Solubility of Hydrocortisone in Organic and Aqueous Media: Evidence for Regular Solution Behavior in Apolar Solvents

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Abstract □ The solubility of hydrocortisone was determined experimentally in a wide variety of solvents. Groups of solvents were selected to emphasize different solute–solvent interactions which can influence the solubility profile of such a large, polyfunctional solute. Regular solution theory for a crystalline solute was shown to be applicable to the solubility behavior of hydrocortisone in solvents that lack strong dipoles and the ability to hydrogen bond. A best-fit solubility parameter of 12.4 $(cal/ml)^{1/2}$ for hydrocortisone was determined from the latter solubilities and the ideal solubility of hydrocortisone. This solubility parameter estimate was significantly higher than estimates calculated from molar-attraction constants. Even though molar volume ratios between hydrocortisone and the solvents ranged from 2.25 to 3.28, the associated Flory–Huggins entropy term did not seem to be a significant solubility-determining factor. In all cases, the solubility of hydrocortisone in solvents capable of dipole–dipole interactions and hydrogen bonding was shown to be higher by logarithmic orders when compared with regular solution theory predictions. Thus, for this solute, regular solution theory was shown to be appropriate only for solvents where London dispersion forces dominate the interactions between solute and solvent molecules.

Keyphrases □ Hydrocortisone—solubility in organic and aqueous media, determination of regular solution behavior in apolar solvents □ Solubility—of hydrocortisone in apolar solvents, regular solution behavior of large polyfunctional solutes □ Regular solution theory—behavior determination for hydrocortisone solubilities in apolar solvents

The physicochemical events responsible for the solubilization of a drug in various solvent systems can be characterized rigorously on a macroscopic scale, if not a molecular scale. For a crystalline nonelectrolyte, the critical factors are the solid-phase activity of the solute and molecular interactions between solute and solvent. The ability to estimate these critical parameters for drug molecules placed in a given vehicle or solution environment has immense importance when deciphering the mechanisms of drug action and delivery. To attain such objectives, macroscopic thermodynamic functions must be coupled with phenomenological interpretations of the processes involved in solubilization. Due to the polyfunctional character of drug molecules, a wide variety of molecular interactions are often simultaneously operative. Current solubility theories are limited to specific types of intermolecular interactions. An example is regular solution theory as proposed by Scathard (1) and Hildebrand (2), which is premised on all intermolecular association being of a nonorientating variety. Although this theory has on occasion been overextended to solvent systems where this fundamental assumption is not true, valid applications have provided basic understanding of solubility behavior for various pharmaceutical systems (3–8).

The purpose of the present study was to characterize the solubility behavior of hydrocortisone in solvents that are capable of a full range of molecular interactions with this polyfunctional solute. Two reference points were employed in the analysis, the primary point being ideal behavior and the secondary point of comparison being regular solution behavior. Furthermore, the values and limitations of regular solution analysis are demonstrated for a typically complex pharmaceutical solute.

THEORETICAL

A reaction of two components, a liquid solvent and an excess of a crystalline solute, is at a state of equilibrium when the thermodynamic activity of the solute in solution (a_2) equals the thermodynamic activity of solid solute (a_2^s). In this case the activity is taken as the ratio of solute vapor pressure to the vapor pressure of pure (supercooled) liquid solute. If this activity also equals the mole fraction composition over the entire concentration range up to and including saturation, the solution is an ideal solution. This only occurs when the solute–solvent adhesiveness is exactly equal to the cohesiveness of the pure liquid components considered on a per unit volume basis. Solubility predictions for ideal solutions require only estimates of a_2^s.

Most solute–solvent mixtures do not behave ideally, and solute mole fractional concentrations often differ greatly from their activities. To establish a relationship between concentration and activity, standard states must be selected for the components. For solubility analysis a convenient selection for the solute is pure liquid solute at the temperature of interest. Unit activity is thus defined as the activity of the pure liquid at a mole fraction of 1.0. The activity of a solute in solution is defined as directly proportional to the mole fractional concentration of the solute (X_2):

$$a_2 = \gamma_2 X_2 \qquad \text{(Eq. 1)}$$

where γ_2 is the proportionality constant or mole fractional activity coefficient. As X_2 approaches unity (the standard state), the ratio a_2/X_2 (or γ_2) approaches unity. The same standard state is also convenient for the solvent. For dilute solutions, the molecular environments of both solute and solvent molecules are predominantly other solvent molecules, and consequently the activity of the solvent is proportional to its fractional composition:

$$a_1 = X_1 \qquad \text{(Eq. 2)}$$

At the same time, solute molecules essentially only interact with solvent, and γ_2 is virtually constant for small changes in solute concentration. For a poorly soluble, crystalline nonelectrolyte, the mole fractional solubility ($X_{2,sat}$) is dependent therefore on molecular interaction differences between solute and solvent, reflected by γ_2, and the activity of the crystal:

$$a_2^s = \gamma_2 X_{2,sat} \qquad \text{(Eq. 3)}$$

From a thermodynamic viewpoint, solubility prediction is possibly based on measurements or estimations of γ_2 and a_2^s.

Crystalline Phase Activity—For solutes that are crystalline at ambient temperature, the selected standard state is a hypothetical state referred to as supercooled liquid solute. The free energy change required to form supercooled liquid solute from the solid solute (ΔG^{sc}) defines the activity of the solid as:

$$a_2^s = e^{-\Delta G^{sc}/RT} \qquad \text{(Eq. 4)}$$

Associated with this process is an enthalpy change ΔH^{sc} and an entropy change (ΔS^{sc}) such that ΔG^{sc} can be expressed as:

$$\Delta G^{sc} = \Delta H^{sc} - T\Delta S^{sc} \qquad \text{(Eq. 5)}$$

It is possible to obtain an expression experimentally suited for estimating

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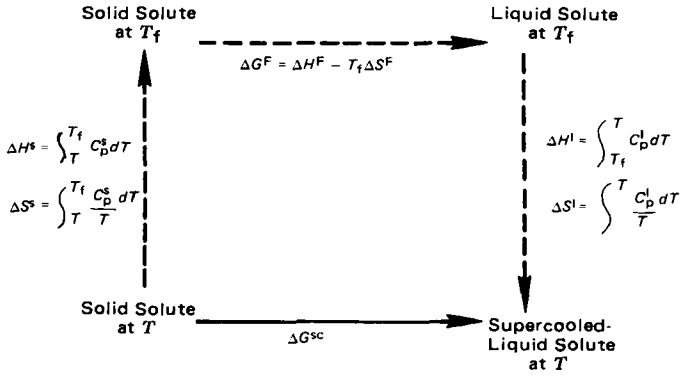


Figure 1—*Thermodynamic pathway for* ΔG^{sc} *at constant pressure.*

ΔG^{sc} at constant pressure. The thermodynamic pathway is given in Fig. 1. Here, a solid is heated to its melting temperature, melted, and the resulting melt is cooled back to the ambient temperature (T). By summing enthalpic and entropic contributions from each step, the total free energy change is obtained and, therefore, the activity of the solid can be expressed as:

$$\ln a_2^s = \frac{-\Delta H_f}{RT}\left(\frac{T_f - T}{T_f}\right) + \frac{\Delta C_p}{R}\left(\frac{T_f - T}{T}\right) - \frac{\Delta C_p}{R}\left(\ln \frac{T_f}{T}\right) \quad \text{(Eq. 6)}$$

where T_f and T are the melting and ambient temperatures, respectively, R is the gas constant, and ΔH_f is the heat of fusion for the solid at the melting point. The term ΔC_p is the difference of heat capacities between the liquid and solid. If ΔC_p and/or the temperature range T_f–T is small, the enthalpy and entropy of fusion are nearly constant, and Eq. 6 reduces to the familiar expression:

$$\ln a_2^s = \frac{-\Delta H_f}{RT}\left(\frac{T_f - T}{T_f}\right) \quad \text{(Eq. 7)}$$

The thermodynamic activity of a crystalline solute is therefore dependent on the *intrinsic properties* of the crystal lattice and can be estimated from experimental measurements of ΔH_f and T_f.

Regular Solutions—Solutions rarely conform to ideal behavior, since slight differences in molecular functionality between solvent and solute can result in large differences in their molecular interactions. Thermodynamically, the extent of deviation from the ideal case is expressed by the ratio a_2/X_2 which is the mole fractional activity coefficient γ_2. In other words, the free energy difference between ideal and nonideal behavior is defined as:

$$\Delta G_2^E = RT \ln (a_2/X_2) \quad \text{(Eq. 8)}$$

where ΔG^E is the excess free energy of mixing. Prediction of ΔG^E is difficult, since it is dependent on both the enthalpy and the entropy associated with molecular interactions for the pure components as well as their mixture. In the regular solution theory, the limiting situation is described as one in which the dominant molecular interactions between solute–solute, solvent–solvent, and solute–solvent are London forces (1, 2). This force is only dependent on the distance between atoms and their instantaneous orientation. The resulting attraction is nonorientating.

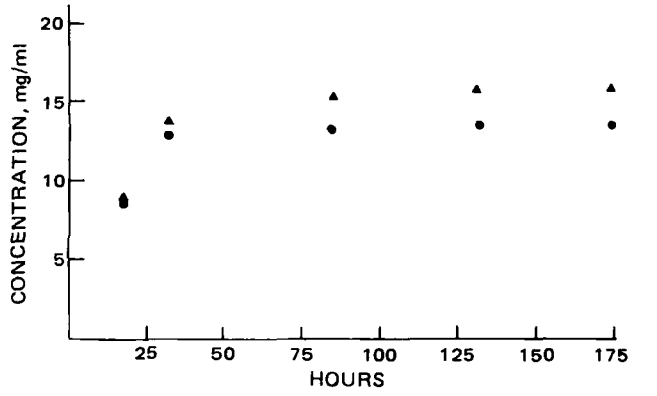


Figure 2—*Formation of saturated solution of hydrocortisone at 25°. Key: (●) 80% propylene glycol in water and (▲) 100% propylene glycol.*

Table I—Group Contributions to Molar Volume for Hydrocortisone

Functional Group or Atom	Number of Groups in Hydrocortisone	Partial Molar Volume Contribution per Group, ml/mole	Total Volume Contribution per Group[a], ml/mole
O—H	3	5.4	16.2
O=	2	5.5	11.0
CH_3	2	19.3	38.6
C	19	9.9	188.1
H	21	3.1	65.1

[a] Molar volume for hydrocortisone = 319 ml/mole.

The molecular model for regular solution behavior, therefore, allows for only an excess enthalpy of mixing arising from differences in cohesive energies between solute and solvent. Completely random mixing is assumed; thus, there is no excess entropy of mixing. The cohesive energy density of a pure liquid component is its internal energy per unit volume. Providing the vapor of a liquid is nearly ideal, the energy of vaporization per unit volume is an acceptable estimate for this internal energy.

The cohesive energy density of a mixture is much more difficult to estimate. By definition, this is the energy necessary to break all intermolecular contacts within the mixture. For these circumstances, Scathard (1) defined the cohesive energy density of a mixture as the geometric mean of the pure components' cohesive energy densities. It is this definition that limits regular solution theory to systems that predominantly interact through London forces.

Using these criteria for regular solution behavior, the energy of mixing for two components ΔE^M is as follows:

$$\Delta E^M = (X_1V_1 + X_2V_2)\left[\left(\frac{\Delta E_1^V}{V_1}\right)^{1/2} - \left(\frac{\Delta E_2^V}{V_2}\right)^{1/2}\right]^2 \phi_1\phi_2 \quad \text{(Eq. 9)}$$

where V is the molar volume, ϕ is the volume fraction, and ΔE^V is the energy of vaporization. As previously defined, the subscripts 1 and 2 designate the solvent and solute, respectively. The square root of the cohesive energy density is more often referred to as the solubility parameter δ. The partial molal energy of transferring liquid solute from pure liquid solute to solution is obtained by differentiating Eq. 9 with respect to n, *i.e.*:

$$\left(\frac{\delta \Delta E^M}{\delta n_2}\right)_{n_1} = V_2\phi_1^2(\delta_1 - \delta_2)^2 \quad \text{(Eq. 10)}$$

Assuming that there is no change in volume on mixing at constant pressure and that the entropy of transfer is ideal, it follows that:

$$\Delta G_2^E = RT \ln (a_2/X_2) = V_2\phi_1^2(\delta_1 - \delta_2)^2 \quad \text{(Eq. 11)}$$

Thus, deviation from ideality arises from the cohesive energy density difference between solvent and solute. This deviation defines the activity coefficient in terms of the excess enthalpy of mixing which, in this model, is identical to the excess free energy of mixing.

For a solid solute in equilibrium with saturated solution, the mole fractional regular solution solubility is as follows:

$$\ln X_2 = \frac{-\Delta H_f}{RT}\left(\frac{T_f - T}{T_f}\right) - \frac{V_2\phi_1^2}{RT}(\delta_1 - \delta_2)^2 \quad \text{(Eq. 12)}$$

In addition to the crystalline properties associated with fusion, application of this theory requires knowledge of the solubility parameters for solute and solvent.

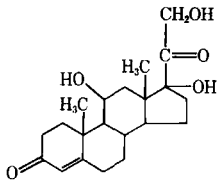
EXPERIMENTAL

Materials—Hydrocortisone was obtained from The Upjohn Company and was used without further purification. For the solubility studies, double distilled water and reagent grade organic solvents[1] were used.

High-Performance Liquid Chromatographic (HPLC) Procedure—A high-performance liquid chromatograph[2], operated at ambient temperature, was equipped with a UV detector for monitoring the column effluent at 254 nm. Chromatographic systems were developed with deaerated methanol–water solvent systems and a μ-Bondapak C-18 column[3]. The flow rate was 1.0 ml/min and the detector sensitivity was

[1] Eastman or Aldrich.
[2] Waters Associates Liquid Chromatographic Systems.
[3] Waters Associates.

Table II—Physical Properties of Hydrocortisone

Molecular Structure	
Molecular weight	362.5 g/mole
Crystalline density	1.24 g/ml
Molar volume, V_2	293 ml/mole
Melting temperature, T_f	212°
Heat of fusion, ΔH_f	8.1 Kcal/mole
Entropy of fusion, ΔS_f	16.7 cal/deg/mole
Activity of solid phase, a_2^s estimated from $\ln a_2^s = \frac{-\Delta H_f}{RT}\left(\frac{T_f - T}{T_f}\right)$	5.2×10^{-3}
Solubility parameter	12.4 $(cal/ml)^{1/2}$

adjusted as needed for each sample. Standard solutions of hydrocortisone were prepared for calibrating chromatographic peak heights. Injection volumes for standard and unknown solutions were equivalent, and internal standards were used when necessary. The sensitivity range of the chromatographic system for hydrocortisone was determined to be 10–0.01 μg/sample. Standard curves demonstrated excellent linearity over the entire concentration range.

Solubility Determination—The solubility of hydrocortisone in each solvent was obtained by equilibrating large excesses of solute with solvent in sealed glass containers. Temperature was maintained at 25° by a constant-temperature water bath and vigorous stirring was supplied by magnetic bars. An excess of solute was always present in the slurries. Solubilities in hexane and cyclohexane were determined by equilibrating large volumes of solution (300–600 ml) with excess solute for several days. Large samples were taken, filtered[4], measured, and brought to dryness; the residue was reconstituted in 3 ml of methanol with an internal standard and assayed by HPLC. The procedure was repeated three times.

The solubilities of hydrocortisone in the remaining solvents were determined in a similar manner utilizing smaller sample volumes. Samples (1 ml) were drawn from equilibrating solutions and were placed in microcentrifuge tubes. After immediate centrifugation, the supernatant was drawn through glass wool-tipped pipets and diluted in methanol. For solutions with densities greater than solid hydrocortisone, excess solute was first removed by suction. At least four samples were drawn from each solution with ~2-day intervals between samplings. Each time point (sample) was assayed by HPLC at least twice. Concentration *versus* time of equilibration plots indicated that equilibration was obtained rapidly (<24 hr) for all solutions except propylene glycol–water mixtures with high percentages of propylene glycol. Apparently due to the high viscosity of propylene glycol and its concentrated aqueous mixtures, these solutions required longer time periods to reach equilibration, as shown in Fig. 2. For all the solvent systems, once concentration plateaus were established, several values were determined at 2-day intervals to further ensure saturation. The procedure was repeated with new solutions. Dissolution profiles showed no evidence of hydrocortisone undergoing polymorphic transition or solvate formation. No decay products or impurities were detected by the HPLC assay. The specific HPLC assay ensured that only hydrocortisone was being quantified and ruled out the often troublesome complications associated with impurities.

Differential Thermal Analysis—The heat of fusion ΔH_f and the entropy of fusion ΔS_f were determined with a differential thermal analyzer[5] equipped with a standard cell attachment. A finely powdered, accurately weighed sample (1.5–2.0 mg) was spread evenly in a 40-μl aluminum crucible. A pinhole opening in the crucible lid allowed the sample to be in contact with the cell atmosphere of dry nitrogen with a regulated flow rate of 0.5 liter/min. An empty, sealed crucible served as a reference. Samples were heated at 5°/min. Heating curves were recorded at 5°/cm with a measuring range of 20 μV and recorder amplification of 100 mV. Calibration coefficients were determined with accurately weighed samples of indium. The molar heat of fusion was calculated from the area of the melting endotherm, moles of sample used, and the calibration coefficient. The entropy of fusion was obtained by dividing the heat of fusion by the absolute temperature of melting, T_f.

[4] Fluoropore, 0.22 μ, Millipore.

[5] Mettler DTA 2000.

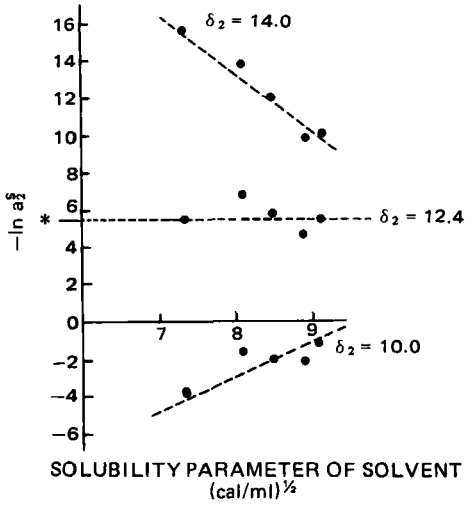


Figure 3—*Ideal solubilities of hydrocortisone (●) obtained from Eq. 14 for varying solute solubility parameters, δ_2. Key: * $-\ln a_2^s$ as calculated from crystalline properties (Table II).*

Melting Point—The melting point of hydrocortisone was determined by two methods: (*a*) controlled-heating thermal microscopy[6] and (*b*) differential thermal analysis. Heating rate for both methods was 5°/min.

RESULTS

Physical Properties—Hydrocortisone is a crystalline solid, which on heating from 25 to 220° undergoes only one thermal transition. This endothermal transition at 212° corresponds to the melting of the crystal. Hot-stage microscopy revealed no crystal morphology changes until melting. However, on cooling the melt below 212°, an amorphous glass was formed instead of the original crystalline solid. This occurrence may be, in part, the result of slight thermal decomposition within the melt. However, the sharpness and symmetrical shape of the endotherm suggest that thermal decomposition apparently is not contributing to the overall energy change during the melting phase. Moreover, melted samples assayed by HPLC showed only trace amounts of decay with essentially 100% retention of hydrocortisone. It is therefore concluded that the endotherm represents primarily energy consumed on melting. The ΔH_f for hydrocortisone is 8.1 kcal/mole and ΔS_f is 16.7 cal/deg mole. These values are averages from five determinations with $SD < \pm 5\%$. The experimental values for ΔH_f, ΔS_f, and T_f are also in good agreement with reported results (3).

A physical parameter that is necessary for solubility analysis is the molar volume of liquid solute. It has been demonstrated for several crystalline steroids that the molecular weight divided by the crystalline density can serve as a suitable molar volume estimate for the supercooled liquid solute (3). Since hydrocortisone has a crystalline density of 1.24 g/ml at 25° (9), the molar volume estimate is 293 ml/mole. An alternative means for estimating molar volume is by the summation of the partial molar volumes of a compound's functional groups (10). Applying this method to hydrocortisone (Table I), a molar volume of 319 ml/mole was obtained. This value is in reasonable agreement with the first estimate. The value of 293 ml/mole for the molar volume of supercooled liquid hydrocortisone will be used to be consistent with previously reported work (3).

The thermodynamic activity of crystalline hydrocortisone at 25° is 5.3×10^{-3}, as obtained from Eq. 7 with the experimental values for ΔH_f and T_f. The value of 5.3×10^{-3} thus represents the mole fractional ideal solubility for hydrocortisone. For a hypothetical solvent with molecular weight of 100 and density of 1.0 g/ml, the solubility of hydrocortisone would be 5.2×10^{-2} moles/liter or 18.9 mg/ml providing the two components formed an ideal mixture. These physical properties, summarized in Table II, are essential for the solubility analysis of hydrocortisone.

Solubility—The solubilities of hydrocortisone at 25°, experimentally determined in the present study, are presented in Table III along with the molar volumes and solubility parameters for the solvents. The solubility parameters for the pure solvents at 25° are taken from Hoy's tables

[6] Mettler Hot Stage with FP5 Temperature Regulator and a Zeiss Standard Microscope.

Table III—Solubilities of Hydrocortisone at 25°

Solvent	Molar Volume of Solvent[a], ml/mole	δ_1[a] (cal/ml)$^{1/2}$	Equilibrium Solubility mg/ml	Equilibrium Solubility moles/liter	Mole Fraction
Hexane	130	7.3	3.45×10^{-5}	9.53×10^{-6}	1.24×10^{-8}
2-Butyl acetate	132	8.0	1.48	4.08×10^{-3}	5.40×10^{-4}
Cyclohexane	108	8.2	8.23×10^{-4}	2.27×10^{-6}	2.24×10^{-7}
Carbon tetrachloride	97	8.6	1.00×10^{-2}	2.84×10^{-5}	2.75×10^{-6}
Isopropyl acetate	117	8.6	1.4	3.86×10^{-3}	4.53×10^{-4}
Ethyl acetate	98	8.9	2.82	7.76×10^{-3}	7.58×10^{-4}
Toluene	106	8.9	9.73×10^{-2}	2.68×10^{-4}	2.85×10^{-5}
Benzene	89	9.1	1.30×10^{-1}	3.59×10^{-4}	3.19×10^{-5}
Chloroform	80	9.2	4.08	1.12×10^{-2}	9.05×10^{-4}
Methyl acetate	79	9.5	5.88	1.62×10^{-2}	1.29×10^{-3}
Octanol	159	10.3	3.40	9.38×10^{-3}	1.49×10^{-3}
Propylene glycol	73	15.0	$1.68 \times 10^{+1}$	4.60×10^{-2}	3.38×10^{-3}
80% Propylene glycol in water	46[b]	16.5[b]	$1.32 \times 10^{+1}$	3.64×10^{-2}	1.68×10^{-3}
60% Propylene glycol in water	33[b]	18.2[b]	5.69	1.59×10^{-2}	5.20×10^{-4}
40% Propylene glycol in water	26[b]	19.8[b]	2.16	5.96×10^{-3}	1.54×10^{-4}
20% Propylene glycol in water	21[b]	21.4[b]	6.99×10^{-1}	1.93×10^{-3}	4.10×10^{-5}
Water	18	23.0	2.97×10^{-1}	8.19×10^{-4}	1.47×10^{-5}

[a] From Ref. 5 except where otherwise indicated. [b] Calculated from the method proposed in Ref. 6.

(10). Values for the cosolvent mixtures of propylene glycol and water were estimated from the expression of Smith *et al.* (11):

$$\delta_{1\text{-}3} = \frac{\phi_1\delta_1 + \phi_3\delta_3}{\phi_1 + \phi_3} \qquad \text{(Eq. 13)}$$

where the subscripts 1 and 3 denote the respective pure solvent parameters and ϕ is the corresponding volume fraction. The validity of the above expression has been demonstrated with binary solvent systems only capable of interacting through London forces (11). Use of the equation must be tentative for mixtures of propylene glycol and water as the molecular interactions of hydrogen bonding and dipole–dipole attractions for those mixtures have yet to be fully delineated.

The solubility parameter scale does provide one indication of the wide range of solvents used for these studies. The solubility parameter for propylene glycol falls roughly between that for hexane [7.3 (cal/ml)$^{1/2}$] and water [23 (cal/ml)$^{1/2}$], which represent the extremes for this solvent scale. Hydrocortisone is extremely insoluble in hexane 9.53×10^{-8} moles/liter and poorly soluble in water 8.19×10^{-4} moles/liter. The maximum molar solubility determined was with propylene glycol 4.63×10^{-2}. The solubility span for hydrocortisone in the evaluated solvents was $>10^5$. Interestingly, all solubility values are below the estimated ideal solubility and are sufficiently low to negate solute–solute interactions.

DISCUSSION

Regular Solution Analysis—It should be mentioned at the onset of this discussion that regular solution behavior, as carefully defined by Hildebrand *et al.* (12), is used as a secondary reference point for the solubility analysis of hydrocortisone. The primary reference point is ideal solution behavior. It is recognized *a priori* that the underlying theory is inapplicable where there is significant hydrogen bonding either between like or unlike species, solute or solvent. However, regular solution behavior provides a norm from which deviations from ideality, other than those derived from differential cohesiveness, can be measured.

Regular solution theory predicts a parabolic relationship between the mole fractional solubility of a given solute and the solubility parameters for solvents which span the solute's value. For a solid solute in equilibrium with its saturated solution, the regular solution solubility is given by Eq. 12. The theoretical maximum solubility is considered to be the ideal solubility where the cohesive energy differential between solute and solvent is zero. In other words, a positive excess enthalpy of mixing and a solubility less than ideal is always associated with regular solution behavior. Solvents were selected which interact within themselves and with hydrocortisone predominantly through London forces, allowing regular solution theory to be applied. Hexane, cyclohexane, carbon tetrachloride, benzene, and toluene were considered appropriate to test the hypothesis that the solubilities of a solute like hydrocortisone would conform to regular solution behavior in apolar solvents. The saturated solutions of hydrocortisone in these solvents are sufficiently dilute to preclude any appreciable solute–solute bonding. The predominant factor contributing to solution phase interaction is London forces. This is also true for cohesion of the pure liquids. The forces binding hydrocortisone in the

Table IV—Estimation of Solubility Parameter for Hydrocortisone[a]

Functional Group	$(EV)^{1/2}$, (cal/ml)$^{1/2}$	Number of Groups	Total $(EV)^{1/2}$ per Group[b], (cal/mol)$^{1/2}$
CH_3	148.3	2	296.6
CH_2	131.5	8	1052.0
—CH<	85.9	4	343.9
>C<	32.0	3	96.0
—CH=	121.5	1	121.5
>C=	84.5	3	253.5
C=O	263.0	2	526.0
OH	226.0	3	678.0
6-Membered ring	−23.4	3	−70.2
5-Membered ring	20.9	1	20.9

[a] $\delta_2 = \frac{(EV)^{1/2}}{V_2} = \frac{3318.2 \text{ (cal/ml)}^{1/2}}{293 \text{ ml}} = 11.4 \text{ (cal/ml)}^{1/2}$. [b] Total $(EV)^{1/2}$ for a mole of hydrocortisone = 3318.2 (cal/ml)$^{1/2}$.

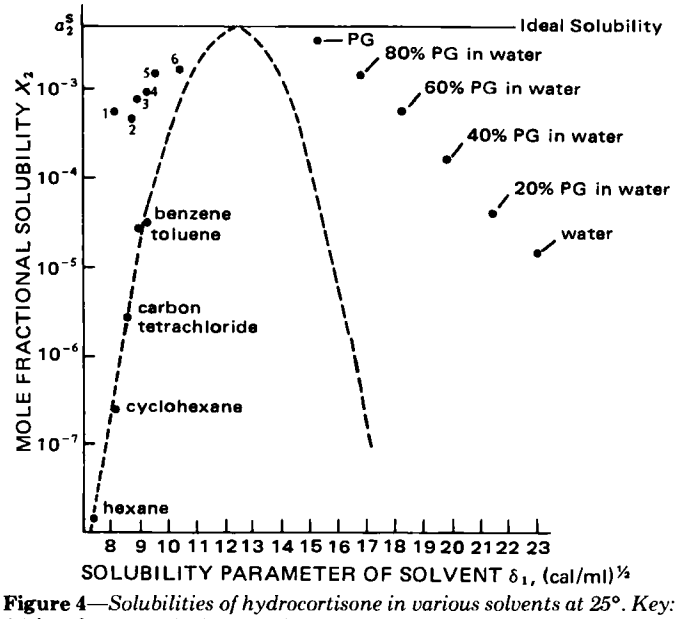


Figure 4—*Solubilities of hydrocortisone in various solvents at 25°. Key: (1) butyl acetate, (2) isopropyl acetate, (3) ethyl acetate, (4) chloroform, (5) methyl acetate, (6) octanol, and (PG) propylene glycol. The dotted line represents the regular solution parabola $\delta_2 = 12.4$ (cal/ml)$^{1/2}$.*

hypothetical supercooled liquid state are indeterminate but are presumed to have significant contributions from hydrogen and dipolar bonding.

Since the net interactions in the hydrocortisone melt include hydrogen bonding, which precludes totally random orientations of its molecules, one primary element required for regular solution behavior is missing. There is an excess entropy of mixing implicitly associated with the freeing of the hydrocortisone molecules from bonds restricting their relative motions and positions in the supercooled liquid state. However, regular solution behavior for alkyl-*p*-aminobenzoate homologues (4), which suffer the same theoretical departure, is followed closely for such polar, highly interactive solutes as long as the solvent is strictly apolar. In essence, it seems that potential sources of deviation from regular solution behavior, especially associated with disintegration of the polar solute melt structure, are insignificant against the excess free energy derived from differential cohesiveness. Thus, for the alkyl-*p*-aminobenzoates there are operative solubility parameters, likely related to the true square root cohesive energy densities, which adequately describe their solubilities in hexane. The present work is, in part, an attempt to examine the behavior of hydrocortisone, an even more complex molecular structure, in this regard. The study differs in an important way from the previous study (alkyl-*p*-aminobenzoates) in that the behavior is examined across diverse solvents and not with respect to solute structure within a fixed solvent.

To evaluate the proposed regular solution behavior for hydrocortisone, the following were assumed:

1. The crystalline properties of hydrocortisone were invariant from solvent to solvent such that the activity of the solid phase was the same in each.
2. The volume fraction for each solvent (ϕ_1) was unity.
3. The molar volume of hydrocortisone is 293 ml/mole at 25° and is independent of the solvent.

With the above assumptions and implicit simplifications, Eq. 12 is rewritten as follows:

$$\ln X_2 = \ln a_2^s - 0.5(\delta_1 - \delta_2)^2 \qquad \text{(Eq. 14)}$$

for a saturated solution of hydrocortisone at 25°. Providing the choice of solvents is satisfactory, a_2^s and the solubility parameter for hydrocortisone δ_2 can be simultaneously determined from the mole fractional solubilities of hydrocortisone in the specified solvents. The value of a_2^s, moreover, should be consistant with the value of 5.2×10^{-3} obtained from ΔH_f and T_f.

Values ranging from 7 to 23 $(cal/ml)^{1/2}$ for δ_2 were evaluated using Eq. 14 to determine δ_2 where a_2^s is most constant. Figure 3 shows $\ln a_2^s$ *versus* the solubility parameter of the solvent for three selected values for γ_2. As seen in the graphical display, a_2^s appears most constant for a δ_2 value of 12.4 $(cal/ml)^{1/2}$; however, there is scatter in the data, and based solely on this analysis, the value of δ_2, at best estimate, can be considered to lie between 12 and 13 $(cal/ml)^{1/2}$. The value of 12.4 $(cal/ml)^{1/2}$ for δ_2 predicts a_2^s to be 5.5×10^{-3} which is in excellent agreement with a_2^s as calculated from ΔH_f and T_f. Furthermore, the dashed lines in Fig. 3 show the calculated deviation in a_2^s if the solubility parameter is in fact 12.4 $(cal/ml)^{1/2}$ for hydrocortisone, but was assumed to be either 10 or 14 $(cal/ml)^{1/2}$. While each of these approaches for estimating the solubility parameter has an inherent uncertainty when considered alone, when combined they indicate a solubility parameter of hydrocortisone of 12.4 $(cal/ml)^{1/2}$. This value is consistent with minimum variability in the corresponding a_2^s values from Eq. 14 and has good agreement with a_2^s as independently predicted from crystalline properties Eq. 7.

The functional-group contribution approach provides another way of estimating the solubility parameter for hydrocortisone. In this case, the molar attraction constants for the solute functional groups are summed as originally proposed by Small (13). Using the updated molar attraction constants tabulated by Hoy (10), the solubility parameter for hydrocortisone was estimated to be 11.4 $(cal/ml)^{1/2}$, as outlined in Table IV. This estimate differs significantly from the experimental value of 12.4 $(cal/ml)^{1/2}$. The discrepancy is not unexpected, since there is little evidence that the functional-group contribution approach is suitable for such a large, polyfunctional solute, and its use for hydrocortisone likely represents an overextention of the method.

Flory–Huggins Excess Entropy of Mixing—As previously defined, regular solution theory assumes the entropy of mixing to be an ideal in which the entropy of the process arises strictly from the statistical mixing of the components. A factor not yet considered in the regular solution analysis for hydrocortisone is the inability to statistically mix molecules of unequal size. Flory (14) and Huggins (15) have considered the excess entropy associated with the mixing of molecules of unequal size. A model was designed for dilute solutions with a small molecular volume solvent and a large, polymer solute. The mixing of a liquid polymer with a solvent

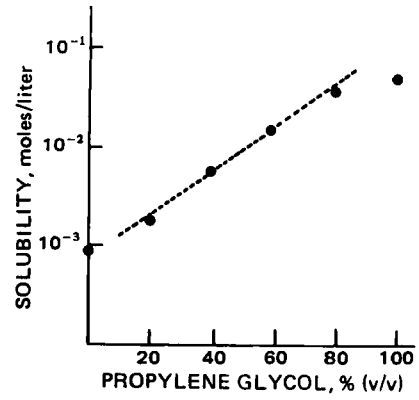


Figure 5—*Solubility of hydrocortisone in propylene glycol–water mixtures at 25°.*

to make a dilute solution with respect to the polymer leads to the total number of possible configurations for the polymer being greatly increased over what exists in the pure polymer state. This large increase in configurational entropy of mixing is expressed in the following equation for the excess free energy of mixing:

$$\Delta G^E = RT[X_1 \ln (\phi_1/X_1) + X_2 \ln (\phi_2/X_2)] \qquad \text{(Eq. 15)}$$

This expression was derived for long-chain molecules with individual segments occupying sites within a liquid lattice consisting of small solvent molecules. This factor should be an additive (independent) function. With this factor incorporated, the general regular solution solubility equation becomes:

$$\ln X_2 = \ln a_2^s - \frac{\phi_1^2 V_2}{RT}(\delta_1 - \delta_2)^2 - [\ln V_2/V_1 + 1 - V_2/V_1] \qquad \text{(Eq. 16)}$$

The validity of the Flory–Huggins model has not been established for compact molecules in a solvent composed of molecules smaller by only several multiples. It has been pointed out (16) that such an evaluation for compact molecules is difficult since possible entropy effects are often obscured by large changes in the enthalpy of mixing. The analysis of the excess entropy due to inequality of size for hydrocortisone appears to be confounded by this difficulty. The hydrocortisone–solvent molar volume ratio, V_2/V_1, is only 2.25–3.28 for those solvents considered for regular solution behavior. To evaluate the impact of the Flory–Huggins entropy correction on the regular solution analysis of hydrocortisone, the appropriate parameters were introduced into Eq. 16, and δ_2 was determined as before. The correction term did not significantly affect the estimation of δ_2, within the sensitivity of the analysis. Thus, the entropy arising from disparate molecular size does not appear to be significant as a solubility-determining factor for these hydrocortisone–solvent systems. This conclusion agrees with the observations of Shinoda and Hildebrand (16) as well as Bowen and James (8), who also noted little or no Flory–Huggins effect for mixtures of nonpolymeric substances of unequal size.

Solubility Profile—The values for the physicochemical properties of hydrocortisone utilized in the subsequent discussion are found in Table II. With appropriate substitution of the above parameters into Eq. 12, the regular solution solubility parabola was calculated for hydrocortisone about the midpoint of 12.4 $(cal/ml)^{1/2}$, where the solution is considered ideal. As expected, the solubilities of hydrocortisone in solvents essentially limited to dispersion molecular interactions conform closely to the curve Fig. 4. These solvents are hexane, cyclohexane, carbon tetrachloride, toluene, and benzene.

Regular solution theory predicts a 50-fold difference in molar solubility between hexane and cyclohexane, and this difference is observed experimentally. However, the inappropriateness of regular solution theory for solvents other than those of the London type is also demonstrated in Fig. 4. It appears inadequate for solubility estimation in all solvents capable of hydrogen bonding or other strong, orientating bonding with hydrocortisone. For example, the experimental solubility of hydrocortisone in isopropyl acetate is nearly 100 times the predicted value. There is also a 20-fold factor unaccounted for by regular solution theory between the solubilities in carbon tetrachloride, a perfectly symmetrical and apolar species, and chloroform, which has a substantial dipole. Thus, for isopropyl acetate, chloroform, and similar solvents, dipole–dipole and hydrogen bonding must contribute significantly to the solution-phase interactions.

The regular solution parabola predicts a solubility of hydrocortisone

in water, where $\gamma_1 = 23.4$ (cal/ml)$^{1/2}$, $\sim 10^{21}$ times less than the observed value. Clearly, simple differential cohesiveness is grossly inadequate to account for the specific intermolecular forces between water and hydrocortisone. Having two ketone moieties and three hydroxyl groups, hydrocortisone is capable of forming hydrogen bonds with water around these centers, which greatly favor its solubility. Contrastingly, the hydrocarbon skeleton and attached methyl groups provide surfaces for hydrophobic association with water, which is unfavorable to solubility. The net results of these additional solution-phase interactions is a large reduction in the excess free energy of transfer of a mole of supercooled liquid hydrocortisone to water. Hence, the solubility in water is orders of magnitude higher than would be expected from the noncritical use of regular solution theory, taking the solubility parameter of water at face value. It should be noted that the solubility parameter of water as a square root cohesive energy density is, in the absolute sense, a legitimate value. However, it can not be used in regular solution treatments because the general behavior of water violates the fundamental assumptions of this theory.

The incremental addition of propylene glycol to an aqueous propylene glycol solvent system is marked by an exponential increase in hydrocortisone solubility and log (solubility) increases roughly linearly with increasing volume fraction of propylene glycol (Fig. 5). This solubility pattern can be compared with the following linear free energy function:

$$\log S_f = \log S_{f=0} + \epsilon f \qquad \text{(Eq. 17)}$$

where ϵ is the incremental change in solubility per volume fraction (f) added. The actual cosolvent profile for hydrocortisone, however, has a slight sigmoidal shape which is most apparent at low and high concentration of propylene glycol. Nevertheless, an estimate for ϵ of 2.1 was obtained from regression analysis with the values for water and propylene glycol excluded because they were out of the linear region. The estimate of ϵ corresponds to an ~100-fold increase in solubility from water to pure propylene glycol, somewhat greater than actually observed.

A similar linear trend is shown in Fig. 4 for log S_f *versus* the solubility parameter estimates for the cosolvent mixtures as calculated from Eq. 12. It might appear that the cosolvent trend is a direct outcome of differential cohesiveness. This would, however, be a superficial and incorrect conclusion. Water, propylene glycol, and their mixtures are extensively hydrogen-bonded systems. Although the experimental cohesive energy densities for these solvents are meaningful as relative measures of the forces of association in the pure liquids, they are meaningless with respect to regular solution calculations. Regular solution theory requires that no significant orientating bonding can occur between solute and solvent, pure solvent, and pure liquid solute. This requirement allows the cohesive energy density of the solute–solvent mixture, C_{12}, to be approximated by $(C_{11}, C_{22})^{1/2}$. These conditions are violated as a consequence of the hydrogen bonding networks in water, propylene glycol, and their mixtures. Based on literature data which indicate that the aqueous solubility of substantially hydrophobic molecules is proportional to the low-energy molecular surface area (17) and that the sensitivity of homologue solubilities in aqueous mixtures is a function of the hydrocarbon chain length (18), it would appear that the solubility trend of hydrocortisone in propylene glycol–water mixtures is principally due to a dilution of the hydrophobically induced self-association of water.

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