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RELATIONSHIP BETWEEN PAPER CHROMATOGRAPHIC R_M VALUES AND HANSCH'S π PARAMETERS IN DISSOCIABLE COMPOUNDS*

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SUMMARY

Logarithms of the partition coefficients and Hansch's π parameters were correlated with R_M values obtained from partition chromatography for three groups of substituted acids: cinnamic, β-aryl-*n*-butyric and α-arylpropionic, which dissociate in the chromatographic system used. It was found that under the conditions used, the degree of dissociation has to be taken into account, either by using partition coefficients corrected for dissociation, or by including Hammett σ constants or pK values in the appropriate correlation equation.

In a series of alkyl- and alkoxyphenols, whose degree of dissociation is negligible, a linear correlation exists between the π parameters and the R_M values.

The correlation equations derived used to calculate some π parameters not previously established, namely for the *p*-dimethylamino group in the series of cinnamic acids, for the *p*-phenoxy group in that of β-aryl-*n*-butyric acids, for the *p*-phenoxy group in that of α-arylpropionic acids, and for the *p*-benzyl, *p*-benzyloxy and *p*-phenyloxy groups in the series of phenols.

The correlation between the chromatographic data and π parameters established for the series of alkyl- and alkoxyphenols show the existence of mutual hydrophobic interactions between the benzene nuclei in *p*-benzyl-, *p*-benzyloxy- and *p*-phenoxyphenols.

INTRODUCTION

Martin and Synge[1] and Consden *et al.*[2] established the relationship between the R_F values obtained from partition chromatography and the partition coefficients. This relationship, modified by Bate-Smith and Westall[3] and extended by Collander[4] is expressed by the equation

$$R_M = a \cdot \log P + b \qquad (1)$$

where a and b are constants for a particular system and P is the partition coefficient.

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The validity of this equation has been studied by a number of workers[5–7] for some series of compounds that do not dissociate in the chromatographic system actually used. Studies[8–12] of the relationship between chemical structure and chromatographic behaviour made use of Martin's postulate[13] of the additivity contributions, ΔR_M, specific for the individual substituents or structural fragments. In this connection, especially worthy of mention is a series of studies conducted by Marcinkiewicz *et al.*[10–12]. Some investigators[8,14–16] have pointed out the influence of dissociation on the chromatographic behaviour of acids and bases. Soczewinski[15] derived an equation which Bush[17] suggested could be used for calculation of the pK values of acids or bases from paper chromatographic data. Some workers[5,18] made indirect use of this relationship in chemical structure–biological activity relationships. The lipophilic nature of substances was expressed by the R_M values obtained from partition chromatography instead of the logarithms of the partition coefficients.

In this study we have confirmed the applicability of Martin's equation to α-alkylcinnamic (I), β-aryl-n-butyric (II), and α-arylpropionic acids (III), which dissociate in the chromatographic system used. As examples of compounds whose degree of dissociation is negligible in the given chromatographic medium, we chose several series of substituted phenols, making use of the experimental data published by Marcinkiewicz *et al.*[10].

The values of the logarithms of experimentally determined partition coefficients in eqn. 1 were replaced by constants π, representing a substituent effect, defined by Hansch *et al.*[19] by the following equation:

$$\pi = \log P_X - \log P_H \tag{2}$$

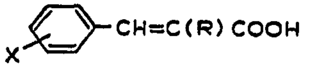
where P_X and P_H are the partition coefficients in the n-octanol–water system for substituted and unsubstituted compounds, respectively; π characterizes the contribution of the substituent to the lipophilic nature of the whole molecule. These π parameters are used as a measure of the lipophilicity in the quantitative chemical structure–biological activity relationships and have been summarized in reviews[20,21].

EXPERIMENTAL

Chromatographic determinations of the acids I, II and III were carried out as follows. A 10-μl volume of a 1% solution of a compound in chloroform was applied on Whatman No. 4 paper, which was then impregnated with a 40% ethanolic solution of formamide containing 5% of ammonium formate. With β-aryl-n-butyric acids (II), Whatman No. 4 paper impregnated with a 5% solution of formic acid in formamide was used as an alternative (in Table III, the former system is designated A and the latter B). After drying for 15 min, downwards one-dimensional chromatography was carried out at a constant temperature of 20° using benzene as the mobile phase. Finally, the chromatogram was allowed to dry at 100°. The cinnamic acids I were rendered visible with a mixture of amylose, potassium iodide and potassium iodate. Each chromatogram contained six to eight compounds, of which one or two were used as reference samples whose R_F values were known from previous chromatograms, and varied by not more than 0.01. The pK_a values of the cinnamic acids IV were determined in aqueous ethanol (1:1) on a recording Titrigraph-Radiometer (Copenhagen, Denmark) SBR-2c potentiometer with a glass electrode and a calomel reference electrode. The correlation equations were calculated by the least-squares method on a Hewlett-Packard (Loveland, Colo., U.S.A.) Model 9820 calculator.

Preparation of compounds

The cinnamic acids (I) were prepared by the Wittig reaction as described elsewhere[22,23]. β-Aryl-*n*-butyric acids (II) were prepared by a series of consecutive reactions from substituted acetophenones according to Asano *et al.*[24]. α-Arylpropionic acids (III) were prepared from arylacetic acids by the method described in the literature[25].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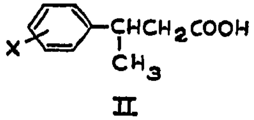
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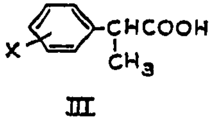
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RESULTS AND DISCUSSION

Experimental results and physico-chemical parameters of the cinnamic acid derivatives are presented in Table I. In the correlation equations 3, 4 and 5, the logarithms of the partition coefficients calculated according to the additivity rule established by Fujita *et al.*[26] and Hansch *et al.*[27] were used. The value of log P for the parent cinnamic acid (log P = 2.13) was taken from Leo *et al.*[20]. For substituents on aromatic ring, the π values valid for substituted benzoic acid were used[*]; the π values for α-alkyl groups were calculated using the following incremental values of π: +0.50 for each carbon atom in a chain and −0.20 for a branch in the chain. The relationship between the calculated log P and R_M values is expressed by eqn. 3. A distinct improvement in correlation was achieved by introduction of pK_a values of these acids (*cf.*, eqn. 4).

	n[**]	s[**]	r[**]	
$\log P = -1.2026\,R_M + 2.8751$	35	0.323	0.917	(3)
$\log P = -1.8431\,R_M - 1.1252\,\mathrm{p}K_a + 9.7825$	35	0.183	0.975	(4)
$\log P' = -1.7148\,R_M + 1.7473$	35	0.192	0.984	(5)

Similarly, correction of the partition coefficients for dissociation at the pH of the chromatographic medium led to an improved correlation. The corrected partition coefficients, P', were calculated from eqn. 6:

$$P/P' = 1 + \operatorname{antilog}(\mathrm{pH} - \mathrm{p}K_a) \qquad (6)$$

where P is the partition coefficient of the undissociated compound and P' is the observed partition coefficient of the compound at the pH of the chromatographic

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[*] Not included in eqns. 3, 4 and 5 are the *p*-dimethylamino derivatives, since π for the *p*-dimethylamino group is not known.

[**] n is the number of compounds included in the correlation, s is the standard deviation and r is the correlation coefficient.

TABLE I

CINNAMIC ACIDS (I), $X\text{-}C_6H_4CH{=}C(R)COOH$

X	R_F				R_M				pK_a				π**	π_{calc}***
	*A**	*B**	*C**	*D**	*A*	*B*	*C*	*D*	*A*	*B*	*C*	*D*		
p-NO_2	0.16	0.28	0.42	0.62	0.72	0.41	0.14	−0.21	5.12	5.72	5.82	5.95	0.02	−0.05
m-NO_2	0.17	0.24	0.46	0.63	0.70	0.50	0.07	−0.23	5.19	5.80§	5.90§	6.00§	−0.05	−0.12
m-Br				0.92				−1.05				6.25	0.99	1.02
m-Cl	0.30	0.70	0.84	0.90	0.36	−0.37	−0.72	−0.95	5.42	6.05	6.20	6.30	0.83	0.83
m-I				0.94				−1.19				6.30	1.28	1.20
p-Br				0.92				−1.05				6.32	0.98	0.92
p-Cl	0.39	0.62	0.83	0.91	0.13	−0.21	−0.69	−1.00	5.52	6.10	6.25	6.35	0.87	0.80
p-I				0.93				−1.12				6.40§	1.14	0.96
H	0.22	0.54	0.75	0.86	0.55	−0.07	−0.48	−0.79	5.68	6.35	6.43	6.55	0	0.12
p-$(CH_3)_2CH$	0.71	0.90	0.94	0.96	−0.39	−0.95	−1.19	−1.38	5.85	6.40	6.53§	6.65	1.40	1.45
p-CH_3		0.74	0.83	0.92		−0.45	−0.69	−1.06		6.45	6.55	6.65	0.42	0.58
p-CH_3O	0.27	0.64	0.80	0.83	0.43	−0.25	−0.60	−0.69	5.90	6.55	6.65	6.70	0.08	0.06
p-$(CH_3)_2N$	0.32	0.61	0.80	0.89	0.34	−0.19	−0.60	−0.93	6.32	6.90§	7.05§	7.15§		−0.28

* A, R = H; B, R = CH_3; C, R = C_2H_5; D, R = *n*-C_3H_7.

** Values taken from ref. 21.

*** Calculated from eqn. 2; for substituents where several values of π were available, the mean values are given

§ Values taken from ref. 23.

medium[28]. We assumed that the pH of the stationary phase of chromatographic system A was 7. Eqn. 5 was obtained from the correlation of the logarithms of the corrected partition coefficients (log *P'*) with the R_M values. Improvements in the correlation are also shown in Fig. 1 (representing eqn. 3) and Fig. 2 (eqn. 5).

Similar results were also obtained for the correlation of the R_M values of both β-aryl-*n*-butyric (eqns. 7 and 8) and α-arylpropionic acids (eqns. 10 and 11) with π. Here, the π values for aromatic *p*- and *m*-substituents derived for arylacetic acids were used. Experimental data and physico-chemical constants for β-aryl-*n*-butyric and for α-arylpropionic acids are presented in Tables II and III. Eqns. 8 and 11 show the

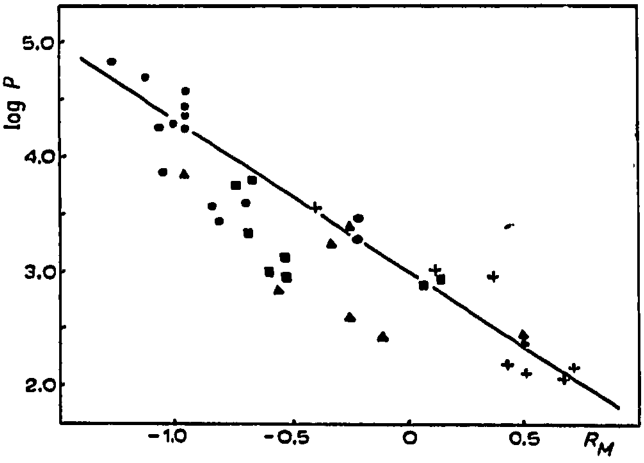


Fig. 1. Relationship between R_M values and log *P* for cinnamic acids. +, α-H; ▲, α-CH_3; ■, α-C_2H_5; ●, α-*n*-C_3H_7.

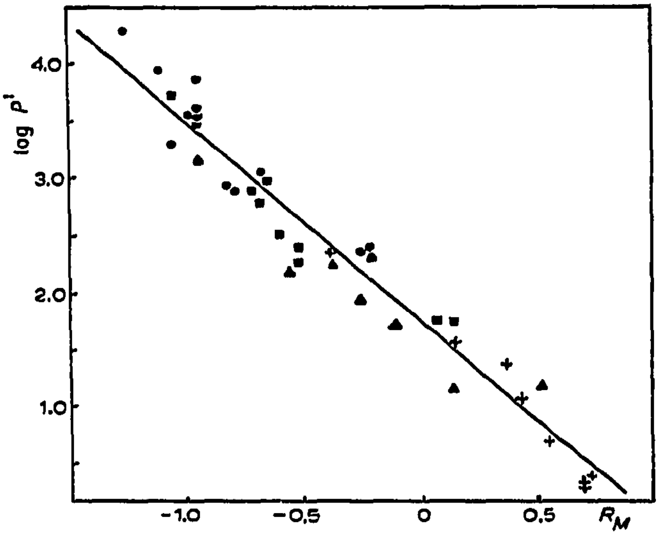


Fig. 2. Relationship between R_M values and log P' for cinnamic acids. +, α-H; ▲, α-CH_3; ■, α-C_2H_5; ●, α-n-C_3H_7.

improvement in the correlation when Hammett σ constants were introduced. The replacement of pK_a values by σ constants is possible owing to the linear dependence between these two quantities. With β-aryl-n-butyric acids, the chromatographic determination was also performed in a system with a stationary phase containing

TABLE II

β-ARYL-n-BUTYRIC ACIDS (II), X-$C_6H_4CH(CH_3)CH_2COOH$

X	R_F*		R_M*		σ**	π**	π_{calc}***
	A	*B*	*A*	*B*			
m-CF_3	0.68	0.80	−0.33	−0.60	0.43	1.16	1.03
m-Br	0.62	0.72	−0.21	−0.41	0.39	0.91	0.79
p-Br	0.64	0.78	−0.25	−0.55	0.27	0.90	0.87
p-Cl	0.65	0.73	−0.27	−0.43	0.23	0.70	0.74
o-I	0.66	0.79	−0.29	−0.58	0.21	0.92	0.91
2-Cl,5-CH_3	0.73	0.82	−0.43	−0.66	0.13§	1.08§§	1.07
H	0.48	0.56	0.03	−0.10	0	0	0.15
p-$(CH_3)_2CHCH_2$	0.90	0.91	−0.95	−1.00	−0.11	1.85	1.74
p-C_2H_5	0.78	0.83	−0.55	−0.69	−0.15	0.90	1.11
p-$(CH_3)_2CH$	0.83	0.88	−0.69	−0.87	−0.15	1.40	1.39
p-CH_3	0.65	0.73	−0.27	−0.43	−0.17	0.45	0.64
2,5-$(CH_3)_2$	0.78	0.84	−0.55	−0.72	−0.24§	1.17§§	1.11
p-CH_3O	0.42	0.51	0.14	−0.02	−0.27	0.01	−0.05
p-C_6H_5	0.84	0.86	−0.73	−0.79	−0.01		1.40

* Chromatographic systems, *cf.*, Experimental.

** Values taken from ref. 21.

*** Mean value of π calculated from eqns. 8 and 9.

§ Sum of σ constants of both substituents.

§§ Sum of π parameters of both substituents; π for *o*-substituents taken from phenoxyacetic acids.

TABLE III

α-ARYLPROPIONIC ACIDS (III), $X\text{–}C_6H_4CH(CH_3)COOH$

X	R_F	R_M	σ^*	π^*	π_{calc}^{**}
m-Br	0.42	0.14	0.39	0.91	0.88
p-Br	0.45	0.09	0.27	0.90	0.84
p-Cl	0.42	0.14	0.23	0.70	0.73
H	0.28	0.41	0	0	0.13
p-$(CH_3)_2CHCH_2$	0.90	−0.95	−0.11	1.85	1.92
p-C_2H_5	0.66	−0.29	−0.15	0.90	0.96
p-$(CH_3)_2CH$	0.79	−0.57	−0.15	1.40	1.36
p-CH_3	0.46	0.07	−0.17	0.45	0.45
p-CH_3O	0.29	0.39	−0.27	0.01	−0.05
p-C_6H_5O	0.88	−0.86	−0.32		1.60

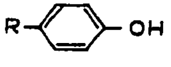
* Values taken from ref. 21.
** Values calculated from eqn. 11.

formic acid. A reduction of the pH inhibits dissociation and hence the correlation between R_M values and π is then satisfactory even without correction for dissociation (*cf.*, eqn. 9).

	n	s	r	
$\pi = -1.5872\ R_M^A + 0.3205$	13	0.208	0.920	(7)
$\pi = -1.6740\ R_M^A + 0.6029\ \sigma + 0.2638$	13	0.150	0.963	(8)
$\pi = -1.7828\ R_M^B - 0.0897$	13	0.150	0.959	(9)
$\pi = -1.2355\ R_M + 0.7395$	9	0.247	0.934	(10)
$\pi = -1.3866\ R_M + 0.9474\ \sigma + 0.7029$	9	0.089	0.993	(11)

The results obtained so far suggest, therefore, that for substances that dissociate in the chromatographic system used, a linear correlation between the R_M values from partition chromatography and π, or the calculated log P value, is only valid if the degree of dissociation is taken into account. The effect of the dissociation can be solved in the following two ways: (a) by using logarithms of partition coefficients (log P') corrected for the dissociation according to eqn. 6; and (b) by including either the pK_a values or Hammett σ constants in the correlation equation.

With acids that do not dissociate in the chromatographic system used, a linear correlation between π and the R_M values is valid even without correction for dissociation. As examples we chose a series of monosubstituted p-alkylphenols (IV) and p-alkoxyphenols (V), whose chromatographic behaviour has been studied in detail by Marcinkiewicz *et al.*[10,11].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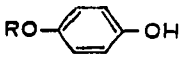
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We correlated their experimental R_M values with π. From the value of π for p-CH_3 (0.48) and p-CH_3O (−0.12), further π parameters were derived using the additive terms[21] $\Delta\pi_{CH_2\,\text{aliph.}} = 0.50$, $\Delta\pi_{CH_2\,\text{cycl.}} = 0.41$, $\Delta\pi_{\text{branching}} = -0.20$ and $\Delta\pi_{\text{double bond}} = -0.30$. For the p-cycloalkyloxy groups, the π parameters were calculated from

$$\pi_{C_nH_{2n-1}O} = \pi_{p\text{-OH}} + n\cdot\Delta\pi_{CH_2\,\text{cycl.}} = -0.87 + n\cdot 0.41 \qquad (12)$$

For p-alkylphenols*, eqn. 13 was formulated and for two series of p-alkoxyphenols that partly differed in their substituents and processed in two different chromatographic systems** eqns. 14 and 15 were derived:

	n	s	r	
$\pi = 1.0100\ R_M + 1.2929$	16	0.102	0.983	(13)
$\pi = 1.1261\ R_M + 1.2997$	13	0.113	0.992	(14)
$\pi = 3.8957\ R_M + 4.2181$	14	0.064	0.999	(15)

The correlation coefficients and standard deviations in eqns. 13–15 not only exhibit a fairly close correlation between the chromatographic data and the π parameters, but also show a high accuracy of the experimental technique used by Marcinkiewicz *et al.*[10–12].

The practical value of the relationships established lies in the possibility of calculating unknown π parameters from appropriate known R_M values. Also, these relationships offer a basis for studies of intramolecular effects, such as the *ortho*-effect, hydrophobic effect and the effect of hydrogen bonds on the lipophilicity of molecules. The accuracy of the determination is enhanced if the value of π is a mean obtained either from several measurements or from measurements made on structurally similar compounds with identical substituents. In the series of cinnamic acids, we obtained the π parameter for the p-dimethylamino group as a mean value from the R_M and pK_a values of the unsubstituted, α-methyl, α-ethyl and α-n-propyl-p-dimethylamino derivatives of cinnamic acid. These values, together with the π parameters for other substituents calculated from eqn. 4, are given in the last column in Table I. From eqns. 8 and 9 for β-aryl-n-butyric acids, the π parameter for the p-phenyl substituent was calculated as the mean of two values obtained from the R_M values found in two chromatographic systems.

Furthermore, from the equations valid for p-alkylphenols (eqn. 13) and p-alkoxyphenols (eqns. 14 and 15), we also calculated the π parameters for several substituents listed in Table IV. A comparison of π values for phenyl (1.89)[26] and benzyl groups (1.83) as well as of those for the phenoxy (average 1.69) and benzyloxy

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* The experimental data were taken from ref. 10. The chromatographic determination was carried out on Whatman No. 1 paper impregnated with ethyl oleate, with 25% aqueous ethanol as the mobile phase[10].

** The data for eqn. 14 were taken from ref. 10, for the chromatographic system, see the above footnote. The data for eqn. 15 were taken from ref. 11. The chromatographic determination was carried out on Whatman No. 4 paper impregnated with a 5% solution of olive oil in light petroleum (b.p. 40–60°), with 70% aqueous ethanol as the mobile phase.

TABLE IV

CALCULATED π PARAMETERS FOR SOME ALKYL- AND ALKOXY-SUBSTITUENTS OF PHENOLS

Substituent	R_M	π_{calc}
$C_6H_5CH_2$	0.530	1.83*
3,4-$(CH_3)_2$	−0.444	0.84*
3-CH_3,4-*n*-C_3H_7	0.396	1.69*
3-CH_3,4-iso-C_3H_7	0.289	1.58*
C_6H_5O	0.311	1.65**
	−0.638	1.73***
$C_6H_5CH_2O$	0.185	1.51**
	0.668	1.61***

* Calculated from eqn. 12.
** Calculated from eqn. 13.
*** Calculated from eqn. 14.

(average 1.56) groups shows that the replacement of phenyl by benzyl does not enhance the lipophilicity. These results are in agreement with the conclusions of Hansch and Anderson[29] and Iwasa *et al.*[6]. According to these workers, the phenomenon may be explained as a consequence of an intramolecular hydrophobic bond, or of an interaction of polarizable electrons present in the aromatic rings. In this connection, it is worth mentioning that the calculated value of π for benzyl (1.83) obviates a disagreement between the R_M and π values for benzyl in a series of substituted penicillins pointed out by Biagi *et al.*[7]. The hydrophobic effect is also likely to be responsible for the distinct decrease in the value of π for the *m*-methyl group in 3,4-disubstituted phenols (Table IV). From the appropriate R_M values, π parameters were calculated which represented totals of the π values valid for each of both alkyls respectively. On subtracting the value of π for the *p*-substituent, the following π values result for the *m*-methyl substituent in these phenols: 3,4 dimethyl, $\pi = 0.36$; 3-methyl-4-*n*-propyl, $\pi = 0.21$; and 3-methyl-4-isopropyl, $\pi = 0.30$. From the value of log *P* for *m*-cresol, that for $\pi_{m\text{-}CH_3} = 0.56$ was calculated[26].

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