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Solvent-dependent lipophilicity and hydrogen-bonding capacity of 2-pyridylalkanols

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Summary

The lipophilicity of homologous 2-pyridylalkanols (2-pyridylmethanol to 5-(2-pyridyl)pentanol) was shown to be strongly solvent-dependent but neither log P values nor partial molar volumes are highly informative in terms of solute–solvent interactions. In contrast, Δ log P values quantitatively express the capacity of the solutes to donate and accept H-bonds to and from the solvent. These capacities are molecular rather than fragmental properties in that they depend not only on the functional groups, but also on their intramolecular relationships.

Introduction

A common approach in quantitative structure–activity relationship (QSAR) studies is to factorize molecular or substituent features such as lipophilic, steric and electronic properties into related descriptors. For example, the electronic Hammett σ constant can be split into an inductive (σ_I) and resonance (σ_R) component. Global steric parameters such as volume have been decomposed in length (L) and width (B_1, B_5) terms (Verloop, 1983). Partition coefficients (log P) have also been factorized into two terms, a volume (cavity) term accounting for hydrophobicity and dispersion forces, and electronic/polarity terms accounting for electrostatic interactions (Van de Waterbeemd and Testa, 1987), e.g. Eqn. 1:

$$\text{lipophilicity} = \text{cavity} + \text{polarity} \quad (1)$$

The bulk (or cavity) term can be described by such parameters as molar volume or molar refractivity. In contrast, the expression of polarity appears much more difficult. Taft and coworkers (1985) have used the parameters π^*, β and α but their approach is limited to liquid and monofunctional compounds.

A promising but long-neglected concept was earlier developed by Seiler (1974) who defined a set of I_H values calculated from Δ log P values obtained from *n*-octanol/water and cyclohexane/water partition coefficients (see later). Very recently Δ log P values have led to a new physicochemical model in the design of brain-penetrat-

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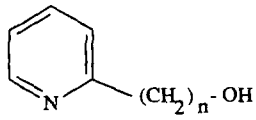

n = 1 - 5

Fig. 1. Structure of the 2-pyridylalkanols investigated.

ing H_2 receptor histamine antagonists (Ganellin et al., 1986; Young et al., 1988). Other authors have demonstrated that Δ log P is a useful parameter in designing percutaneously penetrating drugs (Scott et al., 1986).

In a previous study we examined the lipophilic behaviour of ω-substituted alkylpyridines in the *n*-octanol/water system (Mayer et al., 1982), showing that methylene groups do not contribute a constant increment to the overall molecular lipophilicity, in contradiction with current hydrophobic fragmental systems. To model the deviant behaviour of some molecules, hydration factors were postulated (Van de Waterbeemd and Testa, 1983). The role of water molecules and hydrogen bonds (both inter- and intramolecular) in the partitioning process has been confirmed in a recent thermodynamic study (Repond et al., 1987).

In the present work we investigated the partition behaviour of a homologous series of 2-pyridylalkanols (Fig. 1) in various solvents, the aim being to better understand the role of hydrogen-bonding in lipophilicity.

2-Pyridylalkanols were selected for their capability to accept and donate inter- and intramolecular hydrogen bonds and because they can be expected to display a solvent-dependent conformational behaviour (e.g. intramolecular H-bond in non-polar media). Partial molar volumes were determined by high-precision density measurements in a polar (water) and non-polar (CCl_4) solvent.

Theoretical background

Collander / Seiler concept

It is well-known that solvent systems of a similar nature and polarity produce log P values which are highly correlated, the relationship being described by a Collander equation (Leo et al., 1971):

$$\log P_1 = a \log P_2 + b \tag{2}$$

Strictly, Eqn. 2 is valid only when the two organic solvents are both either inert (e.g. alkanes), H-bond acceptors (e.g. ethers), H-bond donors (e.g. $CHCl_3$), or amphiprotic (e.g. alkanols) (Okada et al., 1985). These restrictions have led to an extention of the Collander equation by adding a corrective term for hydrogen bonding (e.g. Seiler, 1974):

$$\log P_{\text{cyclohexane}} = \log P_{\text{octanol}} + b - \sum I_{\text{H}} \tag{3}$$

or written in another form

$$\Delta \log P = \log P_{\text{octanol}} - \log P_{\text{cyclohexane}} = \sum I_{\text{H}} - b \tag{4}$$

where I_{H} is an additive increment due to the hydrogen bonding capability of a fragment. Thus Δ log P is interpreted as a measure of the hydrogen bonding ability of the total solute molecule.

Molar volume

Partial molar volumes, V^0, are defined as the apparent molar volume, ϕ_v, of a solute in a solvent at infinite dilution and are obtained by extrapolation of experimental values. For non-electrolytes no general theoretical model for such an extrapolation exists (Franks and Smith, 1968) but linear extrapolations are usually the most satisfactory ones.

The experimental partial molar volume is composed of the intrinsic or Van der Waals volume and a number of terms describing solute–solvent and solvent–solvent interactions.

$$V^0 = V_{\text{vdW}} + \sum V_{\text{interactions}} \tag{5}$$

The volume contraction due to solvent–solute interactions is built up of different terms. One of these, called the apparent electrostriction, has been directly correlated with the number of water molecules involved in the hydration of amino acids (Shahidi, 1983).

Materials and Methods

Lipophilicity

Partition coefficients (log P) have been determined at room temperature ($21 \pm 2°C$) by the shake-flask technique in the following systems: *n*-butanol/water, *n*-heptane/water and di-*n*-butyl ether/water. Results in the system *n*-octanol/water were taken from Mayer et al. (1982). Equilibrium concentrations were measured in the aqueous phase by UV after centrifugation. The solvent/water ratio was chosen such that at equilibrium 30–60% of the solute remained in the aqueous phase. A phosphate buffer at pH = 7.5 was used (pK_a of the compounds 4.9–5.9). In preliminary studies it was checked that the log P values were unaffected by ionic strength in the region 0.05–0.3.

Partial molar volumes

Apparent molar volumes, ϕ_v, were calculated from high-precision density values (ρ_{solv} for the solvent and $\rho_{solution}$ for the solution) from eqn. 6:

$$\phi_v = \frac{\text{mol. wt.}}{\rho_{solv}} + \frac{1000(\rho_{solv} - \rho_{solution})}{\rho_{solv} \cdot C} \qquad (6)$$

using an Anton Paar Precision Density DMA 60 and a measuring cell DMA 601. Temperature was maintained at $20 \pm 0.001°C$ by a Lauda RC-20 thermostat placed in a thermostated room. The precision in the density is $\pm 1.5 \times 10^{-6}$ g/cm^3. By making measurements over a range of 6–10 concentrations (C), it was possible to extrapolate linearly to the partial molar volume at infinite dilution.

Calculated molar volumes

Molar volumes have been calculated with the program MOLSV (QCPE 509) on an Apollo DN3000 workstation using Van der Waals radii and interatomic distances according to Testa and Seiler (1981).

Results

Lipophilicity

The experimental shake-flask log P values are reported in Table 1. Applying the approach of Collander for the two alkanol/water systems yielded Eqn. 7:

$$\log P_{oct} = 1.242(\pm 0.027) \log P_{but} - 0.469(\pm 0.024) \qquad (7)$$

$$r = 0.999; \quad n = 5; \quad s = 0.007; \quad F = 38.63$$

Di-*n*-butyl ether is a constitutional isomer of *n*-octanol with only H-bond accepting possibilities. As expected, the correlation with the *n*-octanol/water system is less satisfactory ($r = 0.958$).

Relationships between log P values and the number of carbon atoms in the side-chain are visualized in Fig. 2, showing that $\log P_{but} > \log P_{oct} > \log P_{dbe} > \log P_{hep}$. Fair linear relationships exist ($r > 0.90$) between the various log P values and the chain length, but suppressing 2-pyridylmethanol markedly improves the correlations ($r > 0.98$) due to the deviant behaviour of this homologue. The difference in log P value between the most and least lipophilic homologues is ca. 1.2 in the octanol/water system, ca. 1.0 in butanol/water and dibutyl ether/water systems, and ca. 0.5 in the heptane/water system. These

TABLE 1

Lipophilicity of 2-pyridylalkanols

oct = *n*-octanol; but = *n*-butanol; dbe = di-*n*-butyl ether; hep = heptane; $n = 4$–9.

nC	log P_{oct} [a]	log P_{but}	log P_{dbe}	log P_{hep}
1	0.059	0.425	−1.258	−1.946
	±0.007	±0.006	±0.019	±0.006
2	0.117	0.476	−1.403	−1.944
	±0.015	±0.009	±0.007	±0.009
3	0.578	0.835	−1.136	−1.862
	±0.034	±0.030	±0.012	±0.013
4	0.862	1.070	−0.853	−1.581
	±0.024	±0.020	±0.027	±0.008
5	1.280	1.411	−0.365	−1.437
	±0.024	±0.006	±0.013	±0.013

[a] Results from Mayer et al., 1982.

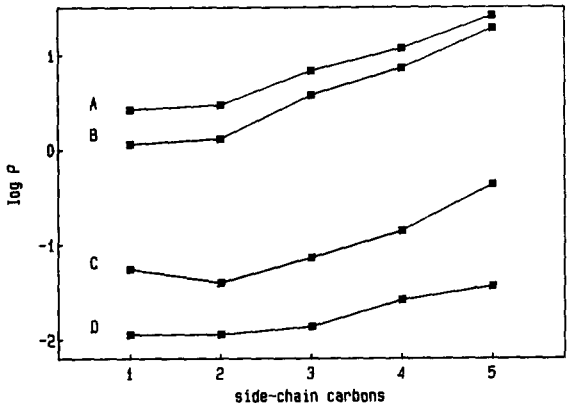

Fig. 2. Log P vs number of carbons for 2-pyridylalkanols. Line A = log P_{but}; line B = log P_{oct}; line C = log P_{dbe}; line D = log P_{hep}.

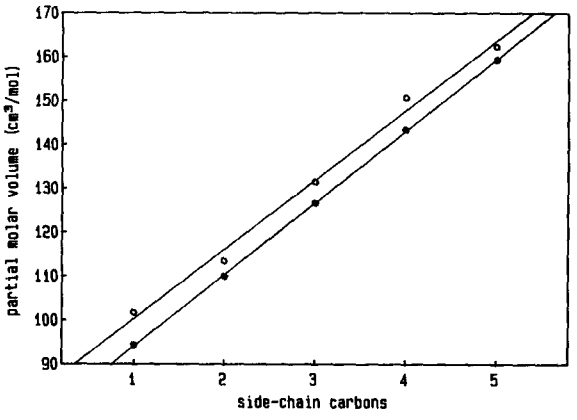

Fig. 4. Partial molar volume of 2-pyridylalkanols in water (●) and carbon tetrachloride (○) at 25 °C.

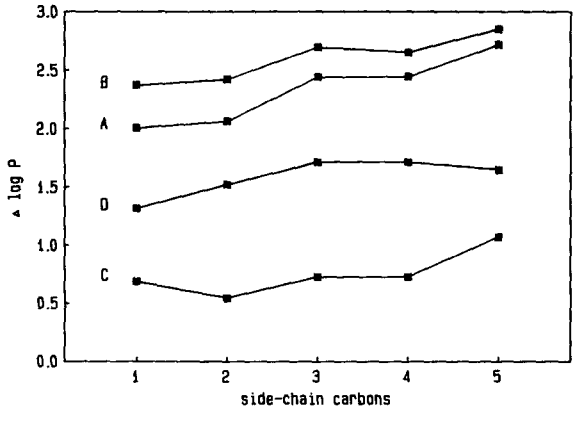

Fig. 3. Δ log P vs number of carbons for 2-pyridylalkanol. Line A = Δ log $P_{oct\text{-}hep}$; line B = Δ log $P_{but\text{-}hep}$; line C = Δ log $P_{dbe\text{-}hep}$; line D = Δ log $P_{oct\text{-}dbe}$.

differences reflect the discriminative power of the various systems (Rekker, 1977).

More information can be extracted from the above data by calculating Δ log P values (Eqn. 4), which define the polarity terms in the various solvent systems (Fig. 3). It appears that the Δ log $P_{oct\text{-}hep}$ and Δ log $P_{but\text{-}hep}$ values display similar behaviour, i.e. a non-linear stepwise increase with increasing chain length. *n*-Octanol and *n*-butanol are able to donate and to accept hydrogen bonds, while no hydrogen bonding between solute and solvent is possible in *n*-heptane. Thus lines A and B in Fig. 3 reflect the capacity of 2-pyridylalkanols to both donate and accept H-bonds, and this capacity visibly increases with increasing chain length. The Δ log $P_{dbe\text{-}hep}$ values

TABLE 2

Experimental and calculated molar volumes of 2-pyridylalkanols (ml / mol)

Experimental values					Calculated values			
nC	V_{aq}	Δ_{aq}	V_{CCl4}	Δ_{CCl4}	Extended conformation		Folded conformation	
					V_{calc}	Δ_{ex}	V_{calc}	Δ_{fol}
1	94.3 ± 0.1	15.7	101.7 ± 1.0	11.8	82.5	14.3	82.8	14.3
2	110.0 ± 0.1	16.8	113.6 ± 0.3	18.0	96.7	13.5	97.0	10.8
3	126.7 ± 0.3	16.7	131.5 ± 0.9	19.2	110.2	14.6	107.9	13.5
4	143.4 ± 0.1	15.9	150.7 ± 0.8	11.6	124.6	13.7	121.4	14.5
5	159.3 ± 0.1		162.3 ± 0.1		138.3		135.9	

(line C in Fig. 3) reflect the capacity of the compounds to donate H-bonds to the solvent. An increase is seen with increasing chain length, excepting 2-(2-pyridyl)ethanol which has the lowest H-bond donating capacity. When the H-bond accepting capacity is considered (line D, Δ log $P_{\text{oct-dbe}}$), an increase is seen up to 3-(2-pyridyl)propanol but not beyond.

Partial molar volumes

Partial molar volumes increase as expected with increasing chain length. As seen in Fig. 4, this increase follows a linear relationship. Fig. 4 and Table 2 reveal that the partial molar volume of a compound may be significantly different when measured in another solvent, in this case a polar versus a non-polar solvent, with V^0_{aq} values being smaller than V^0_{CCl4} values. Different packing densities in the solvent may explain such behaviour, confirming observations made by others (Barlow, 1983; Edward et al., 1978).

The mean incremental value for a CH_2 group in water (16.3 ± 0.5 ml/mol) corresponds to those reported in the literature (ca. 15–16 ml/mol). In carbon tetrachloride this value is 15.1 ± 4.0 ml/mol, while in the literature 17.4 ml/mol has been reported (Edward et al., 1978).

Calculated molar volumes

Since the investigated 2-pyridylalkanols are able to adopt folded conformations, we have examined the relationship between calculated molar volume and conformation. Two conformations were arbitrarily chosen, one with the side-chain in an extended form, the other with the side-chain folded in such a way that a H-bond is created between the hydroxyl group and the pyridyl-nitrogen. The results are given in Table 2. For the molecules with one or two carbon atoms in the side-chain, the volume of the folded molecules is larger than for the extended conformer. However, the situation is reversed for the longer chain homologues. The increment for the extended molecules is quite regular, while an irregularity is noted for the folded molecules. Clearly this calculation demonstrates some role of conformation on molecular volume.

Discussion

The present work examines the solvent-dependent lipophilicity of 2-pyridylalkanols chosen as bifunctional model compounds. The discussion to follow is an attempt to interpret the experimental data in terms of intermolecular (solute–solvent) interactions and intramolecular effects. The latter are conformation- and chain length-dependent and result from the through-bond and through-space interactions between the two functional groups.

The solvent-dependent conformational behaviour of 2-pyridylalkanols does not appear to be known, but a meaningful comparison can be made with 2-pyridylalkanamides (Repond et al., 1987) since both series of compounds are able to exist as intramolecularly H-bonded folded conformers. Thus, while an intramolecular H-bond stabilizes 2-pyridylalkanamides as folded conformers in di-*n*-butyl ether, this H-bond has but a low probability in *n*-octanol (Repond et al., 1987).

As already mentioned, partial molar volumes increase regularly with chain length in water and in CCl_4. While calculated molar volumes of 2-pyridylalkanols are somewhat conformation-dependent, they prove of no help in interpreting the experimental volume variations in conformational terms.

The solvent-dependent log P values (Table 1 and Fig. 2) are rather difficult to interpret. In heptane, no electrostatic solute–solvent interaction occurs, and the range of 0.5 in log P_{hep} values reflects only dispersion forces (cavity term in Eqn. 1). In octanol, butanol and dibutyl ether, the range in log P values is larger (1.0–1.2). This can be interpreted as implying that electrostatic solute–solvent interactions *increase* in the homologous series as the distance between the hydroxyl group and the pyridyl-nitrogen increases.

The Δ log P values in Fig. 3 appear more informative and lead to some interesting rationalisations in terms of both intermolecular and intramolecular effects. Since no intramolecular H-bonded conformers of 2-pyridylalkanols are expected in *n*-octanol (see above), the capacity of these solutes to accept H-bonds from *n*-octanol should not be diminished by an internal H-bond. It is therefore of interest that the parameter ex-

pressing this H-bonding-accepting capacity, namely Δ log $P_{\text{oct-dbe}}$ (Fig. 3, line D), is well correlated ($r = 0.940$) with the pK_a of 2-pyridylalkanols which is itself influenced by intramolecular interactions (Mayer and Testa, 1982). This is a clear indication that the H-bond donation from *n*-octanol occurs mainly on the pyridyl nitrogen.

When the H-bond-donating capacity of 2-pyridylalkanols is considered (Δ log $P_{\text{dbe-hep}}$, Fig. 3, line C), a global increase with chain length is noted, but expectedly no correlation exists with pK_a value ($r = 0.59$). Fig. 3, line C, thus suggests that the greater the chain length between the pyridyl ring and the OH group, the higher the capacity of the latter to donate H-bonds to di-*n*-butyl ether. The case of 2-pyridylethanol is of interest since this compound is the poorest H-bond donor in the series. We believe this behaviour to be due to the existence of a relatively strong intramolecular H-bond, and interpret line C (Fig. 3) as indicating that the stronger the intramolecular H-bond, the weaker the H-bond donation to di-*n*-butyl ether.

The values of Δ log $P_{\text{oct-hep}}$ and Δ log $P_{\text{but-hep}}$ are highly intercorrelated ($r = 0.996$) and express the capacity of 2-pyridylalkanols to both donate and accept H-bonds to and from amphiprotic solvents. The stepwise increase in Δ log $P_{\text{oct-hep}}$ values is difficult to interpret but should not result from conformational factors since intramolecularly H-bonded conformations are not favoured in *n*-octanol (see above).

In summary, this study has used a homologous series of bifunctional solutes to examine their solvent-dependent lipophilicity. The demonstration is made that the capacity of these solutes to donate and accept H-bonds depends not only on the functional groups themselves, but on their intramolecular relationships (distances, interactions, etc). In other words, and just like lipophilicity itself, the capacity for H-bond donation and acceptance is a molecular property originating in functional groups and influenced by their intramolecular relationships. Our main conclusion is thus that Δ log P values are not merely an expression of intermolecular (solute–solvent) interactions, but that they also reflect intramolecular effects.

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