Synthesis and physical properties of novel guanidine containing molecular clips. Strong host-guest binding and formation of a lyotropic liquid crystalline phase

Gerben T. W. Gieling,^a Hans W. Scheeren,^{*a} Randy Israël^b and Roeland J. M. Nolte^{*a}

^a Department of Organic Chemistry, NSR Center, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands ^b Crystallography Laboratory, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands

New guanidine containing molecular clips are described which show a high affinity ($K_a = 25\,000 \text{ dm}^3 \text{ mol}^{-1}$) for aromatic guest molecules; they aggregate to form scrolls when suspended in 1 mol dm⁻³ HCl.

The complexation of neutral molecules by synthetic receptors is a topic of great current interest in supramolecular chemistry.¹ Diphenylglycoluril based molecular clips of type 1 have been shown to be excellent hosts for neutral aromatic guest molecules. Especially dihydroxybenzenes, e.g. resorcinol and 2,7-dihydroxynaphthalene, display a high affinity for host compound 1.2 The main binding sites in the clips are the urea carbonyl oxygen atoms which form hydrogen bonds with the hydroxy groups of the guests. Apart from this interaction, π stacking between the cavity wall of 1 and the guest has been shown to influence the binding strength.2b We expected that transforming the urea functions in 1 into other groups would be an obvious way to modify the complexation behaviour of the clips. Guanidine functions are structurally related to urea and are known to be very strong bases.³ Replacing the urea function by a guanidine group should, therefore, increase the affinity of the clips towards hydroxybenzene guests. A further advantage is that a guanidine group could provide additional possibilities for functionalizing the clips. Its basicity can be controlled by variations in the substituent R (see Scheme 1). Furthermore, on the basis of previous results with basket shaped molecules derived from the clips,⁴ it would be of interest to determine whether lyotropic liquid crystal behaviour can be induced in these simple clip molecules by the attachment of a long aliphatic chain to the guanidine group. This will create the possibility to incorporate the receptor molecules in aqueous bilayer systems. In this communication we report the results of experiments which were performed in this respect.

Initial attempts to replace the urea oxygen atoms of 1 by sulfur or nitrogen atoms by thiation using P_2S_5 or similar reagents, and by alkylation at oxygen (the first required step for replacement with nitrogen) were unsuccessful. It was possible however to synthesize clip 2 from thiourea and benzil in 60% overall yield *via* a route analogous to that published for clip 1.⁵ Only one of the thiourea groups of 2 was alkylated using one of the powerful alkylating reagents methyl triflate (MeOSO₂CF₃) or triethyloxonium tetrafluoroborate (Et₃OBF₄). Compound 3



Scheme 1 Reagents and conditions: i, $MeOSO_2CF_3$ (1 equiv.), CH_2Cl_2 , 16 h; ii, H_2O-Et_3N , 15 min, 84%; iii, $MeOSO_2CF_3$ (1 equiv.), CH_2Cl_2 , 16 h; iv, H_2NR , 15 min, 60–90%

was prepared by treating 2 with methyl triflate, followed by reaction with water and a base. A similar monoalkylation of 2 and subsequent reaction with ammonia or a primary amine provided compounds 4. Using similar procedures clips 5 can be synthesized from 3 in 60–90% yield depending on the substituent R (Scheme 1).† Full experimental details will be reported in a forthcoming paper.

It was possible to obtain crystals of **4b** suitable for X-ray analysis by the slow diffusion of hexane into a chloroform solution of this compound. Refinement of the data to an R value of 0.114 resulted in the structure shown in Fig. 1, which proves that changing the binding sites does not alter the overall shape of the clip molecules.⁶‡ The unit cell contains four molecules of **4b** and two molecules of chloroform. The former are present as two pairs (A and B) having slightly different conformations. The most important difference is the twist in the skeleton, as expressed by the Ph–C–C–Ph torsion angle, which is 24.0° in conformer A and 14.0° in conformer B. In the crystal structure of compound 1 this angle is 22.0°. The centres of the cavity walls are at a distance of 6.84 Å in conformer A and 6.94 Å in conformer B (6.67 Å in compound 1).

The binding properties of hosts 2–5 for the reference guest resorcinol were evaluated by ¹H NMR titrations in chloroform using the H_2 and $H_{4,6}$ resorcinol hydrogens as a probe. The results are presented in Table 1. The association constant of the



Fig. 1 X-ray structure showing two views of conformation A of compound 4b. Hydrogen atoms have been omitted for clarity.

Table 1 Association constants of complexes between various clips and resorcinol^{α}

Clip	$K_a/dm^3 mol^{-1b}$	
1	2600 ^c	
2	50	
3	750	
4a	4500	
5a	25000	

^{*a*} In chloroform, T = 25 °C. ^{*b*} Estimated errors: 20% for 1 and 2, 10% for 3 and 4a, and 50% for 5a. ^{*c*} Value taken from ref. 2*c*.



Fig. 2 (a) Electron micrograph of a dispersion of 4d (0.2 mass%) in 1 mol dm⁻³ HCl, (left) negative staining, (right) platinum shadowing; (b) Proposed arrangement of the clip molecules in a multi-bilayer of 4d

complex between **5a** and resorcinol was very high ($K_a = 25\,000$ dm³ mol⁻¹).§ This is a 10-fold increase compared with the value of $K_a = 2600$ dm³ mol⁻¹ found for the complex of **1** with resorcinol. The guanidine function of **5a** probably deprotonates the resorcinol to give an ion pair. As expected clip **2** had a low association constant, $K_a = 50$ dm³ mol⁻¹, and the K_a value for clip **3** was found to lie in between the values of clip **1** and **2**, $K_a = 750$ dm³ mol⁻¹. The relatively high association constant measured for clip **4a** indicates that the guanidine group more than compensates for the loss of binding energy which results from the replacement of urea by the thiourea group.

The aggregation behaviour of compounds 4d and 5d was then studied. A sample of these clip molecules was suspended in aqueous 1 mol dm⁻³ HCl and electron micrographs were taken by the negative staining/platinum shadowing technique. Both compounds were found to give multi-bilayer sheets which roll up to form scrolls [Fig. 2(a)]. This result is remarkable given the unusual structure of the amphiphilic clip molecules. Electron diffraction experiments proved that the observed structures were aggregates and not crystals (clip 4c, which forms crystals when treated in the same manner, was used as a reference sample). A sample of clip 4d was prepared in the same way as for electron microscopy and then evaporated to dryness to determine the bilayer thickness. The resulting powder was analysed by X-ray powder diffraction. The data revealed a repetitive distance of 40 Å. This result can be explained reasonably if it is assumed that the aliphatic tails of 4d have an intercalated structure. The clips are probably packed as shown in Fig. 2(b) since the positively charged nitrogen centres will prefer to be as close as possible to the water surface. The parallel orientation of the cavity containing head-groups will ensure the closest packing possible with intercalating tails. In the arrangement shown the opposing clips can self associate to form a multilayer.⁷ The reason why this multilayer rolls up to form a scroll is, as yet, unknown. Local deficiencies of counterions or distortions in the packing of the clip molecules may be a possible reason.

Footnotes

† Selected spectroscopic data for **2**: ¹H NMR (CDCl₃, 400 MHz, 25 °C) δ 7.06 (m, 6 H), 6.97 (m, 4 H), 6.72 (s, 4 H), 6.12 (d, 4 H, ²J 15.7 Hz), 4.11

(d, 4 H, ^{2}J 15.7 Hz), 3.82 (s, 12 H); FABMS m/z = 651 (M + 1+, 100%). For 3: 1H NMR (CDCl₃, 400 MHz, 25 °C) & 7.10-6.98 (m, 10 H), 6.65 (d, 2 H, ²J 9.1 Hz), 6.62 (d, 2 H, ²J 9.1 Hz), 6.14 (d, 2 H, ²J 15.7 Hz), 5.56 (d, 2 H, ²J 15.9 Hz), 4.04 (d, 2 H, ²J 15.7 Hz), 3.86 (d, 2 H, ²J 15.9 Hz), 3.80 (s, 6 H), 3.75 (s, 6 H); FABMS $m/z = 635 (M + 1^+, 100\%)$. For 4a; ¹H NMR (CDCl₃, 400 MHz, 25 °C) δ 7.00 (m, 10 H), 6.31 (d, 2 H, ²J 9.2 Hz) 6.60 (d, 2 H, ²J 9.2 Hz), 6.03 (d, 2 H, ²J 15.6 Hz), 5.19 (d, 2 H, ²J 15.8 Hz), 4.15 (d, 2 H, ²J 15.6 Hz), 4.15 (d, 2 H, ²J 15.8 Hz), 3.77 (s, 6 H), 3.75 (s, 6 H), the NH signal could not be found; FABMS $m/z = 634 (M + 1)^+$, 100%. For 4b: ¹H NMR (CDCl₃, 90 MHz, 57 °C) δ 6.94 (s, 10 H), 6.66 (s, 4 H), 6.08 (d, 2 H, ²J 15 Hz), 5.10 (d, 2 H, ²J 14 Hz), 4.30 (2 d, 4 H, ²J 15 Hz), 3.80 (s, 6 H), 3.77 (s, 6 H), 3.41 (s, 3 H); FABMS $m/z = 648 (M + 1^+, 100\%)$. For 4c: ¹H NMR (CDCl₃, 90 MHz, 57 °C) & 7.0 (s, 10 H), 6.63 (s, 4 H), 6.12 (d, 2 H, ²J 16 Hz), 5.2 (d, 2 H, ²J 17 Hz), 4.24 (d, 2 H, ²J 17 Hz), 4.18 (d, 2 H, ²J 16 Hz), 3.75 (s m, 14 H), 1.5 (m, 2 H), 0.95 (t, 3 H, ³J 15 Hz); EIMS $m/z = 689 (M^+, 100\%)$. For 4d: ¹H NMR (CDCl₃, 90 MHz, 57 °C) δ 6.96 (s, 10 H), 6.64 (s, 4 H), 6.13 (d, 2 H, ²J 15 Hz), 5.2 (d, 2 H, ²J 15 Hz), 4.24 (d, 2 H, ²J 15 Hz), 4.18 (d, 2 H, ²J 15 Hz), 3.79 (s, 6 H), 3.77 (s, 6 H), 3.66 (t, 2 H) 1.31 (bs, 24 H), 0.91 (t, 3 H, ${}^{3}J$ 15 Hz); CIMS m/z = 829 (M⁺, 100%). For 5a: ¹H NMR (CDCl₃, 400 MHz, 25 °C) & 7.04 (m, 10 H), 6.47 (d, 2 H, 2J 8.8 Hz) 6.45 (d, 2 H, 2J 8.8 Hz), 5.52 (d, 2 H, 2J 15.9 Hz), 5.31 (d, 2 H, ²J 15.8 Hz), 3.92 (d, 2 H, ²J 15.8 Hz), 3.82 (d, 2 H, ²J 15.8 Hz), 3.72 (s, 6 H), 3.68 (s, 6 H), the NH signal could not be found; FABMS m/z = 618(M + 1)+, 100%. For 5c: ¹H NMR (CDCl₃, 400 MHz, 55 °C) & 7.05 (bs, 10 H), 6.64 (d, 2 H, ³J 9.0 Hz), 6.60 (d, 2 H, ³J 9.0 Hz), 5.54 (d, 2 H, ²J 15.9 Hz), 5.36 (d, 2 H, ²J 15.7 Hz), 4.00 (bs, 2 H), 3.84 (d, 2 H ²J 15.9 Hz), 3.76 (s, 6 H), 3.73 (s, 6 H), 3.65 (t, 2 H, ³J 7.0 Hz) 1.48 (m, 2 H), 1.34 (m, 2 H), 0.92 (t, 3 H, ${}^{3}J$ 7.3 Hz); EIMS m/z = 673 (M⁺, 100%). For 5d: ${}^{1}H$ NMR (CDCl₃, 90 MHz, 57 °C) & 7.00 (s, 10 H), 6.63 (s, 4 H), 5.55 (d, 2 H, ²J 14 Hz), 5.39 (d, 2 H, ²J 16 Hz), 4.04 (d, 2 H, ²J 13 Hz), 3.95 (d, 2 H, ²J 16 Hz), 3.78 (s, 6 H), 3.74 (s, 6 H), 3.66 (t, 2 H) 1.34 (bs, 24 H), 0.92 (t, 3 H, 3J 15 Hz); FABMS m/z = 814 (M + 1⁺, 100%). All compounds gave satisfactory elemental analysis.

‡ Crystal data for **4b**: C₇₅H₇₅N₁₀O₈S₂Cl₃, M = 1414.96, crystal size = 0.31 × 0.16 × 0.11 mm, space group $P\bar{1}$, triclinic, a = 13.5402(7), b = 14.6630(16), c = 18.8913(16) Å, $\alpha = 83.953(8)$, $\beta = 87.081(8)$, $\gamma = 67.454(9)^{\circ}$; Cell volume = 3444.5(6) Å³, z = 2; $D_c = 1.364$ g cm⁻³; radiation Mo-Kα, 0.71073 Å; T 208 K; preliminary R = 0.090 for $F > 6\sigma$. Full details will be reported elsewhere.⁶

§ NMR titrations were performed as described in reference 2c.

References

1 For an overview of the complexation of neutral guest molecules by different hosts see: R. M. Izatt, J. S. Bradshaw, K. Pawlak, R. L. Bruening and B. J. Tarbet, *Chem. Rev.*, 1992, **92**, 1261; R. Liu and W. C. Still,

Tetrahedron Lett., 1993, **34**, 2573; M. M. Conn, G. Deslongchamps, J. de Mendoza and J. Rebek, J. Am. Chem. Soc., 1993, **115**, 3548; B. J. Whitlock and H. W. Whitlock, J. Am. Chem. Soc., 1994, **116**, 2301.

- 2 (a) R. P. Sijbesma and R. J. M. Nolte, J. Org. Chem., 1991, 56, 3122;
 (b) R. P. Sijbesma, A. P. M. Kentgens and R. J. M. Nolte, J. Org. Chem., 1991, 56, 3199; (c) R. P. Sijbesma, A. P. M. Kentgens, E. T. G. Lutz, J. H. van der Maas and R. J. M. Nolte, J. Am. Chem. Soc., 1993, 115, 8999.
- 3 Y. Yamamoto and S. Kojima, in *The Chemistry of Amidines and Imidates*, ed. S. Patai and Z. Rappoport, Wiley-Interscience, Chichester, 1991, vol. 2, p. 505.
- 4 In other papers we have described the aggregation behaviour of azacrown ether modified clips: J. L. M. van Nunen, R. S. A. Stevens, S. J. Picken and R. J. M. Nolte, J. Am. Chem. Soc., 1994, **116**, 8825;

A. P. H. J. Schenning, B. de Bruin, M. C. Feiters and R. J. M. Nolte, Angew. Chem., 1994, **106**, 1741; Angew. Chem., Int. Ed. Engl., 1994, **33**, 1662.

- 5 R. P.Sijbesma and R. J. M. Nolte, *Recl. Trav. Chim. Pays-Bas*, 1993, **112**, 643.
- 6 R. Israël, K. L. Beurskens, G. T. W. Gieling, R.J. M. Nolte, J. M. M. Smits, P. T. Beurskens, manuscript in preparation.
- 7 Self-association was recently found to occur in many of our clip molecules. A. E. Rowan, J. N. H. Reek and R. J. M. Nolte, unpublished results.

Received, 19th July 1995; Com. 5/04737D