Structure−Odor Relationships: Using Neural Networks in the Estimation of Camphoraceous or Fruity Odors and Olfactory Thresholds of Aliphatic Alcohols

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Structure−odor relationships were established for a sample of 99 aliphatic alcohols using a three-layer backpropagation neural network. The molecular structure was described using a common skeleton with six possible substitutions. Substituents were described using only their van der Waals volumes. The discrimination between fruity and camphoraceous odors of 67 compounds gave good results in classification (100%) and prediction (85%) phases. With the global set, the network correctly classified and predicted the camphoraceous character of compounds (100% and 95% respectively) but gave poorer results for the fruity character (87% and 74% respectively). Calculations of pOLs (pOL = −log (olfactory threshold expressed in mol/L)) of 45 camphoraceous compounds were also made. When all camphoraceous compounds were used to establish the model, 91% of the pOLs were correctly estimated. When attempts were made to predict the pOL values of 10% of the compounds from a model designed using 90% of the sample, only 74% of the pOLs were correctly estimated.

1. INTRODUCTION

Odor quality has been related to molecular properties[1−3] or structural elements.[4,5] Recently new approaches to structure−odor relationships have been developed using neural networks.[6−8] Chastrette and Saint-Laumer[9] modeled the structure−odor relationship of 79 nitrobenzene compounds using a multilayer backpropagation network[10,11] and obtained a classification rate of 94% and a prediction rate of 77%.

Chastrette and Zakarya[12] also used neural networks to study a series of 53 tetralins and 15 indans bearing a carbonyl function. All tetralins were correctly classified in the training phase, all indans were subsequently correctly predicted in the test phase, and it was possible to measure the relative contribution of each descriptor to the classification.

Chastrette and El Aïdi[13] extended these methods to a global set of 105 molecules comprising tetralins, indans, and nitrobenzene compounds. The neural network yielded a correct classification rate of 98.1% and a correct-prediction rate of 80%.

Structure−olfactory threshold relationships have been much less studied. Anker et al.[14] correlated the olfactory thresholds of 53 alcohols (selected for their similarity and possessing different odor qualities) with their structure, using the ADAPT software. Four descriptors were selected by a regression analysis. The better results were obtained with two topological descriptors, one geometric descriptor and one geometrical/electronic descriptor ($r = 0.894$; $s = 0.469$). These results were improved by removing four outliers. Zakarya[15] used an autocorrelation method on the same set. Good correlations were obtained with V_0 and V_6 components of the Volume vector and removal of five outliers ($r = 0.91$, $s = 0.43$).

The aim of the present work was to study the potential of neural networks on a series of aliphatic alcohols in a combined approach consisting first of the classification and prediction of camphoraceous and fruity odors and then the calculation of the olfactory thresholds of camphoraceous compounds.

2. MATERIALS AND METHODS

2.1. Materials. The olfactory properties of the alcohols in our sample were taken from a work of Schnabel et al.[16] who described both the odor notes and the olfactory thresholds of 99 aliphatic alcohols. They used 15 notes (or odor qualities) to describe the olfactory properties. The intensity of each note was estimated on a 1−5 scale. The most frequent notes were "etherisch" (defined using camphor as reference and therefore termed camphoraceous in our study) and "fruchtig" (translated as fruity). Alcohols were considered as camphoraceous or fruity if the intensity of the corresponding note was greater than or equal to 3.

Schnabel et al.[16] gave two values for the olfactory thresholds in water, expressed in μmol/L. The first is the concentration at which the odor was still perceptible, and the second the concentration at which the odor was no longer perceptible. These olfactory thresholds were converted into pOLs, defined as pOL = −log (olfactory threshold expressed in mol/L) and gave a minimum pOL (first value) and a maximum pOL (second value). The mean of these two values was used in our calculations.

The set of all 99 alcohols was used to classify and predict the camphoraceous and the fruity notes. We also used a reduced set, designated A, containing only the 67 alcohols which present a camphoraceous or a fruity note with an intensity greater than or equal to 3. A third set, designated B, containing the 45 camphoraceous alcohols was used to calculate the pOLs.

The pOL values, the intensity of camphoraceous and fruity notes, the possible other notes of the 99 alcohols, and the sets to which the compound belong are given in Table 1.

2.2. Description of the Structure. The same description of structure was chosen for the quality and threshold studies.

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Table 1. pOL Values of the 99 Camphoraceous Alcohols Given by Schnabel

no.	compd	min pOL	max pOL	C[a]	F[b]	set	other notes
1	methanol	1.43	1.60				pungent 4, aromatic 1
2	ethanol	3.07	3.47		2		pungent 2
3	propanol	3.89	4.03		2		pungent 4
4	1-butanol	4.57	4.96		4	A	
5	2-methyl-1-propanol	3.57	3.96	3	3	B	
6	1-pentanol	4.34	4.74	1	4	A	
7	2-methyl-1-butanol	5.33	5.55	1	4	A	
8	3-methyl-1-butanol	4.34	5.04	1	4	A	
9	2,2-dimethyl-1-propanol	4.55	5.03	4		A B	acid 1
10	1-hexanol	4.80	5.10	1	4	A	
11	2-methyl-1-pentanol	4.92	5.09		3	A	fresh 2
12	3-methyl-1-pentanol	4.40	5.09		5	A	
13	4-methyl-1-pentanol	4.40	5.10	3	1	A	
14	2-ethyl-1-butanol	5.39	6.10	4		A B	
15	2,2-dimethyl-1-butanol	4.09	4.39	4		A B	metallic 1
16	2,3-dimethyl-1-butanol	4.62	5.09		2		soapy 3
17	3,3-dimethyl-1-butanol	8.08	9.10	3	2		faecal 4
18	1-heptanol	5.30	5.55		3		soapy 3
19	5-methyl-1-hexanol	5.30	5.46		4	A	soapy 1
20	2,2-dimethyl-1-pentanol	6.46	7.15	1	4	A	
21	2,3-dimethyl-1-pentanol	4.85	5.15	4	2	A B	
22	2,4-dimethyl-1-pentanol	5.47	5.68		2		faecal 1
23	1-octanol	6.19	6.49		2		soapy 4
24	2-ethyl-1-hexanol	4.94	5.19	4	2	A B	
25	2,2,4-trimethyl-1-pentanol	5.20	5.49		2		floral 4
26	1-nonanol	6.24	6.54		1		soapy 4
27	1-decanol	7.28	7.38				soapy 5
28	1-undecanol	5.62	6.30				oily 5, soapy 4
29	1-dodecanol	5.66	6.30				soapy 5
30	2-propanol	2.89	3.18				pungent 4
31	2-butanol	3.27	3.66	2	3	A	
32	2-methyl-2-propanol	3.59	3.96	4		A B	metallic 3
33	2-pentanol	3.74	4.04	1	4	A	
34	2-methyl-2-butanol	3.43	3.64	5		A B	
35	3-methyl-2-butanol	5.03	5.34	4		A B	
36	2-hexanol	5.40	6.10	2		B	floral 2
37	2-methyl-2-pentanol	4.10	4.40	4	1	AB	
38	3-methyl-2-pentanol	4.39	5.09	4		A B	
39	4-methyl-2-pentanol	4.40	4.62	4	2	A B	
40	2,3-dimethyl-2-butanol	5.09	6.10	5		A B	
41	3,3-dimethyl-2-butanol	4.40	4.80	5		A B	
42	2-heptanol	6.15	6.46		4	A	sweet 1
43	2-methyl-2-hexanol	4.55	4.85		4	A	sweet 1
44	3-methyl-2-hexanol	5.46	6.15	5	1	A B	
45	5-methyl-2-hexanol	5.25	5.55		4	A	soapy 1
46	3-ethyl-2-pentanol	5.43	5.66	3	1	A B	
47	2,3-dimethyl-2-pentanol	4.44	4.85	4		A B	sweet 1
48	2,4-dimethyl-2-pentanol	4.46	4.68	3		A B	musty 1
49	4,4-dimethyl-2-pentanol	6.15	6.46	3		A B	acid 1
50	2-octanol	6.49	7.22		2		musty 2
51	2-methyl-2-heptanol	5.51	5.92		3		floral 3
52	6-methyl-2-heptanol	5.51	6.52		3		acid 3
53	2,3-dimethyl-2-hexanol	5.29	5.49	4		A B	
54	2,5-dimethyl-2-hexanol	4.89	5.02		1		floral 4
55	3,4-dimethyl-2-hexanol	4.49	5.19	4		A B	
56	2-nonanol	6.24	6.40		4	A	green 1
57	2-decanol	6.59	6.80				soapy 4, acid 2
58	2-undecanol	6.62	7.30				soapy 4
59	2-dodecanol	6.36	6.66				metallic 5
60	3-pentanol	4.03	4.19	4		A B	
61	3-hexanol	4.62	5.10	4		A B	
62	2-methyl-3-pentanol	5.09	5.39	4		A B	
63	3-methyl-3-pentanol	4.40	4.62	5		A B	
64	3-heptanol	5.46	5.68		4	A	
65	2-methyl-3-hexanol	6.15	6.40	4	1	A B	
66	3-methyl-3-hexanol	6.15	6.40	4		A B	musty 1
67	4-methyl-3-hexanol	5.43	5.82	4		A B	
68	5-methyl-3-hexanol	5.15	5.46	4		A B	musty 1
69	3-ethyl-3-pentanol	6.14	6.44	4		A B	musty 1
70	2,2-dimethyl-3-pentanol	6.15	6.46	4		A B	
71	2,3-dimethyl-3-pentanol	5.14	5.44	4		A B	
72	2,4-dimethyl-3-pentanol	5.44	6.15	4		A B	almond 1
73	3-octanol	5.72	6.22	2	4	A	
74	2-methyl-3-heptanol	5.36	5.60	3		A B	musty 2
75	3-methyl-3-heptanol	6.49	7.22		2		floral 3

Table 1 (Continued)

no.	compd	min pOL	max pOL	C[a]	F[b]	set	other notes
76	4-methyl-3-heptanol	5.51	5.74	4	1	A B	
77	5-methyl-3-heptanol	6.22	6.52	1	3	A	
78	6-methyl-3-heptanol	5.49	5.72	1	4	A	
79	4-ethyl-3-hexanol	5.89	6.22	4		A B	
80	2,2-dimethyl-3-hexanol	7.52	8.00	4	1	A B	
81	2,3-dimethyl-3-hexanol	6.49	7.22	4	1	A B	
82	2,4-dimethyl-3-hexanol	5.49	5.72	4		A B	musty 1
83	2,5-dimethyl-3-hexanol	4.89	5.51	4	2	A B	
84	3,5-dimethyl-3-hexanol	5.35	5.49	4		A B	musty 1
85	2,2,4-trimethyl-3-pentanol	6.49	7.22	4		A B	
86	3-nonanol	5.77	6.22		2		soapy 4
87	3-decanol	5.59	6.30		2		soapy 4
88	3-undecanol	6.62	7.30		2		metallic 3
89	3-dodecanol	6.36	6.66		1		soapy 4
90	4-heptanol	5.15	5.45		3	A	floral 2
91	4-octanol	5.20	5.51		3		soapy 2, acid 3
92	2-methyl-4-heptanol	5.21	5.51	4	2	A B	
93	3-methyl-4-heptanol	5.49	6.22	4	2	A B	
94	4-methyl-4-heptanol	5.20	5.36	1	3	A	acid 2
95	4-nonanol	5.54	6.22				green 3
96	4-undecanol	6.32	6.62		3	A	acid 2
97	5-nonanol	5.77	6.22		5	A	
98	5-undecanol	5.32	5.62		1		soapy 4
99	6-undecanol	6.62	7.30				metallic 3, soapy 1

[a] C = camphoraceous. [b] F = fruity.

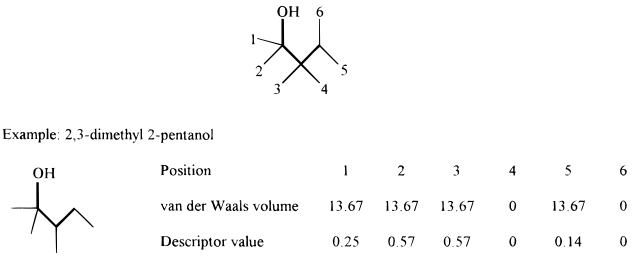

Figure 1. Common skeleton and example of coding.

Eminet and Chastrette[17] have shown that a camphoraceous odor appears in compounds of various structures and functions, only if the molecule has a roughly spherical shape and a convenient volume. Many camphoraceous compounds contain only carbon and hydrogen atoms and this suggests that interactions with the receptors are mainly dispersion interactions. Thus, the substituents are supposed to interact mainly through their volume and polarizability, which are well represented by van der Waals volumes for alkyl substituents of equivalent polarizability.

In a preliminary study[18] of the 99 Schnabel's alcohols we stressed that branched alcohols had a camphoraceous odor, whereas straight-chain alcohols tended to have a fruity odor. The importance of the branching type on carbon atoms in α and β of the function on the olfactory thresholds of the camphoraceous compounds was also noticed.

Thus, to describe the structure in a simple way, we determined a common skeleton with six substitution positions (indicated in bold in Figure 1) for the 99 alcohols and described the substituents 1−6 by their van der Waals volumes.[19] The common skeleton was chosen considering a common pattern, indicated in bold in Figure 2, displayed by compounds with a low olfactory threshold.

The input values were obtained by dividing these volumes by the highest volume found in that particular position.

2.3. Neural Networks. Three-layer backpropagation learning networks[20] with a complete connection among the three layers were used (Figure 3).

The number of neurons in the input layer was six, that is the same as the number of molecular descriptors. The number of neurons in the hidden layer was determined by trial and error, respecting the empirical rule mentioned by So and Richards,[21] based on the ρ ratio: ρ = (number of data points in the training set)/(number of adjustable weights controlled by the network).

The range $1.8 < \rho < 2.2$ has been suggested as an empirical guideline of acceptable ρ values. It has been claimed that, for $\rho << 1.0$, the network simply memorizes the data, while for $\rho >> 3.0$, the network is not able to generalize. So we used a number of neurons in the hidden layer allowing to maintain ρ in the $1 < \rho < 3$ range, to avoid these two problems.

The activation function was a sigmoïd. The number of neurons on the output layer depended on the property studied.

For set A, used to classify and predict the camphoraceous or the fruity odor, the output layer contained one neuron, coded 0.2 for the fruity compounds and 0.8 for the camphoraceous compounds. For the complete set, used to predict both the camphoraceous and the fruity characters, the output layer contained two neurons. The first was used to code the camphoraceous character (0.2 for "not camphoraceous" compounds and 0.8 for camphoraceous compounds) and the second to code the fruity character (0.2 for "not fruity" compounds and 0.8 for fruity compounds). The compounds were considered as correctly classified or predicted if the absolute value of (calculated output−expected output) was lower than or equal to 0.3.

For set B, the output layer contained one neuron with the mean pOL divided by 10, as the expected output value.

Two phases were used: a learning (classification) phase and a prediction (test) phase. The learning phase consisted in reducing the error resulting from the comparison of the output computed by the network to the desired output, by adjusting the weights inside the network through an iterative process of gradient backpropagation. In the test phase a

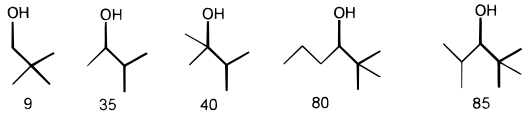

Figure 2. Structure of compounds with the pattern characteristic of low olfactory thresholds.

leave-out procedure was used, and 90% of the compounds were used to train the network and predict the other 10%.

3. RESULTS AND DISCUSSION

All tested configurations had six neurons on the input layer and one or two on the output layer. The best configuration, determined by trial and error, contained a different number of neurons on the hidden layer for each set and the following activation function parameter values: learning rate $\alpha = 0.9$ and momentum $\eta = 0.2$.[21]

Each configuration was tested five to ten times with the number of cycles limited to 5000. In most cases a smaller number of cycles was enough to obtain stable results.

3.1.1. Set A. The hidden layer contained three neurons ($\rho = 2.7$). We also used four neurons on the hidden layer and obtained very similar results, not recorded here.

Discrimination of Compounds with a Camphoraceous or a Fruity Odor. The learning phase was performed on set A comprising 67 compounds with either a camphoraceous (coded 0.8) or a fruity (coded 0.2) odor. All the compounds (100%) were correctly classified in repeated tests.

Prediction of Camphoraceous or Fruity Odors. The predictive ability of the network was tested on 11 test-sets, 10 of which contained six compounds, while one contained seven compounds (that is about 10% of the complete set), making it possible to predict all the compounds of set A. The corresponding training sets comprised 61 and 60 compounds, respectively.

The results were poorer (85% of good predictions) than in the classification phase. Six fruity compounds (7, 20, 43, 77, 90, 94) were predicted as camphoraceous and four camphoraceous compounds (37, 39, 61, 66) as fruity.

Among the 23 compounds of set A with a quaternary carbon atom, 20 were camphoraceous and only three fruity. These three fruity compounds (20, 43, 94) were predicted as camphoraceous, probably due to this peculiar distribution.

Compound 7 was predicted as camphoraceous probably because it displayed a pattern characteristic of many camphoraceous compounds with low olfactory thresholds (Figure 2). Compounds 77 and 90 were wrongly predicted as camphoraceous. They have seven carbon atoms in their longer chain, i.e., only one carbon atom more than compounds 68 and 61 which are camphoraceous, but this seems enough to make them fruity.

The camphoraceous compounds wrong prediction as fruity is probably due to the fact that they have relatively few branchings.

The set A is relatively small, but the olfactory properties were described by Schnabel for 99 alcohols only. This set comprises all the compounds with less than six carbon atoms, 23 out of the 33 C7 alcohols and 39 C8 alcohols. Thirteen unsubstituted alcohols with 9−12 carbon atoms are also described. Olfactory properties of other alcohols with eight carbon atoms were probably given by other authors but were not included in our sets, to keep consistent data.

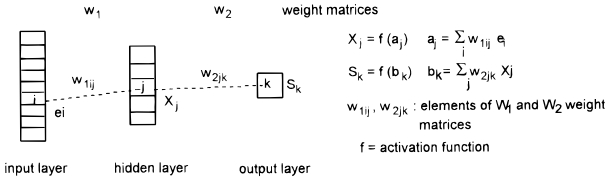

Figure 3. Structure of the multilayer neural network.

3.1.2. The Global Set. The number of neurons on the hidden layer was seven ($\rho = 1.5$).

Classification Phase. The camphoraceous character was correctly estimated for the whole set (100%) and the fruity character almost as well (95%), as only four fruity compounds (51, 52, 56, 96) were classified as not fruity.

Compounds 51 and 52 were described as "fruity 3, floral 3" and "fruity 3, acid 3", respectively. Their misclassification could be related to the fact that the fruity note is not their main note.

In the global set compounds 56 and 96 were similar to long chain compounds 57, 58, 98, and 99, which are not fruity but rather soapy, green, or metallic. However, compounds 56 and 96 were correctly classified when set A, comprising only fruity long chain compounds and not compounds 57, 58, 98, and 99, was used.

Prediction Phase. Camphoraceous Odor. Correct predictions were obtained for 87% of the molecules in the global set. Four "not camphoraceous" (7, 16, 77 and 94) and five "camphoraceous" (21, 24, 44, 61 and 66) alcohols were incorrectly predicted. Compounds 7, 77, and 94 were already incorrectly predicted in set A. Compound 16 which was not in set A was probably predicted as camphoraceous in the global set because of its structural similarity to compound 7. Compounds 61 and 66, which were predicted as fruity in set A, were predicted as "not camphoraceous" in the global set.

Fruity Odor. Correct predictions were obtained for 75 molecules (74%) in the global set. Compounds 20, 43, 77, and 94 were incorrectly predicted in the global set just as in set A. Compounds 51, 52, 56, and 96 were incorrectly predicted as one would expect after their misclassification in the first step. Generally, the relatively long compounds with few branchings, e.g., 23 or 36, were predicted as fruity instead of "not fruity" and, conversely, the short-chain compounds, e.g., 31 or 33, were predicted as "not fruity" instead of fruity.

The poor results obtained for the prediction of fruity odors can be explained by the difficulty of assigning particular structural parameters to fruity compounds, e.g., the odor of long chain compounds is often described as soapy but can also be fruity. Our descriptors are better adapted to camphoraceous odor−structure relationships.

3.2. Estimation of the pOLs. 3.2.1. Learning Phase. First, the network was trained on set B comprising all the 45 camphoraceous alcohols. In most of our computations, 71% of the estimated pOLs were in "min pOL/max pOL" range. To make up for any possible (and probable) inaccuracy in the experimental values, this range was increased to "min pOL−0.3/max pOL + 0.3". Then, correct prediction was obtained for 41 compounds (91%). Only four compounds (41, 49, 65, 71) were slightly out of this range (Figure 4).

The calculated pOLs of alcohols 41 and 71 were higher than the experimental pOLs. Compounds 41 and 71 display

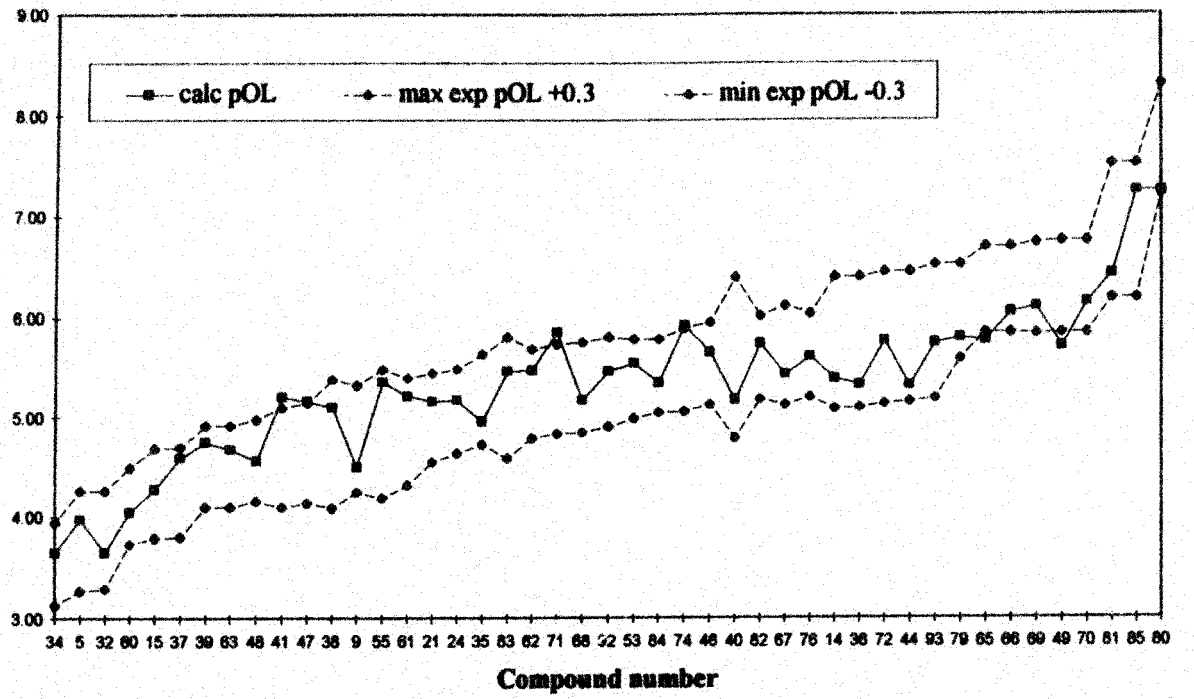

Figure 4. pOLs calculated with the all set B (learning phase).

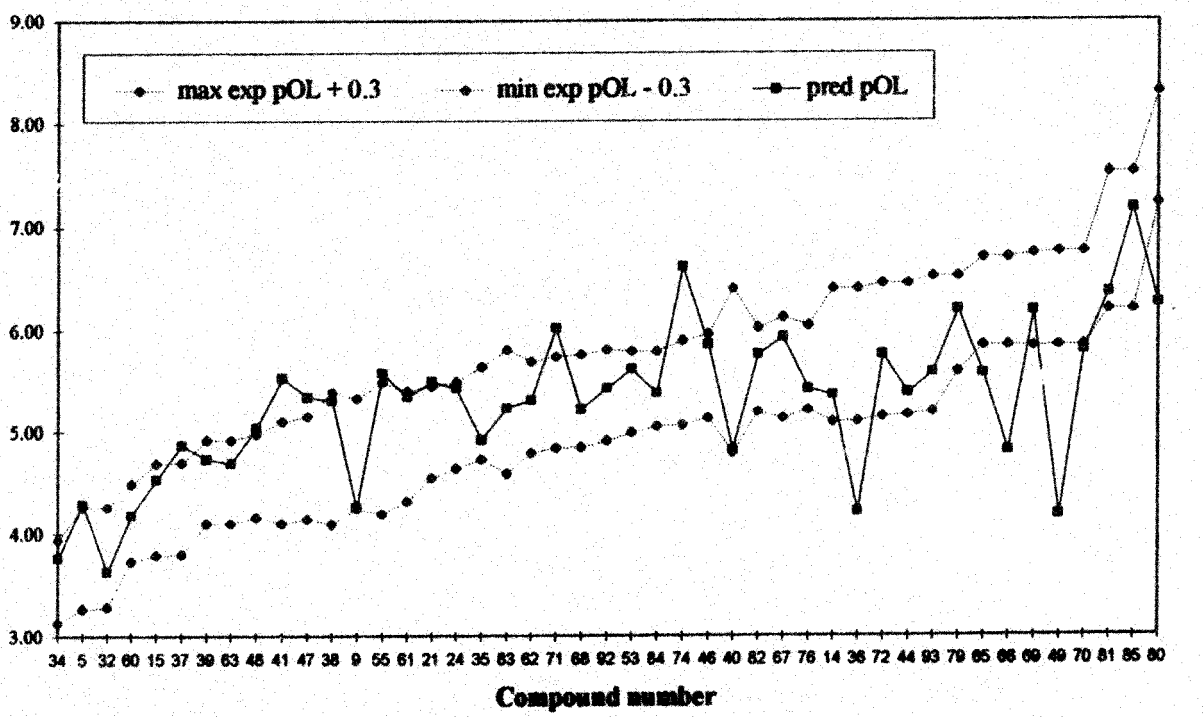

Figure 5. pOLs calculated with reduced sets (test phast).

the common pattern also found in compounds 9, 35, 40, 80, and 85 (Figure 2) characterized by their high pOL values. The high calculated values are consistent with the values of these alcohols.

Compound 49 does not show the same high pOL characteristic pattern, yet the value of its experimental pOL is similar to those of the compounds with the pattern. The network calculated its pOL as if it was a compound without the pattern, thus yielding an underestimated value.

3.2.2. Test Phase. Next, to test for the particular learning that took place, the network was trained on reduced sets comprising 40 or 41 compounds. The trained networks were used to estimate the pOLs of the four or five remaining compounds. Thus, pOLs were calculated for all compounds of the set.

The results were poorer than when the pOLs were calculated from the training of the whole set. The main difference was that the results were less reproducible than with the whole of set B. This phase yielded a rate of 78% of correctly predicted pOLs (Figure 5).

The pOLs of compounds 41, 49, 65, and 71 which were poorly calculated in the first step were again incorrectly estimated. Compounds 41, 47, 71, and 74, all with the characteristic high pOL pattern, were overestimated by the

network. The pOL of compounds 49 and 66 was underestimated. Despite its characteristic pattern, compound 80 display a very high experimental pOL (7.8, the highest of the set), which was underestimated.

4. CONCLUSION

Structure−odor relationships were established for a sample of 99 aliphatic alcohols with various odors including camphoraceous and fruity. The molecular structure was described using a common underlying skeleton with six possible substitutions. Substituents were described using only their van der Waals volumes. This very simple description is well adapted to the description of short-chain branched compounds but proved insufficient for describing longer and more flexible molecules.

In all estimations of odor quality the networks gave good results. Both classification and prediction were quite good (85−100%) when the problem was reduced to the discrimination of 67 compounds that were either camphoraceous or fruity. With the global set where the network had to discriminate among compounds with other notes, the results were less satisfactory (87−100% correct classification and 74−95% correct prediction). However, camphoraceous compounds were in all cases correctly estimated, according to their known structure−odor relationships and to the adequacy of our structural description. Fruity odors are a more difficult problem as compounds with a long chain may be either fruity or soapy. Moreover, our description is not very effective with long chain compounds.

The calculation of pOLs that are continuous values was more difficult. When all camphoraceous compounds were used to establish the model, 91% of the estimated values were in the "min pOL−0.3/max pOL + 0.3" range. When attempts were made to predict the pOL values of 10% of the compounds from a model designed using 90% of the sample, only 74% of the estimated values were in the "min pOL−0.3/max pOL + 0.3" range. However, our estimation of the experimental error in the measurement of pOLs is certainly very moderate, as errors of one order of magnitude are frequently encountered in the literature.

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