Molecular Shape and Size *vs.* Attractancy to Insects in Some Chemically Unrelated Compounds

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Field testing of organic chemicals for insect attractant activity has uncovered two examples of small groups of chemically unrelated compounds whose specific attractancy to certain gnat species seems to correlate with the shapes and sizes of the molecules involved. One such group comprises an ether (octyl-1,1,2,2-tetrafluoroethyl ether), a hydrocarbon (1-phenyloctane), an ester (decyl formate), and a carbamate (decyl diethyl thiolcarbamate). Molecular models of these materials show a striking similarity in size and shape. Relatively minor changes in size have a profound effect upon the ability of these materials to attract *Conioscinella melancholica* and *Tricimba trisulcata*. The results are discussed in the light of some current olfactory theories. It is concluded that the study of behavioral responses in insects towards olfactory stimuli may constitute a useful approach towards elucidating the mechanism of olfactory perception.

During field testing of organic chemicals belonging to many different classes for insect attractant activity, we uncovered a small number of chemicals which were highly specific and highly active attractants for certain species of gnats, namely *Conioscinella melancholica*, *Tricimba trisulcata*, and a species of *Neophyllomyza*. These tests were carried out at test sites near Newark, Del., and Raleigh, N.C., by means of conventional Steiner traps made of cardboard half-gallon ice cream containers (Steiner, 1957). None of the chemicals attracted any other insect species in significant numbers, even though a great many species were known to be present at the test sites. In attempting to correlate the attractant activity of these specific attractants with one or more of their chemical or physical properties, we discovered the existence of correlations between attractancy and molecular size and shape highly reminiscent of similar correlations uncovered by Moncrieff (1951) and especially by Amoore (1964) in the area of organic structures perceived as odorants by the human nose.

EXPERIMENTAL RESULTS

The first example of a correlation found between insect attractant activity and molecular size and shape is provided by the data of Table I. The four compounds shown in this table are, respectively, an ether (I), a hydrocarbon (II), an ester (III), and a thiolcarbamate (IV) and are essentially unrelated chemically. They attracted the gnat species *C. melancholica* and, where present, *T. trisulcata* in large numbers, but did not attract *Neophyllomyza* sp. at any of the sites.

Although the four compounds of Table I are chemically unrelated, Stuart models of their structures show a striking similarity in size and shape. As shown in Figure 1, the four structures are essentially equal in length and have, to some extent, a shape reminiscent of a kite or a frying pan. This shape is particularly well exemplified by compounds I and II, whereby the straight hydrocarbon chain represents the handle of the pan and the $-O-CF_2-CF_2H$ group (I) or the phenyl ring (II) represents the pan, which slopes upward out of the plane of the paper. The pans (functional groups) of III and IV similarly slope upward but are smaller.

Figure 2 shows Dreiding models of the same four compounds photographed against a system of coordinates subdivided in Angström units. Dreiding models show bonds and internuclear distances only, and in some cases give a clearer picture of the steric properties of a molecule than Stuart models. It should be remembered, however, that in order to arrive at the true dimensions of the molecule, the Van der Waals radii of the peripheral atoms should be added. In the absence of special forces, the Van der Waals radius of an atom is about 0.8 Å longer than its covalent single bond radius. Covalent single bond radii of interest here are, in Å: C, 0.77; H, 0.30; O, 0.66; N, 0.70; S, 1.04; F, 0.64. The Dreiding models of Figure 2 and following figures are lined up as accurately as possible with the X- and Y-axes. Apparent extensions beyond these axes are due to photographic distortion (the camera was located $2^1/_2$ ft above the plane of the paper).

All four "projections" of Figure 2 have the dimensions of about 16.5 × 6 Å (including the Van der Waals radii of the peripheral atoms) and possess more or less the same frying pan shape. For the sake of clarity, the pan section of the frying pan shape of II was rotated 90° as compared with Figure 1, and the models are viewed here from the side, rather than from above, as in Figure 1. (The circles are corks supporting the models.) For reasons discussed above, the frying pan shape of compound I is demonstrated more clearly by the Stuart model of Figure 1. The ethyl groups of IV pose a problem in that they render the molecule considerably larger than the other three. However, a comparison with structure III shows that in regard to shape and size, III is essentially identical with IV without its ethyl groups. Originally, Amoore's stereochemical theory of olfaction presumed that the triggering of an olfactory response was due to the fitting of a molecule with the proper size and shape into a complementary hollow in the receptor site. In recent years, this lock and key concept of the odorant-receptor interaction has been deemphasized. Nothing is known with certainty regarding this interaction, and therefore many workers in the field prefer studying and comparing keys without concerning themselves very much with the locks. Nevertheless, the lock and key concept has proved fruitful in explaining other biochemical interactions such as enzyme-substrate (Steitz, 1968), antibody-antigen, and DNA-messenger RNA interactions, and appears to be useful also in the present case. More particularly, it provides a possible explanation for the apparent superfluousness of the ethyl

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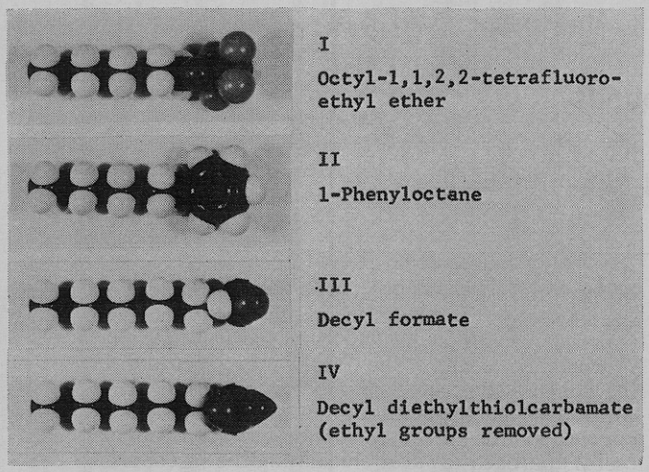


Figure 1. *Stuart models of the compounds of* Table I

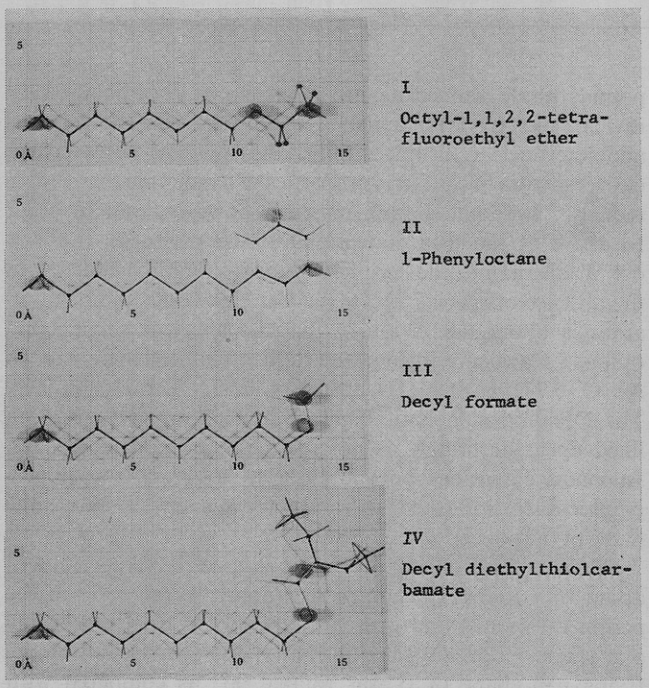


Figure 2. Dreiding models of the compounds of Table I. For the sake of clarity, the pan section of the frying pan shape of II was rotated 90° as compared with Figure 1, and the models are viewed here from the side, rather than from above, as in Figure 1. The circles are corks supporting the models

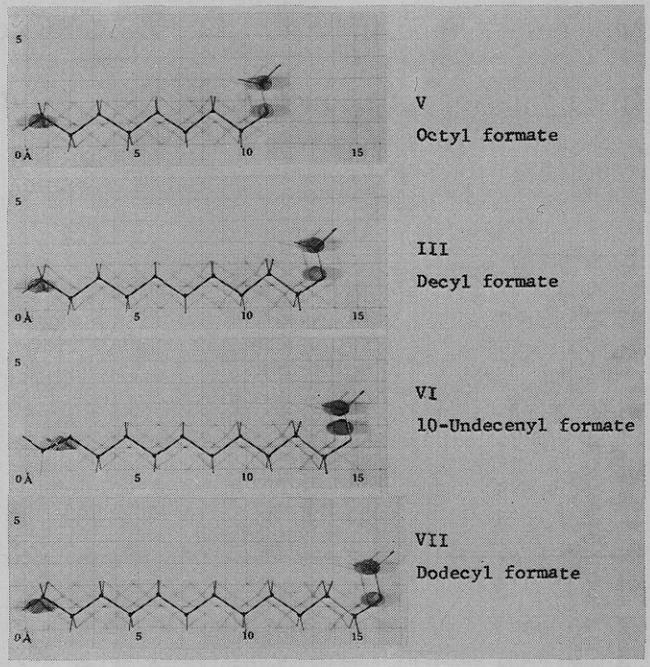


Figure 3. Dreiding models of the compounds of Table II

Table I. Insect Attractant Activity of Compounds I–IV

		Species and numbers of gnats attracted per trap[a]		
No.	Structure	*Con. mel.*	*Tric. tris.*	*Neoph. sp.*
I	$CH_3-(CH_2)_7-O-CF_2-CF_2H$	158	19	0
II	$CH_3-(CH_2)_7-C_6H_5$	55	111	0
III	$CH_3-(CH_2)_9-O-C(=O)-H$	117	0[b]	0
IV	$CH_3-(CH_2)_9-S-C(=O)-N(C_2H_5)_2$	255	0[b]	0

[a] *Mean values of two to four replications.* The insects were killed inside the traps by a volatile insecticide (DDVP) and counted after an exposure period of 1 week. [b] In subsequent tests, it was ascertained that these compounds were capable of attracting *Tricimba trisulcata.* However, no *Neophyllomyza* sp. were ever found in traps baited with these compounds.

groups of IV. These would not prevent the rest of the molecule, which is essentially identical with III in regard to shape and size, from fitting into the appropriate hollow in the receptor site, but would protrude outside this hollow and play no essential part in the interaction. The lock and key concept furthermore reminds us that it is the conformation of the attractant molecule in the attractant-receptor complex rather than its conformation in the free state which is decisive here.

Table II shows the effects of changing the size of one of the structures of Table I (structure III) upon its attractancy, and Figure 3 shows Dreiding models of the structures of Table II. It is clear that a relatively minor change in size has a profound effect upon insect attractancy. Lengthening (VII) as well as shortening (V) the chain of (III) by about 2.5 Å completely abolishes attractancy, whereas VI, which is about 1.2 Å longer than III and has otherwise essentially the same shape, is much less attractive than III. In terms of the lock and key concept, V could easily fit into the hollow complementary to structure III; it could even provide centers of increased electron density (the two oxygen atoms of the functional group) of the same type and at the same location as structure III, only some space at the relatively inert hydrocarbon end would not be filled. Yet, V is inactive.

Table III shows a further example of the effect of changing the size of a structure of Table I upon its attractancy, in this case of structure II. The original test (which produced the data of Table I) included only one other phenylalkane, namely 1-phenyldecane (XI). In this test, XI attracted no *C. melancholica*, only one specimen of *T. trisulcata*, and no *Neophyllomyza* sp., clearly demonstrating again the pronounced effect of relatively minor changes in size. A subsequent test (Table III) included five phenylalkanes. While the conditions of this test were unfavorable (the numbers of insects caught being low), its outcome again demonstrates the specificity of these compounds with respect to two of the

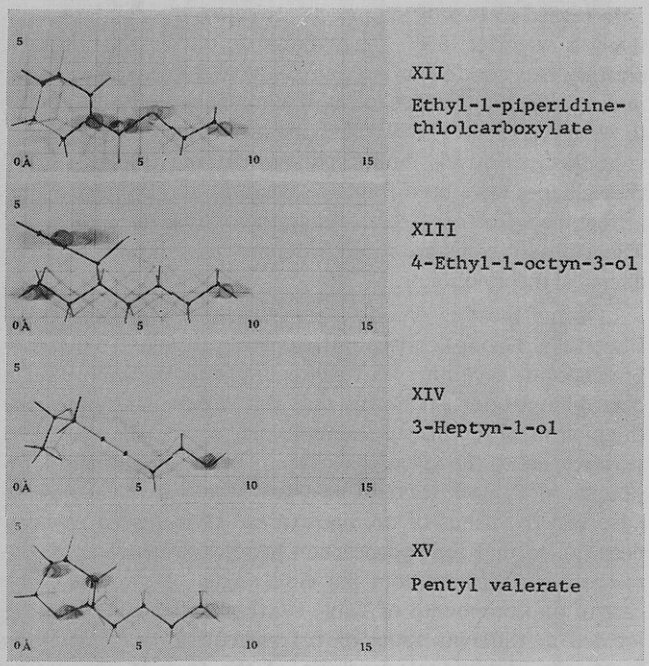


Figure 4. Dreiding models of the compounds of Table IV

Table II. Insect Attractant Activity of Formate Esters

No.	Structure	Species and numbers of gnats attracted per trap[a] *Con. mel.*	*Tric. tris.*	*Neoph. sp.*
V	$CH_3-(CH_2)_7-O-C(=O)-H$	0	0	0
III	$CH_3-(CH_2)_9-O-C(=O)-H$	117	0[b]	0
VI	$H_2C=C(H)-(CH_2)_9-O-C(=O)-H$	19	5	0
VII	$CH_3-(CH_2)_{11}-O-C(=O)-H$	0	0	0

[a] See footnote (a) of Table I. [b] See footnote (b) of Table I.

three insect species, and the importance of molecular size, particularly in regard to the *C. melancholica* catches.

The second example of a correlation found between insect attractancy and molecular size and shape is provided by the data of Table IV. Here, again, we have four seemingly unrelated compounds which, in this case, specifically attract *Neophyllomyza* sp., whereas except for XV which will be discussed in more detail below, they are essentially unattractive to *T. trisulcata* and *C. melancholica*.

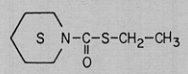
In searching for a molecular shape and size which the four compounds XII–XV might have in common, the ring compound XII, being the least articulated, should be the starting point. Since the ring is not flat, the shape of XII could be compared with that of a mallet. Although a greater stretch of the imagination is required here than in the case of the compounds of Table I, it is possible to twist the Dreiding models of the remaining compounds of Table IV to more or less complete mallet shapes of approximately the same size (11 × 6.5 Å, including the Van der Waals radii) as XII, as shown in Figure 4.

Table III. Insect Attractant Activity of Phenyl Alkanes

No.	Structure	Approx. length	Species and numbers of gnats attracted per trap[a] *Con. mel.*	*Tric. tris.*	*Neoph. sp.*
VIII	$CH_3-(CH_2)_5-C_6H_5$	14Å	0	0	0
IX	$CH_3-(CH_2)_6-C_6H_5$	15.2Å	0	1	0
II	$CH_3-(CH_2)_7-C_6H_5$	16.5Å	4	11	0
X	$CH_3-(CH_2)_8-C_6H_5$	17.7Å	2	6	0
XI	$CH_3-(CH_2)_9-C_6H_5$	19Å	0	3	0

[a] See footnote (a) of Table I.

Table IV. Insect Attractant Activity of Compounds XII–XV

No.	Structure	Species and numbers of gnats attracted per trap[a] *Con. mel.*	*Tric. tris.*	*Neoph. sp.*
XII		0	1	37
XIII	$HC\equiv C-C(OH)(C_2H_5)-C(H)(H)-(CH_2)_3-CH_3$	0	0	96
XIV	$CH_3-(CH_2)_2-C\equiv C-(CH_2)_2-OH$	0	0	26
XV	$CH_3-(CH_2)_3-C(=O)-O-(CH_2)_4-CH_3$	5	44	5

[a] See footnote (a) of Table I.

Since the similarity in shape is not as striking here as it is among the compounds of Table I, it was decided to also compare the far-infrared spectra of the four compounds XII–XV in the hope of finding common bands. Since far-infrared bands (50–500 cm^{-1}) originate from "whole-molecule" vibrations (Wright, 1954, 1966a,b), they are much more characteristic of the whole molecule than are regular infrared bands (1000–4000 cm^{-1}). Accordingly, molecules with approximately the same shape and size may be expected to have at least one far-infrared band in common. The spectra are summarized in Table V.

As shown in Table V, three of the compounds (XII, XIII, and XV) have a band in common (at 223–224 cm^{-1}), and two of the compounds (XII and XIII) show a remarkable similarity in their far-infrared spectra. Thus, these spectra provide support for the shapes of Figure 4 in regard to two and possibly three of the four compounds. In terms of Amoore's stereochemical theory of odor, further support for the shapes of Figure 4 would be provided by a similarity in the odors perceived by the human nose. However, since most of the molecules are quite flexible and might therefore fit into more than one receptor site, the theory would predict at best a common odor component. No attempts have been made to subject the odors of the compounds of Tables I and IV to the judgment of a trained odor panel. In the judgment of the authors, the odors of the compounds of Tables I and IV

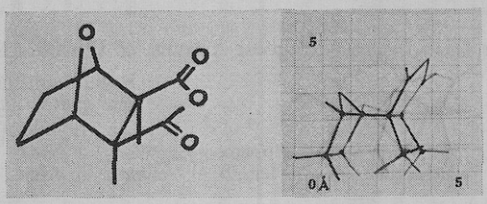
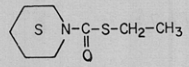
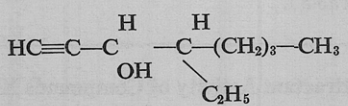


Figure 5. Cantharidin

Table V. Far-Infrared Spectra of the Compounds of Table IV

No.	Structure	Absorption bands, cm^{-1} at liquid N_2 temperature[a]
XII		323, s 276, w 223, ms 159, w 105, w
XIII		320, s 255, w, br 224, ms 162, w 105, w
XIV	$CH_3-(CH_2)_2-C\equiv C-(CH_2)_2-OH$	312, w 248, s, br 123, w 103, w
XV	$CH_3-(CH_2)_3-C(=O)-O-(CH_2)_4-CH_3$	223, br, s 146, w 123, m

[a] The intensities listed are relative to the strongest band in each spectrum. The symbols are: w = weak, m = medium, s = strong, br = broad.

are all different; at best, it may be said that the compounds of Table I have a fatty, rancid note in common, whereas those of Table IV seem to some extent to share a fruity note.

DISCUSSION

It should be pointed out above all that the preliminary nature of these data permits tentative conclusions only. Furthermore, correlations of this type are not found frequently; they are found only within isolated groups of attractants and only among those compounds which under favorable conditions are capable of attracting large numbers of specimens of the species concerned, *e.g.*, "peak" compounds of homologous series such as structure III of Table II. In terms of the lock and key concept, this would indicate that these correlations are found only among compounds which fit the receptor site well.

In view of the flexibility of many of the molecules discussed, it is surprising indeed that their attractancy is so specific, the more so since the literature contains an example of an attractant, namely cantharidin ("Spanish fly"), whose structure is completely rigid (Figure 5) and which is nevertheless capable of attracting numerous entirely unrelated insect species (Görnitz, 1937). One possible explanation for the latter phenomenon might be that these so-called cantharophilic insects, while belonging to different orders, might have one olfactory receptor in common plus the circumstance that only one receptor need be triggered in order to evoke the behavioral response in the insect. (The molecule might fit the receptor site in only one way, most likely with the oxygen atoms directed toward the site.)

In regard to two of the insects attracted, the data are relatively straightforward. They point to direct relationships existing between the frying pan shape and attractancy to *C. melancholica*, and between the mallet shape and attractancy to *Neophyllomyza* sp. To the extent that they have been investigated, relatively minor changes in the dimensions of these shapes have been found to result in abolishment of the attractancy (further work along these lines is indicated). These observations are in accordance with Amoore's stereochemical theory of odor.

In some theories of odor, particularly the PFG (Profile-Functional Group) concept developed by Beets (1957, 1964), presence and location of a functional group are important in determining odor quality in that this group determines the orientation of the rest of the molecular shape (the "profile") with respect to the receptor surface. In the case of the compounds of Table I, it could be argued that the molecules are adsorbed by means of the pans (areas of increased electron density), so that the hydrocarbon handles protrude from the receptor surfaces at about the same angle. However, in the case of the compounds of Table IV, the functional groups are located at different spots of the structures, as depicted in Figure 4. Additional examples of the type of correlation discussed in this paper are obviously needed to bring more clarity.

The results obtained with *T. trisulcata* are more difficult to interpret. This insect is attracted by the frying pan shape, as shown in Table I, and may therefore have a receptor in common with *C. melancholica*. However, there is some indication that it might be attracted by the mallet shape as well, as evidenced by the result obtained with compound XV of Table IV. This compound attracts all three of the insects, and this result may be due to the fact that XV may assume not only the mallet shape but also a shape resembling that of the frying pan. This molecule is the longest one of Table IV; when fully extended, its length is approximately 16.5 Å, the same as that of the compounds of Table I. In terms of the lock and key concept, this "tubular" molecule, while lacking the "complete" frying pan shape, may fit the receptor site to a degree sufficient to attract at least to some extent *C. melancholica* and *T. trisulcata*. In evaluating the data presented here, it should be remembered that the compounds can never be tested under exactly the same conditions. For example, each compound requires a separate trap and is therefore tested at a location different from that of the others. Furthermore, the insect species involved in this study tend to move in swarms, a factor which may affect the insect counts in an unpredictable manner.

There is an additional difficulty in trying to interpret the *T. trisulcata* results. As shown in Tables II and III, a minor change in the overall length of the frying pan shape completely abolishes attractancy toward *C. melancholica*. This is much less true in the case of *T. trisulcata*. As shown in Table III, this insect is attracted over a structural length range of at least 15.2 to 19 Å and thus appears to be much less selective than *C. melancholica* in regard to the permissible length of the attractant molecule. Since the compounds involved are the same, it appears as if the mechanism of odor perception in *T. trisulcata* is in some ways different from that in the other two insects. It would seem almost as if the observations made with *C. melancholica* and perhaps to a lesser extent with *Neophyllomyza* sp. are in some way special, limiting examples of a much broader or more general mechanism of olfactory perception whose nature is as yet unknown. The picture is highly reminiscent of observations made in

in the area of odor quality *vs.* structure relationships. For example, Beets (1957), in reviewing his PFG-model, states: "By reviewing a number of structural classes and by comparing the available data with the requirements of this model, an attempt has been made to assess the value of the latter . . . but the result is not encouraging. It is true that many data agree with the consequences of the model, but (it) is . . . crude and we have . . . little insight into the details . . ."

This similarity between our results and those obtained in odor *vs.* structure studies indicates that the mechanism of odor perception in insects, at least at the receptor level, may not be basically different from that in man. This conclusion is not only intuitively acceptable; there is mounting evidence (Blum, 1969; Amoore *et al.*, 1969) in the literature to support it. Naturally, we are speaking only of the overall mechanism of odor perception, not of specific sensitivities. In terms of the lock and key concept, the shapes of the human locks and keys are likely to be different from those of insects, as evidenced, for example, by the fact that many powerful insect sex attractants are essentially odorless to man.

In view of the above similarity, studies such as the present one may be of value in helping to elucidate the mechanism of odor perception. In the words of Beets (1957): "In short, the only way to study the problem of odor seems to be to get rid of odor itself as the property under consideration in the earliest possible stage of the work." Since this was written, attempts have increasingly been made to eliminate this subjective element from studies of the mechanism of olfactory perception. For example, Amoore (1967) has employed the phenomenon of specific anosmia in attempts to uncover primary odors. The electrophysiological approach to the study of olfactory perception in animals, particularly in insects, has gained greatly in importance, owing to the work of Adrian (1954) and Schneider (1969) and his coworkers. In our opinion, the study of behavioral responses in insects toward olfactory stimuli may constitute another useful, nonsubjective approach toward elucidating the mechanism of of odor perception.

ACKNOWLEDGMENT

We are indebted to Dr. Robert J. Jackobsen, Battelle Memorial Institute, Columbus, Ohio, for determining the far-infrared spectra.

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Received for review July 30, 1970. Accepted October 20, 1970.