Synthesis of 6,13-Bis(thymidinyl)-5,12-dioxocyclams and the Molecular Structure of the (R,S)-Isomer

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The three stereoisomers of the 6,13-bis(thymidinyl)dioxocyclam 6 were synthesized through photoreaction of the chromium alkoxycarbene complex 2 and 1-(benzyloxycarbonyl)-4,4-dimethyl-Δ2-imidazoline. The molecular structure of (R,S)-6 was elucidated by X-ray crystallography.

Introduction

Fourteen-membered 1,4,8,11-tetraaza macrocycles (cyclams) and their 5,7-diones (dioxo cyclams) play important roles as ligands in catalysis as well as in metal complexation chemistry.1-5 Recently, Hegedus et al. have found an unusual and efficient route for the synthesis of the related 1,4,8,11-tetraaza 5,12-dions, which involves the acid-catalyzed cleavage/dimerization of azapenams produced by the photochemical cycloaddition reaction between N-protected imidazolines and chromium (alkoxy)carbene complexes.6-9 This route has the potential to afford cyclams that are not available by other synthetic methods. The utility of this method has been demonstrated in the synthesis of optically active dioxocyclams by employing optically active imidazolines.9 However, optically active chromium carbene complexes have not been attempted in the synthesis of optically active dioxocyclams having substituents at the 6- and the 13-position.

Interesting and novel properties have been found for supramolecular complexes in which interacting components are associated by non-covalent interactions.10 Nucleosides are good candidates for components interacting by hydrogen bonding.11 Here we report the synthesis and photochemical reaction of the chromium alkoxycarbene complex that has a thymidine moiety as the alkoxy substituent at the carbene carbon.

Results and Discussion

The dioxocyclams 6 were synthesized as a mixture of diastereomers through the route shown in Scheme 1: The chromium (pivaloyl)oxycarbene complex 1 was generated by the reaction of pivaloyl chloride and pentacarbonyl[methyl{(tetramethylammonio)oxy}carbene]chromium(0). The pivaloyloxy group was substituted by the thymidine derivative for which the secondary hydroxy group was protected with the tert-butyldimethylsilyl (TBDMS) group to give the alkoxycarbene complex 2.

A dichloromethane solution of carbene complex 2 and 1-(benzyloxycarbonyl)-4,4-dimethyl-Δ2-imidazoline in a Pyrex tube was irradiated under CO pressure (80 psi) with a medium-pressure mercury lamp. The combined yield of N-protected azapenams 3 was high (80%), but a diastereomeric mixture was obtained. The best yield resulted by using slightly less than one equivalent of the imidazoline. Excess imidazoline appeared to induce side reactions with the carbene complex. Each diastereomer was found to exist as a mixture of rotomers about the amide bond.

The benzyloxycarbonyl (BOC) group was removed readily at room temperature by Pd-catalyzed hydrogenolysis reaction in the presence of triethylamine to give free azapenams 4. The formation of hexahydrodiazepinones has been observed under acidic conditions. 9 The virtual 1 : 1 ratio of the diastereomers was clearly determined by 1H NMR, although separation was not feasible.

The 14-membered cyclic compounds 5 were formed in almost quantitative yield by treatment of the free azapenams 4 with camphorsulfonic acid. All three possible diastereomers were produced with insignificant selectivity: (R,R)-5 : (S,S)-5 : (R,S)-5 = 3 : 3 : 4. Interconversion between diastereomers has been known for the methoxy analogues to give the centrosymmetric isomer in high yield by crystallization under acidic conditions.8 Only slow decomposition to unidentified polar species was observed in a similar attempt.
with 5 to obtain one isomer as the predominant product. Fortunately, however, separation of (R,S)-5 from the mixture of (R,R)-5 and (S,S)-5 was achieved by conventional column chromatography on silica gel.

Reduction of 5 with sodium cyanoborohydride gave the dioxocyclams 6. In CDCl₃ solution (R,S)-6 exists as two distinct conformers in about 7 : 3 ratio, as evidenced by doubling of all peaks in the ¹H and ¹³C NMR spectra. However, only one set of resonance peaks was observed in the ¹H and ¹³C NMR spectra for each of the (R,R)- and the (S,S)-isomer. The stereochemistry of (R,S)-6 was confirmed by X-ray diffraction analysis: Details of the X-ray data collection and structural refinement are presented in Table 1. The molecular structure and atom-numbering schemes are given in Figure 1. Selected bond lengths and angles are given in Table 2.

Notable features of the crystal structure are the unsymmetrical interactions of the two thymidine units. One is interacting in an intramolecular fashion through hydrogen bonding between N(8) and O(1) (2.942 Å) while the other is interacting with another molecule through hydrogen bonding between N(6) and O(2) (2.849 Å).

**Experimental Section**

**General.** If not otherwise stated, all NMR spectra were recorded in CDCl₃ at 300 MHz for ¹H and 75.5 MHz for ¹³C. Chemical shifts are given in δ ppm relative to CDCl₃ (δ 7.72, ¹³C) or CHCl₃ (δ 7.26, ¹H) which is present as an impurity in CDCl₃ used. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR.

The following chemicals were prepared according to literature procedures: pentacarbonylmethyl][tetramethy-

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**Table 1. Crystallographic Data for (R,S)-6**

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**Table 2. Selected Bond Lengths (Å) and Angles (deg) for (R,S)-6**

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**Figure 1.** The molecular structure of (R,S)-6.
lammno)(oxy) carbene]chromium(0),12 1-(benzylxycarbonyl)-4,4-dimethyl-A2-imidazoline,13 and the TBDMS-protected thymidine.14

Chromoborne Complex 2. Pentacarbomyl[methyl \{[(tetramethylammonio)oxy] carbene]chromium(0) (583 mg, 1.89 mmol) was dissolved in dry CH2Cl2 (15 mL) under an argon atmosphere, and the solution was cooled to −65 °C. Pivaloyl chloride (0.23 mL, 1.9 mmol) was added dropwise, and the resulting suspension was stirred at −65 °C~−25 °C over 3 h. The suspension was cooled again to −65 °C and a solution of the TBDMS-protected thymidine (565 mg, 1.72 mmol) in dry CH2Cl2 (5 mL) was added through a cannula, and the resulting suspension was stirred at −65 °C~−25 °C over 15 h. The suspension was diluted with CH2Cl2 (60 mL), washed with H2O (40 mL × 2) and brine (40 mL), dried over MgSO4, and the solvent was evaporated to yield a gum which was chromatographed on silica gel (1/1 ethyl acetate/hexane, Rf = 0.69) to give 562 (0.97 mmol, 57%) of complex 2 as yellow-orange solid.1 H NMR δ 9.08 (br s, 1 H, NH), 7.11 (s, 1H), 6.27 (dd, J1 = 6.6 Hz, J2 = 6.3 Hz, 1 H), 5.02 (br m, 2H), 4.56 (br s, 1H), 4.30 (br s, 1H), 3.02 (s, 3 H), 2.32 (m, 2H), 1.90 (s, 3H), 0.91 (s, 3H), 0.105 (s, 3H).13 C NMR δ 361.1, 223.0, 216.4, 163.8, 150.4, 135.5, 111.7, 85.6, 84.2, 71.6, 46.0, 25.9, 18.1, 12.7, −4.46/−4.76, IR (NaCl) ν 3201 (NH), 1719 (C=O), 1678 (C=O), 1605 (C=O). Anal. Calcd for C22H20N6O8Si: C, 56.67; H, 7.94; N, 11.01. Found: C, 56.47; H, 7.88; N, 10.86.

Unsaturated Dioxocyclam 5. The free azapenam 4 (225 mg, 0.442 mmol) and racemic camphorsulfonic acid (27 mg, 0.12 mmol) were dissolved in dry CH2Cl2 (10 mL), and the resulting solution was stirred at 25 °C for 24 h. The solution was diluted with CH2Cl2 (50 mL), washed with aqueous 5% NaHCO3 (20 mL) and brine (20 mL), and dried over MgSO4. The solvent was evaporated to give 216 mg (0.212 mmol, 96%) of a mixture which appeared as two spots (ethyl acetate: Rf = 0.66 and 0.52) on TLC. (R,S)-5:1 H NMR (two conformers, abf/73 δ 9.33(b)/9.32(a) (br s, 2H), 9.08(b)/8.50(a) (s, 2H), 7.89(a)/7.72(b) (s, 2H), 7.66(a)/7.62(b) (s, 2H), 6.40(b)/6.27(a) (dd, J1 = 5.7/6.6 Hz, J2 = 6.4/6.6 Hz), 4.79(b)/4.42(a) (br s, 2H), 4.10(a)/3.95(b) (br s, 2H), 3.90-3.70 (m, 4H), 3.60-3.20 (m, 4H), 2.30-2.05 (m, 4 H), 1.92(a)/1.90(b) (s, 6H), 1.54/1.51/1.47 (s, 12H), 1.22 (s, 6H), 0.87 (s, 18H), 0.88(b)/0.072(a)/0.063(b)/0.054(a) (s, 12H).13 C NMR δ 169.0(a)/168.5(b), 167.9, 164.3, 150.6(b)/150.5(a), 135.6(a)/136.0(b), 110.9(b)/110.8(a), 86.9(b)/86.4(a), 85.9(a)/85.2(b), 80.2(a)/80.1(b), 73.1(b)/72.7(a), 70.6(b)/69.7(a), 65.9(b)/65.6(a), 53.8(a)/53.7(b), 41.3(a)/41.2(b), 25.9(b)/25.8(a), 25.2(b)/25.0(a), 24.8(a)/24.7(a), 24.4, 18.1(a)/18.0(b), 12.8(b)/12.2(a), −4.52(a)/−4.59(b)/−4.69/4.69, −4.72(b). IR (NaCl) ν 3198 (NH), 1688 (C=O), 1678 (C=O) cm−1. (R,R)-5 + (S,S)-5:1 H NMR δ 9.12/9.01 (br s, 2H), 7.91/7.77 (s, 2H), 7.73/7.65 (s, 2H), 7.59/7.50 (s, 2H), 6.37/6.29 (dd, J1 = 6.6/6.6 Hz, J2 = 6.7/6.9 Hz, 2H), 4.62/4.42 (br m, 2H), 4.02/3.97 (br d, J = 2.7/2.1 Hz, 2H), 3.80-3.35 (m, 8 H), 2.30-2.05 (m, 4H), 1.91 (s, 6H), 1.52/1.51 (s, 6H), 1.39/1.37/1.35/1.34 (s, 12H), 0.88 (s, 18H), 0.082/0.076 (s, 12H).13 C NMR δ 168.8, 167.7/167.0, 164.1/163.8, 150.5/150.4, 136.5/135.7, 111.2/110.9, 86.4/86.3, 85.8/85.0, 81.1/80.7, 73.0/72.6, 68.2/67.9, 65.3/64.7, 54.3/54.2, 41.2/41.1, 25.9, 26.1/25.6, 25.5/25.2, 23.1/21.8, 18.1, 12.9/12.3, −4.45/4.54/4.59/4.65. IR (NaCl) ν 3191 (NH), 1688 (C=O) cm−1.

Dioxocyclam 6. The unsaturated dioxocyclam 5 (176 mg, 0.172 mmol), NaBH4CN (23 mg, 0.37 mmol), and a small amount of bromoresol green were dissolved in 1 : 1 MeOH/CH2Cl2 (4 mL). HCI/MeOH (0.9 N) was added dropwise to the cooled (0 °C) blue solution until the yellow-green color remained, and the resulting solution was stirred at 0 °C~25 °C for 24 h. HCl/MeOH (0.9 N) was added, and the resulting yellow solution was stirred for 30 min to destroy NaBH4CN unreacted. Aqueous 5% NaOH was added until the solution turned to blue. The solvents were evaporated, and the resulting residue was dissolved in CH2Cl2 (30 mL).


The solution was washed with H2O (20 mL) and brine (20 mL), and dried over K₂CO₃. The solvent was evaporated to give 101 mg (0.0989 mmol, 57%) of a white solid, which was recrystallized from hexane and a small amount of CH₂Cl₂ to give 77 mg (0.075 mmol, 44%) of white micro crystals. (R,S)-(R,S)-6. 1H NMR (two conformers, a/b ~ 7/3) δ 9.85 (br s, 2 H), 7.20(a)/7.15(b) (s, 2H), 7.11(a)/6.85(b) (s, 2H), 6.11(a)/6.03(b) (dd, J₁ = 6.3,6.6 Hz, J₂ = 6.6/6.6 Hz, 2 H), 4.30 (m, 2H), 3.91 (m, 2H), 3.73-3.45 (m, 4H), 3.45-3.25/2.80-2.60 (m, 6H), 2.20-2.10 (m, 4H), 1.88(a)/1.86(b) (s, 6H), 1.31(b)/1.10(b) (s, 6H), 1.30 (s, 12H), 0.85 (s, 18H), 0.045 (s, 12H). 13C NMR δ 171.6(b)/171.5(a), 164.2(a)/

X-ray Structure Analysis of (R,S)-6. Crystals of (R,S)-6 were grown from a CH₂Cl₂-MeOH-hexane solution at room temperature. Diffraction data were collected by employing graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) at 163 K. A total of 13912 reflections were measured over the following ranges: 2.50 ≤ 2θ ≤ 46.50°, −16 ≤ θ ≤ 17, −12 ≤ k ≤ 12, −19 ≤ l ≤ 20. The crystallographic data and additional details of data collection are summarized in Table 1. The structure was refined by full-matrix least-squares methods. All the non-hydrogen atoms were refined anisotropically. The final cycle of refinement led to the R indices listed in Table 1.

Conclusion

A novel chromium carbene complex 2, which has a thymidine moiety as the alkoxy substituent at the carbene carbon, was synthesized. Its photochemical cycloaddition reaction with an achiral imidazoline produced the corresponding aza- penams 3 in good yield. The unsaturated dioxocyclams 5 were formed by dimerization of the free azapenam 4. Insignificant stereoselectivity was observed in the photochemical cycloaddition as well as in the dimerization. However, the unsaturated dioxocyclam (R,S)-5 was separated from the other isomers. The molecular structure of the dioxocyclam (R,S)-6 was determined by X-ray crystallography.

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Supplementary Material Available. Tables of crystal data, atom coordinates, bond lengths and angles, and anisotropic displacement parameters for (R,S)-6 (7 pages). Ordering information is given on any current masthead page.

References