A Theoretical Study on the Relationship between Nucleophilicity and Ionization Potentials in Solution Phase

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In this paper we describe a method to obtain estimates of the relative nucleophilicity for a series of neutral and charged electron donors from their solution phase ionization potential (I_s). The relationship between nucleophilicity and the solution phase ionization potentials is first tested for experimental I_s values in aqueous solution. On the basis of the meaningful relationship found, the method is then applied to the theoretical solution phase I_s obtained at the IPCM-MP2/6-311G(2d,p) level of theory. The comparison between the experimental nucleophilicity as given by Ritchie's $N+$ scale and the solution phase ionization energy for a series electron donors split out into two families: a first group of marginal and moderate nucleophiles that mainly contains atoms of the first row (H_2O, $NH_2CONHNH_2$, $CF_3CH_2NH_2$, NH_3, CH_3ONH_2, NH_2OH and CH_3O^-), with nucleophilicity number $N+ < 6.0$; a second group of strong nucleophiles, mainly including second-row sulfur atom ($CH_3CH_2S^-$, $CH_3CH_2CH_2S^-$, $OHCH_2CH_2S^-$, $C_6H_5S^-$) and the first-row electron donors piperidine and morpholine, with nucleophilicity number $N+ > 7.0$. An approximate expression for a local nucleophilicity index is proposed. The results show that the nucleophilicity power of the electron donors is consistently shown at the expected nucleophilic sites in these molecules. The solvent effect on the predicted nucleophilicity is also discussed.

1. Introduction

Since the introduction of the electrophilicity and nucleophilicity concepts[1] to describe electron-deficient (electrophile, E^+) and electron-rich (nucleophile, Nu^-) species, respectively, there has been a growing interest in classifying atoms and molecules within empirical scales of electrophilicity and nucleophilicity.[2−6] The availability of quantitative scales of electrophilicity/nucleophilicity provides useful tools for the rationalization of chemical reactivity. The benefits of these scales has been recently illustrated by Mayr et al.[7] They provide for instance quantitative criteria to decide whether a given electrophile−nucleophile combination reaction will take place. The experimental model is based on the following three-parameter equation:

$$\log k = s(N + E) \qquad (1)$$

Here k is the rate constant for the electrophile−nucleophile combination reaction, s is a nucleophile-specific parameter, and N and E are the nucleophilicity and electrophilicity numbers, respectively.[7] The predictive power of this experimental model of reactivity is closely related to the expected reaction rates. It has led to a useful empirical reactivity rule about the kinetic feasibility of the electrophile−nucleophile combination reactions.[7] This model has been further applied to deal with inter- and intramolecular selectivity, by predicting product ratios that result when carbon electrophiles react with two competing nucleophiles, or to predict the preferred sites of electrophilic attacks toward a nucleophile presenting two possible electrophilic sites,[7] respectively.

Theoretical scales of electrophilicity and nucleophilicity are highly desirable as they can be used to rationalize the electronic aspects of reactivity, selectivity, and their variations induced by field effects coming from chemical substitution, solvation, or even conformational changes. A validated theoretical scale of electrophilicity/nucleophilicity may be further extended to describe local reactivity aspects related to selectivity.

From a theoretical point of view, electrophilicity has been recently defined by Parr et al.[8] as the energy stabilization of a chemical species when it acquires an additional fraction of electronic charge from the environment. A useful representation of this property in terms of electronic descriptors of reactivity, namely the electronic chemical potential μ and the chemical hardness η, allowed the authors to define an absolute scale of electrophilicity for atoms and molecules in their ground states.[8] It is based on a second-order model for the changes in electronic energy as a function of the changes in the number of electrons ΔN, at constant external potential $\upsilon(\mathbf{r})$, namely[8]

$$\Delta E = \mu \Delta N + \eta \frac{\Delta N^2}{2} \qquad (2)$$

where

$$\mu = -(I + A)/2 \qquad (3a)$$

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and

$$\eta = I - A \tag{3b}$$

are the electronic chemical potential and chemical hardness defined in terms of the vertical ionization potential I and electron affinity A, respectively. The electronic chemical potential $\mu \approx \Delta E/\Delta N$ of a stable species is always negative. Since an electrophile is a chemical species capable of accepting electrons from the environment, its energy must decrease ($\Delta E < 0$) in the direction of increasing N ($\Delta N > 0$); thus, the condition of negative electronic chemical potential is always fulfilled. This simple argument explain why the definition of the electrophilicity index ω may be consistently obtained from a simple variational calculation as the one described by Parr et al.[8] It consists of minimizing ΔE with respect to ΔN in eq 2 with the following results:

$$\omega = -\Delta E = \frac{\mu^2}{2\eta} \tag{4}$$

The electrophilicity index ω has been successfully applied to classify a series of diene/dienophile pairs participating in Diels−Alder reactions.[9] The theoretical scale of electrophilicity based on Parr's et al. index has also been validated against the kinetic electrophilicity scale of Mayr et al.[10] and the spectroscopic electrophilicity scale of Legon and Millen,[2,3] and recently it has been also validated against the Moss et al. electrophilicity scale for singlet carbenes.[11] Local extensions of expression (4)[12] as well as solvation effects on the electrophilicity power of molecules have been already reported,[13] illustrating the usefulness of the electrophilicity index as a chemical descriptor of reactivity. Other definitions of local electrophilicity and nucleophilicity have been proposed in the literature. For instance, Roy et al.[14] have proposed a local relative nucleophilicity index which is intramolecular in nature, in the sense that it ranks the nucleophilicity power of atomic centers with reference to the other atomic regions within the same molecule.

The definition of nucleophilicity cannot be deduced from a variational framework similar to that leading to the definition of electrophilicity based on eq 2. This is because bound systems that release electronic charge to the environment ($\Delta N < 0$) must increase their energy to maintain a negative value of the electronic chemical potential. On the other hand, the nucleophilicity index ω^- cannot be defined as the inverse of electrophilicity in a mathematical sense: $\omega^- = 1/\omega$ or $\omega^- = 1 - \omega$. The first relationship fails because it has not a clear physical definition (the inverse of power), and the second one fails because the quantity ω is not normalized to unity. This means that electrophilicity and nucleophilicity may be not the opposite ends of a unique scale. Nucleophilicity is however an inverse of electrophilicity on physical grounds: while ω measures the energy stabilization of a chemical species upon accepting electronic charge from the environment, the quantity ω^- measures the energy changes (no necessarily leading to a minimum), when the charge flux with the environment is in the opposite direction. In this work we propose an empirical relationship between an experimental nucleophilicity scale and the vertical ionization potential of the molecule in the solution phase.

2. Model

2.1. Relationship between Nucleophilicity and Solution Phase Ionization Potentials. Consider for instance a nucleophile that transfers one electron to the environment (i.e. $\Delta N = -1$). According to eq 2 and using eqs 3a,b, the energy change will be given by

$$\Delta E \cong -\mu + \frac{\eta}{2} = I \tag{5}$$

which shows that the energy will be increased, as expected, in an amount that exactly gives the ionization potential of the nucleophile. Note that expression (5) entails, with respect to the equivalent expression for $\Delta N = 1$, the inversion of the sign of μ (i.e. the inversion of the electronic charge flux) and that the contribution of the chemical hardness remains invariant in both cases, thereby reinforcing the concept of chemical hardness as a resistance to the electronic charge flux between the system and the environment.[8] From this expression, we may think of the best nucleophile as the one that minimizes the energy increase $\Delta E = I$. A possible empirical definition of a nucleophilicity index that roughly satisfies this condition is $\omega^- = -I$. This definition guarantees that the higher the ionization potential, the lowest the nucleophilic power of the molecule will be, and conversely, the best nucleophile will be the one presenting the lowest value in ionization potential. This result is encouraging as it has been thought for some time that the solution phase ionization potentials helped to determine the nucleophilic potential of electron donors in nucleophilic substitution reactions,[15,16] yet a quantitative relationship between both quantities has not been proposed to date.

The prediction of solution phase ionization potentials may be however a difficult task for some particular cases, mainly those involving negatively charged species. Within the present approach, the relationship between intrinsic (gas phase) nucleophilicity index ω_o^- and the solution phase nucleophilicity ω_s^- is given by

$$\omega_s^- = \omega_o^- + \delta\Delta E_{solv} \tag{6}$$

where

$$\delta\Delta E_{solv} = \Delta E_{solv}(N) - \Delta E_{solv}(N-1) \tag{7}$$

is the difference between the solvation energy of the nucleophile with N electrons and its ionized form with $N - 1$ electrons. In eq 6, $\omega_o^- = -I_o$. According to this model, two sources of errors must be considered concerning the correct prediction of the solution phase nucleophilicity $\omega_s^- = -I_s$. They are the intrinsic ionization potential I_o in the absence of the solvent and the solvation energies of the nucleophile and its ionized counterpart. The first one, and perhaps the most important of them, is the accurate calculation of I_o.

2.2. Solvent Effects on Nucleophilicity. A final remark concerning the role of the solvent in the nucleophilicity pattern of neutral and charged electron donors is worth mentioning. According to eq 6, the second contribution to the solution nucleophilicity index is the difference in solvation energy between the electrophile and its corresponding ionized form. The solvent effects will influence neutral and charged nucleophiles differently. Consider for instance the negatively charged nucleophiles. For these systems, the ionized form corresponds to a neutral radical for which the solvation energy is predicted to be negligible respect to the solvation energy of the corresponding anion.[15] In this case, the solution phase nucleophilicity will be approximately given by $\omega_s^- \approx \omega_o^- + \Delta E_{solv}(N)$. Since $\Delta E_{solv} < 0$ for negatively charged species, it follows that solvation effects will in general attenuate the electrophilicity power of negatively charged electrophiles. For neutral nucleo-

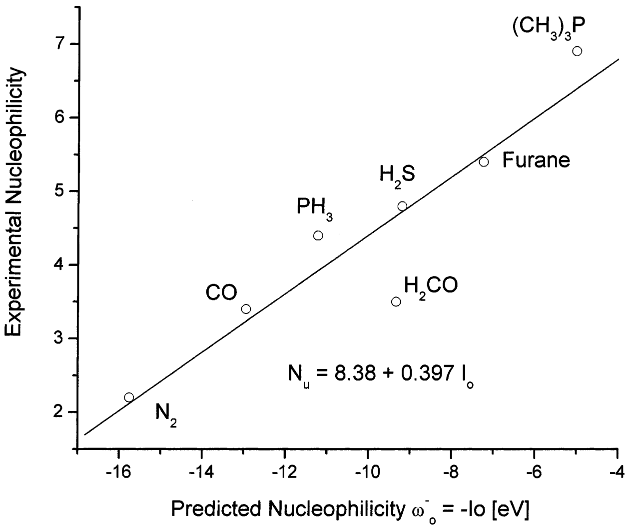

Figure 1. Comparison between experimental gas phase nucleophilicity (from refs 17 and 18) and the negative of the gas phase ionization potential obtained at the MP2/6-311G(2d,p) level of theory.

philes on the other hand, the leading term in eq 7 will be $\Delta E_{\mathrm{solv}}(N - 1)$ and the solution phase nucleophilicity will be approximately given by $\omega_s^- \approx \omega_o^- + \Delta E_{\mathrm{solv}}(N - 1)$. Note that, in this case, the solvation effects will work in favor of the nucleophilicity power in the solution phase in an amount proportional to the solvation energy of the ionized form, which corresponds to positively charged species. Since with the only exception of piperidine and morpholine these neutral electron donors behave as marginal and moderate nucleophilic species, it follows that their nucleophilicity pattern in solution is mostly driven by the intrinsic ionization energy contribution.

3. Results and Discussion

3.1. Global Intermolecular Nucleophilicity. To first test the model of intrinsic nucleophilicity $\omega_o^- = -I_o$, we selected a series of electron donors for which there exist an experimental scale of gas phase nucleophilicity relative to water, built up from spectroscopic data recorded by Legon and Millen.[17,18] The series include N_2, CO, PH_3, H_2CO, H_2S, furan, $(CH_3)_3P$, H_2O (the reference), NH_3, and CH_3OCH_3. MP2/6-311G(2d,p) calculations were performed to evaluate the quantity I_o. The comparison with the experimental scale for the whole series including the reference molecule was fair, mainly because ammonia and dimethyl ether strongly deviated from a linear relationship. However, when the comparison was made for 7 out of the 9 compounds within the series shown in Figure 1, a reasonable good correlation ($R = 0.93$) was obtained. Note that, for the case of NH_3, the authors of the experimental scale report different nucleophilicity values.[17,18] The failure in the correct description of dimethyl ether is intriguing, but no attempts to improve it were made.

To test the model incorporating solvent effects we first compared the experimental scale of nucleophilicity in aqueous solution reported by Ritchie[19] with the negative of the experimental ionization potential in water $-I_s$ reported by Pearson.[15] Unfortunately, the overlap between both databases is scarce, yet they provide sufficient information for the purpose of probing the relationship between both properties. The results are shown in Figure 2 for the short series of charged nucleophiles OH^-, OOH^-, CH_3O^-, N_3^-, $CF_3CH_2O^-$, and $C_6H_5S^-$. The correlation between both variables ($R^2 = 0.95$) reveals a meaningful relationship between Ritchie's nucleophilicity numbers $N+$[19] and the negative of the experimental aqueous ionization potential reported by Pearson.[15] This result is encouraging in the sense that if reliable solution phase ionization potential can be made available from suitable theoretical methods, then an absolute theoretical scale of nucleophilcity may be proposed. Note however that CN^-, for which both experimental $N+$ and I_S data exist, significantly deviates from the approximately linear relationship between both quantities (see Figure 2).

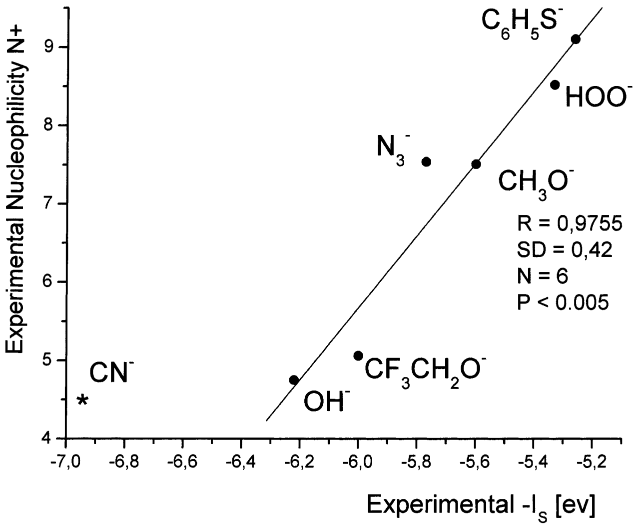

Figure 2. Comparison between experimental nucleophilicity $N+$ (from ref 19) and the negative of the experimental ionization potentials I_s (from ref 15).

TABLE 1: Experimental and Predicted Ionization Potentials in the Gas Phase (I_o) and in Aqueous Solution (I_s) for a Series of Negatively Charged Electron Donors[a]

	exptl		predicted	
species	I_o	I_s	I_o	I_s
OH^-	1.83	6.22	0.19	3.93
OOH^-	1.19	5.33	0.06	3.48
N_3^-	2.70	5.77	2.95	5.79
CH_3O^-	1.59	5.60	0.92	3.99
$CF_3CH_2O^-$	2.22	5.78	2.19	4.90
$C_6H_5S^-$	2.47	5.26	3.12	5.45
CN^-	3.82	7.88	4.04	6.97

[a] All values in eV. Experimental ionization potentials are from ref 20. Predicted quantities from MP2/6-311G(2d,p)//MP2/6-311G(2d,p) calculations; see the text for further details.

As stated before, there are two contributions to the solution nucleophilicity within the model condensed in eqs 6 and 7. On one hand, there is the intrinsic contribution $\omega_o^- = -I_o$, depending on the gas-phase ionization potential. Gas-phase ionization potentials may be evaluated from the energy difference between the systems with N and $N - 1$ electrons, namely, $I_o = E(N - 1) - E(N)$. The calculations are performed for the systems with N and $N - 1$ electrons, for the ground state of the systems in their fully optimized geometry at the MP2/6-311G(2d,p) level of theory. Experimental and theoretical ionization energies in the gas phase are given in Table 1. They are further compared in Figure 3. It may be seen that, at this level of theory, the experimental and theoretical ionization energies are only comparable on qualitative basis. Note that here again the CN^- system shows the most significant deviation from the experimental values. The calculation of accurate ionization potentials has been the matter of interest in the past.[20,21] Several methods including electron correlation at different levels of theory have been tested for this purpose. All of them agree in that

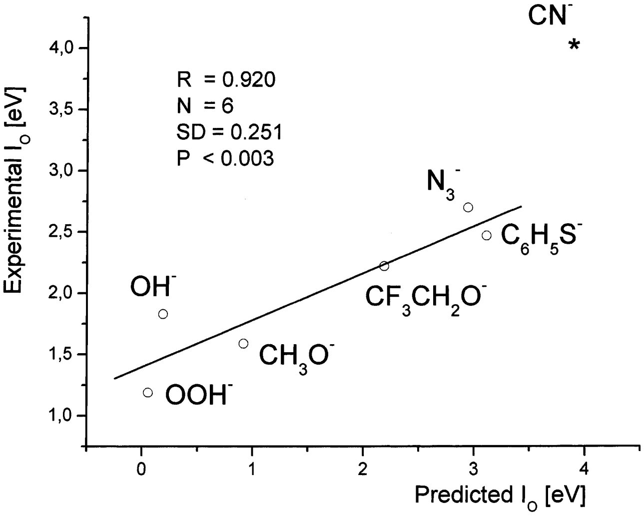

Figure 3. Comparison between experimental ionization potential I_o (from ref 15) and the predicted I_o obtained at the MP2/6-311G(2d,p) level of theory.

quantitative ionization energies are only possible to obtain at higher computational levels.[20] However for the purpose of qualitatively relating the ionization energy and the nucleophilic power of electron donors, the MP2/6-311G(2d,p) level seems to be adequate, if we consider that anions are the upper limit of increasing difficulty to quantitatively represent this property.

Inclusion of solvent effects has been done by means of continuum models using the IPCM model of Tomasi et al.[22] The calculation of the solution phase ionization potential I_S was performed from the energy difference between the system with N and $N - 1$ electrons in the external potential of the system with N electrons (i.e. vertical ionization energy). The I_S quantity is directly obtained by comparing the total energies of the system with N and $N - 1$ electrons in the presence of a polarizable medium characterized by a dielectric constant $\epsilon = 78.5$ to mimic water as solvent. The results are summarized in Table 1. Note that, with the only exception of $C_6H_5S^-$ species, the IPCM-MP2/6-31G(2d,p) method systematically underestimate the solution phase ionization potentials. The largest deviation is observed for the smallest anions for which a high solvent effect is expected. Since for the intrinsic contribution I_o the theoretical values systematically underestimate the experimental value, it may be concluded that both I_o and I_s may be consistently compared with their experimental counterparts without having systematic compensation of errors; thus, the order relationships within a family of anions may be reliably represented at this level of theory.

The preliminary study made on negatively charged electron donors, for which there exist both experimental values of nucleophilicity and solution phase ionization potentials, allowed us to illustrate the major difficulties encountered in the construction of a theoretical scale of nucleophilicity on the basis of the simple model condensed in eqs 6 and 7. Both quantities are compared in Table 2. Despite the fair comparison between the experimental and predicted nucleophilicity for negatively charged electron donors, the following points are worth mentioning: For small anions (OH^-, OOH^-, N_3^-, and CH_3O^-), the solvation energy drives the nucleophilicity power in the solution phase. Note that the abnormally high nucleophilicity predicted for OH^-, the anion experimentally evaluated as the weakest nucleophile within the series, may be traced almost exclusively to the extremely low intrinsic ionization energy I_o predicted for this nucleophile, as its solvation energy is correctly evaluated as the highest within the series. The other point worth mentioning is the failure of the model to reproduce the correct nucleophilicity power of $C_6H_5S^-$, the anion experimentally evaluated as the strongest nucleophile within the series. Here the wrong result may again be traced to a poor representation of I_o, as the IPCM model reproduce its experimental solvation energy almost quantitatively.

TABLE 2: Predicted Nucleophilicity in the Gas (ω_o^-) and in Solution (ω_s^-) Phases and Experimental Nucleophilicity Number ($N+$) in Aqueous Solution for a Series of Negatively Charged Electron Donors[a]

	predicted nucleophilicity[b]			exptl nucleophilicity[c] and solvation energy	
species	ω_s^-	ω_o^-	$\delta\Delta E_{solv}$	$N+$	ΔE_{solv}[d]
OH^-	−3.93	−0.19	−3.74	4.75	−4.55 (−3.94)
OOH^-	−3.48	−0.06	−3.42	8.52	−4.12 (−3.68)
N_3^-	−5.79	−2.95	−2.84	7.54	−3.25 (−2.90)
CH_3O^-	−3.99	−0.92	−3.07	7.51[e]	−4.03 (−3.20)
$CF_3CH_2O^-$	−4.91	−2.19	−2.72	5.06	−3.64 (−2.85)
$C_6H_5S^-$	−5.45	−3.12	−2.33	9.10	−2.95 (−2.47)
CN^-	−6.97	−4.04	−2.93	4.12	−3.21 (−3.09)

[a] All values in eV. [b] $\omega_s^- = \omega_o^- + \delta\Delta E_{solv}$. Evaluated from eqs 4 and 5); see the text for details. [c] Experimental nucleophilicity in water from ref 19. [d] Experimental solvation energies of anions in eV units. The predicted solvation energies are given in parentheses. [e] Experimental nucleophilicity evaluated in methanol from ref 19.

The difficulties outlined above for the representation of the solution nucleophilicity of electron donors in terms of the solution phase ionization potentials may be significantly alleviated for the case of neutral nucleophiles. Having this hypothesis in mind, we evaluated the nucleophilicity power of a series of first row neutral electron donors (i.e. neutral nucleophiles containing N and O atoms) including some second-row charged nucleophiles (i.e. containing sulfur atoms). When we compared the nucleophilicity index $\omega_s^- = -I_s$, incorporating solvent effects with the experimental nucleophilicity number $N+$ reported by Ritchie,[19] two well-defined families of nucleophiles clearly emerged: one family of marginal and moderate nucleophiles with a nucleophilicity number $N+ < 7.0$ in the experimental scale; a second series of nucleophiles with nucleophilicity number $N+ > 7.0$, which we arbitrarily classified as strong nucleophiles. The results of this comparison are shown in Figures 4 and 5, respectively. Included in the first group of marginal and moderate nucleophiles (Figure 4) are water, ammonia, and a series of neutral amines including hydroxylamine. Piperidine and morpholine are borderline between both groups, and they are included in Figure 5 in the group of strong nucleophiles. Note that this family is mainly composed of sulfur-containing anions that have been recognized as strong nucleophilic species in a series of chemical processes.[23,24]

The location of CH_3O^- within the range of strong nucleophiles (i.e. $N+ > 7.0$) in Figure 4 is somehow striking, because according to our model eq 7 the high solvation energy expected for this anion would strongly attenuate its nucleophilicity in aqueous solution. Unfortunately, the experimental nucleophilicity number $N+$ of CH_3O^- in water is not available. The reported $N+$ value for this anion was measured in methanol,[19] a solvent having a markedly lower polarity respect to water. This species is expected to nucleophilically behave in a manner closer to that of OH^-, i.e. as a marginal nucleophile in aqueous solution. To test the predictive power of the present model, we evaluated the nucleophilicity of CH_3O^- from the regression equation: $\omega_s^- = 9.74 - 1.28I_s$ (see Figure 4). Using the predicted ionization energy in water 3.99 eV quoted in Table 1, we obtain $\omega_s^- = 4.63$, in an excellent agreement with an

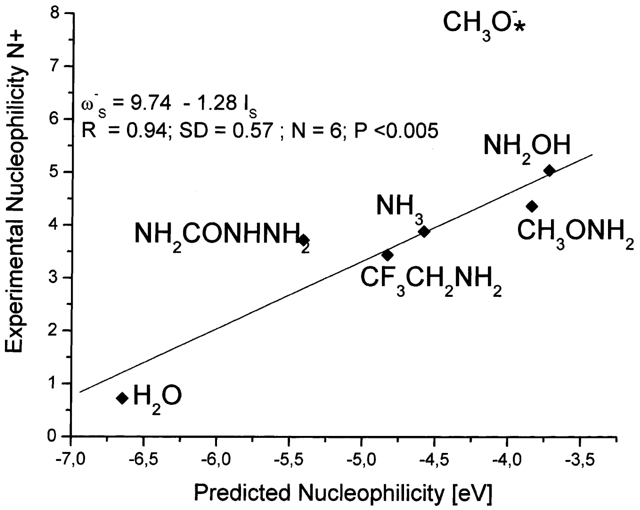

Figure 4. Comparison between experimental nucleophilicity *N*+ (from ref 19) and the predicted solution nucleophilicity obtained at the IPCM-MP2/6-311G(2d,p) level of theory for a series of first-row electron donors (marginal and moderate nucleophiles). *R* is the regression coefficient, SD is the standard deviation, *N* is the number of points in the regression, and *P* is the probability that the relationship between the variables is randomly obtained.

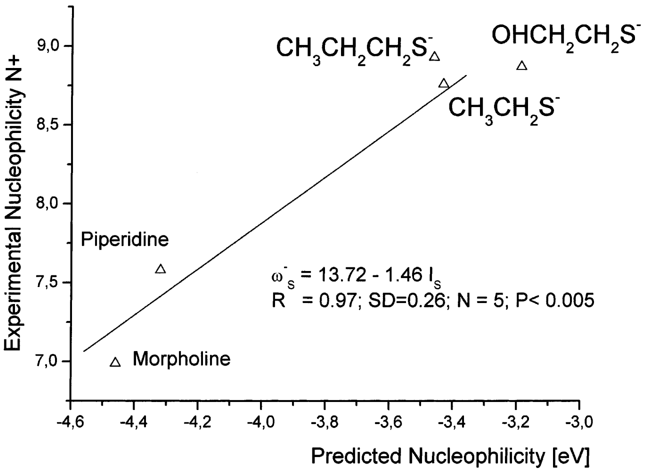

Figure 5. Comparison between experimental nucleophilicity *N*+ (from ref 19) and the predicted solution nucleophilicity obtained at the IPCM-MP2/6-311G(2d,p) level of theory for a series of second- and first-row electron donors (strong nucleophiles). *R* is the regression coefficient, SD is the standard deviation, *N* is the number of points in the regression, and *P* is the probability that the relationship between the variables is randomly obtained.

expected nucleophilicity power close to that experimentally evaluated for OH^- (4.75 eV).

3.2. Local Nucleophilicity. A final remark concerning the local counterpart of the intramolecular global nucleophilicity introduced here is worth mentioning. On intuitive grounds, one would expect the global nucleophilicity power to be mostly located around the nucleophilic centers of the electron donor molecule. Since the global nucleophilicity index is defined here as the negative of the vertical ionization potential *I*, a natural local extension should be based on a local version of this quantity, *I*(**r**) for example. Such a definition has been already proposed in the literature by Politzer:[25]

$$I(\mathbf{r}) = \sum_i \frac{\rho_i(\mathbf{r})|\epsilon_i|}{\rho(\mathbf{r})} \tag{8}$$

TABLE 3: Nucelophilic Sites for Electron Donors and Contributions to the Regional Nucleophilicity Index $\omega_s^-(k)$ Obtained from Eq 10

species	nucleophilic sites (k)	ω_s^-	f_k^-	$\omega_s^-(k)$ (eV)
HO^-	O	−3.93	0.99	−3.89
HOO^-	O	−3.48	0.74	−2.58
$N_3^{-\,a}$	N_1	−5.79	0.49	−2.84
	N_2		0.02	−0.12
	N_3		0.49	−2.84
CH_3O^-	O	−3.99	0.73	−2.91
$CF_3CH_2O^-$	O	−4.91	0.75	−3.68
$C_6H_5S^-$	S	−5.45	0.62	−3.38
CN^-	C	−6.97	0.39	−2.72
	N		0.61	−4.25
NH_2OH	N	−3.72	0.71	−2.64
	O		0.27	−1.00
NH_3	N	−4.58	0.97	−4.44
$NH_2CONHNH_2$	O	−5.41	0.48	−2.60
H_2O	O	−6.65	0.98	−6.52
$CF_3CH_2NH_2$	N	−4.83	0.78	−3.77
CH_3ONH_2	N	−3.84	0.68	−2.61
	O		0.23	−0.88
$CH_3CH_2CH_2S^-$	S	−3.46	0.94	−3.25
$CH_3CH_2S^-$	S	−3.43	0.95	−3.26
$OHCH_2CH_2S^-$	S	−3.15	0.94	−2.96
piperidine	N	−4.32	0.66	−2.85
morpholine	N	−4.46	0.49	−2.19
	O		0.13	−0.58

[a] N_2 is the central atom.

Here $\rho_i(\mathbf{r})$ is the electronic density of the *i*th atomic or molecular orbital at the point **r**, ϵ_i is the orbital energy, and $\rho(\mathbf{r})$ is the total electron density function. Even though eq 8 is not directly amenable to a condensed to atom quantity, the following *anzats* is a reasonable approximation to the quantity I_k, measuring the contribution of the region associated with atom *k* to the average ionization energy:

$$I_k = f_k^- I \tag{9}$$

Here f_k^- is the condensed Fukui function associated with the HOMO. Since the Fukui function is almost unaffected by solvent effects,[26] the intrinsic gas phase values suffice to distribute the quantity $\omega_s^- = -I_s$ on each atomic center *k*. There results the following:

$$\omega_s^-(k) = -f_k^- I_s \tag{10}$$

Equation 10 is our working expression for the regional nucleophilicity index $\omega_s^-(k)$ condensed to atom *k*. The local nucleophilicity pattern for the series of electron donors considered in this study is displayed in Table 3. It may be seen that the $\omega_s^-(k)$ index correctly distributes the global electrophilicity values on those atomic centers that are expected to be the most nucleophilic sites in these molecules.

4. Concluding Remarks

The results reported in this work are to be taken as a first step toward a quantitative description of nucleophilicity, in the form of a reactivity index. It becomes clear that the major difficulty to achieve this goal resides in the accurate description of the intrinsic ionization energy I_o. However, the present model may be still corrected along a different line. For instance, attempts to build up quantitative scales on nucleophilicity have been made in the past on the basis of experimental data that incorporate thermodynamic, kinetic, and electrochemical parameters. The double basicity scale proposed by Edwards[27,28] to describe the chemical reactivity of electron donors is an excellent example of how the nucleophilicity concept has been handled in the past. This author suggested that the nucleophilic strength of a donor particle was probably related to its polarizability.[27] Polarizability as a measure of nucleophilicity was modeled through the electrode potentials of the electron donors[27] and by means of the molar refraction indices.[28] However, a quantitative relationship between nucleophilicity and polarizability was never characterized. Pearson proposed an empirical relationship between nucleophilicity and the oxidation potential for neutral and anionic bases.[29] He found that there was a little correlation with the nucleophilic reactivity toward methyl iodide. In summary, it may be that the quantitative evaluation of the nucleophilicity requires the consideration of both ionization energies and polarizability. The present approach has shown that the former contribution may contain a significant piece of information, in the form of a first-order energy variation, equivalent but not similar to the first-order energy changes associated to the variational definition of electrophilicity. The second contribution related to polarizability may be further modeled through modern concepts such as chemical softness, which represents, within perturbation theory, second-order variations in energy. Work along this line is in progress in our group.

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