Journal of Chromatography, 361 (1986) 63–69
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

CHROM. 18 619

QUANTUM CHEMICAL PARAMETERS IN CORRELATION ANALYSIS OF GAS–LIQUID CHROMATOGRAPHIC RETENTION INDICES OF AMINES

II*. TOPOLOGICAL ELECTRONIC INDEX

KRZYSZTOF OŚMIAŁOWSKI, JAN HALKIEWICZ and ROMAN KALISZAN*
Faculty of Pharmacy, Medical Academy, K. Marksa 107, Gdańsk 80-416 (Poland)
(Received February 11th, 1986)

SUMMARY

Quantitative structure–retention relationships (QSRRs) have been studied for a diverse group of aliphatic and heterocyclic amines subjected to gas–liquid chromatography on three stationary phases of different polarities. As a numerical descriptor of the ability of the solutes to take part in non-specific interactions with stationary phase, a quantum-chemically calculated (by the CNDO/2 method) total energy, E_T, is employed. To characterize quantitatively the differences in specific or polar properties of the solutes, a new topological electronic index, T^E, is proposed. This index is calculated by summation of the absolute differences in electronic excess charges on all atomic pairs in a given molecule, divided by the squares of the respective interatomic distances. The resulting two-parameter QSRR equations involving E_T and T^E are highly statistically significant for retention data determined on either non-polar or polar stationary phases. The index T^E is a better descriptor of molecular polarity than other measures previously reported.

INTRODUCTION

Recently, for studies of quantitative structure–retention relationships (QSRRs), we have proposed a quantum-chemically derived submolecular parameter, Δ, representing the largest difference in atomic charges in a given solute molecule[1–3]. This parameter has been designed as a non-empirical molecular descriptor of the ability of a particular solute to undergo the so-called polar or specific interactions with the chromatographic phases. When used together with the "bulky" non-specific molecular descriptors in a two-parameter regression equation, it improved the quality of structure–retention correlations as compared to other polarity descriptors, *e.g.*, total dipole moments[4,5]. Such correlations were good but only in the case of non-polar stationary phases.

* For Part I see ref. 1.

0021-9673/86/$03.50

THEORETICAL

Highly statistically significant regression equations were reported previously[1–3] which related the retention data for diverse sets of solutes to the CNDO/2 calculated quantum-chemical indices, namely the total energy, E_T, and the polarity descriptor, Δ. The retention data, which have successfully been correlated with both E_T and Δ, were obtained by gas–liquid chromatography (GLC) of a set of aliphatic and heterocyclic amines[1] as well as by high-performance liquid chromatography (HPLC) of a set of benzene derivatives with different polar functional groups[2,3]. In the case of HPLC, the reversed-phase technique was employed, whereas for GLC retention data, satisfactory correlations were found only when the non-polar methyl silicone (OV-101) stationary phase was used. Attempts to correlate with E_T and Δ the Kováts indices determined on polar GLC phases, methyl phenyl cyanopropyl silicone (OV-225) and neopentyl glycol adipate (NGA), were unsuccessful.

It may be assumed that, in the case of more polar phases, the specific interactions with solute molecules become more important for retention. From our studies as well as those of others[6] it may be concluded that E_T well characterizes the ability of a solute to undergo non-specific interactions with chromatographic phases. Thus, in the case of closely congeneric solutes chromatographed on non-polar phases, E_T alone may suffice for the prediction of retention. However, for the description of retention data determined on polar phases, in addition to E_T, another parameter is required which reflects the specific chemical properties of the solutes. The significance of that specific parameter is expected to increase with increasing polarity of the chromatographic phase and with the structural diversity of the solutes.

The quantitation of the specific or polar properties of a given solute is the most difficult problem in attempts to relate structure to retention. Following the early suggestions by Kováts, the dipole moments of solutes were used as polarity measures, either determined electrostatically[5,7–9] or calculated quantum chemically[5,10]. The reported QSRR equations obtained by means of total dipole moments and "bulk" parameters are not considered satisfactory, however.

Bearing in mind the failures when employing total dipole moments in QSRR studies, we came to the conclusion that a local, submolecular polarity of a certain structural fragment of the solute was decisive for polar interactions with chromatographic phases, rather than the overall dipole moment. Thus we turned our attention to the quantum-chemically calculated distribution of electronic excess charges on individual atoms in a solute molecule. The maximum difference in electronic excess charge for two atoms appeared to be a statistically significant descriptor of the retention of diverse sets of solutes in GLC on non-polar phases[1] and in HPLC on chemically bonded hydrocarbonaceous phases[2,3]. Still, however, we could not get satisfactory QSRR equations in the case of polar GLC phases. We have analysed further the electronic charge distribution in solute molecules, believing that information may be extracted from it which reflects in a numerical form the specific/polar properties of the solutes. Impressed with the numerous successful applications of various topological indices in quantitative structure–property relationships[11], we attempted to express topological information concerning the solute molecule in terms of the distribution of the electronic charge on individual atoms and interatomic distances.

EXPERIMENTAL

Chromatography

The details of the procedure applied were as reported previously[1] for the OV-101 phase. The only difference is that here the solutes were chromatographed on the polar phases OV-225 and NGA, purchased from Applied Science. The Kováts retention indices calculated are given in Table I for all the three phases studied.

Topological electronic index calculations

At first the calculations of the electronic charge distribution in solute molecules were done by the CNDO/2 molecular orbital method. The program[12,13] was adapted for the RIAD computer. Standard values of the bond lengths and angles were assumed[14].

The topological electronic index, T^E, proposed here has been calculated as follows. For individual atoms of the solute, cartesian coordinates are determined assuming the same geometry as applied for the CNDO calculations. To each individual vertex atom a number, q, is assigned, equal its electronic excess charge. Next, the distances, $r_{i,j}$, between each pair of vertices are calculated. For every pair of vertices the absolute value of the excess charge difference is divided by the square of the respective interatomic distance. The resulting numbers are summed for all the possible atomic pairs in the molecule:

$$T^E = \sum_{(i,j)} \frac{|q_i - q_j|}{r_{i,j}^2}; \qquad i \neq j \tag{1}$$

The procedure applied is illustrated in Fig. 1. All the calculations of T^E are easily accomplished by means of a small personal computer (the details may be obtained on request from the authors).

RESULTS AND DISCUSSION

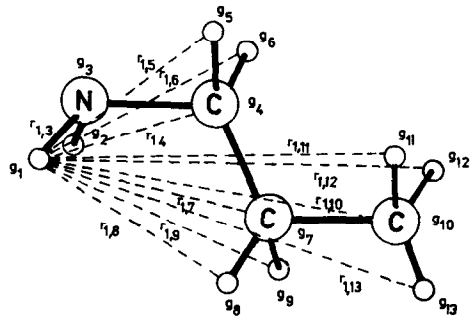
In the previous communication[1] we reported for the Kováts retention indices of amines, normalized to 130°C, $I_{OV\text{-}101}$, a two-parameter regression equation with the total energy, E_T, and the polarity parameter, Δ, as independent variables. The statistical value of that equation derived for $n = 22$ solutes was characterized by the multiple correlation coefficient, $R = 0.93$, the standard deviation from the regression, $s = 67$, and the significance level, $p < 0.0001$.

Here we recalculated the QSRR for retention data determined on the OV-101 phase (Table I), replacing the polarity parameter, Δ, by the topological electronic index, T^E. The resulting equation has the form:

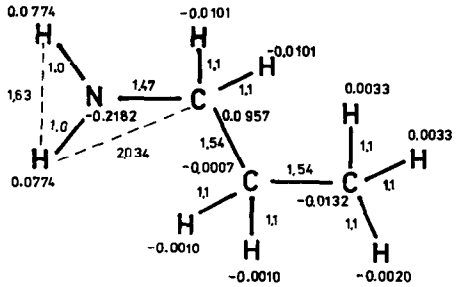
$$I_{OV\text{-}101} = (160.6 \pm 95.8) - (13.39 \pm 1.38)E_T - (149.6 \pm 35.7)T^E \tag{2}$$
$$n = 22,\ s = 35.29,\ R = 0.9810$$

Eqn. 2 is significant at the $p = 10^{-15}$ significance level, whereas the p values for the variables E_T and T^E are 0.0002 and 0.0024 respectively.

The one-parameter equation relating $I_{OV\text{-}101}$ to E_T is significant at the $p =$



$$T^E = \sum_{(i,j)} \frac{|g_i - g_j|}{r_{ij}^2} \quad ; \; i \neq j$$



$$T^E = \frac{[0.0774 - 0.0774]}{1.63^2} + \frac{[0.0774 - (-0.2182)]}{1.0^2} + \frac{[0.0774 - 0.0957]}{2.034^2} + \cdots = 1.532$$

Fig. 1. Determination of the topological electronic index, T^E.

$2 \cdot 10^{-7}$ level and the correlation coefficient is $R = 0.8954$. The similar equation relating $I_{OV\text{-}101}$ to T^E is of low statistical significance: $p = 0.39$, $R = 0.3064$. In spite of that, the introduction of T^E into a regression of the type 2 is fully justified statistically.

As pointed out already, the previous attempts[1] to correlate Kováts retention indices for the same group of solutes, but determined on the polar phases NGA and OV-225, were unsuccessful. Two-parameter equation relating I_{NGA} or $I_{OV\text{-}225}$ to E_T and Δ were of low statistical value. This is because the importance of the E_T term for retention on the polar phases is decreased compared to OV-101. At the same time the parameter Δ is unable to reflect quantitatively the increasing importance of specific, polar solute–stationary phase interactions.

Using the topological electronic index, T^E, instead of Δ, along with E_T, in two-parameter regression analysis, we obtained the following statistically valid equations:

TABLE I

KOVÁTS RETENTION INDICES NORMALIZED TO 130°C AND DETERMINED ON THREE STATIONARY PHASES, QUANTUM CHEMICAL INDICES AND TOPOLOGICAL ELECTRONIC INDICES OF THE AMINES STUDIED

No.	*Solute*	*Retention indices**			*Total energy,* E_T *(a.u.)***	*Energy of HOMO* E_{HOMO} *(a.u.)*	*Topological electronic index,* T^E
		$I_{OV\text{-}101}$	$I_{OV\text{-}225}$	I_{NGA}			
1	Allylamine	463	409	548	−38.100	−0.4964	1.5866
2	*n*-Butylamine	553	588	800	−48.597	−0.4843	1.6746
3	*sec.*-Butylamine	471	575	729	−48.596	−0.4847	1.9182
4	*tert.*-Butylamine	501	574	600	−48.593	−0.4895	2.1516
5	*n*-Pentylamine	635	805	877	−57.381	−0.4767	1.7722
6	*n*-Propylamine	466	457	521	−39.917	−0.4936	1.5321
7	Isopentylamine	615	715	883	−57.272	−0.4793	1.9085
8	Isopropylamine	469	494	521	−39.921	−0.5048	1.8751
9	Diallylamine	660	797	885	−62.519	−0.4686	2.1312
10	Di-*n*-propylamine	694	753	906	−65.964	−0.4655	2.1720
11	Diethylamine	527	467	600	−48.602	−0.4767	2.1247
12	Methyl-*n*-pentylamine	706	819	961	−65.963	−0.4626	1.9765
13	Methyl-*n*-hexylamine	871	875	1032	−74.583	−0.4590	2.0512
14	Methyl-*n*-butylamine	630	616	816	−57.279	−0.4670	1.8866
15	Di-*n*-butylamine	943	1020	1069	−83.242	−0.4595	2.4639
16	Pyrazine	696	940	1115	−54.621	−0.4564	1.0181
17	Pyridine	692	867	1086	−50.866	−0.4707	0.9799
18	*β*-Picoline	841	1059	1156	−59.554	−0.4652	0.9722
19	3-Chloropyridine	890	1134	1280	−66.356	−0.4757	1.1006
20	Chloropyrazine	895	1180	1365	−70.038	−0.4658	1.2350
21	2-Chloropyridine	870	1198	1455	−66.245	−0.4737	1.1321
22	4-Cyanopyridine	955	1640	1675	−68.643	−0.4809	1.3142

* Retention indices extrapolated to 130°C.
** a.u. = Atomic unit.

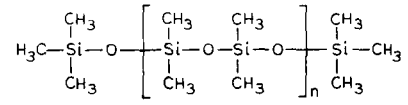
$$I_{NGA} = (456.5 \pm 290.5) - (20.85 \pm 4.17)E_T - (424.5 \pm 108.2)T^E \quad (3)$$
$$n = 22,\ s = 107.0,\ R = 0.9484$$

$$I_{OV\text{-}225} = (270.4 \pm 359.2) - (20.19 \pm 5.15)E_T - (369.5 \pm 133.7)T^E \quad (4)$$
$$n = 22,\ s = 132.2,\ R = 0.9145$$

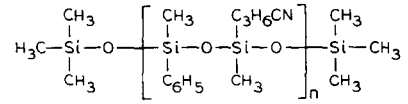
Eqn. 3 is significant at $p = 3.3 \cdot 10^{-9}$ and eqn. 4 at $p = 2.8 \cdot 10^{-7}$. The p values for the variables E_T and T^E in eqn. 3 are 0.0015 and 0.0029, respectively, and 0.0030 and 0.0070 in eqn. 4.

The one-parameter equation relating I_{NGA} to E_T is significant at the $p = 0.0009$ level, correlation coefficient $R = 0.7295$. For the OV-225 phase, E_T is significant at $p = 0.0007$ and $R = 0.7295$.

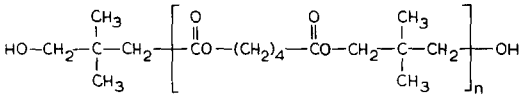
One-parameter equations relating Kováts indices determined on the polar phases NGA and OV-225 to the index T^E are of higher statistical significance than in the case of the non-polar phase OV-101. For the equation $I_{NGA} = f(T^E)$ the statistics are $p = 0.04$ and $R = 0.5338$, whereas for the relationship $I_{OV\text{-}225} = f(T^E)$ the corresponding values are $p = 0.09$ and $R = 0.4733$.



Methylsilicone: OV-101



Methyl Phenyl Cyanopropyl Silicone: OV-225



Neopentyl Glycol Adipate: NGA

Fig. 2. The chemical formulae of the stationary phases employed for the retention index determinations.

The parameters E_T and T^E are nearly completely orthogonal, *i.e.*, for their intercorrelation, $R = 0.1031$. For that reason the two variables are ideally suitable for multiple regression analysis. Another quantum-chemical index which could be very informative for structure–retention studies is the energy of the highest occupied molecular orbital of the solute, E_{HOMO} (Table I). E_{HOMO} is often related to the ability of the solutes to form charge-transfer complexes with chromatographic phases[6,15]. Unfortunately, for the present solutes there is a high intercorrelation between the quantum-chemical indices E_T and E_{HOMO}, namely $R = 0.7665$. Such a situation precludes, for statistical reasons, the unequivocal discussion of QSRR equation comprising both E_T and E_{HOMO}. Anyway, we should note perhaps that E_{HOMO} introduced as a third parameter into eqns. 3 and 4 resulted in an increase of the multiple correlation coefficients. This increase is very significant in the case of the OV-225 phase, *i.e.*, $R = 0.9445$ for the three-parameter equation $I_{OV\text{-}225} = f(E_T, T^E, E_{HOMO})$ and the equation is significant at the $p = 5.2 \cdot 10^{-8}$ level. One would expect marked charge-transfer interactions between the electron-acceptor OV-225 molecules (Fig. 2) and the donor amines. Such interactions should be less evident for the remaining two phases OV-101 and NGA (Fig. 2). The problem of quantitation of the charge-transfer interaction will be studied further, based on the implications of the previous[1–3] and the present work.

The topological electronic index, T^E, proposed here enables progress to be made in numerical differentiation of the polar or specific properties of the solutes. This index is calculated in such a way that it reflects (at least to some extent) differences in solute size, shape and constitution. This is so because the elemental constitution as well as the molecular shape and size undoubtedly affect the electronic charge

distribution in the molecule and the interatomic distances. Formally, the units of the topological electronic index are electron/Å^2. The available topological indices comprise some information related to interatomic distances but do not utilize the information concerning the electronic structure of the solutes. When the quantum-chemical calculations can be done routinely, the toplogical electronic indices may became more readily accessible. Most probably, the quantum-chemical data may be transformed into various topological indices of even better information value than T^E.

The QSRR equations involving non-empirical molecular descriptors, non-specific, *i.e.*, total energy, E_T, and polar, *i.e.*, topological electronic index, T^E, are still lacking in precision, especially in the case of diverse non-congeneric solutes chromatographed on polar phases. Certainly, neither E_T nor T^E is an ideal structural descriptor, all the more so as the CNDO/2 molecular orbital method yields only approximate data and the geometry assumed for the calculations may differ from the actual one in the chromatographic system. Nonetheless, at least for some chromatographic phase systems, interactions other than non-specific and polar interactions should be considered in deriving QSRRs *e.g.*, charge-transfer interactions.

Bearing in mind that the dynamic, reversible drug–receptor interactions resemble chromatographic processes, we expect the successful application of topological electronic indices to medicinal chemistry.

REFERENCES

1 K. Ośmiałowski, J. Halkiewicz, A. Radecki and R. Kaliszan, *J. Chromatogr.*, 346 (1985) 53.
2 R. Kaliszan, K. Ośmiałowski, S. A. Tomellini, S.-H. Hsu, S. D. Fazio and R. A. Hartwick, *Chromatographia*, 20 (1985) 705.
3 R. Kaliszan, K. Ośmiałowski, S. A. Tomellini, S.-H. Hsu, S. D. Fazio and R. A. Hartwick, *J. Chromatogr.*, 352 (1986) 141.
4 R. Kaliszan, *Chromatographia*, 12 (1979) 171.
5 R. Kaliszan and H.-D- Höltje, *J. Chromatogr.*, 234 (1982) 303.
6 F. Saura-Calixto, A. Garcia-Raso and M. A. Raso, *J. Chromatogr. Sci.*, 22 (1984) 22.
7 R. P. W. Scott, *J. Chromatogr.*, 122 (1976) 35.
8 B. L. Karger, L. R. Snyder and C. Eon, *J. Chromatogr.*, 125 (1976) 71.
9 M. Gassiot-Matas and G. Firpo-Pamies, *J. Chromatogr.*, 187 (1980) 1.
10 L. Buydens and D. L. Massart, *Anal. Chem.*, 55 (1983) 738.
11 A. Sabljić and N. Trinajstić, *Acta Pharm. Jugosl.*, 31 (1981) 189.
12 J. A. Pople and G. A. Segal, *J. Chem. Phys.*, 44 (1966) 3289.
13 P. A. Dobosh, *Quantum Chemistry Program Exchange*, 11 (1969) 141.
14 *Tables of Interatomic Distances and Configurations in Molecules and Ions, Suppl. 1956–1959*, The Chemical Society, London, 1965.
15 L. Nondek and R. Ponec, *J. Chromatogr.*, 294 (1984) 175.