Analysis of the chemical reactivity of aminocyclopyrachlor herbicide through the Fukui function

LUIS HUMBERTO MENDOZA-HUIZAR*

Universidad Autónoma del Estado de Hidalgo, Área Académica de Química Químicas, Mineral de la Reforma, Hidalgo, C.P. 42186, México

Abstract: The global and local DFT reactivity descriptors were calculated at the MP2/6-311++G (2d,2p) level of theory for aminocyclopyrachlor herbicide in the aqueous phase. Global reactivity descriptors, such as ionization energy, molecular hardness, electrophilicity and total energies, were calculated to evaluate the reactivity of aminocyclopyrachlor. The local reactivity was evaluated through the Fukui function. The obtained results suggest that the cationic and dipolar forms of aminocyclopyrachlor exhibit similar global reactivity and are susceptible to de-amination and decarboxylation. In addition, opening of the ring might become feasible through free radical attacks on the neutral form, while a similar process is caused by nucleophilic attacks on the anionic form.

Keywords: aminocyclopyrachlor; reactivity; Fukui; MP2; PCM.

INTRODUCTION

Rangelands and pastures (RP) are the major source of high quality protein and fat for human beings through the meat obtained from animals that graze thereon.[1–3] However, the incidence of weeds on these RP reduces the grass density, and forage production.[1–3] Weed control on RP is realized with specific herbicides. However, some of these herbicides used to control many forb species in pastures may also injure desirable native grass species.[4,5] In this sense, potassium 6-amino-5-chloro-2-cyclopropylpyrimidine-4-carboxylate (aminocyclopyrachlor), see Fig. 1, is used to control or suppress several broad-leaved weeds and woody plant species in pastures, rangelands and various non-crop sites,[6] with a less injury to the native grasses in comparison to other herbicides.[4] According to EPA, this herbicide poses very low risk to humans, including workers and the general population, due to its low toxicity and low volatility.[7] Moreover, it was reported that an evaluation of the available scientific infor-

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* E-mail: hhuizar@uaeh.edu.mx

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mation found that this herbicide does not present an unacceptable risk to human health or the environment.[8,9] However, the signs of toxicity associated with aminocyclopyrachlor involve decreased body weight, decreased weight gain, decreased food consumption, and decreased food conversion efficiency.[10] The mechanism by which aminocyclopyrachlor causes decreased food conversion efficiency has not yet been clarified.[10] Additionally, it is important to mention that aminocyclopyrachlor is environmentally persistent, soluble in water, non-volatile, and with a low sorption potential. Pesticides with such features tend to move easily through the soil profile into groundwater.[11,12] Hence, extensive application of this herbicide may increase its concentration in the soil and groundwater and thus aminocyclopyrachlor is recognized as having the potential to pollute groundwater.[13–15]
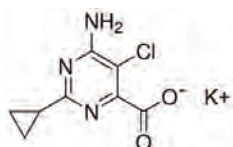

Fig. 1. Potassium 6-amino-5-chloro-2-cyclopropylpyrimidine-4--carboxylate.

Aminocyclopyrachlor slowly degrades by aerobic microbial metabolism with half-lives ranging from 114–433 days in different soils and it is stable to degradation *via* other pathways.[13,16] However, in some cases, this half-life is more related to transport losses from runoff and leaching rather than degradation.[9] Furthermore, the leaching potential of aminocyclopyrachlor is similar to that exhibited by picloram, which is recognized as an emerging water contaminant.[11] Due to its dissociation constant ($pK_a = 4.65$), aminocyclopyrachlor is in the anionic form at typical soil pH levels.[17] Here, it is important to mention that anionic pesticides are generally weakly retained by most soil and sediment components and potentially could reach and contaminate surface and groundwaters.[18,19]

Unfortunately, information on the degradation and metabolic pathways of aminocyclopyrachlor in water is limited, since the main source of information is related to its absorption in soils. Thus, a good understanding of the reactivity of aminocyclopyrachlor would allow the development of efficient degradation methods for its removal from groundwater. To the best of existing knowledge, the reactivity of aminocyclopyrachlor at the molecular level has not hitherto been analyzed. Therefore, in this work, the molecular reactivity of this herbicide is analyzed through the formulation of chemical reactivity based on the density functional theory (DFT).[20] It is considered that this kind of study would contribute to a better understanding of the chemical behavior of this herbicide in aqueous media.

Theory

The formulation of the chemical reactivity theory derived within the framework of the density functional theory has enabled parameters that give information about the general behavior of a molecular system to be defined.[20] These parameters are the electronic chemical potential (μ), the electronegativity (χ) and hardness (η), which can be evaluated through the following equations:[21–26]

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{v(r)} = -\frac{1}{2}(I - A) \tag{1}$$

$$\chi = -\mu \tag{2}$$

$$\eta = \left(\frac{\partial \mu}{\partial N}\right)_{v(r)} = \left(\frac{\partial^2 E}{\partial N^2}\right)_{v(r)} = (I - A) \tag{3}$$

In these equations, E, N and $v(r)$ are the energy, number of electrons and the external potential of the system, respectively. The energy value of the vertical electronic affinity (A) can be calculated as $A = E(N) - E(N+1)$, where $E(N)$ and $E(N+1)$ are the total ground-state energies in the neutral N and the singly charged $(N+1)$ configurations. Moreover, the ionization potential (I) can be calculated as $I = E(N-1) - E(N)$. The chemical potential measures the escaping tendency of an electron and it can be associated with the molecular electronegativity,[27] while η determines the resistance of the chemical species to lose electrons and can be related to the stability and polarizability of the molecular system.[28,29] On the other hand, the global electrophilicity index (ω) is defined as a measurement of the susceptibility of a chemical species to accept electrons and it can be calculated as:[30]

$$\omega = \frac{\mu^2}{2\eta} \tag{4}$$

According to this definition, low values of ω suggest a good nucleophile while higher values indicate the presence of a good electrophile.[30]

Additionally to the global reactivity parameters, it is possible to define local reactivity parameters, which can be used to analyze the reactivity on different sites within a molecule.[31,32] This local reactivity can be evaluated through the Fukui function $(f(\vec{r}))$,[33,34] which is defined as:[35]

$$f(\vec{r}) = \left(\frac{\partial \rho(\vec{r})}{\partial N}\right)_{v(r)} = \left(\frac{\partial \mu(\vec{r})}{\partial v(r)}\right) \tag{5}$$

where $\rho(\vec{r})$ is the electronic density. The Fukui function, Eq. (5), can be evaluated by using a finite difference approximation. However, due to the discontinuity of the electron density with respect to the number of electrons (N), this

approximation leads to three types of Fukui functions for a system, namely, $f^+(\vec{r})$, $f^-(\vec{r})$, and $f^0(\vec{r})$ for nucleophilic, electrophilic, and free radical attacks respectively. These condensed functions can be evaluated as:[31]

$$f^+(\vec{r}) = \rho_{N+1}(\vec{r}) - \rho_N(\vec{r}) \tag{6}$$

$$f^-(\vec{r}) = \rho_N(\vec{r}) - \rho_{N-1}(\vec{r}) \tag{7}$$

$$f^0(\vec{r}) = \frac{1}{2}\left[\rho_{N+1}(\vec{r}) - \rho_{N-1}(\vec{r})\right] \tag{8}$$

However, for studying the reactivity at the atomic level, a more convenient way of calculating the Fukui function is through the condensed forms of the Fukui function for an atom j in a molecule which are expressed as:[31]

$$f_j^+(\vec{r}) = q_{j(N)} - q_{j(N+1)} \tag{9}$$

$$f_j^-(\vec{r}) = q_{j(N-1)} - q_{j(N)} \tag{10}$$

$$f_j^0(\vec{r}) = \frac{1}{2}\left\{q_{j(N-1)} - q_{j(N+1)}\right\} \tag{11}$$

In these equations, q_j is the atomic charge (evaluated from the Mulliken population, electrostatic-derived charge, *etc*.) at the jth atomic site in the neutral (N), anionic (N+1) or cationic (N–1) chemical species.

METHODOLOGY

The optimal conformations of aminocyclopyrachlor chemical species were subjected to full geometry optimization in aqueous phase employing the hybrid functional B3LYP,[36-38] the basis set 6-311++G(2d,2p),[39,40] and the PCM solvation model.[41,42] The optimized geometries in the aqueous phase were re-optimized employing the second order Moller Plesset theory[43] and the basis set 6-311++G(2d,2p). The final atomic charges for aminocyclopyrachlor studied in the aqueous phase were obtained within the framework of the MP2 theory. In all calculations of these atomic charges, the Density=MP2 option was used in order to ensure that the charges were calculated at the MP2 level. All the calculations reported here were performed with the package Gaussian 09,[44] and visualized with the GaussView ver. 3.09 packages.[45]

RESULTS AND DISCUSSION

Aminocyclopyrachlor rapidly dissociates into the acid form (6-amino-5--chloro-2-cyclopropyl-4-pyrimidinecarboxylic acid) with the addition of water at pH 4.65,[46] see Fig. 2a. Furthermore, it is important to consider that in an aqueous environment at pH ≈7, the carboxyl groups are usually deprotonated, meaning they lose an H$^+$ and become negatively charged, see Fig. 2b. Moreover, the nitrogen of the pyrimidine ring can be protonated at pH 1.23 and the protonated and the dipolar forms may exist at acid pH values,[47,48] see Fig. 2c.
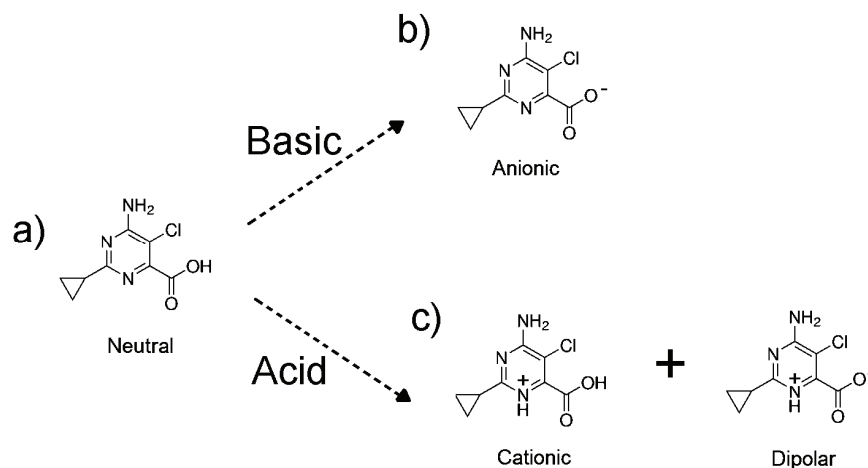
Fig. 2. Chemical species of aminocyclopyrachlor at different pH values.

Under these considerations, the chemical species shown in Fig. 2 were optimized, at the B3LYP/6-311++G (2d,2p) level, in the aqueous phase without any symmetry constraints employing the PCM solvation model. A frequency analysis was applied to the optimized geometries to verify the stability criterion and in all cases, the frequency values were positive and their values were similar to those reported in the literature for pyrimidine.[49] The optimized geometries at the B3LYP/6-311++G (2d,2p) level were re-optimized at the MP2/6-311++G (2d,2p) level. The optimized geometries of the neutral form at the MP2/6--311++G (2d,2p) level are depicted in Fig. 3. Note the existence of two possible conformers for this neutral form in which the cyclopropyl is oriented in a position either *cisoid* (Fig. 3a) or *transoid* (Fig. 3b). The electronic energies for the *cisoid* and *transoid* conformers are –1082.672645 and –1082.672819 hartrees, respectively. Note that there is an energy difference of 0.11 kcal* mol^{-1} between both conformers, which could be expected for two isoenergetic conformers. In addition, the optimized geometries of the anionic, cationic and dipolar forms are reported in Figs. 4–6, respectively. For the anionic, cationic and dipolar forms, the energy differences between the *cisoid* and *transoid* conformers are 0.07, 2.32 and 1.76 kcal mol^{-1}, respectively. These results suggest the existence of two isoenergetic conformers for aminocyclopyrachlor chemical species. However, it is important to mention that a conformer may be converted into another *via* an inversion symmetry operation. Thus, under the Born–Oppenheimer approximation, these conformers must have identical electronic structures and energy and the observed differences may be due exclusively to numerical imprecision.[50]
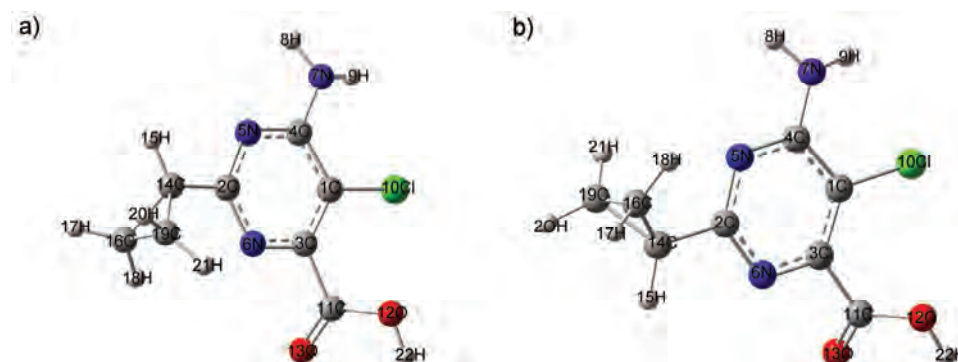
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* 1 kcal = 4186 J

Fig. 3. Neutral aminocyclopyrachlor. a) Bond distances (Å): 1C–10Cl = 1.74, 1C–3C = 1.38 , 3C–11C = 1.50, 3C–6N = 1.34, 11C–13O = 1.21, 11C–12O = 1.34 , 12O–22H = 0.97, 6N–2C = 1.34, 2C–14C = 1.47, 2C–5N = 1.34 , 5N–4C = 1.34 , 4C–7N = 1.36, 7N–8H = 1.01, 7N–9H = 1.01, 14C–15H = 1.08, 14C–16C = 1.52, 14C–19C = 1.52, 16C–19C = 1.50 , 16C–17H = 1.08, 16C–18H = 1.08, 19C–20H = 1.08 and 19C–21H= 1.08, dihedral angles (°): 19C–14C–2C–5N = –145.65 and 6N–3C–11C–13O = 58.43. b) The bond distances were the same as in conformer (a) but the dihedral angles were 19C–14C–2C–5N = –34.80 and 6N–3C–11C–13O = 59.15.
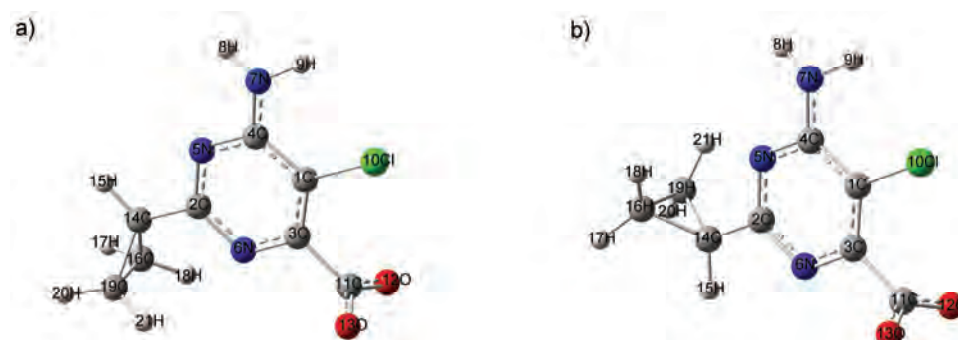

Fig. 4. Anionic aminocyclopyrachlor. a) Bond distances (Å): 1C–10Cl = 1.74, 1C–3C = 1.38 , 3C–11C = 1.52, 3C–6N = 1.35, 11C–13O = 1.26, 11C–12O = 1.26 , 6N–2C = 1.34, 2C–14C = = 1.48, 2C–5N = 1.34, 5N–4C = 1.34 , 4C–7N = 1.37, 7N–8H = 1.01, 7N–9H = 1.01, 14C–15H = 1.08, 14C–16C = 1.52, 14C–19C = 1.52, 16C–19C = 1.50 , 16C–17H = 1.08, 16C–18H = 1.08, 19C–20H = 1.08 and 19C–21H = 1.08, dihedral angles (°): 19C–14C–2C–5N = –145.69 and 6N–3C–11C–13O = 89.76. b) The same bond distances were the same as in conformer (a) but the dihedral angles were 19C–14C–2C–5N = –34.63 and 6N–3C–11C–13O = 89.85.

Global reactivity descriptors

The values of the global reactivity descriptors (μ, η and ω) were calculated at the MP2/6-311++G(2d,2p) level of theory employing Eqs. (1), (2) and (3), respectively, see Table I. From the results reported in this Table, it may be observed that the global hardness of the aminocyclopyrachlor chemical species

increases with increasing pH value. This result suggests an increment in the stability of aminocyclopyrachlor in the aqueous phase in terms of the pH value. In addition, note that the values of μ and ω decrease and increase, respectively. This behavior suggests that the electronegativity and nucleophilic behavior of aminocyclopyrachlor diminishes with increasing pH.
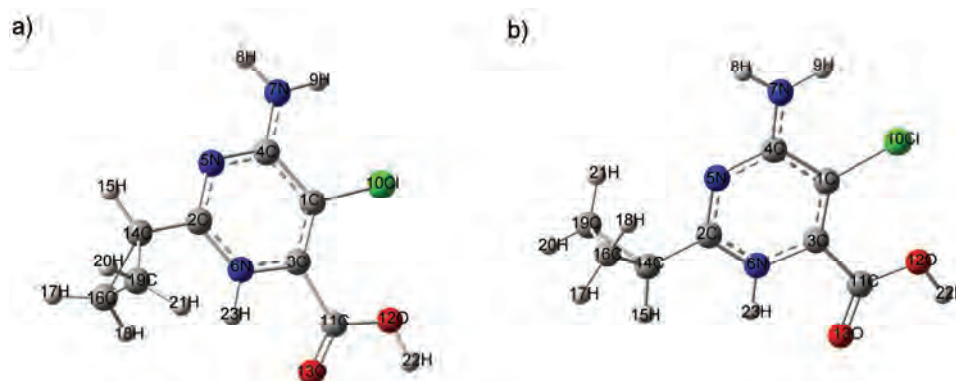

Fig. 5. Cationic aminocyclopyrachlor. a) Bond distances (Å): 1C–10Cl = 1.72, 1C–3C = 1.37 , 3C–11C = 1.50, 3C–6N = 1.36, 6N–23H = 1.02, 11C–13O = 1.22, 11C–12O = 1.33, 12O–22H = 0.97, 6N–2C = 1.35, 2C–14C = 1.46, 2C–5N = 1.32 , 5N–4C = 1.35 , 4C–7N = = 1.32, 7N–8H = 1.01, 7N–9H = 1.01, 14C–15H = 1.08, 14C–16C = 1.52, 14C–19C = 1.52, 16C–19C = 1.50 , 16C–17H = 1.08, 16C–18H = 1.08, 19C–20H = 1.08 and 19C–21H = 1.08, dihedral angles(°): 19C–14C–2C–5N = –145.80 and 6N–3C–11C–13O = –0.004. b) The bond distances were the same as in conformer (a) but the dihedral angles were 19C–14C–2C–5N = –33.42 and 6N–3C–11C–13O = 0.007.
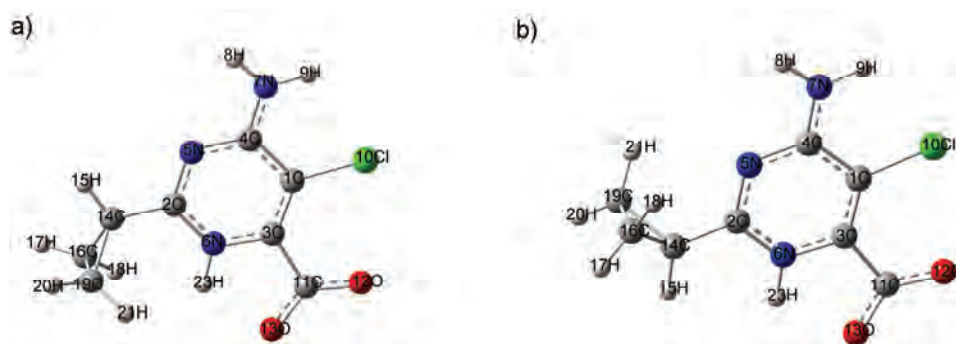

Fig. 6. Dipolar aminocyclopyrachlor. a) Bond distances (Å): 1C–10Cl = 1.72, 1C–3C = 1.37 , 3C–11C = 1.54, 3C–6N = 1.36, 6N–23H = 1.03, 11C–13O = 1.26, 11C–12O = 1.25, 6N–2C = = 1.34, 2C–14C = 1.46, 2C–5N = 1.32 , 5N–4C = 1.35 , 4C–7N = 1.33, 7N–8H = 1.01, 7N–9H = 1.01, 14C–15H = 1.08, 14C–16C = 1.52, 14C–19C = 1.52, 16C–19C = 1.50, 16C–17H = 1.08, 16C–18H = 1.08, 19C–20H = 1.08 and 19C–21H = 1.08, dihedral angles(°): 19C–14C–2C–5N = –145.46 and 6N–3C–11C–13O = –0.008. b) The bond distances were the same as in conformer (a) but the dihedral angles were 19C–14C–2C–5N = –33.69 and 6N–3C–11C–13O = 0.

TABLE I. Global reactivity descriptors for aminocyclopyrachlor chemical species at the MP2/6-311++G(2d,2p) level of theory

Descriptor	I / eV	A / eV	η / eV	μ / eV	ω / eV
Cationic	9.55	3.11	6.44	–3.22	0.80
Dipolar	8.93	2.01	6.92	–3.46	0.86
Neutral	8.48	1.53	6.95	–3.47	0.87
Anionic	7.96	0.51	7.45	–3.73	0.93

Local reactivity descriptors

In order to evaluate the reactivity at atomic resolution, the Fukui function was evaluated through Eqs. (9)–(11). It is well known that the Fukui function allows the determination of the pinpoint distribution of the active sites on a molecule. However, the value of this function is completely dependent on the scheme of charges used. A variety of schemes to evaluate atomic charges has been reported.[42] However, atomic charges derived from the electrostatic potential (*MEP*) have found good acceptance to calculate the condensed Fukui function and good agreement with the experimental results was obtained.[50–52] The values of the Fukui function in terms of *MEP* charges for the *cisoid* and *transoid* conformers of aminocyclopyrachlor in its neutral form are reported in Table S-I of the Supplementary material to this paper. Observe that for neutral *cisoid*-aminocyclopyrachlor, the more reactive sites for electrophilic, nucleophilic and free radical attacks are the 2C, 3C, and 3C atoms, respectively. On the other hand, 7N, 3C, and 6N are the more reactive sites for electrophilic, nucleophilic and free radical attacks respectively in the case of the neutral *transoid*-amino-cyclopyrachlor conformer. Note that even though the *cisoid* and *transoid* conformers are isoenergetic, the local reactivity is different when electrophilic and free radical attacks are considered.

The values of the condensed Fukui function for the anionic, cationic and dipolar forms are reported in Tables S-II–S-IV, respectively. The more reactive sites for neutral, anionic, cationic and dipolar forms are summarized in Table II. From these results, observe that the cationic and dipolar forms are susceptible to de-amination (7N) and decarboxylation (3C). In the neutral *cisoid* form, an elec-

TABLE II. The more reactive sites for aminocyclopyrachlor chemical species; 7N (de-amination), 3C (decarboxylation), 2C (electrophilic substitution), 5N (opening of the ring), 1C (dechlorination), 6N (opening of the ring)

Form	*Cisoid*			*Transoid*		
	Electrophilic	Nucleophilic	Free radical	Electrophilic	Nucleophilic	Free radical
Cationic	7N	3C	7N	7N	3C	7N
Dipolar	7N	3C	7N	7N	3C	7N
Neutral	2C	3C	3C	7N	3C	6N
Anionic	2C	5N	1C	2C	1C	1C

trophilic substitution is expected on 2C and decarboxylation may be caused by either nucleophiles or free radicals by attack on 3C. In the neutral *transoid* form, de-amination, decarboxylation and opening of the ring processes are expected through electrophilic, nucleophilic and free radicals attacks, respectively. At basic pH values, electrophilic, nucleophilic and free radicals attacks on the anionic *cisoid* form would cause electrophilic substitution, opening of the ring and dechlorination, respectively. For the anionic *transoid* form, electrophilic substitution is expected through electrophilic attacks, while dechlorination process may be caused by either nucleophilic or free radicals attacks. These results suggest that a degradation process that involves the opening of the ring might be feasible through free radical attacks to the neutral *transoid* form and nucleophilic attacks on the anionic *cisoid* form. Theoretical analyses of the possibility of more reactive free radicals and nucleophiles to open the pyrimidine ring are beyond of the scope of this paper, however they will be analyzed in future works.

CONCLUSIONS

In the present work, DFT reactivity descriptors for aminocyclopyrachlor herbicide in the aqueous phase were calculated. The cationic and dipolar forms of aminocyclopyrachlor showed similar values of the global reactivity parameters, which is indicative of equivalent global chemical behavior under acid aqueous conditions. Under these acid conditions, the values of the Fukui function suggest that attacks by free radicals and electrophiles on 7N would cause a de-amination process, while a nucleophilic attack would cause decarboxylation. For the neutral form, nucleophilic and free radical attacks would cause a decarboxylation process, while electrophilic substitution is expected on 2C. The neutral *transoid* form is susceptible to de-amination, decarboxylation and opening of the pyrimidine ring through electrophilic, nucleophilic and free radical attacks, respectively. At basic pH values where the anionic form of aminocyclopyrachlor is predominant, the *cisoid* form is susceptible to electrophilic substitution (2C), opening of the ring (5N) and dechlorination (1C). On the other hand, the *transoid* form would be vulnerable to electrophilic attacks on 2C, and a possible dechlorination through nucleophilic and free radical attacks on 1C.

SUPPLEMENTARY MATERIAL

Values of the condensed Fukui function, Tables S-I–S-IV, are available electronically from http://www.shd.org.rs/JSCS/ or from the corresponding author on request.

ИЗВОД

АНАЛИЗА ХЕМИЈСКЕ РЕАКТИВНОСТИ ХЕРБИЦИДА АМИНОЦИКЛОПИРАХЛОР ПОМОЋУ ФУКУИЈЕВЕ ФУНКЦИЈЕ

LUIS HUMBERTO MENDOZA-HUIZAR

Universidad Autónoma del Estado de Hidalgo, Área Académica de Química Químicas, Mineral de la Reforma, Hidalgo, C.P. 42186, México

Израчунати су глобални и локални DFT реакциони дескриптори за хербицид ами-ноциклопирахлор на MP2/6-311++G (2d,2p) нивоу теорије у воденој фази. Глобални реакциони дескриптори су енергија јонизације, молекулска тврдођа, електрофилност и укупна енергија. Локална реактивност је процењена помоћу Фукуијеве фунције. Доби-јени резултати указују на то да катјонске и диполарне форме аминоциклопирахлора имају сличну глобалну реактивност, и подлежу деаминовању и декарбоксилацији.

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