Synthetic Molecular Receptor for Piperazine and Related Diamines

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The new tailored tetrahydroxycyclophane **4b** is shown to be a selective host compound for piperazine **6** and structurally related diamines **7** and **8**; association constants for the 1 : 1 complexes have been measured by ^{1}H NMR titration experiments.

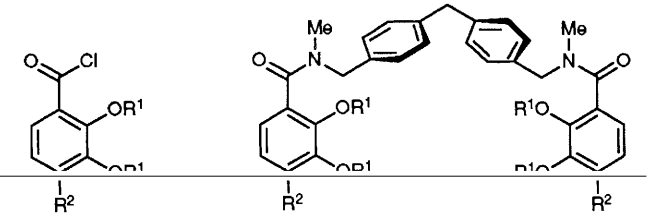
A few years ago we reported on macrobicyclic host molecules which form complexes extremely strongly with metal cations such as Fe^{3+} by preorganization of three catechol units.[1] Enlarging the cavities by spacer units yields endo-acidic macrobicyclic host molecules which show molecular recognition and transport of nucleic bases.[2] Using a similar modular strategy we have now synthesized the macromonocyclic bis(catechol) host **4b** by cyclisation of the diamine **2** and the diacid dichoride **3c** to yield the tetramethoxy-macrocycle **4a** (45% yield).† With its cavity size and endo-acidic functional groups **4b**, from model considerations, should be a hydrogen bond receptor for piperazine-type guest molecules in organic solution.

In ^{1}H NMR titration experiments the shift of host protons was determined at different concentrations of the guest.[3] At the 'coalescence point' the degree of the observed chemical shift of a proton, $\Delta\delta$, is proportional to the percentage of the complexed host relative to the total concentration.[4] The association constant was determined using the relationship: $1/\Delta\delta = 1/(K\cdot\Delta\delta_{max})\cdot 1/[\text{guest}] + 1/\Delta\delta_{max}$. For piperazine **6** and 1,4-diazacycloheptane **7** as guests there is an acceptable fit of the titration curve, suggesting that simple 1 : 1 complexation occurs (Fig. 1). The resulting association constants K_a for the guests **6** and **7** are 1.4×10^2 (±20%) and 1.2×10^2 (±40%) $dm^3\ mol^{-1}$, respectively.

The selective complexation of the guests **6** and **7** is underlined by comparison measurements with the mono(catechol) host reference compound **5b**‡ and the potential guests **9–15**; compound **5b**, bearing analogous acidic functions but without the preorganization of a macrocyclic ring compared to host **4b**, did not show any up- or down-field shifts during NMR titration with piperazine **6**.[5] On the other hand, for the potential guests *cis*- or *trans*-2,5-dimethylpiperazine **11** and *N*,*N*′-dimethylpiperazine **12**, where the methyl groups were intended to disturb the host–guest interactions, no NMR shifts were observed with the host **4b**; the N–H (guest) or O–H (host) proton signals are broad or not observed (rapid exchange). The guest substrates **13–15** do not effect up- or down-field shifts, also.

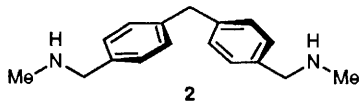
Consequently the fitting guests **6–8** exhibit specific hydrogen-bond shifts caused not only by complexation effects but also from donor-anisotropy effects (Table 1).[6]

DABCO **9** shows a downfield shift of 0.15 ppm. This suggests a proton transfer from the host **4b** (H-5: $\Delta\delta = -0.05$ ppm) to this guest, whereas the complexation takes place at the periphery of **4b** (no or weak anisotropy effect). We expected a similar behaviour for hexacyclen **8** as guest, but an



1a; R^1 = Me, R^2 = CO_2Me
b; R^1 = Me, R^2 = COCl

3a; R^1 = Me, R^2 = CO_2Me
b; R^1 = Me, R^2 = CO_2Na
c; R^1 = Me, R^2 = COCl



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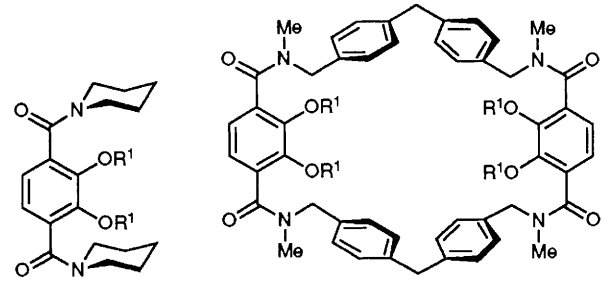

5a; R^1 = Me
b; R^1 = H

4a; R^1 = Me
b; R^1 = H

† *Preparations*: Benzoyl chloride **1**: *cf.* F. L. Weitl, K. H. Raymond and P. W. Durbin, *J. Med. Chem.*, 1981, **24**, 203.

N-Methylamine **2**: prepared by treatment of bis(4-bromomethylphenyl)methane with 20 equiv. of methylamine (33% in ethanol) and 5 equiv. of Na_2CO_3 in ethanol (room temperature, 12 h); yield 79%; yellow oil; ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 35.7 (CH_3), 41.0 ($C^{-3.93}H_2$), 55.5 ($C^{-3.67}H_2$), 128.1 (CH), 128.6 (CH), 137.6 (quat. C) and 139.6 (quat. C); (in this notation, $C^{-3.93}H_2$ indicates the carbon atom attached to the proton resonating at δ_H 3.93, *etc.*) ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.74 (s, 2 H, NH), 2.41 (s, 6 H, Me), 3.67 (s, 4 H, $ArCH_2N$), 3.93 (s, 2 H, $ArCH_2Ar$), 7.14 (d, 4 H, ^3J 6.8 Hz, ArH) and 7.22 (d, 4 H, ^3J 6.8 Hz, ArH); *m/z* 254 (30%, M^+), 225 (100%, $M^+ - CH_3N$) and 194 (40%, $M^+ - 2\ NHCH_3$).

Dimethyl ester **3a**: yield 67%; HRMS calc. for $C_{39}H_{42}N_2O_{10}$ 698.2839; found 698.2857; MS *m/z* (electron impact) 698 (5%, M^+), 667 (15%, $M^+ - OCH_3$), 636 (20%, $M^+ - 2\ OCH_3$), 475 (65% M^+ – 223) and 223 (100%) 4-carbonyl-2,3-dimethoxy-1-methoxycarbonylbenzene cation).

Macrocyclic tetramethoxy-tetraamide **4a**: treatment of **3a** with 2 equiv. of NaOH in methanol–water (90 °C, 12 h), yield 96% of **3b**, m.p. >230 °C; treatment of **3b** with 50 equiv. of $SOCl_2$ in a general procedure; yield of **3c** is quantitative; cyclization of 0.7 mmol of **3c** with 1.4 mmol of **2** in 1.2 dm^3 of chlorobenzene and catalytic amounts of 4-*N*,*N*′-dimethylaminopyridine (DMAP) (50 °C, 12 h) yielded 45% of **4a**, m.p. 157 °C; satisfactory C, H and N analyses. 5,6,30, 31-Tetrahydroxy-2,11,27,36-tetramethyl-2,11,27,36-tetraaza[3.3.1–3.3.1]paracyclophane-3,10,28,35-tetraone **4b**: prepared by treatment of **4a** with 20 equiv. of BBr_3 in dichloromethane (room temperature, 12 h) (*cf.* D. L. Manson and O. C. Musgrave, *J. Chem. Soc.*, 1963, 1011); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 35.8 (CH_3), 41.4 ($C^{-3.95}H_2$), 53.5 ($C^{-4.63}H_2$), 118.5 ($C^{-6.82}H$), 122.2 (quat. C), 128.1, 129.3 ($C^{-7.18}H$), 134.6 (quat. C), 140.9 (quat. C) and 170.1 (C=O); ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.93 (s, 12 H, NCH_3), 3.95 (s, 4 H, $Ar–CH_2–Ar$), 4.63 (s, 8 H, $Ar–CH_2–N$), 6.82 (s, 4 H, ArH) and 7.18 (s, 16 H, ArH); FAB-MS: *m/z* 833.3 (M^+).

‡ Prepared from **1b** and piperidine and subsequent methoxy cleavage with BBr_3; yield 78%; m.p. 196–198 °C; ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 24.5 ($C^{-1.65}H_2$), 26.1 ($C^{-1.65}H_2$), 46.4 ($C^{-3.59}H_2$), 118.2 ($C^{-6.76}H$), 121.5 (quat. C), 144.9 (quat. C) and 168.5 (C=O); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.65 (br, 12 H, CH_2), 3.59 (br, 8 H, $N–CH_2$) and 6.67 (s, 2 H, ArH); *m/z* (electron impact) 332 (14%, M^+), 221 (28%), $M^+ - CONC_5H_{10}$), 84 (100%, $C_5H_{10}N^+$); HRMS calc. for $C_{18}H_{24}N_2O_4$ 332.1736, found 332.1735.

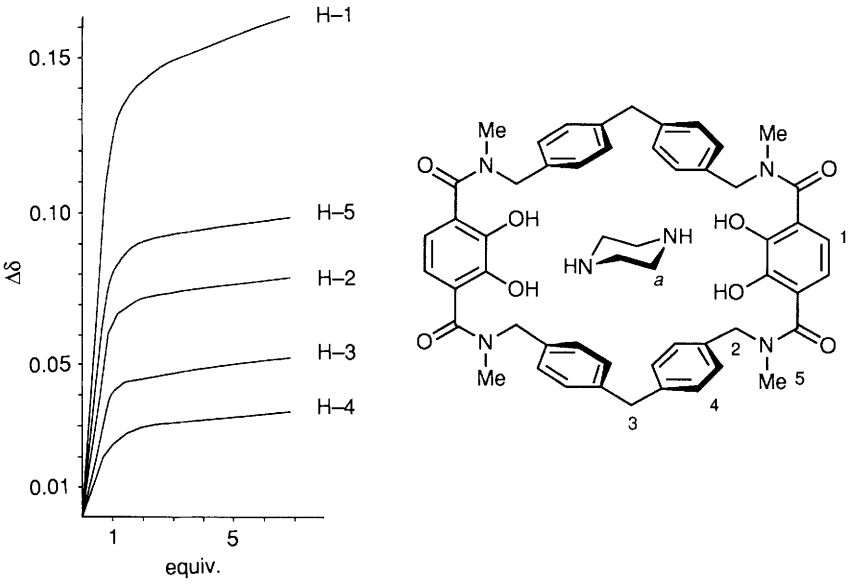

Fig. 1 ^{1}H NMR titration curves. A solution of the guest (G) (10^{-5} mol in 20 mm^3) was added to a solution of host (H) **4b** (10^{-5} mol in 0.5 cm^3; 2 × 10^{-2} mol dm^{-3}) in the same solvent ($CDCl_3$). The change of volume, *e.g.* from H:G = 1:0 to H:G = 1:2 amounts to 40 mm^3 (= 8%) and was neglected. ^{1}H NMR studies at 250 MHz supported the assumption that there is no self-association of the amines under the conditions of these experiments.

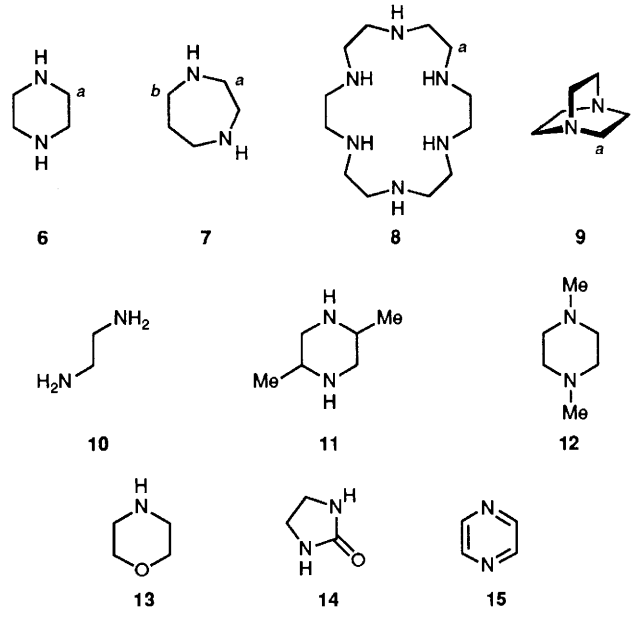

Table 1 Interactions of host **4b** with guest type compounds **6–9**

Substrate	Chemical shifts (Δδ) of host (H-1 to H-5) and guest (*a* and *b*) protons[a]	
	Host protons	Guest protons
Piperazine **6**	1, −0.16; 2, −0.08; 3, −0.05; 4, −0.03; 5, −0.10	*a*, −0.16
1,4-Diazacycloheptane **7**	1, −0.21; 2, −0.09; 3, −0.06; 4, −0.04; 5, −0.12	*a*, −0.18 *b*, −0.08
Hexacyclen **8**	1, −0.34; 2, −0.15; 3, −0.05; 4, −0.07 5, −0.12	*a*, −0.22[b]
DABCO **9**	1, −0.06; 2, −0.05; 3, −0.03; 4, 0; 5, −0.05	*a*, +0.15

[a] In ppm; + downfield, −upfield. [b] ^{1}H NMR signals are broadened.

upfield shift of 0.22 ppm occurs. We conclude that this guest is bound with one NH–$(CH_2)_2$–NH unit and its other parts interact with the aromatic units of the host **4b**.

Ethylenediamine **10** as guest led to salt-type precipitates. The biological relevant nucleic bases[2] are sparingly soluble in $CDCl_3$, so that comparable NMR titration experiments were not possible.

In conclusion the new synthetic receptor molecule **4b** exhibits selectivity in its interactions with piperazine **6** and related amines.

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