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GAS CHROMATOGRAPHIC DETERMINATION OF MOLECULAR POLARITY AND QUANTUM CHEMICAL CALCULATION OF DIPOLE MOMENTS IN A GROUP OF SUBSTITUTED PHENOLS

ROMAN KALISZAN*

Pharmacodynamics and Biopharmaceutics Unit, Medical Academy, 80-416 Gdańsk (Poland)

and

HANS-DIETER HÖLTJE

Institute of Pharmaceutical Chemistry, Johann Wolfgang Goethe University, 6000 Frankfurt am Main (G.F.R.)

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SUMMARY

A chromatographic polarity parameter, $I - b \cdot \mathrm{MR}$, has been calculated, where I is a gas–liquid chromatographic retention index, MR is the molar refractivity of the compound analysed and b is the stationary phase polarizability coefficient. To determine b, retention data are obtained on two phases of different polarities. The polarity parameter has been shown to correlate well with quantum chemically calculated dipole moments in the case of phenols without space-consuming substituents.

INTRODUCTION

During the past decade chromatography has become a powerful tool for the determination of molecular structural data employed in studies of quantitative structure–activity relationships (QSARs)[1,2].

To apply the linear free energy relationship based on Hansch's approach in QSAR, quantitative data are required concerning partitioning, electronic and steric characteristics of the compounds considered. Of the so-called electronic data, the most commonly used are individual Hammett's substituent constants (or their various modifications), dipole moments, pK_a values, spectroscopic data and quantum chemical parameters. The capacity of a drug for dipole–dipole interaction with the biological receptor is often assumed to be of importance for its bioactivity. As determinations of dipole moments are rather tedious there is a need to develop a convenient method for evaluation of dipole moments or a quantity related to them. The recently reported[2] gas chromatographic (GC) polarity parameters are used here with substituted phenols. The polarity parameters are compared to dipole moments calculated by a quantum chemical method.

THEORETICAL

Gas–liquid chromatographic GLC retention indices of fatty acid methyl esters[3] on SE-30 and SILAR 5 CP stationary phases are related by the empirical equation

$$I = K_1 N + K_2 \chi + K_3 \tag{1}$$

where N is a parameter related to the molecular polarity of the solutes, χ (connectivity index[4,5]) characterizes the ability of the solutes to undergo dispersive interactions with stationary phases and K_1–K_3 are constants. The dispersion effect is expected to be important even in the interactions between molecules with large dipole moments.

The connectivity index, χ, is a convenient parameter for the characterization of molecular polarizability. It is easily calculated for hydrocarbons and organic compounds containing nitrogen and oxygen. However, in the case of other atoms, e.g., halogens, χ values are uncertain and generally the molecular refractivity, MR, seems to be the more reliable parameter for the description of molecular polarizability. Thus, our starting relation has the form

$$I = a\mu^2 + b \cdot MR + c \tag{2}$$

where a can be considered as a measure of the stationary phase polarity and b as a measure of its polarizability. The equation is similar to that recently proposed by Gassiot-Matas and Firpo-Pamies[6]. Rearranging eqn. 2 one gets:

$$I - b \cdot MR = a\mu^2 + c \tag{3}$$

Thus, if eqn. 2 holds, the quantity $I - b \cdot MR$ should be linearly related to μ^2 and describe the polarity of the solute. The molecular refractivity, MR, can easily be calculated for any given molecule as a sum of substituent[7] or bond[8] refractivities. Thus, if the retention indices can be determined and the value of b is known, we have a convenient, quantitative measure for the polarity of the solutes.

The constant b is calculated as follows. If one has retention indices for any given compound on two phases of different polarity then one can write

$$I_P = a_1\mu^2 + b_1 \cdot MR + c_1 \tag{4}$$

$$I_{NP} = a_2\mu^2 + b_2 \cdot MR + c_2 \tag{5}$$

where I_P and I_{NP} are retention indices on polar and non-polar phases, respectively. Taking μ^2 from eqn. 5

$$\mu^2 = (I_{NP} - b_2 \cdot MR - c_2)/a_2 \tag{6}$$

eqn. 4 can be rewritten as:

$$I_P = a_1 (I_{NP} - b_2 \cdot MR - c_2)/a_2 + b_1 \cdot MR + c_1 \tag{7}$$

After rearrangement one gets

$$I_P = \frac{a_1}{a_2} \cdot I_{NP} - \left(\frac{a_1}{a_2} \cdot b_2 - b_1\right) MR + k_3 \tag{8}$$

or

$$I_P = k_1 I_{NP} - k_2 \cdot MR + k_3 \tag{9}$$

where k_1–k_3 are constants. These can be determined and statistically evaluated from regression analysis of experimental retention indices and molecular refractivity data for a sufficiently large set of compounds. A statistically significant relation of the type 9 proves the validity of the assumptions expressed by eqn. 2. With knowledge of k_1 and k_2 one can then undertake to calculate b.

Let us first consider the situation when $b_1 = b_2$, i.e., the two phases, polar and non-polar, are of equal polarizability. To a first approximation one can assume this to be the case when the two phases have similar molecular weights. Then:

$$b_1 = b_2 = b = k_2 / (k_1 - 1) \tag{10}$$

After calculation of b one can use eqn. 3 to determine the chromatographic polarity parameter, $I - b \cdot MR$.

If the polarizabilities of the phases, b_1 and b_2, differ significantly, the polarizability of one of the two phases must be known. Then:

$$b_1 = k_1 b_2 - k_2 \qquad \text{or} \qquad b_2 = (k_2 + b_1)/k_1 \tag{11}$$

A possible way to obtain data related to the polarizability of a chosen standard phase would be to find a relation between the molecular refractivity and retention indices for a group of non-polar compounds. The phase chosen should be as non-polar as possible. Alternatively different values of b calculated from eqn. 11 can be compared with those obtained from eqn. 2. In order to get a statistically significant relationship for an equation of the type 2 a certain number of retention indices, dipole moments and molecular refractivities is required. Substituted phenols offer a group of compounds for which quite a few such data are available in the literature. Additionally, these compounds exhibit polar interactions with stationary phases. Retention indices for 43 phenols on three stationary phases of different polarities have recently been reported by Grzybowski et al.[9]. For 20 of them, dipole moment values have been determined experimentally in benzene[10–16].

It seemed interesting to compare the chromatographic polarity parameter, $I - b \cdot MR$, with quantum chemically calculated dipole moments for these 43 phenols. The dipole moments were calculated using the CNDO/2-MO method[17,18], which for this purpose is well established. The results are shown in Table I. In order to obtain reliable values, comparable to those in the literature for solutions in benzene[10–16], we first calculated the most stable conformations of all the phenols. In cases where more than one energetically favoured conformer exists, the value μ_{calc} represents the arithmetic mean of the μ values of the corresponding conformers. For the molecular geometries of the phenols, standard values were used[19].

TABLE I

RETENTION INDICES, MOLAR REFRACTIVITIES, EXPERIMENTAL AND CALCULATED DIPOLE MOMENTS AND CHROMATOGRAPHIC POLARITY PARAMETERS FOR A GROUP OF SUBSTITUTED PHENOLS

No.	Phenol	Kovats retention indices*			Molar refractivity, MR**	Dipole moment values		Chromatographic polarity parameters, $I_{SGA} - 21.3825\,MR$
		SE-30	OV-225	NGA		μ_{obs}***	μ_{calc}	
1	2-CH$_3$	1035	1587	1742	32.83	1.45[10]	1.72	1040
2	4-CH$_3$	1059	1654	1813	32.83	1.61[10]	1.87	1111
3	3-CH$_3$	1065	1648	1782	32.83	1.58[10]	1.79	1080
4	2,6-(CH$_3$)$_2$	1098	1593	1716	37.45	1.38[11]	1.69	915
5	2,4-(CH$_3$)$_2$	1134	1660	1825	37.45	1.39[11]	1.77	1024
6	3-C$_2$H$_5$	1160	1742	1898	37.48	–	1.60	1096
7	4-C$_2$H$_5$	1162	1746	1890	37.48	–	1.85	1088
8	3,5-(CH$_3$)$_2$	1163	1706	1877	37.45	1.55[11]	1.82	1076
9	2,3-(CH$_3$)$_2$	1169	1693	1857	37.45	1.25[11]	1.74	1056
10	2,4-Cl$_2$	1183	1708	1877	38.21	1.59[12]	2.12	1060
11	4-Cl	1192	1922	2058	33.21	2.19[13]	2.36	1348
12	3-Cl	1194	1911	2061	33.21	2.14[13]	2.03	1351
13	2,4,6-(CH$_3$)$_3$	1204	1621	1778	42.07	1.40[13]	1.78	878
14	2,6-Cl$_2$	1206	1727	1871	38.21	–	3.20	1054
15	4-OCH$_3$	1210	1930	2050	35.05	1.92[13]	2.21	1300
16	3-OCH$_3$	1211	1940	2083	35.05	–	2.30	1334
17	2,3,5-(CH$_3$)$_3$	1260	1823	1960	42.07	–	1.78	1060
18	4-Br	1274	2054	2191	36.06	2.19[13]	2.70	1420
19	3-CH$_3$,-4-Cl	1283	2025	2135	37.84	–	2.02	1326
20	4-NH$_2$	1314	2154	2277	32.60	–	2.50	1580
21	4-OH	1334	2330	2515	28.03	1.40[14]	1.61 (3.21)	1916

22	3-NH_2	1335	2219	2352	32.60	1.83[16]	2.53 (2.61)	1655
23	2,4,6-Cl_3	1349	1928	2067	43.21	1.62[15]	1.67	1143
24	2,4,5-Cl_3	1362	2039	2158	43.21	—	1.99	1234
25	3-OH	1368	2371	2576	28.03	2.07[14]	3.49	1977
26	3,5-Cl_2	1391	2217	2343	38.21	2.18[13]	2.17	1526
27	4-I	1398	2230	2348	41.02	2.13[13]	—	1471
28	4-CO_2CH_3	1500	2376	2461	40.05	—	2.71	1604
29	4-$COCH_3$	1578	2478	2529	38.36	—	3.15	1709
30	2-NH_2	1242	2039	2196	32.60	—	2.85	1499
31	3-Br	1270	2069	2214	36.06	—	2.34	1443
32	2-iso-C_3H_7-5-CH_3	1271	1776	1932	45.75	—	1.82	954
33	2,6-($tert.$-C_4H_9)$_2$-4-CH_3	1494	1782	1830	70.01	—	1.75	333
34	2-OCH_3	1095	1544	1627	35.05	—	2.12	878
35	2-NO_2	1149	1556	1703	34.54	3.10[16]	3.82	964
36	2,6-(OCH_3)$_2$	1347	1936	2014	41.89	—	3.00	1118
37	2-OCH_3-4-C_3H_7	1392	1810	1884	48.98	—	2.28	837
38	2-OCH_3-4-CHO	1447	2199	2235	40.90	—	3.39	1360
39	2,6-(OCH_3)$_2$-4-CH_3	1473	2076	2106	46.51	—	3.07	1112
40	2-OCH_3-4-$COCH_3$	1531	2283	2326	38.36	—	2.89	1506
41	2,6-(OCH_3)$_2$-4-C_3H_7	1624	2254	2256	55.82	—	3.20	1062
42	2,6-(OCH_3)$_2$-4-$COCH_3$	1849	2685	2683	52.04	—	4.49	1570
43	2-OCH_3-4-CH_2-CH = CH_2	1367	1848	1923	48.51	—	2.18	886

* Data from ref. 9.

** Calculated according to Hansch *et al.*[7].

*** Determined in benzene solution at 25°C if not specified otherwise.

† Arithmetic mean of the μ values for the energetically favourable conformers.

†† Determined in benzene at 20°C.

RESULTS AND DISCUSSION

Correlations between retention indices on polar and non-polar phases

In Table I the Kovát's retention indices are shown for 43 phenols on dimethyl-polysiloxane (SE-30), 3-cyanopropylmethylpolysiloxane (OV-225) and polyneopen-tyl glycol adipate (NGA) coated on Chromosorb W HMDS (80–100 mesh)[9]. Molar refractivites have been calculated as a sum of fragmental refractivites according to Hansch *et al.*[7]. The dipole moment values μ_{obs} were taken from the literature[10-16], and are for benzene solutions at 25°C (or at 20°C in four cases). The data are from several sources, but seem to be reliable as the values obtained for the same com-pounds by independent authors are very similar. Besides, the data are in accord with the calculated values.

The relationship between retention indices on OV-225 and SE-30 has the form

$$I_{OV-225} = 1.95 \ (\pm \ 0.16) \ I_{SE-30} \ - \ 22.08 \ (\pm \ 3.56) \ MR \ + \ 285.76$$
$$n = 43, \ R = 0.9691, \ s = 71 \tag{12}$$

where n is a number of compounds considered, R is the multiple correlation coef-ficient and s is the standard deviation from the regression equation. The numbers in parentheses are 95 % confidence limits. All the equations presented are statistically significant at least at the 99.9 % significance level, as are the variables used. The corresponding equation in the case of the phases NGA and SE-30 has the form:

$$I_{NGA} = 1.81 \ (\pm \ 0.20) \ I_{SE-30} \ - \ 24.50 \ (\pm \ 4.36) \ MR \ + \ 682.59$$
$$n = 43, \ R = 0.9472, \ s = 87 \tag{13}$$

Determination of the stationary phase polarizability coefficients

· After determination of eqns. 12 and 13 we undertook to calculate the chroma-tographic polarity parameter, $I - b \cdot MR$, as defined by eqn. 3.

We have found experimental dipole moments for a group of 20 compounds. For four compounds, dipole moments determined in benzene at room conditions did not fit eqn. 2. These are 4-OH, 3-OH and 3-NH$_2$ substituted phenols for which the experimental dipole moments are significantly lower than expected from eqn. 2, and

TABLE II

CORRELATION COEFFICIENTS, R, AND STANDARD DEVIATIONS, s, FOR LINEAR EQU-ATIONS $I = \alpha X + \beta$ RELATING RETENTION INDEX, I, TO DIPOLE MOMENTS OR MOLAR REFRACTIVITIES, X, FOR A GROUP OF PHENOLS

α and β are constants.

I	X	R	s
I_{SE-30}	μ_{obs}^2	0.6065	95
I_{OV-225}	μ_{obs}^2	0.8692	114
I_{NGA}	μ_{obs}^2	0.8641	110
I_{SE-30}	MR	0.6479	91
I_{OV-225}	MR	0.2330	225
I_{NGA}	MR	0.2463	213

2-nitrophenol, the experimental dipole moment of which is to high to fit eqn. 2. The cause of the much higher polarity of the first three compounds in comparison with their polarity in benzene solutions is probably partial ionization at high-temperature chromatographic conditions. As far as 2-nitrophenol is concerned its low polarity under chromatographic conditions may be due to an increase in intramolecular bonding. The dipole moments of the remaining 16 compounds under chromatographic conditions are (to a first approximation) linearly related to the experimental ones. Bearing in mind all the limitations, the following equations can be considered as supporting the hypothesis:

$$I_{SE-30} = 66.67 \ (\pm \ 14.42) \ \mu_{obs}^2 + 25.34 \ (\pm \ 5.22)MR + 57.53$$
$$n = 16, \ R = 0.9679, \ s = 31 \qquad \qquad (14)$$

$$I_{V-225} = 164.72 \ (\pm \ 36.61) \ \mu_{obs}^2 + 24.48 \ (\pm \ 12.90) \ MR + 408.33$$
$$n = 16, \ R = 0.9472, \ s = 77 \qquad \qquad (15)$$

$$I_{NGA} = 155.69 \ (\pm \ 33.63) \ \mu_{obs}^2 + 23.99 \ (\pm \ 12.19) \ MR + 599.81$$
$$n = 16, \ R = 0.9477, \ 2 = 73 \qquad \qquad (16)$$

The two-parameter eqns. 14–16 are highly statistically significant. The correlation coefficients for the corresponding one-parameter equations relating the retention indices to μ_{obs}^2 and MR are much lower or of no statistical value (Table II).

Next it was of interest to compare b values obtained from eqns. 14–16 with those calculated from the coefficients in eqns. 12 and 13. For calculation of b_1 by eqn. 11, the value $b_2 = 25.3412$ has been assumed as obtained from eqn. 14. Then, from eqn. 12, b for the OV-225 phase was calculated as 27.3510. The corresponding value for the NGA phase calculated from eqn. 13 is 21.3825.

Relationship between the chromatographic polarity parameter and the calculated dipole moments

As can be concluded from reports by Karger et al.[20] and Scott[21], the polar term in equations of the type 1 reflects more than just the charge distribution in the molecule. It includes a steric component and reflects the ability to form hydrogen
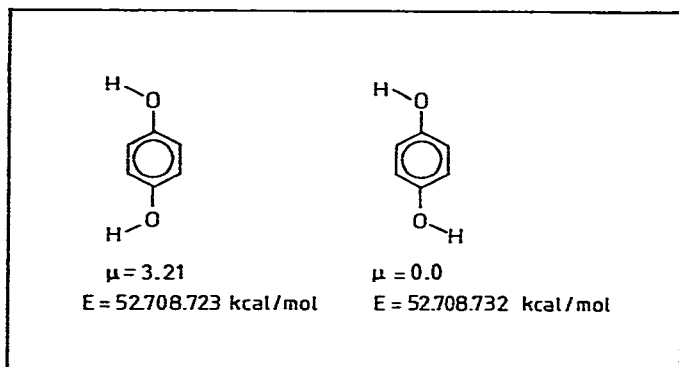

Fig. 1. Dipole moments and conformational energies (E) for energetically favoured conformations of hydroquinone.

bonds between the solutes and the stationary phases. Therefore a chromatographic polarity parameter might be able to simulate the capacity of a molecule to approach an unspecific binding site; this is of great importance in drug–receptor interactions.

The chromatographic polarity parameter, being dynamic in nature, reflects the actual dipole moment of the solute under chromatographic conditions. On the other hand, calculated dipole moments represent the molecular conformations in the gas phase which may well differ from those in the adsorbed state. This can be demonstrat-
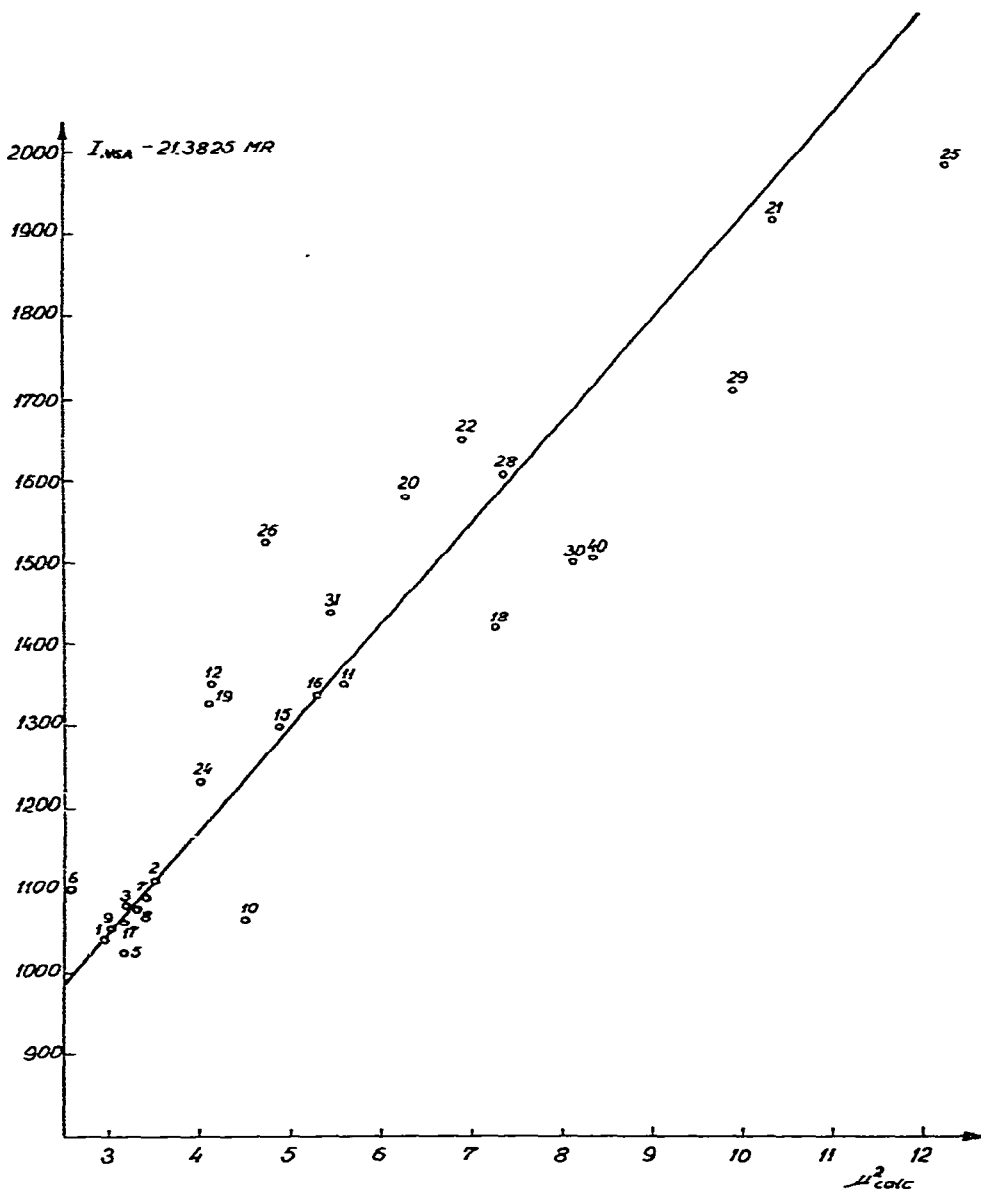

Fig. 2. Correlation between the chromatographic polarity parameter. $I - b \cdot MR$, and calculated dipole moments for phenols without space-consuming substituents.

ed with 4-hydroxyphenol. For this compound μ_{obs} and μ_{calc} are in a very good agreement but there is no correlation with the chromatographic polarity parameter; μ_{calc} is the arithmetic mean for the two conformers (Fig. 1). If one takes the μ_{calc} of only one conformer ($\mu_{calc} = 3.21$) there is a very good correlation with the polarity parameter. This means that in the gas phase and benzene solution we have a mixture of two conformers, whereas at the stationary phase only one conformer is bound. A similar situation can be expected at the surface of a biological receptor.

The idea that the chromatographic polarity parameter reflects more than the charge distribution in the molecule seems to be supported by the correlation shown in Fig. 2:

$$I_{NGA} - 21.3825 \text{ MR} = 98.85 \, \mu_{calc}^2 + 810.62$$
$$n = 27, \, R = 0.919, \, s = 8.47 \tag{17}$$

The good correlation between the chromatographic polarity parameter and μ_{calc} described by eqn. 17 was obtained after elimination of all phenols with space-consuming substituents (33,37,41,43) as well as 2,6-disubstitution (4,13,14,23,33,36,39,41,42), also 34 (steric hindrance and hydrogen bonding), 35 (hydrogen bonding) and 38 (thermal reactions?), leaving 27 phenols. This procedure seems to be reasonable because in the remaining 27 phenols the interaction between the phenol and the stationary phase is dominated by the electronic properties of the molecule (dipole moments), whereas in all the excluded cases additional factors play a significant rôle.

The easily determined chromatographic polarity parameter seems to be a convenient numerical measure of the molecular polarity and might be of importance in medicinal chemistry. Application of it to QSAR will be published elsewhere[22].

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