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Relationship between π and R_m Values of Sulfonamides†

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The chromatographic R_m values of sulfonamides in several reversed phase tlc systems were shown to be very well correlated with the Hansch π values in an isobutyl alcohol-water system. On the other hand, when the π values were calculated from the partition data obtained with chloroform, toluene, or ethylene dichloride as organic phases the correlation coefficients were much lower. By comparing R_m values of sulfonamides, cephalosporins, and penicillins, it was pointed out that sulfonamides are more hydrophilic than both series of antibiotics. Therefore, sulfonamides and penicillins could be considered as being represented respectively by molecules falling on the left and right side of the theoretical parabola relating lipophilic character and antibacterial activity.

The relation between physicochemical properties and biological activity of sulfonamides has been studied by Bell and Roblin,[1] Cowles,[2] Seydel,[3] Seydel, *et al.*,[4] and many others.[5] However, Fujita and Hansch,[6] Fujita,[7] and Seydel[3a] seemed to obtain the best results. The correlation between biological activity and chemical structure was analyzed by means of substituent constants such as the Hammett σ constant, the pK_a value, and the hydrophobicity constant π. Hansch, *et al.*,[8] defined $\pi = \log P_X - \log P_H$ where P_X and P_H are the partition coefficients, determined in the system 1-octanol-water, of the substituted and unsubstituted compounds, respectively. However, because of the practical difficulties of the determination of the partition coefficient, Boyce and Milborrow[9] had proposed the chromatographic R_m value as an expression of the lipophilic character of molecules. The R_m values resulted to be useful in correlating biological activity and lipophilic character of *N*-*n*-alkyltritylamines,[9] bis(dichloroacetamides) and vitamin K analogs,[10] penicillins,[11a,12] cephalosporins,[11a] and testosterone esters.[11b] The contributions of Martin and Synge,[13] Consden, *et al.*,[14] and Brenner, *et al.*,[15] are very important in understanding the relationship between log P and the chromatographic R_m value.

The partition coefficient P of a solute between two immiscible phases can be expressed by

$$P = C_s/C_m \quad (1)$$

where C_s and C_m are the concentration of solute, at equilibrium, in the organic and aqueous phase, respectively. Since $C_s = q/V_s$ and $C_m = p/V_m$, eq 2 is obtained

$$P = (V_m/V_s)\cdot(q/p) \quad (2)$$

where q and p are the fractions of solute in the organic and aqueous phase, and V_s and V_m are the volumes of the organic and aqueous phase, respectively. However $q + p = 1$ and $q = 1 - p$. Therefore, by substituting and taking the logarithms

$$\log P = \log V_m/V_s + \log (1/p - 1) \quad (3)$$

where V_m/V_s can be taken as an arbitrary constant for a given system.

Martin and Synge[13] and Consden, *et al.*,[14] had shown that in a chromatographic system the partition coefficient can be expressed by

$$\log K = \log A_1/A_s + \log (1/R_f - 1) \quad (4)$$

where A_1/A_s, which is the ratio of the volumes of the mobile and stationary phase, has the same meaning of V_m/V_s in eq 3, and R_f is the ratio of the distances traveled by the solute and the front of the mobile phase. Equation 4 indicates that in reversed-phase tlc the R_f value is related to the partition coefficient of the substance between the nonpolar stationary phase and the polar mobile phase.

Since Brenner, *et al.*,[15] had shown that in a chromatographic system $p = R_f$, eq 3 and 4 are clearly related. A proper choice of the volumes V_m and V_s, A_1 and A_s, should make possible to obtain the same value for K and P.

Consden, *et al.*,[14] choose such a water content of the paper that the partition coefficient of several amino acids was close to that found by England and Cohn[16] by means of a direct measurement. Bate-Smith and Westall[17] introduced the term

$$R_m = \log (1/R_f - 1) \quad (5)$$

which cannot be considered as an expression of the true partition coefficient as it does not account for $\log A_1/A_s$. However, it was possible to show very good correlations between R_m and π values,[11b,c,18] the latter being derived from the experimental log P values. In particular, since $\Delta R_m = R_{m(X)} - R_{m(H)}$, where $R_{m(X)}$ and $R_{m(H)}$ are the chromatographic R_m values of the substituted and unsub-

†Dedicated to Professor Alfred Burger for his many outstanding contributions to medicinal chemistry.

stituted compounds, respectively, ΔR_m has the same meaning of π.

In the case of acids or bases, provided that the degree of association in the organic phase can be ignored, the corresponding equation is

$$R_m = \log (1/R_f - 1) + \log (K_A + [H^+])/[H^+] \quad (6)$$

where $[H^+]$ is the hydrogen ion concentration of the mobile phase and K_A is the dissociation constant of solute.

The purpose of the present paper was to show the relationship between π and R_m values and the usefulness of the latter in structure-activity studies with sulfonamides.

Materials and Methods

(1) R_m **Values Determination.** The test compounds obtained from drug companies are reported in Table I. The R_m values were measured by means of a reversed phase thin-layer chromatography technique. The details were already described.[19] The sulfonamides were partitioned between a polar mobile phase and a nonpolar stationary phase. The mobile phase was an aqueous buffer (sodium acetate-Veronal buffer 1/7 *M*) at pH 7.4. In order to obtain a better control of the pH of the stationary phase the slurry of silica gel G was obtained with 0.09 *N* NaOH. The stationary phase was obtained by impregnating a silica gel G layer with a 5, 10, or 20% (v/v) silicone oil or 1-octanol solution in ether. Silicone DC 200 (350 cSt) from Applied Science Laboratories was used. The impregnation was carried out by developing the plates in 5, 10, or 20% silicone or 1-octanol solution in ether. Eight plates could be impregnated in a single chromatographic chamber containing 200 ml of the impregnating solution. The plates were left in the chamber for 12 hr, that is, for several hours after the silicone or 1-octanol solution had reached the top of the plates. The actual amount of silicone oil or 1-octanol in the stationary phase was determined by extracting the impregnated layer with ether. The influence of the nature of the stationary phase on the R_m values was also shown by impregnating a silica gel G layer with a 5, 10, or 20% (v/v) solution in petroleum ether of liquid paraffin, undecane, or squalane, from Merck Co. (Darmstadt), as above described. The sulfonamides were dissolved in acetone (1 mg/ml) and 1 μl of solution was spotted on the plates in randomized allocations. The developed plates were dried and sprayed with *p*-dimethylaminobenzaldehyde (0.1% in ethanol)-concentrated hydrochloric acid (99:1).[20] Yellow spots appeared on a white background. The experimental R_m values were calculated and corrected for their ionization at pH 7.4 by means of eq 6.

(2) π **Values Calculation.** Rieder[21] had obtained partition data for a series of sulfonamides by partitioning the compounds between an aqueous phase represented by 0.154 m*M* Na-Phosphate buffer at pH 7.4 and an organic phase represented by isobutyl alcohol ($C_4H_{10}O$), chloroform ($CHCl_3$), toluene (C_7H_8), or ethylene dichloride ($C_2H_4Cl_2$). The logarithms of the experimental partition coefficients of 16 sulfonamides, in the above systems, were calculated from the data of Rieder[21] and then corrected for the degree of ionization at pH 7.4. For the correction the pK_a values were taken from Yamazaki, *et al.*,[22] Rieder,[21] and Bell, *et al.*[1]

The Hansch π values were finally calculated in the usual way, $\pi = \log P_X - P_H$.

Results and Discussion

Relationship between π(*i*-Bu) and R_m Values. The R_m values obtained with different silicone concentrations in the stationary phase and corrected for their ionization at pH 7.4 are reported in Table I. The π values in the isobutyl alcohol-water system, as calculated and corrected for ionization from the partition data of Rieder,[21] are reported in Table II. There is a very good linear relationship between π and R_m values (eq 7-9).

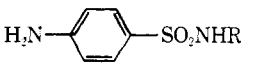
A t test showed that the *b*'s of eq 7-9 are highly significant. In Table III are reported the data showing the actual amount of silicone oil in the stationary phase after the impregnation procedure with 5, 10, or 20% silicone oil solution in ether. The plots of Figure 1 show that the R_m values increased with the concentration of silicone oil in the stationary phase. In other words the increased lipid content of the stationary phase provokes a shorter migration of the sulfonamides. Fujita and Hansch[6] pointed out that the value of the partition coefficient of a sulfonamide would be larger in isobutyl alcohol-water than in the 1-octanol-water system, as the solubility of the polar sulfanilamides is expected to be greater in isobutyl alcohol than in 1-octanol. Therefore, in our system the increase of the R_m values with the oil content can be explained only with the increased volume of the stationary phase. In fact, in eq 4 increasing A_s would reduce R_f and raise R_m. The R_m values obtained with different 1-octanol concentrations in the stationary phase and corrected for their ionization at pH 7.4 are reported in Table I. Equations 10-12 show that they are well correlated with the π values.

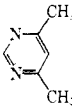
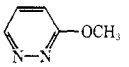
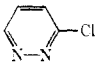
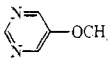
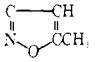
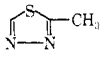
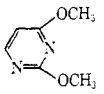
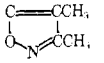
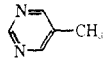
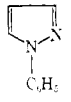
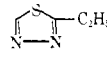
The slopes of eq 10-12 are quite close to those of eq 7-9. Therefore, it does not seem that 1-octanol can provide significantly different correlations. The higher R_m values provided by the impregnation with a 20% solution of 1-octanol (see Table I or intercepts of eq 10-12) can be explained as in the case of the R_m values obtained with silicone oil, with an increased volume of the stationary phase. In fact, the extraction procedure showed a content of 11.2, 19.2, and 48.4% in the stationary phase, when one had impregnated respectively with a 5, 10, and 20% solution of 1-octanol (Table III). However, the correlation coefficient provided by eq 12 is higher than those obtained with eq 10 and 11. This could be due to the fact that a 20% 1-octanol solution is more likely to completely avoid adsorption phenomena on the silica gel G layer. On the other hand, in the case of silicone oil there is a more regular increasing of the R_m values with the concentration of the impregnating medium.

In a different set of experiments, the silica gel G layers were impregnated with several lipophilic substances. In Table IV are reported the equations calculated from the data obtained in such experiments. As the data on the lipophilic character of isosulfamerazine, sulfisomidine, sulfaphenazole, and sulfaethidole were not available in all the test systems, for the analysis of the relationship between π and R_m values only 12 compounds were used. The highest and lowest R_m values are those provided by the

	n	*r*	*s*	
$\pi(i\text{-Bu}) = 0.485(\pm 0.147) + 0.973(\pm 0.150)R_{m(sil,\ 5\%)}$	16	0.961	0.191	(7)
$\pi(i\text{-Bu}) = 0.399(\pm 0.148) + 0.931(\pm 0.135)R_{m(sil,\ 10\%)}$	16	0.962	0.189	(8)
$\pi(i\text{-Bu}) = 0.070(\pm 0.167) + 0.901(\pm 0.116)R_{m(sil,\ 20\%)}$	16	0.974	0.156	(9)
	n	*r*	*s*	
$\pi(i\text{-Bu}) = 0.663(\pm 0.188) + 1.032(\pm 0.240)R_{m(oct,\ 5\%)}$	16	0.925	0.262	(10)
$\pi(i\text{-Bu}) = 0.578(\pm 0.168) + 1.098(\pm 0.210)R_{m(oct,\ 10\%)}$	16	0.947	0.221	(11)
$\pi(i\text{-Bu}) = 0.477(\pm 0.154) + 1.091(\pm 0.175)R_{m(oct,\ 20\%)}$	16	0.961	0.189	(12)

Table I. R_m Values of Sulfonamides



Compounds	R	pK_a	Log (K_A + [H$^+$])/[H$^+$][a]	R_m[b] Silicone oil 5%	Silicone oil 10%	Silicone oil 20%	1-Octanol 5%	1-Octanol 10%	1-Octanol 20%
N^1-Acetylsulfanilamide	$COCH_3$	5.40[c]	2.00	0.78	0.78	1.32	0.83	0.70	0.75
Sulfamerazine		6.93[c]	0.60	0.41	0.49	0.90	0.25	0.36	0.41
Sulfamethazine		7.70[d]	0.18	0.40	0.49	0.74	0.16	0.33	0.43
Sulfathiazole		7.10[c]	0.48	0.32	0.43	0.79	0.06	0.07	0.22
Sulfanilamide	H	10.45[c]	0.00	−0.70	−0.48	−0.36	−0.71	−0.76	−0.68
Sulfamethoxypyridazine		7.05[c]	0.51	0.54	0.64	1.08	0.24	0.38	0.46
Sulfachloropyridazine		6.10[d]	1.32	0.92	1.13	1.42	0.64	0.60	0.69
Sulfamethoxydiazine		7.02[d]	0.53	0.28	0.32	0.87	0.01	0.19	0.26
Sulfamethoxazole		5.81[c]	1.60	0.95	1.15	1.64	0.78	0.85	0.89
Sulfadiazine		6.15[c]	1.27	0.72	0.74	1.24	0.71	0.69	0.74
Sulfamethizole		5.45[e]	1.95	1.49	1.71	1.97	1.15	1.16	1.21
Sulfadimethoxine		6.05[c]	1.37	1.24	1.43	1.91	1.03	1.00	1.24
Sulfisoxazole		4.62[c]	2.78	2.22	2.45	2.75	1.95	1.90	1.99
Sulfisomidine		7.38[c]	0.31	0.28	0.41	0.64	0.10	0.19	0.27
Isosulfamerazine		6.77[d]	0.72	0.60	0.62	1.16	0.44	0.52	0.63
Sulfaphenazole		5.91[c]	1.50	1.30	1.44	1.97	0.81	1.04	1.23
Sulfaethidole		5.65[d]	1.76	1.62	1.84	2.11	1.12	1.10	1.18
Sulfapyridine		8.37[c]	0.04	0.15	0.27	0.46	−0.04	0.05	0.12

[a] Correction term for ionization at pH 7.4. [b] Corrected for ionization at pH 7.4. [c] From Yamazaki.[22] [d] From Rieder.[21] [e] From Bell.[1]

chromatographic systems where the stationary phase is represented by liquid paraffin 20% and silicone 5% (v/v), respectively (see intercepts of equations in Table IV). A measurement of the volume of each of the stationary phases of Table IV could indicate which tlc system is the most hydrophilic one, *i.e.*, which really gives the highest R_m values. From the data of Table IV it could seem that a silica gel G layer impregnated with a 5% solution of liquid paraffin or squalane represents a system more hydrophilic than that provided by the impregnation with a 5% solution of silicone oil or undecane. However, the π values obtained in the isobutyl alcohol-water system are equally correlated with each of the sets of R_m values used for calculating the equations of Table IV. In fact, the slopes of

Table II. π Values of Sulfonamides as Calculated from the Log *P* Values Determined by Rieder[21]

Compounds	π(*i*-Bu) Obsd[a]	π(*i*-Bu) Calcd Eq 12	π(*i*-Bu) Calcd Eq 13	π(*i*-Bu) Calcd Eq 14	π($CHCl_3$) obsd[a]	π(C_7H_8) obsd[a]	π(C_2H_4Cl) obsd[a]
N^1-Acetylsulfanilamide	1.01	1.24	1.12	1.26	1.42	1.35	1.24
Sulfamerazine	0.94	0.88	0.85	0.88	2.14	1.67	1.74
Sulfamethazine	0.76	0.87	0.85	0.74	1.08	1.33	1.78
Sulfathiazole	0.82	0.80	0.80	0.78	0.91	0.87	0.66
Sulfanilamide	0.00	−0.20	−0.05	−0.25	0.00	0.00	0.00
Sulfamethoxypyridazine	1.02	1.01	0.99	1.04	2.42	1.34	1.82
Sulfachloropyridazine	1.28	1.38	1.45	1.35	1.65	0.97	1.49
Sulfamethoxydiazine	0.71	0.76	0.70	0.85	1.52	1.02	1.71
Sulfamethoxazole	1.55	1.41	1.47	1.55	2.19	1.98	1.94
Sulfadiazine	1.11	1.18	1.09	1.19	1.97	1.85	1.76
Sulfadimethoxine	1.86	1.69	1.73	1.79	3.39	2.51	2.87
Sulfisoxazole	2.61	2.64	2.68	2.55	2.94	3.11	2.41
Sulfisomidine	0.40	0.76	0.78	0.65	1.21	0.54	1.61
Isosulfamerazine	1.19	1.07	0.98	1.11	2.42	1.23	2.01
Sulfaphenazole	2.15	1.75	1.74	1.84	1.14	2.60	3.76
Sulfaethidole	1.89	2.06	2.11	1.97	1.90	1.11	2.56

[a] Corrected for ionization at pH 7.4.

Table III. Amount of Silicone Oil or 1-Octanol Present in the Stationary Phase (g/100 g of Silica Gel G) after Impregnation with 5, 10, or 20% Solution in Ether

Concn of impregnating ether soln	Silicone, % in stationary phase	1-Octanol, % in stationary phase
5	5.4	11.2
10	14.9	19.2
20	28.4	48.4

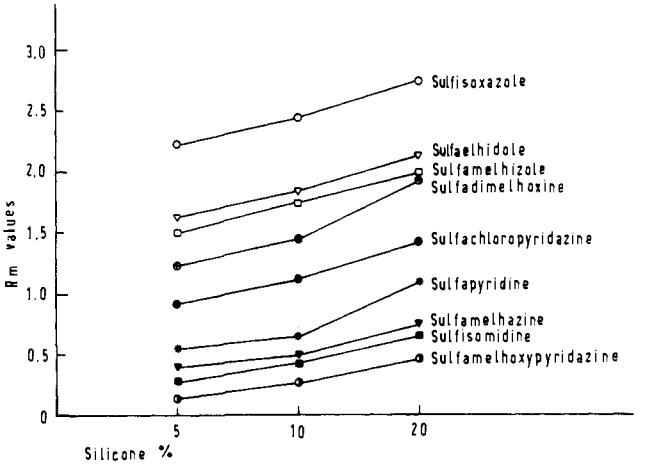


Figure 1. Relationship between R_m values and silicone oil (%) in the impregnating solution.

the equations of Table IV are quite close. One can conclude that the hydrophobic characteristics of the test chromatographic systems are very similar.

The corrected R_m and π values of Table I and II, used for deriving eq 7-9, were obtained by means of the pK_a values of Yamazaki, *et al.*,[22] for some compounds and by means of those of Rieder[21] for some other ones. In order to check the influence of slightly different pK_a values the above equations were derived with π and R_m values corrected by means only of the pK_a values of Rieder.[21] Equation 13-15 resulted to be very similar to the corresponding eq 7-9.

Relationship between π($CHCl_3$), π(C_7H_8), π($C_2H_4Cl_2$), and R_m Values. The π values calculated from partition coefficients measured with chloroform, toluene, and ethylene dichloride, as the organic phase (Table II), are much more poorly correlated with the R_m values sets of Table I. Equation 7 can be compared with eq 16-18 as examples of such poorer correlations.

On the other hand, Fujita[7] showed that in humans the best correlation between renal excretion of sulfonamides and lipophilic character of their molecules is obtained when the latter is expressed by π values derived from a $CHCl_3$-water system instead of those obtained from an isobutyl alcohol-water system. The poorer correlations of eq 16-18 indicate a qualitative difference between the hydrophobic characteristics of the chromatographic systems presently used and those of partitioning systems with $CHCl_3$, toluene, or ethylene dichloride as the organic phase.

Yamazaki, *et al.*,[22] found a rather low correlation coefficient (r = 0.832) between the π values of sulfonamides derived from the true partition coefficient in a chloroform-water system and those derived from a 1-octanol-water

	n	r	s	
$\pi(i\text{-Bu}) = 0.482(\pm 0.139) + 0.973(\pm 0.165)R_{m(sil,\ 5\%)}$	16	0.953	0.191	(13)
$\pi(i\text{-Bu}) = 0.471(\pm 0.168) + 0.870(\pm 0.178)R_{m(sil,\ 10\%)}$	16	0.936	0.223	(14)
$\pi(i\text{-Bu}) = 0.107(\pm 0.173) + 0.877(\pm 0.135)R_{m(sil,\ 20\%)}$	16	0.959	0.177	(15)
	n	r	s	
$\pi(CHCl_3) = 1.144(\pm 0.526) + 0.841(\pm 0.536)R_{m(sil,\ 5\%)}$	16	0.666	0.644	(16)
$\pi(C_7H_8) = 0.754(\pm 0.404) + 0.961(\pm 0.412)R_{m(sil,\ 5\%)}$	16	0.796	0.499	(17)
$\pi(C_2H_4Cl_2) = 1.117(\pm 0.482) + 0.967(\pm 0.491)R_{m(sil,\ 5\%)}$	16	0.747	0.588	(18)

Table IV. Relationship between π Values in Isobutyl Alcohol–Phosphate Buffer System and R_m Values Obtained with Different Stationary Phases

$\pi(i\text{-Bu}) =$	n	r	s
$0.254\ (\pm0.156) + 0.826\ (\pm0.120)\ R_{m(sil,\ 5\%)}$	12	0.975	0.152
$0.100\ (\pm0.175) + 0.826\ (\pm0.180)\ R_{m(sil,\ 10\%)}$	12	0.972	0.159
$-0.025\ (\pm0.186) + 0.846\ (\pm0.180)\ R_{m(sil,\ 20\%)}$	12	0.978	0.142
$0.055\ (\pm0.153) + 0.795\ (\pm0.098)\ R_{m(paraf,\ 5\%)}$	12	0.979	0.138
$-0.035\ (\pm0.167) + 0.774\ (\pm0.098)\ R_{m(paraf,\ 10\%)}$	12	0.979	0.137
$-0.101\ (\pm0.173) + 0.783\ (\pm0.098)\ R_{m(paraf,\ 20\%)}$	12	0.978	0.139
$0.099\ (\pm0.154) + 0.765\ (\pm0.098)\ R_{m(squal,\ 5\%)}$	12	0.981	0.131
$-0.003\ (\pm0.115) + 0.778\ (\pm0.069)\ R_{m(squal,\ 10\%)}$	12	0.984	0.121
$0.202\ (\pm0.136) + 0.803\ (\pm0.098)\ R_{m(undec,\ 5\%)}$	12	0.979	0.136
$0.110\ (\pm0.146) + 0.799\ (\pm0.098)\ R_{m(undec,\ 10\%)}$	12	0.981	0.129

system. They also pointed out a better correlation with bacteriostatic activity of sulfonamides when using π values from the 1-octanol–water system instead of those from chloroform–water.[22] In conclusion, the above results seem to contrast with Collander's[23a,b] findings that there is a linear relationship between partition coefficients measured with two different sets of solvents. Collander[23c] claimed that the nature of the phases used for the determination of partition coefficients should not affect the results in a qualitative sense, when correlating penetration through biological membranes and lipophilic character. He showed that ether–water and olive oil–water partition

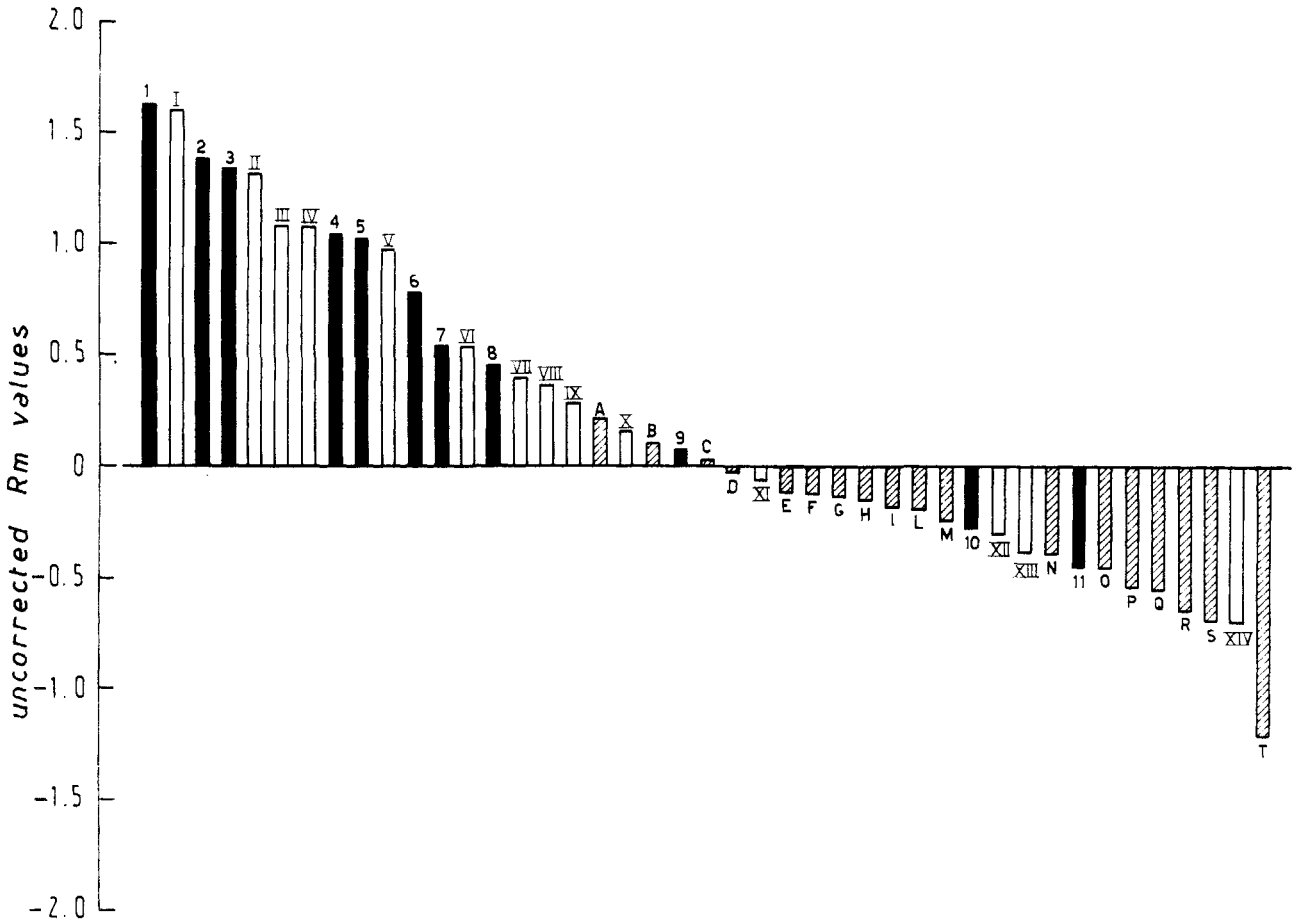


Figure 2. R_m values of penicillins 1–11, cephalosporins I–XIV, and sulfonamides A–T. In order to compare the R_m values of sulfonamides with those of penicillins and cephalosporins, the former were not corrected for ionization at pH 7.4.

1, dicloxacillin
2, nafcillin
3, cloxacillin
4, oxacillin
5, phenethicillin
6, phenoxymethylpenicillin
7, benzylpenicillin
8, methicillin
9, ampicillin
10, methylenampicillin
11, carbenecillin

I, acid
II, acid
III, Na salt
IV, Na salt
V, cephaloridine acid
VI, cephaloram Na salt
VII, cephalotin Na salt
VIII, acid
IX, cephaloglycin acid
X, acid
XI, acid
XII, acid
XIII, 7-aminocephalosporanic acid
XIV, cephalosporin C K salt

A, sulfamethazine
B, sulfapyridine
C, sulfamethoxypyridazine
D, sulfisomidine
E, isosulfamerazine
F, sulfadimethoxine
G, sulfaethidole
H, sulfathiazole
I, sulfamerazine

L, sulfaphenazole
M, sulfamethoxydiazine
N, sulfachloropyridazine
O, sulfamethizole
P, sulfadiazine
Q, sulfisoxazole
R, sulfamethoxazole
S, sulfanilamide
T, N^1-acetylsulfanilamide

coefficients are equally correlated with penetration into Nitella cells.[23c]

In Figure 2 are represented the R_m values of penicillins and cephalosporins, as obtained with a stationary phase impregnated with 5% silicone oil,[11] as well as those of sulfonamides. The R_m values of both series of antibiotics ranged respectively from −0.46 to 1.63 and from −0.71 to 1.60. The experimental R_m values of sulfonamides, *i.e.*, uncorrected for their degree of ionization, were used. In this way the R_m values of sulfonamides could be compared with those of penicillins and cephalosporins. Sulfonamides are more hydrophilic than most of the penicillins and cephalosporins. In fact, only two penicillins and four cephalosporins are on the negative side of the plot. In previous work with penicillins and cephalosporins there was shown, respectively, a linear and parabolic relationship between R_m values and antibacterial activity against *Escherichia coli* in a solid medium.[11a] In particular it was shown that the bacteriostatic activity of penicillins increases with decreasing R_m values. On the other hand, Fujita and Hansch,[6] when analyzing the data of Krüger-Thiemer and Bünger,[24] found a positive slope in the equation relating π values of sulfonamides and their activity in *E. coli*. Penniston, *et al.*,[25] pointed out that such linear relationships hold only within certain limits of partition data. They suggested that in a wider range of compounds there should be evidence of a parabolic relationship as biological activity increases with increasing lipophilic character, reaches a maximum, and then decreases. In fact, the relatively wide range of R_m values of cephalosporins gave a parabolic relationship between log $1/C$ and R_m values. Therefore, while penicillins seem to be represented by molecules falling on the right side of the theoretical parabola, sulfonamides seem primarily to fall on the left side. This would be in agreement with Figure 2 where penicillins and sulfonamides are respectively on the positive and negative side of the plot. Cephalosporins, with four members on the negative side of the plot, which means a wider range of R_m values, would fit the theoretical parabola. In conclusion, the present results show that the R_m values can be useful in structure–activity studies of sulfonamides. Moreover, tlc allows to obtain partition data of different sets of chemotherapeutic agents, which can be thus compared. The general advantages of the tlc technique have been already pointed out.[19] In the present work it was not possible to find a stationary phase providing R_m values best correlated with activity. However, further work is presently carried out on this particular aspect, because such a chromatographic system would be a closer biological model.

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