

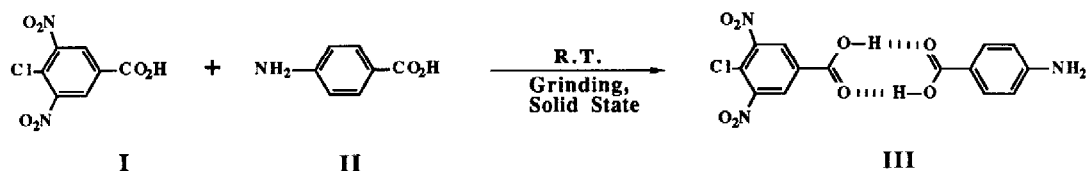
## SOLID-STATE NUCLEOPHILIC AROMATIC SUBSTITUTION REACTION OF A CARBOXYLIC ACID COCRYSTAL

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**Summary:** A facile thermally activated aromatic nucleophilic substitution reaction is shown to take place in the solid state in cocrystals of 4-chloro-3,5-dinitrobenzoic acid and 4-aminobenzoic acid. The cocrystals are also made in the solid state by grinding the two acids together at room temperature.

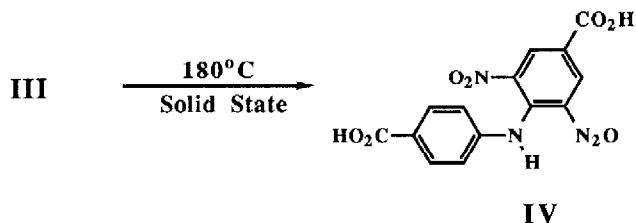
As part of a project on solid-state preparation of hydrogen-bonded organic cocrystals,<sup>1</sup> we attempted to prepare a 1:1 cocrystal (**III**) of 4-chloro-3,5-dinitrobenzoic acid (**I**) and 4-aminobenzoic acid (**II**) by grinding the two compounds together. This process has proven to be a very efficient method for preparing a wide variety of cocrystals, particularly when one component is a good proton donor and the other is a good proton acceptor. For carboxylic acid pairs, solid-state cocrystal formation involving heterodimer association appears to be favored when the two acids have quite different  $pK_a$ 's. We found that **III** could be prepared either in solution, by rapid cooling of an equimolar solution of **I** and **II** in ethanol/methanol, or in the solid state by grinding **I** and **II** in a mill for about twenty minutes at room temperature. Mass spectroscopy, solid-state IR, and X-ray powder pattern analyses were used to characterize the complex.<sup>2</sup>

### Step 1

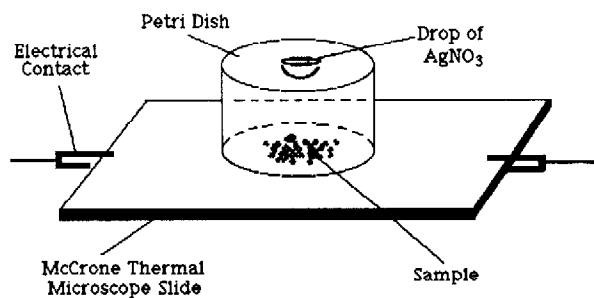


Samples of **III** darken when heated, and melt at 290°C (mp **I**, 159°C; **II**, 188°C). Differential scanning calorimetry (Mettler FP84/80) on **III** shows that an irreversible exothermic phase change ( $10 \pm 2$  kJ/mole) occurs at 180°C, at which time the sample has turned dark yellow-orange. IR spectra, solution NMR spectra, X-ray powder patterns, and mass spectra taken from samples of **III** after they have been heated to 180°C are all consistent with formation of the nucleophilic aromatic substitution product (**IV**).

## Step 2



Loss of HCl during step 2 was monitored by use of a simple device, shown below. The set-up, which is designed for use on a microscope stage, consists of a heated microscope slide which holds the sample,<sup>3</sup> and a drop of AgNO<sub>3</sub> suspended over the sample on an inverted Petri dish. As the sample is heated and HCl is evolved, a white AgCl precipitate is readily seen in the suspended solution. A negative Beilstein test confirmed that chlorine was not present in the sample after HCl evolution ceased.

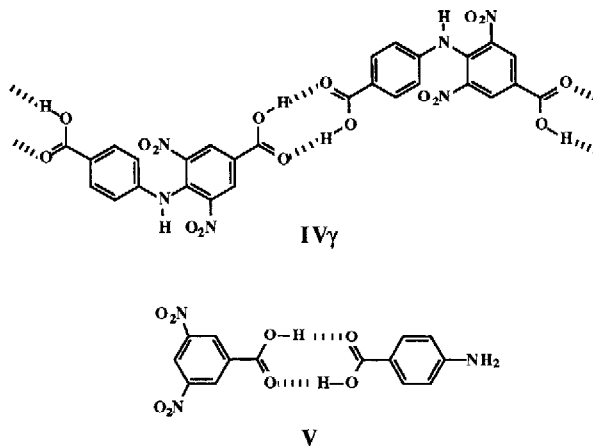


Compound **IV** was prepared independently in solution using the method of Clemo and Dalglish.<sup>4</sup> Compound **IV** was produced in high yield by both the solid-state and solution methods. The solid-state method is the superior preparative technique because it eliminates the need for solvents and specialized glassware. The solid-state technique also eliminates the need for acidification of the product.

Crystals obtained by the solution method are a different polymorph (**IV** $\alpha$ ) than those obtained in the solid-state reaction (**IV** $\beta$ ). High quality crystals of **IV** were obtained as a third form (**IV** $\gamma$ ) from benzene/methanol solution. Both **IV** $\gamma$  and **IV** $\beta$  may be recrystallized to **IV** $\alpha$  from ethyl acetate. Compound **IV** $\alpha$  can easily be distinguished from **IV** $\beta$  and **IV** $\gamma$  by the position of the -NH peak in its IR spectrum.<sup>5</sup> The different crystal forms are characterized by unique X-ray powder patterns.<sup>6</sup>

Crystal structure analysis shows that **IV** $\gamma$  is a benzene solvate of **IV**.<sup>7</sup> The molecules pack in a heterodimer hydrogen-bond pattern, as expected. Because the two different carboxylic acid groups bond to one another in **IV** $\gamma$ , it is reasonable that they may also bond in that pattern in crystals of **III**. Further evidence that **III** is in the heterodimer form comes from the crystal structure of a closely related cocrystal (**V**) of **II** and 3,5-dinitrobenzoic acid, where the heterodimer pattern is again found.<sup>1</sup> Because the -NH and carbonyl stretching

bands of **III** and **V** are shown by IR analysis to be identical,<sup>8</sup> the hydrogen-bond patterns are assumed to be similar. Attempts to grow single crystals of **III** for X-ray structural analysis continue.



This work is an example of a two-step solid-state organic synthesis that proceeds in quantitative yield in both steps. The products formed at the completion of reaction are homogeneous. The reaction of **III** to give **IV $\beta$**  occurs at high temperatures where mobility of the reagents prior to reaction should be substantial. It is not clear that the heterodimer is maintained during the course of reaction, nor is it clear whether the reaction mechanism follows the principles of least motion.<sup>9</sup> Because the reaction reported here proceeds at quite a high temperature, large molecular motions including diffusion as well as reorientation should be possible.<sup>10</sup>

Solid-state organic reactions occur frequently,<sup>11</sup> yet no methodology exists for making these reactions generally useful. The work presented here shows that the scope of reactions possible in the solid state can be increased significantly by using cocrystals containing two or more of the necessary reagents. There is only one other known solid-state nucleophilic aromatic substitution reaction<sup>12</sup> which, like ours, was discovered serendipitously. A conscious effort to design cocrystals of other compounds capable of reacting in the solid state should prove fruitful, particularly if the effort is coupled with a study of solid-state packing patterns. The experimental simplicity of solid-state reactions, as shown here, is a compelling reason to use these reactions as preparative procedures.

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### References

† On leave from the Department of Chemistry, Ben-Gurion University of the Negev, Beer Sheva, Israel.

1. M.C. Etter and G.M. Frankenbach, *Chemistry of Materials* **1989**, *1*, 10-12.

2. Mass spectra (AEI MS-30) of both preparations of **III** have two parent peaks at 246 and 137 characteristic of **I** and **II**. FTIR spectra (Nicolet 5DXB) on solid-state and solution preparations of **III** are identical, and distinctly different than the spectra of **I** and/or **II**. Peaks characteristic of **III** include -NH stretches at 3488 and 3392  $\text{cm}^{-1}$ . X-ray powder patterns (Siemens D500) showed no evidence of **I** or **II** in the final product. Peaks characteristic of **III** include:  $d(I/I_0) = (6.08, 72\%), (5.21, 40\%), (3.72, 32\%), (3.45, 97\%), (3.31, 100\%)$ .
3. The thermal microscope slide was purchased from the McCrone Research Institute, Inc., Chicago, Ill.
4. A solution of **I** (2.2 g.), **II** (1.2 g.), and sodium carbonate (0.7 g.) in water (85 ml.) was refluxed for two hours. After cooling, the product was acidified. Compound **IV** was recrystallized in ethyl acetate. (G.R. Clemo, A.F. Dalglish, *J. Chem. Soc.* **1950**, 1481-1485. This reaction begins to occur in most organic solvents, after several hours, even at room temperature. The formation of **IV** in solution is partly responsible for the difficulty in preparing cocrystals of **III**).
5. The -NH peak from IR for **IV $\alpha$**  is at 3283  $\text{cm}^{-1}$ , while the -NH peaks for **IV $\beta$**  and **IV $\gamma$**  are both at 3323  $\text{cm}^{-1}$ .
6. X-ray powder patterns include the following peaks: **IV $\alpha$** ,  $(d, I/I_0) = (7.10, 94\%), (5.88, 52\%), (4.73, 97\%), (4.14, 81\%), (4.06, 100\%), (3.91, 53\%), (3.56, 57\%), (3.42, 55\%), (3.31, 50\%)$ ; **IV $\beta$** ,  $(d, I/I_0) = (5.40, 75\%), (5.15, 60\%), (4.54, 45\%), (4.39, 78\%), (3.37, 48\%), (3.09, 100\%)$ . The X-ray powder pattern for **IV $\gamma$**  was calculated from the X-ray single crystal data using POWD (Written by Deane K. Smith and Mark Holomany, Materials Research Laboratory, Pennsylvania State University) and includes the following peaks:  $(d, I/I_0) = (11.86, 100\%), (7.99, 52\%), (4.83, 57\%), (3.95, 60\%), (3.11, 45\%)$ .
7. A paper on the crystal structure of **IV $\gamma$**  is in preparation by M.C. Etter, G.M. Frankenbach, J. Bernstein, and D. Britton.
8. Characteristic IR peaks of **III** and **V** include -NH peaks at 3488 and 3392  $\text{cm}^{-1}$  and a sharp carbonyl stretch at 1687  $\text{cm}^{-1}$ .
9. a) F.L. Hirshfeld and G.M.J. Schmidt, In *Solid-State Photochemistry*; Ginsburg, D., Ed.; Verlag Chemie: New York; 1976; Vol. 8, pp 56-60. b) G.M.J. Schmidt, *ibid.*, pp 61-91.
10. I.C. Paul and D.Y. Curtin, *Acc. Chem. Res.* **1973**, 6, 217-225.
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12. R.W. Trimmer, L.R. Stover and A.C. Skjold, *J. Org. Chem.* **1985**, 50, 3612-3614.

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