Synthesis, X-ray structure and binding properties of molecular clips based on dimethylpropanediurea

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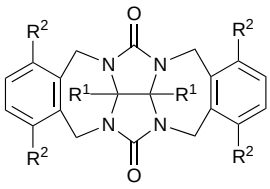
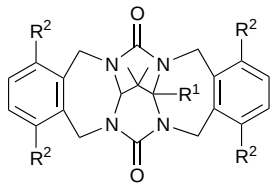
New concave host molecules show strong noncovalent binding of hydroxybenzene derivatives by an induced fit mechanism (K_a up to 3.4 × 10^6 dm^3 mol^{-1}).

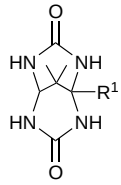
The design and synthesis of host molecules for neutral guests continues to be an area of great interest in supramolecular chemistry.[1] In recent years a series of receptors derived from the concave molecule glycoluril (see **1**) have been developed in our



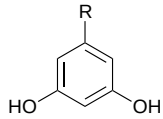
1a R^1 = Ph, R^2 = H
b R^1 = Ph, R^2 = OMe
c R^1 = Me, R^2 = H



2a R^1 = H, R^2 = H
b R^1 = Me, R^2 = H
c R^1 = H, R^2 = OMe



3a R^1 = H
b R^1 = Me



4a R = Me
b R = H
c R = OMe
d R = $CO_2C_6H_{13}$
e R = Cl
f R = CN

laboratory.[2] These receptors, which are U-shaped, bind dihydroxybenzenes by hydrogen bonding interactions between the hydroxy groups of the guest and the urea carbonyl groups of the host and by π–π stacking interactions between the guest and the host side-walls. Although the supramolecular chemistry of glycoluril-based clips has been widely explored, and their sidewalls extensively varied,[2] relatively little attention has been given to variations in the diphenylglycoluril part of the clip molecules. Here we describe the synthesis, X-ray structures and binding properties of a new type of related molecular clips derived from 2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione (propanediurea, see **2**). Molecular modelling studies suggested that the *o*-xylylene side walls of these new clips would be more parallel than the walls of glycoluril derived clips, which would result in better π–π stacking interactions with an aromatic guest molecule sandwiched between the side walls of the clip and hence lead to increased binding affinities for aromatic molecules. Here we show that compound **2** indeed binds aromatic guest molecules with very high association constants (K_a > 10^6 dm^3 mol^{-1}).

Clip molecules **2a**,**b** were prepared in *ca.* 20% yield by reacting the respective propanediurea derivatives **3a**,**b** with α,α′-dibromo-*o*-xylene in DMSO in the presence of NaH. Compound **3a** was accessible following a literature procedure,[3] and compound **3b** was synthesized in 90% yield by refluxing 2,2-dimethyl-3-oxobutanal with urea in toluene in the presence of TFA with azeotropic removal of water. Clip molecule **2c** could be obtained in 20% yield by reacting **3a** with 2,3-bis-(bromomethyl)-1,4-dimethoxybenzene in DMSO in the presence of NaH. The latter compound was prepared from 3,6-dimethoxyphthalic anhydride[4] by reduction with $LiAlH_4$ followed by reaction with PBr_3. Full experimental details will be reported in a forthcoming paper.‡

Single crystals of **2a** were obtained by vapour diffusion using $CHCl_3$ as the solvent and hexane as the precipitant and of **2c** by vapour diffusion using CH_2Cl_2 as the solvent and Et_2O as the precipitant. The crystal structure of **2a** revealed that this clip molecule has a U-shaped cavity similar to that of diphenylglycoluril derived clips.[2a] In contrast to previous clip molecules of type **1** the crystal structure of **2c**§ shows an asymmetric geometry with respect to the side walls (Fig. 1), which is attributed to its greater flexibility. The clip molecule dimerizes to give a 'head-to-head' packing, with the wall of one clip molecule being buried in the cavity of another clip. This dimerization was not observed in $CDCl_3$ solution.

The binding properties of hosts **2** and, for comparison, hosts **1** with a number of hydroxybenzene derivatives (**4a**–**f**, **5**–**7**), were measured by NMR titration experiments in $CDCl_3$ using the outer wall protons of the host and the aromatic protons of the guest as probes.¶ The results are summarized in Table 1. The new clip molecules bind resorcinol derivatives significantly more strongly than diphenylglycoluril molecular clips. The binding constant is a factor of three higher for hosts **2a**,**b** when compared to host **1a**.‖ In the case of **2c** the increase in binding constant strongly depended on the type of guest used (see Table 1). For guests **4a**–**c** the binding was increased by a factor of three, five and twelve respectively when compared to host **1b**. For guests **4d**–**f** the binding constants were so large that they could not be measured by standard NMR titrations.[5] We therefore determined the binding constants of **4d**,**e** by competition experiments with **4c**, and of **4f** by a competition experiment with **4e**.[6] A plot of the binding free energies of guests **4a**–**f** as a function of the Hammett parameter [σ_m (R)] of the guest's substituent (Fig. 2) reveals a linear correlation which has been previously observed for clip **1b**.[2b] From the gradients of the

Fig. 1 X-Ray structure showing a dimer of clip **2c**

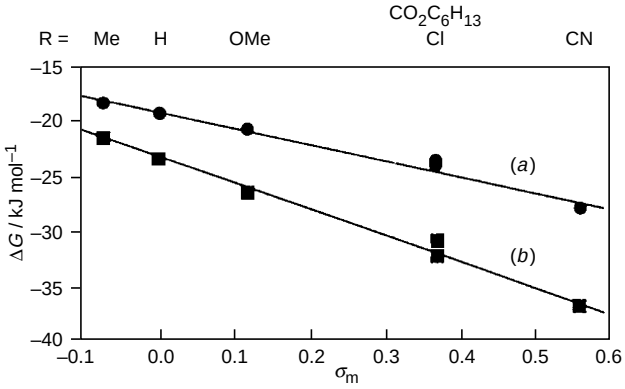


Fig. 2 Binding free energies of guests **4a**–**f** in clips (*a*) **1b** and (*b*) **2c** as a function of the Hammett parameter [σ_m(R)] of the guest's substituent

plots it is clear that binding of guests in clip **2c** is more sensitive to the substituent on the guest than binding in clip **1b**. Previous analysis of the binding properties of clips of type **1** showed that the steeper the gradient the greater the hydrogen bonding contribution is to the overall binding.[2b] One of the reasons for the stronger binding of **2c** is the fact that the carbonyl oxygens atoms are situated slightly higher with respect to the cavity walls than the carbonyl oxygens atoms in clip **1b**, as is clear from the X-ray structures. Previously it has been shown that the optimal distance for π–π interaction of a guest in clips **1** is at a position further out of the cavity than that for optimal hydrogen bonding.[2b] This means that in clip **2c** the complexation geometry is more ideal for optimum π–π interactions than in clip **1b**. Furthermore, the carbonyl–carbonyl distance in clip **2c** (5.2 Å) is closer to the ideal value for resorcinol binding (3.9 Å)** than this distance in clip **1b** (5.5 Å). Although the difference is small, it is significant since **1b** is shown to be better suited for binding of guest molecules with relatively large OH–OH distances such as 2,7-dihydroxynaphthalene **5** than **2c** (Table 1); this guest prefers a carbonyl–carbonyl distance of 6.3 Å.** The enhanced binding of catechol **6** in **2c** can be explained by the smaller carbonyl–carbonyl distance.‖ Other factors, apart from the position of the carbonyl groups, also contribute to the difference in binding properties of the clips. The binding of 4-nitrophenol **7**, which has only one hydroxy group and hence forms one strong optimum hydrogen bond, is stronger in clip **2c** than in clip **1b** (Table 1), suggesting that additional factors, *e.g.* the possibility of a guest to adopt a more parallel orientation with respect to the cavity walls, play a role in the enhanced binding.††

The NMR data suggest that the binding of a guest in clips of type **2** takes place *via* an induced fit mechanism, which is in agreement with the increased flexibility predicted by molecular modelling and suggested in the asymmetry observed in the X-ray crystal structures. The signals due to the benzylic protons of clip **2c** were found to shift considerably upon binding of a guest (**4d**: up to +0.44 ppm for the upfield benzylic proton signals and −0.29 ppm for the downfield benzylic proton signals), in contrast to those of clips **1**, for which virtually no shifts were observed. These shifts indicate that the conformation of the clip's side walls changes upon binding of a guest and are consistent with a tightening of the cavity upon binding of an aromatic guest.

In conclusion, a new type of molecular clips is presented which show enhanced binding of aromatic guest molecules. Applications of these receptor molecules in the construction of new supramolecular architectures are under investigation.

Table 1 Association constants of complexes between various host and guest molecules in $CDCl_3$, T = 25 °C

	Host	
Guest	**2c**	**1b**
4a	5500[a]	1900[b]
4b	14000[a]	2600[c]
4c	53000[a]	4400[b]
4d	$2.7\cdot10^5$[d]	16500[b]
4e	$4.2\cdot10^5$[d]	16000[b]
4f	$3.4\cdot10^6$[e]	$1\cdot10^5$[b]
5	2300[a]	7100[b]
6	130[d]	60[c]
7	4400[a]	1200[c]

[a] Estimated error, 20%. [b] Values taken from ref. 2(*a*). [c] Values taken from ref. 2(*b*). [d] Estimated error, 30%. [e] Estimated error, 40%.

Footnotes and References

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‡ All new compounds were fully characterized by ^{1}H and ^{13}C NMR and mass spectroscopy and elemental analysis. *Selected data* for **2c**: δ_H (300 MHz) 6.74 (s, 4 H), 5.43 (d, 2 H, ^2J 15.1), 4.32 (s, 2 H), 3.90 (d, 4 H, ^2J 15.2), 3.78 (s, 12 H), 1.35 (s, 6 H).

§ *Crystal data and data collection parameters* for **2c**: $C_{27}H_{32}N_4O_6$, M = 508.57, monoclinic, a = 11.760(2), b = 15.300(3), c = 14.574(7) Å, β = 106.849(12)°, V = 2509.7(14) Å^3, T = 293(2) K, space group $P2_1/a$, λ = 1.54184 Å, Z = 4, D_c = 1.346 Mg m^{-3}, F(000) = 1080, colourless crystal with dimensions 0.29 × 0.19 × 0.16 mm, μ(Cu-Kα) = 0.791 mm^{-1}, Enraf-Nonius CAD4 diffractometer, θ–2θ scans, 3.17 < θ < 62.19°, +h, +k, ±l, maximum drift 14.526%, 4186 reflections measured, 3967 unique (R_{int} = 0.0098). The structure was solved using the program CRUNCH (ref. 8), and refined anisotropically, by full-matrix least squares on F^2 [program SHELXL (ref. 9)]. The final $wR(F^2)$ was 0.1991, with conventional $R(F)$ 0.0549.

¶ NMR titration experiments were performed as described in ref. 2(*a*). The chloroform used was standard NMR grade and predried on molecular sieves (4 Å) before use. The NMR spectra used for the determination of the binding constants showed only a small water peak.

‖ For example: for **4d**: K_a = 2000 M^{-1} with clip **2a** and 600 M^{-1} with clip **1c**; for **4b**: K_a = 550 M^{-1} with clip **2b** and 165 M^{-1} with clip **1c**.

** Assuming that the hydrogen bonds are linear and that the O–H–O distance is 2.7 Å (ref. 7).

†† Since clip molecules **1a** and **1c** have different groups at their convex sides, we compared the binding affinities of **1a** and **1c** with guests **4b**, **4d** and **4f**. The binding constants were the same within the experimental error (*e.g.* K_a = 165 and 175 M^{-1}, respectively, for **1a** and **1c** with guest **4b** and K_a = 3600 and 3500 M^{-1}, respectively, with guest **4f**), which indicates that the groups at the convex side of clips **1** do not contribute significantly to the binding. Clip molecule **1c** was prepared in 60% yield from dimethylglycoluril and α,α′-dibromo-*o*-xylene in DMF at room temperature in the presence of NaH.

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