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NO. 365

EFFECT OF INTRAMOLECULAR HYDROGEN BONDING ON PARTITION COEFFICIENTS (U)

by

H.L. Holmes and C.E. Lough

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ABSTRACT

Hansch favours the use of 1-octanol-water for partitioning organic compounds. The advantage ascribed to this and other alcohol-water systems is that the same equation serves to calculate log $P_{alc\text{-}water}$ values for compounds with and without intermolecular hydrogen bonding. Hansch and others have attempted, without much success, to develop equations for calculating the effect of intermolecular hydrogen bonding upon partition coefficients determined in hydrocarbon-water systems.

In this paper, attention is directed towards a similar study of phenols with a functional group at C_2 or C_4. Using conjugative effects, $\Delta\lambda_A$(mμ units), and steric effects, $\Delta\lambda''_A$(mμ units), developed for calculating long-wavelength U.V. absorption maxima of the conjugated heteroenoid compounds, permitted the development of equations relating log P (in the system cyclohexane-water) and log P' (in the system 1-octanol-water) for 2-hydroxy-derivatives to those for the respective isomers with the hydroxyl at C_4.

Incorporation of pK_A into equations analogous to those above related log P_{para} and log P'_{para} for the 4-hydroxy derivatives respectively

to log P_H and log P'_H for the parent compounds. Addition of the appropriate equations from the above two sets permits the calculation of log P_{ortho} values for 2-hydroxy derivatives in the system cyclohexane-water, where intramolecular hydrogen bonding occurs, from log P_H values.

Methods for calculating log P_H and log P'_H values have already been outlined.

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INTRODUCTION

Equations have been developed for conjugated heteroenoid compounds and catechol monomethyl ethers (1a) relating the logarithms of their biological activities to the logarithms of their *in vitro* partition coefficients, P(cyclohexane-water), *in vitro* rate parameters and *in vitro* rates of wastage. Holmes and Reichert (1b) have since discussed why compounds containing intramolecular hydrogen bonds usually are not accommodated by the above equations. Hansch (2) claims that the partitioning system, 1-octanol-water (P') is superior to a system involving hydrocarbon solvents because the water dissolved in the 1-octanol (3) destroys the hydrogen bonding so that log P' values can be calculated for compounds with and without intermolecular hydrogen bonds by equation 1.

$$\log P' = \Sigma \Pi' \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad 1$$

Furthermore, he claims that almost any alcohol could be substituted for 1-octanol. To support this he developed equations relating the logarithms of partition coefficients in another system (e.g. n-butanol-water) to the independent variable log P'. For those organic solvents which dissolve about the same amount of water as does 1-octanol, the relation between log $P_{solvent}$ and log P' is linear and has a slope of 1. For solvents which dissolve more water (e.g. butanol) than 1-octanol, a similar relationship obtains but the slope is less than unity (equation 2).

$$\log P_{\mathrm{butanol}} = 0.70 \log P' + 0.38$$
$$n^* = 57,\ r^* = 0.993,\ s^* = 0.123 \ldots\ldots \qquad 2$$

The compounds involved in the above correlation included those that could participate in intermolecular hydrogen bonding and those that could not. Apolar solvents, such as cyclohexane, do not dissolve water to the same extent as does 1-octanol so the coefficient of log P' is greater than one (4). It will also be seen from equation 3 that the correlation is not nearly as good as that for equation 2.

$$\log P = 2.00 \log P' - 4.86$$
$$n = 9,\ r = 0.791,\ s = 0.391 \ldots\ldots\ldots\ldots \qquad 3$$

$$\log P = 1.00 \log P' - 1.20 \log K_{HB} - 2.35$$
$$n = 9,\ r = 0.979,\ s = 0.140 \ldots\ldots\ldots\ldots \qquad 4$$

If a term for hydrogen bonding, log K_{HB} (5), is introduced as in equation 4, then the correlation is improved and the slope of the line is unity. From this, Hansch (2) concludes that the partitioning processes in the two systems are quite similar except for hydrogen bonding. The above conclusions are based upon a small number of compounds and are misleading. Holmes (6), using 91 compounds, demonstrated that the relation between log P and log P' is not linear (equation 5) but is more likely second or third order with respect to log P**(equations 6 and 7).

$$\log P' = 1.85 \log P - 2.53$$
$$n = 91,\ r = 0.91 \ldots\ldots\ldots\ldots\ldots\ldots \qquad 5$$

$$\log P' = -\ 0.28\ (\log P)^2 + 2.98 \log P - 3.50$$
$$n = 91,\ r = 0.93 \ldots\ldots\ldots\ldots\ldots\ldots \qquad 6$$

$$\log P' = -\ 0.088\ (\log P)^3 + 0.23\ (\log P)^2 + 2.22 \log P - 3.34$$
$$n = 91,\ r = 0.93 \ldots\ldots\ldots\ldots\ldots\ldots \qquad 7$$

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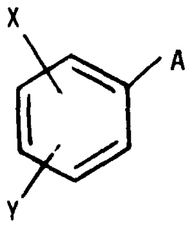
* In these equations, "n" is the number of compounds involved in the correlation, "r" is the correlation coefficient and "s" is the standard deviation.

** The polynomial regression program used is the program LRS03, December 1968, developed by A. Lagler *et al.* and based upon the work of Draper and Smith (22) and Williams (23).

Furthermore, equation 5, when transformed into the form of equation 3, does not have a slope greater than one.

The limited number of data points used in equation 4 is due to the difficulty encountered in calculating K_{HB}. Higuchi *et al.* (5) have been able to assign a relative H-donor capacity to a series of substituted phenols, and Taft *et al.* (9) have measured the H-acceptor capacity of a series of 55 bases of widely different chemical structure. However, from these data it is not possible to assign an H-bonding parameter to more than a small fraction of the solutes common to partitioning work. Moreover, Leo and Hansch (4) state that there appears to be little agreement in the relative H-bonding ability of each of the common functional groups except for the well-known qualitative rules (10) based upon the electronegativity and the size of the two atoms bound by the hydrogen atom. Moreover, no combination of Π, σ, σ^+, σ^-, σ^* or Taft's E_S (11) constant have been found to evaluate adequately the effect of hydrogen bonding upon log P'.

Some compounds with intramolecular hydrogen bonding are similarly examined in this paper. Log P, log P' values and the O-H stretching vibrations, $\gamma(\text{cm}^{-1})$, have been determined for the parent I compounds and their 2- and 4-hydroxy derivatives, where A = CHO, $COCH_3$, COC_2H_5, COC_3H_7-n, COC_6H_5, CO_2CH_3, CN and NO_2. Equations are developed relating log P' to log P and log P_{ortho} - log P_{para} to log ($\gamma_{para} - \gamma_{ortho}$). Finally, log P_{ortho} values are calculated from log P_{para} by the use of conjugative effects, $\Delta\lambda_A$ (21) and steric effects, $\Delta\lambda''_A$ (21).



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EXPERIMENTAL

Log P and log P' values were determined by the method of Currie *et al.* (12) for a number of I compounds where X and Y are H, 2-OH, 4-OH and 3-CH_3O. These values are catalogued in Table 1.

Infrared spectra for the compounds listed in Table 1 were recorded on a Perkin Elmer model 621 grating infrared spectrophotometer. For the 2-hydroxy derivatives 0.10 M solutions in carbon tetrachloride were used, while 0.02 M solutions in carbon tetrachloride were employed in the case of the 4-hydroxy derivatives. The frequencies for the O-H stretching vibration for these compounds are listed in Table 2 along with the values reported in the literature.

DISCUSSION

The plot of log P' against log P for the 22 compounds listed in Table 1 led to equation 8 (see Table 3 for summary of statistical data) for which there was no correlation between these parameters. As well,

$$\log P' = 0.20 \log P + 1.91$$
$$n = 22,\ r = 0.556,\ F = 8.97 \ldots\ldots\ldots\ldots \quad 8$$

calculation of log P' from log P by equations 5 - 7, and plotting log P'_{calc} vs log P'_{obs}, gave very poor correlation coefficients*. This is undoubtedly due to the influence of intermolecular (C_4-OH) and intramolecular (C_2-OH) hydrogen bonding in the I compounds in the system cyclohexane-water and their limited, if any, influence upon the log P' values of these compounds in the system 1-octanol-water. The effect of the two types of hydrogen bonding in the two different partitioning systems is manifest in the values of log P_{ortho} - log P_{para} and log P'_{ortho} - log P'_{para} listed in Table 1. These differences are primarily due to hydrogen bonding in the 2- and 4-hydroxy derivatives of the I compounds and to steric factors.

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* Statistical data for these plots are listed in Table 3 under equations 5a, 6a and 7a.

The extent of intramolecular hydrogen bonding in the 2-*hydroxy* derivatives will be reflected in the frequencies of the O-H stretching vibration of these compounds relative to that of the corresponding 4-hydroxy derivatives. This has been related to $\log P_{ortho} - \log P_{para}$ in equations 9 and 10.

$$\log P_{ortho} - \log P_{para} = 2.71 \log(\gamma_{para} - \gamma_{ortho}) - 3.58$$
$$n = 5,\ r = 0.996,\ F = 364.4 \quad \ldots\ldots \quad 9$$

$$\log P'_{ortho} - \log P'_{para} = 0.42 \log(\gamma_{para} - \gamma_{ortho}) - 0.67$$
$$n = 5,\ r = 0.914,\ F = 15.23 \quad \ldots\ldots \quad 10$$

If there is no intramolecular hydrogen bonding in 1-octanol-water, then the $\log P'_{ortho} - \log P'_{para}$ must be primarily due to steric factors in the 2-hydroxy derivatives. The plot of $\log P'_{ortho} - \log P'_{para}$ against the logarithm of the steric factor $\Delta\lambda''_A$ (21) is expressed mathematically in equation 11.

$$\log P'_{ortho} - \log P'_{para} = 0.50 \log |\Delta\lambda''_A| - 0.047$$
$$n = 5,\ r = 0.950,\ F = 26.62 \quad \ldots\ldots \quad 11$$

Equations 10 and 11 indicate that the steric factor gives a more favourable correlation coefficient and F value than does hydrogen bonding, evaluated by $\log(\gamma_{para} - \gamma_{ortho})$; however, equation 12 demonstrates that covariance exists between $\log(\gamma_{para} - \gamma_{ortho})$ and $\log |\Delta\lambda''_A|$.

$$\log(\gamma_{para} - \gamma_{ortho}) = 1.14 \log |\Delta\lambda''_A| + 1.54$$
$$n = 5,\ r = 0.976,\ F = 59.84 \quad \ldots\ldots \quad 12$$

Since steric factors, $\Delta\lambda''_A$, give as good a correlation with $\log P'_{ortho} - \log P'_{para}$ as does $\log(\gamma_{para} - \gamma_{ortho})$ this suggests that equation 11 adequately represents the true situation. The indication is, then, that the effect of intermolecular hydrogen bonding (C_4-OH) is the same as that of intramolecular hydrogen bonding (C_2-OH)* and that the difference in log P'_{ortho} - log P'_{para} is related to steric effects of the A groups.

From electronic considerations alone, the pK_A values of the 2-hydroxy derivatives should be about the same as those for their C_4-isomers and their magnitude should be related to the conjugative effect, $\Delta\lambda_A$ (21), of the A groups. Evaluation, as well, of the electron-donating powers of the A groups by the conjugative effects, $\Delta\lambda_A$ (21), and steric effects of the A groups by $\Delta\lambda''_A$ (21), the log Ps for 2-hydroxy derivatives should be equal to log Ps for the 4-hydroxy derivatives plus the contributions of the conjugative effects, log $\Delta\lambda_A$, and steric effects, $\log|\Delta\lambda''_A|$. In spite of approximations having to be made for $\Delta\lambda''_A$ for several of the groups, the correlation coefficients** for equation 13 is good.

$$\log P_{ortho} = \log P_{para} - 0.18 \log \Delta\lambda_A + 3.15 \log |\Delta\lambda''_A| + 0.83$$

$$n = 5,\ r = 0.97,\ F = 31.2 \ldots\ldots\ldots\ldots \quad 13$$

The large coefficient of the $\log|\Delta\lambda''_A|$ term relative to that for log $\Delta\lambda_A$ in equation 13 suggests that steric factors play a more dominant role in determining the extent of hydrogen bonding (and blanketing of the phenolic hydroxyl at C_2) than does the electron-donating power of the A group in I, as evaluated by the conjugative effect, log $\Delta\lambda_A$. This is confirmed when equation 13 is factored into equations 14 and 15. The correlation coefficient for equation 15 is much larger than that for equation 14.

$$\log P_{ortho} = \log P_{para} + 12.20 \log \Delta\lambda_A - 15.32$$

$$n = 5,\ r = 0.76,\ F = 4.20 \ldots\ldots\ldots\ldots \quad 14$$

$$\log P_{ortho} = \log P_{para} + 3.12 \log |\Delta\lambda''_A| + 0.58$$

$$n = 5,\ r = 0.98,\ F = 93.5 \ldots\ldots\ldots\ldots \quad 15$$

Comparing the statistical data for equations 13 and 15, it is obvious

---

* It may be that neither one has any effect in the system 1-octanol-water.

** The linear regression analysis program used in this work was the IBM [illegible] 11/360 New York, 1970.

that the log $\Delta\lambda_A$ term of equation 13 contributes nothing to the goodness of fit of log $P_{ortho(calc)}$ with log $P_{ortho(obs)}$. Equation 16 expresses the relationship for the system 1-octanol-water analogous to that in equation 15.

$$\log P'_{ortho} = \log P'_{para} + 0.50 \log |\Delta\lambda''_A| - 0.05$$
$$n = 5,\ r = 0.95,\ F = 26.6 \ldots\ldots\ldots\ldots \quad 16$$

These results suggest that, for the system cyclohexane-water, the effect of intramolecular hydrogen bonding, in the 2-hydroxy-derivatives of I, upon log P is the same as that due to intermolecular hydrogen bonding in the 4-hydroxy-derivatives of I and that the difference in log P stems from a steric effect of the A group. The positive coefficient of the log $|\Delta\lambda''_A|$ term in equation 15 suggests that the steric effect is inhibiting the intermolecular hydrogen bonding in the 4-hydroxy-derivatives of I. For the system 1-octanol-water, where hydrogen bonding is not a factor, the differences in log P' for the 2- and 4- hydroxy-derivatives of I are small. This small difference, as reflected in 0.50 log $|\Delta\lambda''_A|$ of equation 16, is probably due to blanketing of the phenolic hydroxyl group at C_2 by the A group.

Attempts to relate log P_{para} and log P'_{para} respectively to log P_H and log P'_H by the same method failed, as is evident from equations 17 and 20.

$$\log P'_{para} = \log P'_H - 0.66 \log \Delta\lambda_A + 0.86$$
$$n = 5,\ r = 0.39,\ F = 0.52 \ldots\ldots\ldots\ldots \quad 17$$

$$\log P'_{para} = \log P'_H - 0.005\ pK_A - 0.098$$
$$n = 5,\ r = 0.010,\ F = 0.000 \ldots\ldots\ldots\ldots \quad 18$$

$$\log P'_{para} = \log P'_H - 0.045\ pK_A + 1.326 \log \Delta\lambda_A - 0.496 \log |\Delta\lambda''_A| - 1.369$$
$$n = 5,\ r = 0.975,\ F = 6.38 \ldots\ldots\ldots\ldots \quad 19$$

$$\log P_{para} = \log P_H + 1.00 \log \Delta\lambda_A - 0.30 \log |\Delta\lambda''_A| - 4.59$$

$$n = 5,\ r = 0.53,\ F = 0.38 \ldots\ldots\ldots\ldots \qquad 20$$

$$\log P_{para} = \log P_H + 0.36\ pK_A - 0.15 \log |\Delta\lambda''_A| - 6.18$$

$$n = 5,\ r = 0.988,\ F = 41.38 \ldots\ldots\ldots\ldots \qquad 21$$

$$\log P_{para} = \log P_H + 0.34\ pK_A + 0.37 \log \Delta\lambda_A - 0.21 \log |\Delta\lambda''_A| - 6.57$$

$$n = 5,\ r = 0.996,\ F = 42.16 \ldots\ldots\ldots\ldots \qquad 22$$

Neither the log $\Delta\lambda_A$ term of equation 17 nor the pK_A term of equation 18 adequately transformed log P'_H into log P'_{para}. The pK_A term will reflect the hydrophilicity of the compound due to ionization of the phenolic hydroxyl, while the log $\Delta\lambda_A$ term will evaluate the degree of hydrogen bonding with water. Since the degree of hydrogen bonding will also be dependent upon steric factors, then a log $|\Delta\lambda''_A|$ term must also be included as in equation 19 which leads to a satisfactory correlation.

Intermolecular hydrogen bonding can occur in the system cyclohexane-water, so steric hindrance must be introduced into equations 20 and 21 which are analogous to equations 17 and 18. The correlation coefficient and F value for equation 21 are good and are surpassed only slightly by those of equation 22. Hence the dominant factors governing the log P value for para-hydroxy derivatives where intermolecular hydrogen bonding occurs are 1) the acidity of the phenolic hydroxyl and 2) the steric effect of the A group of the I compounds.

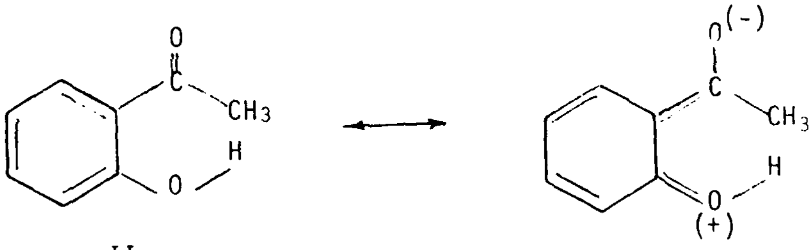
Adding equations 15 and 21 leads to equation 23, thus accounting for log P for ortho-hydroxy compounds where intramolecular hydrogen bonding is involved.

$$\log P_{ortho} = \log P_H + 0.36\ pK_A + 2.97 \log |\Delta\lambda''_A| - 5.60 \ldots \qquad 23$$

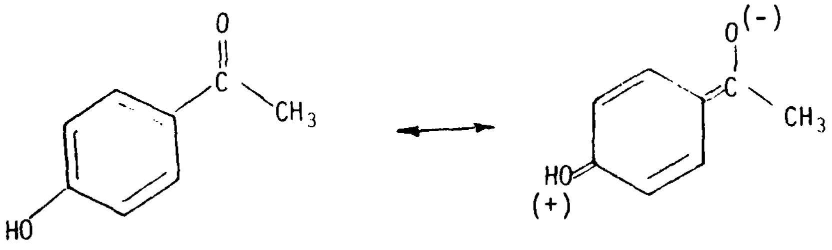
CONCLUSIONS

The frequency differentials ($\gamma_{para} - \gamma_{ortho}$) for the O-H stretching vibration in the 2- and 4-hydroxy derivatives in carbon tetrachloride suggest that, at the concentrations employed, intramolecular hydrogen bonding occurs in the 2-hydroxy derivatives to a much greater extent than does intermolecular hydrogen bonding in the 4-hydroxy derivatives. This accounts for the better correlation coefficient for equation 9 than that for equation 10. Equation 12 reveals that steric effects of the A group of the I compounds restrict intermolecular hydrogen bonding more than they do intramolecular hydrogen bonding. The large positive coefficient of the log $|\Delta\lambda''_A|$ term of equation 15 supports the above statement. If neither intermolecular nor intramolecular hydrogen bonding occurs in the system 1-octanol-water, then the 0.50 log $|\Delta\lambda''_A|$ term of equation 16 is a measure of the blanketing of the phenolic hydroxyl group at C_2, thus enhancing the lipophilicity of these compounds.

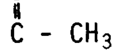
2- and 4-Hydroxyacetophenones are benzologs of acetic acid and should be strong acids. Resonance in these two compounds will involve at least the following cononical structures II↔III and IV↔V.



II III



IV V

The positive charge upon the phenolic oxygen atoms of III and V will repulse the protons enhancing ionization. From equations 9, 12, 13, 14 and 15, the electronic effect of the  $\overset{\overset{O}{\|}}{C} - CH_3$ group of II and IV upon the OH group must be about the same. However, modification of acidity in the parent I compounds cannot occur in the same way, so an analogous relationship between log P_{para} and log P_H is hardly to be expected.

Water in the 1-octanol supplants the phenol in the intermolecular hydrogen bonding of the 4-hydroxy derivatives of the I compounds. Hence the log P' value for these compounds should be governed by 1) the acidity of the phenol, 2) the electron donor properties of the A group and 3) the steric effect of the A group upon the approach of water molecules to the A group. This is expressed mathematically in equation 19.

Intermolecular hydrogen bonding occurs in the above compounds when cyclohexane-water is the partitioning system,so the same factors should operate here to a greater or lesser extent. This is mathematically confirmed by equation 22.

Methods have already been outlined (25, 3, 26) for calculating log P and log P' values for the parent I compounds. This, combined with equation 23 derived from the addition of equations 15 and 21, provides a method for calculating log P and log P' values even when intramolecular hydrogen bonding occurs.

The present work indicates that the effect of intermolecular and intramolecular hydrogen bonding upon partition coefficients can be calculated.

REFERENCES

1a. H.L. Holmes, Structure-Activity Relationships, DRES, Ralston, Alberta, 1975. p 349.

1b. H.L. Holmes and C.R. Reichert, Unpublished Special Publication. 1976.

2. C. Hansch, I.E.P.T. Section 5, Pergamon Press, Oxford and New York, 1973. p 75.

3. H.L. Holmes, Suffield Report No. 282, April 1976. p 18. UNCLASSIFIED.

4. A. Leo and C. Hansch, J. Org. Chem. 36, 1539 (1971).

5. T. Higuchi, J.H. Richards, S.S. Davis, A. Kamada, J.P. Hou, M. Nakano, N.I. Nakano and I.H. Pitman, J. Pharm. Sci. 58, 661 (1969).

6. H.L. Holmes, Structure-Activity Relationships, DRES, Ralston, Alberta, 1975. p 112.

7. H.L. Holmes, Structure-Activity Relationships, DRES, Ralston, Alberta, 1975. p 754.

8. H.L. Holmes, Structure-Activity Relationships, DRES, Ralston, Alberta, 1975. p 100.

9. R.W. Taft, D. Gurka, J. Loris, P.R. Schleyer and J.W. Rakshys, J. Amer. Chem. Soc. 91, 4794, 4801 (1969).

10. G. Pimentel and A. McClellan, The Hydrogen Bond, Reinhold Publishing Corp., New York, 1960. p 229.

11. R.W. Taft, in M.S. Newman, Steric Effects in Organic Chemistry, John Wiley and Sons, New York, 1956. pp 556-675.

12. D.J. Currie, C.E. Lough, R.F. Silver and H.L. Holmes, Can. J. Chem. 44, 1035 (1966).

13. M.S.C. Flett, Spectrochim. Acta, 10, 21 (1957).

14. R.A. Nyquist, Spectrochim. Acta 19, 1655 (1963).

15. A. Allerhand and P.R. Schleyer, J. Amer. Chem. Soc. 85, 866 (1963).

16. S. Forsen and B. Akermark, Acta Chem. Scand. 17, 1907 (1963).

17. J.C. Dearden and W.F. Forbes, Can. J. Chem. 38, 1837 (1960).

18. K.U. Ingold, Can. J. Chem. 38, 1092 (1960).

19. P.M.G.Bavin and W.J. Canady, Can. J. Chem. 35, 1555 (1957).

20. J. Durmis, M. Karvas and Z. Manasek, Collect. Czech. Chem. Commun. 38, 243 (1973).

21. H.L. Holmes, Structure-Activity Relationships, DRES, Ralston, Alberta, 1975. p 1076.

22. N.R. Draper and H. Smith, Applied Regression Analysis, John Wiley and Sons, New York, 1966.

23. E.J. Williams, Regression Analysis, John Wiley and Sons, New York, 1959.

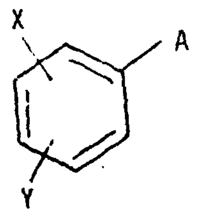
24. G. Socrates, Trans. Faraday Soc. 66, 1052 (1970).

25. T. Fujita, K. Iwasa and C. Hansch, J. Amer. Chem. Soc. 86, 5175 (1964).

26. H.L. Holmes, Structure-Activity Relationships, DRES, Ralston, Alberta, 1975. p 81.

TABLE 1

Log P(Cyclohexane-Water), Log P'(1-Octanol-Water) Values for some Phenols with Intramolecular Hydrogen Bonding



Cmpd No.	A	X	Y	Log P	Log P_{ortho} - Log P_{para}	Log P'	Log P'_{ortho} - Log P'_{para}
1	CHO	H	H	+1.13	-	+1.43	-
2		2-OH	H	+1.37	+3.30	+1.62	+0.27
3		4-OH	H	-1.93		+1.35	
4		2-OH	3-CH_3O	+0.65	+1.31	+1.33	+0.12
5		4-OH	3-CH_3O	-0.66	-	+1.21	-
6	$COCH_3$	H	H	+1.25		+1.68	
7		2-OH	H	+1.75	+3.93	+1.92	+0.47
8		4-OH	H	-2.18	-	+1.45	-
9	COC_2H_5	H	H	+2.02		+2.21	

TABLE 1 (Contd)

Cmpd No.	A	X	Y	Log P	Log P_{ortho} - Log P_{para}	Log P'	Log P'_{ortho} - Log P'_{para}
10	COC_2H_5*	2-OH	H	+2.39	+3.86	+2.54	+0.51
11		4-OH	H	-1.47		+2.03	
12	COC_6H_5	H	H	+3.29	-	+3.58	-
13		2-OH	H	+3.75	+4.18	+3.52	+0.45
14		4-OH	H	-0.43		+3.07	
15	CO_2CH_3	H	H	+2.08	-	+2.23	-
16		2-OH	H	+2.37	+3.61	+2.46	+0.54
17		4-OH	H	-1.24		+1.92	
18	CN*	H	H	+1.15	-	+1.56	-
19		2-OH	H	-1.70	+0.44	+1.61	-0.05
20		4-OH	H	-2.14		+1.66	
21	NO_2	2-OH	H	+1.58	+3.59	+1.77	-0.31
22		4-OH	H	-2.01		+2.08	

* Log $|\Delta\lambda''_A|$ values used for CN and COC_2H_5 were CN = 0.00, COC_2H_5 = 1.161.

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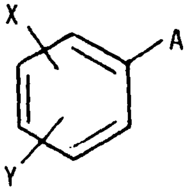
TABLE 2

Frequencies (cm^{-1}) for the O-H Stretching Vibrations of some 2- and 4-substituted phenols: Solvent CCl_4.



A	X	Y	O-H Stretching Vibration (cm^{-1})		
			DRES	Literature	Reference
CHO	2-OH	H	3180	3185	14
	4-OH	H	3590	3595	18
	2-OH	3-CH_3O	3060	3160	16
	4-OH	3-CH_3O	3540	3542	13
$COCH_3$	2-OH	H	3050	3050	14
	4-OH	H	3600	(3591*	19
				(3580**	20
COC_2H_5	2-OH	H	3046	-	-
	4-OH	H	3595	-	-
COC_6H_5	2-OH	H	3060	∿3100	14
	4-OH	H	3598	3587**	20
CO_2CH_3	2-OH	H	3200	3200	14
	4-OH	H	3597	3590*	19
CN	2-OH	H	3560	3559	15
	4-OH	H	3592	3595	18
NO_2	2-OH	H	3238	3243	13,17
	4-OH	H	3594	(3592	18
				(3590	13
				(3578	20

* The solvent is CS_2. ** The solvent is $CHCl_3$

TABLE 3

Summary of Statistical Data*

Eq. No.	No. of Cmpds.	r^2**	r**	F**	Standard Deviation of			Error of Estimate	b**	a**
					1st Term	2nd Term	3rd Term			
5a	22	0.310	0.556	8.99	0.671	-	-	2.985	2.908	-7.449
6a	22	0.219	0.469	5.626	0.671	-	-	4.769	3.679	-10.434
7a	22	0.282	0.531	7.87	0.671	-	-	3.074	2.806	-7.441
8	22	0.309	0.556	8.97	1.895	-	-	0.571	0.197	1.912
9	5	0.992	0.996	364.4	0.538	-	-	0.153	-	-
10	5	0.835	0.914	15.2	0.538	-	-	0.115	-	-
11	5	0.900	0.950	26.6	0.463	-	-	0.090	-	-
12	5	0.952	0.976	59.8	0.463	-	-	0.136	-	-
13	5	0.968	0.984	31.21	0.092	0.463	-	0.366	0.968	0.094
14	5	0.584	0.764	4.20	0.092	-	-	1.094	0.583	1.261
15	5	0.969	0.984	93.49	0.463	-	-	0.299	0.969	0.094
16	5	0.899	0.948	26.62	0.463	-	-	0.090	0.899	0.035
17	5	0.148	0.385	0.523	0.092	-	-	0.168	0.148	-0.119

* The compounds used in these determinations are listed in Table 3a.

** The symbols are defined as follows: r^2 is the coefficient of determination, r is the correlation coefficient and F is the value for the F. test. The symbol b is the slope of the line for the plot of calculated values against observed values and "a" is the intercept of this line.

TABLE 3 (Contd)

18	5	0.000	0.010	0.000	0.421	-	-	0.182	0.000	-0.139
19	5	0.950	0.975	6.38	0.424	0.092	0.463	0.070	0.950	-0.007
20	5	0.277	0.527	0.384	0.092	0.463	-	0.199	0.277	-2.397
21	5	0.976	0.988	41.38	0.421	0.463	-	0.036	0.976	-0.078
22	5	0.992	0.996	42.16	0.421	0.092	0.463	0.029	0.992	-0.025

TABLE 3a

Compounds Involved in Statistical Analysis

Equation No.	Compound Numbers in Table 1
5,6,7,8	Compounds 1 - 22.
9 - 16	2, 3, 7, 8, 10, 11, 16, 17, 19, 20.
17 - 22	1, 3, 6, 8, 9, 11, 15, 17, 18, 20.

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Hansch favours the use of 1-octanol-water for partitioning organic compounds. The advantage ascribed to this and other alcohol-water systems is that the same equation serves to calculate log $P_{(alc\text{-}water)}$ values for compounds with and without intermolecular hydrogen bonding. Hansch and others have attempted, without much success, to develop equations for calculating the effect of intermolecular hydrogen bonding upon partition coefficients determined in hydrocarbon-water systems.

In this paper, attention is directed towards a similar study of phenols with a functional group at C_2 or C_4. Using conjugative effects,* ~~$\Delta\lambda_A$ (mμ units)~~, and steric effects,* ~~$\Delta\lambda_A''$ (mμ units)~~, developed for calculating long-wavelength U.V. absorption maxima of the conjugated heteroenoid compounds, permitted the development of equations relating log P (in the system cyclohexane-water) and log P' (in the system 1-octanol-water) for 2-hydroxy-derivatives to those for the respective isomers with the hydroxyl at C_4

Incorporation of pK_A into equations analogous to those above related log P_{para} and log P'_{para} for the 4-hydroxy derivatives respectively to log P_H and log P'_H for the parent compounds. Addition of the appropriate equations from the above two sets permits the calculation of log P_{ortho} values for 2-hydroxy derivatives in the system cyclohexane-water, where intramolecular hydrogen bonding occurs, from log P_H values.

Methods for calculating log P_H and log P'_H values have already been outlined

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