Quantitative Structure Odor Intensity Relationship

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Dependence of Odor Intensity on the Hydrophobic Properties of Molecules. A Quantitative Structure Odor Intensity Relationship

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The relationship between odor intensity and physicochemical properties of odorants was investigated using the Hansch approach, a quantitative structure–activity relationship technique which utilizes linear free energy relationship (LFER) parameters and multiple regression analysis. Literature odor threshold and suprathreshold data for homologous series of compounds whose members had noncolinear hydrophobic, steric, and polar parameters were successfully correlated only with the hydrophobicity parameter log P, the log [1-octanol/water partition coefficient]. Poor correlations were achieved with steric and polar parameters. This indicated that odor intensity depended upon the hydrophobic and not the odorant's steric or polar properties. Log P also correlated well with odor intensity data for a wide variety of odorants of different functionality. Addition of a hydrogen-bonding indicator parameter, HB, to equations relating odor intensity for nonhomologous series significantly improved the correlations. The successful correlations with the hydrophobicity term, log P, indicates that the ability of an odorant to partition from the medium in which it is dissolved into the atmosphere and its ability to partition through mucus and membrane layers to reach olfactory receptor sites are the important factors in determining odor intensity.

Olfaction, like other biological processes, involves a substrate and receptor site interaction. The nature of the substrate receptor interaction and how this interaction leads to a perceived odor has yet to be elucidated. Many studies have produced theories relating molecular shape to perceived odor quality. For example, Amoore (1952), Beets (1957), Davies (1965), and Wright (1954) have been active in this particular area. Recently, Brugger and Jurs (1977), using pattern recognition techniques, determined 13 structural descriptors to predict odor quality of musk odorants. The general consensus of these studies is that molecular shape is an important factor in determining odorant descriptors or odor quality.

Relatively little work has been reported on how odor intensity is dependent upon odorant physical–chemical properties. Guadagni et al. (1963) related molecular weight with the odor threshold values of aliphatic aldehydes in water. Beck (1964) assumed that a factor determining an odorant's threshold is its volume, shape, and axis (produced by the odorant's functional group "anchored" at a receptor site) around which the molecule rotates. Davies and Taylor (1959) related threshold to the cross-sectional areas and adsorption constants at an oil–water interface of the odorant molecules. However, these observed and calculated thresholds frequently varied by ±1 logarithmic units and sometimes as much as ±2.5 units. In another study, odor thresholds were related to odorant hydrogen bonding, molecular volume, and polarizability by Laffort (1969).

In still another study, Dravnieks (1974) correlated 14 structural features with odor threshold and suprathreshold data. More recently, Dravnieks (1977) correlated odor intensity equivalent to 87 ppm (v/v) of 1-butanol with 20 structural features represented by Wiswesser line notation. The molecular weight term, $(\log M_r)^2$, was reported to be the most statistically significant term.

The use of computer techniques in the correlation of biological activity with substrate physical–chemical properties has received much attention in the area of medicinal chemistry. The use of these techniques, denoted quantitative structure–activity relationships (QSAR), were developed mostly by Hansch and his co-workers and have been reviewed by Tute (1971), Purcell et al. (1973), and Dunn (1973).

The QSAR techniques involve correlating the logarithm of the reciprocal molar concentration of a bioactive compound required for a specific biological response such as ED_{50} or LD_{50} values with linear free energy constants such as the Hammett σ constant, a measure of aromatic substituent electronic effects, Taft polar constant (σ^*), a measure of substituent polar effects, the logarithm of the 1-octanol/water partition coefficient (log P), a measure of hydrophobic–lipophilic effects, and the Taft steric constant (E_s), a measure of substituent steric effects.

In the area of taste these techniques were used by Hansch and Deutsch (1966) to show that the relative sweetness to cane sugar of a series of substituted nitroanilines depended upon the hydrophobicity and electron-donating ability of the substituents. Recently QSAR was applied by Boelens (1976) to study compounds with bitter almond and musk odors. A significant relationship between almond odor quality and the 1-octanol/water partition coefficients and a molecular shape–volume parameter was achieved. A significant relationship between the partition coefficients and musk odor quality was reported for 16 musk odorants.

The object of this paper is to report the applicability of QSAR techniques such as those used by Hansch and his co-workers in establishing the primary physical–chemical property(s) important for determining odor intensity and to rationalize how this contributes to the olfactive process. A secondary objective is to establish whether these techniques can be used to predict odor intensity regardless of odor descriptor within and between homologous series of organic compounds. The premises for pursuing this study are: (1) odor intensity depends upon the odorants ability to partition from a medium in which it is dissolved into the atmosphere from which it must partition through mucus and membrane layers within the nasal tract until it reaches a receptor site. (2) The hydrophobicity of the odorant as measured by the log [1-octanol/water partition coefficient] (log P) can be used to quantitate these partitioning processes. (3) A relationship can be developed between log P and odor intensity by using multiple regression analysis. (4) The physical–chemical properties

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Table I. Equations Relating Alcohol Odor Intensity to Hydrophobic, Steric, and Electronic Parameters

intensity type (medium)	eq no.	equation	n	R	S	source
suprathreshold (air)	1	$\log(1/c) = 1.50 \pm (0.66)\log P - 1.34 \pm (1.25)$	13	0.83	1.25	a
suprathreshold (air)	2	$\log(1/c) = -0.53 \pm (0.71)(\log P)^2 + 3.03 \pm (2.16)\log P - 1.76 \pm (1.18)$	13	0.87	1.16	a
suprathreshold (air)	3	$\log(1/c) = 1.40 \pm (0.51)\log P + HB - 2.81 \pm (1.5)$	13	0.88	1.09	a
suprathreshold (air)	4	$\log(1/c) = -0.37 \pm (1.44)E_s + 0.35 \pm (2.38)$	9	0.22	1.80	a
suprathreshold (air)	5	$\log(1/c) = 0.30 \pm (3.20)\sigma^* - 0.36 \pm (1.88)$	9	0.11	1.35	a
threshold (air)	6	$\log(1/c) = 0.78 \pm (0.39)\log P + 3.06 \pm (0.93)$	11	0.83	0.97	b
threshold (air)	7	$\log(1/c) = -0.29 \pm (0.15)(\log P)^2 + 1.84 \pm (0.60)\log P + 3.91 \pm (2.01)$	11	0.95	0.55	b
threshold (air)	8	$\log(1/c) = -1.27 \pm (1.92)E_s + 8.16 \pm (4.43)$	11	0.45	1.56	b
threshold (water)	9	$\log(1/c) = 1.82 \pm (0.40)\log P + 6.08 \pm (0.50)$	6	0.99	0.37	c
threshold (water)	10	$\log(1/c) = -0.29 \pm (0.18)(\log P)^2 + 2.31 \pm (0.36)\log P + 6.48 \pm (0.22)$	6	0.99	0.14	c

^{a} Dravnieks (1976). ^{b} Laffort (1968). ^{c} ASTM (1973).

such as the Taft steric constant (E_s) and polar constant (σ^*) can be used to determine the importance of odorant steric and polar effects on odor intensity. (5) The derived regression equations can be used to predict odor intensity of untested compounds.

PROCEDURES

The procedures for doing this particular quantitative structure–activity relationship involve the following: (1) searching the chemical literature for odor detection threshold values and suprathreshold values of classes of chemical compounds whose members have noncolinear steric, polar, and hydrophobic constants; (2) calculating or using reported steric (Taft steric constant), polar, and hydrophobic ($\log P$) constants; and (3) correlating the log of the reciprocal millimolar concentration required for a threshold value or suprathreshold value denoted $\log(1/c)$ with the corresponding Taft polar, steric, and $\log P$ values.

Classes of chemical compounds having different functional groups and odor descriptors, some of which are useful to the flavor or perfume industries were selected for this initial study. For example, alcohols, aldehydes, pyrazines, and various benzenoid compounds which have been isolated in the volatiles of cooked meat as reviewed by Hornstein (1971) were studied. For each class of chemical compounds literature threshold values obtained only from one laboratory were used in order to prevent errors associated with technique or methodology between laboratories that occur for threshold determinations as discussed by Guadagni et al. (1963) and Powers and Ware (1976).

Suprathreshold odor intensity data from Dravnieks (1977) equating odor intensity equivalent to 87 ppm (v/v) of 1-butanol was used since it eliminated errors between laboratories which occur for threshold measurements and the 1-butanol reference scale has been approved by the ASTM (1975) as a standard method of measuring odor intensity.

The log [1-octanol/water partition coefficients] ($\log P$) for compounds selected for this study were obtained from those reported by Hansch et al. (1971) or were calculated from fragmental constants as reported by Nys and Rekker (1974). The Taft steric (E_s) and polar (σ^*) constants were obtained from those values reported by Taft (1956).

For alcohols, the E_s and σ^* values for the substituents bonded to the carbinol moiety were each summed and correlated against $\log(1/c)$. For aldehydes and ketones the E_s and σ^* values for substituents bonded to the carbonyl group were each summed and correlated against $\log(1/c)$. The use of E_s and σ^* has been reviewed by Shorter (1972).

The use of a hydrogen bonding indicator parameter (HB) in quantitative structure–activity relationships has recently been reviewed by Fujita et al. (1977). In that study it was found that an indicator parameter (HB) which represents the "extra" hydrogen-bonding effect on the biological activity is required in the Hansch-type correlations when the relative hydrogen-bonding effect of bioactive compounds on phases involved in the binding at the site of biological action differs from that in the 1-octanol–H_2O partitioning phases used as the reference to estimate hydrophobicity. Examples were presented in which the HB indicator parameter was used in correlating activity of gaseous anesthetics and the binding of phenyl 1-methyl carbamates with acetylcholinesterase inhibition. In this study HB was used to ascertain whether it would improve the correlations involving series of congeners with substituents having appreciable association capability. Nonhydrogen bonders were assigned an HB value of 0 while hydrogen acceptors or donors were each assigned an HB value of 1.

Regression studies of the odor intensity data were carried out using the Continental Can Co. stepwise multiple regression program and the PDP-11-45 minicomputer (Digital Equipment Corp.).

RESULTS AND DISCUSSION

The results found relating literature odor intensity data to $\log P$, E_s, and σ^* are presented in Tables I–IV. For each equation N is the number of compounds in the data set, R is the correlation coefficient, and S is the equation standard deviation. The numbers in parentheses are the calculated confidence intervals at the 95% level of confidence.

From the eleven sets of data in Tables I–IV, very good correlations were achieved between $\log(1/c)$ and $\log P$ or $\log P$ and HB with ten sets having an equation with a correlation coefficient greater than 0.88 which was at least significant at the 95% level of confidence. Very good correlations with $\log P$ were found using literature threshold data as well as suprathreshold data. Thus two different odor intensity parameters correlated well with

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Table II. Equations Relating Aldehyde–Ketone Odor Intensity to Hydrophobic, Steric, and Electronic Parameters

intensity type (medium)	eq no.	equation	n	R	S	source
suprathreshold (air)	1	$\log(1/c) = 1.49 \pm (1.58)\log P - 0.06 \pm (2.19)$	9	0.64	1.66	a
suprathreshold (air)	2	$\log(1/c) = 1.89 \pm (0.66)\log P + 2.23 \pm (0.88)HB - 3.23 \pm (0.89)$	9	0.96	0.66	a
suprathreshold (air)	3	$\log(1/c) = -0.47 \pm (1.61)(\log P)^2 + 2.64 \pm (4.33)\log P - 0.44 \pm (1.88)$	9	0.68	1.72	a
suprathreshold (air)	4	$\log(1/c) = -1.08 \pm (1.44)\,\Sigma E_s + 0.07 \pm (1.70)$	7	0.65	1.38	a
suprathreshold (air)	5	$\log(1/c) = 0.31 \pm (4.86)\,\Sigma\sigma^* + 0.63 \pm (1.79)$	7	0.48	1.79	a
threshold (water)	6	$\log(1/c) = 0.19 \pm (0.04)\log P + 3.88 \pm (0.24)$	8	0.97	0.21	b
threshold (water)	7	$\log(1/c) = 0.15 \pm (0.51)(\log P)^2 + 0.15 \pm (0.15)\log P + 3.81 \pm (0.24)$	8	0.98	0.22	b
threshold (water)	8	$\log(1/c) = -3.90 \pm (6.82)E_s + 1.09 \pm (4.33)$	8	0.50	0.79	b
threshold (water)	9	$\log(1/c) = 0.42 \pm (0.25)\log P \pm 3.60 \pm (0.64)$	7	0.97	0.42	c
threshold (water)	10	$\log(1/c) = 0.02 \pm (0.11)(\log P)^2 + 0.36 \pm (0.36)\log P + 3.64 \pm (0.25)$	7	0.97	0.22	c
threshold (water)	11	$\log(1/c) = -3.24 \pm (6.00)E_s + 3.49 \pm (1.83)$	7	0.53	0.72	c

a Dravnieks (1976). b Guadagni et al. (1963). c Ahmed et al., (1978).

Table III. Equations Relating Odor Intensity to Hydrophobic, Steric, and Electronic Parameters for Various Compounds

compounds	intensity type (medium)	eq no.	equation	n	R	S	source
alkanes	threshold (air)	1	$\log(1/c) = 0.76 \pm (0.42)\log P + 1.20 \pm (1.81)$	7	0.89	0.69	a
alkanes	threshold (air)	2	$\log(1/c) = -0.24 \pm (0.18)(\log P)^2 + 2.57 \pm (1.42)\log P + 1.36 \pm (1.08)$	7	0.97	0.39	a
alkanes	threshold (air)	3	$\log(1/c) = 10.42 \pm (24.0)E_s + 8.12 \pm (1.55)$	7	0.51	0.60	a
ethyl esters	threshold (air)	4	$\log(1/c) = 0.42 \pm (0.15)\log P + 5.43 \pm (0.63)$	7	0.96	0.27	a
ethyl esters	threshold (air)	5	$\log(1/c) = -0.05 \pm (0.12)(\log P)^2 + 0.45 \pm (0.50)\log P) + 5.37 \pm (0.83)$	7	0.96	0.30	a
3-alkyl-2-methoxy-pyrazines	threshold (water)	6	$\log(1/c) = 2.37 \pm (1.49)\log P + 4.4 \pm (2.16)$	7	0.88	1.46	b
3-alkyl-2-methoxy-pyrazines	threshold (water)	7	$\log(1/c) = -1.04 \pm (0.77)(\log P)^2 + 5.05 \pm (2.19)\log P + 3.38 \pm (1.23)$	7	0.97	0.77	b
benzenoids and heteroaromatics	threshold (water)	8	$\log(1/c) = 0.93 \pm (0.61)\log P - 0.48 \pm (1.35)$	11	0.75	0.68	c
benzenoids and heteroaromatics	threshold (water)	9	$\log(1/c) = 1.12 \pm (0.41)\log P + 1.21 \pm (0.72)HB - 1.92 \pm (0.86)$	11	0.92	0.43	c

a Laffort (1968). b Seifert et al. (1970). c ASTM (1973).

Table IV. Equations Relating Hydrophobicity to Odor Intensity for a Wide Variety of Odorants

compounds	intensity type (medium)	eq no.	equation	n	R	S	source
aldehydes, ketones	suprathreshold (air)	1	$\log(1/c) = 0.38 \pm (0.37)\log P + 0.12 \pm (0.45)$	50	0.29	1.75	a
acids, esters		2	$\log(1/c) = -0.55 \pm (0.22)(\log P)^2 + 2.46 \pm (0.91)\log P - 0.85 \pm (0.55)$	50	0.63	1.43	a
ethers, alcohols, hydrocarbons, benzenoids		3	$\log(1/c) = -0.38 + (0.19)(\log P)^2 + 2.12 \pm (0.74)\log P + 1.18(0.48)HB - 5.23 \pm (0.45)$	50	0.80	1.17	a

a Dravnieks (1976).

$\log P$. Odor intensity of homologous series as well as for compounds with different functional groups were found to correlate well with $\log P$, although correlations of the latter were improved by the addition of the hydrogen bonding parameter HB. For example, the results in Table IV indicated that $\log P$ and HB correlated well with suprathreshold data for a data set of 50 compounds which

include hydrocarbons, benzenoids, heteroaromatics, aliphatic ethers, ketones, aldehydes, acids, and esters.

Odor intensity was poorly related to E_s or ΣE_s for literature data sets whose hydrophobic and steric properties were not colinear. The results of these correlations are presented in Table I (eq 4 and 8), Table II (eq 4, 8, and 11), and Table III (eq 3). The results in Table I indicate

Table V. Squared Correlation Coefficients for Equations Relating LFER Parameters to Alcohol Odor Suprathreshold Data

	$\log (1/c)$	$\log P +$ HB	ΣE_s	$\Sigma \sigma^*$
$\log (1/c)$	1.00	0.77	0.05	0.01
$\log P + HB$	0.77	1.00	0.15	0.12
ΣE_s	0.05	0.15	1.00	0.42
$\Sigma \sigma^*$	0.01	0.12	0.42	1.00

Table VI. Squared Correlation Coefficients for Equations Relating LFER Parameters to Alcohol Odor Threshold Data

	$\log (1/c)$	$\log P$	ΣE
$\log (1/c)$	1.00	0.69	0.20
$\log P$	0.69	1.00	0.12
ΣE_s	0.20	0.12	1.00

Table VII. Squared Correlation Coefficients for Equations Relating LFER Parameters to Aldehyde-Ketone Odor Suprathreshold Data

	$\log (1/c)$	$\log P +$ HB	E_s	σ^*
$\log (1/c)$	1.00	0.92	0.42	0.23
$\log P + HB$	0.92	1.00	0.01	0.23
E_s	0.42	0.01	1.00	0.02
σ^*	0.23	0.23	0.02	1.00

Table VIII. Squared Correlation Coefficients for Equations Relating LFER Parameters to Aldehyde Odor Threshold Data

	$\log (1/c)$	$\log P$	E_s
$\log (1/c)$	1.00	0.90	0.25
$\log P$	0.90	1.00	0.16
E_s	0.25	0.16	1.00

Table IX. Squared Correlation Coefficients for Equations Relating LFER Parameters to Alkane Odor Threshold Data

	$\log (1/c)$	$\log P$	E_s
$\log (1/c)$	1.00	0.79	0.26
$\log P$	0.79	1.00	0.30
E_s	0.26	0.30	1.00

that ΣE_s correlated poorly with $\log (1/c)$ for alcohols whose odor intensity were determined by two different methods. Thus the bulkiness of the substituents on the carbinol moiety does not determine the level of odor intensity. Similar results were found for the aldehyde-ketone data in Table II for two different types of odor intensity measurement. This indicates that the bulkiness of the substituents bonded to the carbonyl group does not determine the level of odor intensity for aldehydes and ketones. The data presented in Table III (eq 3) indicate that for alkanes E_s correlated poorly with odor intensity. Thus the bulkiness of the substituents bonded to the terminal methyl group does not determine the level of odor intensity for alkanes. The correlation matrix in Tables V-IX summarize all correlations of $\log (1/c)$ vs. E_s and verify the fact that E_s and $\log P$ are not colinear.

Poor correlations between $\log (1/c)$ and σ^* (the Taft polar constant) were observed for alcohol odor intensity data presented in Table I (eq 5). This indicates that the polar effects of the groups bonded to the carbinol moiety do not affect the level of odor intensity as measured by suprathreshold methods. Similar results were observed for the aldehyde-ketone suprathreshold data in Table II (eq 5), indicating polar effects of groups bonded to the carbonyl moiety are not important in determining odor intensity. Other correlations with σ^* values were not possible because of the lack of σ^* values in the literature; however, the effect on σ^* of branching at the B carbon or of lengthening the carbon chain beyond three atoms for homologous series is relatively small. Thus series of saturated alcohols, aldehydes, ketones, etc. have members with similar σ^* values and different $\log (1/c)$ values. The correlation matrix in Tables V-IX summarize all correlations of $\log (1/c)$ vs. σ^*. These tables verify the fact that $\log P$ and σ^* are not colinear.

The concept of odorant hydrophobicity, as measured by $\log P$, determining the level of odor intensity offers insight into the mechanism of olfaction. As discussed by Wright and Burgess (1977), it is known from electron microscopy that in vertebrates the olfactory epithelium contains a tangle of cilia floating in a mucus layer. At any instant the cilia which contains many receptor cells may be totally or partially immersed in this mucus layer. Surely the ability of an odorant to partition through the mucus layer and membrane layers of the cilia will affect the concentration of the odorant that reaches the binding sites and thus odor intensity. An odorant may still partition through membrane layers of cilia not in the mucus layer or membrane layer of receptor cells in the trigeminal nerve until it reaches the receptor site.

The $\log P$ term will also contain a contribution owing to the ability of an odorant to partition from the media in which it is dissolved into the atmosphere. This volatility contribution has been measured by Buttery et al. (1969, 1971) and Nawar (1971) for compounds in dilute aqueous solutions and is called the air/water partition coefficient (A/W). Table X presents equations relating $\log P$ with $\log (A/W)$ for homologous series of methyl ketones, alcohols, and aldehydes. For each homologous series $\log P$ is linearly related to $\log A/W$. These equations indicate that volatility of odorants in aqueous solutions increases with increasing homologue hydrophobicity. The alcohol (Table I eq 9) and aldehyde (Table II eq 5) threshold data indicate that the more hydrophobic alcohols and aldehydes have more intense odors because of their high volatility in aqueous solutions and their ability to partition through biolayers to reach olfactory receptor sites. On the other hand, the 3-alkyl-2-methoxypyrazine threshold data (Table III, eq 4) indicate that there is an optimum $\log P$ value of 2.43 for maximum odor intensity. This indicates that pyrazines with $\log P$ values greater than 2.43 are more volatile in aqueous solutions but have a weaker odor intensity than a pyrazine with a $\log P$ value of 2.43; therefore, with a congeneric series the analogues with the highest

Table X. Equations Relating Log P with Volatilities of Organic Molecules in Dilute Water Solutions by Log Air-Water Partition Coefficients (Log A/W)

compounds	eq no.	equation	n	R	S	source
methyl ketones	1	$\log P = 5.50 \pm (1.54) \log A/W + 14.08 \pm (3.43)$	7	0.96	0.30	a
normal aliphatic alcohols	2	$\log P = 4.98 \pm (0.59) \log A/W + 17.89 \pm (1.91)$	8	0.96	0.15	b
normal aliphatic aldehydes	3	$\log P = 3.31 \pm (0.73) \log A/W + 8.11 \pm (1.44)$	6	0.99	0.10	c

^{a} Nawar (1971). ^{b} Buttery et al. (1971). ^{c} Buttery et al. (1969).

volatilities are not necessarily the most intense odorants. For odorants in air this point is further illustrated by considering vapor pressure data and eq 2 in Table II which indicate that over 2000 times more acetone (vapor pressure = 202 torr at 25 °C) is needed to produce the same odor intensity of acetophenone (vapor pressure = 1.09 torr at 25 °C) based on molar concentration needed to produce odor intensity equivalent to 87 ppm 1-butanol.

The use of log P and HB parameters as a tool for predicting odor intensity seems promising. Although many excellent correlations were obtained as presented in Tables I–IV, further studies are needed to investigate several unresolved areas. The question on whether log P is linearly or parabolically related to odor intensity for a specific medium needs to be resolved. Six equations in Tables I–IV linearly related log P to odor intensity, while five parabolic relationships were observed which had an optimum hydrophobicity (log P) associated with maximum odor intensity, log P_o values observed were 3.17 (eq 7, Table I), 3.98 (eq 10, Table I), 5.35 (eq 2, Table III), 2.43 (eq 4, Table III), and 2.79 (eq 3, Table IV), thus with the exception of the esters, compounds with log P values around 2.8 seem to have maximum odor intensity based upon data from four different laboratories using two different media and measuring two different odor intensity parameters (odor threshold and suprathreshold values).

As discussed by Cammarata and Rogers (1972) the more complex the biological system on which a series of bioactive compounds is tested, the more likely the biological activities will be found to be nonlinear with respect to partition coefficients. The rationale for this is that compounds with a particular partition coefficient (P_o) value achieve sufficient concentrations in a receptor compartment to lead to a maximum in biological response. Compounds with partition coefficients greater or less than P_o tend to become involved in kinetic or energetic processes which cause decreased concentrations of the bioactive compound in the receptor compartment. The biological activities of simple test systems may at times show a nonlinear dependence with respect to partition coefficients, but this usually occurs when the bioactive substances are intrinsically of high lipophilicity, and a wide range of log P values is represented by the series. It is possible that the observed linear relationships between odor intensity and log P would become parabolic if the authors would have studied data sets with compounds having larger log P ranges such as 5–6.

The equations in Table I indicate that for alcohols odor intensity is parabolically dependent upon log P for threshold values determined in air (eq 7) and in water (eq 10) and linearly dependent upon log P for suprathreshold values in air (eq 1). The alcohol odor intensity may be parabolically dependent upon log P for the suprathreshold values in air, if the authors would have studied additional compounds having log P values of 3.75–5.00 since the log P value that gives optimum odor intensity in eq 7 is 3.17. The log P range for the suprathreshold in air data is (–0.32 to 3.25) which have few data points with log P values greater than the optimum log P value of 3.17.

Another area of further study is the reproducibility and accuracy of derived predictive equations. Two different data sets of aliphatic aldehyde threshold values in water were subjected to QSAR techniques to determine whether log P can be used to accurately reproduce predictive equations for odor intensity data of a compound in a given medium determined by two different laboratories. Results in Table II indicate that eq 6 and 9 have slopes, intercepts, correlation coefficients, and standard deviations which are

not statistically different at the 95% level of confidence. Both data sets also produced equations giving poor correlations of E_s and log $(1/c)$ which were not statistically significant.

A similar study is needed for a wide variety of organic compound suprathreshold data to verify the reproducibility of eq 3 in Table IV.

SUMMARY

The use of QSAR techniques such as the Hansch Approach in the investigation of odor intensity and odorant physicochemical properties has indicated that hydrophobic properties of homologous series of compounds, not steric or polar properties, are highly correlated to the level of odor intensity. This was shown to be the case for literature odor threshold and suprathreshold data determined at different laboratories using various media. The hydrophobicity term as measured by log P, the log [1-octanol/water partition coefficient], indicates that the ability of an odorant to partition from the medium in which it is dissolved into the atmosphere and its ability to partition through mucus and membrane layers to reach olfactory receptor sites is highly correlated to odor intensity. Results of this study also indicated that within a congeneric series, the analogues with the highest volatilities are not necessarily the most intense odorants.

The ability of these techniques to predict odor intensity of organic compounds in a given medium seems promising. Many good correlations between literature odor intensity data and log P were observed for different media and for two different methods of measuring odor intensity, odor threshold, and suprathreshold techniques. Log P correlated well with homologous and nonhomologous series. The addition of a hydrogen-bonding indicator parameter, HB, to equations relating odor intensity to log P for nonhomologous series of compounds resulted in significantly improved correlations in four cases. The reproducibility of the predictive power of the derived equations was shown to be very good. This was demonstrated by predictive equations for literature aldehyde threshold values determined in water by two different laboratories. The derived equations were shown to be statistically equivalent at the 95% level of confidence.

Further work is needed in this area before a general predictive equation can be derived relating odor intensity of compounds in a given media to log P and HB. The question on whether log P is linearly or parabolically related to odor intensity needs to be resolved. Data sets of odorants having large log P ranges of 5–6 need to be studied to resolve this issue.

Hopefully, further evaluations of log P as an odor intensity predicting tool will generate general equations relating log P to odor intensity for a wide range of important flavor compounds in specific media. These equations would be of great help to synthetic organic chemists in designing novel flavor compounds with optimum odor intensity.

LITERATURE CITED

Ahmed, E. M., Dennison, R. A., Dougherty, R. H., Shaw, P. E., J. Agric. Food Chem. 26, 187 (1978).

352 *J. Agric. Food Chem.,* Vol. 27, No. 2, 1979

Hoffman, Salb

Amoore, J. E., *Perfum. Essent. Oil Rec.* **43**, 321 (1952).

ASTM E544, "Recommended Practice for Odor Suprathreshold Intensity Referencing", Am. Soc. Test. Materials, Philadelphia, PA 1975.

ASTM DS48, "Compilation of Odor and Taste Threshold Values Data", Stahl, W. H., Ed., Am. Soc. Test. Materials, Philadelphia, PA, 1973.

Beck, L. H., *Ann. N.Y. Acad. Sci.* **116**, 228 (1964).

Beets, M. G. J., in "Molecular Structure and Organoleptic Quality", Society of Chem. Industry, Macmillan, New York, NY, 1957, pp 54–90.

Boelens, H., in "Structure Activity Relationships in Chemoreception", Benz, G., Ed., Information Retrieval Limited, London, 1976, pp 197–206.

Brugger, W. E., Jurs, P. C., *J. Agric. Food Chem.* **25**, 1158 (1977).

Buttery, R. G., King, L. C., Guadagni, D. G., *J. Agric. Food Chem.* **17**, 385 (1969).

Buttery, R. G., Bomben, J. L., Guadagni, D. G., King, L. C., *J. Agric. Food Chem.* **19**, 1045 (1971).

Cammarata, A., Rogers, K. S., in "Advances in Linear Free Energy Relationships", Chapman, N. B., Shorter, J., Ed., Plenum Press, New York, NY, 1972, pp 420–435.

Davies, J. T., *J. Theor. Biol.* **8**, 1 (1965).

Davies, J. T., Taylor, F. H., *Biol. Bull. Woods Hole* **117**, 222 (1959).

Dravnieks, A., *Ann. N.Y. Acad. Sci.* **237**, 144 (1974).

Dravnieks, A., *ACS Symp. Ser.* **No. 51**, 11–28 (1977).

Dunn, W. J., *Ann. Rep. Med. Chem.* **8**, 313 (1973).

Fujita, T., Nishioka, T., Nakajima, M., *J. Med. Chem.* **20**, 1071 (1977).

Guadagni, D. G., Buttery, R. G., Okano, S., *J. Sci. Food Agric.* **14**, 761 (1963).

Hansch, C., Deutsch, E. W., *Nature (London)* **211**, 75 (1966).

Hansch, C., Leo, A., Elkins, D., *Chem. Rev.* **71**, 525 (1971).

Hornstein, I., in "The Science of Meat and Meat Products", Price, J. F., Schweigert, B. S., Ed., W. H. Freeman, San Francisco, CA, 1971, pp 348–363.

Laffort, P., *C. R. Seances Soc. Biol.* **162**, 1704 (1968).

Laffort, P., in "Olfaction and Taste III", Pfaffmann, C., Ed., Rockefeller University Press, New York, NY, 1969, pp 150–151.

Nawar, W. W., *J. Agric. Food Chem.* **10**, 1057 (1971).

Nys, G. G., Rekker, R. F., *Eur. J. Med. Chem.* **9**, 361 (1974).

Powers, J. J., Ware, G. O., *Chem. Senses Flavor* **2**, 241 (1976).

Purcell, W. P., Bass, G. E., Clayton, J. M., "Strategy of Drug Design: A Guide to Biological Activity", Wiley, New York, NY, 1973.

Seifert, R. M., Buttery, R. G., Guadagni, D. G., Black, D. R., Harris, J. G., *J. Agric. Food Chem.* **18**, 246 (1970).

Shorter, J., in "Advances in Linear Free Energy Relationships", Chapman, N. B., Shorter, J., Ed., Plenum Press, New York, NY, 1972, pp 71–119.

Taft, R. W., "Steric Effects in Organic Chemistry", Newman, M. S., Ed., Wiley, New York, NY, 1956, p 556.

Tute, M. S., *Adv. Drug Res.* **6**, 1 (1971).

Wright, R. H., *J. Appl. Chem.* **4**, 611 (1954).

Wright, R. H., Burgess, R. E., *Method. Chemicum.* **11**, 268 (1977).

Isolation and Stable Isotope Ratio Analysis of Vanillin

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A method has been developed for the routine determination of the origin of vanillin found in vanilla extracts and products. This method uses gas chromatographic isolation coupled with C-13/C-12 stable isotope ratio analysis to differentiate between vanillin from vanilla beans and that produced synthetically from lignin, eugenol, and guaiacol.

One of the world's most important and desirable flavors is vanilla, formed by the extraction of the cured fruit of an orchid plant. In 1976, 2.23 million pounds of vanilla beans were imported into the United States at an approximate value of fifteen million dollars. A large majority of the beans came from the Malagasy Republic (Madagascar). With the high demand and limited supply of quality beans and the continuing increase in their cost, the use of inexpensive vanillin from lignin in vanilla extracts and products has become attractive. To insure the quality of vanilla extracts and flavors, it is important to develop techniques to verify their authenticity.

Several methods have been developed for this purpose. The most commonly used methods are found in the Association of Official Analytical Chemists' "Methods of Analysis" (1975). However, the composition of an altered sample can be adjusted to mimic the authentic sample, reducing the usefulness of these methods. Furthermore, changes in the source of vanilla beans in the past few years requires additional experimentation to use some of these techniques. For instance, Indonesia (Java) has become the second largest exporter of vanilla beans and was not included in developing these methods. Recently, Martin et al. (1975, 1977) developed a method which uses identification ratios determined from the vanillin, potassium, nitrogen, and inorganic phosphate content of each type of vanilla extract. This method is applicable but requires sophisticated equipment, a significant input of time, and regular determination of the ratios for authentic standards; e.g., extracts of Java beans in 1975 had an undetectable vanillin content whereas the 1976 crop has about 500 ppm. Therefore, a procedure dependent upon an intrinsic property of the compound vanillin (the major flavor constituent of vanilla) and one which could also determine the origin of the vanillin would be more advantageous and consistent. This procedure would, in addition, be applicable to vanilla products as well as extracts.

It is known that photosynthesis is accompanied by isotopic fractionation of carbon in favor of carbon-12. Stable isotope ratio analysis (SIRA) of carbon, used earlier for correcting radiocarbon dating, was developed by Bender (1971) and Smith and Epstein (1971) into a method for determining biosynthetic pathways since it was found that plants discriminate differently against car-

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