

Kinetic and theoretical study on nucleofugality in the phenolysis of 3-nitrophenyl and 4-nitrophenyl 4-cyanophenyl thionocarbonates

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ABSTRACT

The phenolysis of 3-nitrophenyl 4-cyanophenyl thionocarbonate (**1**) and 4-nitrophenyl 4-cyanophenyl thionocarbonate (**2**) are subjected to a kinetic investigation in order to evaluate the nucleofugality of the corresponding leaving groups. For the reaction of **2** only 4-nitrophenoxide is obtained as leaving group. For the reaction of **1** the nucleofugality ratio 3-nitrophenoxide/4-cyanophenoxide is 1/3 from the corresponding T⁻ intermediate. Theoretical calculations confirm the experimental results. From these results it can be concluded that the non-leaving group affects the nucleofugality ratio.

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1. Introduction

Leaving groups are defined as fragments that detach bearing the bonding electron pair during a heterolytic bond breaking process. These fragments, termed as nucleofuges, are present in two important classes of reactions, namely nucleophilic substitution and elimination. There have been several works concerning leaving ability (nucleofugality) of different groups both from the experimental [1–5] and theoretical points of view [6–10].

Stirling has stated that for the proposal of reliable scales of nucleofugality, the involvement of the leaving group in the rate-determining step is a crucial requisite for this purpose [1]. Concerning this subject, Mayr and co-workers [5] have established a scale of leaving group abilities based on the S_N1 solvolysis reactions of benzhydryl derivatives, which yield a carbocation and the nucleofuge. As the rate constants of these reactions are affected by the solvent, [11–12], these nucleofugality values correspond to the nucleofuge–solvent pair [5,11,12]. The latter apparently is not a problem because it was demonstrated that the solvent change does not alter the nucleofugality trend [5,11,12]. Furthermore, it has been established that in S_N1 solvolysis, the rate constants are influenced by steric and electronic interactions in the substrates [13,14].

On the other hand, good leaving groups are in general conjugate bases of strong acids. Therefore, nucleofugality also depends on the pK_a (H₂O) of the conjugate acid of the leaving group. At this respect

there are several studies that show linear free energy relationships between log *k_N* vs. pK_a of the conjugate acid of the leaving group (LG) [15].

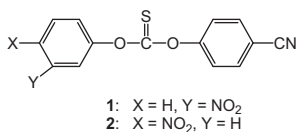
In this Letter we hypothesize that useful nucleofugality ordering may be achieved by working in the same environment (solvent) condition and fixing the nucleophile. Under these conditions, the detachment of specific leaving groups may easily be implemented by choosing nucleophilic reactions of substrates with two potential nucleofuges of the same nature (e.g., both phenoxides).

We are interested in the study of nucleofugality involved in nucleophilic reactions, in which the nucleofuge departure is not necessarily involved in the rate-determining step. A question can be formulated: when the nature of both possible nucleofuges is the same, how the non-leaving group affects the nucleofugality of the nucleofuge? The answer can be found by studying nucleophilic reactions of diaryl carbonates or thionocarbonates, where both possible leaving groups belong to the same family (both phenoxides). This is because if there is a small difference in the pK_a values of the nucleofuges, it could be possible that both nucleofuges depart in parallel paths and not necessarily that the less basic one leaves alone. In the latter reactions the non-leaving group could act by favoring or not the departure of the nucleofuge.

In order to evaluate the nucleofugality of groups of the same nature we performed an integrated kinetic and theoretical study for the phenolysis of 3-nitrophenyl 4-cyanophenyl thionocarbonate (**1**) and 4-nitrophenyl 4-cyanophenyl thionocarbonate (**2**) (see Scheme 1). A HPLC analysis of the reaction products in both series was carried out in order to identify the nucleofuge(s) at different times.

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Scheme 1. General structures of the compounds used in this study.

2. Experimental

2.1. Materials

Synthesis and analytical properties of thionocarbonate **1** are shown in [Supplementary material](#). Thionocarbonate **2** was prepared as reported [16].

2.2. Determination of pK_a

The pK_a values of 3-nitrophenol and 2,3,5,6-tetrafluorophenol were determined spectrophotometrically by the reported method [17]. The experimental conditions used were the same as those for the kinetic measurements: 44 wt% ethanol–water, 25.0 ± 0.1 °C and ionic strength 0.2 M (maintained with KCl). The pK_a values obtained for 3-nitrophenol and 2,3,5,6-tetrafluorophenol are 9.3 and 7.0, respectively.

2.3. Kinetic measurements

The kinetics of the reactions were analyzed through a diode array spectrophotometer in 44 wt% ethanol–water, at 25.0 ± 0.1 °C and an ionic strength of 0.2 M (maintained with KCl). The reactions were followed at the 300–500 nm wavelength range. All reactions were studied under at least a 10-fold phenol excess over the substrate, with the initial concentration of the latter being 2.5×10^{-5} M.

The reactions of **1** were followed at 400 nm and the absorbance vs. time curves were adjusted with an equation derived by considering a parallel and consecutive reactions model (see [Scheme S1 in Supplementary material](#)). The k_{obsd} values calculated and the experimental conditions for the reactions of **1** are shown in [Tables S1–S7, in Supplementary material](#). In all the reactions the pH was maintained constant either by the buffer formed by partial protonation of the nucleophile or by the addition of an external buffer. For the reactions of **2**, pseudo-first-order rate coefficients (k_{obsd}) were found throughout, the kinetics being measured for at least five half-lives at 400 nm, following 4-nitrophenoxide ion formation. The k_{obsd} values obtained and the experimental conditions for these reactions are shown in [Tables S8–S13 in Supplementary material](#).

2.4. Product studies

These were carried out by UV–vis spectrophotometry, by comparison of the spectra at the end of the reactions with those corresponding to authentic samples. Also employed for the products analysis was HPLC with a diode array detector, provided with LiChroCART® 250–4 HPLC-RP-18e (5 μm), HPLC Cartridge LiChrosphere® 100 RP 8, mobile phase 50% v/v CH₃CN:phosphate buffer (0.01 M/pH = 7.00), flow rate: 1.5 mL/min. The products were identified by comparison of their spectra and retention times (r.t.) with those of authentic samples.

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2.4.1. At long times

The HPLC analysis performed at the end of the reactions of thionocarbonates **1** and **2** with phenol at the end of the reactions showed the formation of bis(phenyl) thionocarbonate (r.t. = 15.6 min, λ_{max} = 215 nm). These analyses were carried out by comparison with authentic samples. In the reactions of thionocarbonates **1** and **2** also 4-cyanophenol (r.t. = 3.16 min, λ_{max} = 282 nm) and the corresponding nitrophenoxide were found (3-nitrophenoxide ion, r.t. = 4.04 min, λ_{max} = 416 nm; 4-nitrophenoxide ion, r.t. = 1.6 min, λ_{max} = 400 nm).

2.4.2. At short times

The kinetics of thionocarbonate **1** with phenol (1.0×10^{-3} M, pH 10.0) was followed point-to-point through HPLC analysis and the complex kinetics was confirmed. This showed the presence of 3-nitrophenoxide (r.t. = 4.04 min, λ_{max} = 416 nm) and 4-cyanophenoxide (r.t. = 3.16 min, λ_{max} = 282 nm) anions during the time of the kinetic measurements, by comparison with authentic samples. These were quantified by comparison with calibration curves for 4-cyanophenol and 3-nitrophenol in the presence of phenol (to simulate the same conditions of the kinetics). The quantitative analysis for thionocarbonate **1** showed 75% of 4-cyanophenoxide and 25% of 3-nitrophenoxide anions.

For the reactions of thionocarbonate **2**, 4-nitrophenoxide was identified spectrophotometrically, as well as by HPLC, as one of the products during the time of the kinetic measurements. The presence of 4-cyanophenol in the reactions of **2** was not detected during these times. At much longer times, the presence of 4-cyanophenol was found by HPLC analysis (see above).

3. Results and discussion

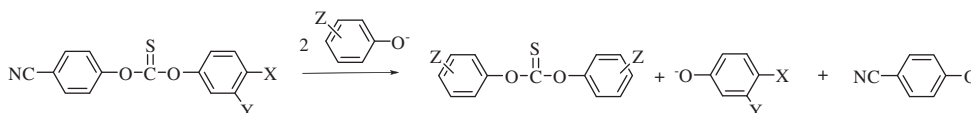
The HPLC analysis at the end of the reactions suggests that the phenolysis reactions of thionocarbonates **1** and **2** proceed as shown in [Scheme 2](#).

The phenolysis of thionocarbonate **1** follows the pathway illustrated in [Scheme S1 \(in Supplementary material\)](#). The nucleofugality of the two possible leaving groups determines one of the two possible pathways. The parallel reaction pathway is also possible.

[Figure 1](#) illustrates the absorbance vs. time curves (400 nm) for the reactions of **1** with phenol.

This spectrophotometric behavior suggests the appearance of 3-nitrophenoxide in a reaction involving two consecutive steps (see [Scheme in Supplementary material](#)). The rate law for this process is described by Eq. (1) (this equation is derived in detail in [Supplementary material](#)). In this equation, A , ε and $[S]_0$ are the absorbance (400 nm) at time t , the molar absorption coefficient of 3-nitrophenoxide (at 400 nm) and the substrate initial concentration, respectively. The constants $k_{\text{obsd}1}$, $k_{\text{obsd}2}$ and $k_{\text{obsd}3}$ are the rate constants defined in [Scheme S1](#) in [Supplementary material](#). The $k_{\text{obsd}4}$ channel is not considered in this equation because this reaction does not contribute to the absorbance at 400 nm:

$$A = \varepsilon \left([S]_0 - [S]_0 e^{-(k_{\text{obsd}1} + k_{\text{obsd}2})t} \frac{k_{\text{obsd}2} [S]_0}{k_{\text{obsd}3} - (k_{\text{obsd}1} + k_{\text{obsd}2})} (e^{-(k_{\text{obsd}1} + k_{\text{obsd}2})t} - e^{k_{\text{obsd}3}t}) \right) \quad (1)$$



Scheme 2. General scheme for the phenolysis of thionocarbonates **1** and **2** and their reaction products.

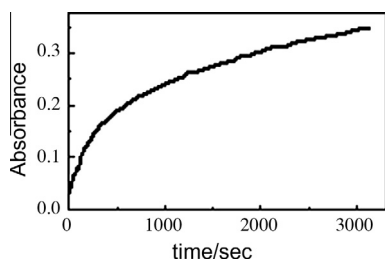


Figure 1. Plot of absorbance (at 400 nm), due to 3-nitrophenoxide appearance, vs. time for the reactions of **1** with phenol (at pH 10.00, $[\text{phenol}]_{\text{total}} = 3.22 \times 10^{-2}$), in 44% ethanol–water, at 25.0 ± 0.1 °C and an ionic strength of 0.2 M (KCl).

The curves of absorbance (A) versus time (t) were satisfactorily adjusted with Eq. (1). Figure S1 (in Supplementary material) shows, as an example, the fitting of Eq. (1) to the experimental kinetic points. The values of $k_{\text{obsd}1}$ and $k_{\text{obsd}2}$ for the phenolysis of thionocarbonate **1** are summarized in Tables S1–S7, all of them in Supplementary material. These and are in accordance with Eq. (2), where k_0 and k_N are the rate coefficients for solvolysis and phenolysis of the substrate, respectively. The values of k_0 and k_N showed no dependence on pH within the pH range employed, disregarding an acid–base catalysis. These values were obtained as the intercept and slope, respectively, of linear plots of k_{obsd} against free phenoxide concentration, at constant pH. The k_0 values were much smaller than the k_N [free phenoxide] term in Eq. (2), disregarding the solvolysis reaction:

$$k_{\text{obsd}(1 \text{ or } 2)} = k_0 + k_{N(1 \text{ or } 2)} [\text{free phenoxide}] \quad (2)$$

From the slope of linear plots of $k_{\text{obsd}1}$ and $k_{\text{obsd}2}$ against free phenoxide concentration the second-order nucleophilic rate coefficients (k_{N1} and k_{N2}) were determined. The k_N values are shown in Table 1 for compound **1**. For the phenolysis of **1** the Brønsted-type plots for k_{N1} and k_{N2} (Figure S2 in Supplementary material) are in accordance with a stepwise mechanism with a change in the rate-determining step, from the formation of the anionic tetrahedral intermediate to its breakdown, as the phenoxide basicity decreases [18–20]. Taking into account that in these reactions there are two nucleofuges, 3-nitrophenoxide and 4-cyanophenoxide anions (see product analysis in Section 2), and only one anionic tetrahedral intermediate (T^-) can be formed initially, the most likely mechanism is that shown in Scheme 3. In this scheme the tetrahedral intermediates involved in paths 3 and 4 have been omitted for clarity reasons. Applying the steady state condition to the anionic tetrahedral intermediate (T^-) in Scheme 3, Eq. (3) is obtained:

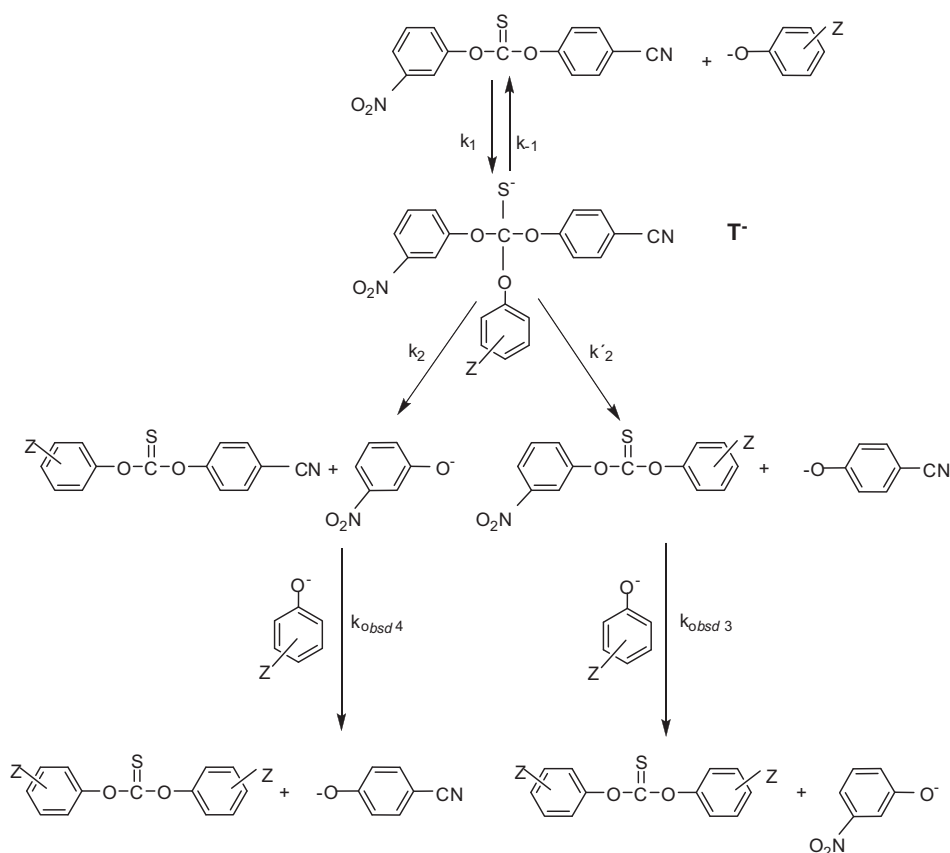
Table 1

Values of pK_a for the phenols and nucleophilic rate constants (k_{N1} and k_{N2}) for the phenolysis of **1**.^{a,b}

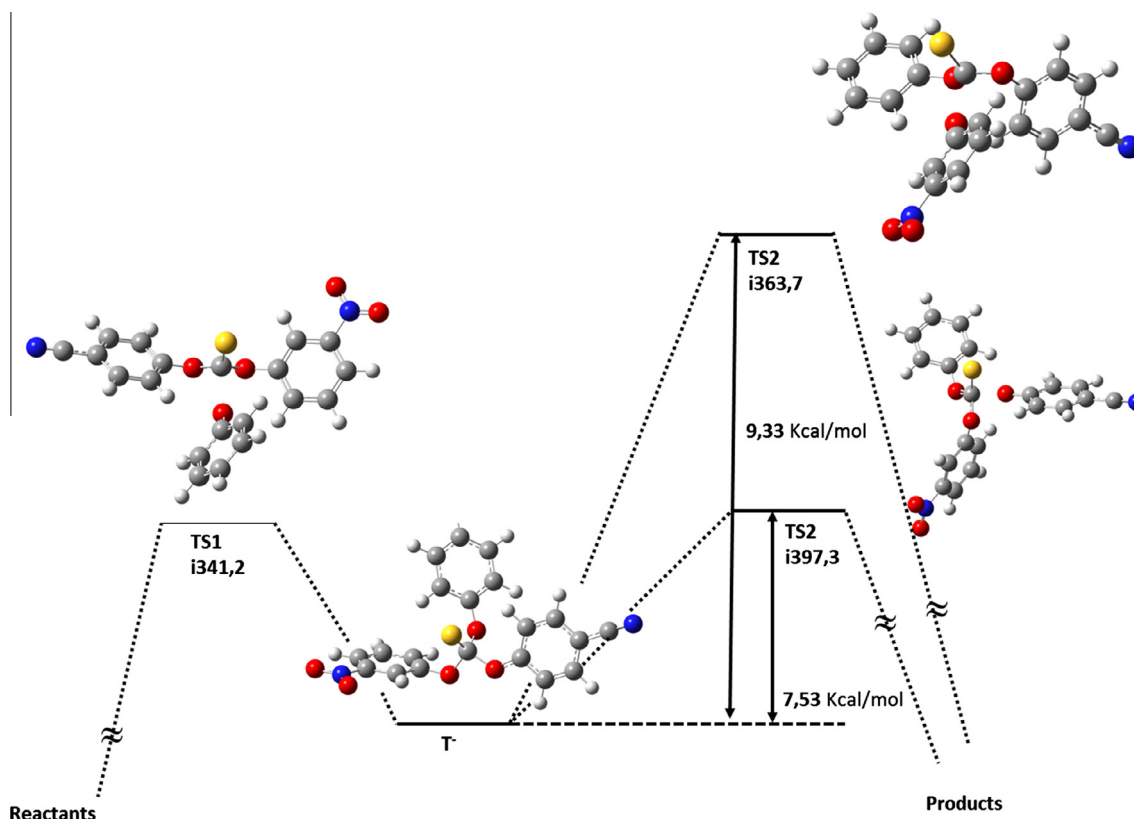
Phenol	pK_a	$10^2 k_{N1}$ ($M^{-1} s^{-1}$)	$10^2 k_{N2}$ ($M^{-1} s^{-1}$)
4-Methoxyphenol	11.55	68 ± 3	370 ± 30
Phenol	11.16	71 ± 3	278 ± 19
4-Chlorophenol	10.47	23 ± 1	136 ± 8
4-Cyanophenol	8.40	8.5 ± 0.4	–
2,6-Difluorophenol	8.21	6.2 ± 0.3	8.6 ± 0.3
2,3,5,6-Tetrafluorophenol	7.02	0.68 ± 0.04	2.3 ± 0.2
2,3,4,5,6-Pentafluorophenol	5.45	0.19 ± 0.01	0.11 ± 0.01

^a Both the pK_a and k_N values were obtained in 44 wt% ethanol–water, at 25.0 ± 0.1 °C and an ionic strength of 0.2 M.

^b Errors shown are standard deviations.



Scheme 3. Probable mechanism for the phenolysis of **1**.



Scheme 4. Potential energy profile for the reaction of compound **1** with phenoxide anion as nucleophile.

$$k_N = k_1(k_2 + k'_2)/(k_{-1} + k_2 + k'_2) \quad (3)$$

For the more basic phenols, $k_{-1} \ll (k_2 + k'_2)$ in Eq. (3) and $k_N = k_1$: the formation of T^- is the rate determining step [18–20]. As only one anionic tetrahedral intermediate can be formed initially, the nucleophilic rate constant for the reactions with these more basic phenols is $k_1 = k_{N1} + k_{N2}$. On the other hand, for the reactions with the less basic phenols, the breakdown to products of T^- is the rate-determining step, ($k_{-1} \gg k_2 + k'_2$) and $k_N = K_1(k_2 + k'_2)$, where K_1 is the equilibrium constant for formation of T^- [18–20]. In this case, $k_{N1} = K_1 k_2$ and $k_{N2} = K_1 k'_2$. The ratio of formed products is $k_{N1}/k_{N2} = k_2/k'_2$. For the reaction of unsubstituted phenol with **1** this ratio has been found to be 0.3 (see Section 2); namely, 4-cyanophenoxide is expelled three times faster than 3-nitrophenoxide from the anionic tetrahedral intermediate. For the phenolysis of **1**, both phenoxide anions are nucleofuges (see Section 2), even though the difference in pK_a is 0.9 unit: the pK_a of 4-cyanophenol and 3-nitrophenol are 8.4 [21] and 9.3 (this work), respectively. Note that the effect of the nucleophile on the k_{N2}/k_{N1} ratio within the series of nucleophiles compiled in Table 1 is mostly associated with the position of the substituent, taking phenol as reference. For instance, the k_{N2}/k_{N1} ratio for substitution at position four enhances this ratio, whereas substitution at the ortho position has a marginal effect. However, a linear relationship in terms of Hammett substituent constants can not be cleanly established.

In order to confirm the kinetic results obtained for compound **1**, we performed a potential energy surface (PES) exploration in the gas phase, associated with the phenoxide anion attack and leaving group abilities of 4-cyanophenoxide and 3-nitrophenoxide anions, (see Scheme 4). Note that the energy gaps between the anionic tetrahedral intermediate (T^-) and the transition state (TS) structures associated to the leaving groups departure are: 7.5 kcal/mol and

9.3 kcal/mol for 4-cyanophenoxide anion and 3-nitrophenoxide anion, respectively. The major stabilization of the TS structure is associated to 4-cyanophenoxide anion departure, which is in agreement with the kinetic results, thereby reinforcing the mechanism proposed for the reaction of compound **1** in Scheme 3.

Until this point, we have referred to the basicity concept as Brønsted basicity, i.e. the affinity of phenoxides toward a proton. However, as Swain and Scott [22] pointed out, the term basicity is related to equilibrium measurements and as such it is to be considered as a thermodynamic concept. Nucleophilicity and its parent concepts, nucleofugality and electrofugality, as well as electrophilicity [23] on the other hand, are kinetic concepts related to rate constants [24]. Parker elaborated a useful concept termed carbon basicity to describe affinity of bases towards positively charged carbon groups, such as an alkyl cation [25]. Subsequently, it was pointed out that carbon basicities or even sulphur basicities are usually greater than their hydrogen basicities (i.e., pK_a values) or the corresponding oxygen basicity [26]. Apart from its intrinsic interest, the basicities of nucleophiles towards elements other than hydrogen may become significant because it can affect rates of substitution reactions involving mechanisms of intermediate complexity, as is the case of the present study. More recently, Mayr's group as persuasively argued in favor of C-basicities as one of the factors that may significantly affect reaction barriers [27,28]. Therein, enhanced nucleophilicity effect induced by C-basicities was examined for a series of nucleophiles reacting toward benzydryl cations as reference electrophiles.

Therefore, in order to introduce this concept we have evaluated the carbon basicity of the phenoxide leaving groups attached to the central carbonyl carbon of the electrophile (compound **1**). The reaction channel for compound **1** may lead to two products, as sketched in Scheme 3. Carbon basicities have been approached by the free energy of the reaction of compound **1** with unsubstituted

Table 2

Values of pK_a for the phenols and nucleophilic rate constants (k_N) for the phenolysis of **2**.^{a,b}

Phenol	pK_a	$10^2 k_N$ ($M^{-1} s^{-1}$)
Phenol	11.16	354 ± 9
4-Chlorophenol	10.47	216 ± 4
4-Cyanophenol	8.40	65 ± 2
2,6-Difluorophenol	8.21	25 ± 1
2,3,5,6-Tetrafluorophenol	7.02	1.5 ± 0.1
Pentafluorophenol	5.45	0.10 ± 0.01

^a Both the pK_a and k_N values were obtained in 44 wt% ethanol–water, at 25.0 ± 0.1 °C and an ionic strength of 0.2 M.

^b Errors shown are standard deviations.

phenoxide, leading to the products associated to the departure of 4-cyanophenoxide and 3-nitrophenoxide anions. The outcome is $\Delta G^\circ = 2.1$ kcal/mol and $\Delta G^\circ = 2.9$ kcal/mol, respectively, thereby showing that in these cases the contribution of carbon basicity to the nucleofugality of the leaving group (LG) almost parallels that of the Brønsted basicity given by their corresponding pK_a : 8.4 and 9.3, respectively. In other words, the relative carbon basicity effect is approximately negligible in these systems. The change of net charge on the carbonyl carbon in the reactant is: 0.5 and 0.41 for the channels leading to the products associated to the departure of 4-cyano and 3-nitro phenoxides, respectively. All structures were optimized using HF/6-311G(d,p) level of theory, using the GAUSSIAN 03 suite of programs [29]. The stationary points were characterized by frequency calculations in order to verify that the transition state structures had one and only one imaginary frequency (Tables S14–S16 in Supplementary material).

In order to compare the LG abilities respect to compound **1**, the phenolysis reactions of **2** were studied. In these reactions only 4-nitrophenoxide ion is observed as leaving group (see Section 2). Furthermore, a clean first order kinetics was found, by following the absorbance increase at 400 nm. The pseudo-first-order rate constants (k_{obsd}) for the reactions of **2**, obtained under phenoxide excess, are summarized in Tables S8–S13, all in Supplementary Material. The values of k_N for the phenolysis of **2** are shown in Table 2 and the Brønsted type-plots is shown in Figure S3 in Supplementary material. The transition state structure oriented to validate the leaving group ability was performed using HF/6-31G(d) level of theory and corrected by single point at HF/6-311G(d,p). The energy gap associated with the leaving group ability for 4-nitrophenoxide (8.72 kcal/mol) and 4-cyanophenoxide anion (10.29 kcal/mol) are in agreement with experimental evidences. (The complete characterization of the TS structures for compound **2** are shown in Supplementary material.)

The Brønsted plot for the phenolysis of **2** is biphasic, with slopes 0.30 and 1.36 and a curvature centre at pK_a 7.5 (5.45–11.16 pK_a range). The data are in accordance with a stepwise mechanism, through a tetrahedral intermediate (T^-) and a change in the rate-determining step, from breakdown of T^- to its formation, as phenoxide basicity increases [19,20].

Finally, it is noteworthy that in the phenolysis of **2** there is only one nucleofuge: 4-nitrophenoxide anion (see Section 2) albeit the difference in pK_a of the corresponding phenols is only 0.9 unit (the pK_a of 4-cyanophenol and 4-nitrophenol are 8.4 and 7.5, respectively, in 44 wt% ethanol–water) [21]. This result is in contrast to that found for the phenolysis of thionocarbonate **1**, whereby 4-cyanophenoxide leaves threefold faster than 3-nitrophenoxide, despite their pK_a difference is the same (0.9 unit, see above). Namely, for the phenolysis of **2** the less basic group leaves ‘infinitely’ faster than the other group, in great contrast to the phenolysis of **1**, where the less basic group leaves only threefold faster than the other, being in both cases the same pK_a difference

between the two potential nucleofuges. From these results it can be concluded that the nonleaving group plays an important role in the nucleofugality of the leaving group [30].

4. Concluding remarks

By studying the phenolysis of thionocarbonates **1** and **2** we have introduced two competing nucleofuges (of the same nature) to assess the role of the worse leaving group role in determining the nucleofugality ratio. For the phenolysis of **2** the less basic group (4-nitrophenoxide, 100%) leaves ‘infinitely’ faster than the other group (4-cyanophenoxide), in great contrast to the phenolysis of **1**, where the less basic group (4-cyanophenoxide, 75%) leaves only threefold faster than the other (3-nitrophenoxide, 25%), being in both cases the same pK_a difference between the two potential nucleofuges. From these results it can be concluded that the nonleaving group plays an important role in the nucleofugality of the leaving group. These kinetic results were confirmed by a potential energy surface study in gas phase for compound **1**. Ratifying that, the major energy stabilization of the (TS) structures is associated to 4-cyanophenoxide anion departure, reinforcing the proposed mechanism. Finally, was applied the Carbon-basicities concept for the same system as one of the factors that may significantly affect reaction barriers, been found that the contribution of carbon basicity associated to the nucleofugality of the leaving group negligible.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.cplett.2013.04.002>.

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