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Strong Hydrogen Bond-Mediated Complexation of $H_2PO_4^-$ by Neutral Bis-Thiourea Hosts

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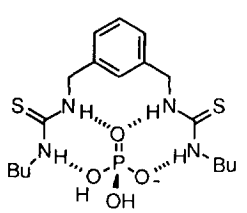
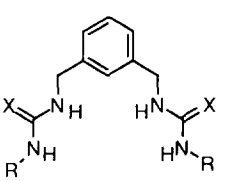
Abstract: Highly preorganized bis-thiourea receptors based on a xanthene spacer selectively ($H_2PO_4^-$ > CH_3COO^- > Cl^-) bind dihydrogenphosphate via multitopic hydrogen bonding, giving stronger complexes with $H_2PO_4^-$ than any synthetic neutral receptor known so far. The high complexation strengths are rationalized by the hydrogen bond donor strength of the thiourea groups and by host preorganization. The hydrogen bond acceptor strengths of the guest anions and, for small ions, guest solvation explain the observed selectivity of complexation in dimethyl sulfoxide (DMSO).

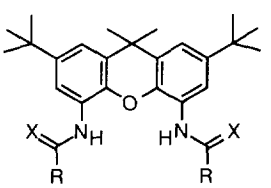
INTRODUCTION

Whereas several electrically charged receptors for phosphate have been reported,[1] the number of neutral compounds complexing this guest is still very limited even though they are of special interest for applications in aprotic media. The design of such neutral receptors is usually based on a Lewis acid and/or hydrogen bond donor groups.[2-4] Using the latter principle, we have previously shown that very simple hosts with two thiourea units are well suited for recognition of $H_2PO_4^-$ in non-aqueous solvents because they dissolve better, self-associate much less[5] and bind $H_2PO_4^-$ stronger than corresponding bis-ureas (e.g. **1**).[4] Evidence from ^1H NMR spectroscopy suggested the formation of complexes with $H_2PO_4^-$ as shown in Figure 1 for bis-thiourea **2** and showed a preferential complexation of $H_2PO_4^-$ by these hosts ($H_2PO_4^-$ > CH_3COO^- > Cl^- > HSO_4^- > NO_3^- > ClO_4^-), which was interpreted in terms of the guest basicity and geometry. While complex strengths were only moderate for these hosts, we now show that $H_2PO_4^-$ complex stabilities can be very significantly increased by using thiourea groups with acidity enhancing substituents and by preorganizing the receptors with a rigid spacer linking the two thiourea groups.





1 X=O, R=Bu; **2** X=S, R=Bu
3 X=S, R=Ph
4 X=S, R=1-naphthyl



5 X=S, R=NHBu
6 X=S, R=NHPh
7 X=O, R=OCH_2Ph

Figure 1.

RESULTS AND DISCUSSION

The relatively flexible bis-thiourea hosts **2** to **4** were prepared from the appropriate isothiocyanate and 1,3-bis(aminomethyl)benzene.[4] The more rigid hosts **5** and **6** with the xanthene spacer, which has previously been used by Rebek et al. in carboxylate receptors, were obtained from 2,7-di-*tert*-butyl-9,9-dimethyl-4,5-xanthenediamine.[6] Association constants of these hosts with guest anions were then, unless mentioned otherwise, measured by ^{1}H NMR titration or dilution experiments with DMSO-d_6 as solvent.[7] To minimize possible effects of ion-pair formation on the determination of these association constants, the bulky tetrabutylammonium ion was chosen as counterion for $H_2PO_4^-$. For hosts **5** and **6** the stabilities of the $H_2PO_4^-$ complexes were too large to be determined by simple titrations. The stabilities of the weaker chloride ion complexes were therefore determined first and then $H_2PO_4^-$ titrations in the presence of a constant chloride background were used to measure the strengths of the dihydrogenphosphate complexes (competitive spectrometry).[7] This was easily possible because several hydrogens bound to the aromatic rings showed different chemical shifts in the $H_2PO_4^-$ and Cl^- complexes (Fig. 2). A conventional titration of a solution of host **5** (Fig. 2, curve a) with $H_2PO_4^-$ was however also performed, giving a distinct titration endpoint at a 1:1 ratio of host and guest and excluding the formation of 1:2 or 2:1 complexes in the investigated range of host and guest concentrations.

As can be seen by comparison of the association constants (Table **1**) of $H_2PO_4^-$ with **2** and **3**, the replacement of the butyl by phenyl substituents leads to much stronger complex stabilities. The same effect is also observed for the analogous pair of **5** and **6**. This can be understood by considering the electron withdrawing effect of the phenyl groups. We have previously reported that the stronger affinity of the bis-thioureas for $H_2PO_4^-$ as compared to bis-ureas can be rationalized in terms of their lower pK_a in DMSO. The phenyl groups enhance this trend by further increasing the acidity of the thiourea (pK_a((H$_2$N)$_2$CO) 26.9;

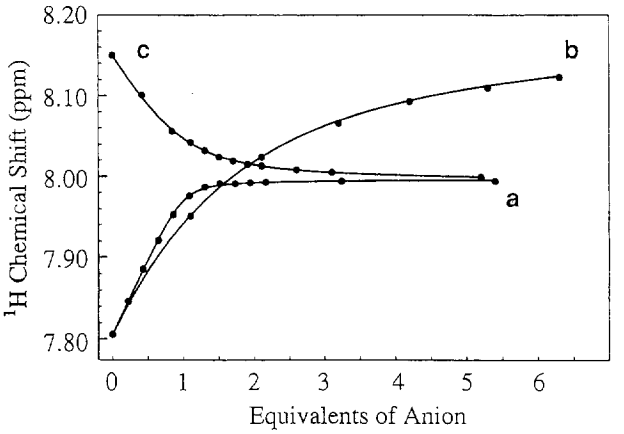


Figure 2. Chemical shift of the aromatic hydrogen adjacent to the thiourea group of bis-thiourea **5** (1.0 mM, in DMSO-d_6 , 300 K) upon increasing the concentration of a) $H_2PO_4^-$ (clearly showing 1:1 stoichiometry) and b) Cl^- in the absence of another anion as well as c) under competitive conditions upon increasing the concentration of $H_2PO_4^-$ in a host solution already containing 10.3 mM Cl^- (counter-ion in all cases $N(C_4H_9)_4^+$; (•) experimental data, (——) non-linear fit).

Table 1. Association constants (K_{11}, M^{-1}, in DMSO-d_6) of hosts **2** to **6** with $H_2PO_4^-$, CH_3COO^- and Cl^-.

anion[a]	host **2**	host **3**	host **4**	host **5**	host **6**
$H_2PO_4^-$	820	4 600	1 000	55 000	195 000
CH_3COO^-	470	2 300	350	38 000	[b]
Cl^-	9	10	5	840	1 000

[a] Counter-ion: $N(C_4H_9)_4^+$; [b] not determined.

pK_a($(H_2N)_2CS$) 21.0; pK_a($(PhNH)_2CS$) 13.5; in DMSO at 25 °C).[8] Similar effects have recently also been observed for complexes between aryl thioureas and a zwitterionic sulfonic acid[9] and for complexes between calix[6]arene receptors and halide ions.[10]

Table 1 also shows that the influence of the naphthyl group is less beneficial for complexation. CPK models indicate that without hindering the complexation of $H_2PO_4^-$ coplanarity of the naphthyl ring with the thiourea group is not possible. Rotation of the naphthyl group out of the common plane and therefore a decrease in conjugation between the thiourea group and its aromatic substituent is the likely reason for the relatively small observed association constants found for host **4**.

Several explanations for the success of xanthene as spacer between the two thiourea groups may be considered. The conjugation of the thiourea group with the aromatic ring of xanthene seems not to account sufficiently for the large increase in the association constant when going from **2** to **5** or from **3** to **6**. These increases are very large as compared to the above observed influence of the phenyl groups and are not expected in the presence of the electrondonating oxygen atom in the xanthene spacer. The latter is expected to weaken the complex, as analogously shown for example by the weaker binding of a sulfonate to a 4-ethoxyphenyl-substituted mono-thiourea than to the corresponding phenylthiourea.[9] Also a hypothetical hydrogen bond between the xanthene oxygen and the guest $H_2PO_4^-$ does not explain the high stabilities of the complexes of hosts **5** and **6** with $H_2PO_4^-$ because the small basicity of the xanthene oxygen suggests only a small strength for such a bond. Furthermore, the increases in complex stabilities in the series of hosts **2** to **6** are very similar for $H_2PO_4^-$, CH_3COO^- and Cl^- even though the latter two guests have no hydrogen that could interact with the host oxygen. It follows that the rigidity of the xanthene spacer is the primary reason for the high stabilities of the $H_2PO_4^-$ complexes of **5** and **6**, giving these hosts a high degree of preorganization.[11,12] The strength of the guest binding can also be seen from the extent of complex formation with **5** in a protic solvent, namely a 1:9 mixture of ethanol and dichloroethane, which was chosen because **5** was not soluble in more polar solvents. A Job's plot experiment[7] based on UV spectrometry (246 nm) showed 1:1 complex stoichiometry and titration (246 nm; host 0.11 mM) gave the association constant K_{11} as 210 M^{-1} for this quite competitive hydrogen bonding medium.

The association constant K_{11} for the complex of $H_2PO_4^-$ and bis-urethane **7**, which was obtained as an intermediate of the synthesis of **5** and **6**, was found to be smaller than 10 M^{-1} in DMSO-d_6. A hypothetical complex in which hydrogen bonds are formed between one guest oxygen and the two NH of **7** as well as between two guest OH and the carbonyl groups of **7** must therefore be very weak. This agrees well with our previous conclusion[4] that the carbonyl groups of bis-urea **1** are not involved in hydrogen bonds to $H_2PO_4^-$ and indeed would be expected also from the presence of unfavorable secondary interactions in this hydrogen bonding pattern.[13]

In view of possible applications, selectivity is one of the most interesting properties of anion receptors. To interpret the observed selectivity in the formation of the complexes between bis-thioureas and various anions, we have previously used the pK_a values of acids, HX, in aqueous solution as a rough measure of the hydrogen bond acceptor strength of the corresponding guests anions, X^-. While differences of the hydration energies of X^- and HX are well known to influence pK_a values[14] and limit the adequacy of pK_a(in water) values as a measure of hydrogen bond acceptor strengths, gas phase acidities for H_3PO_4, which evidently are not affected by solvation effects, seem not to be known yet. Fortunately, electrospray mass spectroscopy has very recently made free energies of hydration, $\Delta G°_{n-1,n}$, for the hydration equilibria $X^-(H_2O)_{n-1} + H_2O \rightleftarrows X^-(H_2O)_n$ in the gas phase available also for $H_2PO_4^-$.[15-17] $\Delta G°_{n-1,n}$ being a much better measure of the hydrogen acceptor strength than pK_a(in water), an improved analysis of the complexation selectivity of bis-thiourea hosts has become possible.[18]

Comparison of the free energies of hydration $\Delta G°_{0,1}$ (in kcal/mol) in the gas phase for the anions reported previously[4] as possible guests (CH_3COO^-: 9.4; Cl^-: 8.2; $H_2PO_4^-$: 7.6; NO_3^-: 7.1; HSO_4^-: 5.9; ClO_4^-: 4.8)[15,16,19] and the constants K_{11} (M^{-1}, in DMSO-d_6) for the 1:1 complexation of host **2** with these anions (CH_3COO^-: 470; Cl^-: 9; $H_2PO_4^-$: 820; NO_3^-: <1; HSO_4^-: 2; ClO_4^-: no binding) confirms our former explanation[4] of weak binding of NO_3^-, HSO_4^- and ClO_4^- due to their relatively low hydrogen bond acceptor strength. On the other hand, the high value of $\Delta G°_{0,1}$ explains why Cl^- binds to hosts **2** to **6** (Table 1) much stronger than would have been expected from the pK_a(in water) of this anion, which is -6.1. Indeed, complexation of host **2** and Cl^- in 1,2-dichloroethane gives complexes that are nearly as stable as those of $H_2PO_4^-$ (K_{11} (M^{-1}): $H_2PO_4^-$: 1.9×10^4; CH_3COO^-: 1.3×10^4; Cl^-: 1.2×10^4; NO_3^-: 2.2×10^3; HSO_4^-: 5.5×10^3; ClO_4^-: no binding; see Experimental Section for details of measurement), suggesting that the discrimination of Cl^- in DMSO is partly a solvation effect. It is known that Cl^- interacts fairly strongly with DMSO via ion-dipole interactions ($\Delta G°$ for the equilibrium $Cl^- + DMSO \rightleftarrows Cl^-(DMSO)$ in the gas phase: 12.5 kcal/mol).[20,21] To do so, it must approach the sulfur center, on which the partial positive charge of the DMSO dipole is located. Because of steric hindrance from the two methyl groups of DMSO, it is easier for the small Cl^- than for larger anions to approach the sulfur center. Considering anion size and the possibility for charge delocalization over more than one atom,[21] weakening of the bis-thioureas complexes by DMSO solvation of the free anion seems therefore largest for Cl^- and CH_3COO^-, may still play a role for NO_3^- but probably hardly affects $H_2PO_4^-$, HSO_4^- and ClO_4^- binding.

To the best of our knowledge, no published neutral receptor forms $H_2PO_4^-$ complexes that are stronger than those of bis-thioureas **5** and **6**. While the extent of complexation selectivity of bis-thioureas was found to depend significantly on the solvent, complexes of all other investigated anions were weaker than those of $H_2PO_4^-$. Bis-thioureas might also be interesting receptors for HPO_4^{2-} and PO_4^{3-}, which due to a higher charge are expected to form even stronger complexes. While the absence of strong hydrogen bond acceptor groups prevents self-association of these receptors to a large extent, which is particularly important for efficient guest binding in aprotic media, the efficient preorganization due to the xanthene spacer results in appreciable complexation even in a protic solvent mixture. We are now trying to further increase association strengths by using more acidic thioureas and to improve the complexation selectivity by using a larger number of hydrogen bonds.

EXPERIMENTAL

Syntheses

α,α'-Bis(*N'*-butylthioureylene)-*m*-xylene (2): 1,3-Bis(aminomethyl)benzene (2.0 g, 15 mmol) was dissolved in EtOH (dried over molecular sieves 3Å, 600 mL) and cooled to 0 °C. A solution of *n*-butyl isothiocyanate (3.4 g, 30 mmol) in EtOH (30 mL) was added slowly while keeping the solution temperature at 0 °C. The reaction solution was stirred for 3 h at 0 °C and then for another 12 h at room temperature. The precipitate that formed was filtered off and washed with EtOH and recrystallized twice from hexane/EtOAc/EtOH (5/2/5) to give white crystals (0.89 g, 16%). IR (KBr): 3225*s*, 3088*w*, 3018*w*, 2960*m*, 2932*m*, 2864*w*, 1563*s*, 1519*m*, 1467*w*, 1466*w*, 1431*w*, 1278*m*, 1210*s*, 1085*w*, 948*w*, 798*w*, 706*w*, 642*w*, 562*w*. ^{1}H NMR (DMSO-d_6): 7.80 (*s*, br., 2H, N<u>H</u>$(CH_2)_3CH_3$), 7.51 (*s*, br., 2H, N<u>H</u>CH_2ar), 7.32 (*t*, J = 8, 1H, NHCH$_2$CCHC<u>H</u>), 7.23 (*s*, 1H, NHCH$_2$CC<u>H</u>C), 7.20 (*d*, J = 6, 2H, NHCH$_2$CC<u>H</u>CH), 4.68 (*s*, br., 4H, NHC<u>H$_2$</u>ar), 1.51 (*quint.*, J = 6, 4H, NHCH$_2$C<u>H$_2$</u>), 1.35 (*sext.*, J = 6, 4H, NH$(CH_2)_2$C<u>H$_2$</u>), 0.93 (*t*, J = 6, 6H, CH_3). Elemental analysis: calc. for $C_{18}H_{30}N_4S_2$ (366.59): 58.98% C, 8.25% H, 15.28% N, 17.49% S. Found: 58.93% C, 8.31% H, 15.25% N, 17.92% S.

α,α'-Bis(*N'*-phenylthioureylene)-*m*-xylene (3): This compound was synthesized analogously to **2** using phenyl isothiocyanate. It was recrystallized twice from EtOH/acetone to give the product as white crystals (9%). IR (KBr): 3378*w*, 3278*m*, 3162*m*, 3059*w*, 3004*w*, 2933*w*, 2869*w*, 1597*m*, 1534*s*, 1497*s*, 1461*w*, 1451*m*, 1427*w*, 1350*m*, 1313*m*, 1298*m*, 1269*m*, 1235*m*, 1186*m*, 1091*w*, 948*w*, 746*w*, 707*w*, 694*m*, 656*w*, 605*w*. ^{1}H NMR (DMSO-d_6): 9.67 (*s*, 2H, NHar), 8.21 (*s*, 2H, N<u>H</u>CH_2ar), 7.48 (*d*, J = 8, 4H, NHCC<u>H</u>), 7.37 (*d*, J = 8, 4H, NHCCHC<u>H</u>), 7.37 (*t*, J = 8, 1H, NHCH$_2$CCHC<u>H</u>), 7.35 (*s*, 1H, NHCH$_2$CC<u>H</u>C), 7.28 (*d*, J = 8, 2H, NHCH$_2$CC<u>H</u>CH), 7.16 (*t*, J = 7, 2H, NHCCHCHC<u>H</u>), 4.79 (*d*, J = 5, 4H, NHC<u>H$_2$</u>ar). Elemental analysis: calc. for $C_{22}H_{22}N_4S_2$ (406.57): 64.99% C, 5.45% H, 13.78% N, 15.77% S; found: 64.73% C, 5.48% H, 13.71% N, 15.57% S.

α,α'-Bis(*N'*-1-naphthylthioureylene)-*m*-xylene (4): Host **4** was synthesized analogously to **2** using naphthyl isothiocyanate. It was purified by flash chromatography with $CHCl_3$/EtOH (20/1) as eluent and three recrystallizations from $CHCl_3$/EtOH, giving the product as white crystals (5%). IR (KBr): 3378*m*, 3182*m*, 2979*w*, 1596*w*, 1541*s*, 1501*s*, 1437*w*, 1396*w*, 1339*m*, 1301 *m*, 1272*m*, 1236*m*, 1207*m*, 1168*w*, 988*m*, 763*m*, 522*m*. ^{1}H NMR (DMSO-d_6): 9.78 (*s*, 2H, N<u>H</u>ar), 8.02 (s, 2H, N<u>H</u>CH$_2$ar), 8.01 (*d*, J = 8, 2H, ar), 7.98 (*d*, J = 8, 2H, ar), 7.95-7.90 (*m*, 2H, ar), 7.66-7.54 (8H, ar), 7.31 (*t*, J = 10, 1H, NHCH$_2$CCHC<u>H</u>), 7.24 (*s*, 1H, NHCH$_2$CC<u>H</u>C), 7.21 (*d*, J = 5, 2H, NHCH$_2$CC<u>H</u>CH), 4.75 (*d*, J = 5, 4H, NHC<u>H$_2$</u>ar). Elemental analysis: calc. for $C_{30}H_{26}N_4S_2$ (506.69): 71.12% C, 5.17% H, 11.06% N, 12.65% S; found: 70.71% C, 5.61% H, 11.47% N, 12.55% S.

2,7-Di-*tert*-butyl-9,9-dimethyl-4,5-xanthenediylbiscarbamic acid dibenzyl ester (7): 2,7-Di-*tert*-butyl-9,9-dimethyl-4,5-xanthenedicarboxylic acid (4.0g, 0.01 mol), diphenyl phosphoryl azide (5.63 g,0.02 mol), triethylamine (2.02 g,0.02 mol), benzyl alcohol (2.16 g,0.02 mol) and 80 mL toluene were heated to 80°C for 22 hours. Upon evaporation of the solvent, a yellowish oil was obtained. Recrystallization from toluene/ethyl acetate (4:1) gave the product as white crystals (0.90 g; 22%). IR (KBr): 3433*m*, 3316*m*, 2966*s*, 2908*m*, 2869*m*, 1729*s*, 1693*s*, 1654*w*, 1626*s*, 1592*w*, 1543*s*, 1435*s*, 1397*m*, 1365*s*, 1324*s*, 1282*s*, 1108*s*, 1075*s*, 981*s*, 889*w*, 871*w*. ^{1}H NMR (DMSO-d_6): 9.61 (*s*, 2H, NH), 7.77 (*s*, 2H, NHCC<u>H</u>), 7.48-7.39 (*m*, 10H, phenyl), 7.24 (*s*, 2H, NHCCHCC<u>H</u>), 5.24 (*s*, 4H, arC<u>H$_2$</u>O), 1.65 (*s*, 6H), 1.31 (*s*, 18H). Elemental analysis: calc. for $C_{39}H_{44}N_2O_5$ (620.80): 75.46% C, 7.14% H, 4.51% N; found: 75.26% C,

7.14% H, 4.62% N.

2,7-Di-*tert*-butyl-9,9-dimethyl-4,5-xanthenediamine: Host 7 (0.86 g) was dissolved in 200 mL EtOH, saturated with KOH, and heated to 100°C for 23 hours. After washing the resulting solution with water until the pH of the water phase was 7, the solvent was evaporated to give a slightly brown solid (0.32 g, 65%). IR: 3450*w*, 3387*w*, 2996*s*, 2874*w*, 1630*s*, 1377*w*, 1352*w*, 1273*w*, 1215*w*, 1051*s*, 780*w*. ^{1}H NMR: 6.67 (*s*, 2H, NHCC<u>H</u>), 6.62 (*s*, 2H, NHCCHCC<u>H</u>), 5.20 (*s*, 4H, NH), 1.57 (*s*, 6H, $C(CH_3)_2$), 1.28 (*s*, 18H, $C(CH_3)_3$). Elemental analysis: calc. for $C_{23}H_{32}N_2O$ (352.52): 78.37% C; 9.15% H; 7.95% N; found: 77.79% C; 9.15% H; 7.89% N.

2,7-Di-*tert*-butyl-9,9-dimethyl-4,5-bis(*N'*-butylthioureylene)-xanthene (5): This compound was synthesized analogously to **2** from the xanthenediamine and butyl isothiocyanate. After storing the reaction solution overnight at 4 °C, crystals precipitated. The product were recrystallized once from hexane/ethanol/chloroform (5:4:4) and a second time from ethanol/chloroform (3:1) to give white crystals (28%). IR (KBr): 3378*m*, 3269*w*, 2965*s*, 2847*m*, 2874*m*, 1654*w*, 1623*m*, 1595*w*, 1541*s*, 1485*s*, 1458*s*, 1365*s*, 1344*s*, 1273*s*, 1116*w*, 1090*w*, 978*w*, 888*w*, 867*w*, 642*w*. ^{1}H NMR ($CDCl_3$): 9.02 (*s*, br., 2H, NH, CNH), 8.00 (*s*, br., 2H, NH, N<u>H</u>CH_2), 7.81 (*s*, 2H, NHCC<u>H</u>), 7.33 (*s*, 2H, NHCCHCC<u>H</u>), 3.54 (*br.*, 4H, NHC<u>H</u>$_2$), 1.66 (*s*, 6H, $C(CH_3)_2$), 1.59 (*quint.*, 4H, $NHCH_2C\underline{H}_2$), 1.39 (*sext.*, 4H, $C\underline{H}_2CH_3$), 1.34 (*s*, 18H, $C(CH_3)_3$), 0.94 (*t*, 6H, $CH_2C\underline{H}_3$). Elemental analysis: calc. for $C_{33}H_{50}N_4S_2O$ (582.34): 68.00% C, 8.65% H, 9.61% N, 11.00% S; found: 67.71% C, 8.58% H, 9.91% N, 11.05% S.

2,7-Di-*tert*-butyl-9,9-dimethyl-4,5-bis(*N'*-phenylthioureylene)-xanthene (6): This compound was synthesized analogously to **2** using phenyl isothiocyanate. It was recrystallised from hexane/ethanol/chloroform. ^{1}H NMR ($CDCl_3$): 10.00 (s, br., 2H, NHCCO), 9.43 (s, 2H, N<u>H</u>CCHCH), 7.85 (s, 2H, NHCC<u>H</u>), 7.55 (d, 4H, NHCC<u>H</u>CH), 7.38 (s, 2H, CHCCO), 7.32 (t, 4H, CCHC<u>H</u>), 7.14 (t, 2H, CCHCHC<u>H</u>), 1.68 (s, 6H, $C(CH_3)_2$), 1.35 (s, 18H, $C(CH_3)_3$). HRMS (m/z (FAB with *m*-nitrobenzylalcohol as matrix) $(M+H)^+$ 623): calc. for M^+: 622.280; found: M^+ 622.282.

Binding Studies

Reagents: All inorganic anions were commercially available as tetrabutylammonium (TBA) salts. Recrystallization was performed for TBA dihydrogen phosphate and hydrogen sulfate from EtOAc/acetone, for TBA acetate, nitrate and perchlorate from EtOAc and for TBA chloride from EtOAc/hexane. DMSO-d_6 was dried over molecular sieves (3Å) and 1,2-dichloroethane purified by passing through a column of basic alumina before use.

Determination of Complexation Constants by ^{1}H NMR Spectroscopy: ^{1}H NMR spectra were obtained on a Bruker AM500 spectrometer (500 MHz; Bruker, Fällanden, Switzerland). All chemical shift values (δ) are reported in parts per million (ppm), using as reference tetramethylsilane (TMS) for $CDCl_3$ and the residual solvent signal (2.55) for DMSO-d_6 solutions. Before measuring association constants of the present hosts with guest anions, it was confirmed that hosts **2** to **7** do not self-associate in DMSO-d_6. For ^{1}H NMR titrations, two stock solutions were prepared in DMSO-d_6, one of them containing host only and the second one guest and an equal concentration of host. Aliquots of the two solutions were mixed directly in NMR tubes. To ensure complete mixing of the rather viscous DMSO solutions, the solutions were repeatedly shaken very carefully and spectra taken not earlier than 1 hour after mixing. For dilution experiments, solutions containing receptor and guest (equimolar) were diluted with pure DMSO-d_6. The very large association constants of hosts **5** and **6** with $H_2PO_4^-$ were determined by competitive spectrometry,[7] which was easily possible due to

different chemical shifts of the aromatic ring hydrogens in the Cl^- and $H_2PO_4^-$ complexes (exact chemical shifts for the complexes were determined by analysis of ^1H NMR titrations). Because the chemical shifts of the aromatic hydrogens were found to be very similar for the complexes of Cl^- and CH_3COO^-, K_{11} for the complex of **5** and CH_3COO^- was determined by a dilution experiment. All experimental data obtained by these methods were analyzed using Mathematica® 2.2 with an appropriate binding isotherm model[7] and a nonlinear regression package.

Determination of Complexation Constants by UV-VIS Spectroscopy: Bis-thiourea host **2** (≈ 0.2 mM in water-saturated 1,2-dichloroethane) was titrated with a solution containing an equal concentration of host **2** and additionally guest (0 ~ 6 mM). The changes in UV absorption at 260, 255, 245, 240 and 236 nm were monitored as a function of the guest concentration. In the case of the titration with NO_3^-, the changes in absorption at 260 and 255 nm were monitored because NO_3^- ions absorb up to 245 nm. The resulting titration curves for all wavelengths were analyzed by nonlinear regression, and the obtained values for association constants were averaged. An algorithm for a system with 1:1 and 1:2 host:guest complexes was employed for analyzing the titration with $H_2PO_4^-$ as guest,[4] while a 1:1 system was employed in the case of all other anions, for which an isosbestic point was observed.

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REFERENCES AND NOTES

1. Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991**, *91*, 1721.
2. Raposo, C.; Pérez, N.; Almaraz, M.; Mussons, L.; Caballero, C.; Moran, J. R. *Tetrahedron Lett.* **1995**, *36*, 3255. Rudkevich, D. M.; Stauthamer, W. P. R. V.; Verboom, W.; Engbersen, J. F. J.; Harkema, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1992**, *114*, 9671. Beer, P. D.; Chen, Z.; Goulden, A. J.; Graydon, A.; Stokes, S. E.; Wear, T. *J. Chem. Soc., Chem. Commun.* **1993**, 1834. Carey, C. M.; Riggan, W. B. *Anal. Chem.* **1994**, *66*, 3587. Glazier, G. A.; Arnold, M. A. *Anal. Chem.* **1991**, *63*, 754. Rudkevich, D. M.; Verboom, W.; Brzozka, Z.; Palys, M. J.; Stauthamer, W. P. R. V.; van Hummel, G. J.; Franken, S. M.; Harkema, S.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1994**, *116*, 4341. Rudkevich, D. M.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1994**, *59*, 3683. Beer, P. D.; Chen, Z.; Goulden, A. J.; Grieve, A.; Hesek, D.; Szemes, F.; Wear, T. *J. Chem. Soc., Chem. Comm.* **1994**, 1269. Valiyaveettil, S.; Engbersen, J. F. J.; Verboom, W.; Reinhoudt, D. N. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 900.
3. Raposo, C.; Almaraz, M.; Martin, M.; Weinrich, V.; Mussons, L.; Alcazar, V.; Caballero, C.; Moran, J. R. *Chem. Lett.* **1995**, 759.
4. Nishizawa, S.; Bühlmann, P.; Iwao, M.; Umezawa, Y. *Tetrahedron Lett.* **1995**, *36*, 6483.
5. Laurence, C.; Berthelot, M.; Questel, J.-Y. L.; Ghomari, M. J. E. *J. Chem. Soc. Perkin Trans. 2* **1995**, 2075.
6. Hamann, B. C.; Branda, N. R.; J. Rebek, J. *Tetrahedron Lett.* **1993**, *34*, 6837.

7. Connors, K. A. *Binding Constants*; John Wiley & Sons: New York, 1987.
8. Bordwell, F. G.; Algrim, D. J.; Harrelson, J. A., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 5903.
9. Wilcox, C. S.; Kim, E.-I.; Romano, D.; Kuo, L. H.; Burt, A. L.; Curran, D. P. *Tetrahedron* **1995**, *51*, 621.
10. Scheerder, J.; Engbersen, J. F. J.; Casnati, A.; Ungaro, R.; Reinhoudt, D. N. *J. Org. Chem.* **1995**, *60*, 6448.
11. Though not directly comparable, it seems interesting to note that Rebek et al.[6] determined K_{11} for the benzoate complexes (in $CDCl_3$) of a monophenyl urea and a bis-urea with a xanthene spacer to be $4x10^2$ M^{-1} and $2x10^5$ M^{-1}, respectively, while we determined $2.9x10^2$ M^{-1} and $3.8x10^4$ M^{-1} for the acetate complexes (in DMSO-d_6) of *N,N'*-dimethylthiourea and bis-thiourea **5** with the xanthene spacer.
12. Independently of our work, a PO_4^{3-} receptor with three phenylsubstituted thiourea groups, derived from tris(2-aminoethyl)amine, has been reported only very shortly after our first communication on bis-thioureas.[3] The complex of that host and the triply charged PO_4^{3-} (K_{11} 1600 M^{-1}, in DMSO-d_6) is appreciably less stable than the complexes of hosts **5** and **6** with $H_2PO_4^-$. The opposite may have been expected from the charge of the guests[22] and the number of thiourea groups in these receptors. While this finding could be mainly explained by the formation of an intramolecular hydrogen bond to the tertiary amine group, which is a very strong hydrogen bond acceptor (intra- and intermolecular hydrogen bond formation has recently also been suggested to be responsible for the relatively weak binding of Cl^-, Br^-, I^-, CN^- and SCN^- by a calix[4]arene with four phenylthiourea substituents),[23] and the lower extent of preorganization in that host, the extent to which the binding strength is decreased is surprising. Ion pair formation involving the triply charged PO_4^{3-} may have made K_{11} appear smaller than it truly is.
13. Jorgensen, W. L.; Pranata, J. *J. Am. Chem. Soc.* **1990**, *112*, 2008.
14. Viggiano, A. A.; Henchman, M. J.; Dale, F.; Deakyne, C. A.; Paulson, J. F. *J. Am. Chem. Soc.* **1992**, *114*, 4299.
15. Blades, A.; Ho, Y.; Kebarle, P. *J. Phys. Chem.* **1996**, *100*, 2443.
16. Blades, A. T.; Klassen, J. S.; Kebarle, P. *J. Am. Chem. Soc.* **1995**, *117*, 10563.
17. Blades, A. T.; Ho, Y.; Kebarle, P. *J. Am. Chem. Soc.* **1996**, *118*, 196.
18. A linear relationship[16,24] between the gas phase acidities[16,24,25] and the free energies of hydration $\Delta G^\circ_{0,1}$ in the gas phase[16,19] of CH_3COO^-, Cl^-, NO_3^-, HSO_4^- and ClO_4^- confirms that the gas phase acidities of the anions would be equally appropriate for the assessment of the hydrogen bond acceptor strengths for the present case, the only problem being that such a value seems not to be known for H_3PO_4.
19. Arshadi, M.; Yamdagni, R.; Kebarle, P. *J. Phys. Chem.* **1970**, *74*, 1475.
20. Magnera, T. F.; Caldwell, G.; Sunner, J.; Ikuta, S.; Kebarle, P. *J. Am. Chem. Soc.* **1984**, *106*, 6140.
21. Taft, R. W.; Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 463.
22. Blades, A. T.; Kebarle, P. *J. Am. Chem. Soc.* **1994**, *116*, 10761.
23. Scheerder, J.; Fochi, M.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Org. Chem.* **1994**, *59*, 7815.
24. Yamdagni, R.; Kebarle, P. *J. Am. Chem. Soc.* **1971**, *93*, 7139.
25. Cumming, J. B.; Kebarle, P. *Can. J. Chem.* **1978**, *56*, 1.
26. Koppel, I. A.; Taft, R. W.; Anvia, F.; Zhu, S.-Z.; Hu, L.-Q.; Sung, K.-S.; DesMarteau, D. D.; Yagupolskii, L. M.; Yagupolskii, Y. L.; Ignat'ev, N. V.; Kondratenko, N. V.; Volkonskii, A. Y.; Vlasov, V. M.; Notario, R.; Maria, P.-C. *J. Am. Chem. Soc.* **1994**, *116*, 3047.

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