

Hydrogen bonding, steric effects and thermodynamics of partitioning

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ABSTRACT: The descriptors in the Abraham solvation equation, especially the solute hydrogen bond acidity descriptor, *A*, have been compared to values of ΔH° and ΔS° for partitioning in the water–cyclohexane and water–octanol systems obtained by Dearden and Bresnen. It is shown that effects on ΔH° and ΔS° due to internal hydrogen bonding parallel very closely effects on *A* values for substituted phenols and substituted benzoic acids, thus suggesting a common structural origin. Steric effects of *ortho*-substituted methyl groups in phenols, benzoic acids and acetanilides on ΔH° and ΔS° also parallel effects on the Abraham solvation parameters. Some of these steric effects, such as those in 2,6-dimethylacetanilide, can be very large. Both the thermodynamics of partitioning and the Abraham descriptors suggest that in 2,6-dihydroxybenzoic acid there is only one internal hydrogen bond, and that 2-nitroresorcinol behaves as though it had two internal hydrogen bonds. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: partition; water–cyclohexane; water–octanol; thermodynamics; solvation equation; hydrogen bonding

INTRODUCTION

Structural effects of solutes are reflected in water–solvent partition coefficients as $\log P$,¹ equivalent to the standard Gibbs energy change ΔG° . However, not all water–solvent partitioning systems reflect structural effects to the same extent. One of the classic cases of internal hydrogen bonding is that of 2-nitrophenol, whereas in 4-nitrophenol there is no possibility of internal hydrogen bonding. Values of $\log P$ in the water–cyclohexane system, $\log P_{\text{cyc}}$, and in the water–octanol system, $\log P_{\text{oct}}$, are given in Table 1. These are from the recent work of Dearden and Bresnen,² or are taken from the Medicinal Chemistry Data Base of Leo.³ For a few compounds, observed $\log P_{\text{oct}}$ values were not available and they were then calculated using the ClogP program.⁴

Although values of $\log P_{\text{cyc}}$ for the 2- and 4-nitrophenols differ very considerably, at 1.40 and –1.90, respectively, the $\log P_{\text{oct}}$ values are quite close, at 1.75 and 1.91, respectively. This can be explained through equations that dissect $\log P$ values into their constituent parts.^{1,5,6} One such equation is the general solvation equation of Abraham:

$$SP = c + eB + sS + aA + bB + vV \quad (1)$$

In Eqn (1) the dependent variable, *SP*, is a set of solute properties in a given system, for example *SP* could be $\log P_{\text{oct}}$ for a series of solutes. The independent variables in Eqn (1) are solute descriptors as follows:^{5,6} *E* is the solute excess molar refractivity in units of $(\text{dm}^3 \text{mol}^{-1})/10$, *S* is the solute dipolarity/polarizability, *A* and *B* are the overall or summation hydrogen bond acidity and basicity and *V* is the McGowan characteristic volume in units of $(\text{dm}^3 \text{mol}^{-1})/100$. The coefficients in Eqn (1) are evaluated through multiple linear regression analysis (MLR).

The two partition equations that we shall be concerned with are water–octanol and water–cyclohexane, for which the application of Eqn (1) yielded:

$$\begin{aligned} \log P_{\text{oct}} &= 0.088 + 0.562E - 1.054S \\ &\quad + 0.034A - 3.460B + 3.814V \\ N &= 613, R = 0.9972, SD = 0.116, \\ F &= 23162 \end{aligned} \quad (2)$$

$$\begin{aligned} \log P_{\text{cyc}} &= 0.127 + 0.816E - 1.731S - 3.778A \\ &\quad - 4.905B + 4.646V \\ N &= 370, R = 0.9982, SD = 0.124, \\ F &= 20236 \end{aligned} \quad (3)$$

In Eqns (2) and (3) *N* is the number of compounds, *R* is the correlation coefficient, *SD* is the standard deviation and *F* is the *F*-statistic.

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Table 1. Values of the Abraham descriptors and $\log P_{\text{cyc}}$ and $\log P_{\text{oct}}$ for phenol and some substituted phenols

Solute	No.	<i>E</i>	<i>S</i>	<i>A</i>	<i>B</i>	<i>V</i>	$\log P_{\text{cyc}}$		$\log P_{\text{oct}}$		Cyclohexane		Octanol	
							Calc.	Obs.	Calc.	Obs.	ΔH°	ΔS°	ΔH°	ΔS°
Phenol	1	0.80	0.89	0.60	0.30	0.7751	-0.88	-0.74	1.54	1.49	15	53	-8	18
2-Nitro	2	1.02	1.05	0.05	0.37	0.9493	1.53	1.40	1.90	1.75	6	61	-2	43
3-Nitro	3	1.05	1.57	0.79	0.23	0.9493	-1.40	-1.57	1.88	2.00	12	24	-15	3
4-Nitro	4	1.07	1.72	0.82	0.26	0.9493	-1.89	-1.90	1.63	1.91	23	56	-19	-10
3-Me, 2-NO ₂	5	1.03	1.01	0.14	0.48	1.0902	1.37	1.32	2.10	2.15	-6	21	-13	16
4-Me, 2-NO ₂	6	1.03	1.04	0.06	0.40	1.0902	2.01	1.99	2.35	2.24	-10	20	-2	53
5-Me, 2-NO ₂	7	1.03	1.05	0.10	0.42	1.0902	1.75	1.74	2.27	2.33	-6	29	-3	51
6-Me, 2-NO ₂	8	1.03	1.01	0.14	0.36	1.0902	1.96	1.95	2.54	2.54	-1	49	7	90
2-Chloro	9	0.85	0.88	0.32	0.31	0.8975	0.73	0.82	2.00	2.12	9	59	-8	29
3-Chloro	10	0.91	1.06	0.69	0.15	0.8975	-0.12	-0.05	2.41	2.45	10	48	-11	26
4-Chloro	11	0.92	1.08	0.67	0.20	0.8975	-0.32	-0.30	2.22	2.36	14	56	-10	27
2-CHO	12	0.96	1.05	0.12	0.33	0.9317	1.34	1.38	1.94	1.66	-4	30	-4	37
3-CHO	13	0.99	1.38	0.73	0.40	0.9317	-1.82	-1.96	1.38	1.35	8	4	-9	14
4-CHO	14	1.01	1.39	0.80	0.44	0.9317	-2.28	-2.29	1.25	1.35	15	23	-10	12

Now in the internal hydrogen bond form of 2-nitrophenol, the hydrogen bond acidity of the —OH group will be very considerably reduced. However, although the hydrogen bond basicity of the nitro group will be reduced, that of the phenolic oxygen will be increased. It turns out that the hydrogen bond basicity of 2-nitrophenol is actually larger than that of 4-nitrophenol. Values of the descriptors in Eqn (1) are given for various series of solutes in Tables 1–4; the descriptors have either been taken from the Absolv database⁸ or have been calculated (recalculated) in the present work. The internal hydrogen bond ring system leads to a considerable reduction in polarity of the molecule; hence *S* is much smaller for 2-nitrophenol. With Eqn (2) there is no effect of hydrogen bond acidity at all, and the effects of *S* and *B* somewhat cancel out between the 2- and 4-nitrophenols, leading to a quite small change in the $\log P$ values. However, in the water–cyclohexane system the term in *A* is very large and the decrease in hydrogen

bond acidity from *A* = 0.82 to *A* = 0.05 will itself lead to a decrease of 2.9 \log units in $\log P_{\text{cyc}}$. Similar considerations apply to the 2- and 4-hydroxy benzaldehydes (Table 1) and to the 2- and 4-hydroxybenzoic acids (Table 2). In general, intramolecular hydrogen bonding will not affect $\log P_{\text{oct}}$ in the same way as it affects $\log P_{\text{cyc}}$.

Steric effects on $\log P$ values are known^{9,10} to be much more subtle. Table 3 lists the Abraham parameters and values of $\log P_{\text{cyc}}$ and $\log P_{\text{oct}}$ for all the methylphenols. Values of $\log P_{\text{cyc}}$ are larger for the phenols with one and, especially, two *ortho*-substituted methyl groups, although $\log P_{\text{oct}}$ is little affected. Thus for 2,4,6-trimethylphenol the values are 1.62 and 2.73 for $\log P_{\text{cyc}}$ and $\log P_{\text{oct}}$ but for 3,4,5-trimethylphenol they are 0.56 and 2.75, respectively. This suggests that the main effect is a reduction in hydrogen bond acidity for the *ortho*-substituted methylphenols, as is shown by the corresponding *A* values (Table 3).

Table 2. The Abraham descriptors, $\log P_{\text{cyc}}$ and $\log P_{\text{oct}}$, and thermodynamic parameters for partitioning for benzoic acid and some substituted benzoic acids

	<i>E</i>	<i>S</i>	<i>A</i>	<i>B</i>	<i>V</i>	$\log P_{\text{cyc}}$		$\log P_{\text{oct}}$		Cyclohexane		Octanol	
						Calc.	Obs.	Calc.	Obs.	ΔH°	ΔS°	ΔH°	ΔS°
Benzoic acid	0.73	0.90	0.59	0.40	0.9317	-0.69	-0.85	1.74	1.87	7	21	-8	24
2-OH	0.89	0.78	0.75	0.30	0.9904	-0.60	-0.50 ^a	2.25	2.30	12	27	-18	1
3-OH	0.91	0.88	0.86	0.58	0.9904	-2.15		1.47	1.60			-19	-17
4-OH	0.93	0.90	0.81	0.56	0.9904	-1.88		1.53	1.55			-23	-30
2-Methyl	0.73	0.84	0.42	0.44	1.0726	0.49	0.98	2.20	2.10	3	17	-12	19
3-Methyl	0.73	0.89	0.60	0.40	1.0726	-0.07	0.36	2.29	2.35	20	90	-13	19
4-Methyl	0.73	0.89	0.60	0.40	1.0726	-0.31	-0.53	2.29	2.30	7	27	-12	22
2,6-Dimethyl	0.73	0.86	0.72	0.64	1.2139	-1.01	-0.98	2.03	1.82 ^b	14	43	-6	37
3,5-Dimethyl	0.73	0.92	0.65	0.44	1.2139	0.14	0.06	2.66	2.85	-9	-15	-12	34

^a Value from Ref. 3 (-1.42 from Ref. 1).

^b Value is 2.21 from Ref. 3.

Table 3. The Abraham descriptors, $\log P_{\text{cyc}}$ and $\log P_{\text{oct}}$, and thermodynamic parameters for partitioning for phenol and methyl phenols

Solute	<i>E</i>	<i>S</i>	<i>A</i>	<i>B</i>	<i>V</i>	$\log P_{\text{cyc}}$		$\log P_{\text{oct}}$		Cyclohexane		Octanol	
						Calc.	Obs.	Calc.	Obs.	ΔH°	ΔS°	ΔH°	ΔS°
Phenol	0.80	0.89	0.60	0.30	0.7751	-0.88	-0.74 ^a	1.54	1.49	15	53	-8	18
2-Methyl	0.84	0.86	0.52	0.30	0.9160	0.14	0.15	2.13	1.90	16	70	-8	28
3-Methyl	0.82	0.88	0.57	0.34	0.9160	-0.29	-0.16 ^b	1.96	1.93	19	76	-8	27
4-Methyl	0.82	0.87	0.57	0.31	0.9160	-0.13	-0.15	2.07	1.98	15	63	-8	27
2,3-Dimethyl	0.85	0.82	0.51	0.37	1.0569	0.52	0.49	2.47	2.30 ^c	15	76	-9	31
2,4-Dimethyl	0.84	0.79	0.52	0.40	1.0569	0.42	0.66	2.39	2.32	13	70	-10	31
2,5-Dimethyl	0.84	0.83	0.50	0.38	1.0569	0.72	0.72	2.33	2.32	14	77	-10	29
2,6-Dimethyl	0.84	0.79	0.39	0.38	1.0569	1.00	0.97	2.46	2.23	9	64	-4	49
3,4-Dimethyl	0.83	0.90	0.55	0.38	1.0569	0.21	0.21	2.34	2.24	19	83	-10	27
3,5-Dimethyl	0.83	0.86	0.55	0.37	1.0569	0.32	0.26	2.42	2.34	16	75	-11	27
2,3,4-Tri	0.86	0.86	0.52	0.42	1.0569	0.86		2.80	2.82 ^d				
2,3,5-Tri	0.86	0.76	0.51	0.43	1.1978	1.01	1.08	2.87	2.70	15	87	-7	48
2,3,6-Tri	0.86	0.78	0.36	0.41	1.1978	1.64	1.72	2.91	2.56	18	108	-6	48
2,4,5-Tri	0.86	0.79	0.51	0.44	1.1978	0.91	0.94 ^d	2.80	2.80 ^d				
2,4,6-Tri	0.86	0.81	0.30	0.45	1.1978	1.62	1.69	2.73	2.60	20	113	-4	56
3,4,5-Tri	0.83	0.89	0.58	0.42	1.1978	0.56	0.63 ^d	2.75	2.82 ^d				
2,3,4,5-Tetra	0.86	0.88	0.55	0.43	1.3387	1.31		3.28	3.32 ^d				
2,3,4,6-Tetra	0.86	0.80	0.38	0.44	1.3387	2.04		3.34	3.32 ^d				
2,3,5,6-Tetra	0.88	0.81	0.38	0.44	1.3387	2.03	1.79	3.32	2.77 ^e	14	95	-6	51
Penta-	0.90	0.90	0.35	0.43	1.4796	2.70		3.82	3.82 ^d				

^a Value is -0.89 from Ref. 3.^b Value is -0.22 from Ref. 3.^c Value is 2.48 from Ref. 3.^d From Ref. 3.^e Value is 3.32 from Ref. 3.

In the case of the methylacetanilides (Table 4), *ortho*-substitution now decreases $\log P_{\text{cyc}}$ and $\log P_{\text{oct}}$. In terms of the descriptors, this is because *ortho*-substitution decreases *A* (as for the phenols) but now increases both *S* and *B*. The effect of *ortho*-substitution on methylbenzoic acids is even odder. One *ortho*-methyl group increases $\log P_{\text{cyc}}$ but two *ortho*-methyl groups decrease $\log P_{\text{cyc}}$ and $\log P_{\text{oct}}$.

Quite recently, Dearden and Bresnen² have suggested that determination of the thermodynamics of partitioning might contribute to a knowledge of structural effects. In particular, they determined not only $\log P$ values

(standard Gibbs energy changes, ΔG°) for partition into cyclohexane and octanol but also the corresponding standard enthalpy (ΔH°) and entropy (ΔS°) changes. Because the descriptors in Eqn (1), especially the hydrogen bond descriptors *A* and *B*, also reflect structural effects, there should be some connection between *A* and *B* and the thermodynamic parameters for partition. It is the aim of the present work to see if the values of ΔH° and ΔS° found by Dearden and Bresnen² for a large number of substituted phenols, benzoic acids and acetanilides correlate with the hydrogen bond parameters, *A* and *B*. We are especially

Table 4. The Abraham descriptors, $\log P_{\text{cyc}}$ and $\log P_{\text{oct}}$, and thermodynamic parameters for partitioning for acetanilide and some methyl acetanilides

Solute	<i>E</i>	<i>S</i>	<i>A</i>	<i>B</i>	<i>V</i>	$\log P_{\text{cyc}}$		$\log P_{\text{oct}}$		Cyclohexane		Octanol	
						Calc.	Obs.	Calc.	Obs.	ΔH°	ΔS°	ΔH°	ΔS°
Acetanilide	0.90	1.37	0.48	0.67	1.1137	-1.40	-1.37	1.16	1.20	23	66	-4	30
2-Methyl	0.87	1.27	0.31	0.92	1.2546	-1.25	-1.25	0.88	0.88	15	43	8	62
3-Methyl	0.87	1.10	0.57	0.73	1.2546	-0.99	-0.99	1.68	1.61	23	73	-4	37
4-Methyl	0.87	1.11	0.56	0.73	1.2546	-0.90	-0.90	1.70	1.61	33	110	-5	33
2,6-Dimethyl	0.85	1.56	0.37	0.95	1.3955	-1.48	-1.48	0.97	0.97	31	90	7	61
3,5-Dimethyl	0.85	1.14	0.54	0.73	1.3955	-0.32	-0.31	2.18	2.17 ^a	31	112	-4	44

^a Ref. 3; 2.06 from ref. 2.

interested in the phenols, because Dearden and Bresnen² obtained thermodynamic parameters for no fewer than 28 substituted phenols.

RESULTS

Values of ΔH° and ΔS° for partitioning of phenols in the water–cyclohexane and water–octanol systems, and the corresponding *A* and *B* parameters, are given in Table 1. It is clear, just by inspection, that there are indeed connections between the thermodynamic parameters and the hydrogen bond parameters. As an example, we show in Fig. 1 the values of ΔH° for partitioning in the water–cyclohexane system of phenol substituted with the NO₂, Cl and CHO groups, and the corresponding values of *A*. The latter are given as 10*A* to have the same scale for ΔH° and 10*A*. There is very good agreement between the substitution patterns for ΔH° and for *A*, confirming the suggestion of Dearden and Bresnen.² This might be expected in the water–cyclohexane system, where the substitution pattern is reflected in $\log P_{\text{cyc}}$. However, there is little effect of substitution pattern on $\log P_{\text{oct}}$ (see Table 1) and yet there is a very large effect on ΔH° and ΔS° in the water–octanol system (see Table 1). In Fig. 2 we show the substitution pattern on $-\Delta S^\circ$ and 100*A* and again there is very considerable similarity. This is remarkable considering the lack of effect on $\log P_{\text{oct}}$ itself.

Across all the substituted phenols in Table 1 (14, including phenol itself) there are considerable connections between the thermodynamic parameters and the hydrogen bond descriptor *A*. We show the connections between ΔH° and ΔS° for the water–octanol system and *A* in Figs 3 and 4. The data for phenol no. 8, 6-methyl-2-nitrophenol, seem out of line but possibly this might be due to compensating errors in ΔH° and ΔS° . However, this is the only compound where there is steric

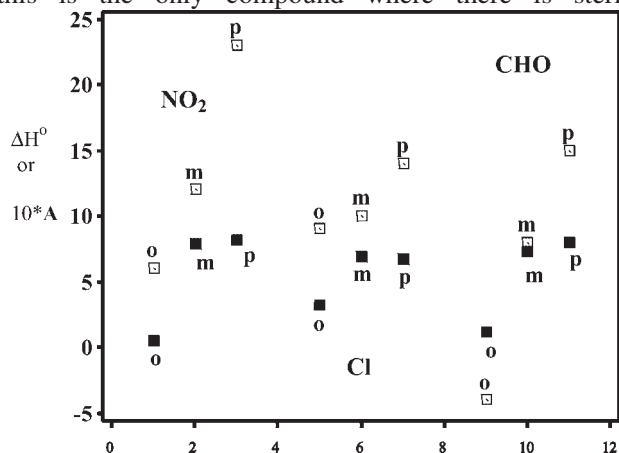


Figure 1. Variation of ΔH° in the water–cyclohexane system (or the descriptor 10*A*) with *o*-, *m*- or *p*-substituent in nitro-, chloro- and formyl-phenols; □ ΔH° , ■ 10*A*

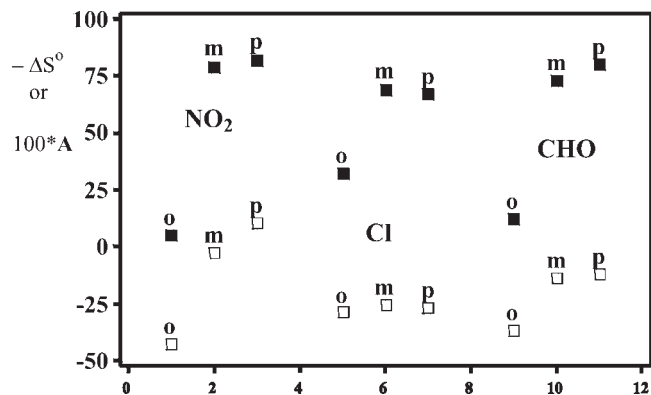


Figure 2. Variation of $-\Delta S^\circ$ in the water–octanol system (or the descriptor 100*A*) with *o*-, *m*- or *p*-substituent in nitro-, chloro- and formyl-phenols; □ $-\Delta S^\circ$, ■ 100*A*

enhancement of intramolecular hydrogen bonding, which might explain the discrepancy. Riebesehl and Tomlinson¹¹ have compared values of ΔH° for partitioning of a number of phenols, as obtained by the temperature dependence of equilibrium constants. They find differences from 8–9 kJ mol⁻¹ in ΔH° , so the possibility of experimental error must always be borne in mind. For thermodynamics of partition in the water–cyclohexane system a plot (not shown) of ΔS° against *A* is almost random, but a plot of ΔH° against *A* is a scattered line (see Fig. 5). Thus the general conclusion is that both the thermodynamics of partition and the hydrogen bond descriptors do indeed reflect the internal hydrogen bond structures of the phenolic 2-NO₂, 2-Cl and 2-CHO groups. A referee has suggested that the data in Figs 3 and 4 could be represented as falling on two straight lines, for compounds with and without 2-substitution respectively. However, we note that without the presence of 4-nitrophenol (the compound represented by the lowest and farthest right-hand point in both

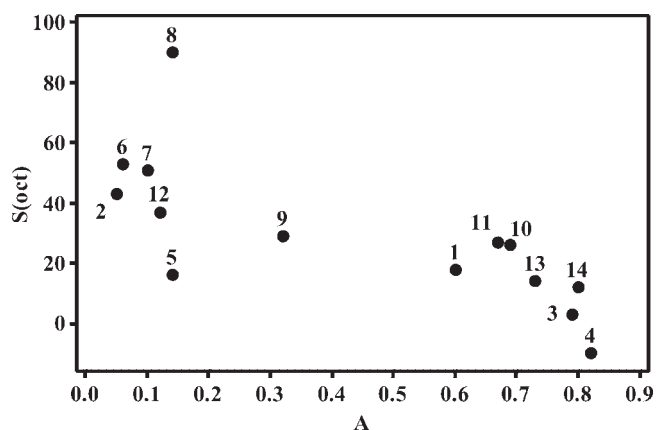


Figure 3. Plot of ΔS° in the water–octanol system, $S(\text{oct})$, against *A* for substituted phenols. Compounds are numbered as in Table 1

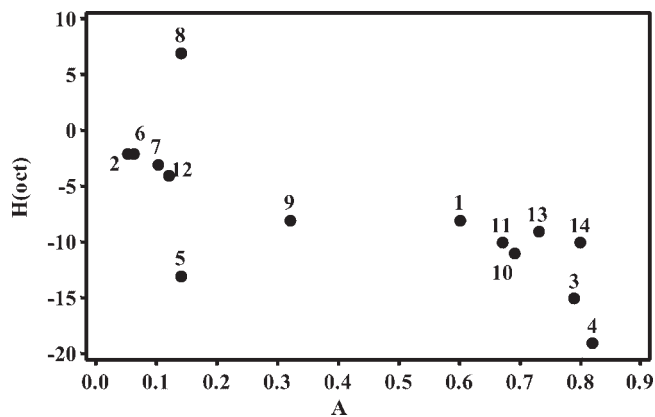


Figure 4. Plot of ΔH° in the water–octanol system, $H(\text{oct})$, against A for substituted phenols. Compounds are numbered as in Table 1

figures) the case for two separate correlations looks much less strong, and hence we prefer to postulate that the data lie on a single line, with 4-nitrophenol being considered an outlier.¹²

For the hydroxybenzoic acids (Table 2) there are not enough data to analyse thermodynamics in the water–cyclohexane system. However, just as for the phenols, there are effects in the water–octanol system. Here, the value of ΔS° for the 2-hydroxy acid is much more positive than that for the 3-hydroxy or the 4-hydroxy acid, and values of A and especially B for the 2-hydroxy acid are substantially different from those for the 3- and 4-hydroxy acids. These results are consistent with the presence of an intramolecular hydrogen bond in the 2-isomer.

Steric effects of *ortho*-methyl groups are more difficult to analyse, because the effects on partition are usually much smaller than effects of internal hydrogen bonding. In Table 3 the thermodynamics of partitioning for a number of methyl-substituted phenols, are given, together with the A and B parameters. There is little effect with increasing methyl substitution until 2,6-dimethylphenol, when ΔH° and ΔS° are unusually low in the water–cyclohexane system and unusually high in the water–octanol system. These effects correspond to a marked reduction in the A value. The A value is also low for 2,3,6- and 2,4,6-trimethylphenol as compared to 2,3,5-trimethylphenol (and 3,4,5-trimethylphenol, see Table 3), but now ΔS° is unusually high in the water–cyclohexane system and there is not much effect in the water–octanol system. Thus, where there are effects of *ortho*-substitution on ΔH° and ΔS° the A parameter is always lower than expected, although the thermodynamic effects are not consistently high or low.

The methyl-substituted benzoic acids also present a difficult situation (Table 2). Values of ΔH° and ΔS° are more negative for 2-methylbenzoic acid compared to 3- or 4-methylbenzoic acid in the water–cyclohexane system but there is little effect in the water–octanol

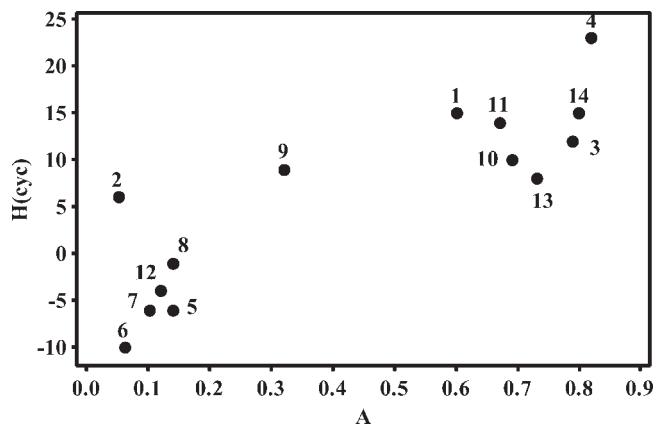


Figure 5. Plot of ΔH° in the water–cyclohexane system, $H(\text{cyc})$, against A for substituted phenols. Compounds are numbered as in Table 1

system. However, ΔH° and ΔS° are more positive for 2,6-dimethylbenzoic acid compared to 3,5-dimethylbenzoic acid in the water–cyclohexane system, and ΔH° is more positive in the water–octanol system. These rather peculiar effects almost exactly parallel effects on A and B . Whereas A is unusually small for 2-methylbenzoic acid, it is unusually large for 2,6-dimethylbenzoic acid. Although the reasons for these *ortho* effects may not be evident, it is clear that the thermodynamic effects parallel effects on hydrogen bond parameters; hence, both of these effects must derive from structural effects that probably involve steric shielding and/or twisting of the carboxylic group.

There is no evidence of any steric shielding or twisting in 2-methylbenzoic acid in the water–octanol system, because the thermodynamic parameters for all three isomers are very similar. There is some evidence of steric shielding from the water–cyclohexane data, with ΔH° being less positive and ΔG° being slightly more negative, for 2-methylbenzoic acid compared with the 4-isomer, as is the case for the xylenols. However, the low ΔS° value for 2-methylbenzoic acid in the water–cyclohexane system is not in line with dimethylphenol behaviour and could indicate some twisting of the carboxyl group, thereby reducing the extent of water-structuring in the aqueous phase. Cisarova *et al.*¹³ have shown by x-ray diffraction that the carboxyl group of 2,3-dimethylbenzoic acid is non-planar. The thermodynamic data for 3-methylbenzoic acid appear to be anomalous, and we have no explanation for this other than that the data might be erroneous.

2,6-Dimethylbenzoic acid, however, shows clear evidence of steric twisting of the carboxyl group, leading to loss of conjugation of the group with the aromatic ring. This renders the group more hydrophilic,¹⁴ and hence ΔG° values in both water–solvent systems are less negative than are the corresponding values for 3,5-dimethylbenzoic acid. Similarly, ΔH° values in both water–solvent systems are less negative than are those of

Table 5. The Abraham descriptors, $\log P_{\text{cyc}}$ and $\log P_{\text{oct}}$, and thermodynamic parameters for partitioning for some polyhydroxy compounds

Solute	<i>E</i>	<i>S</i>	<i>A</i>	<i>B</i>	<i>V</i>	$\log P_{\text{cyc}}$		$\log P_{\text{oct}}$		Cyclohexane		Octanol	
						Calc.	Obs.	Calc.	Obs.	ΔH°	ΔS°	ΔH°	ΔS°
2,6-Dihydroxy benzoic acid	1.10	1.05	1.26	0.56	1.0491	-3.41	-3.35	1.71	1.65	12	-7	-18	-10
3,5-Dihydroxy benzoic acid	1.10	1.25	1.70	0.75	1.0491	-6.33		0.85	0.80			-23	-39
2-Nitroresorcinol	1.21	1.35	0.01	0.48	1.0080	1.05	1.02	1.53	1.50	-3	23	-7	42

3,5-dimethylbenzoic acid, which may be attributed to strong interaction of the hydrophilic non-planar carboxyl group of 2,6-dimethylbenzoic acid with water. There is little effect of non-planarity of the carboxyl group on ΔS° in the water–octanol system. The ΔS° value of 3,5-dimethylbenzoic acid in the water–cyclohexane system is anomalously low, which may be attributable to self-association of this compound in cyclohexane (benzoic acids are known to undergo self-association at very low concentrations¹⁵). 2,6-Dimethylbenzoic acid would not be expected to self-associate because its carboxyl group is shielded.

Details for the methylacetanilides are given in Table 4. Compared to the *meta*- or *para*-substituted derivatives, the *ortho*-substituted acetanilides have lower values of ΔH° and ΔS° in the water–cyclohexane system but larger values of ΔH° and ΔS° in the water–octanol system. The effects on the thermodynamic parameters again parallel those on the hydrogen bond descriptors; *A* is low and *B* is high for the *ortho*-methyl substituents. This is reflected in effects on $\log P_{\text{cyc}}$ and $\log P_{\text{oct}}$, which are nearly two log units and one log unit, respectively. These are extraordinarily large for *ortho* effects of methyl groups, and show how difficult it is to construct schemes for the calculation and prediction of $\log P$ values.

Dearden and O'Hara¹⁰ drew attention to the unusual partitioning behaviour of 2-methyl acetanilide in the water–octanol system, and attributed it to loss of planarity of the acetamido group. It can be seen from Table 4 that the thermodynamic data confirm this, because ΔG° values in both water–solvent systems are less negative than the corresponding values for the 3- and 4-isomers, indicating the greater hydrophilicity of the non-planar acetamido group. ΔH° value in the water–octanol system is less negative (more positive), which probably indicates a reduced ability of octanol to interact with a shielded acetamido group; the high ΔS° value in the water–octanol system confirms this, being indicative of greater disorder in octanol than in aqueous solution. The ΔH° value in the water–cyclohexane system is, however, less positive, suggesting a partial screening of polarity and thus greater interaction with cyclohexane. Again, the entropy data confirm this, with ΔS° indicating a lower increase

in disorder on water–cyclohexane transfer than for the 3- and 4-isomers. The data for 2,6-dimethyl acetanilide, relative to its 3,5-isomer, are entirely consistent with the above explanations.

We may generalise the above as demonstrating that both the thermodynamics of partitioning and the Abraham descriptors can be used to establish the existence of steric effects in *ortho*-substituted benzene derivatives.

Dearden and Bresnen² also determined the thermodynamics of partitioning for a number of polyhydroxylic compounds. These are given in Table 5, which lists the descriptors and values of ΔH° and ΔS° . For the dihydroxybenzoic acids, Dearden and Bresnen² suggested that 2,6-dihydroxybenzoic acid forms only one intramolecular hydrogen bond. Certainly the difference in the thermodynamic parameters between the 2,6- and the 3,5-dihydroxybenzoic acids is the same as those between 2- and 4-hydroxybenzoic acids. The *A* value for the 2,6-dihydroxybenzoic acid is quite large, almost the same as for a free carboxylic group and a free phenolic group, and is in agreement with the assignment of only one intramolecular hydrogen bond.

For 2-nitroresorcinol, lack of data prevents comparison with an analogue that has no intramolecular hydrogen bond involving the nitro group, e.g. 5-nitroresorcinol. Dearden and Bresnen² suggested that in non-polar solvents 2-nitroresorcinol exists as a planar structure with two intramolecular hydrogen bonds, but that in polar solvents only one intramolecular bond is formed. Our calculations lead to *A* = 0.01, which indicates that in terms of partitioning 2-nitroresorcinol behaves as a completely non-acidic compound with two intramolecular hydrogen bonds. However, we note that the method of determination of descriptors yields macroscopic parameters that reflect the general behaviour of a solute in a variety of partitioning systems. This does not preclude differences in intramolecular hydrogen bonding from one system to another.

In conclusion, we show that two different methods of assessment of factors involved in water–solvent partitions lead to essentially the same conclusions about structural effects due to internal hydrogen bonding and steric effects of *ortho*-methyl groups.

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