LETTER

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# Facile synthesis of novel macrocyclic polyamines derived from diphenylglycoluril†

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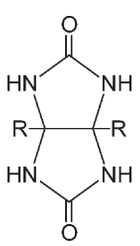
**Three novel macrocyclic polyamines and an unexpected macrocycle have been synthesized by the one-step condensation of diethylenetriamine (or triethylenetetraamine) with formaldehyde and rigid diphenylglycoluril. The X-ray crystal structure of the unexpected macrocycle is provided.**

Macrocyclic polyamines not only can act as host molecules for binding transition metal ions and heavy metal ions,[1] but also have been studied widely as anion hosts by a number of researchers.[2] Recently, many studies have been focused on metal complexes of macrocyclic polyamines, which cleave phosphodiesters, RNA, DNA, dipeptides and proteins.[3]

The rigid concave shape of glycoluril (**1**), coupled with the facile tetrafunctionalization of its ring nitrogen atoms and the availability of two urea carbonyl hydrogen bond acceptors, makes it a versatile progenitor on which to build synthetic host molecules. Many macrocyclic receptor units based on glycoluril have been used as the basis for molecular capsules, molecular clips, self-complementary facial amphiphiles,[4] and the synthesis of the cucurbit[*n*]uril (CB[*n*]) family.[5]




**1a** R = H
**1b** R = $CH_3$
**1c** R = Ph

Many synthetic routes have been developed to prepare macrocyclic polyamines. Martell and coworkers reported the synthesis of macrocyclic and macrobicyclic Schiff bases by condensation of dialdehydes with diamines, subsequent hydrogenation of the Schiff bases provides the corresponding binucleating polyaza macrocyclic ligiands.[6] Earlier, Mock *et al.* reported the formation of hexacyclic rings from **1a** (1 equiv.), formaldehyde (6 equiv.) and alkanediamines (ethane through butane; 2 equiv.), but the ring in these compounds is too small to bond guest molecules or ions.[7] Based on their elegant work, we have designed a one-step condensation procedure to synthesize a novel kind of [2 + 2] macrocyclic polyamines derived from diphenylglycoluril. The X-ray crystal structure of an unexpected macrocycle is provided.

Slow addition of diethylenetriamine **2** to a refluxing mixture of diphenylglycoluril and formaldehyde in methanol yielded a pale yellow solution. The normal product **5a** (Scheme 1) was obtained in 42% yield after separation by silica gel column chromatography. The structure of **5a** was clearly confirmed by its NMR data ($^1$H, $^{13}$C given below) and the electrospray ionisation (ESI) mass spectra (see the Electronic supplementary information). The $^1$H NMR spectrum of **5a** in $CDCl_3$ displays one pair of well-defined doublets for methylene protons (derived from formaldehyde) at $\delta$ 4.95 and 3.95 ($J$ = 15 Hz). However, an unexpected macrocyclic polyamine **5b** was also obtained in 6% yield from the mixture. Its crystal structure is shown in Fig. 1 and Fig. 2. When substituting tris(2-aminoethyl)amine for **2**, we did not find any **5b** in the reaction mixture.

The new synthesis appears to have some generality. An analogous structure (**6**) was obtained employing 2,2′-methyliminodiethylamine **3**[8] and formaldehyde with **1c** in a good yield of 76%. A bigger cyclic polyamine **7** was separated in 24% yield when employing triethylenetetramine **4**; no [1 + 1] macrocyclic polyamine was detected by mass spectral analysis of the crude reaction mixture. Unfortunately, when substituting **1a** or **1b** for **1c**, we found that this reaction could not be carried out.

As for the details of the assembly mechanism of **5a**, **6** and **7**, we surmise that these reactions are general Mannich reactions (Scheme 2).[9] Since amino groups are rather more nucleophilic than are the urea nitrogens of **1c**, the intermediate **8** forms initially and subsequently condenses with **1c** (which slowly dissolves as the reaction proceeds) to yield the intermediate **9**. Then the process repeats itself again to yield the ultimate product.

Preliminary transition metal cation binding studies were undertaken using ESI-MS.[10] The results showed macrocyclic polyamine **6** could bind two metal $Ni^{2+}$ ions ($m/z$ = 1035.3 for $[M + 2Ni]^+$ and 518.3 for $[M + 2Ni]^{2+}$) while the peak for the binding one metal $Ni^{2+}$ ion was not observed (see Electronic supplementary information).

In summary, we have described a facile synthesis of a novel kind of [2 + 2] macrocyclic polyamines by a straightforward condensation of diamines with formaldehyde and rigid diphenylglycoluril. We know that due to the presence of the polarized carbonyl groups, cucurbit[*n*]urils can form complexes by ion-dipole interactions with cationic substances[4f,5f,11] and azamacrocycles also have been used as host molecules for binding

† Electronic supplementary information (ESI) available: ESI mass spectra of **5a**, **6**, alone and with added $Ni(CH_3COO)_2$, and **7**. See http://www.rsc.org/suppdata/nj/b4/b400123k/

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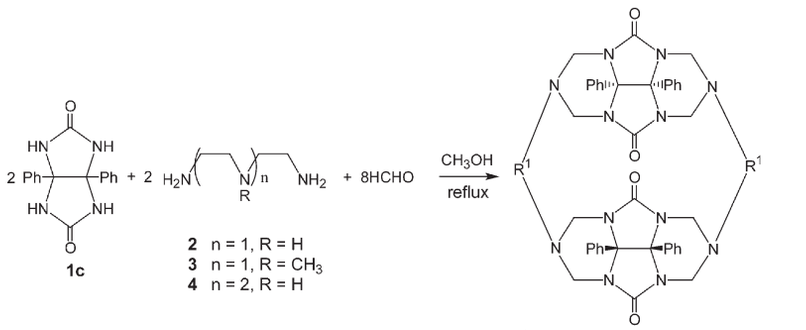



**Scheme 1**

cationic ions due to the presence of electron-rich nitrogen atoms. These new macrocycles combine the binding ability of glycoluril derivatives with those of aza macrocycles, which is expected to result in novel molecular recognition properties. Research into their metal complexes and their complexation with a variety of guest molecules is in progress.

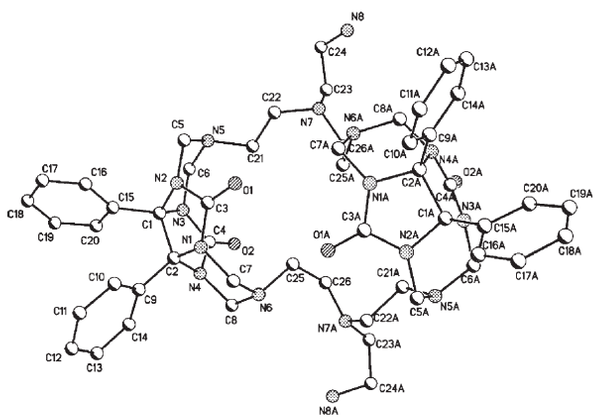


**Fig. 1** The molecular structure **5b** (hydrogen atoms deleted for clarity).

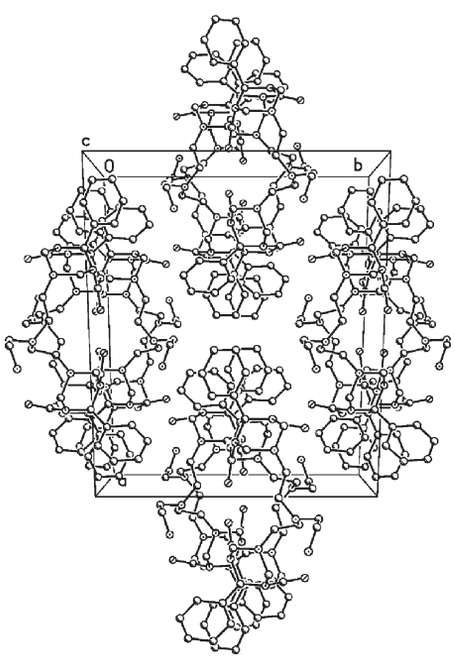



**Fig. 2** View of the packing along the *c* axis of compound **5b**.

## Experimental

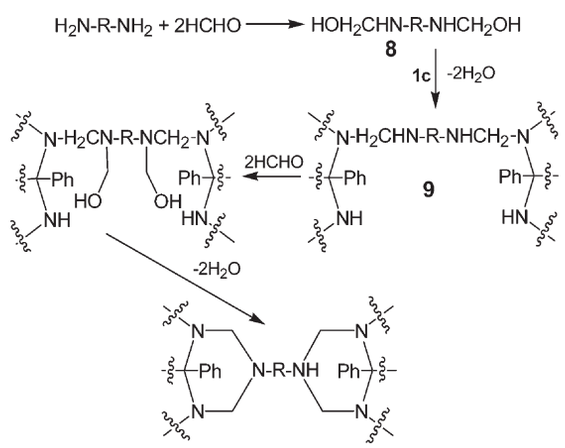
$^1$H NMR spectra were recorded on Mercury VX-300 (Varian, 300 MHz) and Inova-600 (Varian, 600 MHz) spectrometers. The solvent used was $CDCl_3$ with TMS serving as internal standard. ESI-MS measurements were performed on a Thermo Finnigan LCQ Deca XP at room temperature. FAB-MS measurements were carried out on a Finnigan MAT 95 mass spectrometer.

### Typical procedure for the preparation of the novel macrocyclic polyamines

A suspension of diphenylglycoluril (10 mmol) in 37% aqueous formaldehyde (6 mL) and 120 mL methanol was brought to reflux with magnetic stirring. To the mixture was added slowly a solution of diamine (20 mmol) in 60 mL methanol dropwise (over 3 h). Then refluxing was continued overnight. The solvent was removed under reduced pressure. The yellow oily mixture was dissolved in $CHCl_3$ (30 mL), then washed with $H_2O$. The organic extract was dried over $Na_2SO_4$ and concentrated under reduced pressure. The product was separated by silica gel column chromatography (methanol: chloroform = 1:2).

**5a.** $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.03–7.15 (m, 20H), 4.95 (d, 8H, $J$ = 15.0 Hz), 3.95 (d, 8H, $J$ = 15.0 Hz), 2.95 (t, 8H, $J$ = 12.6 Hz), 2.84 (t, 8H, $J$ = 12.6 Hz). $^{13}$C NMR ($CDCl_3$, 300 MHz): $\delta$ = 160.51, 133.53, 128.94, 128.50, 127.91, 81.29, 60.51, 51.60, 48.04. ESI-MS: $m/z$ = 913.5 $[M + Na]^+$, 891.4 $[M + H]^+$, 446.3 $[M + 2H]^{2+}$.

**5b.** $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.05–7.16 (m, 20H), 5.08 (d, 8H, $J$ = 13.2 Hz), 4.20 (m, 2H), 4.08 (d, 8H,




**Scheme 2**

$J = 13.2$ Hz), 3.29 (m, 2H), 2.92–3.19 (m, 16H). $^{13}$C NMR ($CDCl_3$, 300 MHz): $\delta = 160.62$, 134.27, 128.85, 128.52, 128.14, 89.27, 80.93, 59.52, 55.35, 49.63, 49.39.

**6.** $^1$H NMR ($CDCl_3$, 600 MHz): $\delta = 7.06$–7.16 (m, 20H), 5.04 (d, 8H, $J = 13.8$ Hz), 4.07 (d, 8H, $J = 13.8$ Hz), 3.04 (t, 8H, $J = 13.8$ Hz), 2.80 (t, 8H, $J = 13.8$ Hz), 2.42 (s, 6H). $^{13}$C NMR ($CDCl_3$, 600 MHz): $\delta = 160.71$, 133.91, 129.00, 128.65, 128.10, 80.99, 59.41, 53.76, 47.20, 43.35. ESI-MS: $m/z = 941.5$ $[M + Na]^+$, 919.5 $[M + H]^+$, 460.3 $[M + 2H]^{2+}$.

**7.** $^1$H NMR ($CDCl_3$, 300 MHz): $\delta = 7.04$–7.16 (m, 20H), 5.06 (d, 8H, $J = 13.5$ Hz), 4.46 (d, 8H, $J = 13.5$ Hz), 2.50–3.09 (m, 24H). $^{13}$C NMR ($CDCl_3$, 300 MHz): $\delta = 160.54$, 133.87, 128.73, 128.46, 127.94, 81.25, 59.15, 56.53, 50.40, 30.44. FAB-MS: $m/z = 1000$ $[M + Na]^+$.

### X-Ray crystallography

A colorless rod-like single crystal with dimensions of $0.5 \times 0.2 \times 0.2$ mm$^3$ was mounted on a Rigaku RAXIS-RAPID X-Ray diffractometer with graphite monochromated Mo-K$\alpha$ radiation ($\lambda = 0.71073$ Å). A total of 22 137 reflections were collected in the range of $2.49° \leq \theta \leq 27.48°$ at 293 K, 5474 were independent ($R_{int} = 0.0480$) and 2269 observed for $I > 2\sigma(I)$. The structure was determined by direct methods (SHELXS97) and successive difference Fourier syntheses. The structure was refined by full-matrix least-squares techniques with anisotropic thermal parameters for all non-hydrogen atoms. All hydrogen atoms (excepted for hydrogen of N8 and N8A) were located theoretically and refined with riding mode position parameters and fixed isotropic thermal parameters (SHELXL97).

**Crystal data for 5b.** $C_{52}H_{64}N_{16}O_4$, $M = 977.20$, monoclinic, space group $C2/c$, $a = 20.736(4)$, $b = 15.807(3)$, $c = 16.385(3)$ Å, $\beta = 116.93(3)°$, $U = 4788.0(17)$ Å$^3$, $Z = 4$, $D_c = 1.356$ g cm$^{-3}$. Final $R1 = 0.0579$ and $wR2 = 0.1435$ (all data).‡

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‡ CCDC reference number 223521. See http://www.rsc.org/suppdata/nj/b4/b400123k/ for crystallographic data in .cif or other electronic format.