Relationship between the electrophilicity and σ_p Hammett constant in Baeyer–Villiger reactions

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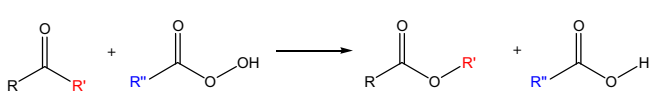
A B S T R A C T

The Baeyer–Villiger oxidation of some aldehydes and ketones has been revised by using the electrophilicity as a descriptor of reactivity. The global electrophilicity index evaluated at the ground state of a series of aromatic aldehydes and ketones shows a linear relationship with the σ_p Hammett substituent constants. The theoretical scale correctly accounts for the electrophilic activation/deactivation effects promoted by electron withdrawing and electron releasing substituents in these molecules.

1. Introduction

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 [1–4]. The reaction is often applied to cyclic ketones to give lactones [5]. Enantioselective synthesis of chiral lactones from achiral ketones has been achieved by use of enzymes, and other asymmetric reactions are known [6–8]. In the Baeyer–Villiger oxidation of aldehydes, the products are two carboxylic acids, one from aldehyde and the other one from the peroxyacid.

The carbonyl carbon in ketones and aldehydes is attacked by the hydroxyl group of the peroxyacid, the result is an analog of an hemiacetal with a peroxide group. Those products are non-stables and they discompose through an eight electrons transition state.



The mechanism is similar to those of analogous reaction with hydrazoic acids and diazomethane [9]. In the first step, the peroxyacid adds to the carbonyl group of the carbonyl compound. This step is a nucleophilic addition analogous to gem-diol and hemiacetal formation. In a second step, the intermediate from the last step undergoes rearrangement. Cleavage of the week O–O bond of the peroxyester is assisted by migration of one of the substituents from de carbonyl group to oxygen. The group R migrates with its pair of electrons in much the same way as alkyl groups migrate in carbocation rearrangements. In general, it is the more substituted group that migrates. The concerted O–O heterolysis and migration is usually the rate-determining step [10–12].

For acyclic compounds, R′ must usually be secondary, tertiary or vinylic, although primary R′ has been rearranged [13]. When the reaction involves an unsymmetrical compound, the structure of the product depends on which group migrates. A number of studies have been directed at ascertaining the basis of migratory preference in Baeyer–Villiger oxidation. From these studies, a general order of migration has been established: tertiary alkyl > secondary alkyl > aryl > primary alkyl > cyclopropyl > methyl [14]. The migrating ability of aryl groups is increased by electron donating and decreased by electron withdrawing substituents, because of the ability to accommodate partial positive charge [15]. Steric and conformational factors are also important, especially in cyclic compounds [16].

Some theoretical studies have been made in Baeyer–Villiger oxidations in order to show the influence of the catalyst [17], the effect of the halo-substituents [18], and the role of the hydrogen bonds in the mechanism of the reaction [19]. However, in those works, they do not classify the substrates in order of their reactivity, which is the aim of this work. We propose here the first reactivity study for substrates involved in Baeyer–Villiger oxidations by using DFT reactivity index.

In this Letter we present a theoretical model to quantitatively describe the σ_p Hammett substituent constants in terms of the global electrophilicity of aldehydes and ketones involved in Baeyer–Villiger oxidation reaction, using a global electrophilicity index [20,21]. We rank, within an absolute scale, the global electrophilicity of a series of (11) ketones and (6) aldehydes. The usefulness of

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the theoretical scale is illustrated for the rationalization of substituent effects on the electrophilic activation/deactivation reagents.

2. Theory

The concept of electrophilicity viewed as a reactivity index was introduced by Maynard et al. [20] to study the reaction of the human immunodeficiency virus type 1 (HIV-1) nucleocapsid protein p7 (NCp7) with a variety of electrophilic agents. It was reformulated by Parr et al. [21] using a second order expansion of the electronic energy with respect to the charge transfer ΔN at fixed geometry. Since 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 [21]:

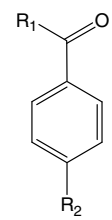
$$\omega = \frac{\mu^2}{2\eta} \tag{1}$$

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 [21]. It has been successfully used to describe 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 cycloadditions reactions [22,23]. It was also found that the difference in electrophilicity for the diene/dienophile pair determined the nature of the reaction mechanism (non-polar or polar character of the process), thereby reinforcing the reliability of the ω index as a kinetic descriptor of reactivity [22] This index is almost insensitive to solvent effects in neutral electrophiles, thus gas phase calculations suffice to establish the electrophilic power of molecules [24]. It has be shown that the intrinsic electronic contribution to the substituent σ_p Hammett constants, $\sigma_e(\omega)$, can be estimated from the ω index calculated for a series of substituted ethylenes [25]. Domingo et al. [25] found that electron withdrawing substitution increased the electrophilicity power of ethylene, and that the corresponding $\sigma_e(\omega)$ 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 [26]. The aim of this work is to 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.

3. Computational details

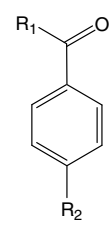
All the structures included in this study are shown in Chart 1. They were optimized at the B3LYP/6-311G** level of theory using the Gaussian03 package of programs [27]. The frontier orbital energies were obtained using the Hartree–Fock (HF) method and the 6-31G* basis set as was suggested by Vargas et al. [28]. 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, [29]. With these quantities, the global electrophilicity at the ground state of molecules was obtained using Eq. (1).

A 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

B 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.

4. Results and discussion

The global electrophilicity patterns of the substituting aldehydes (A) and ketones (B), 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 (ω = 0.562 eV), substitution at R2 by the weak electron releasing $-CH_3$ group results in an electrophilic deactivation in compound A5 (ω = 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 (ω = 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 (ω = 1.088 eV).

For the series of ketones, a similar picture is obtained. In this case, the structures are divided into two groups, the first one 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 (ω = 0.559 eV), substitution at R2 with chlorine and bromine atoms results in an electrophilic activation in compounds B2 (ω = 0.634 eV) and B3 (ω = 0.629 eV). The most activation effect is achieved by $-NO_2$ substitution at R2, in compound B1 (ω = 1.060 eV). In this series, it is clear the electrophilic deactivation promoted by electron releasing groups. Substitution at R2 by

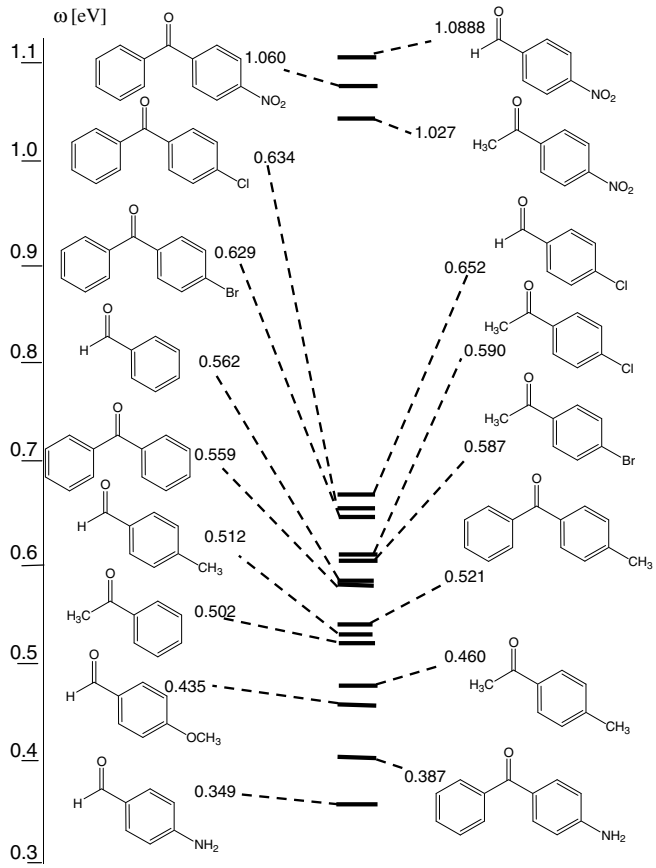


Chart 2. Theoretical scale of global electrophilicity for aldehydes and ketones involved in Baeyer–Villiger oxidation reactions.

$-CH_3$ group causes a deactivation in compound B5 (ω = 0.521 eV). As expected, the substitution by the stronger electron releasing $-NH_2$ group at position R2 in compound B6 (ω = 0.387 eV), results in a higher electrophilic deactivation. 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. For instance, the reference compound B10 (ω = 0.502 eV), substitution at R2 with chlorine and bromine atoms results again in an electrophilic activation in compounds B8 (ω = 0.590 eV) and B9 (ω = 0.587 eV). Also, the most activation effect is achieved by $-NO_2$ substitution at R2, in compound B7 (ω = 1.027 eV). Substitution at R2 by the weak releasing $-CH_3$ group causes a deactivation in compound B11 (ω = 0.460 eV). Table 1 shows the global electrophilicity values for the whole series of aldehydes and ketones for the GS of the substituting agents, and the σ_p Hammett substituent constants.

The usefulness of a reactivity scale has been clearly illustrated by Mayr et al. [30,31]. A reactivity scale should be able of answering fundamental questions about reaction feasibility, intramolecular selectivity and other important aspects of reactivity. First of all we observe in Figs. 1–3, that the relationship between σ_p Hammett constant and global electrophilicity index shows a positive slope. This is because strongly electrophilic reagents with electron withdrawing substituents lead to more positive σ_p Hammett constant values. We compare in Fig. 1 the σ_p Hammett substituent constant and the global electrophilicity index for the series of aldehydes evaluated at the HF/6-31G* level. The resulting regression equation is

$$\sigma_p = 1.515\omega - 0.827 \quad (2)$$

Table 1
Global electrophilicity values (ω) obtained at the HF/6-31G* level of theory for the ground states of aldehydes (A) and ketones (B)[a]

Compound	ω (eV)	σ_p Hammett
A1	1.088	0,81
A2	0.652	0.24
A3	0.562	0.00
A4	0.435	−0.12
A5	0.512	−0.14
A6	0.349	−0.30
B1	1.060	0.81
B2	0.634	0.24
B3	0.629	0.26
B4	0.559	0.00
B5	0.521	−0.14
B6	0.387	−0.30
B7	1.027	0.81
B8	0.590	0.24
B9	0.587	0.26
B10	0.502	0.00
B11	0.460	−0.14

[a] σ_p Hammett substituent constant from Ref. [12].

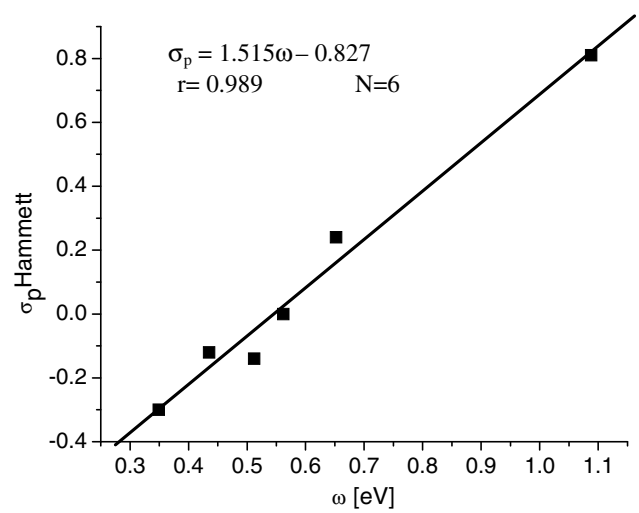


Fig. 1. Comparison between σ_p Hammett substituent constant and global electrophilicity (ω) evaluated at the ground states structure of a series of aldehydes. *r* is the regression coefficient and *N* is the number of points in the regression.

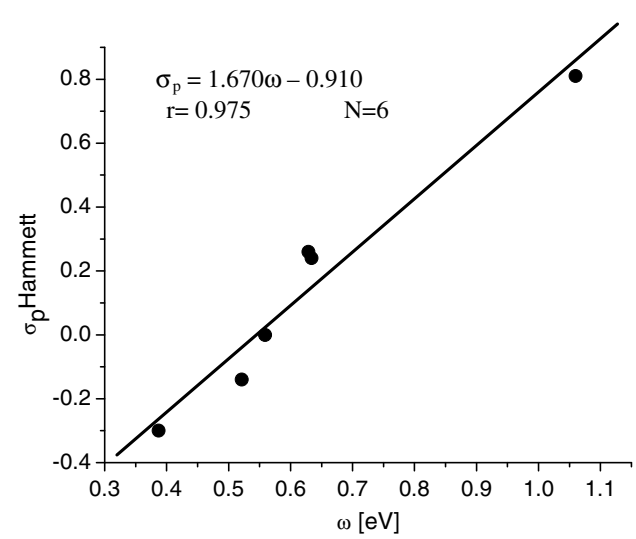


Fig. 2. Comparison between σ_p Hammett substituent constant and global electrophilicity (ω) evaluated at the ground states structure of a first series of ketones. *r* is the regression coefficient and *N* is the number of points in the regression.

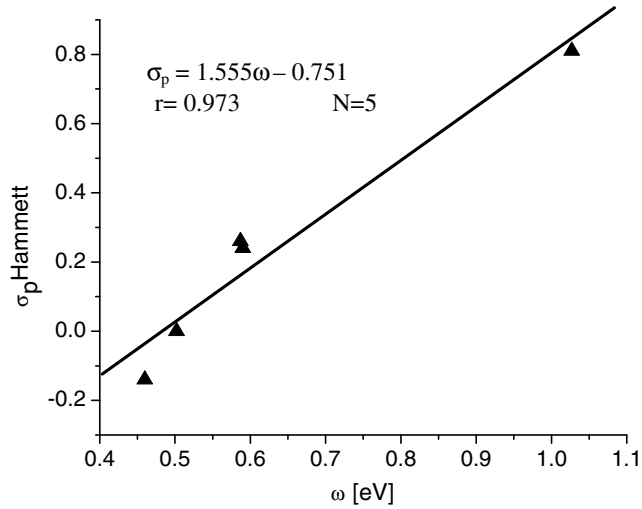


Fig. 3. Comparison between σ_p Hammett substituent constant and global electrophilicity (ω) evaluated at the ground states structure of a second series of ketones. *r* is the regression coefficient and *N* is the number of points in the regression.

The comparison between the σ_p Hammett substituent constant and the global electrophilicity at the ground state of ketones evaluated at the HF/6-31G* level is displayed in Figs. 2 and 3. The comparison yields the following regression equations:

$$\sigma_p = 1.670\omega - 0.910 \quad (3)$$

$$\sigma_p = 1.555\omega - 0.751 \quad (4)$$

In the three figures, it may be seen that in general there exist a true linear relationship between both variables. There remains however some improvements that can be made by explicitly introducing the catalyst, and evaluating the global electrophilicity of molecules at a more realistic stage of the reaction, namely the transition state.

In the ground state of the electrophiles involved in Baeyer–Villiger oxidation reactions, the electrophilicity scale correctly accounts for the electrophilic activation/deactivation effects promoted by the substituents. It is shown that electron withdrawing substituents increase the ability for an oxidation with a peroxyacid more than electron releasing substituents. This is due to the great activation of the carbonyl carbon promoted by resonant effects of electron withdrawing substituent, instead of the great stabilization and deactivation promoted by electron releasing groups in this carbonyl carbon of aldehydes and ketones.

5. Concluding remarks

The global electrophilicity of 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 and the experimental σ_p Hammett substituent constant shows a linear relationship.

Acknowledgments

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