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DFT Study of Dimerization Sites in Imidazo[1,2-a]pyridinyl-chalcone Series

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Abstract

Quantum chemistry methods were performed in order to characterize the chemical reactivity on series of imidazo[1,2-a]pyridinyl-chalcone (IPC). In particular, the B3LYP/6-311G(d) theory level has been used to determine parameters which characterize the global and local reactivity on five molecules of the series. These compounds differ from one to another with the aryl groups. There are: 1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)-3-phenylprop-2-en-1-one, 3-(4-fluorophenyl)-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)prop-2-en-1-one, 3-[4-(dimethylamino)phenyl]-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)prop-2-en-1-one, 3-(2,4-dichlorophenyl)-1-(2-methylimidazo[1,2-*a*] pyridin-3-yl)prop-2-en-1-one, 3-(2,4-dichlorophenyl)-1-(2-methylimidazo [1,2-*a*]pyridin-3-yl)prop-2-en-1-one. All results lead to finding out that local nucleophilicity and electrophilicity of compounds are not substituent-dependant contrarily to their global nucleophilicity which prove to be more sensitive to the electron-donating character of the substituents. 3-[4-(Dimethylamino) phenyl]-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)prop-2-en-1-one was identified as the unique nucleophile compound by global reactivity. Respectively, the carbon atoms C_5 and C_{14} are the prediction sites of electrophilic and nucleophilic attacks in the molecular skeleton of both molecules. Identification of interactions centres on IPC series is of great importance for organic synthesis and medicinal chemistry where the molecular hybridization strategy is very often used to improve biological activities of interesting therapeutic systems.

Keywords

Chemical Reactivity, Conceptual DFT, Imidazopyridinyl-Chalcone, Nematicidal Activity, Quantum Chemistry

1. Introduction

Chalcones bring together a plethora of natural and synthetic compounds, within

which a keto-ethylenic system links two aromatic nuclei (aryl and/or heteroaryl rings) [1] from the carbon atom in β-position and that of the carbonyl function. This family of compounds arouses great interest in various fields of applications. Their true importance is based on the wide spectrum of biological activities [2] [3] [4] and on the many synthetic perspectives offered by their skeleton. The biological activities displayed by these compounds are mainly linked to the functional group *enone* [5] as well as to the electronic nature of the nuclei A and B due to the substituents [6] [7] [8] [9]. Imidazopyridinyl-chalcones (IPC) [10] are synthetic chalcones obtained with imidazo[1,2-a]pyridine as ring A and an aryl as ring B. Imidazopyridine nucleus is the building block in the design of several drugs [11]. In the majority of cases, chalcones have biological activities similar to those of imidazopyridine and derivatives. Undoubtedly, the chalcones carrying imidazopyridine nucleus prove to be potential sources of more biologically active molecules due to the possible conjugation effects of the two entities involved. Imidazopiridinyl-chalcones showed high nematicidal activities against drug-resistant strains of nematodes [10]. Their remarkable therapeutic properties against cancer [12] and certain bacteria [13] are also reported. These biological potentials coupled with the possible molecular diversity define a pharmacological dynamic profile which, increasingly, motivates studies of physicochemical characterizations [14] [15] and structure-activity relationships [16] in IPC series. Also, like most chalcones, the compounds IPC are susceptible to addition reactions [17]. Molecular dimerization based on the IPC entities is therefore a path that deserves serious attention for the development of novel therapeutic agents which could be probably stronger and less toxic. However, any reaction to be carried out requires precise knowledge of the chemoselectivity, the stereoselectivity and the regioselectivity. In this area, the tools of quantum chemistry and quantum theories of chemical reactivity are of great help in predicting and justifying the different selectivity. Among the theories developed and validated, nucleophilicity and electrophilicity concepts have proven to be solid in the study of molecular reactivity [18] [19] [20] [21] [22]. The different parameters defined by these concepts are global and local. In this work, we are interested in five molecules from the IPC series; four of which are substituted from the IPC nucleus by varying the aryl substituents. In **Table 1**, these compounds are summarized with their respective nematicidal potential pLC_{100}.

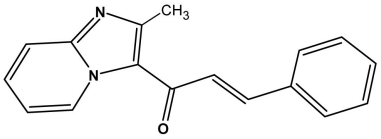
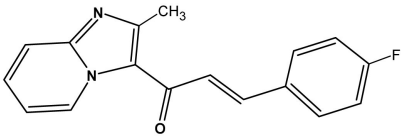
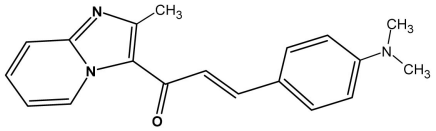
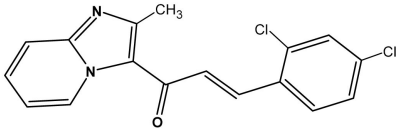
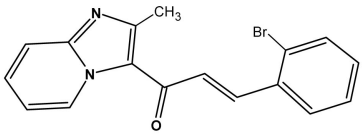
The nematicidal potential pLC_{100} was evaluated following the expression:

$$pLC_{100} = -\log_{10}\left(\frac{LC_{100}}{M} * 10^{-3}\right) \quad \text{(i)}$$

where M (in g/mol) is the molecular molar mass and LC_{100} (in µg/mol), the lowest concentration of tested compound that completely blocked the development of 100% of *Haemonchus contortus* larvae [12].

Depending on the chemistry family of substituent directly linked to carbon in the aryl, the substituted compounds could be divided into two groups: amino group (*Chalc*3) and halogen group (*Chalc*2, *Chalc*4, *Chalc*5). Moreover, the

Table 1. Molecular structures of the studied imidazo[1,2-a]pyridinyl-chalcones.

Code	Molecules	pLC_{100}
*Chalc*1		2.79
	1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)-3-phenylprop-2-en-1-one	
*Chalc*2		8.15
	3-(4-fluorophenyl)-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)prop-2-en-1-one	
*Chalc*3		8.78
	3-[4-(dimethylamino)phenyl]-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)prop-2-en-1-one	
*Chalc*4		8.82
	3-(2,4-dichlorophenyl)-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)prop-2-en-1-one	
*Chalc*5		8.23
	3-(2-bromophenyl)-1-(2-methylimidazo[1,2-*a*]pyridin-3-yl)prop-2-en-1-one	

different substituents of the aryls (Table 1) are electron-withdrawing by inductive effect or electron-donating by mesomer effect. Furthermore, according to the difference in electronegativity between two fragments engaged in a chemical bond, the fragment rich in electrons because of its electron-withdrawing power is directed towards an electrons poor site while the other electrons deficient fragment points to a site in excess of electrons. They are, respectively, the nucleophilic fragment and the electrophilic fragment. Thus, a chemical bond is made by a nucleophile and its reaction partner (electrophile). Therefore, the very useful chemical concept of electrophilicity and nucleophilicity help the chemist in this quest to rationalize the electronic aspect of reactivity, selectivity and the effect of substituents in a reaction. Moreover, the different nematicidal potentials reflect the effect of substitution on activity in the IPC series. By implementing the methods of quantum chemistry, this work consists in determining the physicochemical properties that characterize the global and local chemical reactivity of five molecules of the IPC series as well as the influence of the aryl substituent. The aim is to identify, for all molecules, the preferential nucleophilic and

electrophilic interaction favourite sites of the IPC nucleus not only to the formation of a covalent bond but also to the protection of the pharmacophore with a view to dimerization in IPC series.

2. Calculation Methods

Several theories have been developed for the study of chemical reactivity. In this work, we have used the indices and descriptors that characterize the reactivity of IPC molecules either isolated (global reactivity: static indices) either in interaction with others molecules (local reactivity: dynamic indices). The concepts of global and local reactivity make it possible to elucidate the main questions of relative reactivity, between molecules or between atoms, of the same molecule. All the reactivity parameters used come from the conceptual DFT [23].

2.1. Static Indices of Overall Reactivity

The calculations related to the global hardness (η) and global electrophilicity index (ω) in the Koopmans approximation using the energies of the frontier molecular orbital HOMO and LUMO [24] [25] according to the expressions below:

$$\mu = \frac{E_{\text{HOMO}} + E_{\text{LUMO}}}{2} = -\chi \quad \text{(ii)}$$

$$\eta = \frac{E_{\text{LUMO}} - E_{\text{HOMO}}}{2} \quad \text{(iii)}$$

$$\omega = \frac{\mu^2}{2\eta} \quad \text{(iv)}$$

These global reactivity descriptors make it possible to rationalize the possible movements of transfer and/ or acquisition of electrons by the isolated molecules. The nucleophilicity of the molecules was defined by calculating the relative nucleophilicity index N [26] [27]. The nucleophilicity scale used is that proposed by Domingo *et al.* [28], referenced in relation to the tetracyanoethylene (TCE) molecule and defined by the relation:

$$N = E_{\text{HOMO}}(\text{IPC}) - E_{\text{HOMO}}(\text{TCE}) \quad \text{(v)}$$

By taking into account their different classification scales, the use of global electrophilicity and nucleophilicity indices makes it possible to solve the problem of compounds which can be both good nucleophiles and good electrophiles.

2.2. Dynamic Indices of Reactivity

The determination of the reactivity sites of the different IPC molecules was based on the Fukui indices calculated according to the method of the approximation of finite differences:

$$f_k^+ = q_k(N+1) - q_k(N) \quad \text{(vi)}$$

$$f_k^- = q_k(N) - q_k(N-1) \quad \text{(vii)}$$

$q_k(N), q_k(N-1), q_k(N+1)$ are the atomic net charges of the site K^{th} in the

neutral, cationic and anionic forms, respectively, of each IPC molecule. f_k^+ and f_k^- are used to identify the most favourable sites for nucleophilic attack and electrophilic attack, respectively. The electrophilic or nucleophilic character of a reactive site is great when the value of the Fukui function is high. However, a site can be both a good nucleophile and a good electrophile. In this case, the ambiguity is removed by determining the canonical dual descriptor, Δf_k, on the one hand. This canonical reactivity descriptor results from the difference between f_k^+ and f_k^- such as $\Delta f_k = f_k^+ - f_k^-$ [29]. The sign of Δf_k defines the reactivity character of the site. A site of the molecule whose electrophilic power is predominant will give a positive value; in the case of a predominant nucleophilic power, Δf_k will be negative. On the other hand, the local reactivity difference index R_k proposed by Chattaraj *et al.* [30] is also used. The values of this index make it possible to characterize the nature of the electrophilic or nucleophilic or ambiphilic power of a site within an organic molecule. The sign + or − or ± which precedes the R_k values indicates, respectively, an electrophilic or nucleophilic or ambiphilic character of the considered site *k*. The character is all the stronger the higher the absolute value of R_k. All these physicochemical parameters constitute, on the whole, solid bases for predicting chemical reactivity in IPC series, both qualitatively and quantitatively. Their determinations can only be made in the fundamental state of each of the molecular species studied, respectively. In this context, all geometry optimization calculations are followed by those of frequencies. The calculations of the electronic structures are carried out with the help of the Gaussian09 software [31] using the DFT method by its functional B3LYP and the functions basis 6-311G(d) implemented in the program. The global reactivity parameters are determined only for the IPC molecules when the local reactivity parameters have concerned both the molecules and their respective ionic states.

3. Results and Discussion

The frequencies calculation which followed the geometric optimization of each molecule IPC made it possible to note the absence of imaginary frequency in all the corresponding Hessian matrices. This confirmed that each geometry of structure obtained, at B3LYP/6-311G (d) level, characterizes the fundamental state of the molecule IPC. All the chemical reactivity parameters, for each molecule, have been determined in this state.

3.1. Study of Global Reactivity

Table 2 presents the energies of the frontier orbital (FO), HOMO and LUMO, as well as the energy gaps ΔE such that $\Delta E = E_{\text{LUMO}} - E_{\text{HOMO}}$ of the molecules IPC studied are highlighted.

We observe a particularly demarcation between FOs levels of the *Chalc*3 compound and those of the other compounds. With reference to the unsubstituted molecule *Chalc*1, the FOs of the amino-aryl derivative (*Chalc*3) are all

Table 2. Energy values (in eV) of frontier molecular orbital of the studied imidazo[1,2-a]pyridinyl-chalcones.

Molécules	E_{HO}	E_{BV}	ΔE_{gap}
*Chalc*1	−6.078	−2.265	3.813
*Chalc*2	−6.125	−2.322	3.802
*Chalc*3	−5.334	−1.892	3.442
*Chalc*4	−6.201	−2.525	3.678
*Chalc*5	−6.147	−2.272	3.874

higher in energy; those of halo-aryl derivatives (*Chalc*2, *Chalc*4 and *Chalc*5) are all lower. Generally, electron-donor substituent increases in the energy level of HOMO or LUMO unlike electron-withdrawing substituent which decreases in the energy level of these frontier orbitals. Substituents of the different aryl groups all have a double electronic effect, *i.e.* attractor by inductive effect and donor by mesomer effect. Consequently, in *Chalc*3, the electron-donor nature of dimethylamine is predominant over its electron-withdrawing nature. This observation is in accordance with the rule in organic chemistry which retains the primacy of the mesomer effect over the inductive effect in the event of a double electronic effect of a substituent. However, in the compounds *Chalc*2, *Chalc*4 and *Chalc*5, this rule is taken in default: the inductive effects of halogens appear to be predominant over their mesomer effects. Taking into account these observations, the substituted molecules can be divided into two groups according to the nature of the electronic effects exerted by the substituents. There is the set of compounds *Chalc*2, *Chalc*4 and *Chalc*5 whose substituents affected compound *Chalc*1 by an electron-withdrawing effect and the second group consisting of compound *Chalc*3 which is marked by an electron-donor effect. Moreover, HOMO or LUMO energies constitute precious indicators for comparing electron-donor or electro-acceptor powers, in a series of molecules. *Chalc*3 displays the higher HOMO energy value (−5.334 eV); it is the best electron-donor. *Chalc*4, which has the lowest LUMO energy (−2.525 eV), is the best electron-acceptor in the series. In the case of *Chalc*4, there are two chlorine atoms attached to the aryl group. This suggests that the higher the number of halogens on nucleus B, the stronger the overall electro-acceptor character. In addition, the electronic configurations of the atoms which constitute IPC molecules indicate that they are Lewis bases. They are therefore structurally electron-donor. The influence of the aryl substituent on this naturally electron-donor character was highlighted from the deviations of the HOMO energies. Figure 1 shows the diagram established according to the values of the HOMO energy variations in relation to the unsubstituted compound *Chalc*1.

The diagram illustrates well the electronic effect of each substituent in the aryl group. On the electron-donating scale, ternary amines are far more electron-donor by resonance than halogens, which are very much less electron-donors. The electron-donating power of the studied molecules is then strong when the aryl

Figure 1. Evolution diagram of HOMO energy of IPC.

substituent is a good electron-donor but very weak when the substituent is a strong electron-withdrawing agent. For example, in the case of halo-aryl compounds (*Chalc*2, *Chalc*4, *Chalc*5), the negative values ΔE_{HOMO} clearly reflect the strong attenuation of the electron-donating character due to the presence of halogens and the tendency of the molecules rather towards the global electro-accepting character. Under these conditions, the compounds *Chalc*2, *Chalc*4 and *Chalc*5 become more susceptible to attack a nucleophile. The compound *Chalc*3 could play the role of electron-donor in IPC intermolecular interactions. Therefore, if we calculate the differences in energies according to the relationship:

$$\Delta E_{Chalc3\to Chalci} = E_{\text{LUMO}}^{(Chalci)} - E_{\text{HOMO}}^{(Chalc3)}, i = 2,4,5 \quad \text{(viii)}$$

the sequence of evolution in increasing order of the strength of intermolecular interactions coded $\text{IPC}_{3\to i}$, between *Chalc*3 and another IPC (*Chalci*), is presented as follows:

$$\text{Interaction} : \text{IPC}_{3\to 1} < \text{IPC}_{3\to 5} < \text{IPC}_{3\to 2} < \text{IPC}_{3\to 4} \quad \text{(ix)}$$

The strongest predicted interaction $\text{IPC}_{3\to 4}$, is associated with an energy difference of 2.809 eV with the substituted molecule *Chalc*4 and that of lesser force, $\text{IPC}_{3\to 1}$, with an energy difference of 3.069 eV implies the unsubstituted molecule *Chalc*1. In fact, polar interaction is all the stronger when the energy difference between nucleophile and electrophile is small. In the case of molecules in the IPC series, any substitution carried out at the level of the aryl group is always favourable to the strengthening of the nucleophilic-electrophilic interactions. The nucleophilic and electrophilic characters of the substituted compounds are then rationalized using the global nucleophilicity and electrophilicity indices. The values of electronegativity χ, of hardness η and of the global electrophilicity ω and nucleophilicity indices N are reported in **Table 3**.

According to the values in **Table 3**, two evolution trends can be defined by following the substituted compounds with reference to the unsubstituted compound *Chalc*1. Either the characterized chemical property is improved or it is degenerated under the substitution effect. Thus, the lowest values displayed by *Chalc*3 in the cases of electronegativity and global hardness show that the substituent dimethylamine not only decreased in the ability of the molecule to attract electrons, but also made it more flexible to the deformation of its electronic cloud in an electric field. This is all the more true because the compound *Chalc*3, identified as the best electron-donor, has the highest global nucleophilicity index (N = 3.879 eV) and the lowest global electrophilicity index (ω = 3.792 eV). In the

Table 3. Values of the global reactivity indices of the studied imidazo[1,2-a]pyridinyl-chalcone.

Molecules	χ	η (eV)	ω (eV)	N (eV)
***Chalc*1**	4.172	1.907	4.564	3.135
***Chalc*2**	4.224	1.902	4.690	3.088
***Chalc*3**	3.613	1.721	3.792	3.879
***Chalc*4**	4.363	1.838	5.178	3.012
***Chalc*5**	4.210	1.938	4.573	3.066

same way, the compound *Chalc*4, best electro-acceptor, displays the higher values of the global electrophilicity (ω = 5.178 eV) and electronegativity (χ = 4.363) indicating a great susceptibility of the latter to attract surrounding electrons. According to the general analysis, the halo-aryl derivatives have their values of electronegativity and of global electrophilicity higher than those of the unsubstituted compound *Chalc*1. Furthermore, their global nucleophilicity values all lower than those of *Chalc*1, confirm the electron-withdrawing effect exerted by the halogens. The sequences of evolution of the indices in the ascending order of the electrophilic and nucleophilic powers of the compounds are established, respectively, as follows:

$$\omega : Chalc3 < Chalc1 < Chalc5 < Chalc2 < Chalc4 \quad \text{(x)}$$

$$N : Chalc4 < Chalc5 < Chalc2 < Chalc1 < Chalc3 \quad \text{(xi)}$$

Analysis of these evolution sequences shows that they are related to the LUMO and HOMO energies evolution orders, respectively. In fact, the electrophilic character becomes stronger and stronger when the LUMO energy is weaker and weaker, unlike the strength of the nucleophilic character which increases with the HOMO energy. This result is very interesting, especially since the energies of the frontier orbital are regularly associated with the electron-donating and electro-accepting powers of the compounds. Thus, for the IPC molecules, the energies of the LUMO and HOMO are presented as good descriptors of their electrophilic and nucleophilic powers, respectively. The compounds IPC are therefore ambiphilic. This character indicates that they aren't only nucleophilic by nature but they have a non-negligible electrophilic character also, especially under the effect of substitution with halogens. In fact, apart from the compound *Chalc*3, the electrophilicity indices of the compounds *Chalc*2, *Chalc*4 and *Chalc*5 are all higher than their respective nucleophilicity indices. For these derivatives, the difference between these indices, which ranges from 1.507 eV (*Chalc*5) to 2.166 eV (*Chalc*4), is very significant whereas it is only 0.077 eV with *Chalc*3. The electrophilic character of compounds *Chalc*2, *Chalc*4 and *Chalc*5 is predominant over their nucleophilic character. The study of reactivity by the global approach of IPCs has made it possible to highlight the relative reactivity of molecules. However, although the global reactivity criteria provide information on the behaviour of a chemical species in its entity, the local

reactivity criteria remain very important for the study of the reactivity and selectivity trends of specific sites within a molecule. The local reactivity approach therefore makes it possible to clearly identify the privileged atoms by which a molecule will establish the bonds during molecular interactions. In the case of this study, the isodensity maps relating to the frontier orbitals (HOMO, LUMO) of the different molecules clearly indicate that the HOMO is located mainly on the imidazopyridine nucleus when the LUMO is largely around of the keto-ethylenic system. This therefore supposes that the probable transfer of the electron density takes place from the atoms of the imidazopyridine nucleus to the atoms which constitute the keto-ethylenic system.

3.2. Study of Local Reactivity

In this study, the interest was focused on the heavy atoms of the basic skeleton of imidazo[1,2-a]pyridinyl-chalcone derivatives. Figure 2 shows the numbering of the atoms in the molecules considered.

The analysis of the isodensity maps of HOMO and LUMO, respectively, allowed identifying the potential interaction sites in the compounds studied. From one molecule to another, the atoms which contribute highly to frontier orbital formation stay the same. In fact, the largest lobes characterize the highest electron density in the case of HOMO and the lowest electron density in the case of LUMO, around the atom implicated. On the maps of HOMOs, the four largest lobes contain the carbon atoms C_2, C_6, C_7, C_9, C_5 and the nitrogen N_3. All of these atoms are the likely nucleophile sites in IPCs. On the maps of LUMOs, the carbon atoms C_{11}, C_{13} and C_{14} which belong to the two largest lobes are the likely electrophile sites. Figure 3, related to the compound *Chalc*1, allows illustrating these observations.

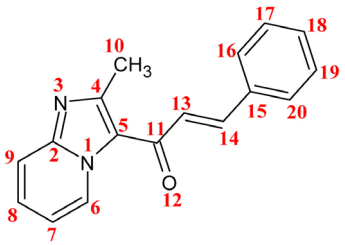
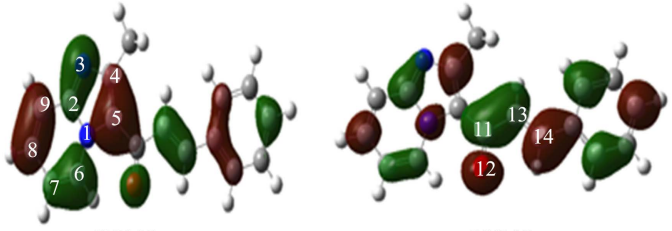


Figure 2. Numbering of the atoms in the basic structural skeleton of imidazo[1,2-a]pyridinyl-chalcones.



HOMO *LUMO*

Figure 3. Isodensity maps of HOMO and LUMO of the compound *Chalc*1.

Regarding the site C_{11}, it belongs to the carbonyl bond, the presence of which is very useful for the manifestation or even the preservation of the biological properties of chalcones. Thus, the different atoms whose reactivity has been demonstrated are the atoms C_2, C_7, C_8, C_9, C_5, C_{13}, C_{14} and N_3 of the imidazo[1,2-a]pyridinyl-chalcone nucleus.

The local reactivity indices of all of the interaction sites are determined according to Fukui theory. Their tendency to behave like an electrophile or a nucleophile will be estimated by following the nature of electrons movement caused by the aryl substituents. In Table 4, the different values of the dual index Δf_k,

Table 4. Local reactivity indices of the interaction sites within the molecules of imidazo[1,2-a]pyridinyl-chalcones calculated at B3LYP/6-311G (d) level.

	atoms	C_{14}	C_2	C_{13}	C_8	C_9	C_7	N_3	C_5
	Δf_k	+0.077	+0.031	−0.007	−0.014	−0.043	−0.056	−0.080	−0.195
*Chalc*1	f_k^+	+0.131	+0.039	+0.040	+0.066	+0.007	+0.014	+0.024	−0.039
	f_k^-	+0.054	+0.008	+0.047	+0.080	+0.050	+0.070	+0.104	+0.156
	R_k	+0.428	+0.153	±0.165	±0.276	−0.124	−0.156	−0.218	−0.667
	atoms	C_{14}	C_2	C_{13}	C_8	C_9	C_7	N_3	C_5
	Δf_k	+0.083	+0.032	−0.007	−0.013	−0.044	−0.055	−0.079	−0.192
*Chalc*2	f_k^+	+0.133	+0.039	+0.041	+0.066	+0.005	+0.014	+0.024	−0.039
	f_k^-	+0.050	+0.008	+0.048	+0.079	+0.049	+0.069	+0.102	+0.153
	R_k	+0.469	+0.158	±0.170	±0.277	−0.126	−0.147	−0.205	−0.655
	atoms	C_{14}	C_2	C_8	C_7	C_9	C_{13}	N_3	C_5
	Δf_k	+0.157	+0.027	+0.017	−0.048	−0.014	−0.091	−0.028	−0.100
*Chalc*3	f_k^+	+0.141	+0.039	+0.067	+0.014	+0.008	+0.019	+0.024	−0.036
	f_k^-	−0.016	+0.016	+0.049	+0.032	+0.023	+0.110	+0.052	+0.062
	R_k	+0.597	+0.086	±0.222	−0.071	−0.570	±0.249	−0.112	−0.377
	atoms	C_{14}	C_2	C_{13}	C_8	C_9	C_7	N_3	C_5
	Δf_k	+0.049	+0.029	+0.028	−0.021	−0.043	−0.058	−0.084	−0.201
*Chalc*4	f_k^+	+0.108	+0.035	+0.056	+0.059	+0.008	+0.013	+0.023	−0.039
	f_k^-	+0.058	+0.006	+0.028	+0.080	+0.016	+0.072	+0.108	+0.163
	R_k	+0.384	+0.163	+0.205	±0.273	−0.113	−0.150	−0.204	−0.693
	atoms	C_{14}	C_2	C_{13}	C_8	C_9	C_7	N_3	C_5
	Δf_k	+0.053	+0.030	+0.022	−0.021	−0.045	−0.060	−0.087	−0.201
*Chalc*5	f_k^+	+0.115	+0.037	+0.049	+0.063	+0.007	+0.014	+0.022	−0.039
	f_k^-	+0.062	+0.007	+0.028	+0.083	+0.052	+0.074	+0.109	+0.167
	R_k	+0.336	+0.147	+0.138	±0.271	−0.129	−0.163	−0.233	−0.690

of the Fukui functions f_k^+ and f_k^- and of the local reactivity difference index R_k obtained for each of these atoms within the molecules are reported. The listed atoms are ordered (from left to right) according to the decrease in the values of the dual index Δf_k so considered either in a decreasing order of their nucleophilic reactivity or in an increasing order of their electrophilic reactivity, within each molecule considered.

The dual reactivity index $\Delta f_k = f_k^+ - f_k^-$ is one of the very precious and useful parameters for rationalizing the sensitivity of a site within a given molecule to an electrophilic or nucleophilic attack, especially when this site displays a double tendency of reactivity. Also, based on the indices analysis, Δf_k and R_k, the sign provides information on the charge inequalities between nucleus and electronic cloud and, consequently, on the predominant reactivity of site k within the molecule. According to **Table 4**, and considering all five molecules of the series, the higher Δf_k values are observed for the carbon atom C_{14} followed closely by the nitrogen atom N_3 when the lower values are found with the atoms of carbon C_2 and C_5, within each molecule. Concerning the atom C_{14}, the Δf_k values are all positive, thus showing that this atom has a great susceptibility to increase its electronic density in the event of electrons gained by the molecule. C_{14} is then an electron deficient site and its reactivity is therefore very strong towards a nucleophile. Moreover, the Fukui function f_k^+ which makes it possible to highlight the electrophilic reactivity of a site relatively to a nucleophilic attack displays its highest values with the atom C_{14} whatever the molecule. Regarding the atom C_5, the Δf_k negative values reflect its susceptibility to have a high electron density even if the molecule loses electrons; it is then rich in electrons and therefore the most reactive centre towards an electrophile. Also, the higher values of the Fukui function f_k^- recorded at this site, whatever the substitution, corroborate this observation. Consequently, the carbon atoms C_{14} and C_5 constitute, in the order, the most reactive electrophilic and nucleophilic centres, in the IPC series. All the sites k with positive values of Δf_k and R_k indicate the potentially electrophilic centres, while the negative values characterize the potentially nucleophilic centres, within the molecules. Thus, analysing Δf_k and R_k values, in the decreasing order of electrophilic reactivity, the site C_2 directly follows the site C_{14} when the site N_3 occupies the second place of nucleophilic reactivity after the site C_5, in the decreasing order, on all the molecules. Indeed, and particularly within the compound *Chalc*3, although $\left|\Delta f_{C_{13}}\right| = 0.091 > \left|\Delta f_{C_7}\right| = 0.048$ indicates a higher nucleophilic reactivity of C_{13} relatively to C_7, the value $R_k = \pm 0.249$ eV for atom C_{13} rather reflects a no less stable nucleophilic behaviour. In fact, the value $R_k = \pm 0.249$ eV is characteristic of an ambiphilic site, *i.e.* which behaves as both nucleophile and electrophile. This result agrees with the local chemical reactivity in α, β-unsaturated keto-ethylenic systems where the localization of π electrons due to conjugation keep the α-position carbon C_{13} in the same ethylenic environment; this carbon atom doesn't lose or gain electrons during the movement of electrons. Another notable remark concerns the R_k values for site C_8. Another remarkable observation is the ± sign which pre-

cedes all the R_k values for C_8 site, on all of the studied molecules. The presence of this sign reveals that the carbon C_8 is an ambiphilic site within the compounds IPC. In addition, the inductive and resonant effects exerted by the substituents attached to the aryl nuclei can possibly influence the sensitivity to attack of the predicted privileged sites C_5 and C_{14}. The sense of influence on the reactivity of the sites is then highlighted for the best prediction of intermolecular interactions in the IPCs series. The comparative study was carried out based on the local reactivity difference index R_k. The higher the absolute value of the index R_k of site k, the greater the activation of the site nucleophilicity. At the C_5 site, the evolution sequence observed in ascending order of the absolute values of this index is presented below:

$$\left|R_{C_5}\right| : Chalc3 < Chalc2 < Chalc5 < Chalc4 \quad \text{(xii)}$$

Absolute indices of the halo-aryl compounds IPC are all higher than that of the amino-aryl compound IPC. Thereby, the nucleophilic reactivity of the site C_5 within the molecules IPC is higher in the presence of halogens. This sequence of evolution is opposite to that of global nucleophilicity for these same compounds. The nucleophilic character of the site C_5 is more and more strengthened when the compound IPC becomes less and less nucleophilic. The high nucleophilicity of the site C_5 within a molecule is therefore not directly linked to the high nucleophilicity of the molecule. The best electron-donor compound in the series, *Chalc*3, has the weak electron-donor nucleophilic site C_5 while the best electro-acceptor compound in the series, *Chalc*4, has the best electron-donor nucleophilic site C_5. Consequently, substitution with a group having a strong electron-donating character proves unfavourable to the nucleophilic reactivity of site C_5. For example, in the case of *Chalc*3, the substituent group of dimethylamine (strongly electron-donor) caused the nucleophilicity of the site to regress by around 43.48% compared to 1.80% in *Chalc*2 with fluorine (weakly electron-donor).

As regards the electrophilic site C_{14}, considering the index R_k values, the increasing order of electrophilic reactivity within the different molecules is:

$$\left|R_{C_{14}}\right| : Chalc5 < Chalc4 < Chalc2 < Chalc3 \quad \text{(xiii)}$$

This sequence of evolution for the electrophilic reactivity of the site C_{14} within the compounds IPC is not in agreement with the evolution of the global electrophilic behaviour of the studied molecules. However, it seems to correspond to the nucleophilic behaviour evolution of these compounds. The highest electrophilic reactivity of the site C_{14} is recorded with the best nucleophilic compound *Chalc*3 in the series when the weakest is found with *Chalc*5, a less nucleophilic compound. Consequently, substitution on the aryl nucleus with a strongly electron-donating fragment is favourable to strengthening the ability of the electrophilic site C_{14} to bind to a nucleophilic site. For example, the improving effect of the electrophilic reactivity of C_{14} is around 39.49% with dimethylamine compared to 9.58% with fluorine, by substitution.

Furthermore, a structure-activity study was undertaken according to the local reactivity descriptors of the identified preferential sites C_5 and C_{14} and the nematicidal potentials of the molecules. In general, no clearly established relationship could be identified with the series of five molecules. However, with the subgroup of halo-aryl derivatives, (*Chalc*2, *Chalc*4 and *Chalc*5), structure-activity relationships are revealed. The sites C_5 and C_{14} evolution sequences were therefore analysed relatively to that of nematicidal potentials of the compounds. Higher nematicidal potential corresponds to the more biologically active molecule against *Haemonchus contortus* larvae. The nematicidal activity sequence of evolution following the increasing values of nematicidal potentials pLC_{100} can be defined as below:

$$pLC_{100} : Chalc2 < Chalc5 < Chalc4 \quad \text{(xiv)}$$

The above sequence is opposite to that of the global nucleophilicity N in the subgroup of halogenated derivatives of IPC. In other words, in the series of halogenated IPCs, a weaker global nucleophilic character leads to better nematicidal molecule. Regarding the sites reactivity within the halogenated derivatives, the sequences of evolution according to the increasing values of local difference reactivity index R_k and Fukui positive function f_k^+ are presented, respectively:

$$\left|R_{C_5}\right| : Chalc2 < Chalc5 < Chalc4 \quad \text{(xv)}$$

$$f_{C_{14}}^+ : Chalc4 < Chalc5 < Chalc2 \quad \text{(xvi)}$$

The evolution sequences (xv) and (xvi) are opposite to each other. However, the first is similar to that of nematicidal activity. In this case, the nematicidal activity increases with the sensitivity of the site C_5 towards an electrophile site. In the second case, more the halogen strengthens the electrophilicity of the site C_{14}, less the nematicidal activity of the molecule is strong. In other words, the nematicidal activity of IPCs becomes strong as the sensitivity of the site C_{14} to a nucleophile becomes weaker and weaker. Therefore, under the substitution effect, the strength of the electrophilic nature of carbon atom C_{14} appears as a modulating parameter of the nematicidal activity in the IPCs series.

Moreover, the substitution effects on the nucleophilicity of nitrogen atom N_3 have been demonstrated. Previous studies reported that atom N_3 was the preferential site for protonation as well as for hydrogen bonding in the IPC series [14] [15]. In the present study, this nitrogen atom appears as the only heteroatom among the potential sites of reactivity identified. And, it is the second best nucleophilic centre of reactivity within the studied substituted IPCs. Its nucleophilic character is therefore of particular importance for the intermolecular interactions involving IPC molecules. In the increasing order of Fukui negative function f_k^- values, the sequence of evolution for the nucleophilic reactivity of nitrogen N_3 is the following:

$$f_{N_3}^- : Chalc3 < Chalc2 < Chalc4 < Chalc5 \quad \text{(xvii)}$$

*Chalc*3 is the IPC derivative with dimethylamino-aryl while the compounds

*Chalc*2, *Chalc*4 and *Chalc*5 belong to the halo-aryl group. Thereby, the above sequence indicates that halogens better promote the nucleophilic character of nitrogen in the IPCs series by the substitution. Nevertheless, the sequence (xvii) of evolution for the nucleophilic character of the site N_3 is in the opposite direction to that of the electrophilic character of the site C_{14} (xiii) defined following the index R_k values. This fact means that any substitution which reinforces the nucleophilic character of nitrogen N_3 disadvantages the electrophilic character of the carbon C_{14}. Such a phenomenon is therefore beneficial to the improvement of the nematicidal activity in the IPC series.

All of these observations are very interesting. They could help in the implementation of strategies for improving nematicidal properties in the IPC series.

4. Conclusion

The chemical reactivity of the compounds in imidazo[1,2-a]pyridinyl-chalcone series is predictable by quantum chemistry methods using conceptual DFT reactivity descriptors. In this series, the effects of substitution on the determined parameters of chemical reactivity are notable especially at the molecular level. On the one hand, the determination of the global descriptors made it possible to show that the presence of electron-donor substituent reinforces the nucleophilic nature of the imidazo[1,2-a]pyridinyl-chalcone compounds. The molecule 3-[4-(dimethylamino)phenyl]-1-(2-methylimidazo[1,2-a]pyridin-3-yl)prop-2-en-1-one has been identified as the most reactive towards electrophilic molecule among the five molecules in the series. On the other hand, the presence of electron-withdrawing substituents such as halogens makes the imidazo[1,2-a] pyridinyl-chalcone compounds more sensitive to nucleophilic molecule attacks. The molecule 3-(2,4-dichlorophenyl)-1-(2-methylimidazo[1,2-a]pyridin-3-yl)prop-2-en-1-one was identified as the most reactive towards any nucleophilic molecule. However, based upon nucleophilicity and electrophilicity index scales, calculations predicted an ambiphilic behaviour of molecules in imidazo[1,2-a]pyridinyl-chalcone series. Thus, these compounds can participate in polar reactions as well as electrophile and nucleophile. From a local point of view, the Fukui indices have made it possible to identify the two preferential nucleophilic and electrophilic centres of interaction for these molecules. The carbon C_5 of the imidazo[1,2-a]pyridine nucleus which is directly linked to the carbonyl carbon has been identified as the more potential nucleophilic centre. The carbon C_{14}, in β-position in the keto-ethylenic system was designated as the more potential electrophilic centre. From one molecule IPC to another, the electrophilic or nucleophilic natures as well as the order position of these two preferential sites were independent of the substituents nature and electronic effects. Therefore, in attractive intermolecular interactions in the IPC series, the most likely bond will be established between carbon atoms C_{14} and C_5, regardless of the molecules. This observation was of capital importance in the sense that the formation of dimers based on the IPCs obeyed the same mode of connection

whatever the substitution on the aryl group. Finally, the structure-activity analysis revealed that the inactivation of the electrophilic character of the site C_{14} by substitution on the B nucleus or by formation of a bond with this site would be favourable for improving the IPC series. The results of this study provide an interesting basis for the study of dimerization in the IPC series.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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