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NEW [2+2] AND [4+4] PHOTODIMERIZATIONS OF 2-PYRIDONES IN AN INCLUSION COMPLEX WITH A SIMPLE CARBOXYLIC ACID HOST: A MODEL OF DNA DAMAGE BY PHOTODIMERIZATION OF ITS THYMINE COMPONENT

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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**).[1] Although some [4+4] photodimerizations of 2-pyridones to *trans*-*anti*-dimers have been reported,[2] 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**).[3] 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

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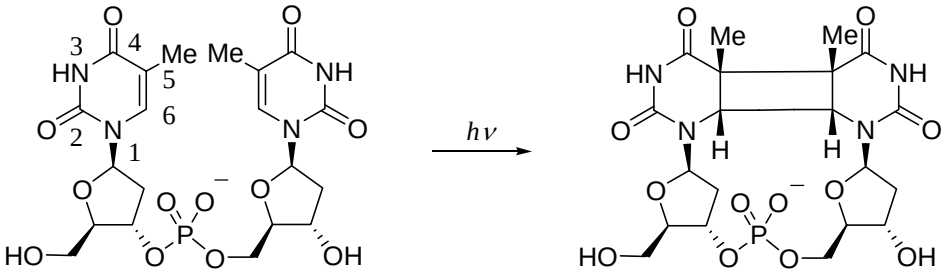
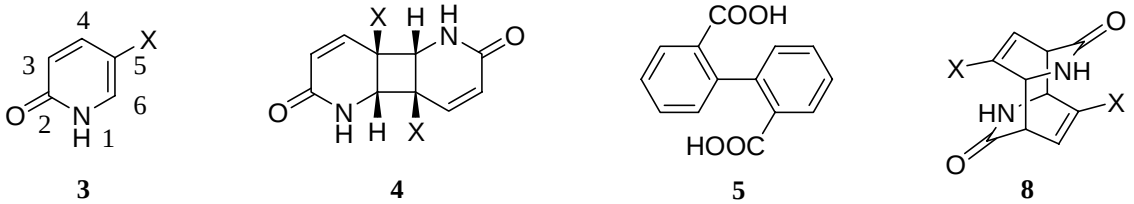
This paper is dedicated to Dr. Pierre Potier on the occasion of his 70th birthday.

(**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.

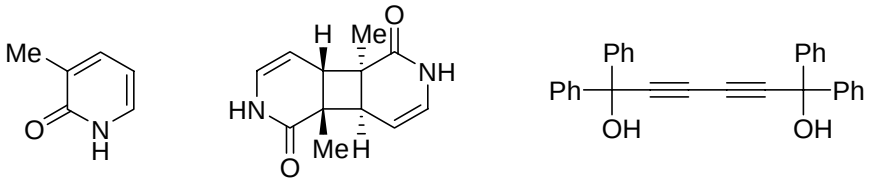


1 **2**

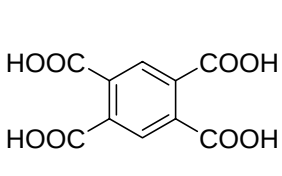


3 **4** **5** **8**

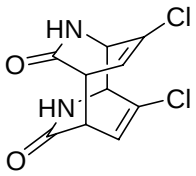
a: X = H
b: X = Cl
c: X = Me



9 **10** **11**



12



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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**).[2] 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.[4] Photoreaction of **3a** in solution for 72 h gave **8a** in 40% yield.[5] 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.[6] 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 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.[7] In this case, however, the dimerization reaction occurred at the C3-C4 double bond, but not at C5-C6.

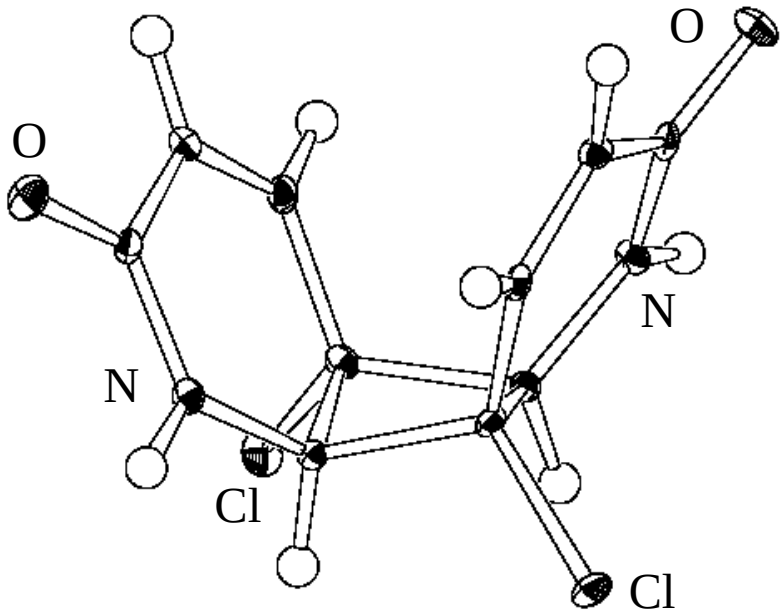

Figure 1. X-Ray structure of **4b**.

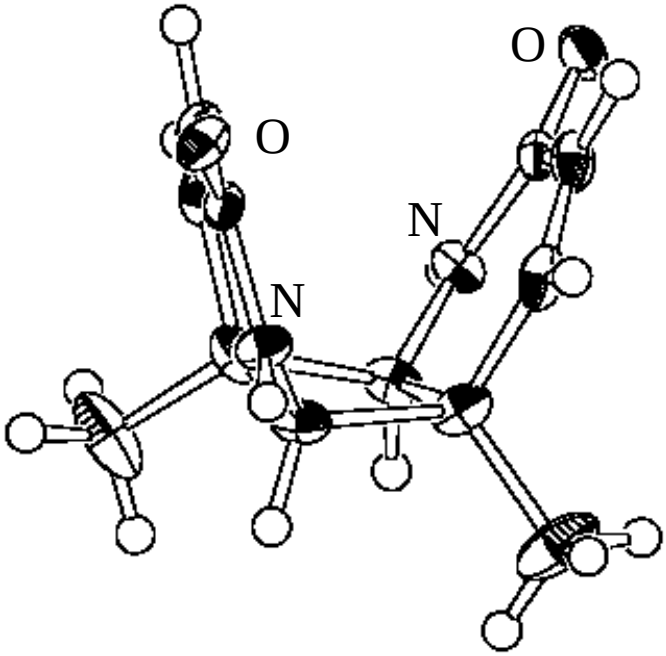

Figure 2. X-Ray structure of **4c**.

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**.

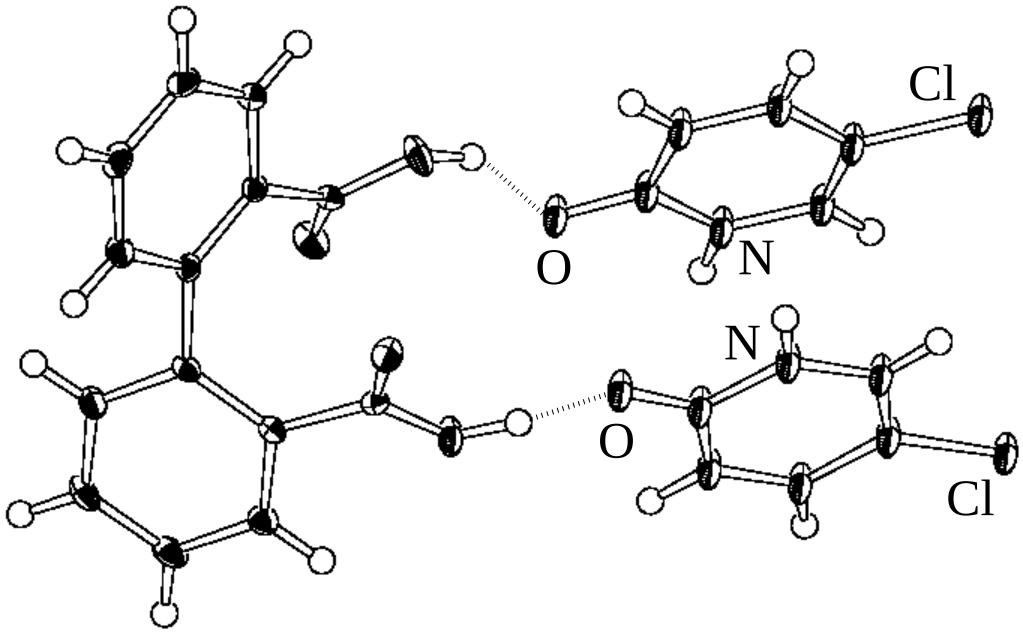

Figure 3. X-Ray structure of **6**.

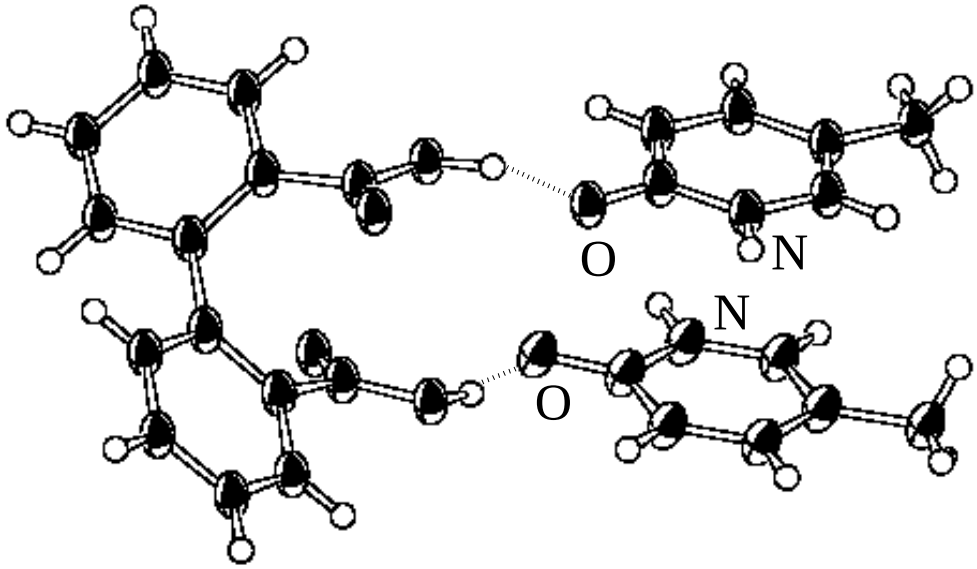

Figure 4. X-Ray structure of **7**.

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.[5] 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 ^{1}H 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 moleclules 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.

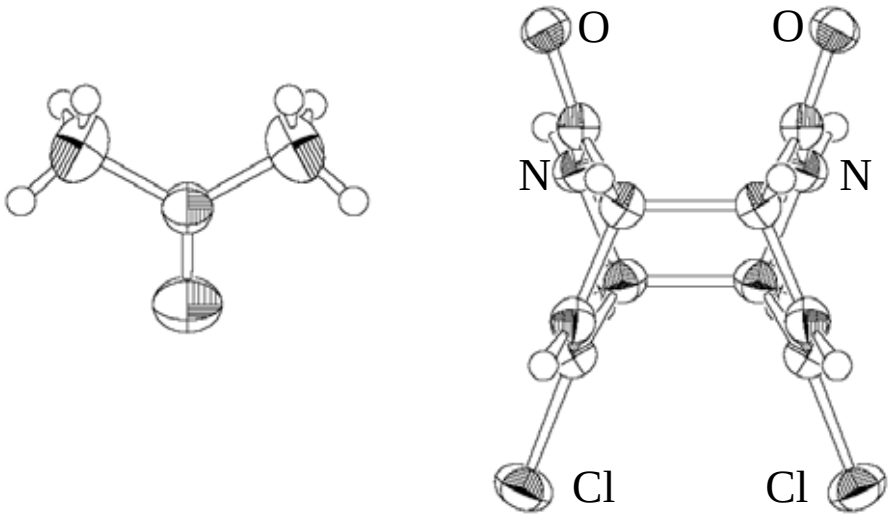

Figure 5. X-Ray structure of a 1:1 complex of **14** and acetone.

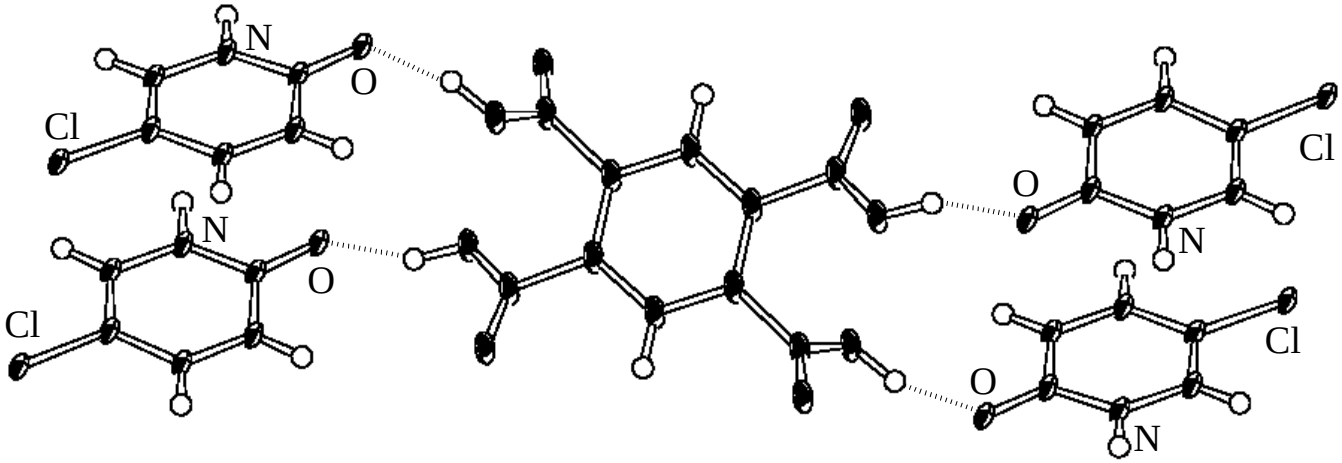

Figure 6. X-Ray structure of **13**.

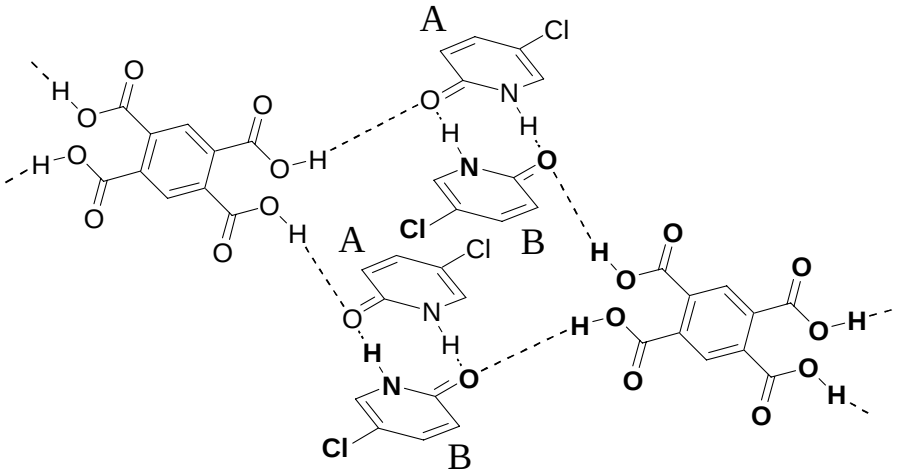

Figure 7. A schematic structure of **13** in which A-A and B-B photodimerizations occur.

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 $_{TE}X_{SAN}$ 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 rr 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 $NaHCO_3$ 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 $C_{10}H_8N_2O_2Cl_2$: 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_3COOD, 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_3COOD, 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 $CHCl_3$-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 ºC). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.22; H, 6.19; N, 12.76. ^1H NMR (500 MHz, CF_3COOD, 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_3COOD, 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, CF_3COOD, δ): 3.78 (2H, dd, *J* = 2.4 and 4.6 Hz), 4.47 (2H, m), 5.94 (2H, m); ^{13}C NMR (125 MHz、CF_3COOD, 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 = $C_{10}H_8N_2O_2Cl_2$, 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, *Dcalc* = 1.676 g/cm^3, *T* = 93 K, number of unique reflection = 1129, *Rint* = 0.0190 up to a 2θ = 55 °, number of parameters = 146, R_1 = 0.0227, *wR* = 0.0653, Gof = 1.157 for 1115 reflections.

Crystallographic data for 4c: Formula = $C_{12}H_{14}N_2O_2$, 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, *Dcalc* = 1.312 g/cm^3, *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 = $C_{14}H_{10}O_4 \cdot 2(C_5H_4NOCl)$, 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, *Dcalc* = 1.488 g/cm^3, *T* = 113 K, number of unique reflection = 10228, *Rint* = 0.039 up to a 2θ = 55 .0 °, number of parameters = 613, R_1 = 0.0345, *wR* = 0.0917, Gof = 1.073 for 7910 reflections.

Crystallographic Data for 7: Formula = $C_{14}H_{10}O_4 \cdot 2(C_6H_7NO)$, 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 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 = $C_{10}H_6O_6 \cdot 4(C_5H_4NCl)$, 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 = $C_{10}H_8N_2O_2Cl_2 \cdot C_3H_6O$, 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.

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