Theoretical Studies of Reactivity and Selectivity in Some Organic Reactions

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ABSTRACT: Some organic reactions with biological or commercial interest have been studied by using reactivity and selectivity indices proposed in the density functional theory. The reactions studied include the electrophilic additions, the Baeyer-Villiger oxidations, and the nucleophilic substitutions. For the study, the concepts of electrophilicity and nucleophilicity have been applied as reactivity descriptors. The local hardness has been applied as well as a selectivity descriptor. In this way, the reactivity and selectivity patterns have been studied for the reactants involved in these organic reactions. They have been ranked in theoretical scales which are comparable with experimental scales obtained from kinetic data. ©2010 Wiley Periodicals, Inc. Int J Quantum Chem 110: 2360–2370, 2010

Key words: reactivity; selectivity; DFT

1. Introduction

Density functional theory (DFT) of chemical reactivity offers an elegant way to predict and interpreted the outcome of a chemical reaction in terms of the properties of the reactants. The properties of interest are usually response functions with respect to perturbations. The DFT has been successful in the development of global and local reactivity indices [1, 2] that have helped significantly in the study of reactivity and selectivity for a wide number of systems [3–6]. A comprehensive review about this theme has been published [7] together with a specific review about the electrophilicity index [8].

The electrophilic addition reactions of hydrogen halides H—X to asymmetric olefins $CH_2{=}CHR$ usually occur regiospecifically leading to the predominant formation of $CH_3{-}CHRX$. In those chemical processes, two groups are selectively added to each carbon atom participating in the double bond of alkenes. This is the well-known Markovnikov's

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rule [9], considered as one of the most important developments in the modern mechanism of organic chemistry. This rule states that in the addition of a hydrogen halide to the double bond of the asymmetric olefin, the acidic hydrogen is bonded to the carbon atom which contains the major hydrogen atoms bonded [10–12].

The recently defined local hardness index has been very useful as an intramolecular selectivity descriptor in the orientation of electrophilic aromatic substitution reactions and alkylation and acylation of lithium enolates [13]. In this article, it is shown that the Markovnikov's rule may be also interpreted applying the local hardness index to substituted ethylenes taking in account the electronic effects of the substituent groups [14].

To perform a complete analysis of the addition reactions and the empirical Markovnikov's rule, the reaction energy for each addition reaction of hydrogen chloride to asymmetric ethylenes in the Markovnikov and in the anti-Markovnikov positions have been obtained. We have also obtained the activation energy for the Markovnikov-type transition state, and for the anti-Markovnikov-type transition state.

Therefore, the selectivity analysis of addition reactions to asymmetric ethylenes has been done in terms of electronic indices, thermodynamic, and kinetic parameters.

The treatment of carbonyl compounds with peroxyacids in presence of acid catalysts, gives carboxylic esters by insertion of oxygen and the carboxylic acid parent of the peroxyacid as a by-product. The reaction is called the Baeyer-Villiger oxidation, and became one of the most well-known and widely applied reactions in organic synthesis [15–18]. The reaction is often applied to cyclic ketones to give lactones [19]. Enantioselective synthesis of chiral lactones from achiral ketones has been achieved using enzymes [20–22]. In the Baeyer-Villiger oxidation of aldehydes, the products are two carboxylic acids, one from aldehyde and the other one from the peroxyacid [10].

Some theoretical studies have been made in Baeyer-Villiger oxidations in order to show the influence of the catalyst [23], the effect of the halo-substituents [24], and the role of the hydrogen bonds in the mechanism of the reaction [25]. However, in those works, they do not classify the substrates in order of their reactivity, which is the aim of this work. We show here the first reactivity study for substrates involved in Baeyer-Villiger oxidations by using DFT reactivity index [6].

In this article, we rank within an absolute theoretical scale the global electrophilicity [26] of a series of (11) ketones and (6) aldehydes. The usefulness of the theoretical scale is illustrated for the rationalization of substituent effects on the electrophilic activation/deactivation reagents [6]. We present here as well, a theoretical model to quantitatively describe the rate constants in terms of the global electrophilicity of a series of aliphatic ketones involved in Baeyer-Villiger oxidation reaction, using the global electrophilicity index [26].

Nucleophilic substitution at carbon is of broad synthetic utility and has received exceptionally detailed mechanistic study by organic [27, 28] and theoretical chemists [29]. The area of nucleophilic substitution illustrates the fact that as a broad conceptual framework can outline the general features to be expected for a given system, precise details will reveal aspects that are characteristic of specific systems. Those reactions may involve several different combinations of charged and uncharged species as reactants. The reactions include two limiting cases: ionization mechanism (S_N1, substitution-nucleophilic-unimolecular) and the direct displacement mechanism (S_N2, substitution-nucleophilic-bimolecular).

The direct displacement (S_N2) mechanism is concerted, without an intermediate, and proceeds through a single rate-determining transition state. The concerted displacement mechanism implies both kinetic and stereochemical consequences. The reactions will exhibit second-order kinetics, first-order in both reactant and nucleophile [30]. In depends on the strong of the nucleophile, the solvent and the type of the alkyl halides. The substitution reactions are competitive with the elimination reactions following the conditions: strength of the nucleophile, the solvent and the type of the alkyl halide.

In this work, we propose a nucleophilicity and basicity pattern through a thermodynamic study of a series of anions, which participate with alkyl halides in substitution and elimination reactions. We also obtained the nucleophilicity [29] values for a small series of anions and we compared them with the experimental values of efficiency for the substitution reactions [31].

2. Theory

2.1. LOCAL HARDNESS

The empirical local hardness has been proposed in terms of the frontier molecular orbital theory, taking in account the Koopmans' theorem [32] in order to perform the selectivity analysis using only information of the neutral molecule. The condensed local hardness on atom k will be given by [13]:

$$\eta_{\mathrm{k}} = \varepsilon_{\mathrm{l}} f_{\mathrm{k}}^{+} - \varepsilon_{\mathrm{H}} f_{\mathrm{k}}^{-} \tag{1}$$

where ε_{L} and ε_{H} are the frontier orbital energies LUMO and HOMO, respectively, and f_{k}^{-} and f_{k}^{+} are the condensed Fukui functions for electrophilic and nucleophilic attacks, respectively [33, 34].

Under the validity of the HSAB principle, one should expect that a hard reagent will attack the site with the greatest value of local hardness. As it has been stated before [13], the proposed local hardness is an empirical one which cannot be derived from the hardness kernel, because of the known ambiguities in the grand canonical ensemble definitions. Note also that usually the hardness is associated with charged-controlled reactions. However, here through the use of the Fukui function, the importance of the orbital overlap is highlighted. On the other side, the use of the Fukui function alone could not help for an intermolecular analysis [35]. In the following, the local hardness of Eq. (1) will be evaluated as an orientation index for electrophilic addition reactions [14].

To validate the efficiency of the new selectivity index, the energy of addition reactions and the activation energy for the transition states in reactions of hydrogen chloride to substituted alkenes have been evaluated. With these two quantities, it will be possible to describe the electronic effects that produce the substituents on the double bond of the alkenes, and to compare with the selectivity results obtained by the local hardness.

2.2. ELECTROPHILICITY INDEX

The concept of electrophilicity viewed as a reactivity index was formulated by Parr et al. [26] using a second-order expansion of the electronic energy with respect to the charge transfer ΔN at fixed geometry. Because electrophiles are species that stabilize upon receiving an additional amount of electronic charge from the environment, there exist a minimum of energy for a particular ΔN^* value. Using this simple idea, Parr et al. performed a variational calculation that led to the definition of the global electrophilicity index as $\omega = -\Delta E(\Delta N^*)$, which may be rewritten into the more familiar form [26]:

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

In terms of the electronic chemical potential μ and the chemical hardness η. The ω index establishes an absolute scale of electrophilicity in the sense that the hierarchy of electrophilicity is built up from the electronic structure of molecules, independent of the nucleophilic partner, which is replaced by an unspecified environment viewed as a sea of electrons [26]. It has been successfully used to describe the reactivity in different organic systems. For instance, the global electrophilicity values obtained from ω have been used to rank the electrophilicity of reagents participating in Diels-Alder and 1,3-dipolar cycloaddition reactions [36, 37]. It was also found that the difference in electrophilicity for the diene/dienophile pair determined the nature of the reaction mechanism (nonpolar or polar character of the process), thereby reinforcing the reliability of the ω index as a kinetic descriptor of reactivity [36]. This index is almost insensitive to solvent effects in neutral electrophiles, thus gas phase calculations suffice to establish the electrophilic power of molecules [8]. It has be shown that the intrinsic electronic contribution to the substituent σ_{p} Hammett constants, $\sigma_{\mathrm{e}}(\omega)$, can be estimated from the ω index calculated for a series of substituted ethylenes [38]. Domingo et al. found that electron withdrawing substitution increased the electrophilicity power of ethylene, and that the corresponding $\sigma_{\mathrm{e}}(\omega)$ values were consistently predicted as positive numbers. More recently, we have illustrated how the electrophilicity index quantitatively accounts for the observed substrate selectivity in Friedel-Craft benzylation and acylation [4]. In this work, we show how the electrophilicity index permits to estimate the activation/deactivation effects promoted by electron-withdrawing and electron-releasing substituents in aldehydes and ketones involved in the Baeyer-Villiger oxidation reactions [6].

2.3. NUCLEOPHILICITY INDEX

Jaramillo et al. [29] have proposed a new empirical model that takes into account the specific electrophilic substrate. A specific electrophile would accept a specific amount of charge and another electrophile a different one. In a very simple model, this amount of charge transfer will be given by the following equation:

$$N = \frac{\mu_A - \mu_B}{\eta_A + \eta_B} \tag{3}$$

where μ_A and μ_B are the chemical potentials of the nucleophilic and electrophilic molecules, respectively. η_A and η_B are the respective hardness's. This equation has been derived by Parr and Yang [1] and the factor of 2 has been omitted for convenience according to the currently accepted definition of the hardness without the factor of one-half. This amount of transferred charge is fixed and different for each couple of reactants. Because the amount of charge is fixed, the scenery is the grand canonical ensemble, where the independent variables are the chemical potential and the external potential [29].

Hence, it is proposed to use as the nucleophilicity index the following expression [29]:

$$\omega^- = \frac{1}{2}\frac{(\mu_A - \mu_B)^2}{(\eta_A + \eta_B)^2}\eta_A \tag{4}$$

Note that the proposed index depends on the electrophilic system and, therefore, there is not a unique nucleophilic scale. It will vary from one electrophile to another. Notice that opposed to the electrophilicity index [26] which is absolute, this one is relative. As for all other indices derived in DFT, one needs a practical scheme to calculate it. As usual, the frozen orbital and the finite difference approximations are used to obtain the respective μ and η [1]. Therefore, the results will also depend on the quality of the respective HOMO and LUMO. The proposed empirical nucleophilicity index was evaluated in a series of anions that participate as nucleophiles in S_N2 substitution reactions.

3. Computational Details

All the calculations were performed at the optimized ground states of the molecules, at the B3LYP/6-311G** level of theory, implemented in the GAUSSIAN 03 package of programs [39]. The frontier orbital energies and the condensed Fukui functions were obtained using the Hartree-Fock (HF) method and the 6-31G* basis set, as was suggested by Vargas et al. [40] in order to obtain well-described reactivity indices. The values of the electronic chemical potential and the chemical hardness were obtained from the approximated expressions $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx \varepsilon_L - \varepsilon_H$, in terms of the one electron energies of the HOMO and LUMO frontier molecular orbitals, ε_H and ε_L, respectively [1]. The condensed local hardness was evaluated using Eq. (1). The energy of addition reactions and the activation energy were obtained as described in literature [30]. The global electrophilicity at the ground state of molecules was obtained using Eq. (2). To obtain the energies of the substitution and the elimination reactions, the structures were optimized at the B3LYP/6-31G* level of theory and then a single point at CCSD(T) level of theory was performed using different basis set. The global nucleophilicity was obtained using Eq. (4).

4. Results and Discussion

4.1. ELECTROPHILIC ADDITION REACTIONS

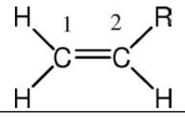
The local hardness values, η_k, for some substituted alkenes of general formula CH_2CHR which contains π bond and participate in addition reactions, are shown in Table I. In this table, the corresponding activation and reaction energies are also included.

The original Markovnikov's rule [9] states that the addition of an acidic proton to a double bond of an alkene yields a product where the proton is bounded to the carbon atom bearing the largest number of hydrogen atoms. Following this empirical rule, the molecules studied in this work should present the greatest value of local hardness, η_k, at the carbon C_1, the less substituted one. From Table I, it may be seen that the η_k values nicely reproduce these trends, as much with electron-donating groups as with electron-withdrawing groups. Clearly, it can seen that the activated carbon for a electrophilic attack is the carbon C_1, showing differences in the condensed local hardness between carbons C_1 and C_2 of 0.14–2.00 eV.

The molecules CH_2CHCOF and CH_2CHNO_2, with strong electron-withdrawing substituents do not follow this trend, they show the larger η_k value at carbon C_2. This can be understood because of the high electron-attraction generated by these substituents leading to the distortion of the π-electronic cloud. Hence, it becomes more reactive for a electrophilic attack, the carbon C_2 instead of C_1, suggesting an anti-Markovnikov mechanism. However, note that the differences in the local hardness between carbon C_1 and C_2 are low [14].

TABLE I

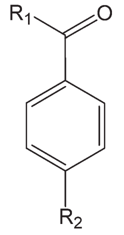
Local hardness (η_K), reaction (ΔE), and activation (E_a) energies for CH_2CHR systems [14].



R	Position (k)	η_K (eV)	ΔE (kcal/mol)	E_a (kcal/mol)
$N(CH_3)_2$	1	5.56	−19.0	1.3
	2	3.67	−8.9	45.4
$NHCH_3$	1	5.99	−20.8	0.6
	2	4.18	−9.9	44.3
NH_2	1	6.25	−19.9	6.0
	2	4.25	−10.5	44.7
$NHNH_2$	1	5.68	−21.2	1.0
	2	3.70	−9.8	44.8
OH	1	7.33	−19.9	18.3
	2	5.78	−11.9	43.2
NHOH	1	6.05	−19.5	10.8
	2	4.18	−12.0	42.9
OCH_3	1	6.84	−20.7	13.6
	2	5.20	−13.0	42.7
CH_3	1	7.31	−18.8	30.1
	2	6.43	−16.4	37.8
CH_2CH_3	1	7.06	−17.6	28.6
	2	6.15	−15.3	37.5
$CHCH_2$	1	3.96	−13.4	29.0
	2	2.10	−10.9	42.6
H	1	7.53	−20.0	36.1
	2	7.53	−20.0	36.1
CCH	1	4.39	−12.6	33.5
	2	2.76	−12.3	41.8
F	1	7.79	−19.2	32.4
	2	6.60	−14.8	45.7
CHO	1	5.62	−12.8	38.4
	2	5.00	−11.7	39.0
COOH	1	5.83	−15.1	41.6
	2	5.69	−13.0	44.5
$COCH_3$	1	5.70	−14.2	37.7
	2	5.03	−13.3	38.2
OCN	1	6.32	−17.8	34.9
	2	5.09	−15.0	47.4
NO	1	5.24	−20.4	52.3
	2	4.88	−20.2	54.1
COF	1	5.68	−10.9	44.8
	2	5.80	−13.1	41.2
NO_2	1	5.47	−13.5	47.0
	2	6.17	−15.4	42.6

The thermodynamical analysis of the reaction energies involved in the Markovnikov and anti-Markovnikov-type addition processes are shown in Table I. The electron-donating groups and the weak electron-withdrawing groups prefer to yield Markovnikov products, whereas the strong electron-withdrawing groups leads to anti-Markovnikov products. Note, however, that the difference between the Markovnikov-type reaction energy and the anti-Markovnikov-type reaction energy in the ethylenes with electron-donating groups are greater than in the ethylenes with electron-withdrawing groups. Again, the molecules CH_2CHCOF and CH_2CHNO_2 follow the anti-Markovnikov's rule [14].

The electronic effect of the substituents has been observed by studying the transition states of the substituted ethylenes with hydrogen chloride. Their activation energies (E_a) are shown in Table I. We found that the CH_2CHR system presents a preference toward electrophilic addition Markovnikov-type when *R* is an activator or electron-

General Structure Aldehydes		R1	R2
	A1	H	NO_2
	A2	H	Cl
	A3	H	H
	A4	H	OCH_3
	A5	H	CH_3
	A6	H	NH_2

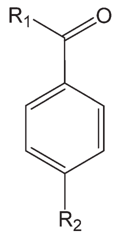
General Structure Ketones		R1	R2
	B1	Ph	NO_2
	B2	Ph	Cl
	B3	Ph	Br
	B4	Ph	H
	B5	Ph	CH_3
	B6	Ph	NH_2
	B7	CH_3	NO_2
	B8	CH_3	Cl
	B9	CH_3	Br
	B10	CH_3	H
	B11	CH_3	CH_3

CHART 1. General structure of aldehydes (A) and ketones (B) involved in Baeyer-Villiger oxidations studied in this work [6].

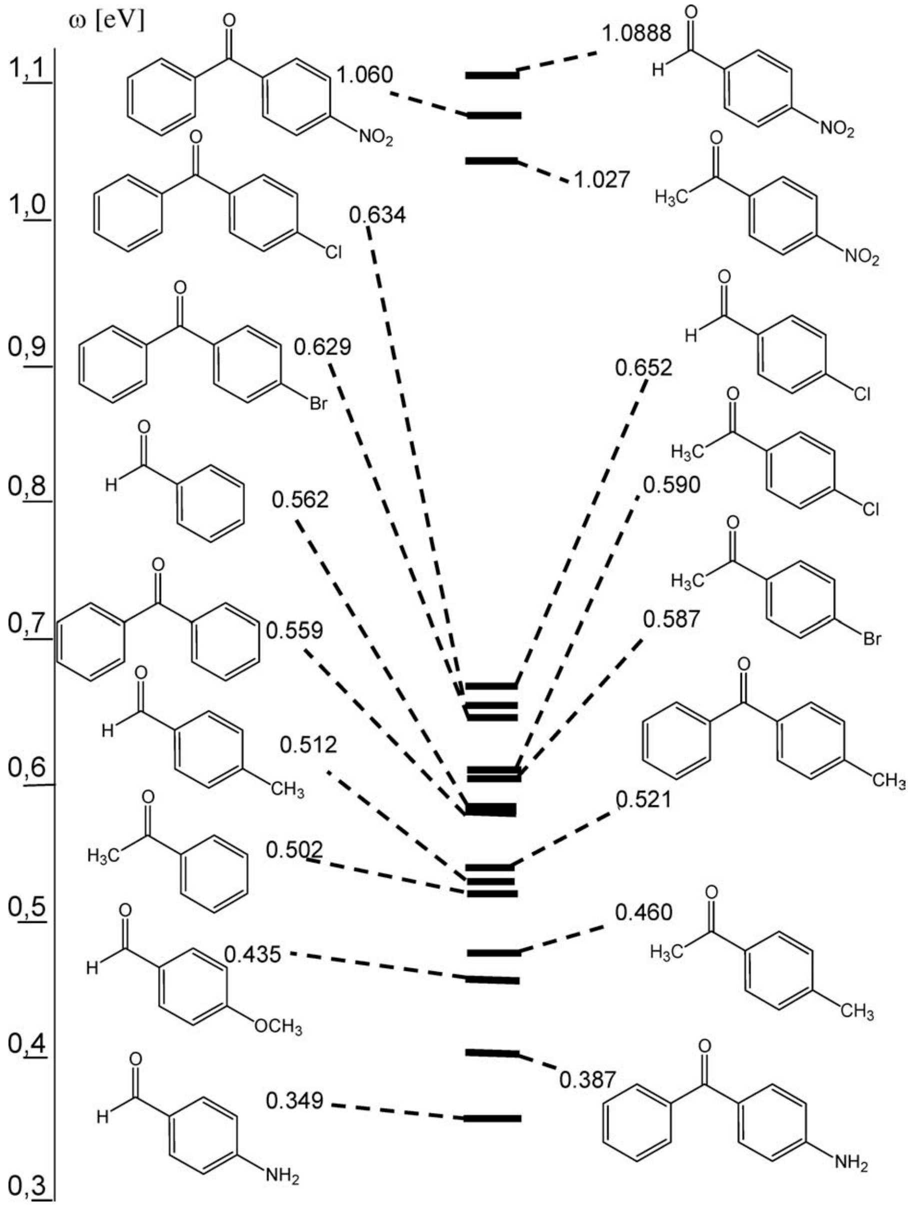


CHART 2. Theoretical scale of global electrophilicity for aldehydes (A) and ketones (B) involved in Baeyer-Villiger oxidation reactions [6].

donating group. This is in agreement with previous works about this theme [35, 41]. However, it should be notice that this is the only density functional descriptor, which works well using only information of the reactant. It can be seen that the activation energy differences between the Markovnikov and the anti-Markovnikov mechanisms in ethylenes with electron-donating groups are greater than in the ethylenes with electron-withdrawing groups. This is due to the stabilization of the carbocation by the electron-donating groups, whereas the electron-withdrawing groups destabilize the formed carbocation, and prefer to form a primary carbocation in spite of being less stable. Note that the activation energies for the ethylenes with electron-donating groups are lower than the activation energy for the addition of the HCl to ethylene, whereas the activation energies of the ethylenes with electron-withdrawing groups are greater than the one for ethylene [14].

Experimental activation energies of the addition of hydrogen chloride to CH_2CHR systems are

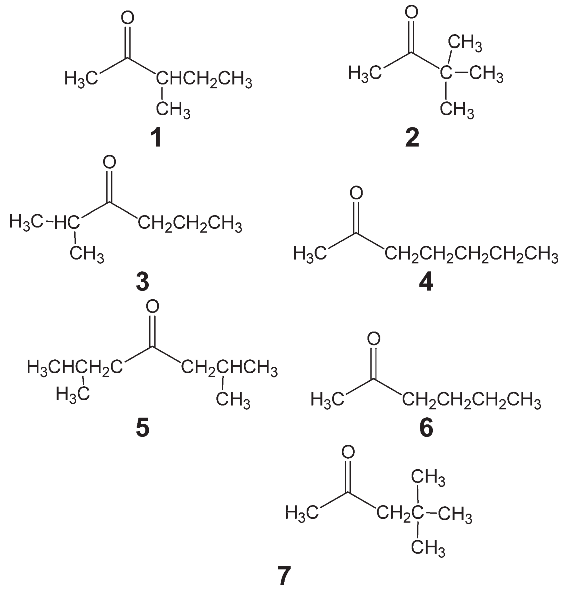


CHART 3. General structure of aliphatic ketones studied in this work.

reported in the reference [42]. The value for the addition of HCl to ethylene is 39.7 kcal/mol, for the Markovnikov addition of HCl to propene is 34.5 kcal/mol, and for the anti-Markovnikov addition is 41.3 kcal/mol. The experimental values are correctly predicted by the theory and the theoretical E_a values are around 3.0 kcal/mol smaller than the experimental data.

4.2. BAEYER-VILLIGER OXIDATION REACTIONS

The structures of aldehydes (A) and ketones (B) included in this study are shown in Chart 1. The global electrophilicity patterns of the substituting aldehydes and ketones, commonly used in Baeyer-Villiger oxidations are ranked in Chart 2. It can be seen that compounds with electron withdrawing substituents appears on the top of the scale, and compounds with electron releasing groups are in the bottom. Ketones display slight lower electrophilicity values than aldehydes with similar substituent. In this case, they are grouped in two groups depending on the substituent R1. If R1 is a phenyl group, the electrophilicity is a little higher than if it is aliphatic. In both, aldehydes and ketones, it is possible to rationalize the electrophilic activating/deactivating effects promoted by substituent group in these molecules. For instance, if we start from the unsubstituted reference compound A3 ($\omega = 0.562$ eV), substitution at R2 by the weak electron releasing —CH_3 group results in an electrophilic deactivation in compound A5 ($\omega = 0.512$ eV). Substitution at the same position with the stronger electron releasing —NH_2 group results in an even higher electrophilic deactivation in compound A6 ($\omega = 0.349$ eV). Substitutions with electron withdrawing groups show, as expected, electrophilic activation. For instance, with reference to compound A3, substitution at R2 with chlorine causes an activation of about 0.09 eV in compound A2, whereas the most efficient activation with reference to compound A3 is achieved by —NO_2 substitution at R2, in compound A1 ($\omega = 1.088$ eV) [6].

For the series of ketones, a similar picture is obtained. In this case, the structures are divided into two groups, the first 1 with phenyl group at R1, and the other one with methyl group at this position. If we start with the first group, starting from the reference compound B4 ($\omega = 0.559$ eV), substitution at R2 with chlorine and bromine atoms results in an electrophilic activation in compounds B2 ($\omega = 0.634$ eV) and B3 ($\omega = 0.629$ eV). The most activation effect is achieved by —NO_2 substitution at R2, in compound B1 ($\omega = 1.060$ eV). Substitution at R2 by —CH_3 group causes a deactivation in compound B5 ($\omega = 0.521$ eV). As expected, the substitution by the stronger electron releasing —NH_2 group at position R2 in compound B6 ($\omega = 0.387$ eV), results in a higher electrophilic deactivation. In this series, it is clear the electrophilic deactivation promoted by electron releasing groups. If we take the second group of ketones included in this study, it can be seen that the trend is similar than in the first group of ketones, however, the electrophilicity values are slightly lower than the ketones with the phenyl group at the R1 position [6]. The usefulness of a reactivity scale has been clearly illustrated by Mayr et al. [43, 44]. A reactivity scale should be

TABLE II

Global electrophilicity values at HF/6-31G* level of theory in the ground state of the molecules.

Compound	ω (eV)	$k_1 \times 10^5$ (Ms^{-1})
1	0.321	10.93
2	0.324	9.34
3	0.327	9.03
4	0.335	3.89
5	0.336	1.98
6	0.339	3.36
7	0.343	1.56

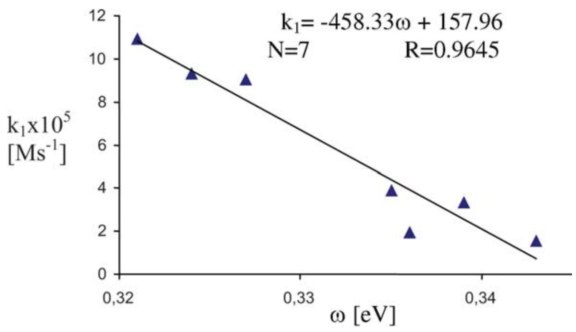


FIGURE 1. Comparison between the first-order rate constant k_1 and the global electrophilicity (ω) evaluated at the ground state of a series of aliphatic ketones. *R* is the regression coefficient and *N* is the number of points in the regression. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

able of answering fundamental questions about reaction feasibility, intramolecular selectivity, and other important aspects of reactivity.

Besides, we have studied the electrophilicity patterns of some aliphatic ketones. Their structures are shown in Chart 3. In Table II, the global electrophilicity values ω for a series of aliphatic ketones are presented. In this Table, the experimental first-order rate constants taken from reference [45] are also included. The kinetic data are from reactions performed in chloroform at 49.7°C and 0.1 MPa. Figure 1 shows the relationship between the first-order rate constant and the calculated global electrophilicity index for the series of aliphatic ketones evaluated at the HF/6-31G* level of theory. It can be seen that there are a good correlation with an $R = 0.9645$. The resulting regression equation is:

$$k_1 = -458.33\,\omega + 157.96 \tag{5}$$

Secondary and tertiary alkyl groups bounded at the carbonyl group show lower electrophilicity values at the ground state of molecules than primary alkyl groups. This is because of the stabilization of the carbonyl group due by those substituents through induction effects, which reduce the reactivity of the ketones. Secondary and tertiary alkyl groups fall dawn the electrophilicity of the carbonyl compound, but they arise their rate constant. This is due to the rate-determining step of the reaction, which involves the migration of the more substituted alkyl group [10].

4.3. NUCLEOPHILIC SUBSTITUTION REACTIONS S_N2

The energy values from substitution (ΔE_s) and elimination reactions (ΔE_e) of some anions which act as nucleophiles against alkyl halides are presented in Tables III–V. In Table III, the analysis is

TABLE III

Substitution (ΔE_s) and elimination (ΔE_e) energy values from a series of anions that react together with ethyl chloride obtained in the CCSD(T) method with different basis set.

	6-31G		6-31G(d)		6-31+G		6-31+G(d)	
Anion	ΔE_s	ΔE_e	ΔE_s	ΔE_e	ΔE_s	ΔE_e	ΔE_s	ΔE_e
CN—	−56.74	−29.60	−40.57	−6.52	−44.49	−18.61	−30.15	2.37
OH—	−88.08	−76.30	−82.51	−62.38	−57.46	−49.35	−91.26	−74.93
CH_3COO—	−45.39	−30.22	−37.00	−14.15	−37.81	−24.16	−15.16	5.58
F—	−70.75	−54.43	−69.17	−44.61	−30.68	−20.06	−30.46	−10.97
SCN—	7.06	32.88	13.00	43.95	3.17	27.95	4.92	31.37
CH_3O—	−73.20	−57.71	−62.70	−37.85	−66.17	−53.30	17.15	37.94
HS—	−25.08	−4.11	−23.48	2.52	−25.59	−5.46	−23.67	1.21
HCC—	−84.27	−59.96	−67.03	−35.72	−70.32	−47.58	−55.61	−26.01
CF_3—	−67.68	−35.22	−73.42	−37.43	−53.37	−22.35	−57.36	−23.86
CH_3S—		−10.81	−30.70	8.90	−34.19	−13.25	−31.93	−5.35
NH_2—	−108.88	−95.64	−96.90	−76.80	−86.08	−74.97	−76.21	−58.12
H—	−136.58	−103.52	−122.15	−83.91	−147.70	−116.20	−133.11	−96.44
NH_2S—	−33.27	−8.65	−34.47	−4.62	−33.47	−9.79		
CF_3CH_2O	−23.75	−25.79	−20.11	−12.11	−16.06	−20.81		

All the values are in kcal/mol.

TABLE IV

Substitution (ΔE_s) and elimination (ΔE_e) energy values from a series of anions that react together with isopropyl chloride obtained in the CCSD(T) method with different basis set.

	6-31G		6-31G(d)		6-31+G		6-31+G(d)	
Anion	ΔE_s	ΔE_e	ΔE_s	ΔE_e	ΔE_s	ΔE_e	ΔE_e	ΔE_s
CN—	−54.25	−28.32	−38.70	−6.12	−42.10	−16.77	−28.23	3.38
OH—	−88.88	−75.03	−83.55	−61.99	−58.28	−47.51	−55.18	−36.46
CH_3COO—	−46.38	−28.95	−38.01	−13.76	−38.63	−22.33	−45.85	−25.38
F—	−72.54	−53.15	−71.28	−44.22	−32.01	−18.22	−31.92	−9.99
SCN—	7.92	34.16	13.87	44.35	4.02	29.79	6.72	36.20
CH_3O—	−73.15	−56.43	−62.46	−37.45	−66.00	−51.46	−54.12	−31.33
HS—	−23.49	−2.84	−66.11	2.91	−24.14	−3.62	−22.54	2.20
HCC—	−81.93	−58.68	−131.08	−101.15	−36.20	−45.74	−53.81	−25.04
CF_3—	−66.11	−33.95	−72.12	−37.04	−51.38	−20.51	−160.89	−128.33
CH_3S—	−31.36	−9.54	−29.40	−2.47	−33.00	−11.42	−30.69	−4.36
NH_2—	−108.51	−94.37	−97.00	−76.41	−85.77	−74.97	−76.27	−51.51
H—	−132.73	−102.25	−119.05	−83.51	−143.51	−114.36	−129.69	−95.49
NH_2S—	−32.95	−7.38	−34.31	−4.22	−33.14	−7.95	−19.84	11.60
CF_3CH_2O	−42.95	−24.51	−37.52	−11.71	−35.27	−18.97	−45.89	−50.70

All the values are in kcal/mol.

for ethyl chloride as electrophile. Table IV shows the analysis for isopropyl chloride and Table V for *tert*-butyl chloride as electrophiles. The three Tables show the energy values obtained by using different basis sets. It can be seen that in the most of the cases the energy of reactions are negative, which indicates exothermic reactions. Only in the case of the SCN^- anion the values are positive. Nevertheless, in the whole cases the energy of the substitution reactions is greater than those of the elimination reactions.

Also, it may be seen that the electrophile shows only a minor influence in the energy values with differences minor than 2 kcal/mol. Only in a few

TABLE V

Substitution (ΔE_s) and elimination (ΔE_e) energy values from a series of anions that react together with *tert*-butyl chloride obtained in the CCSD(T) method with different basis set.

	6-31G		6-31G(d)		6-31+G		6-31+G(d)	
Anion	ΔE_s	ΔE_e	ΔE_s	ΔE_e	ΔE_s	ΔE_e	ΔE_s	ΔE_e
CN—	−52.50	−27.63	−37.56	−6.03	−40.35	−15.29	−27.12	4.14
OH—	−89.63	−74.33	−84.45	−61.89	−58.63	−46.03	−56.13	−35.69
CH_3COO—	−45.24	−28.25	−36.49	−13.66	−37.12	−20.84		−24.61
F—	−64.89	−52.46	−67.56	−44.13	−23.24	−16.74	−33.24	−9.22
SCN—	8.08	34.85	14.02	44.44	4.10	31.27	6.34	36.97
CH_3O—	−72.34	−55.74	−61.36	−37.36	−65.17	−49.98	−57.07	−30.56
HS—	−9.07	−2.14	−12.78	429.09	−9.78	−2.14	−21.83	2.97
HCC—	−80.24	−57.99	−64.15	−101.06	−66.34	−44.26	−52.79	24.27
CF_3—	−64.99	−33.26	−71.33	−36.95	−49.86	−19.03	−159.65	−127.57
CH_3S—	−29.73	−8.85	−16.11	−2.38	−31.63	−9.94	−29.43	−3.59
NH_2—	−108.14	−93.67	−96.98	−76.32	−84.77	−71.65	−75.83	−50.74
H—	−129.92	−101.56	−117.10	−83.42	−140.36	−112.88	−128.35	−94.72
NH_2S—	−32.51	−6.69	−33.93	−4.13	−32.85	−6.47	−33.94	−12.37
CF_3CH_2O	−42.12	−23.82	−36.78	−11.62	−35.10	−17.50		

All the values are in kcal/mol.

TABLE VI

Nucleophilicity values in (eV) and experimental efficiencies [31] for a series of anions.

Nucleophile	ω^- (eV)	Efficiency
OH—	1.54	0.930
F—	1.19	0.910
HS—	0.32	0.001
NH_2S—	0.26	0.043
CF_3CH_2O—	0.21	0.160
$CF_3CF_2CH_2O$—	0.17	0.041

cases, this values change significantly from one to another electrophile.

In the three Tables, it is important to notice the influence of the basis set. The introduction of diffuse and polarization functions change dramatically the energy values in the most of the cases. This is due to the electronic distribution of the anions, which need basis sets with great orbitals to include the electrons of the ion.

To improve this work, it is necessary to use more complete basis set in order to obtain good-built orbitals for the anions.

The nucleophilicity values from a series of anions obtained in gas phase are shown in Table VI. In this Table, the experimental efficiencies values for substitution reactions are also included [31]. Figure 2 shows the relationship between the nucleophilicity and the experimental efficiencies in substitution reactions S_N2. In this figure, it may be seen that there are a good correlation with an $R = 0.9699$. There exists a linear relationship between both variables. Both the global nucleophilicity and the efficiencies values are taken in gas phase. It is important to notice that the nucleophilicity scale is relative, it depends on the electrophile, and it may vary from one electrophile to another.

5. Concluding Remarks

The proposed local hardness index has been validated as a good selectivity descriptor in electrophilic addition reactions to alkenes, demonstrating its utility in hard reactions. The orientation of the electrophilic addition to monosubstituted alkenes has been correctly predicted by the local hardness index. It was demonstrated that in olefins with electron-donating substituents, the empirical Markovnikov's rule is carried out completely, whereas for electron-withdrawing substituents, this rule is carried out only in the cases where the electron attraction is not too strong. This prediction has been confirmed by the reaction and activation energies of the addition of hydrogen chloride to olefins.

The global electrophilicity of aromatic aldehydes and ketones participating in Baeyer-Villiger oxidation reactions has been ranked within an absolute scale using the global electrophilicity index. The theoretical scale correctly accounts for the electrophilic activation/deactivation effects promoted by electron withdrawing and electron releasing substituents in these molecules. The comparison between global electrophilicity of aliphatic ketones and the experimental first-order rate constant shows a linear relationship.

The thermodynamic study of substitution and elimination reactions show that the substitution is prefer over the elimination reaction in gas phase. The structure of the alkyl halide has a less influence in the reaction energy; however, the basis set has great influence in its value.

The global nucleophilicity of a series of anions participating in S_N2 reactions has been ranked within a relative scale using the nucleophilicity index. The comparison between the global nucleophilicity of some anions and the experimental efficiency shows a linear relationship.

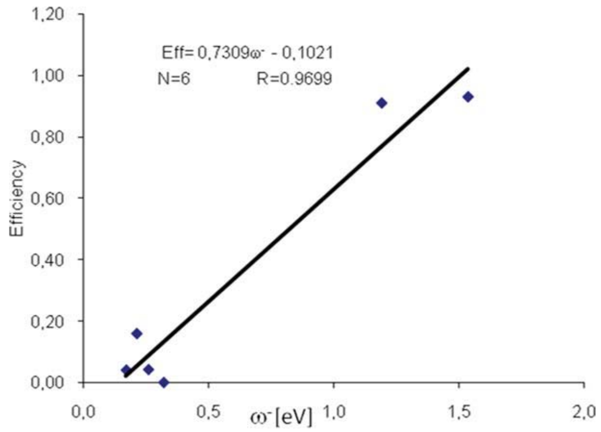


FIGURE 2. Comparison between the efficiency and the global nucleophilicity (ω^-) evaluated at the ground state of a series of anions. *R* is the regression coefficient and *N* is the number of points in the regression. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

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