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Note

Relationships between molecular connectivity indices, partition coefficients and chromatographic parameters

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Good correlations have been found between partition coefficients and molecular connectivity indices¹ for a large number of nitrogen-bridged compounds². Since partitioning and volatility, *i.e.*, boiling point³, are properties governing liquid chromatography and gas chromatography (GC) respectively, it seemed reasonable to examine the relationship between chromatographic parameters and molecular connectivity indices. During the last few years, relationships between molecular connectivity and thin-layer chromatographic (TLC)⁴, high-performance liquid chromatographic⁵ and GC⁶⁻⁹ parameters have been reported, however, these experiments were performed before the complete development of molecular connectivity. Kier and Hall¹⁰, referring to the gas-liquid chromatographic (GLC) data of Michotte and Massart⁶, found a significantly better correlation using regression equations with two variables instead of one. In recent studies, Szász and co-workers^{11,12} pointed out that the differences in GC index values measured on two stationary phases, $I_1 - I_2 = \Delta I$, were linearly correlated with the *n*-octanol-water partition coefficient and this relationship could be interpreted theoretically¹¹. Using molecular connectivity, the GC retention could be described by a regression equation with two retention variables¹²:

$${}^1\chi = aI_1 + b\Delta I + C$$

The present study was undertaken to determine whether molecular connectivity can be employed quantitatively to describe liquid-liquid partitioning, GC and TLC retention of a set of nitrogen-bridged heterocycles.

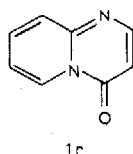
EXPERIMENTAL

Compounds

A series of pyrido[2,1,*a*]pyrimidine and pyrido[2,1,*b*]quinazoline derivatives were used, the chemical structures of which are shown in Tables I-III. Their synthesis has been reported elsewhere¹³. All of the substances were tested for purity by TLC and melting point determination.

TABLE I

CHEMICAL STRUCTURES, CHROMATOGRAPHIC PARAMETERS AND PARTITION COEFFICIENTS OF COMPOUNDS WITH DIFFERENT RING STRUCTURES



Δ indicates the position of the π -bonds.

No.	n_1	n_2	Δ	I	R_F	R_M	$\log P$
1a	1	1	—	1870	0.365	0.240	0.220
b	1	2	—	1973	0.251	0.476	0.805
c	1	3	—	2050	0.171	0.686	1.239
d	1	4	—	2117	0.122	0.856	1.277
e	2	1	—	1961	0.284	0.401	0.707
f	3	1	—	2003	0.176	0.672	1.251
g	1	2	10, 12	1958	0.208	0.582	0.967
h	2	1	6, 8	1968	0.204	0.591	1.188
i	2	2	—	2059	0.176	0.671	1.172
j	2	2	6, 8	2064	0.114	0.890	1.633
k	2	2	6, 8, 10, 13	—	0.077	1.076	2.005
l	3	2	—	2102	0.116	0.884	1.729
m	3	2	12, 14	2101	0.084	1.040	1.977
n	3	3	—	2162	0.075	1.091	2.178
o	4	4	—	2300	0.038	1.400	2.720
p	4	2	—	2165	0.086	1.029	—
r	2	—	6, 8	1577	0.426	0.129	0.203

Chromatography

TLC was carried out by using Desaga "Grundausrüstung" apparatus and Kieselgel-F₂₅₄ silanisiert (Merck) plates. The sample solutions were applied by a Camag "Autoliner". The chromatograms were developed in methanol-water (70:30) as mobile phase; saturation time 60 min. The spots were assigned under UV light, $\lambda = 254$ nm. The R_M values were calculated from the mean of the R_F values from six different developments. GC was carried out using conditions previously described¹².

Connectivity indices

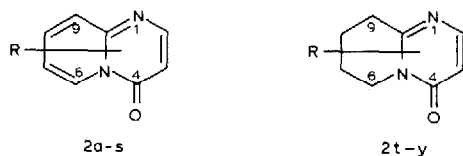
Molecular connectivity calculations are described elsewhere^{1,2}. The following indices were stored in a computer file for further analysis: $^0\chi$, $^1\chi$, $^2\chi$; path indices, $^3\chi_p$ through $^6\chi_p$, $^3\chi_c$, $^4\chi_{pc}$, $^5\chi_{ch}$, $^6\chi_{ch}$; corresponding valence indices for a total of 22 variables. With a standard linear regression computer program* all possible one- and two-variable equations of significant correlations were computed. The equations having the best statistical data were applied for the predictions of chromatographic parameters.

* The computer program CFUNC is available from Dr. Lowell H. Hall (Department of Chemistry, Eastern Nazarene College, Quincy, MA 02170, U.S.A.). It is written in FORTAN IV and is available on cards at a small charge.

TABLE II

CHEMICAL STRUCTURES, CHROMATOGRAPHIC PARAMETERS AND PARTITION COEFFICIENTS OF COMPOUNDS WITH DIFFERENT ALKYL SUBSTITUENTS

Me = Methyl; Et = ethyl; Pr = propyl.



No.	R	I^{OV-1}	R_F	R_M	$\log P$
2a	2-Me	1648	0.344	0.281	0.572
b	3-Me	1638	0.311	0.346	0.771
c	6-Me	1636	0.279	0.412	0.736
d	7-Me	1696	0.311	0.345	0.609
e	8-Me	1703	0.316	0.336	0.562
f	9-Me	1647	0.316	0.335	0.794
g	2,6-Me ₂	1707	0.216	0.561	1.053
h	3,6-Me ₂	1694	0.178	0.666	1.265
i	2,3-Me ₂	1227	0.226	0.536	1.003
j	2-Et,6-Me	1788	0.127	0.837	1.592
k	2-Me,6-Et	1751	0.121	0.861	1.625
l	3-Et,6-Me	1766	0.108	0.918	1.793
m	2-Me,3-Et,6-Me	1821	0.086	1.026	1.856
n	2-Me,3-Pr	1854	0.081	1.054	1.752
o	2-Et,3-Me,6-Me	1839	0.077	1.082	1.867
p	2-Me,3-Pr,6-Me	1896	0.035	1.443	2.221
r	2-Pr,3-Et,6-Me	1948	0.022	1.658	2.375
s	2-Me,3-Et,6-Me,8-Me	1936	0.047	1.306	1.729
t	3-Me	1637	0.350	0.268	0.404
u	6-Me	1578	0.375	0.222	0.299
v	2,3-Me ₂	1726	0.292	0.385	0.597
w	3,6-Me ₂	1636	0.255	0.465	0.822
x	2,6-Me ₂	1656	0.316	0.336	0.688
y	2-Me,3-Et,6-Me	1753	0.139	0.793	1.428

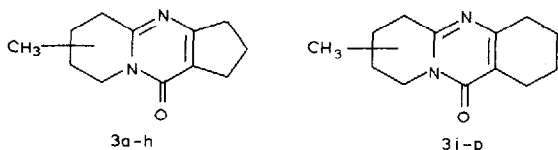
RESULTS AND DISCUSSION

The observed chromatographic data and $\log P$ values² of the compounds are shown in Tables I-III. The equations of regression with the highest correlation coefficients are shown in Table IV. Table V shows the number of such equations providing correlation coefficients higher than 0.9 and the lowest and highest coefficients in the range 0.9-1.0 are included. The correlation between chromatographic parameters and molecular connectivity indices is better than in the case of the partition coefficient² particularly if the differences in the structures of the model substances are considered.

The GC Kováts indices for the 44 compounds fall in the range of 1600-2500. The correlation of these indices is significantly higher with the simple path indices, ${}^m\chi_p$ (Table V), than with the valence indices, ${}^m\chi_p^v$ (Table V). From the 74 equations

TABLE III

CHEMICAL STRUCTURES, CHROMATOGRAPHIC PARAMETERS AND PARTITION COEFFICIENTS OF COMPOUNDS WITH METHYL SUBSTITUENTS



No.	CH ₃	Δ	I^{OV-1}	R_F	R_M	$\log P$
3a	6	6, 8	2020	0.116	0.881	1.773
b	7	6, 8	2084	0.127	0.836	1.614
c	8	6, 8	2089	0.130	0.827	1.648
d	9	6, 8	2023	0.123	0.854	1.711
e	6	—	1953	0.186	0.641	1.207
f	7	—	1998	0.197	0.611	1.193
g	8	—	2000	0.203	0.595	1.205
h	9	—	1978	0.204	0.591	1.206
i	6	6, 8	2120	0.061	1.187	1.907
j	7	6, 8	2189	0.066	1.148	2.068
k	8	6, 8	2190	0.071	1.120	1.860
l	9	6, 8	2123	0.046	1.313	2.441
m	6	—	2045	0.110	0.910	1.674
n	7	—	2095	0.114	0.892	1.701
o	8	—	2097	0.117	0.877	1.674
p	9	—	2071	0.115	0.886	1.759

with a correlation coefficient higher than 0.9, only two were found in which one of the variables was a valence index. Even in these cases the correlation was the poorest (0.902, 0.905). On the contrary, the R_M values and the $\log P$ values are correlated better with equations which involve valence indices (Table V).

By definition, simple connectivity indices are generated as a sum of the σ -bond descriptions of the given fragment types. In order to calculate the valence indices, σ - and π -bonds as well as lone pairs of electrons have to be taken into account¹. As predicted, it is observed that (chromatographic) parameters originating from a (chromatographic) system with polar phase(s), R_M , $\log P$, correlate best with connectivity indices encoding the polar moieties of the molecules, ${}^m\chi^v$. Further, the Kováts indices derived from the interaction with the apolar OV-1 phase are correlated better with

TABLE IV

EQUATIONS OF REGRESSION AND STATISTICAL DATA

y	Equations*			Statistics			
	${}^a x_1$	${}^b x_2$	c	n	s	F	r
R_M	$-0.46^0\chi^v$	$0.77^0\chi$	-1.32	57	0.066	750.5	0.983
I^{OV-1}	$150^6\chi_p$	$140^5\chi_p$	1000	56	36.44	735.0	0.982
$\log P$	$-0.74^4\chi_p^v$	$1.10^1\chi$	-4.74	57	0.167	336	0.962

* Equations, $y = ax_1 + bx_2 + c$, with the highest correlation coefficients (see also Table V).

TABLE V
THE SELECTIVITY OF CORRELATION

y	Number of equations*			
	Total	${}^m\chi$, ${}^n\chi$	${}^m\chi^v$, ${}^n\chi^v$	${}^m\chi^v$, ${}^n\chi$
R_M	9	—	—	9 (0.983)
I	74	72 (0.982)	—	2 (0.905)
log P	10	1 (0.907)	—	9 (0.962)

* $y = ax_1 + bx_2 + c$; $r > 0.9$. The highest correlation coefficients are given in parentheses.

the simple connectivity indices, ${}^m\chi$. These findings provide evidence for the ability of molecular connectivity to characterize numerically the chemical structure of organic compounds.

The good correlation between connectivity indices and chromatographic as well as partitioning parameters offers the possibility to predict chromatographic behaviour and partitioning properties of newly synthesized congeners of a given type of compound. For this purpose, within the structural types investigated, the index pairs ${}^0\chi_p^v$ and ${}^0\chi$ (TLC), ${}^5\chi_p$ and ${}^6\chi_p$ (GLC), ${}^4\chi_p^v$ and ${}^1\chi$ (partitioning) were sufficient to describe structure in the development of the corresponding equations (Table IV).

The quality of the correlations of these physical properties with molecular connectivity reveals the presence of important structural information encoded in the indices, and also suggests a potential for the prediction of approximate values of these properties.

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