Pergamon

Tetrahedron 56 (2000) 6833–6844

TETRAHEDRON

Compelled Orientational Control of the Solid-State Photodimerization of *trans*-Cinnamamides: Dicarboxylic Acid as a Non-covalent Linker

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Received 17 November 1999; accepted 17 February 2000

Abstract—The 2:1 hydrogen-bonded cocrystals **1a·ox**, **1a·su**, **1a·pht**, **1a·fu**, **1b·ox**, **1c·ox**, **1d·ox** between *trans*-cinnamamides (**1a**–**1d**) and dicarboxylic acids (**ox**, **su**, **gl**, **fu**, **pht**) were prepared and characterized by IR and powder X-ray techniques. The crystal structures of **1a·pht**, **1a·ox** and **1a·fu** were solved by single crystal X-ray diffraction. Phthalic acid (**pht**) caused β-type photodimerization of *trans*-cinnamamide (**1a**) in the cocrystal and functioned as a non-covalent linker like gauche 1,2-diamines in photodimerization of *trans*-cinnamic acids. Oxalic acid (ox) enforced **1a** to take a bilayer structure that is suitable for β-type photodimerization. In the case of fumaric acid (**fu**), cross photodimerization with **1a** occurred to give a cycloadduct **4**. For the cocrystals **1a·pht** and **1a·fu**, pedal-like motion was assumed to occur prior to the dimerization.

Introduction

Recently, we have explored compelled orientational control of the solid-state photodimerization of particular compounds like *trans*-cinnamic acids and anthracene-carboxylic acids.[1–7] Our strategy is based on crystalline double salt formation with diamines, which are used as a supramolecular linker to connect two acid molecules in a sort of pre-designed orientation. A series of diamines were investigated. As a result of these studies, it was disclosed that *trans*- and *cis*-cyclohexane-1,2-diamines or gauche 1,2-diamines were useful linkers for preparing double salts of unusual photoreactivity. Evidently, photoreactive overlap configurations are more likely to happen to the gauche conformation of 1,2-diamine.

Upon photolysis in the solid state, *trans*-cinnamamide (**1a**) and its derivatives undergo photodimerization to afford exclusively the corresponding α-truxillamides,[8] whereas in solution only the *trans–cis* photoisomerization was observed to occur as confirmed by us. In this paper, orientational control of the [2+2] photodimerization of *trans*-cinnamamides in the solid state by using a series of dicarboxylic acids as a non-covalent intermolecular linker will be described. The carboxamide group and the carboxyl group can interact in the crystal via hydrogen bonding as was demonstrated by formation of, e.g. a 2:1 hydrogen-bonded cocrystal between benzamide and succinic acid.[9]

Results and Discussion

A 2:1 mixture of *trans*-cinnamamide (**1a**) and each of dicarboxylic acids, which are listed in Scheme 1, was recrystallized from suitable solvent. Cocrystals of **1a** with oxalic acid (**ox**), succinic acid (**su**), phthalic acid (**pht**) and fumaric acid (**fu**) (**1a·ox**, **1a·su**, **1a·pht**, **1a·fu**) were successfully obtained (Table 1). Their melting points were sharp and melted near mp of **1a**. The molar ratio of the constituents was estimated by NMR and was determined by elemental analysis to be 2:1 in all the cocrystals. The IR frequencies of $CONH_2$ and COOH groups for these cocrystal, along with those for the component amide and acid, are summarized in Table 2. The IR spectra of the cocrystals were different from the superposition of the spectra of their components throughout the whole region (4000–600 cm^{-1}).

The identity of the cocrystal between **1a** and glutaric acid (**gl**) (**1a·gl**) is ambiguous. Although its C, H, N analysis was correct as the 2:1 stoichiometry, its melting point was very broad (Table 1) and the carbonyl stretching bands nearly overlapped with the sum of those for **1a** and **gl** (Table 2). In the fingerprint region (1500–600 cm^{-1}), however, the absorption peaks corresponding to **gl** were not discernible, while those to **1a** were clearly visible.

Keywords: cinnamamides; dicarboxylic acids; cocrystals; solid-state photodimerization; hydrogen bond; dynamic disorder.
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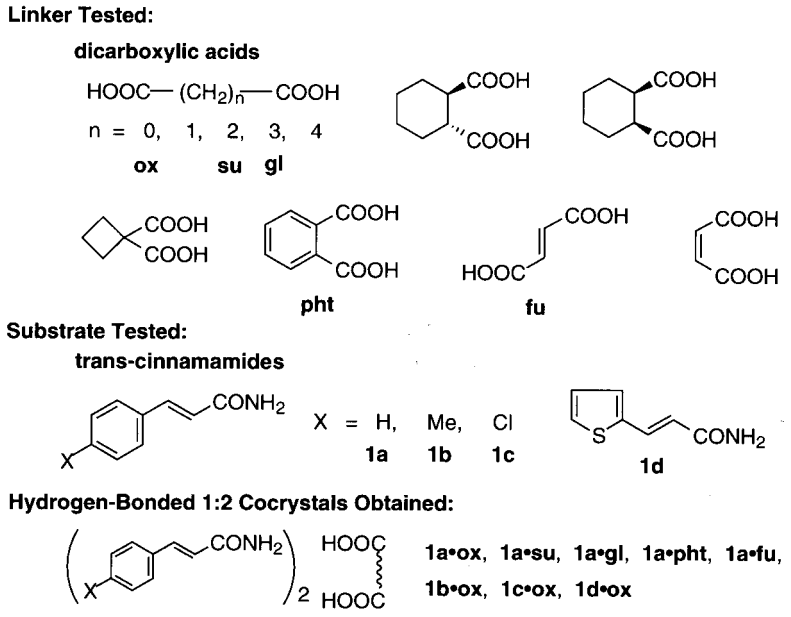
PII: S0040-4020(00)00505-6



Scheme 1.

Table 1. Solvents for recrystallization, melting points and analytical data for the cocrystals prepared from recrystallization of an amide (**1a**, **1b**, **1c**, or **1d**) with a dicarboxylic acid (**ox**, **su**, **gl**, **fu**, or **pht**)

Cocrystal	Recrystzn solvent	Crystal habit, mp, °C[a]	Calcd (%)[b]			Found (%)[b]		
			C	H	N	C	H	N
1a·ox	*i*PrOH	Colorless plates, 159–166.5	62.49	5.25	7.29	62.46	5.29	7.32
1a·su	*i*PrOH	White needles, 150.5–151.5	64.06	5.87	6.79	64.16	5.95	6.86
1a·gl	C_6H_6	Colorless plates+a small amount of prisms, 88.5–124	64.78	6.14	6.57	64.59	6.08	6.47
1a·pht	*i*PrOH	Colorless needles, 142–143.5	67.82	5.25	6.08	67.90	5.23	6.11
1a·fu	*i*PrOH	Colorless needles, 164–166	64.38	5.40	6.83	64.44	5.28	6.69
1b·ox	*i*PrOH	Colorless prisms, 194–202	64.07	5.87	6.79	64.19	5.91	6.83
1c·ox	C_6H_6/*i*-PrOH	Colorless prisms, 207.5–211	53.00	4.00	6.18[c]	53.10	4.02	6.19[d]
1d·ox	*i*PrOH	Pale brown plates, 146–166	48.48	4.07	7.07[e]	48.44	4.10	6.93[f]

[a] Melting points for the components: **1a**, 148–150°C; **1b**, 189–190°C; **1c**, 209–210°C; **1d**, 152–153°C; ox (anhyd), 190°C dec; **su**, 187–189°C; **gl**, 95–98°C; **fu**, 299–300°C subl; **pht**, 210°C dec.
[b] The crystals were dried in vacuo at 35°C for a few days. All samples gave correct C, H, N analyses (within ±0.3%) as (amide)$_2$(dicarboxylic acid).
[c] Cl, 15.64.
[d] Cl, 15.66.
[e] S, 16.17.
[f] S, 16.31.

Table 2. FT IR frequencies in cm^{-1} for $CONH_2$ and COOH groups in KBr

trans-Cinnamamide		Dicarboxylic acid		Cocrystal	
$CONH_2$		COOH		$CONH_2$ and COOH	
1a	1664, 1608	**ox** (anhyd)	1686[a]	**1a·ox**	1682, 1639
		su	1735, 1705	**1a·su**	1700, 1656, 1636
		gl	1701	**1a·gl**	1704, 1663, 1608
		pht	1701, 1682	**1a·pht**	1694, 1655, 1648
		fu	1684	**1a·fu**	1697, 1651, 1628, 1572
1b	1672, 1605			**1b·ox**	1674, 1638
1c	1676, 1613			**1c·ox**	1677, 1637
1d	1671, 1600			**1d·ox**	1671, 1600

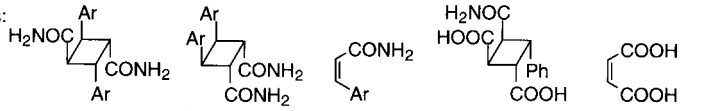
[a] **ox** (dihydrate) 1683 cm^{-1}.

The above results on the melting point and the IR spectrum, combined with the following powder X-ray studies (Fig. 2) and photoreactivities (Table 3), indicate that cocrystals **1a·ox**, **1a·su**, **1a·pht** and **1a·fu** are crystalline complexes, whereas **1a·gl** may possibly be a mixture containing the homocrystal of **1a** and one polymorph of **gl**. The crystal structures of **1a·ox**, **1a·pht** and **1a·fu** could be determined by single crystal X-ray diffraction.

Table 3. Products from solid-state photolyses of the cocrystals (except **1a·fu** (50 h), irradiated for 20 h)

Cocrystals	Products (%)[a,b]				Recovery (%)	
	2	**3**	*cis*-**1**	Others	**1**	Acid
1a·ox	6	42	8		26	ne
1a·su			Photostable		100	100
1a·gl	44	4	2		44	100
1a·pht	3	37	5		51	100
1a·fu	1	5	5	**4**, 50; **ma**, 5	39	45
1b·ox	0	43	0	Polymeric	1	ne
1c·ox	2	86	0		5	ne
1d·ox	0	3	7		83	ne
1a, **1b**, **1c**, or **1d**[c]	18, 100, 100, or 97	0	0		82, 0, 0, 3	–

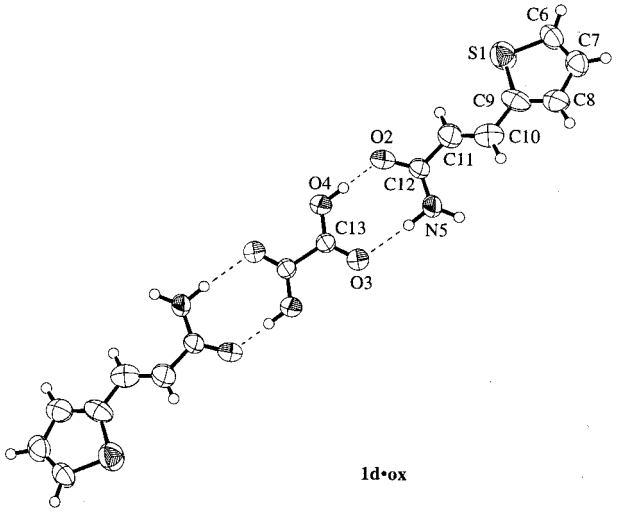
[a] Products:



[b] Yields and recoveries were estimated by NMR and HPLC and calculated as follows: 100 (moles of dimer)/(moles of 2:1 cocrystal)% for α- and β-dimers and **4**, 50(moles of monomer)/(moles of 2:1 cocrystal)% for *trans*- and *cis*-cinnamamides, and 100(moles of acid)/(moles of 2;1 cocrystal)% for dicarboxylic acids; ne=not estimated.

[c] Homocrystals.

Attempts to cocrystallize *trans*-4-methylcinnamamide (**1b**), *trans*-4-chlorocinnamamide (**1c**), and *trans*-β-(2-thienyl)-acrylamide (**1d**) with the above dicarboxylic acids were partly investigated. Cocrystallization with **pht** or with **fu** all failed. In contrast, 2:1 cocrystals with oxalic acid (**1b·ox**, **1c·ox**, **1d·ox**) were successfully obtained. Their data for the recrystallization solvent, mp, elemental analyses, and carbonyl frequencies are also summarized in Tables 1 and 2. Judging from the fairly sharp mp and also from the IR spectra that are distinct from those of the components, cocrystals **1b·ox** and **1c·ox** are undoubtedly a crystalline complex rather than a simple mechanical mixture. From the data given above, the identity of cocrystal **1d·ox** is uncertain, because its mp is broad (Table 1) and its IR spectrum is close to that of **1d** (Table 2). The powder as well as single crystal X-ray studies, however, have demonstrated that **1d·ox** is also a crystalline complex (vide infra).



The diffuse reflectance UV–Vis spectra for cocrystals **1a·ox**, **1a·su**, **1a·gl**, **1a·pht**, **1a·fu** and for the crystals of their constituents were measured (Fig. 1). It can be seen from this figure that the Pyrex-filtered light (>290 nm) incident upon the sample is mainly or exclusively absorbed by the component **1a**. In the spectrum of **1a·fu**, an inflection is observed at ~343 nm, suggesting that the **1a** molecule and the **fu** molecule are interacting not only via hydrogen bonds but also through a π–π interaction. In this case, as described later, cross photodimerization occurred to give **4** (Table 3).

The powder X-ray diffraction (PXD) for cocrystals **1a·ox**, **1a·pht**, **1a·gl**, **1a·fu**, **1a·su** and **1d·ox** were collected (Fig. 2). The diffraction intensities for these cocrystals were much weaker than those for the corresponding components (**ox**, **pht**, **gl**, **fu**, **su**, **1a** and **1d**). This may imply that the crystal structures of these cocrystals are loose. In fact, the X-ray molecular structure for **1a·ox** has proved to be disordered and the photocycloaddition stereoselectivities for **1a·pht** and **1a·fu** could only be rationalized by assuming the dynamic torsional motions (vide infra).

Inspection of Fig. 2 shows that the PXD patterns for **1a·ox**, **1a·pht**, **1a·fu**, **1a·su** and **1d·ox** cannot be represented as a sum of those for the components, indicating that these cocrystals are crystalline complexes. On the other hand, the PXD pattern for **1a·gl** is peculiar like its IR spectrum. Note that the major peaks at 2θ=20.70, 22.28, 23.58, 24.78, 25.58, 26.38, 28.10, 29.42, 33.66 and 37.50° observed for **1a** are still present for **1a·gl** at 2θ=20.66, 22.22, 23.46, 24.78, 25.48, 26.32, 28.00, 29.36, 33.58 and 37.56°, respectively. However, the strong peaks for **gl** at 2θ=22.00, 24.04 and 27.32° are virtually missing for **1a·gl**. It may be likely that the lattice structure of homocrystal **1a** is largely retained after cocrystallization with **gl**, but the crystal packing for the **gl** component in **1a·gl** is different from that of homocrystal **gl**.

Pulverized samples of cocrystals **1a·ox**, **1a·su**, **1a·gl**, **1a·pht**, **1a·fu**, **1b·ox**, **1c·ox** and **1d·ox** were spread between two Pyrex plates and irradiated with a 400 W high pressure mercury lamp under an argon stream. During the irradiation, the photolysis vessel was cooled from the outside with tap

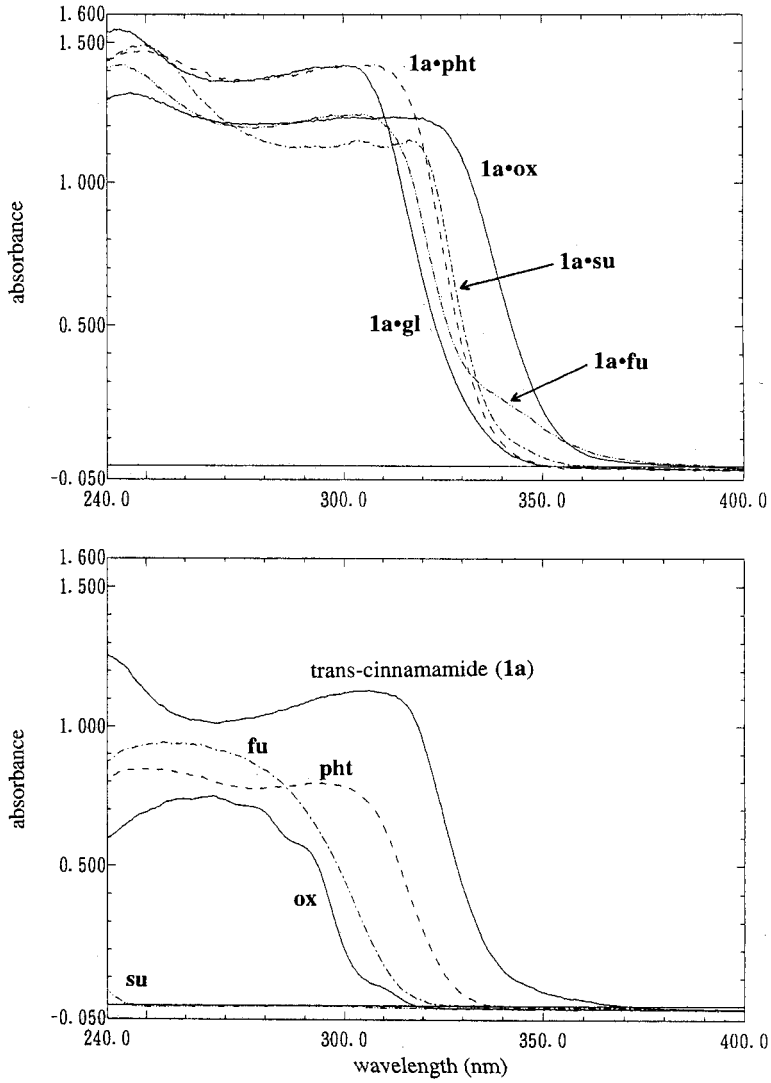


Figure 1. Diffuse reflectance spectra for cocrystals **1a·ox**, **1a·su**, **1a·gl**, **1a·pht**, **1a·fu** and for their constituent crystals **1a**, **ox** (anhyd), **su**, **pht**, and **fu**. The spectrum for **gl**, which is almost the same as that of **su**, is not shown.

water. The photoproducts and their yields are summarized in Table 3. As readily seen from the table, the unusual head-to-head dimer of amides (i.e. β-truxinamide **3** rather than α-truxillamide **2**) was mainly produced by photolyses of the hydrogen–bonded 2:1 complexes formed between the amide and oxalic or phthalic acid **1a·ox**, **1a·pht**, **1b·ox**, **1c·ox** and **1d·ox**, although the reaction was inefficient for **1d·ox**. Noticeably, the cocrystal of **1a** with fumaric acid **1a·fu** afforded a mixed dimer **4** as the predominant photoproduct (50% yield). The cocrystal with succinic acid **1a·su** was completely photostable. Finally, crystal **1a·gl**, like homocrystal **1a**, gave α-truxillamide **2a** as the main product. The formation of the usual photodimer **2a** from **1a·gl** is consistent with the above inference, where **1a·gl** was likened to a mixture comprised of the homocrystal of **1a** and a certain modification of **gl**, on the basis of both the IR spectrum and the PXD pattern.

The structure of **4** was determined after it was hydrolyzed to a tricarboxylic acid **5**, which is unsymmetrical in stereochemical configuration (Scheme 2). A possible symmetrical stereoisomer **5A** could be eliminated by ^{1}H NMR. The compound **5** was subsequently converted to a trimethyl ester **6** and the structure of **6** was established by single crystal X-ray diffraction (see Experimental).

The crystal structures of cocrystals **1a·pht**, **1a·ox** and **1a·fu** and their packing diagrams are displayed in Figs. 3 and 4, respectively. Inspection of the crystal packing for **1a·pht** (Fig. 4a) has revealed that the nearest amide molecules are related in a head-to-head fashion via a supramolecular linker **pht** as shown in Fig. 3a. The ethylene bonds in this pair are anti and are not parallel with the C···C distances 3.82 and 4.85 Å. Although such a twisted arrangement is not ideal for photodimerization,[10] the dimer, if formed from this crystal structure, will be δ-truxinamide, which was not observed (Table 3). In order to accommodate the observed product β-truxinamide **3a**, therefore, a pedal-like dynamic conformational change[11,12] is thought to occur in the crystal prior to cycloaddition into **3a** (Scheme 3).[13] This torsional motion will bring about a parallel orientation that is favorable for the photodimerization. Although molecules of **1a** related by translation along the *c*-direction possess a perfect arrangement for formation of **3a**, the olefine bond separation

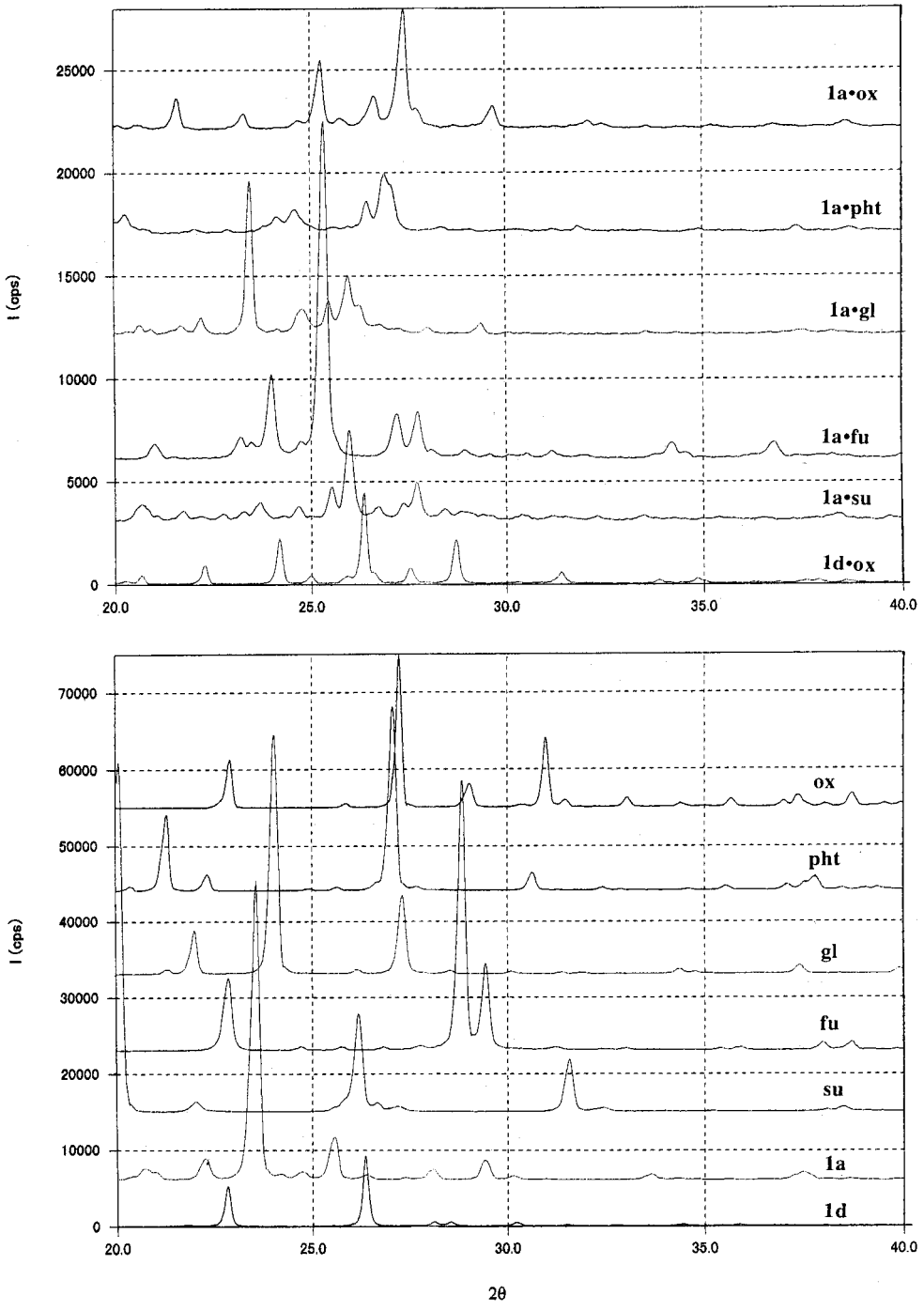
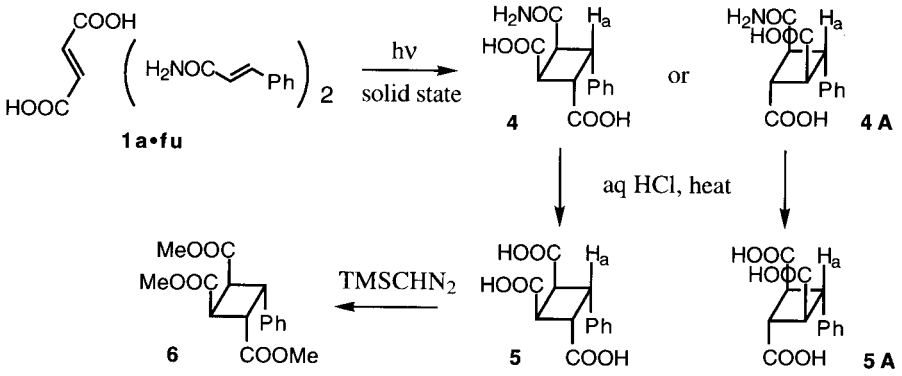


Figure 2. X-Ray powder patterns for cocrystals **1a·ox**, **1a·pht**, **1a·gl**, **1a·fu**, **1a·su** and **1d·ox** and for the constituents **ox** (anhyd), **pht**, **gl**, **fu**, **su**, **1a** and **1d**.

(7.52 Å which is the length of the *c*-axis) is far too long for the reaction to occur.

The X-ray structural features of **1a·ox** are: (a) the presence of disorder at the ethylene carbons (Fig. 3b); and (b) the layered crystal structure (Fig. 4b).[15] The occupancy for C7, C8, C9 and C10 atoms was assumed 50%. The feature (b) is considered to be another mode that can be utilized for the compulsory reaction control. As pictured in Scheme 4, the **1a** molecules are bilayered in a syn head-to-head orientation and are thus in accord with the formation of β-truxinamide **3a**. The photodimerization was not very efficient, however, because of a somewhat long distance between the nearest C═C bonds (C7···C7═C8···C8═C9···C9═C10···C10═4.96 Å).

Fig. 3c shows an ORTEP diagram for **1a·fu**. Scheme 5 depicts the nearest neighbor of **1a** and **fu** in the crystal packing: for example, the pair A and B in the packing diagram Fig. 4c. The distances between the ethylene carbons are 3.82 and 4.22 Å. It is interesting that in order to accommodate the stereochemical configuration of the observed product **4**, a pedal-like conformational change in either **1a** or **fu** (see Scheme 5) is required like in the case of



Scheme 2.

1a·pht (see Scheme 3).[13] There is an array of **1a** and **fu** molecules that are oriented properly to explain the stereochemistry of **4**: for example, A and C′ in Fig. 4c, where C′ is generated by −1 cell translation of C along the *a* axis. However, the ethylene carbons in this array are by far apart, i.e. 7.39 and 7.51 Å. Hence, the nearest separated **1a** and **fu** molecules shown in Scheme 5 will be the reacting partner. Furthermore, there is a good π-overlap between the

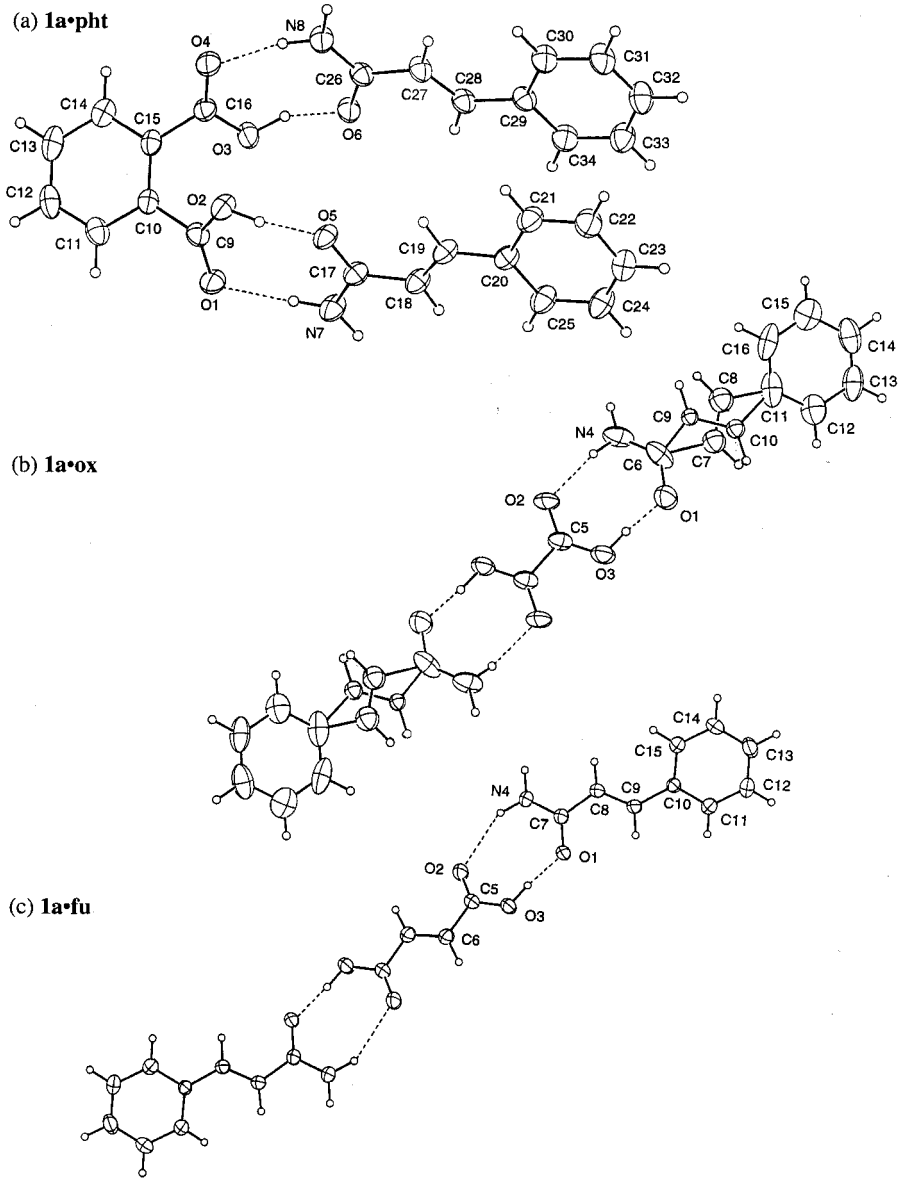


Figure 3. ORTEP drawings of cocrystals: (a) **1a·pht**; (d) **1a·ox**; and (c) **1a·fu**.

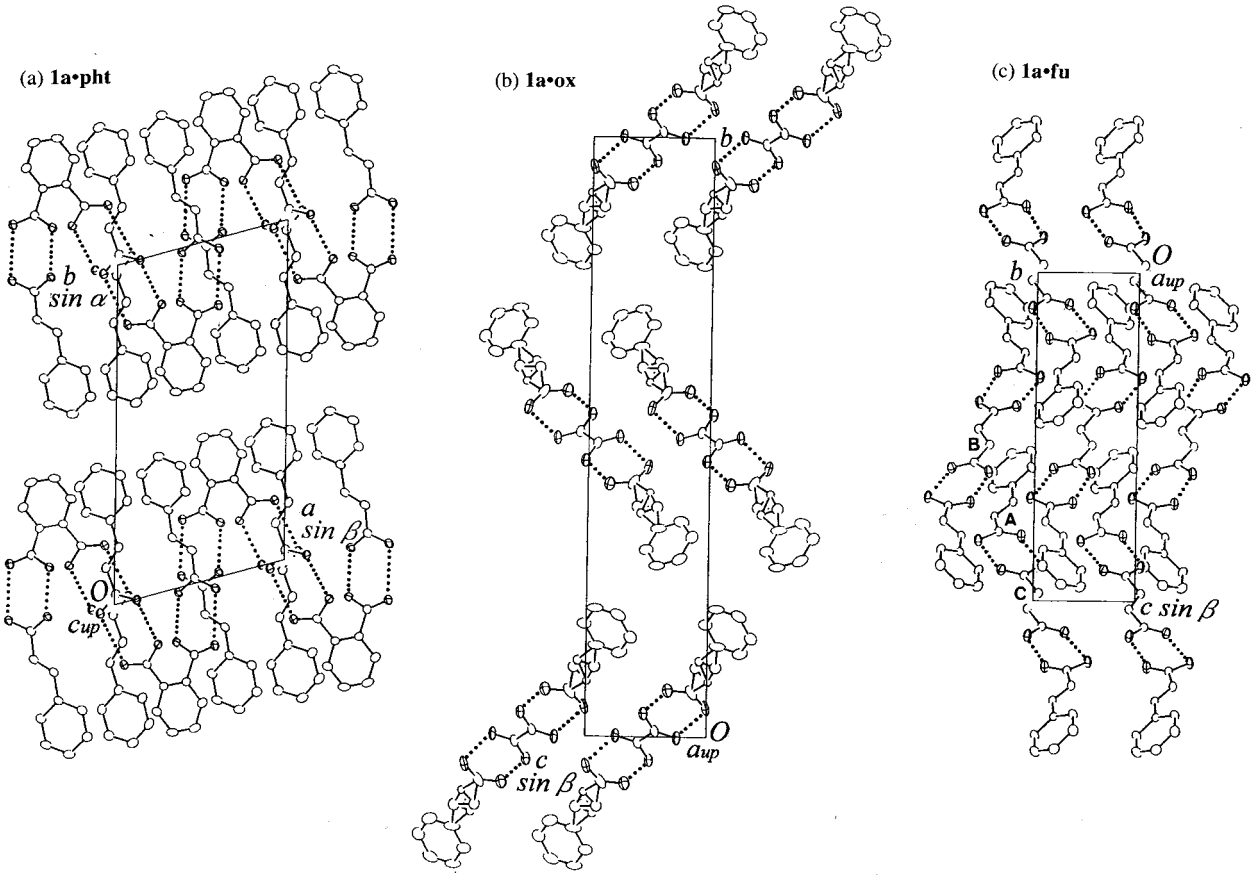
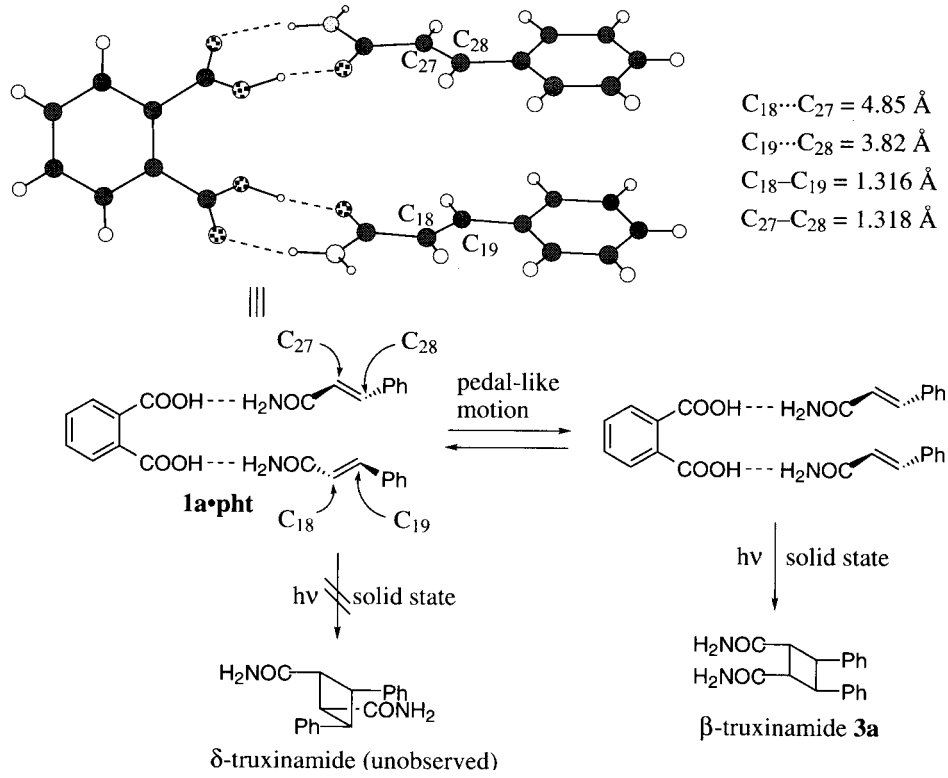
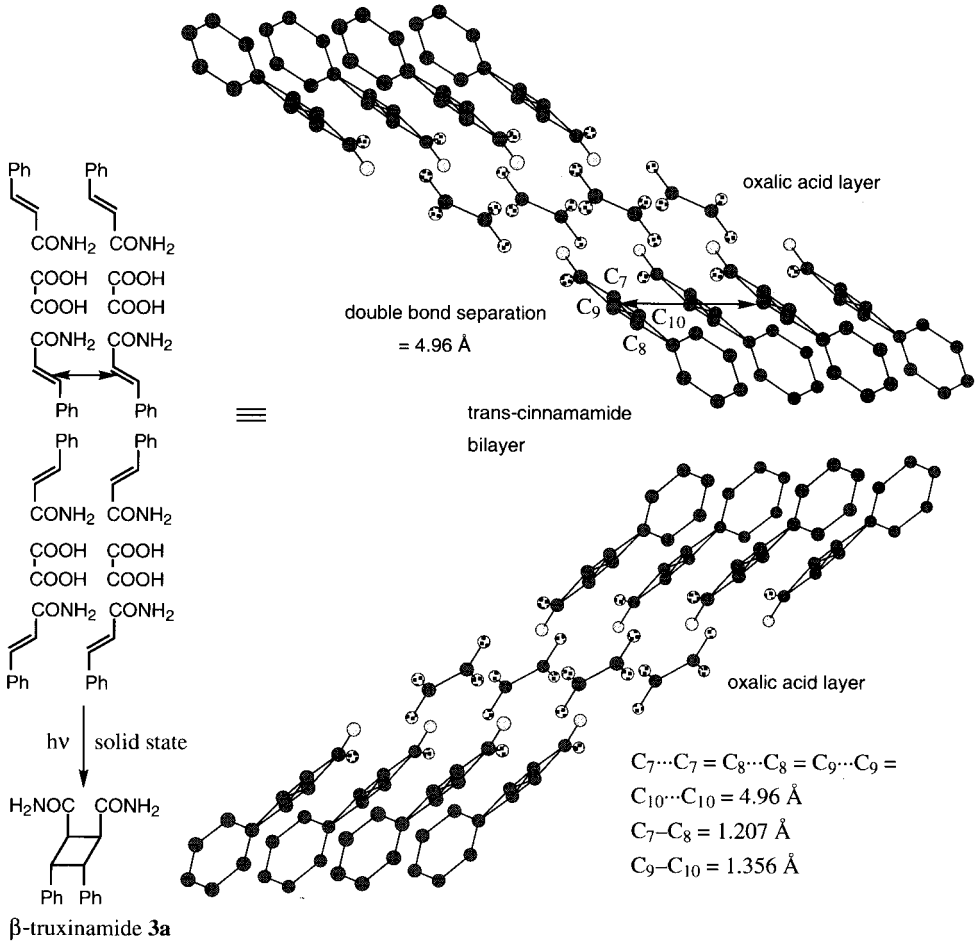


Figure 4. Packing diagrams of cocrystals: (a) **1a·pht**; (b) **1a·ox**; and (c) **1a·fu**, which are projected along the *c*-axis, the *a*-axis and the *a*-axis, respectively.



Scheme 3. A pedal-like dynamic conformational change in cocrystal **1a·pht** and the solid-state photodimerization.



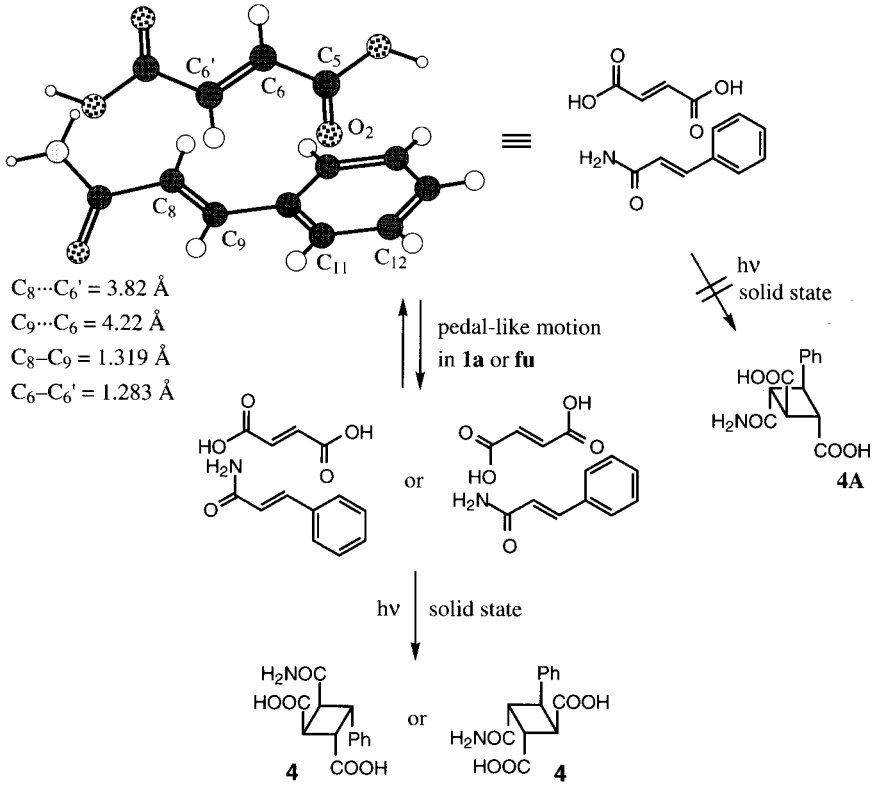
Scheme 4. A layered crystal packing of **1a·ox** and the solid state photodimerization.

phenyl ring and the carbonyl group (O2···C11=3.50 Å, O2···C12=3.43 Å, C11···O2–C5=89°, C12···O2–C5=89°). This overlap should be responsible for the 343 nm inflection which appeared in the diffuse reflectance spectrum of **1a·fu** (Fig. 1). An attractive interaction between the carbonyl and phenyl groups, referred to as C=O···π interaction, was reported to exist and this interaction was utilized for asymmetric dimerization and polymerization.[17] Such a C=O···π interaction could not be recognized in the X-ray structures of cocrystals **1a·ox** and **1a·pht**.

The crystallographically determined lengths of the ethylenic bond in **1a·ox**, **1a·pht**, and **1a·fu** are ~1.28 (disordered), 1.316(2) and 1.318(2) (two **1a** molecules in the asymmetric unit), and 1.319(2) (1.283(2) Å for the **fu** component) Å, respectively. For the **1a** homocrystal, the length was reported to be 1.331(4) Å.[18] For the **fu** homocrystal, it was 1.348 (α form) or 1.315 (β form) Å.[19] Consequently, the ethylene bonds in **1a·pht** and **1a·fu** are considerably shorter than the corresponding ones in the homocrystals. This fact strongly suggests[11] that there is dynamic disorder at the ethylene bond in the hydrogen bonded cocrystals **1a·pht** and **1a·fu**, in line with the pedal-like motion deduced from the product stereochemistry (Schemes 3 and 5 and cf. Ref. 13). Maybe **1a·ox** is an extreme case, since here the static disorder is present at the ethylene bond (Fig. 3b). Facility of the dynamic or static disorder in these cocrystals is not unexpected, because the crystal packing for two-component molecular crystals is often loose.[1,2] The loose crystal packing for **1a·ox**, **1a·pht** and **1a·fu** was also indicated from their weak PXD intensities, as described above.

Although the *R* value was reduced to only 0.141 owing to the poor quality of crystals, the crystal structure for **1d·ox** was found to be very similar to that of **1a·ox**, as expected from identical space group and similar lattice constants.[20] For instance, there are double layers of **1d** and the nearest ethylene bonds are 4.97 Å apart (cf. 4.96 Å apart for **1a·ox**). However, the ethylene bond in **1d·ox** is not disordered. For **1a·ox** (Fig. 3b), disorder is present at the ethylene carbons, indicating that **1a·ox** possesses larger free space[21] around the ethylene bond than **1d·ox**. This difference is apparently reflected on the smaller photodimerization reactivity of **1d·ox** (only 3% yield of **3d**) as compared with that of **1a·ox** (42% yield of **3a**) (Table 3).[22]

In conclusion, a compulsory control of solid-state photodimerization like that by double salts of *gauche* 1,2-diamine[1–7] was also achieved by using **pht** as a hydrogen-bonding intermolecular linker. Furthermore, a new mode of control by **ox** was found. A key point of the latter control was ascribed to the layered crystal structure enforced by **ox**. The crystal structure–reactivity relationship is well investigated and it is believed that the reactivity and the product



Scheme 5. A pedal-like dynamic conformational change in cocrystal **1a·fu** and the mixed photodimerization.

stereochemistry are precisely predictable from the crystal structure.[24] Our study suggests that this is not always the case when there is a dynamic disorder. It seems that this situation is particularly ubiquitous for mixed molecular crystals, because their crystal packings are often loose.[1,2] Torsional vibrations may bring about orientations or configurations that are more favorable for the reaction.

Experimental

General procedures

^{1}H NMR spectra were measured on a Varian Gemini-200, JEOL EX-270J, or JEOL JNM-A400 spectrometer. The solvent employed is DMSO-d_6, unless otherwise specified. IR spectra were recorded in a JASCO FT/IR-5M or SHIMADZU FTIR-8100A spectrometer. Mass spectra were obtained in a JEOL JMS-DX 300 or JEOL JMS-SX 102A spectrometer. Diffuse reflectance spectra were gathered with a SHIMADZU UV-2400PC spectrometer equipped with a diffuse-reflectance attachment and a $BaSO_4$ powder was used as a standard of reflectivity. Powder X-ray diffraction (PXD) patterns were obtained with a MAC Science MX Labo diffractometer equipped with CuKα radiation (1.5406 Å). Data were collected between 20 and 70° in 2θ at a scan rate of 4°/min. HPLC analyses were performed with a SHIMADZU LC-5A chromatograph and a UV detector (fixed at 217 nm) by using a Cosmosil 5C_{18}-AR column (4.6 mm i.d.×150 mm) and were eluted with a mixture of methanol and water, a mixture of methanol and 20 mM acetate buffer (pH 3.6), or a mixture of methanol and 10 mM phosphate buffer (pH 2.6).

Materials

trans-Cinnamamide (**1a**), *trans*-4-chlorocinnamamide (**1c**), oxalic acid (**ox**) (anhydrous and dihydrate), malonic acid, succinic acid (**su**), glutaric acid (**gl**), adipic acid, fumaric acid (**fu**), maleic acid, phthalic acid (**pht**), (±)-*trans*-1,2-cyclohexanedicarboxylic acid, *cis*-1,2-cyclohexanedicarboxylic acid, and 1,1-cyclobutanedicarboxylic acid were commercially available. *trans*-4-Methylcinnamamide (**1b**) and *trans*-β-(2-thienyl)acrylamide (**1d**) were prepared according to the literature method.[8,25] Prior to measuring the diffuse reflectance or PXD spectra, **1a**, **ox** (dihydrate), **su**, **gl**, **fu**, and **pht** were recrystalized from EtOH, water, water, water, water, and EtOH, respectively, while ox (anhydrous) was used as received.

Cocrystallization

A hot solution containing 1.472 g (10.0 mmol) of **1a** in *i*PrOH (15 mL) was mixed with a hot solution containing 0.831 g (5.0 mmol) of **pht** in *i*PrOH (15 mL) and the mixture was filtered immediately. Upon cooling to room temperature, colorless needles crystallized out of the filtrate and were collected by filtration to afford 1.59 g (69%) of **1a·pht**. This was dried in vacuo at 35°C for a few days. Other cocrystals were similarly prepared from mixing 2 equiv. of amides **1a**–**1d** with 1 equiv. of dicarboxylic acids **ox** (dihydrate), **su**, **gl**, and **fu** in appropriate solvent (Table 1).

Small-scale irradiation of cocrystals

Cocrystals of **1a·ox**, **1a·su**, **1a·gl**, **1a·pht**, **1a·fu**, **1b·ox**, **1c·ox**

or **1d·ox** (15–20 mg) were crushed and spread between two Pyrex plates. This sandwiched sample was placed in our solid-state photolysis vessel.[1,2] Irradiation was carried out with a 400 W high-pressure mercury lamp under an argon atmosphere for 20 h. During the irradiation, the vessel was cooled from outside by running water. After the irradiation, the reaction mixture was dissolved in MeOH or DMSO-d_6 for HPLC and ^{1}H NMR analyses, respectively. Yields thus estimated are summarized in Table 3.

Similar irradiation of homocrystals **1a**–**1d** gave cleanly the corresponding α-truxillamides **2a**–**2d**, as was previously reported.[8]

Isolation and characterization of β-truxinamides

(a) Cocrystal **1a·ox** (51 mg) was irradiated for 20 h as described above. The slightly colored photolysate, which contained **3a** with 29% yield (estimated by ^{1}H NMR and HPLC), was taken up in 2 mL of water and was stirred at 45°C for 1 h. After cooling in a refrigerator, an insoluble pale yellow solid was collected by filtration. This was stirred into 2 mL of acetonitrile and an insoluble solid was filtered off to afford 5 mg (13% yield) of **3a** as a white crystalline solid: mp 246–252°C (dec); ^{1}H NMR (200 MHz) δ 3.64 (2H, quasi-d, J=6.5 Hz, cyclobutyl), 4.20 (2H, quasi-d, J=6.5 Hz, cyclobutyl), 6.88–7.18 (10H, m, aromatic); MS (EI) m/z (rel intensity) 277 (42, $M^{+\cdot}-NH_3$), 205 (63), 180 (31, $[PhCH{=}CHPh]^{+\cdot}$), 147 (21, $M^{+\cdot}/2$), 131 (100); IR (KBr) 3430, 3402, 1665, 1605, 1414, 698 cm^{-1}. The stereochemistry of the cyclobutane ring of **3a** was determined on the basis of the characteristic ^{1}H NMR chemical shift and coupling pattern of the cyclobutyl protons, which were similar to those of the corresponding cinnamic acid photodimer. In fact, upon heating 2 mg of **3a** in 0.4 mL of conc HCl at 95°C for 1 h, **3a** was hydrolyzed to β-truxinic acid[3,26] in 81% yield (HPLC).

(b) Cocrystal **1a·pht** (53 mg) was irradiated for 50 h as described above. The resultant white powder, which contained **3a** with 37% yield (estimated by ^{1}H NMR and HPLC), was recrystallized from 5.5 mL of 10:1 acetonitrile–methanol to furnish 10 mg (31%) of **3a** as white needles.

The cyclobutane ring protons for **3b**–**3d** also exhibited the ^{1}H NMR pattern characteristic of the β-type photodimer. Attempts to purify β-truxinamides **3c** and **3d** were not carried out. Their ^{1}H NMR data were derived from the mixtures.

(c) The photolysate from **1b·ox** (50 mg, 40 h irradiation) was recrystallized twice with *i*-PrOH (first 3 mL, then 2 mL) to remove polymeric materials (11 mg). The residue was then recrystallized from MeCN (1 mL) to afford, although still a little contaminated with the polymer, 5 mg of **3b** as pale yellow crystals: mp 188–202°C; ^{1}H NMR (200 MHz) δ 2.11 (6H, s), 3.56 (2H, quasi-d, J=6 Hz, cyclobutyl), 4.11 (2H, quasi-d, J=6 Hz, cyclobutyl), 6.87 (10H, AB with almost vanishing end peaks, J=8 Hz, aromatic); MS (EI) m/z (rel intensity) 305 (3), 233 (12), 208 (7, $[MePhCH{=}CHPhMe]^{+\cdot}$),161 (100, $M^{+\cdot}/2$), 145 (62); IR (KBr) 3394, 3358, 1664, 1516, 1421, 1406, 1245, 811, 722 cm^{-1}.

(d) From the ^{1}H NMR analysis of the photolysate from **1c·ox**, **3c**: ^{1}H NMR (200 MHz) δ 3.61 (2H, quasi-d, J=6 Hz, cyclobutyl), 4.19 (2H, quasi-d, J=6 Hz, cyclobutyl), 7.00 and 7.16 (8H, AB, J=8.4 Hz). This photolysate was directly hydrolyzed with conc HCl as described above. The dimer **3c** was led cleanly to the previously known *p*,*p*′-dichloro-β-truxinic acid.[4,26]

(e) The pale brown photolysate from **1d·ox** (80 mg, 45 h irradiation) was recrystallized first with 10 mL of 1:1 chloroform–MeOH, then with 7 mL of 5:2 EtOH–MeOH. The mother liquor was evaporated and the residue was recrystallized from 11 mL of 10:1 benzene–EtOH. A pale brown solid (16 mg) containing **3d** in ca. 30% (^{1}H NMR) precipitated. **3d**: ^{1}H NMR (CD_3OD, 270 MHz) δ 3.80 (2H, quasi-d, J=6 Hz, cyclobutyl), 4.51 (2H, quasi-d, J=6 Hz, cyclobutyl), 6.81–6.89 (2H, m), 7.16 (1H, d with each peaks slightly split, J=5 Hz). This spectrum was very similar to that of the corresponding dicarboxylic acid previously prepared.[4,27]

Isolation of heterodimer 4. Cocrystal **1a·fu** (101 mg) was irradiated for 90 h as described above. The resultant pale yellow powder, which contained the product **4** with 50% yield (^{1}H NMR and HPLC), was fractionally recrystallized from water (2 mL), then acetonitrile–water, and finally acetonitrile (5 mL). As a result of these recrystallization procedures, fumaric and maleic acids, β-truxinamide **3a**, α-truxillamide **2a**, and *cis*-**1a** could be entirely removed and finally 18 mg of a mixture of **4** and **1a** was isolated as a solid. This mixture was further recrystallized from 7 mL of 4:3 acetonitrile–ether and then 7 mL of 4:3 acetonitrile–benzene to afford 4 mg (6%) of *t*-3-carbamoyl-*c*-4-phenyl-*r*-1,*t*-2-cyclobutanedicarboxylic acid **4** as white small needles: mp 187–190°C; ^{1}H NMR (CD_3OD, 400 MHz) δ 3.74–3.78 (1H, dd, J=10.1 and 6.1 Hz, H_2N–COC*H*), 3.79–3.83 (1H, dd, J=10.1 and 6.1 Hz, $H_2NCOCHCH$-COOH), 3.89–3.3.93 (1H, dd, J=10.7 and 6.1 Hz, PhCHC*H*COOH), 4.09–4.13 (1H, dd, J=10.7 and 6.1 Hz, PhC*H*), 7.19–7.32 (5H, m, aromatic); ^{13}C NMR (CD_3OD, 100 MHz) δ 41.12 (CH), 43.97 (CH), 45.61 (CH), 46.14 (CH), 128.10 (CH), 128.71 (CH), 129.37 (CH), 140.45 (C), 174.84 (CO), 175.16 (CO), 176.69 (CO); IR (KBr) 3425 and >2500 ($CONH_2$ and COOH), 1706 (COOH), 1665 ($CONH_2$), 1648 ($CONH_2$), 1602, 1424, 1301, 1223, 1179, 741, 699 cm^{-1}.

Hydrolysis of 4. (a) Heterodimer **4** (2 mg) in conc. HCl (0.5 mL) was heated at 95°C for 1 h. The reaction mixture was evaporated in vacuo. The residue was essentially pure *c*-4-phenyl-*r*-1,*t*-2,*t*-3-cyclobutanetricarboxylic acid **5** (^{1}H NMR and HPLC).

(b) In order to obtain more **5**, 20 mg of a mixture of **4** and **1a** (molar ratio, ca. 1:1) in conc. HCl (3 mL) was heated at 90°C for 5 h. The reaction mixture was evaporated and the residue was recrystallized with 2 mL of 1:1 methanol–water and then with 5 mL of ether. Relatively insoluble cinnamic acid and other insoluble materials were removed. The resultant soluble part (16 mg) was again recrystallized

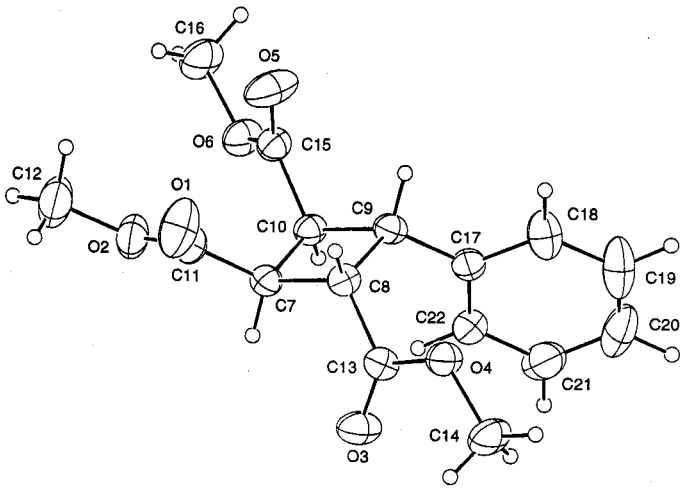


Figure 5. ORTEP drawing of compound **6**.

from $CHCl_3$ (5 mL) to give 9 mg of **5** as white plates: mp 205–208°C; ^{1}H NMR (CD_3OD, 400 MHz) δ 3.72–3.79 (2H, m), 3.82–3.87 (1H, m), 4.22–4.27 (1H, m, PhC*H*), 7.19–7.32 (5H, m, aromatic); ^{13}C NMR (CD_3OD, 100 MHz) δ 41.55 (CH), 44.28 (CH), 44.87 (CH), 45.80 (CH), 128.11 (CH), 128.52 (CH), 129.34 (CH), 140.04 (C), 174.64 (CO), 175.36 (CO), 175.71 (CO); MS (EI) *m/z* (rel intensity) 219 (17, $M^{+\cdot}-COOH$), 200 (18), 174 (45, $M^{+\cdot}-2COOH$), 172 (56), 148 (97, $[PhCH{=}CHCOOH]^{+\cdot}$), 147 (80), 129 (100, $M^{+\cdot}-3COOH$), 128 (93), 103 (44), 77 (50, Ph^+); IR (KBr) 3500–2500 (COOH), 1724 (COOH), 1709 (COOH), 1409, 1272, 1204, 743, 698 cm^{-1}.

In a separate experiment, the photolysate from 539 mg of **1a·fu** (irradiated for 170 h, containing **4** with ca. 75% yield by ^{1}H NMR) was heated in 25 mL of conc. HCl at 95°C for 3 h. The resulting brown to yellow precipitate was filtered off, the filtrate was evaporated to dryness, and then the yellow residue (440 mg) was recrystallized from 18 mL of 5:1 water–methanol. After filtration, a yellow solid (390 mg) was obtained from evaporation of the mother liquor and this was refluxed in $CHCl_3$ (50 mL) for 1 h. Tricarboxylic acid **5** (175 mg, 51% yield on the basis of **1a·fu**) was obtained as an insoluble pale yellow solid.

Esterification of 5. Into a solution containing 10 mg (0.038 mmol) of **5** in 2 mL of 1:1 methanol–benzene was added a 10% hexane solution of (trimethylsilyl)diazomethane (1 mL, ca. 0.8 mmol). The mixture was kept at room temperature for 4 h under stirring. After evaporation, the residue was subjected to preparative TLC (Merck Kieselgel 60 F_{254}, 10:1 $CHCl_3$–acetone) to afford 8 mg (69%) of trimethyl *c*-4-phenyl-*r*-1,*t*-2,*t*-3-cyclobutanetricarboxylate **6**. This was crystallized from 0.6 mL of 5:1 hexane–acetonitrile to afford 4 mg of colorless prisms: mp 88–94°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.29 (3H, s), 3.70 (3H, s), 3.75 (3H, s), 3.8 1–4.02 (3H, m), 4.28–4.40 (1H, m, PhC*H*), 7.16–7.37 (5H, m, aromatic); MS (EI) *m/z* (rel intensity) 306 (11, $M^{+\cdot}$), 275 (16), 246 (44), 214 (41), 187 (35), 162 (100, $[PhCH{=}CHCOOMe]^{+\cdot}$), 131 (96), 113 (42); IR (neat) 1742, 1728, 1436, 1314, 1301, 1274, 1216, 1204, 1172, 1018, 754, 701 cm^{-1}. This compound was successfully analyzed by single crystal X-ray diffraction (Fig. 5).

X-Ray crystal structure determination

X-ray intensities were measured on Rigaku AFC-5 or AFC-7R diffractometer with graphite monochromatized MoKα radiation (λ=0.71073 Å). The structures were solved by direct methods and were refined using CRYSTAN-GM or TEXSAN software.[28]

Crystal data. 1a·pht: triclinic, $P\bar{1}$, a=9.562(1), b=17.402(2), c=7.522(1) Å, α=90.82(1), β=105.71(1), γ=75.50(1)°, V=1164.6(3) Å^3, Z=2, D_x=1.313 g/cm^3, R=0.043. **1a·ox**: monoclinic, $P2_1/n$, a=4.961(5), b=30.536(9), c=6.471(3) Å, β=101.62(5), V=960.2(11) Å^3, Z=2, D_x=1.330 g/cm^3, R=0.052. **1a·fu**: monoclinic, $P2_1/n$, a=11.503(1), b=5.297(1), c=16.888(1) Å, β=94.09(1), V=1026.4(2) Å^3, Z=2, D_x=1.328 g/cm^3, R=0.050. **6**: monoclinic, $P2_1/c$, a=5.789(2), b=17.576(2), c=15.667(2) Å, β=99.85(2), V=1570.6(6) Å^3, Z=4, D_x=1.295 g/cm^3, R=0.061.

Acknowledgements

This work was supported by the grant-in-aid for Scientific Research from the Japanese Government (Nos. 10440215, 10132229, 11119229). The authors also acknowledge Ms Ryoko Yoshihara for her assistance in X-ray work.

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