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Note

Relationship between connectivity indexes of pyrido(1,2*a*)pyrimidin-4-ones and their liquid-liquid partition data obtained by gas-liquid chromatography

GY. SZÁSZ*, K. VALKÓ*, O. PAPP and I. HERMECZ

Institute for Pharmaceutical Chemistry, Semmelweis Medical University, Budapest (Hungary)

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Continuing our systematic studies^{1,2} on the relationship between the chemical structure and physico-chemical properties of pyrido(1,2*a*)pyrimidin-4-one derivatives, in this paper the relationship between partition data measured by gas-liquid chromatography (GLC) and connectivity indexes is considered. The compounds were synthesized by Mészáros and co-workers³⁻⁶. One of the investigated compounds (1j) [2,6-dimethyl-3-ethyl-4H-pyrido(1,2*a*)pyrimidine] is undergoing clinical testing under the name Chinoin 150 (ref. 3).

The connectivity index, proposed by Kier and Hall⁷, is a numerical characteristic of the number of atoms in a molecule and of the connectivity of atoms. It can be easily calculated on the basis of structural formulae, and can be correlated with several physico-chemical properties, such as heat of vaporization, boiling point, density, solubility in water and partition coefficient⁷.

The relationship between GLC retention data and connectivity indices has been studied in detail by Randić⁸ for isoalkanes and other compounds. The relationships between Kováts retention indices and connectivity indices for polycyclic hydrocarbons, ethers, esters, ketones, alcohols and other types of compounds have also been reported⁹⁻¹². According to the results, the following conclusions can be drawn: a linear relationship exists between Kováts retention indices and connectivity indices, and the lower the polarity of the stationary phase the higher is the correlation coefficient between these two indices. In other words, it seems that the relationship is significant only when the retention process is governed mainly by dispersion forces, inductive and/or orientation forces being negligible. In a previous paper¹ it was shown, that the Kováts retention indices of a compound measured on two stationary phases with different polarities, but under the same conditions, are related linearly to the liquid-liquid partition coefficient. In this work the connectivity indices were correlated with GLC partition data.

THEORETICAL

The Kováts retention index is directly proportional to the logarithm of the

* Present address: Institute of Enzymology, Biological Research Centre, Hungarian Academy of Sciences, Budapest, Hungary.

partition coefficient between the carrier gas and the stationary phase (eqn. 3), which can be derived from two well known equations (1 and 2):

$$V_N = KV_L \quad (1)$$

$$I = 100 \cdot \frac{\log V_{N_x} - \log V_{N_z}}{\log V_{N_{z+1}} - \log V_{N_z}} + 100z \quad (2)$$

$$\log K = \frac{bI}{100} + \text{constant} \quad (3)$$

where

- V_N = net retention volume;
- K = gas-liquid partition coefficient;
- V_L = volume of the stationary phase;
- I = Kováts retention index;
- V_{N_x} = net retention volume of the investigated compound;
- V_{N_z} = retention volume of an appropriate n -alkane having z carbon atoms;
- b = $\log V_{N_{z+1}} - \log V_{N_z}$, the slope of the line obtained by plotting the number of carbon atoms against the corresponding $\log V_{N_z}$ values.

There is the following relationship between retention indices measured on two stationary phases with different polarities and liquid-liquid partition coefficient related to the two stationary phase:

$$\log K_1 - \log K_2 = \log P = \frac{b_1 I_1}{100} - \frac{b_2 I_2}{100} + \text{constant} \quad (4)$$

where P is the liquid-liquid partition coefficient related to the two stationary phases. Accepting the validity of eqn. 5, suggested by Kier and Hall⁷:

$$\chi = a \log P + c \quad (5)$$

where a and c can be obtained by the least-squares method, then on the basis of eqns. 4 and 5, eqn. 6 can be written, which is essentially a regression equation with one variable only, if the GLC parameters b_1, I_1, b_2 and I_2 are known:

$$\chi = a \left(\frac{b_1 I_1}{100} - \frac{b_2 I_2}{100} \right) + \text{constant} + c \quad (6)$$

When we intend to study data from the literature, only the retention indices are often available, and in this instance we can use the following regression equation with two variables on the basis of eqn. 7:

$$b_1 I_1 - b_2 I_2 = b_1 (I_1 - I_2) + (b_1 - b_2) I_2 \quad (7)$$

$$\chi = ab_1 I_1 + a(b_1 - b_2) I_2 + a(\text{constant}) + c \quad (8)$$

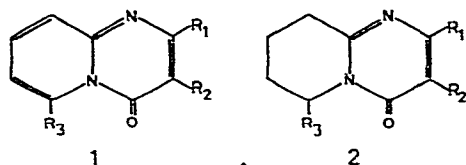
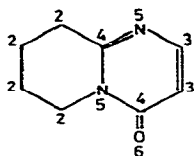


Fig. 1. General formulae of the compounds investigated.



$$\chi^1 = \frac{1}{\sqrt{5 \cdot 3}} \times \frac{2}{\sqrt{3 \cdot 3}} + \frac{1}{\sqrt{3 \cdot 4}} + \frac{2}{\sqrt{4 \cdot 6}} + \frac{1}{\sqrt{4 \cdot 5}} + \frac{1}{\sqrt{5 \cdot 2}} + \frac{1}{\sqrt{2 \cdot 2}} + \frac{1}{\sqrt{2 \cdot 2}} + \frac{1}{\sqrt{2 \cdot 2}} + \frac{1}{\sqrt{2 \cdot 4}} + \frac{1}{\sqrt{4 \cdot 5}} + \frac{2}{\sqrt{4 \cdot 5}} = 4.86$$

Fig. 2. An example of calculation of χ^1 : $\chi^1 = \text{first connectivity index}^7 = \sum (\delta_i \cdot \delta_j)^{\frac{1}{2}}$, where δ is a number assigned to each atom reflecting the number of non-hydrogen bonds connected to it.

Calculating of the statistics of the multiple regression (eqn. 8) can prove the validity of the relationship between connectivity indices and GLC partition data.

EXPERIMENTAL

The connectivity indices of 19 pyrido(1,2a)pyrimidin-4-one derivatives (general formulae in Fig. 1) were calculated. An example of the calculation is presented in Fig. 2. Retention indices of derivatives were determined on four stationary phases under the conditions given in Table I. Special care was taken to avoid adsorption by using silanized glass columns and silanized column packings. Starting data (connectivity indices and I values) are listed in Table II. On the basis of eqn. 8, calculations were carried out by the least-squares method.

RESULTS

Correlation coefficients of the simple linear relationship between χ and I are shown in Table III. Correlation coefficients of the multiple regression equations are given in Table IV.

TABLE I

CONDITIONS OF GAS CHROMATOGRAPHIC PROCEDURE

Chromatograph: Hewlett-Packard 5710 A
 Integrator: Chino In Digint 34
 Column: 6 ft. \times 1/4 in. glass silanized with DMCS
 Column packing: Chromosorb W DMCS
 Stationary phases: 5% OV-1, 5% OV-17, 5% OV-25, 5% Carbowax
 Carrier gas: nitrogen
 Carrier gas flow-rate: 30 ml/min
 Column temperature: 220°C
 Injector temperature: 250°C
 Applications of sample: Hamilton microliter syringes
 Sample size: 1 μ l
 Solvent: chloroform
 Attenuation: 128 \times 10

TABLE II
STARTING DATA (MATRIX)
For general formulae see Fig. 1.

Type	R_1	R_2	R_3	I_{OV-1}	I_{OV-17}	I_{OV-25}	$I_{Carb.}$	χ^2
1a	H	H	H	1577.4	1596.2	2124	2644.6	4.7298
1b	CH ₃	H	H	1648.2	2038.5	2189	2688.6	5.1058
1c	H	H	CH ₃	1636.4	1993.6	2150	2621.8	5.1058
1d	H	CH ₃	H	1638.1	2004.0	2161	2638.5	5.1058
1e	CH ₃	H	CH ₃	1707.3	2056.7	2214	2662.7	5.4819
1f	H	CH ₃	CH ₃	1694.2	2040.5	2198	2622.1	5.4779
1g	CH ₃	H	C ₂ H ₅	1751.0	2087.9	2245	2656.4	6.0426
1h	C ₂ H ₅	H	CH ₃	1787.9	2137.0	2292	2717.6	6.0426
1i	H	C ₂ H ₅	CH ₃	1766.0	2101.1	2255	2658.7	6.0385
1j	CH ₃	C ₂ H ₅	CH ₃	1821.3	2145.4	2297	2673.2	6.4266
1k	C ₂ H ₅	CH ₃	CH ₃	1839.2	2170.6	2325	2695.7	6.4266
1l	CH ₃	C ₃ H ₇	H	1853.5	2199.2	2358	2768.9	6.5505
1m	CH ₃	C ₃ H ₇	CH ₃	1895.6	2219.7	2374	2375.7	6.9266
2a	H	H	H	1581.4	1964.8	2128	2579.6	4.6860
2c	H	H	CH ₃	1578.2	1931.4	2081	2488.1	5.1136
2e	CH ₃	H	CH ₃	1656.1	2008.5	2159	2545.0	5.4897
2f	H	CH ₃	CH ₃	1636.3	1976.3	2121	2483.3	5.4856
2j	CH ₃	C ₂ H ₅	CH ₃	1753.1	2088.2	2241	2539.6	6.4343

DISCUSSION

From the data of Table II, it can be concluded that the lower the polarity of the stationary phase, the higher is the correlation coefficient, which is in accordance with other workers^{7,9}. The highest correlation coefficients are shown by OV stationary phases. All of them are significant at the 95% level. Correlation coefficients of the multiple regression equations are not less than 0.98 when any pair of stationary phases are considered. The larger the difference between polarity of the considered stationary phases, the higher is the correlation coefficient, although the differences are not significant. These results are in agreement with Millership and Woolson's results¹³, although they did not give a theoretical explanation.

TABLE III
CORRELATION COEFFICIENT BETWEEN CONNECTIVITY INDEX AND GLC DATA

GLC data	Correlation coefficient*
I_{OV-1}	0.97001
I_{OV-17}	0.94120
I_{OV-25}	0.92771
$I_{Carb.}$	0.53259
$\Delta I_{Carb.-OV-1}$	-0.81964
$\Delta I_{Carb.-OV-17}$	-0.76569
$\Delta I_{Carb.-OV-25}$	-0.77222
$\Delta I_{OV-25-OV-1}$	-0.85535
$\Delta I_{OV-17-OV-1}$	-0.87475

* Significant at the 95% level.

TABLE IV
MULTIVARIANT REGRESSION EQUATIONS AND THEIR STATISTICS

<i>I</i>	<i>AI</i>	$\chi^2 - aI_1 + bAI + c$			<i>r</i> *	Standard error of the estimate
		<i>a</i>	<i>b</i>	<i>c</i>		
OV-1	OV-17 – OV-1	0.0052	–0.0101	0.3164	0.9834	0.1489
OV-1	OV-25 – OV-1	0.0053	–0.0090	1.2565	0.9865	0.1341
OV-1	Carb. – OV-1	0.0053	–0.0029	–0.7902	0.9931	0.0958
OV-17	Carb. – OV-17	0.0060	–0.0046	–4.0471	0.9903	0.1137
Carb.	Carb. – OV-25	0.0059	–0.0113	–5.1267	0.9883	0.1248

* *r* = correlation coefficient.

In conclusion, the theoretical relationships of χ versus log *P* values and of log *P* versus *AI* and *I* values are also proved by the experimental data. A linear relationship has been found between log *P* (water–1-octanol) and the GLC partition data of these compounds, but the relationship was significant only when the saturated and unsaturated compounds were considered separately. The necessity for separation can be explained as follows: saturated and unsaturated compounds may have essentially different solvations in the two partition systems (water–1-octanol and two stationary phases). On studying the relationship between connectivity indices and GLC retention data after separating saturated from unsaturated compounds, the correlation coefficients did not change significantly. From the relationship between log *P* values (water–1-octanol) and χ values, separation of saturated compounds seems to be necessary in order to obtain a significant regression equation. This leads to the conclusion that relationships between χ and GLC partition data are more general than the relationship between χ and log *P* (water–1-octanol).

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