

Unusual [2+2] Photocycloaddition between Tryptamine and 3-Nitrocinnamic Acid in the Solid State

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A crystalline salt of tryptamine with *trans*-3-nitrocinnamic acid underwent cross photocycloaddition, leading to a cyclobutane adduct **1**. Their solid mixture failed to give **1**. This is the first [2+2] photocycloaddition of alkene to "N-unsubstituted" indoles.

Investigations on the solid-state photoreactivities of two-component crystals are one of current topics in organic photochemistry.¹ These crystals may be treasuries of novel, highly selective bimolecular reactions which are unlikely to be observed in solution. For example, we have reported the photoreductive coupling reaction of the cyano group occurring in the crystalline 1:2 complex between tetracyanobenzene and benzyl cyanide² and the cross photodimerization occurring in the hydrogen-bonded 1:2 cocrystal between fumaric acid and *trans*-cinnamamide.³ There are only a few examples for selective cross photocycloadditions in the solid state.⁴ In the course of our study on the photoreactivity of crystalline salts,⁵ a salt **tpa**·3-**nca** derived from tryptamine (**tpa**) and *trans*-3-nitrocinnamic acid (3-**nca**) had been found to be photoreactive. We now wish to report this reaction.

A crystalline salt **tpa**·3-**nca**⁶ (20 mg) was crushed and spread between two Pyrex plates and this was irradiated with a 400-W high-pressure mercury lamp for 20 h under an argon atmosphere. The irradiation vessel was cooled from the outside by tap water. After the irradiation, the reaction mixture was analyzed by ¹H NMR in DMSO-*d*₆. The only peaks observable were those for the starting materials (**tpa** and 3-**nca**) and a cross photoadduct **1** (47% conversion, 39% yield; 83% yield based on the consumed starting materials) (eq 1), although the presence of weak, very broad absorptions (δ 1.5-8.5) somewhat

raised the base line. In a separate experiment, 105 mg of **tpa**·3-**nca** was irradiated under similar conditions. The product **1** could be isolated simply by fractional recrystallization from ethanol (15 mL). Polymeric products (6 mg) first separated and then 18 mg (17% yield) of nearly pure **1** separated as a pale brown powder: mp 215-225 °C.

The structure of **1** was determined by inspection of its spectral data.⁷ The IR frequencies at 1530 and 1396 cm⁻¹ indicated the presence of a carboxylate anion rather than a carboxyl group. The ¹H NMR spectrum, where each proton was assigned on the basis of its chemical shift with the help of the two-dimensional COSY and ROESY techniques, revealed that the four protons in the CH₂CH₂ moiety (two H_l and two H_m) were all non-equivalent. Therefore, the COOH and CH₂CH₂NH₂ groups were assumed to be on the same side of the cyclobutane ring, forming a salt bridge. Between the two possible structures **1** and **1a**, the former was adopted on the basis of the ROESY data, where ROESY correlations were observed between H_h and H_d and between H_h and H_e. From the molecular mechanics calculation, the two benzene rings in the structure **1** are close enough for observing the NOE effect, i.e., H_h...H_d or H_h...H_e \approx 2.8 Å. On the other hand, those in the structure **1a** are far separated (H...H \geq 4 Å).

Figure 1 shows the solid-state structure of **tpa**·3-**nca**.⁸ The π faces of **tpa** and 3-**nca** are well overlapped. The relevant double bonds are only slightly twisted (8°) and their separation (C7...C12 = 3.83 Å and C8...C13 = 3.61 Å) is well within the Schmidt's critical distance (4.2 Å). Their relative orientation is just in agreement with the stereochemistry of the photoadduct **1**.

In contrast to **tpa**·3-**nca**, other salts⁶ **tpa**·**ca**, **tpa**·2-**nca**, **tpa**·4-**nca**, **tpa**·2-**cca**, **tpa**·2,4-**cca**, **tpa**·3,4-**cca**, **tpa**·4-**fca**, **tpa**·3-**mca**, **tpa**·3,4-**mca** and **tpa**· β -2-**ta** did not give cross-dimers like **1**. Some of these salts were photoinert (**tpa**·**ca**, **tpa**·4-**nca**, **tpa**·2,4-**cca**, **tpa**·3,4-**cca**, **tpa**·4-**fca**, **tpa**·3-**mca**,

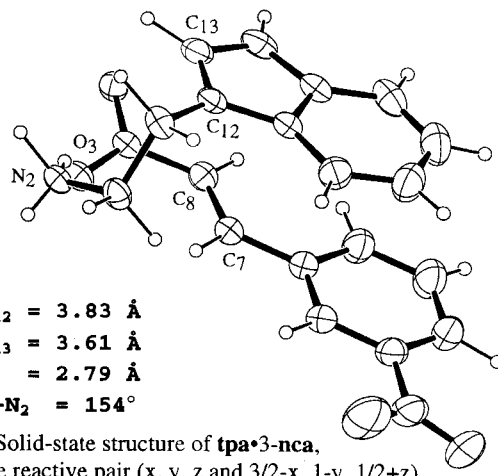
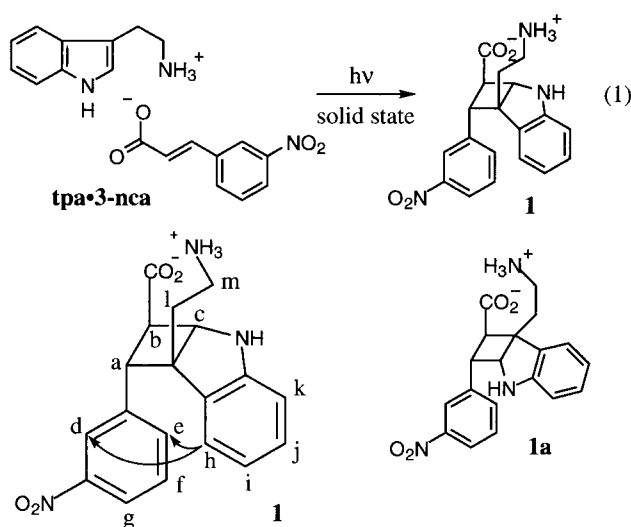


Figure 1. Solid-state structure of **tpa**·3-**nca**, showing the reactive pair (x, y, z and 3/2-x, 1-y, 1/2+z).

tpa-β-2-ta) or only the cinnamic acid component underwent photochemical reactions (5% *cis*-isomer from **tpa-2-cca**, 60% β-truxinic dimer from **tpa-3,4-mca**, or 10% uncharacterized products from **tpa-2-nca**). Based on the published crystal structure⁹ for photostable **tpa-ca** and **tpa-4-nca**, their relevant double bonds are more twisted (53° and 16°, respectively) and the C...C separations are 4.29 and 3.65 Å and 4.00 and 3.69 Å, respectively. Hence, from the topochemical view, these two salts should be less prone to undergo cross additions than **tpa-3-nca**.

Two-component crystals are usually prepared either by traditional cocrystallization or by grinding the two components together in a mortar and pestle.¹ Crystalline salts **tpa-3-nca** and **tpa-ca** which were prepared by cocrystallization and solid mixtures **tpa+3-nca** and **tpa+ca** which were prepared by solid-solid mixing in a mortar and pestle for 90 min, were irradiated as outlined above. Unlike **tpa-3-nca**, **tpa+3-nca** produced a complex mixture (73% conversion) with virtually no cross adduct **1**. Photoreactivities of **tpa-ca** and **tpa+ca** were also very different: **tpa-ca** was photoinert, whereas the **ca** component in **tpa+ca** underwent *trans-cis* isomerization (4%) and dimerization (2%). In ethanol solution, only the *trans-cis* photoisomerization of cinnamic acids occurred for both **tpa-3-nca** and **tpa-ca**.

Figure 2 shows the powder X-ray diffraction for crystalline salts **tpa-3-nca** and **tpa-ca** and for solid mixtures **tpa+3-nca** and **tpa+ca**. The diffraction pattern for the crystalline salt was very different from that for the corresponding solid mixture. IR spectra for the solid mixtures **tpa+3-nca** and **tpa+ca**, however, indicated complete conversion to the ammonium carboxylate salt even by the solid-solid mixing. From these results, a nearly amorphous structure for **tpa+3-nca** appears to be responsible for its complex photoreaction.

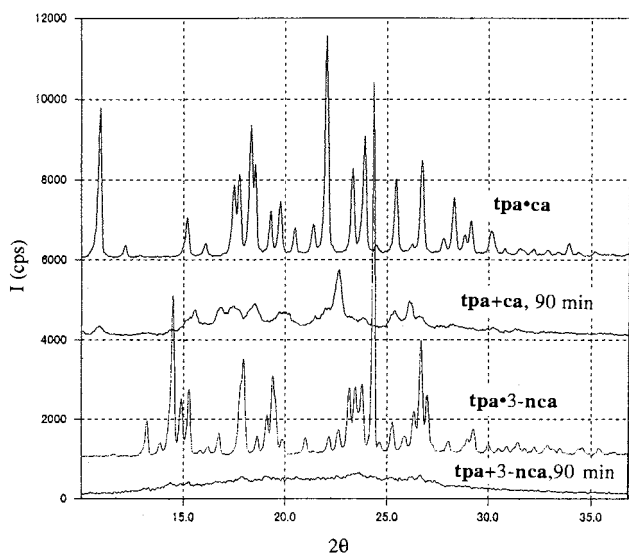
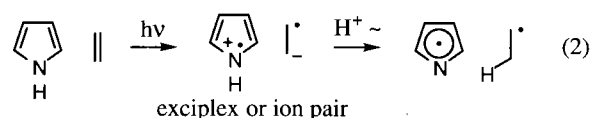


Figure 2. Patterns for powder X-ray diffraction.

A crystalline medium rather than a liquid phase is interesting solvent, since novel intermolecular reactions may be caused in it.¹ Though numerous examples of [2+2] photocycloaddition were reported so far, the reactions involving “*N*-unsubstituted” imidazole or indole are not known, i.e., *N*-substitution by the

alkyl, aryl or acyl group is required for the reaction to occur.¹⁰ This is probably because a transfer of the NH proton to a counter species within an exciplex (or ion pair) (eq 2) is very rapid.¹¹ In this connection, the present bimolecular reaction **tpa-3-nca** → **1** is unusual. We suspect that the rate of cycloaddition can be faster than the proton transfer, depending on geometries in crystal. As to the generality of this [2+2] reaction, however, we must establish as yet unknown protocols for fabricating crystal structures of desired photoreactivity. This goal is still a long way to go.



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References and Notes

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- Crystalline salts of tryptamine (**tpa**) with a series of *trans*-cinnamic acids, i.e., cinnamic acid (**ca**), 2-, 3- or 4-nitrocinnamic acid (2-, 3-, or 4-**nca**), 2-chlorocinnamic acid (2-**cca**), 2,4-dichlorocinnamic acid (2,4-**cca**), 3,4-dichlorocinnamic acid (3,4-**cca**), 4-fluorocinnamic acid (4-**fca**), 3-methoxycinnamic acid (3-**mca**), 3,4-(methylenedioxy)cinnamic acid (3,4-**mca**) and β-(2-thienyl)acrylic acid (β-2-**ta**), could be easily prepared by cocrystallization of **tpa** and the corresponding acid from 2-propanol or ethanol. These were characterized by ¹H NMR, IR and elemental analyses. Melting points were 184-184.5, 158-160, 174-176 (dec), 185-188.5 (dec), 161-163, 175-179, 188-194, 202-203, 148-149.5, 171-174 and 174-177.5 °C, respectively. 3-**nca**, 3,4-**mca** and halogen-substituted cinnamic acids were selected, because they showed a stronger tendency to form an overlapping crystal structure.^{1,5b}
- Spectroscopic data for **1**: ¹H NMR (DMSO-*d*₆, 400 MHz) δ 2.07-2.14 (1 H, m, H₁), 2.19-2.24 (1 H, m, H₁), 2.41-2.49 (1 H, m, H_m), 2.77-2.83 (1 H, m, H_m), 2.91 (1 H, dd, *J* = 9.3 and 5.1 Hz, H_b), 3.97 (1 H, d, *J* = 9.3 Hz, H_a), 4.17 (1 H, d, *J* = 5.1 Hz, H_c), 6.03 (1 H, d, *J* = 7.5 Hz, H₁), 6.27 (1 H, t, *J* = 7.5 Hz, H₁), 6.54 (1 H, d, *J* = 7.5 Hz, H₁), 6.87 (1 H, t, *J* = 7.5 Hz, H₁), 7.49 (2 H, quasi-d, *J* = 5.0 Hz, H_c and H_d), 7.79 (1 H, quasi-s, H_d), 7.99 - 8.03 (1 H, m, H₁); IR (KBr) 3423 (s), 1561 (m), 1530 (s), 1396 (m), 1351 (s), 754 (m) cm⁻¹ (in nujol), 3224 (m), 1554 (m), 1533 (s), 1394 (m), 1355 (s) cm⁻¹; High-resolution FAB MS *m/z* 354.1449 (M+H)⁺, calculated 354.1454 for C₁₉H₂₀O₄N₃.
- Crystal data for **tpa-3-nca**: C₁₉H₁₉N₃O₄, *M* = 353.38, yellow plates, crystal dimensions 0.6 x 0.4 x 0.05 mm, orthorhombic, space group *Pbca*, *a* = 11.712(3), *b* = 36.52(1), *c* = 8.329(3) Å, *V* = 3562(2) Å³, *Z* = 8, *D_x* = 1.318 g/cm³, *μ* (Cu Kα) = 0.776 mm⁻¹, 3378 measured reflections, *R* = 0.052, *R_w* = 0.086 for 2661 reflections [*I* > 3σ(*I*) with 312 parameters].
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