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# Intrinsic Nucleofugality Scale within the Framework of Density Functional Reactivity Theory

**Lies Broeckaert,[†] Jan Moens,[†] Goedele Roos,[†,‡,§] Frank De Proft,[†] and Paul Geerlings*,[†]**

*Eenheid Algemene Chemie, Vrije Universiteit Brussel (VUB), Faculteit Wetenschappen, Pleinlaan 2,
1050 Brussels, Belgium, Department of Molecular and Cellular Interactions, VIB, 1050 Brussels, Belgium,
and Ultrastructure Laboratory, Vrije Universiteit Brussel, Belgium*

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Nucleofugality is a measure of the quality of a leaving group in substitution and elimination reactions. In a conceptual DFT context, the nucleofugality is calculated for an elaborate set of common organic leaving groups, both in the gas phase and in two organic solvents (dichloromethane and methanol). An intrinsic nucleofugality scale is constructed showing fair agreement with the classical trends in leaving group capacity in organic chemistry. The correlation of the results with acidities (tabulated p$K_a$ values) on one hand and experimental solvolysis reaction rate constants (kinetic parameters) on the other hand is discussed. Finally, a conceptual DFT based formula is derived, describing the influence of the solvation energy on the nucleofugality; excellent correlations were found with explicit calculations for the studied leaving groups.

## Introduction

Nucleophilic substitution and elimination reactions constitute two fundamental reaction types in organic chemistry. An important step in their mechanisms is the departure of a leaving group $X^-$ covalently bound in the reactant molecule. In this step, a heterolytic bond cleavage occurs and the leaving group or ‘nucleofuge’ takes up the bonding electron pair from the substrate. The concept of the nucleofugality or leaving group ability was first introduced and quantified experimentally by Stirling[1,2] in 1,2- and 1,3-elimination reactions. Richard et al.[3] presented subsequent research on the nucleofugality of the benzotriazole group in solvolysis reactions. A nucleofugality scale based on experimental kinetic data of the solvolysis reaction of X,Y-substituted benzhydryl derivatives was constructed by Denegri et al.[4] Their scale was interpreted from the following equation (1):

$$\log k_s = s_f(N_f + E_f) \qquad (1)$$

in which $k_s$ is the solvolysis rate constant for a specific reaction. $s_f$ and $N_f$ are nucleofuge-specific parameters while $E_f$ is an electrofuge-specific one. These authors claim that a general nucleofugality scale cannot exist, arguing that relative leaving group abilities depend on the reaction mechanism and within one type of mechanism on the substrate and solvent. Equation 1 was also used by the same authors in the study of phenyl and methyl carbonates.[5] A slightly modified version of eq 1 was proposed by Bentley[6] in order to calculate and interpret nucleofugalities.

Early theoretical work by Boyd et al.[7] mentioned the importance of inductive effects and properties like the electron affinity and polarizability of the nucleofuge. Recently, Ayers et al.[8,9] proposed a theoretical description of the electrofugality and nucleofugality index in the framework of conceptual density functional theory (DFT).[10,11a−c] Since the nucleofugality was solely expressed by the leaving group’s electron affinity and ionization potential, it functioned as an intrinsic, substrate-independent property of the leaving group. Together with the electrophilicity descriptor $\omega$,[12] these indices form a complete family measuring the susceptibility of a molecule to a specific chemical reaction.

We mention that in the past several authors invoked the electrophilicity index $\omega$ as a nucleofugality descriptor. Jaramillo et al.[13] proposed a theoretical nucleofugality scale based on the global electrophilicity $\omega$ of a $CH_3$-X model. Campodónico et al.[14] defined a nucleofugality index by the group electrophilicity of the leaving group and applied this index to nucleophilic substitution reactions of carbonyl and thiocarbonyl derivatives and $\alpha$-elimination reactions.[15] Recently, these authors also proposed an electrofugality index for benzhydryl derivatives.[16]

It is clear from the previous outline that a construction of an absolute, intrinsic nucleofugality scale for a large number of organic leaving groups is still lacking in the literature. The aim of this paper will therefore be the introduction of such a scale based on Ayers’ formulation of the nucleofugality index. The ultimate goal is thereby to create a useful predicting tool for experimental organic chemists. Following our previous research of solvent effects on reactivity descriptors,[17−19] we will examine how nucleofugality values are altered in solution. The construction of this nucleofugality scale bears an analogy with the electrophilicity scale for radicals, previously proposed by De Vleeschouwer et al.[20]

This approach will also enable us to test the rule of thumb in organic chemistry, stating that good leaving groups are the conjugate bases of strong acids.[21] Therefore the correlation between p$K_a$ and leaving group capacity was investigated in some previous nucleofugality studies,[7,13] although it was also stated that care has to be taken when making this comparison. It has been emphasized repeatedly that there is no general correlation of the leaving group ability of $X^-$ with the p$K_a$ of the conjugate acid HX in water. Nevertheless, Stirling et al. demonstrated that a correlation between leaving group ability and p$K_a$ does exist for 1,3-elimination reactions.[22] Because of the kinetic rather than thermodynamic nature of this reactivity

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* Corresponding author. Fax: +32 2 629 3317. E-mail: pgeerlin@vub.ac.be.
[†] Eenheid Algemene Chemie, VUB.
[‡] Department of Molecular and Cellular Interactions, VIB.
[§] Ultrastructure Laboratory, VUB.

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index, most nucleofugality studies, however, are based on experimental reaction rate coefficients $k$. The main problem is that the available kinetic data only cover a narrow range of leaving groups, and the data are restricted to certain solvents and substrates.

This paper is organized as follows. In the next section we will present the theoretical background concerning the nucleofugality descriptor, and we will derive a formula that quantifies the effect of the solvent on this descriptor. After the Methodology and Computational Details section, results are presented and discussed. Finally, conclusions will be drawn.

## Theoretical Background

On the basis of a second-order model for the change of the electronic energy $\Delta E$ as a function of the number of electrons $\Delta N$ at constant external potential $v(\underline{r})$, the energy change is given by eq 2:

$$\Delta E = \mu \Delta N + \frac{1}{2}\eta \Delta N^2 \tag{2}$$

in which $\mu$ is the electronic chemical potential and $\eta$ the chemical hardness. In contact with an electron reservoir at zero chemical potential, the system takes electrons and becomes saturated when $\Delta E/\Delta N$ equals zero. The corresponding gain in energy is given by the electrophilicity descriptor $\omega$:

$$\omega = -\Delta E = \frac{\mu^2}{2\eta} \tag{3}$$

In a finite difference approximation, substituting $\eta$ with $I - A$ and $\mu$ with $-(I + A)/2$, where $I$ represents the ionization potential and $A$ the electron affinity, eq 3 becomes

$$\omega = \frac{(I + A)^2}{8(I - A)} \tag{4}$$

The maximum transfer of electrons that takes place is given by the value of $\Delta N_{\max}$ or $\Delta N_{\text{ideal}}$:

$$\Delta N_{\text{ideal}} = -\frac{\mu}{\eta} \tag{5}$$

**Nucleofugality Descriptor.** An important property of a chemical reagent is the ability to serve as a leaving group. The quality of leaving groups is quantified by means of the nucleofugality concept. Ayers defined the nucleofugality as a measure of the relative stability of an electron acceptor carrying $N + 1$ electrons in comparison with the acceptor fragment with $N + \Delta N_{\text{ideal}}$ electrons, assuming that the leaving group is covalently linked to a perfect electron-donor.[8,9] This energy difference $\Delta E_{\text{nucleofuge}}$, called $\nu$ in the remainder of this paper, has the following form:

$$\Delta E_{\text{nucleofuge}} = \nu = E(N + 1) - E(N + \Delta N_{\text{ideal}}) = -A + \omega \tag{6}$$

Combining eqs 4 and 6, the expression for the nucleofugality in terms of the ionization potential and electron affinity of the nucleofugal fragment becomes

$$\nu = \pm\frac{(\mu + \eta)^2}{2\eta} = \pm\frac{(I - 3A)^2}{8(I - A)} \tag{7}$$

where the positive sign is to be taken when $(I - 3A) \geq 0$, and the negative sign when $(I - 3A) < 0$. If $\Delta N_{\text{ideal}}$ values are larger than 1, the molecular fragment acts as an extremely good leaving group, i.e., an ideal nucleofuge, because energy is released when the leaving group is detached from the molecule. Values of $\nu$ are then negative. If $\Delta N_{\text{ideal}}$ is smaller than 1, energy is needed to liberate the leaving group from the molecule, leading to positive $\nu$ values.

**Solvent Effects on the Nucleofugality.** In a previous study, Pérez et al. examined the solvent effects on the electrophilicity index $\omega$.[23] A first-order variation in $\omega$ was considered (eq 8), induced by the change of phase when going from vacuum to solution, characterized by its dielectric constant $\varepsilon$.

$$\Delta\omega(1 \rightarrow \varepsilon) = \left(\frac{\mu}{\eta}\right)\Delta\mu - \frac{1}{2}\left(\frac{\mu}{\eta}\right)^2\Delta\eta = \Delta\omega^{(1)} + \Delta\omega^{(2)} \tag{8}$$

in which $\Delta\mu$ and $\Delta\eta$ describe the changes in electronic chemical potential and chemical hardness from the gas to the solution phase. A linear relationship was shown to exist for a series of neutral and electrophilic ligands between the change in the electrophilicity descriptor, $\Delta\omega$, and the solvation energy, $\Delta E_{\text{solv}}$:

$$\Delta\omega(1 \rightarrow \varepsilon) = \left(2 + \frac{\Delta N_{\text{ideal}}}{\Delta N}\right)\Delta E_{\text{solv}} = \gamma\Delta E_{\text{solv}} \tag{9}$$

Following this methodology, we derived an expression to describe the solvent effect on the nucleofugality index $\nu$. In analogy with eq 8, the first-order variation in the nucleofugality takes the following form:

$$\Delta\nu(1 \rightarrow \varepsilon) = \frac{\partial\nu}{\partial\mu}\Delta\mu + \frac{\partial\nu}{\partial\eta}\Delta\eta = \Delta\nu^{(1)} + \Delta\nu^{(2)} \tag{10}$$

The corresponding shift in nucleofugality $\Delta\nu$ comprises two contributions, namely $\Delta\nu^{(1)}$ and $\Delta\nu^{(2)}$. The first part of eq 10 in terms of the variation in $\mu$ is given by

$$\Delta\nu^{(1)} = \frac{\partial\nu}{\partial\mu}\Delta\mu = \frac{\mu}{\eta}\Delta\mu + \Delta\mu \tag{11}$$

Rearranging eq 11 in terms of the solvation energy results in the following expression:

$$\Delta\nu^{(1)} = \left(\frac{\Delta E}{\Delta N}\right)\left(\frac{\Delta N}{\Delta\mu}\right)\Delta\mu + \Delta\mu = \Delta E_{\text{ins}} + \Delta\mu = 2\Delta E_{\text{solv}} + \Delta\mu \tag{12}$$

where $\Delta E_{\text{ins}}$ is the insertion energy of the solute into the solvent, identified as twice the solvation energy, $\Delta E_{\text{solv}}$.[24−26] The key parameter in this equation, $\Delta E_{\text{solv}}$, originates from a physical model of ion solvation, presented by Contreras et al.[24]

The energy change associated with a process of transferring a singly charged atom from the gas to the solution phase is defined as the insertion energy $\Delta E_{\text{ins}}$. Pérez et al. presented a DFT formulation of this insertion energy and demonstrated its relationship to the solvation energy $\Delta E_{\text{solv}}$.[26]

The second part of eq 10 in terms of the variation in $\eta$ is given by

$$\Delta\nu^{(2)} = \frac{\partial\nu}{\partial\eta}\Delta\eta = \frac{1}{2}\left(1 - \left(\frac{\mu}{\eta}\right)^2\right)\Delta\eta \tag{13}$$

Substituting the proportionality of the chemical potential and hardness with the $\Delta N_{\text{ideal}}$ value (eq 5) results in

$$\Delta\nu^{(2)} = \frac{1}{2}(1 - \Delta N_{\text{ideal}}{}^2)\Delta\eta \tag{14}$$

Combining expressions 12 and 14 yields eq 15,

$$\Delta\nu = \Delta\nu^{(1)} + \Delta\nu^{(2)} = 2\Delta E_{\text{solv}} + \Delta\mu + \frac{1}{2}\Delta\eta(1 - \Delta N_{\text{ideal}}{}^2) \tag{15}$$

in which $\Delta N_{\text{ideal}}$ values are calculated in the solvent phase. The difference between eq 15and Pérez's eq 9 is the presence of an

**TABLE 1: Calculated Nucleofugalities (eV) of the Organic Leaving Groups $X^-$ Considered in This Work, in the Gas Phase, and in Solvent (Dichloromethane ($CH_2Cl_2$) and Methanol ($CH_3OH$)) and the Acidities ($pK_a$)[21,27,30,31] in $H_2O$ (25 °C) of the Acids HX[a]**

| | | $\Delta E_{nucleofuge}$ | | | $pK_a$ |
|---|---|---|---|---|---|
| | leaving group $X^-$ | gas phase | $CH_2Cl_2$ | $CH_3OH$ | HX |
| | (1) halide ions | | | | |
| 1 | $Br^-$ | 0.02 | −4.26 | −6.43 | −9.00 |
| 2 | $Cl^-$ | 0.05 | −3.61 | −5.37 | −7.00 |
| 3 | $F^-$ | 0.47 | −0.92 | −1.43 | 3.17 |
| | (2) alcohols/thiols | | | | |
| 4 | $C_6H_5OH$* | −1.69 | −4.20 | −4.93 | – |
| 5 | $CH_3OH$* | −1.18 | −2.15 | −2.33 | – |
| 6 | $CH_3CH_2OH$* | −1.38 | −2.66 | −2.92 | −2.00 |
| 7 | $H_2O$* | −0.61 | −0.97 | −1.03 | −1.74 |
| 8 | $PhS^-$ | 0.07 | −2.07 | −3.22 | 6.60 |
| 9 | $HS^-$ | 0.35 | −0.76 | −1.21 | 7.05 |
| 10 | $CH_3CH_2S^-$ | 0.42 | −0.77 | −1.30 | 12.00 |
| 11 | $PhO^-$ | 0.11 | −1.55 | −2.36 | 9.90 |
| 12 | $HO^-$ | 1.04 | −0.05 | −0.15 | 15.74 |
| 13 | $CH_3CH_2O^-$ | 0.82 | −0.18 | −0.39 | 16.00 |
| 14 | $(CH_3)_2CHO^-$ | 0.70 | −0.09 | −0.43 | 17.10 |
| | (3) carboxylates | | | | |
| 15 | $CF_3COO^-$ | 0.08 | −1.11 | −1.60 | 0.23 |
| 16 | $CHF_2COO^-$ | 0.13 | −1.01 | −1.48 | – |
| 17 | $CH_2FCOO^-$ | 0.19 | −0.86 | −1.28 | 2.66 |
| 18 | $CCl_3COO^-$ | 0.01 | −2.01 | −2.82 | 0.70 |
| 19 | $CHCl_2COO^-$ | 0.03 | −1.81 | −2.57 | 1.48 |
| 20 | $CH_2ClCOO^-$ | 0.10 | −1.30 | −1.90 | 2.85 |
| 21 | $CBr_3COO^-$ | 0.00 | −2.79 | −3.92 | – |
| 22 | $CHBr_2COO^-$ | 0.01 | −2.52 | −3.60 | – |
| 23 | $CH_2BrCOO^-$ | 0.06 | −1.71 | −2.51 | 2.69 |
| 24 | $HCOO^-$ | 0.27 | −0.78 | −1.19 | 3.75 |
| 25 | $PhCOO^-$ | 0.11 | −1.43 | −2.16 | 4.20 |
| 26 | $p$-$NO_2C_6H_4COO^-$ | 0.03 | −1.47 | −2.11 | 3.41 |
| 27 | $CH_3COO^-$ | 0.30 | −0.67 | −1.05 | 4.76 |
| 28 | $CH_3CH_2COO^-$ | 0.27 | −0.67 | −1.06 | 4.88 |
| | (4) $N_2$ and amines | | | | |
| 29 | $NH_3$* | −0.33 | −0.60 | −0.65 | 9.24 |
| 30 | $(CH_3)_3N$* | −0.48 | −0.85 | −0.92 | 9.80 |
| 31 | $(CH_3)_2NH$* | −0.53 | −0.89 | −0.95 | 10.73 |
| 32 | $CH_3NH_2$* | −0.55 | −0.94 | −1.01 | 10.65 |
| 33 | $N_2$* | −3.14 | −5.76 | −6.24 | – |
| | (5) sulfonates | | | | |
| 34 | $p$-$CF_3C_6H_4O_2SO^-$ | −0.03 | −3.89 | −5.48 | – |
| 35 | $p$-$CH_3C_6H_4O_2SO^-$ | −0.01 | −4.77 | −7.04 | 0.70 |
| 36 | $^-OSO_2C_4F_9$ | −0.09 | −3.52 | −4.61 | – |
| 37 | $^-OSO_2F$ | −0.02 | −3.36 | −4.49 | – |
| 38 | $^-OSO_2CF_3$ | −0.03 | −3.21 | −4.32 | – |
| 39 | $^-OSO_2CH_3$ | 0.00 | −2.54 | −3.49 | – |

[a] Groups indicated with an asterisk are charged when bound in the molecule.

extra term in $\Delta\mu$ and $(1/2)\Delta\eta$. This is due to the definition of $\nu$ in which the electron affinity besides $\omega$ appears. Consequently, the term $\Delta\mu + (1/2)\Delta\eta$ corresponds to the change of the electron affinity when going from the gas phase to solution.

## Methodology and Computational Details

Calculations were performed using the nucleofugality index as shown in eq 7, both in the gas phase and in two commonly used organic solvents with different polarities, i.e., dichloromethane ($\varepsilon = 8.93$) and methanol ($\varepsilon = 32.63$). Next, the relationships with both $pK_a$ values and available experimental solvolysis rate constants $k$ were examined.[21,27]

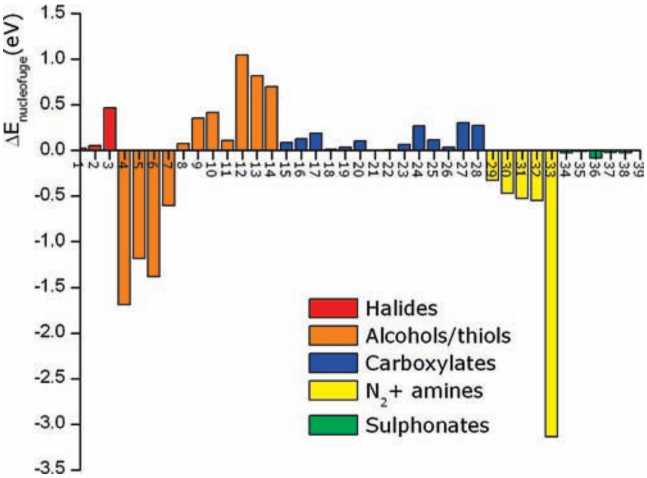


**Figure 1.** Calculated nucleofugalities in the gas phase (values in Table 1). The values on the *x*-axis correspond to the numbers of the leaving groups listed in Table 1.

Geometry optimizations of the radical and positively charged leaving groups, when covalently bound in the molecule, were performed at the 6-311++G(d,p) level using the B3LYP functional. Vertical ionization potentials and electron affinities were calculated at the same level of theory. Frequency calculations were performed to ensure that the structures correspond to minima of the potential energy surface. The groups were embedded in a polarizable continuum solvent model (PCM) in order to mimic the solvent.[28] All calculations were done using the Gaussian 03 program.[29]

Solvent effects on values of the nucleofugality index are estimated through eq 15. The decomposition in different terms makes it possible to evaluate the relative importance of the various contributions.

## Results and Discussion

**Trends in Nucleofugality.** The organic leaving groups are divided into five classes, and their nucleofugalities are listed in Table 1, together with the $pK_a$ values of their conjugate acids: (1) halide ions, (2) alcohols and thiols, (3) carboxylates including halogenated acetic acid derivatives ($CH_nX_{3-n}COOH$, X = F, Cl, Br), (4) $N_2$ and amines, and (5) the sulfonates (or sulfonic acid esters). As could be expected, the leaving groups are stabilized in solvent as compared to the gas phase. All nucleofuges have higher nucleofugalities in the more polar solvent methanol ($\varepsilon = 32.63$) than in the less polar dichloromethane ($\varepsilon = 8.93$). A detailed explanation concerning this topic will be given in the Solvent Effect on the Nucleofugality section. In a first step, the interpretation of our results is based on a comparison with the thermodynamic data (Table 1). Trends in the values of the nucleofugality within the different classes of leaving groups are compared to the expected sequences. The calculated gas phase nucleofugalities of all leaving groups are graphically represented in Figure 1.

An excellent correlation can be found between gas and solution phase nucleofugalities of the charged leaving groups (indicated with an asterisk in Table 1, $R^2 = 0.96$). No linear correlation exists between gas and solution phase nucleofugalities of the neutral nucleofuges. As explained further in the text (Solvent Effect on the Nucleofugality section), charged leaving groups bear a positive charge when they are covalently bound in the molecule. Neutral leaving groups are uncharged when bound in the molecule, and anions are formed upon dissociation.

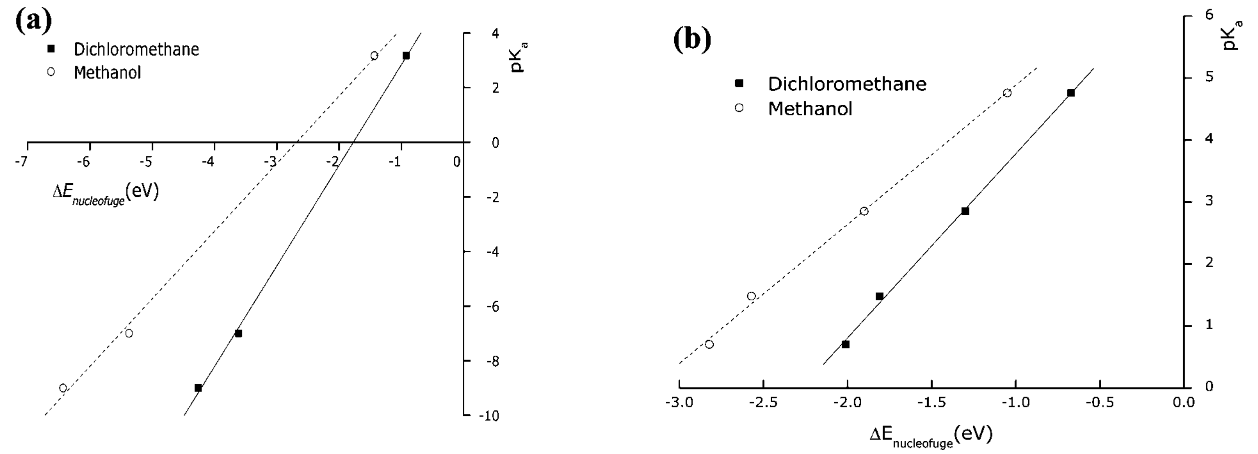


**Figure 2.** Linear relationship between the calculated nucleofugalities of (a) the halides F$^-$, Cl$^-$, and Br$^-$ and (b) the chlorinated carboxylates (acetate anion and its chlorinated derivatives), in $CH_2Cl_2$ and $CH_3OH$, as a function of the acidities of their conjugate acids (p$K_a$ in water, at 25 °C).[21,27]

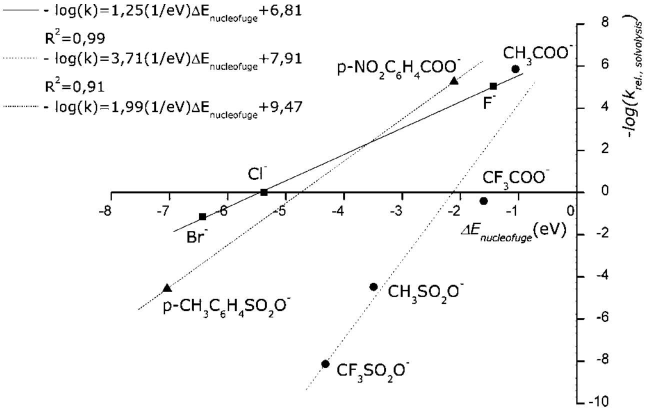


**Figure 3.** Linear correlation for the groups in Table 2 between the negative of the logarithm of $k_{\text{rel.,solvolysis}}$ and $\Delta E_{\text{nucleofuge}}$. A separate correlation was made for the leaving groups 1 to 3 (halides), 4 to 7, and 8 and 9 (two mixed series of carboxylates and sulfonates of comparable size).

**TABLE 2: Relative Rates of Solvolysis of 1-Phenylethyl Esters and Halides in an 80% Ethanol–Water Mixture at 75 °C**[37] [a]

| no. | leaving group | relative solvolysis rate | $\Delta E_{\text{nucleofuge}}$ in $CH_3OH$ (eV) |
|---|---|---|---|
| 1 | F$^-$ | $9 \times 10^{-6}$ | −1.43 |
| 2 | Cl$^-$ | 1.0 | −5.37 |
| 3 | Br$^-$ | 14 | −6.43 |
| 4 | $CH_3COO^-$ | $1.4 \times 10^{-6}$ | −1.05 |
| 5 | $CF_3COO^-$ | 2.5 | −1.60 |
| 6 | $CH_3SO_2O^-$ | $3.0 \times 10^{4}$ | −3.49 |
| 7 | $CF_3SO_2O^-$ | $1.4 \times 10^{8}$ | −4.32 |
| 8 | *p*-$NO_2C_6H_4COO^-$ | $5.5 \times 10^{-6}$ | −2.11 |
| 9 | *p*-$CH_3C_6H_4SO_2O^-$ | $3.7 \times 10^{4}$ | −7.04 |

[a] Calculated values of $\Delta E_{\text{nucleofuge}}$ in methanol are reported in eV.

***(a) Halide Ions.*** Within the halogen family, the nucleofugality order is Br$^-$ > Cl$^-$ > F$^-$ in the gas phase as well as in dichloromethane and methanol. This is the well-known nucleofugality sequence and reproduces the strength of the halic acids: HBr > HCl > HF.

***(b) Alcohols and Thiols.*** In the family of the alcohols and thiols, the neutral molecules and water are found to be excellent leaving groups due to their overall negative values of $\Delta E_{\text{nucleofuge}}$. On the other hand the alkoxides have positive nucleofugalities in the gas phase. Consequently, the neutral molecules, ethanol and water, are better nucleofuges than their corresponding anionic leaving groups, ethoxide and hydroxide, confirming that poor alkoxide leaving groups can be converted into better leaving groups by protonation. In general, RS$^-$ should be a better leaving group than RO$^-$, because the conjugate acid RSH is a stronger acid than ROH. This is confirmed by comparing the gas phase nucleofugalities of PhS$^-$ (0.07 eV) and PhO$^-$ (0.11 eV). The same result is found in both organic solvents. The same trends were observed for HS$^-$ and HO$^-$ in the gas phase as well as in methanol and dichloromethane.

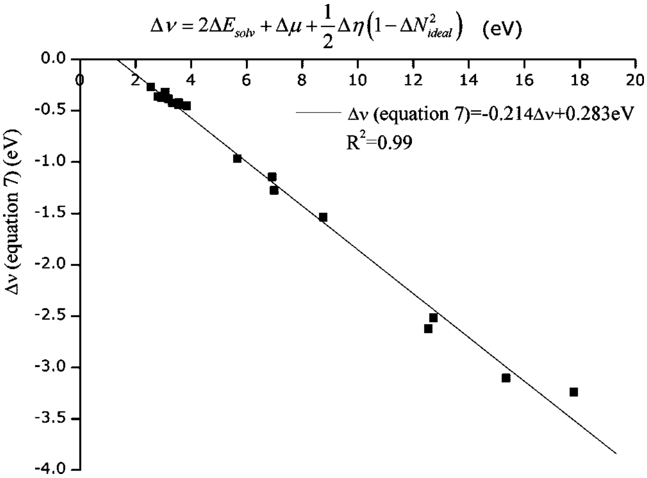
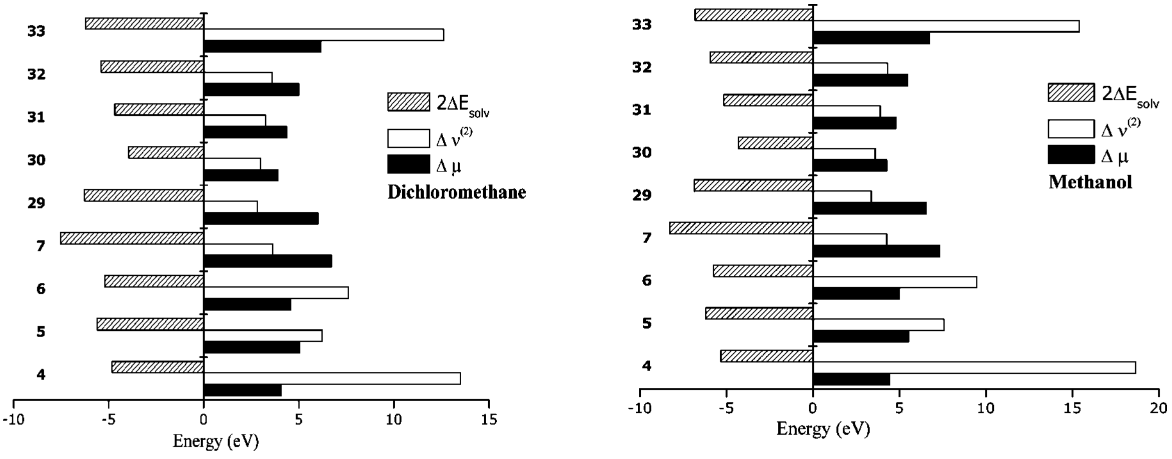


**Figure 4.** Regression line of the nucleofugality difference $\Delta\nu$ of the charged groups calculated through eq 7 and the values obtained by eq 15 in dichloromethane and methanol.

***(c) Carboxylates.*** Within the family of the carboxylic acids, the order of decreasing strength in leaving group capacity corresponds to following order: $CX_3COO^-$ > $CHX_2COO^-$ > $CH_2XCOO^-$ (X = F, Cl, or Br). The delocalized negative charge of the acetate anion becomes more stabilized with inductive electron-withdrawing substituents. This order is consistent with the strength of the carboxylic acids $CX_3COOH$ > $CHX_2COOH$ > $CH_2XCOOH$. Analyzing the computed results, this trend is again found in the nucleofugality descriptor. Between the different families of the carboxylic acids, $CBr_3COO^-$ appears to be the best leaving group with respect to $CCl_3COO^-$ and $CF_3COO^-$. However we expect to see the reverse sequence in solvent phase, based on the decreasing inductive strength of the halogens, when going down in the periodic table. We ascribe this shortcoming to the absence of the solvent assistance effect



**(a)** **(b)**

**Figure 5.** Size of the different contributions to eq 15 for the charged leaving groups in (a) dichloromethane and (b) methanol.

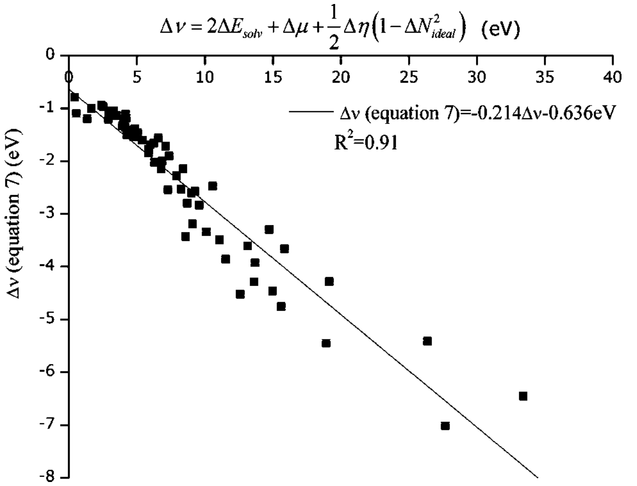


**Figure 6.** Regression line of the nucleofugality difference ($\Delta\nu$) of the neutral groups calculated through eq 7 as a function of the values obtained by eq 15 in dichloromethane and methanol.

since solute−solvent interactions are not considered explicitly in the chosen solvent model.

***(d) $N_2$ and Amines.*** In the series of the amines, the observed nucleofugality sequence in the gas phase, as well as in solvent, is as follows: $N_2$ > $CH_3NH_2$ > $(CH_3)_2NH$ > $(CH_3)_3N$ > $NH_3$. As expected, $N_2$ is the best leaving group of the amine series due to its high stability. The internal sequence between the nucleofugalities of $CH_3NH_2$, $(CH_3)_2NH$, and $(CH_3)_3N$ can be explained by considering the following reaction:

$$R{-}NR'^{+}_{3} \rightarrow R^{+} + NR'_{3}$$

The leaving group ability of $NR'^{+}_{3}$ depends on the relative stability of $NR'_3$ versus $R\text{-}NR'^{+}_{3}$. Before leaving the molecule, the positive charge on the nitrogen atom of the nucleofuge is stabilized by the inductive effect of the methyl substituents. Therefore, $CH_3NH_2$, which has only one methyl group, is a better leaving group than $(CH_3)_3N$ with three methyl substituents. The results show that among the charged molecules, $N_2$ is expected to be the best nucleofuge, both in the gas phase as well as in the organic solvents.

***(e) Sulfonates.*** The series of sulfonates are known to be among the best leaving groups in organic chemistry.[21] The corresponding sulfonic acids are extremely strong acids. The nucleofugality values in the gas phase are all slightly negative, which shows that the sulfonates are retrieved as the best nucleofuges among the anionic leaving groups (see Table 1 and Figure 1). The same observation applies for the results in solvent. Note, however, that the internal nucleofugality order of the sulfonates in the gas phase, in dichloromethane, and in methanol only partially corresponds with the expected leaving group ability.[21]

**Relationship between Nucleofugality and p$K_a$.** A rule of thumb within organic chemistry states that good leaving groups are the conjugate bases of strong acids.[32] We have tried to identify the existence of a relationship between the p$K_a$ of the conjugate acids and the nucleofugality of the studied leaving groups. Although no general trend was seen between these two quantities, an excellent correlation between $\Delta E_{\text{nucleofuge}}$ and the p$K_a$ was found for certain groups. Good qualitative trends were observed for the halide ions and the halogenated carboxylates. Figure 2 presents the results for the halide ions and the group composed of the acetate ions and its chlorinated derivatives in dichloromethane ($CH_2Cl_2$) and methanol ($CH_3OH$) with respect to the p$K_a$ values of their conjugate acids.

Within the different families of leaving groups, the trends in the nucleofugality mostly correspond to correct p$K_a$ sequences. For example, in the group of the alcohols and thiols the nucleofugality reproduces the acid strength of PhOH and PhSH [$\Delta E_{\text{nucleofuge}}$: $PhS^-$ < $PhO^-$], $CH_3CH_2SH$ and $CH_3CH_2OH$ [$\Delta E_{\text{nucleofuge}}$: $CH_3CH_2S^-$ < $CH_3CH_2O^-$], $H_2S$ and $H_2O$ [$\Delta E_{\text{nucleofuge}}$: $HS^-$ < $HO^-$], and $CH_3CH_2OH_2^+$, $CH_3CH_2OH$, and $(CH_3)_2CHOH$ [$\Delta E_{\text{nucleofuge}}$: $CH_3CH_2OH$ < $CH_3CH_2O^-$ < $(CH_3)_2CHO^-$]. In the group of the carboxylates, this descriptor correctly predicts the sequence in acid strength for singly, doubly, and triply halogen-substituted acetic acids. It fails, however, in resolving correct trends in some cases, e.g., in the group of the amines and $N_2$.

Concerning this p$K_a$−nucleofugality relationship it should be stressed that this is only a rule of thumb based on empirical data. The fact that some groups are deviating from this rule therefore does not seem that unexpected, e.g., the formiate versus benzoate leaving group. Within some families of leaving groups, the nucleofugality and acid strength are clearly correlated; however, a general correlation cannot be found and deviations can occur. This was also stressed by Ayers et al.,[8] stating that nucleofugality is not Brønsted acidity. We believe that this model can be improved by using the effective fragment potential (EFP) methodology,[33,34] investigated previously by our group,[35,36]

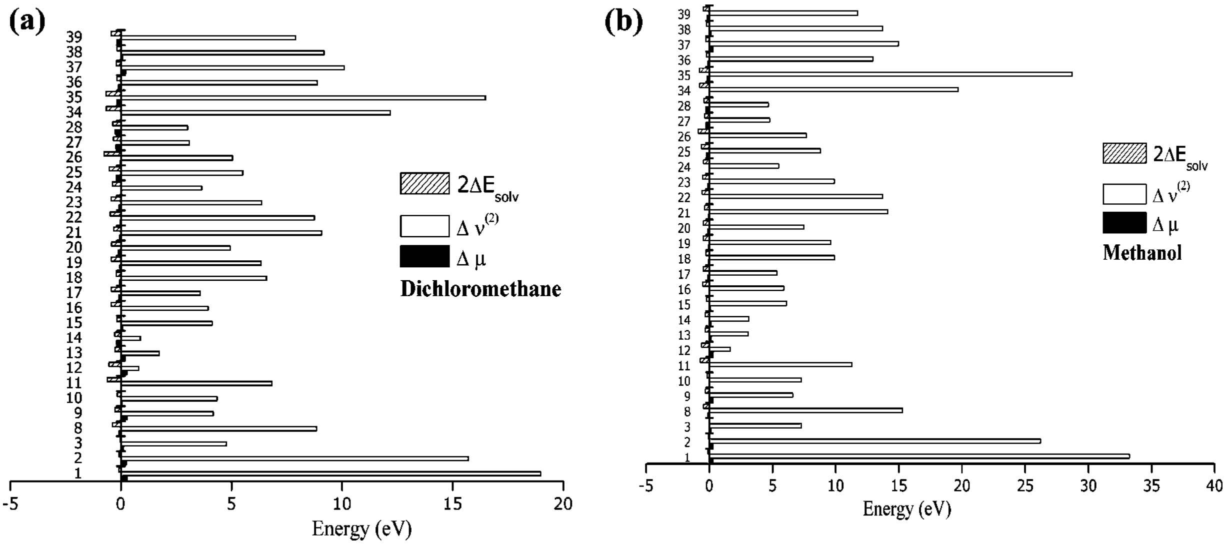


**Figure 7.** Size of the different contributions to eq 15 for the neutral systems in (a) dichloromethane and (b) methanol.

which involves direct solute−solvent interactions. These calculations are far from trivial in organic solvents, such as methanol and dichloromethane, or in mixed solvents, such as the 80% aqueous ethanol mixture in the kinetic study (Relationship between Nucleofugality and Solvolysis Rate Constants section). Note that this approach, however, reduces the transparency and the simplicity of the proposed model.

**Relationship between Nucleofugality and Solvolysis Rate Constants, $k_{\mathrm{solvolysis}}$.** The existence of a linear relationship between the computed nucleofugality and all experimental solvolysis reaction rate constants was examined, thus permitting a broader point of view as compared to an initial study by Ayers on the halides only.[8] Unfortunately, the available kinetic data only cover a limited range of the leaving groups that are considered in our study. Support for the proposed utility of the nucleofugality as measure of solvolysis rate constants is based on experimental $k_{\mathrm{solvolysis}}$ values of 1-phenylethyl esters and halides in an 80% ethanol−water mixture at 75 °C, presented by Noyce et al.[37] This solvent mixture ($\varepsilon = 36.26$) has a comparable polarity to methanol, used in the PCM calculations ($\varepsilon = 32.63$). Relative solvolysis rate constants and corresponding nucleofugalities are presented for some leaving groups in Table 2.

In the same vein as Ayers,[8] we looked for a correlation between the solvolysis rate constant and a nucleofugality descriptor. Starting from Eyring's transition state theory,[38] relating the rate constant and the Gibbs free energy of activation, one obtains

$$-\log k = a\Delta H^{\dagger} + b \qquad (16)$$

where $b$ involves the activation entropy, and $a$ equals $1/(2.303RT)$.

If a linear relation is put forward between $\Delta H^{\dagger}$ and $|\Delta E_{\mathrm{nucleofuge}}|$, eq 16 turns into

$$-\log k = a'\Delta E_{\mathrm{nucleofuge}} + b' \quad \text{with} \quad a' > 0 \qquad (17)$$

Figure 3 shows that the nine cases considered can be divided in three groups (halides, as also found by Ayers,[8] carboxylates and sulfonates, and the two aromatic compounds) showing fair linear relationship for the three- and four-membered series. The fact that not a single straight line could be drawn can, in our opinion, be traced back to the nature of the $b'$ term. Its positive sign is an indication of a negative activation entropy, in agreement with higher ordering of the solvent molecules.[39] Moreover, the sequence of the $b'$ values is in line with the size of the molecules. The difference in slope is less evident, but following LFER type arguments,[40] it could be conjectured to contain information about the transition state position along the reaction path. On the basis of the data in Figure 3 the trend between the $F^-$ and $CF_3COO^-$ leaving group capability can be discussed. Although their nucleofugality values are almost similar, the higher slope of the regression line for $CF_3COO^-$ compared to $F^-$ kinetically favors the solvolysis process.

**Solvent Effect on the Nucleofugality: A Conceptual DFT Approach.** Solvent assistance plays an important role in the study of nucleophilic substitution and elimination reactions. Characteristics such as the polarity and hydrogen-bonding ability of the solvent are decisive for the stabilization of full or partial anions and cations. In case of the $S_N1$ reaction, its rate will be increased by a polar solvent since the rate-determining step usually involves the formation of ions. In this paper, nucleofugality values were computed in two solvents with increasing polarity, i.e., dichloromethane and methanol. These solvents were modeled through a dielectric continuum model (PCM), that includes long-range electrostatic interactions, neglecting, however, hydrogen-bond interactions. As previously noted, the $\Delta E_{\mathrm{nucleofuge}}$ values decrease when going from the gas phase to dichloromethane and methanol, thereby improving the capability of the leaving groups to become dissociated. In order to examine the different contributions to this change in nucleofugality, we derived eq 15 in the Theoretical Background. This formula divides the transition from the gas to the solution phase into three terms, namely the solvation energy $\Delta E_{\mathrm{solv}}$, the change in the chemical potential $\Delta\mu$, and the change in the chemical hardness, $^1/_2\Delta\eta(1 - \Delta N_{\mathrm{ideal}}^2)$, scaled with the value of $\Delta N_{\mathrm{ideal}}$ in solvent. In the following discussion, we distinguish between charged and neutral leaving groups. We will denote charged leaving groups as those groups that bear a positive charge when they are covalently bound in the molecule (groups indicated with an asterisk in Table 1). Neutral leaving groups are uncharged when bound in the molecule; anions are formed upon dissociation.

For the series of the charged leaving groups an excellent correlation can be found between the change in nucleofugality going from the gas phase to solvent, calculated by eq 15 and by eq 7. As depicted in Figure 4 the slope of the regression line is negative, which is due to the initial formula used for deriving eq 15. Since $\Delta N_{\mathrm{ideal}}$ values in solvent are higher than 1, the negative sign of eq 7 should be used as a starting point for the derivation of eq 15. Note, however, that this will only affect the sign of the calculated differences in nucleofugality. Higher values of eq 15 can therefore be interpreted as more negative differences in nucleofugality values, resulting from eq 7.

The enhancement of the leaving groups to become dissociated in the solvent phase can be assigned to the different contributions to eq 15. Charged systems become more stabilized in polar solvents, resulting in a more negative sign for their solvation energies $\Delta E_{\mathrm{solv}}$. The chemical potential increases from the gas to the solvent phase, thereby showing greater resistance to charge transfer. The chemical hardness shows opposite behavior. Lower values of the chemical hardness in solvent indicate that leaving groups become softer in polar solvents, thereby showing a lower resistance to charge transfer. $\Delta N_{\mathrm{ideal}}$ values increase from dichloromethane over methanol, due to dominance of the lower hardness values over the increased chemical potential. As a result the $\Delta\nu^{(2)}$ value augments when the leaving groups are transferred to more polar solvents. The increase in $\Delta\nu^{(2)}$ and $\Delta\mu$ values enhances the leaving group capacity defined in eq 15, while the solvation energy moderates this capacity. As shown in Figure 5a,b the three terms in eq 15 are equally important to describe the change in nucleofugality from the gas phase to solvent.

Concerning the series of the neutral leaving groups, Figure 6 shows the accuracy of the difference in nucleofugality from the gas to the solvent phase, approached by eq 15 with respect to the values calculated with eq 7. Compared to the charged leaving groups a lower correlation is achieved, accompanied by a larger systematic error. Important to note is that the slope of the regression lines for charged and neutral leaving groups are identical, validating the physics behind this proposed formula.

The contribution of the solvation energy to the change in nucleofugality is low since its value is negligible for neutral groups. Second, we find that the difference in chemical potential, when transferring the nucleofuges from gas to the solution phase, is low. This is consistent with Pearson's prediction that the electronegativity of neutral systems is unaffected by solvation.[41] The dominant contribution to eq 15 is given by the value of $^{1}/_{2}\Delta\eta(1 - \Delta N_{\mathrm{ideal}}{}^{2})$, showing that the change in hardness, scaled with $\Delta N_{\mathrm{ideal}}$, directs the leaving group capacity. The size of the different terms is presented in Figure 7a,b.

## Conclusion

In conclusion, we constructed an intrinsic nucleofugality scale, based on the definition introduced by Ayers et al.,[8,9] both in the gas phase and in solution. Our scale is largely in good qualitative agreement with the classical trends in leaving group capacity in organic chemistry. However, some exceptions occur, which can be ascribed to shortcomings in the nonspecific solvent model. Within some families of compounds, $\Delta E_{\mathrm{nucleofuge}}$ and $\mathrm{p}K_{\mathrm{a}}$ are shown to be quantitatively related. The overall results are mostly consistent with solvolysis reaction rate constants and could be interpreted in terms of a linear realtionship between the logarithm of $k_{\mathrm{solvolysis}}$ and $\Delta E_{\mathrm{nucleofuge}}$, based on Eyring's transition state theory and a linear relationship between the activation enthalpy and $\Delta E_{\mathrm{nucleofuge}}$.

The formula we derived in a conceptual DFT context, to describe the solvent effect on the nucleofugality, yields excellent correlations between the changes in nucleofugality and the computed values for all calculated leaving groups in both solvents. The contribution of the three terms in this equation shows that the change in hardness is the dominant contribution in the case of neutral leaving groups, whereas for charged nucleofuges, all terms contribute equally.

The methodology presented opens a perspective to evaluate in a straightforward way the leaving group capacity of a wide variety of groups in a wide variety of solvents, thus being of help for practical organic chemists in designing reaction schemes.

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