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A Model for Odor Thresholds

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Abstract

Odor detection thresholds, that we have previously obtained, have been analysed by a general equation for selective transport. It is shown that such selective transport can account for some 77% of the total effect. The remainder is due to a specific size effect, that might involve odor-binding proteins, and a specific effect for aldehydes and carboxylic acids. Our analysis raises the question of whether selective transport is physically separable from the specific effects of receptor activation. The model predicts a chemical cut-off in odor detection along any homologous series.

Introduction

There have been a number of correlations of odor detection thresholds with various properties of odorants, the study by Laffort and Patte (1987) being one of the first to employ a physicochemical analysis. Chastrette (1997) has reviewed work up to 1996; many studies involved sets of odorants of similar structure, and none led to any conclusions of mechanistic significance. Two subsequent studies related odor detection thresholds (ODT) to properties of homologous series of odorants. Yamanaka (1995) showed that odor thresholds of Davos et al. (1990) for several homologous series could be correlated with the odorant activity coefficient in water, γ_W, through a

set of equations of the type,

$$\log (1/\mathrm{ODT}) = a \log \gamma_W + b \qquad (1)$$

where *a* and *b* differ for each homologous series. A much more detailed analysis was carried out by Hau and Connell (1998) who used the following representation of a possible mechanism,

$$[\mathrm{VOC}]\mathrm{air} \xrightarrow{K^{AM}} [\mathrm{VOC}]\mathrm{mucus} \xrightarrow{K_{MB}} [\mathrm{VOC}]\mathrm{bio} \xrightarrow{K_R} [\mathrm{VOC\text{-}R}] \qquad (2)$$

where [VOC]air is the concentration of an odorant, or volatile organic compound (VOC) in air, [VOC]mucus is the concentration in the mucus, [VOC]bio is the VOC concentration in the biophase that contains the olfactory receptor, and VOC-R is the concentration of the VOC-receptor complex. The equilibrium constants for the three stages are denoted here as K^{AM}, K_{MB} and K_R. From Equation (2), a connection between ODT values and VOC partition coefficients was deduced as,

$$\log [\{\mathrm{ODT}\}K^W] = - a \log \mathrm{Poct} + b \qquad (3)$$

where K^W is the air-water partition coefficient, also known as the Ostwald solubility coefficient, and Poct is the water-octanol partition coefficient. The ODT values were from the AlHA compilation (AlHA 1989); the coefficients *a* and *b* vary from one homologous series to another. The interpretation of Equation (3) was that K^W is an approximation for K^{AM}, since both refer to the equilibrium between the gas phase and an aqueous condensed phase, and that K_{MB} and K_R are both functions of Poct.

Both Equations (1) and (3) suffer from shortcomings as predictive equations, in that only homologous series can be considered. This excludes numerous types of important VOCs such as inhalation anaesthetics and terpenes that do not fall into any homologous series. The model of Hau and Connell (1998) is significant, however, because it is the only real attempt to correlate ODT values on any mechanistic basis.

There have been studies using sets of varied structural types of VOCs, rather than restriction to homologous series. Dravnieks (1974) correlated four sets of threshold data of vapors, using various structural features as the independent variables, but results were not very good, with r^2 ranging from 0.42 to 0.58 with four

independent variables. Such methods may be useful as empirical correlations, but yield little mechanistic information.

In order to investigate odor thresholds in more detail, it is important to understand the way in which olfactory perception is processed, via the relationship between odor stimuli and the receptive surface (Pearce *et al*., 1998). Once in the airspace above the olfactory mucosa, the molecules must diffuse through a layer of mucus (10-30 microns thick) to gain final access to the receptors themselves (Hornung and Mozell, 1981; Snyder *et al*., 1988). Such diffusion, or transport, may involve (at least in part) odorant binding proteins (OBPs) that can act as carriers (Bianchet *et al*., 1996; Brownlow and Sawyer, 1996; Tegoni *et al*., 1996; Löbel *et al*., 2001). The central pocket in the OBP has dimensions of 11×10×7 A (ie 770 A^3) with an opening size of 6×7 A (Tegoni *et al*., 1996), although a much larger cavity of 1100-1300 A^3 has been suggested (Bianchet et al., 1996). Once transported across the mucosal layer to a receptor area or biophase, the VOC (or the VOC/OBP complex) can then interact with odor receptors at the surface of the cilia membrane of the olfactory neuron. The actual binding pocket in the rat OR5 receptor, however, is no less than 12 A from the extracellular surface of the receptor (Singer and Shepherd, 1994). A general model that we suggest is shown in Figure 1. It is useful to consider two types of interaction. Simple transport processes are selective, in that different VOCs will have different equilibrium constants, depending on their structure. However, small changes in structure or small positional changes of functional groups have rather small effects on such processes. On the other hand, in processes such as ligand/receptor interactions, small changes in structure can have very large effects; we refer to these processes as having specific effects. In Figure 1 we indicate which processes may be selective and which may be specific in nature.

Whether the VOC/OBP interactions and the VOC/R interactions are general interactions that can be modelled by a physicochemical transport process, or whether they are more specific interactions, is a crucial point. The analysis of Hau and Connell (1998) certainly supposes that the VOC/R interaction is a general interaction that can be modelled by a simple physicochemical descriptor, such as log Poct.

Our approach is first to use a model that simply reflects a passive physicochemical transport property. Comparison with physicochemical transport to various solvents or to various biophases will then indicate whether or not such passive transport can

model all or part of the odor detection process.

Methodology

We have devised a very general equation for the correlation of a variety of processes in which VOCs are transferred from the gas phase to some condensed phase (Abraham *et al.*, 1991; Abraham, 1993),

$$\log SP = c + e\mathbf{E} + s\mathbf{S} + a\mathbf{A} + b\mathbf{B} + l\mathbf{L} \quad (4)$$

The dependent variable, log SP, is some property of a series of volatile organic compounds (VOCs) in a given system. The independent variables in Equation (4) are (Abraham, 1993) properties of the VOCs. We use a simplified nomenclature, with the original nomenclature in parentheses: **E** (R_2) is an excess molar refraction, **S** (π_2^H) is the dipolarity/polarizability, **A** ($\Sigma\alpha_2^H$) and **B** ($\Sigma\beta_2^H$) are the overall or effective hydrogen-bond acidity and basicity, and **L** ($\log L^{16}$) is defined through L^{16}, the solute Ostwald solubility coefficient on hexadecane at 298K. The **L**-descriptor is itself a combination of two solute properties, (i) a general measure of solute size, and (ii) the ability of a solute to interact with a solvent phase through dispersion forces. The units of **E** are $cm^3/10$; the other descriptors have no units because they are all derived from the logarithm of an equilibrium constant. The coefficients *c*, *e*, *s*, *a*, *b* and *l* are found by multiple linear regression analysis. They reflect the complementary properties of the receptor phase. The *e*-coefficient gives the tendency of the phase to interact with VOCs through polarizability-type interactions, mostly via electron pairs. The *s*-coefficient is a measure of the phase dipolarity/polarizability. The *a*-coefficient represents the complementary property to VOC hydrogen-bond acidity and so is a measure of the phase hydrogen-bond basicity. Likewise, the *b*-coefficient is a measure of the phase hydrogen-bond acidity. Finally, the *l*-coefficient is a measure of the hydrophobicity of the phase. Equation (4) has been applied to numerous gas-solvent partitions (Abraham *et al.*, 1994b, 1998b, 1999a, 1999b), to gas-biophase partitions (Abraham and Weathersby, 1994), and to a very large number of gas chromatographic systems (Abraham *et al.*, 1999c), so it is a well tried and tested equation.

We have previously used Equation (4) to correlate nasal pungency threshold values (NPT, in ppm) for 43 varied compounds (Abraham *et al.*, 1998a), resulting in

Equation (5),

$$\log (1/NPT) = -8.519 + 2.154\,\mathbf{S} + 3.522\,\mathbf{A} + 1.397\,\mathbf{B} + 0.860\,\mathbf{L} \quad (5)$$

$n = 43$, $r^2 = 0.955$, SD = 0.27, F = 201

Here and elsewhere, n is the number of data points (i.e. the number of VOCs), r is the correlation coefficient, SD is the standard deviation in the dependent variable, and F is the F-statistic. The *e*-coefficient of the independent variable, **E**, was statistically not significant. The reciprocal of NPT values were used, so that the more potent the VOC the larger is the value of log(1/NPT).

The coefficients in Equation (5) can be compared to those for various gas-condensed phase partitions that take place by simple transfer mechanisms, as shown in Table 1 (Abraham *et al*., 1994b, 1998b, 1999a, 1999b). There is considerable similarity between the NPT equation and equations for the solubility of gaseous VOCs in solvents such as wet 1-octanol and methanol. There is also some similarity with equations for the solubility of gaseous VOCs in a number of biophases (Abraham and Weathersby, 1994). There is therefore nothing extraordinary about Equation (5), which can be regarded as an equation for simple transfer of VOCs from the gas phase to a biophase. It is noteworthy that Equation (5) encompasses a wide variety of VOCs, including carboxylic acids, aldehydes, ketones, alcohols, etc., with but one outlier - acetic acid. Following the analysis of Abraham *et al*. (1994a), Equation (5) could be interpreted as arising from transport of VOCs to a biophase, followed by activation of a receptor through an 'on-off' mechanism that was independent of the structure of the VOC.

Our strategy is to apply the general Equation (4) to ODT values, in the hope that we might deduce whether or not the resulting equation is consistent with simple transfer of VOCs from the gas phase to a biophase.

Results and Discussion

General analysis - Odor detection thresholds, ODT, for a series of 64 compounds, including esters, aldehydes, ketones, alcohols, carboxylic acids, aromatic hydrocarbons, terpenes and a number of other VOCs, have been determined by Cometto-Muniz and Cain (1990, 1991, 1993, 1994, 1995) and by Cometto-Muniz *et*

al.(1998a, 1998b), using a standardized protocol. This protocol entails direct measurement of vapor phase concentration of the VOCs for as many steps on the dilution series of each VOC as the sensitivity of an FID gas chromatographic detector (or sometimes a PID detector) allows; this is a rarity in olfactory research. The average standard deviation for all odor thresholds, expressed as log (1/ODT) is 0.63 log unit. The VOCs used in these studies are listed in Table 2, together with log (1/ODT) values, where ODT is in ppm. The corresponding VOC descriptors are given in Table 3. As a first step we applied Equation (4) to all the VOCs except the carboxylic acids and aliphatic aldehydes that were clearly out-of-line. The VOCs, propanone, 1-octanol, methyl acetate and t-butyl acetate were then also revealed to be outliers, and were removed to yield the correlation equation,

$$\text{Log (1/ODT)} = -5.154 + 0.533\,\mathbf{E} + 1.912\,\mathbf{S} + 1.276\,\mathbf{A} + 1.559\,\mathbf{B} + 0.699\,\mathbf{L} \qquad (6)$$

$$\qquad\qquad\qquad 0.410 \quad 0.455 \quad 0.623 \quad 0.775 \quad 0.732 \quad 0.072$$

$n = 50$, $r^2 = 0.773$, $q^2 = 0.603$, SD = 0.579, F = 28.7

Here, and elsewhere, q^2 is the coefficient of cross-validation, a useful measure of internal self-consistency. The SD values of the coefficients themselves are given below the coefficients. It is of considerable interest to compare the coefficients in the above equation with the coefficients for the other processes shown in Table 1. It can be seen that the coefficients in Equation (6) are of the same sign and similar order of magnitude as those for transfer from the gas phase to organic solvents. For example, Equation (6) compares well with the equations for gas/methanol or gas/wet 1-octanol, as well as with the NPT Equation (5). Results of our analysis are therefore compatible with the possibility that simple transfer from the gas phase to a biophase might play a substantial role in the relationship of odor thresholds to the structure of VOCs, of the order of 77% of the total effect.

The closeness of Equation (6) to Equation (5), shows also that values of log (1/NPT) and log (1/ODT), except for the aldehydes and carboxylic acids, will be reasonably well correlated, which is indeed the case. Inspection of Table 1 also leads to the conclusion that the aqueous mucus layer that covers the olfactory epithelium does not influence the transport process, because the equation for gas/water transfer (Abraham *et al*., 1994b) is completely different to Equation (6). The latter equation is

also in agreement with the finding that the odor receptor binding pocket, at least for the OR5 receptor, is a considerable distance away from the extracellular surface of the receptor (Singer and Shepherd, 1994).

In order to ascertain what other factors, as well as simple transport, influence the ODT values, it is instructive to plot the residuals in Equation (6), ie [log(1/ODT)obs - log(1/ODT)calc] against the 'size' parameter, **L**. The residuals are not random, and both small VOCs and large VOCs are less potent than expected. An even more informative plot, shown in Figure 2, is of the residuals vs. the maximum length, **D**, of the VOC. The latter was obtained by means of a computer-assisted molecular-modelling program, (Molecular Modeling Pro, 1992). The maximum value for **D** in a VOC was obtained after geometry optimization. In Figure 2, only the residuals for some homologous series are given, for clarity. It can then be seen that the residuals follow a 'parabolic-like' curve: as molecular size increases, the residual value increases to a maximum value and then decreases.

We suggest that the pattern of residuals in Figure 2 is due to an extra effect, in addition to simple transfer. The effect can be quantified and incorporated into an equation for log(1/ODT) through addition of a parabolic term in ($\mathbf{D} - \mathbf{D}^2$),

$$\log (1/ODT) = -6.757 + 0.533\mathbf{E} + 1.912\,\mathbf{S} + 1.276\,\mathbf{A} + 1.559\,\mathbf{B} + 0.699\,\mathbf{L} + 0.297\,\mathbf{D} - 0.013\,\mathbf{D}^2 \quad (7)$$

$n = 50,\ r^2 = 0.82,\ SD = 0.511$

The statistics of Equation (7) are quite good, bearing in mind the experimental error in the ODT values. We can include the carboxylic acids and aliphatic aldehydes into the regression equation by means of an indicator variable, **H**, chosen as 2.0 for the carboxylic acids and aldehydes and zero for all other VOCs,

$$\log (1/ODT) = -7.445 + 0.304\mathbf{E} + 1.652\,\mathbf{S} + 2.104\,\mathbf{A} + 1.500\,\mathbf{B} + 0.822\,\mathbf{L} + 0.369\,\mathbf{D} - 0.016\,\mathbf{D}^2 + 1.000\,\mathbf{H} \quad (8)$$

$n = 60,\ r^2 = 0.84,\ SD = 0.601$

Equation (8) is a general equation for log (1/ODT) values, and could be used to predict further values to about 0.6 log units (see later), of the order of experimental

error. Four compounds are again outliers to Equation (8), viz. propanone, methyl acetate, t-butyl acetate and 1-octanol. We shall use Equation (8) as the basis of our model of odor detection, but suggest that an alternative predictive equation can be constructed by using a parabolic term in **L**, rather than in **D**,

$$\log (1/\mathrm{ODT}) = -7.720 - 0.060\,\mathbf{E} + 2.080\,\mathbf{S} + 2.829\,\mathbf{A} + 1.139\,\mathbf{B} + 2.028\,\mathbf{L} - 0.148\,\mathbf{L}^2 + 1.000\,\mathbf{H} \qquad (9)$$

$n = 60$, $r^2 = 0.85$, $q^2 = 0.536$, SD = 0.598, F = 44

In Equation (9) the indicator variable for aldehydes and carboxylic acids takes the value **H** = 1.6. The advantage of Equation (9) over Equation (8) is that it is not necessary to obtain the maximum length, **D**, in order to predict further values of log (1/ODT).

The necessity for the use of an indicator variable for aldehydes and carboxylic acids arises because these two sets of compounds are more potent than predicted by Equation (7). There is precedent for the extra potency of aldehydes and carboxylic acids. Alarie et al. (1998) have shown that these compounds are more potent than expected in sensory irritation in mice, and suggest that they undergo some actual chemical reaction. However, aldehydes and carboxylic acids (except acetic acid) fit our equation for nasal pungency thresholds (Abraham *et al*. 1998a) without use of any indicator variable, see Equation (5). There is also the problem of the four outliers, propanone, methyl acetate, t-butyl acetate and 1-octanol. There may be extra experimental error with the first three compounds. Loss of propanone and methyl acetate due to their high volatility would result in the compounds appearing to be of lower potency. In the case of t-butyl acetate, the compound seemed to form an emulsion in some experiments, and this would result in an erroneous estimation of the ODT value. However, we have no explanation for the increased potency of 1-octanol.

Very recently, the EVA spectral descriptor has been applied to a selection of ODT values (Turner and Willett, 2000). No details were given other than for 52 ODT values, q^2 was 0.57 and for 44 log ODT values q^2 was 0.71; unfortunately EVA results cannot be interpreted in any chemical way and so cannot lead to any mechanistic conclusions.

Predictive capability – The statistics given for the various equations in log (1/ODT) do not lead to any assessment of their predictive capability, but only of their correlative ability. One method of estimating the predictive power of an equation is to divide total set of data into a training set and a test set. The training set is used to develop a correlation equation which in turn is used to predict the values for the test set. Since the latter values have not been used to set up the correlation equation, a comparison of predicted and observed values for the test set is a very useful guide to the predictive power of the training equation. Equations (7), (8) and (9) cannot be studied in this way, because the parabolic terms have been imposed and are not the result of a straightforward correlation. However, equation (6) is an example of a multiple correlation, and so we have used this equation as an example. In order to have sufficient data points to construct a correlation equation for the training set, we used 38 points for the training set and 12 for a test set. It is important that the test set is a representative sample of the entire set. We listed the 50 compounds in order of increasing values of log (1/ODT) and then selected every fourth compound as a member of the test set, leaving 38 compounds as the training set; we refer to this training/test set as 1(ODT). We then listed the 50 compounds in order of the dependent variable **E**, and chose every fourth compound as a member of a new test set, again leaving 38 compounds as a training set; the new training/test set is denoted as 2(**E**). A similar process was used to obtain training/test sets by ordering compounds by the other independent variables. This gave six different training/test sets.

A summary of the statistics for the six 38-compound training sets is in Table 5, and a comparison of the predicted (pred) and observed (obs) values of log (1/ODT) for the 12-compound test sets is given in Table 6. We give the usual standard deviation as $\sqrt{\{\sum [(obs) - (pred)]/(n-1)\}}$ where n = 12, the average deviation as AD = $\sum$[(obs) –(pred)/12] and the average absolute deviation as AAD = $|\sum [(obs) - (pred)/12]|$. Also in Tables 5 and 6 are the average values of the various coefficients and statistics for the training and test sets. The six training sets have somewhat different coefficients and statistics to the correlation equation (6), but the average values are within any statistical error the same as those for equation (6). This can be seen from the SD values for the coefficients given in equation (6). The various training sets predict values of log (1/ODT) with an average SD value of 0.608 log

units, as compared to the correlation SD of 0.579 log units, that is only 0.029 units higher. We can therefore take the value of 0.608 as a measure of the predictive capability of equation (6). In Table 6 are listed also values of AD and AAD. The former is negligible, at 0.006 log units, and shows that there is no bias towards too positive or too negative predicted values. The AAD values are always less than the SD values, and simply provide another estimate of predictive capability.

As mentioned above, we cannot apply the training/test set method to estimate the predictive capability of equations (7), (8) and (9), but we think it reasonable to assign estimates as about 0.03 log units higher than the correlation SD values

A model of odor detection - Equation (8) is not only a predictive equation, but can be considered to be compatible with the model shown in Figure 1. A large part of the variation in log (1/ODT) values with the structure of the VOCs is due to simple transport of the VOC from the gas phase to a biophase. In addition, there is an effect that we suggest is due to the size of the VOC, specifically to the maximum length. The potency of VOCs in an homologous series has a maximum deviation from the simple transport equation (6) when the VOC has a maximum length of around 11-12 A. Now this length is almost the same as the maximum dimension of the central pocket in OBPs, viz 11 A (Tegoni *et al*., 1996); the alternative volume of Bianchet *et al*. (1996) suggests a maximum length of the central pocket of 12-13 A. Thus one possible mechanism includes simple transfer from the gas phase to a biophase mediated by transport by OBPs. The exceptions are aldehydes and carboxylic acids that are more potent than calculated by about a factor of 100. We do not suggest that there is only one OBP or even one type of OBP; there may be several types with maximum dimensions around 10-15 A.

Of course, the above is not the only mechanism that fits our data analysis. It is possible that the OBPs have no discrimination at all, and that the 'maximum length' effect takes place on activation of the receptor. In any event, we do suggest that at least two types of interaction contribute to the overall threshold effect.

We can obtain some information as to the role of OBPs from recent work (Vincent *et al*., 2000) in which complexation constants for a number of VOCs with porcine OBP were obtained. Details are in Table 7, with the complexation constants given as log ($1/IC_{50}$). Over the seven VOCs studied, values of log ($1/IC_{50}$) vary by 0.75 log unit, whereas log (1/ODT) varies by no less than 3.99 log units. It is therefore possible

that the effect of OBPs is not the prime reason for the variation of log (1/OTD), but that complexation to OBPs (or possibly the rate of complexation to OBPs) just mediates the effect of transport to, and interactions with, the receptor.

Equation (8) has other consequences, including the effect of homologues. Descriptors for the higher homologues are given in Table 4. The linear dependence of log (1/ODT) on **L**, as in Equation (6), would lead to a regular increase in log (1/ODT) along an homologous series, as shown in Figure 3. However, the parabolic dependence on ($\mathbf{D} - \mathbf{D}^2$) considerably modifies the linear increase and results in the prediction shown in Figure 3. The values of log (1/ODT) gradually become smaller than expected from the linear relationship, and eventually even begin to decrease, see Figure 3. This corresponds to a chemical cut-off in potency, a prediction that is completely outside the scope of previous analyses (Yamanaka,1995; Hau and Connell, 1998). This predicted cut-off effect has a very important consequence. Hau *et al*. (2000) have used their partition model (Hau and Connell, 1998) to predict odor thresholds for VOCs found in the indoor environment. As we have pointed out, above, these partition models do not include any cut-off effect at all, and hence higher homologues will be predicted to be more potent than on our model.

Another, very important, consequence follows from the initial Equation (6). The dependent variable, log (1/ODT), conceptually takes the place of the dependent variable, log K, where K is a gas/biophase equilibrium constant given by

$$K = \frac{[\text{number of molecules of VOC in the biophase}]}{[\text{number of molecules of VOC in the gas phase}]} \qquad (10)$$

The ODT value itself represents the number of molecules in the gas phase, so that the only way that 1/ODT can take the place of an equilibrium constant, K, is if the number of molecules of a VOC in the biophase in equilibrium with the gas phase threshold value of the VOC, is the same for each VOC. This is a more general conclusion than the supposition of Hau and Connell (1998) that the minimum proportion of available receptors necessary for the detection of odors is the same for all members of a homologous series, but differs from series to series.

The odor perception of enantiomers is well known, but invariably in terms of odor quality (Pybus and Sell, 1999; Rossiter, 1996). Rossiter (1996) and Laska *et al*. (1999)

list pairs of enantiomers that elicit different sensations of odor quality. The latter workers tested odor discrimination of 10 pairs of enantiomers and concluded that within their experimental procedure, differences in odor intensity played little or no part in discrimination of the two enantiomeric forms. Other workers have shown that ODTs for *R*(+)- and *S*(-)-nicotine are essentially the same (Thuerauf *et al*., 1999). This again suggests selective, rather than specific, transport of VOCs to the biophase.

Regarding the potential implications of our results for the interpretation of olfactory receptor expression studies, we have shown that an equation set for selective transport of VOCs to the olfactory biophase is able to account for 77% of the total effect, measured as odor detection thresholds (ODT). In order to account for the remaining effect, "specific processes" need to be considered. The addition of a parabolic term in D (a maximum length parameter) or in L (a size parameter) raises the explained effect to about 85%. Thus, our data indicate that additional specific parameters, for example those derived from receptor-ligand studies, might be needed to completely account for the ODT measured. The question of whether selective transport is physically separable from the effects of receptor activation remains to be explored: If transport is not an intrinsic part of the stimulation of the receptors, but merely a filter, then research on receptors may well need to look at the residual after the transport aspects are subtracted.

Note added in proof. Two recent papers have stressed molecular length as an important factor in odor recognition:

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Table 1. Regression coefficients in Equation (4) for gas-solvent (phase) partitions at 298K

Phase	*e*	*s*	*a*	*b*	*l*
Wet 1-octanol	0.002	0.709	3.519	1.429	0.858
Dry methanol	-0.215	1.173	3.701	1.432	0.769
Chloroform	-0.467	1.203	0.138	1.432	0.994
Acetone	-0.277	1.522	3.258	0.078	0.863
Dimethylformamide	-0.189	2.327	4.756	0.000	0.808
Water	0.822	2.743	3.904	4.814	-0.213
Brain [a]	0.427	0.286	2.781	2.787	0.609
Muscle [a]	0.544	0.216	3.471	2.924	0.578
Fat [a]	-0.172	0.729	1.747	0.219	0.895
Nasal pungency [a]	0.000	2.154	3.522	1.397	0.860
ODT, equation (6) [a]	0.533	1.912	1.276	1.559	0.699

[a] At 310 K

Table 2. Values of log(1/ODT) with ODT in ppm

VOCs	Log (1/ODT)
Methanol	-3.180
Ethanol	-1.850
1-Propanol	-1.150
2-Propanol	-2.700
1-Butanol	-0.300
2-Butanol	-1.980
2-Methy-1-propanol	-2.780
1-Pentanol	-0.110
1-Hexanol	0.050
1-Heptanol	1.000
4-Heptanol	-0.910
1-Octanol	2.150
Pyridine	-0.110
Methyl acetate	-3.460
Ethyl acetate	-2.240
Propyl acetate	-1.390
Butyl acetate	-0.380
Pentyl acetate	-0.070
Hexyl acetate	0.200
Heptyl acetate	0.010
Octyl acetate	0.410
Decyl acetate	0.500
Dodecyl acetate	1.360
Propanone	-4.070
2-Pentanone	-0.930
2-Heptanone	0.150
2-Nonanone	0.030
Toluene	-2.190
Ethyl benzene	-1.260
Propyl benzene	-0.470
Butyl benzene	-0.630

Pentyl benzene	-0.004
Hexyl benzene	0.190
Heptyl benzene	0.250
Octyl benzene	0.430
Oct-1-ene	-2.310
Oct-1-yne	-2.130
Chlorobenzene	-1.110
2-Phenylethanol	2.190
s-Butylacetate	-0.670
t-Butyl acetate	-0.110
Butyraldehyde	-0.477
Pentanal	-0.699
Hexanal	1.097
Heptanal	1.523
Octanal	2.398
Formic acid	-0.886
Acetic acid	2.000
Butanoic acid	2.444
Hexanoic acid	2.585
Octanoic acid	4.959
Menthol	1.660
Cumene	-0.033
p-Cymene	-0.121
D-3-Carene	-0.223
Linalool	0.022
1,8-Cineole	0.495
Geraniol	1.070
a-Terpinene	-0.152
g-Terpinene	-0.992
a-Pinene	-1.277
b-Pinene	-1.070
(R) (+) limonene	-0.994
(S) (+) limonene	-0.659

Table 3. VOC parameters used in the present work

Solute	**E**	**S**	**A**	**B**	**L**	**D (A)**
Methanol	0.278	0.440	0.430	0.470	0.970	5.150
Ethanol	0.246	0.420	0.370	0.480	1.485	6.378
1-Propanol	0.236	0.420	0.370	0.480	2.031	7.649
2-Propanol	0.212	0.360	0.330	0.560	1.764	6.634
1-Butanol	0.224	0.420	0.370	0.480	2.601	8.882
2-Butanol	0.217	0.360	0.330	0.560	2.338	7.890
2-Methyl-1-propanol	0.180	0.300	0.310	0.600	1.963	6.638
1-Pentanol	0.219	0.420	0.370	0.480	3.106	10.146
1-Hexanol	0.210	0.420	0.370	0.480	3.610	11.396
1-Heptanol	0.211	0.420	0.370	0.480	4.115	12.654
4-Heptanol	0.180	0.360	0.330	0.560	3.850	11.650
1-Octanol	0.199	0.420	0.370	0.480	4.619	13.910
Pyridine	0.631	0.840	0.000	0.520	3.022	6.814
Methyl acetate	0.142	0.640	0.000	0.450	1.911	7.650
Ethyl acetate	0.106	0.620	0.000	0.450	2.314	8.870
Propyl acetate	0.092	0.600	0.000	0.450	2.819	10.154
Butyl acetate	0.071	0.600	0.000	0.450	3.353	11.340
Pentyl acetate	0.067	0.600	0.000	0.450	3.844	12.760
Hexyl acetate	0.056	0.600	0.000	0.450	4.351	13.880
Heptyl acetate	0.050	0.600	0.000	0.450	4.865	15.150
Octyl acetate	0.029	0.600	0.000	0.450	5.364	16.395
Decyl acetate	0.033	0.600	0.000	0.450	6.373	18.940
Dodecyl acetate	0.012	0.600	0.000	0.450	7.381	21.380
Propanone	0.179	0.700	0.040	0.490	1.696	6.612
2-Pentanone	0.143	0.680	0.000	0.510	2.755	9.110
2-Heptanone	0.123	0.680	0.000	0.510	3.760	11.610
2-Nonanone	0.119	0.680	0.000	0.510	4.735	14.120
Toluene	0.601	0.520	0.000	0.140	3.325	8.080
Ethylbenzene	0.613	0.510	0.000	0.150	3.778	9.303
Propylbenzene	0.604	0.500	0.000	0.150	4.230	10.124
Butylbenzene	0.600	0.510	0.000	0.150	4.730	11.650
Pentylbenzene	0.594	0.510	0.000	0.150	5.230	12.778
Hexylbenzene	0.591	0.500	0.000	0.150	5.720	14.080

Heptylbenzene	0.577	0.480	0.000	0.150	6.219	15.231
Octylbenzene	0.579	0.480	0.000	0.150	6.714	16.466
Oct-1-ene	0.094	0.080	0.000	0.070	3.568	12.808
Oct-1-yne	0.155	0.220	0.090	0.100	3.521	12.771
Chlorobenzene	0.718	0.650	0.000	0.070	3.657	8.360
2-Phenylethanol	0.811	0.910	0.300	0.640	4.628	10.090
s-Butyl acetate	0.044	0.570	0.000	0.470	3.054	10.149
t-Butyl acetate	0.025	0.540	0.000	0.470	2.802	8.943
Butanal	0.187	0.650	0.000	0.450	2.270	8.44
Pentanal	0.163	0.650	0.000	0.450	2.851	9.690
Hexanal	0.146	0.650	0.000	0.450	3.357	10.950
Heptanal	0.140	0.650	0.000	0.450	3.865	12.200
Octanal	0.160	0.650	0.000	0.450	4.361	13.460
Formic acid	0.300	0.790	0.720	0.340	1.400	5.260
Acetic acid	0.265	0.650	0.610	0.440	1.750	6.298
Butanoic acid	0.210	0.620	0.600	0.450	2.830	8.790
Hexanoic acid	0.174	0.600	0.600	0.450	3.920	10.290
Octanoic acid	0.150	0.600	0.600	0.450	5.000	13.800
Menthol	0.400	0.500	0.230	0.580	5.177	10.590
Cumene	0.602	0.490	0.000	0.160	4.084	9.300
p-Cymene	0.607	0.490	0.000	0.190	4.590	10.476
Δ-3-Carene	0.511	0.220	0.000	0.100	4.649	6.930
Linalool	0.398	0.550	0.200	0.670	4.794	12.749
1,8-Cineole	0.383	0.330	0.000	0.760	4.688	8.788
Geraniol	0.513	0.632	0.390	0.660	5.479	13.749
α-Terpinene	0.526	0.250	0.000	0.150	4.715	10.477
γ-Terpinene	0.497	0.320	0.000	0.200	4.815	10.499
α-Pinene	0.446	0.140	0.000	0.120	4.308	9.000
β-Pinene	0.530	0.240	0.000	0.190	4.394	8.828
(R) (+) Limonene	0.488	0.280	0.000	0.450	4.725	9.550
(S) (+) Limonene	0.488	0.280	0.000	0.450	4.725	9.550

Table 4 Descriptors for higher homologous

Solute	**E**	**S**	**A**	**B**	**L**	**D** (A)
1-Nonanol	0.193	0.420	0.370	0.480	5.124	15.160
1-Decanol	0.191	0.420	0.370	0.480	5.628	16.400
1-Undecanol	0.181	0.420	0.370	0.480	6.139	17.670
1-Dodecanol	0.175	0.420	0.370	0.480	6.640	18.910
1-Tridecanol	0.169	0.420	0.370	0.480	7.149	20.110
1-Tetradecanol	0.163	0.420	0.370	0.480	7.656	21.430
Tridecyl acetate	0.000	0.600	0.000	0.450	7.878	22.670
Tetradecyl acetate	0.000	0.600	0.000	0.450	8.380	23.910
Pentadecyl acetate	0.000	0.600	0.000	0.450	8.883	25.180
Hexadecyl acetate	0.000	0.600	0.000	0.450	9.386	26.430
2-Decanone	0.108	0.680	0.000	0.510	5.245	15.390
2-Undecanone	0.101	0.680	0.000	0.510	5.732	16.630
2-Dodecanone	0.103	0.680	0.000	0.510	6.167	17.890
2-Tridecanone	0.100	0.680	0.000	0.510	6.672	19.140
2-Nonadecanone	0.100	0.680	0.000	0.510	9.554	26.650
Nonylbenzene	0.578	0.480	0.000	0.150	7.212	17.640
Decylbenzene	0.579	0.470	0.000	0.150	7.708	18.980
Undecylbenzene	0.579	0.470	0.000	0.150	8.159	20.180
Dodecylbenzene	0.571	0.470	0.000	0.150	8.600	21.390
Tridecylbenzene	0.570	0.470	0.000	0.150	9.132	22.590
Tetradecylbenzene	0.570	0.470	0.000	0.150	9.619	23.950

Table 5. A summary of the training set correlations

Set no	c	e	s	a	b	l	r^2	SD
1(ODT)	-5.331	0.299	2.144	2.135	1.018	0.753	0.772	0.615
2(E)	-5.247	0.659	1.402	1.435	2.284	0.702	0.816	0.553
3(S)	-5.123	0.785	2.010	1.000	1.611	0.646	0.804	0.529
4(A)	-5.284	0.709	1.659	0.722	2.122	0.716	0.793	0.580
5(B)	-5.482	0.452	1.881	1.762	1.493	0.800	0.761	0.622
6(L)	-5.311	0.533	1.656	1.346	1.858	0.728	0.813	0.562
Av	-5.296	0.572	1.792	1.400	1.731	0.724	0.793	0.577

Table 6. Comparison of predicted and observed log (1/ODT) values for test sets

Set no	SD	AD	AAD
1(ODT)	0.537	0.166	0.455
2(E)	0.577	-0.190	0.577
3(S)	0.754	0.252	0.630
4(A)	0.628	-0.109	0.512
5(B)	0.487	-0.265	0.542
6(L)	0.670	0.183	0.555
Av	0.608	0.006	0.545

Table 7 Comparison of complexation of VOCs with porcine OBPs, and odor thresholds

VOC	Log (1/ODT) [a]	Log (1/IC_{50}) [b]
Benzyl benzoate	4.58	-0.59
Benzophenone	4.25	-0.56
Thymol	2.40	-0.40
2-Isobutyl-3-methoxy pyrazine	1.27	0.05
Undecanal	0.73	0.16
Dihydromyrcenol	0.59	0.10

[a] Equation (8). [b] From (Vincent *et al*, 2000).

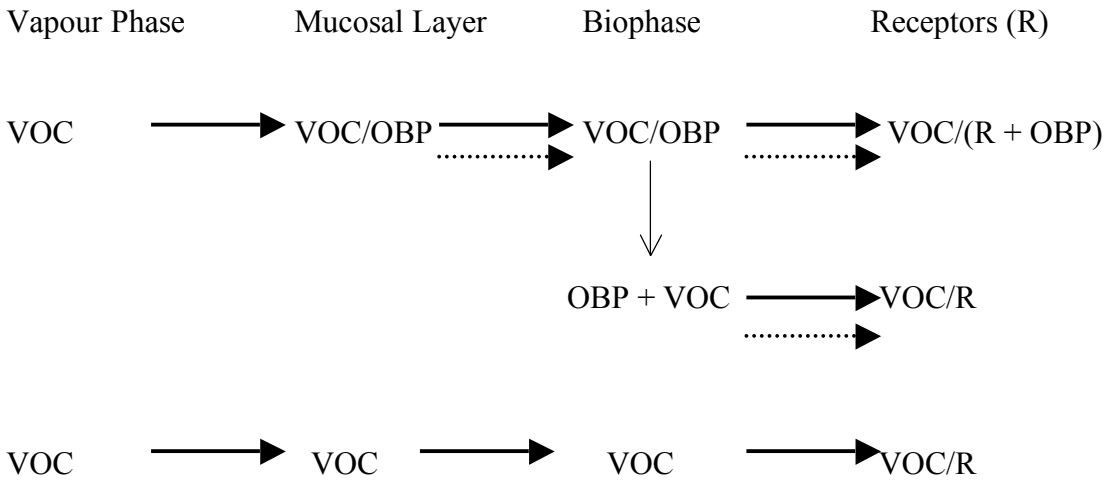

Figure 1. A possible model for odor thresholds. Selective processes ⟶ ; specific processes ⋯⋯▶ .

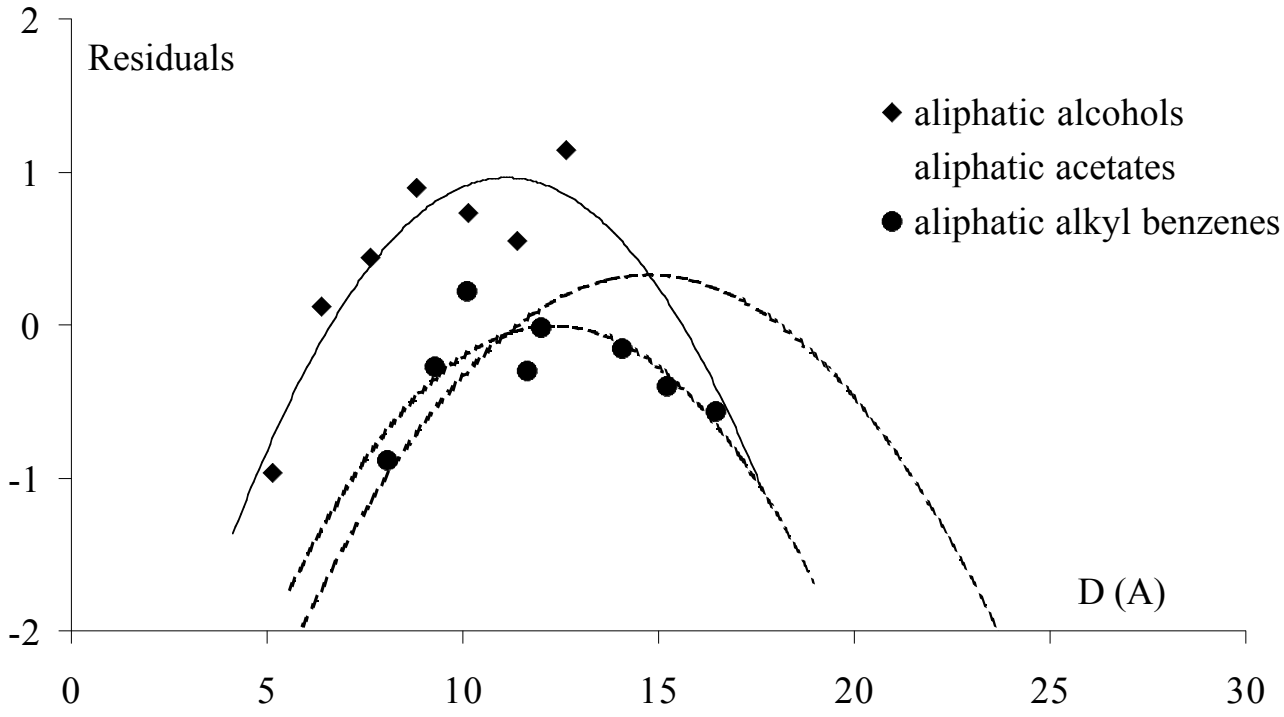

Figure 2. Residuals (observed – calculated values on equation 6) against the VOC maximum length

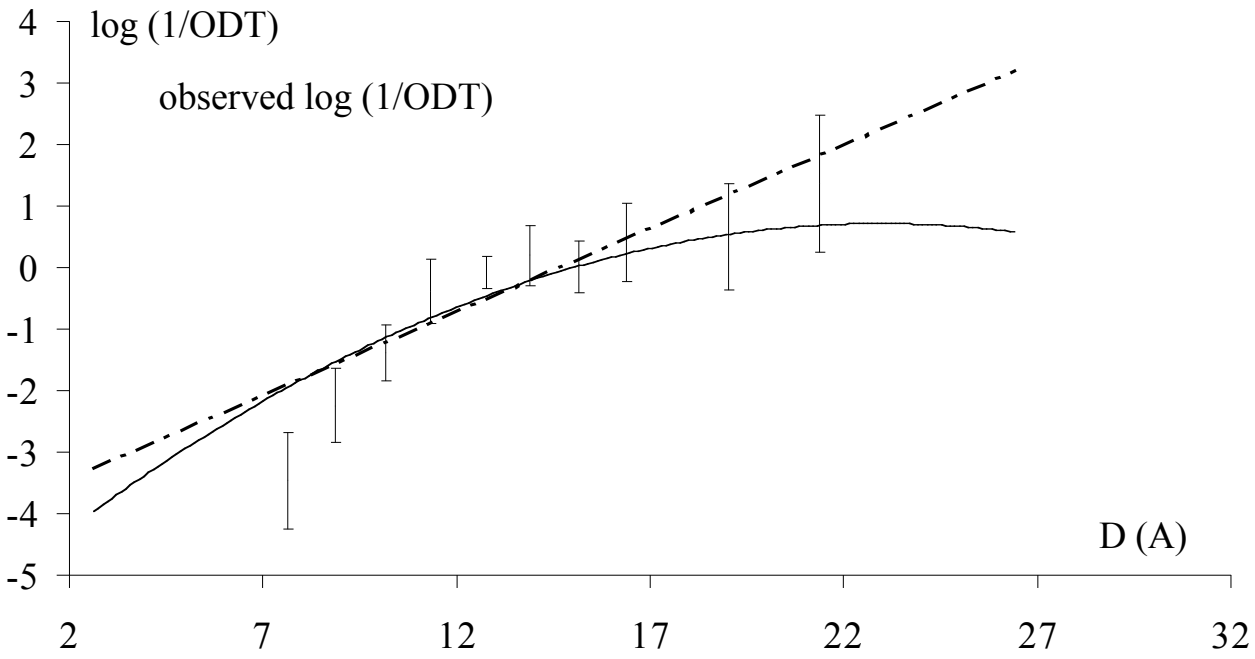

Figure 3. Plot of observed values of log (1/ODT) against the VOC maximum length D, for the homologous series of acetates. ---- Calculated values on equation 6; ____ calculated values on equation 7.