

Olfactory Theories and the Odors of Small Molecules

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Current major theories of olfaction pertaining to odorant-receptor interaction are critically reviewed. The theories dealt with mainly are the Dyson-Wright vibrational theory, the Moncrieff-Amoore site-fitting theory, and Beets' PFG (Profile-Functional Group) concept. It is pointed out that none of the theories is capable of explaining the powerful odors of certain small molecules such as H₂S and NH₃. An attempt is made to explain the odors of such molecules by introducing the concept of in-

herent functional group odor, and to relate the powerful and specific odors of certain functional groups to the latter's electronic properties. It is concluded that in the vast majority of odorants the odor quality observed appears to be the outcome of a complicated interplay of at least three factors, *e.g.*, size-shape, orientation with respect to the receptor surface, and inherent functional group odor. This outcome can at present be predicted only in isolated cases.

During the last 100 years numerous attempts have been made to correlate the odor produced by chemical compounds in some way or another with certain features of their molecular structures. The following review of current knowledge in this area will be limited to those olfactory theories which directly involve the structure of the odorant molecule, and which pertain exclusively to the first stage of odor perception, namely, odorant-receptor interaction, without considering the actual mechanism by which odorant-receptor interaction may or may not give rise to a nerve impulse.

A review of the extensive literature in this field reveals that there appears to be widespread agreement regarding certain requirements an odorant material must meet in order to be clearly odorous. The material must have lipid solubility as well as water solubility; the latter can be very low. It must have sufficient volatility, and must be present in the air surrounding the receptor site in a certain minimum concentration (threshold concentration) which varies enormously for different odorants. Furthermore, it is now generally accepted that there must be direct physical contact between odorant molecule and receptor site (Roderick, 1966) in order for the odor to be perceived, and most workers in the field are of the opinion that the odorant-receptor interaction is a physical rather than a chemical process. In other words, the odorant molecule does not need to undergo a chemical conversion in order to be perceived.

Beyond this area of fairly general agreement, however, there exists great diversity of opinion. On the one end of the spectrum are those who say that there are as many different odors as there are different odorous chemical structures, and that attempts to find general relationships between structure and odor are just as futile as are attempts to find general relationships between structure and any other biological activity, *e.g.*, hormonal or bactericidal activity. On the other side there are those who state that considerable insight has already been gained in regard to certain structural characteristics which play a part in determining odor quality, and that the prognosis for further progress is much better than it is for other structure-activity studies in view of the unique accessibility of the receptor site and the availability of special techniques.

In this connection it is useful to consider the concepts of odor and structural characteristics in a little more detail. In

regard to odor, anyone who spills a bottle of *n*-hexane in a small unventilated room will be of the opinion that he perceives a strong odor. On the other hand, the odor expert knows that the nose is a much finer instrument than the most elaborate gas chromatograph, and that petroleum hydrocarbons contain trace amounts of highly odorous sulfur compounds. Therefore, he will immediately point out that the odor perceived may not be due to *n*-hexane but to an impurity, and further that the concentration of hexane in the air in this case is so high as to render speaking of odor perception in the normal sense rather meaningless. On the other hand, anyone who is asked to compare the odor of *n*-hexane with the odors of, for example, *n*-hexylamine or *n*-hexyl mercaptan at low concentrations will agree that, relatively speaking, *n*-hexane is virtually odorless. Furthermore, no one studying, for example, the relationships of chemical structure to bactericidal activity could expect to get very far by looking at poor bactericides, that is, compounds which have some antibacterial activity only at very high concentrations. Similarly, structure *vs.* odor quality studies should, at least initially, preferably comprise reasonably powerful odorants, that is, odorants with relatively low threshold concentrations, and minor differences in odor nuance between them would, for the time being, probably best be disregarded.

As regards the study of structural characteristics of odorant molecules, it will be necessary to go beyond such attributes as overall dimensions and nature of the functional group. The study will have to include much more subtle structural factors, *e.g.*, increased or decreased electron densities at certain regions of the structure. One is reminded here of the initially rather puzzling relationships between structure and carcinogenic activity of the essentially featureless polynuclear hydrocarbons. Here there is a clear correlation between carcinogenic activity and electron density in the K-region, as evidenced by the influence of a methyl substituent in various positions upon the structural indices, particularly the bond index of that region (Pullman, 1962). Furthermore, it is probably not the distribution of electrical charges in the isolated odorant molecule which is of primary importance in determining odor quality. The approach of the molecule to the receptor site is likely to result in mutual polarization, so that it is the distribution of charges in the transition state (the odorant-receptor complex) which is decisive.

VIBRATIONAL THEORIES

Since it has been established with reasonable certainty that material contact between odorant and receptor is necessary, the older vibrational theories ascribing odor sensation to some

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type of radiation across a distance from odorant to receptor or *vice versa* can be regarded as disproved. More recently, theories have been proposed which involve contact or very close proximity (contiguity) between odorant and receptor, whereby electronic or atomic vibrations of the odorant are somehow transferred to the receptor site, the frequencies of these vibrations determining the odor quality. Thus structures with similar odors might be expected to have at least some of these vibrational frequencies in common. Dyson (1937) proposed that odorants should have vibrations in a frequency range corresponding to the Raman frequency range of 1400–3500 cm^{-1} . These frequencies correspond in most cases to infrared bands in the range between 1400 and 3500 cm^{-1} , the range in which absorption bands due to individual groups in the molecule are found. Dyson's theory was discarded because no correlations could be found between odor quality and infrared absorption bands in the above region. In 1954 Dyson's theory was revived (Wright, 1954a; Wright and Serenius, 1954) in a modified form. Wright proposed that osmically active vibrations (resulting from collisions at room temperature) would be vibrations involving not individual substituents or groups but the whole molecule, and, as a consequence, these vibrations would correspond to absorption bands in lower frequency ranges, *e.g.*, the fingerprint region below 1000 cm^{-1} and more particularly the far infrared region between 50 and 500 cm^{-1} .

In recent years with the advent of far-infrared spectrometers, it became possible to put Wright's theory to the test, and in 1966 Wright (1966a,b) acknowledged that attempts to correlate odor quality with observed spectroscopic frequencies had been quite unsuccessful. He then modified his theory by stating that only certain out-of-plane vibrations of benzenoid structures appeared to be osmically active, and that previous searches for osmic frequencies had not taken into account the possible role of difference frequencies that must arise when two normal vibrational modes are excited in the same molecule at the same time. However, these osmically active difference frequencies may not necessarily appear in the far-infrared spectrum, a circumstance which would tend to render experimental verification of Wright's theory difficult.

Another serious problem connected with the theory is the very fact that far-infrared bands originate from whole-molecule vibrations (Wright, 1954b, 1966a,b). Accordingly, molecules with approximately the same shape and size might be expected to have at least some far-infrared bands in common. Since, as discussed below, similarity in size and shape has been found to correlate with similarity in odor quality, any correlation found to exist between odor quality and far-infrared absorption would not prove Wright's theory as long as the molecules studied were similar in size and shape. In a recent study involving 47 musk odorants belonging to different structural classes (macrocyclic, nitro, benzene, indane, tetraline, and miscellaneous musks) as well as 109 nonmusk compounds with distinctive odors and well defined absorption bands in the 100–500 cm^{-1} range, statistical but no simple direct relationships between presence of musk odor and presence of certain far-infrared bands were uncovered (Wright and Burgess, 1969). Unfortunately, the compounds were coded so that the data cannot be examined for possible correlations between far-infrared bands and/or odor quality on the one hand and molecular size and shape on the other. Furthermore, the vibrational theory cannot explain the fact that certain optical isomers have different odors (Stoll, 1965); neither does it account for the observation that deuteration of an odorant molecule, which shifts its far-infrared absorp-

tion maxima to lower frequencies, does not change its odor (Doolittle *et al.*, 1968). The latter observation does support the stereochemical theory discussed below, since deuteration of a molecule does not materially alter its shape or size.

In discussing Amoore's stereochemical theory, Wright (1966a) stated "... his basic idea gains added force if we picture the out-of-plane movements of the odorous molecule as conforming with corresponding out-of-plane movements of the sensitive surface. To conform in this way, the two molecules must have nearly the same frequencies in nearly the same places, *so that the net effect depends both on shape and on frequency.*" (Italics mine.) It would therefore seem that the so-called controversy between the Dyson–Wright vibrational theory and the Moncrieff–Amoore site-fitting theory is more apparent than real. The vibrational theory concerns itself not only with the initial odorant–receptor interaction but also with the mechanism by which a nerve impulse might be triggered, and in so doing goes one step beyond the site-fitting theory. It is of interest for our following discussion to note that the vibrational theory cannot account for the powerful odors of certain small molecules such as H_2S , NH_3 , and HCN , which possess no low frequency vibrational modes at all (Wright, 1957).

STERIC (SITE-FITTING) THEORIES

In 1951 Moncrieff (1951), after reviewing about 25 theories of olfaction which had been proposed up to 1950, presented an interesting theory of his own. "It seems likely that to be odorous, a substance must have molecules of prescribed shapes which will fit on certain available molecular sites in the olfactory receptors." Although Moncrieff erroneously equated unsaturation and resonance with flexibility, and chemical addition with molecular attraction, he stated significantly: "through flexibility ... the molecule will have a better chance of accommodating itself on a receptor site ... whereas ... if a molecule has a fixed shape it can fit one and only one type of site ...". And further, "In a sense, the adherence of an odorous molecule to a receptor site may be looked upon as an addition reaction that is allowed to take place simply because the shape of the odorous molecule is complementary to that of a receptor site." Similar thoughts were expressed by Timmermans (1954) and by Mullins (1955), who proposed that olfactory excitation takes place only if the size and shape of the stimulant molecule correspond closely with those of the site it occupies, and who showed that rigid molecules are more effective olfactory stimulants than flexible molecules.

Amoore (1952, 1962a,b, 1964; Amoore *et al.*, 1964) deserves much credit for having been the first to undertake a concentrated effort aimed at providing experimental evidence for the site-fitting concept. He made an extensive survey of the literature on compounds with recorded odors, grouped compounds with similar odor descriptions together, and studied the structural characteristics of the compounds within each group with the aid of molecular models. Inspection of these models, particularly the models of the more rigid molecules, showed that in many of the odor classes studied, similarity of odor was associated with likeness of molecular size and shape. It was further concluded that the most common odor descriptions among the rigid molecules would indicate the identity of the corresponding primary odors (*i.e.*, odors perceived when only one type of receptor site is stimulated). Amoore found that they were seven in number; he then devised a set of seven hypothetical receptor sites with complementary properties.

Amoore's seven primary odor configurations did not all

depend on shape and size to the same extent. Amoore found that the ethereal, camphoraceous, and musky odors depended primarily upon size, whereas in the case of the floral and the minty structures the shapes were most important. In the case of minty structures an additional requirement had to be met—namely the presence at the point of the wedge-shaped molecule of an atom capable of forming a hydrogen bond with a hydrogen atom in the receptor site. The remaining two primary odors, quite interestingly, did not depend at all upon molecular size and shape, but upon the electronic status of the odorant molecule, the pungent odor being caused by strongly electrophilic molecules, and the putrid odor by nucleophilic molecules. It is of particular interest to note that these last two classes, which have no shape-size requirements, comprise many small molecules containing heteroatoms, *e.g.*, formaldehyde, trimethylboron, methylamine, methylmercaptan, etc., and that the shape-size concept is also unable to explain the odor of another small molecule, HCN (Amoore, 1963). Thus Amoore's stereochemical theory of olfaction and Wright's vibrational theory both have problems with the same type of small molecules.

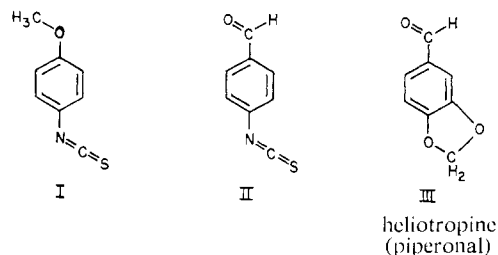
In recent years Amoore has deemphasized his site-fitting concept and has stated that his original seven odor classes are not proven primary odors. Furthermore, he thinks that there may be many more than seven primary odors. Amoore (1968) has recently indicated that in addition to an odorant's molecular size and shape, he regards its functional group as another key parameter in determining the nature and intensity of its odor.

THE PROFILE-FUNCTIONAL GROUP (PFG) CONCEPT

Ruzicka (1920) was one of the first to draw attention to the fact that more than one structural characteristic might be involved in determining odor quality when he wrote: "Für die Geruchsart ist also am wichtigsten das Skelett des Riechstoffs. Durch die Art der Reaktion der Osmophoren Gruppen mit verschiedenen Osmoceptoren wird in der Regel lediglich die Geruchsnuanze bedingt." Tschirsch (1921) proposed a similar hypothesis whereby, however, the functional group determines the odor quality and the overall structure has no more than a secondary influence. Durrans (1919) even went so far as to suggest that the residual affinities of the functional group are solely responsible for the odor quality.

In 1957, Beets (1957) stated: "It is remarkable that a large number of people, working and thinking on very different scientific levels, often 20 years apart, have expressed together a single opinion which, however vague, may be the beginning of a clear concept, *i.e.*, that the odor of a molecule is determined by two separate contributions, one from the form and the bulk of the molecule, the other from its functional group or groups." In the same paper Beets, after reviewing a considerable amount of structure *vs.* odor quality information, further developed this so-called Profile-Functional Group (PFG) concept. Some of this information may be briefly reviewed here.

A comparison of the odors of substituted phenylisothiocyanates shows that the effect of the substituents upon odor quality is far more dependent upon their position than upon their nature. Whether the substituents are acetyl, methoxy (I), or ethoxy, the para position is invariably connected with ethereal odors and the ortho and meta positions with pungency. However, if an aldehyde group is introduced in the para position of phenyl isothiocyanate (II) a strong odor of an entirely different type, namely that of heliotropine (III), is obtained.



These results convey the impression that the odor of a molecule is determined by a competition between functional groups and that one of them wins. In I, the winner is the $-NCS$ group, but in II the aldehyde group wins. The winner determines the orientation of the rest of the molecule with respect to the receptor surface; the loser becomes part of the overall shape of the molecule. Thus it appears that in the transition state the orientation of the molecule at the receptor site is a very important factor in determining odor quality.

Another interesting example concerns the macrocyclic musks. In order for the musk odor to be present in any form, the basic ring structure must contain at least 14 and less than 19 members and at least one functional group, whereby the lactone and the carbonyl group are the most powerful. When additional functional groups are introduced, the musk odor is retained as long as the functional groups are close enough together to act as a single functional group (*e.g.*, anhydride, carbonate), but if a second carbonyl group is introduced at the opposite side of the ring so that the two compete as far as the orientation of the molecule is concerned, the odor disappears completely.

Based on information of the above type, Beets (1957, 1964) proposed the following picture. The functional group determines the orientation of the odorant at the receptor site. The efficiency of the functional group, that is, its ability to determine the orientation of the odorant at the site, is at least in part determined by its tendency to participate in hydrogen bonding. The orientations of all molecules absorbed at the receptor sites are statistically distributed around one or more energetically favored ones and form a pattern which is entirely determined by the nature, position, and steric environment of the functional group or groups in the molecule. The profile of the rest of the molecule, that is, its shape and size as presented to the receptor site in the particular orientation determined by the functional group, is responsible for the odor quality.

THE ODORS OF SMALL MOLECULES

It follows from the above discussion that all three major current olfactory theories have a problem in regard to explaining the powerful odors of certain small molecules which are virtually all functional group and have virtually no profile to offer to the receptor site. It is clear that merely being nucleophilic or electrophilic in character cannot explain the widely divergent and characteristic odors of NH_3 , H_2S , and HCN ; also they do not possess any far-infrared absorption bands at all. To state that these materials as well as others like PH_3 and AsH_3 are not true odorants but merely irritant, receptor-damaging species does not explain away their highly characteristic odors at very high dilutions at which trigeminal stimulation appears to play no role, and at which many a true odorant cannot be perceived.

Another interesting group of small odorant molecules is arrived at by replacing one hydrogen atom of the methane molecule by a series of functional groups, as shown in Table I.

Table I. Monosubstituted Methane Odorants

Structure	Odor	Reference
CH ₃ -H	Odorless	
CH ₃ -Cl	Ethereal, nonirritating	Kirk-Othmer (1947)
CH ₃ -Br	Virtually odorless	Kirk-Othmer (1947)
CH ₃ -I	Pungent	Kirk-Othmer (1947)
CH ₃ -OH	Characteristic, pungent	Kirk-Othmer (1947)
CH ₃ -SH	Highly disagreeable	Kirk-Othmer (1947)
CH ₃ -SeH	Vile	Rodd (1951)
CH ₃ -TeH	Vile	Rodd (1951)
CH ₃ -NH ₂	Characteristic, like NH ₃	Kirk-Othmer (1947)
CH ₃ -PH ₂	Characteristic, like PH ₃ (stinking fish and garlic)	Kosolapoff (1950); Mellor (1929)
CH ₃ -AsH ₂	Characteristic, like AsH ₃ (garlic or rotten cabbage)	Rochow <i>et al.</i> (1957)
CH ₃ -NO ₂	Pleasant	Kirk-Othmer (1947)
CH ₃ -CN	Pleasant, ethereal	Kirk-Othmer (1947)
CH ₃ -NC	Extraordinarily vile	Kirk-Othmer (1947)
CH ₃ -NCS	Characteristic (mustard)	Houben-Weyl (1955)
CH ₃ -HCO	Pungent, suffocating; somewhat fruity and pleasant in dilute solutions	Kirk-Othmer (1947)

Quite a number of these materials have very powerful and characteristic odors, and it appears unlikely that these remarkable differences in odor quality would, for example, be attributable merely to different profiles offered by the methyl group to the receptor surface. In fact in many cases (*e.g.*, the amines, phosphines, arsines, mercaptans, and selenoles) the characteristic odor closely resembles that of the parent element-hydrogen compound and is merely modified when the methyl group is replaced by larger alkyl groups (which of course present different profiles to the receptor surface), and even the phenyl analogs (*e.g.*, thiophenol, phenylisothiocyanate, etc.) in which there is strong interaction between phenyl ring and functional group, retain the respective characteristic odor components in their overall odor qualities. One gains the impression that at least some functional groups make their own characteristic contribution to the odor of the molecule of which they are a part, regardless of any other (orienting) function they may perform.

A pair of molecules which is particularly interesting from the standpoint of this inherent functional group odor concept consists of methyl cyanide (acetonitrile), CH₃-CN, which has a relatively weak, pleasant, ethereal odor, and methyl isocyanide (methyl isonitrile), CH₃-NC, which has an extraordinarily vile and powerful odor.

The diradical structure originally suggested by Nef for isonitriles, R-N=C, does not satisfactorily account for the properties of these materials. The structure now accepted, R-N⁺≡C⁻: or its equivalent R-N⁺≡C⁻·, is supported by all available chemical as well as physical evidence (Sidgwick, 1966).

A comparison of CH₃-C≡N: and CH₃-N⁺≡C⁻· shows that the two molecules have much in common. Both molecules have large dipole moments, with the negative charge located at the same end of the molecule. Both molecules are linear (Sidgwick, 1966) and have virtually the same size and shape. Both molecules, by virtue of the lone pair of electrons on the terminal atom of the functional group, can play the role of acceptor in forming hydrogen bonds (Smith, 1965). Both molecules are essentially neutral. The difference in odor quality cannot be ascribed to mere differences in acidity or basicity. How then can we account for

the remarkable difference in odor quality? There appear to be two possible explanations.

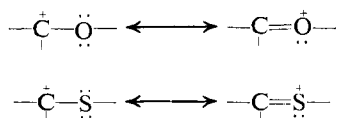
The Difference in Orientation. In nitriles we have just the one electron pair on the terminal (nitrogen) atom, which might be expected to orient the linear CH₃-CN molecule predominantly perpendicular to the receptor surface, whereas in the CH₃-N⁺≡C⁻ molecule we have two charge centers and thus two possible points of contact, as a result of which the CH₃-N⁺≡C⁻ molecule might become oriented predominantly parallel to the receptor surface. At first sight this major difference in orientation would appear to be an attractive possible explanation for the fundamental differences in odor quality. However, the profile (CH₃ group) presented to the receptor surface is very small in both cases and, furthermore, replacing the methyl group by larger *n*-alkyl groups should alter the odor quality much more drastically in the isocyanides than in the cyanides. This is decidedly not the case.

The Difference in Electronic Configuration. Isonitriles, unlike nitriles, readily add chlorine to give compounds of the type R-N=CCl₂, and they react with salts of many heavy metals (Smith, 1965) to form very stable complexes. Isonitriles will even displace carbon monoxide from metal carbonyls to form nonionic complexes of the so-called zero-valent metal (Smith, 1965). This chemical behavior of the isonitrile group is quite unique and differs profoundly from that of nitriles. It seems reasonable to suggest that the unique odor of isonitriles is connected with the unique monoionic-monoradical nature of the strongly exposed carbanion, and to regard the above observations as support for the inherent functional group odor concept.

Another interesting pair of structurally related compounds with greatly different odors consists of methanol, CH₃OH, which is relatively odorless, and methyl mercaptan, CH₃SH, which has a highly powerful and disagreeable odor. As in the case of methyl cyanide and methyl isocyanide, the two molecules have much in common, and the differences in shape, size, and reactivity appear to be differences in degree rather than in kind and cannot account for the vast difference in odor quality. The main difference, namely in acidity, can be eliminated from the discussion by methylating both compounds to give dimethyl ether, CH₃-O-CH₃, and dimethyl sulfide, CH₃-SCH₃, respectively. We may be introducing another problem here, namely the increased size of the molecules, so that now the overall shape and size may begin to play a part. According to Amoore's classification, molecules of this type should have an ethereal odor, which dimethyl ether has, and it has been argued that the foul odor of dimethyl and higher sulfides is due to impurities, the actual odor of pure dimethyl sulfide being ethereal [but at the same time reminiscent of horseradish (Finckh, 1894)]. A similar argument has been applied to the odor of methyl isonitrile, but later studies (Kaufmann and Vorländer, 1910) have not confirmed these findings, and it now appears to be generally accepted that dimethyl sulfide at least has a foul constituent odor quality which is missing in dimethyl ether. How can we explain this difference?

Due to differences in bond length (C-S = 1.82 Å, C-O = 1.43 Å) and bond angle (smaller for the S compound), the steric accessibility of the S atom in CH₃-S-CH₃ is much greater than that of the O atom in CH₃-O-CH₃. However, neither this fact nor the resulting slight difference in orientation of the methyl groups appears capable of explaining so pronounced a difference in odor quality, so that it must rather be assumed that this difference resides in the heteroatoms themselves. In what respects do divalently bound

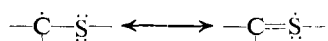
oxygen and sulfur differ? Both of them can readily stabilize adjacent electron-deficient centers such as carbonium ions by releasing electrons:



However, there have been numerous reports that a hydrogen atom attached to carbon adjacent to a sulfide group is considerably more acidic than an α -hydrogen in the corresponding ether (or amine) (Price and Oae, 1962). This acidity has generally been attributed to the ability of sulfur to accept electrons by conjugation, using its vacant 3d-orbitals to accommodate ten electrons in its valence shell.



Similarly, a free radical center with an odd unshared electron can be stabilized by accommodation of nine electrons in the valence shell of sulfur.



Oxygen, however, cannot readily accept electrons by expanding its normal valence shell. It could accept valence electrons beyond eight only by adding them in the third shell which, due to the smaller nuclear charge as compared with sulfur, would provide very little stabilization.

In accordance with this difference is the fact that sulfides such as dimethyl sulfide are capable of forming stable complexes with many metal salts (CuCl, ZnBr₂, CdI₂, HgCl₂, SnCl₄, PdCl₂) and even with Br₂ and I₂ (Beilstein, 1918). These chemical properties are reminiscent of those of the isonitriles.

Thus, the ability of sulfide sulfur and the inability of ether oxygen to use 3d-orbitals to accommodate up to ten electrons in its valence shell most likely constitutes the major difference between the two, and it is again suggested that the difference in odor quality is primarily connected with this basic difference in electronic behavior.

The inherent functional group odor concept can be readily extended to functional groups containing such elements as Se, Te, P, As, and even N (amines). However, it appears to be at best a minor factor in oxygen-containing functional groups, which are the most important from the perfumer's standpoint. The keto group, judging by the fruity odors of such small molecules as acetone and (dilute) acetaldehyde, may have a mild intrinsic odor. In the case of the OH group, however, the existence of any inherent odor is quite doubtful. Methanol is said by some to be odorless when pure; thus, in the higher alcohols, which are definitely odorous, the OH group would primarily have the function of providing adsorption and orientation of the whole molecule. Still further down the line are such substituents as -Cl and -Br which seem to be not much more than part of the overall profile even in the smallest molecule.

CONCLUSION

The picture of the relationship between molecular structure and odor quality which has emerged is a complicated one. It would appear that at least three main factors contribute to the odor quality of a molecule, namely its size and shape, its functional group, and its orientation with respect to the receptor surface. In some instances, the influence of one of

these factors may strongly dominate. This applies, for example, to the functional group of isonitriles. In the case of carbon tetrachloride, orientation plays no part, and since chlorine seems to be of little or no importance as an odor-producing functional group, size and shape dominate. Orientation, of course, does not exist independently of the other two factors mentioned, but its influence might, for example, be seen in 1,1-dimethylcyclohexane. This compound is an unexpectedly powerful odorant as compared with cyclohexane. It has no functional group which could contribute to its odor either directly or through orientation, but a preferred orientation is likely brought about by the increased electron density at the ring carbon atom bearing the two methyl groups.

We have seen that the inherent odor of the functional group in general plays an important role only where this group is an important part of the molecule, *i.e.*, in small molecules. In larger molecules the functional group may tend more and more toward an orienting task, and in still larger molecules its inherent odor may be lost and its orienting function taken over by more favorably situated functional groups, so that in large molecules it is no more than a part of the overall shape. For example, sulfide sulfur, which plays an extremely important role as the functional group carrying the typical odor of small sulfide molecules such as dimethyl sulfide, has completely lost this role in the sulfide analogs of macrocyclic musks (Beets, 1957, 1964) which have a weak musk odor. Here, the sulfide linkage is buried in the rest of the molecule to such an extent that its characteristic odor is completely lost, and it has become not much more than just a part of the overall shape of the molecule, except for its slight orienting activity.

On the other hand, again generally speaking, shape and size alone are not likely to impart an odor to small molecules (*e.g.*, methane), and here we are dealing with a factor which tends to become more important as the molecular size increases.

Thus, in the vast majority of odorants the odor quality observed appears to be the outcome of a complicated interplay of at least three factors, *e.g.*, size-shape, orientation with respect to the receptor surface, and inherent functional group odor, and at the present time our knowledge of this interplay is insufficient to predict its outcome except in isolated cases.

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