Group electrophilicity as a model of nucleofugality in nucleophilic substitution reactions

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Abstract

We propose and test an empirical nucleofugality index to rank the leaving group ability of a series of molecular fragments present in nucleophilic substitution reactions of carbonyl and thiocarbonyl derivatives. The nucleofugality index is defined as the group electrophilicity of the leaving group embedded in the substrate that undergoes the nucleophilic attack. The reliability and usefulness of this new reactivity index is tested against experimental kinetic data.

1. Introduction

Nucleofugality [1] defined as the propensity of an atom or group (the nucleofuge Z) to depart with the bonding electron pair in a heterolytic bond cleavage process, is involved in two kinds of processes, namely the nucleophilic substitution and elimination reactions. Both processes share the same kind of reagents: a nucleophile and a substrate bearing a good leaving group Z [1,2].

The leaving group departure is a complex process involving several aspects that include for instance, the electrophilicity of Z, the reaction mechanism involved, the basicity of the nucleophile, solvent effects, polarizability, and the nucleophile–nucleofuge interactions [3]. Those factors involving intermolecular interactions (solvent effects) or intramolecular (nucleophile–nucleofuge interactions at the transition state) play against the formulation of an universal scale of nucleofugality. Stirling [1] further stated additional aspects to be taken into account before building a coherent nucleofugality scale from kinetic data. The main requisite is that the leaving group Z must be involved in the rate determining step [1]. These considerations apply to both experimental and theoretical models of nucleofugality. Note that this restriction also prevents the possibility of having a universal (substrate-independent) scale of nucleofugality, because the involvement of the chemical environment in the departure of the LG at the transition state. The first attempt to theoretically define the nucleofugality concept in substitution and elimination reactions is that proposed by Ayers et al. [4,5]. These authors related the leaving group (LG) ability to the ionization potential and electron affinity using a quadratic model for the dependence of the energy with the number of the electrons [4,5]. By construction, this scale yields an intrinsic nucleofugality hierarchy based on a nucleofugality index v which is substrate-independent [6]. The theoretical nucleofugality index allowed the authors to qualitatively rank a series of atomic and molecular fragments that include a wide family of well known LG's in organic chemistry. Another theoretical scale of nucleofugality is that recently proposed by Domingo et al. [7] which is based on the global electrophilicity of a model CH_3-LG substrate. These authors have also succeeded in qualitatively classifying the nucleofugality of a series of well known organic leaving groups.

Our aim in this work is somehow different. We propose that by incorporating Stirling's considerations, it is possible

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to build up a more quantitative representation of nucleofugality for a set of fragments present in nucleophilic substitution reactions that are kinetically well described, and their reaction mechanisms unambiguously established [1]. Even though such a scale may have a more limited range of applications, it may become a useful tool as the body of experimental kinetic data grows. In our definition, the substrate-dependent nucleofugality index is taken as the group electrophilicity of the leaving group Z, in conditions of same solvent and same nucleophilic attacking group, piperidine in the present case [8–16].

2. Model equations and computational details

The global electrophilicity index, ω, which measures the stabilization in energy when the system acquires an additional electronic charge ΔN from the environment, has been given the following simple expression [17]:

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

in terms of the electronic chemical potential μ and the chemical hardness η. These quantities may be approached in terms of the one electron energies of the frontier molecular orbital HOMO and LUMO, εH and εL, 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 μ^2 (the square of electronegativity, $\chi = -\mu$), and the resistance of the system to exchange electronic charge with the environment described by η. The global electrophilicity is an extensive property of the system, in the sense that it may be recovered from the semi local contributions condensed to atoms [19],

$$\omega = \Sigma_k \omega_k; \quad \omega_k = f_k^+ \omega \tag{2}$$

where f_k^+ is the electrophilic Fukui function (i.e., the Fukui function for nucleophilic attack [20]).

Within this context, we define the nucleofugality index ν(PG) as the group electrophilicity of the leaving group Z embedded in structurally related substrates that undergo the nucleophilic attack as follows:

$$\nu(\mathrm{PG}) \equiv \omega_Z = \sum_{k \varepsilon Z} \omega_k \tag{3}$$

The notation ν(PG) for the nucleofugality index proposed here is used first to differentiate it from the intrinsic nucleophilic index proposed by Ayers et al. [4,5] and secondly, to stress the fact that this index has a dependence on the permanent groups (PG) of the systems we analyze here [6]. The global electrophilicity and the Fukui functions are not sensitive to solvent effects [21], so that the intrinsic gas phase values suffice to distribute the nucleofugality of LG's within a molecule using Eq. (3).

Ab initio HF/6-311G (d,p) calculations were performed using the Gaussian 98 suite of programs [22] in order to evaluate the electronic quantities required to calculate the ground state electrophilicity index for the series of carbonyl and thiocarbonyl derivatives considered in the present study (26 compounds) [8–16]. The electrophilic Fukui function, f_k^+, needed to project the regional electrophilicity condensed at the LG fragments, were obtained from single point calculations on the optimized ground state structures by a method described elsewhere [23,24].

Note that both, the local and global electrophilicity (and therefore the ν(PG) index) encompass all the three factors proposed by Boyd [25] to be the main determinants of a nucleofugality hierarchy: the electron affinity appears averaged with the ionization potential in a parent concept, namely the electronic chemical potential which is related to electronegativity [18] and chemical softness which is directly related to polarizability [26]. Inductive substituent effects on the other hand have been shown to be well described by local electrophilicity, in the form of local responses at the active site induced by chemical substitution [27].

3. Results and discussion

The nucleophilic substitution reactions of carbonyl [28,29] and thiocarbonyl [30] derivatives in solution with reagents of varying nucleophilicity studied by Castro et al. [8–16,28–30] is a suitable data base for the present study in the sense that the kinetic and mechanisms of these processes have been fully described. Depending on the nature of electrophile–nucleophile pair, two general mechanisms are possible. In the first one, the interaction of the nucleophile with the electrophilic carbonyl carbon may lead to the formation of a tetrahedral intermediate, $T^{\pm}$, from which the leaving group detaches. This mechanism is usually referred to as stepwise [30,31]. Another possibility is the concerted pathway [31]. The reaction mechanism is sketched in Eq. (4):

$$\mathrm{Nu} : + \mathrm{R} - Z \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{Nu}^+ - \mathrm{R} - Z^- \overset{k_2}{\rightarrow} \mathrm{Nu} - \mathrm{R} + : Z(T^{\pm}) \tag{4}$$

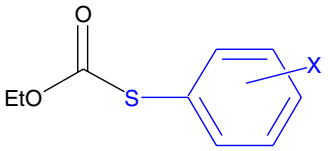
The macroscopic rate coefficient k_N for the aminolysis described in Eq. (4) is given by [30]:

$$k_N = \frac{k_1\ k_2}{k_{-1} + k_2} \tag{5}$$

Two regimes are possible [28–31]: (i) for amines of low basicity $k_{-1} \gg k_2$, and $k_N \approx K_1 k_2$, where K_1 is the equilibrium constant for the first step in Eq. (4) and (ii) for amines of high basicity $k_{-1} < k_2$, and $k_N \approx k_1$). Note that the limiting case $k_N = K_1 k_2$ refers to a situation where Stirling's rule regarding the role of the leaving group in the rate determining step applies, but the limiting case $k_N \approx k_1$ refers to a situation where Stirling's rule does not because the rate determining step is the attack of the nucleophile.

Table 1 displays the kinetic (k_N) as well as the computed nucleofugality index ν(LP) for a series of thiolcarbonates (7 compounds) in reaction with piperidine. Also included in Table 1 are the Hammett substituent constant, σ [32,33].

Table 1
Nucleofugality index v(PG) of thiolcarbonates, evaluated using Eq. (3) at the HF/6-311G (d,p) level of theory

Thiolcarbonate		v(PG) (eV)	k_N^{exptl} (s-1M-1)	σ	k_N^{pred}
1	X:4-NO_2	0.82	2.10[c]	0.78	–
2	X:4-Cl	0.34	0.46[d]	0.37	–
3	X:H	0.27	0.24[d]	0.00	–
4	X:4-CH_3	0.25	0.17[d]	−0.17	–
5	X:4-OCH_3	0.23	0.17[d]	−0.27	–
6	X:2,4,6-triNO_2	1.41	27.0[b]	1.15	–
7	X:2,4-diNO_2	1.03	14.0[a]	0.96	–
8	X:3-NO_2	0.72	–	0.71	1.76
9	X:4-CN	0.69	–	0.66	1.35
10	X:4-CO_2H	0.64	–	0.45	1.23
11	X:4-CF_3	0.61	–	0.54	1.08
12	X:3-CO_2H	0.58	–	0.37	0.94
13	X:3-CF_3	0.54	–	0.43	0.79
14	X:3-CH_3	0.38	–	−0.07	0.39

The LG is highlighted in box.
[a] From Ref. [8].
[b] from Ref. [9].
[c] from Ref. [10].
[d] from Ref. [11].

The comparison between k_N and the nucleofugality index performed for compounds **1**–**7** is shown in Fig. 1. The resulting regression equation is

$$\log k_N = -1.15 + 1.94\ v(\mathrm{PG});\ R = 0.984,\ N = 7,\ P < 0.0001 \quad (6)$$

Compounds **1**–**5** react with piperidine via a stepwise mechanism, with formation of the tetrahedral intermediate $T^{\pm}$. In all five cases, the rate determining step is the departure of the nucleofuges [8–11]. and the nature of the reaction mechanism is the same, so that following Stirling's criteria, the kinetic data contain relevant information about nucleofugality and complications in establishing a nucleofugality order are not expected. Compounds **6** and **7** on the other hand, were proposed to react with piperidine via a concerted pathway [8,9]. It is interesting to stress at this point that Stirling introduces the idea that, even if the leaving group is involved in the rate determining step, the nature of the mechanism (concerted or stepwise) can complicate the correlation between experimental kinetic data and nucleofugality, due to other factors such as interactions between the nucleophile and the nucleofuge. Note that these two thiolcarbonates are predicted to have the highest nucleofugality values within the series **1**–**7**. At the same time, they show rate coefficients one order of magnitude higher than compounds **1**–**5**. This result may highlight the role of the nucleofuges in the kinetics of these two concerted reactions. These two compounds bear multiple substitutions with the strong electron withdrawing –NO_2 group that enhances the group electrophilicity of the nucleofuge on one hand, and that create a strong electrophilic site at the carbonyl carbon which should show a significant sp^2 character at the transition state (vide infra). The higher values of nucleofugality index for compounds **6** and **7** suggest that the nucleophile–nucleofuge interactions are probably weak in these cases.

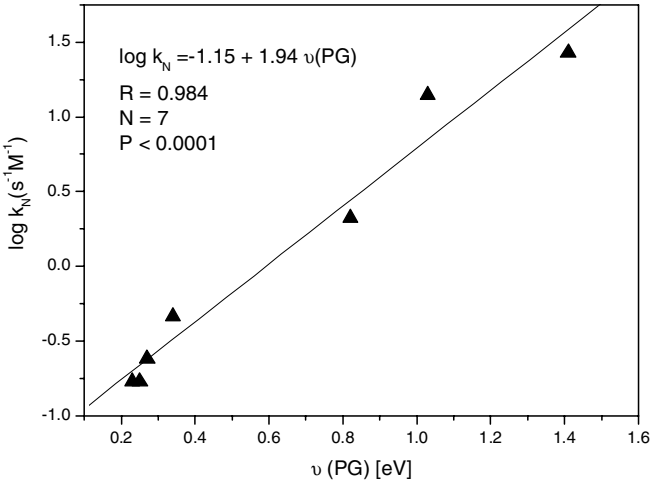


Fig. 1. Comparison between the experimental nucleophilic rate coefficient, k_N, for the reactions of the thiolcarbonates series with piperidine and the nucleofugality index v(PG) evaluated at the HF/6-311G (d,p) level theory. R is the regression coefficient, N is the number of points and P is the probability that the observed correlation was randomly obtained.

The empirical Eq. (6) was also used to predict the k_N values expected for substitution reactions not experimentally evaluated to date (compounds **8**–**14** in Table 1). This series contains compounds bearing *para*- and *meta*-substitution

with moderate electron withdrawing groups, electron releasing groups and single *meta*-substitution with a $-NO_2$ group [32]. It may be seen in Table 1 that these sub series are upper and lower bounded by compounds **1**–**3** (bearing strong nucleofuges) and **4**–**7** (bearing marginal nucleofuges), respectively, in terms of the nucleofugality index v, k_N values and Hammett substituent constant, σ [32,33].

The kinetics and mechanisms of the aminolysis of a parent thionocarbonates series have also been extensively studied. These reactions proceed via a stepwise mechanism, where again the rate determining step is the departure of the nucleofuge [12–15] from a tetrahedral intermediate. Table 2 summarizes the nucleofugality index evaluated for a series of diaryltionocarbonates (7 compounds) and the experimental rate coefficient k_N. Note that in this case the v(PG) values are lower than the values obtained for the thiolcarbonates series in Table 1. This result may be traced to the presence of a sulfur atom at the carbonyl functionality. The softer sulfur atom can stabilize the negative charge more efficiently than the parent thiolcarbonates compounds, a result probably due to the smaller difference in electronegativity between the carbonyl carbon and the sulfur atom present in the thiolcarbonates series. This time, the departure of the thiophenoxide groups from the thionocarbonate framework seems to occur within a more stable σ bonded $T^{\pm}$ intermediate, and therefore with a nucleofugality pattern less favorable than that present in the thiolcarbonates series. The comparison between the experimental k_N values [12–15] and the nucleofugality index is again significant. The comparison is shown in Fig. 2. The resulting empirical equation is:

$$\log k_N = -0.95 + 2.23v(\mathrm{PG});\ R = 0.970,\ N = 7,\ P < 0.0003 \quad (7)$$

From this equation, the rate coefficient k_N, may be predicted from the knowledge of the nucleofugality index. For instance, the k_N values expected for the substitution

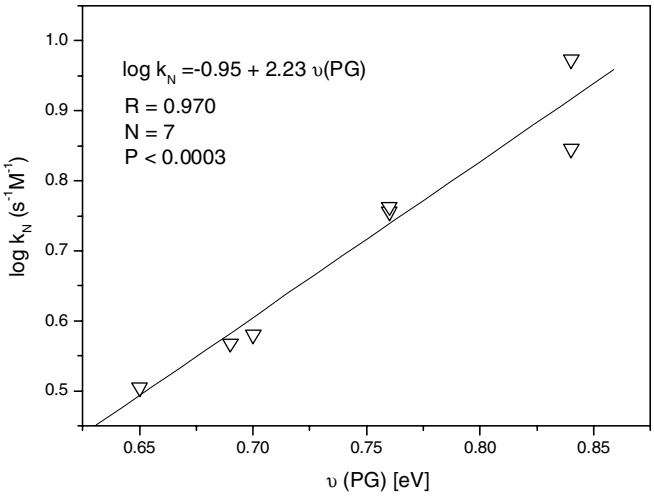
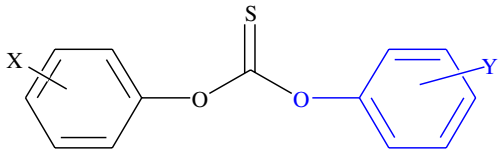


Fig. 2. Comparison between the experimental nucleophilic rate coefficient, k_N, for the reactions of the diarylthionocarbonates series with piperidine and the nucleofugality index v(PG) obtained at the HF/6-311G (d,p) level theory. For definitions of the statistical parameters R, N and P, see footnote in Fig. 1.

reaction of 4-chlorophenyl 4-nitrophenyl thionocarbonate with piperidine in the same experimental conditions is $k_N = 5.06$ ($s^{-1}M^{-1}$). It may be seen that this compound bearing, –Cl *para* substitution appears again upper and lower bounded by compounds **15**–**18** (bearing a strong nucleofuge at -*para* and –*meta* positions) and compounds **19**–**21** (bearing moderates nucleofuges), respectively, in terms of the k_N values.

In order to coherently close the present discussion about the feasibility of defining a quantitative nucleofugality scale in carbonyl compounds, we shall discuss the case of the reactivity of dithiocarbonates with piperidine. In opposition with the previous systems analyzed in this work, these reactions proceed via a stepwise mechanism [16] where the rate-determining step of the reaction is the nucleophilic attack of the amine, k_1 in Eq. (4), not the departure of

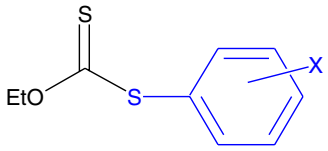
Table 2
Nucleofugality index v(PG) of diarylthionocarbonates evaluated using Eq. (3) at the HF/6-311G (d,p) level of theory



Thionocarbonate	Permanent group	Leaving group	v(PG) (eV)	k_N^{exptl} ($s^{-1}M^{-1}$)
15	X:(4-NO_2)	Y:(4-NO_2)	0.84	7.0[d]
16	X:(3-NO_2)	Y:(3-NO_2)	0.84	9.4[a]
17	X:(3-Cl)	Y:(4-NO_2)	0.76	5.7[b]
18	X:(3-Cl)	Y:(3-NO_2)	0.76	5.8[a]
19	X:(H)	Y:(4-NO_2)	0.70	3.8[c]
20	X:(3-CH_3O)	Y:(4-NO_2)	0.69	3.7[b]
21	X:(3-CH_3O)	Y:(3-NO_2)	0.65	3.2[a]

The LG is highlighted in box.
[a] From Ref. [12].
[b] from Ref. [13].
[c] from Ref. [14].
[d] from Ref. [15].

Table 3
Nucleofugality index v(PG) of dithiocarbonates, evaluated using Eq. (3) at the HF/6-311G (d,p) level of theory

Dithiocarbonate		v(PG) (eV)	k_1^{exptl} ($s^{-1}M^{-1}$)
22	X:H	0.11	1.1[a]
23	X:4-CH_3	0.19	1.3[a]
24	X:4-OCH_3	0.30	1.4[a]
25	X:4-Cl	0.16	1.7[a]
26	X:4-NO_2	0.09	3.0[a]

The LG is highlighted in box.
[a] From Ref. [16].

the nucleofuge. According Stirling's criteria, the kinetic data of these reactions do not contain any information about nucleofugality and then no correlation between the rate coefficients and our reactivity index should be expected [16]. Table 3 summarizes the nucleofugality index evaluated for a series of dithiocarbonates (5 compounds) and the experimental rate coefficient k_1. The comparison between the nucleofugality index and the experimental rate coefficients k_1 for compounds **22**–**26** consistently yields a poorer correlation ($R = 0.381$, $N = 5$, $P < 0.5227$).

4. Concluding remarks

An empirical nucleofugality index defined in terms of the group electrophilicity of the leaving group has been presented. In contrast to previous definitions of nucleofugality, the present substrate-dependent reactivity index does yields quantitative comparisons with the rate coefficients, yet its applicability covers a more narrow range. Even though the proposed nucleophilicity scale is not a universal one, we expect that the accumulation of new experimental kinetic data on substitution and elimination reactions satisfying the Stirling's conditions will allow comparisons between experimental LG abilities and the proposed nucleofugality index, thereby offering the prospect of a better understanding of the nature of nucleofugality in such processes.

Acknowledgments

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