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New supramolecular organization for a glycoluril: chiral hydrogen-bonded ribbons

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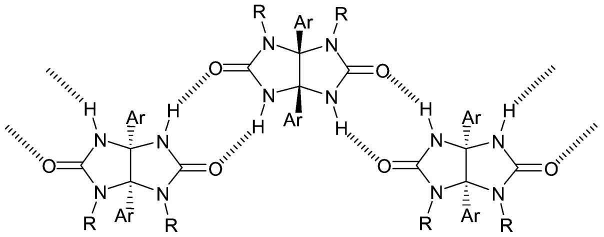
A series of substituted glycoluril molecules exhibits a substantial twist of the fused five-membered rings and assembles exclusively chiral hydrogen-bonded ribbons in the solid-state.

Glycolurils have been the subject of research investigating their use as biotin analogs, fertilizers, bleaching activators, radioiodination agents for biomolecules, psychotropic agents, and catalysts.[1] They have also received attention for their propensity to form varied supramolecular structures arising from the curvature of the fused ring system.[2–6] Despite this intense interest in glycolurils, relatively few crystal structures are known.[1,6–11]

We present a series of three achiral glycolurils (**1**–**3**) that adopt an unusual, severely twisted conformation in the solid state to form chiral hydrogen-bonded ribbons (Fig. 1).†[12] Each glycoluril monomer in this series has only two *syn*-urea N–H groups free for hydrogen bonding. Thus in the solid state structure each monomer is attached to an adjacent glycoluril by two amide N–H to carbonyl oxygen hydrogen bonds (Fig. 1, 2). Such an orientation of monomers forces the *syn*-NH faces of the glycolurils to alternate along the length of the ribbon. Interestingly, the glycoluril is severely twisted about the bridgehead dihedral angle in the ribbon structure resulting in chiral monomers (Fig. 3). This twist gives rise to a stereospecific interaction between adjacent enantiomers—each ribbon consists of identical enantiomers.[13] The dihedral angle between the bridgehead carbons, η,[14] is found to range from 26° to 29° in these structures, which is comparable to the most grotesque twist reported to date where η = 30.5° (Fig. 3).[11]



1: R = PMB, Ar = 4-*t*-BuPh
2: R = PMB, Ar = 4-MePh
3: R = CH_2CO_2Et, Ar = 4-MeOPh

Fig. 1 Chemdraw representation of the ribbon structural motif showing all glycolurils used in this study.

The chemical origin of the twisting of glycolurils has remained elusive, although arguments have been proffered based on either steric interactions or differing electronics of the nitrogen atoms.[1,11,15] The twisting of the glycolurils observed here cannot arise simply from electronic differences between the nitrogens, since they are symmetric. However, the bulky *N*-alkyl groups (*p*-methoxybenzyl or ethyl carboxymethyl) could introduce strain into the glycoluril system, and bridgehead twisting could relieve this putative strain. These glycolurils may also adopt a twisted conformation to maximize separation of the bridgehead phenyls. The closest C_{phenyl}–C_{phenyl} contact in this series is 2.93 Å. While this would explain the observed twisting, it does not account for the absence of twisting in glycolurils with bridgehead methyl groups.[1] In such untwisted glycolurils, the steric repulsion should be at least as great as for the aryl bridgehead case. The twist of the glycoluril does not result from substituent effects of the bridgehead aryl groups, since no systematic variation is observed as the *para* substituent becomes bulkier (methyl to *tert*-butyl) or more electron rich (alkyl to methoxy).

Density Functional Theory (DFT) computational studies were performed to determine if the twisted conformation was the preferred orientation for these glycolurils. All calculations were performed using Jaguar at the B3LYP/6-31G** level.[16] Using twisted glycoluril **2** as a representative example, geometry optimizations were conducted on a series of conformers of **2** varying the constrained dihedral angle η within the range of 0° and 40°, while all other bonds were left unconstrained. These calculations show an energy minimum at η = 22°; the energy of this minimized structure was 2.6 kcal mol^{-1} lower in energy than the untwisted conformer.

The solution structure of these substituted glycolurils was studied by variable temperature (VT) NMR spectroscopy in THF, in which only monomeric species exist. (Due to the low binding constant determined for a model urea, formation of ribbons in non-competitive solvents is unlikely.) Three possible

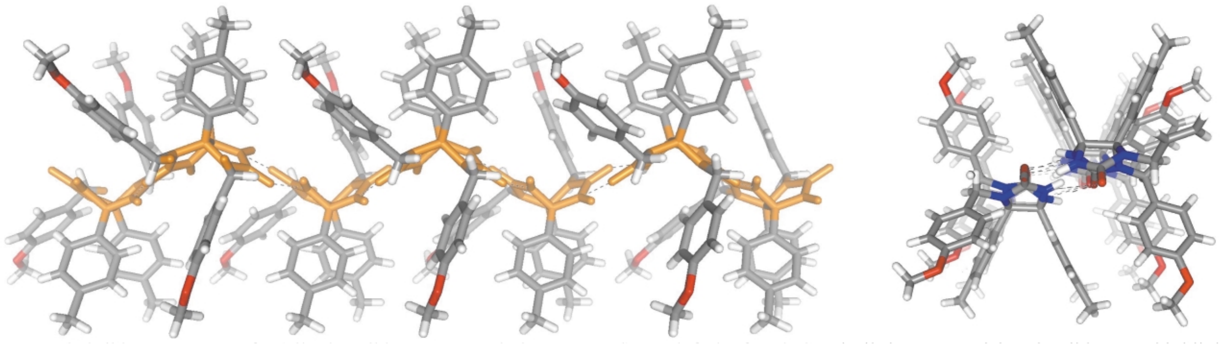


Fig. 2 Extended ribbon structure of **2** (all other ribbons are nearly isostructural). At left the fused glycoluril rings comprising the ribbon are highlighted in orange for clarity. At right is a view down the 2_1 crystallographic screw axis of the tape with the hydrogen bonding between adjacent ureas shown as black dashed lines: N(5)⋯O(2) = 2.860(3) Å, N(7)⋯O(1) = 2.861(3) Å, N(5)–H(5A)---O(2) = 143.8°, N(7)–H(7A)---O(1) = 137.4°.

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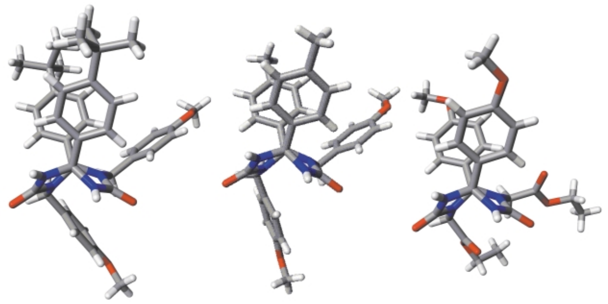

1 2 3

Fig. 3 Wireframe representations of the crystal structures of monomers **1**–**3** viewed down the twist axis of the glycoluril. The bridgehead dihedral angles, η, are: **1**, $\eta = 27.3(3)°$; **2**, $\eta = 25.7(3)°$; **3**, $\eta = 28.9(3)°$.

dynamic processes were considered in the analysis of the VT ^{1}H NMR spectroscopic data: (1) interconversion between the two twisted conformations of these substituted glycolurils, (2) bridgehead aryl ring rotation, and (3) rotation about the N–C$_{\mathrm{PMB}}$ bond. In light of the DFT investigation, possibility (1) was not analyzed further since the energy barrier to interconversion between twisted glycoluril conformations is too low to be studied by solution phase NMR spectroscopy.

The results of the VT ^{1}H NMR spectroscopic study show that upon cooling a THF solution of **2**, the four room temperature doublets of the bridgehead phenyl rings broaden significantly, whereas the resonances corresponding to the PMB aryl ring protons remain sharp. In addition the PMB benzylic protons exhibit broadening between -30 °C and -40 °C until they are completely lost in the baseline at -53 °C. Hindered rotation of the bridgehead phenyl groups with concomitant restricted rotation about the N–C$_{\mathrm{PMB}}$ bond would explain this observation; however, an additional experiment was necessary to verify this.

An isomeric version of compound **2** was prepared featuring *anti*-PMB substitution rather than *syn*.[17] Since rotation about the N–C$_{\mathrm{PMB}}$ bond is presumed to be relatively unrestricted in the *anti*-**2** isomer, any temperature dependent NMR spectral changes can be attributed to hindered bridgehead aryl ring rotation—this essentially isolates one dynamic process. Low temperature ^{1}H NMR spectroscopy on *anti*-**2** corroborates the hindered bridgehead aryl ring rotation in **2**, providing an energy barrier of $\triangle G^{\ddagger} = 12 \pm 1$ kcal mol^{-1} for this process.[18]

The solution phase NMR experiments and complementary DFT calculations suggest that the twisted conformation adopted in these glycolurils reflects a minimization of internal molecular strain rather than crystal packing forces alone. In addition, facile interconversion of the two twisted conformations accompanies restricted bridgehead aryl group rotation in solution.

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Notes and references

† *General X-ray Diffraction Experimental*: Crystallographic data were collected using a Siemens SMART[19] diffractometer equipped with a CCD area detector using Cu-K$_\alpha$ (compounds **1** and **2**, $\lambda = 1.54180$ Å) or Mo-K$_\alpha$ (compound **3**, $\lambda = 0.71073$ Å) radiation. Data were integrated using SAINT[20] and further analysed using XPREP.[21] An empirical absorption correction was applied using SADABS.[22] The structure solution and refinement for **2** were performed using SHELXTL (refining on F^2).[21] For compounds **1** and **3** SIR92[23] was used for the structure solution and SHELXTL was used for all subsequent refinements. See http://www.rsc.org/suppdata/cc/b2/b206648c/ for crystallographic data in CIF or other electronic format.

Crystal Data: **1**, $C_{40}H_{46}N_4O_4$·DMF:[24] thin colorless plate, crystal size 0.40 × 0.10 × 0.02 mm, $M = 719.90$, $T = -153$ °C, monoclinic space group $C2/c$ (no. 15), $a = 34.427(1)$, $b = 10.8215(3)$, $c = 21.6985(6)$ Å, $\beta = 91.115(2)°$, $U = 8082.4(4)$ Å^3, $Z = 8$, μ(Cu-Kα) = 0.622 mm^{-1}, 12629 reflections measured (4776 unique, $R_{int} = 0.030$), $R1$ (3697 reflections $I > 2\sigma(I)$) = 0.048, $wR2$ (all data) = 0.134, $GOF = 1.073$.

2, $C_{34}H_{34}N_4O_4$:[25] colorless block, crystal size 0.21 × 0.13 × 0.06 mm, $M = 562.65$, $T = -152$ °C, monoclinic space group $P2_1/n$, $a = 15.6238(3)$, $b = 10.8061(2)$, $c = 18.8578(4)$ Å, $\beta = 111.229(1)°$, $U = 2967.8(1)$ Å^3, $Z = 4$, μ(Cu-Kα) = 0.672 mm^{-1}, 9856 reflections measured (3549 unique, $R_{int} = 0.035$), $R1$ (3260 reflections $I > 2\sigma(I)$) = 0.059, $wR2$ (all data) = 0.154, $GOF = 1.036$.

3, $C_{26}H_{30}N_4O_8$:[25] colorless block, crystal size 0.35 × 0.12 × 0.08 mm, $M = 526.54$, $T = 25$ °C, monoclinic space group $P2_1$, $a = 11.631(5)$, $b = 10.602(4)$, $c = 11.995(5)$ Å, $\beta = 116.54(3)°$, $U = 1323.3(9)$ Å^3, $Z = 2$, μ(Mo-Kα) = 0.100 mm^{-1}, 4642 reflections measured (3544 unique, $R_{int} = 0.0203$), $R1$ (3306 reflections $I > 2\sigma(I)$) = 0.039, $wR2$ (all data) = 0.099, $GOF = 1.056$.

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