

## Permanent group effect on nucleofugality in aryl benzoates

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### ARTICLE INFO

#### Article history:

Received 19 July 2010

In final form 17 August 2010

Available online 21 August 2010

### ABSTRACT

We herein report on the group electrophilicity of molecular fragments present in the title compounds to describe leaving group abilities in reactions of aryl benzoates toward  $\text{CN}^-$ . It is found that the presence of electron-withdrawing substituents in the permanent group enhances its electrophilicity, thereby contributing to the stabilization of the tetrahedral intermediate involved in the stepwise pathway. On the other hand electron-releasing substituents attached to the permanent group enhance the nucleofugality of the leaving groups in these systems. Substituent effects are used to rationalize the activation/deactivation patterns induced by electron-withdrawing and electron-releasing groups at the aromatic rings.

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### 1. Introduction

In the last time the acyl group has been reported to be involved in biological process as well as in synthetic applications [1]. For these reasons, acyl group transfer reactions of esters have been the subject of extensive experimental and theoretical studies and their mechanisms are well-established [2–8]. Depending on the nature of the electrophile/nucleophile pair, two mechanisms are possible: a concerted pathway [9,10], where the nucleophile attack at the electrophilic carbon in carbonyl group occurs simultaneously with the leaving group departure within a single step. Another possibility is the interaction of the nucleophile with the electrophilic carbon that may lead to the formation of a tetrahedral intermediate,  $\text{T}^\ddagger$ , from which the leaving group detaches. This mechanism is usually referred to as stepwise [7,9,10]. Linear free-energy relationships, such as Brønsted type-plot and Hammett equations, have been most commonly used to determine reaction mechanisms. Curved Brønsted type-plots, often found in the aminolysis of esters bearing good leaving groups, have been interpreted in terms of change in the rate-determining step for stepwise reactions [2,4,7,9,10]. The center of the curve in Brønsted type-plot has been defined as  $\text{p}K_a^0$ , for which the rate breakdown of the zwitterionic tetrahedral intermediate ( $\text{T}^\ddagger$ ) is the same as the rate of its formation [2,4,7,9,10]. The rate-determining step has been suggested to change at  $\text{p}K_a^0$  from breakdown of  $\text{T}^\ddagger$  to its formation, thereby indicating that the  $\text{p}K_a^0$  value is governed by the basicity of the nucleophile, solvent effects, polarizability, the nucleophile–nucleofuge interaction and the nucleofugality of the leaving group [11–15]. However, the effects of the permanent

group (PG) on the reaction mechanism is not yet completely understood. A general picture of the accepted reaction mechanism is depicted in Scheme 1. Castro et al. concluded that the  $\text{p}K_a^0$  values increase as the substituent in the PG bears a strong electron-withdrawing group [16]. These authors concluded that the electron-withdrawing substituent at the PG increased the  $\text{p}K_a^0$  value by decreasing the  $k_2/k_{-1}$  ratio, that is, an electron-withdrawing substituent in the PG favour the nucleophile expulsion, but retards the departure of the leaving groups from  $\text{T}^\ddagger$  [17].

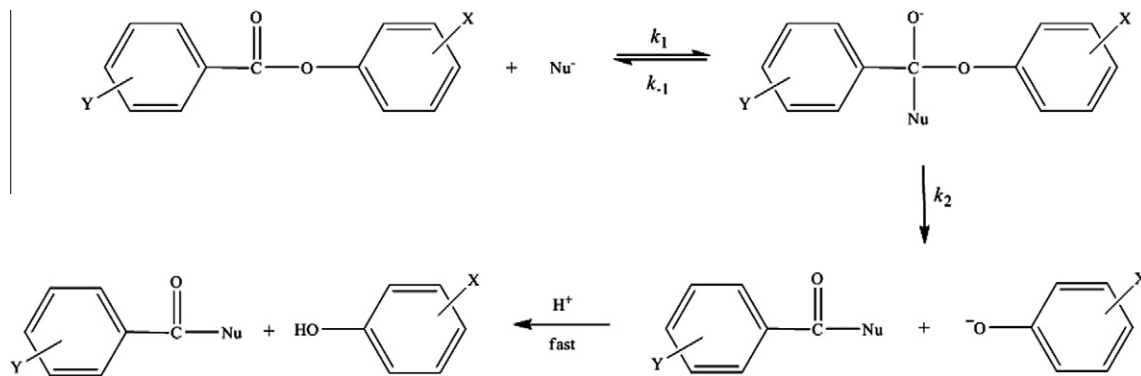
From a theoretical point of view, the chemical concepts introduced from the density functional theory of Parr and Yang [18] as for instance, the global electrophilicity and the electrophilic and nucleophilic Fukui functions, may help to understand the electronic factors that determine a given reaction mechanism. A set of recent review works illustrate well this point [19–22]. Based on these concepts, we have proposed that the regional electrophilicity of a chemical fragment given by the global electrophilicity index weighted by the electrophilic Fukui function can be taken as a measure of its nucleofugality in elimination and nucleophilic substitution reactions of carbonates and thio-derivatives [11–15]. The representation of nucleofugality within the conceptual density functional theory has been proposed on a more formal basis by Ayers et al. [23] These authors have specifically addressed the modelling of leaving groups including the effect of permanent groups which play the role of electrofuge in the heterolytic cleavage process [24,25].

In this work we show that the regional electrophilicity can be used to better understand the reaction mechanisms in a series of aryl benzoates (see Scheme 2) [26–28]. These substrates may schematically be partitioned into three fragments: PG–(CO)–LG where PG is the permanent group, CO is the carbonyl group and LG is the substituted phenoxide leaving group in the molecule. We propose that it is possible to assess the effect of the PG as an activating

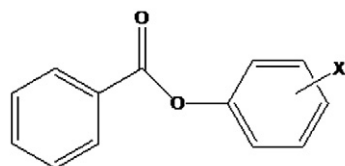
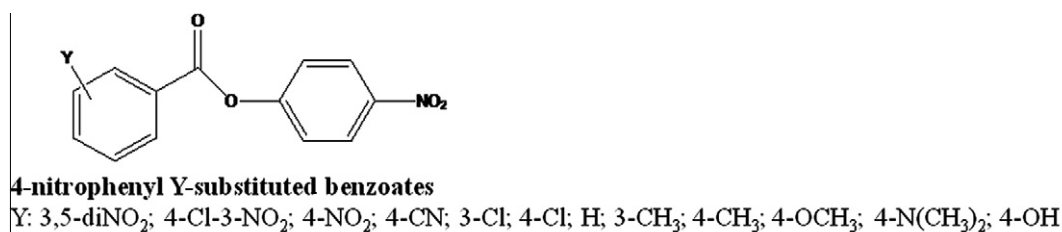
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**Scheme 1.** A general picture of the accepted reaction mechanism from reference [27].



**X-substituted phenyl benzoates**

X: 3,4-diNO<sub>2</sub>; 4-NO<sub>2</sub>; 4-CN; 4-CHO; 4-COCH<sub>3</sub>; 4-CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>; 3-NO<sub>2</sub>; 3-COCH<sub>3</sub>; 4-Cl; H; 4-CH<sub>3</sub>; 4-OCH<sub>3</sub>

**Scheme 2.** Structure of compounds studied in this work.

factor for the nucleophilic attack on one hand; and the group electrophilicity of the LG as a measure of their nucleofugality.

## 2. Model and computational details

The global electrophilicity index  $\omega$  which measures the stabilization in energy when the system acquires an additional electronic charge,  $\Delta N$ , from the environment, has been given the following simple expression: [29]

$$\omega = \frac{\mu^2}{2\eta} \quad (1)$$

in terms of the electronic chemical potential  $\mu$  and the chemical hardness  $\eta$ . These quantities may be approached in terms of the one electron energies of the frontier molecular orbital HOMO and LUMO,  $\varepsilon_H$  and  $\varepsilon_L$ , as  $\mu \approx \frac{\varepsilon_H + \varepsilon_L}{2}$  and  $\eta \approx \varepsilon_L - \varepsilon_H$ , respectively [18]. The electrophilicity index encompasses both, the propensity of the electrophile to acquire an additional electronic charge driven by  $\mu^2$  (the square of electronegativity,  $\chi = -\mu$ ), and the resistance of the system to exchange electronic charge with the environment described by  $\eta$ . The global electrophilicity is an additive property of the system, in the sense that it may be recovered from the semi local contributions condensed to atoms as follows:

$$\omega = \sum_k \omega_k \quad (2)$$

with,

$$\omega_k = f_k^+ \omega \quad (3)$$

$f_k^+$  is the electrophilic Fukui function (i.e. the Fukui function for nucleophilic attack [11–15]). Adding up the atomic electrophilicity over fragments in a molecule a group electrophilicity representing the nucleofugality of the fragment can be obtained as follows:

$$\omega(\text{LG}) \equiv \sum_{j \in \text{LG}} \omega_j \quad (4)$$

The global electrophilicity of the molecule is of course recovered from the sum over the three fragments. Ab initio HF/6-311G (d,p) calculations were performed using the Gaussian03 suite of programs [30] in order to evaluate the electronic quantities required to calculate the ground state electrophilicity index for the series of aryl benzoates considered in the present study (24 compounds) [26–28]. The electrophilic Fukui function,  $f_k^+$ , needed to project the global electrophilicity onto fragments, were obtained from single point calculations on the optimized ground state structures by a method described elsewhere [31,32].

## 3. Results and discussion

The nucleophilic substitution reactions of aryl benzoates in solution with reagents of varying nucleophilicity studied by Um

et al. is a suitable data base for the present study in the sense that the kinetic and mechanisms of these processes have been fully described [26–28]. Tables 1 and 2 display the global electrophilicity values and group electrophilicity values of the LG and the PG for a series of 4-nitrophenyl Y-substituted benzoates (12 compounds) and X-substituted phenyl benzoates (12 compounds) In Tables 1 and 2 the experimental nucleophilic rate coefficients,  $k_N$ , reported by Um et al. are included [26]. In Table 2 we have incorporated the experimentally determined Hammett substituent constants  $\sigma$  [8,33–35]. Experimentally, the reactions of 4-nitrophenyl Y-substituted benzoates and X-substituted phenyl benzoates with negatively charged and neutral nucleophiles ( $\text{CN}^-$ ,  $\text{OH}^-$  or piperidine) proceed with quantitative liberation of 4-nitrophenoxide or the corresponding aryloxyde (LG), respectively [26].

Table 1 summarizes the group properties for the series of 4-nitrophenyl Y-substituted benzoates. The leaving group has been kept constant in order to assess the effect of the group electrophilicity of the phenyl substituted moiety (PG). It may be observed that the group electrophilicity values at the PG decrease as the substituent Y changes from an electron-withdrawing substitution pat-

tern to an electron-releasing substituent pattern from 3,5-diNO<sub>2</sub> to 4-OH. Note that the presence of electron-withdrawing substituents in these substrates improve their reactivity, as it can be seen from their  $k_N$  values. On the other hand, electron-releasing substituents improve the leaving group ability in these substrates, described by their group electrophilicity values at the LG. The enhanced group electrophilicity of the LG (compounds 5–11) is interpreted here as an activating effect that help the nucleophile expulsion from  $\text{T}^\ddagger$  through the channel  $k_{-1}$  thereby retarding the departure of the LG from  $\text{T}^\ddagger$  (see the pre-equilibrium in Scheme 1 and  $k_N$  values in Table 1) [17]. Based on these results, we can conclude that the substituent at the PG has an effect on the nucleofugality of the LG that in some cases may become significant [7,16]. The plot of  $\log k_N$  vs the group electrophilicities at the LG and PG moieties is shown in Figure 1. The comparison shows two straight lines with different slopes. It may be seen that the presence of electron-releasing groups on the PG results in an electrophilic activation at the LG (solid line in Figure 1 for compounds 5–12). On the other hand, the presence of electron-withdrawing groups on the PG (dashed line in Figure 1 for compounds 1–4) increases the reactiv-

Table 1

Electrophilicity index of 4-nitro phenyl Y-substituted benzoates, evaluated at the HF/6-311G (d,p) level of theory.

| Compound | $\omega$ (eV) | Y                                  | $\omega_{\text{PG}}$ (eV) | $\omega_{\text{LG}}$ (eV) | $k_N^a$ ( $\text{M}^{-1} \text{s}^{-1}$ )  |
|----------|---------------|------------------------------------|---------------------------|---------------------------|--|
| 1        | 1.23          | 3,5-diNO <sub>2</sub>              | 1.23                      | 0.00                      | 42.5                                       |
| 2        | 1.01          | 4-Cl-3-NO <sub>2</sub>             | 0.93                      | 0.08                      | 8.17                                       |
| 3        | 1.11          | 4-NO <sub>2</sub>                  | 1.10                      | 0.01                      | 6.25                                       |
| 4        | 0.98          | 4-CN                               | 0.97                      | 0.01                      | 4.47                                       |
| 5        | 0.77          | 3-Cl                               | 0.10                      | 0.67                      | 1.33                                       |
| 6        | 0.79          | 4-Cl                               | 0.10                      | 0.69                      | 0.628                                      |
| 7        | 0.75          | H                                  | 0.10                      | 0.65                      | 0.228                                      |
| 8        | 0.70          | 3-CH <sub>3</sub>                  | 0.09                      | 0.61                      | 0.189                                      |
| 9        | 0.72          | 4-CH <sub>3</sub>                  | 0.14                      | 0.58                      | 0.117                                      |
| 10       | 0.66          | 4-OCH <sub>3</sub>                 | 0.08                      | 0.58                      | 0.046                                      |
| 11       | 0.54          | 4-N(CH <sub>3</sub> ) <sub>2</sub> | 0.09                      | 0.45                      | 0.00265                                    |
| 12       | 0.68          | 4-OH                               | 0.08                      | 0.60                      | $3.57 \times 10^{-4}$ (0.114) <sup>*</sup> |

<sup>a</sup>  $k_N$  values taken from reference [26].

<sup>\*</sup> Predicted values were obtained from Eq. (5).

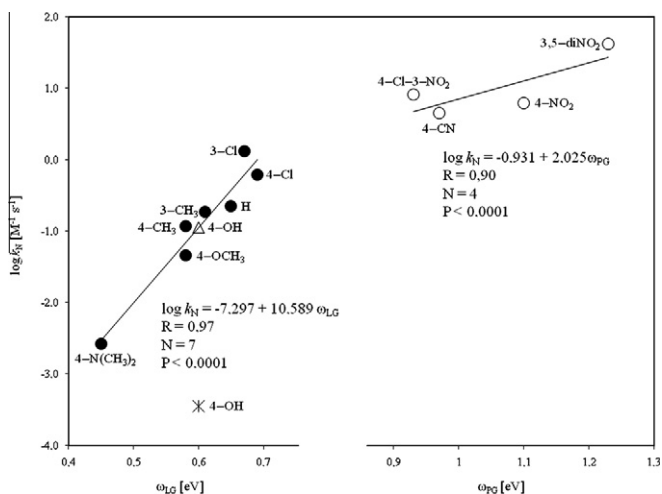
Table 2

Electrophilicity index of X-substituted phenyl benzoates, evaluated at the HF/6-311G (d,p) level of theory.

| Compound | $\omega$ (eV) | X   | $\omega_{\text{LG}}$ (eV) | $\Delta\omega_{\text{LG}}$ (eV) | $\sigma$          | $k_N^a$ ( $\text{M}^{-1} \text{s}^{-1}$ ) |
|----------|---------------|---|---------------------------|---------------------------------|-------------------|---|
| 13       | 0.94          | 3,4-diNO <sub>2</sub>                             | 0.90                      | 0.89                            | 0.83 <sup>*</sup> | 1.92                                      |
| 14       | 0.75          | 4-NO <sub>2</sub>                                 | 0.72                      | 0.71                            | 0.78              | 0.231                                     |
| 15       | 0.61          | 4-CN  | 0.61                      | 0.60                            | 0.66              | –   |
| 16       | 0.61          | 4-CHO   | 0.35                      | 0.34                            | 0.42              | 0.103                                     |
| 17       | 0.57          | 4-COCH <sub>3</sub>                               | 0.20                      | 0.19                            | 0.50              | 0.0768                                    |
| 18       | 0.56          | 4-CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> | 0.09                      | 0.08                            | 0.45              | –   |
| 19       | 0.77          | 3-NO <sub>2</sub>                                 | 0.77                      | 0.76                            | 0.71              | 0.141                                     |
| 20       | 0.56          | 3-COCH <sub>3</sub>                               | 0.21                      | 0.20                            | 0.38              | 0.0359                                    |
| 21       | 0.53          | 4-Cl  | 0.01                      | 0.00                            | 0.23              | –   |
| 22       | 0.66          | H   | 0.01                      | 0.00                            | 0.00              | 0.0102                                    |
| 23       | 0.47          | 4-CH <sub>3</sub>                                 | 0.01                      | 0.00                            | –0.17             | 0.00783                                   |
| 24       | 0.83          | 4-OCH <sub>3</sub>                                | 0.01                      | 0.00                            | –0.27             | 0.00843                                   |

<sup>a</sup>  $k_N$  values taken from reference [26].

<sup>\*</sup> Predicted values were obtained from Eq. (7).



**Figure 1.** Comparison between the experimental nucleophilic rate coefficient,  $k_N$ , for the reactions of the 4-nitrophenyl Y-substituted benzoates series with  $\text{CN}^-$  and the group electrophilicity index evaluated at the HF/6-311G (d,p) level theory.

ity of the substrates. Note that, compound **12** escapes from the solid line in Figure 1 marked with an asterisk. This result may be traced to a regional preferential solvation of the OH- group (80/20 water/DMSO) that diminishes its electron-releasing effect probably expressed as a more facile hydrogen bonding interaction to the solvent.

A regression analysis  $\log k_N$  vs the group electrophilicity at the LG was performed for the set of molecules except compound **12** (compounds **5–11**). The resulting empirical equation is:

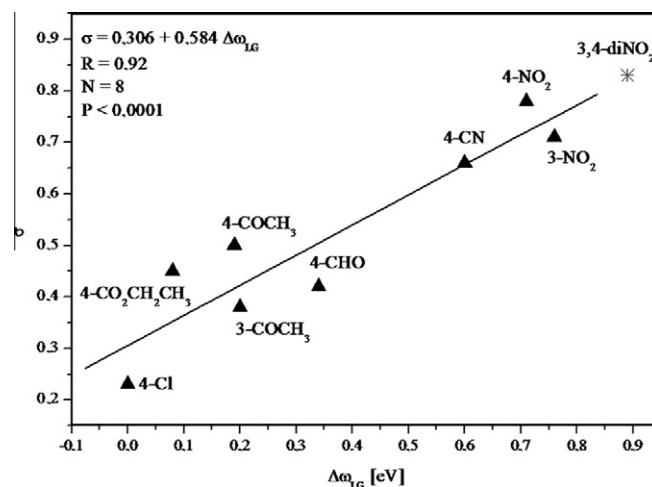
$$\log k_N = -7297 + 10,589 \omega_{LG} \quad R = 0.97 \quad N = 7 \quad P < 0.0001 \quad (5)$$

Based on Eq (5) it is possible to give an estimate for the rate coefficient value for compound **12** ( $k_N = 0114 \text{ M}^{-1} \text{ s}^{-1}$ ). Note that this time compound **12** appears correctly bound by compounds **9** and **10** respects to their corresponding  $k_N$  values. For the second series involving electron-withdrawing substituents (compounds **1–4**); the resulting regression equation is:

$$\log k_N = -0931 + 2025 \omega_{PG} \quad R = 0.90 \quad N = 4 \quad P < 0.0001 \quad (6)$$

From Eq (6) it may be observed that compounds bearing electron-withdrawing groups show an enhanced reactivity with increasing electron accepting power of the substituents at the PG moiety. These results are in agreement with the conclusions drawn by Gresser and Jencks [7] and Castro et al. [16]. One would expect in this case a change on the rate-determining step [26–28] towards the detachment of the LG. However, experimentally, the rate-determining step for the  $\text{S}_{\text{N}}1$  reactions of the title compounds is the nucleophilic attack [26]. The presence of two linear trends may be traced to an electronic substituent effect at the PG: an electron-releasing substituent enhances the electrophilicity of the LG moiety improving the departure of the nucleofuge from the  $\text{T}^\ddagger$ . Therefore, the electrophilic activation at the PG is not sufficient to change the reaction mechanism. The net effect of the group electrophilicity at both the PG and LG moieties is completely consistent with the experimental rate coefficients quoted in Table 1.

In order to assess the effect of the group electrophilicity at the LG, we selected a new series of reactions where this time the PG is kept fixed. Now, the accumulation of electrophilicity at the LG has a different effect on the whole structure. The presence of the strong electron-withdrawing  $-\text{NO}_2$  group results this time in an enhancement of the nucleofugality of the LG (compounds **13**, **14** and **19**). Note that this effect is coherently expressed in terms of



**Figure 2.** Comparison between the experimental Hammett substituent,  $\sigma$ , for the reactions of X-substituted phenyl benzoates with  $\text{CN}^-$  and the group electrophilicity index evaluated at the HF/6-311G (d,p) level theory.

the experimental rate coefficients included in Table 2. Addition of activating substituents on the LG improves the leaving group ability because the net electronic effect is the destabilization of the tetrahedral intermediate,  $\text{T}^\ddagger$ , from which the leaving group detaches.

In Table 2 Hammett substituent constants for a series of X-substituted phenyl benzoates are included. Figure 2 displays the comparison between Hammett substituent constant,  $\sigma$ , and the group electrophilicity values at the LG. We introduce a group electrophilicity difference  $\Delta \omega_{LG}$  with reference to the unsubstituted LG with X = H. The resulting regression equation is:

$$\sigma = 0306 + 0584 \Delta \omega_{LG} \quad R = 0.92 \quad N = 8 \quad P < 0.0001 \quad (7)$$

This series contains compounds bearing *para*- and *meta*-substitution with strong and moderate electron-withdrawing groups. Note further that compounds **16**, **17**, **18** and **20** are predicted to display nucleophilic rate coefficients ( $k_N$ ) smaller than those shown by the  $-\text{NO}_2$  group at the *meta* (compound **19**) and *para* (compound **14**) positions of the phenyl ring. It is interesting to notice that Hammett substituent constant values [33–35] correlate well with the relative electrophilicity index on the LG.[8,33] Based on the empirical Eq. (7) the  $\sigma$  value for compound **13** (3,4-diNO<sub>2</sub>) that have not been experimentally evaluated to date can be predicted ( $\sigma = 0.83$ ). Note that the predicted  $\sigma$  value is consistent with a larger rate coefficient value ( $k_N = 1.92 \text{ M}^{-1} \text{ s}^{-1}$ ). Note also that compounds **23** and **24** break the linear regime obtained. This result may be traced to a change in the rate-determining step for the formation of the tetrahedral intermediate [7,8,17].

#### 4. Concluding remarks

An empirical model based on the group electrophilicity of molecular fragment has been applied to a series of aryl benzoates that follow a stepwise mechanism towards  $\text{CN}^-$ . It is found that the presence of electron-withdrawing substituents in the permanent group enhance the electrophilicity of the permanent group, a result that may be traced to the stabilization of the tetrahedral intermediate involved in the stepwise pathway. Electron-releasing groups attached to the permanent group enhance the nucleofugality of the leaving groups in these systems. Substituent effects are used to rationalize their reaction mechanism and the activation/deactivation patterns induced by electron-withdrawing and electron-releasing groups at the aromatic ring. New Hammett substituent

constants are predicted for compounds that have not been experimentally evaluated to date.

### Acknowledgment

This work received financial support from Fondecyt, Projects 1100492 and 1070715. Support from USM Project 130922 is also acknowledged.

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