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PARTITION COEFFICIENTS AND INTRAMOLECULAR HYDROGEN BONDING. 2. THE INFLUENCE OF PARTITION SOLVENTS ON THE INTRAMOLECULAR HYDROGEN-BOND STABILITY OF SALICYCLIC ACID DERIVATIVES

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The intramolecular hydrogen bonding (chelation) of salicylaldehyde, methyl salicylate, *N,N*-dimethylsalicylamide and 2-hydroxyacetophenone was studied by IR spectroscopy in different phases used for partition coefficient determinations. The extent of chelation was found to be highly sensitive to the solvent and to the substituent on the carbonyl group in the orders carbon tetrachloride = chloroform ≫ octanol > water ≫ dimethyl sulfoxide and OMe ≈ Me > H ≫ NMe_2. These sequences are discussed in terms of hydrogen-bond acidity of the hydroxyl group, hydrogen-bond basicity of the carbonyl group, planarity of the solute molecule and hydrogen-bond acidity/basicity properties of the solvent. Semi-empirical and *ab initio* calculations confirmed the substituent sequence.

INTRODUCTION

In the last decade, significant advances have been made in the treatment of partition coefficients in terms of solute structural parameters.[1–5] General solvation equations have been set up indicating that it is now possible to assign to the solute interpretable structural descriptors that satisfactorily reproduce partition coefficients for a wide diversity of binary phases. However, depending on the nature of the solvent, numerous solute molecules undergo drastic structural modifications such as tautomerization, ionization, self-association or intramolecular hydrogen bonding.When partition coefficients are treated by general solvation equations such as those cited above, 'global' or 'average' descriptors are obtained for all compounds present in two (or more) interconverting forms in the partitioning solvents. This lead to an important loss of structural information on the solute–solvent interactions of the individual forms. In a recent detailed analysis of the partitioning of acetylacetone, Abraham and Leo[6] showed that the individual parameters for the keto and enol structures are accessible provided that the relative amounts of the two forms are known in all phases.

This series of three papers analyses the influence of intramolecular hydrogen bonds* on the hydrogen-bond acidity and basicity abilities of solute molecules with the aim of obtaining a better understanding of their well known action in partition coefficients.[7] Part 1[8] was devoted to the quantitative measurement of the residual hydrogen-bond basicity of chelated systems dissolved in carbon tetrachloride. This paper studies the extent of intramolecular hydrogen bonding (equilibrium **a** ⇌ **b**†) for a set of four salicylic acid derivatives **1**–**4** in carbon tetrachloride, chloroform, water, octanol and dimethyl sulfoxide (DMSO). The methylated compounds **5**–**8** were studied for comparison.

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* For the sake of simplicity, we also use the old term 'chelation' that has been widely used as a synonym of intramolecular hydrogen bonding in salicylic compounds.[9]

† The process **a** → **b** will be called 'dechelation.'

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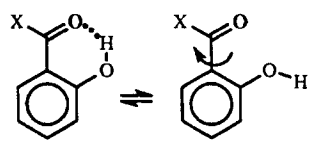
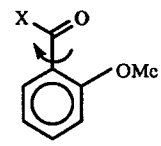


a b

X = H 1
Me 2
OMe 3
NMe_2 4



X = H 5
Me 6
OMe 7
NMe_2 8

The four first solvents were chosen because octanol–water, alkane‡–water and chloroform–water are important systems for the determination of biologically relevant partition coefficients.[10–12] As a pure hydrogen-bond acceptor, DMSO was added to the pure hydrogen-bond donor $CHCl_3$ in order to disentangle the respective contributions of hydrogen-bond acidity and basicity to the amphoteric behavior of octanol and water.

Theoretical calculations show that the salicylic derivatives **1–4** are fully chelated *in vacuo*. IR study of the carbonyl, hydroxyl and ring stretching vibrations demonstrates that this result extends to alkanes CCl_4 and $CHCl_3$ but not to water or octanol, which can, partially or totally, break the chelation. As will be shown in Part 3, this has evident and important consequences on partitioning.

EXPERIMENTAL

We have already described[8] the origin and purification of compounds **1–8** and the measurements of FTIR spectra.

The organic solvents were carefully dried and ethanol was removed from chloroform. Water measurements were carried out with heavy water in order to avoid the absorption of H_2O near 1630 cm^{-1}. This leads to rapid deuteration of the phenolic hydrogen in **1–4** and to significant shifts (*ca* 3–4 cm^{-1}) of the ν(C=O) and ν_{8a} bands toward lower wavenumbers attributed to vibrational decoupling and not to solvation effects. Owing to the low water solubility of methyl salicylate, IR data in pure water were extrapolated from acetonitrile–water mixture data (the amount of water was increased up to 25 M).

The overlapping IR bands were either deconvoluted or mathematically decomposed with a Gauss–Lorentz profile.

The theoretical calculations were performed with the Spartan 4.0 program implemented on a Silicon Graphics Indigo station.

RESULTS AND DISCUSSION

Theoretical calculations *in vacuo*

The ΔH_f^{298} (AM1, PM3) and ΔE_0 (STO-3G, 6–31G) values were calculated for the dechelation (DC) process **a**⟶**b** as the difference between **b** in the most stable dechelated conformation minus **a**. They differ little from the Gibbs free energy ΔG_{DC} since entropy calculations show little or no ΔS_{DC}. Table 1 shows the values of ΔG_{DC} ($\approx \Delta H_{DC} \approx \Delta E_{DC}$).

It is evident that the four compounds are fully chelated *in vacuo* (the equilibrium constants for **a**⇌**b** vary between *ca* 10^{-4} and 10^{-6}). The chelation stability order **4a**(NMe_2) < **1a**(H) < **2a**(Me) < **3a**(OMe) is found by all four calculations (except the inversion of **4a** and **1a** at the 6–31G level). A near planar geometry is found for **1a–3a** but not for **4a**, where the plane of the amide function is not coplanar with the benzene ring.

IR spectra in carbon tetrachloride (alkanes)

Results of calculations *in vacuo* should apply for experiments in alkanes or CCl_4. We have already shown in Part 1[8] that compounds **1–4** are totally present as form **a** in CCl_4. This result extends to alkanes since there is no known example where an intramolecular hydrogen bond is broken on going from CCl_4 to alkanes. The IR conclusion for **1–4** in CCl_4 follows from the fact that no absorption attributed to the free ν(OH) vibrator is observed near 3600 cm^{-1}. This region cannot be analysed in the other solvents (D_2O, octanol, DMSO) because of either a lack of IR transparency and/or the difficulty in distinguishing the stretchings of the OH group engaged in an intramolecular hydrogen bond or in an intermolecular hydrogen bond with the solvent. Therefore, we studied the 1550–1750 cm^{-1} region where the ν(CO) and the two ring absorptions denoted ν_{8a} and ν_{8b} are found. In CCl_4, comparison of compounds **1–4** in form **a** with their methylated analogs **5–8** suggest the following: the chelation provokes a large shift of the carbonyl absorption toward lower wavenumbers and a shift in the opposite direction of the ν_{8a} band (the ν_{8b} absorption remains almost unchanged). Figure 1(A) shows that $\Delta\nu(CO) = -34$ cm^{-1} and

Table 1. Calculated ΔG (kcal mol^{-1}) for the dechelation of salicyclic derivatives **1–4**

Compound	Substituent X	AM1	PM3	STO-3G	6–31G
4	Me_2N	3·1	3·0	7·5	7·0
1	H	3·9	3·4	8·1	6·0
2	Me	5·1	4·2	8·5	7·6
3	MeO	5·8	4·5	11·0	10·9

‡ CCl_4 was used instead of alkanes because of better solubility and IR transparency (see below).

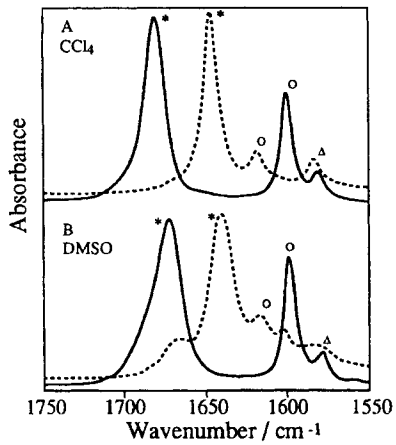
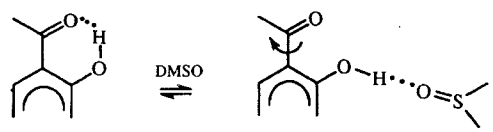


Figure 1. ν(C=O) (*), ν_{8a} (o) and ν_{8b} (Δ) absorptions of 2-hydroxyacetophenone (dotted lines) and 2-methoxyacetophenone (solid lines) in (A) carbon tetrachloride and (B) dimethyl sulfoxide

$\Delta\nu_{8a} = +18{\cdot}3$ cm^{-1} for 2-hydroxy- and 2-methoxyacetophenone (Δ = 2-OMe minus 2-OH).

IR spectra in dimethyl sulfoxide

On going from CCl_4 to DMSO, the ν(CO) band of 2-methoxyacetophenone is shifted from 1679·9 to 1671·5 cm^{-1} by van der Waals forces and the two ν_8 absorptions remain almost unchanged [see Figures 1(A) and 1(B)]. However, the spectrum of 2-hydroxyacetophenone in DMSO [Figure 1(B), dotted line] becomes more complex than in CCl_4 [Figure 1(A), dotted line] since two new bands appear at 1665 and 1601·6 cm^{-1}. These new bands clearly correspond to the ν(CO) and ν_{8a} of **2** in form **b** where the intramolecular hydrogen bond is broken and replaced by an OH···$OSMe_2$ intermolecular hydrogen bond [equilibrium (1)].



a **b** (1)

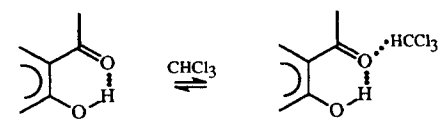
Assuming that the extinction coefficients of the carbonyl bands at 1665 and 1639 cm^{-1} in DMSO, corresponding to forms **2b** and **2a**, respectively, are roughly the same, the amount of dechelation can be estimated, from the band intensity ratio, to be *ca* 15%.

The IR spectra of the three other salicylic acid derivatives **1**, **3** and **4** dissolved in DMSO were analysed using the same method. Methyl salicylate (**3**), salicylaldehyde (**1**), and *N*,*N*-dimethylsalicylamide (**4**) are 25%, 70% and 100%, respectively, present as form **b** in which the intramolecular hydrogen bond has been broken by DMSO.

DMSO appears clearly as a powerful 'intramolecular hydrogen-bond breaker.' This is probably due to its strong hydrogen-bond basicity, form **b** being stabilized by an intermolecular hydrogen bond with the sulfoxide group, as revealed by the appearance of a broad ν(OH···O=S) band in the spectrum of **4**. The spectra of **1**, **2** and **3** are less clear because of the superposition of ν(OH···O=C) and ν(OH···O=S) absorptions.

IR spectra in chloroform

On passing from CCl_4 to neat or to water-saturated chloroform (the actual phase in water–chloroform partition), there is no appearance of any carbonyl, hydroxyl or ring stretching absorptions characteristic of the **b** form in compounds **1**–**4**. We only observe a slight shift (**3**–**4** cm^{-1}) of the carbonyl band toward lower wavenumbers, which indicates the attachment of a chloroform molecule to the second carbonyl lone pair of species **a** [equilibrium (2)] or its replacement by a water molecule in wet chloroform.

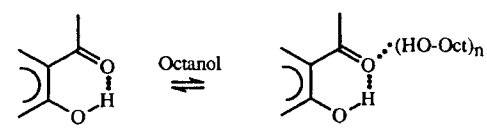


(2)

Clearly, the hydrogen-bond donor chloroform does not break the stable intramolecular hydrogen bond of salicylic acid derivatives. This does not mean that chloroform never acts as an 'intramolecular hydrogen-bond breaker.' We have analysed the ν(OH) region of guaiacol (2-methoxyphenol), a molecule with a weaker intramolecular hydrogen bond than in salicylic derivatives (see Part 1[8]). This compound is fully chelated in carbon tetrachloride whereas 50% of the intramolecular hydrogen bonds are broken in chloroform.

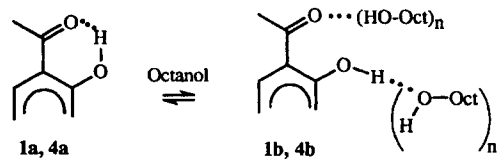
IR spectra in octanol

Two situations arise on going from CCl_4 to octanol. The intramolecular hydrogen bond of 2-hydroxyacetophenone (**2**) and methyl salicylate (**3**) is not broken by octanol. We only observe slight changes in the IR spectra, a weak shoulder appearing on the low-frequency side of the carbonyl bands. As for $CHCl_3$, this shoulder is attributed to the fixation of octanol to the second carbonyl lone pair of species **a** [equilibrium (3)].



2a, 3a (3)

In contrast, the characteristic ν(CO) and ν_{8a} absorptions of species **b** are observed for salicylaldehyde (**1**) and *N*,*N*-dimethylsalicylamide (**4**) . The proportions of species **1b** and **4b** are given in Table 2. The amphoteric properties of octanol must account for the octanol-solvated **b** form shown in equilibrium (4).



1a, 4a **1b, 4b**

The above results are for dry octanol. In wet octanol, the real phase in water–octanol partition, we do not observe significant changes in the IR spectra but a minor intensity rise of a carbonyl absorption attributed to **1a** or **4a** with their second carbonyl lone pair hydrogen bonded to the OH solvent groups. This observation provides confirmation that water saturation has small effects on the bulk properties of neat octanol, possibly because water molecules are trapped in octanol clusters.[13,14]

IR spectra in water

While the intramolecular hydrogen bond is found to be totally broken for **4** (i.e. it is present as form **b** in water), it appears to be very stable for **1**–**3**, which are present as form **a** at 90–100% (see Table 2).

Solvent and substituent effects on equilibrium a ⇌ b

The extent of intramolecular hydrogen bonding in **1**–**4** depends on the free energy difference between forms **a** and **b**. The stability of **a** appears to depend more on the strength of the *intra*molecular hydrogen bond than on molecular *inter*actions with solvents, since the hydrogen-bond acidity of **a** (towards a hydrogen-bond acceptor solvent such as DMSO) is almost zero and its hydrogen-bond basicity (towards a hydrogen-bond donor solvent such as $CHCl_3$) has been greatly reduced.[8] Among the various substituent effects that influence the strength of the intramolecular hydrogen bond we note the following:

(i) The electron-donating effect of X, which increases the hydrogen-bond basicity of the carbonyl groups in the order H ≈ OMe < Me ≪ NMe_2 estimated from the pK_{HB} values of the 4-methoxy analogs of **1**–**4**:[8] 4-

Table 2. Carbonyl frequencies and relative intensities of the two forms of salicyclic acid derivatives **1**–**4**

Compound	Solute	Solvent	ν(C=O)/cm^{-1} Form **b**	ν(C=O)/cm^{-1} Form **a**	Form **a** (%)[a]
1	2-OHC_6H_4CHO	CCl_4		1664·4[c]	100
		$CHCl_3$[b]		1659·8[c]	100
		Octanol[b]	~1680	1661·0[c]	90
		D_2O[e]	~1678	1651·0[c]	90
		DMSO	1682·2	1655·9[c]	30
2	2-OHC_6H_4COMe	CCl_4		1646·1	100
		$CHCl_3$[b]		1642·1	100
		Octanol[b]		1645·8–1634·6[d]	100
		D_2O[e]	~1636	1631·1	90
		DMSO	1665·0	1639·0	85
3	2-OHC_6H_4COOMe	CCl_4		1682·0	100
		$CHCl_3$[b]		1678·2	100
		Octanol[b]		1681·6	100
		D_2O[e]		1673·0[f]	100
		DMSO	1723·2–1697·0[g]	1675·7	75
4	2-$OHC_6H_4CONMe_2$	CCl_4		1632·8	100
		$CHCl_3$[b]		1629·0	100
		Octanol[b]	~1625	~1625	35[h]
		D_2O[e]	1624·4		0
		DMSO	1629·3		0

[a] Extent of form **a** determined from the intensity ratio of the two carbonyl absorptions (estimated accuracy ± 15%).
[b] Experimental data are given for dry chloroform and octanol. Very little change is found in wet solvents (see text).
[c] Corrected from a Fermi resonance following Ref. 22.
[d] Shoulder corresponding to the 1 : 1 association.
[e] Absorptions corresponding to the deuterated solute (see Experimental).
[f] Extrapolated from acetonitrile–heavy water mixtures.
[g] Two bands corresponding to rotational isomers.
[h] Determined from the intensity ratio of the ν_{8a} bands.

$MeOC_6H_4COOMe$ (1·08) ≈ 4-$MeOC_6H_4COH$ (1·10) < 4-$MeOC_6H_4COMe$ (1·33) ≪ 4-$MeOC_6H_4CONMe_2$ (2·31);

(ii) The electron-withdrawing effect of COX, which increases the hydrogen-bond acidity of the hydroxyl group in the order of the field and resonance substituent constants[15] (σ_F and σ_R^- respectively, in parentheses): $CONMe_2$ (0·19, 0·14) ≪ COOMe (0·24, 0·16) < COMe (0·26, 0·17) ≪ COH (0·31, 0·19);

(iii) The steric effect of X, which may prevent an optimum geometry of the intramolecular hydrogen bond, in the order of the steric substituent constant $|S^\circ|$:[16] H(0) < Me (0·73) < OMe (1·28) < NMe_2 (2·32); in fact, *N,N*-dimethylsalicylamide (**4**) is non-planar as a result of steric interactions between the NMe_2 group and the *ortho* hydrogen atom of the phenyl ring, whereas **1**–**3** are near planar (solid-state[17,18] and *in vacuo*, see above).

In contrast, the stability of **b** could depend more on the molecular interactions with the solvent via:

(iv) the hydrogen-bond acidity of the hydroxyl group, which gives intermolecular hydrogen bonds with solvents in the order of their HB acceptor ability:[19,20] $CCl_4 = CHCl_3$ ≪ water < octanol < DMSO; this is, however, coupled with effect (ii);

(v) the hydrogen-bond basicity of the carbonyl group, which gives intermolecular hydrogen bonds with solvents in the order of their HB donor ability:[20] DMSO = CCl_4 < $CHCl_3$, octanol ≪ water; this is, however, coupled with effect (i).

The orders of extent of intramolecular hydrogen bonding originate from a blend and interplay of effects (i)–(v), with the following highlights:

(a) the absence or the weakness of the solute–solvent interactions [effects (iv) and (v)] which stabilize the dechelated form explain why the chelations are not broken in carbon tetrachloride and chloroform;

(b) the main factor that accounts for the lower stability of the chelation in **N,N**-dimethylsalicylamide (**4**) is its non-planarity [effect (iii)] since other effects such as (i) and (ii) counterbalance each other in form **a** as well as in form **b** and would give to **4** roughly the same stability as the other salicylic derivatives in octanol and water;

(c) the importance of interaction (iv) explains why DMSO breaks the intramolecular hydrogen bond the most effectively for all compounds. An enthalpy of −6·4 kcal mol^{-1}, measured[21] for the hydrogen-bond formation between 4-hydroxyacetophenone and DMSO, compares very well with the calculated dechelation energetic cost of 7·6 kcal mol^{-1} (at the 6–31G level) for 4-hydroxyacetophenone.

CONCLUSION

As expected, IR hydrogen-bond studies give a clear description of the structure and solvation of salicylic acid derivatives. A different approach to the problem is the analysis of partition coefficients by the linear solvation energy relationships method.[1–5] Partition coefficient determination in intramolecular hydrogen-bonded systems, their analysis via linear solvation energy relationships and their comparison with IR results are the subject of Part 3.

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