

# Nucleophilicity scale for n- and $\pi$ -nucleophiles

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## Abstract

A recently introduced empirical nucleophilicity index for a series of n- and  $\pi$ -nucleophiles was evaluated. The index is based on the frontier molecular orbital information of the nucleophile and its electrophilic partner. The model is validated against kinetic data of alkenes, phosphanes, phosphites and amines interacting with the corresponding electrophilic partner. The predictive character of this index is tested for some nucleophiles.

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## 1. Introduction

The introduction of concepts like electrophilicity and nucleophilicity to define electron deficient (electrophile) and electron rich (nucleophile) species has gained a continuous interest to construct empirical scales classifying atoms, molecules and charged species [1–6]. The availability of empirical scales of electrophilicity and nucleophilicity, usually based on kinetic parameters, have been very useful to rationalize the chemical reactivity, in terms of selectivity, reaction mechanisms, solvent, substituent effects, etc. [4]. While both concepts have been defined in a kinetic sense [4,7,8], the theoretical electrophilicity concept was defined as a stabilization of the energy when electron deficient species acquires an additional electronic charge from the environment [9]. Quantitative descriptions of nucleophilicity have been more limited and the constructed scales and its applicability have been scarce. Up to now, a universal nucleophilicity scale has been unachievable. It seems to be necessary to establish whether or not the nucleophilicity (or electrophilicity) can be defined without taking into account the counterpart electrophile (nucleophile), leaving group, solvent, reaction mechanisms, the

intrinsic properties of the nucleophile alone or whatever experimental condition [10]. From of the theoretical point of view, a nucleophilicity definition is even a more difficult task. When a nucleophile loses electron charge, its total energy will increase, having a total energy versus electron numbers plot with a curvature of opposite sign. Therefore, the variational model of Parr et al. [9] used to define the electrophilicity cannot be used.

Experimentally, Mayr and Patz [4] have contributed making nucleophilicity/electrophilicity scales based on the rate constants of the electrophile–nucleophile combination reactions. These scales have been successfully applied to a wide variety of electrophile–nucleophile interactions [7,8]. In the last years, several attempts to construct nucleophilicity scales have been done. Nucleophilicity has been related with  $pK_a$  values [10], polarizability [11] and the HSAB principle [12]. One important model of nucleophilicity has been the experimental scale proposed by Legon and Millen [3] based on low-frequency hydrogen bond stretching modes measures for several B–HX dimers (B is a Lewis base; HX with X = F and Cl). The strength of the interaction between the nucleophile and the electrophile is provided from the vibrational spectroscopy in gas phase. This model has recently applied to different interacting systems [13,14].

From the theoretical point of view, the minimum values of the molecular electrostatic potential (MEP) [15] at the electrophilic site of HX,  $V_H$ , have been used to postulate

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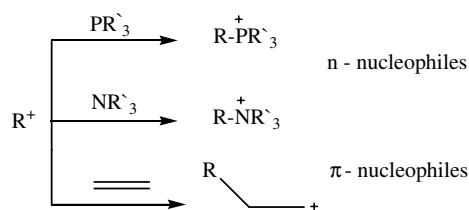


Chart 1. Single step reactions for the studied system.

a nucleophilicity scale [13,14,16]. Roy et al. [17] have proposed a local relative nucleophilicity index which is intramolecular in nature. Additionally, Chattaraj and Maiti [18] have proposed the concept of philicity, stressing the idea that a particular molecular site may undergo more likely an electrophilic attack or another site undergoes a nucleophilic attack. Other attempts show a relationship between nucleophilicity and solution phase ionization potentials [19]. Recently, Jaramillo et al. [13] have proposed a new empirical nucleophilicity index based on the first order energy changes due to changes in the electron number for a soft-soft interaction.

In this letter we test the empirical nucleophilicity index recently introduced [13] for n-nucleophiles (electrons making a new bond are located in a n type orbital) as phosphanes, phosphites, and amines, and  $\pi$ -nucleophiles (electrons making a new bond are located in a  $\pi$  type orbital) as alkenes, interacting with a specific cationic electrophile (see Chart 1). Our aim is validate the empirical index in other different nucleophile-electrophile interactions and to stress that nucleophilicity concept needs to contain information about the electrophilic partner. The model is validated against kinetic data reported by Mayr and Patz [4]. The predictive character of the nucleophilicity index is evaluated.

## 2. Model equations and computational details

Assuming that A is the nucleophile and B is the electrophile, the empirical nucleophilicity index, within the grand canonical ensemble was defined by Jaramillo et al. [13] as

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

where  $\mu_A$  and  $\mu_B$  are the corresponding chemical potentials, and  $\eta_A$  and  $\eta_B$  are the respective hardnesses. Eq. (1) was derived considering that the electronic charge transferred between A and B species is given by  $N = \frac{\mu_A - \mu_B}{\eta_A + \eta_B}$ . This amount of transferred charge is fixed and different for each couple of reactants. Note that the index depends on the electrophilic system and, therefore, there is not a unique nucleophilic scale. It will vary from one electrophilic to the other. Notice, that opposed to the absolute electrophilicity index [9], our index is relative.

The quantities contained in Eq. (1) may be approached in terms of the one electron energies of the frontier molec-

ular 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 [20]

The nucleophiles studied are shown in Chart 1. The electrophilic partners are AnPhCH<sup>+</sup> (An: abbreviation for Ph-OCH<sub>3</sub>) for substituted ethene series [4], (C<sub>6</sub>H<sub>7</sub>)(CO)<sub>3</sub>Fe<sup>+</sup> for the phosphane and phosphite families [4], and (Ph-N(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>PhC<sup>+</sup> for the amines [4]. Full geometry optimization for the whole series of nucleophiles and electrophiles were performed at the B3LYP/6-31+G(d,p) level of theory implemented in the GAUSSIAN98 package of programs [21]. The nucleophilicity, the chemical potential and hardness indexes for the ethene family (and its corresponding electrophile) were calculated in solution phase, using gas phase geometries at the same level of theory mentioned above. The molecules solvated by dichloromethane was treated in terms of polarized continuum model PCM [22], where the solvent is included as an infinite dielectric continuum.

## 3. Results and discussion

The hardness, chemical potential, charge transfer and the nucleophilicity index are shown in Tables 1–3 for alkenes, amines, phosphanes and phosphites, respectively. The kinetic data available from the literature [4] for the single step (see Chart 1) nucleophile-electrophile reactions are also displayed in Tables 1–3. At first glance of Tables 1–3, the chemical potential ( $\mu$ ) of the nucleophiles is always greater than the corresponding for the electrophiles in all of three series. This is right because the electron charge will

Table 1

Experimental rate constants and calculated properties of substituted ethenes in CH<sub>2</sub>Cl<sub>2</sub> using 1-Methoxyphenyl 1-phenyl carbenium ion as electrophile<sup>a</sup>

substituted ethenes	log k	$\eta$ (au)	$\mu$ (au)	N	$\omega^-$ (eV)	
	E1	-3.027	0.262	-0.129	-0.223	0.177
	E2	-2.733	0.256	-0.129	-0.226	0.178
	E3	1.265	0.248	-0.124	-0.243	0.200
	E4	1.367	0.251	-0.123	-0.244	0.204
	E5	2.412	0.249	-0.123	-0.246	0.206
	E6	2.456	0.241	-0.124	-0.251	0.206
	E7		0.205	-0.218	0.020	0.001
	E8		0.195	-0.171	-0.132	0.046
	E9		0.230	-0.182	-0.088	0.025
	E10		0.240	-0.114	-0.278	0.254
	E11		0.213	-0.095	-0.359	0.373
	E12		0.252	-0.113	-0.271	0.252
	E13		0.240	-0.112	-0.284	0.263
Electrophile AnPhCH <sup>+</sup>			0.112	-0.212		

<sup>a</sup> All calculations were performed at B3LYP/6-31+G(d,p) level of theory. PCM model was used to calculate properties in CH<sub>2</sub>Cl<sub>2</sub>.

Table 2

Experimental rate constant ( $\log k$ ) and calculated properties for amines using malachite green as electrophile<sup>a</sup>

		$\log k$	$\eta$ (au)	$\mu$ (au)	$N$	$\omega^-$ (eV)
Nucleophiles						
CF <sub>3</sub> CH <sub>2</sub> NH <sub>2</sub>	A1	-1.260	0.269	-0.140	-0.333	0.405
MeONH <sub>2</sub>	A2	-0.018	0.278	-0.128	-0.357	0.483
NH <sub>3</sub>	A3	-0.523	0.284	-0.126	-0.356	0.490
MeO(CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub>	A4	0.556	0.246	-0.123	-0.405	0.549
NH <sub>2</sub> NH <sub>2</sub>	A5	1.623	0.274	-0.118	-0.388	0.561
<i>n</i> PrNH <sub>2</sub>	A6	1.114	0.242	-0.118	-0.426	0.595
Electrophile						
Malachite green			0.095	-0.261		

<sup>a</sup> All calculations were performed at B3LYP/6-31+G(d,p) level of theory.

Table 3

Experimental rate constant ( $\log k$ ) [4] and calculated properties for phosphanes and phosphites using tricarbonylcyclohexadienyliron cation as electrophile<sup>a</sup>

		$\log k$	$\eta$ (au)	$\mu$ (au)	$N$	$\omega^-$ (eV)
Nucleophiles						
P(2-OMeC <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>	P1	5.833	0.177	-0.112	-0.695	1.164
PBu <sub>3</sub>	P2	5.526	0.225	-0.110	-0.593	1.074
PAn <sub>3</sub>	P3	4.808	0.179	-0.119	-0.663	1.070
PTol <sub>3</sub>	P4	4.452	0.185	-0.119	-0.646	1.050
PPh <sub>2</sub> Tol	P5	3.908	0.186	-0.125	-0.625	0.988
PPh <sub>3</sub>	P6	3.873	0.187	-0.127	-0.612	0.954
P(OBu) <sub>3</sub>	P7	2.004	0.252	-0.120	-0.513	0.903
P(OEt) <sub>3</sub>	P8	1.662	0.251	-0.122	-0.509	0.885
P(OMe) <sub>3</sub>	P9	1.473	0.252	-0.126	-0.495	0.839
P(OPh) <sub>3</sub>	P10	-1.384	0.218	-0.135	-0.521	0.807
Electrophile						
(CO) <sub>3</sub> (C <sub>6</sub> H <sub>7</sub> )Fe <sup>+</sup>			0.079	-0.290		

<sup>a</sup> All calculations were performed at B3LYP/6-31+G(d,p) level of theory.

flux from the donor to acceptor electron species [20]. For the ethene series, all descriptors were calculated using the PCM model [22] to compare with the experimental kinetic data obtained in CH<sub>2</sub>Cl<sub>2</sub> as solvent [4]. However, reaction rates between carbocations and uncharged nucleophiles like alkenes are hardly affected by the nature of solvent [23]. Therefore the comparisons between properties in some aprotic solvent and those in gas phase are a good approximation to the intrinsic properties. A plot of the logarithm of the rate constant ( $\log k$ ) vs. the nucleophilicity index ( $\omega^-$ ) yields a good linear correlation (see Fig. 1,  $r = 0.994$ ) for the six alkyl-substituted ethenes (E1–E6). It may be seen that once the interaction nucleophile–electrophile has occurred a secondary carbenium ions (E1 and E2) is formed. These carbenium ions are lesser reactive than the tertiary ones (E3–E6, see values of  $\log k$  and  $\omega^-$  from Table 1). In order to validate the empirical nucleophilicity index with other different alkyl substituent, we have calculated the nucleophilicity index for electron-withdrawing and electron-releasing substituted ethenes. Those ethylenes substituted by (–NO<sub>2</sub>, –COCH<sub>3</sub>, –COOH) display low  $\omega^-$  values (see Table 1). It is known that electron withdrawing

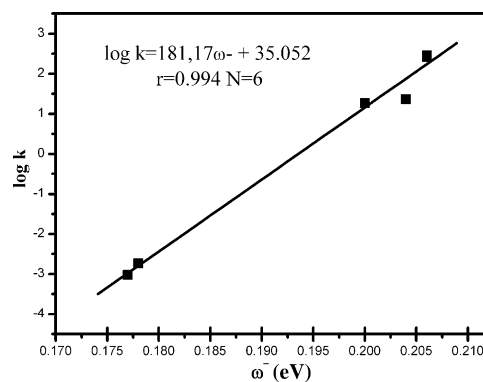


Fig. 1. Comparison between logarithm of the rate constant ( $\log k$ ) [4] and the calculated nucleophilicity for alkyl-substituted ethenes.

groups decrease the nucleophilic character by inductive and conjugation effects. Therefore, these kinds of ethenes can be classified as poor nucleophiles. On the other hand, when the ethylene is substituted by electron donating groups (–OCH<sub>3</sub>, –NH<sub>2</sub>, –OH, –OEt), the nucleophilic reactivity increases noticeably (see  $\omega^-$  values in Table 1). These groups enhance the nucleophilic reactivity of a double bond toward electrophilic addition [24]. For instance, ethylenamine (E11) presents the highest nucleophilic value ( $\omega^- = 0.373$  eV) of the series. Both results are consistent with previous results about the reactivity of substituted ethylenes in Diels–Alder reactions [25,26].

Fig. 2 shows the comparison between the nucleophilicity index and experimental rate constant ( $\log k$ ) for the amine series. Even though the comparison is not as good as the ethene family ( $r = 0.924$ ), it can be observed that amines are more reactive nucleophiles than the alkyl-substituted ethenes in addition reactions [24]. This behavior is reflected in their greater  $\omega^-$  values. On the other hand, it may be noted that the calculated substituted amines nucleophilicity trend is in agreement with the observed one obtained with diarylmethyl cations as electrophiles in acetonitrile/water solutions [27]. The observed nucleophilicity trend is: CF<sub>3</sub>CH<sub>2</sub>NH<sub>2</sub> < CH<sub>3</sub>O(CH<sub>2</sub>)<sub>2</sub>NH<sub>2</sub> < *n*PrNH<sub>2</sub> in complete agreement with the respective  $\omega^-$  values (see Table 2).

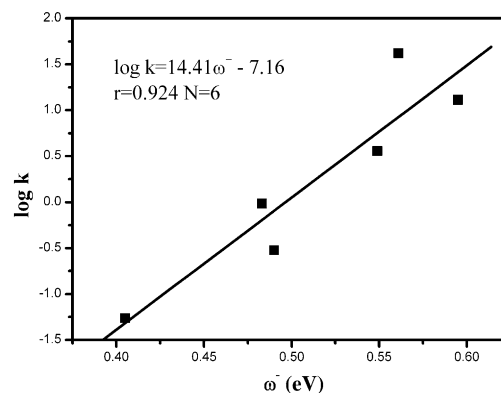


Fig. 2. Comparison between logarithm of the rate constant ( $\log k$ ) [4] and the calculated nucleophilicity for amines.

For some amines presenting alpha effect [28] as hydrazine,  $\text{NH}_2\text{NH}_2$ , and methoxyamine,  $\text{CH}_3\text{ONH}_2$ , the  $\omega^-$  values ( $\omega^- = 0.561$  eV for hydrazine and  $\omega^- = 0.483$  eV for methoxyamine) are also consistent with experimental data using acetyl chloride as electrophile [28]. For this group of molecules is more difficult to find a nucleophilicity scale because the reactivity of these amines is affected by solvent effects, basicity, substituents steric effect and several other conditions reactions [29]. However, the main interest in this work is showing general trends of our calculated index of nucleophilicity with experimental information with other electrophiles than malachite green utilized in this study [4].

Fig. 3 shows a good correlation between the calculated nucleophilicity and rate constants ( $r = 0.942$ ) for phosphanes and phosphites interacting with tricarbonylcyclohexadienyliron cation in acetone [30]. As was mentioned above [23], the rate constants of carbocations/uncharged nucleophiles in aprotic solvents are almost independent of the solvent polarity, therefore the experimental rates for phosphanes and phosphites can be considered as intrinsic properties [4]. The system P(2-MeOC<sub>6</sub>H<sub>4</sub>)<sub>3</sub> (P1) presents the highest nucleophilicity value ( $\omega^- = 1.164$  eV) in agreement with the highest rate constant. The highest reactivity of P1 compared for instance with  $\text{PPh}_3$  (P6) could be explain by the enhancement of the electronic density on the phosphorous atom by mesomeric interactions with

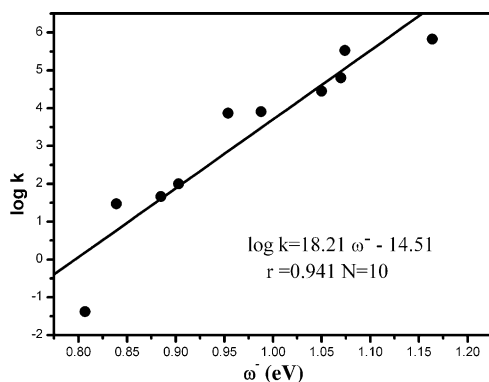


Fig. 3. Comparison between logarithm of the rate constant ( $\log k$ ) [4] and the calculated nucleophilicity for phosphanes and phosphites.

the substituents [4]. Phosphites are less reactive than phosphanes (see Table 3). In this case, it was explained that the mesomeric effect is diminished by the strong inductive effect of the electronegative oxygen atom [4]. The nucleophilicity values in Table 3 reflect the experimental result.

In order to test the predictive power of the model and the quality of the linear relationship between logarithm of the rate reaction and  $\omega^-$  values, eight of 10 nucleophiles included in the regression of Fig. 3 were selected as training set of molecules (see Table 4). The empirical equation for a first regression (line 1) is  $\log k = 17.784 \omega^- + 14.163$  ( $r = 0.933$ ) predicting a  $\log k$  for P2 of 4.937 ( $\omega^-(\text{P2}) = 1.074$  eV) and for P8 a value of 1.575 ( $\omega^-(\text{P8}) = 0.885$  eV), which are in excellent agreement with the experimental values of 5.526 and 1.662 [6], respectively. By selecting other set of eight nucleophiles (line 4), the regression is  $\log k = 18.367 \omega^- + 14.651$  ( $r = 0.937$ ), predicting a  $\log k$  for P4 of 4.635 ( $\omega^-(\text{P4}) = 1.050$  eV) and for P7 a value of 1.934 ( $\omega^-(\text{P7}) = 0.903$  eV), which are consistent with the experimental values of 4.452 and 2.004 [4], respectively. In Table 4 there is more statistical analysis to validate the nucleophilicity model used. Although these comparisons were arbitrarily chosen, allow us to validate the predictive character of the proposed nucleophilicity model. The predictive power of the generated linear relationships is considered very well because the error is smaller than of 12.0%.

#### 4. Concluding remarks

An empirical nucleophilicity index was used to test the nucleophilic trend of three families of nucleophiles. The model is validated against kinetic data of alkenes, phosphanes, phosphites and amines interacting with the corresponding electrophilic partners. The nucleophilicity order obtained with the calculated  $\omega^-$  shows good correlations with the experimental rate constants in all of three studied systems. Substituted ethenes with releasing electron groups increase markedly the nucleophilic reactivity. In addition, the nucleophilicity index has a predictive character being tested in some phosphane and phosphite species. The nucleophilicity order is electrophile-dependent as is shown in this work.

Table 4  
Statistical data for different correlations between nucleophilicity ( $\omega^-$ ) and the rate constant of the reactions ( $\log k$ )

Line	Nucleophiles	Constant	Slope	$r$	$N$	Predicted $\log k^a$
1	P1–P3–P4–P5–P6–P7–P9–P10	14.163	17.784	0.933	8	P2: 4.937 (5.526) P8: 1.575 (1.662)
2	P1–P2–P4–P5–P6–P7–P9–P10	14.696	18.415	0.934	8	P3: 5.007 (4.808) P8: 1.601 (1.662)
3	P1–P2–P3–P5–P6–P7–P9–P10	14.654	18.370	0.936	8	P4: 4.635 (4.452) P8: 1.603 (1.662)
4	P1–P2–P3–P5–P6–P8–P9–P10	14.651	18.367	0.937	8	P4: 4.634 (4.452) P7: 1.934 (2.004)
5	P1–P2–P3–P4–P6–P8–P9–P10	14.592	18.229	0.941	8	P5: 3.418 (3.908) P7: 1.869 (2.004)

<sup>a</sup> Values in parentheses are the experimental data. They are taken from Ref. [4].

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