Electrostatic and Stereochemical Aspects of Insect Juvenile Hormone Active Compounds: A Clue for High Activity

Tetsuyoshi Hayashi, Hajime Iwamura,* and Toshio Fujita

Department of Agricultural Chemistry, Faculty of Agriculture, Kyoto University, Kyoto 606, Japan

The electrostatic potentials were computed for a variety of functional groups found in active insect juvenile hormone (JH) mimetics; they are nonaromatic ester, carbamate, and oxime functions and aromatic phenyl, phenoxy, pyridyl, and pyridyloxy groups. The contours of the potentials commonly had a negative peak when viewed in the plane that perpendicularly bisects their skeletal plane. The site of the peak was at the position where the oxygen atom is located in the ethers, but in the multiatomic oximes it was at the nitrogen atom site rather than the oxygen site. In the benzene and pyridine functions, the negative peak was located at the site within the aromatic ring. The stereochemical interpretations made on the basis of this revealed that the most active members of the aromatic compounds are the entities the dimensions of which well fit the receptor cavity, and their negative peak is on the same site as that of the most active members of the nonaromatic classes of compounds.

We have developed classes of insect juvenile hormone (JH) mimetic compounds having a nonterpenoid structure; they are (4-phenoxyphenoxy)- and (4-benzylphenoxy)-alkanaldoxime *O*-ethers (Niwa et al., 1988), their ether (Niwa et al., 1989) and hydroxylamine (Niwa et al., 1990) congeners, and (4-alkoxyphenoxy)- and (4-alkylphenoxy)-alkanaldoxime *O*-ethers (Hayashi et al., 1989). Through these studies, the common, important features that confer activity have been shown to be the overall length of the molecule and the position of a functional group built in the molecule. The optimum length has been estimated to be 21–22 Å, and the position-specific interaction site with the receptor to be at δ from the central phenoxy oxygen atom or alternatively at the site about 4.6 Å distant from the side-chain end in the optimum molecules.

In the paper that immediately precedes this one (Hayashi et al., 1990), we have developed 4-alkylphenyl phenylalkyl and phenoxyalkyl ethers and related pyridine compounds. They are the compounds where the oxime function of previous (4-alkyl- and 4-alkoxyphenoxy)-alkanaldoxime *O*-ethers is replaced by a benzene or pyridine function. In these, the "common structural features" mentioned above were seemingly in disturbance. The compounds with an optimum length and a heteroatom, a phenoxy or pyridyloxy oxygen atom, at the δ-position were not necessarily highly active. The most active member of the class, 4-(2-ethylbutyl)phenyl 2-(2-pyridyloxy)ethyl ether, was the compound whose molecular length is not an optimum one but about 1.5 Å short. Moreover, the compound has a heteroatom as a pyridyloxy oxygen atom, but it is not at the right, δ-position, but at γ from the central oxygen atom. Moreover, the benzene congener of this compound, 4-(2-ethylbutyl)phenyl phenoxyethyl ether, was not the most potent member in the benzene subseries, irrespective of the similitude of the structures. The situation is further complicated by introducing a substituent at various positions of the aromatic rings; in most cases it lowers the potency even if it makes them an optimum length.

These circumstances prompted us to find explanations in their electrostatic and stereochemical properties. As a result, the contour maps of electrostatic potentials were shown to have a feature that is common between the nonaromatic and aromatic functions and characterized by a negative potential peak, when the molecules are constructed in the extended or energy minimum conformation, and patterns of the potentials are compared in the plane that bisects perpendicularly their skeletal plane. On this basis, stereochemical interpretations were made to show that the negative peak of the potentials lies at the δ-position in the most active members of both the aromatic and nonaromatic classes of compounds, but that of poorer members misses the point.

METHODS

Table I shows the ether (Niwa et al., 1989) and oxime (Niwa et al., 1988; Hayashi et al., 1989) compounds studied, and Table II lists the representatives of the aromatic compounds reported in our preceding paper (Hayashi et al., 1990). The pI_{50} expresses the activity against *Culex pipiens* larva. It is the logarithm of the reciprocal of the molar concentration at which 50% inhibition of metamorphosis is observed, and the data are taken from the literature listed above. The *D* in Table II is the overall length of the molecule. It has been reported in the literature, but Figure 2 explains its definition for the readers' convenience. It is measured in the extended or energy minimum conformation along the axis that passes through the central phenoxy oxygen atom and has an angle of 40.02° to the bond that connects the phenoxy oxygen atom and the rest of the molecule.

The stable conformation of compounds was studied by molecular orbital methods. The computation was done by using AMPAC (QCPE No. 523) with AM1 parameterization (Dewar et al., 1985; Dewar and Stewart, 1986). The starting coordinates were obtained from ANCHOR (Kureha Chemical Industry Co., Ltd., and Fujitsu Ltd., Tokyo, Japan), a program system for molecular modeling. The electrostatic potentials were calculated for the optimum geometries from the point charges on the atomic centers and plotted as shown in Figure 3.

RESULTS AND DISCUSSION

Provisional Aspects. The compounds in Table I are those with the optimum *D* for activity (21–22 Å), and the position-specific interaction site is shown by shadowing. Accordingly, in the set of the first three ether compounds, the most potent is the one with the heteroatom at the δ-position. In the multiatom oximes, the favorable compounds have been shown to be those with a δ-nitrogen atom

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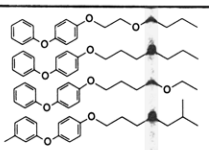
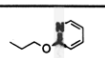
Table I. Structure and Activity against *C. pipiens* of 4-Phenoxyphenoxy and 4-Alkylphenoxy Types of Compounds Having Ether, Oxime, and Hydroxylamine Functions[a]

Structure	pI_{50}[b]
	8.08
	9.47
	7.93
	10.49
	8.48
	9.68
	10.00
	7.81
	8.79
	10.76

[a] The shadowing made on the δ-position from the phenoxy oxygen atom shows the position-specific interaction site with the receptor. [b] The logarithm of reciprocal of the molar concentration at which 50% inhibition of metamorphosis is observed.

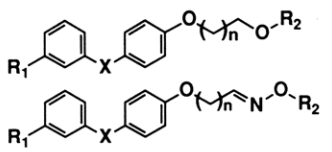
Table II. Structure and Activity against *C. pipiens* of 4-(2-Ethylbutyl)phenyl Pyridyloxyalkyl Ethers and Related Benzene Compounds[a]

	Structure[b]	pI_{50}[c]	D[d]
1		10.04	19.55
2		6.73	19.55
3		5.04	19.55
4		7.80	19.55
5		9.10	20.77
6		8.44	20.78
7		5.26	20.63
8		9.04	20.76
9		8.79	19.71
10		4.96	20.70
11		7.15	19.55
12		7.17	20.77
13		5.96	20.77
14		7.56	20.78
15		8.96	19.55

[a] See footnote *a* of Table I. [b] Shown by the energy minimum conformation of aralkyloxyalkyl moiety. [c] See footnote *b* of Table I. [d] The overall length of the molecule defined in Figure 2.

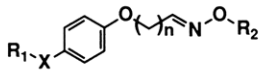
rather than the δ-oxygen compounds. This has come from the observation that the oxime compounds having the nitrogen atom at the δ-position are more potent than those with the δ-oxygen atom, and this situation is reproduced in Table I. What the physiochemical basis is, however, has remained unclear. The last compound in each subclass in Table I shows the most active member.

The δ-site of the aromatic series of compounds in Table II is also indicated by shadowing, and for this purpose the structures are shown in the depiction of the energy minimum conformation. The set of compounds epitomizes

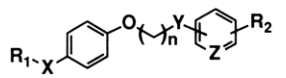


R_1 = H, Me R_2 = Alkyl

X = CH_2, O



R_1, R_2 = Alkyl X = CH_2, O



R_1 = Alkyl R_2 = Alkyl, Alkoxy

X, Y = CH_2, O Z = CH, N

Figure 1. Generic formulas of classes of JH-active compounds studied.

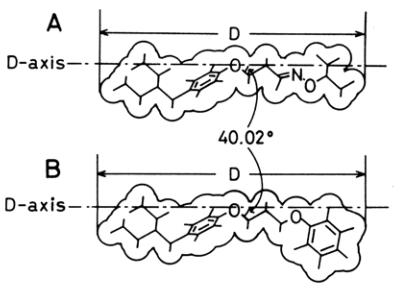


Figure 2. Definition of length parameter *D*. The model compounds are (A) [4-(2-ethylbutyl)phenoxy]propionaldoxime *O*-propyl ether (Hayashi et al., 1989) and (B) 4-(2-ethylbutyl)-phenyl phenoxypropyl ether (**14**). The ends of the bars of the structure represent hydrogen atoms.

the structure–activity problems reported in our preceding paper (Hayashi et al., 1990). The most active member of the class, 4-(2-ethylbutyl)phenyl 2-(2-pyridyloxy)ethyl ether (**1**), for example, has about 1.5 Å shorter molecular length (19.55 Å) than its optimum (21–22 Å). Moreover, the compound seems to have the point-interactive heteroatom as a pyridyloxy oxygen atom, but it is at the γ-position from the central phenoxy oxygen atom. 4-(2-Ethylbutyl)phenyl 2-(2-pyridyloxy)propyl ether (**6**), which is one methylene unit longer than **1**, has about the right length (20.78 Å) and the pyridyloxy oxygen at the δ-position. Nevertheless, it has about 40 times less activity than **1**. The benzene congener of **1**, 4-(2-ethylbutyl)-phenylphenoxyethyl ether (**11**), is not the most potent member in the benzene subseries, which was 4-isopropoxybenzyl ether (**8**). Compound **8** has a molecular length of about the optimum (20.76 Å), but the site of the "heteroatom" interaction is someplace buried in the benzene ring. Introduction of a substituent at positions of the aromatic rings confuses the situation further. The (3- or *m*-methylphenoxy)ethyl compound **12** is more than 10 times more active than its 4- or *p*-methyl congener **13**. The situation is, however, the reverse in the pyridine congeners, 2-[(6-methylpyridyl)oxy]ethyl (**4**), i.e., the *m*-methyl congener, being about 20 times less active than 5- or *p*-methyl **5**.

We sought explanations for these problems in their electrostatic and stereochemical properties to be shown below.

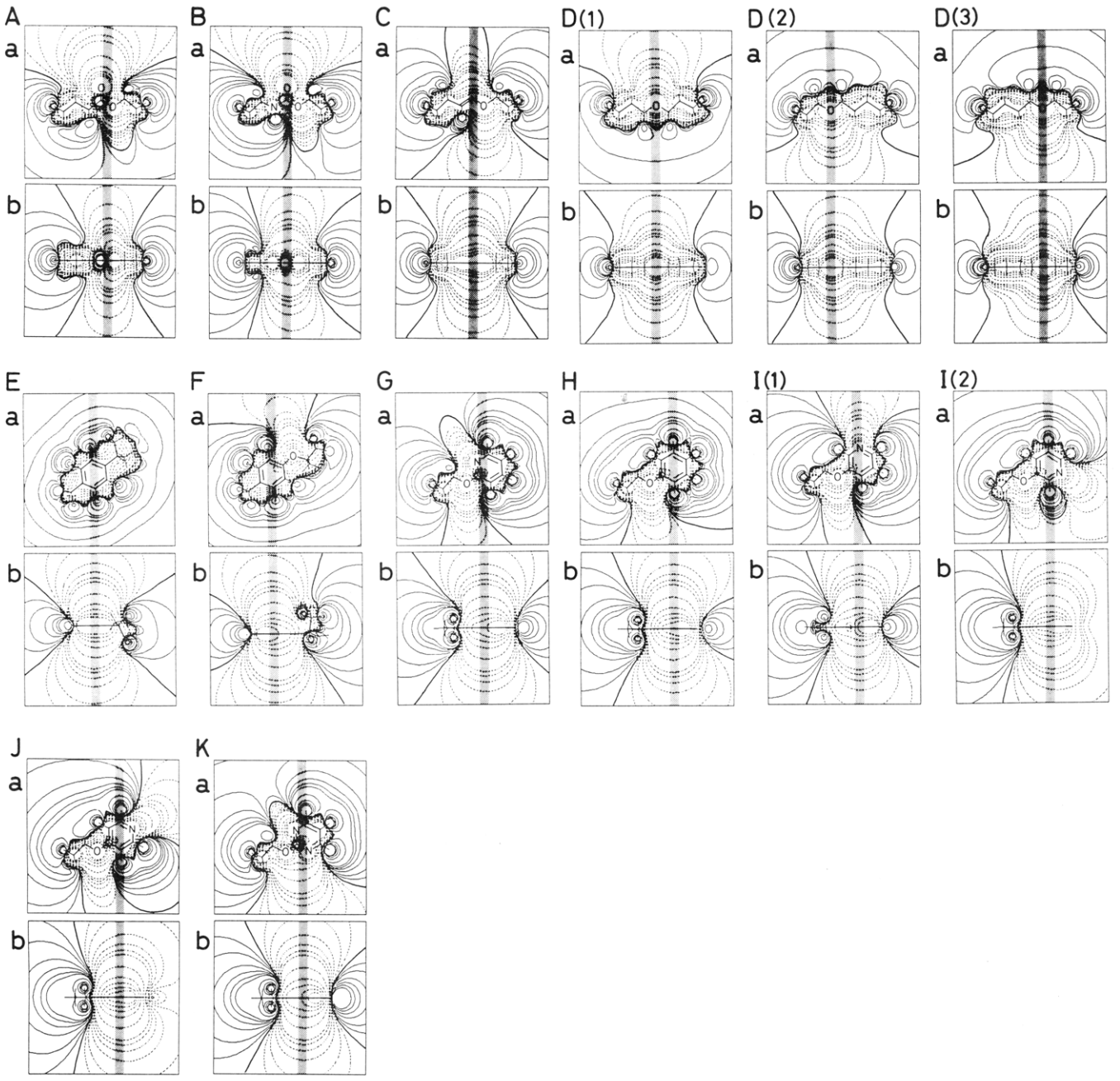


Figure 3. Contours of electrostatic potentials. (—) Positive contours; (- - -) negative contours: (—) zero contour. The a series of figures shows the map in the zigzag, extended molecular plane, and the b series shows the map in the plane that bisects the molecule vertically. The horizontal line in the middle of the b series shows the molecular skeleton on which the component atoms line up. The ends of bars vertical to this line and those of the structures in the a series indicate hydrogen atoms. The shadowing in the a series is an extension of that in the b series and indicates where the site of the negative potential peak found in the b series locates on the molecules shown in the a series.

Electrostatic Potentials. Nakayama and Richard (1987) have explored the electrostatic similarities between ester, carbamate, and oxime functions that are found in active JH mimetics in terms of the similarity index that compares the similitude of space of a certain expanse. Within these functions, the patterns of the contour maps of their electrostatic potentials are obviously similar when they are viewed in the zigzag plane of the molecules. They are reproduced by our calculation in Figure 3Aa,Ba,Ca. Figure 3Aa represents the α,β-unsaturated ester function of methoprene [isopropyl (2*E*,4*E*)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate] and its congeners including natural JHs. Figure 3Ba represents the carbamate function found in fenoxycarb [ethyl *N*-(4-phenoxyphenoxy)-ethylcarbamate] (Fisher et al., 1979). Figure 3Ca represents oxime function found in our previous series of compounds (Niwa et al., 1988, 1989; Hayashi et al., 1989). The negative region of the potentials commonly passes through one side of the molecule to the other, showing a "straitlike" pattern between the positive "islands". The b series of Figure 3 is the view in the vertical plane that bisects the zigzag molecules to be discussed below. The horizontal line in the middle of each of those figures shows the molecular skeleton on which the component atoms line up, and the ends of bars vertically oriented to the line indicate hydrogen atoms.

With interests in the electrostatic characteristics of the simplest function, ether, and of the aromatic functions in Table II, we examined their electrostatic potential maps in reference to those of the functions mentioned above. The calculation was made on the rest of the molecules from which the common 4-substituted phenoxy moiety was subtracted, and the conformation adopted is the energy minimum one calculated as mentioned above. The

compounds in Figure 3D–J were so drawn that the first three atoms from the common phenoxy oxygen atom overlapped as closely as possible to those of the oxime in Figure 3C, according to the least-squares fitting.

The maps of the zigzag plane are shown in the a series of Figure 3, and those of potential isomers of the ethers in Figure 3Da showed on the upper side of the plane a pattern similar to those of the ester (Figure 3Aa), carbamate (Figure 3Ba), and oxime (Figure 3Ca) functions, but it was very different on the lower side. More dissimilarity was observed for the 4-isopropylbenzyl function of the active **9** in Figure 3Ea, and the pattern of 4-isopropoxybenzyl in Figure 3Fa of the highest active **8** in the benzene series also looked unlike. Though the (2-pyridyloxy)ethyl part in Figure 3Ga of the most active member of the present class, compound **1**, showed rather similar features with those of Figure 3Aa–Ca, the set of results indicates that the comparison of the electrostatic nature is not necessarily adequate in the zigzag plane.

We suggest that the comparison is better done by viewing the contours from the rectangular direction in the plane that bisects the zigzag molecule at its geometrical center. All of the compounds have a similar pattern as seen through the b series of Figure 3 (Ab–Kb), with the contour lines symmetrically distributed with a negative peak through the upper and lower sides of the molecule. The site of the peak is indicated by shadowing, and it is extended upward to the a series of figures to show which atom is just at the site. Note that the site of the peak was found on the contour at about the van der Waals surface of the molecule that could be assumed to be the frontier of the contact with the receptor. Since the contours correspond to the level of potential energy relative to a positive charge, the negative sign means that the site of the molecule has a tendency to be drawn toward a positive site of the receptor.

The site of peak moves to the right in the γ-ether in Figure 3D(2) and to the left in the ϵ-ether in Figure 3D-(3) from the site of the δ-ether in Figure 3D(1). This relationship coincides with the site of the oxygen atom vs potency relationship of these ethers in Table I, the δ-compound being most potent, and the others being less. Thus, the electrostatic, complementary interaction with the receptor, if any, is considered to be best when a function is built in a molecule so that the negative potential peak is on the δ-position. Moreover, the peak is more at the nitrogen site than at the oxygen site in the oximes, as seen from Figure 3C. This provides the answer to the question raised in Table I, why the oxime compounds with the nitrogen atom at the δ-position are more active than those having it at other positions. The most active of the ethers and oximes listed in Table I are the compounds that have dimensions stereochemically best, or at least nearest best, complementary with the receptor cavity, in addition to the electrostatic fit at the δ-site. The aromatic functions of the molecules in Table II, however, could have more or less conformational as well as bulkiness problems in the stereochemical fit, and this may cause a distortion of the electrostatic fit leading more or less to a poorer potency, as discussed below.

Stereochemical and Electrostatic Aspects. In our previous paper, we have drawn a "mode-of-action map" of JHs and JH-mimetic molecules that would be of value in examining the structural correspondence between classes of compounds as well as in elucidating structural profiles that confer activity (Niwa et al., 1989). Figure 4A is the reproduction of the map, and the compound accommodated as model is 3-[4-(3-methylphenoxy)phenoxy]-propyl isobutyl ether (Niwa et al., 1989), one of the most active of the compounds we have developed. The structure

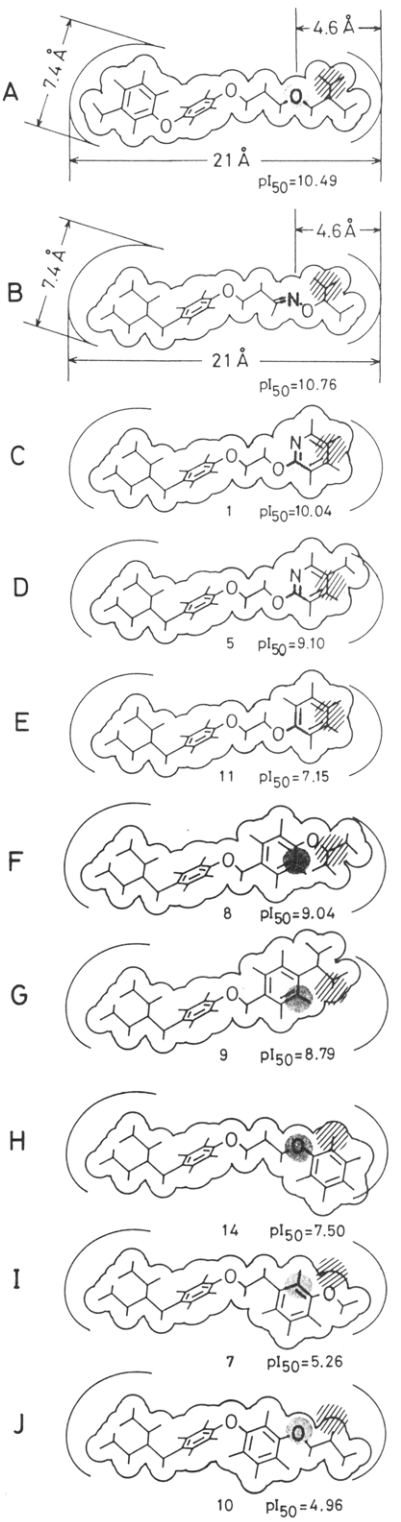


Figure 4. Accommodation of JH-mimetic compounds in the mode-of-action map. The solid lines indicate the steric interaction site or the receptor walls. The striped region at the right is the site where the receptor walls are located in vertical directions. The shadowed circle at the right indicates the position-specific, electrostatic interaction site with a heteroatom or a functional group of the JH molecule. The compound accommodated in (A) is 3-[4-(3-methylphenoxy)phenoxy]-propyl isobutyl ether (Niwa et al., 1989), and the compound in (B) is [4-(2-ethylbutyl)phenoxy]proipionaldoxime *O*-isopropyl ether (Hayashi et al., 1989). The end of the bars of the structures represent hydrogen atoms. (A) is reproduced from our previous paper (Niwa et al., 1990) with permission from the American Chemical Society.

was constructed as a CPK molecular model in the stable, extended conformation. The solid lines indicate the steric interaction site or the receptor walls that encompass the molecule of optimum length, about 21 Å. The striped region at the right is the site where the receptor walls are located in vertical directions, plausibly constituting a cavity. There is also a cavity at the left, and it has been suggested to have a diameter of about 7.4 Å, just encompassing the *m*-methoxyphenyl residue. The shadowed circle at the right indicates the position-specific interaction site with a heteroatom of the JH molecules. It is at the position δ from the central phenoxy oxygen atom or at 4.6 Å distant from the right edge.

The compound accommodated in Figure 4B is [4-(2-ethylbutyl)phenoxy]propionaldoxime *O*-isopropyl ether, which is one of the most active members of the (4-alkylphenoxy)propionaldoxime series (Hayashi et al., 1989) and is the immediate parent of the aromatic series of compounds (Hayashi et al., 1990) in Table II. The oxime nitrogen atom, rather than the oxygen atom, has been suggested to be the point interaction site of this molecule and is at the shadowed δ-position. In Figure 4C–J, we interpreted the steric aspects of this series of compounds, together with consideration of their electrostatic nature. The compounds were also constructed by the prevalent CPK model by the same principles adopted in Figure 3. The bond angle and bond length of the rigid CPK model do not necessarily coincide completely with those calculated, but the difference is so slight that the van der Waals contours almost overlap between the two models. The accommodation was made so that the 4-(2-ethylbutyl)-phenoxy moiety occupied the same place as it does in Figure 4B.

The most active member of this class, compound 1, fits the framework of the receptor well (Figure 4C), irrespective of its about 1 Å shorter *D* than optimum value. If *D* becomes optimum with the introduction of a substituent at the 4- or 5-position of the pyridine ring, the results would be that the substituent invades the right wall at its upper or lower part. The situation is shown by Figure 4D, where the 5-methyl congener of 1, compound **5**, is accommodated.

If reference with the contour map of Figure 3Gb, the peak of the negative potentials of 1 is thought to be at the left edge of the pyridine ring or at the position where the C=N function is and is just on the shadowed δ-position in Figure 4C. This is considered to be another factor for its high potency. Why the benzene analogue of 1, compound 11 in Figure 4E, is less potent could be attributed to the fact that the electrostatic peak of 11 is somewhat off to the right since it is at about the center of the benzene ring as seen from the potential map of its phenoxyethyl moiety in Figure 3 Hb. The N-position isomers of **1**, 3- and 4-pyridyloxy **2** and **3**, could have similar electrostatic problems like 11. They may fit the receptor sterically as well as compound 1 does (figures not shown), but the electrostatic peak does not come in the right place as seen from Figure 3Ib,Jb. There are calculated to be two possible conformations for **2** with a small difference of the conformational energy, 1.6 kcal/mol (Figure 3Ia(1),(2)]. Whichever conformation the molecule may take, the negative peak is between the center and right edge of the ring and thus does not fit the δ-point. The pyrimidine derivative **15** is also the entity that fits the receptor as well as 1 and 11 (figure not shown, but refer to Figure 4C,E of the pyridine and benzene congeners). Its potency, pI_{50} = 8.96, is 10 times less than that of 1 but about 60 times more than that of 11. Figure 3K shows that the negative peak of **15** lies between the two aromatic nitrogen atoms or between the sites where the peaks of **1** and 11 lie. The hydrophobic character of the aromatic ring surface may be somewhat different between benzene, pyridine, and pyrimidine, and thus may have some consequence on the binding. Still, the position of the peak in the map explains the intermediate potency of **15** well. It is quite likely that the electrostatic interaction is very directional or very sensitive to the distortion of the face-to-face contact with the receptive point.

Compound **8**, the most active compound in the benzene subseries, rather tightly fits the map (Figure 4F) and the electrostatic peak is at the region somewhat slipped off to the left as seen from the preceding Figure 3F. If it moved to the right to catch the point interaction site, then the right end of the molecule would invade the receptor wall. A congeneric but a little shorter **9** is thought to invade the wall at the upper side (Figure 4G).

The higher potency of (*m*-tolyloxy)ethyl **12** relative to that of *p*-**13** (tolyl congeners of **11** in Figure 4E) is considered to be due to the fact that the substituent invades the wall less when it is at the meta position than when it is at the para position (figures not shown), since the cavity at the right is thought to be deeper in the meta direction, as supposed from Figure 4E for unsubstituted 11. On the contrary, in the pyridine congeners **4** and **5**, the *p*-methyl **5** in Figure 4D is thought to fit the receptor less tightly than *m*-methyl **4** (figure not shown). This comes from the fact that the energy minimum conformation of *m*-**4** is calculated to be the one that stands as it is in Table II, rather than the one where the aromatic ring rotates 180° with respect to the connecting axis to the body of the molecule (the energy difference is about 5.1 kcal/mol). The *m*-methyl substituent of **4** is thought to be oriented differently from that of **12**. The "favorable" conformation of **4** could be unfavorable when it fits the receptor, because the projection of the meta (or 6) substituent is so large toward the upper direction.

Through the interpretations made above for the pyridyloxyethyl, phenoxyethyl, and benzyl compounds (Figure 4C–F), it seems that the bulkiness of the aromatic plane itself is not so serious when it is at the β- or δ-position from the central phenyl oxygen atom. However, when it is at other positions, the bulkiness effect is thought to be more or less unfavorable for activity, in addition to the missing of the electrostatic fit. The phenoxypropyl compound **14** in Figure 4H has the bulkiness at the terminal with the missing of the point; Figure 3Hb shows that in the phenoxyalkyls the electrostatic peak is on the benzene moiety rather than on the oxygen atom. The δ-oxygen atom of **14** right on the shadowed circle in Figure 4H is thus a false appearance. The fact that the phenethyl compound **10** in Figure 4I has about a correct *D* (20.7 Å) but shows a poor potency (pI_{50} = 4.96) suggests that the bulge toward the lower direction at the position where the benzene ring exists is inconvenient in interaction with the receptor, plausibly invading a wall that was not evident in the previous interpretations (Niwa et al., 1989; Hayashi et al., 1989). Propoxyphenyl **7** in Figure 4J has a bulge in the downward direction at about the center of the molecule. It is also a molecule that has the negative peak far from the point interaction site. Whichever effect is the cause of its poor potency, the propoxy oxygen atom at the point interaction site is again a deceptive appearance.

Although not shown, similar apparent anomalies observed in the rest of the aromatic compounds reported in our preceding paper (Hayashi et al., 1990) can be explained as well by the similar stereoelectrostatic as well as stereochemical considerations.

Concluding Remarks. Through the examination of the electrostatic properties of the aromatic compounds in Table II and those of the previous nonaromatic classes of mimetics, we found that the electrostatic contour maps have a common feature, the negative peak, when they are viewed and compared in the section that bisects the zigzag plane of the molecules. The considerations of the electrostatic potentials have been rather directed toward grasping the features or the effects of certain space areas. This study suggests another aspect that originates from the view that the electrostatic interaction could be highly position specific and directional.

The peak of the negative contour lines was observed to be at the oxygen atom site in the JH-active ethers and at the nitrogen atom site in the oximes. Together with the previous finding that the potency is highest when these sites are at the δ-position in the molecules of optimum dimensions, this fact indicates that the point interaction is an electrostatic one in nature and most favorable when the negative peak is on the δ-site. On this basis, stereochemical and electrostatic interpretations were made on the aromatic series of compounds, showing that it is the benzene of pyridine moiety that substitutes in the role of the heteroatoms; some of the compounds have an aryloxy oxygen at the pertinent δ-position, but the negative potential peak does not lie there. The inference of whether or not the negative point lies at the right place in the binding molecule was made possible by doing the examination within the framework of the mode-of-action map, and this could be extended to obtain a clue what structure of compounds should be designed and how a lead compound should be modified for high activity; inspection of a prospective molecule on the map will show whether or not it has optimum dimensions and the negative peak at the right place, whatever function it has. Referring to the present results, the inspection could be extended to the molecules active against species other than *C. pipiens* as well as to other JH-active compounds.

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Registry No. 1, 128550-32-3; 2, 128550-33-4; 3, 128550-34-5; 4, 128550-35-6; 5, 128550-36-7; 6, 128550-37-8; 7, 125796-67-0; 8, 125796-81-8; 9, 125796-73-8; 10, 125796-86-3; 11, 125796-89-6; 12, 125796-91-0; 13, 125796-90-9; 14, 125796-97-6; 15, 125796-63-6; PhO-*p*-C_6H_4-OCH_2CH_2OBu, 57650-83-6; PhO-*p*-C_6H_4-$OCH_2CH_2CH_2OPr$, 119454-88-5; PhO-C_6H_4-*p*-$OCH_2CH_2CH_2CH_2OEt$, 119437-18-2; Me-*m*-C_6H_4-$OCH_2CH_2CH_2OBu$-i, 118358-10-4; $PhCH_2$-*p*-C_6H_4-OCH_2CH=NOBu-i, 112597-68-9; $PhCH_2$-*p*-C_6H_4-OCH_2CH_2CH=NOPr-i, 112597-77-0; Me-*m*-C_6H_4-O-C_6H_4-*p*-OCH_2CH_2CH=NOPr-i, 112597-81-6; i-PrO-*p*-C_6H_4-OCH_2CH=NOPr, 116799-50-9; i-PrO-*p*-C_6H_4-OCH_2CH_2CH=NOEt, 116799-75-8; $(CH_3CH_2)_2CH$-*p*-C_6H_4-OCH_2CH_2CH=NOPr-i, 118358-19-3; 3-[4-(3-methylphenoxy)phenoxy]propyl isobutyl ether, 118358-10-4.