Electroneutral Artificial Hosts for Oxoanions Active in Strong Donor Solvents

Michael Berger and Franz P. Schmidtchen*

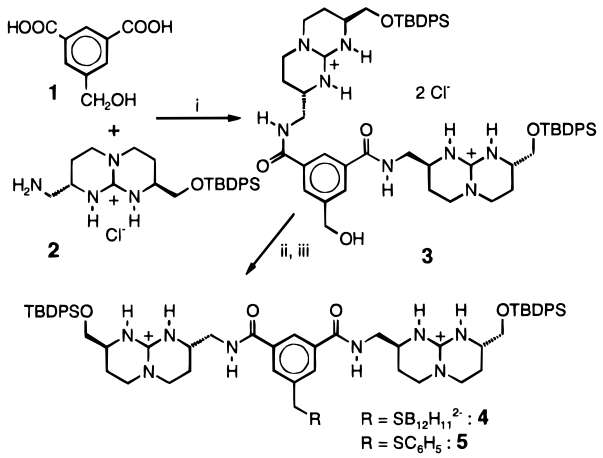
Institut für Organische Chemie und Biochemie
Technische Universität München
D-85747 Garching, Germany

Received March 13, 1996

Strongly solvating solvents like dimethyl sulfoxide (DMSO) or water are severe competitors in the complexation of oxoanions (carboxylates, phosphates, sulfates etc.) by artificial receptors. Any exploitation of such molecular recognition processes for, e.g., anion sensing or separation by membrane transport depends on the proper balance of selective complexation capabilities of the molecular host under these restrictive conditions and its pronounced lipophilicity in order to avoid loss of the receptor or the host−guest complex to the hydrophilic layer of an aqueous/organic two-phase mixture. Current concepts for the construction of anion hosts[1] (anti-crown receptors,[2] polycationic macrocycles,[3] zwitterionic cage compounds,[4] multiple metal coordination[5]) in general serve only one or the other of these putatively opposing requirements.

A guideline for a successful design concept of an abiotic host meeting these criteria may use the same principles as the natural enzymes. Though being quite flexible chain molecules they manage to extract well-solvated anions (e.g. phosphate, sulfate) from water and transfer them to a hydrophobic environment (the interior of the protein) by virtue of multiple strong and preponderantly electrostatic interactions[6] and a peculiar folding process which leaves suitable solvating groups exposed to the outer environment.

Starting from a foldable bis(guanidinium) module of proven utility in oxoanion complexation,[7] the covalent attachment of an anionic *closo*-borane cluster moiety should annihilate the net charge but conserve utmost hydrophobicity of the resulting zwitterion. Icosahedral borane clusters are chemically stable quasiaromatic compounds[8] having a lipophilic periphery with very poor hydrogen bond and Lewis acid acceptor properties (i.e., they figure as noncoordinating anions[9]). Yet they house a 2-fold negative charge which cannot be screened by protonation. If the covalent framework assures the segregation of the oppositely charged moieties prohibiting charge neutralization by internal collapse, a high-affinity anion binding site between the guanidinium substructures can be formed, capable of complexing the negatively charged guest by multiple H-bonding and Coulombic interactions.[10] The peculiar folding of the flexible host on guest binding leaves the complex with an exceedingly hydrophobic surface warranting high distribution ratios in two-phase systems in favor of the more hydrophobic liquid phase. Here we report on the synthesis and fundamental complexation behavior of the foldable electroneutral anion host **4** and also of the cationic receptor **5** lacking the anionic borane cluster and having a phenyl residue of comparable size instead. The latter compound was synthesized to get some insight into the role played by the borane cluster in the overall complexation abilities of the ditopic receptors.



i. HBTU, NMM, DMF/CH_3CN, N_2, 20°; ii. MesCl, TEA, CH_2Cl_2, N_2, -10°
iii. **4** : $Na_2B_{12}H_{11}SH$, TBD, DMF, N_2, 20°; **5** : C_6H_5SH, CH_2Cl_2, TBD, N_2, 20°

Condensation of the bicyclic chiral (aminomethyl)guanidinium salt **2**[11] with 5-(hydroxymethyl)isophthalic acid **1**[12] using HBTU[13] in DMF/acetonitrile afforded the bis(amide) **3** in 72% yield after purification by flash chromatography on C_8-reverse phase silica. Conversion of the benzylic hydroxy group into the mesylate was followed by nucleophilic substitution with sodium borocaptate $Na_2[HSB_{12}H_{11}]$ in DMF to yield **4** in 32% (two steps). The moderate yield is likely due to the formation of a bis-alkylated sulfonium compound also found in analogous alkylations[14] and mandated cleanup by preparative HPLC.[15] The hydrophobicity expected was evident from nonsolubility of **4** in water and very low solubility in methanol. Likewise, mesylation and substitution with thiophenol were followed by flash chromatography (silica, RP-8). Redissolving of the

* Fax: ++49-89-28913345.

(1) (a) Pierre, J.-L.; Baret, P. *Bull. Soc. Chim. Fr.* **1983**, *II*, 367. (b) Kimura, E. *Top. Curr. Chem.* **1985**, *128*, 113. (c) Dietrich, B. In *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNichol, D. D., Eds.; Oxford University Press: Oxford, 1984; Vol. 2, pp 373−405. (d) Dietrich, B. *Pure Appl. Chem.* **1993**, *65*, 1457. (e) Schmidtchen, F. P. *Nachr. Chem., Tech. Lab.* **1988**, *36*, 8. (f) Schmidtchen, F. P. *Pure Appl. Chem.* **1989,** *61*, 1535. (g) Reinhoudt, D. N.; Rudkevich, D. M.; Verboom, W. *Pure Appl. Chem.* **1994**, *66*, 679.

(2) (a) Zhang, Z.; Knobler, C. B.; Hawthorne, M. F. *J. Am. Chem. Soc.* **1995**, *117*, 5105−5113. (b) Tikhonova, I. A.; Dolgushin, F. M.; Yanorski, A. I.; Struchkov, Y. T.; Gavrilova, A. N.; Saitkulova, L. N.; Skubina, E. S.; Epstein, L. M.; Furin, G. G.; Shur, V. B. *J. Organomet. Chem.* **1996**, *508*, 271−273. (c) Newcomb, M.; Horner, J. H.; Blanda, M. T.; Squatritto, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 6294−6301. (d) Jurkschat, K.; Rühlemann, A.; Tzschach, A. *J. Organomet. Chem.* **1990**, *381*, c53−c56. (e) Takenchi, Y.; Tanaka, K.; Aoyagi, S. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1549−1553.

(3) (a) Bencini, A.; Bianchi, A.; Paoletti, P.; Paoli, P. *Pure Appl. Chem.* **1993**, *65*, 381−386. (b) Hosseini, M. W.; Lehn, J. M. *Helv. Chim. Acta* **1988**, *71*, 749−756. (c) Cudic, P.; Zinic, M.; Tomisic, V.; Simeon, V.; Vigneron, J. P.; Lehn, J. M. *J. Chem. Soc., Chem. Commun.* **1995**, 1073−1075. (d) Sessler, J. L.; Cyr, M.; Furuta, H.; Král, V.; Mody, T.; Morishima, T.; Shionoya, M.; Weghorn, S. *Pure Appl. Chem.* **1993**, *65*, 393−398. (e) Schmidtchen, F. P. *J. Am. Chem. Soc.* **1986**, *108*, 8249−8255.

(4) (a) Worm, K.; Schmidtchen, F. P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 65−66. (b) Worm, K.; Schmidtchen, F. P.; Schier, A.; Schäfer, A.; Hesse, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 327−329.

(5) Lacy, S. M.; Rudkevich, D. M.; Verboom, W.; Reinhoudt, D. N. *J. Chem. Soc., Perkin Trans 2* **1995**, 137−139.

(6) (a) Mangani, S.; Ferraroni, M.; Orioli, P. *Inorg. Chem.* **1994**, *33*, 3421−3423. (b) Luecke, H.; Quiocho, F. A. *Nature* **1990**, *347*, 402−406.

(7) (a) Peschke, W.; Schmidtchen, F. P. *Tetrahedron Lett.* **1995**, *36*, 5155−5158. (b) Schiessl,P.; Schmidtchen, F. P. *J. Org. Chem.* **1994**, *59*, 509. (c) Stephan, H.; Gloe, K.; Schiessl, P.; Schmidtchen, F. P. *Supramolec. Chem.* **1995**, *5*, 273−280. (d) De Mendoza, J.; Galán, A.; Seel, C. T*op. Curr. Chem.* **1995**, *175*, 101.

(8) Plesek, J. *Chem. Rev.* **1992**, *92*, 269−278.

(9) Strauss, S. H. *Chem. Rev.* **1993**, *93*, 927−942.

(10) Hannon, C. L.; Anslyn, E. V. *The Guanidinium Group: Its Biological Role and Synthetic Analogs;* Bioorganic Chemistry Frontiers 3; Dugas, H., Schmidtchen, F. P., Eds.; Springer: Heidelberg, 1993; pp 193−255.

(11) Peschke, W.; Schiessl, P.; Schmidtchen, F. P. *J. Org. Chem.* **1995**, *60*, 1039−1043.

(12) Benning, A.; Grosskinsky, O. *Chem. Ber.* **1954,** *87*, 54−57.

(13) Dourtoglou, V.; et al. *Synthesis* **1984**, 572.

(14) Gabel, D.; Moeller, D.; Harfst, S.; Rösler, J.; Ketz, H. *Inorg. Chem.* **1993**, *32*, 2276−2278.

(15) HPLC conditions: 250×4 Purospher (Merck) RP-18, 5 μm; 90% CH_3CN/30 mM H_3PO_4, 30 mM $NaClO_4$; all spectroscopic analyses (^1H,^{13}C,^{11}B-NMR, IR) are consistent with the structures proposed (see supporting information).

S0002-7863(96)00818-9 CCC: $12.00

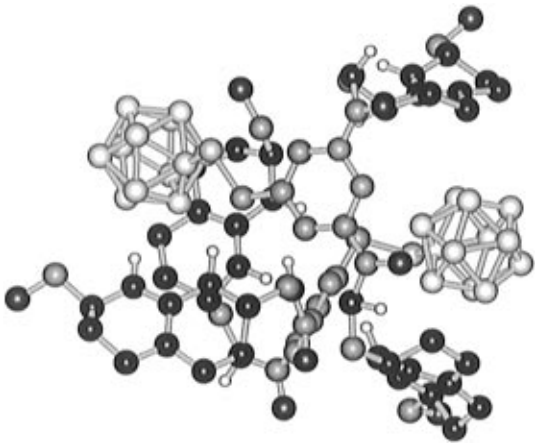


Figure 1. Structure of the **4** dimer as obtained from Hyperchem 3 force field calculations in vacuo.The hydrogens (except for N−H) and the silyl protecting groups have been omitted for clarity. The bicyclic guanidinium moieties are shown in black.

product thus obtained in methylene chloride and precipitation with diethyl ether was repeated two times to give pure **5** in 30% yield (two steps) as the chloride salt.

Despite the divergent extension from the central hub, the guanidinium anchor groups of **4** might fold back to associate electrostatically to the anionic cluster moiety. Molecular modeling in vacuo (Hyperchem 3, MM 2 force field employing atomic charges obtained by semiempirical AM1 calculations followed by a dynamics run with subsequent minimization) showed this process not to be an energetically favorable option. Instead, intermolecular dimerization with mutual interaction of the opposing charges (Yin−Yang principle) appeared to be the dominating process (Figure 1).

Dilution experiments in DMSO as monitored by ^{1}H-NMR measurements confirmed this dimerization (K_{dim}(**4**) = 250 M^{-1} (DMSO)), whereas the cationic host **5** (used as the perchlorate) showed no sign of dimerization at all. Certainly, the behavior of **4** largely originates from unspecific coulombic attraction, since addition of 50 mM neutral electrolyte (TBA ClO_4) diminished K_{dim} to 100 M^{-1}. Similar NMR studies revealed no effect on addition of singly charged anions like NO_3^- or Br^-. With sulfate, however, several proton signals showed marked shifts depending on guest concentration and displaying a distinct saturation behavior thus indicating a host−guest equilibrium with fast exchange kinetics. The guanidinium and amido NH resonances experienced the strongest downfields shifts, which were quite small however (0.3 ppm), along with some broadening. The changes were best analyzed by a nonlinear regression fit encompassing complexes of 1:1 and 1:2 host−guest stoichiometries[16] (HOSTEST 5.1, C. S. Wilcox) taking the dimerization into account (Table 1). Similar shifts were observed when **5** was titrated with sulfate, and regression analysis gave the same binding constant (1×10^{-3} M^{-1}). It is remarkable that in this case the introduction of the anionic borane cluster does not seem to influence the overall complexation ability.

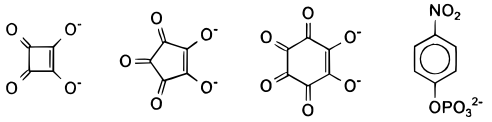
In contrast, HPO_4^{2-}, adenosine monophosphate, and oxalate gave clear evidence of strong binding to **4**, too, but the NH signals rapidly broadened with increasing guest concentrations and finally vanished completely. Most probably the basicity of these anions promoted the proton exchange kinetics enough to thwart all attempts to evaluate the binding constants. Nonexchangeable proton signals showed nonmonotonous shifts strongly suggesting the formation of complexes of higher order.

Seeking simplification of the confusing multiple-binding equilibria, we investigated more dilute solutions in a concentration domain not amenable to NMR measurements. The UV spectra of some conjugated oxoanions proved sensitive to complexation by **4**.

Table 1. Binding Constants K_A (M^{-1}) for Receptor **4** in DMSO at 298 K

anion	K_A(1:1)[d]	*p* range[h]
NO_2^-, Br^- [a]	no effect[e]	
SO_4^{2-} [b]	1.0×10^3 [e]	0.43−0.89
p-nitrophenyl phosphate **9**[c]	7.0×10^3 [f]	0.33−0.61
squarate **6**[b]	3.1×10^4 [g]	0.22−0.83
croconate **7**[c]	2.5×10^4 [g]	0.41−0.76
rhodizonate **8**[c]	1.8×10^4 [g]	0.35−0.73

[a] Monosodium[2.2.2]cryptates. [b] Tetraethylammonium salts. [c] Disodium[2.2.2]cryptates. [d] In all cases 1:2 complexes (host:guest) were taken into account; $K_{A(1:2)}$ values obtained are in the range of 10−100 M^{-1}. [e] NMR titration. [f] UV titration at 436 nm. [g] UV titration at 313 nm. [h] See ref 19.



6 **7** **8** **9**

The cyclic oxoanions squarate **6**, croconate **7**, and rhodizonate **8** showed progressive hyperchromic effects at λ = 313 nm, whereas complexation of *p*-nitrophenyl phosphate **9** resulted in a hypochromic effect at λ = 436 nm.[17] Thus, analysis of the underlying host−guest complexation event using Benesi−Hildebrandt conditions[18] but also direct fitting of the data by nonlinear regression was possible. The latter was especially useful since the results indicated that even in more dilute solutions formation of higher complexes had to be considered. NMR titration of squarate, on the other hand, indicated that this concentration domain (10^{-3} M) was much too high to obtain any reliable results.[19]

The data given in Table 1 indicate quite strong binding (K_{assoc} $\sim 10^4$ M^{-1} (DMSO)) of these anions to **4** and thus place this flexible host in similar ranks as recently introduced electroneutral hosts of alternative design.[20] Judicious choice and the remote implementation of a chemically inert anionic substructure into a foldable bis(guanidinium) host adapt the natural way of receptor design. This concept allows exploitation of the inherently strong affinity of cationic guanidinium anchor groups for anion binding under highly competitive solvation conditions while conserving overall host hydrophobicity.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and the Fond der Chemischen Industrie. We are particularly grateful to Prof. C. S. Wilcox, University of Pittsburgh, for supplying and providing assistance with his data analysis and fitting program HOSTEST.

Supporting Information Available: Spectral data of **4** and **5**; HOSTEST output and HPLC chromatogram of **4** (13 pages). See any current masthead page for ordering and Internet access instructions.

JA960818D

(16) Software: HOSTEST 5.1, C. S. Wilcox and the University of Pittsburgh, 1993.

(17) Ishida, H.; Suga, M.; Donowaki, K.; Ohkubo, K. *J. Org. Chem.* **1995**, *60*, 5374−5375.
(18) Connors, K. A. *Binding Constants*; John Wiley: New York, 1987; p 141 ff.
(19) Wilcox, C. S. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H. J., Dürr, H., Eds.; VCH: Weinheim, 1991; p 132 ff.
(20) (a) Raposo, C.; Pérez, N.; Almaraz, M.; Mussons, M. L.; Caballero, M. C.; Morán, J. R. *Tetrahedron Lett.* **1995**, *36*, 3255−3258.