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Communications

First Carbamoyloxa-Bridged Cyclophane: Synthesis and Crystal Structures of Two Isolable Conformers

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Summary: Conformational control of a cyclophane with intermolecular hydrogen bonding was accomplished through the first synthesis of a carbamoyloxa-bridged cyclophane **3**, with the result that the crystal structures of two isolable conformers **3a** and **3b** were elucidated to be *anti*-(*E*,*E*) and *anti*-(*Z*,*Z*) by X-ray analysis. The convenient conversion of **3a** to **3b** was carried out with hydrogen bonding assisted by polar solvents.

Conformational control of molecules with weak nonbonding interactions is one of the most attractive fields in organic chemistry.[1] Much attention has been paid to a search for a strategy to control the conformations of cyclophanes as effective receptors for molecular recognition.[2] Major advances in fixing the conformations of cyclophanes have been made in designing various bridges,[3] substituents on aromatic rings,[4] and rigid systems,[5] including polycyclophanes[6] constructed with covalent bonds. However, no attempt to control the conformations of cyclophanes by hydrogen bonding employing functionalized bridges has been reported. In this study, we achieved this novel method through the first synthesis of the carbamoyloxa-bridged[7] cyclophane **3**. The new bridge brought not only the rotational barrier around the N–C(=O) bonds but also the potential of the distinct intermolecular hydrogen bonding patterns[8] into the cy-

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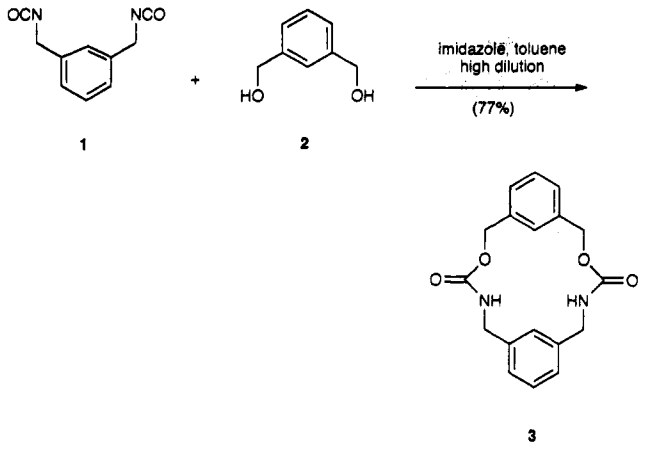
Scheme 1. Synthesis of Cyclophane 3



clophane, with the result that the two conformers were easily isolated as single crystals. Several attempts to isolate a pair of conformers of medium-sized (8–12-membered) cyclophanes were reported,[9] where it was difficult to isolate the conformers of macro-sized cyclophanes due to the low barrier to conformational inversion.[10] Owing to the rigidity and the intermolecular hydrogen bonding, the macro-sized cyclophane **3** showed a behavior similar to the medium-sized cyclophanes, in which conformers exchanged slowly at ambient temperature with a high interconversion barrier (>15 kcal/mol).[4,9c,11] Our 16-membered system is the first example of a conformationally isolable macro-sized cyclophane containing only two benzene rings.

A direct synthesis of the target cyclophane **3** was carried out through coupling of *m*-xylylenediisocyanate (**1**) and *m*-xylylenediol (**2**)[12] with a modified polyurethane synthesis.[13] A good yield (77%) of **3**[14] was obtained by using imidazole[15] under high dilution conditions (2.38×10^{-3} M) in refluxing toluene (Scheme 1).[16-18]

^{1}H NMR spectrum of **3** in methanol-d_4 at 20 °C indicated the presence of two conformers in the ratio of 4.9:1.[19] By a variable-temperature ^{1}H NMR study focused on a set of singlets of methylene protons adjacent to oxygen,[20] the conformational inversion barrier $\Delta G^{\ddagger}$ was estimated to be 16.1 kcal/mol.[21]

Crystallization of **3** from dichloromethane/chloroform (1:1) gave a single conformer **3a** (245 mg, 95%, plates, mp 219 °C). Its *anti*-(*E*,*E*) structure was confirmed by X-ray analysis (Figure 1).[22,26] Intramolecular hydrogen bonding is impossible between the distant bridges. Figure 2 indicates that the molecules are linked by two kinds of interactions between neighboring carbamoyloxa moieties: N1H1···O1 (distance 2.046 Å, angle 143.9°), and

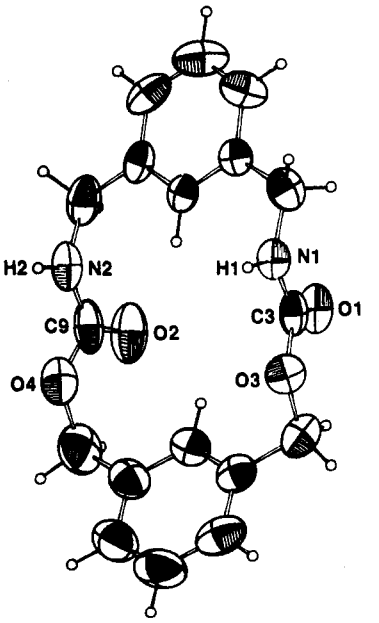


Figure 1. Perspective ORTEP view of **3a**.

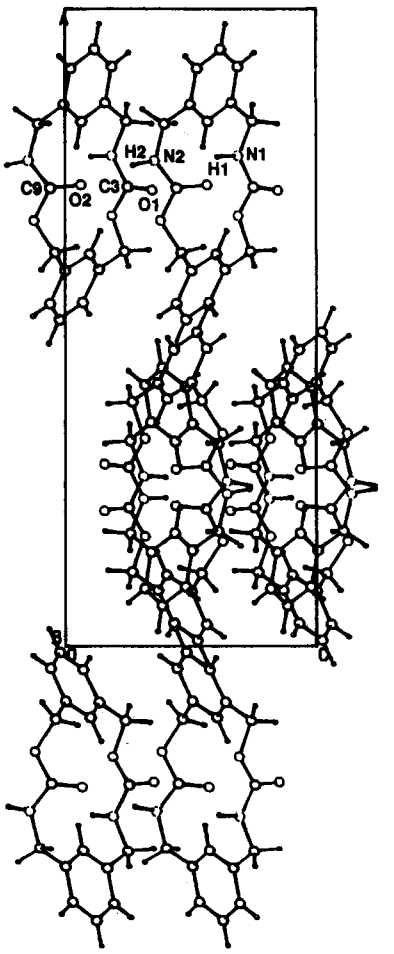


Figure 2. Packing Diagram for **3a**.

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(12) The starting materials **1** and **2** were commercially available.

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(14) Spectral data of 5,13-diaza-3,15-dioxatricyclo[15.3.1.1^{17,11}]docosa-1(21),7,9,11(22),17,19-hexaene-4,14-dione (**3**): IR ($CHCl_3$) 3470 (NH), 1730 (C=O) cm^{-1}; ^{1}H NMR (methanol-d_4, 300 MHz) (for the major conformer) δ 4.34 (s, 4H), 5.20 (s, 4H), 7.04–7.47 ($8H_{arom}$ and $2H_{NH}$, m); ^{13}C NMR (DMSO-d_6, 75 MHz, INEPT) δ 43.34 (CH_2), 64.11 (CH_2), 122.6 (CH), 123.1 (CH), 125.2 (CH), 125.9 (CH), 127.7 (CH), 128.0 (CH), 138.8 (C), 140.3 (C), 156.4 (C=O); MS (FAB) 327 (MH^+), 349 (MNa^+), 365 (MK^+), 459 (MCs^+), 325 (neg). Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 65.94; H, 5.52; N, 8.51.

(15) When triethylamine or pyridine was used as a base, the coupling reaction became complexed.

(16) Polymers were obtained as minor products, but 32-membered cyclophane (dimer) was not detected.

(17) In contrast to the example given for this reaction, coupling of **1** with *p*-xylylenediol gave only polymeric products under the same condition.

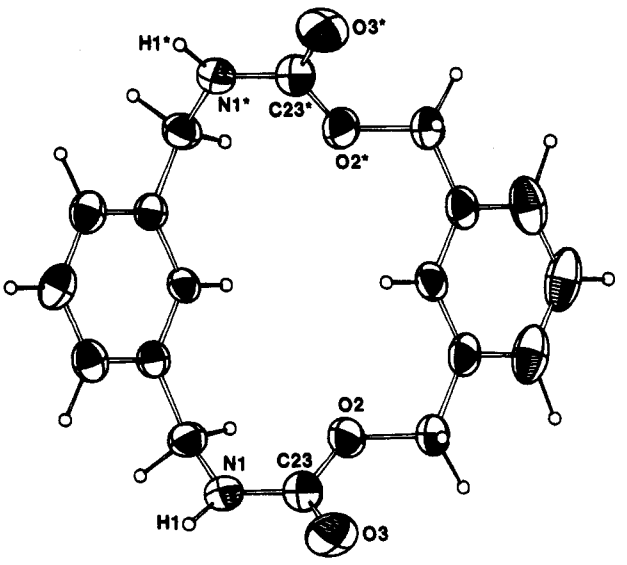

Figure 3. Perspective ORTEP view of **3b**.

N2H2···O2 (2.458 Å, 135.2°). Therefore, the IR spectrum in the solid state (KBr) showed two sets of absorptions corresponding to the carbamoyloxa moieties: 3330, 1690 cm^{-1} (for N1H1···O1=C3), and 3380, 1718 cm^{-1} (for N2H2···O2=C9).

In order to demonstrate the utility of carbamoyloxa bridges, a conformational change of **3a** was tried. Since amide–amide hydrogen bonding in polar solvents was known,[23] alcohols would be suitable for freezing the *Z* conformation of carbamoyloxa moieties forming cyclic intermolecular hydrogen bonding. Recrystallization from methanol/ethanol solution (3:7, 32 mL) of **3a** (28.1 mg, 0.086 mmol) gave the desired conformer **3b** (26.3 mg, 94%, columns, mp 225 °C). The conformational change was clearly observed from the IR spectrum (KBr): 3320 and 1700 cm^{-1}. The X-ray crystallographic analysis reveals the *anti*-(*Z*,*Z*) conformation of **3b** (Figure 4).[24,26] The carbamoyloxa bridges are strongly linked by cyclic intermolecular hydrogen bonding[25] (N1H1···O3, 1.939 Å, 148.25°, and N1*H1*···O3*, 1.939 Å, 148.25°). This controlled conformational inversion is remarkable as a characteristic of the carbamoyloxa bridges.

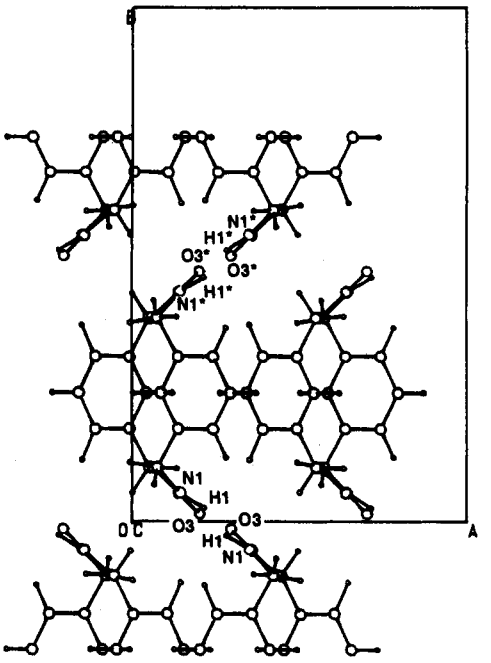

Figure 4. Packing Diagram for **3b**.

Our new approach described here would be one of the general methods to control the conformations and molecular crystals of cyclophanes. Further studies are in progress.

Supplementary Material Available: Experimental procedure, characterization data, and ^1H and ^{13}C NMR spectra of **3** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(18) The established optimal reaction conditions are as follows: To stirred refluxing toluene (360 mL) was added simultaneously over 9 h a solution of **1** (138 mg, 1.0 mmol) and imidazole (136 mg, 2.0 mmol) in THF (30 mL) and a solution of **2** (188 mg, 1.0 mmol) in toluene (30 mL). After the addition was completed, the mixture was refluxed for an additional 2 h and then evaporated. The resulting crude product was chromatographed over silica gel using EtOAc/hexane to yield **3** (259 mg, 77%) as a white solid (mp 209–213 °C).

(19) The ratio was determined by the integration of the ^1H NMR spectrum.

(20) The ^1H NMR spectrum for **3** was recorded at 20, 30, 40, 50, and 60 °C in methanol-d_4. After the sample was cooled to 20 °C, the ratio of the conformers was back to that before heating.

(21) $\Delta G^{\ddagger}$ was calculated by the following equation $\Delta G^{\ddagger}$ (cal/mol) = $RT_c(22.96 + \ln T_c - \ln \Delta\delta)$. **3**: $\Delta\delta$ = 36 Hz, T_c = 323 K.

(22) Colorless crystals of **3a** are orthorhombic, the space group is *Pbcn* with a = 23.299(3) Å, b = 15.026(2) Å, c = 9.250(1) Å, V = 3238.4 Å^3, Z = 8, and d_{calcd} = 1.33 g/cm^3. The final residuals were R = 0.037 for 1172 data with $F_o^2 > 3.0\sigma(I)$.

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(24) Colorless crystals of **3b** are monoclinic, the space group is *Pnam* with a = 11.520(2) Å, b = 17.421(2) Å, c = 7.891(1) Å, V = 1583.6 Å^3, Z = 4, and d_{calcd} = 1.37 g/cm^3. The final residuals were R = 0.046 for 1186 data with $F_o^2 > 3.0\sigma(I)$.

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(26) The author has deposited atomic coordinates for **3a** and **3b** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.