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ARTICLE TYPE

X-ray Studies of Conformation: Observation of Conformational Polymorphism of Glycoluril Clip†

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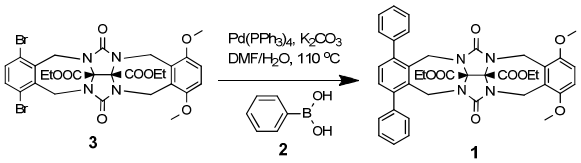
In order to study the conformation behavior of glycoluril clip, compound **1** was synthesized and X-ray crystallography, NMR spectroscopy, and molecular modeling were used in the work. The results of the computational studies revealed the stability of four conformers remained the order *aa*>*as*≈*sa*>*ss* in both gas and solvation models, while solvation decreased the relative energies of each conformer dramatically. In solid phase, X-ray crystallographic analysis indicated compound **1** presented conformational polymorphism when it crystallized in various solvents. We fortunately obtained the single crystal of *aa* and *as* conformers of the same glycoluril clip. The X-ray crystallographic analysis in this report first provided crystallographic evidence of the conformers of glycoluril clip. Unlike to solid state, the conformers interconvert rapidly in solution and therefore cannot be detected on NMR timescale.

INTRODUCTION

Molecular conformation is a subtle but important property in the chemistry of the organic solid state.[1] The conformation or molecular shape plays a critical role in their properties as well as reactivities.[2] Thus, determination and control of the conformation is an important subject to address. For a long time, substantial effort has been devoted to the study of conformation behavior of biomolecules,[3] natural products,[4] pharmaceutical molecules,[5] and many others.[6] In solid state, conformational polymorphism has attracted considerable attention due to the fact that it provides ideal systems for the study of structure-property relationships,[7] the effect of crystal forces on molecular conformation,[8] molecular-level control of crystallization,[9] and the prediction[10] and design[11] of crystal structures. Evidently, among the techniques for the conformation study, X-ray crystallographic analysis has the potential advantage because it can provide a complete molecular conformation from experimental data.[3c]

Glycoluril and its derivatives has become popular building blocks to construct a variety of molecular and supramolecular objects,[12] such as molecular clips,[13] molecular capsules,[14] and the cucurbit[*n*]uril family of macrocycles.[15] Among these versatile structures, glycoluril-derived clips attracted much interesting due to their diverse function including acting as excellent receptors,[16] as components of supramolecular vesicles and organogel,[17] and as enzyme mimics.[18] However, the function of these privileged struture, especially their binding properties, always affected by their conformation.[19] It was Nolte who detailed investigated the conformation behavior and their related binding features of 3*U* (one glycoluril framework unit and two atomic sidewall unit) glycoluril clips.[19a-d,20] Unfortunately, only the single crystal structure of the *aa* conformation (Figure. 1), which was calculated to have the lowest energy in all the cases, was obtained in experiments as yet. Thus, it is still of great significance to understand the molecular information of other conformations via the X-ray crystallography. In this paper, we present the conformational polymorphism of a novel 3*U* glycoluril derived clip. To the best of our knowledge, the X-ray crystallographic analysis in this report first provided crystallographic evidences of the 3*U* glycoluril clip conformers.



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Scheme 1. Synthesis of compounds 1.

Compound **1** was chosen for our study because its appropriate solubility in various solutions, which was suitable for crystal growth. This 3*U* glycoluril clip was synthesized by Pd-catalyzed Suzuki coupling reaction.[21] Each of the two pairs of methylene bridges of **1** can adopt two different conformations. These conformations differ in the disposition of their *o*-xylylene rings with respect to the adjacent diethoxycarbonyl substituents on the convex face of the glycoluril framework. Following the convention of Nolte,[20] we denote the conformation as *syn* (*s*) when the substituted *o*-xylylene ring orients the ring in the same direction as the adjacent diethoxycarbonyl groups and *anti* (*a*) when they point in the opposite direction. Figure 1 shows schematic representations of 4 different conformations, that *aa*, *as*, *sa*, *ss* of compound **1**.

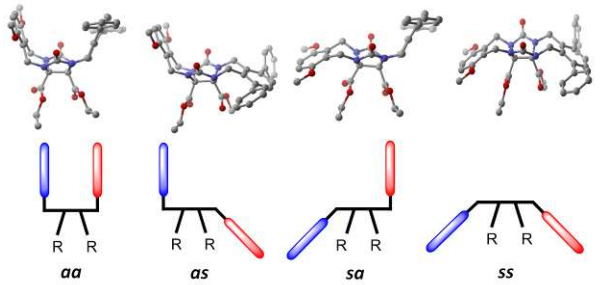


Figure. 1 The possible conformations of **1**. The descriptors "*a*" and "*s*" refer to the *anti* or *syn* relationship between the xylylene rings and the diethoxycarbonyl groups on the convex face of the molecule. R = CO_2Et.

As guidance for our X-ray studies of conformation, density functional theory (DFT) calculations were used to optimize the geometry structures to understanding the thermodynamic stabilities of the conformers.[22] First, we did geometry optimization for four kinds of conformers in gas phase and obtained the most stable geometry structures (Table 1). The order of stability in gas phase is *aa*>*as*≈*sa*>*ss*, which is consistent with the past researches.[19a-d,20] The *aa* conformer is over 3 kcal/mol more stable than others which partially explains the reason of no crystals of other conformers obtained in the past. Then we explored the optimized structures in the solvation models. Four solvents ($CHCl_3$, CH_2Cl_2, EtOAc and MeOH) were chosen as models in DFT studies (Table 1). In every solvent, the stability of the four conformers remained the order in gas phase. The *as*, *sa* and *ss* conformational isomers are still less stable than *aa* the conformation, while their relative energies decreased dramatically. For example, in the solvates of CH_2Cl_2, $CHCl_3$ and EtOAc, the relative energies between *as* and *aa* conformers are about 2 kcal/mol, which have decreased at least 1 kcal/mol. Specially, in the solvent of MeOH, the value decreases further to only 0.6 kcal/mol. It indicates that the stability of *as* conformer is about the same as *aa* conformer in solvent of methanol. It suggested that we may have a chance to obtain a crystal of *as* conformer in methanol.

Table 1. Comparison of the relative sum of electronic and zero-point energies (ΔE) in gas and different solvation models of each conformer.

Conformer	*aa*	*as*	*sa*	*ss*
ΔE_{gas} (kcal/mol)	0.0	3.3	3.4	6.2
ΔE_{CHCl3} (kcal/mol)	0.0	2.1	3.3	5.4
ΔE_{CH2Cl2} (kcal/mol)	0.0	1.9	3.1	5.2
ΔE_{EtOAc} (kcal/mol)	0.0	1.7	3.0	4.9
ΔE_{MeOH} (kcal/mol)	0.0	0.6	2.3	3.5

In our X-ray studies of conformation, a colorless crystal of compound **1** was initially obtained from a solution in $CHCl_3$ at room temperature. Diffraction data was collected at 200 K and compound **1** was crystallized as a **1**-$CHCl_3$ solvate (**1**a).‡ X-ray crystallographic analysis shows solvate **1**a presented the *aa* conformation (Figure 2a), which was the energetically favorable conformational isomer in $CHCl_3$ solvation model. Following this result, the solvent CH_2Cl_2 was also selected for crystal growth. After slow evaporation of the CH_2Cl_2 solution of **1** at room temperature, colorless crystal of **1** suitable for X-ray analysis was obtained in another penicillin bottle. The **1**-CH_2Cl_2 solvate (**1**b) also adopts the lowest energy *aa* comformation (Figure 2b).‡ The glycoluril framework of **1**a and **1**b remained similar structural features with the reported structures.[13,16-20] For example, the distances between the centroids of the substituted *o*-xylylene rings (6.543 and 7.059 Å) and the angles between the mean planes of the *o*-xylylene ring (35.74 and 55.22°) in **1**a and **1**b were both ranged in those reported structures (6.11-7.11 Å and 30-60 °). As shown in table 1, the relative energie of other conformers were 1.9-5.4 kcal/mol higher than the *aa* conformer in the $CHCl_3$ and CH_2Cl_2 solvation model, which suggested that they were unstable and thus the crystals were hard to obtained.

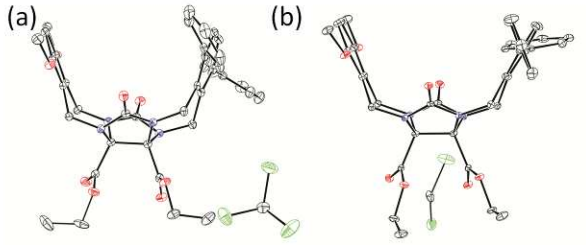
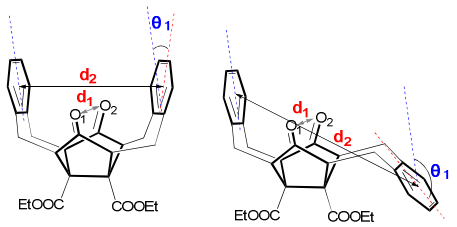


Figure. 2 Crystalline structure of solvates **1**. (a) **1**a (**1**-$CHCl_3$), (b) **1**b (**1**-CH_2Cl_2). Color coding: C, gray; N, blue; O, red; Cl, green. Hydrogen atoms have been omitted for clarity.

Table 2. Growth conditions, conformation and selected parameters from the x-ray crystal structures **1**a-e.



Solvates	**1**-$CHCl_3$ (**1a**)	**1**-CH_2Cl_2 (**1b**)	**1**- MeOH (**1c**)	**1**-EtOAc (**1d**)	**1**-EtOAc (**1e**)
Growth solvent	$CHCl_3$	CH_2Cl_2	MeOH	EtOAc	EtOAc
Growth Temp (°C)	25	25	25	25	5
Conformation	*aa*	*aa*	*as*	*aa*+*as*	*as*
dimensions	0.15×0.12×0.10	0.15×0.12×0.10	0.15×0.12×0.10	0.15×0.12×0.10	0.15×0.12×0.10
d_1 (Å)	5.659	5.550	5.618	5.591(*aa*) 5.503(*as*)	5.540
d_2 (Å)	6.543	7.059	8.539	6.801(*aa*) 8.464(*as*)	8.632
θ_1 (°)	35.74	55.22	136.37	43.21(*aa*) 136.52(*as*)	141.09

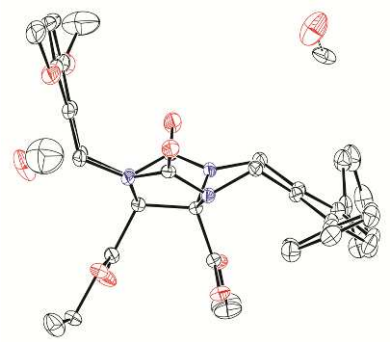


Figure. 3 Crystalline structure of solvates **1**c (**1**-MeOH). Color coding: C, gray; N, blue; O, red; Cl, green. Hydrogen atoms have been omitted for clarity.

The direct experimental observation of the *aa* conformer crystals of clip **1** correlating well with the results of computational studies. Accordingly, our continuing work was focus on catching the crystal structure of other conformers, which were never observed (or obtained) before. The solvent methanol was selected for crystal growth because the value of relative energies between *as* and *aa* conformers decreased dramatically to only 0.6 kcal/mol in the methanol solvation model. In practice, a colorless crystal of compound **1** was fortunately obtained from a mixed solution in $CHCl_3$/MeOH(v/v=4/1) at room temperature. After about 5 days, compound **1** was crystallized as a **1**-MeOH solvate (**1**c) and presented in its *as* conformation (Figure 2a).‡ The glycoluril framework part of **1**c remained similar structural features with the abovementioned structures. However, the geometrical shape of this *as* conformation was quite different to those reported methylene bridges 3*U* clips. In the x-ray structure of **1**c, one methylene bridged substituted *o*-xylylene ring (*p*-diphenyl substituted phenyl) orients the ring in the same direction *as* the adjacent diethoxycarbonyl groups while the other (*p*-dimethoxy substituted phenyl) point in opposite directions. The distances between the centroids of the substituted *o*-xylylene rings (d_2) was 8.539 Å, which was larger than those reported *aa* conformation 3*U* clips (range from 6.11 to 7.11 Å). As the distance between the centroids of the aromatic rings change, so does the angle between the mean planes of the *o*-xylylene ring (Table 2, θ_1 = 136.37°). Although, this *as* conformation of glycoluril 3*U* clips have ever been predicted early to 1987,[13b] our results first provided the crystallographic evidences of the this conformation.

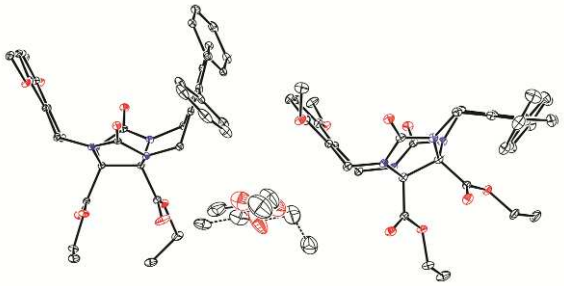


Figure. 4 Crystalline structure of conformational isomorphism solvates **1**d. Color coding: C, gray; N, blue; O, red; Cl, green. Hydrogen atoms have been omitted for clarity.

In our further studies of conformation via X-ray crystallography, we were unexpected to get a mixed crystal of their *aa* and *as* conformation as a EtOAc solvate **1**d (Figure 4).‡ The solvate **1**d exhibited conformational isomorphism,[1b] which coexistence of the *aa* and the *as* conformers in the same crystal structure. In each asymmetric unit, one of the two independent molecules present in *aa* conformation and the other present in *as* conformation. The geometrical characters of each conformer were both similar to their corresponding conformation crystallized separately. In the *aa* conformation independent molecule of **1**d, the distances between the centroids of the substituted *o*-xylylene rings was 6.780 Å and the angle between the mean planes of the *o*-xylylene ring is 42.12°, which were similar to the *aa* conformer crystallized separately in $CHCl_3$ (6.543 Å and 35.74° in **1**a) and CH_2Cl_2(7.059 Å and 55.22° in **1**b). In the *as* conformation of **1**d, the distances between the centroids of the substituted *o*-xylylene rings was 8.433 Å and the angle between the mean planes of the *o*-xylylene ring is 136.65°, which were similar to the *as* conformer crystallized separately in MeOH (8.539 Å and 136.37° in **1**c). In the crystal structures of **1**d, the existence of high energy *as* conformer (ΔG_{EtOAc}=1.7 kcal/mol) can be explained in terms of 'crystal forces',[23] where an improvement in intermolecular interactions compensates for this energetically unfavorable conformation. The attention of solvent molecule EtOAc or the cocrystallization of two different conformers within the crystal lattice played as important factor for lattice stabilization by increasing the packing efficiency.[24] As an accidental experiment, when the EtOAc solution of **1** was standing in the refrigerator (about 5 °C), some colorless crystals obtained after 30 days. X-ray crystallographic analysis shows the EtOAc solvate **1**e presented in *as* conformation separately (Figure 5).‡ In this *as* conformation of **1**e, the distances between the centroids of the substituted *o*-xylylene rings was 8.632 Å and the angle between the mean planes of the *o*-xylylene ring is 141.09°, which were similar to the independent *as* conformer in **1**d (8.464 Å and 136.52 °). The result suggested that the temperature also plays an important role to conformation in the crystal growth.

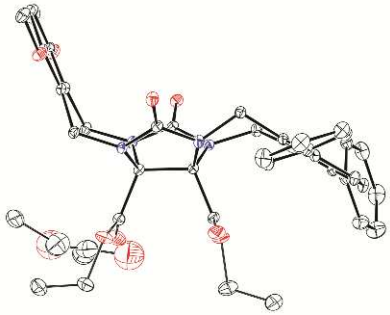


Figure. 5 Crystalline structure of solvates **1**e. Color coding: C, gray; N, blue; O, red; Cl, green. Hydrogen atoms have been omitted for clarity.

The abovementioned crystal structures of conformational isomers inspired us to study their interconvert and the stability factors of the conformers. Our ^{1}H NMR studies on compound **1** were performed in various solvents (eg. CD_2Cl_2, $CDCl_3$, DMSO, C_6D_6, $C_6D_5CD_3$), but no signals that indicating the presence of another conformational isomer as nolte mentioned (Figure S1) [15c,16b]. The variable-temperature ^{1}H NMR spectra employed from -40 to 25 °C in $CDCl_3$ (Figure S2) also tried but failed to observed other conformational isomers. According to the X-ray structures of the *aa* conformation obtained from $CHCl_3$ and the *as* conformation obtained from CH_3OH, we assume that adding

CD_3OD to the $CDCl_3$ solution of **1** should cause the appearing of another conformer. Thus, ^1H NMR spectrum data were recorded when CD_3OD was added stepwise to the $CDCl_3$ solution of compound **1**. As shown in Figure S3, ^1H NMR signals of compound **1** is almost no change and there were no new signals observed in the mixed solution of compound **1**. We suspect that the conformational isomers of compound **1** were interconvert fast over the NMR timescale.

In this report, molecular modeling, X-ray crystallography and NMR spectroscopy were used for the study of conformation behavior of a novel glycoluril based clip **1**. The results of the computational studies revealed the stability of four conformers in the order *aa*>*as*≈*sa*>*ss* in gas and solvation models. However, solvation effects decreased the relative energies of each conformer dramatically, and especially narrowed the energy gap between *aa* and *as* conformers. In addition to solvation effects, the crystal growth condition also plays some influence for the crystallization of different conformations. In the X-ray studies of conformation, we were fortunately observed the conformational polymorphism of glycoluril clip **1**. Unlike to solid state, different conformers may interconvert rapidly in solution and therefore cannot be detected on NMR timescale. Despite the solvent effect remained intricate and elusive in the process of crystallization, to the best of our knowledge, the X-ray crystallographic analysis in this report first provided crystallographic evidences of the *as* conformation and observed conformational polymorphism of glycoluril clip. Further studies of the conformational behavior and structure−property relationship in these glycoluril based clips are currently underway in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Preparation and characterization of **1**, Crystallographic data and refinement details, ^1H NMR and ^{13}C NMR spectra and NMR studies. Computational methods. CCDC 1032703-1032707. For ESI and crystallographic data in CIF, See DOI: 10.1039/b000000x/.

‡ Crystal data of **1**a: $C_{41}H_{39}N_4O_8Cl_3$, Mr = 822.11, space group P-1, a = 10.014(1) Å, b = 11.679(1) Å, c = 17.704(1) Å, α = 82.360(1)°, β = 87.038(1), γ = 69.440(1), V = 1921.5(2) Å^3, ρ = 1.47 g\cm^3, Z = 2, final R_1 = 0.0765, (Rint = 0.0306) for 14870 independent reflections [I >2σ(I)]. Crystal data of **1**b: $C_{41}H_{37}N_4O_8Cl_2$, Mr = 821.11, space group P-1, a = 11.262(1) Å, b = 12.427(1) Å, c = 15.957(1) Å, α = 68.170(1)°, β = 74.522(1) °, γ = 65.900(1) °, V = 1874.8(2) Å^3, ρ = 1.395 g\cm^3, Z = 2, final R_1 = 0.0722, (Rint = 0.0206) for 13311 independent reflections [I >2σ(I)]. Crystal data of **1**c: $C_{41}H_{42}N_4O_9$, Mr = 734.79, space group P-1, a = 8.706(1) Å, b = 11.058(1) Å, c = 20.271(2) Å, α = 99.383(2)°, β = 98.246(2) °, γ = 95.472(2) °, V = 1891.4(4) Å^3, ρ = 1.290 g\cm^3, Z = 2, final R_1 = 0.0261, (Rint = 0.0306) for 13231 independent reflections [I >2σ(I)]. Crystal data of **1**d: $C_{43}H_{44}N_4O_{9.5}$, Mr = 768.82, space group P-1, a = 9.902(1) Å, b = 14.573(2) Å, c = 27.372(3) Å, α = 94.424(2) °, β = 97.048(2) °, γ = 100.801(2) °, V = 3830.2(8) Å^3, ρ = 1.333 g\cm^3, Z = 2, final R_1 = 0.0261, (R_{int} = 0.0249) for 28344 independent reflections [I >2σ(I)]. Crystal data of **1**e: $C_{43}H_{43}N_4O_9$, Mr = 746.80, space group P2(1)/c, a = 13.371(2) Å, b = 24.587(3) Å, c = 13.486(2) Å, α = 90 °, β = 117.750(2) °, γ = 90 °, V = 3923.5(9) Å^3, ρ = 1.264 g\cm^3, Z = 4, final R_1 = 0.1003, (Rint = 0.0249) for 6819 independent reflections [I >2σ(I)].

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