

Solution Thermodynamics of Alkyl *p*-Aminobenzoates

PETER A. SCHWARTZ and ANTHONY N. PARUTA *

Abstract □ Equilibrium solubilities of the first four homologous alkyl *p*-aminobenzoate esters were determined in methanol, ethanol, and 1-propanol at 25, 33, and 40°; the esters and the alcohols comprise separate homologous series. The solution process of a solute may be considered to be the summation of two sequential steps, melting and mixing, and the magnitude of solubility depends upon temperature and the extent of interactions between solute and solvent molecules. Quantitative solute concentrations, obtained from spectrophotometric analysis, were converted to mole fractions. Statistical analysis of the logarithmic mole fraction solubilities of the aminobenzoates, which were linear with respect to both reciprocal absolute temperature and the logarithm of absolute temperature, generated enthalpies and entropies of solution, respectively. The heats of fusion and the melting points of these aminobenzoates were determined to calculate their ideal solubilities. Excess free energies and partial molal free energies of each solution were calculated from the activity coefficients of the solutes; the thermodynamic elements for these systems are discussed.

Keyphrases □ *p*-Aminobenzoates—equilibrium solubilities of four alkyl esters in alcohols, solution thermodynamics □ Thermodynamics, solution—four alkyl *p*-aminobenzoate esters, equilibrium solubilities in alcohols

Solubility results principally from interactions between solute and solvent molecules (1). The extent of these interactions, *i.e.*, the magnitude of solubility, depends partially upon the polarity and the hydrogen bonding characteristics of the solution components with respect to each other and to themselves; it depends also on the temperature of the system.

Solutes studied included four normal alkyl *p*-aminobenzoate esters (methyl, ethyl, propyl, and butyl), chosen because these esters comprise a series differing in structure from each other by one methylene (CH₂) group. The solvents were methanol, ethanol, and 1-propanol; this homologous series was chosen because it would provide a range of solvent polarity. The equilibrium solubilities of each solute in these solvents were determined at several temperatures to provide enthalpies and entropies of solution with respect to fundamental thermodynamic relationships.

BACKGROUND

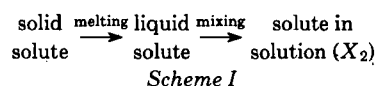
The solubility of nonelectrolytes has often been interpreted on the basis of polarity differences between solutes and solvents (2-9). An incremental increase in the length of a hydrocarbon side chain effects a polarity difference between consecutive members of a homologous series. These structural differences result in altered physical properties such as boiling-point elevation, increased partition coefficient (lipid solubility), decreased aqueous solubility, and increased surface tension.

Since many properties of a homologous series change according to a geometric progression (10), the plot of the logarithm of these properties against the carbon number of the nonpolar hydrocarbon chain is linear. Solubility studies (11) on the first four homologs of the alkyl *p*-aminobenzoate esters demonstrated such linearity for semilogarithmic plots of solubility in silicone oil and hexane, two nonpolar solvents, as well as of their partition coefficients with water against alkyl carbon numbers. The solubility increased with alkyl carbon number equal to four and decreased thereafter. The heats of fusion, melting points, and solubility parameters were

used to generate expected values for molar solubility, all of which agreed well with the experimental values for hexane. However, poor agreement was found with experimental data for water, a polar, hydrogen-bonding solvent.

The similar series of homologous esters, alkyl *p*-hydroxybenzoates, was studied (3, 4) in several alcohols, *i.e.*, polar, hydrogen-bonding solvents. The Hildebrand and Scott (5) solubility parameter theory was used to predict the points of maximum solubility in each solvent. However, the magnitude of solubility depends upon specific solute-solvent interactions (6) and is not always predictable.

Solubility is a colligative property and is related to the temperature-dependent thermodynamic equation for freezing-point depression (12). At any temperature, the concentration of pure solid solute is constant and is in equilibrium with the liquid state. The solution process is considered to occur in two steps as shown in Scheme I:



where X_2 is the solute mole fraction. The enthalpy change for melting is the heat of fusion, ΔH^F , and the enthalpy for the second step is the heat of mixing, ΔH^M (12). For ideal solutions, the enthalpy of the second step is zero, since, by definition, no heat is evolved or absorbed (13).

The equation for the ideal mole fraction solubility of a solute, X_2^i , at a temperature below its melting point, T_m , is given in terms of the natural logarithm of the solubility, *i.e.*:

$$\ln X_2^i = \frac{-\Delta H^F}{R} \left(\frac{1}{T} - \frac{1}{T_m} \right) \quad (\text{Eq. 1})$$

when it is assumed that the heat of fusion is constant with respect to temperature, and the gas constant, R , equals 1.987 cal/degree. The solubility at any given temperature should be the same for all solvents with which it forms an ideal solution. From Eq. 1, it is apparent that a solute with a low heat of fusion and a low melting point will have a high ideal solubility, that the solubility of a solute increases as the melting point decreases, and that solubility appears to be independent of the nature of the solvent.

Hildebrand and Scott (14) equated the activity of a solute, a_2 , with X_2^i for ideal solutions. The activity is a relative quantity and represents the deviation from a designated reference state. The most useful standard state for solubility is one in which the pure liquid solute, extrapolated below the melting point as a supercooled liquid (15), has a value of unity when its mole fraction is unity. The ratio of the activity to the mole fraction is the activity coefficient, γ , *i.e.*:

$$\gamma = a/x \quad (\text{Eq. 2})$$

Because the activity varies with composition, the activity coefficients, which remain relatively constant, are more suitable parameters for expressing deviations from ideal solutions.

Equation 1 is valid only when the heat of fusion is constant with respect to temperature. From the heat of fusion at the melting point, ΔH_m^F , and the change in molal heat capacity between liquid and solid solute, ΔC_p , also extrapolated below the melting point, the heat of fusion at any temperature can be derived (16):

$$\Delta H^F = \Delta H_m^F - \Delta C_p(T_m - T) \quad (\text{Eq. 3})$$

Substitution of this heat expression in Eq. 1 gives the following for ideal mole fraction solubility:

$$\ln X_2^i = [\Delta H_m^F/R(T_m - T/T_m)] + [\Delta C_p/R(T_m - T/T)] [\Delta C_p/R(\ln T_m/T)] \quad (\text{Eq. 4})$$

For the ideal solution, the plot of the natural logarithm of the mole fraction solubility, $\ln X_2$, versus the reciprocal of the abso-

Table I—Structure and Thermal Properties of Alkyl *p*-Aminobenzoate Esters

Ester ^a	Melting Point		Differential Scanning Calorimetry	Heats of Fusion, cal/mole	Entropy of Fusion, cal/mole deg
	Literature	Capillary Tube			
Methyl	112 ^b , 114 ^c	110.5–111 ^o	112.5 ^o	5180	13.5
Ethyl	89 ^d , 90 ^c , 92 ^b	88–90 ^o	89.7 ^o	5030	13.9
<i>n</i> -Propyl	73 ^d , 73–74 ^b , 75 ^c	73–74 ^o	73.0 ^o	5000	14.5
<i>n</i> -Butyl	57 ^d , 58 ^{b,c}	56–58 ^o	55.8 ^o	5290	16.1

^aC. O. Wilson, O. Gisvold, and R. F. Doerge, "Textbook of Organic, Medicinal and Pharmaceutical Chemistry," 5th ed., Lippincott, Philadelphia, Pa., 1966, p. 602. ^b"Dictionary of Organic Compounds," 4th rev., Oxford University Press, New York, N.Y., 1965. ^c"Handbook of Chemistry and Physics," 51st ed., Chemical Rubber Co., Cleveland, Ohio, 1970. ^dR. Adams, E. K. Rideal, W. B. Burnett, R. L. Jenkins, and E. E. Dreger, *J. Amer. Chem. Soc.*, 48, 1758 (1926).

lute temperature, $1/T$, has a slope proportional to the heat of fusion at the melting point and an intercept proportional to the entropy of fusion, *i.e.*, $\Delta H_m^F/T_m$. Data from nonideal solutions plotted in this manner have slopes and intercepts proportional to the differential heats and entropy of solution, respectively (12).

Hildebrand and Scott (17) showed that the heat capacity is not negligible and can be approximated by the entropy of fusion. Substitution of ΔS_m^F for ΔC_P in Eq. 4 cancels out the first two terms on the right side and leaves the ideal mole fraction solubility equation as:

$$\ln X_2^i = (\Delta S_m^F/R) (\ln T/T_m) \quad (\text{Eq. 5})$$

Accordingly, a plot of $\ln X_2$ versus the natural logarithm of the absolute temperature, $\ln T$, is linear with a slope proportional to the entropy of fusion. For nonideal data, the entropy of solution can be obtained from the slope of this line (18).

Since orienting and chemical effects, such as hydrogen bonding, solvation, and association, are absent in regular solutions (19) and molecules are randomly distributed as in ideal solutions, the two types of solutions have equal entropies. The deviation from ideality for a regular solution represents the magnitude of the enthalpy of mixing, since no heat is evolved in the formation of an ideal solution.

The free energy, F , represents the maximum of work that can be obtained from a process and applied to useful purposes (20). At equilibrium, the total free energy is at a minimum (21) with no separation of enthalpic and entropic components (22). Nonideal solutions have an excess free energy of mixing, which can be regarded as "the excess of the nonideal free energy of mixing over the ideal free energy of mixing" (23); *i.e.*, in terms of free energy:

$$\bar{F}^E = RT \ln \gamma_2 \quad (\text{Eq. 6})$$

A partial molal quantity is defined as "the rate of increase in the content of the system in that particular quantity while the component is being added to the system" (24). However, Hildebrand and Scott (25) warned that the physical property of partial molal quantities cannot be attributed to molecules of one species alone and that it is a property of the solution as a whole—not of the particular component.

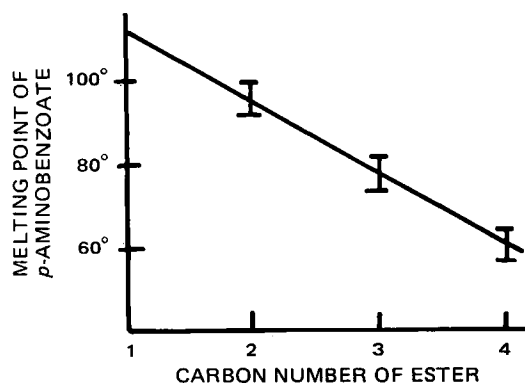


Figure 1—Plot of the range of melting points for the alkyl *p*-aminobenzoate esters as a function of the alkyl carbon number of the ester.

The $\log \gamma_2$ term for the excess free energy of regular solutions is due to the intermolecular forces of the solute and solvent that are not present in ideal solutions. These forces can be characterized by considering the solubility parameters of the solute and solvent, the volume fraction of the solvent, ϕ_1 , and the molar volume of the solute, V_2 , so that the deviation from the ideal is:

$$\ln \gamma_2 = (\delta_1 - \delta_2)^2 V_2 \phi_1^2 / RT \quad (\text{Eq. 7})$$

Since the solubility parameter is a measure of polarity, the greater the differences in polarity between solute and solvent, the greater is the deviational term of the activity coefficient.

Entropy is related to structure (12) and indicates the probability of a combination between solute and solvent. An increased entropy of solution denotes a more probable state for such a system than do the separate pure solute and solvent. As the degree of randomness and disorder for a system increases, the entropy increases, but the free energy decreases. For example, at increased temperatures there is more randomness, *i.e.*, increased entropy, while the amount of useful work or free energy is diminished. For alcohols in solution with nonpolar components, there is a decreased entropy due to specific interactions, *i.e.*, ordering due to hydrogen bonding, and large positive deviations from ideality are expected (26).

Highly nonideal solubility with such large entropy terms cannot be calculated from Eqs. 1–7 and are best calculated in terms of free

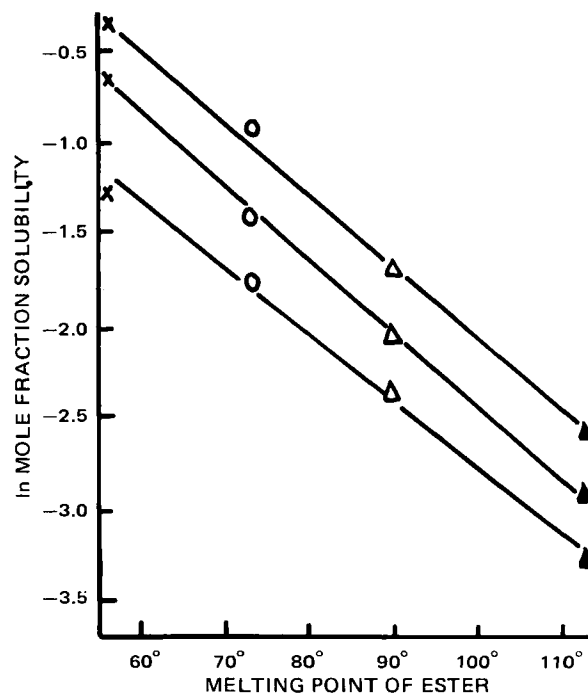


Figure 2—Plot of the \ln mole fraction solubility in methanol versus the melting point of the aminobenzoate ester at the three temperatures noted. Key: \blacktriangle , methyl *p*-aminobenzoate; \triangle , ethyl *p*-aminobenzoate; \circ , propyl *p*-aminobenzoate; and \times , butyl *p*-aminobenzoate.

Table II—Average Mole Fraction Solubilities of Alkyl *p*-Aminobenzoate Esters in Each Solvent at 25, 33, and 40°

Ester	Temperature	Solvent			Ideal A ^a	Ideal B ^b
		Methanol	Ethanol	1-Propanol		
Methyl	25°	0.0367	0.0419	0.0306	0.1369	0.1752
	33°	0.0524	0.0545	0.0428	0.1722	0.2096
	40°	0.0730	0.0740	0.0586	0.2084	0.2442
Ethyl	25°	0.0945	0.0895	0.0836	0.2195	0.2539
	33°	0.1256	0.1276	0.0953	0.2741	0.3054
	40°	0.1811	0.1843	0.1455	0.3299	0.3576
<i>n</i> -Propyl	25°	0.1709	0.1634	0.1826	0.3100	0.3376
	33°	0.2402	0.2177	0.2485	0.3866	0.4093
	40°	0.4016	0.4018	0.3680	0.4648	0.4825
<i>n</i> -Butyl	25°	0.2779	0.2212	0.2544	0.4319	0.4507
	33°	0.5247	0.4319	0.3705	0.5457	0.5586
	40°	0.7030	0.6220	0.6205	0.6632	0.6709

^a Calculated from Eq. 1. ^b Calculated from Eq. 5.

Table III—Enthalpies and Entropies of Alkyl *p*-Aminobenzoates in Alcohols

Ester	Solvent	Enthalpy, cal/mole			Entropy, cal/mole deg				
		ΔH_s	ΔH_m^F	ΔH^M ^a	ΔS_s^b	ΔS_m^F	ΔS^M ^c	S_s^d	S_s^d/S_s^b
Methyl	Methanol	8,470	5180	3280	21.9	13.5	8.4	27.7	1.27
	Ethanol	7,000	5180	1810	17.2	13.5	3.7	22.9	1.34
	1-Propanol	7,990	5180	2800	19.9	13.5	6.4	26.2	1.34
Ethyl	Methanol	7,990	5030	2960	22.1	13.9	8.2	26.2	1.19
	Ethanol	8,900	5030	3870	25.1	13.9	11.2	29.2	1.16
	1-Propanol	6,710	5030	1680	17.5	13.9	3.6	22.1	1.26
<i>n</i> -Propyl	Methanol	10,460	5000	5460	31.5	14.5	17.0	34.3	1.09
	Ethanol	10,970	5000	5970	33.1	14.5	18.6	36.0	1.09
	1-Propanol	8,610	5000	3610	25.5	14.5	11.0	28.2	1.15
<i>n</i> -Butyl	Methanol	11,570	5290	6280	36.3	16.1	20.2	37.8	1.04
	Ethanol	12,850	5290	7560	40.2	16.1	24.1	42.1	1.01
	1-Propanol	10,940	5290	5650	33.9	16.1	17.8	35.9	1.06

^a $H^M = H_s - H_m^F$. ^b R times intercept of $\ln X_2$ versus $1/T$. ^c $S^M = S_s - S_m^F$. ^d R times intercept of $\ln X_2$ versus $\ln T$.

energies. This approach avoids serious errors of oversimplification and does not separate enthalpic and entropic effects (22).

EXPERIMENTAL¹

Chemicals—The following chemicals were used: methyl *p*-aminobenzoate²; ethyl *p*-aminobenzoate³; propyl *p*-aminobenzoate⁴; butyl *p*-aminobenzoate⁵; methanol, anhydrous, spectrophotometric grade solvent⁶; absolute alcohol USP, reagent quality⁷; 1-propanol⁸; ethanol⁹ 95%, USP grade; stearic acid¹⁰, 99.8% pure; and water, distilled and deionized.

Calorimeter Calibration—The calorimeter cell of a differential scanning calorimeter, used to determine heats of fusion, was calibrated with stearic acid, 99.8% pure. Three samples of the acid, in amounts empirically chosen to produce endothermic fusion peaks of maximum area, were accurately weighed (± 0.002 mg) on an electrobalance into tared aluminum pans. The pans were subsequently sealed to prevent volatilization.

The samples were heated in a nitrogen atmosphere in the calo-

rimeter cell over a temperature range of 60–75° at a heating rate of 5°/min and at a chart recording speed of 304.8 cm (120 in.)/min. Each sample was melted twice, and calibration constants were calculated from only those curves having essentially straight baselines for both pre- and postfusion.

The value of H_m^F , the heat absorbed by a sample during fusion, is proportional to the area under the curve defined by the endothermic peak and by a line drawn between the point of departure from the baseline (onset of fusion) to the point of baseline return after fusion (27). The thermograms generated by the samples were reproduced on paper of a uniform thickness, and each area was carefully cut out and weighed (28). The stearic acid calibration coefficient, 0.0641969 (0.0642), is the average of the determinations from each sample calculated according to the following equation:

$$K = \frac{H_{sa}^F M}{Wr} \quad (\text{Eq. 8})$$

where:

- K = calibration coefficient, millicalories per milligram of paper
- H_{sa}^F = heat of fusion for stearic acid, -47.54 mcal/mg
- M = weight of stearic acid sample, milligrams
- W = weight of stearic acid sample, milligrams of paper
- r = power coefficient of the instrument

Because the instrument does not provide readings in Celsius degrees, the fusion endotherms of stearic acid were used to determine a calibration constant for temperature correction. The melting point for a solid is best represented by the extrapolation to the prefusion baseline of its endotherm (28). The known melting point of 68.82° was subtracted from the average value of the instrument readings for the onset of fusion for stearic acid to produce a correction constant of 378.4°.

Melting-Point Determinations—The average of the two calorimeter melting points for each aminobenzoate ester was converted to Celsius melting points by subtracting the temperature correction constant. Since there was a close agreement in melting points

¹ The following equipment was used: Thomas-Hoover capillary melting-point apparatus, No. 6404, A. H. Thomas Co., Philadelphia, Pa.; Cary model 16 spectrophotometer, Cary Instruments, Monrovia, Calif.; Precision-Porta-Temp unit, Precision Scientific Co., Chicago, Ill.; Mettler balance, type H6T, Mettler Instrument Corp., Princeton, N.J.; rotating sample holder with small motor, Department of Pharmacy, University of Rhode Island; Pyrex Corning glass wool, Corning Glass Works, Corning, N.Y.; Cahn gram electrobalance, model 18, Cahn Instruments, Paramount, Calif.; and Perkin-Elmer differential scanning calorimeter, DSC-18, Perkin-Elmer Corp., Instrument Division, Norwalk, Conn.

² Lot 3403, Eastman Chemical Co., Rochester, N.Y.

³ Lot EX 305, Matheson, Coleman and Bell, Norwood, Ohio.

⁴ Lot 3, City Chemical Co., supplied through the courtesy of Astra Pharmaceutical Products, Worcester, Mass.

⁵ Lot 7, Matheson, Coleman and Bell, Norwood, Ohio.

⁶ Lot VNM, Mallinckrodt Chemical Works, St. Louis, Mo.

⁷ U.S. Industrial Chemicals Co., New York, N.Y.

⁸ Analyzed reagent, Lot 39420, J.T. Baker Chemical Co., Phillipsburg, N.J.

⁹ Lot TM 288671, Industrial Chemicals Co., Littleton, Mass.

¹⁰ Applied Sciences, State College, Pa.

Table IV—Ideal, Actual, and Excess Free Energy of Alkyl *p*-Aminobenzoates in Alcohols

Ester	Solvent	Free Energy, cal/mole		
		ΔFA	ΔFI	ΔFE
Methyl	Methanol	1790	1063	+727
	Ethanol	1754	1063	+691
	1-Propanol	1920	1063	+863
Ethyl	Methanol	1250	790	+460
	Ethanol	1244	790	+454
	1-Propanol	1372	790	+582
<i>n</i> -Propyl	Methanol	852	577	+275
	Ethanol	874	577	+297
	1-Propanol	832	577	+255
<i>n</i> -Butyl	Methanol	498	379	+119
	Ethanol	587	379	+210
	1-Propanol	600	379	+221

between experimental and literature values for the esters, these compounds were used directly and without further purification. The purity of the solutes was accepted from the label claiming greater than 99.8% in all cases, since the melting point of these materials did not differ from ethanolic recrystallized samples of these solutes.

Heats of Fusion—Samples of the four aminobenzoate esters were carefully weighed into aluminum volatile sample pans, and thermograms of a 10° pre-fusion baseline and a fusion endotherm were recorded. Because direct remelts of the same sample indicated an apparent formation of liquid crystals after fusion, each fused sample was cooled to 0° for 30 min prior to remelting. Recordings were analyzed for melting points and endothermic areas in the same manner as for stearic acid.

Solubility Determinations—The solubility of the four aminobenzoate esters in several alcohols and water was determined by the following procedure. Each solute, in an amount in excess of its solubility, was placed in screw-capped glass vials¹¹ with each solvent. The vials were sealed with adhesive tape. Vials were rotated at 28 rpm in a large constant-temperature ($\pm 0.2^\circ$) water bath maintained successively at 25, 33, and 40°.

After an equilibrium solubility was attained by at least 24 hr of continuous rotation¹², each of six¹³ sample vials was removed in succession for assay. The exterior of the vial was quickly dried, the sealing tape was removed, and the cap was carefully unscrewed to prevent water contamination. A filtered aliquot of the saturated solution was pipetted into tared containers, weighed, and appropriately diluted for spectrophotometric assay with 95% ethanol to give a final concentration of solute in the range of 1–5 $\mu\text{g/ml}$. All pipets were prewarmed to prevent thermal precipitation, and each had a pledget of fiber glass wrapped around its tip to act as a filter. The variation in solubility values was about 5% for the methyl derivatives and fell to about 3% for the butyl derivative.

Spectrophotometric Determination—The spectrophotometer was calibrated for each aminobenzoate ester at its wavelength of maximum absorbance, at concentrations up to 15 $\mu\text{g/ml}$ in 95% ethanol, in matched silica cells. A least-squares method was used to determine the statistical significance ($\alpha = 0.0001$) of the linear relationship between absorbance and concentration, *i.e.*, the Beer's law equation.

The molar absorptivities for the esters were very close in value, varying from 2.05 for the methyl, ethyl, and propyl esters to 2.07 for the butyl ester.

RESULTS AND DISCUSSION

The chemical structures of the alkyl *p*-aminobenzoate esters and their thermal properties are shown in Table I. Experimentally determined differential scanning calorimetric and capillary tube melting points in Table I agree well with literature values shown there and are the same as those recently reported (11). The heats

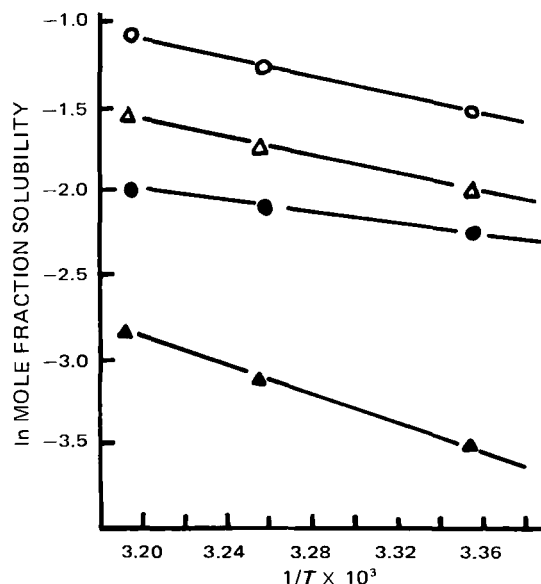


Figure 3—Plot of the \ln mole fraction solubility in 1-propanol versus the reciprocal temperature, $^\circ\text{K}$. The ideal curves are from heat of fusion data, and the actual curves are from experimental data. Key: O, ethyl *p*-aminobenzoate, ideal; ●, ethyl *p*-aminobenzoate, actual; Δ, methyl *p*-aminobenzoate, ideal; and ▲, methyl *p*-aminobenzoate, actual.

of fusion show the same trend as do the Yalkowsky *et al.* (11) data; *i.e.*, enthalpies for the methyl and butyl esters are higher than for the ethyl and propyl esters.

The average mole fraction solubilities of these esters in methanol, ethanol, and 1-propanol and the ideal solubilities predicted by both Eqs. 3 and 7 at 25, 33, and 40° are summarized in Table II and show an expected direct relationship between the magnitude of solubility and the temperature for each solvent.

In Fig. 1, the melting-point range for the alkyl *p*-aminobenzoates is plotted *versus* the alkyl carbon number. This relationship is approximately linear and reflects a regularity on the structural differences between homologs.

Figure 2 shows a plot of the \log_e mole fraction solubility in methanol at the three temperatures studied *versus* the melting points of the solutes. The decrease in solubility at any temperature is linear with increasing melting point for carbon numbers less than or equal to four. The parallelism observed for the three temperatures indicates similar solute-solvent interactions and a constant dissolution mechanism for these solutes.

In Fig. 3, the $\ln X_2$ in 1-propanol for each solute is plotted *versus* the $\ln T$ at the temperatures studied. The heats of fusion, heats of solution, and heats of mixing were obtained from the slopes of the lines generated from observed and calculated data as shown in Fig. 3. The entropy of fusion, entropy of solution, and entropy of mixing were obtained as intercepts of Figs. 3 and 4.

The entropies of solution in Table III were determined from a least-squares analysis of the mole fraction data in Table II. The value of S_s^b was obtained from the intercepts of $\ln X_2$ *versus* the reciprocal absolute temperature shown graphically in Fig. 3 for 1-propanol solutions. The Hildebrand entropy of solution, S_s^d , was obtained from the slopes of $\ln X_2$ *versus* the natural logarithm of the absolute temperature, shown graphically in Fig. 4 for 1-propanol solutions. These graphs are similar to the graphs of the other alcohol solutions and were chosen as representative examples of the solute behavior.

Hildebrand's entropy of solution for the solid solutes, S_s^d , which includes the heat of fusion of the solute, has values several entropy units (calories per mole degree) higher than the corresponding values of entropy of solutions, S_s^b (Table III). However, Hildebrand applied a correction factor to his experimental data from solutions with mole fractions greater than 0.1, *i.e.*, good solvents (29). The "Henry's law" factor (the change in solute activity per change in solute mole fraction) could not be calculated for the aminobenzoates because the solutions were not considered dilute systems. Thus, the Hildebrand entropy of solution values are uncor-

¹¹ Lined with Teflon.

¹² Previous studies showed that this time was sufficient to obtain saturated solutions at 25°.

¹³ Only three samples of propyl *p*-aminobenzoate were used because of its scarcity.

Table V—Activity Coefficients for Alkyl *p*-Aminobenzoates Based upon the Ideal Solubilities from Eq. 3

Ester	Temperature	Solvent		
		Methanol	Ethanol	1-Propanol
Methyl	25°	3.7	3.3	4.5
	33°	3.3	3.2	4.0
	40°	2.8	2.8	3.6
Ethyl	25°	2.3	2.5	2.6
	33°	2.2	2.2	2.9
	40°	1.8	1.8	2.3
<i>n</i> -Propyl	25°	1.8	1.9	1.7
	33°	1.6	1.8	1.6
	40°	1.2	1.2	1.3
<i>n</i> -Butyl	25°	1.6	2.0	1.7
	33°	1.0	1.3	1.5
	40°	1.0	1.1	1.1

rected, and actual values of the entropy of solution, S_s^d , would be less than those given in Table III.

The diminishing difference between the two values for entropy of solution as the alkyl chain length increases is shown by the decrease in the ratio S_s^d/S_s^b in Table III. Since the two values of the ideal solubilities from Eqs. 1 and 5 in Table II are reasonably close, the ideal values from Eq. 1 were chosen as a basis for comparison in the activity coefficient determinations. The choice of the entropy of solution obtained from plots of Eq. 1, $\ln X_2$ versus $1/T$, was due to its conventional and generally accepted use.

The maximum entropy of solution within a group of solvents denotes the best solvent for that solute, and comparison between groups illustrates the effect of the alcohols upon the solubility of each ester. As the solute alkyl chain length increases, the molecules become less polar and the entropy of solution increases. Although the methyl ester, the most polar of these solutes (11), has a maximum entropy in methanol, the most polar alcohol, all other esters have their entropic maxima in ethanol, a less polar solvent.

The heats of solution in Table III can be compared with the heats of fusion in Table I to show that a positive heat of mixing, ΔH_{mix} , was generated for all solutions in the alcohols and that the magnitudes of these heats increased as the alkyl chain length increased. This excess heat above ideal also showed the most increase in methanol for the methyl ester and in ethanol for all other esters, *i.e.*, the same result observed for the entropy of solution data.

Since values for the entropy and heat of solution are determined

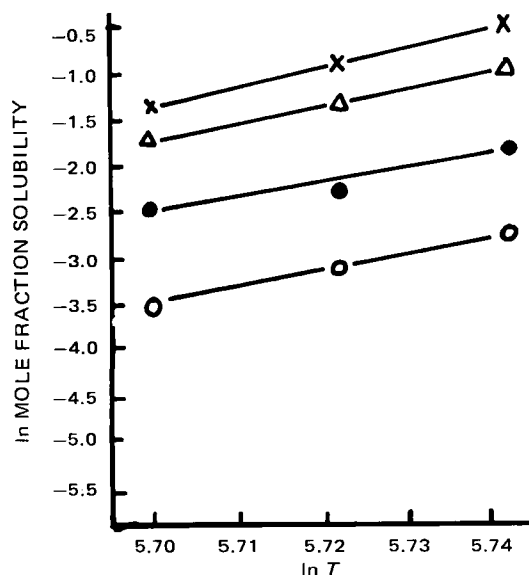


Figure 4—Plot of the \ln mole fraction solubility in 1-propanol for each solute as a function of the \ln temperature, °K. Key: X, butyl *p*-aminobenzoate; Δ, propyl *p*-aminobenzoate; ●, ethyl *p*-aminobenzoate; and O, methyl *p*-aminobenzoate.

Table VI—Partial Molal Excess Free Energies Calculated from the Activity Coefficients of Alkyl *p*-Aminobenzoates

Ester	Temperature	Solvent		
		Methanol	Ethanol	1-Propanol
Methyl	25°	-34	-30	-40
	33°	-40	-38	-48
	40°	-44	-43	-55
Ethyl	25°	-33	-36	-40
	33°	-39	-38	-60
	40°	-35	-33	-55
<i>n</i> -Propyl	25°	-30	-34	-25
	33°	-29	-39	-26
	40°	-5	-5	-12
<i>n</i> -Butyl	25°	-30	-58	-41
	33°	-1	-16	-38
	40°	-2	-2	-3

as averages over a narrow temperature range, they do not reflect the temperature change upon the solubility parameters or the dielectric constant of the solutes. This objection limits the usefulness of separate entropic or enthalpic interpretations of solubility (22).

From the values presented in Table III, various free energy values can be calculated. Table IV presents the ideal, actual, and excess free energies for each solute in each solvent. As expected from the solubility data, the excess free energies decrease with increasing size. The closer the ideal and actual free energies, the smaller are the excess free energy terms and the actual mole fraction solubility approaches the ideal mole fraction solubility.

The activity coefficients in Table V are based upon the ideal mole fraction solubilities of Eq. 1 and were used to calculate the partial molal excess free energy of the solutes (Table VI). Since the activity coefficients are high for the methyl ester (2.82–4.47) and decrease progressively to near unity for the butyl ester (1.96–0.95), the excess free energies also decrease proportionally. Although free energies near zero were obtained for several butyl solutions at high temperatures, the high entropy of solution values indicate increased molecular disorder and prevent these from being classed as regular solutions.

SUMMARY

The magnitudes of the solubility of these esters dissolved in the normal alcohols increased with increased temperatures, indicative of an endothermic dissolution process. The conventional relationship between the natural log mole fraction data and the reciprocal temperature was linear for all solutions and produced values for the enthalpy and entropy of solution. The Hildebrand entropy of solution values were obtained from the linear relationship between the natural log mole fraction solubility and the log of the absolute temperature. The Hildebrand entropy values include the heat capacity of the solute.

Thermodynamic data for the aminobenzoates dissolved in the normal alcohols indicate increased entropy of solution as the alkyl chain length increases. There was no significant difference between the conventional entropy of solution values and the Hildebrand entropy of solution values.

The butyl ester was highly soluble in the alcohols. From the heat of fusion and the melting-point data determined for these solutes, their ideal mole fraction solubilities were calculated. Activity coefficients of the solutes compare ideal to actual solubilities and were used to calculate partial molal excess free energies. These free energies were near zero in some cases, but the high entropy of solution values for these solutions do not indicate regular solutions.

REFERENCES

- (1) T. Higuchi, in "Pharmaceutical Compounding and Dispensing," R. Layman, Ed., Lippincott, Philadelphia, Pa., 1949, chap. 7.
- (2) M. Sax and J. Pletcher, *Science*, **166**, 1546(1969).
- (3) F. A. Restaino and A. N. Martin, *J. Pharm. Sci.*, **53**, 636(1964).
- (4) A. N. Paruta, *ibid.*, **58**, 216(1969).

- (5) J. H. Hildebrand and R. L. Scott, "The Solubility of Non-electrolytes," 3rd ed., Reinhold, New York, N.Y., 1949.
- (6) A. N. Paruta, B. J. Sciarrone, and N. G. Lordi, *J. Pharm. Sci.*, **53**, 1349(1964).
- (7) M. J. Chortkoff and A. N. Martin, *J. Amer. Pharm. Ass., Sci. Ed.*, **49**, 444(1960).
- (8) W. G. Gorman and G. D. Hall, *J. Pharm. Sci.*, **53**, 1017(1964).
- (9) J. H. Hildebrand, J. M. Prausnitz, and R. L. Scott, "Regular and Related Solutions," Van Nostrand Reinhold, New York, N.Y., 1970.
- (10) J. Ferguson, *J. Proc. Roy. Soc. (Ser. B)*, **127**, 397(1939).
- (11) S. H. Yalkowsky, G. L. Flynn, and T. G. Slunick, *J. Pharm. Sci.*, **61**, 853(1972).
- (12) B. H. Mahan, "Elementary Chemical Thermodynamics," W. A. Benjamin, New York, N.Y., 1963, chap. 4.
- (13) J. H. Hildebrand and R. L. Scott, "The Solubility of Non-electrolytes," 3rd ed., Reinhold, New York, N.Y., 1949, p. 47.
- (14) J. H. Hildebrand and R. L. Scott, "Regular Solutions," Prentice Hall, Englewood Cliffs, N.J., 1962, p. 132.
- (15) *Ibid.*, p. 13.
- (16) *Ibid.*, p. 270.
- (17) *Ibid.*, p. 20.
- (18) J. H. Hildebrand, J. M. Prausnitz, and R. L. Scott, "Regular and Related Solutions," Van Nostrand Reinhold, New York, N.Y., 1970, p. 144.
- (19) J. H. Hildebrand, *J. Amer. Chem. Soc.*, **51**, 66(1929).
- (20) G. N. Lewis and M. Randall, "Thermodynamics," McGraw-Hill, New York, N.Y., 1923, p. 158.
- (21) J. H. Hildebrand and R. L. Scott, "The Solubility of Non-electrolytes," 3rd ed., Reinhold, New York, N.Y., 1949, p. 44.
- (22) *Ibid.*, p. 136.
- (23) J. H. Hildebrand, J. M. Prausnitz, and R. L. Scott, "Regular and Related Solutions," Van Nostrand Reinhold, New York, N.Y., 1970, p. 17.
- (24) J. H. Hildebrand and R. L. Scott, "The Solubility of Non-electrolytes," 3rd ed., Reinhold, New York, N.Y., 1949, p. 5.
- (25) *Ibid.*, p. 14.
- (26) *Ibid.*, p. 218.
- (27) J. K. Guillery, *J. Pharm. Sci.*, **56**, 72(1967).
- (28) R. Reubke and J. A. Mollica, *J. Pharm. Sci.*, **56**, 822(1967).
- (29) A. E. Lewis, "Biostatistics," Reinhold, New York, N.Y., 1966, p. 76.

ACKNOWLEDGMENTS AND ADDRESSES

Received March 20, 1974, from the *College of Pharmacy, University of Rhode Island, Kingston, RI 02881*

Accepted for publication May 9, 1975.

Abstracted in part from a dissertation submitted by P. A. Schwartz to the Graduate School, University of Rhode Island, in partial fulfillment of the Master of Science degree requirements.

* To whom inquiries should be directed.

Simultaneous Determination of Pilocarpine and Isopilocarpine in Pharmaceutical Preparations by Liquid Chromatography

T. URBÁNYI*, A. PIEDMONT, E. WILLIS, and G. MANNING

Abstract □ A liquid chromatographic assay method is described for the simultaneous determination of pilocarpine and isopilocarpine in pharmaceutical preparations. The method involves separation of the isomers on a high-resolution ion-exchange column, followed by detection of pilocarpine and isopilocarpine by UV absorption in the 217-nm region. The specificity of the method is such that pilocarpine and isopilocarpine can be assayed separately in the presence of one another and in the presence of the excipients commonly found in commercial pilocarpine solutions. Its sensitivity for isopilocarpine is at least 25 ppm (independent of the concentration of pilocarpine). In contrast, USP methods lack both specificity and sensitivity. It is concluded that this method is applicable to the routine analysis of commercial pilocarpine preparations and is an improvement over the official methods.

Keyphrases □ Pilocarpine—chromatographic separation and UV analysis, pharmaceutical preparations, in presence of isopilocarpine, compared to USP methods □ Isopilocarpine—chromatographic separation and UV analysis, pharmaceutical preparations, in presence of pilocarpine, compared to USP methods □ Chromatography—separation of pilocarpine and isopilocarpine in pharmaceutical preparations □ UV analysis—pilocarpine and isopilocarpine in pharmaceutical preparations

It is almost a century since the pilocarpine alkaloid was isolated from the plant *Pilocarpus microphyllus* Stapf (1), and its highly effective therapeutic appli-

cation for glaucoma (2) treatment was soon realized. After the isolation of pilocarpine, its structure was well defined. However, the isolated alkaloid contains an inactive stereoisomer, which is not purely an artifact formed during the isolation process but occurs in the natural plant (3).

The common isomer is isopilocarpine, differing from pilocarpine only in the position of the ethyl substitution at the α -carbon on the lactone ring. Isopilocarpine has been reported to be therapeutically inactive (4). A literature review revealed only one paper reporting the determination of isopilocarpine (5). Isopilocarpine is thermodynamically more stable than pilocarpine in most environments (5) and readily forms from pilocarpine upon heating or in neutral or alkaline solutions (4, 6).

DISCUSSION

The lactone ring in pilocarpine is very labile (7); even under mild conditions, it can be opened, forming another inactive product, pilocarpic acid. While pilocarpic acid can be detected by the official methods (8-10), neither isomerization to isopilocarpine nor differentiation from pilocarpine in pharmaceutical preparations has been reported until now.