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GENERAL INDEX OF MOLECULAR COMPLEXITY AND CHROMATOGRAPHIC RETENTION DATA

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SUMMARY

The general index of molecular complexity (GIMC) is presented in relation to chromatographic retention data. Its calculation method for various compounds and series of homologues is given, and its use to linearize liquid and gas chromatographic data is discussed. Results obtained for alcohols, fatty acids, and fatty acid silyl derivatives indicate that log k' *vs.* GIMC plots are linear, and permit an ordering of retention data. The use of the GIMC to study retention mechanisms and to predict retention under a given set of experimental conditions is also discussed.

INTRODUCTION

Theoretical as well as practical reasons have caused chromatographers to relate retention data to some basic characteristic properties of molecules. Such a process permits the ordering of molecules, and this may be used to predict the retention behaviour of unknown solutes. The use of a molecular index for scaling compounds in relation with their structure may: (1) facilitate the choice of the right strength of solvent to elute a given compound satisfactorily; (2) help in judging the feasability of a given separation; and (3) permit a fast optimization of the chromatographic conditions.

There are known examples where variations in retention are predictable. This is the case when series of homologues are examined, because t_R values for such compounds vary in a regular and predictable manner[1]. For instance, the variation of retention in a homologous carboxylic acid series is described by Martin's rule:

$$\log k' = A + Bn$$

where k' is the capacity factor, A and B are constants and n is the number of repetitive groups in the molecule. These may be the number of alkyl carbons, the number of double bonds, or any repeating pattern in the skeleton. Accurate prediction of retention times using Martin's rule is often possible. In reversed-phase chromatography, because the retention mechanism is very similar to the liquid–liquid partition

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mechanism, chromatographers have used data from solvent extraction systems to help predict retention. Thus, log k' values are represented as a function of the so-called "hydrophobicity" of molecules[2], a measure of partition between octanol and water. Hydrophobicity can be calculated from the fragmental hydrophobic constants, and tables of these have been published[3]. Kovat's retention indices are widely used[4] for reporting gas chromatographic (GC) retention data, but their values[5] are based on experimental data. Other approaches to describe the retention of molecules are based on molecular topology. Thus, connectivity indices[6], Wiener numbers[7], and Balaban indices[8] have been proposed for various solutes and chromatographic conditions. These indices are not of universal applicability, and some require experimental data.

The diversity of applications makes it desirable to search for an index that would have as wide an applicability as possible, and would not require the use of any experimental nor empirical data. The general index of molecular complexity (GIMC) fits these requirements.

THEORY

The GIMC[9–11] is derived from a combination of concepts taken from graph theory and from statistical information theory. It takes into account features that make a molecule more or less complex: size, symmetry, branching, rings, multiple bonds and heterogeneity in the atoms. A molecule is represented by its skeletal molecular graph, and the complexity of this representation is then derived from Shannon's formula[12]:

$$I = -\sum p_i \log_2 p_i \tag{1}$$

where I represents the information content of a point on a graph, defined in terms of probability p_i.

Methods based on statistical information theory are defined by means of probability, and are quite useful whenever there is some uncertainty about the choice of elements in a set. In its most general definition, the degree of uncertainty of a given outcome i is expressed by its entropy, $S(i)$, which is a function of the probability p_i that event i will occur. Hence, one can write:

$$S(i) = -\log_2 p_i \tag{2}$$

Use of base 2 for the logarithm expresses the entropy in bits, known as "logon" or "Shannon"[13]. Entropy as a measure of any kind of disorder (or uniformity) is a more general concept than thermodynamic entropy, the latter being a measure of the disorder in atomic and molecular motions.

Shannon's formula gives the mean entropy $S(P)$ of the probability distribution $[P(p_1,p_2,\ldots p_k]$ of all k possible outcomes in a given situation. Thus,

$$S(P) = -\sum_{i=1}^{k} p_i \log_2 p_i \tag{3}$$

The difference in the general entropy value before, $S(P_0)$, and after, $S(P_1)$, an event has occurred is expressed as follows:

$$I = S(P_0) - S(P_1) \tag{4}$$

The event referred to could be anything: the building of a bridge starting from steel beams or the building of a molecule starting from atomic arrays. Bertz[9] has shown that the application of this formula to a molecule gives the measure of the complexity of the graph skeletal molecular graph, $C(n)$. The equation is:

$$C(n) = 2n \log_2 n - \sum_{i=1}^{k} n_i \log_2 n_i \tag{5}$$

Here, n represents any graph-theoretical invariant. Gordon[14] defines a "graph-theoretical" invariant as the number of distinct ways in which skeleton i can be cut out of skeleton j. Bertz[9] proposes η, the number of connections, as the graph-theoretical invariant. The connectivity number takes into account branching as well as size and symmetry and, $C(\eta)$ is therefore one measure of molecular complexity.

The above treatment does not suffice to describe complexity when heteroatoms are present in the skeleton of a molecule. Complexity increases with the number of heteroatoms by amounts calculated from the following expression[9]:

$$C(E) = E \log_2 E - \sum_{i=1}^{j} E_i \log_2 E_i \tag{6}$$

where E is the total number of atoms (other than hydrogen), and E_i is the number of atoms of species i amongst the j different types of atom. This simple molecular invariant is valid as long as the heteroatoms are the same as is the case in series of homologues. When substances containing different heteroatoms (F, Cl, Br, I, ...) are compared, or non-homologous compounds are considered, additional terms have to be included. This is presently under investigation for systems such as polyhalogenated hydrocarbons and will be discussed in a separate report.

As a general approach, the above two contributions, connectivity and heterogeneity, will usually suffice to describe the structure, and the GIMC is given by:

$$\text{GIMC} = C(\eta) + C(E) \tag{7}$$

Any observable related to the complexity of a molecule should be a function of the GIMC. Therefore, chromatographic retention data should also be related to the GIMC.

Calculation of the GIMC

The calculation of the GIMC will be illustrated using the following molecules: benzene, phenylacetonitrile, and the normal fatty acids.

The calculation necessitates the establishment of the correct number of connections in a molecule. This is easily achieved as follows. A graph skeletal represen-

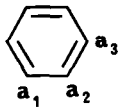

Fig. 1. Graph skeletal representation of benzene.

tation of the molecule is first drawn, although hydrogen atoms may be omitted (the effect of this omission will be discussed later). Equivalent atoms are designated by a letter, and bonds by two letters representing each bonded atom. Thus, a connection, made of two adjacent bonds, is designated by three letters, *e.g.* aaa, abd... The total number of connections, η, is given by the number of pairs of adjacent bonds necessary to construct the molecule. A connection is therefore a bond–atom–bond structural element linking two atoms that are not adjacent; a bond links two adjacent atoms. A double bond is equivalent to one connection, and a triple bond to three connections. When all the possible structural elements have been written, the actual number of connections may be determined by visual inspection of the skeletal representation.

Benzene. This molecule was chosen to illustrate the calculation of molecular complexity when double bonds are present. The graph skeletal representation is shown in Fig. 1. In this case, all carbon atoms are equivalent and can thus be designated by a single letter, a. The subscripts 1, 2, 3, ... are helpful in determining the connections. Thus, between say a_1 and a_3, the number of connections is determined as follows: a_1 and a_3 are connected by two paths involving single C–C bonds, and furthermore, the double bond offers an additional connection between a_2 and a_3, which is $a_2a_3a_2$. Therefore, the graph representation indicates that there are three connections between a_1 and a_3. For the whole molecule, we have,

$$\eta = 12(aaa) + 3DB_{aa} = 15$$

From eqn. 5, $C(\eta)$ is then calculated to be:

$$C(\eta) = 2 \times 15 \log_2 15 - 12 \log_2 12 - 3 \log_2 3 = 69.43 \text{ Shannons}$$

Since hydrogen atoms are neglected in the calculations, there is only one type of atom in the molecule, thus $C(E) = 0$ and GIMC = 69.43 Shannons.

Phenylacetonitrile. This compound contains a heteroatom as well as two double bonds and a triple bond. Equivalent carbons on the phenyl ring (those that have the same NMR environment) are designated by the same letter. The skeleton of the molecule with the proper designation of atoms is shown in Fig. 2. By inspection of this molecule,

$$\eta = 2(aaa) + 4(aab) + 4(abc) + 2(bcb) + 3(bcd) + (cde) + 3(def) + 1\,DB_{aa} + 1\,DB_{ab} + 1\,DB_{bc} + 1\,TB_{ef}(\equiv 3) = 25$$

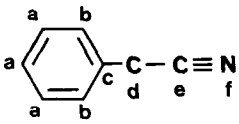

Fig. 2. Graph skeletal representation of phenylacetonitrile.

The number of connections in a benzene derivative is the number of connections in benzene, 15, plus three connections for each monoatomic substituent. For a polyatomic substituent, we add this value, 18, to the number of connections of the substituent obtained by including benzene in its skeleton but considering it as an atom, different from the other atoms of the substituent. Thus, for j substituents,

$$\eta = 15 + 3j + \sum_{i=1}^{j} \eta_i$$

For phenylacetonitrile, $C_6H_5CH_2CN$, this gives

$$\eta = 15 + 3 + 7 = 25$$

From eqn. 5,

$$C(\eta) = 2 \times 25 \log_2 25 - (2 \times 4) \log_2 4 - (3 \times 3) \log_2 3 - (2 \times 2) \log_2 2 - (4 \times 1) \log_2 1 = 198.0 \text{ Shannons}$$

The total complexity must include the complexity due to the heteroatom as calculated from eqn. 6. Thus:

$$C(E) = 9 \log_2 9 - 8 \log_2 8 - 1 \log_2 1 = 4.53 \text{ Shannons}$$

Therefore, GIMC = 202.5 Shannons.

Fatty acids. The general formula for normal fatty acids is $C_nH_{2n+1}COOH$. The graph skeletal representation is shown in Fig. 3. A general formula to calculate the GIMC for any normal fatty acid as a function of the total number of carbons in the aliphatic chain may be derived. Inspection of the representation indicates the following connections:

$$\eta = 1(abc) + 1(bcc) + (n-5)(ccc) + 1(ccd) + 1(cde) + 1(def) + 2(deg) + 2(feg) + 1\,DB_{eg}$$

Thus, $\eta = (n-5)(ccc) + 10 = (n+5)$ connections and,

$$C(\eta) = 2(n+5) \log_2 (n+5) - (n-5) \log_2 (n-5) - (2 \times 2) \log_2 2 - 6 \log_2 1$$

Similarly, for the heterogeneity,

$$C(E) = (n+3) \log_2 (n+3) - (n+1) \log_2 (n+1) - 2 \log_2 2$$

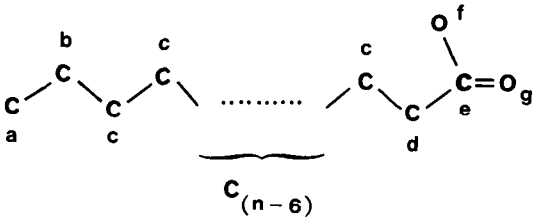

Fig. 3. Graph skeletal representation of normal fatty acids.

TABLE I

FORMULAE TO CALCULATE GIMC OF HOMOLOGOUS SERIES OF COMPOUNDS

Compounds	*Chemical formulae*	*GIMC*
n-Alkanes	C_nH_{2n+2} $n>6$	$2(n-2)\log_2(n-2) - (n-6)\log_2(n-6) - 4.000$
n-Alcohols	$C_nH_{2n+1}OH$ $n>5$	$2(n-1)\log_2(n-1) + (n+1)\log_2(n+1) - n\log_2 n - (n-5)\log_2(n-5)$
n-Fatty acids	$C_nH_{2n+1}COOH$ $n>5$	$2(n+5)\log_2(n+5) + (n+3)\log_2(n+3) - (n-1)\log_2(n-1) - (n-5)\log_2(n-5) - 6.000$
9-Unsaturated fatty acids	$C_nH_{2n-1}COOH$ $n>11$	$2(n-8)\log_2(n-8) + (n+3)\log_2(n+3) - (n+1)\log_2(n+1) - (n-11)\log_2(n-11) - 18.000$
n-Fatty acid trimethylsilanes	$C_nH_{2n+1}COOSi(CH_3)_3$ $n>5$	$2(n+12)\log_2(n+12) + (n+7)\log_2(n+7) - (n+4)\log_2(n+4) - (n-5)\log_2(n-5) - 15.510$
n-Fatty acid cyanoethyldimethylsilanes	$C_nH_{2n+1}COOSi(CH_3)_2C_2H_4CN$ $n>5$	$2(n+21)\log_2(n+21) + (n+10)\log_2(n+10) - (n+6)\log_2(n+6) - (n-5)\log_2(n-5) - 19.510$

TABLE II

VALUES OF GIMC FOR VARIOUS COMPOUNDS

Compound	*GIMC*	*Compound*	*GIMC*
Propane	0.00	*n*-Ethyl alcohol	2.75
n-Butane	2.00	*n*-Propyl alcohol	7.25
n-Pentane	7.51	*n*-Butyl alcohol	13.12
n-Hexane	12.00	*n*-Pentyl alcohol	19.90
n-Heptane	19.22	*n*-Hexyl alcohol	27.36
2-Methylbutane	14.00	*n*-Pentanoic acid	59.1
2,2-Dimethylpropane	15.51	*n*-Hexanoic acid	62.44
2-Methylpentane	21.22	Palmitoleic acid	193.1
3-Methylpentane	19.22	Oleic acid	210.1
2,2-Dimethylbutane	24.26	9-Eicosenoic acid	226.4
2,3-Dimethylbutane	25.02	Linoleic acid	247.8
Azulene	220.3	Linolenic acid	273.0
Acenaphtene	328.7	Arachidonic acid	312.1
1,2-Dichlorobenzene	155.0	Tetrahydrofuran	22.83
1,3-Dichlorobenzene	161.5	Acetonitrile	24.26
1,4-Dichlorobenzene	141.5	Chrysene	563.8
3,4-Benzphenanthrene	593.5	Indene	196.4
Biphenylene	327.9	Indan	182.1
Isoprene	51.06	Pyrene	537.0
Naphthalene	225.2	Anthracene	401.1
Naphthacene	567.1	Pentacene	735.9
Phenanthrene	420.1	Hexacene	904.4
Cholesterol	581.1	Biphenyl	286.7

Adding the two values,

$$\text{GIMC} = 2(n+5)\log_2(n+5) + (n+3)\log_2(n+3) - (n+1)\log_2(n+1) - (n-5)\log_2(n-5) - 6.000$$

The formula permits calculation of the GIMC for any normal fatty acid with n greater than 5 and no double bond in the alkyl chain. Similar equations can be derived for other series of compounds, and some are given in Table I. The GIMC was also calculated for several types of different molecules, and some of these are given in Table II. The latter table contains values of the index for isomeric compounds. These indicate that the GIMC is sensitive to different isomers, as expected. Notice in particular the pentane isomers, whose GIMC changes from 7.51 for *n*-pentane to 14.00 for 2-methylbutane, and to 15.51 for 2,2-dimethylpropane. Similar differences are observed with the dichlorobenzene isomers (GIMC = 155.0, 161.5 and 141.5, respectively, for the *ortho, meta,* and *para* isomer). Finally, differences in the GIMC for isomers of condensed polyaromatic compounds are also observed. For instance, the GIMC for 3,4-benzphenanthrene is 593.5 whereas for its isomer, chrysene, it is 563.8. Table II also gives the GIMC for complex molecules, such as cholesterol and several polyaromatics. Results that illustrate the potential usefulness of this molecular parameter in the linearization of gas as well as liquid chromatographic retention data are given and discussed in terms of retention mechanisms.

EXPERIMENTAL

Chemicals

Solvents used for high-performance liquid chromatography (HPLC) were all HPLC grade; water was distilled-in-glass and further purified through a Milli-Q system (Millipore, Bedford, MA, U.S.A.). All other chemicals used as solutes were reagent grade and came from various sources. The fatty acid esters were prepared according to a method described elsewhere[15].

Instruments

Liquid chromatographic data were obtained using a modular system consisting of a Waters pump, Model 6000A (Waters Assoc., Milford, MA, U.S.A.) coupled to a Hitachi spectrophotometer, Model 100-20 (Hitachi, Mountain View, CA, U.S.A.) equipped with an 8-μl flowthrough cell or to a differential refractive index detector, Waters, Model R-401. A universal injector, Rheodyne, Model 905-12, was used. The ODS columns (20 cm × 3.2 mm I.D.) were packed with Johns-Manville (Denver, CO, U.S.A.) LC-7 particles.

All GC data were obtained with a Perkin-Elmer (Norwalk, CT, U.S.A.) Model Sigma 2B chromatograph equipped with dual detectors (flame ionization and nitrogen–phosphorus). The capillary column, 30 m × 0.25 mm I.D., was a bonded polydimethylsiloxane phase DB-1. The split injector (I&W Scientific) was maintained at 275°C and the detector temperature was 300°C. The column was operated at 200°C, with helium as the carrier gas.

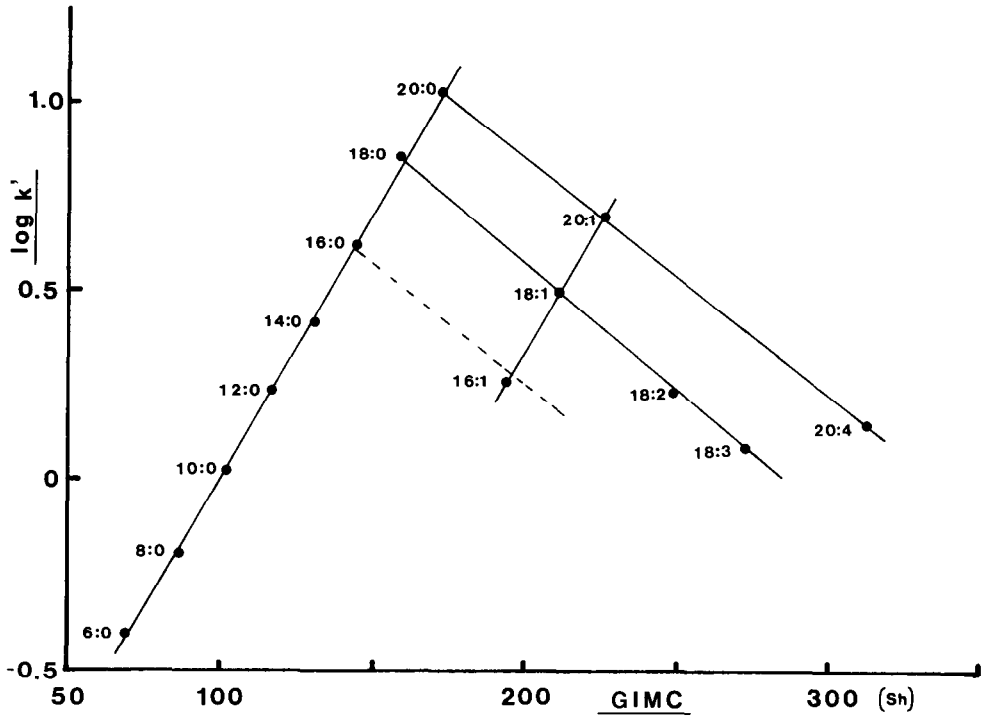

Fig. 4. Retention as a function of GIMC for HPLC of fatty acids in acetonitrile–water (1:1) over an ODS stationary phase.

RESULTS AND DISCUSSION

The linear relationship between HPLC retention data and hydrophobicity has previously been reported[2]. It was shown, for various compounds, that log k' values are linearly related to the hydrophobic factors of molecules. Most of the compounds were on a single straight line and some on lines that were close to each other. Such behaviour is not surprising since hydrophobicity is a parameter derived from experimental partition coefficients of solutes between *n*-octanol and water. Hydrophobicity takes into account various interactions and effects and thus is a global property. Among those compounds, alcohols followed a linear relationship which was, however, very distant from that of most chemicals. The normal fatty acids were on a straight line, but fatty acids containing double bonds appeared randomly distributed on the graph. For these substances, hydrophobicity did not explain the differences observed. A representation of these retentions (log k') as a function of their GIMC is shown in Fig. 4. Systematic, non-random linear relationships are clearly observed.

A careful examination of the data shows that double bonds lower the retention by predictable amounts that could not be accounted for using hydrophobicity. In acetonitrile–water (1:1), the first double bond (on the ninth carbon) lowers the log k' values by 0.34 unit, the second (k on the twelfth carbon) by 0.26 unit, and the third (on the fifteenth carbon) by 0.17 unit. The larger the number of double bonds

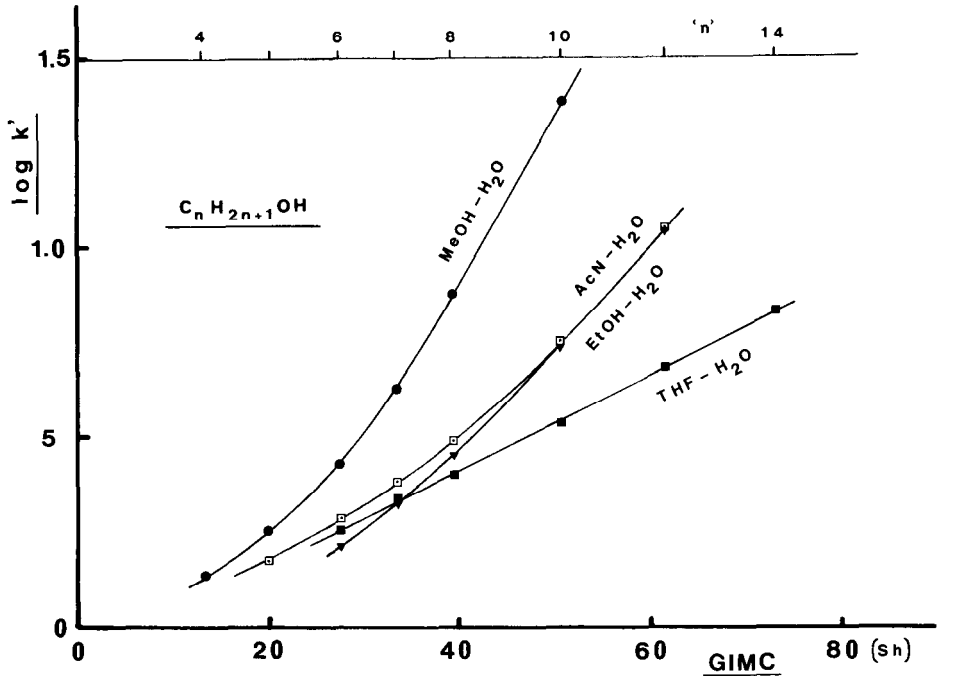

Fig. 5. Retention as a function of GIMC for HPLC of alcohols over an ODS stationary phase. Mobile phases are mixtures (1:1) of organic modifier in water.

on a molecule, the larger the dipole–dipole interaction with the mobile phase. The variation of retention is controlled by the extent of the interaction of the solutes with the mobile phase. The interaction mechanism in retention should be related to the GIMC, a structure-sensitive parameter that represents various reactive attributes of a molecule.

As a second example of application, consider Fig. 5. This shows log k' *vs.* GIMC for the lower alcohols in various solvents, analysed over an ODS stationary phase in HPLC. The variation of log k' with the GIMC is linear except for the first members ($n < 5$) of the series in alcohols.

The polarity of the mobile phase, P', calculated from the Rohrschneider parameter, is: tetrahydrofuran–water, 7.1; ethanol–water, 7.2; methanol–water, 7.6 and acetonitrile–water, 8.0. The retention should increase with a decrease in polarity as one goes from acetonitrile–water to tetrahydrofuran–water, but a different order is observed: retention increases from tetrahydrofuran–water to methanol–water. According to the mechanism proposed by Stahlberg and Almgren[16], the polarity of the surface increases when the mobile phase is changed from methanol–water to acetonitrile–water. It is suggested that methanol molecules enter the long alkyl chain, and are hydrogen-bonded to the free silanols of the packing. The overall effect is to decrease the polarity of the surface. These authors conclude that the concentration of freely moving methanol between the alkyl chains is very low, since an increase in methanol above *ca.* 25% does not increase the polarity of the surface. On the other hand, with acetonitrile–water mobile phases, the polarity of the ODS surface increas-

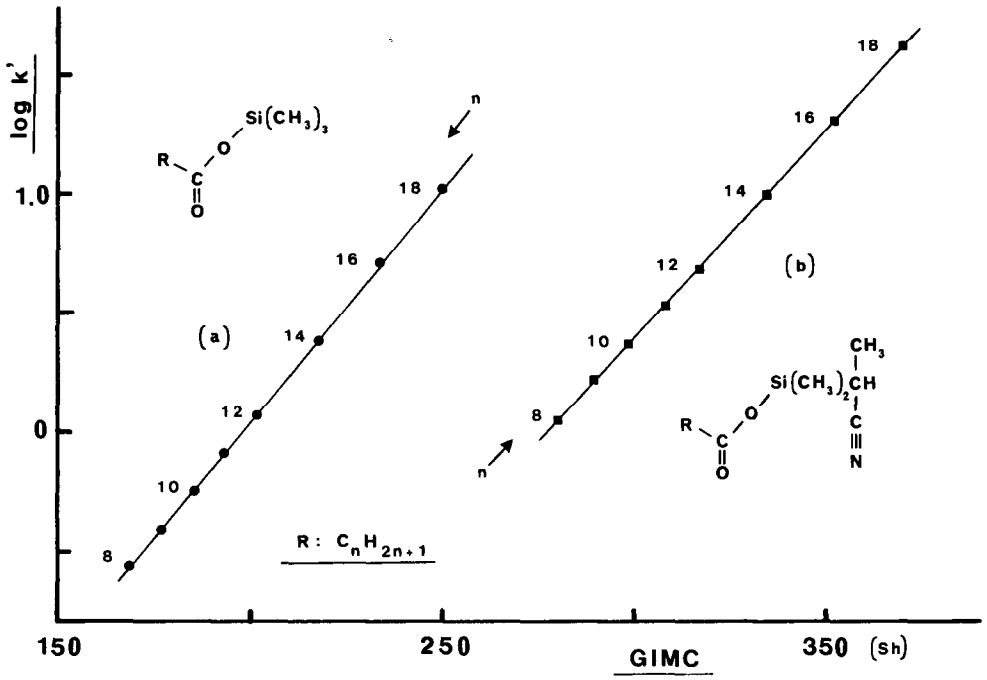

Fig. 6. Gas chromatography of volatile fatty acid derivatives: log k' as a function of GIMC.

es when the acetonitrile content increases above 14%. It is believed that the acetonitrile hydrogen-bonds to the free silanols of the surface in the first place; then, after saturation, addition of acetonitrile in the mobile phase increases the polarity of the surface because some acetonitrile molecules enter between the alkyl chains where they move more or less freely. Since alcohols are more retained in methanol–water, *i.e.* on the less polar surface, it seems reasonable to assume that the aliphatic part of the solutes is oriented "outside" the eluent, towards the alkyl chain of the stationary phase. The aliphatic moiety is thus more likely to interact with the less polar surface, therefore retention in methanol–water should be higher than in acetonitrile–water. The results indicate that the mechanism in ethanol–water is very similar to the one observed in acetonitrile–water. The small retention of alcohols in tetrahydrofuran–water is due to the fact that alcohols have a strong proton donor–acceptor ability, thus competing successfully with tetrahydrofuran in hydrogen-bonding with water. In this case, the alcohols interact more effectively with the mobile phase, and thus elute sooner.

Use of the GIMC with GC retention data has also been examined. Retention (log k') values for two series of fatty acid derivatives are shown in Fig. 6. In these examples, the retention behaviour of trimethylsilyl and cyanoethyldimethylsilyl derivatives of normal fatty acids were studied on a polydimethylsiloxane surface.

The linear relationship (log k' *vs.* GIMC) is an excellent model, which explains all of the variance (R^2 = 99.98%). This retention behaviour in GC shows the same general features as those observed in liquid chromatography (LC), as shown in Fig. 4. The slopes of the two sets of data are slightly, but significantly ($F_{8,8}$ = 1.26,

t = 38), different, their ratio being 1.13. For a given complexity, it can be seen that a trimethylsilyl derivative has a retention time 20–25 times longer than the cyanoethyldimethylsilyl derivative. These relationships can again be used to indicate differences in retention behaviours of different structures on a stationary phase. Comparison of HPLC and GC data for fatty acids discloses that introduction of double bonds in the system produces a predictable change in the retention. Although the changes observed in GC and LC with fatty acids are not explained by the same arguments, the plots indicate that use of the GIMC offers an invariant basis for comparison. Such linear relationships can definitely provide important analytical utility, as shown in Fig. 4. This demonstrates that the GIMC may be used to predict the retention behaviour of the fatty acids system.

The above examples were given as an illustration of the applicability of the GIMC to the study of retention mechanisms. Numerous other compounds were examined under various chromatographic conditions, and it was found that linearization was always observed with at least 99.5% of the variance explained by the linear model.

CONCLUSION

The results of this study indicate that, as an invariant parameter, the GIMC can be a useful tool as regards chromatographic data. It can not only, be used to study retention mechanisms and linearize retention data, but it also appears to have potential as an analytical parameter in predicting separations. This is specially true since *n*-alkanes, which are the basis of calculation for Kovat's RI indices, are a series of homologues which can be included in the log k' *vs.* GIMC plane. This makes it possible to transpose existing data, and correlate different homologous series of compounds.

The GIMC takes into account branching, size, degree of bond saturation, and heteroatoms. Since it does not rely on experimental data, it can be used to correlate experimental data at a very fundamental level. Calculations done on several types of molecule (*e.g.* Table II) indicate that the index can be calculated from first principles for any type of chemical structure, and that it is sensitive to changes of isomeric structures. Although the examples treated in this paper support the general applicability of the structural index as an invariant parameter in chromatography, problems still remain. Among these, is the difficulty related to the applicability of the index, as described, to molecules containing different heteroatoms (O, S, F, Cl, Br, I...) similarly bonded. The prediction of retention for compounds belonging to non-homologous series, and the correlation of data between different stationary phases, are also problems deserving investigation. Further studies on these aspects are presently being conducted and results will be published in a later report.

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