A Quantitative Structure–Activity Relationship (QSAR) Study of Alkylpyrazine Odor Modalities

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The odor strength of a series of alkylpyrazines has been quantitatively investigated applying molecular connectivity, molecular shape, and the recently developed electrotopological state indices. The successful use of the latter parameters indicates that both electronic and topological features contribute to the odor strength of the compounds under study, while the specific role of the two nitrogen atoms is revealed.

KEY WORDS: alkylpyrazines; odor strength; molecular connectivity; molecular shape; electrotopological state index.

INTRODUCTION

According to Amoore's postulation, odor characteristics of chemicals depend on the structure of the whole molecule. Thus molecular size and shape should play a predominant role in the mechanism of olfaction (1). Based on this assumption, a quantitative investigation of the relationships between odor strength and structure implies the use of whole molecule descriptors. Kier and Hall's molecular connectivity chi and molecular shape kappa indices represent suitable sets of such descriptors and have been successfully applied in QSAR studies (2–5).

Recently the electrotopological state indices for atoms in molecules have been developed by Kier and Hall (6–9). The new indices encode information about the topological as well as the electronic structure of an atom in a molecule. Since every atom is considered unique because of differences in its electronic and topological environment, the structure of the whole molecule is taken into account in order to calculate the values associated with the individual atoms. Thus the introduction of those indices in a QSAR study concerning the odor strength does not contradict Amoore's arguments, while at the same time it may clarify the involvement of specific atoms in activity.

In the present work the above-mentioned arsenal of molecular descriptors has served to analyze the odor strength of a series of alkylpyrazines. The aim of the study was to evaluate the use of the different indices and explore the contribution of the topology, the shape, and the electronic features of the molecules in odor modalities.

CALCULATION AND METHODS

The odor thresholds of 13 alkylpyrazine derivatives, expressed as parts per billion, are taken from the literature (10) and are converted to their logarithms (Table I).

The calculation of molecular connectivity chi indices is based on the hydrogen-suppressed graph of the molecules and is described in Ref. 2. The molecular shape indices were calculated according to Kier (3–5) from expressions (1)–(4).

$$^1\kappa_\alpha = (A + \alpha)(A + \alpha - 1)^2/(^1P_i + \alpha)^2 \quad (1)$$

$$^2\kappa_\alpha = (A + \alpha - 1)(A + \alpha - 2)^2/(^2P_i + \alpha)^2 \quad (2)$$

$$^3\kappa_\alpha = (A + \alpha - 1)(A + \alpha - 3)^2/(^3P_i + \alpha)^2 \quad \text{when } A \text{ is odd} \quad (3)$$

$$^3\kappa_\alpha = (A + \alpha - 3)(A + \alpha - 2)^2/(^3P_i + \alpha)^2 \quad \text{when } A \text{ is even} \quad (4)$$

where A is the number of atoms (other than hydrogens) of the molecular skeleton, and ^1P_i, ^2P_i, and ^3P_i are the numbers of possible subgraphs formed by two, three, and four vertices. The modifier α accounts for the atom-specific contribution to shape and represents the ratio of covalent radii r_x to the carbon C-sp^3 radius as shown in Eq. (5).

$$\alpha_x = (r_x/r_{C\text{-}sp^3}) - 1 \quad (5)$$

In order to obtain the electrotopological state indices, again a hydrogen-suppressed graph is used to represent the structure of the molecule and the calculations are performed as described by Kier and Hall (6–9). An intrinsic value I is assigned to each atom as $I = (\delta^v + 1)/\delta$, in which δ^v and δ are the counts of the valence and sigma electrons, excluding those bonding hydrogens, respectively. Each atom pair $i \ldots j$ defines a compartment the dimension r of which corresponds to the count of atoms in a contiguous path beginning with atom i and ending with atom j. The influence of the structural environment upon the intrinsic value I of an atom i may be considered as a summation of the interaction of all atom pairs $i \ldots j$. This interaction is assumed to be a function of the difference in the intrinsic values I_i and I_j. Its effect is less for widely separated atoms and is assumed to decrease with the square of the graph separation r^2. The overall influence is quantitated by expression (6).

$$\Delta I = \Sigma(I_i - I_j)/r^2_{ij} \quad (6)$$

The electrotopological state S of an atom is an estimate of the result of this influence on I and is defined as shown in Eq. (7).

$$S = I + \Delta I \quad (7)$$

All computations were performed with a new version of the MOLCONN2 software.[4] Multiple regression analysis has been performed in order to seek correlations between the odor thresholds and the computed structural descriptors. Table II includes the most important regression equations that have been established. All data used in those equations are reported in Table III.

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[4] The program MOLCONN2 can be obtained from Prof. L. H. Hall, Hall Associates Consulting, 2 Davis St., Quincy MA 02170.

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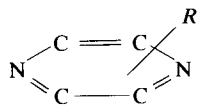
Table I. Structures and Odor Thresholds of the Alkylpyrazines Under Study



Compound no.	R	logppb
1	—	5.24
2	2-Methyl	4.78
3	2-Ethyl	3.78
4	2-Isobutyl	2.60
5	2-Methyl,5-ethyl	2.00
6	2,5-Diethyl	1.30
7	2,6-Diethyl	0.78
8	2,3 Dimethyl	3.40
9	2,5-Dimethyl	3.26
10	2,6-Dimethyl	3.18
11	2-Methyl,3-ethyl	2.11
12	2-Methyl,3-isobutyl	1.54
13	2,5-Dimethyl,6-ethyl	−0.40

RESULTS AND DISCUSSION

Equations (8) and (9) (Table II) indicate that molecular shape expressed by the κ_α indices, although an important attribute, is not a sufficient condition in determining the odor strength of the alkylpyrazines, since at least 23% of the cases remain unexplained and compound 13 is an outlier. Exclusion of that compound from the statistical analysis improves the quality of the equations [Eqs. (8*) and (9*)] considerably. Better results are obtained using higher-order molecular connectivity indices [Eqs. (10) and (11)]. Equation (10) shows satisfactory statistics, however, it cannot serve as a model for the entire series, since compound 13 remains a distinct outlier. It should be noted that compound 13 is the most potent member of the series. Structurally it differs from the other members in that it is the only trisubstituted derivative. Therefore we considered it important to seek an equation of more general validity, accounting for a larger potency range and structural differentiation. The influence of the electronic characteristics in odor strength has been explored introducing the differential molecular connectivity indices $\Delta^m\chi$ (11). The $\Delta^m\chi$ indices represent the difference between the simple and the valence connectivity indices of the same order. They

Table II. Regression Equations

	r	s	Eq. no.
logppb = $-1.00(\pm0.16)^1\kappa_\alpha + 8.54(\pm1.01)$	0.887	0.796	(8)
logppb = $-0.89(\pm0.12)^1\kappa_\alpha + 8.06(\pm0.74)$	0.916	0.576	(8*)[a]
logppb = $13.98(\pm3.22)^3\kappa_\alpha + 3.67(\pm0.97)(^3\kappa_\alpha)^2 + 14.36(\pm1.78)$	0.860	0.862	(9)
logppb = $-11.70(\pm2.32)^3\kappa_\alpha + 3.00(\pm0.70)(^3\kappa_\alpha)^2 + 12.82(\pm1.78)$	0.914	0.614	(9*)[a]
logppb = $-2.96(\pm0.32)^3\chi_p + 10.13(\pm0.82)$	0.942	0.554	(10)
logppb = $-4.30(\pm0.55)^{3v}\chi_p + 7.49(\pm0.65)$	0.920	0.649	(11)
logppb = $51.76(\pm6.33)\Delta^1\chi - 61.66(\pm7.85)$	0.927	0.623	(12)
logppb = $39.12(\pm6.33)\Delta^1\chi - 3.20(\pm1.08)^{4v}\chi_{pc} - 44.91(\pm8.09)$	0.951	0.491	(13)
logppb = $24.55(\pm3.82)\Delta^0\chi - 1.25(\pm0.23)^2\kappa_\alpha - 17.62(\pm3.89)$	0.947	0.512	(14)
logppb = $-10.49(\pm0.86)S_N + 45.09(\pm3.48)$	0.965	0.434	(15)
logppb = $94.87(\pm22.20)S_N - 13.17(\pm2.77)(S_N)^2 - 165.38(\pm44.38)$	0.991	0.252	(16)

[a] Compound 13 not included.

Table III. Molecular Shape, Connectivity, and Electropological State Indices Used in the Regression Equations in Table II

Compound no.	$^1\kappa_\alpha$	$^2\kappa_\alpha$	$^3\kappa_\alpha$	$3\chi_p$	$^{3v}\chi_p$	$^{4v}\chi_{pc}$	$\Delta^0\chi$	$\Delta^1\chi$	S_N
1	3.28	1.50	0.76	1.50	0.48	0.00	1.04	1.30	3.722
2	4.24	1.69	0.96	1.89	0.69	0.13	0.99	1.27	3.870
3	5.22	2.40	1.28	2.30	0.98	0.18	0.99	1.25	3.964
4	7.19	3.30	2.48	2.53	1.23	0.35	0.99	1.25	4.066
5	6.20	2.58	1.49	2.71	1.20	0.32	0.93	1.22	4.111
6	7.19	3.30	1.78	3.12	1.48	0.37	0.93	1.20	4.206
7	7.19	3.30	1.78	3.05	1.46	0.36	0.93	1.20	4.206
8	5.22	1.90	1.04	2.54	1.13	0.45	0.93	1.26	4.016
9	5.22	1.90	1.28	2.30	0.91	0.26	0.93	1.25	4.016
10	5.22	1.90	1.28	2.20	0.88	0.24	0.93	1.25	4.016
11	6.20	2.58	1.25	2.81	1.32	0.43	0.93	1.24	4.111
12	8.18	3.46	2.30	3.06	1.58	0.60	0.93	1.24	4.126
13	7.19	2.78	1.54	3.15	1.51	0.55	0.88	1.21	4.258

Table IV. Experimental and Calculated Data According to Eq. (16)

Compound no.	logppb(exp.)	logppb(calc.)	Residual
1	5.24	5.32	−0.08
2	4.78	4.57	0.21
3	3.78	3.79	−0.01
4	2.60	2.69	−0.09
5	2.00	2.11	−0.11
6	1.30	0.72	0.58
7	0.78	0.72	0.06
8	3.40	3.26	0.14
9	3.26	3.26	0.00
10	3.18	3.26	−0.08
11	2.11	2.11	0.00
12	1.54	1.90	−0.36
13	−0.40	−0.15	−0.25

convey electronic information concerning the presence of π and/or lone-pair electrons, which is the source of most chemical and biological activities. In addition, the $\Delta^0\chi$ values inform about the degree of substitution on heteroatoms or double bonds, while the $\Delta^1\chi$ values encode the presence and nature of all α substituent atoms (11). The introduction of $\Delta^m\chi$ as a single parameter leads to Eq. (12), which indicates a significant electronic influence in odor strength. Combining the electronic component with a higher-order connectivity or a shape term, Eqs. (13) and (14) are obtained with satisfactory statistics and no outliers. Equations (12) and (13) reveal the importance of the electronic component as influenced by the α atoms of the alkyl substituents. The path cluster connectivity index in Eq. (13) further emphasizes, in terms of topology, the contribution of molecular branching in activity. According to Eq. (14), the degree of substitution on the pyrazine nucleus may be considered as another major factor next to the molecular shape governing the odor strength of the alkylpyrazines.

Both electronic and topological features can be more efficiently described by means of the recently developed electrotopological state indices. The use of the average electrotopological state values S_N of the two nitrogen atoms—the key structural elements of the alkylpyrazine molecules, which carry most electronic information—leads to the high-quality one-parameter Eq. (15) with no outliers. Equation (15) confirms the physical meaning of Eqs. (13) and (14) and provides better information revealing the predominant role of the heteroatoms in odor strength. A parabolic relationship with S_N expressed by Eq. (16) shows even higher statistics than the linear one and accommodates compound 13 better. In this equation the disubstituted compound 6 appears to be a marginal outlier. However, since the standard deviation of Eq. (16) is very low, the absolute value of the residual obtained for compound 6 may be considered to remain within the experimental error of the data. Thus, despite this shortcoming, we suggest that Eq. (16) offers a better and more general model suitable for the description of the alkylpyrazine odor modalities. Calculated logppb values derived according to Eq. (16) and their deviations from the experimental data are reported in Table IV. Table V includes the residuals obtained for compound 13 when calculations are performed using Eqs. (10)–(16). The standard deviations of the equations are also given for reasons of comparison.

Table V. Calculated Data for Compound 13

logppb (calc.)	Residual	s	Eq. no.
0.82	−1.22	0.554	(10)
1.00	−1.40	0.649	(11)
0.88	−1.28	0.623	(12)
0.58	−0.98	0.491	(13)
0.57	−0.97	0.512	(14)
0.42	−0.82	0.434	(15)
−0.15	−0.25	0.252	(16)

CONCLUSIONS

The odor strength of the alkylpyrazines depends to a great extent on molecular shape and topology, as implied by Amoore's theory on olfaction. However, electronic features of the molecular structure proved to constitute another important attribute. From this general formalism a more specific model is generated by the use of the electrotopological state indices, and the decisive contribution of the two nitrogen atoms in odor strength is revealed.

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