Journal of Chromatography, 286 (1984) 63–67
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

CHROMSYMP. 225

GAS CHROMATOGRAPHIC BEHAVIOUR OF CARBOXAMIDE DERIVATIVES

ÉVA JÁNOS*, BARNA BORDÁS and TIBOR CSERHÁTI
Research Institute for Plant Protection, Hungarian Academy of Sciences, Budapest (Hungary)

SUMMARY

Gas–liquid chromatographic retention indices of 28 substituted carboxamide derivatives were measured on apolar (Apolan 87) and polar (Carbowax 20M) stationary phases. Relationships were sought between these retention indices and the lipophilicities of the compounds. The influence of the structural elements on retention indices and lipophilicity was studied.

INTRODUCTION

Quantitative structure–activity relationships (QSARs) are widely used for the design of bioactive molecules. These approaches often use lipophilicity indices as independent variables to characterize the investigated molecules. The lipophilicity of a molecule can be measured in several ways: partition in octanol–water system[1,2] giving log *P*; reversed-phase thin-layer chromatography (RPTLC)[3,4]; reversed-phase high-performance liquid chromatography[5,6] and recently gas chromatography (GC)[7,8].

We have studied the GC behaviour of 28 substituted carboxamide derivatives and tried to find relationships between the retention indices, I_A and I_C, or differences between retention indices and lipophilicity (characterized by measured RPTLC R_M values and calculated octanol–water partition values, log *P*. We also tried to find those structural elements which correlated well with the chromatographic and lipophilic data using "stepwise" regression analysis.

Earlier, Clifford and Watkings[9] reported the correlation of GC retention times with log *P* values. Later Papp *et al.*[10] showed that differences between GC retention indices correlated well with lipophilicity (log *P*). We obtained similar results in the case of certain *s*-triazine herbicides[11].

EXPERIMENTAL

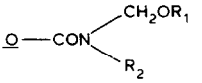
The carboxamide derivatives are listed in Table I.

For measuring the retention indices the following GC apparatus was applied: gas chromatograph, Packard 7400 equipped with a flame ionization detector; columns, 120 cm × 2 mm I.D. glass, packed with 3% Apolan 87 on Supelcoport (80–

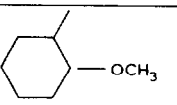
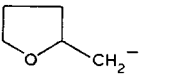
0021-9673/84/$03.00

TABLE I

THE CARBOXAMIDE DERIVATIVES INVESTIGATED



Q = Irrelevant substructure identical for each compound.

No.	R_1	R_2	*No.*	R_1	R_2
1	$H_3COCH_2CH_2$–	–CH_2–CH=CH_2			
2	$H_5C_2OCH_2CH_2$–	–CH_2CH=CH_2	18		–CH_2-CH=CH_2
3	$H_5C_6OCH_2CH_2$–	–CH_2-CH=CH_2			
4	$H_9C_4OCH_2CH_2$–	–CH_2-CH=CH_2			
5	$H_3COCH_2CH_2$–	–CH_2–CH_2–CH_3			
6	$H_5C_2OCH_2CH_2$–	–CH_2-CH_2-CH_3	19		–CH_2-CH=CH_2
7	$H_5C_2OCH_2C$–$\overset{H}{CH_3}$	–CH_2-CH_2-CH_3			
8	H_3COCH_2C–$\overset{H}{CH_3}$	–CH_2-CH_2-CH_3			
9	$H_3COCH_2CH_2$–	–CH_3	20	$H_5C_2OCH_2CH_2$–	–CH_2-CH_2-$CH(CH_3)_2$
10	$H_5C_2OCH_2CH_2$–	–CH_3	21	$H_9C_4OCH_2CH_2$–	–CH_2-CH_2-$CH(CH_3)_2$
11	$H_9C_4OCH_2CH_2$–	–CH_3	22	C_3H_7–	–CH_2-CH=CH_2
12	H_3COCH_2C–$\overset{H}{CH_3}$	–CH_3	23	$H_3COCH_2CH_2$–	–CH_2-CH_3
13	$H_3COCH_2CH_2$–	–CH_2-CH_2-OCH_3	24	$H_5C_6OCH_2CH_2$–	–CH_2-CH_3
14	$H_5C_2OCH_2CH_2$–	–CH_2-CH_2-OCH_3	25	$H_5C_2OCH_2CH_2$–	–CH_2-CH_3
15	$H_9C_4OCH_2CH_2$–	–CH_2-CH_2OCH_3	26	C_4H_9–	–CH_2-CH_3
16	$H_3COCH_2CH_2$–	HC–$\overset{CH_3}{CH_3}$	27	$H_9C_4OCH_2CH_2$–	–CH_2-CH_3
17	$H_5C_2OCH_2CH_2$–	HC–$\overset{CH_3}{CH_3}$	28	C_4H_9–	–CH_2-CH=CH_2

100 mesh) (1), 120 cm × 2 mm I.D. glass, packed with 3% Carbowax 20M on Supelcoport (80–100 mesh) (2). The retention indices were measured at three different column temperatures and extrapolated to 130°C.

R_M values were measured on Kieselgel HF_{254} impregnated with 5% paraffin oil in *n*-hexane. The eluent system was methanol–water (1:1). The spots were detected by spraying with 0.5 g diphenylamine and 0.5 g $ZnCl_2$ in 100 cm^3 acetone, and then heating for 5 min at 200°C.

Adsorption heats, ΔH, were calculated from retention times, t_1 and t_2, measured at different temperatures, T_1 and T_2, by:

$$\Delta H = \frac{\ln t_2 - \ln t_1}{1/T_1 - 1/T_2} \cdot 1.98 \text{ cal/mol} \qquad (1)$$

log *P* values were calculated as described by Hansch and Leo[12].

To get maximum information from our data set, principal component analysis[13] and stepwise regression analysis were used.

RESULTS AND DISCUSSION

Relationships were sought between the measured GC (I_A, I_C) and TLC (R_M) data and the calculated log *P* and ΔH values. The best fits containing the variables (Table II) selected by principal component analysis are shown in Table III. The statistical significance is >99.9% for the relationships between the following parameter pairs:

TABLE II

THE VARIABLES STUDIED

1	R_M (measured by RPTLC)
2	log P (calculated according to Hansch and Leo)
3	I_A (retention indices measured on Apolan 87)
4	α_A (measure of temperature dependence of I_A)
5	I_C (retention indices measured on Carbowax 20M)
6	α_C (measure of temperature dependence of I_C)
7	ΔI ($I_C - I_A$)
8	ΔH measured on Apolan 87
9	ΔH measured on Carbowax 20M

(a) R_M and log P
(b) retention indices measured on columns 1 and 2
(c) retention indices on column 1 and ΔH values on the same column
(d) retention indices on column 2 and ΔH values on column 1
(e) retention indices on column 2 and ΔH on the same column
(f) α for retention indices on column 2 and ΔH on the same column
(g) ΔH measured on columns 1 and 2

The highly significant relationship between R_M and log P values is expected, and the correlation of retention indices measured on the different columns can also be explained. As the ΔH values are calculated from the retention data, their correlation with retention indices is expected. The same is true for the four other equations where the relationship is highly significant.

However, we could not find significant relationships between the GC retention data and R_M or log P values (lipophilicity) of the compounds: neither for retention indices on Apolan 87 nor on Carbowax 20M, nor for the difference between the two parameters correlated with the R_M or log P values. This means that, contrary to our expectation, GC retention data may not be used to characterize the lipophilicity of the carboxamide derivatives investigated.

Non-linear mapping of the result of principal component (PC) analysis (Fig. 1) showed that only two "clusters" are separated on the graph of the PC loadings. One cluster was formed by the retention indices determined on both columns and by

TABLE III

STATISTICAL PARAMETERS OF THE REGRESSION EQUATIONS CONTAINING THE VARIABLES SELECTED BY PRINCIPAL COMPONENT ANALYSIS

x	y	a	b	s_b	n	r	s	F
1	2	2.68	3.414	0.758	28	0.662	0.794	20.276
3	5	933.31	0.818	0.136	28	0.762	108.5	36.037
3	8	−1487.35	9.019	1.687	28	0.724	1343.2	28.581
3	9	5401.14	5.490	1.595	28	0.560	1426.7	11.850
5	8	−2713.52	7.208	1.786	28	0.621	1233.6	16.296
5	9	−1709.30	7.067	1.137	28	0.773	971.4	38.650
6	9	11,571.41	3299.1	713.260	28	0.672	1134.6	21.390
8	9	8282.64	0.471	0.124	28	0.599	1266.7	14.540

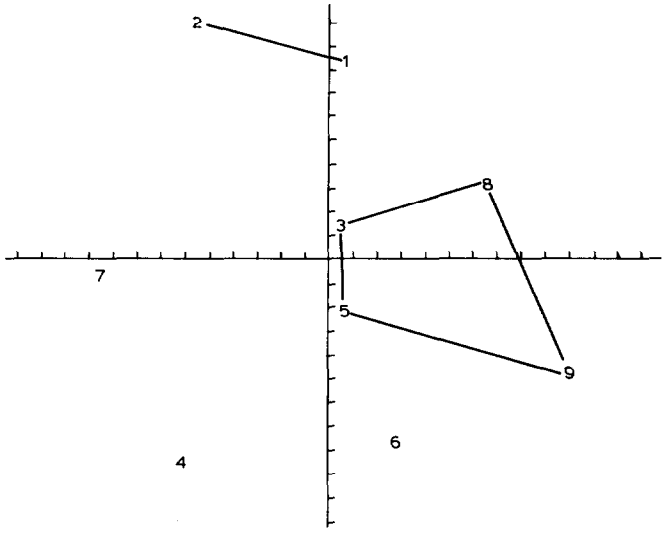


Fig. 1. Graph of the PC loadings. For numbers see Table II.

the adsorption heats. This finding can be explained because the adsorption heats are calculated from the retention times. The other cluster contained the R_M and log P values. Both variables characterize the lipophilic character of a molecule, so that their appearance in a cluster is expected. We obtained the same result by varimax rotation of the PC loadings[14].

On the map of the PC variables (Fig. 2) – obtained by non-linear mapping – the chromatographic behaviour of 28 carboxamide derivatives is illustrated. Here there are no clusters, which would indicate the existence of groups of compounds

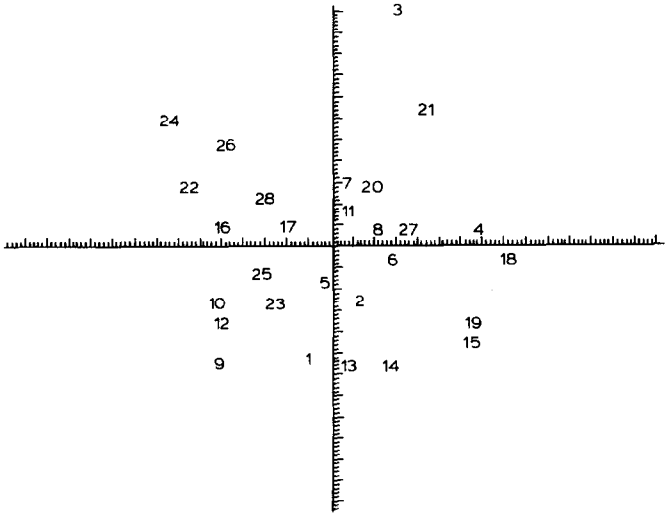


Fig. 2. Graph of the PC variables. For numbers see Table I.

which could be separated from the rest according to their chromatographic behaviour.

Finally we searched for structural elements which influence the retention indices, I_A and I_C, and the lipophilic character, R_M and log P. The following structural elements were taken into consideration: 1, number of carbon atoms; 2, number of oxygens; 3, presence of phenyl rings; 4, branching; 5, double bonds. Stepwise regression analysis was used to find the best fits.

The most significant structural elements selected by the analysis of retention indices measured on the Apolan 87 column were 1–3. Retention indices on Carbowax 20M were influenced by structural elements 1, 2 and 5. The index differences, ΔI, were not influenced significantly by the number of carbon atoms, but they were affected by the number of oxygen atoms, the presence of phenyl rings and double bonds. Only two structural elements were important from the point of view of the R_M values: the number of carbon atoms and the presence of phenyl rings. All the five structural elements were selected by the analysis as significantly influencing log P, but of these only three (the number of C atoms, the number of O atoms and the presence of phenyl rings) were highly significant. As the log P values were calculated from structural fragments, we expected all the structural elements to be important. In fact, all the structural elements except branching had an important rôle in the retention behaviour of our carboxamide derivatives.

REFERENCES

1 T. Fujita, J. Iwasa and C. Hansch, *J. Amer. Chem. Soc.*, 86 (1964) 5175.
2 C. Hansch and S. M. Anderson, *J. Org. Chem.*, 32 (1967) 2583.
3 C. B. C. Boyce and B. V. Milborow, *Nature (London)*, 208 (1965) 537.
4 G. L. Biagi, A. M. Barbaro, M. T. Gamba and M. C. Guerra, *J. Chromatogr.*, 41 (1969) 371.
5 J. M. McCall, *J. Med. Chem.*, 18 (1975) 549.
6 M. S. Mirrlees, S. J. Moulton, C. T. Murphy and P. J. Taylor, *J. Med. Chem.*, 19 (1976) 615.
7 K. Boček, *J. Chromatogr.*, 162 (1979) 209.
8 K. Valkó and A. Lopata, *J. Chromatogr.*, 252 (1982) 77.
9 D. R. Clifford and D. A. M. Watkins, *Pestic. Sci.*, 2 (1971) 41.
10 O. Papp, K. Valkó, Gy. Szász, I. Hermecz, J. Vámos, K. Hankó and Zs. Ignáth-Halász, *J. Chromatogr.*, 252 (1982) 67.
11 É. János and T. Cserháti, *Acta Phytopathol.*, in press.
12 C. Hansch and A. Leo, *Substituent Constants for Correlation Analysis in Chemistry and Biology*, Wiley, New York, 1979.
13 K. V. Mardia, J. T. Kent and J. M. Bibby, *Multivariate Analysis*, Academic Press, London, 1979.
14 E. Weber, *Einführung in die Faktoranalyse*, VEB Gustav Fischer Verlag, Jena, 1974, pp. 140–145.