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Note

Assessment of quantitative relationships between Kováts' retention index and chemical structure: prediction for pyrido-pyrimidine derivatives

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Quantitative relationships between chemical structure and gas chromatographic behaviour of organic compounds have been discussed in several papers[1–12]. Most of these reports concerned relatively simple compounds, such as alkanes, alkenes and aromatic hydrocarbons. The present paper investigates similar relationships for a heteroaromatic group of compounds, pyrido-pyrimidine derivatives, where specific interactions between the ring and heteroatoms may occur (Fig. 1). Pyrido-pyrimidine derivatives, prepared by Mészáros and Hermecz[13], show strong analgesic activities, and one of them is marketed as Probonz®. The results of their gas chromatographic (GC) investigations have already been published[14], and even the relationships between structure and retention indices have been studied.

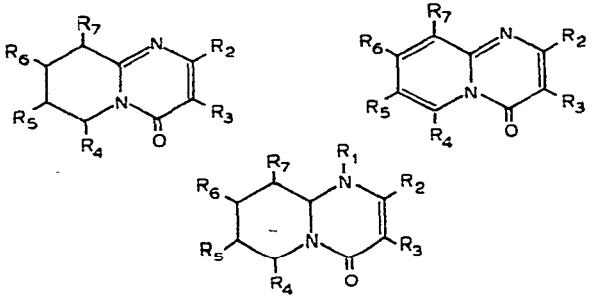

Fig. 1. General structures of investigated compounds. R_1 = H, CH_3, C_2H_5, $COCH_3$, C_4H_9; R_2 = H, CH_3, C_2H_5, C_3H_7; R_3 = CH_3, C_2H_5, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, COO-*tert.*-butyl, $OCH(CH_3)_2$, $CONH_2$, C_6H_5, CN; R_4 = H, CH_3; R_5 = H, CH_3; R_6 = H, CH_3; R_7 = H.

The starting point of our investigations was the assumption that models of the quantitative structure–activity relationship (QSAR) are also applicable to quantitative structure–retention index relationship (QSRR) studies. According to the simplest

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models of Free and Wilson[15] and BEL–Free[16], the biological activity (or in our case, the retention index) can be considered as a sum of increments assigned to the substituents of the derivatives within a congeneric series[15,16].

METHODS

The model proposed by Free and Wilson[15] for QSAR can be adapted for retention indices as follows.

The measured retention indices, I, for all molecules are regarded as the sum of the index increments of the structural part, Q, common to each compound and of the substituents, x_z, attached at z positions in Q. Let us denote by j_z the serial number of an arbitrary substituent in the position z. Then, the measured retention index, I, of a compound can be expressed as follows

$$I = i_0 + \sum_{z=1}^{n} \sum_{j_z=1}^{m} i_{j_z} x_{j_z} \tag{1}$$

where n is the number of substitution positions, m is the number of substituents in position z, x_{j_z} is a structural parameter, assuming a value of 0 or 1 depending on whether substituent j_z is absent or present in the molecule investigated, i_0 is the increment of the skeleton, *i.e.*, Q, and i_{j_z} is the retention index increment. Our purpose is to calculate the i_0 and i_{j_z} values.

For the values of i_{j_z} the following relationship is assumed:

$$\sum_{j_z=1}^{m} i_{j_z} = 0 \tag{2}$$

If q molecules are investigated, q equations of the above type can be set up, according to the model. Since the number of equations is greater than the number of variables, the values of i_{j_z} in eqn. 1 can be calculated by regression analysis. Eqn. 1 can then be applied for prediction of retention indices for new compounds.

The results can more easily be interpreted if the index increments of the substituents are related to the unsubstituted case, *i.e.*, to the atom, by subtraction. The δi_{j_z} increments can be obtained, for substituent w and substituent position z, as follows:

$$\delta i_{wz} = i_{wz} - i_{Hz} \tag{3}$$

($i_{H_z} = i$ value with a H atom in position z).

The BEL–Free method is a specific procedure for improving the predictive ability of the Free–Wilson method. It is based essentially on steptwise regression technique, omitting variables which disturb the prediction. First, eqn. 1 is solved as in the Free–Wilson method, but, in our case, without the restriction of eqn. 2. The retention index of the compound selected for prediction (and the corresponding confidence interval) is also estimated. Then the equation is refined by a trial-and-error procedure, variables which increase the prediction confidence interval being gradually eliminated. This process is continued until a minimal confidence interval is found by removing variables or re-entering previously eliminated variables.

The final equation is used for the prediction of the retention index for the selected compound. Since this process eliminates the unnecesary variables from the Free–Wilson equation in "backward" steps, it is called backward elimination from the Free–Wilson equation (BEL–Free method).

EXPERIMENTAL

The Free–Wilson and BEL-Free calculations were carried out by means of our interactive program system, written in FORTRAN, on the Siemens 7755 computer at the Institute for Coordination of Computer Techniques, Budapest. The GC conditions are shown in Table I.

TABLE I

GAS CHROMATOGRAPHIC CONDITIONS

Chromatograph	Hewlett-Packard 5710A, Chinoin Digint 21 Integrator
Column	6 ft. × 1/4 in., glass
packing	Chromosorb W CMDS
stationary phases	3% OV-17, 3% OV-1
Carrier gas	nitrogen, 30 ml/min
Temperatures	
column	240°C
detector	300°C
injector	300°C
Sample	1 μl, applied with Hamilton syringes
solvent	chloroform
Attenuator	128 × 10

RESULTS AND DISCUSSION

Table II contains the statistics of the calculations. Table III compares the calculated and measured retention indices for the two new molecules. The differences between the measured and calculated values can be considered as acceptable, bearing in mind that the compounds are fairly polar and contain three heteroatoms and regarding the conditions of measurement.

TABLE II

STATISTICS OF CALCULATIONS

	OV-1	*OV-17*
Multiple correlation coefficient, R	0.9921	0.9965
Lower 95% confidence interval for R	0.9784	0.9905
R^2	0.9842	0.9931
Amount of explained variance	0.9703	0.9876
Significance of regression, F ratio (%)	0.0000	0.0000
Standard error of the dependent variable	307.0688	351.4068
Standard error of the estimate	52.9056	39.0522

TABLE III

MEASURED AND CALCULATED INDEX VALUES OF THE TWO NEW COMPOUNDS

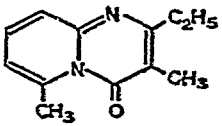
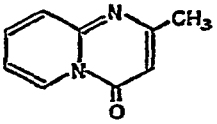
Compound	*OV-1*		*OV-17*	
	Meas.	*Calc.*	*Meas.*	*Calc.*
	1874	1886	2170	2162
	1694	1698	2048	2060

TABLE IV

INDEX INCREMENTS OF SUBSTITUENTS ON OV-1 AND OV-17 STATIONARY PHASES

Substituent		*Index increment*	
		OV-1	*OV-17*
R_1	—	−58.36	−60.25
	Ethyl	224.20	254.89
	n-Butyl	375.20	362.89
	Methyl	295.82	298.01
	Acetyl	88.92	114.98
R_2	Methyl	45.89	−4.47
	n-Propyl	131.24	96.21
	H	−19.97	−6.25
	Ethyl	158.49	88.76
R_3	H	−388.47	−394.41
	Ethyl	−212.21	−278.86
	Phenyl	336.97	349.51
	$CONH_2$	223.89	255.35
	CO-Ethyl	167.66	186.11
	CO-*n*-propyl	198.46	245.49
	CO-*n*-butyl	295.46	342.49
	Methyl	−332.03	−393.49
	CN	26.46	40.49
	CO-*tert.*-butyl	127.46	150.49
R_4	Methyl	4.34	2.10
	H	−12.14	−5.74
	Axial methyl	−107.27	−44.02
	Ethyl	120.94	49.34
R_5	H	−1.19	−1.43
	Methyl	38.09	45.79
R_6	H	−4.63	−4.63
	Methyl	71.69	71.82
R_7	H	−20.14	−20.88
		46.33	48.01
Skeleton		2073.48	2483.85

The relative contributions of the substituents to the retention indices, *i.e.* the δi_{Jz} values of eqn. 3, are listed in Table IV. Since δi_{Jz} values are analogous to δI values (obtained by simple subtraction), the retention index contributions of Table IV can formally be compared with δI values published in our previous paper[14]. The results indicate that the mathematical methods used for the investigation of chemical structure–biological activity relationships can be applied with acceptable accuracy for the prediction of retention indices.

The Free–Wilson and BEL–Free methods seem to be suitable for the investigation of structure–retention index relationships and for the prediction of the retention indices of new compounds after measurements on a few members in a congeneric series.

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