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GAS–LIQUID CHROMATOGRAPHY AS A TOOL FOR EVALUATION OF LIPOPHILICITY OF SELECTED ESTERS OF AROMATIC AND ALIPHATIC ACIDS

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SUMMARY

   The use of gas–liquid chromatographic retention values for the determination of lipophilicity was studied for series of esters of aromatic and aliphatic acids and for series of aliphatic alcohols. The regression relationships between the logarithms of the partition coefficients and the retention characteristics measured on two capillary columns, SE-30 and OV-351, differing markedly in polarity, were evaluated. It may be deduced that, for the structurally similar compounds, the stationary phases used simulate the reference partitioning system octanol–water.

INTRODUCTION

   Lipophilicity is an important property of biologically active compounds and much attention has been devoted to its evaluation. Retention indices from partition chromatography are frequently used[1–4] as lipophilicity parameters in quantitative structure–activity relationships (QSARs). They are used either directly or for calculation of log P values. Recently, retention characteristics from gas chromatography were used for such purposes[5–9]; there seem to be some advantages in comparison with high-performance liquid chromatography (HPLC) and thin-layer chromatography (TLC) especially with regard to reproducibility of the results. In gas–liquid chromatography (GLC), the only transition which takes place is that from the gaseous to the liquid phase. If the liquid phase is non-polar, only the part of the distribution process that is characterized by the solvation in an organic solvent is relevant. Contributions from hydration connected with the transition of a compound into the organic solvent, *i.e.*, repulsive interactions between the hydrophobic part of the molecule with water, are absent. The loss of this contribution has a profound effect upon the contribution of the polar groups to separation in GLC. Generally, it cannot be assumed that a relationship exists between the GLC retention indices and log P for structurally similar compounds differing in the polarity of the substituents.

Although there are considerable differences in mechanism of separation in GLC and the partitioning process, ways were sought to apply of GLC in lipophilicity evaluation. Boček[5,6] developed a method of indirect determination of the partition coefficient in the system 9-octadecenol–water. In his method, the ratio of the distribution constants in 9-octadecenol–nitrogen and water–nitrogen is determined by gas chromatography. The method is, however, only suitable for volatile compounds with low boiling points. A similar principle was used by Valkó and Lopata[7]. In their approach, the differences between both types of separation were overcome by use of two stationary phases differing markedly in their polarities.

On the assumption that the distribution constants, K_1 and K_2, in both systems are independent of the concentration of solute, the partition coefficient, $P_{1/2}$, between the liquid phases is expressed as:

$$P_{1/2} = K_1/K_2 \tag{1}$$

The relationships between capacity factors, k', specific volumes, V_g, Kováts indices, I, and the partition coefficients, $P_{1/2}$ are:

$$\log P_{1/2} = \log(k'_1/k'_2) + a \tag{2}$$

$$\log P_{1/2} = \log(V_{g1}/V_{g2}) + b \tag{3}$$

$$\log P_{1/2} = cI_1 - dI_2 + e \tag{4}$$

where a, b, c, d and e are constants. Assuming the validity of the Collander equation[10] between the logarithms of partition coefficients determined in GLC and a suitable system, e.g., octanol–water, then for the Kováts indices:

$$\log P_{o/w} = k_1 I_1 - k_2 I_2 + k_3 \tag{5}$$

where k_1, k_2 and k_3 are constants. The GLC retention characteristics for various series of esters of organic acids using capillary columns with stationary phases of different polarities were determined by Korhonen and co-workers[11-16]. The columns used were a vitreous silica, SE-30, and a fused-silica, OV-351. The experimental data were used for verification of the relationships between the logarithms of the partition coefficients and gas chromatographic values, i.e. the Kováts indices, I, or relative retention times, RRT. .

CALCULATIONS

Experimental log P values were taken from ref. 17. The calculations for alkyl benzoates (I) were based on the log P values of methyl and propyl benzoates. Incremental values of $\Delta f = 0.54$ per methylene group were used for other esters. The parameters π derived[18] for substituted benzoic acids were used for chloro substituents. Phenyl acetate was used as a basis for the calculation of log P values for esters (II). For chloro substitution, the values of π derived for phenols[18] were used. For the esters of alkanoic acids(III), the calculations were based on the log P value for ethyl acetate. The increment for the methylene group was again $\Delta f = 0.54$. The

differences among ethyl, 1-chloroethyl, 1,1-dichloroethyl and 1,1,1-trichloroethyl groups were assumed to be the same as those among ethane (log P = 1.81), 1-chloroethane (log P = 1.43), 1,1-dichloroethane (log P = 1.79) and 1,1,1-trichloroethane (log P = 2.49). Both the experimental values of log P and the increments for the methylene group were used for alcohols(IV). Ethyl propanoate was the starting compound for the alkyl propanoates(V). The increments calculated as the differences between the log P values for the corresponding alcohols were used for the rest of the esters V. The increments for 2-chloro and 3-chloro derivatives (VI and VII) were calculated by the fragmental method[17].

For the branched-chain alkyl esters of benzoic acids, (cf. Table IV), the calculations were based on the log P value (2.12) for methyl benzoate. The increments for other esters were calculated from Σf for the corresponding alkyls, taking into account the difference between Σf and $f(CH_3)$. For example, for 1-methylpropyl benzoate (the branching factor F_{cBr} and the bonding factor F_b were taken from ref. 17):

$$\Sigma f = 2f(CH_3) + f(CH_2) + f(CH) - F_{cBr} - 2F_b$$
$$= 1.78 + 0.66 + 0.43 - 0.13 - 0.24 = 2.50$$
$$\log P = 2.12 + \Sigma f - f(CH_3) = 2.12 + 2.50 - 0.89 = 3.73$$

For the unsaturated esters of benzoic acids, cf., Table V, methyl benzoate was used as a starting compound. The increments for the other esters were taken as the differences between the value for methane and those for the corresponding unsaturated hydrocarbons. For example, for 2-propenyl benzoate:

$$\log P = \log P(\text{methyl benzoate}) + \log P(\text{2-propene}) - \log P(\text{methane})$$
$$= 2.12 + 1.77 - 1.09 = 2.80$$

RESULTS AND DISCUSSION

The relationships between the lipophilicities and GLC characteristics (Table I) for the substituted methyl benzoates(I) and aromatic acetates(II) were found to be:

	n	r	s	F	
$\log P = 0.0046\ I(\text{SE-30}) - 3.105$	18	0.847	0.274	15.3	(6)
$\log P = 0.0026\ I(\text{OV-351}) - 2.430$	18	0.603	0.412	3.4	(7)
$\log P = 0.0104\ I(\text{SE-30}) - 0.0051\ I(\text{OV-351}) - 0.797$	18	0.961	0.156	30.5	(8)

n = Number of compounds; r = regression coefficient; s = standard deviation; F = Fisher-Snedecor criterion. According to the general relationship 5, the lipophilicity of the esters I and II can be expressed by the two-variable eqn. 8. Extension of the series to 2-, 3- and 4-chlorobenzoates yielded the analogous equation:

$$\log P = 0.0092\ I(\text{SE-30}) - 0.0036\ I(\text{OV-351}) - 1.900 \tag{9}$$
$$n = 18, \quad r = 0.999, \quad s = 0.066, \quad F = 5899.3$$

TABLE I

LIPOPHILICITIES AND GLC CHARACTERISTICS OF COMPOUNDS I AND II
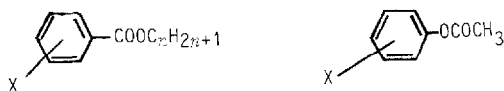
	I			II	
Compound No.	X	n	log P	I(SE-30)*	I(OV-351)*
Ia	H	1	2.12**	1097	1643
Ib	H	2	2.64**	1164	1685
Ic	H	7	5.46	1657	2174
Id	H	9	6.54	1856	2374
Ie	2-Cl	3	3.77	1422	2055
If	2-Cl	9	7.01	2014	2639
Ig	3-Cl	2	3.47	1323	1887
Ih	3-Cl	6	5.63	1714	2251
Ii	4-Cl	2	3.51	1324	1885
Ik	4-Cl	5	5.13	1616	2158
Il	4-Cl	7	6.21	1815	2356
IIa	H		1.49	1008	1633
IIb	2-Cl		2.18	1173	1829
IIc	3-Cl		2.32	1198	1848
IId	4-Cl		2.32	1203	1870

* Values were taken from ref. 11.
** Experimental value taken from ref. 17.

TABLE II

LIPOPHILICITIES AND GLC CHARACTERISTICS OF COMPOUNDS $C_nH_{2n+1}COOCH_2CH_{3-x}Cl_x$ (III)

Compound No.	x	n	log P	RRT(SE-30)*	RRT(OV-351)*
IIIa	0	1	0.73**	0.25	0.36
IIIb		2	1.27	0.27	0.38
IIIc		3	1.81	0.30	0.44
IIId		4	2.35	0.35	0.52
IIIe		5	2.89	0.43	0.66
IIIf	1	1	0.35	0.31	0.84
IIIg		2	0.89	0.37	1.03
IIIh		3	1.43	0.44	1.32
IIIi		6	3.05	0.84	2.77
IIIk	2	1	0.71	0.35	1.16
IIIl		2	1.25	0.44	1.40
IIIm		3	1.79	0.54	1.76
IIIn		5	2.87	0.82	2.72
IIIo		6	3.41	0.98	3.28
IIIp	3	1	1.41	0.42	1.13
IIIr		2	1.95	0.54	1.36
IIIs		3	2.49	0.67	1.69
IIIt		4	3.03	0.82	2.16

* Values were taken from ref. 12.
** Experimental value taken from ref. 17.

The series of ethyl and chloroethyl esters of alkanoic acids(III) also gave a good correlation between log P and the retention values (Table II) in both GLC systems:

$$\log P = 10.813 \log RRT(SE\text{-}30) - 4.415 \log RRT(OV\text{-}351) + 5.695 \quad (10)$$
$$n = 18, \quad r = 0.971, \quad s = 0.237, \quad F = 124.7$$

The equations corresponding to the individual systems have much lower statistical significance:

$$\begin{array}{llll} & n & r & s & F \end{array}$$

$$\log P = 4.157 \log RRT(SE\text{-}30) \quad + 3.249 \qquad 18 \; 0.812 \; 0.563 \; 30.9 \quad (11)$$

$$\log P = 1.723 \log RRT(OV\text{-}351) + 1.778 \qquad 18 \; 0.548 \; 0.806 \; 6.9 \quad (12)$$

TABLE III

LIPOPHILICITIES AND GLC CHARACTERISTICS OF COMPOUNDS $C_nH_{2n+1}OH$ (IV), $CH_3CH_2COOC_nH_{3n+1}$ (V), $CH_3CHClCOOC_nH_{2n+1}$ (VI), $CH_2ClCH_2COOC_nH_{2n+1}$ (VII)

Compound No.	n	log P	I(SE-30)*	I(OV-351)*
IVa	1**	−0.77***	471	978
IVb	2**	−0.31***	513	1015
IVc	3**	0.25***	575	1031
IVd	4**	0.88	649	1124
IVe	5	1.56***	748	1238
IVf	6	2.03***	845	1332
IVg	7	2.60***	950	1427
IVh	8	3.15***	1049	1528
IVi	9	3.65	1147	1627
IVk	10	4.15	1247	1726
IVl	11	4.65	1347	1826
IVm	12	5.13***	1448	1924
Va	1**	0.75	622	1003
Vb	2**	1.21***	684	1031
Vc	3**	1.77	785	1064
Vd	4**	2.40	884	1145
Ve	5	3.08	983	1234
Vf	6	3.55	1081	1330
Vg	7	4.12	1178	1427
Vh	8	4.67	1276	1522
Vi	9	5.17	1376	1618
Vk	10	5.67	1476	1716
VIa	1**	1.26	756	1202
VIb	2**	1.72	832	1229
VIc	3**	2.28	930	1305
VId	4**	2.91	1027	1396
VIIa	1**	1.48	819	1330
VIIc	3**	2.50	996	1450
VlId	4**	3.13	1092	1542
VIIe	5**	3.81	1189	1636

* Values were taken from ref. 13.
** Value used for deriving eqn. 16.
*** Experimental value taken from ref. 17.

The log P values for the series of homologous aliphatic alcohols(IV) as well for the series of alkyl propanoates(V) correlate well with Kováts indices (Table III):

$$\log P = 0.0058\ I(\text{SE-30}) \quad - 3.1091 \qquad \begin{array}{cccc} n & r & s & F \\ 12 & 0.994 & 0.220 & 868.2 \end{array} \qquad (13)$$

$$\log P = 0.0059\ I(\text{OV-351}) - 6.0166 \qquad 12\ \ 0.992\ \ 0.262\ \ 613.3 \qquad (14)$$

$$\log P = 0.0058\ I(\text{SE-30}) \quad - 2.7258 \qquad 10\ \ 0.999\ \ 0.082\ \ 3818.1 \qquad (15)$$

When the series of compounds IV and V and also esters of 2-chloro-(VI) and 3-chloropropanoic acid(VII) are taken as a whole the range of polarity is greater and thus the two-variable equation
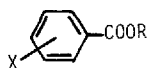
$$\log P = 0.0081\ I(\text{SE-30}) - 0.0024\ I(\text{OV-351}) - 1.9605 \qquad (16)$$
$$n = 16, \quad r = 0.995, \quad s = 0.137, \quad F = 623.9$$

is more suitable for the correlation of log P with Kováts indices I.

TABLE IV

LIPOPHILICITIES AND GLC CHARACTERISTICS FOR BRANCHED-CHAIN ALKYL ESTERS OF BENZOIC ACIDS

X	R	log P	RRT(SE-30)*	RRT(OV-351)*
H	Methylethyl	3.19	0.66	1.69
	1-Methylpropyl	3.73	0.82	1.95
	2-Methylpropyl	3.73	0.85	2.06
	1,2-Dimethylpropyl	4.14	0.93	2.13
	1-Methylbutyl	4.27	0.96	2.20
	3-Methylbutyl	4.27	1.03	2.42
2-Cl	Methylethyl	3.78	0.92	2.50
	1-Methylpropyl	4.32	1.09	2.78
	2-Methylpropyl	4.32	1.13	2.88
	1,2-Dimethylpropyl	4.73	1.21	2.95
	1-Methylbutyl	4.86	1.23	3.01
	3-Methylbutyl	4.86	1.29	3.20
3-Cl	Methylethyl	4.02	0.92	2.24
	1-Methylpropyl	4.56	1.08	2.50
	2-Methylpropyl	4.56	1.12	2.60
	1,2-Dimethylpropyl	4.97	1.20	2.66
	1-Methylbutyl	5.10	1.23	2.74
	3-Methylbutyl	5.10	1.29	2.96
4-Cl	Methylethyl	4.06	0.92	2.23
	1-Methylpropyl	4.60	1.08	2.50
	2-methylpropyl	4.60	1.12	2.62
	1,2-Dimethylpropyl	5.01	1.21	2.68
	1-Methylbutyl	5.14	1.23	2.75
	3-Methylbutyl	5.14	1.30	2.97

* Values were taken from ref. 14.

Similar conclusions can be drawn for the series of esters of benzoic acids with branched-chain aliphatic alcohols (Table IV):

$$\log P = 12.783 \log \text{RRT(SE-30)} - 7.112 \log \text{RRT(OV-351)} + 6.966 \quad (17)$$
$$n = 24, \quad r = 0.979, \quad s = 0.113, \quad F = 238.5$$
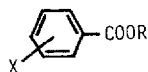
or with unsaturated alcohols (Table V):

$$\log P = 15.787 \log \text{RRT(SE-30)} - 9.741 \log \text{RRT(OV-351)} + 7.598 \quad (18)$$
$$n = 28, \quad r = 0.985, \quad s = 0.160, \quad F = 412.1$$

Striking differences in statistical significance were found for the equations used to correlate the data for esters VIII (Table VI):

TABLE V

LIPOPHILICITIES AND GLC CHARACTERISTICS OF UNSATURATED ALKYL ESTERS OF BENZOIC ACIDS

X	R	log P	RRT(SE-30)*	RRT(OV-351)*
H	2-Propenyl	2.80	0.74	1.99
	2-Propynyl	1.97	0.75	2.52
	3-Butenyl	3.43	0.89	2.24
	1-Methyl-3-butenyl	3.84	0.94	2.18
	(E)-2-Butenyl	3.43	0.95	2.39
	4-Pentenyl	3.97	1.07	2.55
	(E)-3-Hexenyl	4.51	1.24	2.75
2-Cl	2-Propenyl	3.39	1.00	2.78
	2-Propynyl	2.56	1.02	3.30
	3-Butenyl	4.02	1.16	3.02
	1-Methyl-3-butenyl	4.43	1.21	2.95
	(E)-2-Butenyl	4.02	1.21	3.14
	4-Pentenyl	4.56	1.34	3.30
	(E)-3-Hexenyl	5.10	1.50	3.52
3-Cl	2-Propenyl	3.63	1.00	2.54
	2-Propynyl	2.80	1.01	3.06
	3-Butenyl	4.26	1.16	2.78
	1-Methyl-3-butenyl	4.67	1.20	2.70
	(E)-2-Butenyl	4.26	1.21	2.92
	4-Pentenyl	4.80	1.33	3.07
	(E)-3-Hexenyl	5.34	1.49	3.25
4-Cl	2-Propenyl	3.67	1.00	2.52
	2-Propynyl	2.84	1.01	3.04
	3-Butenyl	4.30	1.16	2.76
	1-Methyl-3-butenyl	4.71	1.21	2.69
	(E)-2-Butenyl	4.30	1.22	2.90
	4-Pentenyl	4.84	1.34	3.08
	(E)-3-Hexenyl	5.38	1.49	3.26

* Values were taken from ref. 15.

TABLE VI

LIPOPHILICITIES AND GLC CHARACTERISTICS OF COMPOUNDS VIII

$$\text{benzene ring}—COOCH_2CH_{3-x}Cl_x$$

with X substituent
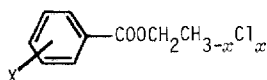
Compound No.	X	x	log P	I(SE-30)*	I(OV-351)*
VIIIa	H	0	2.64**	1157	1695
VIIIb		1	2.26	1380	2123
VIIIc		2	2.62	1470	2213
VIIId		3	3.32	1536	2184
VIIIe	2-Cl	0	3.23	1325	1965
VIIIf		1	2.85	1549	2398
VIIIg		2	3.21	1638	2491
VIIIh		3	3.91	1708	2469
VIIIi	3-Cl	0	3.47	1318	1884
VIIIk		1	3.09	1542	2331
VIIIl		2	3.45	1627	2421
VIIIm		3	4.15	1690	2366
VIIIn	4-Cl	0	3.51	1323	1878
VIIIo		1	3.13	1544	2325
VIIIp		2	3.49	1635	2419
VIIIr		3	4.19	1696	2372

* Values were taken from ref. 16.
** Experimental value taken from ref. 17.

$$\log P = 0.0019\ I(\text{SE-30}) + 0.3963 \qquad n=16\quad r=0.589\quad s=0.497\quad F=7.4 \qquad (19)$$

$$\log P = 0.0008\ I(\text{OV-351}) + 1.6118 \qquad n=16\quad r=0.344\quad s=0.519\quad F=1.9 \qquad (20)$$

$$\log P = 0.0091\ I(\text{SE-30}) - 0.0051\ I(\text{OV-351}) + 0.8278 \qquad n=16\quad r=0.921\quad s=0.224\quad F=36.3 \qquad (21)$$

The high statistical significance of the regression equations 8–10, 16–18 and 21 indicates, that for the structurally similar compounds the stationary phases used simulate the reference system octanol–water. It is suggested that these equations can be used for prediction of the partition coefficients in this system.

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