

THE ROLE OF ADSORPTION AND MOLECULAR MORPHOLOGY IN OLFACTION: THE CALCULATION OF OLFACTORY THRESHOLDS

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The surface of the olfactory nerve cell is folded into a number of delicate, hair-like protoplasmic filaments (Engström and Bloom, 1953; Bloom and Engström, 1952) which have long been considered to be the ultimate sensory processes of the receptor cells. Admirable photographs showing these hairs, a discussion of their possible functions and a description of the anatomy of the entire olfactory epithelium of various vertebrates are given by Le Gros Clark (1957) and by Allison (1953).

The filaments serve to give the olfactory receptors a large surface area. That this enlarged surface readily adsorbs odorants was shown by Moncrieff (1954, 1955) who made direct measurements, using a sheep's head, and found that odorants are adsorbed strongly and rapidly on the olfactory epithelium and that the process is reversible.

Neither the structure nor the exact composition of the human olfactory cell membrane is known. Hopkins (1926) examined the olfactory filaments of the frog which he found to be extensions of the olfactory cell membrane; he noted that the hairs reduce osmic acid and are disrupted by organic lipoid solvents, the proximal parts only remaining intact. The human olfactory membrane will probably resemble that of the frog and, like other nerve cells, will consist of a few layers of oriented lipid and protein molecules. This membrane is continually bathed by mucus (effectively saline) at a pH of about 7.2.

Davies and Taylor (1954) used the erythrocyte membrane as a model for that of the olfactory nerve cell, and showed that a large number of odorous substances act as accelerators of haemolysis by saponin. Moreover, for these substances, the logarithms of the olfactory thresholds (for man) are directly proportional to the logarithms of the haemolytic accelerating powers. This is shown in Figure 1. Some of these compounds which act as haemolytic accelerators have also been shown to cause a leakage of potassium ions across the red cell membrane (Davson and Danielli, 1938). This correlation lends support to theories of olfaction such as those of Ehrensward (1942) and Davies (1953a, 1953b) which postulate that odorant molecules must first adsorb onto the plasma membrane of the olfactory cell. Ehrensward's theory that the potential changes due to adsorption at this interface initiate the nerve impulses ascribes more importance to the specific polar groups of the odorant molecules than does the present work. Further experiments on potentials on the lines of those of Ehrensward and Cheesman (1941) would be of interest in this connection.

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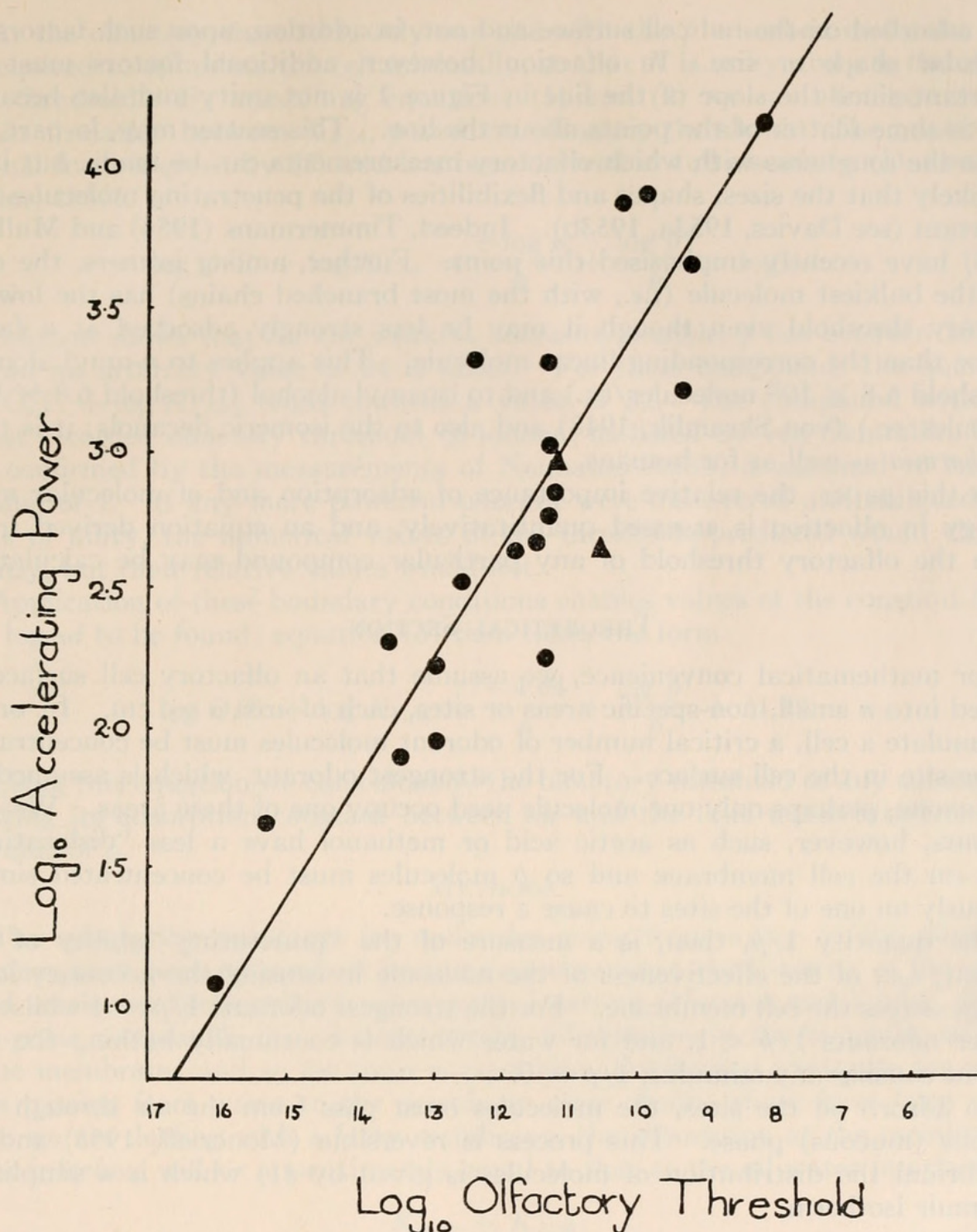


FIGURE 1. Plot of the logarithm of the haemolytic accelerating power against the logarithm of the olfactory threshold (in molecules/cc.). The equation of the line which is drawn in can be deduced from equation (4) if certain approximations are made (Davies and Taylor, 1957).

The present work, following the theory of Davies, assumes that the odorant molecules can simply dislocate the olfactory cell membrane, permitting an exchange of sodium and potassium ions across it. This exchange of ions initiates the nervous impulse as in the general theory of Hodgkin and Katz (1949).

Recently, Rideal and Taylor (1958) have shown that the logarithm of the haemolytic accelerating power of a substance is directly proportional to its free energy of adsorption at the oil-water interface; this means that the effectiveness of compounds as haemolytic accelerators depends only on the number of mole-

cules adsorbed on the red cell surface and not, in addition, upon such factors as molecular shape or size. In olfaction, however, additional factors must be important since the slope of the line in Figure 1 is not unity and also because there is some scatter of the points about the line. This scatter may, in part, be due to the roughness with which olfactory measurements can be made, but it is also likely that the sizes, shapes and flexibilities of the penetrating molecules are important (see Davies, 1953a, 1953b). Indeed, Timmermans (1954) and Mullins (1955) have recently emphasised this point. Further, among isomers, the one with the bulkiest molecule (*i.e.*, with the most branched chains) has the lowest olfactory threshold even though it may be less strongly adsorbed at a fatty surface than the corresponding linear molecule. This applies to *n*-amyl alcohol (threshold 6.8×10^{12} molecules/cc.) and to isoamyl alcohol (threshold 6.8×10^{11} molecules/cc.) (von Skramlik, 1948) and also to the isomeric decanols; it is true for *Phormia* as well as for humans.

In this paper, the relative importance of adsorption and of molecular morphology in olfaction is assessed quantitatively, and an equation derived from which the olfactory threshold of any particular compound may be calculated.

THEORETICAL SECTION

For mathematical convenience, we assume that an olfactory cell surface is divided into n small, non-specific areas or sites, each of area α sq. cm. In order to stimulate a cell, a critical number of odorant molecules must be concentrated on one site in the cell surface. For the strongest odorant, which is assumed to be β ionone, perhaps only one molecule need occupy one of these areas. Weaker odorants, however, such as acetic acid or methanol have a less "dislocating" effect on the cell membrane and so p molecules must be concentrated simultaneously on one of the sites to cause a response.

The quantity $1/p$, then, is a measure of the "puncturing" ability of the odorant, *i.e.*, of the effectiveness of the molecule in causing the necessary ionic leakage across the cell membrane. For the strongest odorants $1/p = 1$ whilst for weaker odorants $1/p < 1$, and for water which is continually bathing the cell without causing any stimulus, $1/p = 0$.

To adsorb on the sites, the molecules must pass from the air through the aqueous (mucous) phase. This process is reversible (Moncrieff, 1955) and at equilibrium the distribution of molecules is given by (1) which is a simplified Langmuir isotherm.

$$\frac{x}{c d} = K_{L/A}. \quad (1)$$

Here x is the average membrane concentration of odorant molecules/sq. cm., c is the average concentration of molecules/cc. in the air, and d is the surface thickness (about 10 \AA). $K_{L/A}$ is the adsorption constant for molecules passing from air to the lipid-water interface. The number of sites, N , per nerve cell containing p molecules where p is greater than the average number αx is given by Poisson's equation:

$$N = \frac{n e^{-\alpha x} (\alpha x)^p}{p!}, \quad (2)$$

where n is the total number of sites/cell.

At the olfactory threshold, only one site with the p adsorbed molecules will be required to stimulate the cell minimally, so that N is unity and c is the olfactory threshold. By combining equations (1) and (2) we can eliminate x and obtain a relation between $K_{L/A}$, p and the olfactory threshold. The relation in its final form is given by (3) and has been derived in full elsewhere (Davies and Taylor, 1957).

$$\log \text{O.T.} + \log K_{L/A} = \frac{-\log n}{p} + \frac{\log p!}{p} - \log \alpha d. \quad (3)$$

Calculation shows that for the weakest odorants possible, p lies between 15 and 30 and an arbitrary value of 24 is taken. For these compounds the quantity $(\log \text{O.T.} + \log K_{L/A})$ tends towards a value of 22. The compound with the lowest recorded olfactory threshold (β ionone; as listed by von Skramlik, 1948, and confirmed by the measurements of Neuhaus, 1953b) is assumed to have a p value of 1. If any more powerful odorant were discovered and assigned a p value of unity, the numerical values of the thresholds predicted would change slightly, but their relative values would not.

Application of these boundary conditions enables values of the constant $\log n$ and $\log \alpha d$ to be found; equation (3) then takes the form:

$$\log \text{O.T.} + \log K_{L/A} = \frac{-4.64}{p} + \frac{\log p!}{p} + 21.19. \quad (4)$$

Using this equation we can calculate the olfactory threshold of any substance, knowing its adsorption constant between air and the lipid-water interface and its value of p .

METHODS

The adsorption constants for molecules going from water to the oil-water interface have been determined from measurements of the lowering of the interfacial tension at the petroleum ether-water interface (Haydon and Taylor, 1959). Non-polar compounds (*e.g.*, hydrocarbons) will dissolve in the lipophilic interior of the membrane, and so for these compounds, distribution constants for molecules passing from water to the petroleum ether (bulk) phase have been used. Since we are dealing with a fatty membrane, the adsorption at the membrane/water interface will be approximately equal to that at the oil-water interface.

$$K_{O/W} = K_{L/W}.$$

In fact $K_{L/W}$ will be slightly less than $K_{O/W}$ by a factor depending on the dielectric constant at the membrane surface. The distribution constant for molecules going from air to the aqueous phase has been found from the ratio of the solubility of the substance in water at 20° C. to its vapour pressure at the same temperature, or, in some instances, from the measurements of partial vapour pressures of aqueous solutions of the substances recorded in the literature.

From $K_{L/W}$ ($= K_{O/W}$) and $K_{W/A}$, the term $K_{L/A}$ ($= K_{O/A}$) required in equation (4) may be obtained directly since

$$K_{L/A} = K_{L/W} \cdot K_{W/A}.$$

Values of $\log K_{O/A}$ are listed in Table I.

TABLE I

Compound	$\log_{10} K_{O/W}$	$\log_{10} K_{W/A}$	$\log_{10} K_{O/A}$	Cross-sectional areas \AA^2	
				a	b
Methanol*	1.235	4.245	5.48	20.0	12.4
Ethanol*	1.80	3.99	5.78	26.7	15.4
Propanol*	2.41	3.81	6.22	32.6	18.3
Butanol	2.85	3.69	6.54	38.0	19.2
Pentanol	3.71	3.42	7.13	43.0	20.0
Hexanol	4.39	3.18	7.57	47.8	20.0
Heptanol	4.82	2.83	7.65	52.3	20.0
Octanol	5.30	3.04	8.34	56.0	20.0
Decanol	6.94	2.04	8.98	64.6	20.0
β ionone	5.79	2.56	8.35	69.7	57.6
Piperonal	3.41	3.48	6.89	47.3	41.4
Menthol	4.505	2.015	6.52	62.8	44.8
Skatol	4.76	3.84	8.60	53.5	42.5
Xylol musk	4.58	3.96	8.54	74.0	56.2
Isoamyl alcohol	3.71	3.50	7.21	43.0	26.0
Isobutanol	2.26	3.81	6.07	38.0	24.0
Camphor	3.335	2.64	5.98	59.7	43.6
Phenol	3.04	4.66	7.70	37.9	24.1
Isoamyl acetate	3.63	1.82	5.45	52.6	30.0
Nitrobenzene	3.85	8.14	6.99	42.2	24.1
Coumarin	2.83	4.48	7.31	48.0	41.3
Pyridine*	3.25	4.78	8.03	36.3	24.0
Cycloheptadecyl lactone	5.33	3.42	8.75	89.0	50.0
Glycerol*	1.93	4.00	5.93	36.5	36.0
Cyclohexanol	3.92	4.05	7.97	45.5	27.0
Water	—	—	—	14.0	8.1
Naphthalene**	4.67	1.82	6.49	48.5	42.0
Benzene**	3.09	0.75	3.84	36.1	24.0
Cyclohexane**	3.56	-0.35	3.21	43.6	27.0
Ethane**	1.23	-0.66	0.66	24.4	15.4
<i>n</i> -butane**	2.40	-0.60	1.80	36.1	20.0
<i>n</i> -pentane**	2.97	-0.66	2.31	41.2	20.0
<i>n</i> -heptane**	4.15	-0.59	3.56	50.6	20.0
<i>n</i> -nonane**	5.33	-0.76	4.57	59.3	20.0
<i>n</i> -undecane**	6.52	-0.74	5.78	67.3	20.0
<i>n</i> -butyric acid*	3.19	6.17	9.36	38.7	20.0
<i>n</i> -valeric acid	3.78	5.04	8.82	43.8	20.0
Caproic acid	4.38	4.85	9.23	84.5	20.0
Oenanthic acid	4.97	4.55	9.52	53.0	20.0

Data needed to calculate olfactory thresholds for a number of odorants.

* $K_{W/A}$ calculated from published data on the partial vapour pressures of aqueous solutions of the substances.

** $K_{O/W}$ for non-polar compounds refers to passage from water to bulk of the oil phase.

The cross-sectional areas in column a have been calculated from the molecular volumes assuming the molecules to be spheres. The molecular volumes have been obtained by assuming the additivity of atomic volumes using data given in Partington (1951).

Areas in column b have been measured from models.

RESULTS AND DISCUSSION

(a) *The calculation of olfactory thresholds*

Since $1/p$ is a measure of the ability of an odorant molecule to "puncture" or dislocate the membrane temporarily, it is expected to be a function of molecular shape and size. These quantities are difficult to define, however, and for present

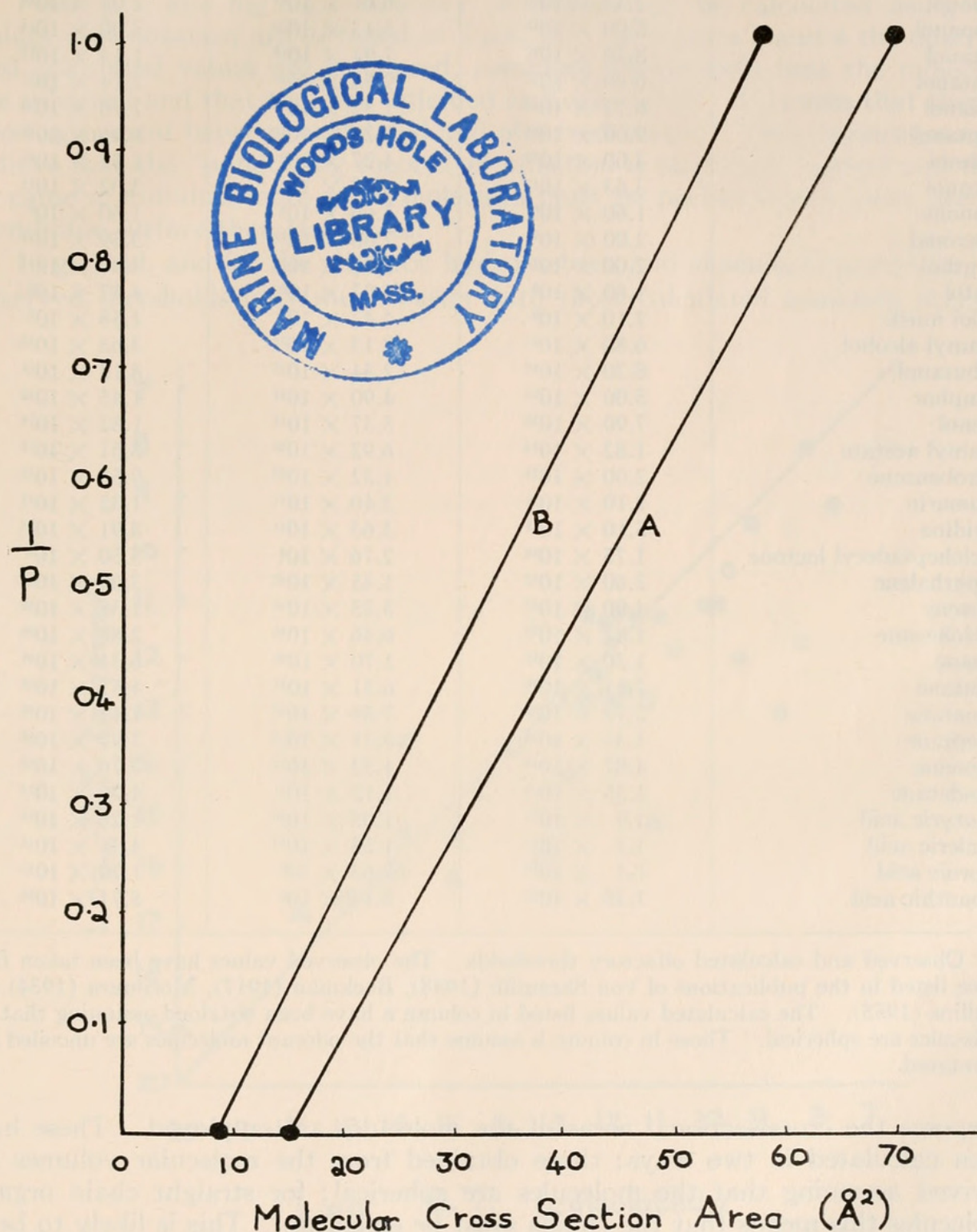


FIGURE 2. The relationships which are assumed to hold between $1/p$ and the molecular cross-sectional areas in the evaluation of $1/p$, when (A) cross-sectional areas derived from molecular volumes are employed (molecules assumed to be spheres). (B) Measurements on models have been employed (molecules uncoiled and orientated in the membrane).

TABLE II

Compound	Olfactory thresholds in molecules/cc.		
	Observed	a	b
Methanol	1.10×10^{16}	8.13×10^{15}	1.15×10^{16}
Ethanol	2.44×10^{15}	6.61×10^{14}	2.04×10^{15}
Propanol	5.00×10^{13}	5.13×10^{13}	3.00×10^{14}
Butanol	8.20×10^{12}	7.94×10^{12}	1.12×10^{14}
Pentanol	6.80×10^{12}	9.78×10^{11}	2.14×10^{13}
Hexanol	6.72×10^{12}	1.32×10^{11}	7.76×10^{12}
Heptanol	9.00×10^{11}	5.25×10^{10}	6.46×10^{12}
Octanol	3.00×10^{10}	4.27×10^9	1.32×10^{12}
Decanol	3.63×10^{11}	1.78×10^8	3.02×10^{11}
β ionone	1.60×10^8	1.60×10^8	1.60×10^8
Piperonal	2.00×10^{11}	7.08×10^{11}	3.39×10^{11}
Menthol	2.00×10^{11}	8.32×10^{11}	3.31×10^{11}
Skatol	1.80×10^9	4.07×10^9	4.47×10^9
Xylol musk	2.10×10^9	4.47×10^7	1.58×10^8
Isoamyl alcohol	6.80×10^{11}	8.13×10^{11}	3.63×10^{12}
Isobutanol	8.20×10^{12}	2.34×10^{12}	8.13×10^{13}
Camphor	5.00×10^{12}	4.90×10^{11}	1.45×10^{12}
Phenol	7.90×10^{12}	5.37×10^{11}	1.82×10^{12}
Isoamyl acetate	1.82×10^{14}	6.92×10^{12}	8.51×10^{13}
Nitrobenzene	2.00×10^{11}	1.32×10^{12}	9.55×10^{12}
Coumarin	2.10×10^{11}	2.40×10^{11}	1.32×10^{11}
Pyridine	3.10×10^{11}	3.63×10^{11}	8.91×10^{11}
Cycloheptadecyl lactone	1.75×10^{10}	2.76×10^6	5.50×10^8
Naphthalene	2.60×10^{12}	1.45×10^{12}	3.09×10^{13}
Benzene	4.00×10^{13}	5.75×10^{15}	1.38×10^{16}
Cyclohexane	1.82×10^{15}	6.46×10^{15}	2.88×10^{16}
Ethane	1.30×10^{19}	1.70×10^{20}	6.31×10^{19}
<i>n</i> -butane	7.11×10^{16}	6.31×10^{17}	4.57×10^{18}
<i>n</i> -pentane	2.73×10^{16}	7.59×10^{16}	1.41×10^{18}
<i>n</i> -heptane	1.32×10^{16}	8.51×10^{14}	7.94×10^{16}
<i>n</i> -nonane	4.87×10^{15}	1.32×10^{13}	7.76×10^{15}
<i>n</i> -undecane	1.35×10^{15}	1.15×10^{11}	4.79×10^{14}
<i>n</i> -butyric acid	1.4×10^{11}	1.05×10^{10}	1.26×10^{11}
<i>n</i> -valeric acid	1.2×10^{11}	1.55×10^{10}	4.37×10^{11}
Caproic acid	1.2×10^{12}	2.63×10^9	1.70×10^{11}
Oenanthic acid	1.35×10^{13}	5.13×10^8	8.71×10^{10}

Observed and calculated olfactory thresholds. The observed values have been taken from those listed in the publications of von Skramlik (1948), Backman (1917), Morimura (1934) and Mullins (1955). The calculated values listed in column a have been obtained assuming that the molecules are spherical. Those in column b assume that the odorant molecules are uncoiled and orientated.

purposes the cross-sectional areas of the molecules are employed. These have been calculated in two ways: those obtained from the molecular volumes are derived assuming that the molecules are spherical; for straight chain organic molecules this means that the chains must be coiled up. This is likely to be so when the molecules are in water but is unlikely in a fatty membrane. In measurements taken from models, therefore, it is assumed that the molecules adsorbed in the membrane are orientated with the hydrocarbon chains completely uncoiled;

in a homologous series the cross-sectional area is thus constant for the higher members.

If it is assumed that the dislocating power $1/p$ varies linearly with the molecular cross-sectional area, then values of $1/p$ can be calculated, since for β ionone $1/p = 1$ and for water $1/p = 0$ (Fig. 2). Values of the areas used for this purpose are listed in Table I.

From $1/p$ and $\log K_{O/A}$ olfactory thresholds can be calculated using (4); values thus obtained are included in Table II. In Figures 3 and 4 the observed and calculated values are compared, assuming respectively that the molecules are spherical and that they are unfolded and orientated. It is seen that there is good agreement between calculated and observed values. This encourages us to believe that the "puncturing theory" of olfaction is essentially correct and that, to cause a stimulus, more small molecules must be packed into a given area of membrane surface than large ones.

In general, and for the aliphatic hydrocarbons and alcohols in particular, the observed thresholds tally much better with those calculated assuming that the

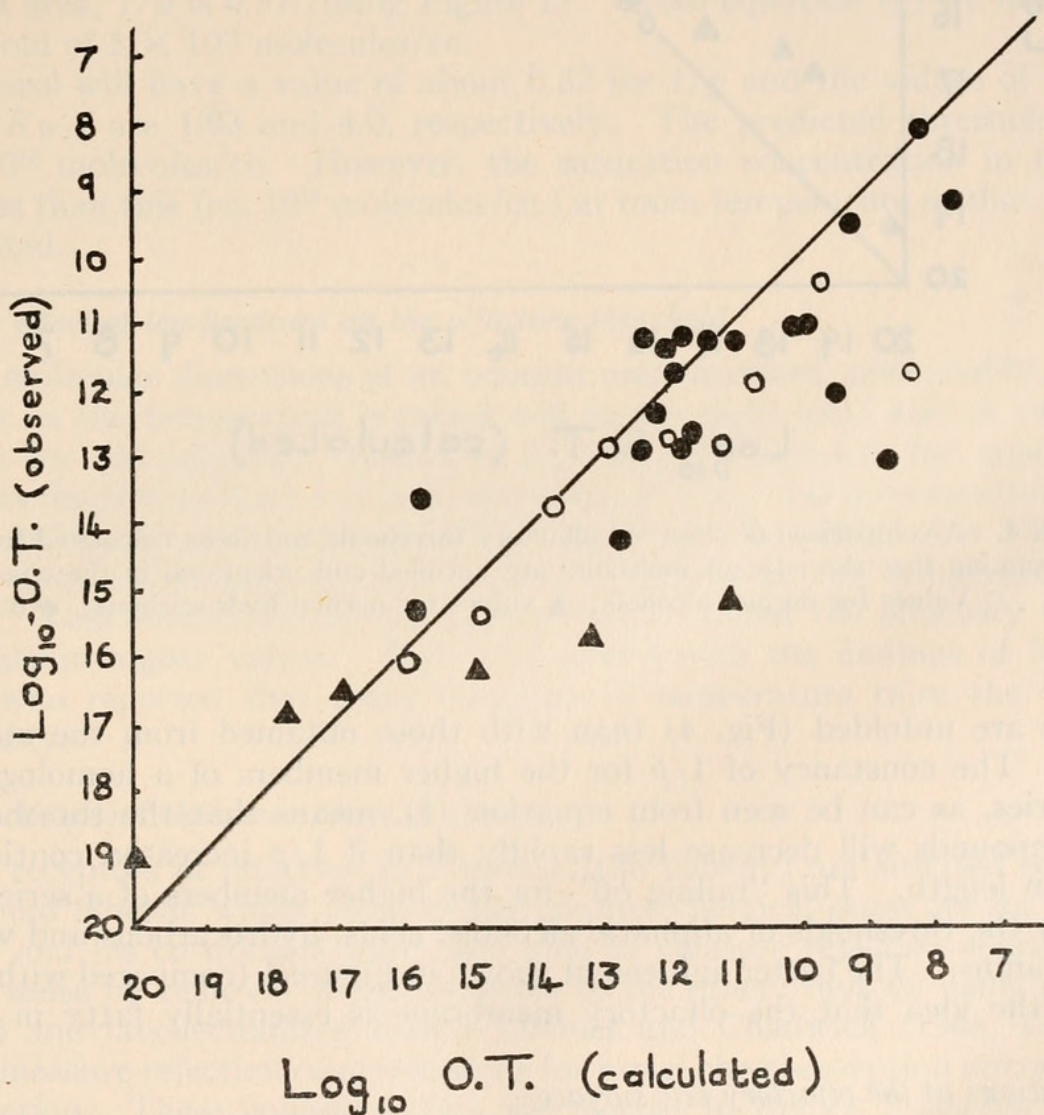


FIGURE 3. A comparison of observed olfactory thresholds and those calculated from equation (4) assuming that the molecules are spherical. ○ Values for normal alcohols; ▲ values for normal paraffins; ● other compounds.

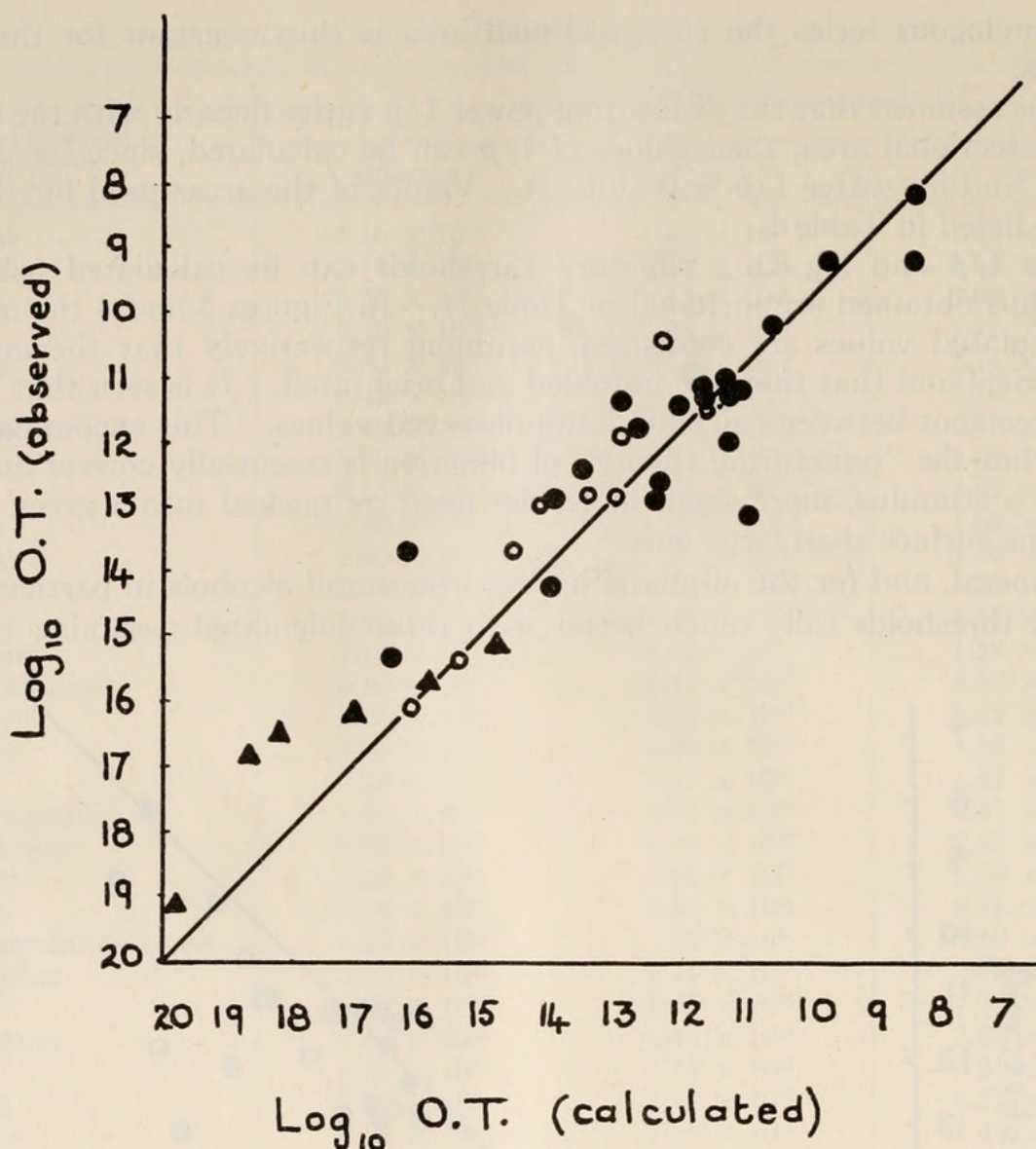


FIGURE 4. A comparison of observed olfactory thresholds and those calculated from equation (4) assuming that the odorant molecules are uncoiled and orientated in the olfactory cell membrane. ○ Values for normal alcohols; ▲ values for normal hydrocarbons; ● other compounds.

molecules are unfolded (Fig. 4) than with those obtained from the molecular volumes. The constancy of $1/p$ for the higher members of a homologous aliphatic series, as can be seen from equation (4), means that the thresholds for these compounds will decrease less rapidly than if $1/p$ increased continuously with chain length. This "tailing off" for the higher members of a series is observed for the thresholds of aliphatic alcohols, acids, hydrocarbons and with the chloroparaffins. The better agreement shown in Figure 4 (compared with Fig. 3) confirms the idea that the olfactory membrane is essentially fatty in nature.

(b) *Conditions at the olfactory cell surface*

In obtaining equation (4) from equation (3) by the use of experimental boundary conditions, values for $\log n$ (where n is the number of "sites" per cell) and α the area of one "site" are obtained. $\log n$ is 4.64 which means that there

are 4.5×10^4 "sites" per cell and α has the value of 64 \AA^2 if the depth of the surface phase is taken to be 10 \AA .

The active adsorbing surface area of each cell then comes to $n\alpha$ or 3×10^{-10} sq. cm. This is much smaller than that which can be calculated from the results of Bloom and Engström (1952) (3×10^{-6} sq. cm.) or those of Le Gros Clark and Warwick (1946) (ca. 10^{-8} sq. cm.). This could either indicate that the active "sites" do not occupy the entire cell surface or that one of the boundary conditions used in deriving (4) is wrong. If, for instance, there is a stronger odorant than β ionone (such that $\log \text{O.T.} < 8.2$), then the surface area predicted would be larger.

(c) *Prediction of olfactory thresholds*

If the values of $K_{O/W}$ and $K_{W/A}$ are determined experimentally for any substance, and if its molecular dimensions are known approximately, then it is possible by use of equation (4) to predict its olfactory threshold. Thus for cyclohexanol $\log K_{O/W}$ is 3.92, $\log K_{W/A}$ is 4.05 and from its molecular cross-sectional area, $1/p$ is 0.37 (using Figure 2). From equation (4) we now predict a threshold of 5×10^{11} molecules/cc.

Glycerol will have a value of about 0.32 for $1/p$ and the values of $\log K_{O/W}$ and $\log K_{W/A}$ are 1.93 and 4.0, respectively. The predicted threshold is then about 10^{14} molecules/cc. However, the saturation concentration in the air is much less than this (ca. 10^{13} molecules/cc.) at room temperature so that it cannot be detected.

(d) *The effect of temperature on the olfactory threshold*

The molecular dimensions of an odorant and therefore, presumably, $1/p$ will not alter as the temperature is raised and so the right hand side of (4) will be constant for any odorant. However, $K_{L/W}(K_{O/W})$ decreases for organic compounds as the temperature is raised; the value of $K_{W/A}$ also decreases numerically (thus at 20°C . $K_{W/A}$ for *n*-hexanol is 1.54×10^3 whilst at 40°C . it is 2.29×10^3).

For most compounds, therefore, $K_{O/A}$ decreases as the temperature is increased. This means that as the temperature is raised the olfactory threshold should attain higher values. This is in accord with the findings of Morimura (1934) who reported that small increases in temperature raise the threshold appreciably.

(e) *Olfaction and chemoreception in insects*

The receptors of olfaction in *Phormia* (the blowfly) are situated on the antennae and labellae whilst those of the contact chemical sense are on the tarsi. Dethier and his co-workers have been able to measure rejection concentrations for one sense by removal of the receptors of the other: thus by using antennectomized and labellectomized insects Dethier and Chadwick (1948, 1950) were able to measure rejection concentrations for tarsal chemoreception uncomplicated by olfaction. These concentrations are plotted in Figure 5 against $\log K_{O/W}$ and there is seen to be a linear relationship between the two quantities, the equation of the line being

$$\log M = 1.17 \log K_{O/W} + 2.83.$$

Here M is the threshold expressed as the molar concentration of test substance *in water* rejected by 50% of the flies. The slope of the line is very near to that expected for adsorption from solution on to a pure lipid membrane (1.0).

The olfactory rejection concentrations, however, (given by the molar concentrations in *the air* rejected by 50% of the insects) when plotted against $\log K_{O/A}$,

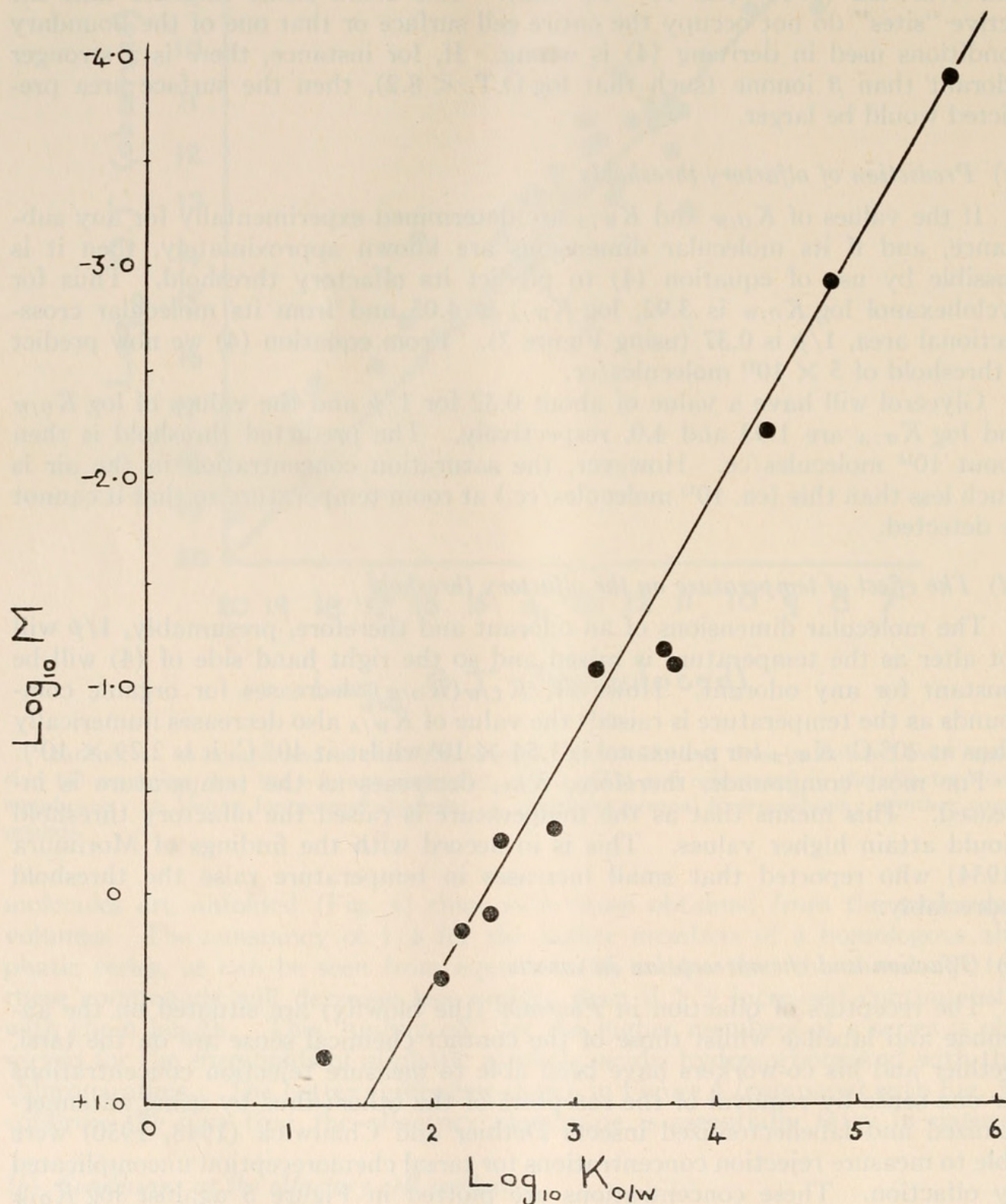


FIGURE 5. Plot of the logarithm of the molar concentration in water rejected by 50% of a number of blowflies against $\log_{10} K_{O/W}$. The concentrations are taken from the publications of Dethier and Chadwick (1948, 1950).

show a levelling off for the higher members of a homologous series (Fig. 6). This confirms that a shape factor in addition to an adsorption factor is significant in olfaction. Unfortunately, results are available only for aliphatic alcohols and aldehydes for *Phormia* (Dethier and Yost, 1952; Dethier, 1954).

Examination of the literature shows that there are many examples of the interaction of small molecules with biological membranes where adsorption is all-important (as with the chemoreception above or in haemolytic acceleration) and others where the effect is dependent on molecular shape or polarity in addition to the membrane concentration. Thus in the action of compounds on *B. typhosus*

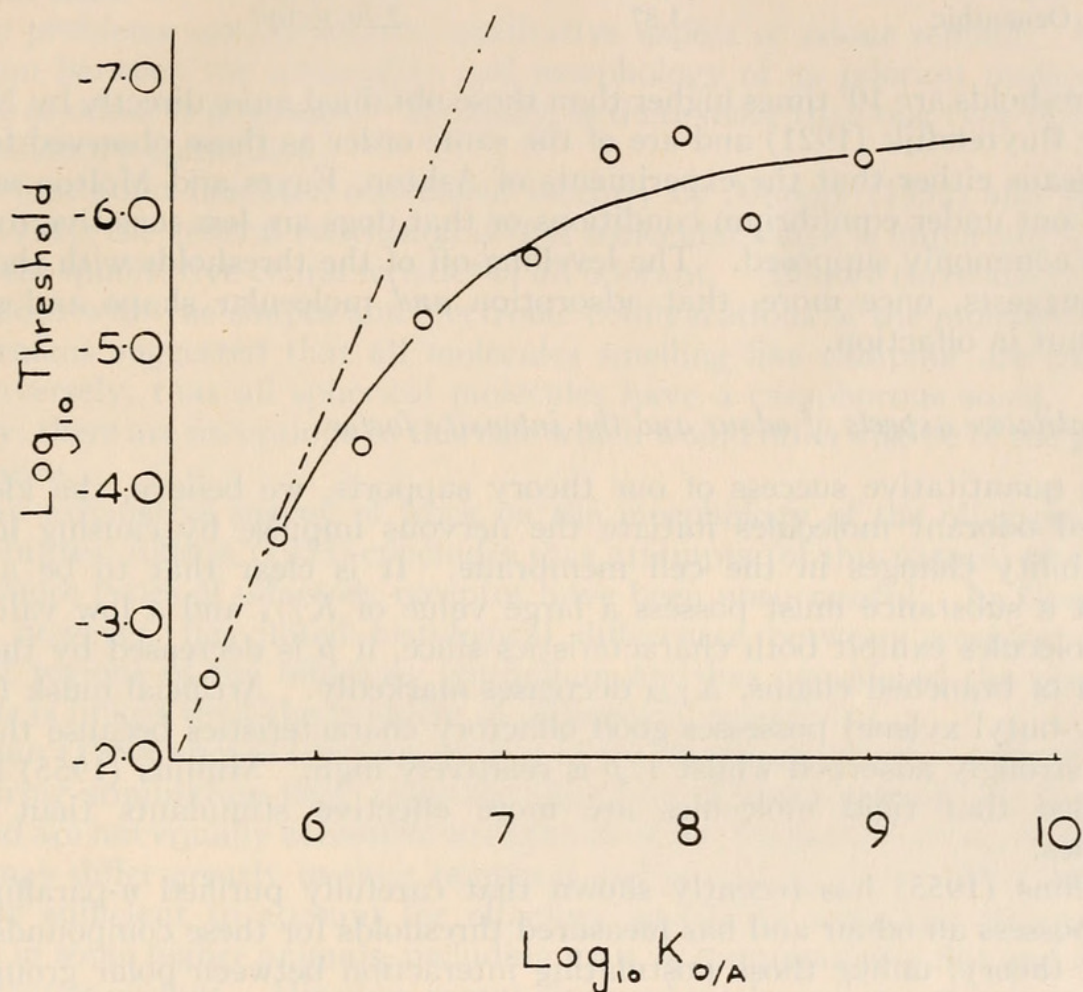


FIGURE 6. Plot of the logarithm of the olfactory rejection concentration for blowflies against $\log_{10} K_{O/W}$. The concentrations are taken from Dethier and Yost (1952). \cdots , line with slope expected if $1/p$ were to increase regularly with chain length for alcohols.

the effect is proportional to $\log K_{O/W}$ (Ferguson, 1939) but the action of similar substances on chloroplast lecithinase systems (Kates, 1957) involves a shape or polarity factor in addition.

(f) *Olfaction in dogs*

Several workers have recently determined olfactory thresholds for dogs (Krushinski, Chuvaev and Vollkind, 1946; Uchida, 1951; Neuhaus, 1953a, 1953b; Ashton, Eayrs and Molton, 1957). The carefully conducted experiments of Ashton, Eayrs and Molton, using solutions of fatty acids, yield thresholds in

terms of gm. mols./liters of *aqueous* solution. From the values of $K_{W/A}$ given in Table I, these can be converted into molecules/cc. in air, assuming that equilibrium conditions prevailed during the experiments. The results for four acids are given below.

Acid	Log molar conc. in water	Thresholds	
		Calculated	Molecules/cc. in air From Neuhaus (1953a, 1953b)
Butyric	-4.38	1.73×10^{10}	9×10^3
Valeric	-3.29	2.82×10^{12}	3.5×10^4
Caproic	-3.56	2.34×10^{12}	4.0×10^4
Oenanthic	-3.87	2.29×10^{12}	—

The thresholds are 10^7 times higher than those obtained more directly by Neuhaus and by Buytendijk (1921) and are of the same order as those observed for man. This means either that the experiments of Ashton, Eayrs and Molton were not carried out under equilibrium conditions or that dogs are less sensitive to odours than is commonly supposed. The levelling-off of the thresholds with the higher acids suggests, once more, that adsorption *and* molecular shape and size are important in olfaction.

(g) *Qualitative aspects of odour and the intensity factor*

The quantitative success of our theory supports, we believe, the idea that adsorbed odorant molecules initiate the nervous impulse by causing localized permeability changes in the cell membrane. It is clear that to be a strong odorant a substance must possess a large value of $K_{L/A}$ and a low value of p . Few molecules exhibit both characteristics since, if p is decreased by the introduction of branched chains, $K_{L/A}$ decreases markedly. Artificial musk (trinitro tertiary-butyl xylene) possesses good olfactory characteristics because the molecule is strongly adsorbed whilst $1/p$ is relatively high. Mullins (1955) has also concluded that rigid molecules are more effective stimulants than flexible molecules.

Mullins (1955) has recently shown that carefully purified *n*-paraffins definitely possess an odour and has measured thresholds for these compounds. The present theory, unlike those postulating interaction between polar groups, predicts this and the threshold values that we have calculated agree well with those observed by Mullins (Figs. 3 and 4).

It should be possible, by an extension of the theory, to investigate the variation in *intensity* of an odour with its concentration in the air about the threshold value. The intensity of an odour, however, is difficult to define or to measure for humans, and little work has been done on this subject. Experiments on *Phormia* or other insects seem more suitable for work on this parameter. The recent electrophysiological experiments of Beidler (1958) have shown that the activity of the olfactory receptors in the rabbit increases with the concentration of odorant until a maximum level of activity is reached.

It is not clear, however, whether excitation of an olfactory cell by an odorant is an all-or-nothing phenomenon (so that the intensity of smell depends on the number of cells stimulated), or whether there are different degrees of stimulation

of one cell (when the intensity would depend on the number of impulses per second, *i.e.*, on the number of small areas per cell occupied by p odorant molecules).

Repeated exposure of the receptors to concentrations of odorant well above the threshold causes a temporary loss of sensitivity. On the theory of olfaction proposed here, this represents a simple depolarization phenomenon, the cell being unable to build up the "equilibrium" ion concentrations in the periods between successive inspirations. This phenomenon of fatigue or adaptation has been discussed by Adrian (1950a) with reference to olfaction in the rabbit and in general (1950b). Kristensen and Zilstorff-Pedersen (1953) discuss olfactory fatigue in man.

Two problems concerning the qualitative aspect of odour remain. Is there a relation between the adsorption and morphology of an odorant molecule and the type of odour it possesses? Secondly, is there more than one type of receptor in the olfactory epithelium?

The first point has been considered recently by Amoore (1952) and Timmermans (1954); the general conclusion is that molecular shape is important in determining the qualitative characteristics of an odorant. Amoore correlated the type of an odour with the shapes and electronic configurations of the molecules whilst Timmermans suggested that all molecules smelling like camphor are spherical, and conversely, that all spherical molecules have a camphorous smell. Unfortunately, there are exceptions to this rule which would otherwise be of the greatest significance.

In an exhaustive survey of work on the morphology of the olfactory region in vertebrates, Allison (1953) concludes that attempts (of this nature) to discover two or more types of olfactory receptor have been unsuccessful. Le Gros Clark (1957), however, has noted histological differences between receptor cells in different regions of the olfactory epithelium and has considered the possibility that this is linked with the problem of differential sensitivity.

Adrian (1950c) noted from his studies of the electrical activity of the olfactory bulb during stimulation that, since the receptors of lower animals are located in folds and are not equally accessible to currents of air, discharges set up by different smells may differ greatly in their temporal and spatial pattern. This fact alone is hardly sufficient to account for olfactory specificity since the olfactory epithelium in some higher animals, including man, is comparatively flat and exposed over its entire surface. His more recent electrophysiological investigations (1951, 1952, 1954) indicated that there are several types of olfactory receptor but that they are specifically sensitive at concentrations only just above the threshold; at concentrations much above this they react to more odorants. Beidler and Tucker (1955) recorded neural activity from isolated bundles of primary olfactory nerves of the opossum. Their results, too, yielded evidence for a certain degree of specificity in the receptors. These techniques, however, because of the difficulties of placing the electrodes, yield indirect and imprecise information about different receptor types. We may conclude (with Allison) that any observed differences in receptor response must be attributed to subtle differences in structure at the physico-chemical level. Certainly, the specificities of the receptors might depend on the ease with which the different membrane layers are distorted: slight differences in their structure could render them more readily disoriented by molecules of certain shapes than by others. If there are only a few types of

olfactory receptor, however, then finer shades of odour must be the result of a complex pattern of impulses arriving in the brain as a result of the different intensities of stimulation of different receptor types as suggested by Adrian. Mullins (1955) and Cheeseman and Mayne (1953) have studied this question with regard to olfaction in humans, by examining the interference of one odorant with the threshold of another. Mullins suggests that since butanol does not disturb the threshold for butane and vice versa, there are at least two types of receptor membrane in the olfactory epithelium.

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SUMMARY

1. It is proposed that a stimulus is initiated in an olfactory receptor cell only when a critical number (p) of odorant molecules is concentrated within one small area of the cell membrane. An equation is derived which relates the olfactory threshold for humans to this number p and to the adsorption constant for molecules passing from air to the oil/water interface. Olfactory thresholds are calculated for a range of odorants on the assumption that $1/p$ is a function of the molecular cross-section area of an odorant. The calculated thresholds agree with the observed values; that predicted for glycerol exceeds the saturation concentration in the air so that this substance is odourless.

2. The equation suggests that olfactory thresholds should increase as the temperature is raised, as has been found experimentally. The results suggest that the olfactory cell membrane is lipoid in nature; the calculated "active surface area" of each olfactory cell is less than the observed total value. The effectiveness of compounds as odorants for *Phormia* and dogs, as well as for humans, depends on the concentration adsorbed on the membrane and upon the shape and size of the odorant molecules. Contact chemoreception in *Phormia*, however, is dependent only upon the appropriate adsorption constant and not upon molecular morphology.

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