

CONTRIBUTION OF ELECTRONIC EFFECTS TO THE LIPOPHILICITY DETERMINED BY COMPARISON OF VALUES OF LOG P OBTAINED BY HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY AND CALCULATION*

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SUMMARY

In a series of 49 aryl sulphoxides, the partition coefficients ($\log P$) estimated by high-performance liquid chromatography were compared with $\log P$ values calculated according to the hydrophobic fragmental method of Rekker and a modification of the method of Moreau. Moderate correlations were found. The introduction of Hammett sigma values as a measure of electronic effects proved to be good correction factors for the calculated $\log P$ values. In the presence of strong electron-withdrawing substituents, the sulphoxide moiety is far less hydrophobic than in the absence of such groups.

INTRODUCTION

The partition of a compound between water and an organic phase, generally expressed as $\log P$, seems to be the most important parameter in quantitative structure activity relationships (QSAR). The $\log P$ values obtained from an *n*-octanol-water system are commonly used because of the ability of *n*-octanol to simulate biological membranes. In order to predict biological activities from equations derived in QSAR experiments, not only experimentally obtained $\log P$ values but also calculated ones are necessary.

Different methods of calculating partition coefficients have been described. In 1973 Rekker introduced the hydrophobic fragmental constant. These constants were obtained from regression analysis of experimental $\log P$ values. Corrections have to be made for proximity effects, cross-conjugation, etc. If correction is necessary, it has to be done by adding a "magic constant"¹ to the original calculated $\log P$. In our study, the Rekker method is one of the procedures used to calculate $\log P$.

The Hansch and Leo approach² is also based upon a fragmental method. Their constants were obtained from very precise $\log P$ measurements on simple molecules. They introduced a lot of correction factors, depending upon the type of binding,

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proximity effects, *ortho-ortho* interactions, the possibility of hydrogen bonds and influences of electronic effects.

Broto *et al.*³ developed a somewhat different method. From about 1800 experimental $\log P$ values, more than 200 atomic contributions were extracted by regression analysis. These atomic constants are defined by their atom type, binding pattern and the character of the bonded atoms. The only correction is for conjugated double bonds. In our laboratory a combined Moreau/Hansch method has been developed and more than 500 atomic constants were calculated from over 2500 experimental $\log P$ values. Corrections are necessary for *ortho-ortho* and hydrogen-bond interactions, and electronic effects⁴. Values of $\log P$ calculated by this method are also used in this study.

Beside calculated $\log P$ values, there is a need for experimentally determined ones. The traditional shake-flask method is time consuming, requires very pure chemicals and can be used only within a certain range of $\log P$ values. Some of these objections are associated with high-performance liquid chromatographic (HPLC) methods.

The prediction of $\log P$ in *n*-octanol-water using HPLC has been shown to be of value^{5,6}, depending on the nature of the compounds⁷. The use of reversed-phase HPLC systems with surfactants in the mobile phase is especially useful for ionizable substances⁸⁻¹⁰. Interaction between different functional groups within the molecule affects the actual lipophilicity. Deviations between HPLC measurements and computer calculated values of $\log P$ have been reported¹¹.

In this study, HPLC $\log P$ values for aryl sulphoxides are compared with calculated ones. The influence of electronic factors is considered by means of regression analysis. As a measure of electronic factors, the Hammett σ and *para* σ values are used.

EXPERIMENTAL

Apparatus

The liquid chromatograph consisted of an high-pressure pump (S1000; Sykam, F.R.G.), an autosampler (231-401; Gilson, U.S.A.) equipped with a 5- μ l loop, a stainless-steel column (50 mm \times 4.6 mm I.D.) and a variable-wavelength UV detector (Kratos, Spectroflow 757, ABI, U.S.A.). The column was thermostatted at $22 \pm 0.1^\circ\text{C}$ by means of a water jacket connected to a cryostat bath (Colora WK 4; Braun Melsungen, F.R.G.). The detector signal at 254 nm was recorded by an integrator (HP 3392; Hewlett-Packard, Avondale, PA, U.S.A.).

Materials

HPLC-grade methanol, acetonitrile (J. T. Baker, U.S.A.) and doubly distilled water were used to prepare the mobile phase, which was sparged with helium before use. All other chemicals were of analytical reagent grade. The solutes were commercially available or made by the Duphar laboratory¹². The stationary phase consisted of chemically modified silica gel, phenyl-Rosil, 5 μm (Alltech, Belgium).

Procedures

The column was packed by a pressurized slurry technique with *n*-propanol-

tetrachloromethane (1:4) as the slurry liquid and *n*-hexane as the displacer liquid. The maximum packing pressure was 60 MPa. The column was washed with tetrahydrofuran followed by methanol-water (9:1) and equilibrated with the mobile phase until the retention was constant.

The mobile phase was prepared by dissolving 0.7 g $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ in 450 ml water, adjusting the pH to 3.0 with phosphoric acid and mixing with 1.0 g sodium dodecyl sulphate and 14.0 g sodium perchlorate dissolved in 550 ml methanol. Potassium dichromate was used as a non-retained compound.

A linear regression was established from $\log k'$ (k' = capacity factor) and literature values of $\log P$ in *n*-octanol-water for neutral (Nos. 1-9) and basic (Nos. 10-14) solutes as given in Table I. The HPLC $\log P$ values were determined from linear regression according to

$$\log P_{n\text{-octanol-water}} = 2.16 \log k' \frac{t \text{ value}}{19.65} + 1.19 \quad (1)$$

$$n = 14 \quad r = 0.985 \quad s = 0.267 \quad F = 386.2$$

where n is the number of data, r is the correlation coefficient, s is the standard error of the estimate, F is a measure of the significance of the correlation and the t value is the Student t test. Each day a calibration was performed twice, before and after a series of seven compounds for which $\log P$ was to be determined. The $\log P$ values were determined from the means of at least two measurements on different days.

RESULTS AND DISCUSSION

Measurements of $\log P_{\text{HPLC}}$ were performed for 49 aryl sulphoxides as described. The correlation coefficient of the linear regression according to eqn. 1 ranged from

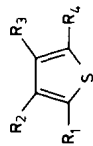
TABLE I
COMPOUNDS USED FOR THE LINEAR REGRESSION

Literature values of $\log P$ in *n*-octanol-water and measured values of $\log k'_{\text{HPLC}}$.

| Code | Compound | $\log P_{n\text{-octanol-water}}$ | $\log k'_{\text{HPLC}}$ |
|------|-----------------------|-----------------------------------|-------------------------|
| 1 | Acetanilide | 1.16 | 0.002 |
| 2 | Indole | 2.14 | 0.347 |
| 3 | Nitrobenzene | 1.85 | 0.450 |
| 4 | Linuron | 3.00 | 0.808 |
| 5 | <i>p</i> -Xylene | 3.18 | 0.885 |
| 6 | Naphthalene | 3.33 | 0.932 |
| 7 | Benzophenone | 3.18 | 1.035 |
| 8 | Biphenyl | 3.91 | 1.269 |
| 9 | 4,4'-Dichlorobiphenyl | 5.28 | 1.827 |
| 10 | Procaine | 1.87 | 0.072 |
| 11 | Atropine | 1.80 | 0.413 |
| 12 | Haloperidol | 4.31 | 1.610 |
| 13 | Imipramine | 4.70 | 1.635 |
| 14 | Pimozide | 6.23 | 2.166 |

TABLE II
STRUCTURES OF THIENYL SULPHOXIDES USED IN THE CORRELATION STUDIES AND VALUES OF HPLC AND COMPUTER CALCULATED
LOG *P*

(*p*) means *para*-substituted.



| No. | <i>R</i> ₁ | <i>R</i> ₂ | <i>R</i> ₃ | <i>R</i> ₄ | <i>log P</i> | <i>σ</i> | | | |
|-----|-----------------------|-------------------------------|-----------------------|---|--------------|----------|--------|--------|------|
| | | | | | | HPLC | Rekker | Moreau | |
| 1 | H | H | NO ₂ | SOCH ₃ | 1.69 | 0.06 | 0.01 | 0.83 | 1.27 |
| 2 | H | H | NO ₂ | SOC ₂ H ₅ | 2.06 | 0.58 | 0.43 | 0.83 | 1.27 |
| 3 | H | H | NO ₂ | SOC ₃ H ₇ | 2.52 | 1.10 | 0.89 | 0.83 | 1.27 |
| 4 | H | H | NO ₂ | SOCH ₂ CH(CH ₃) ₂ | 2.93 | 1.62 | 1.09 | 0.83 | 1.27 |
| 5 | H | CH ₃ | NO ₂ | SOCH ₃ | 2.19 | 0.58 | 0.43 | 0.76 | 1.20 |
| 6 | CH ₃ | CH ₃ | NO ₂ | SOCH ₃ | 2.65 | 1.15 | 0.84 | 0.59 | 1.03 |
| 7 | H | C ₆ H ₅ | NO ₂ | SOCH ₃ | 3.20 | 1.72 | 1.44 | 0.83 | 1.27 |
| 8 | CN | H | CN | SOCH ₃ | 1.31 | -0.42 | -0.80 | 1.37 | 2.00 |
| 9 | CN | H | CN | SOC ₂ H ₅ | 1.78 | 0.10 | -0.38 | 1.37 | 2.00 |
| 10 | CN | H | CN | SOC ₃ H ₇ | 2.18 | 0.62 | 0.08 | 1.37 | 2.00 |
| 11 | CN | H | CN | SOC ₄ H ₉ | 2.64 | 1.14 | 0.55 | 1.37 | 2.00 |

| | | | | | | | | | |
|----|----------------------------------|--|--|---------------------------------|------|-------|-------|------|------|
| 12 | CN | Cl | CN | SOCH ₃ | 2.15 | 0.33 | -0.09 | 1.74 | 2.37 |
| 13 | CN | Cl | CN | SOC ₃ H ₇ | 2.95 | 1.37 | 0.79 | 1.74 | 2.37 |
| 14 | CN | Cl | CN | SOC ₄ H ₉ | 3.44 | 1.88 | 1.25 | 1.74 | 2.37 |
| 15 | COCH ₃ | CH ₃ | NO ₂ | SOC ₂ H ₅ | 2.81 | 0.60 | 0.66 | 1.25 | 2.04 |
| 16 | COCH ₃ | Cl | CN | SOC ₂ H ₅ | 2.64 | 0.95 | 0.55 | 1.57 | 2.24 |
| 17 | CN | CH ₃ | COCH ₃ | SOC ₂ H ₅ | 2.22 | 0.72 | 0.02 | 1.14 | 1.77 |
| 18 | COCH ₃ | CH ₃ | C ₆ H ₅ | SOCH ₃ | 3.26 | 2.22 | 1.89 | 0.48 | 0.87 |
| 19 | COCH ₃ | NH ₂ | CN | SOC ₂ H ₅ | 1.82 | -0.82 | 0.22 | 1.05 | 1.71 |
| 20 | COCH ₃ | C ₆ H ₄ Cl(<i>p</i>) | CN | SOCH ₃ | 3.31 | 2.08 | 1.69 | 1.36 | 2.02 |
| 21 | COOC ₂ H ₅ | H | CN | SOCH ₃ | 2.27 | 0.59 | 0.21 | 1.16 | 1.64 |
| 22 | COCH ₃ | CH ₃ | C ₆ H ₄ Cl(<i>p</i>) | SOCH ₃ | 3.82 | 2.96 | 2.60 | 0.63 | 0.80 |
| 23 | CN | OCH ₃ | CN | SOCH ₃ | 2.02 | -0.33 | -0.47 | 1.49 | 2.12 |
| 24 | CN | CH ₃ | C ₆ H ₅ | SOCH ₃ | 3.36 | 2.12 | 1.58 | 0.64 | 1.00 |
| 25 | CN | CH ₃ | C ₆ H ₄ Cl(<i>p</i>) | SOCH ₃ | 3.80 | 2.86 | 2.29 | 0.72 | 0.92 |
| 26 | COCH ₃ | NH ₂ | C ₆ H ₄ Cl(<i>p</i>) | SOCH ₃ | 3.18 | 1.42 | 2.31 | 0.54 | 0.73 |
| 27 | NO ₂ | H | H | SOCH ₃ | 1.40 | 0.06 | 0.24 | 0.83 | 1.27 |
| 28 | H | H | CN | SOCH ₃ | 0.96 | -0.06 | -0.27 | 0.71 | 1.00 |
| 29 | H | H | SOCH ₃ | H | 0.91 | 0.29 | 0.26 | 0.05 | 0.00 |
| 30 | H | H | H | SOCH ₃ | 0.91 | 0.29 | 0.26 | 0.05 | 0.00 |
| 31 | H | H | Br | SOCH ₃ | 1.71 | 1.23 | 0.92 | 0.28 | 0.28 |
| 32 | COCH ₃ | H | H | SOC ₂ H ₅ | 1.31 | 0.56 | 0.46 | 0.55 | 0.87 |
| 33 | CN | OCH ₃ | CN | SOC ₂ H ₅ | 2.35 | 0.18 | -0.05 | 1.49 | 2.12 |
| 34 | Cl | H | CN | SOC ₂ H ₅ | 2.31 | 1.20 | 0.85 | 0.94 | 1.27 |
| 35 | COCH ₃ | CH ₃ | CN | SOC ₂ H ₅ | 2.22 | 0.72 | 0.38 | 1.21 | 1.77 |

0.984 to 0.988. The reproducibility of the determination was 1.5% ($n = 49$).

In Table II the parameters for 35 thienyl sulphoxides are mentioned. In the column containing the sigma values the sum of the Hammett sigma values is used without the values for the SO-alkyl substituents; for the thienyl S a value of 0.05 is taken and R_1 and R_3 are considered as *para* and *ortho* to R_4 (the sulphoxide position). For the *ortho* and *para* positions the same sigma value is taken. The *para* sigma column contains the sum of the *para* sigma values of R_1 and R_3 and of the normal Hammett *meta para* sigma values of R_2 . *Para* sigma values are also chosen as they are sometimes of importance in reactions containing thiofens¹³. All sigma values are taken from Hansch and Leo¹⁴.

The correlation between both calculated values is expressed in eqn. 2:

$$\log P_{\text{Rekker}} = 1.00 \log P_{\text{Moreau}} + 0.24 \quad t \text{ value } 12.78 \quad (2)$$

$n = 35 \quad r = 0.912 \quad s = 0.372 \quad F = 163.3$

The relative low correlation coefficient, r is caused by two outliers, the compounds 19 and 26 containing a NH_2 group. In our Moreau approach these are electronic corrections so that the NH_2 group is less polar due to the presence of electron-withdrawing substituents. In Fig. 1 the relationship is shown between the calculated values according to Rekker and the HPLC values:

$$\log P_{\text{HPLC}} = 0.75 \log P_{\text{Rekker}} + 1.67 \quad t \text{ value } 9.01 \quad (3)$$

$n = 35 \quad r = 0.843 \quad s = 0.437 \quad F = 81.2$

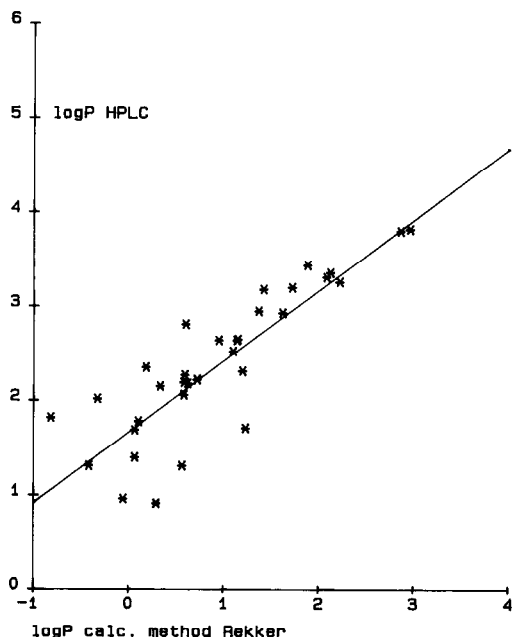


Fig. 1. Relationship between $\log P$ calculated according to Rekker and $\log P_{\text{HPLC}}$ for 35 thienyl sulphoxides.

The intercept is far from zero and the slope is much smaller than the expected value of one. The values of $\log P$ calculated by the Moreau method are plotted against the HPLC values in Fig. 2. Eqn. 4 is the corresponding equation.

$$\log P_{\text{HPLC}} = 0.79 \log P_{\text{Moreau}} + 1.83 \quad t \text{ value } 7.74 \quad (4)$$

$$n = 35 \quad r = 0.803 \quad s = 0.484 \quad F = 59.8$$

The results are less good than those shown in eqn 3. Also the intercept is high and the slope lower than one. One reason for such large deviations may be an underestimate of the contribution of the SO moiety to the calculated $\log P$ values in the presence of strong electron-withdrawing groups. Eqns 5-8 show how the correlations can be improved by adding σ values to the regression analyses:

$$\log P_{\text{HPLC}} = 0.81 \log P_{\text{Rekker}} + 0.64 \sigma + 0.98 \quad t \text{ value } 12.81 \quad (5)$$

$$n = 35 \quad r = 0.919 \quad s = 0.325 \quad F = 87.2$$

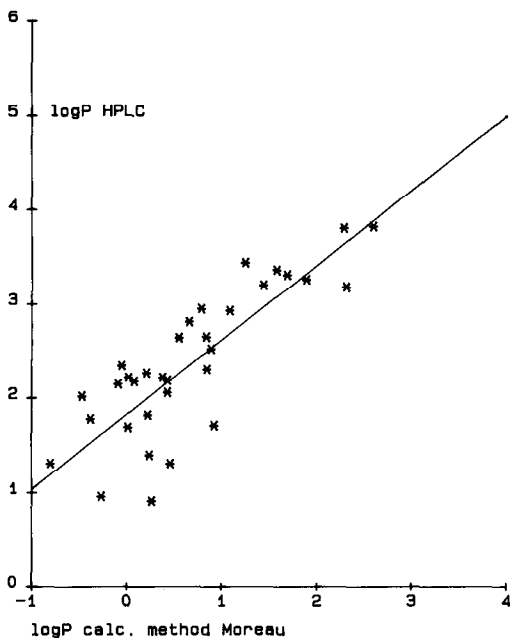


Fig. 2. Relationship between $\log P$ calculated according to Moreau and $\log P_{\text{HPLC}}$ for 35 thienyl sulphoxides.

$$\log P_{\text{HPLC}} = 0.82 \log P_{\text{Rekker}} \quad 13.96 \quad (6)$$

$$\quad + 0.49 \text{ para } \sigma \quad 6.08$$

$$\quad + 0.90$$

$$n = 35 \quad r = 0.931 \quad s = 0.302 \quad F = 103.3$$

$$\log P_{\text{HPLC}} = 0.96 \log P_{\text{Moreau}} \quad 16.84 \quad (7)$$

$$\quad + 0.94 \sigma \quad 9.28$$

$$\quad + 0.80$$

$$n = 35 \quad r = 0.951 \quad s = 0.256 \quad F = 150.2$$

$$\log P_{\text{HPLC}} = 0.97 \log P_{\text{Moreau}} \quad 18.63 \quad (8)$$

$$\quad + 0.68 \text{ para } \sigma \quad 10.48$$

$$\quad + 0.73$$

$$n = 35 \quad r = 0.959 \quad s = 0.233 \quad F = 183.5$$

The result of eqn. 8 is visualized in Fig. 3.

It is obvious that electronic effects strongly influence the hydrophobic character of the sulfoxide moiety. The best correction is effected by sigma constants, especially to the Moreau values. The slope is nearly one, but the intercept is still far from zero. In order to investigate whether this is due to the thienyl basic structure, the log *P* values of some other sulfoxides were estimated. The results are shown in Table III.

The σ value for one aromatic nitrogen is assigned the value for a NO₂ group, and for two nitrogens 1.5 times that value, because of mutual interactions. The results of the regression analyses are shown in eqns. 9–12:

$$\log P_{\text{HPLC}} = 1.09 \log P_{\text{Rekker}} \quad t \text{ value} \quad 5.51 \quad (9)$$

$$\quad + 1.70$$

$$n = 14 \quad r = 0.850 \quad s = 0.601 \quad F = 31.1$$

$$\log P_{\text{HPLC}} = 1.00 \log P_{\text{Moreau}} \quad 7.76 \quad (10)$$

$$\quad + 1.75$$

$$n = 14 \quad r = 0.913 \quad s = 0.465 \quad F = 60.2$$

$$\log P_{\text{HPLC}} = 1.16 \log P_{\text{Rekker}} \quad 6.71 \quad (11)$$

$$\quad + 0.67 \sigma \quad 2.22$$

$$\quad + 0.85$$

$$n = 14 \quad r = 0.899 \quad s = 0.522 \quad F = 23.1$$

$$\log P_{\text{HPLC}} = 1.07 \log P_{\text{Moreau}} \quad 13.12 \quad (12)$$

$$\quad + 0.76 \sigma \quad 4.50$$

$$\quad + 0.78$$

$$n = 14 \quad r = 0.970 \quad s = 0.288 \quad F = 88.3$$

The correlation between the calculated $\log P$ values and the experimental values is much better for $\log P$ derived from the Moreau method. However, the intercept remains approximately. By use of all the compounds and regression analysis with only the Moreau values, eqns. 13 and 14 are obtained:

$$\begin{aligned} \log P_{\text{HPLC}} &= 0.87 \log P_{\text{Moreau}} & t \text{ value} & 10.96 \\ &+ 1.80 & & \\ n = 49 \quad r &= 0.848 \quad s = 0.479 & F &= 120.2 \end{aligned} \quad (13)$$

$$\begin{aligned} \log P_{\text{HPLC}} &= 0.98 \log P_{\text{Moreau}} & 21.23 & \\ &+ 0.86 \sigma & 10.05 & \\ &+ 0.82 & & \\ n = 49 \quad r &= 0.955 \quad s = 0.271 & F &= 238.4 \end{aligned} \quad (14)$$

The results of eqns. 13 and 14 are visualized in Figs. 4 and 5. Fig. 5 shows a very good correlation, but the intercept remains about 0.80, the same as in eqn. 8 and 12. It is known^{11,15} that sulphones and sulphoxides often show disagreement with respect to partition behaviour. The "real" *n*-octanol–water partition coefficient of compound 42 is known^{1,14} as 0.50. So it is possible that all HPLC values are about 0.55 too high in relation to the "shake-flask" values. When corrected in such a way, Fig. 6 shows the result. The remaining intercept of 0.27 is hardly significant and probably caused by the error in the value for atomic sulphur in the Moreau approach.

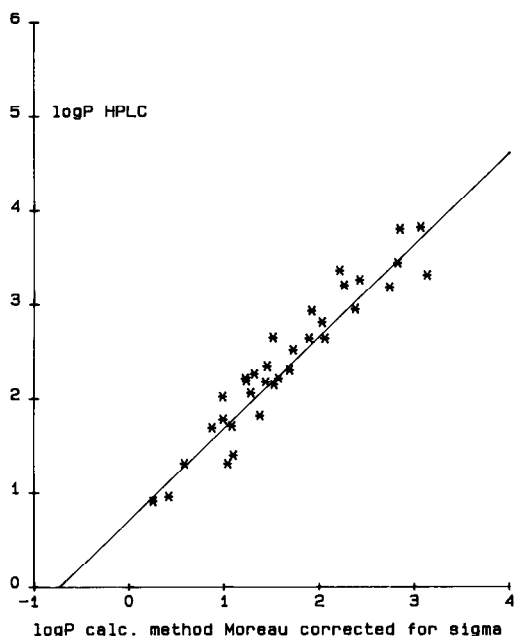
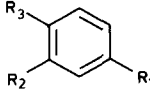

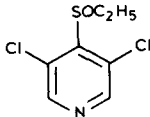
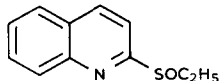
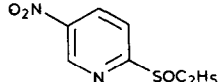
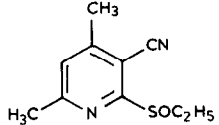
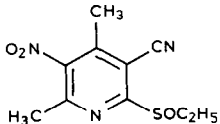
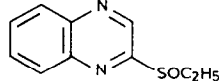
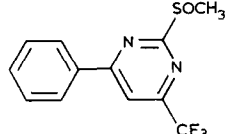


Fig. 3. Relationship between $\log P$ calculated according to Moreau with σ correction factors and $\log P_{\text{HPLC}}$ for 35 thienyl sulphoxides.

TABLE III

STRUCTURES OF ARYL SULPHOXIDES USED IN THE CORRELATION STUDIES AND VALUES OF HPLC AND COMPUTER CALCULATED LOG P

| No. | R_1 | R_2 | R_3 | $\log P$ | | | σ |
|-----|---|---------------------------------|---|----------|--------|--------|----------|
| | | | | HPLC | Rekker | Moreau | |
| |  | | | | | | |
| 36 | COC ₂ H ₅ | NO ₂ | SOC ₂ H ₅ | 2.80 | 1.04 | 0.77 | 1.28 |
| 37 | COC ₅ H ₁₁ | NO ₂ | SOC ₂ H ₅ | 4.36 | 2.59 | 2.16 | 1.28 |
| 38 | COC ₆ H ₅ | NO ₂ | SOC ₂ H ₅ | 3.82 | 1.66 | 1.86 | 1.21 |
| 39 | NO ₂ | CN | SOC ₂ H ₅ | 2.15 | 0.42 | 0.19 | 1.44 |
| 40 |  | NO ₂ | SOC ₂ H ₅ | 5.11 | 2.24 | 3.45 | 0.85 |
| 41 | Cl | SO ₂ CH ₃ | SOC ₂ H ₅ | 2.31 | 0.40 | 0.20 | 0.95 |
| 42 | H | H | SOCH ₃ | 1.04 | 0.49 | 0.32 | 0.00 |
| 43 |  | | | 2.10 | 1.17 | 0.58 | 1.24 |
| 44 | | |  | 2.43 | 0.96 | 1.47 | 0.78 |
| 45 |  | | | 1.74 | -0.55 | -0.16 | 1.56 |
| 46 | | |  | 1.77 | 0.37 | 0.20 | 1.10 |
| 47 |  | | | 2.44 | 0.14 | 0.19 | 2.08 |
| 48 | | |  | 2.29 | 0.31 | 0.61 | 1.17 |
| 49 |  | | | 3.01 | 1.06 | 1.07 | 1.71 |

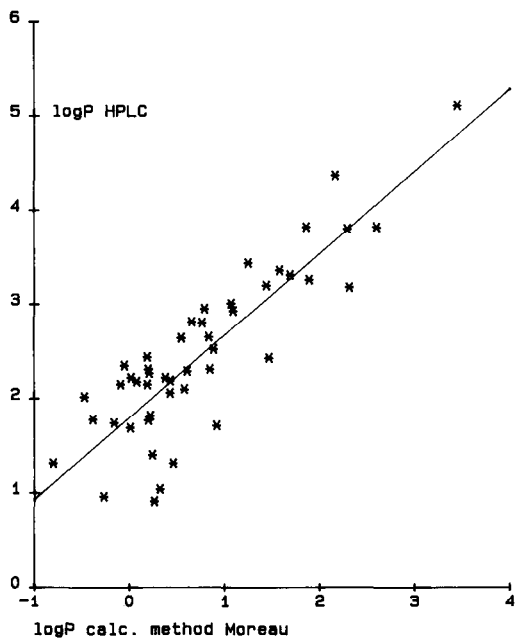


Fig. 4. Relationship between $\log P$ calculated according to Moreau and $\log P_{\text{HPLC}}$ for 49 aryl sulphoxides.

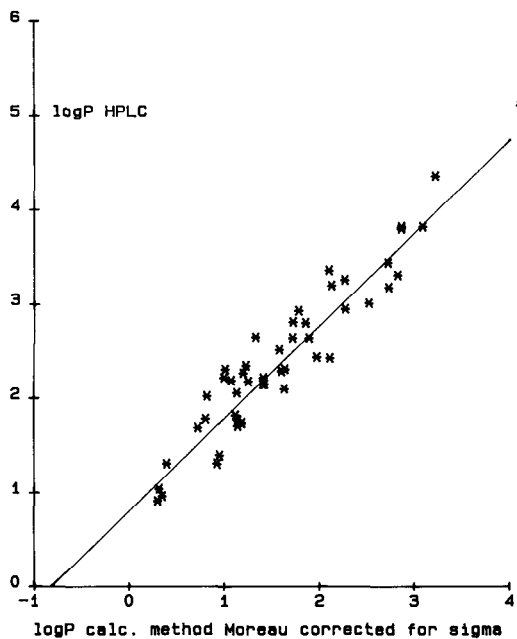


Fig. 5. Relationship between $\log P$ calculated according to Moreau with σ correction factors and $\log P_{\text{HPLC}}$ for 49 aryl sulphoxides.

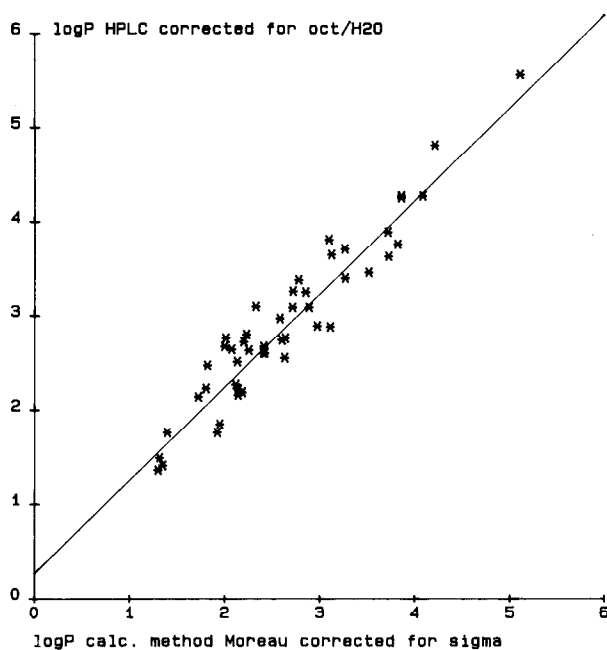


Fig. 6. Relationship between $\log P$ calculated according to Moreau with correction factors for σ and $\log P_{\text{HPLC}}$ corrected for the SO moiety of 49 aryl sulphoxides.

CONCLUSIONS

The hydrophobic properties of the sulphoxide moiety, substituted into an aromatic nucleus, is strongly dependent on the electronic character of other substituents attached to that nucleus. Electron-withdrawing groups increase hydrophobicity. In the case of thienyl derivatives, the *para* σ substituent constants seem to be the best correction factors for calculated $\log P$ values. For aromatic systems in general, the Hammett constants are suitable to correct calculated $\log P$ values in order to get good correlations with $\log P$ values estimated by HPLC. The equation finally obtained for 49 aryl sulphoxides is:

$$\log P_{\text{HPLC}} = 0.98 \log P \text{ calc.} + 0.86 \sigma + 0.82$$

| |
|----------------|
| <i>t</i> value |
| 21.23 |
| 10.05 |

$n = 49 \quad r = 0.955 \quad s = 0.271 \quad F = 238.4$

The remaining intercept of 0.82 is possibly caused by a systematic overestimation of the hydrophobicity of the sulphoxide moiety by HPLC in relation to the "shake-flask" method.

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