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Research Article

Solubility and Related Physicochemical Properties of Narcotic Analgesics

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The physicochemical properties of select opioid and anilinopiperidine narcotic analgesics were investigated. The solubilities of the narcotics in hexane and water and, for morphine, in other organic solvents were determined. Regular solution theory seems to be applicable to the solubility behavior of morphine in solvents that lack strong dipoles and hydrogen bonds. A best-fit solubility parameter of 13.2 $(cal/cm^3)^{1/2}$ for morphine was determined from its solubilities in London solvents and its ideal solubility. Calculation of morphine's solubility parameter from its hexane solubility alone and its melting properties gave a corresponding δ_2 value. These measured solubility parameters were appreciably larger than the solubility parameter estimated from molar attraction constants. Solubility parameters of hydromorphone, codeine, fentanyl, and sufentanil were also calculated from respective hexane solubilities, melting points, and heats of fusion and were 11.7, 10.9, 9.8, and 9.7 $(cal/cm^3)^{1/2}$. For these compounds, experimental solubility parameters agreed with solubility parameters estimated from molar attraction constants. Because meperidine, fentanyl, and sufentanil exhibit low levels of intracrystalline cohesion, as reflected in low melting points and relatively modest heats of fusion, theoretically projected ideal solubilities and actual solubilities in organic solvents measured for them were considerably higher than determined for morphine and its analogues. Consistent with the solubilities, the octanol–water partition coefficients of the two 4-anilinopiperidine analogues and of meperidine were several orders of magnitude larger than those of the opioids, evidencing the fact that meperidine, fentanyl, and sufentanil are substantially more lipophilic than the opioids.

KEY WORDS: narcotics; narcotic analgesics; opioids; morphine; codeine; hydromorphone; fentanyl; sufentanil; meperidine; solubility; solubilities; regular solution theory; solubility parameter.

INTRODUCTION

The clinical use of narcotic analgesics for the relief of pain in terminal cancer patients and postsurgical operations is a long-standing practice (1). The opioids are given either orally or intravenously to achieve therapeutic effects. Conventional ways of delivering these narcotics have some major drawbacks. All have to be given frequently because all have high metabolic clearances. Pharmacologically related 4-anilinopiperidine analgesics have large volumes of distribution in addition to high metabolic clearances and therefore are particularly short acting. Oral absorption of all these narcotics is unpredictable and incomplete due to first-pass metabolism (2–4), so much so in the case of the anilinopiperidines that they are used strictly parenterally. The drugs also tend to be sedative when administered intravenously in pain-relieving doses (5,6). Finding alternative means of delivering these compounds to minimize some of the problems of the drug class, even the tendency for them to be clinically underutilized due to a fear that they may be addictive to patients (7), is desirable. Transdermal delivery offers a particularly attractive option for these compounds, as it promises to provide sustained pain relief at drug levels that remain below sedative levels.

The physicochemical properties of drugs, particularly their absolute and relative solubilities, are crucial to decisions about and the design of novel systems of delivery (8–10). Generally, the greater a drug's innate tendencies to dissolve, the more likely it is that the drug can be delivered at an adequate rate across the skin or, for that matter, any other membrane (11,12). Therefore, the solubilities of morphine, hydromorphone, and codeine (opioids), fentanyl and sufentanil (4-anilinopiperidines), and meperidine, the structures of which appear in Fig. 1, in select solvents have been assessed and such important physicochemical determinants of solubility as melting points, fusion energies, and cohesiveness have also been investigated. As the prototypical narcotic, morphine's solubilities in solvents of wide-ranging polarity have been characterized. These establish an overall picture of the solubility behavior of the class. Hexane and water solubilities were determined for the remaining compounds. Two reference behaviors were employed in the solubility analysis, ideal behavior and, secondarily, regular solution behavior. Using the experimental data and also molar attraction constants, solubility parameters (13,14) were de-

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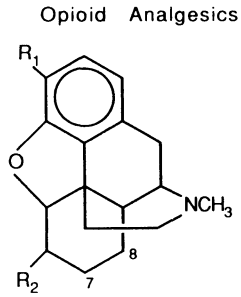

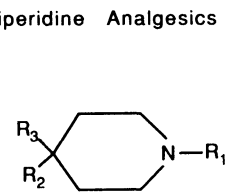

Morphine : R_1: OH; R_2 : OH; double bond between C_7 and C_8
Hydromorphone : R_1: OH; R_2 : =O;
Codeine : R_1: OCH_3; R_2 : OH; double bond between C_7 and C_8

Meperidine : R_1 : CH_3; R_2 : C_6H_5; R_3 : $COOC_2H_5$;
Fentanyl : R_1 : $C_6H_5C_2H_4$; R_2 : H; R_3 : $N(C_6H_5)COC_2H_5$;
Sufentanil : R_1 : $C_4H_3SC_2H_4$; R_2 : $-CH_2OCH_3$; R_3 : $-N(C_6H_5)COC_2H_5$;

Fig. 1. Structures of the opioids and piperidine-type narcotics.

termined for these narcotics, allowing a critical comparison of the two methods of estimation.

THEORETICAL BACKGROUND

Regular Solution Analysis. The thermodynamic activity of a crystalline solute, a_2^s, can be related to its reference super-cooled liquid state through the following equation (13):

$$\ln a_2^s = \frac{-\Delta H_f}{RT}\left(\frac{T_f - T}{T_f}\right) + \frac{\Delta C_p}{R}\left(\frac{T_f - T}{T_f}\right) - \frac{\Delta C_p}{R}\left(\ln\frac{T_f}{T}\right) \quad (1)$$

where ΔH_f is the heat of fusion for a solid having a melting point, T_f. T is the experimental (prevailing) temperature and R is the gas constant. In writing Eq. (1) it is assumed that the term ΔC_p, the differential in heat capacity between the solid and the supercooled liquid states of a material, may be treated as a fixed difference during the process of raising the temperature to T_m to melt the solid and then lowering it back to T to yield the supercooled liquid state at T. Since the heat capacity of the supercooled liquid normally cannot be determined, but is generally not extraordinarily different from the heat capacity of the solid solute, ΔC_p is often assumed to be negligible. This assumption results in the familiar equation:

$$\ln a_2^s = \frac{-\Delta H_f}{RT}\left(\frac{T_f - T}{T_f}\right) \quad (2)$$

Equation (2) suggests that the thermodynamic activity of a crystalline solute depends strictly on the properties of its crystal lattice, allowing it to be estimated from experimental measurements of ΔH_f and T_f. Because the activity coefficient of an ideal solution is unity (by definition), a_2^s also represents the mole fraction ideal solubility. However, solutes rarely exhibit ideal behavior in real solvents because of differences in cohesive energy densities between solute and solvent and also often because strong intermolecular bonding leads to both excess enthalpic and excess entropic contributions to the free energy of solution. When the nonideality arises strictly from differential cohesiveness, it can be shown for a solid solute in equilibrium with its saturated solution that the mole fraction solubility follows

$$\ln x_2 = \frac{\Delta H_f}{RT}\left(\frac{T_f - T}{T_f}\right) - \frac{V_2\,\phi_1^2}{RT}(\delta_1 - \delta_2)^2 \quad (3)$$

where, δ_1 and δ_2 are the solubility parameters or the square-root cohesive energy densities for solvent and solute, respectively. V_2 is the molar volume of the solute and ϕ_1 is the volume fraction of the solvent. Such solutions are known as regular solutions. Equation (3) indicates that if one is armed with (1) knowledge of the solubility of an organic solute in an apolar organic solvent, (2) the solute's heat of fusion, (3) the solute's melting point, and (4) the solubility parameter of the solvent, the solubility parameter of solute, δ_2, can be determined from the experimentally measured mole fraction solubility in the solvent.

MATERIALS AND METHODS

Materials. Fentanyl and sufentanil were a gift from Janssen Pharmaceutica (N.J.). Meperidine hydrochloride, morphine sulfate, codeine phosphate, and hydromorphone hydrochloride were obtained from stocks of the compounds at the University of Michigan Hospital (Ann Arbor). Morphine, codeine, hydromorphone, and meperidine free base were liberated from aqueous solutions of their respective salts by adding a saturated solution of sodium bicarbonate and then extracting with an appropriate organic solvent (CH_2Cl_2 or hexane, depending on the compound). The organic phase containing the isolated free base was evaporated to dryness under a gentle stream of dry nitrogen. Each free base was recrystallized from hexane or from hexane–ethanol mixtures. High levels of purity (not actually quantitated) of the recrystallized solutes were assured by gas chromatography (GC) or high-performance liquid chromatography (HPLC) and by the sharpness of melting points. For the solubility studies, double-distilled deionized water and reagent-grade organic solvents (Fisher Scientific) were used. Buffers were prepared from reagent-grade chemicals.

Solubility Determination. The solubilities of morphine in several organic solvents were obtained by equilibrating large excesses of this solute with each solvent. Temperature was maintained at 35°C by circulating water from a constant-temperature water bath through jackets around the vessels used in the analysis. To hasten the attainment of

equilibrium, each slurry was continuously, vigorously mixed with a magnetic stirring bar. Samples were taken, filtered (Fluoropore, 0.22-μm Millipore), measured with respect to volume, and brought to dryness. The residue was reconstituted in the mobile phase and assayed by HPLC. The initial 25% of each filtrate was discarded to eliminate the possibility that adsorption of morphine on the filter and/or the filtering apparatus might influence the solubility determination. The sampling procedure was repeated twice, for a total of three assays on each sample. Concentration versus time plots indicated that equilibrium was obtained well within 48 hr. Therefore, the equilibration times for all the studies were ≥48 hr. The 35°C solubilities of codeine, hydromorphone, meperidine, fentanyl, and sufentanil in hexane were determined in a similar fashion. Solubilities of the free-base forms of the narcotics were determined in pure water at 25°C.

Chromatographic Procedure. Morphine was assayed by HPLC using UV detection at 254 nm. A μ-Bondapak C_{18} column (Water Associates) was used. Acetonitrile–water (26:74) as a mobile phase was employed for the chromatographic resolution (15). The flow rate was set at 1.2 ml/min, and the absorption wavelength at 254 nm. Calibration curves for morphine were obtained by plotting the peak height ratio of the authentic drug to the internal standard, codeine, as a function of the drug concentration in the standard aqueous sample. Standard curves exhibited excellent linearity over the entire concentration range employed in the assays. The concentrations of the other narcotics were determined by HPLC with only minor modification of these chromatographic conditions.

It proved easier to measure the hexane solubilities of fentanyl and sufentanil gas chromatographically (Hewlett Packard GC-5840 equipped with flame ionization detector). The chromatographic conditions were a glass column (182 × 0.2 cm) packed with 3% OV-17, a column temperature of 282°C, detector and injection temperatures of 300°C, and a nitrogen flow rate of 35 ml/min. Meperidine, codeine, and hydromorphone concentrations in hexane were determined by GC. Peak areas were automatically integrated (HP-1885 integrator). Typical chromatograms are shown in Fig. 2.

Differential Thermal Analysis. The heat of fusion, ΔH_f, and the entropy of fusion, ΔS_f, for morphine, codeine, fentanyl, and sufentanil were determined with a differential thermal analyzer (Mettler Model FP-800) equipped with a standard cell attachment. Values for morphine, hydromorphone, and meperidine were obtained on a Perkin–Elmer DSC II. Comparable values for morphine were obtained on each instrument. In all instances the compounds were in their free-base forms, having been freshly recrystallized from hexane or hexane–ethanol mixtures. A finely powdered, accurately weighed sample of drug (1.5–3 mg) was layered evenly over the bottom of a 40-μl aluminium crucible. Samples were heated at 1.5°C/min. Heating curves were recorded at 1.5°C/min, with a measuring range of 20 μV and a recorder amplification of 100 mV. Instrumental calibration was done 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 calibration coefficient. All tracings were repeated three times, for a total of four estimates. There were no appreciable differences in the thermograms for any compound from run to run. The melting points of the compounds were also determined from the DSC curves.

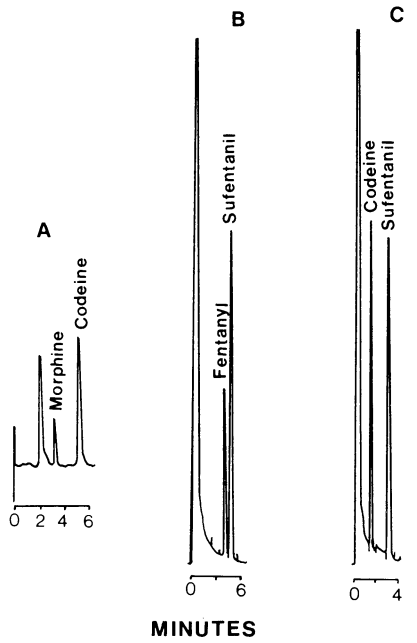

Fig. 2. Representative chromatograms for the assay of morphine, codeine, fentanyl, and sufentanil.

Partition Coefficient Determination. Octanol–water partition coefficients of the narcotics were evaluated by equilibrating aqueous solutions (pH 7.4) of the narcotics with octanol. The samples were equilibrated in a shaker bath at 37°C for 24 hr. The samples were then centrifuged for 10 min and the octanol phase and the octanol and water phases were carefully separated. Using essentially the same sample preparation procedures employed in the solubility studies, the octanol phases were assayed by GC, after appropriate dilution, and the aqueous phases were assayed by HPLC. The HPLC and GC assays described under the solubility studies required only minor adaption for these assessments.

RESULTS

The physical properties of six narcotic analgesics are summarized in Table I. Morphine and its analogues, hydromorphone and codeine, exhibited only one thermal transition. The endotherms at 255, 265, and 155°C correspond to the melting of these crystals. However, morphine and hydromorphone decomposed rapidly upon melting. Meperidine, fentanyl, and sufentanil also underwent a single thermal transition, with melting endotherms at 35, 84, and 97°C, respectively. Melted samples of these drugs assayed by GC showed only trace amounts of decomposition. Enthalpies of fusion, ΔH_f, and entropies of fusion, ΔS_f, calculated from these data are also shown in Table I. These values are the mean of four determinations, all with coefficients of variation <5%.

The molar volumes, V_2, of morphine, hydromorphone, and codeine were determined from their molecular weights divided by the respective crystalline density (16). The values are given in Table I. Alternatively, molar volumes were esti-

Table I. Physicochemical Properties of Narcotic Analgesics

Physical parameter	Morphine	Hydromorphone	Codeine	Fentanyl	Sufentanil	Meperidine
MW (g/mol)	285.3	285.3	299.3	336.5	387.5	247
Crystalline density (g/ml)	1.32	1.32	1.32	1.11	1.12	1.11
Molar volume, V_2 (ml/mol)	216.2	216.2	226.8	303.3	345.2	221.8
MP, T_f (°C)	255	266	155	84	97	35
Heat of fusion, ΔH_f (kcal/mol)	6.90	8.51	4.37	5.38	5.70	5.88
Entropy of fusion, ΔS_f (cal/mol/deg)	13.1	15.8	10.2	15.1	15.4	19.1
Activity of solid phase, a^s_2 at 25°C	6.2×10^{-3}	1.6×10^{-3}	1.1×10^{-1}	2.2×10^{-1}	1.5×10^{-1}	7.2×10^{-1}

mated by the summation of the partial molal volumes of the compound's functional groups (17). Upon applying this method of determination to the opioids, molar volumes of 242, 242, and 256 were obtained for morphine, hydromorphone, and codeine, respectively, in rough agreement with the first estimates. Because no values for the crystalline densities of fentanyl, sufentanil, and meperidine could be found in the literature, the molar volumes of meperidine, fentanyl, and sufentanil listed in Table 1 were estimated by functional-group molar volumes. The thermodynamic activities of the crystalline narcotics at 35°C are also presented in Table I (reference state, the supercooled liquid). These values were calculated using Eq. (2).

The aqueous solubilities and octanol/water partition coefficients (K_p) for the narcotics are summarized in Table II. Hexane solubilities of the narcotics at 35°C are also presented in Table II. Fentanyl and sufentanil were more soluble in hexane than morphine and its analogues. Nevertheless, it can be seen that these solubilities are low, allowing one to make the assumption that ϕ_1, the volume fraction of hexane in their saturated solutions, is unity (14). Using this surmise, the solubility parameters for all the solutes were calculated from Eq. (3). The experimental values for the mole fraction solubilities of narcotics in hexane and the melting points and heats of fusion were used in the calculations.

Morphine's solubility parameter calculated from molar attraction constants (18,19) was compared with its experimentally derived values. The theoretical calculation is illustrated in Table III. Solubility parameters of the other narcotics were calculated in a similar fashion. These values and the experimentally determined solubility parameters of all the narcotics are summarized in Table IV. The solubilities of morphine at 35°C in various organic solvents are presented in Table V, along with the molar volumes and solubility parameters for the solvents. The solubility parameters and molar volumes of the pure solvents at 25°C were taken from Hoy's tables (19).

DISCUSSION

Physicochemical Properties of the Narcotics. Table I summarizes the physicochemical properties of the six narcotics in the study. There are several interesting patterns to the data. First, the naturally occurring opioids, morphine, codeine, and hydromorphone, all have measured crystalline densities of 1.32; the synthetic narcotics, fentanyl, meperidine, and sufentanil, have calculated densities around 1.1. As might be expected, the more tightly molecularly configured opioid solids have higher melting points. There appears to be no particular pattern to the heats of fusion, however. Both the melting points and the crystalline densities reflect a greater ability of morphine and its close analogues to self-associate within the crystalline state. By several measures, these compounds are clearly more polar than the piperidine narcotics. Consequently the opioids have lower octanol/water partition coefficients (Table II) and higher cohesive energy densities in their supercooled liquid states (square of the solubility parameter; Table IV). Figure 3 illustrates an interesting relationship that exists between partitioning and the intrinsic cohesiveness of each of the compounds. A curvilinear relationship between water–octanol partition coefficients ($1/K_p$) and solute solubility parameters, δ_2, is observed but it can also be seen that cohesiveness grows monotonically with increasing polarity. The inverse partition coefficient was chosen for the x axis so that polarity increases from left to right, rather than the reverse, to make

Table II. Solubilities and Partition Coefficients of Six Narcotic Analgesics

Narcotic	Solubility		K_p
	Water (25°C)	Hexane (35°C)	(octanol/water)
Morphine	0.345	1.3×10^{-4}	0.70
Hydromorphone	1.931	6.2×10^{-3}	1.28
Codeine	10.69	2.87	2.95
Fentanyl	0.200	31.96	717.0
Sufentanil	0.076	18.84	2842.0
Meperidine	6.55	—	38.9

Table III. Estimation of Solubility Parameters of Morphine[a]

Functional group	$(E_2V_2)^{1/2}$ (cal$^{1/2}$ cm$^{3/2}$)	No. of groups	Total $(E_2V_2)^{1/2}$ group (cal$^{1/2}$ cm$^{3/2}$)
$-CH_3$	148	1	148
$-CH_2-$	132	3	396
$-CH-$	86	4	344
$-C-$	32	1	32
$>CH-$	121	2	242
Phenyl ring	735	1	735
$-OH$	226	2	452
$-O-$	115	1	115
$-N-$	61	1	61
6 membered	−23.4	2	−46.8
5 membered	21	1	21
Ortho	9.7	1	9.7

[a] $\Sigma(E_2V_2)^{1/2}$ = 2508.9 cal$^{1/2}$ cm$^{3/2}$/mole; V_2 = 216.2 cm^3/mol; δ_2 = 11.6 (cal/cm^3)$^{1/2}$. [a] Values are taken from Hoy's table (17).

this point. The low $1/K_p$ values (or high K_p values) for the 4-anilinopiperidine analogues and meperidine evidence the fact that these narcotics are the most lipophilic of the compounds studied. The plot shows that this corresponds to a low cohesiveness in the liquid state. A dependence of melting temperatures on cohesiveness is to be expected and is also observed. However, we ascribe no fundamental significance to the fact that the solubility parameters of the narcotics decrease systematically as their molecular weights increase.

Table I also contains the calculated solid-state activities of the compounds at 35°C. These are equivalent to the mole fraction solubilities of the respective ideal solutions of the compounds. It can be seen that, as the narcotics become more nonpolar, their activities increase monotonically. This is another reflection that hydrophobicity is associated with lessened cohesiveness in the solid state. Consequently, molecular escape from the crystal surface is easier for meperidine, fentanyl, and sufentanil than it is for the opioids and their ideal mole fraction solubilities are high.

According to regular solution theory, one would expect the solubilities of narcotic analgesics in apolar solvents to be in the order hexane > cyclohexane > carbon tetrachloride > toluene > benzene. This is as observed for morphine. The theory also indicates that solubilities of the anilinopiperidine analogues and meperidine, although low in hexane, are predicatively high enough in the other London solvents to allow appreciable solute self-interaction. In this circumstance, regular solution theory would be difficult to apply. Given that limited supplies of these compounds were available, no attempt was made to measure the solubilities of meperidine, fentanyl, and sufentanil in the other nonpolar solvents.

The aqueous solubility of codeine was high relative to that of morphine, even though codeine lacks morphine's free phenolic functional group, a group that promotes aqueous solubility through hydrogen bonding. Obviously, the lower melting point of codeine more than offsets its lessened ability to interact with water. In contrast, hydromorphone, which has a higher melting point and lower solubility parameter than morphine, both factors unfavorable to aqueous solubility, actually exhibits a higher aqueous solubility than morphine. Here it would appear that possible keto- and enol-tautomers of hydromorphone might lead to its greater association with water. The aqueous solubilities of fentanyl and sufentanil are far less than those of the more crystalline opioid analogues, a direct reflection of their greater hydrophobicities. However, the aqueous solubility of meperidine was quite high. In meperidine's case, the high aqueous solubility is the consequence of its exceptionally low melting point (35°C), as meperidine is a considerably hydrophobic solute based on the value of its octanol/water partition coefficient.

Table IV. Calculated and Experimentally Determined Solubility Parameters of Narcotic Analgesics

Narcotic	$(E_2V_2)^{1/2}$ (cal · cm^3)$^{1/2}$/mol	V_2 (cc/mol)	Solubility parameter, δ_2 (cal/cm^3)$^{1/2}$ Calc.[a]	Solubility parameter, δ_2 (cal/cm^3)$^{1/2}$ Expt. (hexane only)
Morphine	2509	216.2	11.6	12.9[b]
Hydromorphone	2546	216.2	11.8	11.5[b]
Codeine	2546	226.8	11.2	10.9
Fentanyl	2914	303.3	9.6	9.7
Sufentanil	3295	345.2	9.5	9.7
Meperidine	2139	221.8	9.6	—

[a] Calculated from Eq. (4).
[b] Decomposed to black residues upon melting.

Table V. Solubilities of Morphine at 35°C

Solvent	Molar volume of solvent (ml/mol)	δ_1 (cal/cm^3)$^{1/2}$	Equilibrium solubility		
			mg/ml	mol/liter	Mole fraction
Hexane	130	7.3	1.35×10^{-4}	4.73×10^{-7}	5.98×10^{-8}
Cyclohexane	108	8.2	4.41×10^{-3}	1.54×10^{-5}	1.57×10^{-6}
Carbon tetrachloride	97	8.6	1.23×10^{-2}	4.31×10^{-5}	4.02×10^{-6}
Toluene	106	8.9	2.60×10^{-2}	9.11×10^{-5}	9.36×10^{-6}
Benzene	89	9.1	8.67×10^{-2}	3.04×10^{-4}	2.62×10^{-5}
1,3-Butanediol	87	13.8	22.7	7.95×10^{-2}	6.83×10^{-3}
Propylene glycol	73	15.0	28.6	1.00×10^{-1}	7.06×10^{-3}
Water (pH 8.0)	18	23.0	3.25×10^{-1}	1.12×10^{-4}	1.98×10^{-5}
Alcohol (95%)	27	13.3	5.33	1.87×10^{-2}	4.86×10^{-4}
Polyethylene-glycol-400	—	—	11.34	3.97×10^{-2}	—

Regular Solution Analysis of Morphine's Solubilities. The regular solution solubility for a solid solute in equilibrium with its saturated solution is given by Eq. (3). The theoretical maximum solubility is the ideal solubility. This is so because, at the peak of the regular solution curve, the cohesive energy differential between solute and solvent, $\delta_1 - \delta_2$, is zero and

$$\ln a_2^s = \ln x_{2,\text{ideal}} = \frac{\Delta H_f}{RT}\left(\frac{T_f - T}{T_f}\right) \quad (4)$$

In effect, the activity coefficient is unity at the apex of the curve and it follows that $a_2^s = x_{2,\text{ideal}}$.

To show the extent to which morphine's solubility behavior might conform to regular solution behavior, solvents were selected that self-interact exclusively through London forces. Hexane, cyclohexane, carbon tetrachloride, benzene, and toluene are molecules of a high molecular symmetry that contain no hetero atoms capable of imparting a formal dipole. Such solvents are thus held in their condensed states strictly by dispersion forces and are incapable of hydrogen bonding or strong dipolar bonding with polar solutes. They are thus appropriate solvents to substantiate an earlier hypothesis associated with hydrocortisone's solubilities (14) that polar solutes essentially exhibit regular solution behavior in nonpolar solvents. The controlling solution phase interactions in these media are, of necessity, almost strictly London forces. To calculate the solubility parameter, it was assumed that the crystalline properties of morphine are unaffected by the solvents, that solutions are sufficiently dilute to make the volume fraction of each solvent, ϕ_1, unity, and that the effective molar volume of morphine in solution, taken to be 216.2 ml/mol, is solvent independent. Based on these premises, Eq. (3) can be rewritten for saturated solutions in London solvents at 35°C as

$$\ln x_2 = \ln a_2^s - 0.36\,(\delta_1 - \delta_2)^2 \quad (5)$$

The activity, a_2^s, and the solubility parameter for morphine were simultaneously determined by computer from the mole fraction solubilities of morphine in the collection of apolar solvents. The best-fitting set of a_2^s and δ_2 values for the multiple equations associated with the solubilities of morphine in the organic solvents was specifically determined. Solvent solubility parameters, δ_1, ranging from 7 (cal/cm^3)$^{1/2}$, a value slightly less than hexane's, to 23.5 (cal/cm^3)$^{1/2}$, the value for water, were evaluated within Eq. (5). Values of 13.2 (cal/cm^3)$^{1/2}$ for the solubility parameter of morphine, δ_2, and of 9.1×10^{-3} for the activity of solid morphine, a_2^s, were generated by the computer. The latter value for the activity of solid morphine exactly agreed with the value of a_2^s determined independently from fusion data.

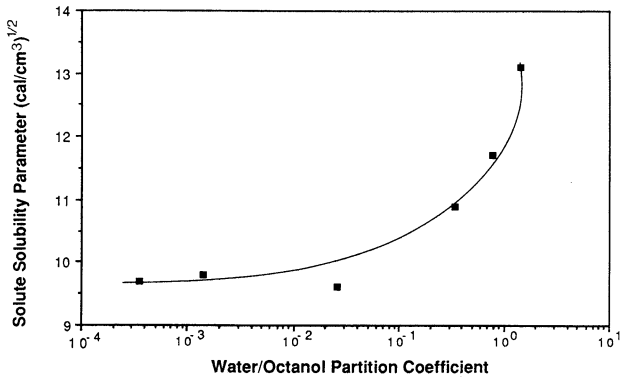

Fig. 3. Plot of the estimated solubility parameters against the experimental water/octanol partition coefficients of the compounds. The inverse partition coefficient was used so that polarity increases as the partition coefficient increases. One can see a monotonic relationship of the solubility parameter with the partition coefficient. This is because both these parameters essentially reflect the level of polarity of the compounds.

Neau and Flynn (20) have demonstrated that the solubility parameters of alkyl *p*-aminobenzoates can be determined accurately and with a deviation of no more than ±0.2 (cal/cm^3)$^{1/2}$ from their solubilities in either *n*-hexane or *n*-heptane and their heats of fusion and melting points. In the present work, as indicated in Table I, the solubility parameter of morphine calculated from its solubility in hexane and its heat of fusion was virtually identical to the best-fit solubility parameter obtained from the solubilities in all London solvents, in agreement with Neau and Flynn. However, when morphine's solubility parameter was calculated from molar attraction constants, a value of 11.6 (cal/cm^3)$^{1/2}$ was obtained, in poor agreement with the experimental values (Table IV). The failure of the group contribution method to predict morphine's solubility parameter indicates that the additive-constitutive method (18,19) becomes overextended when applied to such polar molecular species.

The solubilities of morphine in the various London and

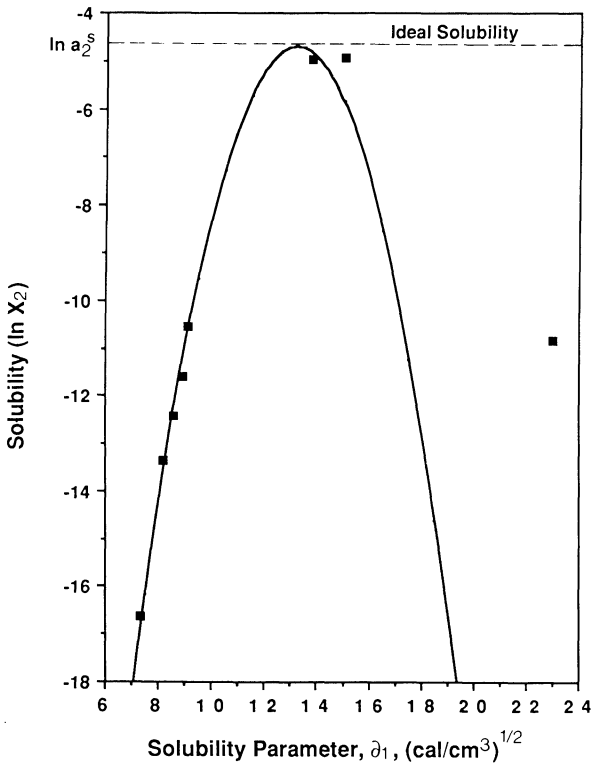

Fig. 4. The smooth line is the regular solution parabola for morphine based on its estimated solubility parameter of 13.2. It can be seen that the curve passes nicely through the solubility data points for hexane (first data point), cyclohexane (second data point), carbon tetrachloride (third data point), toluene (fourth data point), and benzene (fifth data point, from left to right, respectively). The data point for propylene glycol (sixth data point) also fits close to the curve but the solubility values for 1,3-butanediol and water, the seventh and eighth data points, respectively, do not fit to the theoretical line. The value for water is literally over 10 orders of magnitude too large. The later departures reflect the fact that strong bonding causes the solutions to be other than regular.

other solvents are summarized in Table V. Regular solution theory predicts a parabolic relationship between the mole fraction solubility of a given solute and the solubility parameters of "regular" (essentially nonpolar) solvents. The theoretical regular solution parabola shown in Fig. 4 was calculated for morphine about the midpoint of 13.2 (cal/cm^3)$^{1/2}$, where the solution is ideal, using Eq. (3). As anticipated, the solubilities of morphine in hexane, cyclohexane, carbon tetrachloride, benzene, and toluene closely fit to the theoretical curve. The mole fraction solubility of morphine in 1,3-butanediol is near the apex of the parabola and essentially at the place suggested by 1,3-butanediol's solubility parameter. In this case the closeness of the fit to theory is spurious, as one can see that morphine's solubilities in propylene glycol and water, two other polar solvents, are far off scale. In a general way the lack of agreement of regular solution projected solubilities and actual solubilities here illustrates that regular solution theory is inappropriate for solubility estimation in those solvents capable of hydrogen bonding or other strong orienting bonding with the solute. Such intermolecular interaction between solute and solvent violates two fundamental assumptions of regular solution theory, namely, that there is no excess entropy of mixing and that the total enthalpy of mixing is derived from differential cohesiveness.

The group contribution method of estimating solubility parameters worked well with all the other narcotics studied (Table IV). Agreement between the experimental values (hexane method) and those calculated from molar attraction constants was within 0.2 to 0.3 solubility parameter units, roughly the experimental uncertainty in these values. The solubility parameters for fentanyl, sufentanil, and meperidine are low, indicating weak intermolecular association in their respective liquified states. Because this makes them more soluble in all media excepting water and because they also have high oil/water partition coefficients, one can expect that the anilinopiperidine narcotics and meperidine would be more easily delivered through lipoidal membranes such as the skin.

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