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Theoretical Study of Reactivity Based on the Hard-Soft/Acid-base (HSAB) in Isatoic Anhydride and Some Derivatives

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Abstract. In order to utilize the great chemical potential of isatoic anhidryde (ISA) as a precursor of several derived products, it was most important to determine its molecular reactivity. To this end, we have carried out theoretical calculations on ISA and some of its derivatives by using density functional theory (DFT), MP2, HF levels of theory with a correlated augmented basis set aug-cc-pvDZ. The B3LYP/aug-cc-pvDZ level yielded theoretical results that correlated very well with the experimental work. We used this method to get the global and local descriptors with Koopman's approximation, taking into account two main ISA structural components: the aromatic and heterocyclic systems. The Fukui functions were calculated on the formalism of the quantum theory of atoms in molecules (QTAIM) which is a method for condensation. These theoretical calculations allow to study the electron-withdrawing or donating substituent of the aromatic ring. The results showed that, globally, the most reactive compound is ISA with the OCH_3 substituent. Locally, it is confirmed that C2 is the molecular region most susceptible to suffer a nucleophilic attack against ISA.

Key words: Isatoic anhydride (ISA), molecular reactivity, Fukui functions, nucleophilic attack, electrophilic attack.

Resumen. Con la finalidad de utilizar el gran potencial químico del anhídrido isatoico (ISA) como precursor de varios derivados, es importante determinar su reactividad molecular. En ese sentido, llevamos a cabo cálculos teóricos del ISA y algunos de sus derivados usando métodos de la Teoría de Funcionales de la Densidad (DFT), MP2, HF con bases de correlación aumentadas aug-cc-pvDZ. El método B3LYP/aug-cc-pvDZ proporcionó resultados teóricos que correlacionaron muy bien con el trabajo experimental. Utilizamos este método para obtener los descriptores globales y locales con la aproximación de Koopman, tomando en cuenta dos componentes estructurales del ISA: los sistemas aromático y heterocíclico. Las funciones de Fukui fueron calculadas con base al formalismo de la teoría cuántica de átomos en moléculas (TCAEM) que es un método para condensación. Estos cálculos teóricos permitieron estudiar sustituyentes electrodonadores y electroatractores en el anillo aromático. Los resultados mostraron que, globalmente, el compuesto más reactivo es ISA con el sustituyente OCH_3. Localmente, se confirmó que C2 es la región molecular más susceptible de sufrir un ataque nucleofílico en relación al ISA.

Palabras clave: Anhidrido isatoico (ISA), reactividad molecular, funciones de Fukui, ataque nucleofílico, ataque electrofílico.

Introduction

Isatoic anhydride (*2H* 3,1–benzoxacin-2,4 (*1H*)-dione, ISA) is an organic compound that has been used for several years [1-3]. The great importance of this compound is in the organic synthesis field due to its physicochemical properties, which have been very well exploited, therefore, we find a great number of patents related to this system, mainly in the industrial field where it is applied for manufacturing agrochemicals, desiccants, paints, fragrances and drug products, among others [4-6]. Recently, in biological research, this compound has been used as an agent for clinical diagnosis [7], and several derivatives with antimicrobial activity have been synthesized from it [8]. One can find very complete reviews in the literature relating to ISA [5-6] and its derivatives regarding their heterocyclic structures (Figure 1).

The chemical advantages shown by ISA as a precursor of a great amount of derivatives lie mainly in its capacity to react through two fundamental mechanisms: a) the reaction of the aromatic ring at C8 toward electrophilic attack, if this position is available, or at C10 if it is occupied by another atom or functional group, and b) the reactivity of the oxirane ring toward nucleophilic attack in the carbon base of the carbonyl group C2, generally losing a CO_2 group. A third place where a reaction can occur is at the N atom, due to its electronic properties.

According to published literature, ISA is an important precursor of several compounds. Unlike its experimental counterpart, it has been little studied using theoretical models.

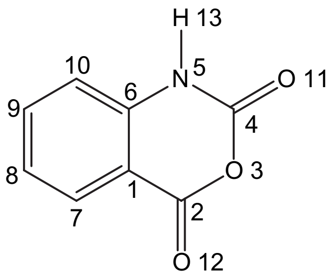


Fig 1. Chemical structure of ISA

We found only two reports in literature: one for determining the aromatic character of ISA [9], realized under the Density Functional Theory (DFT) at B3LYP/6-311G** level of theory, and another for determining its isomerizing energy [10], realized through a level of theory B3LYP and two bases type Pople 6-31G* and 6-311G*. In computational chemistry tools, the DFT offers the fundamentals for interpreting multiple chemical concepts used in different branches of chemistry. In particular, the quantification of descriptors associated with chemical reactivity, like hardness, softness and the Fukui functions [11-15] permits us to make use of powerful methodologies for studying the molecular reactive sites of interest in both organic and inorganic chemistry fields. Global hardness and softness [16-20] characterize the reactivity of a molecule as a whole. On the other hand, local descriptors like the Fukui condensed functions [21], together with local softness, make it possible to quantify the local reactivity of an atom within its molecular surroundings.

Pearson's principle about the hard-soft acid base concept (HSAB) [20, 22-24] indicates that hard-hard and soft-soft interactions are more likely to occur than hard-soft interactions [25-27]. Again it has been found that soft-soft interactions are preferred at the site where the Fukui function has its maximum value [28-30]. On the other hand, hard-hard interactions are more likely to occur at the site where the Fukui function has its minimum value [31-33].

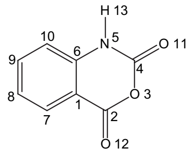
The object of the present study is to carry out a theoretical study on the gaseous phase of the ISA structure to identify its chemical reactivity, using the common methods of quantum chemistry (DFT, MP2, HF) in order to explore the theoretical-experimental consistency that will enable us to understand its versatility as a precursor compound. For that purpose and for comparison, we are also conducting a study of the reactivity of diverse compounds obtained from isatoic anhydride which have electrodonating and electron-withdrawing subtituents in the aromatic ring system.

Results and Discussion

Table 1 shows the values of energy and the optimized and representative linking lengths with the different theoretical methods. The last column corresponds to experimental data. The chemical model B3LYP/aug-cc-pvDZ produces the optimized geometry with the least energy: -588.40 a.u., whereas with RHF/aug-cc-pvDZ we obtained the greatest energy: -585.02 a.u. With the method MP2/aug-cc-pvDZ, all the calculated values of the linking lengths are estimated by excess.

Table 2 shows statistical measurements for the calculated values in Table 1. We include the RMS, mean, absolute mean and maximum errors with respect to the experimental value. We observe that the lowest RMS corresponds to the RHF calculation; however the difference between it and the greatest error, which corresponds to MP2, is 0.007 Å. The distribution of estimates above and below corresponds to RHF and reflects on the magnitude of the mean error. Both B3LYP and MP2 tend to estimate above; therefore, the highest mean errors, 0.024 and 0.029 Å, correspond to them, respectively.

Table 1. Optimized values of the linking lengths (Å) of isatoic anhydride (ISA).



	RHF	LSDA	B3PW91	PBE	B3LYP	MP2	EXP[38]
ENERGY(a.u)	-585.02	-585.25	-588.18	-587.76	-588.40	-586.82	
O3-C2	1.368	1.391	1.397	1.391	1.404	1.409	1.399
O3-C4	1.345	1.367	1.370	1.366	1.376	1.387	1.352
C4-N5	1.362	1.369	1.373	1.371	1.377	1.379	1.342
C6-N5	1.384	1.374	1.384	1.383	1.389	1.395	1.393
C1-C2	1.470	1.473	1.466	1.464	1.469	1.476	1.454
C4-O11	1.182	1.206	1.204	1.202	1.205	1.214	1.213
C2-O12	1.178	1.204	1.201	1.199	1.202	1.211	1.188
N5-H13	0.996	1.020	1.011	1.010	1.011	1.015	0.850
C1-C7	1.396	1.396	1.401	1.399	1.404	1.410	1.406
C7-C8	1.379	1.385	1.388	1.386	1.390	1.400	1.389
C8-C9	1.397	1.399	1.402	1.401	1.405	1.412	1.379
C9-C10	1.382	1.387	1.390	1.389	1.393	1.402	1.389
C10-C6	1.394	1.396	1.400	1.399	1.403	1.409	1.392

Table 2. Statistical data obtained from Table 1 for values of linking lengths calculated with different theoretical methods: RMS error, mean error, absolute mean error, and maximum error.

	RHF	LSDA	B3PW91	PBE	B3LYP	MP2
RMS ERROR	0.045	0.051	0.048	0.048	0.049	0.052
MEAN ERROR	0.007	0.017	0.018	0.016	0.022	0.029
ABSOLUTE MEAN ERROR	0.024	0.025	0.022	0.022	0.024	0.029
MAXIMUM ERROR	0.146	0.170	0.161	0.160	0.161	0.165

Tables 3 and 4 shown the data corresponding to the calculated values of linking angles and to the quantified errors, respectively. In this case, the lowest RMS error of 0.887 corresponds to the calculation made with the B3LYP functional and the highest error with RHF. The evaluation of the linking angles MP2 shows a high symmetry in the estimates above and below, having the lowest mean error of 0.050. The smallest maximum errors correspond to B3LYP and MP2, both methods with maximum errors of 1.6. The greatest maximum errors of 2.0 correspond to RHF and the LSDA functional.

Table 5 shows the values of the global indexes of reactivity, the hardness η, the chemical potential μ and the global softness s. An extra column is added with Hammett's constant σ, an experimental parameter whose value was taken as the criterion for the selection of the substituent used in this study, considering that Hammett's constant characterizes the electronic properties of the diverse substituents [34]. Thus, the negative values are associated with electron-donating species and the positive ones with electron-withdrawing species, so on that scale, the value of Hammett's constant for the compound without a substituent (hydrogen) has been assigned the value of zero.

From the values of global chemical hardness, η, shown in Table 5, it can be seen that the ISA with NO_2 as substituent is the least reactive one in this series of compounds and at global level, having a value of hardness of 5.333. On the other hand, when the substituent is the most electron-donating one, OCH_3, the value of hardness characterizing the globally most reactive compound is 4.639, the lowest of all those studied. The values of global softness, calculated as 0.5 of the reciprocal of hardness, show the same qualitative behavior upon identifying, just as with hardness, the same compounds as the most and least reactive. In accordance with these values calculated for global hardness and softness, it is possible to order the global molecular reactivity in the following manner: $OCH_3 > CH_3 > Br > H > Cl > NO_2$.

Upon analyzing the chemical potential, on the other hand, the tendency observed is that the compound with the most electron-donating substituent has the highest chemical potential, -4.149 eV for OCH_3, in respect to the compound with no substituent taken as reference with a value of -4.435 eV. When the substituent is electro-withdrawing, the chemical potential decreases to -4.979 eV for NO_2, and a relation of reciprocal qualitative behavior is noted between Hammett's constant and the chemical potential. The chemical potential values calculated indicate electron-donating or withdrawing properties as expected, for example, the presence of electron-donating groups decreases the chemical potential, whereas that of electron-withdrawing groups increases the electronegativity in comparison with ISA without a substituent. In addition, it is also observed that the function of the substituent in this family of compounds is that it distinguishes the electron-withdrawing or electro-donating nature in terms of global hardness and softness. In this sense, the global hardness for electron-donating groups decreases in comparison to ISA without a substituent,

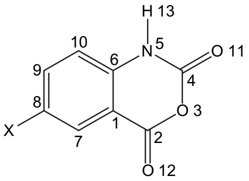
Table 3. Values of the optimized linking angles (°) compared with experimental data.

	HF	LSDA	B3PW91	PBE	B3LYP	MP2	EXP[38]
O3-C2-C1	116.0	115.9	116.0	116.1	115.9	116.2	116.2
C4-O3-C2	126.2	125.4	125.4	125.4	125.4	125.0	125.1
N5-C4-O3	116.1	115.7	115.8	115.9	115.7	115.8	116.5
C8-C7-C1	120.0	120.0	120.1	120.1	120.1	119.7	119.2
C9-C8-C7	119.2	119.5	119.5	119.5	119.5	119.8	119.9
C10-C9-C8	121.4	121.1	121.1	121.1	121.0	120.7	121.2
H13-N5-C4	114.8	114.3	114.5	114.5	114.6	114.4	116.0
O3-C2-O12	118.1	117.8	117.5	117.6	117.5	117.6	116.1
C2-C1-C6	118.9	119.7	119.4	119.4	119.5	119.4	118.5
C2-C1-C7	120.8	120.1	120.6	120.5	120.6	120.2	121.3
C9-C10-C6	118.9	119.2	119.2	119.1	119.2	119.4	118.9
C10-C6-C1	120.2	120.0	120.1	120.1	120.1	120.0	120.6
C10-C6-N5	121.5	121.9	121.6	121.7	121.5	121.5	119.9
C6-N5-H13	120.7	120.5	120.4	120.5	120.3	120.4	120.0

Table 4. Statistical data obtained from the values of the optimized linking angles of ISA. RMS error, mean error, absolute mean error, maximum error.

	RHF	LASD	B3PW91	PBE	B3LYP	MP2
RMS ERROR	0.946	1.074	0.899	0.927	0.887	0.927
MEAN ERROR	0.320	0.121	0.128	0.150	0.107	0.050
ABSOLUTE MEAN ERROR	0.728	0.915	0.714	0.561	0.721	0.721
MAXIMUM ERROR	2.0	2.0	1.7	1.8	1.6	1.6

Table 5. Values of the global indexes of reactivity calculated for ISA.



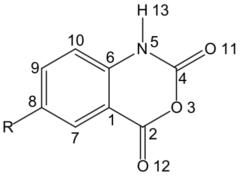
X	σ	η (eV)	μ (eV)	s (1/eV)
OCH_3	-0.27	4.639	-4.149	0.108
CH_3	-0.17	4.816	-4.272	0.104
H	0.00	4.952	-4.435	0.101
Br	0.23	4.966	-4.476	0.100
Cl	0.23	4.925	-4.462	0.102
NO_2	0.78	5.333	-4.979	0.094

whereas that for the electron-withdrawing groups increases when similarly compared.

For analyzing the results of local reactivity, the carbon and nitrogen atoms in both rings were considered. This was done because reports in the relevant literature [5] mention that, experimentally, some of these atomic centers have shown the greatest probability for electrophilic and nucleophilic reactions to take place.

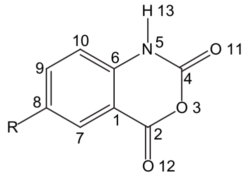
The values of the Fukui condensed functions f_x^+, f_x^- and of local softness s_x^+ and s_x^- for isatoic anhydride and the derivatives studied in this work are shown in Tables 6 and 7. The values for f_x^+ and s_x^+ in ISA and its derivatives shown for the atom C2 are more reactive toward the reaction with a nucleophilic species for these compounds, in consistence with the experimental data. The local behavior at C2 depends on the chemical nature of the substituent present at the C8 position in the aromatic ring, that is, when the most electron-donating functional group (OCH_3) is present, the softness at C2 increases by 0.019 in comparison to ISA without a substituent, where-

Table 6. Local softness and condensed Fukui function in atomic units associated with carbon atoms and nitrogen in both rings of ISA and derivatives associated with a nucleophilic attack, calculated on the basis of population in the theory of atoms in molecules (AIM).



	R = OCH_3		CH_3		H		Br		Cl		NO_2	
x	fx^+	s_x^+	fx^+	s_x^+	fx^+	s_x^+	fx^+	s_x^+	fx^+	s_x^+	fx^+	s_x^+
C_1	0.025	0.072	0.024	0.068	0.027	0.073	0.027	0.076	0.029	0.079	0.028	0.073
C_2	0.124	0.365	0.121	0.342	0.126	0.346	0.118	0.325	0.119	0.325	0.048	0.124
O_3	0.040	0.117	0.041	0.116	0.041	0.114	0.038	0.105	0.041	0.111	0.032	0.082
C_4	0.010	0.028	0.012	0.033	0.012	0.033	0.013	0.035	0.011	0.031	0.027	0.070
N_5	0.018	0.053	0.018	0.049	0.017	0.048	0.016	0.045	0.019	0.052	0.022	0.057
C_6	0.035	0.102	0.040	0.114	0.042	0.116	0.038	0.106	0.037	0.101	0.056	0.136
C_7	0.057	0.169	0.048	0.132	0.054	0.148	0.044	0.122	0.047	0.128	0.022	0.055
C_8	0.058	0.171	0.018	0.051	0.027	0.075	0.028	0.078	0.038	0.105	-0.003	-0.007
C_9	0.064	0.187	0.071	0.200	0.070	0.192	0.058	0.161	0.062	0.171	0.048	0.123
C_{10}	0.039	0.115	0.034	0.097	0.040	0.110	0.039	0.107	0.039	0.108	0.026	0.067
O_{11}					0.072	0.197						
O_{12}					0.111	0.305						
H_{13}					0.036	0.098						
H_{14}					0.074	0.204						
H_{15}					0.075	0.206						
H_{16}					0.098	0.269						
H_{17}					0.078	0.214						
Σ =					**1.000**	**2.748**						

Table 7. Local softness and condensed Fukui function in atomic units associated with carbon atoms and nitrogen in both rings of ISA and derivatives associated with a electrophilic attack, calculated on the basis of population in the theory of atoms in molecules (AIM).



	R = OCH_3		CH_3		H		Br		Cl		NO_2	
x	f_x^-	s_x^-	f_x^-	s_x^-	f_x^-	s_x^-	f_x^-	s_x^-	f_x^-	s_x^-	f_x^-	s_x^-
C_1	0.025	0.074	0.250	0.071	-0.062	-0.171	0.025	0.069	0.028	0.075	0.032	0.081
C_2	0.035	0.104	0.035	0.099	0.038	0.105	0.033	0.091	0.035	0.097	0.036	0.091
O_3	0.033	0.098	0.037	0.103	0.039	0.108	0.034	0.094	0.036	0.097	0.039	0.099
C_4	0.023	0.067	0.022	0.062	0.029	0.080	0.018	0.050	0.021	0.056	0.021	0.053
N_5	0.051	0.149	0.065	0.183	-0.165	-0.453	0.059	0.163	0.058	0.158	0.078	0.198
C_6	0.038	0.113	0.035	0.099	-0.131	-0.360	0.032	0.089	0.034	0.092	0.031	0.078
C_7	0.030	0.089	0.009	0.027	0.001	0.002	0.022	0.061	0.025	0.068	0.019	0.049
C_8	0.049	0.144	0.018	0.050	-0.201	-0.551	0.028	0.078	0.041	0.111	0.048	0.122
C_9	0.032	0.094	0.027	0.077	0.020	0.055	0.024	0.065	0.024	0.065	0.026	0.065
C_{10}	0.035	0.102	0.035	0.098	-0.068	-0.188	0.031	0.085	0.033	0.090	0.034	0.087

as the presence of the most electron-withdrawing group (NO_2) decreases it by 0.222. This suggests that, under experimental conditions, one can influence the nuclophilic attack on atom C2 in the heterocyclic ring of either ISA or its derivatives, specifically by incorporating electron-donating or electron-withdrawing groups at C8 in the aromatic ring. The results relating to the nitrogen atom are less indicative of its reactive character, and this is corroborated by experimental studies in which the substituent of this atom is present [5] before the ISA is made to react with some other molecule, thus making it easy to obtain the derivatives with functional groups joined to the heterocyclic nitrogen atom.

Table 7 shows the values of f_x^- and s_x^- for ISA and its derivatives. In this Table we can see that some of the values are negative for the ISA without a substituent, which is our reference compound. The interpretation of these negative values ranges from not having a physical meaning to interpretations supported by experimental and theoretical calculation on redox-induced electron rearrangement (RIER) [50], which consider that taking orbital relaxation into account can explain how, although the molecular system globally loses one electron, the electron density increases in some regions of the molecule, thereby giving rise to negative values for the condensed electrophilic Fukui function.

Due to the sensitivity of the Fukui function regarding the type of populational analysis to be performed, we consider it appropriate to carry out a study of ISA and its derivatives in a later work, basing ourselves on the electronic population given by the load-partitioning «stockholder» (Hirshfeld's analysis), with which non-negative values are always obtained for the Fukui function [51].

From the experimental point of view, the interest lies mostly in the characterization of local reactivity in the heterocyclic ring of isatoic anhydride (ISA). The values shown in Table 6 for the nucleophilic attack show the expected theoretical-experimental consistency. On the other hand, the negative values in Table 7 associated with atoms in the aromatic ring do not permit a clear interpretation of the reactivity toward electrophilic attack; therefore the consistency between theory and experiment can not be determined with this approach, and this makes the refinement of the calculation with the model of Hirshfeld necessary.

Conclusions

Globally, the least reactive compound turned out to be the ISA derivative with the most electron-withdrawing substituent (NO_2), whereas the most reactive was the one with the most electron-donating substituent (OCH_3). The ISA compound without a substituent has a reactivity value between the extremes previously mentioned. The global hardness values allow us to differentiate between the electron-withdrawing or electron-donating properties of the substituents. The electron-donating groups yield compounds with less hardness or more reactivity in comparison to that without a substituent (ISA), whereas the electron-withdrawing groups yield less reactive compounds because they increase the hardness values in comparison to the reference compound.

The data obtained in this work make it possible to explain the local reactivity that has been observed experimentally in the molecule of isatoic anhydride and its derivatives by analyzing C2 and C4 in the heteroring. These results permit the quantitative explanation of the differences in reactivity toward nucleophilic attack that give rise to the versatility of ISA as a precursor in different processes of synthesis.

Complementarily, it was determined that, locally, the action of the most electron- donating substituent is to increase the value of the local Fukui and softness at C2, whereas the electron-withdrawing substituent decreases them. This confirms the experimental data reported in relevant literature.

Experimental

The DFT has been extensively used to study and explain diverse chemical problems and concepts derived from this theory, like electronegativity and hardness, which are two important molecular properties, useful for interpreting and understanding the stability and reactivity of molecular systems [11]. According to the Hohenberg and Kohn (HK), theorems [35], there is a functional relationship between the energy of the basic state of an electronic system and the electronic density of same. The process of minimization of said functional through the method of Lagrange multipliers, with the restriction that the integral of electronic density over all the space is equal to the total number of electrons N of the molecule, leads directly to the Euler-Lagrange equation [11] of chemical electronic potential, μ. This amount measures the tendency of the system, in its basic state, to attract and retain electrons, it being accepted as a global index of reactivity and defined as the slope of the curve of energy against the number of electrons maintaining the external potential constant.

In the approximation of finite differences, this slope can be described in terms of the ionization potential I, and the electronic affinity A. Thus, the chemical potential can be associated with the negative of Mulliken's electronegativity (χ) [36] in the form

$$\mu = -\frac{I+A}{2} = -\chi \tag{1}$$

The dependency of the chemical potential on both the number of electrons and the external potential to which they are attached determines the expression to describe their change due to the variation of these two variables, which leads to the definition of two other very important indicators of reactivity: the global hardness and the local indicator of reactivity called the Fukui function [12]. The definition of global hardness η provided by Parr and Pearson [6] permits us to interpret it as the resistance of the chemical potential to change due to variations in the number of electrons; thus, an increase in the number of electrons in the molecule decreases its tendency to withdrawing electrons from nearby systems and vice versa. This tendency is measured by the chemical potential. Like the chemical potential, hardness is also expressed in terms of I and A as follows:

$$\eta = \frac{I-A}{2} \tag{2}$$

On the other hand, global softness *s* is defined as 0.5 times the inverse of global hardness [13]. Both global hardness and softness are concepts that have been used to explain chemical reactivity [17]. Gázquez and Vela [38] have demonstrated that when softness is applied to atoms, it lineally correlates with polarizability. The approximation provided by the Koopman theorem makes it possible to write the chemical potential, global hardness and softness in terms of the frontier molecule orbital energies (ε_{Homo} and ε_{Lumo}), which represent the energy of the occupied molecular orbital with more energy and the energy of the unoccupied molecular orbital with less energy, respectively. With this approximation, the potential of ionization I is identified with the negative of ε_{Homo} and the electronic affinity, A, with the negative of ε_{Lumo}.

The local indicator of reactivity called the Fukui function is a measurement of the sensitiveness of the chemical potential due to the change in the external potential at a particular point r of the molecule, the number of electrons [28-30] remaining constant. The Fukui function measures the nucleophilicity and electrophilicity at different sites of a molecule. The expressions for determining such nucleophilicity and electrophilicity are the Fukui functions f_x^+ (r) and f_x^- (r) condensed to *x* atom in a molecule with N electrons [12, 31] and are given as follows:

$$f_X{}^+ = [q_X(N+1) - q_X(N)] \tag{3}$$

$$f_X{}^- = [q_X(N) - q_X(N-1)] \tag{4}$$

where q_x represents the electronic population of *x* atom in the molecule.

Another local descriptor is the local softness *s* condensed to *x* atom and is defined as the product of the condensed Fukui function $f_x^{+/-}$ times the global softness s. Thus this descriptor has the same information as the Fukui function, plus additional information provided by the global molecular softness.

The expressions for local softness in each atom in the x position of the molecule will be

$$s_X{}^+ = f_X{}^+ s \tag{5}$$

$$s_X{}^- = f_X{}^- s \tag{6}$$

which describe nucleophilic and electrophilic local attacks, respectively.

In this work, we initially realized a structural study starting from the atomic positions of ISA obtained by the diffraction of X-rays [39]. The geometry was totally optimized at the theoretical level RHF [40], MP2 [41] and various DFT methods like B3LYP [42], LSDA [43], B3PW91 [44], PBE [45], with a correlated, augmented aug-cc-pvDZ [46] base, as they are implemented in the GAUSSIAN 03 package [47]. The vibrational frequencies calculated with the same level of theory assure that the geometries obtained correspond to a local minimum of energy.

For the study of reactivity, in the optimized geometry of ISA at the level of B3LYP/aug-cc-pv-DZ, we carried out the substitutions in the C8 position of the functional groups (OCH_3, CH_3, H, Cl, Br, NO_2), totally reoptimizing the resulting geometry (Figure1).

The global indexes of reactivity were calculated with Koopman´s approximation. To obtain said indexes, we realized single-point calculations of the anion and the cation at the optimized geometry of the neutral molecule to guarantee the condition of maintaining the external potential constant. For the single-point calculation of the ionic structures we used the chemical model UB3LYP/aug-cc-pVDZ, thereby obtaining results without spin contamination. The condensed Fukui functions and the atomic softness were evaluated by using the set of equations 3, 4, and 5, 6, respectively. The electronic population for calculating the Fukui functions was based on the formulation of the quantum theory of atoms in molecules (QTAIM) [48], first calculating the wave function for each one of the neutral and ionic systems based on the optimized geometry for the neutral molecule. Starting from the wave function, we calculated the electronic population by integrating the electronic density on the basin of each atom of interest and with the accuracy criterion that the integration of the Laplacian of the electronic density in the same region should be lower than 10^{-3}; we used the Morphy98 package to do this [49].

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