^{-1}]	K_a [M^{-1}]	ΔG°_{a} [kcal mol^{-1}]	$T\Delta S^{\circ}_{a}$ [kcal mol^{-1}]
1[b]	0.47	+1.50	284	−3.40	+4.90
3	1.03	+7.71	6.8×10^{6}	−9.47	+17.18
5	0.95	+7.07	4.9×10^{6}	−9.27	+16.34
6	1.12	+7.28	4.4×10^{5}	−7.82	+15.10
7	0.94	+5.46	2.7×10^{6}	−8.91	+14.37
9	0.54	+3.76	313	−3.43	+7.22
10	0.46	+2.76	553	−3.80	+6.56

[a] Sulfate: bis(tetramethylammonium) sulfate, solvent: methanol, unless otherwise stated. [b] Bis(tetraethylammonium) sulfate, DMSO.

introduction of a fluorine substituent in the 2-position of the aromatic core together with the removal of the silyl ether functionalities to give the free hydroxyl groups in **6** yields an inferior host for sulfate binding. Though enthalpy appears unaffected, which suggests an almost identical guest-binding mode in the receptors discussed so far, the entropy is diminished. This reflects some solvophobic interactions between the silyl moieties in hosts **2**, **3**, and **5** on binding, which is not available in **6**. The hydroxyl groups apparently do not participate in the complexation of sulfate ions in methanol. The relief of some of the folding strain on going from **6** to the monocyclic guanidinium receptor **7** seemingly allows a better mutual fit, which is expressed as a more negative (less positive) ΔH°_{a} value, whereas ΔS°_{a} is hardly affected. The quite respectable association constant in methanol (K_a (**7** in CH_3OH) $= 2.7\cdot10^{6}$ M^{-1}) was initially believed to also allow the complexation of sulfate ions with this host in water. However, the heat effects turned out to be vanishingly small, and we could not derive a titration curve. ^{19}F NMR spectroscopy proved helpful, and the titration of **7** with sulfate ions in D_2O gave $K_a = 84$ M^{-1} at 298 K.



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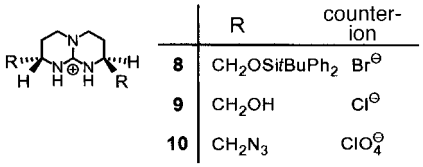
Since both the guanidinium group and the sulfate anions are solvated very effectively in protic solvents, the positive ΔH°_{a} value observed reflects the endothermic reorganization of the solvent shell upon complexation. The complex is less solvated than the sum of its free components, and the release of solvent molecules thus leads to the entropic overcompensation of the unfavorable positive ΔH°_{a} of desolvation. This effect is smaller in the more hydrophilic host **6** and results in a smaller entropy contribution and weaker binding.

The low solubility of the electroneutral zwitterionic host **1** in protic solvents thwarted the direct comparison to the cationic guanidinium receptors. Titration in DMSO, however, uncovered the unexpected host–guest stoichiometry of 0.5. As host **1** dimerizes under these conditions[6] this result is compatible with the sulfate ions binding to the host dimer without disrupting its aggregate structure.[11] Because this binding event most likely displaces one weekly bound anionic borane cluster rather than strongly bound solvent molecules from the first guanidinium binding site in the yin–yang dimer,[6] the enthalpy and entropy of guest association are more negative than found with cationic hosts. Nevertheless, complex formation remains entropy-driven even in this case.

In an effort to compare and quantify the virtue of combining two guanidinium groups in a ditopic host, the monotopic parent bicyclic guanidines **8** and **9** were tested in



DMSO. Neither produced a heat effect on titration with sulfate ions, which suggested a total lack of complexation and underlined the benefit of the covalent linkage in the ditopic hosts. In water the bishydroxyl anchor group **9** does not show any enthalpic interaction with sulfate ions either, but in methanol some endothermic association is observed ($\Delta H^{\circ}_{a} = +3.76$ kcal mol^{-1}) with $K_a = 313$ M^{-1}. The replacement of the hydroxyl groups by non-hydrogen-bonding azido substituents roughly doubles K_a (553 M^{-1}), primarily because of a favorable enthalpic effect. However, the binding affinity of the monotopic guanidinium anchor groups are still four orders of magnitude lower than that of their ditopic counterparts. The calorimetric results of the binding of sulfate ions to guanidinium hosts attest to the dominating role of solvation and calls for solvation design as a profitable way to improve guest-binding affinity and selectivity.

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[8] a) I. Wadsö, *Chem. Soc. Rev.* **1997**, 79–86; b) J. E. Ladbury, B. Z. Chowdhry, *Chem. Biol.* **1996**, *3*, 791–801.
[9] Details about the syntheses of the hosts will be published in a full paper.
[10] The measurements were performed with a MCS-ITC instrument (MicroCal). In all cases, the sulfate solution was injected into the cell containing the host. The heat of dilution was corrected for by injecting

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the sulfate solution into neat solvent and subtracting this data from that of the host–guest titration. The data was analyzed and fit by the Origin software (MicroCal).[12]

[11] Close inspection of the multidimensional error hypersurface of the NMR binding data in the reaction of **1** and sulfate ions revealed no minimum that would justify accounting for a 1:2 host–guest complex.[6] Recalculation of the primary data with host dimerization and 1:1 host–guest complexation incorporated gave $K_a = 680\ M^{-1}$, which is in reasonable agreement with the present determination conducted at a slightly higher temperature.

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A Soluble C_{60} Graphite Segment**

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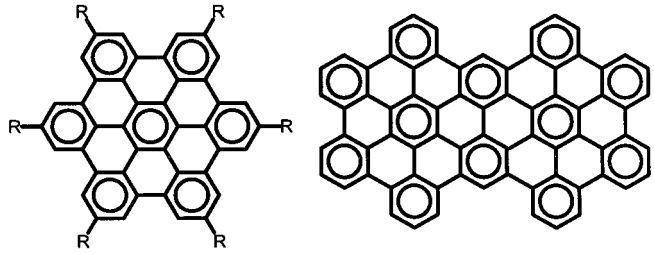
We recently described an efficient cycloaddition-cyclodehydrogenation route to obtain very large polycyclic aromatic hydrocarbons (PAHs) such as **1a** (C_{42}) and **2** (C_{72}).[1–3] Owing to the extremely low solubility of the parent compounds, the soluble hexa-*n*-alkyl derivatives **1b** were synthesized in order to perform complete spectroscopic characterization of these compounds. Discotic meso phases with stacked discs were thereby observed. Physisorption of **1b** onto substrate surfaces gave rise to the formation of monomolecular adsorbate layers, which were characterized by scanning tunneling microscopy (STM).[1–3]



1a: R = H
1b: R = *n*-alkyl

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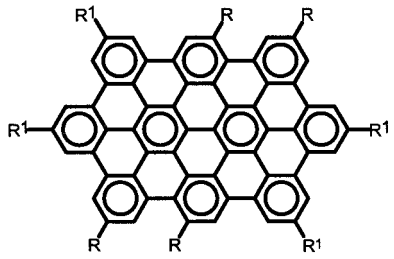
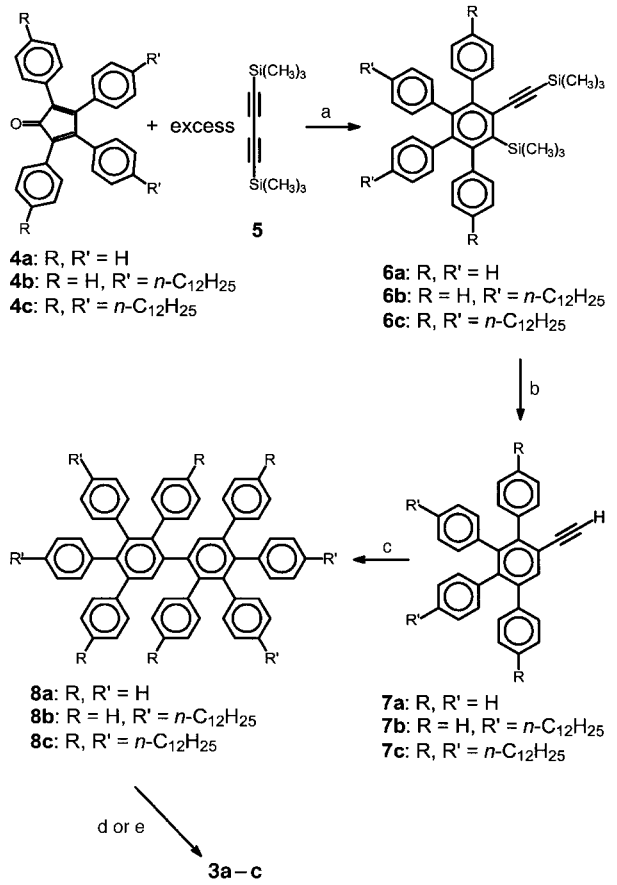


3a: R, R^1 = H
3b: R = H, R^1 = *n*-$C_{12}H_{25}$
3c: R, R^1 = *n*-$C_{12}H_{25}$

A comparable protocol is impossible with larger discs (e.g. C_{72}, C_{78}, C_{96}, C_{132}) since the synthetic strategies are not readily transferable to the respective *n*-alkyl derivatives. We describe here the remarkable C_{60} hydrocarbon **3a**,[4, 5] which, as a homologue of **1a**, is predicted to be the most thermodynamically stable of the $C_{60}H_{22}$ PAH isomers.[6] The synthesis of **3a** in gram or even decagram quantities is surprisingly straightforward. More importantly, however, soluble tetra- and octa-*n*-alkyl derivatives (**3b** and **3c**, respectively) of this large disk can be prepared, and the formation of monolayers from solution is possible even with discs of that size. This could prove to be a central step for the electronic characterization of molecular graphite models.

Following the construction principle reported by our group for larger PAHs, an oligophenyl precursor of **3** is available by a twofold Diels–Alder reaction between butadiyne and tetraphenylcyclopentadienone (**4a**, Scheme 1). The reaction



Scheme 1. a) **4a**, **4b**, or **4c** (1 equiv), 250 °C, Ph_2O, 3–6 h, ca. 100%; b) $nBu_4N^+F^-$ (10 equiv), THF, **6a**: 85%, **6b**: 86%, **6c**: 88%; c) **4a**, **4b**, or **4c** (1.1 equiv), 250 °C, Ph_2O, 3–6 h, ca. 100%; d) $Cu(OSO_2CF_3)_2$ (60 equiv), $AlCl_3$ (60 equiv), 25 °C, CS_2, **3a**: >90%; e) $FeCl_3$, CH_3NO_2, CH_2Cl_2, Ar, 15–30 min, **1a**: >80%, **3b**: 75%.

of **4a** with a large excess of 1,4 bis(trimethylsilyl)butadiyne (**5**)—both starting materials are commercially available—resulted in the formation of **6a** in nearly quantitative yield.

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