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Short Communication

Chromatographic behaviour of dipyridylsulphides

Relationship between log k' values and structure by reversed-phase high-performance liquid chromatography*

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ABSTRACT

Relationships between the structure and retention time in a group of dipyridylsulphides have been investigated. The retention time has been determined by high-performance liquid chromatography on a chemically bonded octadecylsilica column with methanol–13 m*M* phosphate buffer (pH 7) as the mobile phase, using UV detection. From the values of the logarithm of the capacity factor the contributions of the half-molecular fragments have been calculated. The contributions of the fragments can be used to calculate the capacity factors of other dipyridylsulphides. One example of the study of the structure–antituberculous activity relationship from the carbothioamides series is presented.

INTRODUCTION

The hydrophobicity of substances is undoubtedly the most important physical property affecting their biological activity. Since the time when Hansch and Fujita [1] formulated a general equation for the relationships between hydrophobicity, expressed in terms of the logarithm of the partition coefficient for the octanol–water system, and quantitatively expressed biological activity, many systems have been developed for estimation of hydrophobicity. Partition chromatography has played an important role [2–4]. The purpose of this work was to study the relationship between the structure and retention parameter obtained by high-performance liquid chromatography (HPLC) measurement (the logarithm of the capacity factor, log k') on a chemically bonded octadecylsilica column in a series of substituted dipyridylsulphides. The thioamides of this group are potential antituberculous drugs [5,6].

EXPERIMENTAL

Materials

Substances were prepared as described previously [5,6]. Solvents were of analytical reagent quality and were used without further purification.

High-performance liquid chromatography

The chromatographic system consisted of a Varian 8500 pump, a Varian Varichrom UV–VIS detec-

* Dedicated to Professor Roland Mayer on the occasion of his 65th birthday.

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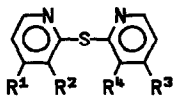
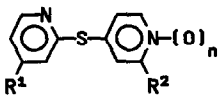
TABLE I

LOGARITHM OF THE CAPACITY FACTOR FOR DIPYRIDYLSULPHIDES



Type I



Type II

Compound No.	Type	R^1	R^2	R^3	R^4	n	Log k'
1	I	CN	H	CN	H	–	1.0625
2	I	$CSNH_2$	H	$CSNH_2$	H	–	0.9669
3	I	$CONHNH_2$	H	$CONHNH_2$	H	–	−0.00505
4	I	$CONH_2$	H	$CONH_2$	H	–	0.0964
5	I	H	CN	H	CN	–	0.8230
6	I	H	$CSNH_2$	H	$CSNH_2$	–	0.1493
7	I	CN	H	H	CN	–	0.9609
8	I	$CSNH_2$	H	H	$CSNH_2$	–	0.4952
9	II	CN	CN	–	–	0	1.0641
10	II	$CSNH_2$	$CSNH_2$	–	–	0	0.8819
11	II	CN	CN	–	–	1	0.5291
12	II	$CSNH_2$	$CSNH_2$	–	–	1	1.1180

tor, operated at 254 nm, and a Spectra-Physics SP 4100 integrator. The column (250 × 4 mm I.D.) was packed with Silasorb C_{18} 7.5 μm particle size (Lachema, Brno, Czechoslovakia). The pyridylsulphide solutions in methanol were injected into the column via a 10-μl loop. The mobile phase was methanol–13 m*M* phosphate buffer, pH 7 (30:70, v/v), at a flow-rate of 1 ml/min. The experiments were performed at room temperature. The retention time of potassium iodide was taken as t_0. The capacity factor, k', was evaluated from the t_0 value and the retention time of the solute, t_R, by eqn. 1.

$$k' = (t_R - t_0)/t_0 \quad (1)$$

The results are summarized in Table I.

TABLE II

VALUES OF THE LOGARITHM OF THE CAPACITY FACTOR FOR THE HALF-MOLECULAR FRAGMENTS

$r = 0.994$, $s = 0.002$, $n = 12$.

Fragments R–$S_{1/2}$[a]	Log k'
R	
(a) 4-Cyano-2-pyridyl	0.531
(b) 3-Cyano-2-pyridyl	0.411
(c) 2-Cyano-4-pyridyl	0.533
(d) 4-Thiocarbamoyl-2-pyridyl	0.476
(e) 3-Thiocarbamoyl-2-pyridyl	0.068
(f) 2-Thiocarbamoyl-4-pyridyl	0.406
(g) 4-Carbamoyl-2-pyridyl	0.048
(h) 4-Carbazoyl-2-pyridyl	−0.003
(l) 1-Oxido-2-cyano-4-pyridyl	−0.002
(j) 1-Oxido-2-thiocarbamoyl-4-pyridyl	0.642

[a] $S_{1/2}$ = one half of a sulphur atom.

Calculations

The regression equations were calculated on an IQ-151 personal computer (ZPA Nový Bor, Czechoslovakia) using a Multireg-H program.

The values of log k' for the half-molecular fragments were calculated by the iteration procedure (see Table II). For symmetrical sulphides, the half-molecular fragment value was obtained by dividing the log k' value by two. For unsymmetrical sulphides, *e.g.* Nos. 7, 8, 9, 10, 11 and 12, the values obtained for the symmetrical substituents served as the basis and, furthermore, these values were modified in the whole group to obtain the least standard deviation.

DISCUSSION

Structure–capacity factor relationships

The method used is based on the assumption that the mutual interaction between the pyridine rings is neglibible and therefore the use of the contributions corresponding to the half-molecular fragments is justified. On the basis of these fragment contributions, log k' can be calculated for other dipyridylsulphides not investigated in the present paper, *e.g.* for *bis*(2-thiocarbamoylpyridine-1-oxide-4-yl)sulphide log $k' = 2 \times 0.068 = 0.136$.

Interactions, however, can occur between the substituents on the pyridine ring. For instance, a comparison of the values in Table I for compounds 9 and 11 shows that the presence of 1-oxide results in a decrease in lipophilicity. In contrast, comparison of the values for compounds 10 and 12 shows that the presence of 1-oxide results in an increase in lipophilicity. In this case there is, however, a strong non-binding interaction between the thioamide and oxide groups (a hydrogen bond formation). From the values of half-molecular contributions the values of capacity factors were calculated for some other compounds studied from the standpoint of the structure–antituberculous activity relationships.

Structure–antituberculous activity relationships

The structure–antituberculous activity relationships were investigated only in the group of thioamides.

The values of the minimal inhibitory concentrations (MIC) were taken from the literature [5,6]. For the group of five thioamides, eqn. 2 was found to hold:

$$\text{Log MIC} = -0.5477 \log k' + 1.241 \qquad (2)$$

$$n = 5 \quad r = 0.800 \quad s = 0.187$$

The antituberculous activity increases with increasing lipophilicity.

Similar conclusion have been reached when other thioamides of the dipyridylsulphides group have been examined [7].

CONCLUSION

The approach outlined in this paper for calculating the logarithm of the capacity factor from half-molecular contributions has not been employed in the literature hitherto. It can also be useful in other groups of isosteric compounds, such as other diarylsulphides, diarylethers, diarylmethane derivatives, etc. As log k' from chromatography on octadecyl silica columns can be considered a parameter of lipophilicity, the approach can be utilized in the quantitative structure–activity relationship (QSAR) method.

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