Solubility of Phenylacetic Acid, *p*-Hydroxyphenylacetic Acid, *p*-Aminophenylacetic Acid, *p*-Hydroxybenzoic Acid, and Ibuprofen in Pure Solvents

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The solubility of phenyl acetic acid, *p*-hydroxyphenylacetic acid, *p*-aminophenylacetic acid, *p*-hydroxybenzoic acid, and ibuprofen in water and in a range of organic solvents of relevance to industrial processing is reported. The solvents used are water, methanol, ethanol, 2-propanol, acetone, 4-methyl-2-pentanone, ethyl acetate, chloroform, and toluene. Solubility data are discussed from the standpoint of molecular aspects of solute−solvent interactions and by estimated solid-phase activity.

Introduction

The solubility of solid compounds in solvents and solvent mixtures plays a key role in all crystallization processes. Crystallization is a crucial step in the manufacturing of many pharmaceuticals, agrochemicals, dyestuffs, catalysts, zeolites, proteins, and food products. The solubility at the conditions of the process determines the production rate and the yield. The solubility also determines the method by which supersaturation is generated in the process and how the supersaturation varies during the course of operation. In the present work solubility data are reported for phenylacetic acid at 20 °C, *p*-hydroxyphenylacetic acid at 10, 15, 20, and 25 °C, *p*-aminophenylacetic acid at 16, 20, 25, and 30 °C, *p*-hydroxybenzoic acid at 25 °C, and ibuprofen at 10, 15, 20, 30, and 35 °C. Only a few solubility data of these substances in the solvents studied are available in the literature. Solutes were chosen as candidates to represent organic intermediates and pharmaceutically important compounds, and for their industrial relevance and/or structural interest. All but one of the test substances are disubstituted (*p*-position) benzenes with one or usually two polar groups attached directly to the benzene ring or via a nonpolar group (Figure 1).

Experimental Section

Materials. Ibuprofen (CAS Registry Number 15687-27-1; fine powder of pharmaceutical grade, 99.4% on dry basis determined as specified by the European Pharmacopè) was obtained from AstraZeneca AB and was used without further purification. Phenyl acetic acid (CAS Registry Number 103-82-2; purity 99%), *p*-aminophenylacetic acid (CAS Registry Number 1197-55-3; 98%), *p*-hydroxyphenylacetic acid (CAS Registry Number 156-38-7; purity 98%), and *p*-hydroxybenzoic acid (CAS Registry Number 99-96-7; purity 99%) were supplied by Sigma-Aldrich Sweden AB. The water used was distilled, deionized, and filtered (0.2 μm). Eight organic solvents are included in the study. They are of pro analyse quality and purchased from Merck, except for ethanol, which is from Kemetyl AB, Sweden, having >99.5% purity.

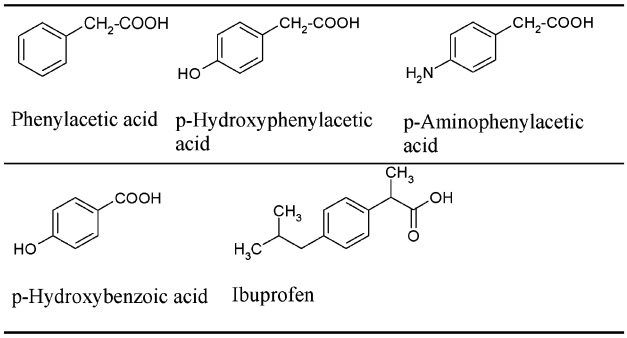

Figure 1. Solute molecules.

Solubility Measurements. The solubility was determined gravimetrically using the same procedure as previously.[1,2] The experimental setup consists of a thermostatic water bath standing on a multiple position magnetic stirrer. Erlenmeyer flasks (250 cm^3) with a Teflon-coated magnetic stirrer were filled with an excess of solute in a solvent. The flasks were placed in the thermostat bath and agitated for at least 72 h at each temperature. The temperature was kept within ±0.02 °C of the desired temperature and was checked with a Pt-100 resistance thermometer. The Pt-100 thermometer was calibrated against a calibrated mercury precision thermometer (Thermo-Schneider, Wertheim, Germany) having an uncertainty of ±0.01 °C. After the equilibration, excess solid solute was allowed to settle for at least 4 h with no agitation. A sample of the clear saturated solution (approximately 10 cm^3) was then transferred with a preheated syringe into a previously weighed sample vial with mass m_v. The vials had Teflon septums to prevent solvent evaporation during the weighing procedure. The mass of the sample vial with the saturated solution, m_{vs}, was measured. (m_v and m_{vs} both denote masses without the Teflon septum.) Then, the septums were removed and the solvent was allowed to evaporate in a vacuum oven at 20 °C for approximately 1 week until the remaining mass of the sample did not change with time (or until no further mass loss was observed if the drying is continued at 30 °C for 72 h).

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Table 1. Solubility, *S*, of Phenylacetic Acid in Different Solvents at the Temperature 20 °C Given in g/kg of Solvent on a Solute Free Basis

solvent	*S*	sd
water	15.8	2.5
methanol	2915	2.2
ethanol	2064	5.5
2-propanol	1382	3.9
acetone	1720[a]	9.6
mibk	803.5	0.2
chloroform	637.1	12.9
ethyl acetate	825.4[a]	10.3
toluene	377.9	1.5

[a] The average of two samples from the same solution.

Table 2. Solubility, *S*, of *p*-Hydroxyphenylacetic Acid in Different Solvents at Temperatures between 10 and 25 °C Given in g/kg of Solvent on a Solute Free Basis

	T = 10 °C		*T* = 15 °C		*T* = 20 °C		*T* = 25 °C	
solvent	*S*	sd	*S*	sd	*S*	sd	*S*	sd
water	29.6	0.1	37.1	0.1	46.31	0.1	60.7	0.1
methanol	934.4	2.2	1061	1.8	1608	0.1	2658	51.5
ethanol	567.8[a]	0.6	702.3	3.2	937.5	6.9	1466	0.4
2-propanol	314.5	1.0	398.9	0.9	496.3	0.4	601.4	0.2
acetone	475.4	0.4	608.6	1.9	693.0	1.3	744.5	2.0
4-methyl-2-pentanone	148.8[a]	0.6	161.2	1.8	179.7	0.6	200.3[a]	0.2
chloroform	1.3	0.1	2.5	0.1				
ethyl acetate	134.2	0.7	147.7	0.1	164.3	0.5	183.6[a]	0.2
toluene	1.7[b]		2.07[a]	0.0				

[a]The average of two samples from the same solution. [b] One sample.

Then the constant "dry residue" mass, m_{vdr}, was determined. The solubility, expressed in grams of solute per kilogram of solvent (on a solute free basis), was calculated by eq 1

$$S = 10^3 \frac{(m_{vdr} - m_v)}{(m_{vs} - m_{vdr})} \quad (1)$$

DSC Measurements. Melting points, enthalpies of fusion, and heat capacities were determined by differential scanning calorimetry using a TA Instruments MDSC-2920. For the measurements of melting point and enthalpy of fusion, the calorimeter is calibrated against the melting point and enthalpy of fusion of indium. Samples (normally 2−8 mg) are heated at 2 and 5 °C /min starting from 25 °C and ending at 20 °C above the melting point in hermetic Al-pans while being purged with nitrogen. Six measurements were performed on each compound. For the measurements of the heat capacities, the calorimeter is calibrated with sapphire and indium. The samples (10−13 mg) were heated from 35 to 50 °C above the melting point in hermetic Al-pans while being purged with nitrogen at the heating rate 2 °C/min. The modulation amplitude was ±1 °C, and the modulation period was 60 s.

Results and Discussion

Tables 1−5 list experimental results for the solubilities of the five solutes in eight or nine different solvents. The solubilities of ibuprofen and *p*-aminophenylacetic acid in water are below the limit of accurate determination of the present work. The solubility, *S*, is given as grams of solute per kilogram of solvent on a solute free basis, and it represents the average of three samples from the same equilibrated solution, unless otherwise stated. The corresponding standard deviation, sd, for each mean value is also reported. Some results are presented in Figures 2−4.

Table 3. Solubility, *S*, of *p*-Aminophenylacetic Acid in Different Solvents at Temperatures between 16 and 30 °C Given in g/kg of Solvent on a Solute Free Basis

	T = 16 °C		*T* = 20 °C		*T* = 25 °C		*T* = 30 °C	
solvent	*S*	sd	*S*	sd	*S*	sd	*S*	sd
methanol	3.7	0.1	4.3	0.1	4.7	0.3		
ethanol	1.1[a]	0.0	1.4[a]	0	1.8	0.6	2.3	0.2
2-propanol	0.4	0.0	0.6[a]	0			1.0	0.1
acetone	6.79[a]	0.2	8.8[a]	0	9.3	0.4	12.6	0.2
4-methyl-2-pentanone	1.1	0.4	2.2	0.2	2.5	0.0		
chloroform	0.9	0.3			1.4	0.3	1.9	0.4
ethyl acetate	0.6	0.3	1.2	0.2	18	0.1		
toluene	1.2	0.1			1.4[a]	0.3		

[a] The average of two samples from the same solution. [b] One sample.

Table 4. Solubility, *S*, of *p*-Hydroxybenzoic Acid in Different Solvents at Temperature 25 °C Given in g/kg of Solvent on a Solute Free Basis

solvent	*s*	sd
water	6.1	0.1
methanol	555.8	4.4
ethanol	432.7	10.2
2-propanol	362.0	0.2
1-octanol	131.4	1.2
acetone	322.3	0.2
mibk	153.4	0.2
ethyl acetate	117.7	1.5
toluene	1.5	0.9

The solubility of phenylacetic acid (PAA), Table 1, is very high in the low molecular weight alcohols and in acetone, is low in water, and is fairly high in the nonpolar toluene. The low solubility in water should be due to the aromatic ring of the solute. The solubility of *p*-hydroxyphenylacetic acid (*p*-HPAA) at 20 °C, Table 2, is high in methanol and ethanol but only fairly high in propanol and in acetone. The solubility is low in water but is higher than that of PAA. In toluene and chloroform the solubility is below the limit of determination of this work. In comparing the solubility of *p*-HPAA with that of PAA, the hydroxy group of the former obviously leads to a lower solubility in the alcohols and in acetone, a somewhat higher solubility in water, and a strong reduction of the solubility in nonpolar solvents. The solubility of a compound is determined by the conditions for the solute in the solution and by the properties of the pure solid state in equilibrium with the solvent. The expected increased preference for alcohols and water is hampered by the fact that the solid-phase properties of *p*-HPAA are such that the solubility tends to be lower than that for PAA. A higher melting point temperature and a higher enthalpy of melting suggest a lower solubility**.** As given in Table 6, the melting point of *p*-HPAA is about 70 °C higher and the enthalpy of melting is almost twice that of PAA.

The tendency of the solid phase to exhibit solubility is best described by the molar Gibbs free energy change upon fusion at the temperature of interest. The higher the Gibbs free energy change upon fusion, the higher is in a sense the "stability" of the solid phase, and the lower is the solubility. By standard thermodynamic relations the molar Gibbs free energy change upon fusion is directly related to the solid-phase activity where the supercooled melt is used as the state of reference. The higher the Gibbs free energy change, the lower is the solid-phase activity. The solid-

Table 5. Solubility, S, of Ibuprofen in Different Solvents at Temperatures between 10 and 35 °C Given in g/kg Solvent on Solute Free Basis (*a* = the average of two samples from the same solution, *b* = one sample)

	$T = 10$ °C		$T = 15$ °C		$T = 20$ °C		$T = 30$ °C		$T = 35$ °C	
solvent	S	sd	S	sd	S	sd	S	sd	S	sd
methanol	725.8	6.1	922.3	1.9	1035	4.5	1752[a]	12.7	2730[b]	
ethanol	592.6	4.6	765.8	4.3	886.5[a]	1.3	1420[a]	11.0	2230[b]	
2-propanol	505.3	2.0	658.8	3.3	793.8	5.0	1297	13.0	1540	32.3
acetone	587.6	3.6	713.9[a]	4.8	883.3	0.9	1357	1.9	1679	2.9
4-methyl-2-pentanone	315.3	0.9	390.9	1.0	487.7	1.0	763.7	7.3	953.4	0.9
chloroform	457.5	6.8	554.5[a]	3.0	644.8	1.6				
ethyl acetate	327.2	0.5	414.8	0.5	531.6	1.4	856.4	4.3	1084	2.2
toluene	258.3	0.1	343.1	0.1	457.1	1.1	749.7	2.1	957.0	0.6

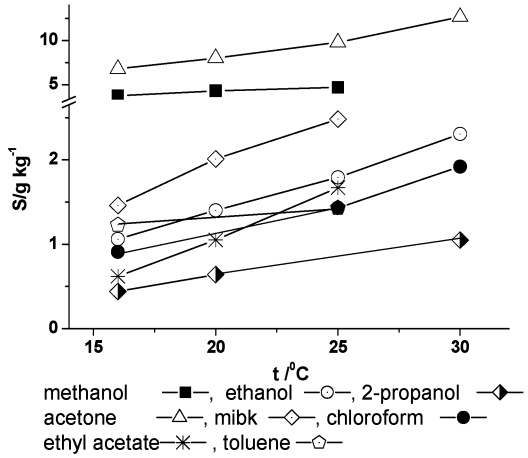

Figure 2. Solubility, *S*, of *p*-aminophenylacetic acid.

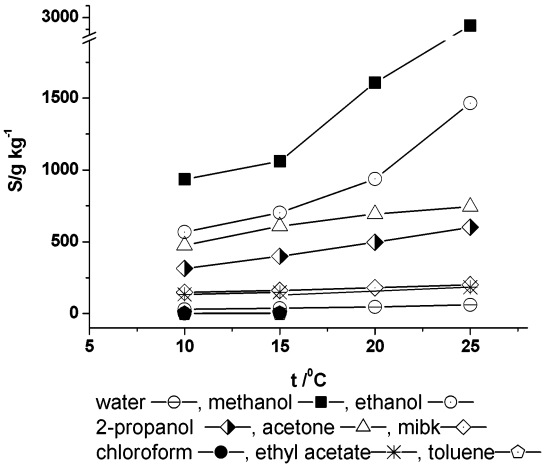

Figure 3. Solubility, *S*, of *p*-hydroxyphenylacetic acid.

phase activity, $a^s(T)$, at temperature T can be estimated by

$$a^s(T) = \exp\left[\frac{\Delta H^f_m}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) - \frac{\Delta C_p}{R}\left(\ln\frac{T_m}{T} - T_m/T + 1\right)\right] \quad (2)$$

where ΔH^f_m is the enthalpy of fusion at the melting point, T_m. In eq 2, it is assumed that the heat capacity difference between the melt and the solid state $(C^m_p - C^s_p) = \Delta C_p$ is independent of temperature.[3] This assumption is not always justified. However, the reference state is a supercooled melt, the properties of which cannot, in general, be determined by experiment but only from extrapolation of data from above the melting point.[3] Hence, the assumption is usually accepted. In the chemical engineering literature,

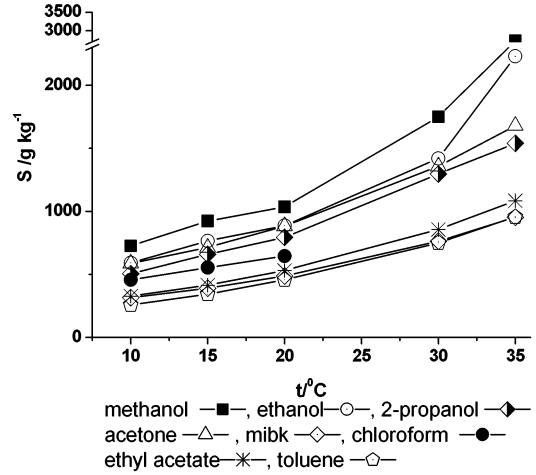

Figure 4. Solubility, *S*, of ibuprofen.

often the heat capacity term is entirely neglected, by which we obtain

$$a^s(T) = \exp\left[\frac{\Delta H^f_m}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right)\right] \quad (3)$$

Our experimental results for melting points and enthalpies of fusion at the melting point are presented in Table 6, as the mean value of six measurements, together with the corresponding standard deviations. The available data from the literature[5] are also given for comparison. Results on heat capacities are presented in Table 7. Data are extrapolated for determination of the difference in heat capacity between the melt and the solid at the melting point. For *p*-aminophenylacetic acid (*p*-APAA), this calculation is not performed, since the compound decomposes close to the melting point. Solid-phase activities at 25 °C are given in Table 8, on the basis of eq 2 (except for *p*-aminophenylacetic acid) and, for comparison, also when the heat capacity term is neglected, eq 3. Quite clearly, the neglect of the heat capacity term is questionable for *p*-HPAA and for *p*-HBA, while it seems reasonable for PAA and for ibuprofen.

The activity of solid *p*-HPAA is less than $^1/_7$ that of PAA, and hence the ideal mole fraction solubility is correspondingly less than $^1/_7$. When a Raoult's law standard state is used, the activity coefficient of the solute in the saturated solution, γ_i^{sat}, is defined as

$$a_i^{sat} = x_i^{sat}\gamma_i^{sat} = a^s \quad (4)$$

where a_i^{sat} is the activity of the solute *i* in the saturated solution and x_i^{sat} denotes the mole fraction solubility. Activity coefficients are calculated from the experimental

Table 6. Melting Points and Enthalpies of Fusion[5]

solute	T_m/°C	sd	lit. value	$\Delta_{fus}H_m$/kJ mol^{-1}	sd	lit. value
phenylacetic acid	76	0.8	75−79	15.5	0.2	na[a]
p-hydroxphenylacetic acid	149.7	0.7	139−154	28.0	0.7	na
p-aminophenylacetic acid	195	0.9	183−204	42.7	2.1	na
p-hydroxybenzoic acid	214	0.5	191−220	31.4	0.8	31.44
ibuprofen	74	0.9	72−77.5	25.5	0.4	25.5−25.8

[a] na = not applicable.

Table 7. Heat Capacities of Solids and Melts

solute	crystal heat capacity	liquid heat capacity	$\Delta_{fus}C_p$/J·mol^{-1}
phenylacetic acid	$0.5724T + 148.8$	$0.6265T + 199.6$	54.9
p-hydroxphenylacetic acid	$0.5777T + 159.85$	$0.8977T + 171.88$	59.7
p-aminophenylacetic acid	$0.889T + 134.71$	decomposition	
p-hydroxybenzoic acid	$0.6883T + 119.93$	$0.1243T + 303.69$	63.1
ibuprofen	$0.9702T + 190.89$	$0.8342T + 248.08$	50.3

Table 8. Solid State Activity at 25 °C

solute	solid state activity eq 2	solid state activity eq 3
phenylacetic acid	0.4375	0.4012
p-hydroxphenylacetic acid	0.0584	0.0356
p-aminophenylacetic acid		0.0019
p-hydroxybenzoic acid	0.0216	0.0073
ibuprofen	0.2509	0.2341

solubility data and the estimated solid-phase activity (eq 2, except for *p*-APAA) and are given in Table 9. In examining solubility data for the same solute in different solvents, the activity coefficient completely accounts for the effect of the solvent. In examining the solubilities of different solutes in the same solvent, the solid-phase activity reflects the "stability" of the solid in the sense described above. The higher the stability, the lower is the solid-phase activity and the lower is the solubility.

Except for water (and toluene), the activity coefficients of PAA and *p*-HPAA are below unity in all solvents studied. This means that the solubility exceeds the ideal solubility, and hence the solute exhibits a reasonable affinity to these solvents. We may also notice for PAA that the activity coefficient is essentially the same in all the solvents except for in water and in toluene. Hence, in terms of mole fraction, the solubility is roughly the same. Also for *p*-HPAA the variation in solubility is much less in terms of mole fraction. In water the activity coefficient of PAA in particular, but also of *p*-HPAA, is much higher than unity. Hence, the solubility is much lower than the ideal solubility, which reflects that the solutes overall do not exhibit much affinity for water, or perhaps rather that the water does not exhibit affinity for the solute. In water the activity coefficient of PAA is about 25 times higher than that of *p*-HPAA. Hence, despite the fact that the solid phase of *p*-HPAA has a much higher Gibbs free energy change upon fusion, that is, exhibits a higher "stability", the solubility ends up being higher for *p*-HPAA in water. Hence, from a thermodynamic point of view the hydroxy group makes the crystalline phase more "stable", but in water the interaction between the solute and the solvent is favorable enough to override this, leading to a higher solubility compared to that of PAA. In the other solvents (besides toluene and chloroform) the activity coefficient of *p*-HPAA is lower than that of PAA. However, the difference is smaller than the difference in solid state activity, and hence the solubility of *p*-HPAA is lower than that of PAA.

For *p*-aminophenylacetic acid (*p*-APAA), the highest solubility is found in acetone, but in all solvents the solubility is very low. By replacing the hydroxy group of the *p*-HPAA by an amino group in *p*-APAA, the solubility decreases dramatically in all the solvents, because the solid phase of *p*-APAA is significantly more "stable" than that of *p*-HPAA. The melting point is about 45 °C higher, and the enthalpy of melting is 43 kJ/mol as compared to 28 kJ/mol for *p*-HPAA. The solid-phase activity is only about 1/20 of that of *p*-HPAA. However, in addition, the hydroxy group in *p*-HPAA is more strongly hydrogen bond donating and accepting than the amino group in *p*-APAA. Hence, the activity coefficients of *p*-APAA in alcohols and in water are expected to be higher, and this would contribute to lower solubilities. In fact, as shown in Table 9, the activity coefficients are always higher for *p*-APAA, and they are actually above unity in all solvents except for acetone. However, activity coefficients and the solid-phase activity are more uncertain for *p*-APAA, since the heat capacity correction could not be done.

The general trend of the solubility of *p*-hydroxybenzoic acid (*p*-HBA) in the different solvents is similar to that of *p*-HPAA. However, the solubility is in general significantly lower, especially in water and in the lower alcohols. It is initially surprising to find that the removal of the CH_2 group that is inserted between the aromatic ring and the carboxylic group in *p*-HPAA leads to a clearly lower solubility in water, in the alcohols, and in the nonpolar solvents. The first reason for this is that the solid phase of

Table 9. Activity Coefficients γ

		γ								
solute	T/°C	water	methanol	ethanol	2-propanol	acetone	4-methyl-2-pentanone	ethyl acetate	chloroform	toluene
PAA	20	209	0.64	0.63	0.72	0.60	0.74	0.82	0.78	1.71
p-HPAA	20	8.41	0.14	0.16	0.23	0.17	0.39	0.48		
p-HPAA	25	8.13	0.10	0.13	0.25	0.21	0.44	0.55		
p-APAA[a]	25		1.93	3.52	6.06	0.52	1.16	1.84	1.29	2.26
p-HPA	25	27.1	0.17	0.15	0.14	0.16	0.19	0.29		21.6
IB	20		1.56	1.27	1.08	1.01	1.06	1.10	0.67	1.23

[a] From eq 3.

p-HBA is more "stable". *p*-HBA has a clearly higher melting temperature, even somewhat higher than that of *p*-APAA. The enthalpy of melting is also higher, and the solid-phase activity is about 40% of that of *p*-HPAA. However, in addition, as shown in Table 9, in water the activity coefficient of *p*-HBA is higher than that of *p*-HPAA. This means that the CH_2 group of *p*-HPAA allows the molecule a higher affinity for water, compared to the conditions in the the corresponding supercooled melt, than is the case for *p*-HBA. This is opposite to our expectation. A possible explanation, however, is that the CH_2 group reduces the charge displacement in the molecule. When directly attached to the aromatic ring, the carboxylic group tends to draw electrons via aromatic ring from the hydroxy group leading to reduced hydrogen bond donating and accepting capabilities.[5] If the CH_2 group reduces this effect, it leads to the electrostatic potential of the surface of the molecule exhibiting stronger positive and negative domains in *p*-HPAA and the molecule interacting more strongly with water. The activity coefficients also reveal that the removal of the CH_2 group does give the *p*-HBA molecule a slightly lower affinity for methanol, essentially unchanged affinity for ethanol, and somewhat higher affinity for the other solvents**.** The activity coefficients for *p*-HBA in the different solvents reveal that, besides the cases of water and toluene, the mole fraction solubility only varies by up to a factor of 2.

Ibuprofen contains a carboxylic acid group but is otherwise quite nonpolar and has a high molecular weight. This leads to the solubility in water being very low. For ibuprofen the enthalpy of melting per mole is clearly higher than that of PAA, but the melting point temperature is the same. The solid state activity is about half of that of PAA, and the activity coefficients are usually higher than those of PAA especially in methanol and in ethanol, and hence the solubility is lower for ibuprofen. The solubility in chloroform and ethyl acetate is fairly high because of the nonpolar character of the molecule, and the solubility in toluene actually exceeds that of PAA.

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