Stereoselective Thermal Conversion of s-*trans*-Diallene into Dimethylenecyclobutene via s-*cis*-Diallene in the Crystalline State

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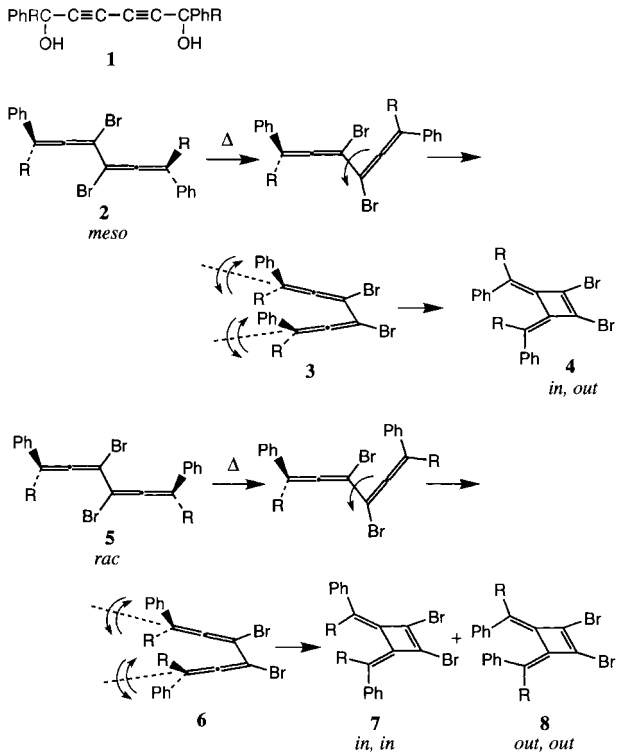
It has been well established that thermal bimolecular organic reactions proceed efficiently in the solid state by mixing the powdered substrate and reagent.[1] However, no thermally irreversible unimolecular reaction from crystal to crystal has been reported, although reversible reactions such as thermochromism and single crystal to single crystal thermal conversion of a cyclic photodimer of a styrylpyrylium derivative to its monomer[2] are known. We report the thermal crystal-to-crystal conversion of s-*trans*-1,1,6,6-tetraaryl-3,4-dibromo-1,2,4,5-hexatetraenes (**2a**, **2b**, and **5b**) into the corresponding 3,4-bis(diarylmethylene)-1,2-dibromocyclobutenes (**4a**, **4b**, and **7b** and **8b**) via s-*cis*-diallenes (**3a**, **3b**, and **6b**). These thermal conversions involve two crystal-to-crystal reactions. First the s-*trans* configuration of **2a** (**2b** or **5b**) is rearranged to the s-*cis* conformer in the crystal to give **3a** (**3b** and **6b**, respectively; Scheme 1). In the second step the cyclization of **3a** occurs in the crystal to give **4a**. This cyclization proceeds stereoselectively; compound **2b** gave **4b**, and **5b** gave a 1:1 mixture of **7b** and **8b**, through a [2+2] conrotatory cyclization. It is surprising that the thermal rearrangement and stereoselective cyclization occur so readily despite the necessary movement of a sterically bulky group in the crystal, although single crystal to single crystal photodimerization of a styrylpyrylium derivative[2] and of cinnamic acid[3] to the corresponding dimer is known.



Scheme 1. Thermal conversion of s-*trans*-diallenes into dimethylenecyclobutenes via s-*cis*-diallenes. **a**: R = Ph; **b**: R = *p*-MeC_6H_4.

Heating the colorless crystals of s-*trans*-1,1,6,6-tetraphenyl-3,4-dibromohexa-1,2,4,5-tetraene (**2a**) at 150 °C, prepared from 1,1,6,6-tetraphenylhexa-2,4-diyne-1,6-diol (**1a**) and aqueous HBr according to the reported method,[4] gave 3,4-bis(diphenylmethylene)-1,2-dibromocyclobutene (**4a**) (m.p. 199 °C) in quantitative yield. The differential scanning calorimetry (DSC) measurement of the crystal of **2a** showed a peak for an exothermic process at around 156 °C and one for an endothermic process at 198 °C. The cyclization to **4a** occurs at around 156 °C. Thermal cyclizations of **2a** to **4a**,[5] and of unsubstituted and alkyl-substituted diallenes to the corresponding dimethylenecyclobutenes[6] in solution have been described. However, the cyclization of diallene in the solid state has never been reported. Since no liquid state was observed during the conversion of **2a** to **4a**, the reaction in the crystal is a real solid-state reaction. The s-*trans* conformation of **2a** was elucidated by an X-ray structural analysis. The structure is not unreasonable because even 1,2,4,5-hexatetraene exists in a s-*trans* form both in the gas phase[7] and in solution.[8] In order to cyclize to **4a**, **2a** should first isomerize to its s-*cis* isomer (**3a**) in the crystal. The conformational change of **2a** to **3a** requires a rotation of the sterically bulky 1,1-diphenylallene moiety around the single bond connecting the two allene groups in the crystalline state (see Scheme 1). A similar conformational change of s-*trans*-diallene to s-*cis*-diallene in solution, followed by the addition of SO_2 to give a cyclic sulfone derivative has been discussed.[9] Furthermore, thermal conversion of the s-*cis*-diallene **3a** to **4a** should also be accompanied by a molecular motion of the 1,1-diphenylmethylene groups. This dynamic behavior of the molecules in the crystalline state is very interesting. To verify whether the rearrangement of s-*strans*-diallene to s-*cis*-diallene and the cyclization of the latter to dimethylenecyclobutene proceed stereoselectively, the thermal reactions of *meso*- (**2b**) and *rac*-s-*trans*-1,6-diphenyl-1,6-di(*p*-tolyl)-3,4-dibromohexa-1,2,4,5-tetraene (**5b**) were studied.

The reaction of a mixture of *meso*- and *rac*-1,6-diphenyl-1,6-di(*p*-tolyl)hexa-2,4-diyne-1,6-diol (**1b**) with aqueous HBr gave a mixture of **2b** and **5b**, which upon fractional recrystallization gave pure **2b** and **5b** as colorless crystals (see Experimental Section). The structures of these were elucidated by X-ray analyses (Figure 1).[10] Heating crystals of **2b** at 135 °C gave the *in,out* isomer **4b**, while heating **5b** at 145 °C gave a 1:1 mixture of the *in,in* isomer **7b** and the *out,out*-3,4-bis(phenyl-*p*-tolylmethylene)-1,2-dibromocyclobutene (**8b**) in quantitative yields. Although the structures of all the products were elucidated by X-ray analyses, only the representative structure of **8b** is shown in Figure 2.[11] The structures of the products can also be determined easily from their ^{1}H NMR spectra: although the spectrum for **4b** shows

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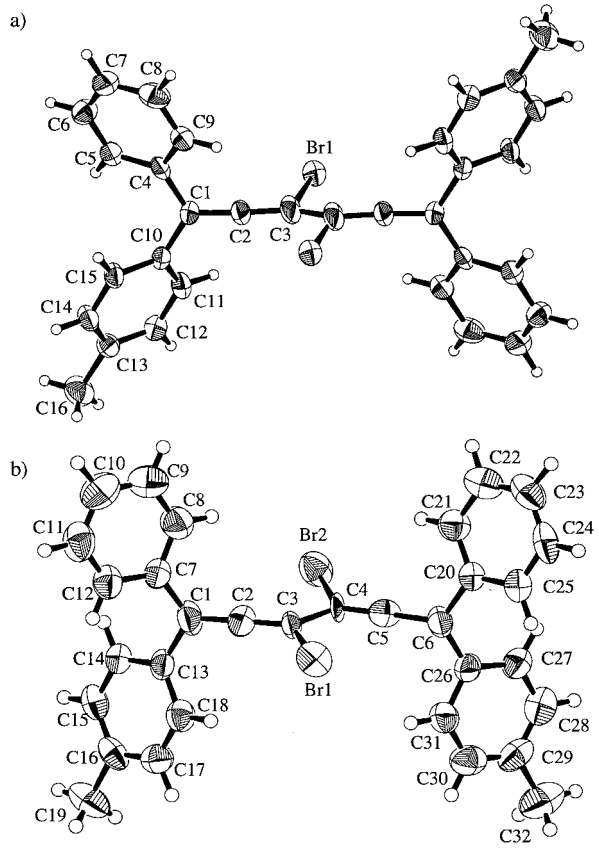

Figure 1. Crystal structure of (a) **2b** and (b) **5b**. Selected bond lengths [Å] and angles [°]: for **2b**: Br1 – C3 2.16(2), C1 – C2 1.30(1), C1 – C4 1.49(1), C1 – C10 1.47(1), C2 – C3 1.28(1), C3 – C3′ 1.21(2); C2-C1-C4 119.9(8), C2-C1-C10 119.3(8), C4-C1-C10 120.8(7), C1-C2-C3 175(1), Br1-C3-C2 111(1), Br1-C3-C3′ 98(1), C2-C3-C3′ 149(2); for **5b**: Br1 – C3 1.94(2), Br2 – C4 1.87(2), C1 – C2 1.33(5), C1 – C7 1.48(1), C1 – C13 1.49(1), C2 – C3 1.26(6), C3 – C4 1.51(3) C4 – C5 1.19(4), C5 – C6 1.42(4), C6 – C20 1.506(9), C6 – C26 1.465(9); C2-C1-C7 118(2), C2-C1-C13 120(2), C7-C1-C13 119.9(6), C1-C2-C3 172(3), Br1-C3-C2 115(2), Br1-C3-C4 113(1), C2-C3-C4 131(2), Br2-C4-C3 113(1), Br2-C4-C5 116(1), C3-C4-C5 130(2), C4-C5-C6 176(2), C5-C6-C20 117(1), C5-C6-C26 120(1), C20-C6-C26 120.2(6).

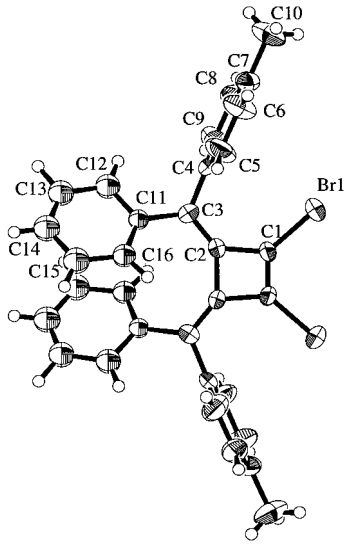

Figure 2. Crystal structure of **8b**. Selected bond lengths [Å] and angles [°]: Br1 – C1 1.858(8), C1 – C1′ 1.30(2), C1 – C2 1.48(1), C2 – C2′ 1.52(2), C2 – C3 1.32(1), C3 – C4 1.50(1), C3 – C11 1.58(2); Br1-C1-C1′ 131.7(3), Br1-C1-C2 134.0(6), C1′-C1-C2 94.2(5), C1-C2-C2′ 85.8(5), C1-C2-C3 132.7(8), C2′-C2-C3 141.5(6), C2-C3-C4 119.6(9), C2-C3-C11 120.1(10).

both the shielded and normal methyl signals at $\delta = 2.07$ and 2.39, respectively, whereas those of **7b** and **8b** show only a signal for a shielded methyl group at $\delta = 2.10$ and a normal methyl signalat $\delta = 2.39$, respectively.

The thermal reaction of **2b** and **5b** in boiling xylene gave the same products. The steric course of the solid-state reaction is shown in Scheme 1. Compounds, **2b** and **5b** rearrange first to **3b** and **6b**, respectively, and their conrotatory [2+2] ring closure gives **4b** and a 1:1 mixture of **7b** and **8b**, respectively. Mechanistic studies of the thermal conversion of diallene to dimethylenecyclobutene in solution and in the gas phase have revealed that it is an electrocyclic conrotatory process has been established.[12]

To verify that these reactions really occur in the solid state and not in the liquid state, the thermal reaction of **5b** in the crystal was studied by taking DSC measurements and recording IR spectra, and by monitoring the course of the reaction through a microscope. In the DSC diagram of **5b** revealed an peak for an exothermic reaction at around 150 °C which is attributable to the rearrangement of **5b** to **6b** followed by cyclization to a mixture of **7b** and **8b** and a peak for an endothermic conversion at around 193 °C, which is attributable to the melting point of the product (Figure 3). This

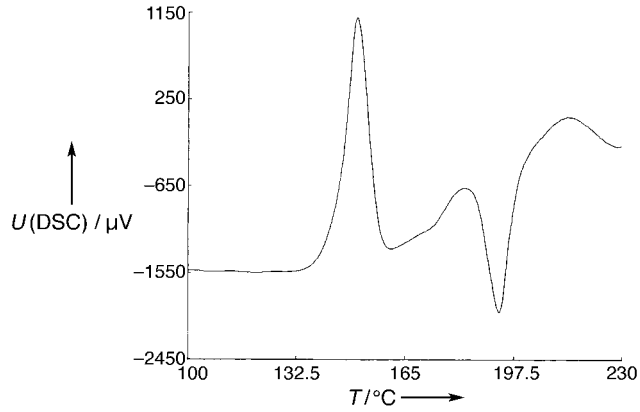

Figure 3. DSC diagram of **5b**.

assignment is resonable, since a 1:1 mixture of **7b** and **8b** showed a peak for an endothermic process at 194 °C in the DSC measurement. On the other hand, **2b** showed a peak for an exothermic conversion at around 178 °C and one for an endothermic one at 216 °C that is attributable to the melting point of **4b** (m.p. 214 – 215 °C). When the IR spectrum of a single crystal of **5b** was measured continuously every minute for 50 min at 125 °C, the signal at $\tilde{\nu} = 1927\ cm^{-1}$ (C=C=C) gradually decreased and finally disappeared (Figure 4). By heating **5b** in the crystalline state at 135 °C on a hot plate for 80 min, it was completely converted to **7b** and **8b** without melting. This conversion from crystal-to-crystal was monitored through a microscope, and a molten state was not observed throughout the reaction, although the reaction product was no longer a single crystal (Figure 5). These findings clearly support that the conversion of s-*trans*-diallene into dimethylenecyclobutene via s-*cis*-diallene really occurs in the crystalline state and not in the molten state. They also

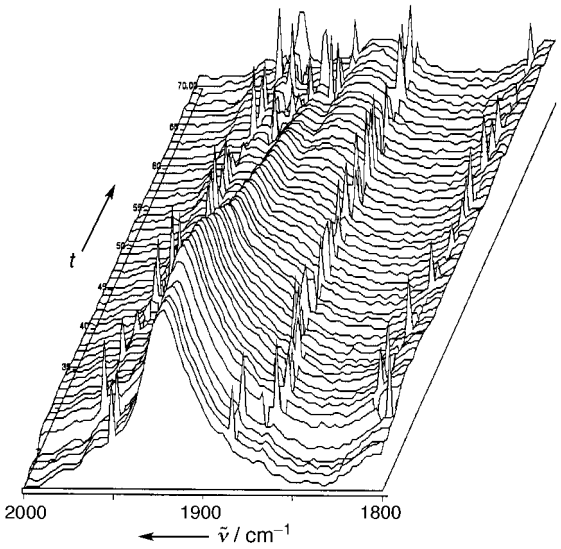

Figure 4. IR spectra showing the thermal reaction of **5b** in the crystalline state at 125 °C. The spectrum was measured every minute for 50 min.

verify that the molecular motion of the sterically bulky 1,1-diarylallene group in the rearrangement of s-*trans*-diallene to its s-*cis* isomer and that of the 1,1-diarylmethylene group in the cyclization of s-*cis*-diallene to dimethylenecyclobutene occur in the crystal.

Experimental Section

2b and **5b**: Aqueous HBr was added to a solution of **1b** (10 g) in AcOH (200 mL) at room temperature to give crystalline material. The crystals formed were filtered, washed with water, and air dried. The dried crystals were suspended in diethyl ether and filtered to give insoluble **2b** and an solution of **5b** in diethyl ether. Recrystallization of **2b** and **5b** from AcOEt gave pure **2b** as colorless needles (4 g, 30% yield) and **5b** as colorless prisms (4 g, 30% yield). **2b**: IR: $\tilde{\nu}$ = 1929 cm^{-1} (C=C=C); ^{1}H NMR: δ = 2.40 (s, 6H, Me), 7.20–7.48 (m, 18H, Ar); elemental analysis calcd for $C_{32}H_{28}Br_2$: C 67.63, H 4.26; found: C 67.84, H 4.13. **5b**: IR: $\tilde{\nu}$ = 1927 cm^{-1} (C=C=C); ^{1}H NMR: δ = 2.40 (s, 6H, Me), 7.20–7.48 (m, 18H, Ar); elemental analysis calcd for $C_{32}H_{28}Br_2$: C 67.63, H 4.26; found: C 67.70, H 7.24.

4b: Compound **2b** (0.2 g) was heated in the crystalline state at 135 °C for 1.5 h to give **4b** (0.2 g, 100% yield) as colorless needles after recrystallization from AcOEt. M.p. 214–215 °C; ^{1}H NMR: δ = 2.07 (s, 3H, Me), 2.39 (s, 3H, Me), 6.45–6.85 (m, 9H, Ar), 7.13–7.35 (m, 9H, Ar); elemental analysis calcd for $C_{32}H_{24}Br_2$: C 67.63, H 4.26; found: C 67.89, H 4.13.

7b and **8b**: Compound **5b** (0.4 g) was heated in the crystalline state at 125 °C for 1.5 h to give a 1:1 mixture (by ^{1}H NMR spectroscopy) of **7b** and **8b** (0.4 g, 100% yield). Fractional recrystallization of the mixture gave pure **7b** as colorless needles (m.p. 180–183 °C) and pure **8b** as colorless needles (m.p. 215–218 °C). **7b**: ^{1}H NMR: δ = 2.10 (s, 6H, Me), 6.48–6.52 (d, 4H, Ar), 6.70–6.74 (d, 4H, Ar), 7.23–7.26 (m, 10H, Ar); elemental analysis calcd for $C_{32}H_{24}Br_2$: C 67.63, H 4.26; found: C 67.46, H 3.97. **8b**: ^{1}H NMR: δ = 2.39 (s, 6H, Me), 6.66–6.87 (m, 10H, Ar), 7.10–7.25 (m, 8H, Ar); elemental analysis calcd for $C_{32}H_{24}Br_2$: C 67.63, H 4.26; found: C 67.66, H 4.13.

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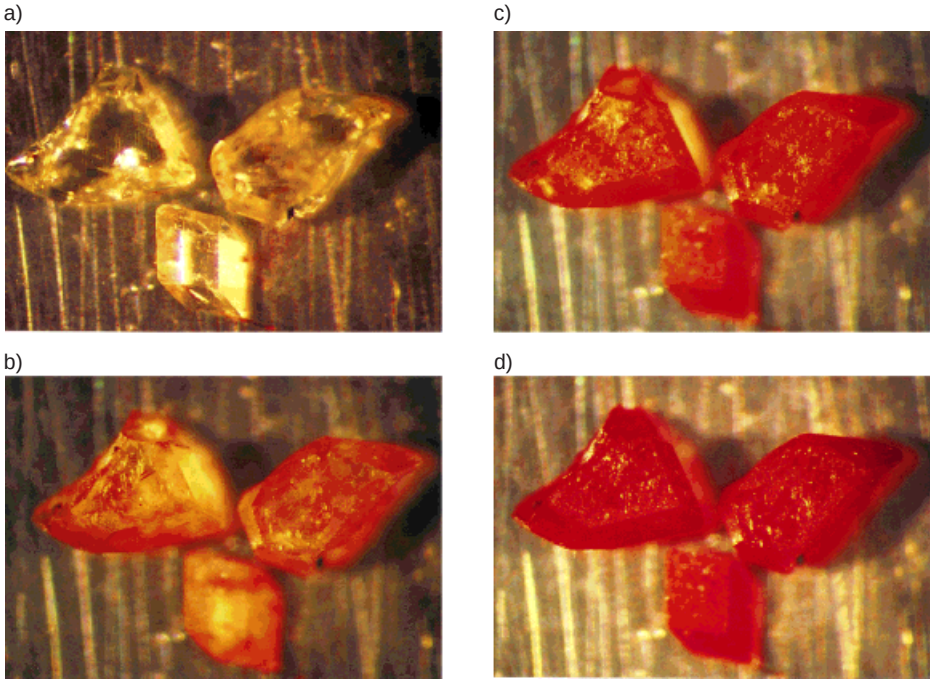

Figure 5. The thermal reaction of a crystal of **5b** to a crystal of a 1:1 mixture of **7b** and **8b** as observed through a microscope. The photos show the crystal before heating (a), as well as after 15 (b), 40 (c), and 80 min at 135 °C (d).

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[10] a) Crystal data for **2b**: $C_{32}H_{24}Br_2$, M_r = 568.35, triclinic, space group $P\bar{1}$ (No. 2), a = 8.547(3), b = 13.633(5), c = 6.049(2) Å, α = 102.34(3), β = 104.80(3), γ = 96.10(3)°, V = 656.0(5) Å^3, Z = 1, ρ_{calcd} = 1.439 g cm^{-3}, crystal dimensions 0.50 × 0.10 × 0.02 mm, μ = 31.16 cm^{-1}, T = 293 K, R = 0.050, wR = 0.065, and S = 1.43 for 154 parameters and 1174 unique observed reflections with $I > 3\sigma(I)$, $\Delta\rho_{max}$ = 0.68 e Å^{-3}. **5b**: $C_{32}H_{24}Br_2$, M_r = 568.35, monoclinic, space group

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$P2_1/n$ (No. 14), $a = 10.979(6)$, $b = 14.897(5)$, $c = 16.606(4)$ Å, $\beta = 101.28(3)^\circ$, $V = 2663(1)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.417$ g cm^{-3}, crystal dimensions $0.36 \times 0.32 \times 0.18$ mm, $\mu = 30.70$ cm^{-1}, $T = 293$ K, final $R = 0.048$, $wR = 0.062$, and $S = 1.45$ for 307 parameters and 2158 unique observed reflections with $I > 3\sigma(I)$, $\Delta\rho_{max} = 0.58$ e Å^{-3}. Diffraction data for **2b** and **5b** were collected on a Rigaku AFC-7R diffractometer with graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å) to $2\theta_{max} = 55^\circ$. The structures of **2b** and **5b** were solved by direct methods and heavy-atom Patterson methods, respectively, and expanded with Fourier techniques. The diallene moiety of **5b** was found to be disordered. All calculations were carried out with the teXsan crystallographic software package from the Molecular Structure Corporation. b) Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101408. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[11] Crystal data for **8b**: $C_{32}H_{24}Br_2$, $M_r = 568.35$, monoclinic, space group $C2/c$ (No. 15), $a = 6.641(7)$, $b = 28.502(4)$, $c = 13.773(5)$ Å, $\beta = 96.66(5)^\circ$, $V = 2589(2)$ Å3, $Z = 4$, $\rho_{calcd} = 1.458$ g cm^{-3}, crystal dimensions $0.34 \times 0.06 \times 0.04$ mm, $\mu(Mo_{K\alpha}) = 31.58$ cm^{-1}, $T = 295$ K, $R = 0.057$, $wR = 0.075$, and $S = 1.67$ for 145 parameters and 969 unique observed reflections with $I > 3\sigma(I)$, $\Delta\rho_{max} = 0.68$ e Å^{-3}. Data collection and analysis were carried out in a similar way to those for **5b**. The phenyl groups were refined with two disordered positions.[10b]

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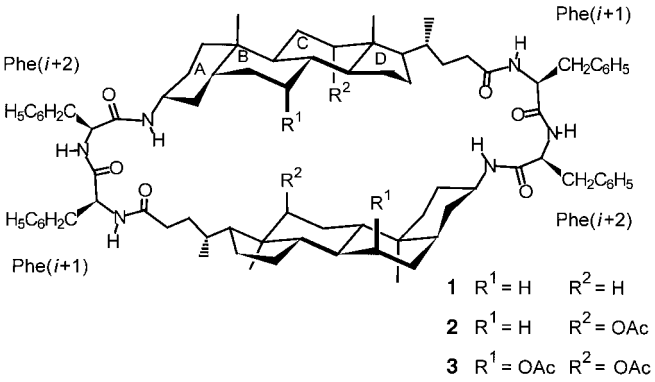
Crystal Structure of a Peptide–Steroid Macrocycle—Intramolecular Attraction between Steroids and Peptidic β(I) Turns**

Dieter Albert, Martin Feigel,* Jordi Benet-Buchholz, and Roland Boese

The concave surface of cholanic acids seems to be preorganized to bind molecular guests through weak interactions. Examples are the cholaphanes—synthesized by Davis, Bonar-Law, and co-workers from cholanic acid derivatives and aromatic spacers—which encapsulate carbohydrates and anions in solution.[1] Other researchers have used the hydroxyl groups on the α side of the steran residue to position covalently attached units such as peptides, carbohydrates, or polycyclic arenes.[2]

We intend to develop molecular hosts of designed characteristics by combining the rigid, concave surface of cholanic acids with the flexibility and functionality of amino acids.[3, 4] Analyzing the NMR spectra of compounds **1**–**3**, we found



1 $R^1 = H$ $R^2 = H$
2 $R^1 = H$ $R^2 = OAc$
3 $R^1 = OAc$ $R^2 = OAc$

that substitution of the cholanic surfaces by acetoxy groups influences the conformation of the peptide part.[4] The present work describes for the first time the solid-state structure of such a macrocycle (**1**) containing a steroid (lithocholic acid) and a dipeptide (Phe-Phe). The structure demonstrates that an optimal approach between the two steroidal surfaces in the molecule is achieved when the peptide parts fold to form two β(I) turns.

Compound **1** was obtained by cyclodimerization of the pentafluorophenol ester of bis(phenylalaninyl)-3-amidolithocholic acid.[4] Crystallization of **1** from chloroform yielded prisms which were suitable for X-ray diffraction. The structure was solved using the Patterson search method of Egert and Sheldrick;[5] the steran residue of lithocholic acid was used as a structural fragment. The macrocycle **1** adopts a compressed form of C_2 symmetry in the crystal. The two lithocholic acid units of the molecule are in van der Waals contact (Figure 1). The close contact between the α surface of

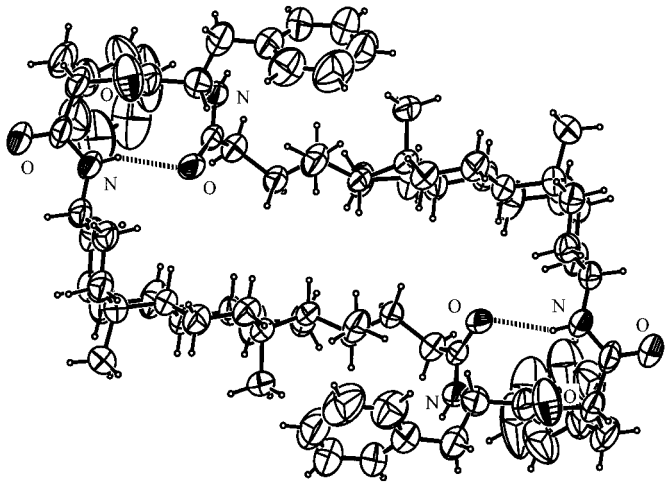


Figure 1. Structure of **1** in the crystal.

rings C and D and the branched side chain of the opposite lithocholic acid is particularly visible in Figure 1. The approach is achieved since the peptide parts of the molecule fold into β loops. The dihedral angles ϕ and ψ of the peptide parts (Phe$(i+1)$: $\phi/\psi = -75.7/-12.2$; Phe$(i+2)$: $\phi/\psi = -81.2/-3.5$) correspond to those found in a β(I) turn (residue$(i+1)$: $\phi/\psi = -60/-30$; residue$(i+2)$: $\phi/\psi = -90/0$).[6]

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