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SOLUBILITY FACTORS IN GAS-LIQUID CHROMATOGRAPHY

COMPARISON BETWEEN TWO APPROACHES AND APPLICATION TO SOME BIOLOGICAL STUDIES

PAUL LAFFORT and FRANÇOIS PATTE

Groupe de Laboratoires du C.N.R.S., 91190 Gif-sur-Yvette (France)

SUMMARY

Solubility factors in gas-liquid chromatography have mainly been determined by the work of two groups of workers: Snyder, Karger and Eon through an expanded version of the Hildebrand solubility parameter, and Laffort, Patte and Etcheton through a computer program related to factor analysis. An experimental comparison between these two approaches has been made, giving a mutual improvement (approximately 80% of mutual agreement). Some applications in biology are considered, especially in olfaction.

INTRODUCTION

Several workers have attempted to characterize the cohesion of solutions from factors of solutes and of solvents. In the more restricted field of gas-liquid chromatography (GLC), Rohrschneider proposed in 1965¹ a linear equation to calculate the Kováts retention indices:

$$I = I_0 + ax + by + cz \quad (1)$$

where I_0 is the retention index for squalane, a , b and c are the solute factors and x , y , z the solvent factors. Rohrschneider himself extended this equation to six terms in 1966² and McReynolds proposed one of eight terms in 1970³.

The general purpose of these approaches was to classify stationary phases simply, without attempting to obtain factors mutually independent or "orthogonal".

Weiner and Howery, in 1972^{4,5}, obtained from the experimental data of Rohrschneider and McReynolds eight abstract orthogonal factors by using factor analysis. They then tried to superimpose a physico-chemical space on the mathematical space defined. They had some success: in their two papers, three of the eight factors were identified. In one, the molar polarizability, the square of dipole moment and the heat of vaporization were identified, and in the other the "gas imperfection term using the Van der Waals equation of state", an "alcohol-like character" and an "electron donor ability" were given. There is, of course, a large overlap between these

two groups of properties, and there remain five factors to be identified in both instances.

Also in 1972, Dravnieks and Laffort⁶ proposed to characterize this space by a linear equation of only four terms, in which the solute factors were identified as: α , the molecular volume (or apolar factor); ρ , the receptor of proton ability; π , the proton donor ability; and ε , an index of local volume polarizability (or electron factor). Numerical data for 31 substances were obtained, and highly significant correlations between these physico-chemical properties and a biological property (olfactory) were found.

In 1974, Laffort, Patte and Etcheto⁷ improved the method. They derived these molecular properties with good accuracy from only 4 stationary phases instead of 25 and gave numerical data for 85 substances.

Let us consider the different numbers of factors involved according to the several workers quoted*. The number of factors to be taken in account depends on their orthogonality, on the sample of substances and phases, and on the mean accuracy of the calculated retention indices. This accuracy has to be comparable to the mean experimental accuracy, which most of the workers estimate to be within 6 and 9 Kováts index units. An accuracy of 3 index units found by Weiner and Howery with 8 orthogonal factors must be considered as illusory.

In a parallel direction to this empirical progress from 1965 to 1974, there is a semi-theoretical approach, elaborated by Snyder in 1971⁹ and further developed in 1975 by Snyder and co-workers^{10,11}. They expanded the "solubility parameter" of Hildebrand and Scott's theory^{12,13} to five partial parameters, which they called parameters of dispersion (δ_d), orientation (δ_o), induction (δ_{in}), basicity (δ_b) and acidity (δ_a). They developed from this a general theory of retention, valid for the several kinds of chromatography: by partition or adsorption, in the gaseous phase or in a liquid, which takes into account the partial solubility parameters of the solutes, solvents and adsorbents, and the molar volume of the solutes. An equation with five terms was proposed for GLC.

The purpose of the present work is to compare this semi-theoretical approach and the empirical approach of Laffort *et al.*⁷, in order to try to realize the suggestion made by Keller in 1973¹⁴: "It seems clear that factor analysis needs to be applied to test the value of extended solubility parameters once a more complete set becomes available".

Note

We mention the topological approach only as a reminder, because it implies that a limited number of physico-chemical factors cannot explain the solutions and the adsorptions. To our knowledge, this approach has been fruitful only in pharmacology, when families of very similar substances are involved. For GLC, Lenfant *et al.*¹⁵ in 1971, by using the DARC system, proposed an equation of seven terms to predict the retention times of saturated ketones, which is not valid, of course, for substances with other functional groups. It is to be hoped, however, that in the future a comparison between topology and thermodynamics will be made, similar to

* Dupuis and Dijkstra⁸ studied the classification of phases and estimated that 10 factors are necessary.

the physico-chemical comparison between theoretical and empirical approaches that we are analyzing in this paper.

MATERIALS AND METHODS

The methods used were the same as those used by Dravnieks and Laffort⁶ and Laffort *et al.*⁷, with the numerical partial solubility parameters given by Snyder⁹ in addition.

Kováts retention indices

Kováts retention indices were measured by McReynolds in 1970¹⁶ for the interaction of 68 substances on 25 phases at 120°. We added seven *n*-alkanes in order to make the computations easier.

Computer program

The program used was established by Robin and Laffort in 1971¹⁷. It is related to the programs of factor analysis, but it requires an initiation by values that approximate to the real solution. Fig. 1 shows how it works.

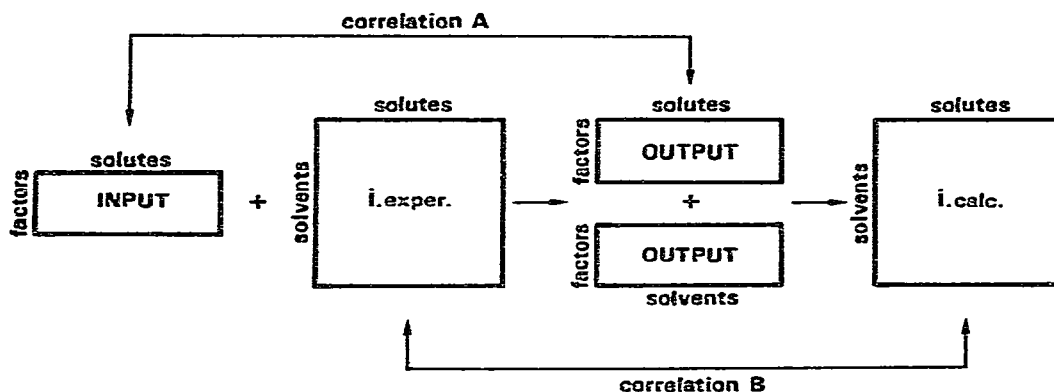


Fig. 1. Representation of the Robin-Laffort computer program¹⁷. Correlation B depends only on the number of factors, whereas correlation A depends on the INPUT solutes factors matrix for a given number of factors (see text).

The correlation A depends, for a given number of factors, on the initiation of solute factors; if the matrix INPUT is made with randomized digits, the correlation will be bad. If, on the other hand, it is made with molecular factors involved in the phenomenon, the correlation will be good. The correlation B between experimental and calculated Kováts indices depends only on the number of factors chosen. It will be unity if the number of factors is the same as the number of solvents (25 in our case). Fig. 2 shows how Dravnieks and Laffort⁶ estimated, in 1972, that the number of factors involved is four. Instead of a correlation coefficient, they calculated the "standard error" between the calculated and experimental retention indices using eqn. 2,

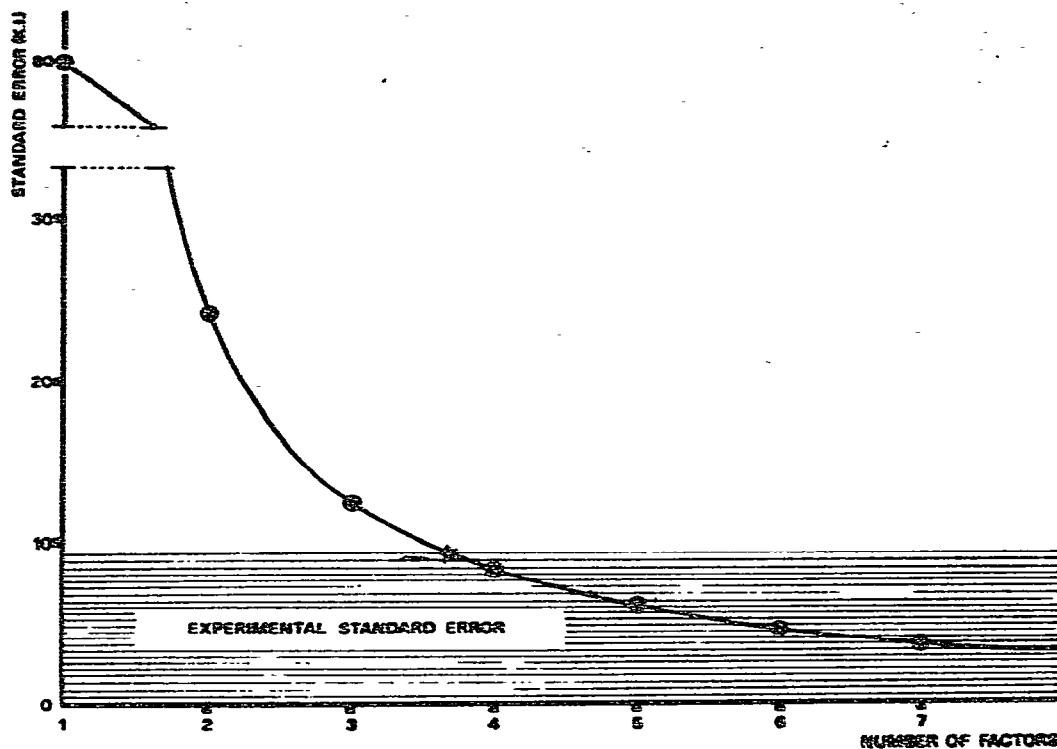


Fig. 2. Comparison between the "standard error" of calculated retention indices in GLC and the "experimental standard error". The latter, being found to be equal to 9 index units, seems to indicate that four factors are sufficient to explain the phenomenon. Index range, 200–1600; mean, 900. (From Dravnieks and Laffort⁶, modified.)

which they compared to the value of the "experimental standard error" given by eqn. 3.

$$\text{Standard error} = \sqrt{\sum (I_{\text{calc.}} - I_{\text{exp.}})^2 / (n - 1)} \quad (2)$$

$$\text{Experimental standard error} = \sqrt{\sum (I_{\text{exp.}} - I_{\text{exp.}})^2 / (n - 1)} \quad (3)$$

The experimental standard error, on the basis of numerical experimental data, was evaluated as 9 Kováts' index units. The consequence was the assumption that four factors were involved. A hypothesis of an experimental standard error of six index units would have implied five factors, etc.*

Partial solubility parameters

Let us consider briefly how Snyder *et al.*¹⁰ define the components of the Hildebrand solubility parameter (δ):

$$\Delta E^v = V_{20} \delta^2 = V_{20} (\delta_d^2 + \delta_o^2 + 2\delta_{in} \delta_d + 2\delta_a \delta_o) \quad (4)$$

* The method of Rohrschneider (six non-orthogonal factors) for a matrix of 20 solutes by 25 solvents gives also, by using eqn. 2 on McReynolds data, a standard error of 9 Kováts index units.

where ΔE° is the free enthalpy of vaporization.

The calculation of the free enthalpy of solubility of a binary mixture gives, according to these workers, in the particular case of GLC, the following equation, in which i is related to the solute and j to the stationary phase:

$$I = -[100 V_i / (\Delta E_{me})_i] [2\delta_a^i \delta_d^j + 2\delta_o^i \delta_a^j + 2\delta_{in}^i \delta_d^j + 2\delta_{in}^i \delta_a^j + 2\delta_a^j \delta_b^i + 2\delta_a^i \delta_b^j] \quad (5)$$

If we take into account in a first stage only the solute factors as variables, the solvents factors can be gathered in arbitrary constants. Under these conditions

$$I = V_i (A\delta_d^i + B\delta_o^i + C\delta_{in}^i + D\delta_a^i + D\delta_b^i) \quad (6)$$

Therefore, the experiments we made were essentially an initiation of the Robin-Laffort program by $V_{20} \delta_d$, $V_{20} \delta_o$, $V_{20} \delta_{in}$, $V_{20} \delta_a$ and $V_{20} \delta_b$, on the basis of retention indices established by McReynolds.

RESULTS AND DISCUSSION

First stage

The 25 substances for which both Kováts indices on 25 phases and partial solubility parameters were available are given in Table I. Also reported are the partial solubility parameters, the products $V_{20} \delta$ and $(V_{20}/V_b) \delta_a$ (V_b being the molar volume at the boiling point)*.

Preliminary examination of Table I suggests that the products $V_{20} \delta_o$, $V_{20} \delta_a$ and $V_{20} \delta_b$ are relatively constant for a given functional group and environment. This will be confirmed later by the values found for substances included in larger homologous series. It is also evident that the product $(V_{20}/V_b) \delta_a$ is constant for a given functional group. This can be explained easily. From Snyder *et al.*¹⁰, we have the approximate relationship

$$\delta_a = 30.7 \left(\frac{n^2 - 1}{n^2 + 2} \right) \quad (7)$$

that is

$$\delta_a = 30.7 \frac{R_m}{V_{20}}$$

from which

$$\delta_a \frac{V_{20}}{V_b} = 30.7 \left(\frac{R_m}{V_{20}} \cdot \frac{V_{20}}{V_b} \right) = 30.7 \frac{R_m}{V_b}$$

Because R_m and V_b are both additive properties, the ratio will be virtually

* δ_a , δ_o , δ_a and δ_b were given by Snyder⁹; δ_{in} was calculated from eqn. 4; the global value of δ was also given by Snyder⁹.

TABLE I
 PARTIAL SOLUBILITY PARAMETERS ACCORDING TO SNYDER⁸, AND DERIVED TERMS USED TO INITIATE THE COMPUTER PROGRAM, FOR 25 SUBSTANCES (SEE TEXT)

Compound	δ_d	δ_o	δ_b	δ_a	δ_{in}	V_{20}	V_o	$\frac{V_{20}}{100} \delta_d$	$\frac{V_{20}}{100} \delta_o$	$\frac{V_{20}}{100} \delta_b$	$\frac{V_{20}}{100} \delta_a$	$\frac{V_{20}}{100} \delta_{in}$	$\frac{V_{20}}{V_o} \delta_d$
Methanol	6.2	5.0	7.5	7.5	-0.8	41	42	2.5	2.0	3.0	3.0	-0.3	6.0
Ethanol	6.8	4.0	5.0	5.0	1.0	58	62	4.0	2.3	2.9	2.9	0.6	6.4
1-Propanol	7.2	2.5	4.0	4.0	1.0	77	81	5.6	1.9	3.1	3.1	0.8	6.8
Acetone	6.8	5.0	2.5	0.0	1.3	73	77	5.0	3.7	1.8	0.0	0.9	6.4
2-Butanone	7.1	3.7	2.0	0.0	1.4	90	100	6.4	3.3	1.8	0.0	1.3	6.3
Chloroform	8.1	3.0	0.5	3.0	0.3	81	85	6.6	2.4	0.4	2.4	0.3	7.7
Carbon tetrachloride	8.6	0.0	0.5	0.0	0.0	97	102	8.3	0.0	0.5	0.0	0.0	8.1
Ethyl bromide	7.8	3.0	0.0	0.0	0.5	75	77	5.8	2.2	0.0	0.0	0.4	7.5
Methyl iodide	9.3	2.0	0.5	0.0	0.4	62	65	5.8	1.3	0.3	0.0	0.3	8.9
Nitromethane	7.3	8.0	1.0	0.0	0.3	54	63	3.9	4.3	0.5	0.0	0.1	6.2
Acetonitrile	6.5	8.0	2.5	0.0	2.5	52	58	3.4	4.2	1.3	0.0	1.3	5.9
Pyridine	9.0	4.0	5.0	0.0	0.6	81	93	7.3	3.2	4.0	0.0	0.5	7.8
Benzene	9.2	0.0	0.5	0.0	0.0	89	98	8.2	0.0	0.4	0.0	0.0	8.4
Toluene	8.9	0.0	0.5	0.0	0.0	106	118	9.5	0.0	0.5	0.0	0.0	8.0
2,4-Dimethylpentane	7.1	0.0	0.0	0.0	0.0	149	159	10.6	0.0	0.0	0.0	0.0	6.6
2-Methylheptane	7.4	0.0	0.0	0.0	0.0	164	180	12.1	0.0	0.0	0.0	0.0	6.7
3-Methylheptane	7.4	0.0	0.0	0.0	0.0	162	180	12.0	0.0	0.0	0.0	0.0	6.6
2,2,5-Trimethylhexane	7.4	0.0	0.0	0.0	0.0	182	201	13.4	0.0	0.0	0.0	0.0	6.7
1,4-Dioxane	7.8	4.0	3.0	0.0	1.2	85	89	6.6	3.4	2.6	0.0	1.1	7.5
Anisole	9.1	2.5	2.0	0.0	0.3	109	126	9.9	2.7	2.2	0.0	0.3	7.9
Cyclohexane	8.2	0.0	0.0	0.0	0.0	108	117	8.9	0.0	0.0	0.0	0.0	7.6
Hydrindane	8.5	0.0	0.0	0.0	0.0	144	161	12.2	0.0	0.0	0.0	0.0	7.6
Decalin	8.7	0.0	0.0	0.0	0.0	154	178	13.4	0.0	0.0	0.0	0.0	7.5
1-Octane	7.4	0.0	0.0	0.0	0.0	163	187	12.0	0.0	0.0	0.0	0.0	6.4
Tetradecane	7.9	0.0	0.0	0.0	0.0	260	319	20.6	0.0	0.0	0.0	0.0	6.4

constant for a given homologous series. For example, for C_4 – C_{18} *n*-alkanes the δ_d values lie in the range 6.4–8.1, but the product $\delta_d (V_{20}/V_b)$ is always 6.4.

Table II indicates the method used by Kopp (quoted by Partington¹⁸, pp. 17–28) to calculate V_b . The original list of increments was expanded by Laffort in 1969¹⁹ and Laffort and Dravnieks in 1973²⁰.

TABLE II

LIST OF INCREMENTS FOR EVALUATING MOLAR VOLUMES AT BOILING POINT, V_b , ACCORDING TO KOPP, LOSSEN, SCHIFF AND ZANDER AND LE BAS (ALL QUOTED BY PARTINGTON¹⁸)

The balance between authors and additional increments are from Laffort¹⁹ and Laffort and Dravnieks²⁰.

Group	Increment (ml)	Group	Increment (ml)
H—	5.5	—O—	7.8
$\begin{array}{c} \\ -C- \\ \end{array}$	11.0	O=	10.2
$\begin{array}{c} \diagup \\ C= \\ \diagdown \end{array}$	13.0	—S—	22.6
=C= and —C≡	15.0	S=	28.6
N (in CN and NO ₂)	15.6	F—	12.6
Ring of 6 atoms	–15.0	Cl—	22.8
Ring of 5 atoms	–11.5	Br—	27.8
Ring of 4 atoms	–8.5	I—	37.5
Ring of 3 atoms	–6.5	P(III) and P(V)	25.4

Second stage

The Robin–Laffort computer program was initiated by three sets of random numbers for the substances in Table I. The correlation coefficients between the INPUT and OUTPUT solute factors are reported at the top of Table III. According to this table, it seems that an initiation has to generate correlations close to 0.9 in order to be valid.

The same program was then initiated by $V_{20} \delta_d$, $V_{20} \delta_o$, $V_{20} \delta_{in}$, $V_{20} \delta_a$ and $V_{20} \delta_b$ according to Snyder *et al.*¹⁰. All of the initiations, as seen from Table III, seems to be accurate except for $V_{20} \delta_{in}$.

If the product $(V_{20}/V_b) \delta_d$ takes the place of $V_{20} \delta_{in}$, all initiations are good (see also the results in Table III). Useful conclusions can be drawn from these results: on the one hand, it appears that five factors have to be taken into account, instead of four as Laffort *et al.* believed; on the other hand, Snyder *et al.*'s theory, in its application to GLC is verified at 80% (4 out of 5 initiation terms) and becomes easy to verify at 100% with a slight adjustment. The degree of overlapping between these results and the factors proposed by Laffort *et al.* in 1974⁷ will be seen later.

* In the particular case of *n*-alkanes, V_b can be calculated by the very simple equation

$$V_b \text{ (ml)} = 22n + 11 \quad (8)$$

in which *n* is the number of carbon atoms.

TABLE III

CORRELATIONS BETWEEN THE INPUT AND OUTPUT SOLUTE FACTORS FOR 25 SUBSTANCES

See explanation in text.

	1st factor	2nd factor	3rd factor	4th factor	5th factor
Random numbers	0.22 0.19 0.38	0.04 0.05 0.29	0.56 0.00 0.39	0.15 0.15 0.39	0.10 0.12 0.05
Strict Snyder <i>et al.</i> theory	$V_{20} \delta_a$ 0.99	$V_{20} \delta_o$ 0.93	$V_{20} \delta_{1a}$ 0.56	$V_{20} \delta_a$ 0.87	$V_{10} \delta_b$ 0.92
Adapted Snyder <i>et al.</i> theory	$V_{20} \delta_a$ 0.98	$V_{20} \delta_o$ 0.93	$(V_{20}/V_b) \delta_a$ 0.89	$V_{20} \delta_a$ 0.93	$V_{20} \delta_b$ 0.94

Third stage

As can be seen in Fig. 1, the program also generates solvent factors matrix. With the matrix obtained in the last case of the second stage, we found easily (by regression analysis the solute factors for the 75 substances, the retention indices of which were available on 25 phases.

Fourth stage

At this stage, we selected the five stationary phases reproducing with accuracy the results of the third step. As in 1974, according to Laffort *et al.*⁷, no set including an apolar phase was acceptable. The five phases selected were Zonyl E7 (DuPont, Wilmington, Del., U.S.A.), Carbowax 1000, tricyanoethoxypropane, polyphenyl ether (6 rings) and diethylene glycol succinate (Applied Science Labs., State College, Pa., U.S.A.). The first four are the same as those previously selected.

Fifth stage

The solute factors obtained at this stage were compared with an "index of cohesive energy" (ICE) defined by eqns. 9 and 9a.

$$\text{ICE}_{25} = -(\log \text{ vapour pressure at } 25^\circ \text{ in atm}) \text{ if } t_b \geq 25^\circ \quad (9)$$

$$\text{ICE}_{25} = \left[\frac{T_b}{402.8} + 0.6168 \right]^3 - 2.45 \quad \text{if } t_b < 25^\circ \quad (9a)$$

The comparison was made with a polynomial regression program. Eqns. 10 reproduce the definition of the primary factors in GLC in this "1976 version", as we have proposed.

$$\left. \begin{aligned} \alpha &= 0.503 Z - 0.119 C + 0.016 T + 1.602 P - 1.514 D \\ \omega &= 0.286 Z + 0.433 C - 0.220 T - 0.041 P - 0.458 D \\ \varepsilon &= -0.737 Z + 0.651 C + 0.905 T - 0.654 P - 0.165 D \\ \pi &= -0.031 Z - 0.127 C - 0.283 T + 0.567 P - 0.126 D \\ \beta &= 0.273 Z - 0.816 C - 0.596 T - 0.008 P + 1.147 D \end{aligned} \right\} \quad (10)$$

in which

$$\begin{aligned} Z &= (I - 100)/100 \text{ on Zonyl E7;} \\ C &= (I - 100)/100 \text{ on Carbowax 1000;} \\ T &= (I - 100)/100 \text{ on tricyanoethoxypropane;} \\ P &= (I - 100)/100 \text{ on polyphenyl ether (6 rings);} \\ D &= (I - 100)/100 \text{ on diethylene glycol succinate.} \end{aligned}$$

According to this definition, each factor has the same weight in its contribution to the "index of cohesive energy", as shown in eqn. 11:

$$\text{ICE}_{25}(\text{X}) - \text{ICE}_{25}(\text{CH}_4) = \alpha + \omega + \varepsilon + \pi + \beta - 1.2 \varepsilon\pi \quad (r = 0.99). \quad (11)$$

The ICE_{25} value for methane is -1.74 . The values of α , ω , ε , π and β in the 1976 version for the 75 substances studied are reported in Table IV.

Our approach suggests two comments about the global solubility parameter as defined by Hildebrand and Scott^{12,13}. The first comment was implicit in the first stage of the present work: why is V_{20} instead of V_b used as an approach to the actual molar volume? The second comment concerns the choice of the free enthalpy of vaporization, ΔE° , rather than the saturated vapour pressure as a criterion of "cohesion energy". Several forces of cohesion are not necessarily implied in the same proportions at different temperatures, because of molecular motion. The following experiment confirmed this hypothesis.

The saturated vapour pressure at 120° for the same 75 substances was treated by a polynomial regression program. We obtained ($r = 0.99$):

$$\begin{aligned} -(\log \text{ vapour pressure at } 120^\circ \text{ in atm}) &= 0.62 \alpha + 0.55 \omega + 0.66 \varepsilon + \\ &+ 0.27 \pi + 0.62 \beta - 0.44 \varepsilon\pi - 5.0 \quad (12) \end{aligned}$$

To simplify, we can say that the factor π (proton donor) is proportionally half as involved, in comparison with the other factors, at 120° as at 25° (coefficient of proportionality is 0.3 instead of 0.6). Therefore, it seemed to us more precise to choose an index of cohesion, determined at a given temperature. However, for the substances too near their critical temperature, we preferred to derive this index of cohesion from boiling points rather than saturated vapour pressures. We estimated that this was the case for all substances in the gaseous state at 25° .

Sixth stage

We believe that solute factors are expressed in an easier form in terms of α , ω , ε , π and β rather than δ , because four out of five factors characterize only the functional group and its environment, whereas only the last one characterizes the molar volume. On the other hand, eqn. 11, relating the "index of cohesive energy" to these factors, is simple, with no squared terms and only one cross-product. However, while waiting to see more clearly which kind of expression will be the most useful, we established eqns. 13 in order to pass easily from one expression to another:

TABLE IV

SOLUTE FACTORS IN GLC DERIVED FROM FIVE PHASES, EXPRESSED IN TERMS OF α , ω , ε , π , AND β (1976 VERSION) ACCORDING TO EQNS. 10 AND IN TERMS OF V_{20} , δ_a , δ_b , δ_c , δ_d , AND δ_e ACCORDING TO EQNS. 13 FOR 75 SUBSTANCES

No.	Compound	α	ω	ε	π	β	V_{20}	δ_a	δ_b	δ_c	δ_d	δ_e
1	Methanol	0.26	0.78	-0.14	0.64	0.97	45	6.01	5.76	7.73	5.86	
2	Ethanol	0.53	0.69	0.02	0.55	0.88	55	6.71	4.01	5.22	4.18	
3	Propanol	1.09	0.67	0.0	0.56	0.88	73	7.15	2.69	3.69	2.90	
4	Isopropanol	0.89	0.72	-0.14	0.45	0.86	69	6.42	3.25	3.33	3.18	
5	Butanol	1.64	0.67	-0.02	0.57	0.90	92	7.40	2.07	2.88	2.28	
6	tert.-Butanol	1.08	0.75	-0.27	0.30	0.85	77	6.03	3.03	1.99	2.81	
7	1-Hexanol	2.80	0.63	-0.18	0.62	1.02	131	7.21	1.31	2.11	1.73	
8	2-Hexanol	2.40	0.67	-0.17	0.42	0.91	119	7.04	1.57	1.61	1.74	
9	3-Hexanol	2.32	0.64	-0.02	0.37	0.79	117	7.47	1.54	1.45	1.55	
10	Allyl alcohol	0.79	0.68	0.12	0.70	1.00	61	7.60	1.88	1.14	1.72	
11	2-Methyl-2-pentanol	2.12	0.73	-0.22	0.27	0.82	112	6.70	1.84	0.92	1.71	
12	3-Methyl-3-pentanol	2.01	0.69	-0.04	0.21	0.78	108	7.22	1.84	0.92	1.71	
13	2-Methyl-2-heptanol	3.12	0.67	-0.32	0.29	0.92	146	6.63	1.28	0.90	1.43	
14	3-Methyl-3-heptanol	3.03	0.66	-0.15	0.23	0.83	142	7.16	1.29	0.73	1.32	
15	Cyclopentanol	1.79	0.55	0.34	0.50	0.97	95	8.70	1.60	2.38	2.31	
16	Acetone	0.78	1.41	-0.11	-0.15	0.39	64	6.48	6.83	-1.19	1.55	
17	2-Butanone	1.29	1.35	0.05	-0.19	0.26	81	7.31	4.89	-1.13	0.77	
18	2-Pentanone	1.78	1.33	-0.02	-0.20	0.30	98	7.31	3.88	-0.95	0.72	
19	2-Hexanone	2.32	1.34	-0.05	-0.21	0.30	116	7.41	3.22	-0.83	0.59	
20	3-Hexanone	2.27	1.28	0.17	-0.23	0.11	115	8.07	3.13	-0.92	0.22	
21	1-Fluorooctane	3.41	0.67	-0.05	-0.09	0.13	160	7.30	1.19	-0.26	0.19	
22	1,1-Difluorotetrachloroethane	2.49	0.26	-0.48	0.10	0.82	133	5.60	0.59	0.37	1.53	
23	1,2-Difluorotetrachloroethane	2.45	0.26	-0.49	0.09	0.85	132	5.56	0.60	0.34	1.60	
24	Chloroform	1.26	0.13	0.59	0.43	0.64	83	8.61	0.48	2.59	1.93	
25	Carbon tetrachloride	1.70	0.04	0.46	0.06	0.48	104	8.03	0.12	0.30	1.18	
26	1-Chlorohexane	2.72	0.44	0.54	-0.05	0.07	135	9.00	0.93	-0.17	0.12	
27	1,1,2,2-Tetrachloroethane	2.00	0.16	0.94	0.58	0.94	101	10.80	0.43	2.55	2.06	
28	Ethyl bromide	0.91	0.35	0.77	0.03	0.09	73	8.49	1.56	0.22	0.33	
29	1-Bromopentane	2.38	0.37	0.84	-0.05	0.02	122	9.87	0.87	-0.19	0.04	
30	Methyl iodide	0.64	0.12	1.18	0.09	0.09	63	9.32	0.64	0.79	0.39	
31	1-Iodobutane	2.13	0.23	1.24	-0.04	-0.10	112	11.05	0.59	-0.17	-0.21	
32	2-Iodobutane	2.04	0.29	1.08	-0.05	-0.06	110	10.46	0.77	-0.22	-0.13	
33	Propional	0.90	1.10	0.19	-0.08	0.22	69	7.30	4.94	-0.59	0.81	

$$\begin{array}{l}
 V_b = 45\alpha + 33 \\
 V_{20} = 33\alpha - 12\omega - 9\varepsilon - 9\pi - 5\beta + 55 \\
 \delta_d = (2.6\varepsilon + 6.4) V_b/V_{20} \\
 \delta_o = 330\omega/V_b \\
 \delta_x = 540\pi/V_b \\
 \delta_b = 270\beta/V_b
 \end{array}
 \left.
 \begin{array}{l}
 (r = 0.98, N = 75) \\
 (r = 0.98, N = 75) \\
 (r = 0.84, N = 25) \\
 (r = 0.92, N = 25) \\
 (r = 0.89, N = 25) \\
 (r = 0.85, N = 25)
 \end{array}
 \right\} (13)$$

The last four columns in Table IV show the numerical data we obtained with these equations for the 75 substances studied. Workers in thermodynamics should be able to say if these data seem precise. Theoretical adjustments could perhaps allow a new initiation of our program that is more accurate.

The first four factors proposed in this work are closely related to those of Laffort *et al.* ("1973 version"), as shown in Fig. 3. [We changed the letter ρ (receptor of protons) into ω (orientation), which seems more appropriate.] The new factor β (of basicity) is not well correlated with any of the old factors.

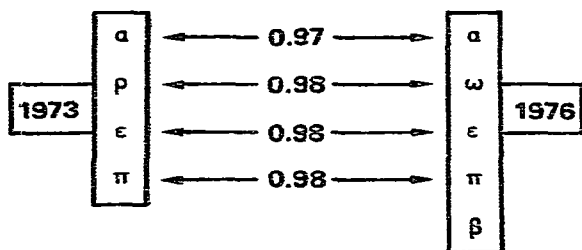


Fig. 3. Correlation coefficients (according to Pearson) between the 1973 version of molecular factors and the 1976 version for 75 substances.

APPLICATIONS IN BIOLOGY

Among the molecular properties used by some pharmacologists (Hansch²¹) for correlation with biological properties, only one is "polychromatic", *e.g.*, valid for various families of substances at once, namely the partition coefficient of octanol-water, P . This coefficient P , established for 31 of the 75 substances studied above, can be calculated from the five molecular factors with good accuracy ($r = 0.95$) by means of the equation

$$\log P = \alpha - 0.93\omega + 0.80\varepsilon - 0.29\pi - 0.22\beta + 0.38 \quad (14)$$

Therefore, the present work could perhaps be applied in pharmacology, but there is the limitation, inherent in GLC, that it cannot be used for substances of low volatility. We are now attempting to extrapolate the results obtained in gas chromatography to liquid chromatography, for the purpose of studying slightly volatile substances, but we have not yet achieved consistent results.

In fact, our general purpose is to attempt to identify the significant molecular characteristics for the neuroreceptors of the olfactory system. Highly significant cor-

relations have been established between experimental and calculated human olfactory thresholds, on the basis of the "1973 version" of molecular factors. Fig. 4 (according to Etcheto²²) shows the results obtained so far. The accuracy is comparable to that of the experiment, except for three substances. Unfortunately, these three substances are not included in the set studied in the present work. Using a five-column system filled with the five phases described above, we are therefore measuring experimentally the retention indices of the 180 substances previously studied with only four phases. We are expecting that the three exceptions in Fig. 4 will disappear.

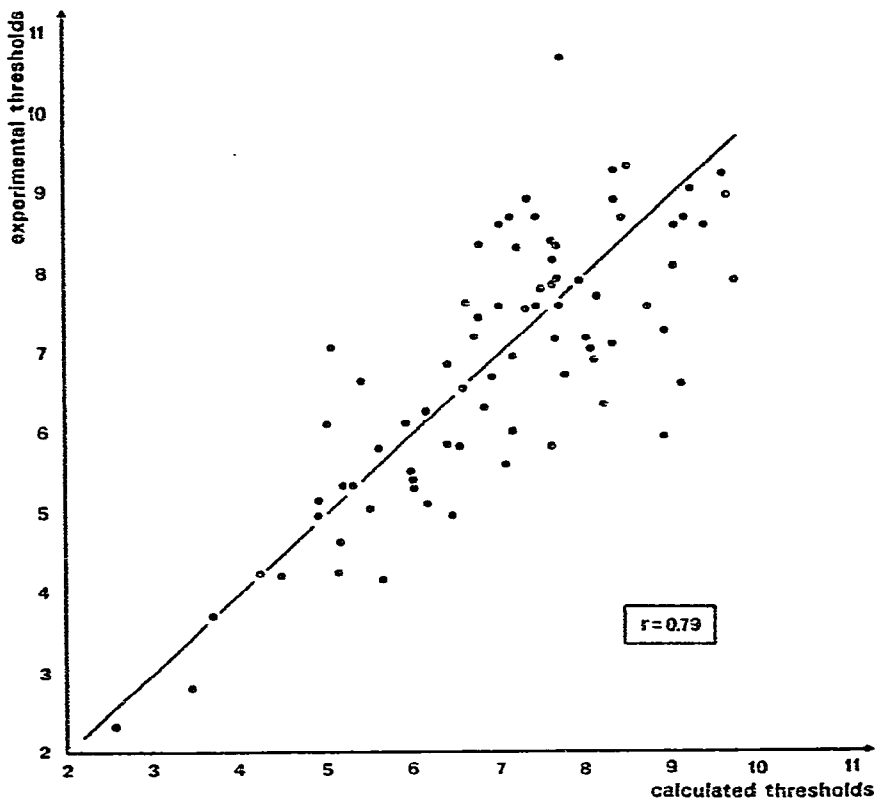


Fig. 4. Comparison between experimental and calculated human olfactory thresholds on the basis of the "1973 version" of molecular factors for 79 substances. Data are expressed as $-(\log \text{molar fractions})$. (From Etcheto²².)

Fig. 5 was proposed by Patte in 1974²³, and represents similarities and differences in the distribution of molecular factors (1973 version) for substances with various qualitative olfactory notes. It seems that a given distribution pattern can characterize only one qualitative note, even if the results are not numerous enough to be absolutely sure. We are also expecting that the taking into account of five factors will improve the correspondences.

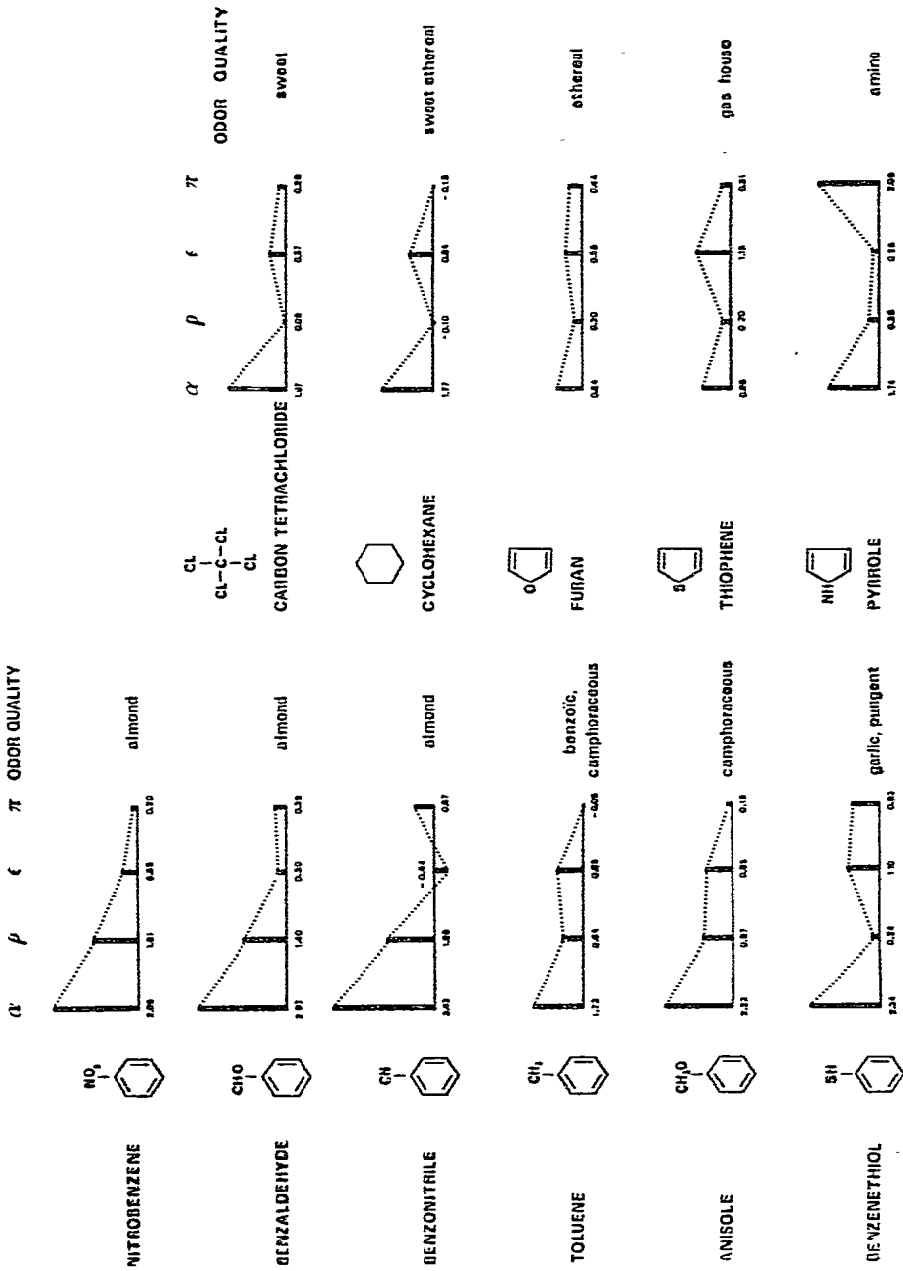


Fig. 5. Developed formulae, "physico-chemical patterns" and qualitative olfactory notes of 11 substances. It seems that similarity of odour is more related to a similarity of the "physico-chemical pattern" than to a similarity of shape (From Patte²³).

CONCLUSION

The comparison between the semi-theoretical approach of Snyder and co-workers^{10,11} and the empirical approach of Laffort *et al.*⁷ indicates confidence in each and also a mutual improvement. It is clear that on the one hand the induction solubility parameter δ_{in} does not seem to be correctly defined, and that on the other hand five factors instead of four have to be considered. However, for the remaining factors, a very good correspondence has been established. On the basis of the overlapping observed, simple equations have been proposed in order to establish the numerical values of factors in both approaches from the retention indices compared on five polar phases.

We hope that this cooperation is only a first step. Workers in thermodynamics should now be able to further refine these data, and topologists to compare them with their own approach. It will, perhaps, be possible that working together in this way will be useful not only in olfaction, but also in other scientific fields.

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