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Solid-State Phase Transition of an Inclusion Complex of 5-Methyl-2-pyridone with 1,3,5-Benzenetricarboxylic Acid**

*Shinya Hirano, Shinji Toyota, Fumio Toda,**
*Kotaro Fujii, and Hidehiro Uekuasa**

Efficient and selective inter- and intramolecular photoreactions of guest compounds in their inclusion complexes with a host compound have long been studied.[1] We reported that photoirradiation of a 1:2 inclusion complex of 5-methyl- (**1a**) and 5-chloro-2-pyridone (**1b**) with a 2,2′-biphenyldicarboxylic acid host (**2**) gives the corresponding *rac-cis-anti* dimer **3a** and **3b**, respectively.[2,3] These [2+2] photodimerization reactions of 2-pyridone derivatives are important as models for DNA damage; this damage occurs by photodimerization of the thymine component of DNA, which is the cause of skin cancer. We also reported [4+4] photodimerizations of 2-pyridone itself (**1c**) and **1b** in their inclusion complexes with **2** and a 1,2,4,5-benzenetetracarboxylic acid host (**4**), respectively, which give the *rac-trans-anti* dimer **5c** and the *meso-cis-syn* dimer **6b**, respectively.[3,4] X-ray analyses of these inclusion complexes showed that the 2-pyridone molecules are ordered at reasonable positions for the corresponding photodimerization reactions in all cases.[2–4]

In some cases, however, the guest molecules are not located at appropriate positions for a photodimerization. Schmidt's rule states that for efficient photodimerization in the solid state, two olefin molecules should be arranged parallel and closer than 4.2 Å in the crystal.[5] Nevertheless, we found that a photochemically unreactive molecular aggregate of **1a** in an inclusion complex with a 1,3,5-benzenetricarboxylic acid host (**7**) can be transformed in the solid state into a reactive aggregate by heating or by contact with MeCN vapor. The mechanism of this novel phase transition was clarified by X-ray analysis.

A 1:1:1 inclusion complex (**8**) of **7**, **1a**, and MeOH, which was prepared as colorless crystals by recrystallization of **7** and **1a** from MeOH, was inert to photoirradiation. Very interestingly, however, the crystal of **8** was transformed by heating or by contact with MeCN vapor into a reactive powder of **9**, the solid-state photoirradiation of which gave the *meso-cis-syn* [4+4] dimer **6a** (Scheme 1). This is the first report of a phase transition in the solid state from photochemically unreactive molecular aggregate into a reactive aggregate caused by heating or contact with solvent vapor.

The phase transition of **8** into **9** did not occur by contact with vapor of EtCN, PhCN, tetrahydrofuran, acetone, CH_2Cl_2, $CHCl_3$, or *n*-hexane. This is an interesting example of a solvent effect in the solid state. A similar solvent effect was reported for a solid-state reaction that was accelerated in the presence of a small amount of solvent vapor.[6]

Since **6a** is thermally labile and can be converted easily into the *meso-cis-syn* [2+2] dimer **11**, **6a** was isolated as its stable 1:1:1 inclusion complex **10** consisting of **7**, **6a**, and H_2O, which was prepared by recrystallization of the photoirradiated powder of **9** from MeOH. The structure of **6a** was elucidated by comparison of its IR and ^1H NMR spectra with those of **6b**.[3] The structure of **6a** was finally confirmed by X-ray analysis of **10** (Figure 1). However, the simulated powder X-ray diffraction (PXRD) pattern of **10** was different from that of photoirradiated powder of **9** (see the Supporting Information). Heating of the thermally labile **6a** as **10** in CD_3COOD at 70 °C for 2 h gave **11** in quantitative yield. The structure of **11** was elucidated by comparison of its ^1H and ^{13}C NMR spectra with those of **3a**.[2,3] The *meso-cis-syn* dimer **11** is the first example of a [2+2] photodimer of 2-pyridone that has a *cis-syn* configuration. Compound **11** has the same configuration as that of the thymine dimer produced by photodimerization of the thymine component of a nucleotide in DNA.[7]

To know the mechanism of the unreactive-to-photoreactive phase transition of **8** into **9**, the crystal structure of **8** was studied by X-ray analysis. As shown in the packing diagram of **8** (Figure 2), molecules of **1a, 7**, and MeOH aggregate by forming four kinds of hydrogen bonds: COOH(**7**)···O=C(**1a**), C=O(**7**)···HN(**1a**), COOH(**7**)···OHMe, and C=O(**7**)···HOMe. The shortest contact between the reaction centers of two symmetry-related molecules of **1a** is C3–C6′ (= C6–C3′) = 5.04 Å. This distance is too far for reaction. Even if a [4+4] photodimerization of **1a** can be effected, the *trans-anti* dimer **5a** should be produced instead of *cis-syn* dimer **6a**, as is expected from the molecular ordering shown in Figure 2.

As the crystal of **8** did not retain its single crystalline form after the thermal phase transition at 120 °C, attempts to obtain single crystals suitable for X-ray diffraction were unsuccessful. The results of thermogravimetry and differential thermal analysis (TG/DTA) show that the phase transition is associated with the loss of MeOH molecules from **8** (see the Supporting Information), which is the cause of the disintegration of the single crystal. The decreasing weight corresponded to one MeOH molecule in the asymmetric unit. The phase transition was confirmed by the PXRD pattern of **8**

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[*] S. Hirano, Prof. Dr. S. Toyota, Prof. Dr. F. Toda
Department of Chemistry
Okayama University of Science
Ridai-cho, Okayama 700-0005 (Japan)
Fax: (+81) 86-256-9604
E-mail: toda@chem.ous.ac.jp

K. Fujii, Prof. Dr. H. Uekuasa
Department of Chemistry and Materials Science
Tokyo Institute of Technology
Ookayama 2, Meguro-ku, Tokyo 152-8551 (Japan)
Fax: (+81) 3-5734-3529
E-mail: uekusa@cms.titechl.ac.jp

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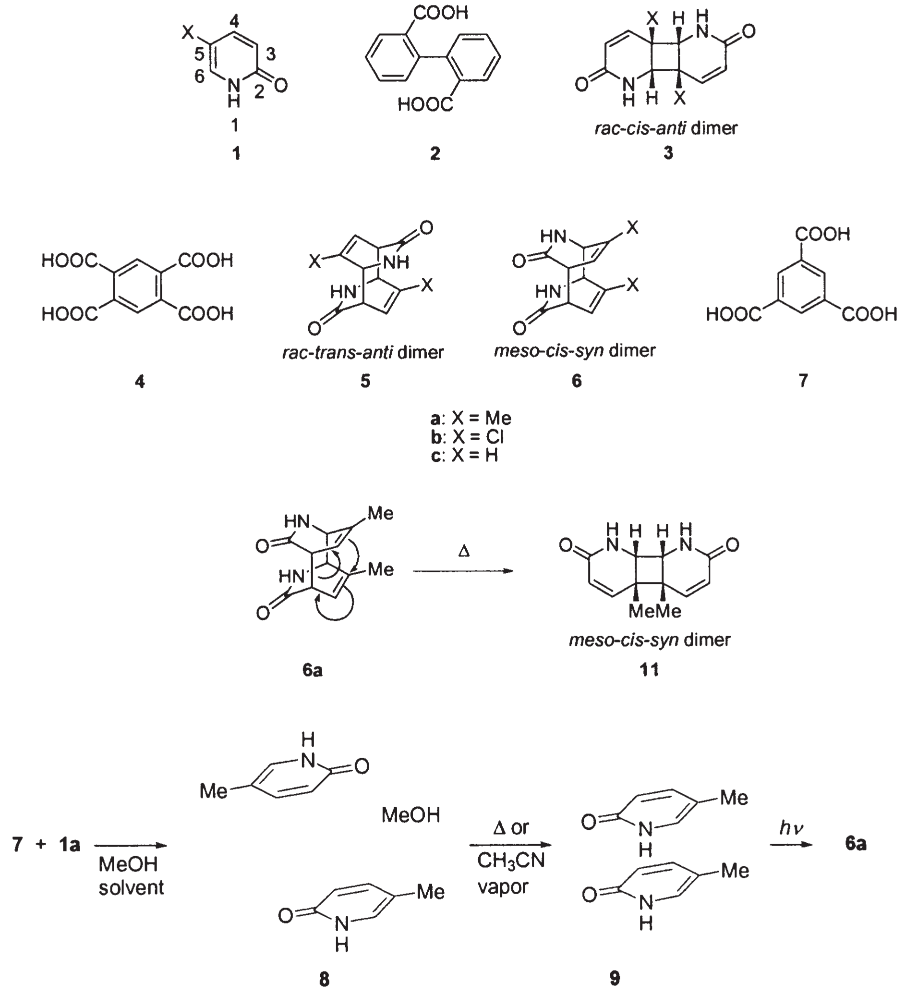
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. Transformation from photochemically unreactive **8** into reactive **9** in the solid state. Host **7** is omitted for clarity.

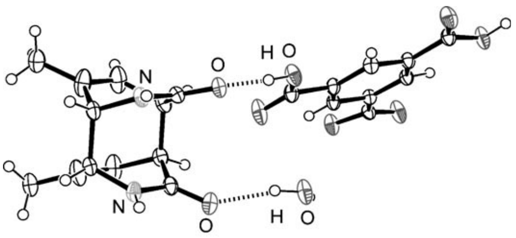


Figure 1. X-ray crystal structure of **10**.

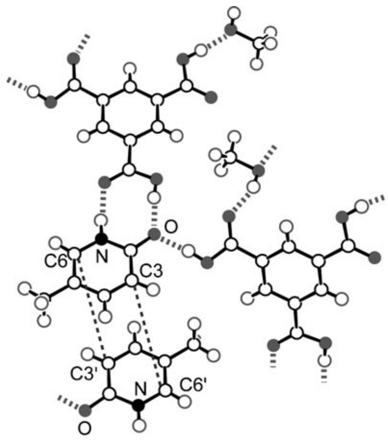


Figure 2. X-ray crystal structure of **8**.

and **9** (Figure 3). As the pattern of **9** is significantly different from that of **8**, we determined the crystal structure of **9** from the PXRD data by using the ab initio method of the program EAGER;[8,9] this program adopts the direct-space strategy[10] for structure solution from powder diffraction data[11] and is based on the use of the genetic algorithm technique[9] for global optimization. The crystal structure was refined by the Rietveld method.

As shown in the packing diagram of **9** (Figure 4), molecules of **1a** and **7** aggregate by forming the four kinds of hydrogen bonds: two COOH(**7**)···O=C(**1a**) bonds, COOH(**7**)···O=C(**7**), and C=O(**1a**)···HN(**1a**). The shortest contact between the reaction centers of two translationally related **1a** molecules is C3–C3′ (=C6–C6′) = 3.84 Å. This distance is close enough for reaction to occur, and two **1a** molecules are arranged so as to give the *cis-syn*-dimer **6a**. These data show that the transformation of **8** into **9** should occur through removal of a methanol molecule and turning of one **1a** molecule about 180° by heating or by contact with MeCN vapor. Photochemically unreactive chalcone derivatives are known to transform both in the solid state and in solution into reactive species in the molten state, and a [2+2] stereoselective photodimerization of chalcones occurrs in the molten state to give *rac-anti*-head-to-head dimers.[12] However, the transformation from the photochemically unreactive **8** into the reactive **9** in the solid state is much more interesting and important.

Although host–guest inclusion crystals are useful for stereoselective template reactions of the guest compounds, the guest molecules are not always ordered at appropriate positions for effective reaction. For example, for [2+2] or [4+4] photodimerization of olefins, the two olefin molecules should be ordered close and parallel to each other. The unsuitable positioning of olefin molecules in the inclusion complex can be changed into an appropriate molecular ordering by phase transition in the solid state. This finding should encourage chemists who have been disappointed with the failure of template reactions because of inappropriate ordering of the guest molecules.

Knowledge of the three-dimensional crystal structure is of vital importance for the discussion of crystalline-state reaction mechanisms. However, the structural phase transition is

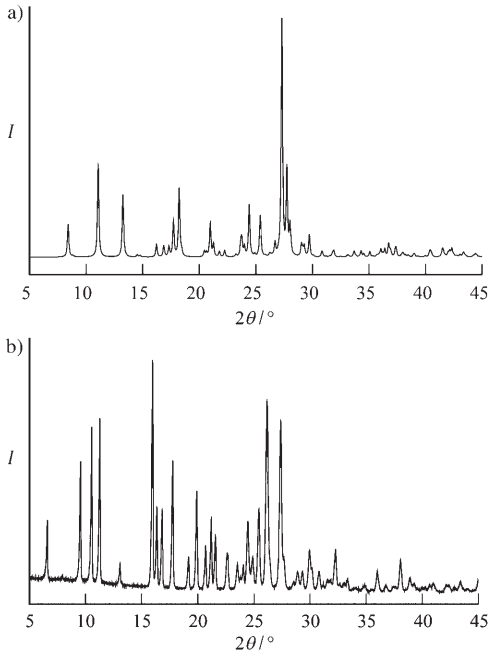


Figure 3. Powder X-ray diffraction pattern of a) **8** (simulation from single-crystal data) and b) **9**.

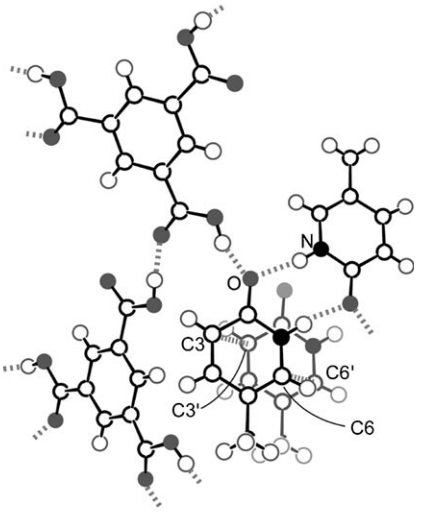


Figure 4. X-ray crystal structure of **9**.

often associated with loss of crystal integrity, and the crystal structure after the phase transition may not be accessible by single-crystal analysis. Even in such a case, a method that enables the ab initio structure determination from a PXRD pattern can be used to elucidate the crystal structure of polycrystalline materials.

Experimental Section

The single-crystal X-ray diffraction data were collected on a Rigaku RAXIS RAPID Imaging Plate diffractometer with $Mo_{K\alpha}$ radiation ($\lambda = 0.71075$ Å) to a maximum 2θ value of 55.0°. The reflection data were corrected for the Lorentz-polarization effects and secondary extinction. No absorption correction was applied. The structure was solved by direct methods using the Sir2004[13] program and refined by the full-matrix least-squares method by using the SHELXL97[14] program. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located from the difference Fourier map and refined.

Crystal data for **8**: $C_9H_6O_6{\cdot}C_6H_7NO{\cdot}CH_4O$, $M_r = 351.31$, monoclinic, space group $P2_1/n$, $a = 13.3645(14)$, $b = 7.4825(5)$, $c = 15.9942(19)$ Å, $\beta = 92.852(5)°$, $V = 1597.4(3)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.461$ g cm^{-3}, $T = 173$ K, number of unique reflections = 3650, $R_{int} = 0.027$ up to $2\theta = 55.0°$, number of parameters = 294, $R_1 = 0.0349$, $wR = 0.0915$, $Gof = 1.056$ for 3124 reflections.

Crystal data for **10**: $C_9H_6O_6{\cdot}C_{12}H_{14}N_2O_2{\cdot}H_2O$, $M_r = 446.41$, triclinic, space group $P\bar{1}$, $a = 7.0942(9)$, $b = 9.6224(8)$, $c = 14.467(2)$ Å, $\alpha = 92.634(6)$, $\beta = 93.240(7)$, $\gamma = 95.754(6)°$, $V = 979.7(2)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.513$ g cm^{-3}, $T = 173$ K, number of unique reflections = 4505, $R_{int} = 0.026$ up to $2\theta = 55.0°$, number of parameters = 357, $R_1 = 0.0616$, $wR = 0.1559$, $Gof = 1.064$ for 4054 reflections. The large maximum residual electron density (1.2 e Å^{-3}) was caused by decomposition of the *meso-cis-syn* [4+4] dimer (**6a**).

The powder X-ray diffraction data of **9** were collected at ambient temperature on a Panalytical X'Pert PRO MRD with reflection mode (parallel $Cu_{K\alpha}$ radiation, $\lambda = 1.54184$ Å; 2θ range 5–70°; step size 0.006°; data collection time 12 h). The powder X-ray diffraction pattern was indexed by using DICVOL04[15] to give the monoclinic unit cell $M_{25} = 45.0$, $F_{25} = 136.2$. The space group was assigned from the results of LeBail fitting ($R_{wp} = 0.0839$) as $P2_1/a$. The space group and cell volume indicates that there is one pair of molecules **1a** and **7** in the asymmetric unit. The genetic algorithm calculation was performed using the program EAGER to solve the structure and determine a total of 15 variables for **1a** and **7**. Final Rietveld refinement was carried out with the GSAS[16] program. $a = 16.713(6)$, $b = 22.089(8)$, $c = 3.8294(14)$ Å, $\beta = 93.631(2)°$, $V = 1409.2(15)$ Å^3, $R_{wp} = 0.0780$, $R_p = 0.0581$, $R_B = 0.0505$, 2θ range 5.0–55.0°, 8332 profile points, 124 refined variables. CCDC-263741, -263742, and -602110 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

The ^{1}H and ^{13}C NMR spectra were measured on a JEOL Lambda-500 spectrometer at 500 MHz. IR spectra were measured on a JEOL FT/IR-460 Plus instrument. Melting points were measured on a Stuart Scientific SMP3 instrument. TG/DTA was performed on a Rigaku Thermo Plus 2 instrument.

Preparation of **8**: A solution of **7** (101 mg, 0.478 mmol) and **1a** (104 mg, 0.948 mmol) in MeOH (4.0 mL) was kept at room temperature for 24 h to give the 1:1:1 inclusion complex **8** as colorless needles (127 mg, 0.361 mmol, 75 % yield, m.p. 284–286 °C).

Transformation of **8** into **9**: Compound **8** was heated at 120 °C for 10 min to give the 1:1 inclusion complex **9** as a white crystalline powder (m.p. 289–289.5 °C) in quantitative yield. Contact of **8** with MeCN vapor for 24 h at room temperature also gave **9** quantitatively.

Photoreaction of **9** in the solid state: The crude product obtained by photoirradiation (400-W high-pressure Hg lamp) of powdered **9** (100 mg, 0.313 mmol) in the solid state for 30 h was recrystallized from MeOH to give **10** as colorless block crystals (45.1 mg, 0.101 mmol, 64 % yield, m.p. 245.5–282.5 °C (decomp)). ^{1}H NMR (500 MHz, CF_3COOD): $\delta = 5.75$ (brm, 2 H), 4.37 (brm, 2 H), 3.81 (dd, J (H,H) = 2.5 and 4.3 Hz, 2 H), 2.13 ppm (d, J (H,H) = 1.5 Hz, 6 H); ^{13}C NMR (125 MHz, CF_3COOD): $\delta = 20.89$, 50.12, 62.52, 125.02, 148.92, 186.03 ppm.

Thermal conversion of **6a** into **11**: A solution of **10** in CD_3COOD was heated at 70 °C for 2 h to give **11** in quantitative yield. ^{1}H NMR (500 MHz, CF_3COOD): $\delta = 6.51$ (d, J (H,H) = 10 Hz, 2 H), 6.00 (d, J (H,H) = 10 Hz, 2 H), 4.23 (s, 2 H), 1.38 ppm (s, 6 H); ^{13}C NMR

(125 MHz, CF_3COOD): $\delta = 22.71$, 48.09, 59.83, 120.52, 151.45, 171.18 ppm.

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