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Desolvations of Solvated Organic Crystals

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Desolvations of Solvated Organic Crystals

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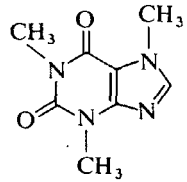
The appearance of water of hydration is common in crystals of both organic and inorganic compounds. A review of Molecular Structures and Dimensions[1] indicates that more than 1000 crystal structures of solvates have been determined and water is by far the most frequent solvating species. A more restricted review of inorganic crystallography showed that 282 structures of hydrates had been reported through 1970.[2]

In our earlier communication we reported the macroscopic behavior of caffeine hydrate and dihydrophenylalanine hydrate crystals upon standing in air.[3] In this communication we extend our studies to three other crystal solvates: theophylline hydrate, bis(salicylaldehyde)ethylenediimine cobalt(II) chloroformate and cycloserine hydrate. The behavior of these crystals is consistent with our earlier studies and indicates that crystal packing and the presence of nucleation sites control these reactions.

A typical crystal of caffeine hydrate (grown by slow evaporation of a water



Caffeine

solution) with the ends removed by cutting with a blade is shown in Figure 1. Upon standing the ends of the crystal become opaque (black as viewed with transmitted light through the microscope) and the opaque region proceeds

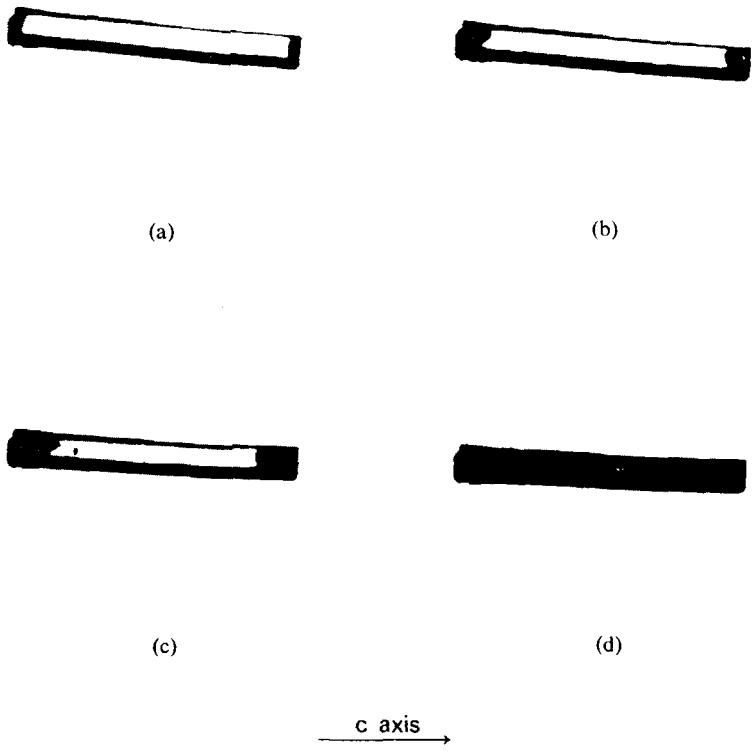


FIGURE 1 Desolvation of a crystal of caffeine hydrate in air at room temperature after both ends were removed with a razor blade: (a) Immediately after cutting; (b) After 4 hr at room temperature; (c) After 24 hr at room temperature and (d) After 72 hr at room temperature.

toward the center in a well defined front. Crystals without the ends removed and crystals cut parallel to the *c* crystal axis (elongated direction) were still preferentially desolvated from the ends. Several reports in the literature[4,5,6] and our own studies on phloroglucinol dihydrate indicate that the opaque region of the crystal is due to loss of solvent. We were able to grow a large single crystal of phloroglucinol dihydrate and weigh it as the front moved through the crystal. There was a reasonable correlation between the estimated percent of the crystal which was opaque and weight loss due to dehydration.

Examination of the crystal packing of caffeine monohydrate (Figure 2) showed that there were tunnels of water molecules parallel to the long axis of the crystal (*c* axis).

The anisotropic behavior is explained by the preferential escape of water molecules along the tunnels. Desolvation from other crystal directions would

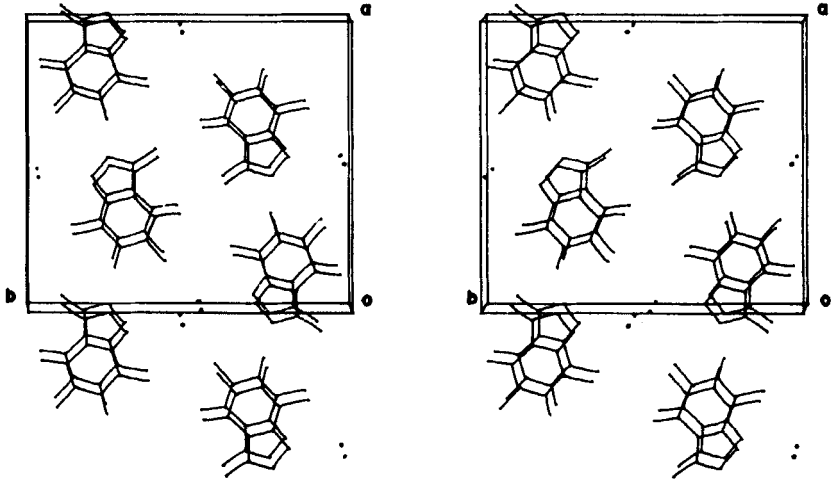
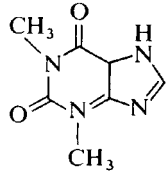


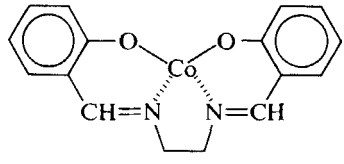
FIGURE 2 Crystal packing of caffeine monohydrate viewed perpendicular to the (001) face.

require the water molecules to penetrate the somewhat closely packed layers of nonpolar groups in the other two crystallographic directions. Crystals which were not cut with a razor blade behaved in the same way but the desolvation reaction was slower as determined by rate of front advancement.

In order to determine whether crystal packing and nucleation sites produced by cutting with a razor blade influenced other solid state desolvations, we have studied the loss of solvent from theophylline hydrate and bis(salicylaldehyde) ethylenediimine cobalt (II) chloroformate.



theophylline



bis(salicylaldehyde)ethylenediimine cobalt(II)

Figure 3 shows the behavior of crystals of theophylline monohydrate which were obtained from water solution. As with caffeine monohydrate the opaque region moves from the ends toward the middle although some reaction on the side crystal face can be observed. Precession photography showed that the crystals were elongated along the *c* crystallographic axis.

The crystal packing of theophylline hydrate is quite similar but not identical to that of caffeine monohydrate[7] with tunnels of water molecules parallel to

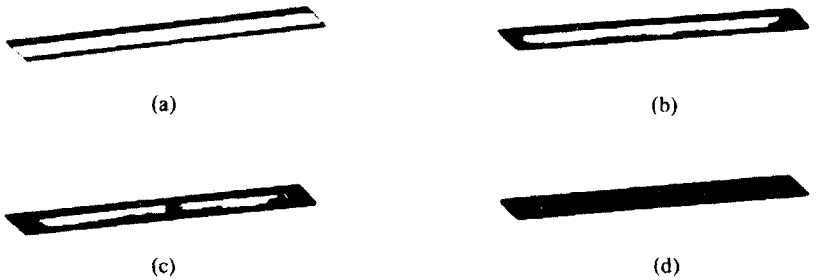


FIGURE 3 Desolvation of a crystal of theophylline monohydrate in air at 35°: (a) At start; (b) After 24 hr; (c) After 48 hr; (d) After 5 days.

the *c* crystal axis ($c = 4.50$ Å). The crystals were elongated along the *c* crystal axis; thus the tunnels of water molecules were parallel to the long axis.

The water of solvation appears to exit the crystal of theophylline hydrate along the tunnel axis similarly to caffeine hydrate. Crystals with their ends removed reacted faster than uncut crystals, but theophylline hydrate always reacted slower than caffeine hydrate even though they have similar crystal packing.

Crystals of the chloroform solvate of bis(salicylaldehyde)ethylenediimine cobalt (II) reversibly bind oxygen after the chloroform of solvation leaves the crystal.[8] Examination of the crystal packing of this chloroform solvate shows that there are tunnels of chloroform molecules running parallel to the *b* crystal axis.[8] Optical goniometry and precession photography showed that the *b* crystal axis was parallel to the needle axis of the crystal and indeed desolvation at room temperature proceeded from the ends of cut crystals towards the center as shown in Figure 4. Crystals which had not been cut began to react from the top face but the reaction was still faster along the tunnel direction. The presence of artificially induced nucleation sites obviously plays an important role in this reaction.

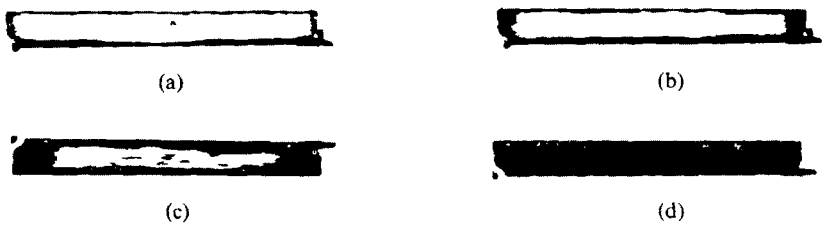
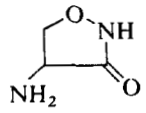


FIGURE 4 Desolvation of a crystal of bis(salicylaldehyde)ethylenediimine cobalt (II) chloroformate which had its ends removed at room temperature: (a) At start; (b) After 12 hr, (c) After 28 hr and (d) After 48 hr.

In a related case where the crystal structure is unknown, we have obtained cycloserine monohydrate by allowing a solution of cycloserine in ethanol-isopropanol-water stand in a refrigerator. The hydrate crystals desolvated



cycloserine

at 40 or 45° as shown in Figure 5. The front moves parallel to the needle axis but the spot and time at which the reaction of an individual crystal begins is variable and indicates that this reaction is very sensitive to the presence of nucleation sites.

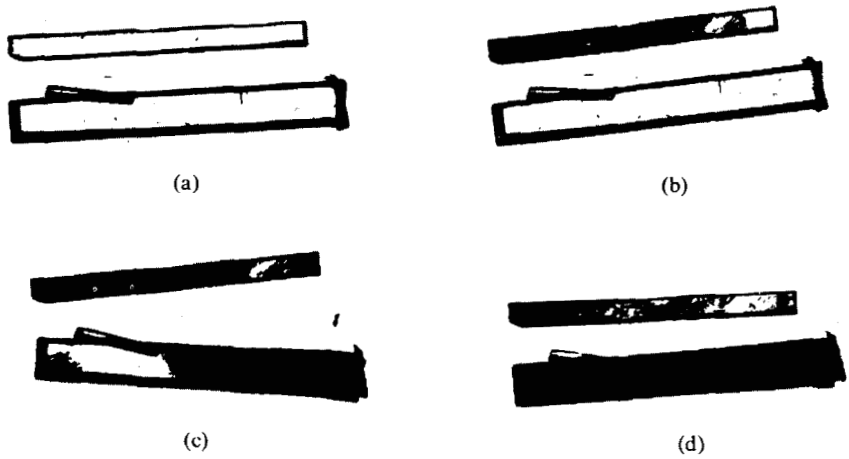


FIGURE 5 Desolvation of a pair of crystals of cycloserine monohydrate at 40°: (a) At start; (b) After 165 min; (c) After 190 min; (d) After 200 min.

In conclusion, the behavior of crystals of caffeine monohydrate, theophylline monohydrate, and bis(salicylaldehyde)ethylenediimine cobalt (II) chloroformate show that crystal packing is apparently responsible for the direction of front movement. Furthermore, cutting causes some crystals (e.g. bis(salicylaldehyde)ethylenediimine cobalt (II) chloroformate) to behave somewhat differently from uncut crystals and accelerates the rate of desolvation. These differences and the behavior of the cycloserine monohydrate crystals illustrate the role nucleation sites play in these reactions. The studies reported here may have important implications for the behavior of solvates of pharmaceuticals.

Acknowledgments

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