Determination of the lipophilicity of arylsulphonylalkanoic and arylsulphonylcycloalkanecarboxylic acids by thin-layer chromatography

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ABSTRACT

   The R_M values of arylsulphonylalkanoic and arylsulphonylcycloalkanecarboxylic acids were measured by thin-layer chromatography on a polyamide layer. The R_M *vs.* Rekker hydrophobicity relationship was analysed and some excellent correlations, especially within strictly congeneric sub-series, were established.

INTRODUCTION

   Lipophilicity is one of the basic properties discussed in quantitative structure–activity relationship (QSAR) studies of biologically active compounds [1]. However, because of the complexity of the phenomena involved, no individual and simple procedure can be recommended as a unique quantitative measure of this property [2]. One of the parameters that appears to fit into the QSAR models of lipophilicity is the R_M value determined on polyamide layers [2,3]. This parameter has been found even more suitable for the description of the biological activity of some compounds than the Hansch hydrophobic constant [4], apparently owing to the similarity between the polyamide and the protein structures [5]. On the other hand, it has been established that the retention mechanism on the polyamide layers involved both partition and adsorption through the hydrogen bonds [6], the phenomena omnipresent in most natural processes.

   The aim of this work was to study the dependence between the R_M parameters measured on polyamide layers and the Rekker hydrophobic constants for the series of α-arylsulphonylalkanoic and α-arylsulphonylcycloalkanecarboxylic acids (I–III), some of which have been found to stimulate a sweet taste receptor [7].
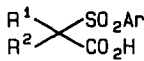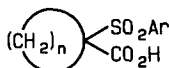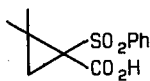
EXPERIMENTAL

The title compounds were synthesized according to procedures described elsewhere [8].

For the determination of R_M values, polyamide 11 F_{254} (Merck, Darmstadt,

TABLE I

LIPOPHILICITY INDICES OF THE ACIDS I–III[a]

No.	Type of structure	Ar[b]	R¹/R²[b] or n	R_M	$S(R_M)$[c]	Σf
1	III	Ph	H/H	−0.31	0.062	0.453
2	III	Ph	Me/H	0.15	0.064	0.860
3	III	Ph	Et/H	0.41	0.043	1.390
4	III	Ph	n-Pr/H	0.61	0.033	1.920
5	III	Ph	i-Pr/H	0.57	0.052	1.797
6	III	Ph	s-Bu/H[d]	0.81	0.077	2.327
7	III	Ph	c-Pn/H	0.93	0.050	2.513
8	III	Ph	Bz/H	1.07	0.051	2.740
9	III	Ph	n-Bu/H	0.84	0.021	2.450
10	III	Fc	i-Pr/H	0.88	0.041	—[e]
11	III	Ph	Me/Me	0.40	0.065	1.477
12	III	Ph	Et/Et	0.79	0.067	2.537
13	III	Ph	n-Pr/n-Pr	1.16	0.055	3.597
14	III	Ph	n-Pr/Et	0.98	0.124	3.067
15	III	Ph	Et/Me	0.58	0.087	2.007
16	III	Ph	i-Pr/Me	0.70	0.054	2.414
17	II	Ph	2	0.47	0.067	1.133
18	I	Ph	—	0.54	0.044	2.157
19	II	Ph	3	0.48	0.022	1.663
20	II	Ph	4	0.70	0.052	2.193
21	II	Ph	5	0.91	0.010	2.723
22	III	4-Me-Ph	i-Pr/H	0.72	0.056	2.301
23	III	4-Cl-Ph	i-Pr/H	0.88	0.044	2.521
24	III	4-Br-Ph	i-Pr/H	1.05	0.039	2.730
25	III	4-Et-Ph	i-Pr/H	0.90	0.022	2.831
26	III	4-t-Bu-Ph	i-Pr/H	1.16	0.041	3.855
27	III	4-i-Pr-Ph	i-Pr/H	1.05	0.016	3.238
28	III	4-MeO-Ph	i-Pr/H	0.70	0.035	1.868
29	III	3,4-Cl-Ph	i-Pr/H	1.22	0.022	3.186
30	II	4-MeO-Ph	5	1.05	0.009	2.794
31	II	4-Me-Ph	4	0.81	0.045	2.697
32	II	4-MeO-Ph	4	0.81	0.034	2.264
33	III[f]	Ph	Me/H	−0.35	0.084	0.680
34	II	Fc	4	0.96	0.020	—[e]

[a] The synthesis has been detailed elsewhere [8].

[b] Ph = phenyl; Me = methyl; Et = ethyl; Pr = propyl; Bu = butyl; Fc = ferrocenyl; c-Pn = cyclopentyl; Bz = benzyl; 3,4-Cl-Ph = 3,4-dichlorophenyl.

[c] Relative standard deviations of R_M (n = 8–10).

[d] Compound 6 consists of two diastereoisomers [7] which do not separate under the chromatographic conditions.

[e] The Rekker fragmental constant f for the ferrocene unit is not available in the literature.

[f] 2-Phenylsulphinylpropionic acid.

Germany) 20×20 cm plates were used as the stationary phase. The tested compounds were dissolved in methanol ad $40\text{-}\mu g$ samples were spotted randomly on the plates in order to avoid any systematic error. Four chromatographic plates placed in a holding frame were developed to a height of 15 cm after 2 h of saturating the chromatographic tank, and using citric buffer (pH 2)–methanol (1:1, v/v) as the mobile phase. The plates were then dried and spots were detected under UV light (254 nm). The reported R_M values, calculated from equation $R_M = \log(1/R_F - 1)$, are the averages of 8–10 measurements.

The Rekker hydrophobic constants, Σf, were calculated according to ref. 9.

RESULTS AND DISCUSSION

Table I gives the R_M values obtained from our experiments and the calculated Rekker hydrophobic constants, Σf. The relative standard deviations of the R_M values range from 1.0 to 12.4%.

Table II shows the established regression relationships for all the derivatives considered (eqn. 1) and for limited sub-sets of these compounds (eqns. 2–4a).

TABLE II

CORRELATION EQUATIONS[a] BETWEEN R_M AND Σ_f VALUES

$R_M = a\Sigma f + b$

Eqn. No.	a	b	n	r	s	F	Compounds considered
1	0.435	−0.272	32	0.937	0.132	216	All[b]
2	0.468	−0.262	8	0.995	0.033	588	2–9
3	0.364	−0.147	6	0.998	0.019	1064	11–16
4	0.406	−0.193	3	1.000[c]	0.004	5547	19–21
4a	0.291	0.080	4	0.951	0.079	19.10	17, 19–21

[a] All calculations were performed on a Texas Instruments SR 51 A calculator.
[b] Excluding 10 and 34: ferrocene derivatives whose f values are not available in the literature.
[c] 0.9999.

The relationship R_M vs. Σf for all the 32 derivatives considered is show in Fig. 1. The correlation coefficient is $r = 0.937$.

Fig. 2 shows the relationship R_M vs. Σf for the mono-($R_2 = H$) and disubstituted ($R^1, R^2 \neq H$) phenylsulphonylalkanoic acid derivatives. The results can be arranged in two separate straight-line plots, one for each type of derivative. The respective correlation coefficients are remarkably high (above 0.99) (eqns. 2 and 3, Fig. 2). It seems justified to conclude that these significantly good correlations indicate the congenericity of the aforementioned sub-sets of derivatives, as obtained from the definition of the congenericity [10]. Hence it seems reasonable to assume that within the two discussed sub-sets the adsorption processes are alike to such an extent that the retention differences are due to the differences in the partition mechanism only.

In contrast, a significantly poorer correlation is observed within the cyclic
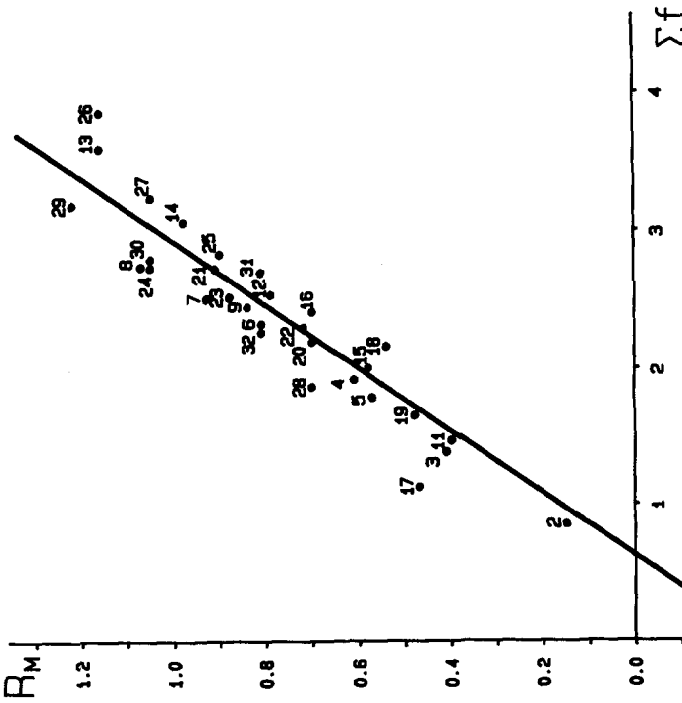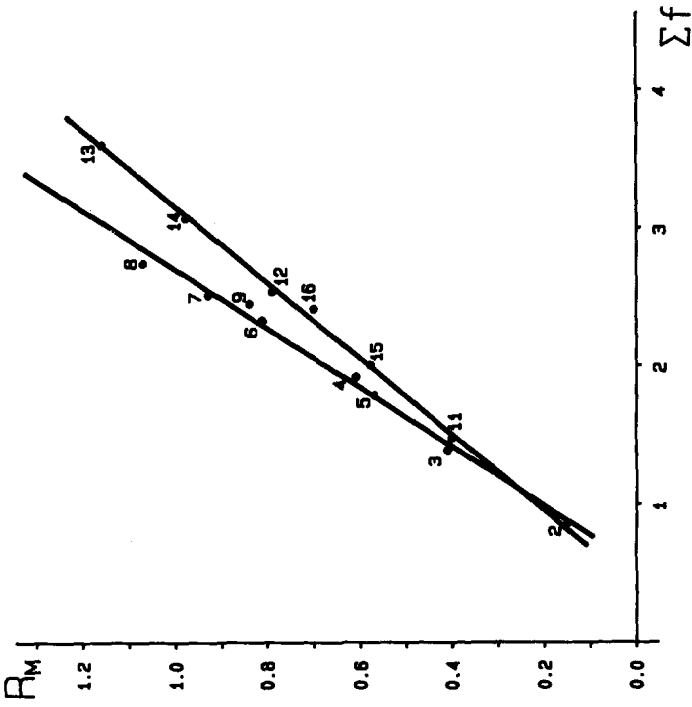
Fig. 1. Relationship between R_M and Σf values for all the 32 derivatives considered, as described by eqn. 1.

Fig. 2. Relationship between R_M and Σf values for mono- and disubstituted phenylsulphonylalkanoic acid derivatives, as described by eqns. 2 and 3, respectively.
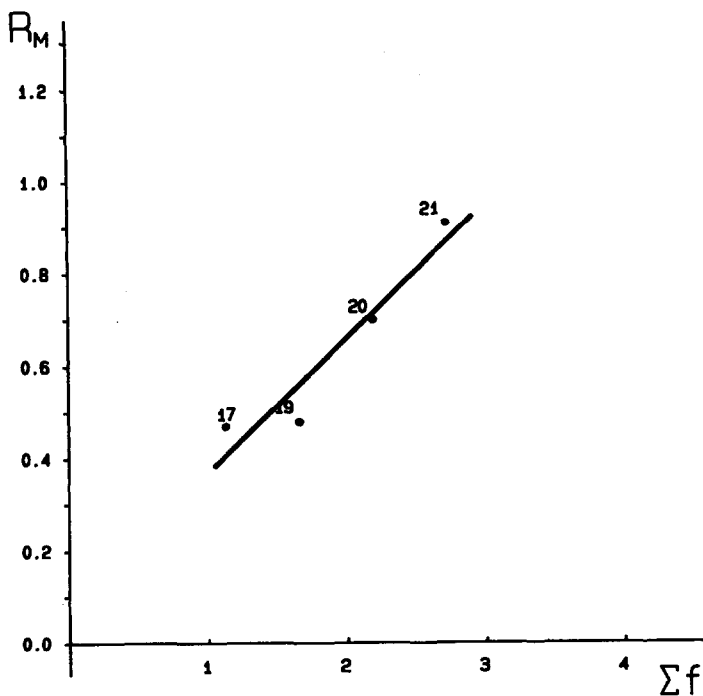
Fig. 3. Relationship between R_M and Σf values for phenylsulphonylcycloalkanecarboxylic acids, as described by eqn. 4a.
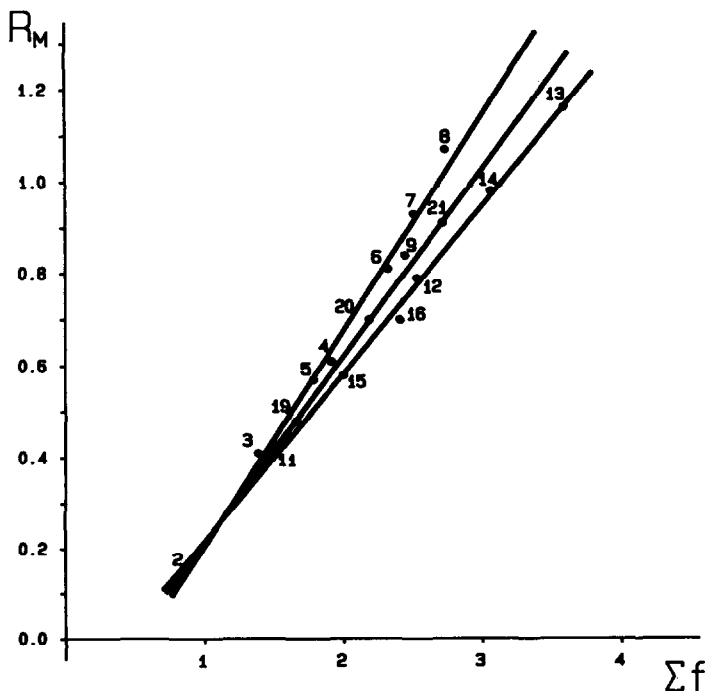

Fig. 4. Relationship between R_M and Σf values for mono-, disubstituted and cyclic phenyl derivatives, as described by eqns. 2, 3 and 4, respectively.

derivatives sub-set (eqn. 4a, Fig. 3). This phenomenon probably results from the change in the geometry of the polar $COOH/SO_2$ moiety induced by the cyclopropane ring. Hence the consecutive cyclic derivatives differ in respect of both the partition and adsorption mechanisms. Neglecting the cyclopropane derivative 17 gives eqn. 4, which describes excellently the R_M vs. Σf relationship for the cyclobutane to cyclohexane analogues. It is worth mentioning also that the three aforementioned straight-line plots (eqns. 2–4) intersect precisely at one point (Fig. 4).

CONCLUSIONS

The intermolecular interaction through hydrogen bonds and partition effects in the retention mechanism on polyamide seem to be similar and may simulate the intermolecular interaction in living systems which are usually based on lipophilicity and hydrogen bond effects. In fact, probably owing to the importance of these two factors in chemoreception processes [11], the established R_M values provide a significantly better fit in our QSAR (structure–taste) model than do the hydrophobicity constants [7,12].

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