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STUDY OF THE LIPOPHILIC CHARACTER OF XANTHINE AND ADENOSINE DERIVATIVES

I. R_M AND LOG P VALUES

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SUMMARY

The R_M values of a series of xanthine and adenosine derivatives were measured using silicone reversed-phase thin-layer chromatographic (TLC) and C_{18} reversed-phase high-performance TLC systems. The two series of data were well correlated. Both were compared with experimental log P and calculated CLOGP values. For xanthine derivatives a good linear relationship was shown between the R_M values from the two chromatographic systems and the log P or CLOGP data. For adenosine derivatives the CLOGP values had to be corrected in order to fit the data to the same equation. The TLC data proved to be reliable parameters for describing the lipophilic properties of the test compounds.

INTRODUCTION

Purine (I) and its derivatives xanthine (2,6-dioxopurine), adenine (6-aminopurine) and guanine (2-amino-6-oxopurine) are the parent compounds of several very important classes of biologically active chemicals. Purine and guanine derivatives, such as 6-mercaptopurine and 6-thioguanine, are potential anticancer agents[1]. Allopurinol is an isomer of hypoxanthine (6-oxopurine), which decreases uric acid production by inhibiting xanthine oxidase[1].

The pharmacological actions of the classical natural methylxanthines, such as caffeine, theobromine and theophylline, and a few other synthetic derivatives, such as etofylline and enprofylline, are well known, *e.g.*, stimulation of the central nervous system, tachycardia, bronchodilatation and increased diuresis[1]. Inhibition of phosphodiesterase was postulated as the mechanism by which xanthines elicit these effects.

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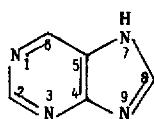
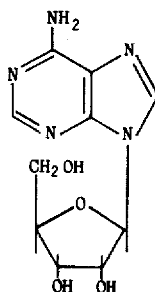


(I)



(II)

Recently, the role of xanthines as antagonists of adenosine binding emerged as an alternative explanation for these effects. In fact, in recent years, several important roles for adenosine (II) in the control of many physiological processes have been delineated, *e.g.*, vasodilatation, cardiodepressant effects, relaxation of smooth muscle, stimulation of steroidogenesis in adrenal cells, depression of the central nervous system and inhibition of neurotransmitters release[2]. From a biochemical point of view, adenosine inhibits adenylate cyclase via a high-affinity receptor and activates adenylate cyclase via a low-affinity receptor. These receptors, called A_1 and A_2, respectively, show different profiles for activation by adenosine analogues[3]. The limited use of drugs acting on the adenosine system is mainly due to the lack of selectivity, which is typical of these drugs, and to the numerous sites of action of adenosine throughout the body. Studies on quantitative structure–activity relationships have been reported for xanthine derivatives in the above mentioned pharmacological areas. Silipo and co-workers[4–6] studied the inhibition of xanthine oxidase and other enzymes by 9-phenylguanines. The bronchodilator activity of 6-mercaptoxanthines was investigated by Bowden and Wooldridge[7]. Lien *et al.*[8] examined the phosphodiesterase inhibition and cytotoxicity of xanthine analogues. Olaru and Simon[9,10] investigated the inhibition of human erythrocytic ipoxanthine phosphoribosyltransferase. Hamilton *et al.*[11] analysed the influence of several physico-chemical parameters on the adenosine A_1 receptor affinity of a series of 8-phenylxanthines. Neiman and Quinn[12,13] studied the activity against adenocarcinoma CA755 and the acute toxicity in mice of a series of 2,6-mono- and disubstituted purines.

In the above-mentioned papers, the lipophilic character, which was shown to affect variously the different biological activities, was expressed by means of the Hansch π values and only a very few log P values were measured and reported[11]. Gaspari and Bonati[14] were the first to study the correlation between the experimental octanol–water partition coefficients and the high-performance liquid chromatographic (HPLC) retention data of 18 xanthine derivatives. They also found some correlations between the lipophilicity of xanthines and their pharmacokinetic parameters in rats.

Walther and co-workers[15,16] determined the HPLC log k' values of a series of substituted xanthines and compared them with the log P values calculated by means of the Rekker's fragmental method. The differences between the two lipophilicity indexes were attibuted to the conformational behaviour of the compounds. They found that

lipophilicity plays a role in determining the phosphodiesterase inhibition of N-7-unsubstituted compounds.

Despite these more recent contributions, there is still a lack of experimental data describing the lipophilicity of xanthine and adenosine derivatives. In view of a QSAR study dealing with adenosine receptors binding, the main purpose of this work was to study the lipophilic character of a number of adenosine and xanthine derivatives. The lipophilic character was expressed by means of the R_M values obtained from reversed-phase silicone thin-layer chromatography (silicone RP-TLC) and C_{18} high-performance TLC (C_{18} RP-HPTLC). The R_M values were compared with calculated and experimental octanol–water log P values. A further purpose of this work was to show the usefulness of the R_M values in checking the reliability of calculated log P values.

EXPERIMENTAL

Chemicals

Xanthine and adenosine derivatives 8–42 were purchased from RBI (Natick, MA, U.S.A.); compounds 1–7 and 43 were obtained from Sigma (St. Louis, MO, U.S.A.). All other chemicals and solvents were of analytical-reagent or HPLC grade. In the following we shall refer to any purine derivative as xanthines and to any nucleoside as adenosines or guanosines.

Determination of R_M values by silicone RP-TLC

The details of the reversed-phase chromatographic technique were described previously[17]. Glass plates measuring 20 × 20 cm were coated with silica gel GF_{254} in the usual manner. In order to obtain a better control of the pH of the stationary phase, the slurry of silica gel GF_{254} was obtained with 0.09 or 0.36 *M* sodium hydroxide solution or 0.09 *M* hydrochloric acid when the pH of the mobile phase had to be 7.0, 9.0 or 1.2, respectively. A non-polar stationary phase was obtained by impregnating the silica gel GF_{254} layer with silicone DC 200 (350 cS) from Applied Science Labs., (State College, PA, U.S.A.). The impregnation was carried out by developing the plates in a 5% silicone solution in diethyl ether. Eight plates could be impregnated in a single chromatographic chamber containing 200 ml of the silicone solution. The plates were left in the chamber for 12 h, *i.e.*, for several hours after the silicone solution had reached the top of the plates.

The mobile phases, saturated with silicone, were aqueous buffers alone or mixed with various amounts of acetone. Glycine buffer at pH 9.0 and sodium acetate–Veronal buffer (1/7 *M*) at pH 7.0 were used. The R_M values of compounds 4, 8, 22 and 27 were also measured at pH 1.2 (glycine buffer). Two plates were developed simultaneously in a chromatographic chamber containing 200 ml of mobile phase. The test compounds were dissolved in 0.1 *M* sodium hydroxide solution, water or acetone (1–2 mg/ml), and 1 μl of solution was spotted randomly on the plates in order to avoid any systematic error. The developed plates were dried and the spots detected under UV light (254 nm). The R_M values were calculated by means of equation $R_M = \log[(1/R_F) - 1]$.

Determination of R_M values by C_{18} RP-HPTLC

The HPTLC determinations were carried out on Whatman KC18F plates[18]. A Camag (Berlin, F.R.G.) Nanomat was used to spot the compounds on the plates (about 100 nl of each compound solution). The solutes were detected under UV light (254 nm). Solvent mixtures of methanol–phosphate buffer at pH 7.0 were used. A mobile phase at pH 1.2 was used for compounds 4, 8, 22 and 27. The methanol concentration ranged from 30 to 80%.

Octanol–water partition coefficients

Most of the log *P* values in Table I were calculated by means of the CLOGP program developed by the Pomona College group[19]. The experimental log *P* values of compounds 1, 2, 3, 4, 9, 12, 15 and 30 were taken from the STARLIST file of the Pomona College database[20]. The log *P* of guanosine (compound 43) was measured in our laboratory using the classical shake-flask method[21]. For the adenosine derivatives a log *P* value was calculated by adding a correction factor to the CLOGP value of each compound. This was obtained by averaging the difference between the experimental and the CLOGP values of adenosine and guanosine:

$$\log P_{\mathrm{adenosine}} - \mathrm{CLOGP}_{\mathrm{adenosine}} = -1.23-(-3.51) = 2.28$$

$$\log P_{\mathrm{guanosine}} - \mathrm{CLOGP}_{\mathrm{guanosine}} = -1.85-(-4.42) = 2.57$$

$$\bar{x} = 2.42$$

RESULTS

R_M values from silicone RP-TLC

In the first step the R_M values of most of the compounds in Table I were measured with a mobile phase represented by the Veronal buffer at pH 7.0, alone or mixed with various amounts of acetone. RP-TLC showed that for each compound there was a linear relationship between R_M values and a certain range of acetone concentrations in the mobile phase. The equations of the straight lines were used to calculate a theoretical R_M value at 0% acetone in the mobile phase. The intercepts of the equations are reported in Table I to represent the theoretical R_M values at 0% acetone. These extrapolated R_M values at 0% could be considered as a measure of the partitioning of the compounds between an aqueous buffer and the hydrophobic stationary phase, *i.e.*, in a standard system where all the compounds could be compared on the basis of their lipophilic character. At acetone concentrations higher than 12% all the compounds tended to migrate with the solvent front. Therefore, the equations were calculated by means of the R_M values obtained at acetone concentrations only up to 12%. The only exceptions were compounds 18, 23 and 29, which were much more lipophilic and did not migrate at 0% acetone. Their extrapolated R_M values were calculated from higher ranges of acetone concentrations in the mobile phase.

However, in the present instance, except for compounds 18, 23 and 29, all the compounds migrated in a reliable way even at 0% acetone. Therefore, in Table I both the experimental and the extrapolated R_M values are reported for 33 compounds. The

TABLE I

LIPOPHILICITY INDICES OF XANTHINES AND ADENOSINES

No.	Compound	$R_{M\ exp.}$ (pH 7.0)	$R_{M\ extrap}$ (pH 7.0)	$R_{M\ exp.}$ (pH 9.0)	$R_{M\ C_{18}}$ (pH 7.0)	Log P
	Xanthines:					
1	Purine	0.25	–	−0.37	0.50	−0.58[b] −0.37[c]
2	Adenine	0.35	–	−0.01	0.83	−0.33[b] −0.09[c]
3	Guanine	−0.08	–	−0.44	–	−1.28[b] −0.91[c]
4	Xanthine	−0.72 0.02[a]	–	−0.81	−0.13 0.57[a]	−1.65[b] −0.73[c]
5	1-Methylxanthine	−0.30	–	−0.83	0.42	−1.25[b]
6	3-Methylxanthine	−0.08	–	−0.63	0.40	−1.00[b]
7	7-Methylxanthine	−0.12	–	−0.83	0.26	−1.32[b]
8	1,3-Dimethyluric acid	−0.73 −0.08[a]	−0.71	–	0.60[a]	–
9	Theophylline (1,3-dimethylxanthine)	0.38	0.33	−0.20	1.19	−0.05[b] −0.02[c]
10	1,7-Dimethylxanthine (paraxanthine)	0.39	0.35	−0.24	1.06	−0.92[b]
11	1,9-Dimethylxanthine	−0.21	−0.21	−0.41	0.28	−0.92[b]
12	Theobromine (3,7-dimethylxanthine)	0.26	0.22	0.04	0.92	−0.67[b] −0.78[c]
13	3,9-Dimethylxanthine	0.04	−0.01	0.02	0.50	−0.67[b]
14	7,9-Dimethylxanthine	−0.73	−0.76	–	−0.46	–
15	Caffeine (1,3,7-trimethylxanthine)	0.79	0.77	0.61	1.54	0.26[b] −0.07[c]
16	Thiocaffeine	1.14	1.15	0.97	2.14	–
17	3-Isobutyl-1-methylxanthine	1.03	1.05	0.31	2.36	1.41[b]
18	1,3-Diethyl-8-phenylxanthine	–	1.45	0.78	2.95	3.10[b]
19	3-Propylxanthine (enprofylline)	0.35	0.29	−0.10	1.29	0.05[b]
20	7-Propylxanthine	0.25	0.23	−0.13	1.07	−0.26[b]
21	9-Propylxanthine	0.04	0.09	−0.35	0.65	−0.26[b]
22	1,3-Dipropyl-8-(*p*-sulphophenyl)xanthine	1.12 –	1.11 1.57[a]	0.10	2.51 3.18[a]	2.31[b]
23	1,3-Dipropyl-8-(2-amino-4-chlorophenyl)xanthine	–	2.24	0.92	3.57	4.05[b]
24	7-(β-Hydroxyethyl)theophylline (etofylline)	0.39	0.35	0.11	0.86	−1.20[b]
25	7-(β-Chloroethyl)-theophylline	1.03	1.00	0.74	1.70	0.50[b]
26	8-Phenyltheophylline	1.11	1.11	0.60	2.08	2.05[b]
27	8-(*p*-Sulphophenyl)-theophylline	0.15 0.52[a]	0.00	−0.52	1.26 1.50[a]	0.19[b]
28	8-Cyclopentyltheophylline	1.03	1.06	0.77	2.55	2.16[b]
29	8-Cyclopentyl-1,3-dipropylxanthine	–	1.94	1.05	3.61	4.28[b]
	Adenosines					
30	Adenosine	0.24	0.26	0.36	0.42	−3.51[b] −1.23[c]
31	2-Chloroadenosine	0.19	0.15	0.41	0.66	−2.76[b] −0.34[d]

(Continued on p. 184)

TABLE I (continued)

No.	Compound	$R_{M\ exp.}$ (pH 7.0)	$R_{M\ extrap}$ (pH 7.0)	$R_{M\ exp.}$ (pH 9.0)	$R_{M\ C_{18}}$ (pH 7.0)	Log P
32	2-Phenylaminoadenosine	0.96	0.97	1.22	1.83	−0.55[b] 1.87[d]
33	6-Methyladenosine	0.41	0.28	0.51	0.80	−2.78[b] −0.36[d]
34	6-Cyclopentyladenosine	1.12	1.18	1.08	2.29	−1.31[b] 1.11[d]
35	6-Cyclohexyladenosine	1.14	1.16	1.02	2.44	−0.75[b] 1.67[d]
36	6-Phenyladenosine	0.96	0.96	1.16	1.86	−0.80[b] 1.62[d]
37	6-Phenylethyladenosine	1.30	1.30	1.20	2.94	−0.68[b] 1.74[d]
38	6-(2-Phenylisopropyl)-adenosine	1.34	1.31	1.38	2.87	−0.37[b] 2.05[d]
39	6-Benzyladenosine	0.93	0.92	0.89	1.98	−1.08[b] 1.34[d]
40	5′-N-Methylcarboxamido-adenosine	0.41	0.34	0.41	0.72	−3.62[b] −1.20[d]
41	5′-N-Ethylcarboxamido-adenosine	0.67	0.61	0.82	1.13	−3.09[b] −0.67[d]
42	5′-N-Cyclopropylcarbox-amidoadenosine	0.89	0.90	0.55	2.02	−3.26[b] −0.84[d]
43	Guanosine	−0.38	—	−0.83	−0.16	−4.42[b] −1.85[c]
44	1-Methylisoguanosine	−0.33	−0.39	−0.20	0.08	—

[a] Measured at pH 1.2.
[b] CLOGP.
[c] Experimental log P in octanol–water.
[d] Calculated log P values (see text).

very good correlation between the experimental and extrapolated R_M values is described by the equation

$$R_{M\ \text{exptl}} = 0.036\ (\pm\ 0.010) + 0.972\ (\pm\ 0.013)\ R_{M\ \text{extrap}}$$
$$(n = 33;\ r = 0.997;\ s = 0.043;\ F = 5523;\ P<0.005) \quad (1)$$

The intercept and slope, very close to 0 and 1 respectively, show the validity of the extrapolation technique. Because of eqn. 1, in the second step of our work the R_M values of compounds 1–7 and 43 were measured with a mobile phase represented only by the buffer and therefore their extrapolated R_M values were not available for Table I. Further, a mobile phase at pH 1.2 (glycine buffer) was also used for compounds 4, 8, 22 and 27 in order to measure the R_M value of their non-ionized form.

The above mobile phase of pH 7.0 was chosen on the basis of the ionization profiles of the test compounds. Owing to their structure, the xanthine derivatives are amphoteric compounds that exhibit acidic and basic ionization constants; substituents

on different positions of the heterocyclic ring may variously affect the pK_a values[22]. However, basic pK_a values <4 and acidic pK_a values >9 are reported for the most representative compounds of this class[23]. Xanthine (pK_a = 7.4), 1,3-dimethyluric acid (uric acid: pK_a = 5.4), 1,3-dipropyl-8-(*p*-sulphophenyl)xanthine ($pK_a < 2$) and 8-(*p*-sulphophenyl)theophylline (1,3-diethyl analogue: pK_a <2) are exceptions, showing "stronger" acidic properties[11,22,23]. The purine nucleosides appear to be even weaker acids than the 9-unsubstituted purines, whereas their basic properties are similar to those of the above-mentioned group (adenosine has basic pK_a = 3.58, acidic pK_a = 12.5). At pH 7.0 most of the compounds we examined should therefore be non-ionized or ionized to only a very small extent.

In order to illustrate this point, the R_M values of all the compounds in Table I (except compound 8) were also measured at pH 9.0 by means of a glycine buffer without the addition of acetone. The data reported in Table I show that at pH 9.0 compounds 18, 23 and 29 also migrated in a reliable way without the addition of acetone to the mobile phase. In contrast, it was not possible to measure reliable R_M values for compounds 8 and 14 as these migrated with the solvent front. In any event at pH 9.0 all the xanthine derivatives are characterized by longer migrations, *i.e.*, lower R_M values, which means that ionization occurred at some extent, according to their acidic pK_a values. The relationship between the R_M values of xanthine derivatives at pH 7.0 and those at pH 9.0 is described by

$$R_{M\ \mathrm{pH}\ 7.0} = 0.481\ (\pm\ 0.057) + 1.079\ (\pm\ 0.100)\ R_{M\ \mathrm{pH}\ 9.0}$$
$$(n = 27;\ r = 0.907;\ s = 0.298;\ F = 116.7;\ P<0.005) \quad (2)$$

If all the derivatives had the same pK_a value, one should have obtained an equation characterized by an intercept higher than 0 and a slope equal to 1, *i.e.*, very close to eqn. 2. However, the standard deviation is rather high, suggesting that not all the compounds are equally affected by the increased pH of the chromatographic system.

In contrast, for the series of adenosine derivatives an increase in pH did not seem to have any significant influence on their chromatographic migration. This behaviour might be explained by considering the higher acidic pK_a value of adenosine (and presumably of the adeonsine derivatives), which prevents the ionization of the compounds even under strongly basic conditions. The only exception is guanosine, which shows a lower R_M value at pH 9.0. In fact, guanosine has a lower acidic pK_a of 9.2[8], which should induce ionization at pH 9.0. The relationship between the R_M values at pH 7.0 and 9.0 is described by the equation

$$R_{M\ \mathrm{pH}\ 7.0} = -0.062\ (\pm\ 0.092) + 1.027\ (\pm\ 0.105)\ R_{M\ \mathrm{pH}\ 9.0}$$
$$(n = 14;\ r = 0.943;\ s = 0.168;\ F = 96.15;\ P<0.005) \quad (3)$$

which was calculated with the exclusion of guanosine. The intercept and slope are very close to 0 and 1, respectively. As a consequence of its pK_a value, guanosine could be incorporated into eqn. 2 as shown by the following equation, calculated with 28 compounds:

$$R_{M\ \mathrm{pH}\ 7.0} = 0.482\ (\pm\ 0.055) + 1.076\ (\pm\ 0.094)\ R_{M\ \mathrm{pH}\ 9.0}$$
$$(n = 28;\ r = 0.913;\ s = 0.292;\ F = 130.5;\ P<0.005) \quad (2a)$$

In conclusion, eqns. 2 and 3 show that at pH 7.0 both xanthine and adenosine derivatives are mainly in their non-ionized form, except compounds 4, 8, 22 and 27. Therefore, in any subsequent correlation the R_M values at pH 7.0 or 1.2 (compounds 4, 8, 22 and 27) were used.

R_M values from C_{18} RP-HPTLC

The chromatographic work carried out at pH 7.0 with Whatman KC18F plates showed the usual linear relationship between R_M values and methanol concentrations for each compound. The compounds did not migrate without the addition of methanol to the mobile phase. The equations of the straight lines yielded the extrapolated R_M values at 0% methanol (Table I). The relationship between the silicone RP-TLC (R_M) and C_{18} RP-HPTLC ($R_{M\,C_{18}}$) data for the xanthine and adenosine derivatives at pH 7.0 or 1.2 is shown in Fig. 1 and described by

$$R_M = -0.272\ (\pm\ 0.040) + 0.610\ (\pm\ 0.023)\ R_{M\,C_{18}}$$
$$(n = 43;\ r = 0.972;\ s = 0.154;\ F = 706.8;\ P < 0.005) \quad (4)$$

The very good correlation coefficient explains 94% of the variance in the silicone RP-TLC R_M values.

Although in silicone RP-TLC acetone was added to the mobile phase and in C_{18} RP-HPTLC methanol was used, the R_M values are very well correlated. In previous papers it was shown that the extrapolated R_M values were very similar whether one used acetone or methanol in the mobile phase[24,25]. Therefore, the present data seem to confirm that the nature of the organic solvent added to the mobile phase does not

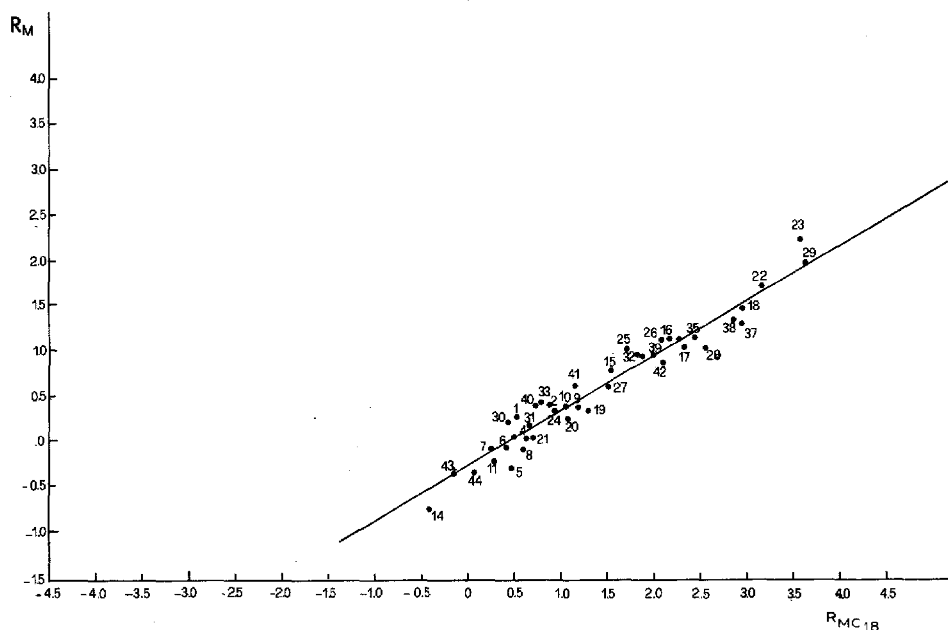


Fig. 1. Relationship between R_M and $R_{M\,C_{18}}$ values, as described by eqn. 4.

affect the results in a qualitative way. An intercept lower than zero is due to the difference in the stationary phase. The C_{18} RP-HPTLC system seems to be more lipophilic. In fact, both xanthine and adenosine derivatives have higher $R_{M\ C_{18}}$ values. A slope lower than 1 is due to the narrower range of the silicone RP-TLC R_M values. It can be also pointed out that the extrapolated C_{18} RP-HPTLC R_M values are very well correlated with the silicone RP-TLC experimental R_M values. This again indicates the reliability of the extrapolation technique.

Log P values

The experimental log P values of caffeine, theophylline, theobromine, guanine, xanthine, purine and adenine, and also the CLOGP values of these and other xanthines derivatives, are reported in Table I. The relationship between the R_M values at pH 7.0 or 1.2 and the log P values is described by eqn. 5, which was calculated with the CLOGP values, or the experimental log P values when available (compounds 1, 2, 3, 4, 9, 12 and 15). Eqn. 5 and all the subsequent equations in this section are given in Table II.

Owing to the acceptable agreement between the CLOGP and experimental log P values for the above seven compounds, eqn. 5 does not change when calculated with the CLOGP values for all the 26 xanthine derivatives.

In the series of the adenosine derivatives there is a striking difference between the experimental log P and the CLOGP values of adenosine and guanosine. In fact, an equation calculated with the CLOGP values or the experimental log P values, when available (compounds 30 and 43), yielded a very low correlation coefficient (r = 0.523). Therefore, eqn. 6 was calculated by means of the CLOGP values of all the adenosine derivatives, showing a much better correlation coefficient.

The regression coefficient of eqn. 6 is not much different from that of eqn. 5, and eqns. 5 and 6 describe two almost parallel straight lines. However, the two correlations cannot be combined in one equation, because of the much higher intercept of eqn. 6. This is due to the very low CLOGP values for the adenosine derivatives as calculated by the CLOGP program. As described under Experimental, a log P value was calculated for each of the twelve adenosines for which an experimental log P value was

TABLE II

CORRELATION EQUATIONS BETWEEN R_M AND LOG P VALUES

Equation	*a*	*b*	*n*	*r*	*s*	*F* (*P*<0.005)	*Eqn. No.*
$R_M = a + b \log P$	0.423 (±0.044)	0.390 (±0.027)	26	0.947	0.221	209.8	5
	1.360 (±0.125)	0.306 (±0.050)	14	0.868	0.255	36.58	6
	0.620 (±0.072)	0.305 (±0.052)	14	0.861	0.261	34.46	7
	0.490 (±0.041)	0.367 (±0.026)	40	0.916	0.250	199.4	8
	0.468 (±0.037)	0.376 (±0.023)	39	0.935	0.224	257.6	13
$R_{M\ C_{18}} = a + b \log P$	1.184 (±0.061)	0.609 (±0.036)	25	0.962	0.294	283.0	9
	2.784 (±0.247)	0.592 (±0.100)	14	0.863	0.503	35.13	10
	1.348 (±0.140)	0.595 (±0.101)	14	0.862	0.507	34.75	11
	1.243 (±0.062)	0.604 (±0.040)	39	0.929	0.379	232.4	12
	1.202 (±0.053)	0.622 (±0.033)	38	0.952	0.315	348.9	14

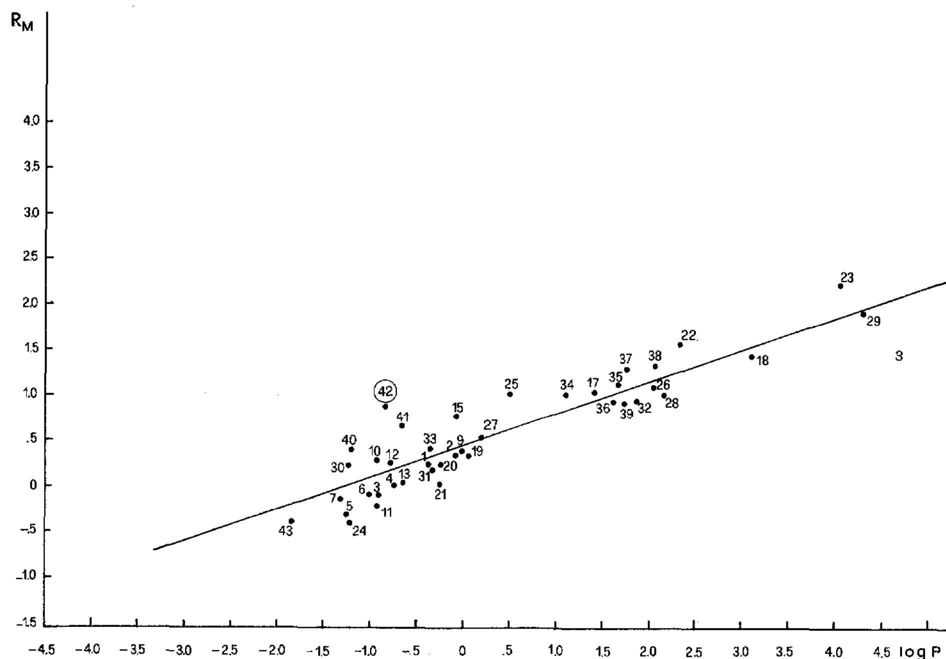


Fig. 2. Relationship between R_M and log P values, as described by eqn. 13 (compound 42 was not used in calculating the equation).

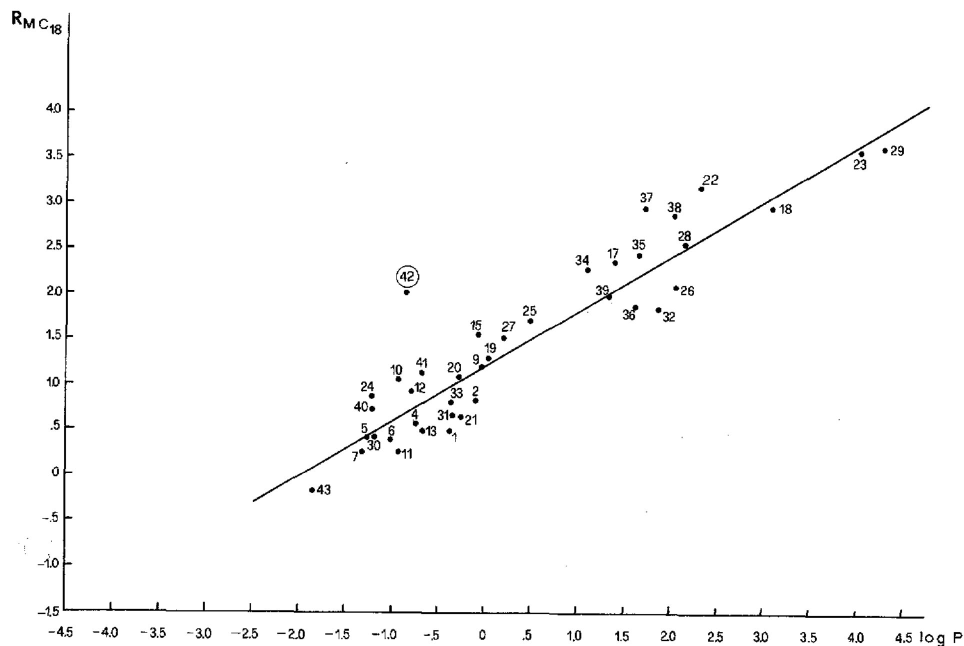


Fig. 3. Relationship between $R_{M\ C_{18}}$ and log P values, as described by eqn. 14 (compound 42 was not used in calculating the equation).

not available. The relationship described by eqn. 7 between the R_M values and the calculated (compounds 31–42) or experimental (compounds 30 and 43) log P values for the adenosine derivatives is closer to that described by eqn. 5 for the xanthine derivatives. Finally, eqns. 5 and 7 were incorporated into eqn. 8.

Following the same procedure that led to eqns. 5–8, the corresponding eqns. 9–12 were calculated using the same log P values and the $R_{M\ C_{18}}$ instead of the R_M values.

Eqns. 8 and 12 are shown graphically in Figs. 2 and 3. From the plots it can be seen that in both equations compound 42 is an outlier. When it is excluded, eqns. 13 and 14 are obtained. The reason why compound 42 has to be excluded from eqns. 13 and 14 might be that the carboxamido group in the sugar moiety can interact via hydrogen bonding with free OH groups of the stationary phases. This hypothesis is supported by the fact that in the silicone RP-TLC system the same behaviour, although at a lesser extent, is shown also by the analogous compounds 40 and 41.

DISCUSSION AND CONCLUSIONS

The results show a very good correlation between the R_M values from two different chromatographic systems. It is interesting that the correlation described by eqn. 4 holds over a wide range of lipophilicity. This justifies our confidence in the use of chromatographic data as lipophilic parameters.

At the same time, the very good correlations described by enqs. 5 and 9 show that the calculated CLOGP value of the xanthine derivatives is a reliable lipophilic index for these compounds. In fact, eqns. 5 and 9 were calculated using the experimental log P values for seven compounds and the CLOGP values for the remaining derivatives.

In the adenosine series the CLOGP values could not be used with the experimental log P values in the same equation. A correction had to be made in order to allow the calculation of eqns. 8 and 12 and also eqns. 13 and 14. In fact, the CLOGP program does not correctly estimate the partition coefficient of nucleosides. The program might not be able to take into account interactions between the purine ring and the sugar moiety. On the other hand, a disadvantageous aspect of the silicone RP-TLC and C_{18} RP-HPTLC systems is the interaction with the stationary phases causing the deviation of compound 42 from eqns. 8 and 12. As a final remark, it is pointed out that Gaspari and Bonati[14] and Walther and co-workers[15,16] did not obtain very good correlations when they considered their whole series of derivatives. In contrast, the present R_M and $R_{M\ C_{18}}$ values allowed two structurally different series of compounds, such as xanthines and adenosines, to be combined in one equation. Work is in progress in our laboratory to measure the HPLC log k' values of the present series of compounds for further investigation of the relationships among different lipophilic descriptors.

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