X-ray structure of an unusual glycoluril derivative conformation: Structural analysis and influencing factors

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Abstract
The synthesis and X-ray structure of a novel glycoluril derivative are described. The crystal of the glycoluril derivative is obtained by slow evaporation in a refrigerator at about 5 °C. X-ray crystallographic analysis revealed that the compound crystallized in an unusual as conformation instead of the usual clip-shaped aa conformation. Structural analysis shows that the solvation effect, hydrogen bonding, and space-occupying effect influenced the crystallization conformation of the derivative. The X-ray crystallographic analysis in this work provides additional crystallographic evidence for the as conformation of the 3U glycoluril derivative and shows the effect of solvent water on the conformational behavior.

Keywords
conformation, crystal engineering, glycoluril derivative, hydrogen bonds, solvation effect

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Introduction
In chemistry, molecular conformation is an enigmatic but important property to the organic solid state and plays critical role on the physicochemical properties.1–3 The importance of the molecular conformation of biomolecules,4 natural products,5 pharmaceutical agents,6,7 and many other organic compounds8 has long been recognized. As an interesting research objective, glycoluril units are widely used to design interesting supramolecular structures due to their concave skeletons.9–12 These versatile molecules are designed as host molecules with cavities such as molecular capsules,13,14 the cucurbit[n]uril family of macrocycles15–17 and analogues,18 or with semi-cavities such as molecular clips.19,20 Among them, clip-shaped glycoluril derivatives have attracted much interest due to their ability to function as excellent receptors.21,22 However, the molecular conformation will affect the formation of the clip-shaped semi-cavity and thus affect the binding property of the glycoluril host molecule.23 According to our knowledge, most of the reported molecules crystallize in the clip-shaped aa conformation because of its stability. In our recent work in 2015, an asymmetric 3U glycoluril derivative was synthesized and X-ray structure of its as conformation was obtained via the MeOH solvate, which provided the first crystallographic evidence of the as conformation of a 3U glycoluril derivative.24 Since then, we have been trying to obtain more crystal structures of the as conformation of 3U glycoluril derivatives. In this work, a novel symmetrical 3U glycoluril derivative was designed and synthesised, and the obtained X-ray structure of its as conformation via the H2O solvate provided an additional crystallographic evidence for the as conformation of a 3U glycoluril derivative.

Results and discussion
Compound 1 was chosen for our study because of its suitable solubility for crystal growth. The 3U glycoluril derivative was synthesized by a Pd-catalyzed Suzuki coupling reaction (Scheme 1).25 In compound 1, each of the two pairs of methylene bridges adopts two different conformations. These conformations differed in the disposition of their phenyl-substituted aromatic rings with respect to the adjacent diethoxycarbonyl (–COOEt) substituents on the convex face of the glycoluril framework. Following the convention of Nolte and co-workers,26 we denoted the conformation as syn (s) when the phenyl-substituted aromatic ring was oriented in
Scheme 1. Synthesis of compound 1.

Figure 1. The possible conformations of 1. The descriptors “a” and “s” refer to the anti or syn relationship between the xylylene rings and the diethoxycarbonyl groups on the convex face of the molecule. R = CO2Et.

Figure 2. The molecular structure of compound 1 showing the atom-numbering scheme. The displacement ellipsoids are drawn at the 20% probability level. Hydrogen atoms are deleted for convenience.

was 8.569 Å, which is larger than those reported for the aa conformation 3U clips (ranging from 6.11 to 7.11 Å). As the distance between the centroids of the aromatic rings changed, the angle between the mean planes of the o-xylylene ring (θ = 145.94°) was also different from those of the reported clip-shaped aa conformation.

In order to understand the conformational behavior of compound 1, density functional theory (DFT) calculations were used to optimize the structure geometries to understand the thermodynamic stabilities of the conformers.27 The most stable geometry structure of the as conformer was optimized in the gas phase and using the H2O solvation model. The calculated data show that the sum of the energies of the as conformer in the H2O solvation model (−2602.0100329 Hartree) was significantly decreased at about 0.0388572 Hartree compared to the value in the gas phase (−2601.9711757 Hartree). This indicates the significant impact of the solvation effect in stabilizing the crystallization of this conformation.28,29

In addition, some other factors also played important roles in the crystallization of the as conformation. As seen in Figure 3, an intramolecular hydrogen-bond (C5–H5⋯O2, H–O distance: 2.27 Å; C–H–O angle: 157°) was observed between the carbonyl oxygen atom O2 and the aromatic hydrogen atom H5, which appeared beneficial in bringing them closer to each other and thus keeping the p-diphenyl substituted o-xylylene ring oriented in the opposite direction to the adjacent –COOEt groups. At the same time, a water molecule was found occupying the position of the other clamp arm and pushing the p-diphenyl-substituted o-xylylene ring so that it was oriented in the same direction as the adjacent –COOEt groups. Therefore, the 1–H2O solvate crystallized in the as conformation rather than the clip-shaped aa conformation. In the supramolecular structure of the solvate 1–H2O (Figure 4), the water molecules fill the cavity in the packing arrangement of compound 1, which indicates that the space-occupying effect28 and the crystal environment21 were likely to play a critical role in stabilizing the conformation.
Finally, the crystallization temperature may also affect the conformational behavior of this compound, but unfortunately, we failed to obtain the crystal structure of the compound at room temperature or at a lower temperature.

### Conclusion

In conclusion, the synthesis and X-ray structure of a novel 3U glycoluril derivative are described. The compound crystallized as a H$_2$O solvate and adopted a rarely seen conformation. The results of computational study revealed that the solvation effects of water decreased the sum of the energies of the conformation. In addition to the solvation effects, hydrogen bonding and space-occupying effects also influenced the crystallization of different conformations. Although the factors affecting the conformation remain intricate and elusive in the process of crystallization, the X-ray crystallographic analysis discussed in this work provides additional crystallographic evidence of the as conformation of the 3U glycoluril derivative and shows the solvation effect of water on the conformational behavior. Further studies on the conformational behavior and structure-property relationships in these glycoluril-based clips are currently underway in our laboratory.

### Experimental

Compound 2 was prepared according to literature procedures.$^{22}$ Other reagents were obtained from commercial suppliers and were used without further purification. Melting points were determined using an XT-4 apparatus and are not corrected. Column chromatography was performed on silica gel (200–300 mesh) and silica gel GF254 used for thin-layer chromatography (TLC) analysis purchased from Qingdao Chemical Company, China. Infrared (IR) spectra were recorded on a PE-983 spectrophotometer as KBr pellets and are reported in cm$^{-1}$. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury 400 or 600 MHz spectrometer and chemical shifts are reported in ppm relative to the internal standard tetramethylsilane (TMS). High resolution mass spectra (HRMS) were obtained on a Bruker Apex-Ultra 7.0 T Fourier transform mass spectrometry (FTMS) utilizing atmospheric-pressure chemical ionization (APCI).

#### Preparation of 1

To a solution of Pd(PPh$_3$)$_4$ (35 mg, 0.03 mmol), Na$_2$CO$_3$ (106 mg, 1 mmol), and 2 (161 mg, 0.20 mmol) in dimethylformamide (DMF) (10 mL) and H$_2$O (1 mL) under an Ar atmosphere at room temperature, phenylboronic acid was added (122 mg, 1.00 mmol). The mixture was heated at 110 °C for 2 h (monitored by TLC). After cooling, the solvent was removed under reduced pressure. The solid residue was purified by flash chromatography (SiO$_2$, petroleum ether (b.p. 60–90 °C)/EtOAc, 30:1) to give 1 (136 mg, 0.18 mmol, 86%) as a white solid. M.p. 251.1–252.3 °C. IR (KBr, cm$^{-1}$): 2933 (w), 1725 (s), 1485 (s), 1460 (m), 1446 (s), 1300 (m), 1261 (s), 1154 (w), 1137 (w), 1079 (m), 920 (m), 703 (m). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ (ppm), 7.47–7.35 (m, 20H), 4.66 (d, $J = 15$ Hz, 4H), 4.56 (d, $J = 14.4$ Hz, 4H), 3.91 (q, $J = 7.2$ Hz, 4H), 1.06 (t, $J = 7.2$ Hz, 6H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ (ppm) 166.4, 157.2, 142.3, 140.3, 132.7, 130.1, 129.3, 128.3, 127.4, 114.4, 63.2, 43.1, 13.8. HRMS (APCI): $m/z$ [M + H]$^+$ calcd for C$_{50}$H$_{43}$N$_4$O$_6$: 795.3177; found: 795.3182. Crystal data for 1: C$_{50}$H$_{42}$N$_4$O$_6$·H$_2$O, Mr = 803.88. Triclinic, space group P-1, $a = 11.4679(12)$, $b = 11.7972(13)$, $c = 15.4308(17)$ Å, $Z = 2$, $V = 1999.2(4)$ Å$^3$, $D_c = 1.335$ g cm$^{-3}$, $\mu = 0.089$ mm$^{-1}$, $\theta_{\text{max}} = 23.39^\circ$, $F(000) = 846$, reflections collected/unique, 4916/7395 ($R_{int} = 0.0447$), final $R$ indices ($I > 2\sigma(I)$) $R_1 = 0.0460$, $wR_2 = 0.1204$, $R$ indices (all data) $R_1 = 0.0805$, $wR_2 = 0.1402$, goodness-of-fit (GOF) = 1.007 for all data. CCDC 2020784 for compound 1 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
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