A new [2 + 2] photodimerization of 5-chloro- and 5-methyl-2-pyridone in their inclusion complexes with 1,1′-biphenyl-2,2′-dicarboxylic acid as a model for DNA damage by photodimerization of its thymine component

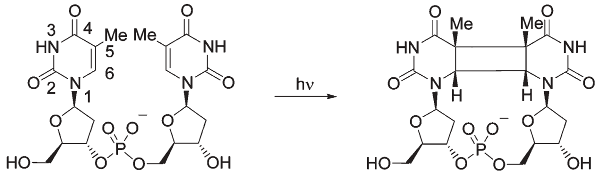
Shinya Hirano, Shinji Toyota and Fumio Toda*

Received (in Cambridge, UK) 16th September 2004, Accepted 27th October 2004
First published as an Advance Article on the web 13th December 2004
DOI: 10.1039/b414134b

As a model for DNA damage by photodimerization of its thymine component, a new [2 + 2] photodimerization of 5-chloro and 5-methyl-2-pyridone to the corresponding *cis-anti*-dimers as their inclusion complexes with 1,1′-biphenyl-2,2′-dicarboxylic acid was found, and the mechanism of this stereoselective solid state reaction was studied by X-ray analysis.

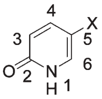
In relation to the damage of DNA caused by [2 + 2] photodimerization of its basic thymine nucleotide component (**1**) to the *cis-syn*-dimer (**2**), photodimerization reactions of thymine and 2-pyridone derivatives are a very important research subject. However, no adequate [2 + 2] photodimerization of thymine and 2-pyridone derivatives as a model for the thymine photodimerization reaction has been reported so far. We report [2 + 2] photodimerizations of 5-chloro- (**3b**) and 5-methyl-2-pyridone (**3c**) to the *cis-anti*-dimers **4b** and **4c**, respectively, as their inclusion complexes with a simple carboxylic acid host, 1,1′-biphenyl-2,2′-dicarboxylic acid (**5**). The mechanism of the stereoselective reaction was studied by X-ray analysis. Nevertheless, thymine was inert to the photoreaction in its single crystal. Although photodimerization of thymine itself has been reported to occur in its thin film form, the reaction occurs only in the presence of water.[1]

Recrystallization of **5** and **3b** from AcOEt gave a 1 : 2 inclusion complex (**6**) of **5** and **3b**. Photoirradiation of powdered **6** for 30 h gave the *cis-anti*-dimer (**4b**) in 93% yield. Similar photoirradiation of the 1 : 2 inclusion complex (**7**), which had been prepared by recrystallization of **5** and **3c** from MeOH, gave the *cis-anti*-dimer (**4c**) in 86% yield.†



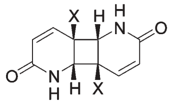
1

2

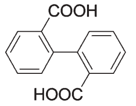


3

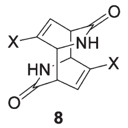
a: X = H
b: X = Cl
c: X = Me



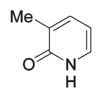
4



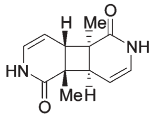
5



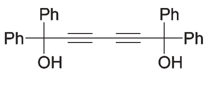
8



9



10



11

The *cis-anti*-dimer structure of **4b** and **4c** was elucidated by X-ray analysis. The structures of **4b** and **4c** are comparable. In Fig. 1, the crystal structure of **4c** is shown. In the photoreaction of **3b** and **3c** to **4b** and **4c**, respectively, as their inclusion complexes with **5**, the following three interesting things were found. First, the Cl- or Me-substituent at the C5 of **3** is important in causing the photodimerization reaction to proceed in the [2 + 2] manner, since photoirradiation of the 1 : 2 inclusion complex of **5** and the unsubstituted 2-pyridone (**3a**) gave [4 + 4] *trans-anti*-dimer (**8a**) but not the [2 + 2] dimer **4a**.[2] Secondly, photoreaction of **3b** and **3c** is strongly controlled so as to proceed in the [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,[3] and since photoirradiation of **3b** in EtOH containing a half molar amount of **5** also gave **8b**. Reaction of **3c** in solution gave the similar product, **8c**.[4] Photoirradiation of powdered **3b** in the solid state for 30 h gave **8b** in 73% yield. X-ray structural analysis of **3b** showed that the **3b** molecules are located in positions so as to yield **8b** by the dimerization reaction.[5] However, photoreaction of **3c** did not occur in the solid state. Thirdly, it is also a unusual that the [2 + 2] photodimerization of **3b** and **3c** occurs at their C5–C6 double bond but not at the 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.[6] In this case, however, the dimerization reaction occurred at C3–C4 double bond, but not at C5–C6 one.

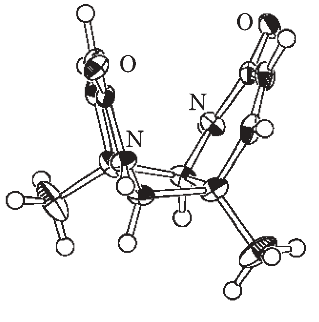


Fig. 1 X-ray structure of **4c**.

---

*toda@chem.ous.ac.jp

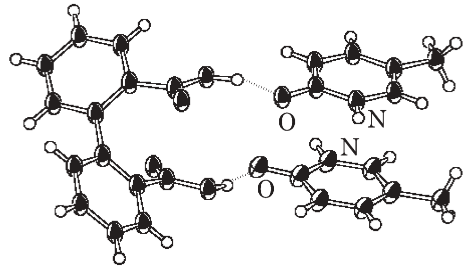


Fig. 2 X-ray structure of **7**.

In order to clarify this 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 Fig. 2, the crystal structure of **7** is shown. In **7**, two **3c** molecules bind to one host molecule **5** through the formation of –COOH···O=C– hydrogen bonds and these two **3c** molecules are arranged at close positions so as to give the *cis-anti*-dimer (**4c**) on photodimerization. The distance between the two C5–C6 double bonds of **3c** molecules is very short, 3.46 Å. This is the reason why photoirradiation of **6** and **7** give the *cis-anti*-dimer (**4**) by the [2 + 2] dimerization between C5–C6 double bonds of **3**.

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 Fig. 2. It has been reported that electron density on the C5 increases by a sustituent on C5 and then reactivity of the C5–C6 double bond increases.[7] 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.

Shinya Hirano, Shinji Toyota and Fumio Toda*
Department of Chemistry, Faculty of Science, Okayama University of Science, Ridai-cho 1-1, Okayama, 700-0005, Japan.
E-mail: toda@chem.ous.ac.jp; Fax: +81-86-256-9604;
Tel: 81-86-256-9604

Notes and references

† Experimental: When a solution of **5** (102 mg) and **3b** (107 mg) in AcOEt (0.8 ml) was kept at room temperature for 24 h, a 1 : 2 inclusion complex (**6**) of **5** and **3b** was obtained as colorless crystals (148 mg, 71% yield, mp 128.0–128.5 °C). Crude product obtained by photoirradiation of powdered **6** (95 mg) in the solid state using a 400 W Hg-lamp for 30 h, was washed with aqueous NaHCO$_3$ followed by recrystallization from MeOH to give **4b** as colorless crystals (45.7 mg, 93% yield, mp > 360 °C). Anal. Calcd for C$_{10}$H$_8$C$_{12}$N$_2$O$_2$: C, 46.36; H, 3.11; N, 10.81%. Found: C, 46.66; H, 3.03; N, 10.75%. ^{1}H NMR (500 MHz, CF$_3$COOD, δ): 4.94 (2H, s), 6.17 (2H, d, J = 10.1 Hz), 6.80 (2H, d, J = 10.1 Hz); ^{13}C NMR (125 MHz, CF$_3$COOD, δ): 59.3, 71.24, 126.67, 142.13, 168.46. When a solution of **5** (102 mg) and **3c** (90.9 mg) in MeOH (1.2 ml) was kept at room temperature for 24 h, a 1 : 2 inclusion complex (**7**) of **5** and **3c** was obtained as colorless crystals (119 mg, 62% yield, mp 162.0–163.0 °C). Crude product obtained by similar photoirradiation of **7** (106 mg) for 100 h, was column chromatographed on alumina using CHCl$_3$–MeOH (9 : 1) as solvent followed by recrystallization from MeOH to give **4c** as colorless crystals (43.1 mg, 86% yield, mp 299.5–300 °C). Anal. Calcd for C$_{12}$H$_{14}$N$_2$O$_2$: C, 66.04; H, 6.47; N, 12.84%. Found: C, 66.22; H, 6.19; N, 12.76%. ^{1}H NMR (500 MHz, CF$_3$COOD, 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); ^{13}C NMR (125 MHz, CF$_3$COOD, δ): 27.19, 47.12, 66.06, 123.04, 151.49, 169.99. The diffraction data were collected on a Rigaku RAXIS-IV imaging plate diffractometer with Mo Kα 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 direct methods and refined by the full-matrix least-squares method by using a $_{\mathrm{TE}}$X$_{\mathrm{SAN}}$ program. The non-hydrogen atoms were refined anisotropically. Crystallographic data for **4b**: Formula = C$_{10}$H$_8$Cl$_2$N$_2$O$_2$, 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) Å^3, Z = 4, D_{calc} = 1.676 g cm^{-3}, T = 93 K, number of unique reflections = 1129, R_{int} = 0.0190 up to a 2θ = 55°, number of parameters = 146, R_1 = 0.0228, wR = 0.0610, gof = 1.648 for 1115 reflections. Crystallographic data for **4c**: Formula = C$_{12}$H$_{14}$N$_2$O$_2$, 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) Å^3, Z = 8, D_{calc} = 1.312 g cm^{-3}, T = 173 K, number of unique reflections = 1295, R_{int} = 0.020 up to 2θ = 55°, number of parameters = 1151, R_1 = 0.0362, wR = 0.1699, gof = 1.009 for 1242 reflections. Crystallographic data for **6**: Formula = C$_{14}$H$_{10}$O$_4$·2(C$_5$H$_4$ClNO), 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) Å^3, Z = 8, D_{calc} = 1.488 g cm^{-3}, T = 113 K, number of unique reflections = 10228, R_{int} = 0.039 up to 2θ = 55°, number of parameters = 613, R_1 = 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, D_{calc} = 1.339 g cm^{-3}, T = 173 K, number of unique reflections = 7812, R_{int} = 0.036 up to 2θ = 55°, number of parameters = 154, R_1 = 0.0520, wR = 0.1675, gof = 1.013 for 2609 reflections. CCDC 251193–251196. See http://www.rsc.org/suppdata/cc/b4/b414134b/ for crystallographic data in .cif or other electronic format.

1 S. Y. Wang, *Nature*, 1963, **200**, 879.
2 M. Yagi, S. Hirano, S. Toyota, F. Toda, P. Giastas and I. M. Mavridis, *Heterocycles*, 2003, **59**, 735.
3 W. L. Dilling, N. B. Tefertiller and A. B. Mitchell, *Mol. Photochem.*, 1973, **5**, 371.
4 E. C. Taylor and R. O. Kan, *J. Am. Chem. Soc.*, 1963, **85**, 776.
5 A. Kvick and S. S. Booles, *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.*, 1972, **28**, 3405.
6 M. Kuzuya, A. Noguchi, N. Yokota, T. Okuda, F. Toda and K. Tanaka, *J. Chem. Soc. Jpn.*, 1986, 1746.
7 M. Kuzuya, A. Noguchi and T. Okuda, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 3454.