HETEROCYCLES, Vol. 59, No. 2, 2003, pp. 735 - 744, Received, 15th November, 2002

PHOTOREACTIONS OF 2- AND 4-PYRIDONES IN THEIR INCLUSION CRYSTAL WITH A HOST COMPOUND

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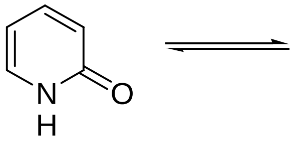
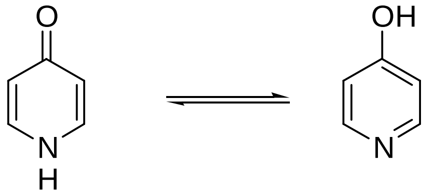
Abstract – Photoirradiation of a 2:1 inclusion crystal of 2-pyridone with biphenyl-2,2'-dicarboxylic acid in the solid state gave its trans-*anti*-dimer. Since photoirradiation of a mixture of biphenyl-2,2'-dicarboxylic acid and an excess of 2-pyridone in the solid state gave the trans-*an*ti-dimer in a quatititative yield, it is clear that inclusion complexation of the two components occurs followed by photodimerization in the inclusion complex and that the host compound is used as a catalyst. However, a 2:2 inclusion crystal of 4-pyridone with *rac*-2,2'-dihydroxy-1,1'-binaphthyl was inert to the photoirradiation. Crystal structures of these inclusion compounds were studied by X-Ray analysis.

Photodimerization reactions of 2- (**1a**) and 4-pyridone (**2a**) are very important research subject in relation to damage of DNA by photodimerization of its basic components, guanine, cytosine and thymine. Nevertheless, photodimerization reactions of **1a** with **2a** have not been successful, since **1a** and **2a** exist as an equilibrium mixture with the corresponding enol forms, 2- (**1b**) and 4-hydroxypyridine (**2b**), respectively.[1] For example, photoirradiation of an equilibrium mixture of **1a** and **1b** in solution for 72 h gave the *trans-anti*-dimer (**7**) in 40% yield.[2] In the crystal, only the keto-form (**1a**) exists,[3] but its photoirradiation in the solid state does not give any photodimer. Regarding **2**, no successful photodimerization of **2a** has been reported so far. In this paper, some efficient photodimerization reactions of **1a** as an inclusion complex in the crystalline state are reported. In contrast, **2a** did not dimerize even as an inclusion complex in which two molecules of **2a** are arranged at appropriate positions for the dimerization. As host compounds for the inclusion complexes, biphenyl-2,2'-dicarboxylic acid (**3**),[4] *rac*-2,2'-dihydroxy-1,1'-binaphthyl (**4a**)[5] and the chiral host compound (*R,R*)-(-)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.4]nonane (**5**)[6] which can easily be derived from tartaric acid, were used.

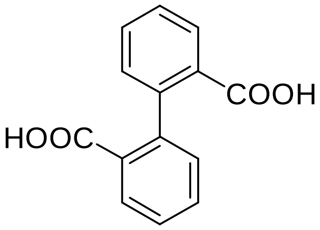


1



2

a = keto-form
b = enol-form



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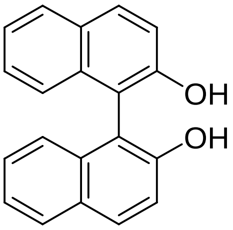
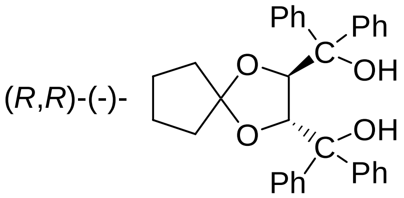


4

a = *rac*-form
b = (+)-form
c = (-)-from



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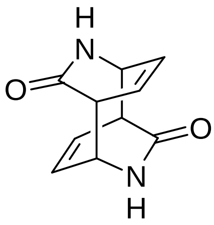

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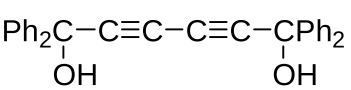
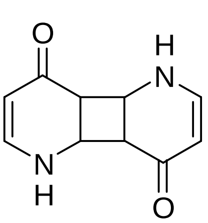


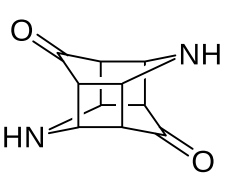
$$\underset{OH}{Ph_2C}-C\equiv C-C\equiv C-\underset{OH}{CPh_2}$$

8



10

a = *syn*-form
b = *anti*-form



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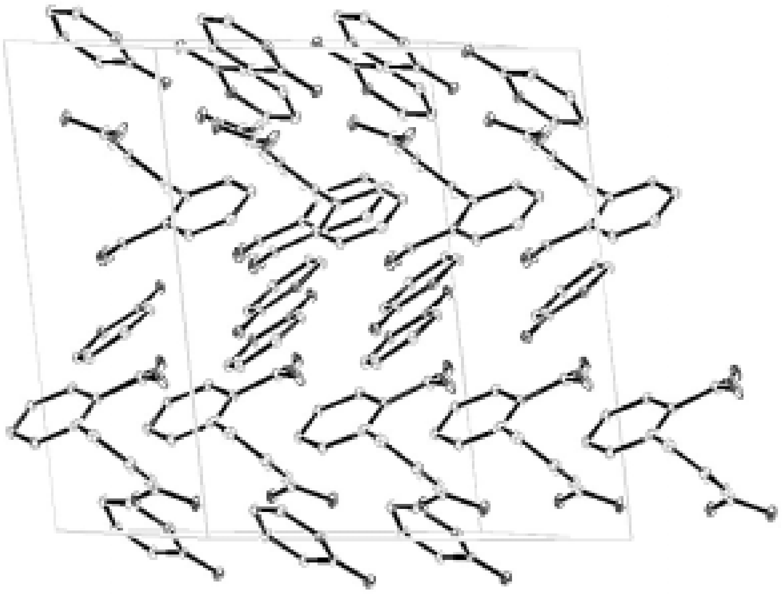

Figure 1 ORTEP diagram[11] showing the packing of complex (**6**) where a central channel of guest pairs is shown.

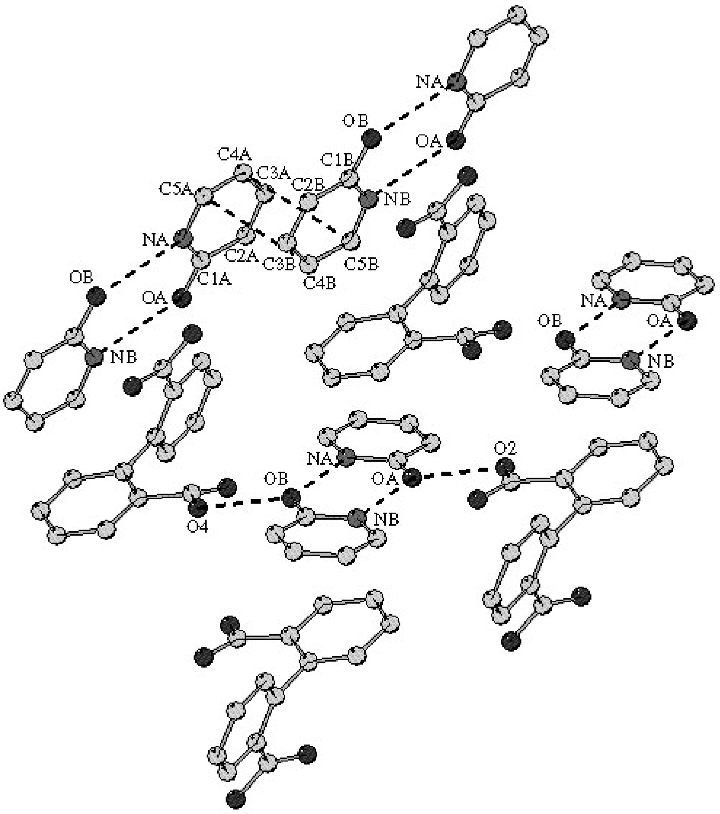

Figure 2 Details (drawn by MOLSCRIPT[12]) of the environment around a coplanar 2-pyridone pair (shown in the middle) of complex (**6**). This pair belongs to a channel almost perpendicular to the plane of the figure. In the upper left corner an adjacent channel is shown with two pairs of guests and their closest π-π interactions between their respective atoms C4 and C5.

Table 1. Hydrogen bonding of guest molecules with neighboring host, solvent molecules or among themselves

	Distance (Å) O… H	Distance (Å) O…O(or N)	Angle (°) O… H-O(or N)
Complex (**6**)			
OA$_{\text{(guest)}}$ HNB-NB$_{\text{(guest)}}$	2.170	2.928	159.8
OB$_{\text{(guest)}}$ HNA-NA$_{\text{(guest)}}$	1.785	2.900	171.9
OA$_{\text{(guest)}}$ HO2-O2$_{\text{(host)}}$	1.856	2.568	141.0
OB$_{\text{(guest)}}$ HO4-O4$_{\text{(host)}}$	1.579	2.591	152.3
Complex (**9**)			
O$^{i}_{\text{(guest)}}$ HO1- O1	1.776	2.657	171.15
O$^{ii}_{\text{(guest)}}$ HO2-O2	1.873	2.695	169.36
O1 HN-N$_{\text{(guest)}}$	1.954	2.888	135.19
Complex (**12a**) [**5**·**2a** (pyridone)]			
O5A$^{iii}_{\text{(guest)}}$ HO4- O4	1.758	2.606	153.00
O5A$_{\text{(guest)}}$ HOS-OMe	1.868	2.716	164.82
OMe^{iv} HNA-NA$_{\text{(guest)}}$	1.829	2.689	141.35
Complex (**12a**) [**5**·**2b** (hydroxypyridine)]			
O5B$^{iii}_{\text{(guest)}}$ HO4-O4	1.814	2.696	161.29
O5B HOMe-OMe	1.841	2.668	158.64

(i) –2-x, -1-y, 1-z; (ii) -1.5-x, -0.5+y, 1-z; (iii)-x, 0.5+y, -z; (iv) 1+x, y, z

When a solution of **3** and **1** in EtOH was kept at room temperature, a 1:2 inclusion complex (**6**) of **3** with**1a** was obtained as colorless crystals in 83% yield. The inclusion complex (**6**) can also be prepared easily by grinding powdered **3** and **1a** by a pestle and mortar for 5 min. IR spectrum of the complex prepared by the recrystallization method was identical to that of the complex prepared by the mixing method. X-Ray analysis of **6** showed that 2-pyridone molecules are trapped in channels of hosts (Figure 1). Four host molecules surround coplanar pairs of guest molecules (**1a**), which are forming mutual weak hydrogen-bonds. Additionally, two carboxylic groups of opposite hosts form hydrogen-bonds with each 2-pyridone molecule of the pair (Table 1 and Figure 2). The rest of the carboxylic groups are hydrogen-bonded to other pairs of **1a** in adjacent channels. Each 2-pyridone pair exhibits limited π-π interactions with neighboring antiparallel pairs above and below along the channel. Specifically, atoms C4A and C5A of one molecule are at distances of 3.63 and 3.69 Å from atoms C5B and C4B respectively of the molecule below. Thus a steplike procession of guest molecules (**1**) is formed along the channel as indicated in Figure. 2. This arrangement in the crystal would suggest a [2+2] reaction. However, a [4+4] reaction actually occurs (vide *infra*) that involves bond formation between atoms C2A and C5B and C5A and C2B. Distances between atoms C2A and C5B and C5A and C2B involved in the [4+4] reaction are 4.20 and 4.21 Å respectively. Therefore, it seems that during irradiation antiparallel molecules in different steps slip in such a way as to overlap better and bring atoms C2 and C5 closer to give the *trans-anti*-dimer (**7**). Actually, a [2+2] reaction has never been known, although intramolecular [2+2] reaction, which gives β-lactam has been reported.[7]

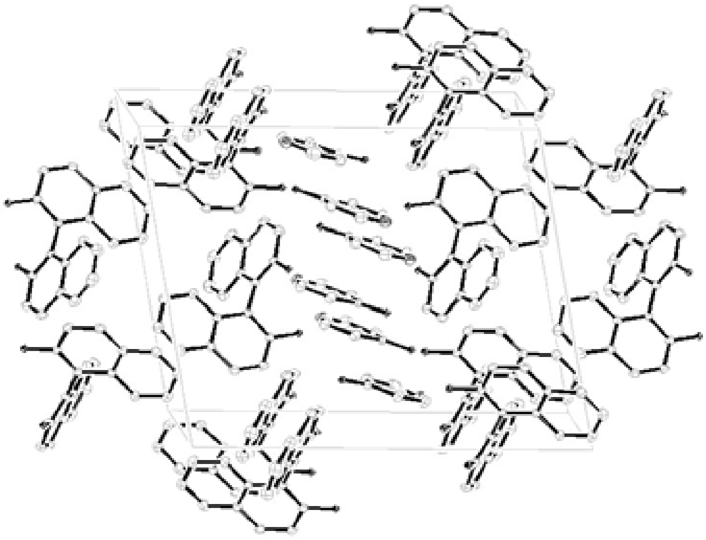

Figure 3 ORTEP diagram of the packing of complex (**9**) where the layers of host and guest molecules are exhibited.

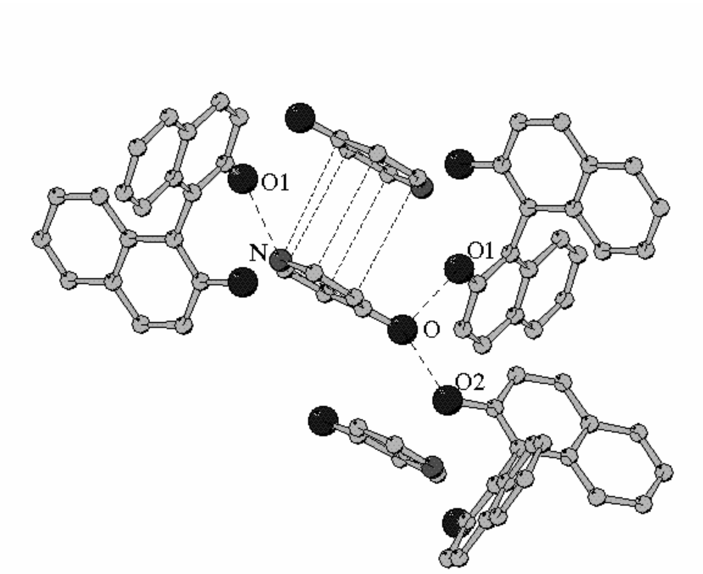

Figure 4 Details of the environment around each 4-pyridone pair of complex (**9**). Hydrogen-bonds are indicated by dotted lines between corresponding non-hydrogen atoms (drawn by MOLSCRIPT).

Photoirradiation of powdered **6** for 20 h gave the *trans-anti*-dimer (**7**) in 92% yield. Compound (**7**) was characterised by comparison of its spectral data with those reported for the sample prepared previously by photoreaction of a 1:2 inclusion compound of **1a** with 1,1,6,6-tetraphenyl-2,4-hexadiyne-1,6-diol (**8**).[8] Formation of **7** in 53% yield by a photoirradiation of a 1:1 inclusion complex of **1a** with 2-naphthylacetic acid in the solid state for 48 h has also been reported.[9] Nevertheless, it is an important finding that the commercially available simple aromatic acid (**3**) can be used as a host for the selective inclusion of **1a** from its equilibrium mixture with **1b** and for its efficient photodimerization to **7**. Therefore, since an inclusion complex between **3** and **1a** easily occurs by simple mixing of both components in the solid state, an interesting photochemical synthetic process can be established by combining the mixing and photoirradiation procedures in the solid state. For example, photoirradiation of a 1:2 mixture of powdered **3** and **1** for 20 h under grinding occasionally by pestle and mortar gave **7** in 90% yield. Since the photodimerization of **1a** does not occur in its own crystal, it is very clear that the inclusion complex of **1a** with **3** is formed before the photodimerization reaction. A much more interesting catalytic reaction process in the solid state was accomplished. Photoirradiation of a 1:4 mixture of **3** and **1** for 20 h in the solid state gave **7** in 81% yield. These data clearly show that molecules of **3** worked twice as a host. Namely, the mixing of **3** and **1** produces **6** and its photoirradiation gives **7** and **3**. By further mixing, excess **1** is included with **3** to give **6**, which upon continuous irradiation forms **7**

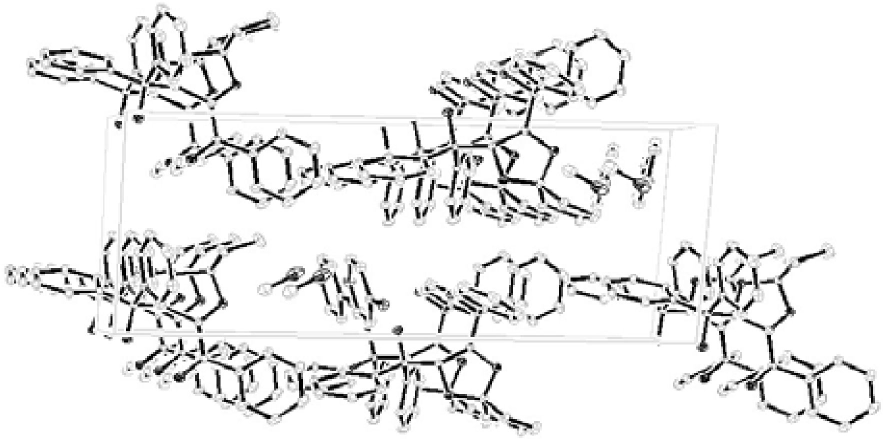

Figure 5 ORTEP diagram of the packing of complex (**12a**) where it is shown that the guest and methanol molecules are inside the channels formed by the host molecules.

Photodimerization of 4-pyridone (**2a**) has never been successful, thus photodimerization of **2** as an inclusion complex in the crystal was studied. First, a 1:1 inclusion complex (**9**) of **2** with **4a** was prepared in 78% yield by recrystallization of these components from MeOH. X-Ray structural study of **9** showed that the crystal packing is composed of alternating host and guest layers (Figure 3). Within a guest layer, pairs of pyridone molecules are formed surrounded by four host molecules as inside a kind of nanovessel (Figure 4). Each guest molecule is forming very strong hydrogen-bonds with three different host molecules (Table 1). On the one side, the pyridone oxygen atom O forms two strong H-bonds with the hydroxyl groups (HO_1 and HO_2) of two different host molecules. On the other side, the N-H group is H-bonded to the O_1H group of a third host. Moreover, there are many C-H… π interactions (at distances around 3 Å) between the guest and the aryl groups of the host. The pyridone molecules in each pair are antiparallel with a mean interplane distance of 3.69 Å, thus in an appropriate geometry to give cyclic dimer (**10** or **11**) by photodimerization. However, irradiation of **9** in the solid state did not give any photoproduct and the crystal structure cannot give an explanation for that.

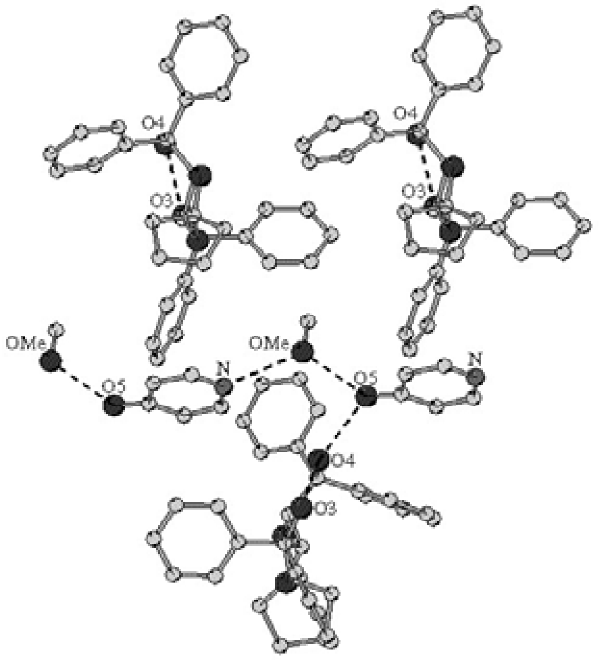

Figure 6 Details of the guest in the channels of complex (**12a**) (view perpendicular to that of Figure 5). The linear arrangement of the 4-pyridone guest molecules and their H-bonding is shown (drawn by MOLSCRIPT).

In addition to the above, inclusion complexes of **2** with **5** were prepared. Recrystallization of **2** and **5** from MeOH gave a 1:1:1 inclusion complex of **2**:**5**:MeOH (**12**). X-Ray structural analysis of **12** showed that the host molecules form cylindrical channels of approximate diameter 8-9 Å that enclose the guest as well as solvent methanol molecules (Figure 5). The guest is disordered, composed of 56.1% pyridine (**2a**) and 43.9% hydroxypyridine (**2b**), forms. The position of the latter almost coincides with that of the pyridone form, as the distances of the hydroxypyridine atoms from the host atoms indicate (Table 1). Figure 6 shows that the arrangement of the guest within the host channel is linear. No pairs of guests are formed therefore, complex (**12**) was inert to photoirradiation. The crystal structure explains the non specificity of this host towards the pyridone form of the guest, as opposed to complex (**9**): The pyridone - host interactions are limited to one strong H-bond between the keto oxygen-atom to the host hydroxyl O4H

(Table 1 and Figure 6). The guest is also interacting with the solvent hydroxyl, HOMe, by two more H-bonds both via its keto oxygen and the N-H atoms (Table 1 and Figure 6). The enol tautomer is stabilized also by similar H-bonds. Therefore, due to the entrapped solvent molecules, the keto form is not as stabilized as in the previous complex and it exists in equilibrium with the hydroxypyridine form in the crystal.

EXPERIMENTAL

General Procedures

Photoreactions were carried out by irradiation with using 100W High Pressure Hg-lamp under air at room temperature.

X-Ray crystallography- Diffraction data were collected at T = 291K with Cu Kα radiation (= 1.5418 Å) by θ-2θ scanning method on a Syntex P21 diffractometer equipped with Rigaku rotating anode and graphite monochromator. Intensities for unique reflections were collected using a theta-2theta scan up to a 2θ = 117°. The data were corrected for Lorentz and polarization effects but not for absorption. The structures were solved by direct methods using SHELXS and refined by SHELXL 97[10] based on F^2. All non-H atoms were treated anisotropically unless otherwise stated.

Preparation of A 1:2 Inclusion (6) of 1a with 3.

When a solution of **3** (0.2 g, 0.8 mmol) and **1** (0.15 g, 1.6 mmol) in ethanol (5 mL) was kept at rt, a 1:2 inclusion compound (**6**) of **3** with **1a** was obtained as colorless crystals (0.29 g, 83%); mp 140-142 ℃. Mixing of **3** (0.2 g, 0.8 mmol) and **1** (0.15 g, 1.6 mmol) by a pestle and mortar gave **6** (0.35 g, quantitative yield) which shows the same IR spectrum with that of the authentic sample prepared by the recrystallization method.

Photoreaction of 6 in the Solid State.

Irradiation of **6** (0.25 g) was carried out for 20 h under grinding by pestle and mortar every 2 h. The reaction mixture was chromatographed on silica gel (bezene-MeOH) to give **7** (0.10 g, 92%), mp 225.5-227.5 ℃ (lit.,2,8 225.5-227.5 ℃). IR and ^{1}H NMR spectra were identical to those of the authentic sample.[2,8]

Preparation of Inclusion Compounds of 2 with 4a, 5, and 8.

When a solution of **4a** (0.2 g, 0.7 mmol) and **2** (0.07 g, 0.7 mmol) in ethanol (5 mL) was kept at rt, a 0.5:0.5:1 inclusion compound (**9**) of 4b:4c:2a was obtained as colorless crystals (0.21 g, 78%); mp 117-127 ℃.

When a solution of **5** (0.2 g, 0.7 mmol) and **2** (0.04 mg, 0.4 mmol) in methanol (0.5 mL) was kept at rt, a 1:1:1 inclusion compound (**12**) of 5:2:MeOH was obtained as colorless crystals (0.20 g, 82%); mp is not clear. X-Ray analysis of **12** showed that both the **2a** (56.1%) and **2b** (43.9%) are included in **12**.

When a solution of **8** (0.2 g, 0.5 mmol) and **2** (0.05 g, 0.5 mmol) in methanol (5 mL) was kept at rt, a 1:1 inclusion compound of **8** and **2** was obtained as colorless crystals. However, its structure has not been analyzed.

Photoreaction of Inclusion Compounds of 2.

All inclusion compounds of **2** with **4a**, **5** and **8** were inert to photoirradiation in the solid state.

Crystal and refinement data for 6, $C_{14}H_{10}O_4 \cdot 2C_5H_5ON$, $MW_1 = 432.42$. The substance was crystallized at space group Cc, a = 10.568(3), b=14.080(4), c = 14.968(4)Å, ß = 106.019(8), V =2140.7(11)Å^3, Z = 2, Dc = 1.342 gcm^{-3} and crystal size = 0.4x0.3x0.25mm. Number of unique reflections = 1564, $R_{int} = 0.039$ up to a $2\theta = 117^o$, number of parameters = 368, $R_1 = 0.0382$, $wR_2 = 0.0953$, Gof = 1.072 for 1110 reflections with $F_o > 4\sigma(F_o)$. A final difference electron density map showed no distinct features with ρmax=0.17eÅ^{-3}, ρmin =-0.15eÅ^{-3}. Hydrogen atoms were given isotropic temperature factors and were refined independently

Crystal and refinement data for 9, $C_{20}H_{14}O_2 \cdot C_5H_5ON$, $MW_1 = 381.41$. The substance was crystallized at space group $P2_1/a$, a = 14.326(2), b=8.8599(17), c=16.057(3)Å, ß = 100.265(5)o, V =2005.4(6)Å^3, Z = 4, Dc = 1.263 gcm^{-3} and crystal size = 0.3x0.3x0.25mm. Number of unique reflections = 2839. $R_{int} = 0.0125$ up to a $2\theta = 117^o$, number of parameters = 338, $R_1 = 0.0413$, $wR_2 = 0.1123$, Gof = 1.027 for 2251 reflections with $F_o > 4\sigma(F_o)$. A final difference electron density map showed no distinct features with ρmax=0.28eÅ^{-3}, ρmin =-0.16eÅ^{-3}. Hydrogen atoms were given isotropic temperature factors and were refined independently

Crystal and refinement data for 12, $C_{33}H_{32}O_4 \cdot C_5H_5NO \cdot CH_3OH$, MW = 617.17. The complex was crystallized at space group $P2_1$, a = 8.408(4), b = 22.311(8), c = 9.454(4) Å, ß = 108.878(18), V = 1678.2(12)Å^3, Z = 2, Dc = 1.222 gcm^{-3} and crystal size =0.6x0.20x0.12mm. Number of unique reflections = 2612 and 512 parameters, $R_1=0.0349$ for 2539 $F_o > 4\sigma F_o$ reflection, $wR_2 = 0.0953$ and Gof = 1.038. Guest hydrogen atoms were put at geometrically generated positions and they were refined riding on the corresponding non-H-atoms with $U_{eq} = 1.25U'_{eq}$ of the corresponding atom. The final difference Fourier map showed $\rho_{max} = 0.22e/Å^3$, and $\rho_{min} = -0.14e/Å^3$.

REFERENCES AND NOTES

1. P. Beak, *Acc. Chem. Res.*, 1977, **10**, 186; P. Beak, J. B. Covington, and J. M. White, *J. Org. Chem.*, 1980, **45**, 1347; P. Beak, J. B. Covington, J. M. White, and J. M. Zeigler, *J. Am. Chem. Soc.*, 1980, **102**, 1354; M. Kuzuya, A. Noguchi, and T. Okuda, *J. Chem. Soc., Chem. Commun.*, 1985, 435; M. Kuzuya, A. Noguchi, and T. Okuda, *J. Chem. Soc., Perkin Trans.* 2, 1985, 1423.
2. E. C. Taylor and R. O. Kan, *J. Am. Chem. Soc.*, 1963, **85**, 776.
3. B. R. Penfold, *Acta Cryst.*, 1953, **6**, 591.
4. This is the first finding that the biphenyl-2,2'-dicarboxylic acid works as a host compound.
5. F. Toda, K. Tanaka, and K. Nagamatsu, *Tetrahedron Lett.*, 1984, **25**, 4929; F. Toda and K. Tanaka, *J. Org. Chem.*, 1988, **53**, 3607.
6. F. Toda and K. Tanaka, *Tetrahedron Lett.*, 1988, **29**, 551; D. Seebach, A. K. Beck, R. Imwinkelried, R. Rogo, and A. Wannacott, Helv. *Chim. Acta,* 1987, **70**, 954.
7. K. Tanaka and F. Toda, *Tetrahedron Lett.*, 1988, **29**, 4299; T. Fujiwara, N. Tanaka, K. Tanaka, and F.Toda, *J. Chem. Soc., Perkin Trans.* 1, 1989, 663.
8. K. Tanaka and F. Toda, *Nippon Kagaku Kaishi*, 1984, 141.
9. T. Odani and A. Matsumoto, *CrystEngComm.*, 2002, **4**, 467.
10. G. M. Sheldrick, University of Göttingen, Germany, 1997

11. Johnson, C. K. *ORTEPI, ORNL-5138*. Oak Ridge National Laboratory, Tennessee, USA, 1973.

12. P. Kraulis, *J. Appl. Cryst.*, 1991, **24**, 946-950