Biosci. Biotechnol. Biochem., **62** (6), 1216–1224, 1998

Imidacloprid and Related Compounds: Structure and Water Solubility of *N*-Alkyl Derivatives of Imidacloprid†

Shinzo KAGABU, Kazuhito YOKOYAMA, Kazuko IWAYA, and Masahiro TANAKA

Department of Chemistry, Faculty of Education, Gifu University, Yanagido, Gifu 501-1193, Japan

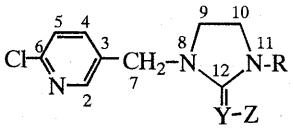
Received January 23, 1998

An intramolecular hydrogen bond between NH···O_2N in insecticide, imidacloprid (1), and its nitromethylene analog 15 was proved by NMR and IR spectra. That electron delocalization over their planar moieties was disrupted by alkylation at the imidazolidine nitrogen atom is demonstrated by the hypsochromic shifts in UV and deshielding effect in NMR spectra. Interestingly, the *N*-alkyl derivatives (C1-5) had greater water solubility than 1, although increasing alkyl chain length decreased the solubility. The hydrophilicity of the alkyl derivatives would result from remote charge heads being formed as a result of the conjugation disruption by alkylation, while the hydrophobicity of 1 could be ascribed to the charge distribution over the conjugated system coupled with the intramolecular H-bonding. The greater water solubility of 15 than 1 and contrastively small solubility of the cyanoimine analogue are discussed based on the difference in their steric crowding.

Key words: imidacloprid; log *P*; water solubility; molecular surface area; hydrogen bonding

A new insecticide class called chloronicotinyls represented by imidacloprid (**1**), 1-(6-chloronicotinyl)-2-nitroiminoimidazolidine, has been added to the pest control tools which have hitherto been based almost exclusively on the organophosphorus esters, carbamates and pyrethroids, and an evaluation of this insecticide class has been pointed to the newly-established agrotechnology of seed-dressing and box-treatment applications.[1-3] The performance characteristics of these compounds are linked in part to their appropriate systemic properties, *i.e.* adequate hydrophilicity.[3,4] According to the results of electrophysiological studies, imidacloprid acts on the postsynaptic nicotinic acetylcholine receptor. It polarizes the cockroach motor neuron at a dose level of 10^{-7} M.[5-10] Such extremely highly intrinsic potency from the first product of this class will be a trigger to make up successive active molecules by modifying the original structure.[1,3]

Appending a lipophilic increment to the hydrophilic tip of the parent compound is the conventional strategy to design a molecule with different biological spectra or transport properties by altering the original solubility parameters. Methylation at the imidazolidinyl nitrogen of imidacloprid (**1**) has also been attempted to devise a more lipophilic molecule along this line.[11] However, *N*-methylimidacloprid (**2**) turned out to have unexpectedly low lipophilic properties with a log *P* value, the partition coefficient between octanol and water, of −0.06 being much smaller than the value of 0.60 for the NH mother compound. A closer value of −0.19 for **2** has also been reported by another group.[7]



Compound	R	Y-Z
1 (imidacloprid)	H	NNO_2
2	CH_3	NNO_2
3	C_2H_5	NNO_2
4	*n*-C_3H_7	NNO_2
5	*i*-C_3H_7	NNO_2
6	$CH_2CH{=}CH_2$	NNO_2
7	$CH_2C{\equiv}CH$	NNO_2
8	*n*-C_4H_9	NNO_2
9	*i*-C_4H_9	NNO_2
10	*s*-C_4H_9	NNO_2
11	*n*-C_5H_{11}	NNO_2
12	*i*-C_5H_{11}	NNO_2
13	*n*-C_6H_{13}	NNO_2
14	$CH_2C_6H_5$	NNO_2
15	H	$CHNO_2$
16	CH_3	$CHNO_2$
17	H	NCN
18	CH_3	NCN

Fig. 1. Imidacloprid and Related Compounds.

This unusual phenomenon of increasing hydrophilicity by methylation prompted us to examine how the water solubility of the imidacloprid skeleton could be varied by systematic alkylation and to see if such an anomaly by methylation would also be apparent in the nitromethylene and cyanoimine analogues of imidacloprid. For this study, we first compared the structural properties of a set of related molecules listed in Figure 1 based on their molecular spectra.

Corresponding author. Shinzo Kagabu. Fax: +81-058-293-2207, E-mail: kagabus@cc.gifu-u.ac.jp

† Chloronicotinyl Insecticides, Part X. For Part IX, see ref. 36.

Materials and Methods

Chemicals. Typical preparation procedures for the *N*-alkylimidacloprids (**2–14**) are represented by compound **3**. To a stirred solution of imidacloprid (1.03 g, 4 mmol) in DMF (20 mmol) was added sodium hydride (0.17 g of a 60% oil dispersion, 4.3 mmol) at 0°C. After 1 h, ethyl iodide (1.56 g, 10 mmol) was added dropwise, and stirring was continued for 12 h at ambient temperature. After evaporating DMF *in vacuo*, the residue was extracted with chloroform, and the chloroform layer was washed with water and dried over anhyd. magnesium sulfate. After evaporating the solvent, the product was separated by silica gel column chromatography with ethyl acetate/ethanol (15:1) as the eluent. Recrystallization of the crude product from ethanol gave 727 mg in a 68% yield for an analytically pure sample. The percentage yields for the similarly prepared other compounds are in parentheses: **2** (60), **4** (53), **5** (18), **6** (66), **7** (73), **8** (48), **9** (3), **10** (25), **11** (44), **12** (35), **13** (20), **14** (84).

Preparation of 1-methyl-3-(6-chloronicotinyl)-2-nitromethylene-imidazolidine (**16**). A solution of 6-chloronicotinealdehyde (1.42 g, 10 mmol) in benzene (15 ml) was added dropwise to a stirred solution of *N*-methylethylenediamine in benzene (15 ml) while ice cooling. After 30 min, the benzene solution was heated at refluxing temperature while removing the water through a Dean-Stark separator. Heating was continued until water no longer collected in the separatory funnel (*ca.* 2 h). The benzene was distilled off and the cooled residue was dissolved in 50% ethanol (20 ml). To the ice-cooled solution was added portionswise sodium borohydride (1.0 g, 26 mmol), and the mixture was stirred overnight at ambient temperature. The content was acidified to pH 1 with conc. HCl and washed with hexane. The hexane solution was discarded. The aqueous layer was strongly alkalized with solid NaOH, and the solvent was distilled off with a rotary evaporator at 60–70°C. The residual liquid was extracted with acetonitrile (3 × 15 ml), and the insoluble material was filtered off. Evaporation of acetonitrile left 1.89 g of crude *N*-methyl-*N'*-6-chloronicotinyl-ethylenediamine, which was used for the next step without further purification. A solution of the foregoing diamine (1.70 g, *ca.* 8.5 mmol) and 1,1'-bis(methylthio)-2-nitroethylene (1.42 g, 8.5 mmol) in ethanol (50 ml) was heated under reflux for 18 h. After evaporating the solvents, the residual mixture was separated by silica gel column chromatography with ethyl acetate/ethanol (15:1) as the eluent. The fractions containing the product were collected, and the combined content was subjected to preparative TLC. Recrystallization of the crude product from ethyl acetate gave an analytically pure sample (100 mg, 4.4% yield). Similarly, 1-methyl-3-(6-chloronicotinyl)-2-cyanoiminoimidazolidine (**18**) was prepared from *N*-methyl-*N'*-6-chloronicotinyl-ethylenediamine and *S,S'*-dimethyl-*N*-cyanoiminocarbonate in a 10% yield.

All melting point (mp) data are uncorrected. NMR spectra for a sample solution of 20 mg of a compound in 0.7 ml of deuterated solvent and for the solid sample were obtained by a Varian Gemini 2000 C/H instrument (400 MHz). IR spectra were measured (as KBr discs) with a Perkin Elmer FTIR 1600 spectrometer and a JASCO A-100 spectrometer. Mass spectra were recorded (EI, 70 eV) with a Shimadzu QP 1000 mass spectrometer unless otherwise noted. UV spectra were measured with a Shimadzu UV-180 instrument. The analytical and spectral data for the prepared compounds are given in Tables 1–3.

Measurement of water solubility and Log P. The water solubility (WS) was measured by the flask method according to the procedure listed in OECD guidelines,[12] and the dissolved mass was estimated by UV. Sample concentration to determine the log *P* value was measured at 25±1°C by HPLC with an ODS column (Merck, LiChrosorb RP-18) and acetonitrile/water (30:70, v/v) as the mobile phase. The solubility data and log *P* values are listed in Table 4.

Calculations. The hydrophilic fragment constant (f-value) and van der Waals surface area (SA) were calculated according to methods of Rekker[13] and Bondi,[14] respectively, and are listed in Table 4.

Results and Discussion

Crystallographic analyses of imidacloprid (**1**) and its nitromethylene (**15**) and cyanoimine (**17**) analogues revealed a coplanar relationship of the imidazolidine ring to the functional groups, and planarity has been argued based on the electron delocalization in a push-pull olefin system.[16] In the mass spectrum of imidacloprid, the positively charged molecular ion was detected as only a trace by the conventional electron ionization method (EI) because of the facile $N-NO_2$ fragmentation (Fig. 2), whereas the recently developed chemical negative ionization method through an atmospheric pressure interface (LC-APCI)[17] displayed the molecular ion as a virtually single peak (Fig. 3), which would advocate stabilization of the formed radical anion in this conjugated system.

The planarity of the frameworks of **1** and **15** would be supplemented by the intramolecular hydrogen bonding, $NH\cdots O_2N$, with suitable geometry (Fig. 4).[16] For **17**, even if H-bonding may be possible from the distance between NH and the C≡N π-bond face, the magnitude would be small, if any, by considering the less-polarizable p-electrons. The IR spectra of **1** and **15** show highly chelated NH absorption by intense bands at frequency of 3356 and 3310 cm^{-1}. A strong absorption band at a frequency in the range of 1500–1600 cm^{-1} can be assigned to the stretching vibration of the double bond coupled with the stretching vibration of the N–N or C–N bonds. Wennerbeck and Sandström[18] and Kumpler[19] have found similar mixed vibrations in push-pull olefins and *N*-nitroguanidines, respectively. That these compounds are strongly polarized is clear from the much lower frequency (1600–1570 cm^{-1}) of the C=C or C=N bond in the skeletal vibration of the C=C–N or C=N–N grouping than in normal ethylene (1640 cm^{-1}) or imine (1650 cm^{-1}). The intense absorption due to C≡N conjugated with C=N of **17** and **18** at 2165–2230 cm^{-1}

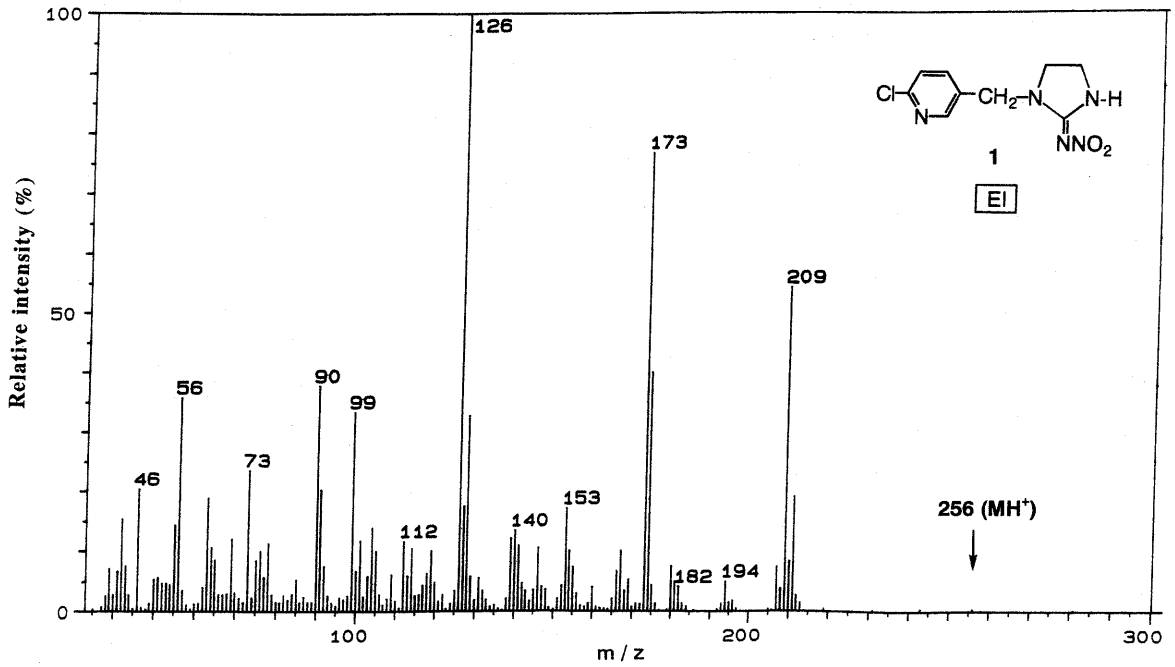


Fig. 2. EI Mass Spectrum of Imidacloprid (**1**).
70 eV; 180°C ion chamber temperature.

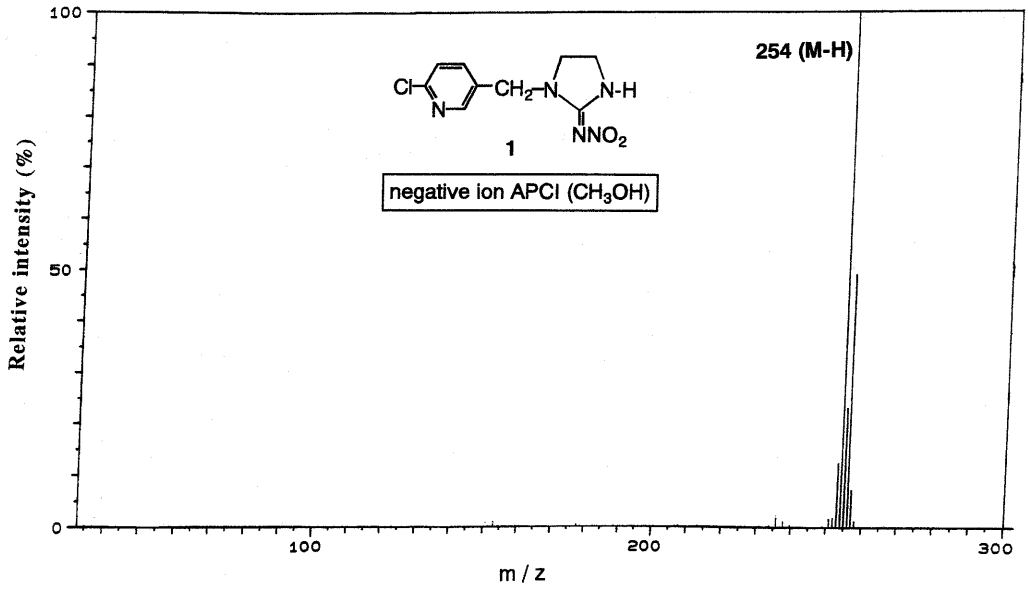


Fig. 3. APCI Mass Spectrum of Imidacloprid (**1**).
Methanol, 170°C nebulizer temperature, 50 V drift voltage.

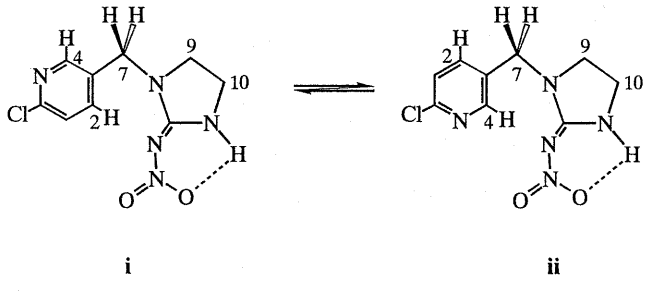


Fig. 4. Hydrogen Bonding and Rotamers of Imidacloprid (**1**).

is characteristic of the cyanoguanidine structure.[20,21]

Rajappa *et al.* have analyzed by NMR 1-methyl-2-nitromethylene-imidazolidine and several nitromethylene nitrogen-heterocycles, showing that the chemical shift due to the NH proton was around 8.2 ppm in $CDCl_3$ and somewhat lower in DMSO-d_6 for the (*E*)-configuration where intramolecular H-bonding $NH\cdots O_2N$ was presupposed.[22] The reported deshielding of the NH proton in DMSO will be brought about by increasing the N–H bond length in the polar solvent of H-accepting nature, which would reduce the electron

Table 1. Elementary Analysis, UV, MS and IR Data of Prepared Compounds

Compound	Mp (°C)	Formula[a]	λ_{max} (log ε)[b]	MS (m/e, rel int)	IR[c]
1[d]	143–144	$C_9H_{10}ClN_5O_2$ (255.7)	269 (4.17)	209 (M^+-NO_2, 55), 173 (80), 126 (100)	3355, 1580, 1565, 1300, 1280
2	107–108	$C_{10}H_{12}ClN_5O_2$ (269.7), C: 49.17 (49.25), H: 4.88 (4.89), N: 20.85 (21.00)	255 (4.10)	270 (M^++1, 33), 223 (100), 187 (71), 126 (24)	1600, 1585, 1525, 1300, 1270
3	100–101	$C_{11}H_{14}ClN_5O_2$ (283.7), C: 46.57 (46.60), H: 4.97 (4.96), N: 24.69 (24.52)		284 (M^++1, 23), 237 (100), 201 (45), 173 (15), 126 (40)	1600, 1585, 1555, 1310, 1295
4	68–69	$C_{12}H_{16}ClN_5O_2$ (297.7), C: 48.40 (48.40), H: 5.42 (5.41), N: 23.52 (23.55)		298 (M^++1, 23), 251 (100), 215 (20), 174 (16), 126 (38)	1580–1530, 1280, 1250
5	145–147	$C_{12}H_{16}ClN_5O_2$ (297.7), C: 48.40 (48.15), H: 5.42 (5.55), N: 23.52 (23.33)		298 (M^++1, 34), 251 (100), 215 (24), 174 (16), 126 (38)	1560, 1530, 1290, 1260
6	103–105	$C_{12}H_{14}ClN_5O_2$ (295.7), C: 48.73 (48.80), H: 4.77 (4.70), N: 23.68 (23.54)		296 (M^++1, 23), 251 (83), 249 (93), 235 (15), 126 (51), 41 (100)	1645, 1570, 1540, 1300, 1280, 1010, 955
7	101–102	$C_{12}H_{12}ClN_5O_2$ (293.7), C: 49.07 (49.27), H: 4.12 (4.00), N: 23.85 (23.79)		294 (M^++1, 27), 247 (100), 211 (38), 167 (78), 126 (91)	3220, 2100, 1590, 1560–1520, 1300–1250
8	63–65	$C_{13}H_{18}ClN_5O_2$ (311.8), C: 50.08 (50.21), H: 5.82 (5.59), N: 22.47 (22.67)		312 (M^++1, 12), 267 (50), 224 (83), 173 (14), 126 (100)	1580, 1540, 1280–1260
9	92–94	$C_{13}H_{18}ClN_5O_2$ (311.8), C: 50.08 (50.29), H: 5.82 (5.70), N: 22.47 (22.65)		312 (M^++1, 22), 267(31), 265 (89), 238 (46), 209 (56), 173 (35), 126 (64), 56 (100)	1575, 1550, 1300, 1280
10	77–78	$C_{13}H_{18}ClN_5O_2$ (311.8), C: 50.08 (49.97), H: 5.82 (5.90), N: 22.47 (22.70)		312 (M^++1, 13), 267 (27), 265 (63), 224 (59), 173 (23), 126 (100)	1600, 1580, 1545, 1290, 1270
11	60–62	$C_{14}H_{20}ClN_5O_2$ (313.8), C: 51.60 (51.70), H: 6.19 (6.18), N: 21.50 (21.52)		326 (M^++1, 18), 279 (100), 224 (40), 209 (18), 173 (13), 126 (52)	1580–1530, 1290–1280
12	62–63	$C_{14}H_{20}ClN_5O_2$ (313.8), C: 51.60 (51.55), H: 6.19 (6.08), N: 21.50 (21.79)		326 (M^++1, 22), 279 (100), 223 (40), 209 (25), 126 (47)	1580–1520, 1290–1260
13	93–94	$C_{15}H_{22}ClN_5O_2$ (315.8), C: 53.01 (53.12), H: 6.53 (6.50), N: 20.61 (20.52)		340 (M^++1, 13), 295 (43), 293 (100), 223 (28), 209 (21), 126 (39)	1570, 1555, 1280–1260
14	89–90	$C_{16}H_{16}ClN_5O_2$ (345.8), C: 55.57 (55.80), H: 4.66 (4.56), N: 20.26 (20.32)		346 (M^++1, 9), 302 (38), 210 (19), 175 (52), 126 (26), 91 (100)	1590, 1560, 1535, 1290–1260, 740, 695
15[e]	166–167	$C_{10}H_{11}ClN_4O_2$ (254.7)	323 (4.09)	254 (M^+, 25), 208 (70), 172 (40), 126 (100)	3310, 3130, 1600, 1580, 1540, 1250, 1215
16	121–122	$C_{11}H_{13}ClN_4O_2$ (268.7), C: 49.17 (48.98), H: 4.88 (4.86), N: 20.85 (20.75)	306 (4.01)	268 (M^+, 7), 238 (20), 222 (100), 186 (89), 126 (78)	3115, 1550, 1255
17[d]	174–175	$C_{10}H_{10}ClN_5$ (235.7)	268 (3.56)	235 (M^+, 45), 234 (65), 200 (25), 126 (75), 84 (100)	3230, 2180, 1600, 1545
18	105–106	$C_{11}H_{12}ClN_5$ (249.7), C: 52.91 (52.88), H: 4.85 (4.69), N: 28.05 (28.12)	268 (3.94)	249 (M^+, 35), 248 (52), 214 (15), 126 (44), 123 (46), 98 (100)	2165, 1600, 1540

[a]Calculated C, H and N compositions with found values in parentheses. [b]In water at 25°C. [c]KBr, ν, cm^{-1}. [d]Ref. 11. [e]Ref. 15.

density at the proton. The chemical shifts for NH of compounds **1** and **15** in $CDCl_3$ and DMSO fell in line with the reported range of the H-bond. In the case of **17**, however, significantly different chemical shifts of the NH proton were observed in both solvents. It is generally acknowledged that both an intra- and intermolecular H-bonding-capable molecule such as nitroanilins is overwhelmingly intramolecularly H-bonded in $CDCl_3$ and intermolecularly H-bonded in DMSO.[23] The lower signal of **17** would be in response to intermolecular H-bonding, while the upfield signal in chloroform does not clarify whether it is an intramolecularly H-bonded proton or a non-H-bonded amine proton. The H-D exchange rates ($\tau_{1/2}$) of these NH protons with D_2O in $CDCl_3$ were about 180 min and 120 min at 10°C for **1** and **15** respectively, and shorter than 5 min for **17**, so the slow reaction for the former two would further support the notion of intramolecular H-bonding, and the spontaneous

Table 2. ^{1}H-NMR Dpectral Data of the Prepared Compounds[a)]

Compd.	2	4	5	CH_2	NCH_2CH_2NR[c)]	R and YZ
1	8.32 (d, J=2.6)	7.70 (dd, J=7.0/2.2)	7.35 (d, J=8.4)	4.55	3.54 (m), 3.83 (m)	8.20 (bs, NH)
1[b)]	8.37 (d, J=2.9)	7.79 (dd, J=8.1/2.9)	7.52 (d, J=8.1)	4.48	3.50 (m), 3.64 (m)	8.95 (bs, NH)
2	8.30 (d, J=2.5)	7.71 (dd, J=8.4/2.5)	7.35 (d, J=8.4)	4.50	3.56 (m), 3.77 (m)	2.97 (s, 3H)
2[b)]	8.30 (d, J=2.5)	7.71 (dd, J=8.4/2.5)	7.35 (d, J=8.4)	4.50	3.56 (m), 3.77 (m)	2.97 (s, 3H)
3	8.32 (d, J=2.5)	7.72 (dd, J=8.4/2.5)	7.36 (d, J=8.4)	4.48	3.58 (m), 3.75 (m)	3.38 (q, J=7.0, 2H), 1.24 (t, J=7.0, 3H)
4	8.32 (d, J=2.5)	7.72 (dd, J=8.2/2.5)	7.36 (d, J=8.2)	4.47	3.58 (m), 3.74 (m)	3.29 (t, J=7.6, 2H), 1.65 (tq, J=7.6/7.3, 2H), 0.94 (t, J=7.3, 3H)
5	8.32 (bs)	7.73 (bs, J=8.0)	7.31 (bd, J=8.0)	4.46	3.58 (m), 3.71 (m)	4.20 (m, 1H), 1.23 (d, J=6.5, 6H)
6	8.31 (d, J=2.6)	7.71 (dd, J=8.4/2.6)	7.35 (d, J=8.4)	4.45	3.58 (m), 3.69 (m)	5.79 (m, 1H), 5.33 (dd, J=1.4/1.1, 1H), 5.30 (d, J=5.1/1.1, 1H), 3.91 (d, J=6.2, 2H)
7	8.32 (d, J=2.6)	7.71 (dd, J=8.0/2.6)	7.36 (d, J=8.0)	4.50	3.61 (m), 3.86 (m)	4.16 (d, J=2.5, 2H), 2.42 (t, J=2.5, 1H)
8	8.31 (d, J=2.6)	7.72 (dd, J=8.0/2.6)	7.36 (d, J=8.0)	4.47	3.56 (m), 3.73 (m)	3.32 (t, J=7.5), 1.59 (m, 2H), 1.34 (m, 2H), 0.93 (t, J=7.4, 3H)
9	8.32 (d, J=2.6)	7.74 (dd, J=8.1/2.6)	7.36 (d, J=8.1)	4.46	3.66 (m), 3.96 (m)	3.95 (m, 1H), 1.54 (m, 2H), 1.22 (d, J=6.9, 2H), 0.91 (t, J=7.3, 3H)
10	8.32 (d, J=2.6)	7.74 (dd, J=8.0/2.6)	7.36 (d, J=8.0)	4.46	3.58 (m), 3.76 (m)	3.16 (d, J=8.7, 2H), 1.96 (m, 1H)
11	8.32 (d, J=2.8)	7.73 (dd, J=8.4/2.8)	7.36 (d, J=8.4)	4.42	3.60 (m), 3.73 (m)	3.31 (t, J=7.7, 2H), 1.61 (m, 2H), 1.31 (m, 4H), 0.90 (t, J=7.1, 3H)
12	8.31 (d, J=2.6)	7.72 (dd, J=8.5/2.6)	7.36 (d, J=8.5)	4.47	3.60 (m), 3.74 (m)	3.33 (t, J=8.0, 2H), 1.4-1.6 (m, 3H), 0.92 (d, J=6.6, 6H)
13	8.31 (d, J=2.5)	7.72 (dd, J=8.0/2.5)	7.36 (d, J=8.0)	4.47	3.57 (m), 3.74 (m)	3.31 (t, J=7.3), 1.6 (m, 2H), 1.3 (m, 6H), 0.88 (t, J=7.0, 3H)
14	8.32 (d, J=1.8)	7.73 (dd, J=7.7/1.8)	7.28 (d, J=7.7)	4.49 (s, 4H)	3.54 (bs, 4H)	7.4 (m, 5H)
15	8.31 (d, J=2.5)	7.59 (dd, J=8.1/2.5)	7.37 (d, J=8.1)	4.33	3.59 (m), 3.81 (m)	8.73 (bs, NH), 6.66 (s, $CHNO_2$)
15[b)]	8.37 (d, J=2.2)	7.77 (dd, J=8.3/2.2)	7.53 (d, J=8.3)	4.49	3.53 (m), 3.65 (m)	8.88 (bs, NH), 6.76 (s, $CHNO_2$)
16	8.33 (d, J=2.5)	7.77 (dd, J=7.7/2.5)	7.35 (d, J=7.7)	4.63	3.57 (m), 3.69 (m)	3.04 (s, 3H), 6.45 (s, $CHNO_2$)
17	8.31 (d, J=2.6)	7.66 (dd, J=7.7/2.6)	7.34 (d, J=7.7)	4.42	3.62 (m), 3.65 (m)	6.73 (bs, NH)
17[b)]	8.34 (d, J=2.2)	7.76 (dd, J=8.2/2.8)	7.52 (d, J=8.2)	4.40	3.32 (m), 3.47 (m)	8.03 (bs, NH)
18	8.31 (d, J=2.4)	7.72 (dd, J=8.2/2.4)	7.35 (d, J=2.4)	4.58	3.36 (m), 3.50 (m)	3.20 (s, 3H)

[a)] δ (ppm), J=Hz; $CDCl_3$ unless otherwise noted. [b)] DMSO-d_6.

Table 3. ^{13}C-NMR Spectrum Data of the Prepared Compounds[a)]

Compd.	2	3	4	5	6	7	9	10	12	R	YZ
1	149.3	129.8	139.1	124.8	151.6	48.5	46.6	42.4	161.3		
1[b)]	149.4	131.5	139.3	124.2	149.2	45.0	44.4	41.5	160.3		
1[c)]	152.9	132.7	142.0	125.3	149.1	{44.4 (broad)}			160.4		
2	149.3	129.3	139.0	124.8	151.7	46.9	44.6	48.7	161.3	34.4	
2[b)]	149.3	130.8	139.3	124.2	149.6	45.7	44.8	48.2	160.8	33.4	
2[c)]	149.8	130.0	141.5	125.2	148.8	{47.4 (broad)}			159.3	32.5	
3	149.3	129.1	139.1	124.8	151.7	45.1	44.8	47.2	160.9	41.9, 11.9	
4	149.3	129.1	139.2	124.8	151.8	45.4	45.0	47.3	161.2	48.4, 20.1, 11.0	
5	149.4	128.9	139.3	124.9	151.8	47.4	45.1	39.9	160.5	47.3, 19.6	
6	149.3	129.0	139.1	124.8	151.7	45.4	44.9	47.2	160.8	130.2, 120.7, 49.8	
7	149.3	128.8	139.1	124.8	151.8	45.2	45.1	47.5	160.4	75.3, 75.0, 36.7	
8	149.3	129.0	139.2	124.9	151.8	45.4	44.9	47.3	161.2	46.7, 28.8, 19.8, 13.6	
9	149.4	129.0	139.3	124.9	151.8	47.4	45.1	39.8	161.2	53.1, 26.8, 17.4, 10.8	
10	149.4	129.0	139.2	124.9	151.8	45.7	45.1	47.5	161.6	53.9, 26.3, 19.8	
11	149.4	129.1	139.2	124.9	151.8	45.5	45.0	47.3	161.2	46.9, 28.6, 26.4, 22.2, 13.9	
12	149.4	129.1	139.2	124.9	151.9	45.5	45.0	47.4	161.2	56.7, 35.4, 25.9, 22.4	
13	149.4	129.1	139.2	124.9	151.9	45.5	45.0	47.3	161.2	47.0, 31.3, 26.8, 26.2, 22.5, 13.9	
14	149.4	129.1	139.2	124.9	151.9	45.1	44.7	47.5	161.2	133.6, 128.9, 128.6, 128.5, 50.7	
15	148.8	129.2	140.5	124.9	151.9	48.5	46.6	42.4	159.4		96.7
15[b)]	149.5	131.3	139.1	124.2	149.1	45.1	42.4	47.9	158.5		95.7
15[c)]	149.5	132.1	141.8	125.5	149.8	{47.5 (broad)}			159.3		95.7
16	149.1	129.9	138.9	124.6	149.0	50.7	47.8	50.1	160.9	35.6	95.4
17	149.3	130.2	138.9	124.7	153.1	46.4	45.2	40.3	164.0		118.5
17[b)]	149.4	131.7	139.3	124.2	149.2	46.2	44.2	40.1	163.4		117.8
18	149.2	130.3	139.0	124.7	151.4	46.4	44.2	47.9	159.1	33.3	116.3

[a)] δ (ppm), $CDCl_3$ unless otherwise noted. [b)] DMSO-d_6 [c)] Solid state.

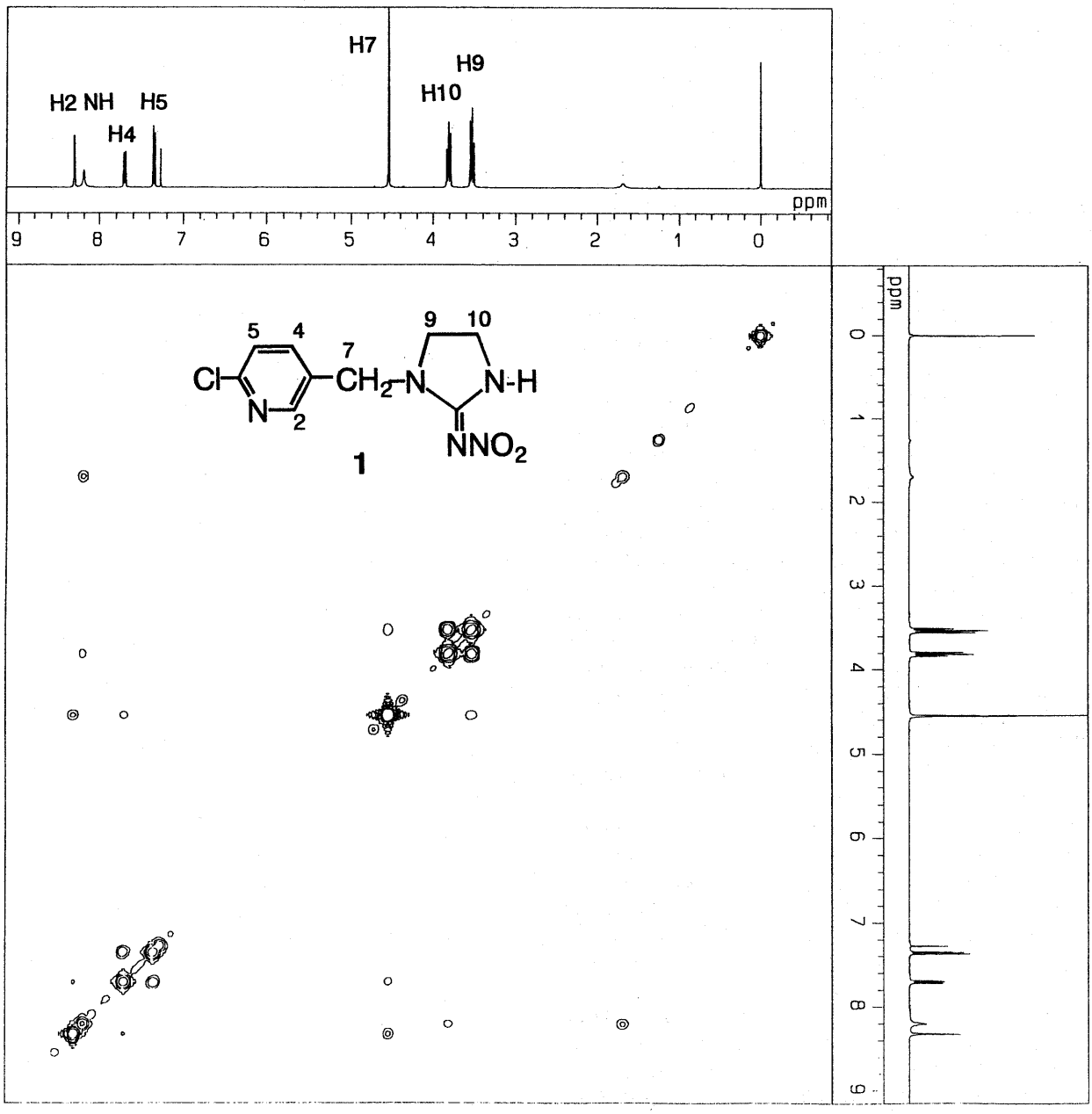


Fig. 5. NOESY Spectrum of Imidacloprid (**1**).
(δ, ppm, $CDCl_3$).

exchange for the latter would suggest the free amine proton.

In crystalline **2**, the N-NO_2 bond is twisted almost perpendicularly from the guanidine [(-N)(-N)C=N-] plane by steric constraints around the guanidine region produced by methylation,[16] and a more crammed situation could be expected in $CHNO_2$ analogue **15**. The electron absorption in water showed, in fact, a hypsochromic shift in the π-π^* absorption of 14 nm for **2** and of 17 nm for **16** from the unsubstituted compounds. On the other hand, cyanoimino compounds **17** and **18** displayed close wavelengths, suggesting that the linear functional group contained would not produce a significant skeletal distortion around the chromophore in the ground state.

The proton and carbon NMR data are summarized in Tables 2 and 3, the chemical shift assignment being performed by using H-H and C-H COSY, and NOESY techniques. The H-H NOESY spectrum of imidacloprid is given in Fig. 5. From the NOE relationships to the C7 protons, the signal at 3.54 ppm was assigned to C9 protons. The C10 protons at 3.83 ppm had NOE correlation to the N-H proton. Interestingly, the chemical shift due to the C7 protons turned out to be closer to the proton in the 2-position on the pyridine ring than to that in the 4-position, indicating that rotamer **ii** is predominated over rotamer **i** under the measuring conditions (Fig. 4). The downfield shifts due to the C10 carbon of *N*-methyl derivatives **2**, **16** and **18** at 48.7, 50.7 and 47.9 ppm in $CDCl_3$ *vs.* those of **1**, **15** and **17** at 42.4, 42.4 and 40.3

ppm, respectively, would have been caused by the α-effect of the introduced methyl group on the *N*-atom, as generally stated for α-alkylation on an aminomethylene moiety.[24,25] The other *N*-alkyl derivatives showed similarly a deshielding resonance, except for isopropyl and *s*-butyl derivatives **5** and **9**, in which the upfield shifts due to the γ-hydrogen effect of these bulky alkyl groups were noted.[25] The ^{13}C chemical shifts in the solid state of compounds **1**, **2** and **15** were not significantly different from those in solutions.

Judging from the confirmed intramolecular H-bonding in the spectra and the supporting crystal structures, unsubstituted molecules of **1**, **15** and **17** would most probably have an *E*-configuration about the exocyclic C=Y axis also in a solution. On the other hand, the recognizable magnitude of the downfield shifts due to C7 in the *N*-isopropyl (**5**), *s*-butyl (**9**) and *N*-methyl nitromethylene (**16**) compounds implicates their geometry being different from that of the unsubstituted compounds. However, although the ^{13}C- and ^{1}H-NMR spectra in the solvents used gave rise to only one set of signals, we are unable to decide the definite configuration of the individual *N*-alkyl derivatives in solution at room temperature, because the rotation barrier about C=C of push-pull olefins is in the range 42–84 kJ/mol,[26,27] so that fast interconversion among rotamers could possibly have taken place. Nevertheless, judging from the crystallography reflecting that even the smallest substituent like a methyl induced steric strain to a considerable extent and from the different spectroscopic features of the methyl derivatives in a solution from the patterns for *E*-configuration that the unsubstituted species possess, we could safely say that C=Y and/or Y–Z would be forced out of an in-plane conformation by appending an alkyl group larger than a methyl to the unsubstituted molecules, so that the fully conjugated network would have been disrupted in these molecules.

The results of the water solubility are puzzling at the first glance (Table 4). The *N*-alkyl derivatives (**2**–**11**) of imidacloprid (**1**) all had greater solubility than imidacloprid, except for the benzyl derivative (**14**). In particular, the methyl (**2**) and ethyl (**3**) derivatives were more soluble by 17 and 11 times, respectively, and the isopropyl (**5**) and *s*-butyl (**9**) derivatives were 9 times more soluble than **1**. Even compound carrying such a long alkyl chain as the pentyl (**11**) derivative recorded greater water solubility.

Molecular size, like the surface area of a nonelectrolytic solute, is taken as one determinant of its water solubility and has been studied by many workers.[14,28–30] This concept considers that the major factor in solubility relationships is the energy required to create a cavity in water into which the solute is placed. The energy needed for this hole formation should be proportional to the molecular size of the solute. In accordance with this, the set of imidacloprid alkyl derivatives show a linear relationship between the logarithms of water solubility (WS) and the surface area (SA) of the alkyl increment, except for three outliers (Fig. 6), and a parallel relationship was also obtained for hydrophobic parameter value Σf.[13] It may not be immediately understandable that the

Table 4. Water Solubility (WS), log *P*, Sum of the Fragmental Constants (Σf) and van der Waals Surface Areas (SA) of the Prepared Compounds

Compound	WS[a]	log *P*	Σf[b]	SA[c]
1	0.49	0.6	0.20	0.57
2	8.36	−0.06	0.70	2.12
3	5.48	0.23	1.23	3.47
4	3.15	0.59	1.75	4.82
5	4.25	0.46	1.64	4.81
6	2.05	0.51	1.46	4.29
7	1.21	0.29	1.04	4.07
8	2.30	1.13	2.28	6.17
9	4.62	0.81	2.17	6.15
10	2.57	0.95	2.17	6.16
11	1.26	1.68	2.81	7.52
12	—[d]	1.52	2.70	7.51
13	—[d]	1.94	3.34	8.87
14	0.34	1.49	2.43	6.98
15	3.58	−0.19	—[e]	—[e]
16	18.20	−0.94	—[e]	—[e]
17	0.55	0.72	—[e]	—[e]
18	1.84	0.82	—[e]	—[e]

[a]Water solubility (g/l). [b]Sum of the hydrophobic fragmental constants of increment R.[13] [c]van der Waals surface area (cm²) of increment R by Bondi.[14] [d]Not measured. [e]Not calculated.

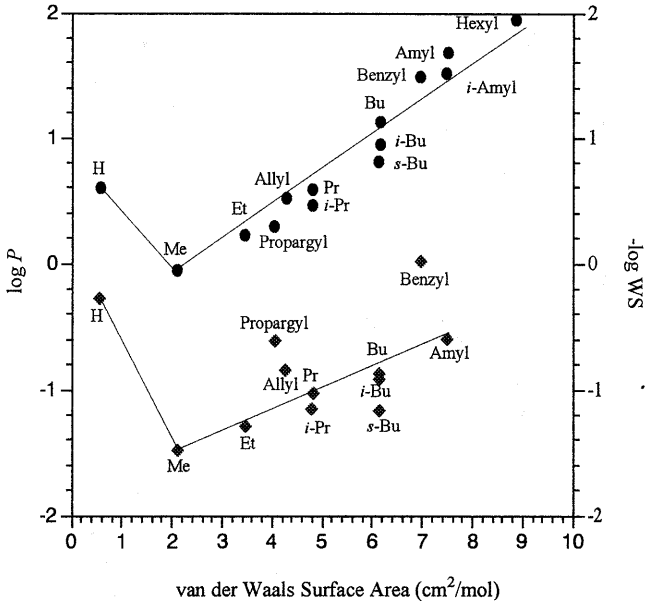
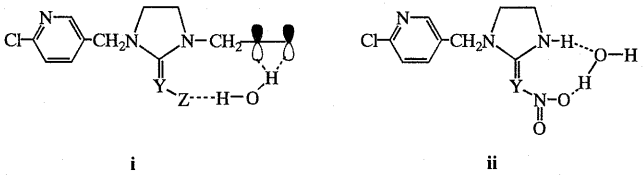


Fig. 6. Relationships of log *P* and Water Solubility with van der Waals Surface Area of Incremental Substituents of *N*-Alkyl Imidacloprids.

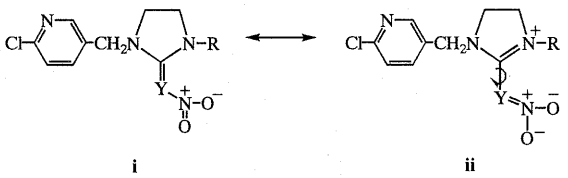
WS, water solubility (mmol/l); ● log *P*; ■ log WS.

outlying allyl (**6**), propargyl (**7**) and benzyl (**14**) derivatives were less soluble in water than predicted from the WS-SA slope, because all these unsaturated fragments can be taken to have rather hydrophilic nature owing to their proton-accepting properties. The unexpected deviations could be rationalized because it has been generally stated[14,28–30] that, during the dissolving process, the forces holding together the solute molecules in a solid gradually disappear, intermolecular interaction of



i ii

Fig. 7. Possible Solute-Water Addition Product (**i**) for Compounds **6**, **7** and **14**, and (**ii**) for Compounds **1**, **16** and **17**.



i ii

Fig. 8. Resonance of Imidacloprid (**1**) and Related Compounds.

nonelectrolites is dominantly exerted by dispersion forces which, in turn, are the result of intermolecular electron correlation, and that these dispersion forces are most noticeable between loose electron pairs such as lone pairs, π lectrons and outer electrons of large atoms. It is conceivable that linear C≡C, a planar benzene ring or C=C would force the molecule in the solid state to self-associate. Alternatively, the phenomenon can be also ascribed to these molecules binding with a limited number of water molecules to form an inclusion product as depicted by **i** in Fig. 7. This cohesive or adhesive interaction would shrink the molecular area exposed to the surrounding solvent molecules and, as a result, greater energy would be needed for dissolving. On the other hand, the linear relationship between the surface area of the alkylated compounds and log *P* was obtained without any apparent outliers (Fig. 6), suggesting that these thermodynamic parameters during fusion of the solid molecules were offset in both phases.

The water solubility of NH compound **1** should be discussed from another viewpoint, considering the conspicuously large deviation from the slope relationship for the *N*-alkyl derivatives. The difference in this molecule from the alkyl derivatives is its extended conjugated makeup with an intramolecular H-bonding facility. A solute molecule bearing localized charge heads would be solvated to a greater extent than the solute where the charge is distributed over tandem atoms. With intramolecular H-bonding, the charge is not located at two incorporated atoms, but rather is spread over the chelated domain, as a decreased dipole moment has been reported for such molecules.[31] It is generally accepted that the behavior of a substance containing intramolecular H-bonds is much closer to that of a non-H bonded substance, which does not involve molecular association, change in molecular polarity, if any, little enhancement of solubility in solvent capable of intermolecular H-bonding.[32]

By referring to the molecular figure for the crystalline *N*-methyl derivative (**2**), the following geometry for the *N*-alkyl derivatives is more likely in a solution in which the C–Y bond is elongated toward a single bond length and the angle R–N(11)–C(12) is increased toward an sp^2 (120°) angle from the sp^3 (109°) angle to lessen the steric strain between R and the nitro oxygen atom. Thus, the molecules can be expected to partake of the nature of the canonical structure **ii** with remote charge heads, where two hydration sites are available, allowing much more hydration than structure **i** in which the charge dispersed which compound **1** dominates (Fig. 8). Additionally, being liberated from the H-bonding yoke, the *N*-alkylated molecules become flexible where rotation about the C–Y axis can occur without any significant restriction. It is a well-documented phenomenon that flexible molecules are more soluble in water than rigid molecules because of weaker packing forces in the crystal.[33]

Water solubility of *N*-methylnitromethylene compound (**16**) was 18.20 g/l. The enhanced solubility compared with 8.36 g/l of nitroimino derivative (**2**) would be ascribed to the sterically crammed skeleton. On the other hand, the solubility was evidently lower for cyanoimine (**17**) where neither an influential intramolecular H-bond nor any significant steric constraint is calculated, and the solubility enhancement by methylation was modest (0.55 g/l and 1.84 g/l for **17** and **18**, respectively).

Our foregoing discussion is based on the results of spectral analyses in solid and nonaqueous media. There may be an argument that intramolecular H-bonding is not prevalent in the bulk of water. Nagy *et al.* have recently addressed the issue of competing intra- and intermolecular H-bonds for organic solutes in an aqueous solution, and advocated the maintenance of the intramolecular H-bond favored over formation of more H-bonds to the water in case of 2-hydroxybenzoic acid and histidine.[34] Alternatively, it is also plausible in molecules capable of intramolecular H-bonding that hydration takes place to form a 1:1 addition product like **ii** (Fig. 7), and such chelation could contribute to reducing the water solubility.[35]

In conclusion, the lower hydrophilicity of imidacloprid and its related unsubstituted nitromethylene and cyanoimine compounds than their *N*-alkyl derivatives was due to the less hydration accommodation in the electron-delocalized conjugated system which could be reinforced by intramolecular H-bonding, whilst the greater water solubility of the *N*-alkyl derivatives is ascribed to the de-coupling of resonance.

Acknowledgments

The authors are indebted to Nihon Bayer Agrochem Ltd. for presenting imidacloprid, to Mr. Haruo Ito of Hitachi Keisoku Engineering Ltd. for measuring the LC-APCI MS spectra, and to Mr. Jun Ashida of Varian Japan Ltd. for measuring the solid state NMR spectra.

References

1) Yamamoto, I. and Tomizawa, M., New development of nicotinoid insecticides. In "Pesticides/Development: Molecular Biological Approaches," eds. Mitsui, T., Matsumura, F., and Yamaguchi, I., Pesticide Sci. Soc. Jpn., Tokyo, pp. 67–83 (1993).
2) Leicht, W., Imidacloprid-a chloronicotinyl insecticide biological

activity and agricultural significance. *Pflanzenschutz Nachr. Bayer*, **49**, 71–84 (1996).
3) Kagabu, S., Study on the synthesis and insecticidal activity of neonicotinoid compounds. *J. Pesticide Sci.*, **21**, 231–239 (1996).
4) Kagabu, S. and Medej, S., Chloronicotinyl insecticides-stability comparison of imidacloprid and related compounds under simulated sunlight, hydrolysis conditions, and to oxygen. *Biosci. Biotech. Biochem.*, **59**, 980–985 (1995).
5) Bai, D., Lummis, S. C. R., Leicht, W., Breer, H., and Sattelle, D. B., Actions of imidacloprid and related nitromethylene on cholinergic receptors of an identified insect motor neuron. *Pestic. Sci.*, **33**, 197–204 (1991).
6) Liu, M.-Y. and Casida, J. E., High affinity of [^{3}H]imidacloprid in the insect acetylcholine receptor. *Pestic. Biochem. Physiol.*, **46**, 40–46 (1993).
7) Nishimura, K., Kanda, Y., Okazawa, A., and Ueno, T., Relationship between insecticidal and neurophysiological activities of imidacloprid and related compounds. *Pestic. Biochem. Physiol.*, **50**, 51–59 (1994).
8) Zwart, R., Oortgiesen, M., and Vijverberg, H. P. M., Nitromethylene heterocycles: selective agonists of nicotinic receptors in locust neurons compared to mouse NIE-115 and BC3H1 cells. *Pestic. Biochem. Physiol.*, **48**, 202–213 (1994).
9) Sone, S., Naghata, K., Tsuboi, S., and Shono, T., Toxic symptoms and effect of a new class of insecticide, imidacloprid, on the American cockroach. *J. Pesticide Sci.*, **19**, 69–72 (1994).
10) Narahashi, T., Neuronal ion channels as the target sites of insecticides. *Pharmacol. Toxicol.*, **78**, 1–14 (1996).
11) Moriya, K., Shibuya, K., Hattori, Y., Tsuboi, S., Shiokawa, K., and Kagabu, S., 1-(6-Chloronicotinyl)-2-nitroiminoimidazolidines and related compounds as potential new insecticides. *Biosci. Biotech. Biochem.*, **56**, 364–365 (1992).
12) OECD guideline for testing of chemicals; No. 105, Water solubility, pp. 1–15 (May 12, 1981).
13) Rekker, R. F., "The Hydrophobic Fragmental Constant," Elsevier, Amsterdam (1977).
14) Bondi, A., "Physical Properties of Molecular Crystals, Liquids, and Glasses," Wiley, New York, Chapter 15 (1968).
15) Kagabu, S., Moriya, K., Shibuya, K., Hattori, Y., Tsuboi, S., and Shiokawa, K., 1-(6-Halonicotinyl)-2-nitromethylene-imidazolidines as potential new insecticides. *Biosci. Biotech. Biochem.*, **56**, 362–363 (1992).
16) Kagabu, S. and Matsuno, H., Crystal and molecular structures of imidacloprid and analogous compounds. *J. Agric. Food Chem.*, **45**, 276–281 (1997).
17) Kato, Y., Environmental science and mass spectrometry (in Japanese). Proc. 13th Symp. Envir. Sci. Pestic. (Kyoto), No. 3, pp. 73–89 (1995).
18) Wennerbeck, I. and Sandström, J., Studies of polarized ethylenes-IV: Barriers to rotation around formal double bonds and formal single bonds in 1,1-bis-dimethylaminoethylenes. *Org. Mag. Res.*, **4**, 783–809 (1972).
19) Kumpler, W. D., The infrared spectra of nitroguanidine and related compounds. *J. Am. Chem. Soc.*, **76**, 814–816 (1954).
20) Horiguchi, H., "Compiled Infrared Spectra Charts" (in Japanese), Sankyo Pub., Tokyo (1973).
21) Gante, J. and Mohr, G., Neue Aminosäure-Derivate. *Chem. Ber.*, **108**, 174–180 (1975).
22) Rajappa, S., Nagarajan, K., Venkatesan, K., Kamath, N., Padmanabhan, V.-M., von Philipsborn, W., Chen, B.-C., and Müller, R., Studies on the streochemistry of 2-(nitromethylene)-heterocycles. *Helv. Chim. Acta*, **67**, 1669–1680 (1984).
23) Axenrod, T. and Wieder, M. J., Nitrogen-15 magnetic resonance spectroscopy. Solvent effects on $^1J(^{15}NH)$ and hydrogen bonding in ortho-substituted anilines. *J. Am. Chem. Soc.*, **93**, 3541–3542 (1971).
24) Jackman, L. M. and Sternbell, S., "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon, Oxford, Chapter 3-2 (1969).
25) Breitmaier, E. and Voelter, W., "Carbon-13 NMR Spectroscopy," VCH, Weinheim, Chapter 4 (1987).
26) Isaksson, G. and Sandström, J., Internal rotations, dipole moments, and ultraviolet spectra of nitroethylenes, experimental results and PPP calculations. *Acta. Chem. Scand.*, **27**, 1183–1191 (1973).
27) Sandström, J., Static and dynamic stereochemistry of push-pull and strained ethylenes. *Topic. Stereochem.*, **14**, 83–181 (1983).
28) Hildebrand, J. H. and Scott, R. L., "The Solubility of Nonelectrolites, 3rd Ed.," Dover Pub., New York, Chapters 2, 3 and 17 (1964).
29) Yalkowsky, S. H., Solubility and solubilization of nonelectrolites. *Drugs Pharm. Sci.*, **12**, 1–14 (1981).
30) Shinoda, K., "Solution and Solubility" (in Japanese), Maruzen, Tokyo, Chapters 2, 6, 9 and 13 (1991).
31) Kvitko, S. M., Perekalin, V. V., Vasil'eva, V. N., Bobovich, Y. S., and Slovokhotova, N. A., Synthesis and structures of derivatives of nitrobutadiene. Dokl. Akad. Nauk SSSR (*English ed.*), **143**, 193–195 (1962).
32) Vinogradov, S. N. and Linnell, R., "Hydrogen Bonding," van Nostrand Reinhold, New York, Chapter 2 (1970).
33) Anderson, B. D., Thermodynamic considerations in physical property involvement through prodrugs. In "Physical Properties of Drugs," eds. Yalkowsky, S. H., Sinkula, A. A., and Valvani, S. C., Marcel Dekker, New York, Chapter 7 (1980).
34) Nagy, P. I., Durant, G. J., and Smith, D. A., Competing intra- and intermolecular hydrogen bonds for organic solutes in aqueous solution. In "Modeling the Hydrogen Bond," ed. Smith, D. A., Am. Chem. Soc., Washington, Chapter 5 (1994).
35) Fujita, T., Substituent effects in the partition coefficient of disubstituted benzenes: Bidirectional Hammett-type relationships. *Prog. Phys. Org. Chem.*, **14**, 75–113 (1983).
36) Kagabu, S. and Akagi, T., Quantum chemical consideration of photostability of imidacloprid and related compounds. *J. Pesticide Sci.*, **22**, 84–89 (1997).