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Conformational Analysis of a Novel Neonicotinoid Insecticide Bearing an Amide Moiety by Molecular Mechanics Calculations

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Abstract

A novel neonicotinoid insecticide, (*E*)-2-{1-[(6-Chloropyridin-3-yl)methyl]-imidazolidin-2-ylidene}-2-cyano-*N*-(2-methylphenyl)acetamide, is known to act on the central nervous system of insects. In this paper its structure was built and *E* and *Z* imidazolidine isomers with respect to the cyano group were obtained by molecular mechanics calculations using the MMFF94s force field included in the Omega software. The title compound isomers, 984 conformers and 4 types of stereoisomers, thus obtained were compared to the experimental data of the X-ray experimental data. The *E* isomer was found to be closer to the structure of the X-ray data.

Keywords: neonicotinoid insecticides, molecular mechanics, conformational analysis, Omega

1. Introduction

Neonicotinoids are the newest of the five major classes of insecticides (the others are chlorinated hydrocarbons, organophosphorus compounds, methylcarbamates, and pyrethroids), and they make up approximately one-fourth of the world insecticide market (Tomizawa & Casida, 2011). The neonicotinoids show reduced toxicity compared to previously used organophosphate and carbamate insecticides. Shinzo Kagabu is the principal discoverer and therefore father of the neonicotinoid insecticides.

They act on the central nervous system of insects and are widely used in agriculture due their broad spectrum activity and low mammalian toxicity (Nishimura et al., 1994; Bai et al., 1991; Wu et al., 2011). As a result of this mode of action, there is little or no cross-resistance to older insecticide classes such as pyrethroids, chlorinated hydrocarbons, organophosphates, and carbamates, for which neonicotinoids are now supplanting for

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insect control on many major crops (Nauen & Denholm, 2005). Neonicotinoid insecticides act as selective agonists at insect nicotinic acetylcholine receptors (Mori et al., 2002).

The distinctive molecular feature of neonicotinoids is an electronegative nitro- or cyanoimino moiety, which is coplanar with the guanidine or amidine plane, yielding electronic conjugation to facilitate partial negative charge flow toward the tip, in this manner enabling hydrogen-bonding and π-stacking with the receptor subsites (Tomizawa et al., 2011). Interestingly, the nitrosoimino (=NNO) analogues retain the receptor potency of the nitroimino compounds, thereby defining the functional tip oxygen. However, the formylimino [=NC(O)H] congeners showed greatly reduced potency. It was stated that the clear potency difference between the two functional groups [=NNO versus =NC(O)H] can be attributable to their pharmacophore orientations. The =NNO tip oxygen substantially faces the descending direction (active form) for H-bonding formation with the subsite. In contrast, the =NC(O)H oxygen possibly takes two flexible directions under biological conditions, that is, the alternative upward oxygen orientation (inactive form) and the active one as with the =NNO tip. Thus, the direction of the oxygen tip presumably determines the binding constant of these pharmacophore types. However, the =NC(O)H moiety can be replaced by extended and hydrophobic substituents, conferring an incentive to explore novel chemotype pharmacophores.

Between neonicotinoids and insect nicotinic acetylcholine receptors electrostatic interactions and possibly hydrogen bond formation are important for the selectivity of these chemicals (Matsuda et al., 2005).

In this paper a conformational study of (*E*)-2-{1-[(6-Chloropyridin-3-yl)methyl]-imidazolidin-2-ylidene}-2-cyano-*N*-(2-methylphenyl)acetamide is performed by molecular mechanics calculations using the MMFF94s force field, the resulted structures being compared to experimental X-ray data (Wu, 2011).

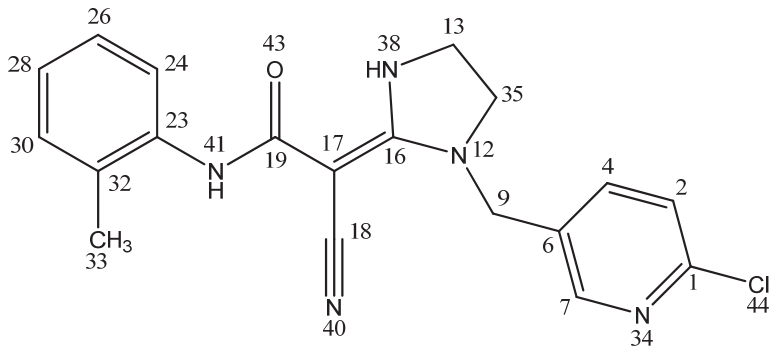

Figure 1. (*E*)-2-{1-[(6-Chloropyridin-3-yl)methyl]-imidazolidin-2-ylidene}-2-cyano-*N*-(2-methylphenyl) acetamide structure

2. Materials and Methods

Monomer structure simulation by OMEGA software

The molecular structure of (*E*)-2-{1-[(6-Chloropyridin-3-yl)methyl]-imidazolidin-2-ylidene}-2-cyano-*N*-(2-methylphenyl)acetamide was modelled by the conformational search ability of the Omega v.2.5.1.4 (OpenEye Scientific Software, Santa Fe, NM. http://www.eyesopen.com) program (Hawkins et al., 2010; Hawkins et al., 2012). Isomeric SMILES notation was used as program input in order to avoid any influences on conformational model generation by presenting 3D seed structures. Omega employs a rule-based algorithm (Tresadern et al., 2009) in combination with variants of the Merck force field 94 (Halgren, 1999).

For the generation of conformers, following parameters were used: a maximum of 400 conformers per compound, an energy cut-off of 10 kcal/mol relative to global minimum identified from the search. The force field used was the 94s variant of the MMFF (Merck Molecular force field) (Halgren, 1999) with coulomb interactions and the attractive part of the van der Waals interactions. The RMSD fit value 0.5 Å was used to avoid redundant conformers.

The root-mean-square-deviation (RMSD) overlay procedure

All conformations in a given ensemble were superimposed on the corresponding unmodified X-ray structure (Wu, 2011) by a least-squares superimposition procedure. Only non-hydrogen atoms were matched.

3. Results and Discussion

Omega generated 984 conformers and 4 types of stereoisomers. The minimum energy conformer obtained for each type is presented in Table 1. Four stereoisomer types of the imidazolidin-2-ylidene-*N*-(2-methylphenyl)acetamide molecular structure, with respect to the ylidene group and N12 imidazolin atom (Figure 1) more stable were obtained: 1*ZS*; 2*ES*; 3*ZR* and 4*ER*. Same lowest molecular energy was noticed in case of two stereoisomers: the 2*ES* and 4*ER* conformers (see Table 1). The energy minimized structures are presented in Figure 2).

According to the RMSD values conformer 2*ES* is the most stable one (Table 1). Small geometric differences can be observed between structures of close energy (Figure 2e and 2f).

Correlations between the torsion angles of experimental X-ray structure and those of the respective conformers were performed by Statistica software (StatSoft, Inc. (2005). STATISTICA (data analysis software system), version 7.1. www.statsoft.com.) in order

Table 1. RMSD values and energy of the lowest molecular energy structures

Conformer	RMS	$E_{MMFF94s}$ (kcal/mol)
1*ZS*	2.449	72.34
2*ES*	0.794	69.86
3*ZR*	2.545	72.36
4*ER*	1.058	69.86

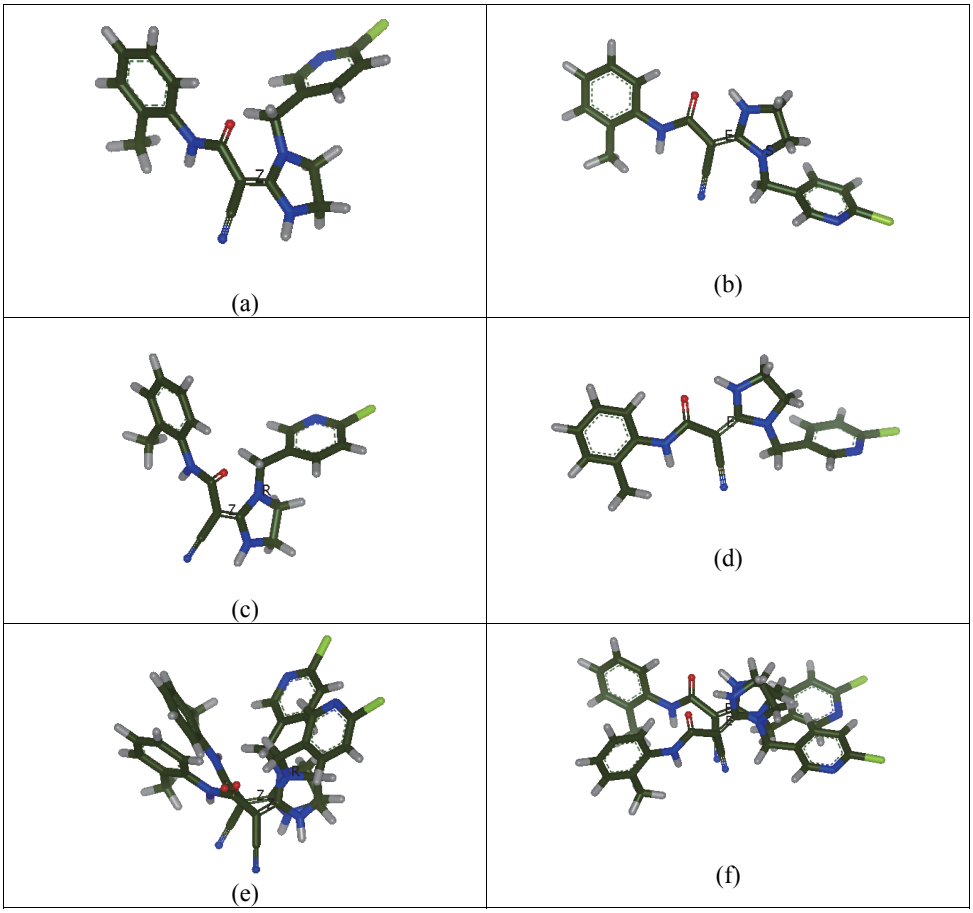

Figure 2. Energy minimized conformers: 1*ZS* (a), 2*ES* (b), 3*ZR* (c), 4*ER* (d), 1*ZS* superposed over 3*ZR* (e), 2*ES* superposed over 4*ER* (f)

to differentiate the minimum energy conformers of close structure. Table 2 presents the torsion angles and the respective statistical parameters.

Correlations of torsion angles between the experimental and computed structures

Table 2. Torsion angles (degrees) of experimental X-ray structure and of the minimum energy conformers*

Torsion angle	X-ray	1*ZS*	2*ES*	3*ZR*	4*ER*
C24C23N41C19	27.2264 (sp)	0.0256 (sp)	0.0256 (sp)	0.0256 (sp)	0.0256 (sp)
C23N41C19C17	170.1082 (ap)	-180.03 (ap)	180.0256 (ap)	180.0256 (ap)	180.0256 (ap)
C23N41C19O43	-8.26 (sp)	0.0256 (sp)	0.0287 (sp)	0.0256 (sp)	0.0256 (sp)
N41C19C17C18	-10.28 (sp)	-90 (-sc)	0.0256 (sp)	-90 (-sc)	-0.0256 (sp)
N41C19C17C16	-179.023 (ap)	89.9137 (+sc)	-180.084 (ap)	89.915 (+sc)	-180.085 (ap)
C19C17C16N38	4.8948 (sp)	-179.9 (ap)	0.0839 (sp)	180.0256 (ap)	0.0772 (sp)
C18C17C16N12	12.53 (sp)	-180.24 (ap)	-0.252 (sp)	-180.1893 (ap)	-0.1912 (sp)
C35N12C9C6	77.1416 (+sc)	-11.23 (sp)	-11.2358 (sp)	-11.5285 (sp)	-11.5285 (sp)
N12C9C6C7	30.8853 (sp)	104.5328 (+ac)	104.5328 (+ac)	104.5402 (+ac)	104.5402 (+ac)
r^2		0.236708	0.8110571	0.0203693	0.810472
SE		85.63	42.6	97.01	42.67
F(1,7)		2.171	30.05	0.146	29.93

* r – correlation coefficient; SE – standard error of estimates; F – Fischer test

indicate similar results for conformers 2*ES* and 4 *ER*. Same information results from the steric arrangements of atoms (see Table 2).

4. Conclusion

Following general structural features were derived from the inspection of the minimized energy structures:

- The *E* stereoisomer type of the imidazolidin-2-ylidene-*N*-(2-methylphenyl)acetamide molecular structure, with respect to the ylidene group and N12 imidazoline atom (Figure 1) was more stable energetically, being in accordance to X-ray experimental data.
- Conformations having the trans form with respect to the ylidene group have similar

steric arrangements of atoms.

- The ylidene group is situated in the same plane with the phenyl and imidazoline rings in the most stable structures.
- Most of the torsion angles including the phenyl ring are of synperiplanar and antiperiplanar type in both experimental structure and most stable conformers.
- One hydrogen bond between the carbonyl oxygen atom (O43) and the hydrogen atom connected to the N38 atom from the imidazoline ring (Figure 1) was noticed in all trans conformations, as well as in the X-ray structure.

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和文要旨

アミド基を有するネオニコチノイド系農薬分子の分子力場計算による立体配座の安定性の解析

鈴木孝弘，Simona FUNAR-TIMOFEI

ネオニコチノイド農薬は、昆虫の神経伝達物質アセチルコリンの受容体に結合し、神経を興奮状態にして方向感覚を狂わせ、筋肉を収縮させて死に至らしめる効果がある。本研究では、アミド基を有するネオニコチノイド農薬である、(*E*)-2-{1-[(6-Chloropyridin-3-yl)methyl]-imidazolidin-2-ylidene}-2-cyano-*N*-(2-methylphenyl)acetamide について，MMFF94s を使った分子力場計算による分子の立体配座の安定性を検討した。X 線構造解析の結果から、シアノ基についてのシス - トランス異性体のうち、*E* 体の方が実際の構造に近いことがわかった。