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Energies and selectivities for anion binding as a function of host conformational preorganisation†

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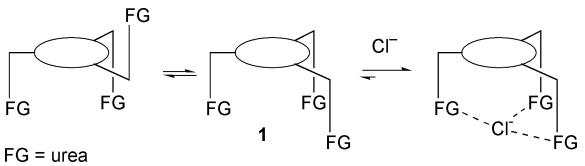
The anion binding of tripodal hosts 2–4 has been studied. Increasing levels of conformational preorganisation of the side arms of the hosts led to increased (Cl^-) unaltered (Br^-) or decreased (NO_3^-) binding; it was thus possible to change guest selectivities by about an order of magnitude through conformational preorganisation of the flexible host.

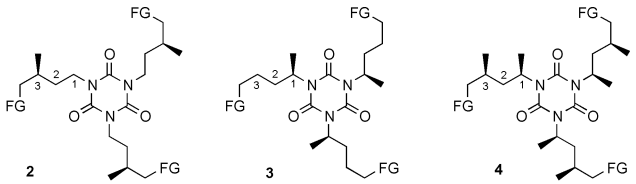
Conformational preorganisation is a key feature in many natural products of polyketide biogenetic origin.[1,2] It is therefore interesting to ask, which advantage nature gained during evolution by choosing flexible conformationally preorganised molecules over flexible non-preorganised structures. This question has been addressed *e.g.* by monitoring the biological activity of bleomycine on gradually reducing the conformational preorganisation in the linker segment which unites the two pharmacophoric regions of bleomycine.[3] Biological activity is often triggered in a chemical sense by molecular recognition between a drug and the appropriate receptor, a process, that can be described by a binding constant. The effect of (conformational) preorganisation of a host molecule on binding properties has been a focus of research since the pioneering studies by Cram.[4] Recent examples can be found in refs. 5–7. But for the most part it was not possible to clearly single out the effects of conformational preorganisation from other effects. For this reason we initiated a study in which we used a series of 'receptors' differing solely in the level of conformational preorganisation. We wanted to learn, how this affects binding constants as well as binding selectivities.

For our studies we chose a tripodal receptor (host) of the general structure **1** with three side arms at a central platform. As guests we envisaged spherically symmetrical anions[7,8] such as Cl^- and Br^-, as they do not require any special coordination geometry. To complex these anions the side arms were armed with urea moieties as sticky groups at their ends, *cf.* Scheme 1.



Scheme 1 Schematic overview of the hosts, in which the conformational preorganisation of the side arms can be controlled by the number and position of methyl substituents.

We started with the host molecule **2** (Scheme 2), which is devoid of any conformational preorganisation. Binding of tetrabutylammonium chloride and bromide by **2** in $CDCl_3$ was followed by ^{1}H-NMR-spectroscopy monitoring the chemical shifts of the NH-protons. In addition, complexation to nitrate was also investigated. Job-plots showed that in all cases 1 : 1 complexes were formed. The binding constants (Table 1) were found to be in the order of 10^3 M^{-1} (ΔG *ca.* 4 kcal mol^{-1}, Table 1), *i.e.* they are significantly larger than the self-association of **2** which was determined by dilution experiments to be in the order of 20 M^{-1}. A binding constant in the order of 10^3 M^{-1} is unexceptional for a tris-urea receptor[7] and was judged to be optimal to assess the effects of conformational preorganisation, because conformational effects on binding constants so far reported[5,7] have a range of about 1 kcal mol^{-1}.



FG = NH-CO-NH-(*p*)C_6H_4-^{n}C_4H_9

Scheme 2

Our aim was to stepwise increase the level of conformational preorganisation in **2**, while maintaining the same coordination geometry of the constructs. The level of conformational preorganisation in the side arms and in the total constructs is adjusted by the number and location of the methyl-substituents. This is exemplified by a change from host **2** to host **3**. In **2** the side arms are free to adopt almost any conformation within themselves and relative to the platform. By shifting of the methyl groups from C-3 to C-1 of each side chain, the orientation of the side chain relative to the platform can be controlled. In order to avoid 1,3-allylic strain[9] the side chains in **3** are now arranged orthogonal to the platform. Either all three arms are on the same side of the platform, or, statistically favoured by 3 : 1, two arms are on one side and one on the other. These two forms are obviously in rapid equilibrium (Scheme 1). The conformational preorganisation attained in **3** at the junction between the platform and the side arms leads to a moderate increase in the binding of chloride and bromide, but to a decrease in the case of nitrate, relative to the reference values of **2** (Table 1). Apparently the binding of the larger nitrate anion requires conformational adjustments in the side chains of the host **3**, which lead to destabilizing interactions to and from the methyl groups at C-1 of the side chains. The reason is, that the methyl groups at C-1 favor a distinct folding of the host molecule **3**. Complexation to nitrate requires a different and, hence, higher energy conformation of the host molecule, which cannot so readily be adapted in host **3** than in host **2**, which is lacking the methyl groups at C-1.

Table 1 Binding energies (kcal mol^{-1}) and binding constants (M^{-1}) for complexation of Cl^-, Br^- and NO_3^- by the hosts **2**, **3** and **4** at rt in $CDCl_3$

Guest/host	**2**	**3**	**4**
Bu_4N^+ Cl^-	−5.27 (±0.02)	−5.80 (±0.07)	−5.84 (±0.06)
	7400 (±280)	18300 (±2270)	19500 (±2160)
Bu_4N^+ Br^-	−4.56 (±0.02)	−4.76 (±0.03)	−4.57 (±0.03)
	1990 (±50)	3100 (±160)	2260 (±100)
Bu_4N^+ NO_3^-	−4.45 (±0.02)	−4.17 (±0.02)	−3.95 (±0.02)
	1840 (±40)	1150 (±13)	800 (±10)

† Electronic supplementary information (ESI) available: NMR data and binding isotherms. See http://www.rsc.org/suppdata/cc/b2/b200605g/

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Next, we introduced a second methyl group at C-3 of each side arm in going from **3** to **4**. The configuration at the additional stereogenic centres was chosen such, as to favour a distinct conformation within the side arms,[10] which is nicely illustrated by an X-ray crystal structure of host **4** (Fig. 1).‡

In solution, the conformational preorganisation along the C-1/C-2 bond is manifest in the $^3J_{H,H}$-coupling constant between H-1 and H-2a of 10.0 Hz (*cf*. also the $^3J_{C,H}$-coupling constants[11] for **H**-2/C-2/C-1/**C**H$_3$ of 2.0 and 2.8 Hz). Conformational preorganisation about the C-2/C-3 bond is somewhat lower (*cf*. $^3J_{C,H}$ = **H**-2/C-2/C-3/**C**H$_3$ = 6.1 and 4.6 Hz), probably as a consequence of intra- and intermolecular self-interaction between the urea groups in **4** (Fig. 1). It can be expected that the conformational preorganisation in the side chains of **4** should increase further on binding to an anion. However attendant line broadening of the NMR-signals prevented us from demonstrating this by determination of the coupling constants.

The change in going from **3** to **4** is reflected in only minor alterations in the binding constants, but these changes illustrate, how the additional element of conformation design (the methyl groups at C-3 of the side chains) helps to fine-tune binding selectivities: The dimethyl-substitution makes it more difficult for the side chains in **4** than in **3** to accommodate an unfavourable folding geometry on complexation of an anion, such as that necessary to bind nitrate. Hence, ligand **4** becomes the one with the highest anion selectivity of the three ligands studied. In consequence, it is possible to increase (Cl^-) or to decrease (NO_3^-) the binding of a guest by conformational preorganisation of the host (other factors remaining constant). This is reflected in guest selectivities, *e.g*. Cl^-/NO_3^-, which increase from 4 in the case of **2** to over 16 for **3** and to 24 in the case of **4**. This exemplary case therefore shows that distinct advantages can be gained in molecular recognition by using a conformationally preorganised (**4**) *vs*. a non-preorganised (**2**) host. The effects observed may appear small, but nature for the most part also relies on small effects which it often combines to attain sizeable effects. Conformation design[2] is certainly one of the tools used by nature to optimise molecular recognition.

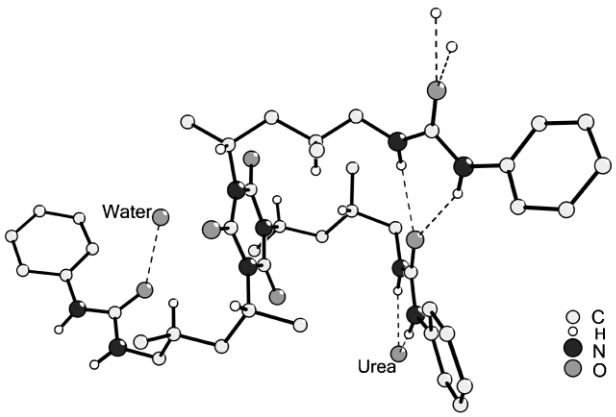

Fig. 1 Key features of the X-ray crystal structure of **4** (butyl groups omitted): side arms orthogonal to the platform; side arms in extended conformation; intra- and intermolecular hydrogen bonds.

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Notes and references

‡ *Crystal data*. $(C_{54}H_{80}N_9O_6)_2{\cdot}H_2O$, M = 1922.58, triclinic, a = 9.3553(8), b = 15.9882(15), c = 19.585(2) Å, α = 103.119(12), β = 90.298(12), γ = 102.334(10)°, U = 2782.6(5) Å^3, T = 193 K, space group $P\bar{1}$ (No. 1), Z = 1, μ(Mo-K$_\alpha$) = 0.076 mm^{-1}, 34183 reflections measured, 20133 unique (R_{int} = 0.133) which were used in all calculations. The structure was solved with SHELXD (G. M. Sheldrick, University of Göttingen, Germany, 2001). The final $wR(F^2)$ was 0.1017 (all data). CCDC 178240. See http://www.rsc.org/suppdata/cc/b2/b200605g/ for crystallographic files in .cif or other electronic format.

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