Solid-State Chemistry of Drugs

Second Edition

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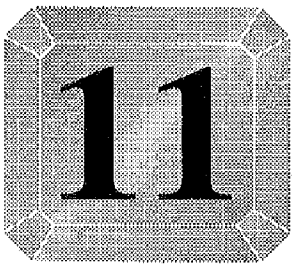
Cover illustration: The figures are space-filling representations of prednisolone 21-*tert*-butylacetate crystal packing diagrams. On the top is Form IV illustrating the densely packed crystal lattice. On the bottom is Form V showing the oxygen-accessible tunnels produced by desolvation.



Hydrates and Solvates

The occurrence of hydrated or solvated crystal forms (see Table 11.1), crystals in which solvent molecules occupy regular positions in the crystal structure, is widespread but by no means universal among drug substances. Some classes of drugs (*e.g.*, steroids, antibiotics, and sulfonamides) are particularly prone to form solvates, but this impression may be partly related to the considerable attention these drugs have received. In her classic book on thermomicroscopy, Kuhnert-Brandstätter

Table 11.1 Partial List of Drugs Discovered Prior to 1971 that Form Solvates

Drug	Reference
Ampicillin	Austin *et al.*, 1965
Cephaloridine	Chapman *et al.*, 1968; Pfeiffer *et al.*, 1970
Chloramphenicol	Himuro *et al.*, 1971
Cholesterol	Shefter and Higuchi, 1967
Cortisone acetate	Carless *et al.*, 1966
Eluprednisolone	Haleblian *et al.*, 1971
Erythromycin	Rose, 1955
Estradiol	Kuhnert-Brandstatter and Gasser, 1971
Fluorohydrocortisone acetate	Shefter and Higuchi, 1967
Gramicidin	Olsen and Szabo, 1959
Griseofulvin	Sekiguchi *et al.*, 1968
Hydrocortisone 21-acetate	Shell, 1955
Hydrocortisone 21-*tert*-butylacetate	Biles, 1963
Nitrofurmethone	Borka *et al.*, 1972
Prednisolone 21-*tert*-butylacetate	Biles, 1963
Succinylsulfathiazole	Shefter and Higuchi, 1967
Sulfabenzamide	Yang and Guillory, 1972
Sulfaguanidine	Yang and Guillory, 1972
Sulfameter	Moustafa *et al.*, 1971
Sulfanilamide	Lin, 1972

(Kuhnert-Brandstätter, 1971)

(1971) summarized in tabular form some of these examples (see Table 11.2). Nevertheless, many drugs, including some members of the aforementioned classes, even after intensive investigation, are found to always crystallize without solvent inclusion (*e.g.*, aspirin and ibuprofen).

In a classic study, Kuhnert-Brandstatter (1971) characterized the behavior of hydrates of pharmaceuticals known at that time using thermomicroscopy (see Table 10.2). Many of the hydrates listed in this table show unusual behavior that may be caused by dehydration prior to melting. Many of these crystals are reported to become opaque, and appear dark when viewed by transmitted light (see Chapter 14). Some of these hydrates crack and "jump" during dehydration. This behavior is characteristic of rapid solid-state reactions that produce gaseous products.

Another aspect of solvate formation is that virtually any laboratory solvent can be involved; Table 11.3 lists solvents in solvates reported in the crystal structure literature on organic compounds which, naturally, includes many crystalline drugs. In some solvates, two or even three different solvents occupy their own positions in the structure. Furthermore, a compound may form solvates with a given solvent in different ratios, 2:1, 1:1, etc., and in rare cases, a fixed ratio in polymorphic forms.

Because prediction of crystal structures is not yet generally possible, we must be content with examining the crystal structures of compounds after the fact in looking for explanations of why solvates do or do not form. On doing so, however, we are left with only vague impressions, to wit:

- Certain molecular shapes and features favor the formation of crystals without solvent. These structures tend to be stabilized by an efficient packing that also utilizes intermolecular hydrogen bonding and other bonding capacity to a maximum extent. The slightest molecular differences may conceivably interfere with this cooperative effect. As a result, solvate formation within a series of related compounds tends to lack a discernible pattern—each compound has a unique response to solvate formation.
- Including specific solvent molecules can stabilize a crystal structure by improving either the packing or the intermolecular bonding, especially hydrogen bonding. Some of the solvents listed in Table 11.3 are nonhydrogen-bonding solvents and thus must serve only in a space-occupying capacity. The hydrogen-bonding capacity of included solvent molecules is usually fully exploited, although some structures are known where such bonding capacity is not exercised at all.
- Lower temperatures favor formation of solvates and also higher stoichiometric amounts of a given solvent. This is probably due to the increased strength of hydrogen bonding at lower temperatures.
- The ease with which solvent is lost varies widely among solvates. At one extreme some retain solvent at temperatures well above the boiling point of the solvent, at the other extreme, others lose solvent readily at room temperature. In the latter case, the formation of a solvate may be overlooked unless special precautions are taken to preserve the composition of the crystals.

Table 11.2 Thermomicroscopic Behavior of Drug Hydrates

Drug	Mp (°C)	Remarks
Apomorphine hydrochloride	220–260	From 220 °C, turbidity and carbonization
Atropine sulfate	190–193	Substance partially dehydrates
Brucine	170	Crystals are rarely clear
Brucine sulfate	130–165	Gradual loss of water
Chloroquine sulfate	209–213	
Citric acid	152–155	Loss of H_2O and turbidity at 60–70 °C
Cocaine nitrate	55–59	Needles of decomposition product appear
Codeine	156	Loss of water with turbidity
Codeine hydrochloride	260–275	
Codeine phosphate	225–240	
Cyclophosphamide	40–47	Melts as hydrate
Dihydrocodeinone bitartrate	115–130	
Dipropylbarbituric acid	148	Commercial product partly dehydrated
Emetine hydrochloride	205–215	
L-Ephedrine	38–40	
Heroine hydrochloride	218–232	Turbidity of crystals from 115–120 °C
Histidine monohydrochloride	155–176	
Hydrocortisone hemisuccinate	198–205	From 85 °C, loss of water with turbidity
Hyoscyamine hydrochloride	152–155	Turbidity with loss of water during heating
Lidocaine hydrochloride	65–78	
Mercaptopurine	300–325	From 160 °C, turbidity of crystals
Mescaline sulfate	230–250	From 125 °C, water escapes with turbidity
Methicillin sodium	182–186	Loss of birefringence
Morphine	245–255	At 115–140 °C, loss of water with turbidity
Morphine hydrochloride	285–310	From 80 °C, loss of water with turbidity
Morphine sulfate	230–240	
Ouabain	178–184	Loses H_2O from 90 °C
Oxycodone hydrochloride	245–260	From 70 °C, loss of water with turbidity
Phloroglucinol	218–220	At 55–90 °C, turbidity with loss of water
Pyrogallol	133	Turbidity
Quercetin	300–320	
Quinidine hydrochloride	262–265	From 90 °C, loss of water
Quinidine sulfate	205–210	
Quinine bisulfate	155–160	Turbidity at 60 °C
Quinine hydrobromide	145–152	Water evolved at 90 °C
Raffinose pentahydrate	132–135	Transforms to anhydrous
Reserpine hydrochloride	125–225	From 180 °C, turbidity of crystals
α-Rhamnose	70–95	
Succinylsulfathiazole	190–193	
Sulphaguanidine	187–191	From 90 °C loss of water
Terpin hydrate	105.5	Transforms to anhydrous
Theophylline	274	At 70–80 °C, loss of water
L-Thyroxine sodium	195–202	From 70 °C, effervescence with jumping

(Kuhnert-Brandstätter, 1971)

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