

Thermodynamics of Water-octanol and Water-cyclohexane Partitioning of some Aromatic Compounds

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To my good friend Marvin Charton, whom I hold in the greatest respect and admiration for his untiring efforts over many years to clarify molecular processes, I dedicate this paper on the occasion of his 70th birthday.

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Abstract: The Gibbs free energy, enthalpy and entropy of partitioning of 45 simple aromatic compounds (phenols, benzoic acids and acetanilides) from water to octanol and from water to cyclohexane have been determined using the filter-probe method. This involved the measurement of partition coefficients over the temperature range 20-45°C. The aim of the work was to explore the effects of intramolecular hydrogen bonding and steric factors on the partitioning process. It was found that the intramolecular hydrogen bond is intact in 2-nitrophenol and salicylic acid, and possibly in 2-hydroxybenzaldehyde, in all three solvents, but 2-chlorophenol is intramolecularly hydrogen bonded only in inert solution. The evidence indicates that 2-nitroresorcinol and 2,6-dihydroxybenzoic acid possess only one intramolecular hydrogen bond, although they are theoretically capable of possessing two. There is evidence of steric shielding in 2,6-dimethylphenol, whilst 2,6-dimethylbenzoic acid and *ortho*-substituted acetanilides show evidence of steric twisting of the carboxyl and acetamido groups respectively out of the plane of the aromatic ring. Unusual steric effects are displayed in the methyl-2-nitrophenols whereby, depending upon the position of the methyl group, the intramolecular hydrogen bond is either weakened or strengthened.

Keywords: Partition coefficient, thermodynamics of partitioning, intramolecular hydrogen bond, steric effect

Introduction

The partition coefficient (P) of a compound has been shown over the years to be the single most important property controlling the transport in living organisms of xenobiotics such as drugs and environmental pollutants. Thousands of quantitative structure-activity relationships (QSARs) have been derived that utilise log P as a descriptor [1]. The 1-octanol-water system is generally used for the measurement or calculation of log P, although many other solvent pairs have also been used, especially the cyclohexane-water system. P is an equilibrium constant, and thus, from the van't Hoff isotherm, is a free energy term:

$$\Delta G = 2.303 \log P \quad (1)$$

where ΔG is the Gibbs free energy of transfer from water to pinguid solvent. However, it should be remembered that the Gibbs free energy is the difference between the enthalpy (ΔH) and the entropy (ΔS) of transfer:

$$\Delta G = \Delta H - T\Delta S \quad (2)$$

where T is the temperature (K). It is thus possible for two compounds with very similar log P values to have widely differing enthalpies and entropies of partitioning, indicating different partitioning mechanisms. Indeed, it is sometimes said that the log P term hides more than it reveals, at least so far as partitioning mechanisms are concerned. Because of this it is important, in considering partitioning mechanisms, to examine not only the free energy of partitioning but also the enthalpy and entropy of partitioning.

In an investigation of the effects of hydrogen bonding and steric effects on partitioning behaviour, we have determined the thermodynamics of partitioning of 45 compounds, comprising 34 phenols, 5 benzoic acids and 6 acetanilides, in both the water-octanol and the water-cyclohexane systems. We have used the van't Hoff approach, which involves measuring the partition coefficient of a chemical at a number of different temperatures, and obtaining from the van't Hoff isochore (eq. 3) the enthalpy of partitioning.

$$\text{Log } P = - 2.303 \Delta H/RT + \text{constant} \quad (3)$$

The method relies on the enthalpy of partitioning being constant over the temperature range used, which may not be the case when there is considerable mutual solubility of the two solvents [2], as in the case of octanol and water (Water-saturated octanol contains about 27 mole % water at 25°C).

Results and Discussion

The Gibbs free energy, enthalpy and entropy of partitioning of each of the 45 chemicals in the water-octanol and water-cyclohexane systems are given in Table 1. All of the van't Hoff plots of log P vs. 1/T for water-cyclohexane, and most of those for water-octanol, were rectilinear. For six compounds with non-rectilinear plots (see Experimental), tangents were taken at 25°C. It is accepted

that for these compounds the thermodynamic parameters probably contain greater error. We believe, however, that the consistency of the results means that they are reasonably accurate. Figure 1 depicts van't Hoff plots for nine of the chemicals, including some with non-rectilinear plots.

Table 1. Thermodynamic parameters (mole fraction scale) of partitioning from water to octanol (w→o) and from water to cyclohexane (w→c)

Compound	$\Delta G_{w \rightarrow o}^a$	$\Delta H_{w \rightarrow o}^a$	$\Delta S_{w \rightarrow o}^b$	$\Delta G_{w \rightarrow c}^a$	$\Delta H_{w \rightarrow c}^a$	$\Delta S_{w \rightarrow c}^b$
Phenol	-13.7	-8.4	17.7	-0.3	15.3	52.5
2-Chlorophenol	-17.0	-8.4	28.9	-9.1	8.6	59.4
3-Chlorophenol	-18.6	-10.9	26.4	-4.2	10.2	48.3
4-Chlorophenol	-18.6	-10.5	26.9	-2.8	14.0	56.4
2-Nitrophenol	-15.4	-2.5	43.3	-12.5	5.7	61.0
3-Nitrophenol	-16.2	-15.3	3.0	4.5	11.5	23.6
4-Nitrophenol	-16.1	-19.2	-10.3	6.4	23.0	55.5
2-Nitroresorcinol	-19.8	-7.3	41.9	-10.2	-3.3	23.4
2-Hydroxybenzaldehyde	-14.7	-3.7	37.1	-12.3	-3.5	29.6
3-Hydroxybenzaldehyde	-13.2	-8.9	14.4	6.7	7.9	3.8
4-Hydroxybenzaldehyde	-13.3	-9.6	12.4	8.5	15.3	22.8
Benzoic acid	-15.6	-8.4	24.1	0.4	6.6	20.8
2-Hydroxybenzoic acid	-18.0	-17.9	0.6	3.6	11.5	26.5
3-Hydroxybenzoic acid	-14.1	-19.2	-16.9	c	c	c
4-Hydroxybenzoic acid	-13.9	-23.0	-30.4	c	c	c
2,6-Dihydroxybenzoic acid	-14.8	-17.9	-10.3	14.6	12.5	-7.2
3,5-Dihydroxybenzoic acid	-11.3	-23.0	-39.1	c	c	*
3-Methyl-2-nitrophenol	-17.6	-12.8	16.3	-12.0	-5.7	20.9
4-Methyl-2-nitrophenol	-18.1	-2.2	53.4	-15.9	-9.9	20.2
5-Methyl-2-nitrophenol	-18.6	-3.4	51.2	-14.3	-5.7	28.6
6-Methyl-2-nitrophenol	-20.0	6.8	89.8	-15.6	-1.0	48.8
2-Methylphenol	-15.9	-7.7	28.3	-5.3	15.6	70.1
3-Methylphenol	-16.2	-8.1	27.5	-3.6	19.2	76.2
4-Methylphenol	-16.1	-8.4	26.7	-3.6	15.3	63.4
2,3-Dimethylphenol	-18.3	-9.1	30.9	-7.3	15.3	75.9
2,4-Dimethylphenol	-18.8	-9.6	31.4	-8.2	12.8	70.2
2,5-Dimethylphenol	-18.5	-9.9	29.1	-8.6	14.3	76.7
2,6-Dimethylphenol	-18.1	-3.6	48.6	-10.0	9.2	64.4
3,4-Dimethylphenol	-18.0	-10.1	27.2	-5.5	19.2	82.6
3,5-Dimethylphenol	-18.6	-10.5	26.9	-6.0	16.4	75.0
2,3,5-Trimethylphenol	-20.6	-6.7	47.6	-10.6	15.3	86.9
2,3,6-Trimethylphenol	-19.8	-5.7	47.9	-14.3	17.9	107.9
2,4,6-Trimethylphenol	-20.1	-3.8	55.7	-14.0	19.7	113.0

Table 1. Cont.

Compound	$\Delta G_{w \rightarrow o}^a$	$\Delta H_{w \rightarrow o}^a$	$\Delta S_{w \rightarrow o}^b$	$\Delta G_{w \rightarrow c}^a$	$\Delta H_{w \rightarrow c}^a$	$\Delta S_{w \rightarrow c}^b$
2,3,5,6-Tetramethylphenol	-21.1	-6.0	50.7	-14.6	13.8	95.3
2-Methylbenzoic acid	-18.1	-12.5	18.9	-2.2	2.7	16.7
3-Methylbenzoic acid	-19.1	-13.4	19.0	-6.5	20.4	90.4
4-Methylbenzoic acid	-18.7	-12.1	22.0	-1.4	6.7	27.3
2,6-Dimethylbenzoic acid	-16.9	-5.7	37.3	1.3	14.0	42.8
3,5-Dimethylbenzoic acid	-21.6	-11.5	34.0	-4.8	-9.2	-14.9
Acetanilide	-12.4	-3.5	29.9	3.4	23.0	65.8
2-Methylacetanilide	-10.3	8.3	62.2	2.7	15.3	42.5
3-Methylacetanilide	-14.5	-3.5	37.2	1.2	23	73.3
4-Methylacetanilide	-14.5	-4.6	33.3	0.7	33.3	109.6
2,6-Dimethylacetanilide	-11.0	7.2	60.9	3.9	30.6	89.7
3,5-Dimethylacetanilide	-16.9	-3.8	43.9	-2.7	30.6	111.9

^a Units are kJ mol⁻¹

^b Units are J mol⁻¹ K⁻¹

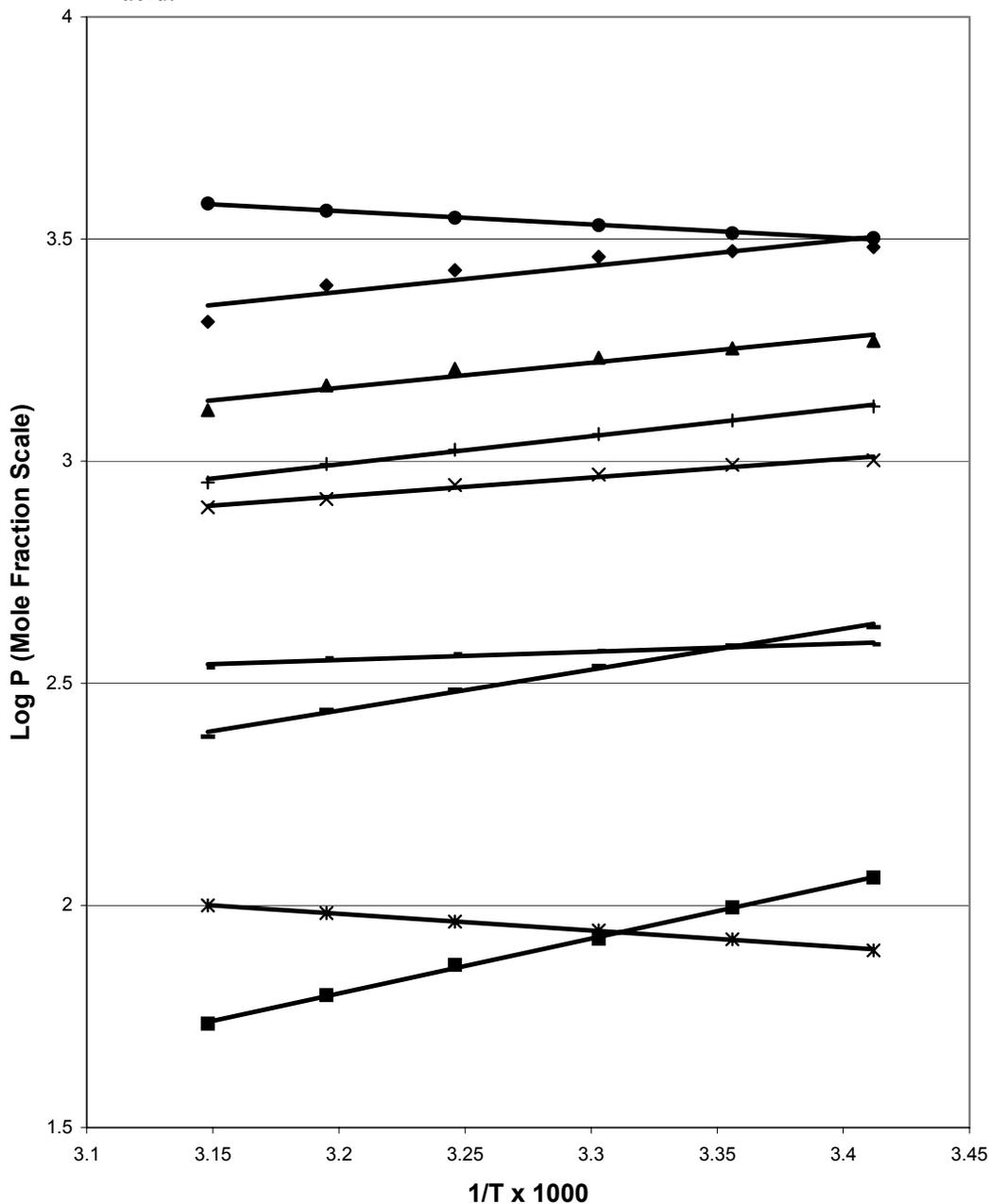
^c Compound too insoluble in cyclohexane for log P to be measured

It has been postulated [3] that ΔH and ΔS should be rectilinearly correlated for a system or process operating by a single mechanism, although it has been pointed out [4] that since ΔH and ΔS are derived from the same set of data, such enthalpy-entropy compensation could be a statistical artefact. The use of ΔG - ΔH is preferred [2] for this reason. In fact, for our data, there is good enthalpy-entropy correlation in the water-octanol system ($n = 45$, $r^2 = 0.852$) but not in the water-cyclohexane system ($n = 42$, $r^2 = 0.529$). There is virtually no ΔG - ΔH correlation in either system; however, when sub-sets of compounds are examined separately, there are good ΔG - ΔH correlations in both systems. For example, for the four methyl-2-nitrophenols in the water-octanol system the coefficient of variation (r^2) is 0.865. We interpret this to mean that our data are valid, and that there are multiple mechanisms of partitioning within our data-set, with distinctions being made even between, for example, methylphenols and dimethylphenols.

Intramolecular Hydrogen Bonding

2-Chlorophenol, 2-nitrophenol and the four methyl-2-nitrophenols, 2-nitroresorcinol, 2-hydroxybenzaldehyde, 2-hydroxybenzoic acid (salicylic acid) and 2,6-dihydroxybenzoic acid are all capable of intramolecular hydrogen bonding. This reduces polarity and intermolecular hydrogen bonding ability, and might therefore be expected to increase partition coefficient. However, there is no consistent effect of intramolecular hydrogen bonding on octanol-water partition coefficients; 2-hydroxybenzaldehyde is more hydrophobic (ΔG more negative) than are its 3- and 4-isomers, whereas 2-nitrophenol is less hydrophobic than are its isomers.

Figure 1. van't Hoff plots for nine of the compounds used in this work: (●) 6-methyl-2-nitrophenol; (◊) 2,3,6-trimethylphenol; (▲) 4-chlorophenol; (+) 3-methyl-2-nitrophenol; (x) 2-chlorophenol; (-) 2-hydroxybenzaldehyde; (–) 2,6-dihydroxybenzoic acid; (*) 2,6-dimethylacetanilide; (■) 3,5-dihydroxybenzoic acid.



The hydrogen bond donor ability of water is much greater than is that of octanol, whilst their hydrogen bond acceptor abilities are about the same [5]. The involvement of the carbonyl oxygen of 2-hydroxybenzaldehyde in intramolecular hydrogen bonding thus reduces its interaction with water more than it reduces its interaction with octanol, thereby increasing hydrophobicity. The involvement of the nitro group of 2-nitrophenol in intramolecular hydrogen bonding still leaves one nitro group oxygen atom available for intermolecular hydrogen bonding with water, thus preventing an increase in hydrophobicity [6]. The situation with salicylic acid is more complex; intramolecular hydrogen

bonding leaves a carbonyl oxygen and a hydroxyl group still available for intermolecular hydrogen bonding, and it is difficult to predict the overall effect on hydrophobicity. In fact, salicylic acid is more hydrophobic (in the water-octanol system) than are its 3- and 4-isomers. This is confirmed by its low aqueous solubility (0.18% w/v at 20°C) relative to that of its 3-isomer (0.92% w/v at 20°C) [7]. Theoretical studies have also shown that salicylic acid is intramolecularly hydrogen bonded in aqueous solution [8]. The rather lower hydrophobicity of 2,6-dihydroxybenzoic acid suggests that this compound may possess only one intramolecular hydrogen bond in the water-octanol system. The similarity of the hydrophobicities and aqueous solubilities [7] of all the chlorophenols suggests that 2-chlorophenol may not be intramolecularly hydrogen bonded in water or octanol. It has also been shown [9] that the intramolecular hydrogen bond in 2-chlorophenol is broken in the presence of the hydrogen bond acceptor ethyl propionate.

In the water-octanol system, the enthalpy and entropy of transfer of 2-chlorophenol, 2-nitrophenol, 2-hydroxybenzaldehyde and 2-hydroxybenzoic acid are in each case less negative than are those of the corresponding 3- and 4-isomers. It is probably better to compare values between the 2- and 4-isomers (Table 2), since the 3-isomers are not capable of classical resonance interaction between substituents.

Table 2. Differences between 2- and 4-substituted phenols of enthalpies ($\Delta\Delta H$) and entropies ($\Delta\Delta S$) of transfer from water to octanol and from water to cyclohexane

Compound	$\Delta\Delta H_{w \rightarrow o}$ ^a	$\Delta\Delta S_{w \rightarrow o}$ ^b	$\Delta\Delta H_{w \rightarrow c}$ ^a	$\Delta\Delta S_{w \rightarrow c}$ ^b
Chlorophenol	1.9	2.0	-5.4	3.0
Nitrophenol	16.7	33.0	-17.3	5.5
Hydroxybenzaldehyde	5.9	24.7	-18.8	6.8
Hydroxybenzoic acid	5.1	3.0	^c	^c

^a Units are kJ mol⁻¹

^b Units are J mol⁻¹ K⁻¹

^c Compound too insoluble in cyclohexane for log P to be measured

The positive $\Delta\Delta H$ values for transfer from water to octanol are a consequence of the weak hydrogen bond donor ability of octanol relative to that of water; since an intramolecularly hydrogen bonded –OH group is unavailable for intermolecular hydrogen bond donation to solvent, there is more solute-solvent interaction in water than in octanol, for intramolecularly hydrogen bonded compounds. Hence transfer from water to octanol is enthalpically less favourable. The positive $\Delta\Delta S$ values for transfer from water to octanol confirm the above, since less solute-solvent interaction in octanol than in water gives rise to greater disorder of solvent molecules consequent upon solute transfer. The negative $\Delta\Delta H$ values for transfer from water to cyclohexane indicate greater interaction of intramolecularly hydrogen bonded compounds with the non-polar solvent, probably reflecting the less polar nature of these compounds relative to their 4-isomers. This greater interaction accounts also for their low $\Delta\Delta S$ values relative to those for transfer from water to octanol.

It can be seen from Table 2 that the $\Delta\Delta H$ and $\Delta\Delta S$ values for transfer of 2-chlorophenol from water to octanol are close to zero. We interpret this to indicate that the intramolecular hydrogen bond in 2-chlorophenol is very weak or non-existent in water and octanol, as already suggested by

consideration of hydrophobicities. However, the negative $\Delta\Delta H$ value for transfer from water to cyclohexane indicates at least partial intramolecular hydrogen bonding of 2-chlorophenol in cyclohexane, leading to greater interaction with the non-polar solvent. In support of this, there is infrared spectroscopic evidence of such hydrogen bonding of 2-chlorophenol in tetrachloromethane [10]. Entropically, the increased interaction with cyclohexane is more than offset by the release of structured water upon transfer from the aqueous phase.

The strongly positive $\Delta\Delta H_{w\rightarrow o}$ and $\Delta\Delta S_{w\rightarrow o}$ values for transfer of 2-nitrophenol indicate that the intramolecular hydrogen bond is intact in this compound in both solvents, as found also by Abraham *et al.* [6]. The significantly negative $\Delta\Delta H_{w\rightarrow c}$ value, indicating strong solute-cyclohexane interaction, also confirms the existence of the intramolecular hydrogen bond of 2-nitrophenol in cyclohexane solution. As with 2-chlorophenol, the effect of such increased interaction is more than offset by the release of structured water upon transfer from the aqueous phase, leading to a slightly positive $\Delta\Delta S_{w\rightarrow c}$ value.

Similar interpretations can be placed on the thermodynamic parameters for phase transfer of 2-hydroxybenzaldehyde. The low $\Delta\Delta H_{w\rightarrow o}$ value for this compound may indicate that its intramolecular hydrogen bond is not wholly intact in polar solvents, in agreement with the findings of Berthelot *et al.* [11]. The $\Delta\Delta H_{w\rightarrow c}$ and $\Delta\Delta S_{w\rightarrow c}$ values, however, confirm that it is intact in cyclohexane solution.

The $\Delta\Delta H_{w\rightarrow o}$ and $\Delta\Delta S_{w\rightarrow o}$ values for transfer of 2-hydroxybenzoic acid are, like those of 2-chlorophenol, quite close to zero. However, as pointed out above, aqueous solubility values indicate that salicylic acid is intramolecularly hydrogen-bonded in water, and therefore presumably also in octanol. The low $\Delta\Delta H_{w\rightarrow o}$ and $\Delta\Delta S_{w\rightarrow o}$ values for 2-hydroxybenzoic acid are probably due to the fact that the compound still has an -OH group able to form intermolecular hydrogen bonds with both water and octanol.

Both 2-nitroresorcinol and 2,6-dihydroxybenzoic acid are theoretically capable of forming two intramolecular hydrogen bonds. The increase in hydrophobicity in the water-octanol system of 2-nitroresorcinol relative to that of 2-nitrophenol implies that the compound does possess two intramolecular hydrogen bonds. However, the lower $\Delta H_{w\rightarrow o}$ value of the former suggests that only one intramolecular hydrogen bond exists in 2-nitroresorcinol in water and octanol solutions, as does the close similarity of the $\Delta S_{w\rightarrow o}$ values of 2-nitrophenol and 2-nitroresorcinol. Berthelot *et al.* [12] have shown that compounds with the potential to form two intramolecular hydrogen bonds actually form only one in the presence of a polar hydrogen bond donor.

The situation appears different for 2-nitroresorcinol in cyclohexane solution. Its $\Delta H_{w\rightarrow c}$ value is more negative than is that of 2-nitrophenol, which suggests that the compound possesses two intramolecular hydrogen bonds in cyclohexane solution. Its relatively low $\Delta S_{w\rightarrow c}$ value confirms this, since it suggests that there is relatively little structured water around 2-nitroresorcinol molecules in aqueous solution, leading to a relatively small entropy increase upon transfer to cyclohexane. Boykin [13] has observed both intramolecular hydrogen bonds of 2-nitroresorcinol to be intact in toluene solution. Ultraviolet spectroscopic data support the above hypothesis. In contrast to the behaviour of 2-nitrophenol, we found a pronounced hypsochromic shift of the spectrum of 2-nitroresorcinol on going from cyclohexane to ethanolic or aqueous solution, consistent with breaking of an intramolecular hydrogen bond and consequent loss of planarity of the nitro group.

The lower hydrophobicity of 2,6-dihydroxybenzoic acid relative to that of salicylic acid suggests that this compound also has only one intramolecular hydrogen bond in water and octanol. Its entropy

of transfer from water to octanol is considerably lower than that of salicylic acid, suggesting hydrogen bond donation to octanol. The enthalpies of transfer of the two compounds are the same, arising presumably from the very similar hydrogen bond acceptor abilities of water and octanol. That there is certainly one intramolecular hydrogen bond present in 2,6-dihydroxybenzoic acid is shown by the compound's greater hydrophobicity and less negative $\Delta H_{w \rightarrow o}$ and $\Delta S_{w \rightarrow o}$ values relative to 3,5-dihydroxybenzoic acid. The water-cyclohexane data also indicate that, unlike the situation in 2-nitroresorcinol, there is only one intramolecular hydrogen bond present in 2,6-dihydroxybenzoic acid in cyclohexane solution. This follows because the changes in $\Delta G_{w \rightarrow c}$, $\Delta H_{w \rightarrow c}$ and $\Delta S_{w \rightarrow c}$ relative to those for salicylic acid all mirror those for transfer from water to octanol.

Steric effects

In the compounds that we have examined, two main steric effects may be postulated: shielding of a polar group, and twisting of a polar group out of the plane of the aromatic ring, by adjacent alkyl substitution. The $\Delta G_{w \rightarrow o}$, $\Delta H_{w \rightarrow o}$ and $\Delta S_{w \rightarrow o}$ values of the three cresols (methylphenols) are all very similar, suggesting that there is no steric shielding of the -OH group in 2-methylphenol. For transfer from water to cyclohexane a slight effect could be apparent, although, bearing in mind the experimental errors in the determination of thermodynamic parameters by the van't Hoff method, this could be an artefact. If the effect is real, our interpretation is that shielding of the -OH group renders 2-methylphenol less polar, thereby increasing the partition coefficient and lowering $\Delta G_{w \rightarrow c}$. However, this is not confirmed by the $\Delta H_{w \rightarrow c}$ and $\Delta S_{w \rightarrow c}$ values, so our conclusion must be that the data show no consistent indication of steric shielding in 2-methylphenol.

2,6-Xylenol (2,6-dimethylphenol) does, however, show a significant shielding effect. Transfer from water to octanol involves a less negative $\Delta H_{w \rightarrow o}$ value and a more positive $\Delta S_{w \rightarrow o}$ value than those of the other isomers; its $\Delta G_{w \rightarrow o}$ value, however, is very close to those of its isomers. The data are interpreted as indicating more structured water around the molecule in aqueous solution, leading to breaking of hydrogen bonds between water molecules upon transfer to octanol and a consequent increase in disorder. Transfer from water to cyclohexane involves a more negative $\Delta G_{w \rightarrow c}$ value and less positive $\Delta H_{w \rightarrow c}$ and $\Delta S_{w \rightarrow c}$ values than those of the other isomers. These all indicate a significant solute-cyclohexane interaction, consistent with appreciable shielding of the -OH group and lowering of effective polarity.

Additional methyl substitution does not appear to give rise to additional shielding, even in 2,3,6-trimethylphenol and 2,3,5,6-tetramethylphenol, where a buttressing effect of two adjacent methyl groups might have been expected. The methyl-substituted benzoic acids show a somewhat similar pattern to the methyl-substituted phenols. Despite the greater size of the carboxyl group compared with the hydroxyl group, there is no evidence of any steric shielding or twisting in 2-methylbenzoic acid in the water-octanol system, since the thermodynamic parameters for all three isomers are very similar. There is some evidence of steric shielding from the water-cyclohexane data, with $\Delta H_{w \rightarrow c}^0$ being less positive, and $\Delta G_{w \rightarrow c}$ being slightly more negative, for 2-methylbenzoic acid compared with the 4-isomer, as is the case for the xylenols. However, the low $\Delta S_{w \rightarrow c}$ value for 2-methylbenzoic acid 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.* [14] have shown by X-ray diffraction that the carboxyl group of 2,3-dimethylbenzoic acid is non-planar. The data for 3-

methylbenzoic acid appear to be anomalous, and we have no explanation for this, other than that the data are 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 [15], and hence both $\Delta G_{w \rightarrow o}$ and $\Delta G_{w \rightarrow c}$ are less negative than the corresponding values for 3,5-dimethylbenzoic acid. Similarly, $\Delta H_{w \rightarrow o}$ and $\Delta H_{w \rightarrow c}$ are both less negative than those of 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 $\Delta S_{w \rightarrow o}$. The $\Delta S_{w \rightarrow c}$ value of 3,5-dimethylbenzoic acid 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 concentrations [16]. 2,6-Dimethylbenzoic acid would not be expected to self-associate because its carboxyl group is shielded.

Dearden and O'Hara [17] drew attention to the unusual partitioning behaviour of 2-methylacetanilide in the water-octanol system, and attributed it to loss of planarity of the acetamido group. It can be seen from Table 1 that the thermodynamic data confirm this, as $\Delta G_{w \rightarrow o}$ and $\Delta G_{w \rightarrow c}$ are less negative than the corresponding values for both the 3- and 4-isomers, indicating the greater hydrophilicity of the non-planar acetamido group. $\Delta H_{w \rightarrow o}$ is less negative (more positive), which probably indicates a reduced ability of octanol to interact with a shielded acetamido group; the high $\Delta S_{w \rightarrow o}$ value confirms this, being indicative of greater disorder in octanol than in aqueous solution. $\Delta H_{w \rightarrow c}$, however, is less positive, suggesting a partial screening of polarity and thus greater interaction with cyclohexane. Again, the entropy data confirm this, with $\Delta S_{w \rightarrow c}$ indicating a lower increase in disorder on water-cyclohexane transfer than for the 3- and 4-isomers. The data for 2,6-dimethylacetanilide, relative to its 3,5-isomer, are entirely consistent with the above explanations.

A very interesting aspect of steric effects is shown by the methyl-2-nitrophenols. Dearden and Forbes [18] used ultraviolet absorption spectroscopy to show that in 3-methyl-2-nitrophenol steric hindrance by the methyl group puts a strain upon the intramolecular hydrogen bond. In cyclohexane solution this strain is insufficient fully to rupture the hydrogen bond, as was observed by Boykin [13] for the compound in toluene solution. However, in hydrogen bonding solvents such as water and ethanol, competing solute-solvent hydrogen bonding is sufficient to cause rupture of the intramolecular hydrogen bond. In 6-methyl-2-nitrophenol, on the other hand, the effect of the methyl group is to push the hydroxyl group closer to the nitro group, thus strengthening the intramolecular hydrogen bond.

The partitioning data largely support the above. $\Delta H_{w \rightarrow o}$ is much more negative for 3-methyl-2-nitrophenol than for the other isomers, suggesting less structured water present, and therefore fewer water-water hydrogen bonds to be broken on transfer to octanol; this is confirmed by the very low $\Delta S_{w \rightarrow o}$ value for 3-methyl-2-nitrophenol. Conversely, for 6-methyl-2-nitrophenol, with a very strong intramolecular hydrogen bond, $\Delta H_{w \rightarrow o}$ is actually positive and $\Delta S_{w \rightarrow o}$ is much more positive than for the other isomers. The water-cyclohexane transfer data indicate that the intramolecular hydrogen bond in 3-methyl-2-nitrophenol is intact in cyclohexane solution, as $\Delta H_{w \rightarrow c}$ values are similar in 3-, 4- and 5-methyl-2-nitrophenols. The high strength of the intramolecular hydrogen bond in 6-methyl-2-nitrophenol is shown by its less negative $\Delta H_{w \rightarrow c}$ value and its highly positive $\Delta S_{w \rightarrow c}$ value, both of which indicate a high level of structured water in aqueous solution, leading to rupture of water-water hydrogen bonds and concomitant increase in disorder upon transfer to cyclohexane.

Conclusions

Analysis of the thermodynamics of partitioning between water and octanol and between water and cyclohexane has shown that the existence of intramolecular hydrogen bonding in compounds such as 2-nitrophenol, 2-hydroxybenzaldehyde and salicylic acid can be clearly detected. However, in 2-nitroresorcinol and 2,6-dihydroxybenzoic acid a second intramolecular hydrogen bond does not appear to be formed in polar solvents. Our results also show that no intramolecular hydrogen bond exists in 2-chlorophenol in polar solvents, although it appears to exist in cyclohexane solution.

Steric effects such as shielding of polar groups and twisting of conjugated groups out of the plane of the aromatic ring can be seen from the thermodynamics of partitioning of compounds such as 2,6-dimethylphenol, 2,6-dimethylbenzoic acid and 2-methylacetanilide.

Experimental

Compounds were obtained from a variety of commercial sources, and were purified by crystallisation or distillation. Cyclohexane and 1-octanol were of spectroscopic grade quality. Partition coefficients in the octanol-water and cyclohexane-water systems were measured over the temperature range 20-45°C using the filter-probe method modified by Kinkel *et al.* [2] from the original method developed by Cantwell and Mohammed [19]. It comprised a thermostatted mixing chamber whose contents could be vigorously stirred using a magnetic stirring bar; the output from the chamber was passed through either a hydrophilic (Whatman No. 1) or a hydrophobic (Whatman PS) filter paper, and the filtered solution passed into a thermostatted Perkin Elmer 550 ultraviolet absorption spectrophotometer and then returned to the mixing chamber. A full description of the apparatus is given in Kinkel *et al.* [2]. Solvents were pre-equilibrated for 24 hours in order to achieve mutual saturation. All spectrophotometric calibration plots were rectilinear over the concentration ranges used, and all determinations were carried out in duplicate.

Partition coefficients were obtained at six temperatures from 20 to 45°C, and were calculated on a mole fraction basis and converted to ΔG values using eq. 1. ΔH values were obtained from the slope of the $\log P-1/T$ plots, and ΔS values were obtained from eq. 2. Most of the $\log P-1/T$ plots were rectilinear, including all those for the cyclohexane-water system. A few showed a slight convex curvature in the octanol-water system, and for those compounds the slope was taken as the tangent at 25°C. The compounds with non-rectilinear plots were 3-chlorophenol, 4-chlorophenol, 2,3,5-trimethylphenol, 2,3,6-trimethylphenol, 2,4,6-trimethylphenol and 3,5-dimethylacetanilide.

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