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Solution thermodynamics of phenols

J.A. Rogers

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta (Canada)

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Summary

The temperature-dependent solubilities of several series of phenols in a 0.15 M sodium chloride solution have been measured. Experimentally determined heats of solution are compared with calculated values based on solubility principles. The solution process of all phenols is entropy-dominated and functional group contributions to the solubility are attributed mainly to their relative sizes and hydrophobicities. The correlation between experimental and calculated solubilities is excellent within a given series of phenols but not so good between different series. Correlations found between aqueous solubilities and partition coefficients of compounds can be explained in terms of the entropy change of the process in each case.

Introduction

Phenolic compounds are of considerable importance in pharmacy because of their bactericidal activity and because they constitute the nucleus for many other drug molecules (e.g. phenylephrine, hydroxyamphetamine). However, their occurrence as contaminants of the environment, particularly from petroleum wastes, is of particular concern (Lysyj and Russell, 1975). Upon exposure, biological membranes rapidly accumulate these compounds due to their high lipid–water partition coefficients (Rogers and Davis, 1980).

The phenols have a wide range of water solubilities but it is now established that water solubilities and partition coefficients can be correlated for many compounds (Chiou et al., 1977; MacKay et al., 1980). Previously it was reported that the partition coefficients of alcohols and other water-soluble compounds (Katz and Diamond, 1974c) and phenols (Rogers and Davis, 1980; Rogers and Wong, 1980) are quantitatively related to functional group contributions in a homologous series.

Mechanistic approaches to functional group contributions have included studies of the thermodynamics of the process (Katz and Diamond, 1974b; Rogers and Davis, 1980) as well as the penetration of phospholipid monolayers (Kaye and Proudfoot, 1971; Proudfoot and Davdani, 1974). However, the shortcomings of these approaches have been not knowing the solution properties of the compounds in either the aqueous or lipid phases.

Thus, results of the temperature-dependency of the aqueous solubility of phenols and the resultant thermodynamics of the process have been obtained and are presented in this report.

Experimental

Solubilities were measured in a 0.15 M sodium chloride (BDH reagent) solution over the temperature range 10–40°C. Isotonic conditions were employed to enable direct comparisons with results of partitioning in biochemical systems (Katz and Diamond, 1974a; Rogers and Davis, 1980). The phenolic compounds studied have been described previously (Rogers and Wong, 1980). Double-distilled water was used throughout.

A known weight of aqueous phase was measured into glass vials fitted with screw caps and then excess phenolic compound was added. Where the compound was solid, it was previously reduced to fine particles in a mortar before adding. Subsequently, the vials were placed in shaker water-baths (Dubnoff metabolic shaker, Precision Scientific) maintained at the appropriate temperature ±0.2°C. Equilibration of samples containing phenols of low solubility was achieved after approximately 70 h, thus, all samples were shaken for this period of time.

Samples were allowed to stand prior to removing aliquots for analysis. Precautions were taken to ensure that the supernatant solutions were clear before sampling. Mole fraction solubilities (X_2) were determined by measuring UV absorbances in 1 cm cells (Beckman Model 25 Spectrophotometer) after appropriate dilution and interpolation from previously constructed calibration curves for each phenolic compound.

Results

The aqueous solubilities of the several phenolic compounds investigated as a function of temperature may be determined from the parameters of the linear regression analysis of typical Van't Hoff plots presented in Table 1. Normally, experiments were conducted at 4 temperatures but results were obtained at 3 temperatures where a narrower temperature range is indicated. The linear correlation in all but one instance (*o*-methylphenol) was better than 0.95. The pH of the solution was at least two pH units below the pK_a of the respective phenols, thus the solubility is considered as being that of the unionized compound. The results show that $\Delta \ln X_2/\text{deg}$ is less than 1×10^{-3} for phenol, monosubstituted alkylphenols,

TABLE 1

REGRESSION ANALYSIS OF ln X_2 VERSUS 1/T FOR SOLUBILITY OF SUBSTITUTED PHENOLS IN A 0.15 M NaCl SOLUTION [a]

Compound	Slope	Intercept	Correlation
phenol	−626.4	−2.275	−0.962
o-methylphenol [b]	−111.0	−5.098	−0.877
m-methylphenol [c]	−229.0	−4.763	−0.994
p-methylphenol	−402.3	−4.386	−0.972
p-ethylphenol	−495.3	−5.351	−0.984
p-*n*-butylphenol [b]	−844.7	−6.939	−0.988
2,4-dimethylphenol	−459.4	−5.357	−0.956
2,6-dimethylphenol	−1811	−1.105	−0.981
3,5-dimethylphenol	−3952	5.792	−0.982
p-fluorophenol [c]	−457.4	−2.951	−0.994
p-chlorophenol	−402.5	−4.302	−0.983
p-bromophenol	−2072	0.572	−0.987
p-iodophenol	−3306	3.038	−0.975
p-hydroxymethylbenzoate [c]	−2033	−1.245	−0.982
p-methoxyphenol	−2138	1.721	−0.992
p-ethoxyphenol	−3090	3.626	−0.980
p-nitrophenol	−4021	7.240	−0.977

[a] Over the temperature range 10–40°C.
[b] Over the temperature range 20–40°C.
[c] Over the temperature range 10–30°C.

2,4-dimethylphenol, *p*-fluorophenol and *p*-chlorophenol, near 2×10^{-3} for 2,6-dimethylphenol, *p*-bromophenol, *p*-hydroxymethylbenzoate and *p*-methoxyphenol, near 3×10^{-3} for *p*-iodophenol and *p*-ethoxyphenol, and near 4×10^{-3} for 3,5-dimethylphenol and *p*-nitrophenol. This suggests that the type of substituent, the number of substituents and the position of the substituents on the aromatic ring all affect the magnitude of the temperature dependence of phenol solubility in water. The substituent may play a two-fold role in affecting the solubility: (1) it may alter the acidity of the phenolic OH group to some extent; and (2) depending on the nature of the substituent it may also contribute its individual interaction with water to the solubility. For instance, *p*-bromophenol ($pK_a = 9.34$) and *p*-nitrophenol ($pK_a = 7.15$) have approximately equal solubilities at 20°C (Table 3) but ln X_2/deg is 2×10^{-3} and 4×10^{-3}, respectively.

Determination of heats of solution ($\Delta \bar{H}_w$)

The thermodynamics of the solution process is commonly described in terms of the free energy, enthalpy and entropy of solution calculated using standard equations (Martin et al., 1969). The differential enthalpy or heat of solution, $\Delta \bar{H}_w$, may be obtained from the temperature-dependency of the solubility or by independent

TABLE 2

COMPARISON OF HEATS OF SOLUTION OF PHENOLS OBTAINED FROM THE TEMPERATURE-DEPENDENT SOLUBILITY AND FROM SOLUBILITY PRINCIPLES

Compound	$\Delta\bar{H}^*_w$ (cal/mol)	$\Delta\bar{H}_w$ [a] (cal/mol)	$\Delta\bar{H}^0_w$ [b] (cal/mol)
phenol	1245	5106	6550
p-methylphenol	799.3	6068	7320
p-bromophenol	4116	6900	7797
p-nitrophenol	7989	8337	7977

[a] Values represent the average of the range at 20°C using literature values of ΔH_F (Handbook of Chemistry and Physics, 53rd Edn.) and the treatment proposed by Hollenbeck (1980).

[b] Derived from Eqns. 15, 16, 17 and 18 of Hollenbeck (1980) using $\Delta S_F = \Delta H_F/T_M = 13.5$ e.u. for rigid molecules at 20°C (Yalkowsky and Valvani, 1980).

means such as microcalorimetry or from vapor pressure measurements. However, it has recently been pointed out that $\Delta\bar{H}^*_w$ as obtained from the temperature-dependency of the solubility is not necessarily equal to $\Delta\bar{H}_w$ in non-ideal solutions (Hollenbeck, 1980). Since this may be the case with solutions of phenols, values of

TABLE 3

SOLUBILITIES AND THERMODYNAMICS OF SOLUTION OF PHENOLS IN A 0.15 M NaCl SOLUTION AT 20°C

Compound	X_2 ($\times 10^4$)	$\Delta\bar{G}^0_w$ ($kJ \cdot mol^{-1}$)	$\Delta\bar{H}^0_w$ ($kJ \cdot mol^{-1}$)	$\Delta\bar{S}^0_w$ ($J \cdot mol^{-1} \cdot K^{-1}$)
phenol	118	−10.8	27.4	130
o-methylphenol	42.0	−13.3	29.9	148
m-methylphenol	38.9	−13.5	30.1	149
p-methylphenol	31.2	−14.1	30.6	152
p-ethylphenol	8.79	−17.1	33.8	174
p-*n*-butylphenol	0.547	−23.9	40.5	220
2,4-dimethylphenol	9.55	−16.9	33.5	172
2,6-dimethylphenol	6.50	−17.9	34.5	179
3,5-dimethylphenol	5.35	−18.4	35.1	182
p-fluorophenol	109	−11.0	27.6	132
p-chlorophenol	33.9	−13.9	30.5	151
p-bromophenol	14.7	−15.9	32.6	166
p-iodophenol	2.32	−20.4	37.4	197
p-methoxyphenol	38.3	−13.6	30.8	151
p-ethoxyphenol	9.24	−17.0	33.8	173
p-nitrophenol	13.4	−16.1	33.4	169
p-hydroxymethyl benzoate	2.63	−20.1	37.6	197

the heats of solution are compared in Table 2. The first column of figures gives $\Delta\overline{H}^*_w$ for 4 phenols. The second column gives $\Delta\overline{H}_w$ calculated from the ΔH_F (heat of fusion, for which only 4 values could be found in the literature) and these values represent the average over the range when it is assumed that $\Delta C_p = 0$ at the one extreme and $\Delta C_p = \Delta S^M_F$ at the other extreme (Hollenbeck, 1980) where ΔC_p is the heat capacity and ΔS^M_F is the entropy of fusion at the melting point of the compound. The third column gives the heat of solution:

$$\Delta\overline{H}^0_w = 13.5[T_M + T\ln(T/T_M)] - RT\ln X_2 \qquad (1)$$

where T_M is the melting point of the phenol, T is the stated temperature and X_2 is the mole fraction solubility. Eqn. 1 is based on the approximations that:

$$\Delta H_F = \Delta H^M_F = \Delta S^M_F T_M = 13.5\ T_M \qquad (2)$$

Yalkowsky and Valvani (1980) have derived equations which enable the estimation of aqueous solubility solely on the basis of the melting point of the compound. In their treatment they use a value of 13.5 for the entropy of fusion of rigid molecules which is demonstrated to yield a good estimate of the solubility of several series of compounds. Thus, 13.5 is used here to provide a calculation of the heat of solution ($\Delta\overline{H}^0_w$) when the appropriate heats of fusion are not available. The data in Table 2 indicate that the agreement between $\Delta\overline{H}_w$ and $\Delta\overline{H}^0_w$ is at least 78% whereas $\Delta\overline{H}^*_w$ values show poor agreement for 3 of the phenols. This can be attributed to the extent of deviation from ideal behaviour. Thus, as previously stated (Hollenbeck, 1980), $\Delta\overline{H}^*_w$ should not be used to calculate the partial molar free energies or entropies.

In Table 3 solubilities of phenols in 0.15 M sodium chloride at 20°C, and the standard partial molar free energies, enthalpies and entropies of solution are presented. It can be seen that the standard free energy change which occurs when solute transfers from the solute phase to the solution phase is negative. In view of the positive heats of solution, which imply that only weak interactions between the phenols and the aqueous medium occur, the release of free energy is probably due to the breaking of water structure which is required to accommodate each molecule of solute as it is released from the solute phase. The positive entropies in Table 3 reflect this transformation towards a more randomly oriented energetic state of the aqueous phase.

The individual contributions of functional groups to the solubility of phenol may be compared by examining the incremental thermodynamic quantities as shown in Table 4.

(1) p-Alkyl substituents. The addition of a single methyl group decreases the aqueous solubility of phenol entirely through an entropy-dominated process since $\delta\Delta\overline{G}^0_w$ and $\delta\Delta\overline{H}^0_w$ are similar but opposite in sign. Each additional methylene group in the *p*-alkyl chain contributes equally to the thermodynamics of solution suggesting that no special orientation effect of the hydrocarbon chain plays a role in creating a ‘hole’ in the water to accommodate the solute molecule. Furthermore,

TABLE 4

INCREMENTAL THERMODYNAMIC FUNCTIONS FOR SOLUBILITY OF PHENOLS IN A 0.15 M NaCl SOLUTION AT 20°C

Functional group	$\delta\Delta\bar{G}^0_w$ ($kJ \cdot mol^{-1}$)	$\delta\Delta\bar{H}^0_w$ ($kJ \cdot mol^{-1}$)	$\delta\Delta\bar{S}^0_w$ ($J \cdot mol^{-1} \cdot K^{-1}$)
o-methyl	−2.5	2.5	18
m-methyl	−2.7	2.7	19
p-methyl	−3.3	3.2	22
p-ethyl	−6.3	6.4	44
p-*n*-butyl	−13.1	13.1	90
2,4-dimethyl	−6.1	6.1	42
2,6-dimethyl	−7.1	7.1	49
3,5-dimethyl	−7.6	7.7	52
p-fluoro	−0.2	0.2	2
p-chloro	−3.1	3.1	21
p-bromo	−5.1	5.2	36
p-iodo	−9.6	10.0	67
p-methoxy	−2.8	3.4	21
p-ethoxy	−6.2	6.4	43
p-nitro	−5.3	6.0	39
p-$COOCH_3$	−9.3	10.2	67

these results suggest that *p*-alkyl group substitution contributes to the solute–solvent interaction through its intrinsic enthalpy–entropy compensating effect on water without significantly altering the phenol–water interaction. The relative constancy of the pK_a of the *p*-alkylphenols supports this contention.

(2) Methyl isomers. The position of $-CH_3$ on the aromatic ring appears to alter the energetics of solution only slightly. Thus, the solubilities of cresols, which are reported to be lower in 0.1 N sodium chloride solution than in water (Azaz and Donbrow, 1976) decrease in the order ortho → meta → *p*-methylphenol in a 0.15 M sodium chloride solution which suggests a change in state of hydration of the methyl phenol isomers for reasons which are not presently clear.

(3) Dimethyl isomers . The solubilities of the 3 isomers investigated in this study compare closely with that of *p*-ethylphenol but differences in the energetics of solution among the isomers may be related to the differences in energy requirements to transfer solute from the solute phase to the solution phase as the melting points of the compounds would indicate (2,4-dimethyl-, m.p. 27.5°C; 2,6-dimethyl-, m.p. 49°C; 3,5-dimethyl-, m.p. 68°C).

(4)p-Halo substituents. The energetics of solution of phenol following substitution of a *p*-halo group parallels that following *p*-alkyl substitution indicating that aromatic halogens behave similarly to aromatic alkyl groups with respect to their influence on the solubility of phenol in dilute aqueous salt solution. Thus, the interaction between water and a phenolic *p*-chloro group is similar to that between

water and a methyl group; a bromo group behaves similarly to an ethyl group and an iodo group appears to exert its effects in a manner similar to a *n*-propyl group (i.e. between ethyl and *n*-butyl). In other words, a halogen is simply equivalent to a hydrocarbon residue of the same size in its direct effect on the water solubility of phenol.

(5)p-Oxy substituents . As seen in Tables 3 and 4, substituents of methoxy and ethoxy produce similar patterns of behaviour as methyl and ethyl substituents suggesting that there is no significant interaction of water with the oxygen of the 'oxy' substituent. The decrease in solubility of phenol by a *p*-nitro group occurs for the same reasons as for a *p*-ethyl group. Although a nitro group has a higher dipole moment than most other substituent groups, it forms weak hydrogen bonds because of a low resonance contribution to bridge strength (Nagakura and Gouterman, 1957). Finally, it is seen that a methyl ester group results in a solubility of the phenol molecule similar to that produced by the iodo substituent indicating that the size of the group produces the major effect on the solubility in spite of anticipated possible hydrogen bonding forces between this group and water (since $\delta\Delta\overline{H}^0_w$ and $\delta\Delta\overline{S}^0_w$ are greatest for this group among the 'oxy' substituents).

Discussion

There is little doubt that the type of substituted functional group determines to a large extent the physical-chemical behaviour of phenol. The inverse relationship between solubility and oil-water partition coefficient has been demonstrated on several occasions (Chiou et al., 1977; MacKay et al., 1980). Such a correlation can also be found for the phenols in a log-log plot of the solubility data inTable 3 and previously reported *n*-octanol-water partition coefficients (Rogers and Wong, 1980) (correlation coefficient, $r = 0.93$ for 13 para-substituted phenols).

The mole fraction solubility of non-electrolytes in aqueous solution may be predicted based upon an equation (Eqn. 26) by Yalkowksy and Valvani (1980) which incorporates the *n*-octanol-water partition coefficient, the entropy of fusion, ΔS_F, and the melting point of the solute. When ΔS_F is estimated to be 13.5, linear regression analysis yielded the following from a log X_w(obs) versus log X_w(estd) plot:

(1) *methylphenol isomers* $\log X_w(\text{obs}) = 1.19 \log X_w(\text{estd}) + 1.16$

$$n = 4;\ r = 0.97 \tag{3}$$

(2) *p-alkylphenols* $\log X_w(\text{obs}) = 1.20 \log X_w(\text{estd}) + 1.27$

$$n = 4;\ r = 0.99 \tag{4}$$

(3) *disubstituted alkylphenols* $\log X_w(\text{obs}) = 1.16 \log X_w(\text{estd}) + 1.06$

$$n = 4;\ r = 0.99 \tag{5}$$

(4) *p-halophenols* $\log X_w(\text{obs}) = 0.92 \log X_w(\text{estd}) + 0.68$

$$n = 5;\ r = 0.96 \qquad (6)$$

Phenol was included in each calculation. When 17 phenols were pooled the correlation was poorer ($r = 0.87$).

The solubility process is entropy-dominated and a large gain in enthalpy is associated with each substituent. Comparison of results shown in Table 3 indicates that compounds having similar solubilities also have similar enthalpies and entropies of solution. It is possible to suggest, therefore, that the correlations found between solubilities and partition coefficients are based entirely on hydrophobicities of the compounds. The significance in biological systems is that correlations are observed when the biomembrane serves simply as a lipid reservoir for the removal of the phenolic solute from its aqueous environment. However, previous results from artificial membrane systems (Rogers and Davis, 1980) indicate that phenol–phospholipid interactions add a further dimension to the partitioning process. At least in this instance, it does not seem wise to rely solely on aqueous solubilities to evaluate the biological consequences of active compounds.

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