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RETENTION BEHAVIOUR AND MOLECULAR STRUCTURE OF DIOLS IN REVERSED-PHASE LIQUID CHROMATOGRAPHY

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SUMMARY

Correlations between the retention behaviour of diols in reversed-phase liquid chromatography and their molecular structures have been studied using hydrophobicity (log P) and topological indices (χ_R, χ_R^V, W, W^*, J, J^*, C_T). It has been shown that the retention behaviour of diols in an eluent of acetonitrile–water (50:50) is best described by a polynomial equation of second degree involving hydrophobicity. Topological indices fail to predict the elution sequence of diols but the use of a parameterization scheme for topological indices calculated from the distance matrix improves the results. The combination of log P with the Wiener index and the first-order valence molecular connectivity indices gives reliable predicted capacity factors.

INTRODUCTION

Optimization of separations in liquid chromatography and prediction of capacity factors or retention indices for various solutes can be improved by studying the relationship etween the retention behaviour and the molecular structure. In reversed-phase liquid chromatography (RPLC), the retention behaviour of some series of homologous solutes has already been correlated with different numerical descriptors of the molecular structure, such as hydrophobicity factors or topological indices[1–4]. For example, the chromatographic behaviour of alkanes or alkylbenzenes and related products can be relatively well described using molecular topology[5–7]. Also, the capacity factors of some drugs have been correlated with their biological activities by means of hydrophobicity[8]. In spite of some drawbacks, relationships between these molecular descriptors and capacity factors have contributed to improving the understanding of the retention mechanism in RPLC.

Some categories of solutes have not been studied in regard to their retention behaviour. During the development of a chromatographic method to analyse industrial polyether polyols used in the fabrication of rigid polyurethane foams[9], it was found that many diols were present in the mixture either as required components or as impurities. The purpose of this paper is to study the relationship for these diols between the retention behaviour and some molecular descriptors, such as hydrophobicity and topological indices.

EXPERIMENTAL

The chromatographic system consisted of a Varian Model 5000 liquid chromatograph (Varian, Palo Alto, CA, U.S.A.) with an automatic universal injector (10-μl loop), Model 7126 (Rheodyne, Cotati, CA, U.S.A.). The variable-wavelength detector was a Varian Model UV-100 with a 4.5-μl flow-cell, set at 200 nm. Chromatograms were recorded on a Varian Vista 401 data station. The column used was purchased pre-packed and was of the following type: a Hypersil-ODS C_{18} (Chromatography Science Co., Ville Mont-Royal, Canada), 25 cm × 4.6 mm I.D., 5 μm particles.

Acetonitrile was Fisher HPLC grade (Fischer Scientific, Fair Lawn, NJ, U.S.A.). Water was purified through a NANOpure system and UV irradiated with an ORGANICpure system (Barnstead, Boston, MA, U.S.A.). Diols (kit 151C) were obtained from Polyscience (Niles, IL, U.S.A.).

The mobile phase was acetonitrile–water (50:50), and the flow-rate was kept at 1.0 ml/min. The column was maintained at 25°C. The retention time t_0 of an unretained compound was determined by injection of sodium nitrite solution in acetonitrile.

RESULTS AND DISCUSSION

The hydrophobicity of a molecule is calculated on the basis of the hydrophobic fragmental system proposed by Rekker and De Kort[10]. This parameter is estimated for a specific compound from its partition coefficient between an organic solvent and water. In our case, hydrophobic factors, log *P*, which were measured in the octanol–water system by Rekker[10], were used to evaluate the hydrophobicity of a molecule. In RPLC, hydrophobicity describes the affinity of a solute for a non-polar stationary phase[11,12]. Generally, the retention time of a solute increases with an increase of the hydrophobic factor[12].

TABLE I

VARIATION OF MOLECULAR DESCRIPTORS AS A FUNCTION OF CAPACITY FACTORS OF DIOLS

Columns, Hypersil ODS C_{18}, 25 cm × 4.6 mm I.D.; eluent, acetonitrile–water (50:50).

Diols	*No.*	*Log k'*	*Log P*	χ_R	χ_R^V	*W*	*W**	*J*	*J**	C_T
Glycerol	7	−0.602	−1.879	2.808	1.707	31	28.0	2.754	3.068	25.21
1,3-Propanediol	8	−0.502	−1.383	2.414	1.632	20	18.5	2.191	2.384	12.36
Ethyleneglycol	1	−0.496	−1.324	1.914	1.132	10	9.0	1.975	2.257	6.00
1,4-Butanediol	6	−0.487	−0.864	2.914	2.132	35	33.0	2.339	2.479	17.51
1,2-Propanediol	2	−0.468	−0.805	2.270	1.560	18	16.5	2.540	2.808	22.85
1,3-Propanediol	3	−0.455	−0.864	2.770	2.060	32	30.0	2.627	2.809	26.73
1,5-Pentanediol	9	−0.442	−0.345	2.414	2.632	56	53.5	2.447	2.553	25.36
2,3-Butanediol	5	−0.407	−0.286	2.643	2.004	29	28.0	2.994	3.109	30.53
1,2-Butanediol	4	−0.398	−0.286	2.808	2.098	31	29.0	2.754	2.959	26.73
2,4-Pentanediol	10	−0.351	−0.345	3.126	2.488	48	45.5	2.953	3.115	39.34
1,9-Nonanediol	11	−0.064	1.731	5.414	4.632	220	215.5	2.691	2.736	48.97
1,10-Decanediol	12	0.094	2.250	5.914	5.132	286	281.0	2.727	2.766	54.73
1,12-Dodecanediol	13	0.377	3.288	6.914	6.132	455	449.0	2.785	2.814	66.32

TABLE II

CORRELATION MATRIX FOR THE VARIOUS INDICES GIVEN IN TABLE I

	Log P	χ_R	χ_R^V	*W*	*W**	*J*	*J**	C_T	*Log k'*
Log *P*	1.000								
χ_R	0.9499	1.000							
χ_R^V	0.9737	0.9824	1.000						
W	0.9509	0.9732	0.9725	1.000					
*W**	0.9511	0.9727	0.9720	0.9999	1.000				
J	0.4004	0.3995	0.3924	0.3072	0.3062	1.000			
*J**	0.1394	0.1663	0.1344	0.0767	0.0756	0.9487	1.000		
C_T	0.9231	0.9312	0.9383	0.8972	0.8964	0.6672	0.4550	1.000	
Log *k'*	0.9839	0.9627	0.9690	0.9801	0.9805	0.3557	0.1130	0.9144	1.000

Graph theory has led to the proposal of many different topological indices to describe a molecular structure. For the calculation of topological indices related to diols, two kinds of first-order molecular connectivity index[13,14], which are based on the adjacency matrix of a molecular graph, have been evaluated: the molecular connectivity index, χ_R, and the valence molecular connectivity index, χ_R^V. Topological indices based on the distance matrix of a molecular graph, such as Wiener number, *W*, and the Balaban index, *J*, have also been calculated[13,14]. Recently, a more general definition of the distance matrix for molecules with multiple bonds and heteroatoms has been proposed[15]. Hence, it is possible to calculate Wiener and Balaban indices with this new definition to incorporate the effect of the oxygen atoms in diols. In this paper these indices are labelled with asterisks to distinguish them from standard indices. In addition, an information index that is described as a general index of molecular complexity, C_T, has been calculated[16]. The values of C_T and other parameters for some diols are given in Table I. The detailed description of these indices and the methods of calculation are given elsewhere[10,13–16] and will not be repeated here.

A correlation matrix was calculated for the various parameters given in Table I and the results are shown in Table II. Examination of the coefficients shows that hydrophobicity (log *P*) is the best parameter to describe the retention (log *k'*) of diols in RPLC with a binary acetonitrile–water eluent, and that the Balaban index is not suitable for studying the chromatographic behaviour of diols. Strangely, the Balaban index calculated with the heteroatoms parameterization scheme, *J**, correlates less well with log *k'* than the standard Balaban index, *J*. In gas chromatography, with various chlorobenzenes eluting on a non-polar stationary phase, the Balaban index *J** has shown a slightly higher correlation coefficient with the retention indices than the standard Balaban index *J* (ref. 6). However, as for diols, the Balaban index, either *J* or *J**, shows a worse correlation than simpler indices with a lower structural information content and a lower discriminatory power, such as connectivity indices. Sabljic[6] has attributed this phenomenon to the large amount of structural information included in the Balaban indices, which can obscure significant factors in regard to the chromatographic behaviour.

For diols, the hydrophobicity factor is better than the valence molecular connectivity index for the prediction of the retention behaviour. A similar trend has been reported for benzophenones[11]. The linear relation between log k' and log P is:

$$\log k' = -0.308 + 0.181(\log P) \tag{1}$$

with a correlation coefficient equal to 0.9839. The correlation coefficient can be improved by the use of a quadratic equation ($r = 0.9956$):

$$\log k' = -0.357 + 0.150(\log P) + 0.0211(\log P)^2 \tag{2}$$

The variation of log k' as a function of log P is shown in Fig. 1 with the quadratic regression curve. A similar relationship has been found for barbiturates on an octadecyl bonded phase with methanol–water eluent, where a curvature in the plot of log k' *versus* log P was observed[8]. Addition of other polynomial terms to eqn. 2 does not increase the correlation coefficient significantly.

A good correlation between the retention and hydrophobicity for solutes with good hydrogen-bonding capabilities is difficult to obtain[17,18]. The curvature observed on the plot of log k' *versus* log P is explained in terms of diols with small and long alkyl chains having different retention mechanisms. As the number of carbons atoms in the alkyl chain increases, the interaction between the diol and the stationary phase tends to be controlled by hydrophobicity. For example, a linear relationship between retention and hydrophobicity was observed for a series of alcohols (C_4–C_{12}) in acetonitrile–water (50:50) on an octadecyl bonded phase[12]. For small diols, it is reasonable to assume that the solvation of the molecule is influenced by the presence of two hydroxyl groups on the short alkyl chain. Thus, for these molecules, the retention mechanism is not controlled mainly by hydrophobicity and this may explain the deviation from linearity. However, a series of experiments involving various mobile phases and possibly other diols will be necessary to obtain more information on the retention mechanism.

In spite of the excellent correlation coefficient found in eqn. 2, the hydrophobic

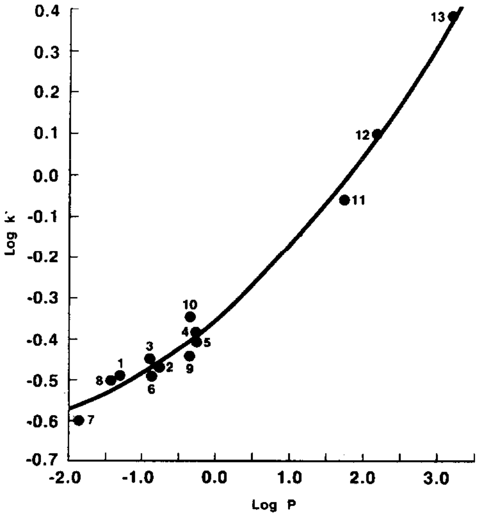

Fig. 1. Variation of log k' of diols as a function of log P. The curve has been calculated with eqn. 2. See Table I for identification of the diols.

factor cannot distinguish between isomers, such as 1,2-butanediol and 2,3-butanediol. According to the correlation table (Table II), the best molecular descriptor after log *P* is the Wiener index. A multiple stepwise regression analysis was performed with topological indices only, and it was found that it is of no interest to use different topological indices in conjunction with the Wiener index. As opposed to log *P* values, the Wiener index with the heteroatoms parameterization scheme gives different values for isomers. The variation of log *k'* as a function of *W** can be described by a linear relation:

$$\log k' = -0.522 + 2.05 \cdot 10^{-3}\,(W^*) \tag{3}$$

The correlation coefficient is 0.9801, and the addition of another term (W^{*2}) does not significantly increase this value. However, in spite of the capability of *W** to describe different isomers, the elution sequence for solutes 1–9 is incorrectly predicted. By comparison, only two solutes (4 and 10) were incorrectly predicted with log *P*.

The incorporation of various topological indices in an equation can be useful in the prediction of retention indices[5,6]. A tentative equation has been established with the best molecular descriptors:

$$\log k' = 0.264 + 0.132(\log P) - 0.0643\,(\chi_R^V) + 0.00134\,(W^*) \tag{4}$$

The correlation coefficient is 0.9963, which is greater than the correlation coefficient found with eqn. 2. Although the elution sequence is identical with the one found with eqn. 2, eqn. 4 has the advantage of being able to distinguish between different isomers.

CONCLUSION

The retention behaviour of some diols has been related to hydrophobicity. The relation between log *k'* and log *P* is best described by a polynomial equation of degree 2. Topological indices have failed to predict correctly the elution sequence of diols in RPLC with acetonitrile–water (50:50). However, topological indices calculated from the distance matrix give better results if the heteroatoms parameterization scheme is used. The combination of log *P* with the Wiener index and the first-order valence molecular connectivity indices gives predicted reliable capacity factors. It would be interesting to observe the behaviour of these indices with other solutes, which are not well described by hydrophobicity or topological indices.

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