

## Solid-state *versus* solution preparation of two crystal forms of [HN(CH<sub>2</sub>CH<sub>2</sub>)<sub>3</sub>NH][OOC(CH<sub>2</sub>)COOH]<sub>2</sub>. Polymorphs or hydrogen bond isomers?

Dario Braga\* and Lucia Maini\*

Dipartimento di Chimica "G. Ciamician", Via Selmi 2, 40126 Bologna, Italy. E-mail: dario.braga@unibo.it; lmaini@ciam.unibo.it

Received (in Cambridge, UK) 20th January 2004, Accepted 23rd February 2004

First published as an Advance Article on the web 16th March 2004

The reaction of [N(CH<sub>2</sub>CH<sub>2</sub>)<sub>3</sub>N] with malonic acid [HOOC(CH<sub>2</sub>)COOH] in the molar 1:2 ratio yields two different crystal forms of the salt [HN(CH<sub>2</sub>CH<sub>2</sub>)<sub>3</sub>NH][OOC(CH<sub>2</sub>)COOH]<sub>2</sub> depending on the preparation technique and crystallization speed: form I, containing malonate anions with intramolecular hydrogen bonds, is obtained by solid-state co-grinding or by rapid crystallization, whereas form II containing intermolecular hydrogen bonds is obtained by slow crystallization. Form I and II do not interconvert, and form I undergoes an order–disorder phase transition on cooling.

The controlled preparation and characterization of crystal polymorphs,<sup>1</sup> e.g. of different crystal forms of the same substance, has become one of the major issues of modern crystal engineering and solid-state chemistry.<sup>2</sup> This is not only because of the economical issues arising from drug patent litigations but also because studies of polymorphism afford fundamental information on molecular recognition, crystal nucleation, crystallization, and the relationship between solid phases.<sup>3</sup> An aspect of relevance in studies of polymorphism is the possibility of preparing crystal forms by means of non-solution methods, such as the solvent-free mechanochemical co-grinding of solids.<sup>4</sup>

In this communication we report the discovery of an intriguing case of polymorphism, namely the formation of different crystal forms of the salt [HN(CH<sub>2</sub>CH<sub>2</sub>)<sub>3</sub>NH][OOC(CH<sub>2</sub>)COOH]<sub>2</sub> depending on whether the crystals are obtained by grinding together the reactants (form I) or by slow crystallization in solution (form II).

The two crystals are nearly isomorphous and differ essentially in the O–H...O hydrogen bonding interactions established by the hydrogen malonate anion [OOC(CH<sub>2</sub>)COOH]<sup>–</sup>. In form I all hydrogen malonate anions show only intramolecular O–H...O hydrogen bonding, whereas in form II one intramolecular hydrogen bond opens up and transforms into an intermolecular hydrogen bond.

The two forms can be separately obtained by reacting the organic base [N(CH<sub>2</sub>CH<sub>2</sub>)<sub>3</sub>N] with malonic acid [HOOC(CH<sub>2</sub>)COOH] in the stoichiometric ratio 1:2. Form I (intra) is easy to prepare by solid-state co-grinding of the diamine and the dicarboxylic acid in the stoichiometric ratio 1:2 using an agate mortar. A similar procedure has been recently used to generate a whole family of acid–base adducts.<sup>5</sup> Form I can also be obtained by dissolving 4 mmol of acid and 2 mmol of base in 20 ml of ethanol at 50 °C and allowing the solution to cool slowly. Within about 12 h this procedure yields crystals suitable for X-ray single crystal diffraction.† The comparison between calculated and measured powder diffraction patterns was used to ascertain that the same phase had formed *via* the two routes.‡

Form II (inter) is obtained by adding at room temperature directly 10 mL of a 0.2 M ethanolic solution of malonic acid to 10 mL of a 0.1 M ethanolic solution of [N(CH<sub>2</sub>CH<sub>2</sub>)<sub>3</sub>N] without stirring. After leaving the solution at room temperature for 24 h without crystal formation, the solution was kept in a fridge for a further seven days and single crystals suitable for X-ray single crystal diffraction were recovered. Manual grinding of the crystals did not cause phase transition.†

As mentioned above, the two forms differ in the hydrogen bonding motifs adopted by the hydrogen malonate anions in the two

crystals. The hydrogen malonate anions in form I [see Fig. 1(a)] form typical intramolecular hydrogen bonds [S(6) in the graph set notation<sup>6</sup>], [O...O 2.4032(5) Å] and interact *via* O...H...N hydrogen bonds [N...O distance 2.7127(5) Å] with the organic base on both sides. Hence the supramolecular motif can be described by the sequence [OOC(CH<sub>2</sub>)COOH]<sup>–</sup><sub>INTRA</sub>...[HN(CH<sub>2</sub>CH<sub>2</sub>)<sub>3</sub>NH]<sup>2+</sup>...[OOC(CH<sub>2</sub>)COOH]<sup>–</sup><sub>INTRA</sub>. The base is affected by orientational disorder around the O...H...N#N...H...O vector.

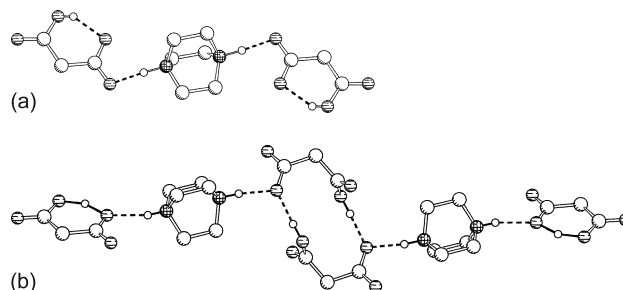
Form I can be cooled down to 214 K without transforming into form II. At low temperature (134 K) the disorder disappears. The orthorhombic–monoclinic order–disorder phase transition is reversible and can be monitored on the same crystal specimen.†

Form II contains 'oligomers' formed of six units: two outer anions [OOC(CH<sub>2</sub>)COOH]<sup>–</sup><sub>INTRA</sub> [S(6)] linked to two [N(CH<sub>2</sub>CH<sub>2</sub>)<sub>3</sub>NH]<sup>+</sup> cations, which are in turn joined by a twelve-membered ring formed of two [OOC(CH<sub>2</sub>)COOH]<sup>–</sup><sub>INTER</sub> [R(12)] anions as shown in Fig. 1(b). The supramolecular sequence is [OOC(CH<sub>2</sub>)COOH]<sup>–</sup><sub>INTRA</sub>...[HN(CH<sub>2</sub>CH<sub>2</sub>)<sub>3</sub>NH]<sup>2+</sup>...([OOC(CH<sub>2</sub>)COOH]<sup>–</sup><sub>INTER</sub>)<sub>2</sub>...[HN(CH<sub>2</sub>CH<sub>2</sub>)<sub>3</sub>NH]<sup>2+</sup>...[OOC(CH<sub>2</sub>)COOH]<sup>–</sup><sub>INTRA</sub>. As expected, the intramolecular O–H...O hydrogen bond is shorter than the intermolecular one [2.429(2) *versus* 2.615(2) Å]. The N...O distances, 2.607(2) and 2.698(2) Å, are both shorter than in form I.

Preliminary studies on the thermodynamic properties show that there is no transition between the two forms. The two forms have the same melting point 118(1) °C and probably we are in presence of a monotropic dimorphic system.<sup>7,8</sup>

Although it is known that [OOC(CH<sub>2</sub>)COOH]<sup>–</sup> can form either intermolecular and intramolecular hydrogen bonds, to the best of our knowledge the ring motif [R(12)] formed by two hydrogen malonate anions (or by two malonic acid molecules) has never been observed before.<sup>9</sup>

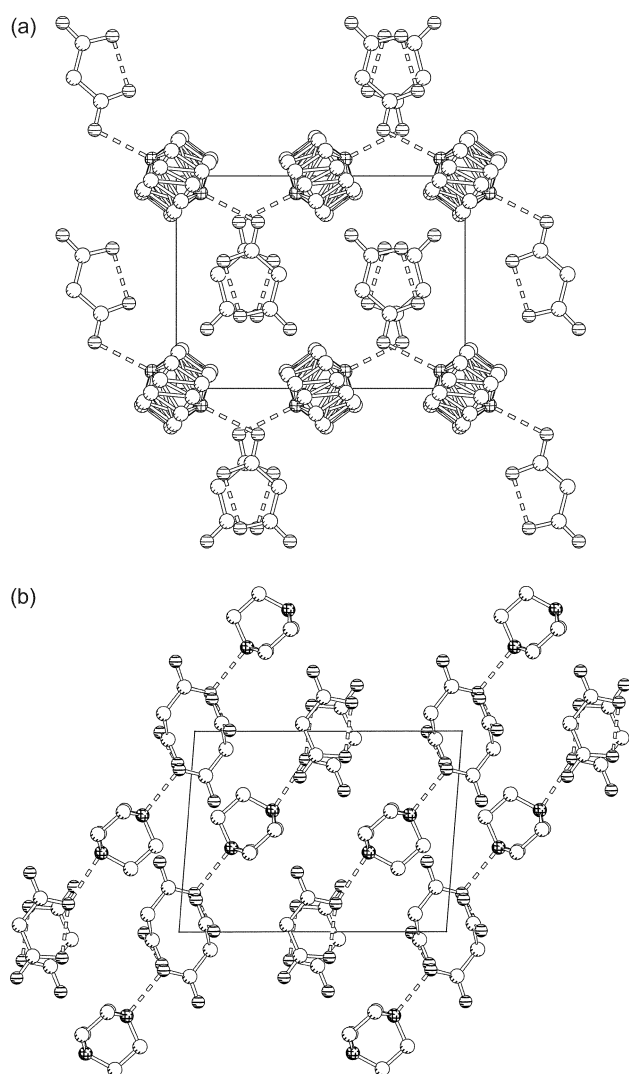
Topologically, form II can be ideally derived from form I upon conversion of two adjacent hydrogen oxalate anions of the type [OOC(CH<sub>2</sub>)COOH]<sup>–</sup><sub>INTRA</sub> into a ring formed by two [OOC(CH<sub>2</sub>)COOH]<sup>–</sup><sub>INTER</sub> anions and formation of the large twelve-membered ring. Fig. 2 shows a comparison between the crystal packings of form I and form II (projection down the *ab* and *bc* planes, respectively). In both crystal structures the two moieties are piled in a very similar geometric arrangement, which suggests the possible topochemical path not only from form I to form II but also from form II to a third hypothetical form III where all next-



**Fig. 1** (a) Hydrogen bond motif in form I. Only one disordered position of the base is shown for clarity. (b) Hydrogen bond motif form II. H<sub>CH</sub> atoms omitted for clarity.

neighbouring pairs of  $[\text{OOC}(\text{CH}_2)\text{COOH}]^-_{\text{INTRA}}$  anions in form I are transformed into twelve-membered rings  $[\text{R}(12)]$  leading to a hydrogen bonded polymer  $[\text{OOC}(\text{CH}_2)\text{COOH}]^-_{\text{INTER}} \cdots [\text{HN}(\text{CH}_2\text{CH}_2)_3\text{NH}]^{2+} \cdots [\text{OOC}(\text{CH}_2)\text{COOH}]^-_{\text{INTER}}$ . However, we have had, thus far, no hint of the formation of this third hypothetical phase.

Whether the two forms can be considered *bona fide* polymorphs or hydrogen bonded isomers might appear a semantic question. Certainly, there will be no chemical difference between the two forms when dissolved in the same solvent because they will equilibrate. On the other hand the rate of interconversion between the isomers, which is under temperature control, can be crucial in determining the composition of the isomeric equilibrium mixture at nucleation time, which will, in turn, determine which crystal form can grow to size. The relationship between polymorphs and interconverting isomers has been commented upon.<sup>10</sup> In this study we have also shown that the seemingly kinetic product can be obtained also by solid-state methods, while the stable thermodynamic form can only be prepared by slow crystallization. Work is



**Fig. 2** Comparison between the crystal packings of form I (a) and form II (b) projected along the *ab* and *bc* planes, respectively, showing the relationship between the hydrogen bonded 'oligomers'. Note the disordered projection of the  $[\text{NH}(\text{CH}_2\text{CH}_2)_3\text{NH}]^{2+}$  cations. Hydrogen atoms omitted for clarity.

in progress to explore the relationship between intra- and inter-molecular hydrogen bonds in solution and to evaluate the packing energy of the two forms.

We thank Professor Joel Bernstein, Professor Gautam Desiraju, Professor Fabrizia Grepioni for useful discussion and Dr Katia Rubini for DSC measurements. The financial support of University of Bologna is gratefully acknowledged.

## Notes and references

† X-Ray data collected on a Nonius-CAD4 diffractometer; MoK $\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ).

*Crystal data.* Form I:  $M = 320.30$ ,  $T = 214 \text{ K}$ , orthorhombic, space group  $Pn\bar{c}m$ ,  $a = 8.946(2)$ ,  $b = 12.144(2)$ ,  $c = 6.684(1) \text{ \AA}$ ,  $V = 715.3(2) \text{ \AA}^3$ ,  $Z = 2$ , 690 independent reflections (1258 measured),  $wR_2 = 0.2428$ ,  $R_1 = 0.0802$ . Form I, ordered:  $M = 320.30$ ,  $T = 134 \text{ K}$ , monoclinic, space group  $P21/a$ ,  $a = 6.417(1)$ ,  $b = 11.861(2)$ ,  $c = 18.164(6) \text{ \AA}$ ,  $\beta = 91.42(9)^\circ$ ,  $V = 1382.1(6) \text{ \AA}^3$ . Form II:  $M = 320.30$ ,  $T = 293 \text{ K}$ , triclinic, space group  $P\bar{1}$ ,  $a = 6.807(3)$ ,  $b = 8.939(4)$ ,  $c = 11.833(7) \text{ \AA}$ ,  $\alpha = 94.54(4)$ ,  $\beta = 90.75(4)$ ,  $\gamma = 94.00(3)^\circ$ ,  $V = 715.9(6) \text{ \AA}^3$ ,  $Z = 2$ , 2499 independent reflections (2631 measured),  $wR_2 = 0.1363$ ,  $R_1 = 0.0460$ . SHELX97<sup>11a</sup> and SCHAAL99<sup>11b</sup> were used for structure solution and graphical representation. In form I the carbon atoms of the dication  $[\text{HN}(\text{CH}_2\text{CH}_2)_3\text{NH}]^{2+}$  are disordered, with occupancies of 0.125 and 0.25 depending on the site symmetry; the corresponding hydrogen atoms were not modelled.

CCDC 229133 and 219134. See <http://www.rsc.org/suppdata/cc/b4/b400901k/> for crystallographic data in .cif or other electronic format.

‡ In view of the poor quality, crystal data of form I (134 K) have not been deposited. The correspondence between the bulk material obtained *via* the two crystallization procedures and the structures obtained by single crystal diffraction experiments was verified by comparing calculated and observed powder diffraction patterns.

- W. C. McCrone, in *Polymorphism in Physics and Chemistry of the Organic Solid State*, D. Fox, M. M. Labes and A. Weisseberger, ed., Interscience, New York, 1965, vol. II, p. 726; T. L. Threlfall, *Analyst*, 1995, **120**, 2435; J. Bernstein, *Polymorphism in Molecular Crystals*, Oxford University Press, Oxford, 2002.
- J. Bernstein, R. J. Davey and J.-O. Henck, *Angew. Chem., Int. Ed.*, 1999, **38**, 3440; see also: N. Bladgen and R. J. Davey, *Chem. Br.*, 1999, **35**, 44.
- J. Dunitz and J. Bernstein, *Acc. Chem. Res.*, 1995, **28**, 193; D. Braga and F. Grepioni, *Chem. Soc. Rev.*, 2000, **4**, 229; N. Bladgen and R. J. Davey, *Cryst. Growth Des.*, 2003, **3**, 873; R. J. Davey, K. Allen, N. Bladgen, W. I. Cross, F. H. Lieberman, M. J. Quayle, S. Righini, L. Seton and G. J. T. Tiddy, *CrystEngComm*, 2002, **4**, 257; R. K. R. Jetti, R. Boese, J. A. R. P. Sarma, L. S. Reddy, P. Vishweshwar and G. R. Desiraju, *Angew. Chem., Int. Ed.*, 2003, **42**, 1963.
- D. Bradley, *Chem. Br.*, September 2002, 42; K. Tanaka and F. Toda, *Chem. Rev.*, 2000, **100**, 1025; G. W. V. Cave, C. L. Raston and J. L. Scott, *Chem. Commun.*, 2001, 2159; G. Rothenberg, A. P. Downie, C. L. Raston and J. L. Scott, *J. Am. Chem. Soc.*, 2001, **123**, 8701; G. Kaupp, *CrystEngComm*, 2003, **5**, 117; K. Tanaka, *Solvent-free Organic Synthesis*, Wiley-VCH, Weinheim, 2003.
- D. Braga, L. Maini, G. de Sanctis, K. Rubini, F. Grepioni, M. R. Chireotti and R. Gobetto, *Chem. Eur. J.*, 2003, **9**, 5538.
- J. Bernstein, R. E. Davis, L. Shimoni and N.-L. Chang, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1555.
- A. Burger, *Acta Pharm. Technol.*, 1982, **28**, 1.
- DSC measurements were carried out with a scan speed of  $0.5 \text{ }^\circ\text{C min}^{-1}$ , closed sample pan. The differences between the calculated densities ( $1.466$  and  $1.486 \text{ g cm}^{-3}$  at room temperature for I and II, respectively) seem to indicate that form II is the thermodynamically stable form.
- A CSD search has not yielded any other example (CSD version 5.24 November 2002). F. H. Allen and O. Kennard, *Chem. Des. Automat. News*, 1993, **8**, 31.
- J. Dunitz, *Acta Crystallogr., Sect. B*, 1995, **51**, 619.
- (a) G. M. Scheldrick, SHELXL97: Program for Crystal Structure Determination, University of Göttingen, Germany, 1997; (b) E. Keller, SCHAAL: Graphical Representation of Molecular Models, University of Freiburg, Germany, 1999.