Polymorphism and Drug Availability

Solubility Relationships in the Methylprednisolone System

By W. I. HIGUCHI†, P. K. LAU, T. HIGUCHI, and J. W. SHELL

The thermodynamic relationships involving polymorphism and solubility were examined in some detail and applied to experimental results with the methylprednisolone system. The solubilities of the two crystal forms of this steroid were determined in water, decyl alcohol, and dodecyl alcohol at various temperatures. The solubility ratios for the two forms were generally found to be independent of the solvent in accordance with theory. At room temperatures the activity of the more energetic form of the drug was found to be the order of 80% greater than that of the more stable form. The heat, entropy, and temperature of transition were calculated from the data, and the possible molecular factors involved in polymorphism were considered. Further work of exploratory nature involving cloudpoint determinations indicate that much more energetic crystal forms are probable.

AMONG THE numerous ways (1) of altering drug availability to the patient, methods involving changing the crystal form of the drug appear to have received proportionately the least detailed examination. Thus it appeared to us that an investigation of this problem would be worthwhile. This report represents the initial phase of a program aimed toward the understanding of factors determining activity, physical stability, and frequency of occurrence (or preparation) of polymorphs.

THERMODYNAMIC THEORY

For simplicity let us assume that a particular drug exhibits only two crystalline forms depending on the conditions of preparation. Let these be form I and form II, the former designating the more thermodynamically stable one at room temperatures.

We may then write

$$F_I^\circ = H_I^\circ - T^\circ S_I \qquad \text{(Eq. 1a)}$$

and

$$F_{II}^\circ = H_{II}^\circ - TS_{II}^\circ \qquad \text{(Eq. 1b)}$$

where F°, H°, and S° are the usual standard state Gibbs free energy, enthalpy, and entropy, respectively, for the two forms, and T is the absolute temperature in °K. For completeness we may also write the corresponding equation for the supercooled liquid

$$F_I^\circ = H_I^\circ - TS_I^\circ \qquad \text{(Eq. 1c)}$$

If now f_I and f_{II} are the drug fugacities (2) or escaping tendencies for the two phases in their standard states, we have then

$$RT \ln f_I/f_{II} = \Delta F_{I.II} = F_I^\circ - F_{II}^\circ \qquad \text{(Eq. 2)}$$

where R is the gas constant. Since fugacities may be equated to the vapor pressures in the limit of low pressures (gas ideality) and since vapor imperfection is generally negligible in our system, we may regard the fugacity ratio expressed in Eq. 2 as simply the vapor pressure ratio for the two forms.

By combining Eq. 1 and Eq. 2 we obtain the following relation

$$RT \ln f_I/f_{II} = \Delta F_{I.II}^\circ = \Delta H_{I.II}^\circ - T\Delta S_{I.II}^\circ \qquad \text{(Eq. 3)}$$

which relates the fugacities with the standard entropy, enthalpy, and free energy changes for the I to II phase transformation. Equation 3 is particularly useful in discussing the relationship between molecular arrangements in the crystals and fugacity of polymorphs.

As our interests are associated with drug availability with respect to solid-solution behavior we must introduce solubility into the theory. Adopting the convention that the activity becomes equal to molality at infinite solute dilution we can write (3)

$$\frac{\partial \ln (\gamma m)}{\partial T} = \frac{H^\infty - H^S}{RT^2} \qquad \text{(Eq. 4)}$$

Here m is the solubility in molal units, γ is the activity coefficient defined by

$$\gamma \to 1 \text{ as } m \to 0$$

H^∞ is the partial molar enthalpy of the solute at infinite dilution and H^S is the mola' enthalpy of the crystal. The difference

$$\Delta H = H^\infty - H^S$$

is the heat of dissolution at infinite dilution per mole of crystal.

Now when Henry's law is obeyed, *i.e.*, for dilute solutions in which solute association is negligible, solute fugacity of the solution will be proportional to the solute concentration. Thus under these conditions $\gamma = 1$ and $f_I/f_{II} = m_I/m_{II}$. Since most systems of interest to us involve dilute solutions, this case is of practical importance. Assuming Henry's law we may write from Eq. 4

$$\frac{\partial \ln m_I}{\partial T} = \frac{H^\infty - H_I^\circ}{RT^2} = \frac{\Delta H_I^\circ}{RT^2} \qquad \text{(Eq. 5a)}$$

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† Present address: University of Michigan, College of Pharmacy, Ann Arbor.

and

$$\frac{\partial \ln m_{II}}{\partial T} = \frac{H^{\infty} - H_{II}^{\circ}}{RT^2} = \frac{\Delta H_{II}^{\circ}}{RT^2} \quad \text{(Eq. 5b)}$$

for each of the two forms in their standard states. Here the ΔH°'s are the heats of solution at infinite dilution.

Equations 5a and 5b may be combined to give

$$\frac{\partial \ln (m_I/m_{II})}{\partial T} = \frac{\Delta H_{I,II}^{\circ}}{RT^2} \quad \text{(Eq. 6)}$$

Equation 6 relates the solubility (or fugacity) ratio to the enthalpy of phase change. It can be seen that

$$\frac{\partial \ln (m_I/m_{II})}{\partial T}$$

should be independent of the solvent as long as Henry's law is obeyed.

At some temperature, T_t, known as the transition temperature the fugacities of the two forms will be equal, *i.e.*, $f_I = f_{II}$ or $m_I = m_{II}$. From Eq. 3 we have the condition

$$\Delta H_{I,II}^{\circ} = T_t \Delta S_{I,II}^{\circ} \quad \text{(Eq. 7)}$$

at $T = T_t$.

It is apparent that the above thermodynamic relationships, if judiciously applied, should be helpful in the characterization and the evaluation of polymorphic systems. In particular, it is noteworthy that by means of solubility measurements alone it is possible to obtain the enthalpy and entropy differences between polymorphic forms of crystals. These thermodynamic quantities are useful in the understanding of the inter- and intramolecular crystalline factors determining the frequencies of occurrence and differences in activities among polymorphs.

EXPERIMENTAL

General Considerations.—Methylprednisolone was selected for this study because only two crystalline forms of this compound are known to exist. Furthermore, these can be easily prepared and characterized by X-ray or infrared methods.

Polymorph I was prepared by recrystallization from acetone and polymorph II by sublimation at 190°. Table I gives the X-ray powder diffraction data for the two forms. The infrared mull spectra (mineral oil) are presented in Fig. 1. Either of these two methods serve to characterize the two forms.

TABLE I.—METHYLPREDNISOLONE, INTERPLANAR SPACINGS, A

Polymorph I		Polymorph II	
9.87	2.81	12.10	3.32
9.21	2.70	8.58	3.26
8.42	2.51	7.37	3.16
7.08	2.44	6.32	3.13
5.94	2.37	6.06	3.10
5.50	2.32	5.79	3.04
5.01	2.25	5.21	2.93
4.59	2.16	5.09	2.89
4.19	2.13	4.71	2.86
3.93	2.08	4.57	2.78
3.67	2.06	4.52	2.72
3.51	1.99	4.27	2.58
3.39	1.92	4.08	2.55
3.29	1.84	3.98	2.43
3.11	1.79	3.88	2.37
2.96	...	3.72	2.34
2.91	...	3.67	...
2.85	...	3.38	...

To permit a test of the solvent independence of f_I/f_{II} (or m_I/m_{II}), three solvents—water, decyl alcohol, and dodecyl alcohol—were selected. The solubilities of methylprednisolone in these solvents are all low enough so that Henry's law is likely to be obeyed by these solutions.

Procedure.—For determinations of solubilities in

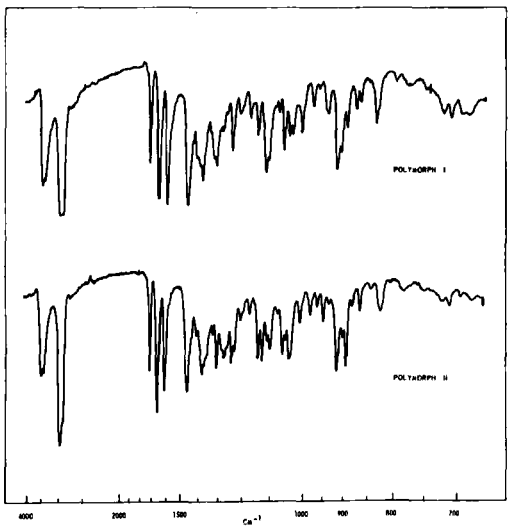

Fig. 1.—Infrared mull spectra of methylprednisolone, polymorphs I and II.

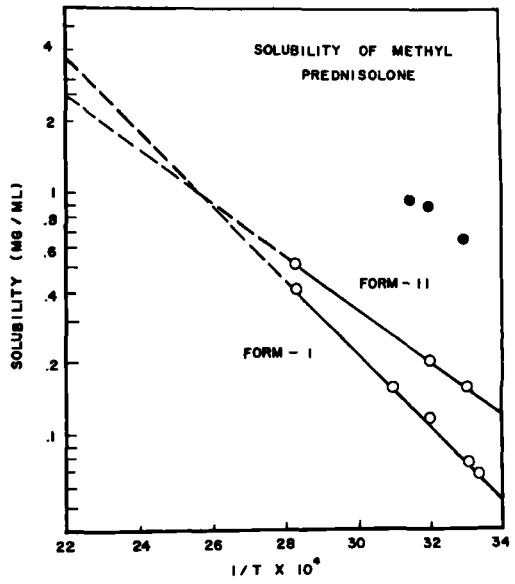

Fig. 2.—Water solubilities of methylprednisolone as a function of temperature: ○ refers to data for form I and Form II; ● is cloudpoint data (see text).

water, 15-ml. vials containing water and excess amounts of the particular form were slowly rotated in a water bath thermostated to ±0.05°. Periodically 5-ml. aliquots of the solution were withdrawn with a pipet fitted with a glass wool plug, diluted with 95% ethanol, and assayed spectrophotometrically. After several days the steroid concentrations in the solution phase were found to be constant.

For determinations in the alcohols, excess amounts of the particular form of the drug were placed with the solvent in a stoppered flask which was water jacketed to maintain a constant temperature within ±0.05°. The mixture was vigorously agitated with a magnetic stirrer. Aliquots of the solution were withdrawn and filtered by a syringe fitted with a hypodermic adapter for Millipore[1] filter paper. Then the solutions were diluted appropriately in 95% ethanol and assayed spectrophotometrically.

In the water system with both forms I and II the steroid concentration always increased with time to a constant value. This was also the general behavior with the alcohol systems at the lower temperatures. However, beyond 50° in the decyl alcohol case involving form II, the steroid concentrations initially increased with time, then reached a maximum value, and then decreased steadily. This can be explained on the basis of relatively rapid conversion of the drug to another form at the higher temperatures in decyl alcohol. Thus for form II in decyl alcohol, data were obtained only up to 60°.

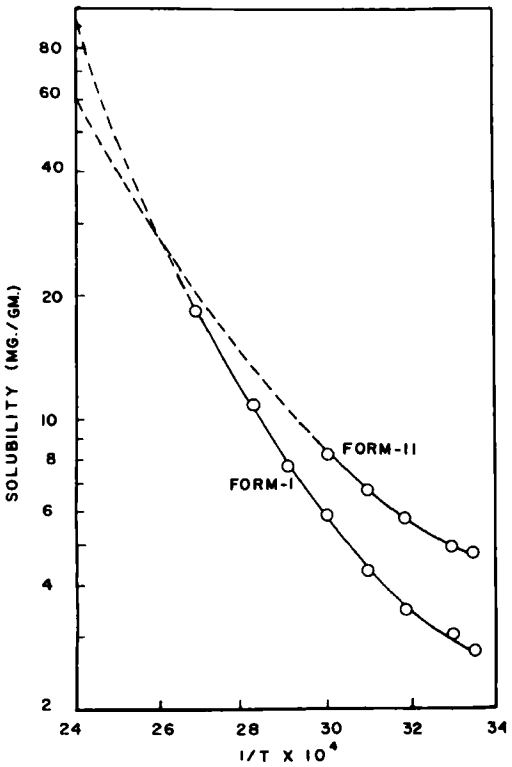

Fig. 3.—Solubility of the two forms of methylprednisolone in decyl alcohol as a function of temperature.

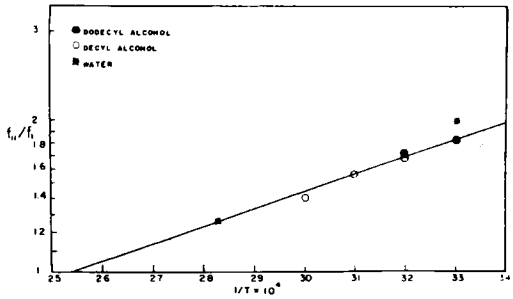

Fig. 4.—A plot of the fugacity or solubility ratio for the two forms of methylprednisolone as a function of solvent and temperature.

RESULTS AND DISCUSSION

The results of the determinations in water and decyl alcohol are shown in Figs. 2 (open circles) and 3, respectively. The data are plotted as log solubility *vs.* $1/T$ rather than *vs.* T. This method of plotting follows from rearranging Eq. 5 to give

$$\frac{\partial \ln m_I}{\partial (1/T)} = \frac{-\Delta H_I^\circ}{R} \qquad \text{(Eq. 8a)}$$

and

$$\frac{\partial \ln m_{II}}{\partial (1/T)} = \frac{-\Delta H_{II}^\circ}{R} \qquad \text{(Eq. 8b)}$$

In Fig. 4, these data and the data for the dodecyl alcohol system are all plotted as log solubility ratio *vs.* $1/T$. This type of plot is suggested by Eq. 6. Except for the results at the lowest temperatures, the solubility ratios appear to be independent of the solvent in accordance with theory. While it appears unlikely, the deviations at the low temperatures are possibly attributable to the deviations from Henry's law.

From the slope of the best straight line drawn through the points in Fig. 4 we may calculate a value for $\Delta H_{I,II}^\circ$. The transition temperature, T_t, may be obtained by extrapolating the curve to

$$\frac{f_I}{f_{II}} = \frac{m_I}{m_{II}} = 1$$

For these quantities we obtain $\Delta H_{I,II}^\circ = 1600$ cal. mole^{-1} and $T_t = 118°$. Then by application of Eq. 7 we obtain $\Delta S_{I,II}^\circ = 4.1$ e.u.

Paucity of data in the literature on entropies of transition and the lack of structural information on the methylprednisolone system preclude a single interpretation of the $\Delta S_{I,II}^\circ$ value in terms of molecular arrangement in the crystals. It appears likely, however, that the entropy difference is a result of greater localization of the functional groups in the side chain in form I resulting either from intermolecular or intramolecular interactions. It is well known (4) that lack of freedom of rotation about the carbon-carbon bond contributes about $R\ln 3$ per methylene group to the entropy of fusion for long chain paraffins. Thus the effects of two or more linkages in the side chain may account for the observed $\Delta S^\circ_{I,II}$.

[1] Millipore Filter Corporation, Bedford, Mass.

These results with form I and form II of methylprednisolone demonstrate that significant differences in solubilities may exist among polymorphs. In the present example the unstable form, II, exhibits a solubility the order of 80% greater than that for the more stable form, I, at room temperature. In order to obtain an idea as to the order of magnitude of the solubility of amorphous methylprednisolone, exploratory studies[2] involving cloudpoint determinations were carried out. The results of these are presented in Fig. 2 (darkened circles). These "solubility" values represent the concentrations of the steroid in aqueous solutions necessary for rapid appearance of turbidity when a concentrated dimethylformamide solution of the steroid was added dropwise to water. If it can be assumed that appreciable supersaturation is unnecessary for nucleation of the supercooled liquid phase, it is reasonable to presume that these values represent a lower limit for the solubility of the supercooled liquid or the amorphous solid. It is noteworthy that these correspond to almost 20 times the solubility of form I. It is hoped that future studies on this problem would lead to preparable crystal forms exhibiting such large differences in solubilities.

[2] Unpublished work.

REFERENCES

(1) See *e.g.*, Wagner, J. G., THIS JOURNAL, 50, 359(1961).
(2) Lewis, G. N., and Randall, M., "Thermodynamics," McGraw-Hill Book Company, Inc., New York, 1923, p. 190.
(3) Guggenheim, E. A., "Thermodynamics," North-Holland Publishing Company, Amsterdam, 1957, p. 292.
(4) For a recent discussion, see Aranow, R. H., Witten, L., and Andrews, D. H., *J. Phys. Chem.*, 62, 812(1958).

X-Ray and Crystallographic Applications in Pharmaceutical Research IV

Modified Procedures for Molecular Weight Determinations

By JOHN W. SHELL†

The modified procedures described in this paper for the determination of molecular weights of crystalline organic compounds differ from conventional procedures in the replacement of film recording by proportional counter recording and by the use of fractional-cell, rather than true unit-cell volumes. These procedures allow the routine determination of molecular weights with relatively small investments of time, yet with errors usually no greater than one hydrogen atom. The general method is presented and detailed procedures for lower symmetry crystal systems, in which most organic compounds fall, are described. The procedures are illustrated by specific examples.

FOR THE precise determination of molecular weights of crystalline compounds, the X-ray diffraction method has long been the method of choice. If one invests sufficient time and all the necessary care, the accuracy of this method need be limited only by errors due to crystal imperfections, which are often of the order of 0.04% if due to void spaces and often less if due in part to inclusions.

The strong relationship between time investment and accuracy appears, for practical purposes, to have a point of diminishing returns. Experience has shown that somewhat less than absolute, but yet fairly accurate determinations can be made with reasonable time investments.

In these laboratories an attempt has been made to develop procedures which assure an acceptable level of accuracy (the error usually approximating one hydrogen atom) with a minimum investment of operator time. This has required differing procedures for crystals of different symmetry, as noted below. It has also required the replacement of film techniques with direct recorder techniques.

GENERAL METHOD

The feasibility of the X-ray method for molecular weight determinations derives from the fact that an exact and determinable numbe; of molecules occupies a *unit cell* which, by three-dimensional repetition, generates the space lattice of the crystal. As the repeat spacings are of the same order of magnitude as X-ray wavelengths, diffraction of X-rays is possible and oriented diffraction procedures permit the measurement of the unit cell volume. An experimentally determined unit-cell density (crystal density) permits then the simple calculation of the unit-cell weight. This is either the molecular weight or some

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† Present address: Allergan Pharmaceuticals, Inc., Santa Ana, Calif.