Chloronicotinyl Insecticides. 8. Crystal and Molecular Structures of Imidacloprid and Analogous Compounds

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The crystal structures of the chloronicotinyl insecticide imidacloprid and related molecules have been determined by three-dimensional X-ray diffraction analysis. In imidacloprid the nitroimino group is coplanar with the imidazolidine ring plane; shorter ring C—N bond lengths and longer exocyclic C═N bond length were observed, suggesting a formation of a fully delocalized diene system. Similar molecular frameworks were seen in the nitromethylene and cyanoimine analogues. The interatomic distances between an imidazolidyl nitrogen and a nitro oxygen or a cyano nitrogen were *ca*. 5.9 Å, a suitable value to bind to the recognition site on nicotinic acetylcholine receptor.

Keywords: *Chloronicotinyl insecticide; imidacloprid; X-ray structure; nicotinic acetylcholine receptor; nitromethylene insecticide*

INTRODUCTION

Chloronicotinyl insecticides represented by imidacloprid (**1**) have ben receiving attention as reliable tools for insect control (Ishii *et al*., 1994; Kagabu, 1993, 1996; Leicht, 1993; Moffat, 1993). Recent biological studies demonstrated that chloronicotinyls and the lead class, nitromethylenes such as nithiazine (**6**), act on the nicotinic acetylcholine receptor (nAChR) of insects. Yamamoto and his colleagues have pointed out commonality of chloronicotinyls with nicotine both in structure and in physiology and have proposed a binding model for these insecticides (Tomizawa and Yamamoto, 1993).

We undertook in this paper a crystallographic study of imidacloprid and related insecticides (Figure 1) to obtain precise three-dimensional structural information. Characteristic molecular features should give insight into the binding mode of these insecticides to nAChR.

MATERIALS AND METHODS

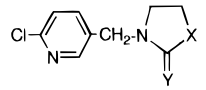
The compounds for X-ray structure determination were prepared according to the previous description (Kagabu *et al*., 1992; Kagabu and Medej, 1995; Moriya *et al*., 1992; Shiokawa *et al*., 1992), and the single crystals were grown by slow evaporation of an ethanol solution at room temperature. The crystal data, data collection, refinement parameters, and atomic coordinates are summarized in Supporting Information.

RESULTS

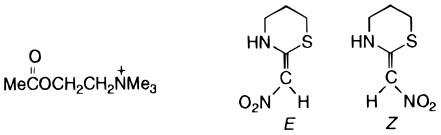
The respective molecular structures resulting from X-ray diffraction studies, together with the numbering of the various atoms, are shown in Chart 1 and Figures 2−5. Selected bond lengths, bond angles, and torsional angles are given in Tables 1 and 2.

The chloropyridyl part of each compound shows the ordinary plane figure for the pyridine ring. In molecule **1**, the C5−C4−C6−N2 and C7−N2−C6−C4 torsional angles are 117.8° and 106.9°, respectively. As a result, the angle between the pyridine and imidazolidine ring planes through a methylene bridge is 75.7°, and the pyridine plane bisects the H4−C6−N2 bond angle, leading the relation between H3 and H5 to be quasi 1,3-diaxial and bringing H2 close to H6 on the imidazolidine ring.

In molecule **2**, the C5−C4−C6−N2 torsional angle becomes larger, 156.4°, probably to evade the repulsion between H10 and the proximal H4/H5. The pyridyl *ortho* hydrogen, H2, is close to H6 at 2.74 Å and at the same time lies obliquely over N2 on the imidazolidine



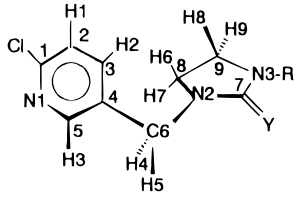
1: Y=NNO_2, X=NH; imidacloprid
2: Y=$CHNO_2$, X=NH
3: Y=NCN, X=NH
4: Y=NNO_2, X=NMe
7: Y=O, X=NH
8: Y=$CHCO_2Et$, X=NH



5: acetylcholine (ACh) **6**: nithiazine

Figure 1. Chemical structures of imidacloprid and related compounds.

Chart 1. Numbering for Crystal Structures



1: Y = N4-N5 O1(O2); R = H10
2: Y = C10(H10)-N5O1(O2); R = H11
3: Y = N4-C10 N5; R = H10
4: Y = N4-N5 O1(O2); R = $C10H_3$

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S0021-8561(96)00075-1 CCC: $14.00

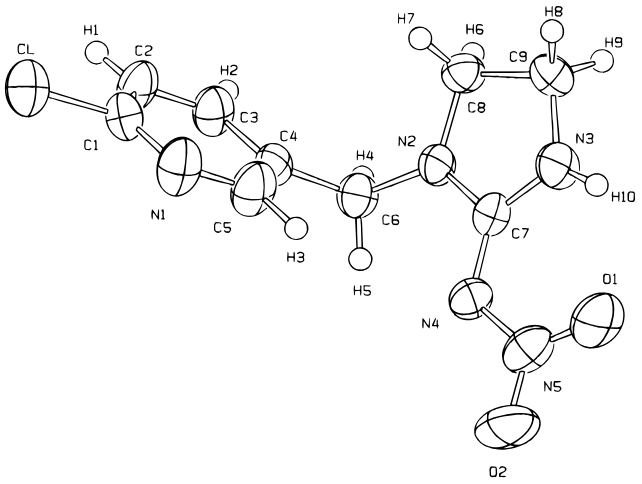

Figure 2. Molecular structure and numbering scheme for imidacloprid (**1**).

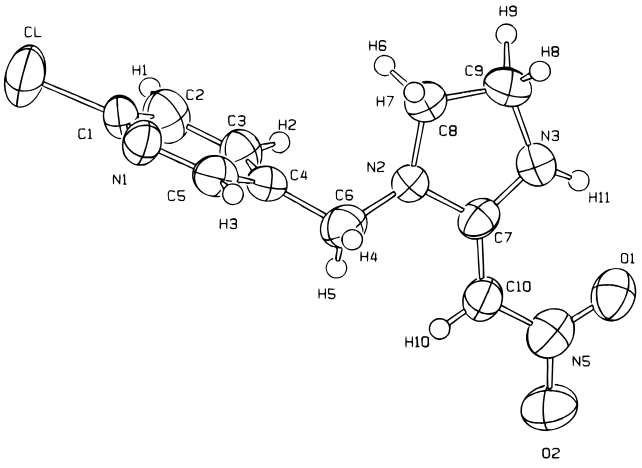

Figure 3. Molecular structure and numbering scheme for **2**.

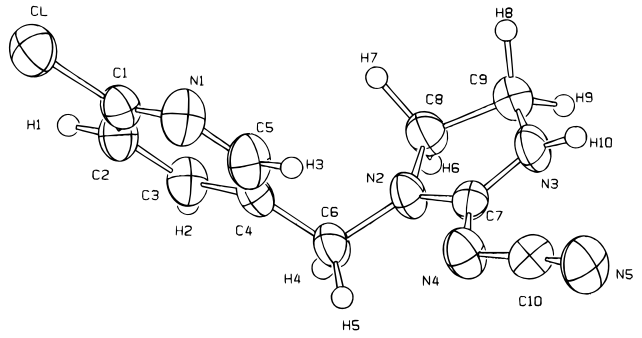

Figure 4. Molecular structure and numbering scheme for **3**.

ring. On the other hand, another *ortho* hydrogen, H3, adopts a cramped 1,3-diaxial relation to H5.

The interatomic situation in molecule **3** is similar to that in molecule **1**, and the pyridyl nitrogen and the functional group (Y) on C7 are likewise on the same molecular side. In contrast, in molecule **4** both entities are to the opposite side of each other, and instead of the H2 hydrogen as in case of **1**, **2**, or **3**, the H3 atom approaches the H6/H7 region on the imidazolidine ring.

Several characteristics are seen in the enamine parts. For molecules **1**−**3** the imidazolidine planes have approximate C_{2v} symmetry, with the symmetry axis passing through the C7−Y bond; the C7−N2 and C7−N3 bond lengths, 1.32−1.34 Å, are remarkably shorter than normal C−N (amine) (1.47 Å) but close to C=N (imine) (1.33 Å) (Sasada, 1984). The double-bond character,

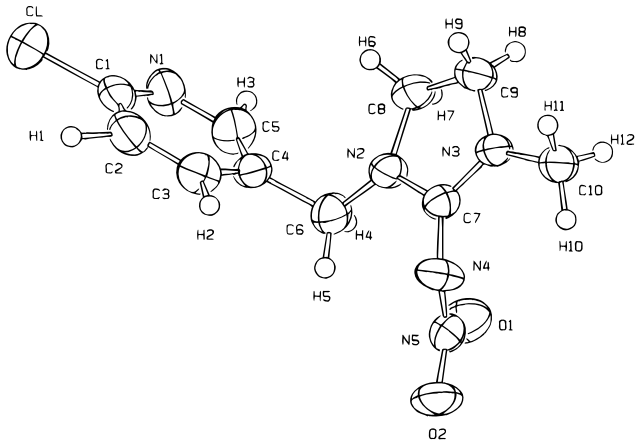

Figure 5. Molecular structure and numbering scheme for **4**.

obviously brought about by the transfer of the lone-pair electrons on the amines, is reconfirmed by the trigonal configuration of the C7 carbon in that the sums of the N2−C7−C10, N3−C7−C10, and N2−C7−N3 bond angles are 360.0°, 359.6°, and 360.0° for molecules **1**, **2**, and **3**, respectively. The delocalization of the electrons extends as far as the strong electron-withdrawing group, NO_2 or CN, forming a coplanar olefin−amine π-electron network. Furthermore, in molecules **1** and **2** are displayed the full patterns of the lengthenings of the center C7=N4 (normal C=N; *vis. supra*) or C7=C10 (normal C=C; 1.34 Å) double bonds and shortenings of N−NO_2 (N−N in NH_2NO_2; 1.43 Å) and C−NO_2 (C−N in CH_3NO_2; 1.49 Å) (Sasada, 1984) single bonds.

Another remarkable feature for the enamine parts in these molecules is the *E* configuration about the exocyclic C7=Y bond. The preference for this geometry is mostly due to the larger steric increment of the picolyl group relative to methyl, on one hand (Taft's steric index, *Es*, for benzyl is −0.38 referred to methyl as 0) (Taft, 1956), and on the other hand, in the cases of **1** and **2** the intramolecular hydrogen bonding between the N3 amine hydrogen and the nitro oxygen to form an ideal six-membered ring with the appropriate H-bond lengths and angles contributes decisively (Table 2) (Vinogradov and Linnell, 1971). The extra ring will also reinforce the coplanarity of the dipolar *s-cis* diene cascades.

The above argument is not the case for molecule **4**, in which the hydrogen bonding is deprived by the methyl substitution on the N3 atom at the imidazolidine ring and this methyl group produces in turn large steric constraints around the guanidine region. The nitro group is pushed up almost perpendicularly out of the guanidine plane at the cost of the conjugation stability, and both N−O bonds in the nitro group are eclipsed with the imine bond (C=Y). An oxygen of the NO_2 is close to the methylene bridge as O1···H4 (2.58 Å), O1···H5 (2.79 Å), and O1···C6 (2.92 Å), suggesting significant repulsion among them, considering the van der Waals distances (O···H, 2.72 Å; O···C, 3.22 Å) (Sasada, 1984). In response to this, the N2 atom at the imidazolidine ring adopts a pyramidal configuration (the sum of its valence bond angles is 356.5°).

DISCUSSION

Vertebrate nAChR is a pentamer of four glicopeptide subunits (α_2, β, γ, δ), and among them the α-subunit carries an ACh binding site. Study to elucidate the binding domains is in progress [*cf.* Clarke *et al.* (1985),

Table 1. Selected Atom Distances and Angles of 1−4

	bond lengths (Å)					bond angles (deg)			
	1	**2**	**3**	**4**		**1**	**2**	**3**	**4**
C1−CL	1.75	1.75	1.75	1.74	N1−C1−C2	125.3	127.6	125.7	125.6
C1−N1	1.31	1.28	1.30	1.32	C1−C2−C3	118.0	115.5	117.4	116.0
C1−C2	1.37	1.39	1.37	1.37	C2−C3−C4	119.6	120.1	120.4	120.5
C2−C3	1.37	1.39	1.38	1.39	C3−C4−C5	116.5	116.3	115.5	118.6
C3−C4	1.38	1.37	1.38	1.36	C4−C5−N1	125.4	126.5	125.8	122.6
C4−C5	1.38	1.38	1.38	1.37	C5−N1−C1	115.2	113.9	115.3	116.7
C5−N1	1.34	1.34	1.34	1.35	N1−C2−CL	115.5	115.2	115.6	115.5
C4−C6	1.50	1.49	1.50	1.53	C3−C4−C6	122.2	115.5	123.2	122.5
C6−N2	1.45	1.46	1.45	1.44	C4−C6−N2	113.1	122.2	112.5	111.3
N2−C7	1.34	1.36	1.35	1.33	C6−N2−C7	125.7	113.1	124.4	125.1
N2−C8	1.45	1.45	1.45	1.47	C6−N2−C8	122.2	125.7	123.1	121.7
C7−N3	1.32	1.33	1.33	1.33	C7−N2−C8	112.0	122.2	112.8	109.7
N3−C9	1.45	1.44	1.46	1.44	N2−C8−C9	102.7	112.0	103.0	102.1
C8−C9	1.53	1.50	1.53	1.52	C8−C9−N3	102.8	102.7	102.7	102.8
					C7−N3−C9	112.5	102.8	112.6	111.1
					N2−C7−N3	109.6	112.5	108.9	111.0
					N2−C7−Y	117.1	117.1	121.2	127.2
					N3−C7−Y	133.3	128.3	129.9	121.3
Y	1.34	1.40	1.32	1.37	Y	116.7	122.1	116.6	114.8
	C7−N4	C7−C10	C7−N4	C7−N4	C7−	N4−N5	C10−N5	N4−C10	N4−N5
	1.35	1.35	1.33	1.32		115.4	118.2	175.2	116.6
	N4−N5	C10−N5	N4−C10	N4−N5	N4/C10[a]−	N5−O1	N5−O1	C10−N5	N5−O1
	1.23	1.27	1.14	1.23		122.9	121.6		121.5
	N5−O1	N5−O1	C10−N5	N5−O1	N4/C10[a]−	N5−O2	N5−O2		N5−O2
R^2	N3−C10			1.44	R^2	C9−N3−C10			123.1

[a] Molecule **2**.

Table 2. Interatomic Distances (Angstroms), Torsional and Interplane Angles θ (Degrees), and Geometric Parameters of Hydrogen Bonds in 1−4

	1	**2**	**3**	**4**
C4−C5−C6−N2	117.8	49.8	117.2	−81.4
C7−N2−C6−C4	106.9	156.4	105.3	125.6
C6−N2−C7−N4/C10[a]	−0.5	21.4	0.9	−19.6
N2−C7−N4/C10[a]	176.3	176.6	176.4	67.2
C7−N4/C10[a]−N5−O1	0.0	0.6	−169.0[c]	−171.3
C7−N4/C10[a]−N5−O2	179.4	179.0		8.5
N4/C10[a]−C7−N2−C8	176.5	175.2	179.7	178.5
N3−C7−N4/C10−N5	−3.0	−0.2	−0.6[d]	−121.7
C9−N3−C7−N4/C10[a]	178.8	176.0	−178.4	−169.8
N1−N2 bond distances[e]	4.35 (5.45)	4.78 (6.06)	4.35 (5.62)	4.56 (5.81)
N2−O1/N2−N5[b,f]	4.47 (5.80)	4.66 (6.00)	4.60 (6.12)	4.12
θg	75.7	78.4	78.4	76.3
hydrogen bond				
N−H···O1 distance	2.10	2.06		
N3−H1−O1 angle	117.4	128.5		

[a] Molecule **2**. [b] Molecule **3**. [c] C7−N4−C10−N5. [d] N3−C7−N4−C10. [e] With the van der Walls surface of N1 in parentheses. [f] With the van der Waals surface of O1. [g] Interplane angles between pyridine and imidazolidine rings.

Galzi *et al*. (1991), and Herz *et al*. (1989)], and the structural homology of nAChRs of vertebrates to insects has been reported [*cf*. Breer and Sattelle (1987)]. Electrophysiological experiments proved that imidacloprid and nithiazine act as an ACh agonist on insect postsynaptic nAChR as does the natural insecticide nicotine (Bai *et al*., 1991; Liu and Casida, 1993; Nishimura *et al*., 1994; Sattelle *et al*., 1989; Schroeder and Flattum, 1984; Tomizawa and Yamamoto, 1993).

Previously, Beers and Reich carried out conformational analyses on several ACh agonists and antagonists and showed that the specific binding of those agents to the receptor is mediated by two elements: (a) a Coulombic interaction involving the positively charged moiety and (b) a hydrogen bond that depends on an acceptor group in the drug and is formed approximately 5.9 Å from the center of the positive charge. As for nicotine, the pyrrolidinium nitrogen, which is protonated by *ca*. 90% under physiological conditions, functions as the cationic center and the pyridyl nitrogen as the hydrogen bond acceptor (Beers and Reich, 1970).

Recently, Tomizawa and Yamamoto pointed out that the imidazolidine nitrogen of imidacloprid and related insecticides should be partially positively charged by force of the neighboring electron-withdrawing group such as nitroimine and could interact with the anionic center on the receptor, as does the corresponding pyrrolidinium cation of nicotine (Tomizawa and Yamamoto, 1993). On the other hand, its chloropyridine part was claimed to be able to participate in the hydrogen bonding like the pyridine ring of nicotine. They had also predicted that the distance between the imidazolidyl nitrogen and 3-pyridylmethyl nitrogen atoms in imidacloprid should correspond to the distance in nicotine. On the basis of these structural considerations in addition to the physiological resemblance, they have proposed a binding model for this new class of insecticides common with nicotine (model i in Figure 6). The deduced electron deficiency of the nitrogen atom of imidacloprid and the analogues has been proved explicitly by the experiment using ^{15}N-NMR technique (Yamamoto *et al*., 1995) and by HPLC measurements (Kagabu and Medej, 1995). The present X-ray data gave the precise distances between the van der Waals surface of the nitrogen of 3-pyridylmethyl and the atomic center of imidazolidyl N2: 5.45, 6.06, 5.62, and 5.81 Å for **1**, **2**, **3**, and **4**, respectively. These distances meet the prediction. Furthermore, this model explains the results clearly that compounds such as 2-pyridylmethyl-, 3-pyridylethyl-, and 3-pyridylimidazolidines composed of longer or shorter N−N distance than specified are lower in insecticidal activity than 3-pyridylmethyl derivatives (Kagabu *et al*., 1992; Moriya *et al*., 1992; Tomizawa and Yamamoto, 1993).

However, an alternative binding model was revealed by analysis of the crystallographic data. In imidacloprid the interatomic distance suitable to the estimation by

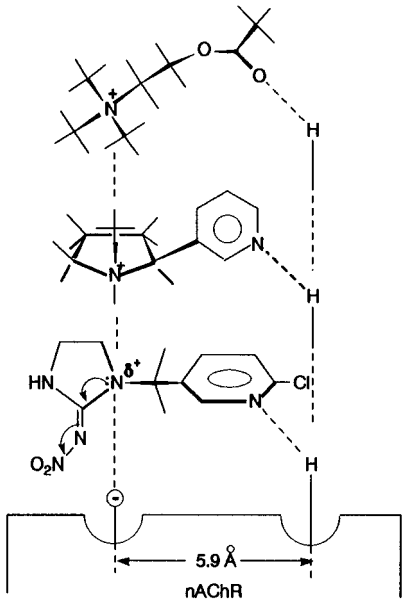

Figure 6. Binding model i for ACh, nicotine, and imidacloprid to AChR.

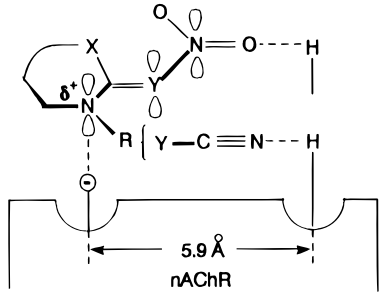

Figure 7. Schematic model ii for binding of chloronicotinyl to AChR.

Beers and Reich is not restricted to between the pyridyl and the imidazolidine nitrogen atoms. The distance of 5.80 Å between the nitro oxygen (with the van der Waals surface) and the N2 atom is also adequate. The corresponding distances, 6.00 and 6.12 Å in molecules **2** and **3** (the cyano nitrogen instead), respectively, are also within a similar range. This means that the NO_2 oxygen or the CN nitrogen can also act as the acceptor for the hydrogen bonding with the receptor in place of the pyridyl nitrogen; thus a π-conjugation system composed of a nitro or cyano group and the tandem amine can be thought of as the essential part for chloronicotinyls to interact with the binding sites on nAChR (model ii in Figure 7). According to this model, the pyridyl part functions merely in a subsidiary way to improve molecular lipophilicity, to affect dipole vectors, or to influence other physicochemical factors connected with the pharmacological processes. This pyridine ring can therefore be replaced by other bioisosteric moieties as evidenced by the reported significant activity of the phenyl and thiazolyl analogues (Kagabu *et al.*, 1992; Shiokawa *et al.*, 1992; Moriya *et al.*, 1993a,b). Nithiazine (**6**) is a good example for which insecticidal activity can be expected by our model, since it has the essential structural elements and an adequate NH···O distance of 5.98 Å (calculated for the *Z* form using the crystal data reported for the *E* form in Figure 1; Camilleri *et al.*, 1988). Its potent agonistic action (Sattelle *et al.*, 1989) may be unassailably explained by model i because it lacks the essential pyridine ring. It has been reported that the insecticidal efficacies and the

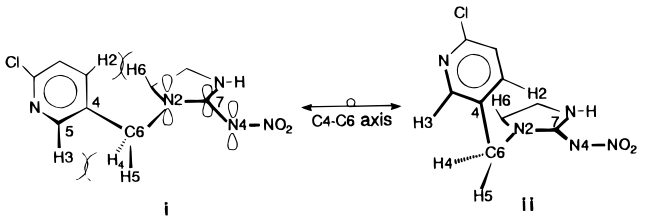

Figure 8. Steric constraints in rotamers of imidacloprid.

binding affinities of chloro-substituted pyridine derivatives such as **1**−**3** are far higher than the unsubstituted ones (Kagabu *et al.*, 1992; Moriya *et al.*, 1992; Tomizawa and Yamamoto, 1993). If we take the pyridine nitrogen as a hydrogen acceptor according to model i, their activity levels should be inverse because of the higher basicity of pyridine relative to 3-chloropyridine (the pK_a of pyridine is 5.2 and that of 3-chloropyridine 2.8; Schofield, 1967). We assume that the chloropyridyl part contributes to the activity enhancement by participation in a certain bonding with the hydrophobic residues near the essential binding site in the receptor peptide segment. On the other hand, urea **7** is known to show no insecticidal activity, despite having a partially positive nitrogen atom at the suitable position (Moriya *et al.*, 1992). Its nil activity is ascribed to the shorter distance to the hydrogen donator on the receptor. In our model the conjugated functional groups with the amidines or guanidines must possess both powerful electron-withdrawing and hydrogen-accepting capacities like NNO_2, $CNNO_2$, and NCN. Hence, considering the rather lower electron-withdrawing power to make the imidazolidyl nitrogen positive enough, the carbethoxymethylenyl derivative **8** would be weak in activity even though it has a hydrogen accepting head (Moriya *et al.*, 1992).

Another remark to be made about this model is that the partial positive N2 nitrogen is of sp^2 nature and the deficient 2p orbital lobes extend vertically with respect to the imidazolidine plane; thus, this nitrogen atom can approach the anionic site on the receptor only from this direction. This mode of interaction may be contrasted with the mode of nicotine and ACh (**5**), which carry, respectively, a pyrrolidinium and a tetramethylammonium nitrogen of the omni-directional *s*-symmetric sp^3 hybrid.

The N2 nitrogen of **4** is rather of sp^3 nature, different from molecules **1**−**3**, and the lone-pair electrons tend to localize on this atom. The electron-rich amine nitrogens do not perform electrostatic attraction with the anionic partners. This reflects the reported far inferior affinity of **4** to **1** to the binding site of honeybee head nAChR (binding affinity to nAChR: 164 μM for **4** *vs* 1.55 μM for **1**; Tomizawa and Yamamoto, 1993). Its nevertheless high insecticidal efficacy is probably caused by metabolic demethylation.

We have also looked at the steric situations around the pyridyl *ortho* hydrogens of imidacloprid (H2/H3 in Figure 8) with an aim to find any cause why the *ortho* substitution on the pyridine ring decreases the insecticidal activity greatly (Kagabu *et al.*, 1992; Moriya *et al.*, 1992, 1993a,b). Hydrogen (H2) in **1** lies closely above the N2 atom (the interatomic atomic distance is 2.42 Å). This value is less than the N−H van der Waals length (2.75 Å), considered the threshold for significant repulsion. Another *ortho* hydrogen (H3) is similarly cramped because of eclipsed relations to H5 (dihedral angle ∼0°) (Figure 8, **i**). If the pyridine ring rotates to become staggered to both H4/H5 hydrogens, H2 approaches the repulsive domain of the N2 atom (Figure

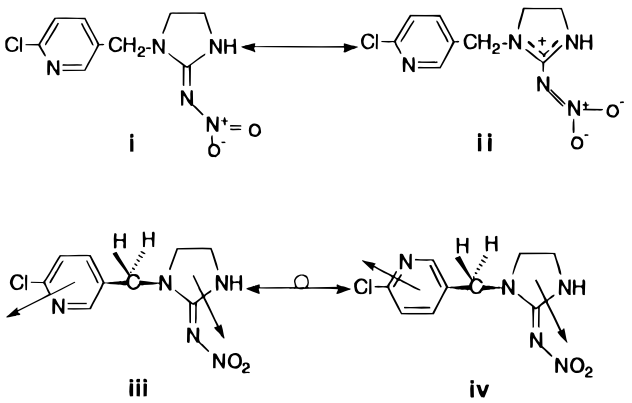

Figure 9. Resonance structures **i/ii** and rotamers **iii/iv** of imidacloprid. The arrows show the dipole directions.

8, **ii**). Because of such steric constraints even in the unsubstituted case, introduction of a substituent to either *ortho* position will compel the conjugated molecular framework to distort substantially. On the other hand, rotation about the C6−N2 axis will not lessen the strain energy either, because the steric constraints due to the proximal relations between H2 and H6 or H2 and H4 occur instead. Thus, in any case the individual conformer bearing a substituent in the *ortho* position of the pyridine ring will be subject to a considerable deformation from the well-fitting structure to the receptor.

We have discussed above the conformation of chloronicotinyl compounds based on the crystal data. There may be an argument that compounds should have different conformations in solution from those in the solid states. It has indeed been stated that the medium can affect conformational equilibria considerably, since the Gibbs energy differences between conformational isomers are generally very small (*ca.* 0−3 kcal/mol) and the solvation enthalpies of dipolar solutes are at least as large as and often much larger than this (Reichardt, 1988). However, as far as the precedent insecticide molecules are concerned, the existence of resonance structures, leading to the coplanar conjugation systems (**ii** in Figure 9) will become more possible also in an aqueous environment due to the stabilization by solvation. Also, equilibrium shifts from the geometry observed in the solid (**iii**) to the rotamer (**iv**) will be unrealistic in physiological milieu, considering the higher dipole moment of the former favored in dipolar media, even though the energy barrier for rotation of the pyridine ring around the C4−C6 axis in imidacloprid is in fact very low (2.8 kcal/mol in our calculation).

To summarize, the crystallographic data show (i) in molecules **1**−**3** the interatomic distances from N2 to pyridyl nitrogen or nitro oxygen/cyano nitrogen are 5.80−6.12 Å (with the value of the van der Waals surface), suitable to respond to an AChR binding site; (ii) the nitroguanidine, nitroamidine, and cyanoguanidine parts in molecules **1**−**3** are planar, (iii) compounds **1** and **2** take the *E* geometry with respect to the C7−Y bond, forming an ideal hydrogen bonding ON−O···H−N3; (iv) imidazolidyl nitrogen atoms of **1**−**3** are of sp^2 nature and electron deficient; and (v) in the *N*-methyl derivative (**4**) the nitro group is twisted nearly to a right angle out of the guanidine plane and the N2 atom is of sp^3 nature.

Supporting Information Available: Crystal data, data collection, refinement parameters, and atomic coordinates for compounds **1**−**4** (5 pages). See any masthead page for ordering information.

LITERATURE CITED

Bai, D.; Lummis, R. C. S.; Leicht, W.; Breer, H.; Sattelle, B. D. Actions of imidacloprid and a related nitromethylene on cholinergic receptors of an identified insect motor neurone. *Pestic. Sci.* **1991**, *33*, 197−204.

Beers, W. H.; Reich, E. Structure and activity of acetylcholine. *Nature* **1970**, *228*, 917−922.

Breer, H.; Sattelle, D. B. Molecular properties and functions of insect acetylcholine receptors. *J. Insect Physiol.* **1987**, *33*, 771−790.

Camilleri, P.; Carey, J. V.; Odell, B.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 2* **1988**, 591−596.

Clarke, P. B. S.; Schwartz, R. D.; Paul, S. M.; Pert, C. B.; Pert, A. Nicotinic binding in rat brain: autoradiographic comparison of [^{3}H]acetylcholine, [^{3}H]nicotine, and [^{125}I]-α-bungarotoxin. *J. Neurosci.* **1985**, *5*, 1307−1315.

Galzi, J.-L.; Revah, F.; Bessis, A.; Changeux, J.-P. Functional architecture of the nicotinic acetylcholine receptor. *Annu. Rev. Pharmacol.* **1991**, *31*, 37−72.

Herz, J. M.; Johnson, D. A.; Taylor, P. Distance between the agonist and noncompetitive inhibitor sites on the nicotinic acetylcholine receptor. *J. Biol. Chem.* **1989**, *25*, 12439−12448.

Ishii, Y.; Kobori, I.; Araki, Y.; Kurogochi, S.; Iwaya, K.; Kagabu, S. HPLC determination of the new insecticide imidacloprid and its behavior in rice and cucumber. *J. Agric. Food Chem.* **1994**, *42*, 2917−2921.

Kagabu, S. New insecticide imidacloprid (in Japanese). *Chem. Biol.* **1993**, *31*, 521−523.

Kagabu, S. Study on the synthesis and insecticidal activity of neonicotinoid compounds. *J. Pestic. Sci.* **1996**, *21*, 231−239.

Kagabu, S.; Medej, S. Stability comparison of imidacloprid and related compounds under simulated sunlight, hydrolysis conditions, and to oxygen. *Biosci., Biotechnol., Biochem.* **1995**, *59*, 980−985.

Kagabu, S.; Moriya, K.; Shibuya, K.; Hattori, Y.; Tsuboi, S.; Shiokawa, K. 1-(6-Halonicotinyl)-2-nitromethylene-imidazolidines as potential new insecticides. *Biosci., Biotechnol., Biochem.* **1992**, *56*, 361−363.

Leicht, W.; Imidacloprid—a chloronicotinyl insecticide. *Pestic. Outlook* **1993**, *4*, 17−21.

Liu, M.-Y.; Casida, J. E. High affinity binding of [^{3}H]-imidacloprid in the insect acetylcholine receptor. *Pestic. Biochem. Physiol.* **1993**, *46*, 40−46.

Moffat, S. New chemicals seek to outwit insect pests. *Science* **1993**, *261*, 550−551.

Moriya, K.; Shibuya, K.; Hattori, Y.; Tsuboi, S.; Shiokawa, K.; Kagabu, S. 1-(6-Chloronicotinyl)-2-nitroimino-imidazolidines and related compounds as potential new insecticides. *Biosci., Biotechnol., Biochem.* **1992**, *56*, 364−365.

Moriya, K.; Shibuya, K.; Hattori, Y.; Tsuboi, S.; Shiokawa, K.; Kagabu, S. Structural modification of the 6-chloropyridyl moiety in the imidacloprid skeleton: introduction of a five-membered heteroaromatic ring and the resulting insecticidal activity. *Biosci., Biotechnol. Biochem.* **1993a**, *57*, 127−128.

Moriya, K.; Shibuya, K.; Hattori, Y.; Tsuboi, S.; Shiokawa, K.; Kagabu, S. 1-Diazinylmethyl-2-nitromethylene- and 2-nitroimino-imidazolidines as new potential insecticides. *J. Pestic. Sci.* **1993b**, *18*, 119−123.

Nishimura, K.; Kanda, Y.; Okazawa, A.; Ueno, T. Relationships between insecticidal and neurophysiological activities of imidacloprid and related compounds. *Pestic. Biochem. Physiol.* **1994**, *50*, 51−59.

Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH Verlag.: Weinheim, 1988; Chapter 4.

Sasada, Y. Molecular and crystal structures. In *Chemistry Handbook* (in Japanese), 3rd ed.; The Chemical Society of Japan, Maruzen: Tokyo, 1984; Chapter 15.

Sattelle, D. B.; Buckingham, S. D.; Wafford, K. A.; Sherby, S. M.; Bakry, N. M.; Elderfrawi, R. T.; Elderfrawi, M. E.; May, T. E. Action of the insecticide 2-(nitromethylene)tetrahydro-

1,3-thiazine on insect and vertebrate nicotinic acetylcholine receptors. *Proc. R. Soc. London* **1989**, *B237*, 501−514.

Schofield, K. *Heteroaromatic Nitrogen Compounds*; Butterworth: London, 1967; Chapter 5.

Schroeder, M. E.; Flattum, R. F. The mode of action and neurotoxic properties of the nitromethylene heterocycle insecticides. *Pestic. Biochem. Physiol.* **1984**, *22*, 148−160.

Shiokawa, K.; Moriya, K.; Shibuya, K.; Hattori, Y.; Tsuboi, S.; Kagabu, S. 3-(6-Chloronicotinyl)-2-nitromethylene-thiazolidine as a new class of insecticide acting against *Lepidoptera* species. *Biosci. Biotech. Biochem.*, **1992**, *56*, 1364−1365.

Taft, R. W. Separation of polar, steric, and resonance effects in reactivity. In *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; Wiley: New York, 1956; Chapter 13.

Tomizawa, M.; Yamamoto, I. Structure-activity relationships of nicotinoids and imidacloprid analogs. *J. Pestic. Sci.* **1993**, *18*, 91−98.

Vinogradov, S. N.; Linnell, R. H. *Hydrogen Bonding*; Van Nostrand Reinhold: New York, 1971; Chapter 6.

Yamamoto, I.; Tomizawa, M. New development of nicotinoid insecticides. In *Pesticides/Environment: Molecular Biological Approaches*; Mitsui, T., Matsumura, F., Yamaguchi, I., Eds.; Pesticide Science Society of Japan: Tokyo, 1993; pp 67−85.

Yamamoto, I.; Yabuta, G.; Tomizawa, M.; Saito, T.; Miyamoto, T.; Kagabu, S. Molecular mechanism for selective toxicity of nicotinoids and neonicotinoids. *J. Pestic. Sci.* **1995**, *20*, 33−40.

Received for review February 1, 1996. Revised manuscript received August 19, 1996. Accepted October 8, 1996.[⊗]

JF960075F

[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1996.