Synthesis of novel unsymmetrical molecular clips derived from glycoluril

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Four novel unsymmetrical molecular clips derived from glycoluril have been designed and synthesised and the structure and conformation of one was also confirmed by single crystal X-ray diffraction.

Keywords: glycoluril, unsymmetrical, molecular clip

The design and synthesis of novel receptors with different molecular cavities is one of the major challenges in host-guest chemistry.[1] Glycoluril is an important building block for supramolecular chemistry and its have been used as the basis for various molecular clips.[2-5] Most molecular clips based on glycoluril were derived from benzene, hydroquinone and their derivatives. They possess suitable symmetry with aromatic walls and show good binding properties for aromatic guests especially for dihydroxybenzene by hydrogen bonding, π–π stacking interactions and a so-called "cavity-effect".[6,7] However, molecular clips derived from glycoluril with two different sidewalls are still rare.[8,9] In the present work, we report the synthesis of novel unsymmetrical molecular clips derived from glycoluril.

The synthesis of title unsymmetrical clip molecules **10a–d** is shown in Scheme 1. The structure and conformations of compound **10d** was also elucidated by single crystal X-ray diffraction.

Crystals of **10d** were obtained by slow evaporation of a solution in chloroform/methanol mixtures. Analysis of the structure shows that in the crystal the asymmetric unit contains two independent molecules A and B (Fig. 1). There are some slight differences in their structures and conformations. In molecule A, the distance between the carbonyl oxygens (O_2–O_3) of the glycoluril ring amounts to 5.363 Å, the dihedral angle between two phenyl rings of the sidewalls is 35.74°, and the distance between the centroids of two phenyl rings of the sidewalls is 6.766 Å. In molecule B, the distance between the carbonyl oxygens(O_5–O_6) of glycoluril ring amounts to 5.415 Å, the dihedral angle between two phenyl rings of the sidewalls is 34.14°, and the distance between the centroids of two phenyl rings of the sidewalls is 6.593 Å.

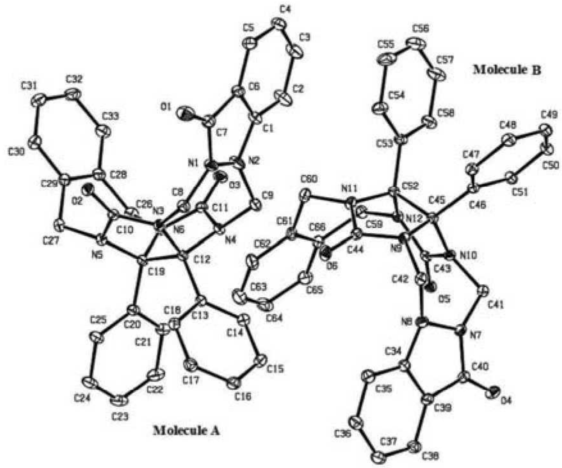
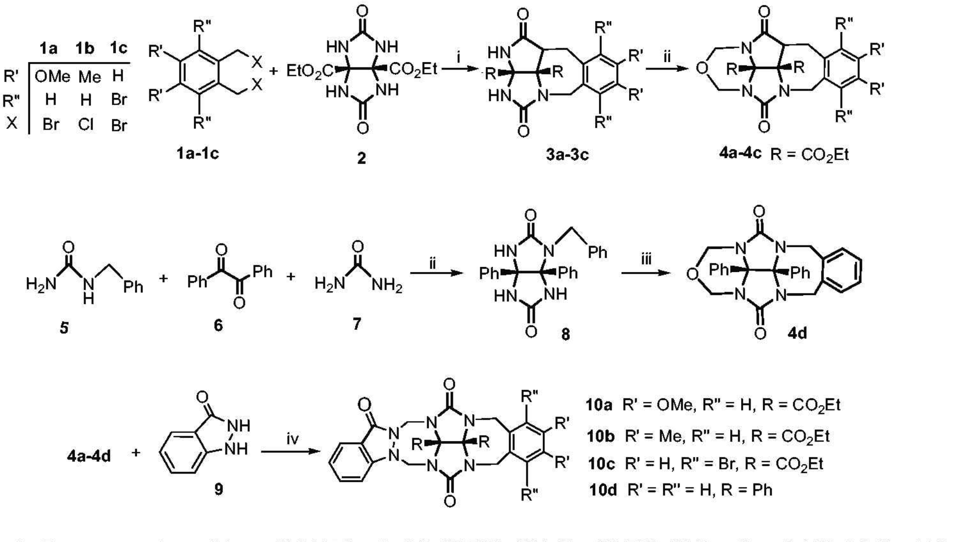


Fig. 1 The crystal structure of 10d, solvent molecules omitted for clarity.

In conclusion, four new unsymmetrical clip molecules derived from glycoluril were designed and synthesised. The structure and conformation of **10d** was also confirmed by single crystal X-ray diffraction. Further studies on their molecular recognition are in progress.



Scheme 1 Reagents and conditions: (i) DMSO, *t*-BuOK; (ii) TFA, $(CH_2O)_n$; (iii) TFA, PhH, reflux; (iv) $MeSO_3H$, 80 °C.

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Experimental

General

All reagents obtained from commercial sources were of AR grade. Melting points was determined with XT4A micromelting point apparatus and were uncorrected. The ^1H NMR spectra were recorded on a Mercury Plus-400 spectrometer with TMS as internal reference and $CDCl_3$ and DMSO-d_6 as solvent. IR spectra were recorded on a Perkin–Elmer PE-983 IR spectrometer as KBr pellets with absorption in cm^{-1}. MS were obtained with Finnigan Trace MS instrument using EI method. Elemental analyses were carried out on a Vario EL III instrument.

Synthesis

Diethoxycarbonyl glycoluril **2**,[10] glycoluril cyclic ether **4a–d**[11,12] were prepared by the literature method.

General procedure for preparation of **10a–d**

Anh. $MeSO_3H$ (10 mL) was added to a flask containing compound **9** (0.18 g, 1.37 mmol), and the mixture was stirred at 80 °C until homogeneous. Compound **4** (1.37 mmol) was added in one portion and the flask was sealed and heated at 80 °C for 3 h. The reaction mixture was allowed to cool and then poured into water (100 mL). The pale precipitate was collected by filtration through a medium fritted funnel and washed with water (50 mL) and dried under vacuum, flash chromatography gave compound **10** as white solid. The physical and spectra data of the compounds **10a–d** are as follows.

10a: M.p.270–272 °C; IR(KBr,cm^{-1}): 3445, 2955, 1731, 1685, 1653, 1456, 1424, 1270, 1142, 1105. ^1H NMR(400 MHz, $CDCl_3$): δ_H 7.79–7.77(m, 1H, ArH), 7.57(m, 1H, ArH), 7.32–7.20(m, 2H, ArH), 6.85–6.82(m, 2H, ArH), 5.80–5.76(m, 1H, NCH), 5.62–5.58(m, 1H, NCH), 4.94(d, 1H, NCH_2), 4.90–4.84(m, 2H, NCH_2), 4.80–4.75(m, 2H, NCH_2), 4.56–4.52(m, 1H, NCH_2), 4.31–4.29(m, 4H, $C\underline{H}_2CH_3$), 3.85(s, 6H, OCH_3), 1.38–1.33(m, 6H, $OCH_2C\underline{H}_3$). EI-MS: *m/z* 607 $[M + H]^+$. Anal. Calcd for $C_{29}H_{30}N_6O_9$ (606.21): C, 57.42; H, 4.99; N, 13.85. Found: C, 57.1; H, 4.88; N, 13.27%.

10b: M.p.250–252 °C; IR(KBr, cm^{-1}): 3429, 3021, 2987, 1734, 1649, 1558, 1461, 1419, 1252, 1148, 1017. ^1H NMR(400 MHz, $CDCl_3$): δ_H 7.78–7.61(m, J = 7.6 Hz, 1H,ArH), 7.57–7.54(m, J = 7.6 Hz, 1H, ArH), 7.31–7.08(m, 4H, ArH), 5.76(d, J = 12.8 Hz, 1H, NCH), 5.58(d, 1H, NCH), 4.98(d, J = 12.8 Hz, 1H, NCH), 4.83–4.77(m, 2H, NCH_2), 4.55–4.50(m, 1H, NCH), 4.40–4.32(m, 2H, NCH_2), 4.31–4.29(m, 4H, J = 3.6 Hz, OCH_2),2.18(s, 6H, $ArCH_3$), 1.38–1.32(m, 6H, J = 3.6 Hz, $OCH_2C\underline{H}_3$). EI-MS: *m/z* 575 $[M + H]^+$. Anal. Calcd for $C_{29}H_{30}N_6O_7$ (574.22): C, 60.62; H, 5.26; N, 14.63. Found: C, 60.33; H, 5.08; N, 14.37%.

10c: M.p. 218–220 °C; IR(KBr,cm^{-1}): 3445, 2996, 1736, 1682, 1620, 1459, 1423, 1255, 1150, 1016. ^1H NMR(400 MHz, $CDCl_3$): δ_H 7.80–7.78(m, 1H, ArH), 7.61–7.59(m, 1H, ArH), 7.37–7.21(m, 4H, ArH), 5.71(d, J = 16.4 Hz, 1H, NCH), 5.65–5.52(m, 3H, NCH), 5.07(m, 1H, NCH), 4.50(d, J = 16.4 Hz, 1H, NCH), 4.40–4.32(m, 2H, NCH_2), 4.30–4.25(m, 4H, OCH_2)1.39–1.33(m, 6H, $OCH_2C\underline{H}_3$). EI-MS: *m/z* 706 $[M + 4H]^{4+}$. Anal. Calcd for $C_{27}H_{24}Br_2N_6O_7$ (702.01): C, 46.04; H, 3.43; N, 11.93. Found: C, 45.89; H, 3.28; N, 11.79%.

10d: M.p. >300 °C; IR(KBr, cm^{-1}): 3428, 2924, 1730, 1713, 1674, 1620, 1461, 1429, 1261, 1151, 1105; ^1H NMR(400 MHz, DMSO-*d*6): δ_H 7.54(d, J = 1.6 Hz, 1H, ArH), 7.52(d, J = 1.6 Hz, 1H, ArH), 7.40–7.04 (m, 16H, ArH), 6.16 (d, J = 14.8 Hz, 1H, NCH), 5.86 (d, J = 14.8 Hz, 1H, NCH), 4.80–4.60 (m, 4H, NCH_2), 4.24–4.22 (m, 2H, NCH_2). ESI-MS: *m/z* 593.0 $[M + K]^+$, 577.3 $[M + Na]^+$, 555.5 $[M + H]^+$. Anal. Calcd for $C_{33}H_{26}N_6O_3$ (554.21): C, 71.47; H, 4.73; N, 15.15. Found: C, 70.93; H, 4.48; N, 15.02%.

X-ray diffraction study of compound **10d**

Crystals were obtained by slow evaporation from chloroform–methanol solution (20:1 v/v). A yellow crystal of the title compound **10d** having approximate dimensions of 0.30 mm × 0.26 mm × 0.18 mm was mounted on a glass fibre in a random orientation at 292(2) K. The determination of unit cell and the data collection were performed with MoKα radiation ($\lambda = 0.71073$ Å) on a Bruker Smart Apex-CCD diffactometer with a ψ-ω scan mode. A total of 16 556 reflections were collected in the range of $1.89<\theta<25.00^\circ$ at room temperature, and 9782 were independent ($R_{int} = 0.0288$), of which 6305 observed reflections with $I>2\sigma(I)$ were used in the structure determination and refinements. The structure was solved by direct methods with SHELXS-97 program and expanded by Fourier technique. The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were determined with theoretical calculation. A full-matrix least-squares refinement gave the final $R = 0.0599$, $wR = 0.1582$. All calculations were performed on a PC with SHELXS-97 program. *Crystal data*: $C_{66}\ H_{54}\ N_{12}\ O_8$, $M = 1143.21$, Triclinic, space group P-1, $a = 11.3011(9)$, $b = 14.9057(12)$, $c = 18.8130(15)$ Å, $\alpha = 68.151(2)^\circ$, $\beta = 74.480(2)^\circ$, $\gamma = 77.1380(10)^\circ$, $V = 2807.2(4)$Å^3, $Z = 2$, $D_c = 1.352$ g cm^{-3}, $\mu = 0.092$ mm^{-1}. The details of the crystal data have been deposited with Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC 734384.

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