Tetrahedron Letters, Vol. 34, No. 15, pp. 2449-2452, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

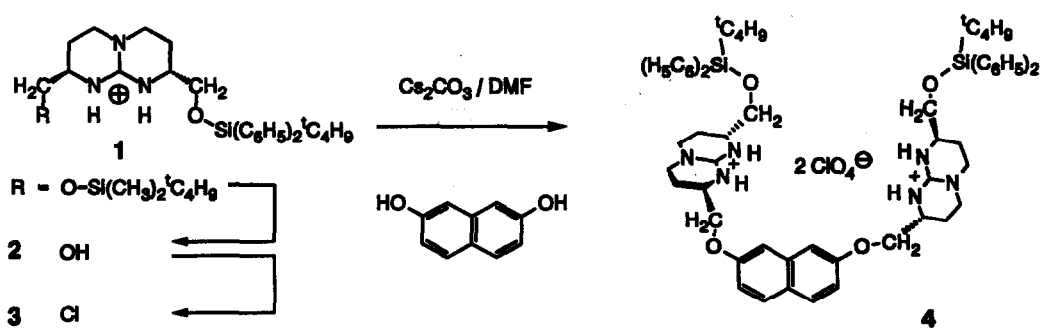
# Abiotic Molecular Recognition of Dicarboxylic Anions in Methanol

**Petra Schießl and Franz P. Schmidtchen***

Lehrstuhl für Org.Chemie und Biochemie, Technische Universität München
Lichtenbergstrasse 4, D-8046 Garching, Fed.Rep. Germany

***Abstract***: The easily accessible open-chain host compound **4** binds the dicarboxylic anions given in Tab.1 and Tab.2 under competitive solvation conditions in methanol with appreciable strength, despite the apparent lack of preorganization of binding sites.[1]

The specific abiotic host-guest complexation of multifunctional biologically relevant compounds under protic solvation conditions has so far been an elusive goal. As we have repeatedly argued[2] a successful approach might require an open-chain host design for various reasons rather than a completely preorganized and rigid macrocyclic structure. Following an analogous path Still et al.[3] prepared podand ionophores, which in spite of their open-chain nature essentially possess only one ground state conformation and are thus preorganized. Their complex stabilities with cations in aprotic solvents are higher by up to 3 kcal compared to regular non-preorganized ethylene glycol ethers. Though this proves the general correctness of the underlying idea it seems unlikely in view of the small margin of energy involved that the subtle design of host folding could *predictibly* govern the selectivity features of host-guest complexation in a protic environment. The latter is rather under the regime of electrostatic and solvophobic host-guest interactions. The design of anchor groups which are to compete with solvation in binding (recognition!) of complementary structural epitopes of a guest should exploit these respective molecular interactions.

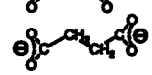
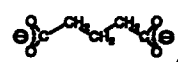
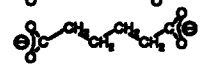
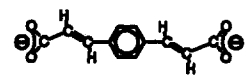


In line with this reasoning we had shown that bicyclic guanidinium salts (parent structure **1**) would complex oxoanionic substrates under less stringent solvation conditions[4]. In protic solvents, however,oxoanions are heavily stabilized by hydrogen bonding and their association with guanidinium salts is very low[5]. The rational extension of our concept of open-chain host molecules calls for successive attachment of more anchor groups to make up a polytopic host in order to outmatch any competition from solvation. Here we report on a flexible ditopic guanidinium host **4** capable to bind dicarboxylates in methanol solution.

Starting from the known chiral heterobicycle **1** [6] the dimethyl-$^t$butylsilyl protection was removed selectively by mild acid hydrolysis to produce the alcohol **2** which was converted to the chloro derivative **3** by $SOCl_2$ / pyridine. The Williamson synthesis starting with **3** and 2,7-dihydroxynaphthalene and using either cesium carbonate or BEMP[7] as bases in DMF gave comparable yields (ca.70%) of **4** along with some monoether product. The bisguanidinium perchlorate **4** was obtained by MLCC purification[8] as an off white powder, which is readily soluble in methanol or chloroform, but not in water[9].

Molecular modeling (Biosym software : Insight/Discover, CVFF forcefield, vacuum) confirmed the trivial chemical intuition: Compound **4** is a flexible molecule that most likely adopts an extended conformation due to the electrostatic repulsion of the positive charges. On interaction with a dicarboxylate (glutarate was the most studied example) a different "secondary structure" is observed in which the dianionic guest is pinched between the guanidinium moieties. A molecular dynamics run ( 100 picosec at 500 K, one structure every picosec was sampled and minimized) finds a great number of distinctly different conformations in the host-guest complex all within 3 kcal above the lowest total energy.

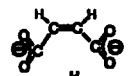
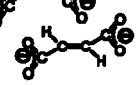
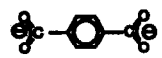
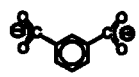
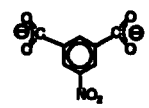
Table 1: Binding Constants of Host-Guest Complexation of **4** with Dimensional Probes in Methanol Measured by $^1$H-NMR

| entry | substrate | $K_{ass}$ [$M^{-1}$] | complex. range [%] |
|---|---|---|---|
| 1 |  | 225 | 5 - 66 |
| 2 |  | 2 540 | 15 - 91 |
| 3 |  | 16 500 | 22 - 98 |
| 4 |  | 854 | 22 - 91 |
| 5 |  | 1 240 | 31 - 93 |
| 6 |  | 833 | 19 - 91 |
| 7 |  | 633 | 19 - 89 |

Host-guest complexation in methanol can be conveniently followed by $^1$H-NMR from the progressive shift of all of the naphthalene signals to higher field and the change of the chemical shift and coupling pattern of the $CH_2$-O-groups at the spacer junction. Almost all of the other signals are little affected by guest binding suggesting a conformational change on complexation which involves mainly the attachment sites of the guanidinium moieties with the spacer unit. The evaluation of the respective titration curves by nonlinear regression[10] furnished the association constants given in tab. 1 and tab.2 [11].

With the monoanions (iodide and acetate) no change in chemical shift was observed at all. The dianions, however, showed complexation induced shifts (CIS) which could cleanly be fitted to a 1:1 host-guest stoichiometry. Though all dicarboxylates were bound by **4** in methanol there are peculiar quantitative differences: Despite its flexibility host **4** exhibits a preference for malonate over the shorter or longer analogs. But even the most rigid and extended guest (entry # 7) is bound with considerable stability indicating the adaptability of the host to the guest structure. This is also reflected in the insensitivity to guest geometry (tab.2). The complex stabilities of the various rigid guests fall all to within 0.6 kcal of each other. If, however, additional opportunities for host-guest interactions are provided e.g. by virtue of improved stacking/charge-transfer in the case of nitro-isophthalate (entry # 13) this shows up as a profoundly enhanced complex stability.

Table 2: Binding Constants of Host-Guest Complexation of **4** with Geometrical Probes in Methanol Measured by $^1$H-NMR

| entry | substrate | $K_{ass}$ [$M^{-1}$] | complex. range [%] |
|---|---|---|---|
| 8 |  | 1 724 | 11 - 89 |
| 9 |  | 4 520 | 33 - 94 |
| 10 |  | 1 805 | 27 - 92 |
| 11 |  | 3 100 | 11 - 94 |
| 12 |  | 6 060 | 19 - 96 |
| 13 |  | 14 500 | 32 - 97 |
| 14 |  | 3 450 | 7 - 91 |

The flexible host **4** clearly demonstrates the feasibility of satisfactory guest binding under stringent competitive solvation conditions while retaining easy accessibility of the host structure by a linear building block synthesis.

***Acknowledgement:***This work was supported by BMFT, project NT 20574; we also acknowledge a generous gift of chiral materials by Degussa AG, Hanau.

***References and Notes***


1. This work was presented on XVII ISMC in Provo,UT, August 1992.

2. a) Schmidtchen,F.P.;*J.Am.Chem.Soc.* **1986**, *108*, 8249-8255; b) Schmidtchen, F.P.; *J.Org.Chem.* **1986**, *51*, 5161-6168; c) Schmidtchen, F.P.; Gleich, A.; Schummer, A.; *Pure Appl.Chem.* **1989**, *61*, 1535-1546;

3. a) Still, W.C.; Wang, X.; Erickson, S.D.; Iimori, T.; *J.Am.Chem.Soc.* **1992**, *114*, 4128-4137; b) Iimori, T.; Erickson, S.D.; Rheingold, A.L.; Still, W.C.; *Tetrahedron Lett.* **1989**, *30*, 6947-6950; c) Li, G.; Still, W.C.; *J.Org.Chem.* **1991**, *56*, 6964-6966; d) Li, G.; Still, W.C.; *Tetrahedron Lett.* **1992**, *33*, 5929-5932; f) Erickson, S.D.; Ohlmeyer, M.H.J.; Still, W.C.; *ibid.* **1992**, *33*, 5925-5928; e) cf. Hoffmann, R.W.; *Angew.Chem.Int.Ed.Engl.* **1992**, *31*, 1124;

4. a) Schmidtchen, F.P.; Müller, G.; Riede, J.; *Angew.Chem.Int.Ed.Engl.* **1988**, *27*, 1516-1518; b) Gleich, A.; Mikulcik, P.; Müller, G.; Schmidtchen, F.P.; *J.Chem.Soc.Chem.Commun.* **1990**, 55-57; c) Echavarren, A.; Galan, A.; de Menddoza, J.; Lehn, J.-M.; *J.Am.Chem.Soc.* **1989**, *111*, 4994-4995;

5. Haake, P.; Springs, B.; *Tetrahedron Lett.* **1977**, 3223-3226;

6. a) Kurzmeier, H.; Schmidtchen, F.P.; *J.Org.Chem.* **1990**, *55*, 3749-3755; b) Schmidtchen, F.P.; *Tetrahedron Lett.* **1990**, *31*, 2269-2272; c) cf. Echavarren, A.; Galan, A.; de Mendoza, J.; Salmeron, A.; Lehn, J.-M.; *Helv.Chim.Acta* **1988**, *71*, 685; d) cf. Gleich,A.; Schmidtchen, F.P.; *Chem.Ber.* **1990**, *123*, 907-915;

7. BEMP = 2-$^{t}$Butylimino-2-diethylamino-1,3-dimethylperhydrodiazaphosphorin (Fluka).

8. MLCC = Ito Multi Layer Coil Chromatograph (Zinsser Analytik).

9. All new compounds gave satisfactory $^{1}H/^{13}C$-NMR and FAB-MS spectra and were obtained in >95% purity as checked by RP-HPLC ($\lambda$ = 254 nm detection). **4** * 2 $ClO_4^-$ : Elem. anal.: calc.: C = 60.16; H = 6.48; N = 7.00; found: C = 59.73; H = 6.31; N = 6.88. - $^{1}$H-NMR (360 MHz; $CD_3CN$) $\delta$ = 7.61-7.64 (m, 8H) C*H*-aromat.; 7.49-7.46 (d,$^{3}$J = 8.9 Hz, 2H) *H*C4, *H*C5; 7.36-7.42 (m, 12H) C*H*-aromat.; 7.29 (d, $^{4}$J = 2.0 Hz, 2H) *H*C1, *H*C8; 6.98-7.01 (dd,$^{3}$J = 8.8Hz, $^{4}$J = 2.3 Hz, 2H) *H*C6, HC3; 6.82 (s, 1H) NH; 6.62 (s, 1H) N*H*; 4.06-4.09 (dd, 2H) C$H_2$O-Naph; 3.77 -3.82 (dd, 2H) C$H_2$O-Naph; 3.63- 3.67 (dd, 2H,$^{3}$J = 5.2 Hz,$^{2}$J = 10.6 Hz) C*H*N-Naph; 3.57-3.52 (m, 4H) C$H_2$O-Si, CHN-Si; 3.39 (m, 2H) C$H_2$O-Si; 2.99 (m, 8H) C$H_2$N; 1.95- 1.86 (m, 4H) C$H_2$; 1.71 -1.17 (m, 2H) C$H_2$-Si; 1.55-1.45 (m, 2H) C$H_2$-Naph; 1.06 (s, 18H) $CH_3$. - $^{13}$C-NMR (90 MHz, $CD_3CN$) $\delta$ = 156.6 (C2,C7); 150.3 (guanidine); 135.5, 132.6, 129.9 , 127.8,(aromatic); 132.0 (C4, C5); 128.5, 124.0 (C9, C10); 116.0 (C3, C6); 106.6 (C1, C8); 69.1 (*C*$H_2$O-Naph); 65.1 (*C*$H_2$O-Si); 47.9 (*C*HN-Si); 45.8 (*C*$H_2$O-Naph); 44.9, 45.4 (*C*$H_2$N); 22.7, 22.2 ($CH_2$); 26.81 (*C*$H_3$-C); 19.03 ($CH_3$-*C*).

10. Software Enzfitter (R.Leatherbarrow) Biosoft, Cambridge,UK;

11. In a typical experiment 2 mmol **4** * 2 $ClO_4$ in 600 ml $CD_3OD$ was titrated with a 0.08 M solution of the guest dianion in the same solvent. $^{1}$H-NMR spectra were recorded (80-200 scans) at 250 MHz. The changes in chemical shift in the spectra of 8 - 16 addition increments were fed to the regression software which could account for the increasing dilution.


(Received in Germany 29 December 1992)