

# Conformational polymorphism of methacrylamide†

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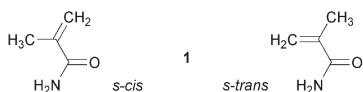
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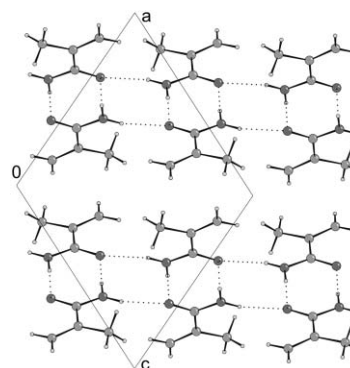
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The industrially important compound methacrylamide crystallizes as concomitant conformational polymorphs; the monoclinic form contains only the *s-cis* conformer, while the orthorhombic form contains only the *s-trans* conformer.

Methacrylamide (**1**) was first synthesized in 1928.<sup>1</sup> The first patent involving **1** appeared in 1935;<sup>2</sup> **1** has appeared in over 1000 patents to date. Methacrylamide sulfate is a key intermediate compound in the acetone cyanohydrin (ACH) process for the manufacture of methyl methacrylate (MMA); the total projected US capacity for MMA production by the ACH process in 2004 was  $8 \times 10^5$  metric tons.<sup>3</sup> Despite the attention that methacrylamide has received, its crystal structure has remained unknown. As part of our interest in the solid-state polymerisation of molecular materials,<sup>4</sup> we set out to establish the crystal structure of **1** and provide a rationale for understanding its sensitivity to ionising radiation.<sup>5</sup> As we attempted to grow and characterise crystals of **1**, it became apparent that there were monoclinic (Form I) and orthorhombic (Form II) polymorphs which crystallised concomitantly.<sup>6</sup> The results of preliminary X-ray structural analyses (linear diffractometry) at 294 K were inconclusive owing to poor crystal quality, but nonetheless suggested that Form I contained only the *s-cis* conformer, while Form II contained only the *s-trans* conformer. While it has not yet been possible to develop procedures for the isolation of the pure phases, reliable procedures for the preparation of *enriched* batches of either Form I or Form II with improved crystal quality (and unambiguous redetermined structures) are now at hand.



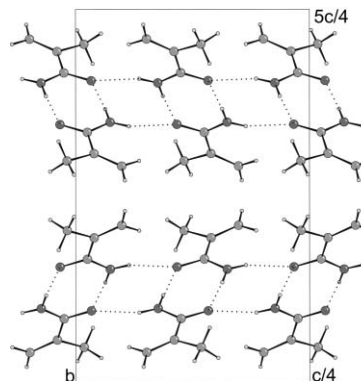
Using the improved material, X-ray structure determinations of both forms were redetermined at 120 and 294 K. Crystals of the first polymorph, Form I, obtained from hot  $\text{CHCl}_3$  solution, are monoclinic, space group  $P2_1/n$ , with  $Z = 4$ .<sup>†</sup> In a typical crystallization, 95–98% of the material appears to be Form I. Inspection of the packing diagram (Fig. 1) shows that Form I consists exclusively of the *s-cis* conformer. The crystal structure contains alternate layers of hydrogen-bonded molecules, with pairs of molecules involved in centrosymmetric  $R_2^2(8)$  hydrogen bonds.<sup>7</sup> The rings are connected by infinite  $C(4)$  chains along [101], as shown in the Figure. The  $C(4)$  chains in Fig. 1 are eclipsed in this view, and are not all at the same level; rather the chains are in a



**Fig. 1** Crystal structure of Form I viewed down the *b* axis. At 120 K, the C=C, C–N and C–C(methyl) distances are 1.335(3), 1.337(2) and 1.498(3) Å, respectively. The  $R_2^2(8)$  hydrogen bond parameters (N $\cdots$ O, N–H $\cdots$ O) are 2.923 Å, 178°, while the analogous parameters for the  $C(4)$  chains are 2.966 Å, 163°.

spiral arrangement around the  $2_1$  screw axes, as observed in many other amide crystal structures (see ESI for a view of the spiral arrangement).<sup>8</sup> A secondary graph set,  $C(8)$ , along [111] (11.88 Å), relates the sets of  $C(4)$  chains along [010].

Crystals of a second polymorph, Form II (Fig. 2), were obtained by slow cooling of a warm aqueous solution; the solid material obtained by this method appears to contain approximately equal amounts of Forms I and II. Form II is orthorhombic, space group  $Pbca$ , with  $Z = 8$ , and contains exclusively the *s-trans* conformer. The crystal structure (Fig. 2) is quite similar to that of Form I, with centrosymmetric  $R_2^2(8)$  hydrogen bonds and infinite  $C(4)$  chains

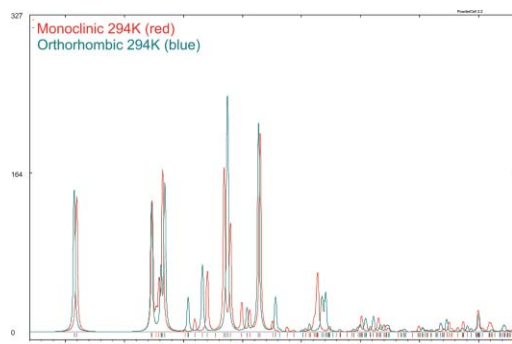


**Fig. 2** Crystal structure of Form II viewed down the *a* axis. At 120 K, the C=C, C–N and C–C(methyl) distances are 1.327(3), 1.331(3) and 1.506(4) Å, respectively. The  $R_2^2(8)$  hydrogen bond parameters (N $\cdots$ O, N–H $\cdots$ O) are 2.952 Å, 176°, while the analogous parameters for the  $C(4)$  chains are 2.980 Å, 165°.

† Electronic supplementary information (ESI) available: calculated (120, 294 K) and experimental (294 K) powder patterns; revised data for ref. 17, packing diagrams. See <http://www.rsc.org/suppdata/cc/b4/b418869a/> \*foxman1@brandeis.edu

along [010]. Once again, the **C(4)** chains in Fig. 2 are eclipsed in this view, and are not all at the same level; rather the chains are in a spiral arrangement around the 2<sub>1</sub> screw axes, as observed in other amide crystal structures (see ESI for a view of the spiral arrangement).<sup>8</sup> A secondary graph set, **C(8)**, along [110] (11.66 Å), relates the sets of **C(4)** chains along [100]. In order to show a view most similar to that of Form **I**, Fig. 2 has been drawn with the *b* axis horizontal and *c* vertical, but with limits of *c*/*a* to 5*c*/*a*. Both Forms **I** and **II** crystallise in the shallow-glide-plane packing motif observed for primary amides.<sup>8</sup> Form **I** has C–N⋯O and C=O⋯N interpair angles<sup>8</sup> of 134.1 and 141.4°; lower-melting Form **II** has C–N⋯O and C=O⋯N interpair angles of 125.7 and 153.1°, respectively.

As described above, X-ray data were first collected at 294 K on a CAD-4 diffractometer, and later at 120 K on a Kappa-CCD instrument in order to confirm the results at the higher temperature. At 120 K, the values of the C=C and C–CH<sub>3</sub> distances (Figs. 1 and 2) clearly indicate that each phase contains a single conformer, and that the two forms are indeed *conformational polymorphs*.<sup>9</sup> This discovery represents a singular example of the isolation of the *s-cis* and *s-trans* conformers of a simple α,β-unsaturated molecule. At 294 K, the C=C (**I**: 1.368(4); **II**, 1.366(6) Å) and C–CH<sub>3</sub> (**I**: 1.403(5); **II**, 1.422(6) Å) distances suggest that reorientation processes or static disorder may be occurring. The unit cell metrics (120 K) of the two polymorphs are remarkably similar. Thus, *a*<sub>II</sub> ≈ *b*<sub>I</sub> (5.72, 6.05 Å); *b*<sub>II</sub> ≈ [101]<sub>I</sub> (10.16, 10.22 Å), and *c*<sub>II</sub> ≈ [101̄]<sub>I</sub> (16.24, 15.49 Å), with an angle between [101]<sub>I</sub> and [101̄]<sub>I</sub> of 92.5°. At 294 K, the differences are even smaller: *a*<sub>II</sub> ≈ *b*<sub>I</sub> (5.93, 6.09 Å); *b*<sub>II</sub> ≈ [101]<sub>I</sub> (10.24, 10.23 Å), and *c*<sub>II</sub> ≈ [101̄]<sub>I</sub> (16.44, 16.14 Å). Accordingly, the X-ray powder diffraction patterns (294 K) are quite similar (Fig. 3), a rare phenomenon;<sup>10</sup> the greatest differences occur for certain of the lower-intensity peaks in the 20–32° 2θ region. Experimental powder patterns (ESI) contain peaks with FWHM values in the range 0.3 to > 0.5°, further blurring the distinction between Forms **I** and **II**. Experimental powder diffraction patterns show correspondence with either Form **I** or **II**; no evidence for additional phases was observed. Consistent with the observed larger differences in cell constants at 120 K, the calculated powder patterns show a greater difference at that temperature (ESI). At 120 K, the molecular volume of Form **I** (239.1 Å<sup>3</sup>) is slightly greater than that for Form **II** (236.0 Å<sup>3</sup>); the difference is smaller at 294 K (251.1, 249.7 Å<sup>3</sup>).



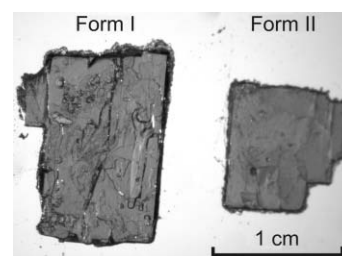
**Fig. 3** Calculated powder diffraction patterns<sup>11</sup> (294 K) of Form **I** and Form **II** obtained by slow growth from CHCl<sub>3</sub> and H<sub>2</sub>O, respectively.

On a Kofler hot-stage microscope, isolated crystals of Form **I** melt at 109–110°, while those of Form **II** melt at 102–104 °C. While it was not possible to detect the melting of any Form **II** material in powder samples of methacrylamide obtained from CHCl<sub>3</sub>, the melting behaviour of methacrylamide obtained from water was consistent with the presence of nearly equal quantities of two forms that melted separately at 102–104° and 109–110°. While DSC measurements were complicated by either sublimation or decomposition processes, results were consistent with the Kofler measurements; neither DSC nor visual inspection revealed any evidence for polymorphic transformations.

Crystals of Forms **I** and **II** were selected by manual separation after crystallization from either CHCl<sub>3</sub> or H<sub>2</sub>O (Fig. 4). All had platelike morphology, with faces corresponding to chemically-equivalent directions. Thus, Form **I** has (101̄) plate faces, with (101) and (010) side faces, while Form **II** has (001) plate faces, with (010) and (100) side faces. As discussed above, these directions correspond to the normal-to-page, vertical and horizontal directions, respectively, in Figs. 1 and 2. As the crystal grows, hydrogen bonds are formed rapidly in the horizontal and normal-to-page directions; hydrophobic bilayers are formed along the slowest growth direction (plate faces).

From single-crystal diffraction measurements, samples of Form **II** have mosaicities *ca.* 60–80% higher than values observed for Form **I**. Owing to the high mosaicity of the orthorhombic form, it has not been possible to obtain a quantitative assay for the amounts of each form present in a given sample by powder diffraction measurements. Manual separations of the two forms, as well as estimates of the relative amounts, have been made based upon the visual appearance of a batch, with a focus on qualitative knowledge of three key properties. First, Form **II** crystals have cleaner and smoother plate faces than those of Form **I** (Fig. 4). Second, crystals of Form **II** are more brittle than those of Form **I**, and often break upon gentle handling. Finally, at temperatures above 40 °C, it is evident that Form **II** sublimates more rapidly than Form **I**. Upon standing in air at ambient temperature for *ca.* 24 h, crystals of Form **II** develop a patina, while those of Form **I** do not, a consequence of the greater tendency of the orthorhombic form to sublime. Crystals selected using the above criteria are *usually* the desired form, based upon evaluation on a single-crystal diffractometer. As might be expected, the success rate is high (perhaps 75–85%), but less than 100%.

Irradiation of solid **I** (Aldrich, m.p. 109 °C) with <sup>60</sup>Co γ-rays (115 kGy) produces polymethacrylamide in 20% yield, as observed previously.<sup>5</sup> It has not yet been possible to quantitatively establish the amount of Forms **I** and **II** in a sample at the outset of a particular irradiation experiment. Thus, experiments are underway



**Fig. 4** Crystals of Form **I**, showing face (101̄) and Form **II**, showing face (001), obtained by slow growth from CHCl<sub>3</sub> and H<sub>2</sub>O, respectively.

to manually separate or crystallise pure quantities of Forms **I** and **II** sufficient to carry out a meaningful study of structure–reactivity relationships in the two forms. Indeed, given the structural and morphological similarity of the two phases, one form may nucleate the other,<sup>12</sup> making manual separation a preferred route. At 294 K, the shortest  $\alpha$ – $\beta'$  carbon–carbon contact is 4.16 Å (Form **I**) and 4.40 Å (Form **II**); thus Form **II** should show lower reactivity upon <sup>60</sup>Co  $\gamma$ -irradiation.

The energy difference between *s-cis* and *s-trans* conformers of  $\alpha,\beta$ -unsaturated carbonyl compounds is expected to be small. Early work on methacrylamide (analysis of UV spectra) proposed greater stability for the *s-cis* form.<sup>13</sup> Recent spectroscopic and theoretical studies of the relative abundances or stabilities of compounds such as methyl methacrylate and methyl *trans*-crotonate support stability of the *s-cis* form by as much as 0.65 Kcal,<sup>14</sup> while an electron diffraction study of MMA showed the *s-trans* conformer to have a mole fraction of 0.64(17) in the gas phase.<sup>15</sup> A search of the Cambridge Structural Database,<sup>16</sup> specifically for the conformations of  $\alpha,\beta$ -unsaturated primary amides, showed that only two of 35 selected entries (omitting duplicates and structures with high R values) were in the *s-trans* form.<sup>17,18</sup> However, only the data for one of the two examples, pinthunamide,<sup>18</sup> are consistent with assignment as a distorted *s-trans* conformer (O=C–C=C torsion angle of 144.8°). For the other, 2-carbamoyl-1-phenylthiolato-ethenyl acetate,<sup>17</sup> the data in CSD strongly suggest an incorrect structure, with a calculated C–NH<sub>2</sub> distance of 1.197 Å and C=O distance of 1.355 Å. Switching the identity of the N and O atoms, and moving the misplaced H atoms to the “new” N atom produce a chemically appropriate structure, with an *s-cis* conformation, and a reasonable hydrogen bonding pattern compared to that derived from the published coordinates (ESI). (By contrast, of 25 *N*-substituted secondary amides in CSD or the recent literature,<sup>19</sup> 4 of 25 had the *s-cis* conformation.) The isolation of an *s-trans* conformer of an  $\alpha,\beta$ -unsaturated primary amide is thus a rare event in itself. The present result, along with the likely small difference in energy of the conformers, suggests that it may be possible to isolate the conformational isomers of other  $\alpha,\beta$ -unsaturated amides by careful choice of solvent and crystallization conditions.

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## Notes and references

‡ Crystal data were measured at 294 K on an Enraf-Nonius CAD-4U diffractometer using CuK $\alpha$  radiation (Waltham) and at 120 K on a Nonius KappaCCD diffractometer (Mainz). Crystal data at 120 K [at 294 K in brackets]:<sup>20–22</sup> Form **I**, C<sub>4</sub>H<sub>7</sub>NO, *M* = 85.11, monoclinic, space group:

*P*2<sub>1</sub>/*n*; *a* = 9.0920(5) [9.365(2)]; *b* = 6.0470(4) [6.086(2)]; *c* = 9.4610(5) [9.743(3)] Å;  $\beta$  = 113.162(1) [115.30(2)]°; *U* = 478.23(5) [502.1(2)] Å<sup>3</sup>; *Z* = 4;  $\rho_{\text{calc}}$  = 1.182 [1.126] g/cm<sup>3</sup>,  $\mu$  = 0.086 [0.67] mm<sup>-1</sup>,  $\theta_{\text{max}}$  = 29° [74°]; plate, 0.13 × 0.30 × 0.45 [0.07 × 0.29 × 0.58] mm; 1251 [1027] unique data, 602 [559] [*I* > 1.96 $\sigma$ (*I*)], 83 [56] parameters;  $\rho_{\text{max}}$  = 0.14 [0.12] e<sup>-</sup>/Å<sup>3</sup>; *R* = 0.0408 [0.0525], *R<sub>w</sub>* = 0.0812 [0.1261]. For Form **II**, C<sub>4</sub>H<sub>7</sub>NO, *M* = 85.11, orthorhombic, space group: *Pbca*; *a* = 5.7200(4) [5.934(7)]; *b* = 10.1600(5) [10.242(5)]; *c* = 16.2410(7) [16.436(3)] Å; *U* = 943.85(9) [998.9(13)] Å<sup>3</sup>; *Z* = 8;  $\rho_{\text{calc}}$  = 1.198 [1.132] g/cm<sup>3</sup>;  $\mu$  = 0.087 [0.67] mm<sup>-1</sup>,  $\theta_{\text{max}}$  = 29° [65°]; plate, 0.07 × 0.20 × 0.40 [0.14 × 0.43 × 0.50] mm; 1222 [843] unique data, 726 [314] [*I* > 1.96 $\sigma$ (*I*)], 83 [56] parameters;  $\rho_{\text{max}}$  = 0.27 [0.10] e<sup>-</sup>/Å<sup>3</sup>; *R* = 0.0548 [0.0435], *R<sub>w</sub>* = 0.1416 [0.1023]. CCDC 258650, 260952–260954. See <http://www.rsc.org/suppdata/cc/b4/b418869a/> for crystallographic data in .cif or other electronic format.

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