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Abstract – A new [2+2] photodimerization of 5-chloro- and 5-methyl-2-pyridones to the corresponding cis-anti-dimer in an inclusion complex with 1,1’-biphenyl-2,2’-dicarboxylic acid was found. This reaction is a good model of thymine dimerization in a nucleotide which causes damage to DNA. A new [4+4] photodimerization of 5-chloro-2-pyridone to the cis-syn-dimer in the inclusion complex with 1,2,4,5-benzenetetracarboxylic acid was also found. The mechanism of these stereoselective photoreactions in the solid state was studied by X-Ray analysis.

In relation to damage to DNA by [2+2] photodimerization of its basic component thymine in nucleotide (1) to the cis-syn-dimer (2), photodimerization reactions of 2-pyridone derivatives represent a very important research subject. However, no adequate [2+2] photodimerization of 2-pyridone derivative as a model of the thymine photodimerization reaction has been reported thus far. We report [2+2] photodimerizations of 5-chloro- (3b) and 5-methyl-2-pyridones (3c) to the cis-anti-dimers (4b) and (4c), respectively, as inclusion complexes with a simple carboxylic acid host, 1,1’-biphenyl-2,2’-dicarboxylic acid (5). Although some [4+4] photodimerizations of 2-pyridones to trans-anti-dimers have been reported, no any photoreaction which gives the cis-syn-dimer has been reported. We succeeded in preparing the cis-syn-dimer (14) of 3b by carrying out the photoreaction of 3b in an inclusion complex with 1,2,4,5-benzenetetracarboxylic acid (12). The mechanism of these stereoselective reaction was studied by X-Ray analysis.

Recrystallization of 5 and 3b from AcOEt gave a 1:2 inclusion complex (6) of 5 and 3b. Photoirradiation of powdered 6 using a 400 W high-pressure Hg-lamp at room temperature for 30 h gave cis-anti-dimer

This paper is dedicated to Dr. Pierre Potier on the occasion of his 70th birthday.
(4b) in 93% yield. Similar photoirradiation of a 1:2 inclusion complex (7), which had been prepared by recrystallization of 5 and 3c from MeOH, gave cis-anti-dimer (4c) in 86% yield.

The cis-anti-dimer structure of 4b and 4c was elucidated by X-Ray analysis. Crystallographic data for 4b and 4c are comparable. In Figures 1 and 2, the crystal structures of 4b and 4c are shown. In the photoreaction of 3b and 3c to 4b and 4c, respectively, as the inclusion complexes with 5, the following three interesting aspects were discovered. Firstly, the Cl- or Me-substituent at the C5 of 3 is important for causing the photodimerization reaction so as to proceed in a [2+2] manner, since photoirradiation of a 1:2 inclusion complex of 5 and the unsubstituted 2-pyridone (3a) gave the [4+4] trans-anti-dimer (8a) but not the [2+2] dimer (4a). Secondly, photoreaction of 3b and 3c is strongly controlled so as to proceed in a [2+2] manner by the crystalline lattice of the inclusion complex. This is also an interesting result, since photoirradiation of 3b in EtOH for 20 h gave the [4+4] trans-anti-dimer (8b) in 42% yield. Photoreaction of 3a in solution for 72 h gave 8a in 40% yield. Photoirradiation of powdered 3b in the
solid state for 30 h also gave $8b$ in 73% yield. X-Ray structural analysis of $3b$ showed that $3b$ molecules are ordered at the positions so as to give $8b$ by the dimerization reaction. However, photoreaction of $3c$ did not occur in the solid state. Thirdly, it is also unusual that the [2+2] photodimerization of $3b$ and $3c$ occurs at their C5-C6 double bond but not at C3-C4 one. As the sole example of a [2+2] photodimerization of a 2-pyridone derivative, photoreaction of 3-methyl-2-pyridone ($9$) in an inclusion complex with 1,1,6,6-tetraphenylhexa-2,4-diyne-1,6-diol ($11$) in the solid state which gives trans-anti-dimer ($10$) in 22% yield has been reported. In this case, however, the dimerization reaction occurred at the C3-C4 double bond, but not at C5-C6.

Figure 1. X-Ray structure of $4b$.

Figure 2. X-Ray structure of $4c$. 
In order to clarify the interesting and unusual photodimerization of 3 to 4, the X-Ray structures of 6 and 7 were analyzed. Crystal structures of 6 and 7 are comparable. In Figures 3 and 4, the crystal structures of 6 and 7 are shown. In Figure 3, two 3b molecules bind to one host molecule (5) through the formation of COOH---O=C- hydrogen bonds and these two 3b molecules are arranged at close positions so as to give the cis-anti-dimer (4b) on photodimerization. The distance between the two C5-C6 double bonds of 3b molecules is very short (3.46 Å). In Figure 4, 3c molecules are similarly ordered as are 3b molecules ordered in Figure 3, by formation of the hydrogen bond. This is the reason why photoirradiation of 6 and 7 gives the cis-anti-dimer (4) by the [2+2] dimerization reaction between the C5-C6 double bonds of 3.

Figure 3. X-Ray structure of 6.

Figure 4. X-Ray structure of 7.
The data described above leads to the following conclusion. For the [2+2] photodimerization of 2-pyridone at its C5-C6 double bond, the 2-pyridone molecules should have a substituent at C5 and should be arranged at appropriate close positions as shown in Figures 3 and 4. It has been reported that electron density on the C5 increases by a substituent on C5 and then reactivity of the C5-C6 double bond increases. This is common to those thymine molecules in 1 which have a Me-group at C5 and are arranged at appropriate positions for photodimerization, although the dimerization of thymine gives the *cis-syn*-dimer. Finally, the [2+2] photodimerization of 3b and 3c in their inclusion complexes with 5 is proven to be a nice model for the thymine photodimerization in the nucleotide of DNA.

As described above, the *trans-anti*-dimer (8) can easily be obtained by the [4+4] photodimerization of 2-pyridones (3) in solution, in the solid state or in the inclusion complex with a host compound. However, preparation of the *cis-syn*-dimer by [4+4] photodimerization of 3 has never been achieved. We succeeded in preparing the *meso-cis-syn*-dimer (14) by photoirradiation of a 1:4 inclusion complex (13) of 1,2,4,5-benzenetetracarboxylic acid (12) and 3b. Photoirradiation of powdered 13 for 100 h gave a mixture of 14, 4b and an unidentified dimeric product in 51, 2 and 18% yields, respectively. Since 14 is labile, its yield was determined together with those of the other two products by 1H NMR spectral analysis of their mixture. However, a single crystal of 14 for X-Ray analysis was obtained by recrystallization of the reaction mixture from acetone as a 1:1 complex with acetone. 14 is stable for X-Ray analysis in its crystal.

The *meso-cis-syn*-structure of 14 was elucidated by X-Ray analysis of its 1:1 inclusion complex with acetone (Figure 5). In order to clarify the steric course of the photodimerization of 3b to 14 in 13, the X-Ray crystal structure of 13 was studied. As shown in Figures 6 and 7, four 3b guest molecules bind to one 12 host molecule through hydrogen bond formation. The two relevant hydrogen bonds, COOH---O=C between the host and the guest molecules and NH---O=C between the guest molecules, are shown schematically in Figure 7. In 13, two 3b molecules are spatially arranged as mirror image and their [4+4] dimerization should give the *meso-cis-cyn*-dimer (14). Since a 1:2 inclusion complex (15) of 12 and 3c, was inert to the photoirradiation, the chlorine atom of 3b would play an important role in the molecular arrangement as shown in Figures 6 and 7 and the efficient photodimerization in the inclusion complex.
Figure 5. X-Ray structure of a 1:1 complex of 14 and acetone.

Figure 6. X-Ray structure of 13.

Figure 7. A schematic structure of 13 in which A-A and B-B photodimerizations occur.
EXPERIMENTAL

GENERAL PROCEDURES
Photoreactions were carried out by irradiation with using 400W High Pressure Hg-lamp under air at room temperature.

X-RAY CRYSTALLOGRAPHY
The diffraction data were collected on a Rigaku RAXIS-IV imaging plate diffractometer with MoKα radiation (λ = 0.71070 Å) to a maximum 2θ value of 55.0°. The reflection data were corrected for the Lorentz-polarization effects and secondary extinction. The readout was performed in the 0.100 mm pixel mode. The structure was solved by the direct method and refined by the full-matrix least-squares method by using a TEXSAN program. The non-hydrogen atoms were refined anisotropically.

Preparation of a 1:2 Inclusion Complex (6) of 3c and 5.
When a solution of 5 (102 mg, 0.421 mmol) and 3b (107 mg, 0.826 mmol) in AcOEt (0.8 mL) was kept at rt for 24 h, a 1:2 inclusion complex (6) of 5 and 3b was obtained as colorless crystals (148 mg, 71%, mp 128.0-128.5 ºC).

Preparation of a 1:2 Inclusion Complex (7) of 3c and 5.
When a solution of 5 (102 mg, 0.421 mmol) and 3c (90.9 mg, 0.833 mmol) in MeOH (1.2 mL) was kept at rt for 24 h, a 1:2 inclusion complex (7) of 5 and 3c was obtained as colorless crystals (119 mg, 62% yield, mp 162-163 ºC).

Preparation of a 1:4 Inclusion Complex (13) of 3b and 12.
When a solution of 12 (99.0 mg, 0.390 mmol) and 3b (101 mg, 0.780 mmol) in MeOH (2 mL) was kept at rt for 24 h, a 1:4 inclusion complex (13) of 12 and 3b was obtained as colorless crystals (103 mg, 34%, mp 202-209 ºC).

Preparation of a 1:2 Inclusion Complex (15) of 12 and 3c.
When a solution of 12 (103 mg, 0.405 mmol) and 3c (85.6 mg, 0.784 mmol) in MeOH (2 mL) was kept at rt for 24 h, a 1:2 inclusion complex (15) was obtained as colorless crystals (100 mg, 54%, mp 195-199 ºC).

Photoreaction of 6 in the Solid State.
Crude product obtained by photoirradiation of powdered 6 (95.0 mg) in the solid state for 30 h was washed with saturated aqueous NaHCO₃ to give crude 4b as colorless powder. Recrystallization of the crude 4b from MeOH gave 4b as colorless crystals (45.7 mg, 93% yield, mp>360 ºC). Anal. Calcd for C₁₀H₈N₂O₂Cl₂: C, 46.36; H, 3.11; N, 10.81. Found: C, 46.66; H, 3.03; N, 10.75. ¹H NMR (500 MHz,
CF3COOD, δ): 4.94 (2H, s), 6.17 (2H, d, J = 10.1 Hz), 6.80 (2H, d, J = 10.1 Hz); 13C NMR (125 MHz, CF3COOD, δ): 59.3, 71.24, 126.67, 142.13, 168.46.

**Photoreaction of 7 in the Solid State.**

Crude product obtained by photoirradiation of 7 (106 mg) in the solid state for 100 h was column chromatographed on alumina using CHCl3-MeOH (9:1) as solvent to give crude 4c as colorless crystals. Recrystallization of the crude 4c from MeOH gave pure 4c as colorless crystals (43.1 mg, 86%, mp 299.5-300 °C). Anal. Calcd for C12H14N2O2: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.22; H, 6.19; N, 12.76. 1H NMR (500 MHz, CF3COOD, δ): 1.48 (6H, s), 4.05 (2H, s), 6.11 (2H, d, J = 10.1 Hz), 6.88 (2H, d, J = 10.4 Hz); 13C NMR (125 MHz, CF3COOD, δ): 27.19, 47.12, 66.06, 123.04, 151.49, 169.99.

**Photoreaction of 3b in the Solid State.**

Photoirradiation of powdered 3b (100 mg) was irradiation in the solid state for 30 h gave 8b, after washing with MeOH (10 mL), as colorless crystals (73.0 mg, 73%).

**Photoreaction of 13 in the Solid State.**

Photoirradiation of powdered 13 (180 mg) in the solid state for 100 h gave a crude reaction mixture. The mixture was washed with MeOH (10 mL) to give a solid. 1H NMR spectral analysis showed that the solid consisted of 14 (61.6 mg, 51%), 4b (2.4 mg, 2%) and an unidentified dimer (21.7 mg, 18%) produced in the yields indicated. For 14, 1H NMR (500 MHz, CF3COOD, δ): 3.78 (2H, dd, J = 2.4 and 4.6 Hz), 4.47 (2H, m), 5.94 (2H, m); 13C NMR (125 MHz, CF3COOD, δ): 49.63, 64.72, 126.43, 143.08, 183.61. Recrystallization of the solid from acetone gave a 1:1 complex of 14 and acetone.

**Crystallographic Data for 4b:** Formula = C10H8N2O2Cl2, MW = 259.08, Crystal System = monoclinic, Space group = Cc (#9), Lattice Parameters a = 13.0410(5) Å, b = 10.8975(4) Å, c = 7.4136(2) Å, β = 102.994(2) °, V = 1026.60(6) Å³, Z = 4, De calc = 1.676 g/cm³, T = 93 K, number of unique reflection = 1129, Rint = 0.0190 up to a 2θ = 55.0 °, number of parameters = 146, R₁ = 0.0227, wR = 0.0653, Gof = 1.157 for 1115 reflections.

**Crystallographic data for 4c:** Formula = C12H14N2O2, MW = 218.25, Crystal System = tetragonal, Space group = I41/a (#88), Lattice Parameters a = 12.9385(1) Å, c = 13.1962(2) Å, V = 2209.11(4) Å³, Z = 8, De calc = 1.312 g/cm³, T = 173 K, number of unique reflection = 1295, Rint = 0.020 up to a 2θ = 55.0 °, number of parameters = 1151, R₁ = 0.0362, wR = 0.1699, Gof = 1.009 for 1242 reflections.

**Crystallographic Data for 6:** Formula = C14H10O4·2(C5H4NOCl), MW = 501.32, Crystal System = monoclinic, Space group = P2/c (#13), Lattice Parameters a = 17.2292(2) Å, b= 15.0443(2) Å, c = 18.9657(2) Å, β = 114.4248(3) °, V = 4475.98(9) Å³, Z = 8, De calc = 1.488 g/cm³, T = 113 K, number of unique reflection = 10228, Rint = 0.039 up to a 2θ = 55.0 °, number of parameters = 613, R₁ = 0.0345, wR = 0.0917, Gof = 1.073 for 7910 reflections.
Crystallographic Data for 7: Formula = C_{14}H_{10}O_{4}·2(C_{6}H_{7}NO), MW = 460.49, Crystal System = monoclinic, Space group = C2/c (#15), Lattice Parameters a = 15.1110(3) Å, b = 15.0153(3) Å, c = 10.1193(3) Å, β = 96.0058(7) °, V = 2283.43(9) Å^{3}, Z = 4, Dcalc = 1.339 g/cm^{3}, T = 173 K, number of unique reflection = 7812, Rint = 0.036 up to a 2θ = 55.0 °, number of parameters = 154, R_{1} = 0.0520, wR = 0.1675, Gof = 1.013 for 2609 reflections.

Crystallographic Data for 13: Formula = C_{10}H_{6}O_{6}·4(C_{5}H_{4}NCl), MW = 772.34, Crystal System = monoclinic, Space group = C2/c (#15), Lattice Parameters a = 22.1471(6) Å, b = 10.2111(3) Å, c = 14.3422(3) Å, β = 90.265(1) °, V = 3243.4(1) Å^{3}, Z = 4, Dcalc = 1.582 g/cm^{3}, T = 173 K, number of unique reflection = 3089, Rint = 0.044 up to a 2θ = 55.0 °, number of parameters = 1151, R_{1} = 0.0347, wR = 0.1069, Gof = 0.0997 for 3560 reflections.

Crystallographic Data for a 1:1 Complex of 14 and Acetone: Formula = C_{10}H_{8}N_{2}O_{2}Cl_{2}·C_{3}H_{6}O, MW = 317.17, Crystal System = orthorhombic, Space group = Pnma (#62), Lattice Parameters a = 7.4908(2) Å, b = 11.9813(4) Å, c = 15.8317(5) Å, V = 1420.89(8) Å^{3}, Z = 4, Dcalc = 1.498 g/cm^{3}, T = 173 K, number of unique reflection = 1573, Rint = 0.038 up to a 2θ = 55 °, number of parameters = 1439, R_{1} = 0.0691, wR = 0.2378, Gof = 1.498 for 1573 reflections.

REFERENCES
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