Nucleophilicity Index from Perturbed Electrostatic Potentials

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We introduce and test a nucleophilicity index as a new descriptor of chemical reactivity. The index is derived from a perturbation model for the interaction between the nucleophile and a positive test charge. The computational implementation of the model uses an isoelectronic process involving the minimum values of the electronic part of the perturbed molecular electrostatic potential. The working expression defining the nucleophilicity index encompasses both the electrostatic contributions and the second-order polarization effects in a form which is consistent with the empirical scales previously proposed. The index is validated for a series of neutral nucleophiles in the gas phase for which the nucleophilicity pattern has been experimentally established within a spectroscopic scale.

1. Introduction

In many polar processes involving electron-rich and electron-deficient species, it is useful to have a qualitative or semiquantitative hierarchy of the propensity of electron acceptors and electron donors to release or accept electronic charge from and to the environment, respectively. The concepts of electrophilicity and nucleophilicity introduced by Ingold[1] in the early 30s to describe electron-deficient (electrophile, E^+) and electron-rich (nucleophile, Nu^-) species were primarily based on the valence electron theory of Lewis[2] and the general acid−base theory of Brönsted and Lowry.[3] From that time, there has been a growing interest in classifying atoms and molecules within empirical scales of electrophilicity and nucleophilicity.[4−13]

In the early 50s, Swain et al.[4] proposed a two-parameter equation that correlated the relative rates of 47 reactions involving several neutral and charged nucleophiles shown in eq 1

$$\log\left(\frac{k}{k_0}\right) = sn \tag{1}$$

where n is the nucleophilic constant of the electron donor and s is a sensitivity parameter characteristic of the substrate (i.e., measuring the discrimination of different substrates among different nucleophiles and electrophiles). On the basis of Swain's equation, Edwards[5] proposed a more explicit double basicity scale condensed in the empirical eq 2

$$\log\left(\frac{K}{K_0}\right) = \alpha E_n + \beta H \tag{2}$$

where K/K_0 is a relative (to water) rate or equilibrium constant, E_n is a nucleophilic constant, characteristic of an electron donor, H is the relative basicity of the donor to protons, and α and β are substrate constants. Specifically, the H scale was set, within a constant, equal to the pK_a of the nucleophile. Prompted by a previous proposal by Foss,[6] the E_n scale considered an empirical relationship between nucleophilicity and the one-electron oxidation potential. This proposal was later confirmed by Ritchie.[7] However, the comparison of new experimental one-electron oxidation potentials from a number of diverse nucleophiles reported by Pearson[8] surprisingly showed little correlation with nucleophilic reactivity toward methyl iodide. A modified version of Edwards's equation[9] considered a relationship between nucleophilicity and polarizability P, according to eq 3

$$E_n = aP + bH \tag{3}$$

where P is the polarizability of the nucleophile, which was estimated as the ratio of the molar refraction of the electron donor relative to that of water, and a and b are constants. Equation 3 is one of the relevant equations to be considered later on, as it gives a useful background to the theoretical model we will present in the next section.

The second experimental scale of nucleophilicity which is closely related to the theoretical model of nucleophilicity, which is introduced in this work is the spectroscopic scale proposed by Legon and Millen.[10] In this scale, the assigned intrinsic nucleophilicity is derived from the intermolecular stretching force constant k_σ, recorded from the rotational and infrared spectra of the dimmer B···HX formed by the nucleophile B and a series of HX species (for X = halogens) and other neutral electrophiles. The nucleophilicity number in this case is obtained from the empirical eq 4

$$k_\sigma = cnE \tag{4}$$

where c is a constant. The implementation of this model is as follows: a nucleophilicity number $n = 10$ for H_2O and an electrophilicity number $E = 10$ for HF were assigned as references. The next step is to use the observed k_σ value for the

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B···HF complex to establish the n values of the remaining nucleophiles in the series under consideration. By this means, the authors provide a limiting gas-phase hierarchy of nucleophilicity for a series of neutral electron donors in the absence of the complex solvent effects. More recently, Mayr et al. have proposed kinetic scales of electrophilicity and nucleophilicity that have been successfully applied for a wide range of neutral and charged electrophiles in different solvents.[11−13]

From a theoretical point of view, the definition of a nucleophilicity index turned out to be a more difficult task than defining an electrophilicity index. Prompted by a former proposal by Maynard et al.,[14] an electrophilicity index was quantitatively introduced by Parr et al.[15] as the stabilization energy when atoms or molecules in their ground states acquire additional 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. The resulting expression is[15]

$$\omega = \frac{\mu^2}{2\eta} \tag{5}$$

where the electronic chemical potential and chemical hardness are computed from the vertical ionization potential I and electron affinity A as $\mu = -(I + A)/2$ and $\eta = I - A$. Recent reviews on these electronic descriptors of reactivity can be found elsewhere.[16] Since the electronic chemical potential $\mu \approx \Delta E/\Delta N$ of stable species is always negative, the energy of an electrophile (a chemical species capable of accepting electrons from the environment) must decrease ($\Delta E < 0$) when N increases ($\Delta N > 0$), while the electronic chemical potential remains negative. A similar argument was used by Parr et al.[15] to connect the electrophilicity power of chemical species with a variational model. Solvent effects on electrophilicity have also been reported elsewhere.[17]

However, the definition of a nucleophilicity index cannot be deduced from a similar framework leading to eq 5. From the negativity of the electronic chemical potential of a bound system, the release of electronic charge ($\Delta N < 0$) always implies an increase in energy. Note that the problems encountered to define nucleophilicity and electrophilicity within a common framework have been already reported in a different approach based on the molecular electrostatic potential (MEP), proposed by Sen and Politzer.[18] The problem discussed therein is somehow opposite in the sense that while the MEP has been widely and successfully used for estimating the reactivity of specific centers in molecules toward electrophiles (i.e., local nucleophilicity), the inverse situation is more complex, as the preferential sites for the interaction with nucleophiles (i.e., local electrophilicity) should be associated with regions of positive potentials. According to these authors, the positive charges of the atomic nuclei in a molecule may produce spurious positive potentials that may outweigh the negative contributions of the dispersed electrons. Thus, while negative potentials at certain regions of a molecule may consistently be associated with sites potentially attractive toward electrophiles, a positive potential does not necessarily has an analogous (but opposite) meaning. Other attempt to define a nucleophilicity index based on a minimum ionization potential criterion has been presented recently.[19] However, in the light of Edwards's eq 3 the nucleophilicity scale reported in reference[19] is incomplete, in the sense that the representation of nucleophilicity in terms of the aqueous ionization potential corrected by solvent effects only assesses (indirectly) the information encompassed in the H scale (second term of eqs 2 and 3).

In this work we propose the definition of a nucleophilicity index based on a perturbation model for the interaction energy between the electron donor and a positive test charge. The resulting theoretical model of nucleophilicity encompasses both electrostatic contributions and second-order polarization effects, in a form which is consistent with the experimental scale proposed by Edwards and quoted here as eq 3.

2. Nucleophilicity Model and Computational Details

Nucleophiles are chemical species that donate electronic charge to a reaction partner, an electrophile. In this process, the presence of the electron attractor perturbs the donor species and the charge transfer becomes feasible. Since electrophiles are electron deficient species, in this work they are modeled by the electron attracting potential of a positive point charge. The interaction energy of a chemical species with a test charge q located at r_0 can be split out in two parts

$$\Delta E = \Delta E_{\mathrm{el}} + \Delta E_{\mathrm{nuc}} \tag{6}$$

where the electronic contribution is given by

$$\Delta E_{\mathrm{el}} \approx \int \rho(r)\Delta v(r)\,\mathrm{d}r + \frac{1}{2}\int \chi(r,r')\Delta v(r)\Delta v(r')\,\mathrm{d}r\,\mathrm{d}r' + ... \tag{7}$$

and the nuclear part is essentially electrostatic

$$\Delta E_{\mathrm{nuc}} = q\sum_{A=1}^{M}\frac{Z_{\mathrm{A}}}{|R_{\mathrm{A}} - r_0|} \tag{8}$$

In the previous equations, $\rho(r)$ represents the electron density in the absence of the test charge, $\Delta v(r)$ is the change in external potential due to the presence of the test charge and $\chi(r,r')$ is the first-order static density response function. By use of a quadratic expansion, the nucleophilicity index ω^- can be defined as the extremal change in the energy (see Appendix 1)

$$\omega^- = -\frac{1}{2}\frac{|\varphi(r_0)|^2}{\langle\chi\rangle_{r_0}} \tag{9}$$

where $\varphi(\mathrm{r}_0)$ is the electrostatic potential at r_0 and the quantity $\langle\chi\rangle_{r_0}$ is defined by

$$\langle\chi\rangle_{r_0} \equiv \int \frac{\chi(r,r')}{|r - r_0||r' - r_0|}\,\mathrm{d}r\,\mathrm{d}r' \tag{10}$$

Note that the proposed index includes both first- and second-order responses. The molecular electrostatic potential represents the first-order (electric) response to the point charge, while the density response function corresponds to a second-order effect, which takes into account the charge reorganization on the molecule induced by the presence of the point charge. It is also interesting to mention that, under particular conditions, eq 9 defining the nucleophilicity index becomes similar (but not equal) to the electrophilicity index, eq 5. This case corresponds to the selection of a point r_0 where the electrostatic potential is equal to the electronic chemical potential.[20] Furthermore, the quantity $\langle\chi\rangle_{r_0}$ within the present approach is the second derivative of the interaction energy with respect to the test charge (see

TABLE 1: Experimental Gas-Phase Nucleophilicity *n*, Minimum Value of the Molecular Electrostatic Potential $\varphi(r_0)$, and the Quantities $\Phi'_e(q)$ and $\langle\chi\rangle_{r_0}$ Needed to Evaluate the Theoretical Nucleophilicity Index ω^- for Neutral Nucleophiles That Have Been Fully Investigated[a]

nucleophile	$\varphi(r_0)$	$\Phi_e(^1/_8)$	$\Phi_e(1/16)$	$\Phi_e(0)$	$<\chi>_{r_0}$	ω^-(eV)	*n*
N_2	−0.020	−3.914	−3.908	−3.901	−0.098	0.056	2.8
	−0.020	−3.947	−3.941	−3.935	−0.097	0.056	2.8
CO	−0.014	−4.043	−4.039	−4.034	−0.073	0.035	3.4
	−0.021	−4.201	−4.196	−4.191	−0.080	0.074	3.4
PH_3	−0.036	−4.695	−4.691	−4.686	−0.078	0.226	4.4
	−0.043	−4.847	−4.843	−4.838	−0.078	0.323	4.4
H_2S	−0.037	−5.061	−5.056	−5.052	−0.070	0.264	4.8
	−0.039	−5.148	−5.144	−5.139	−0.072	0.294	4.8
HCN	−0.072	−4.257	−4.248	−4.239	−0.141	0.500	7.3
	−0.079	−4.339	−4.330	−4.321	−0.143	0.593	7.3
CH_3CN	−0.086	−5.342	−5.332	−5.322	−0.162	0.623	8.1
	−0.093	−5.434	−5.423	−5.413	−0.163	0.724	8.1
H_2O	−0.092	−4.136	−4.129	−4.121	−0.120	0.961	10.0
	−0.100	−4.256	−4.250	−4.243	−0.111	1.220	10.0
NH_3	−0.125	−4.005	−3.996	−3.987	−0.144	1.484	11.5
	−0.130	−4.057	−4.048	−4.039	−0.143	1.623	11.5

[a] See the text for definitions. This series contains compounds that have been completely investigated, i.e., the experimental intermolecular stretching constant k_σ value is available for the B···HX dimmers involving all the six electrophilic dipoles HX, X=F, Cl, CN, Br, C≡CH, and CF_3. For each compound, the first entry corresponds to *B3LYP*/6-311(d,p) calculations and the second entry corresponds to *HF*/6-311(d,p) calculations.

Appendix 1), and even though it is not formally equal to the chemical hardness, it has at least the dimensions of a hardness quantity.

All the calculations needed to compute the nucleophilicity index were performed at two levels of theory, namely, HF/6-311G(d,p) and B3LYP/6-311G(d,p) using the Gaussian98 suite of programs.[21] The evaluation of the electrostatic potential was performed on the minimum energy configuration. The point r_0 was selected as the place where the molecular electrostatic potential has its minimum value. It is worth describing the computational implementation of eq 9. While $\varphi(r_0)$ can be accessible from standard calculations, there remains the problem of calculating the integral $\langle\chi\rangle_{r_0}$. In Appendix 2 it is shown that this quantity can be computed from the change in MEP using an isoelectronic model. This approach leads to the following expression

$$\langle\chi\rangle_{r_0} = \lim_{q\to 0}\frac{\Delta\Phi_e(r_0)}{q} = \lim_{q\to 0}\frac{\Phi'_e(r_0) - \Phi_e(r_0)}{q} \qquad (11)$$

where $\Phi_e(r_0)$ is the electronic contribution to the electrostatic potential of the unperturbed molecule and $\Phi'_e(r_0)$ corresponds to the same quantity but associated to the density of the molecule in the presence of a test charge *q*, at r_0. The $q = 0$ limit can be found by extrapolation of the ratio $\Delta\Phi/q$ for small values of *q*.

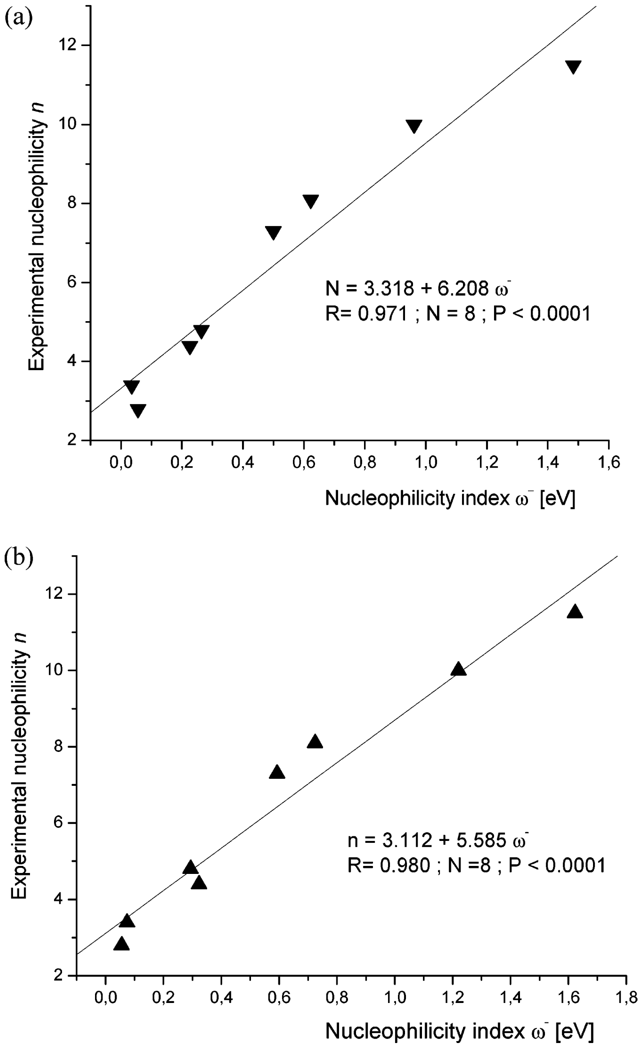

Figure 1. Comparison between experimental gas-phase nucleophilicity *n* and the theoretical nucleophilicity index ω^- evaluated at the (a) B3LYP/6-311(d,p) and (b) HF/6-311(d,p) levels of theory for the series of neutral nucleophiles that have been fully investigated using the experimental spectroscopic scale given in ref 10. *R* is the regression coefficient, *N* the number of points included in the regression, and *P* the probability that the observed correlation was randomly obtained.

3. Results and Discussion

The limiting gas-phase nucleophilicity scale reported by Legon and Millen provided the following order:[10] $N_2 < CO < PH_3 < H_2S < HCN < CH_3CN < H_2O < NH_3$. This series contains compounds that have been completely investigated, i.e., the experimental intermolecular stretching constant k_σ value is available for the dimmers B···HX involving all the six electrophilic dipoles HX (for X = F, Cl, CN, Br, C≡CH, CF_3). Table 1 contains the comparison between the present theoretical scale of nucleophilicity, based on eq 9, and the spectroscopic scale[10] for the fully characterized series. The first entry corresponds to B3LYP/6-311G(d,p) calculations and the second entry corresponds to HF/6-311G(d,p) calculations. Our scale based on the ω^- index correctly reproduces the experimental order of nucleophilicity. We first arbitrarily define three subgroups: marginal nucleophiles with nucleophilicity numbers in the range $2 < n < 4$; moderate nucleophiles with nucleophilicity numbers in the range $4 < n < 8$ and strong nucleophiles with nucleophilicity numbers in the range $n > 8$. The molecules N_2 and CO are correctly predicted as marginal nucleophiles; H_2O and NH_3 are consistently predicted as the most powerful nucleophiles within the series. In addition, moderate nucleophiles follow the experimental order $PH_3 < H_2S < HCN < CH_3CN$. The quantitative comparison between the experimental and theoretical values is depicted in parts a and b of Figure 1at the two levels of theory. It may also be seen that the present model is reasonably stable with respect to the density used to evaluate the electrostatic potential. Table 2 summarizes the results for the series of compounds for which the complete set of intermolecular stretching force constant k_σ is not available from the experiment, and therefore the assigned nucleophilicity number may be less accurate. The comparison within the series shown in Table 2 is qualitatively coherent. However H_2CO, assigned as a marginal nucleophile by the Legon scale, is

TABLE 2: Experimental Gas-phase Nucleophilicity n, Minimum Value of the Molecular Electrostatic Potential $\varphi(r_0)$, and the Quantities $\Phi'_e(q)$ and $\langle\chi\rangle_{r_0}$ Needed to Evaluate the Theoretical Nucleophilicity Index ω^- for Neutral Nucleophiles That Have Not Been Fully Investigated[a]

nucleophile	$\varphi(r_0)$	$\Phi_e(^1/_8)$	$\Phi_e(^1/_{16})$	$\Phi_e(0)$	$<\chi>_{r_0}$	ω^- (eV)	n
H_2CO	−0.059	−4.854	−4.846	−4.838	−0.127	0.368	3.5
	−0.070	−4.991	−4.982	−4.974	−0.132	0.508	3.5
Furane	−0.047	−8.488	−8.478	−8.468	−0.155	0.196	5.4
	−0.057	−8.732	−8.722	−8.712	−0.161	0.278	5.4
$(CN)_2$	−0.042	−5.429	−5.421	−5.411	−0.151	0.155	5.7
	−0.046	−5.549	−5.540	−5.531	−0.147	0.197	5.7
HCCCN	−0.067	−5.568	−5.558	−5.547	−0.171	0.361	6.5
	−0.074	−5.686	−5.675	−5.664	−0.171	0.433	6.5
$P(CH_3)_3$	−0.062	−8.842	−8.832	−8.822	−0.155	0.336	6.9
	−0.075	−9.068	−9.059	−9.049	−0.155	0.490	6.9
$(CH_3)_3CCN$	−0.089	−7.969	−7.958	−7.947	−0.174	0.614	9.0
	−0.097	−8.115	−8.104	−8.093	−0.174	0.731	9.0
$(CH_3)_2O$	−0.079	−7.417	−7.407	−7.396	−0.167	0.510	11.2
	−0.093	−7.573	−7.563	−7.553	−0.166	0.711	11.2

[a] See the text for definitions. This series contains compounds that have not been completely investigated, i.e., the experimental intermolecular stretching constant k_σ value is available for only one B···HX complex. For each compound, the first entry corresponds to *B3LYP*/6-311(d,p) calculations and the second entry corresponds to *HF*/6-311(d,p) calculations.

predicted as a moderate one by our theoretical scale and the highest nucleophilicity number within the sub series of Table 2 is assigned to dimethyl ether. In general, note that the qualitative comparison between both series is chemically meaningful. Consider for instance the case of phosphine PH_3 in Table 1. Substitution of the three hydrogen atoms by methyl groups brings the nucleophilicity of phosphine from the values 0.226 and 0.323 eV (at the HF and DFT levels of theory, respectively) to the values 0.336 and 0.490 eV in trimethylphosphine, respectively. Note that the theoretical scale correctly predicts the enhancement in nucleophilicity in these systems, which may be traced to an electron releasing effect of the methyl groups that renders the phosphorus site more basic than in the PH_3 molecule. Similar inductive effects promoted by increasing substitution by methyl groups in the HCN derivatives may also be verified after comparison of Tables 1 and 2. We next made an attempt to correlate the theoretical and experimental scales for all the 15 compounds included in reference.[10] The best comparison was obtained for 13 out of the 15 nucleophiles after excluding dimethyl ether and formaldehyde. Note that both molecules belong to the series shown in Table 2 for which the set of intermolecular stretching constants is incomplete. The result of this comparison is shown in parts a and b of Figure 2 at the two levels of theory considered here. It may be seen that, with the exception of dimethyl ether and formaldehyde, both scales compare qualitatively well. There is a first subgroup of marginal nucleophiles that includes N_2, CO, PH_3, and H_2S, which concentrates at the bottom of both scales. Also the moderate nucleophiles like furane, HCN and its derivatives $(CN)_2$ and $(CH_3)_3CCN$ are correctly predicted to have a moderate nucleophilicity, greater than N_2, CO, and PH_3 but less than H_2O and NH_3.

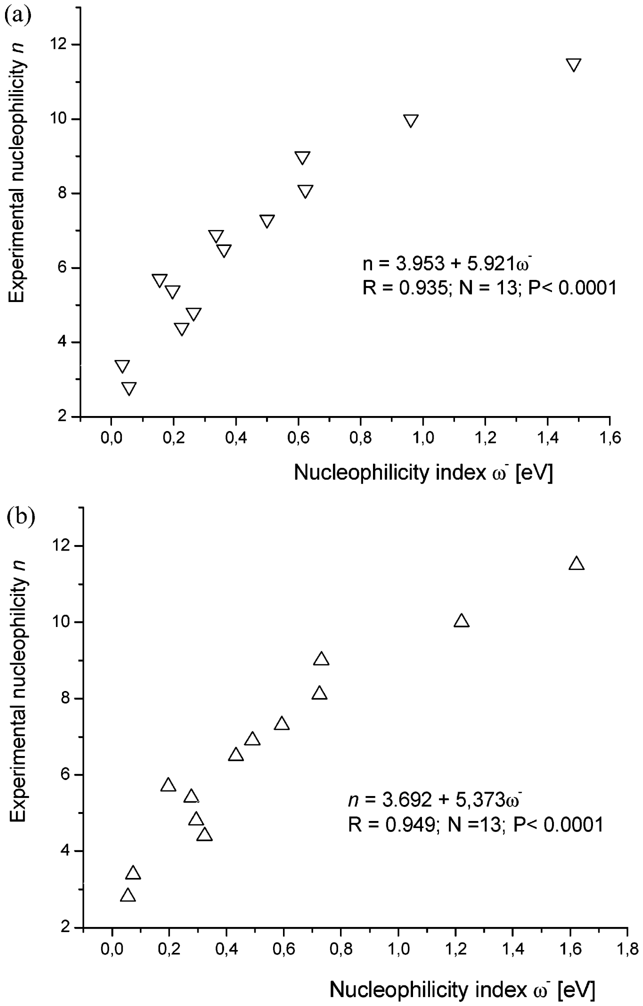

Figure 2. Comparison between experimental gas-phase nucleophilicity n and the theoretical nucleophilicity index ω^- evaluated at the (a) B3LYP/6-311(d,p) and (b) HF/6-311(d,p) levels of theory for the whole series of neutral nucleophiles spectroscopically investigated in ref 10. Dimethyl ether and formaldehyde which significantly deviate from the correlation are not included. R is the regression coefficient, N the number of points included in the regression, and P the probability that the observed correlation was randomly obtained.

In order to further examine the origin of the strong deviations of dimethyl ether and formaldehyde, we first made an attempt to estimate the intermolecular force constant from the theoretical IR spectrum for $(CH_3)_2O\cdots HF$ complex. Note that, from Table 2, the nucleophile $(CH_3)_2O$ displays a high nucleophilicity pattern in the spectroscopic scale, as compared to the water (reference) molecule, with a nucleophilicity value close to that displayed by NH_3. However there are some problems with the assignment of the IR stretching force constant of the intermolecular hydrogen bond in the $(CH_3)_2O\cdots HF$ system which we shall discuss here. We have calculated the IR spectra of $(CH_3)_2O$ at the MP2/6-31+G(d,p) level, following the prescription recommended in the literature.[22] The force constant used by Legon and Millen to derive the nucleophilicity number for $(CH_3)_2O$ was obtained from the IR spectra recorded by Thomas[23] which yields a stretching force constant $k_\sigma = 28.1$ N/m. The calculated IR spectrum for the complex shows two possible intermolecular stretching modes associated to the hydrogen bond. The first one has a frequency $\nu = 205.8\ \text{cm}^{-1}$ and a force constant $k_\sigma = 5.5$ N/m. This mode is slightly contaminated with a twist of the CH_3 group. The second stretching mode has a frequency $\nu = 425.7\ \text{cm}^{-1}$ and a force constant $k_\sigma = 26.3$ N/m. This mode is strongly contaminated by CH_3OCH_3 bending. Note that this last mode has a force constant close to the experimental value reported by Thomas.[23] The IR spectrum of the hydrogen bonded $(CH_3)_2O\cdots HF$ complex has been recently calculated by Perchard et al. at the B3LYP/6-31+G(d,p) level.[22] These authors report an intermolecular stretching mode $k_\sigma = 9.9$ N/m, which is far from the experimental value assigned by Thomas[23] and the one related to the lowest frequency calculated by us. The assignment of these low-energy modes is complicated from the

TABLE 3: Calculated Stretching Force Constants k_σ in N/m and Dissociation Energies ΔE_d of the B···HF Complexes, Proton Affinities PA, and Gas-Phase Basicity Free Energies ΔG of the Nucleophiles B in kcal/mol[a]

nucleophile	k_s	ΔE_d	PA	ΔG
H_2O	27.3	7.4	164.2	158.5
CH_3OH	31.6	8.9	179.7	173.6
$(CH_3)_2O$	34.5	9.6	188.5	182.5
NH_3	34.4	11.3	205.0	199.0
H_2CO	24.0	6.1	166.8	160.7

[a] The force constants are numerically estimated by a three point quadratic model. Both dissociation energies and proton affinities include zero-point energy corrections. Gas-phase basicities come from the ideal gas reaction at 298.15 K. All quantities were computed with the MP2/6-31++G(d,p) model.

experimental spectrum and strongly sensitive to the level of theory used to calculate it. In order to settle this problem we estimated the intermolecular force constant from a simple harmonic model. From the optimized geometry of the B···HF complex, the hydrogen bond length is changed to get a numerical value of the force constant, while all the other geometrical parameters are optimized. Table 3 shows the force constants and dissociation energies for H_2O, CH_3OH, $(CH_3)_2O$, and NH_3 complexes. Note that dimethyl ether and ammonia complexes have similar stretching force constants, larger than that of water. Methyl substitution on water gradually increases the stretching force constant up to a value similar to that of the ammonia complex. The dissociation energies of the same complexes show the same trend with respect to the methyl substitution; however the dimethyl ether complex is not as stable as the ammonia complex. The increase on the complex stability associated with the methyl substitution is a consequence of the inductive effect of the methyl group on the oxygen atom. Each methyl group also increases the negative charge on the oxygen atom as well as the basicity of the nucleophile as one can see from the values of the proton affinities and gas-phase basicities in Table 3. Therefore one can conclude that even when the force constants of the dimethyl ether and ammonia complexes are similar, the nucleophilicity of both compounds must be different, as it is shown by the other computed properties; in fact the nucleophilicity of dimethyleter should be smaller than that of ammonia.

A similar analysis is made for H_2CO and Table 3 shows the computed parameters. In this case one can note that the estimated stretching constant is a bit smaller than that of water. The dissociation energies of the complexes with HF also show the same ordering. On the other hand, from values of the proton affinity and gas-phase basicity, formaldehyde seems to be slightly more basic than water. Therefore one cannot expect large differences on the nucleophilicities of formaldehyde and water, as the spectroscopic scale suggests.

Legon and Millen scale is exclusively based on the force constant and similarity of this spectroscopic quantity does not necessarily imply similar nucleophilicities. In fact, one might expect that the nucleophilicity should be in a better agreement with the stability of the nucleophile−electrophile complex rather than with the corresponding force constant.

A final comment about the kinetic or thermodynamic character of the introduced nucleophilicity index defined in eq 9 is worth making. It is well-known that nucleophilicity is related (but not equal) to basicity. In fact, some efforts have been made to define a nucleophilicity number in the form of a free-energy relationship with the thermodynamic and kinetic contributions separated. Such an expression has been worked out using Marcus equation in the seminal review article reported by Albery for reactions in solution.[24] More recently, Uggerud[25] reported on the relationship between nucleophilicity and basicity in the gas phase. This author concluded that the trends in (kinetic) nucleophilicity, as measured by the activation free energy or rate coefficients and basicity, are opposing, and therefore the resulting nucleophilicity is determined by the relative contribution of the two factors. Only in the limit of strongly exothermic reactions basicity and nucleophilicity may become equivalent. It is clear from the structure of our working eq 9 that both effects are implicitly incorporated in the form of an electrostatic contribution, the MEP, and a polarization term, given by the inverse of $\langle\chi\rangle_{r_0}$, but they cannot by any means to be written as separated contributions. The same arguments apply for the kinetic or thermodynamic nature of the electrophilicity index defined in eq 5.

4. Concluding Remarks

To the extent that the limiting gas-phase nucleophilicity data derived from the spectroscopic results presented in ref 10 are reliable, the nucleophilicity index introduced in this work seems to qualitatively assess the intrinsic nucleophilicity order expected for these neutral electron donors. Comparison with previous approaches to model nucleophilicity as a reactivity index is not immediate, but one of the main results issued here is that any theoretical model of nucleophilicity needs to consider first and second-order energy contributions. This result, yet not directly comparable with Edwards's eq 3, is consistent with Edwards's empirical scale of nucleophilicity in the sense that it is built up from the model interaction energy given in eq 7, in which the second-order contribution is related to the electronic polarization. To have a reasonable and reliable model of nucleophilicity for a general situation, the introduction of solvent effects is mandatory, and it is in this sense that the present contribution must be considered as an initial step that takes into account the electronic responses in the absence of solvent. The results presented here, even taken as a starting point, are quite satisfactory, and they encourage further work in the direction of the introduction of the solvent effects which certainly will improve the description of the electrophile−nucleophile combination reactions in solution. This task deserves a substantial effort since the kind of solvent effects involved in this problem include the partial desolvation which is expected to occur prior to the formation of the bond in the solution phase. Work along this line is in course.

Appendix

Appendix 1. Derivation of Eq 9 of the Text. The change on the molecular energy coming from the presence of a point charge q at r_0 can be written as

$$\Delta E \approx q\sum_{A=1}^{M}\frac{Z_A}{|R_A - r_0|} + \int \rho(r)\Delta v(r)\,dr + \frac{1}{2}\int \chi(r,r')\Delta v(r)\Delta v(r')\,dr\,dr' + ... \quad (A1)$$

where the perturbative potential correspond to the point charge field

$$\Delta v(r) = -\frac{q}{|r - r_0|} \quad (A2)$$

In this case, the energy change corresponds to

$$\Delta E(q) \approx q\varphi(r_0) + \frac{q^2}{2}\langle\chi\rangle_{r_0} + ... \quad (A3)$$

where $\varphi(r_0)$ represents the molecular electrostatic potential at r_0 and the response function contribution takes the form

$$\langle\chi\rangle_{r_0} \equiv \int \frac{\chi(r,r')}{|r-r_0||r'-r_0|}\,\mathrm{d}r\,\mathrm{d}r' \qquad \text{(A4)}$$

It is important to notice that ΔE explicitly depends on r_0 and q. Therefore it can be thought as a local index. Additionally, it becomes a quadratic function of q, if one only keeps terms up to second order, and an extreme exists for this coordinate

$$\frac{\partial\Delta E}{\partial q} = \varphi(r_0) + q\langle\chi\rangle_{r_0} = 0 \qquad \text{(A5)}$$

Such extreme defines a critical charge

$$q_{\mathrm{cr}} = -\frac{\varphi(r_0)}{\langle\chi\rangle_{r_0}} \qquad \text{(A6)}$$

For a given r_0, the corresponding energy is

$$\Delta E_{\mathrm{cr}} = \Delta E(q_{\mathrm{cr}}) = -\frac{1}{2}\frac{|\varphi(r_0)|^2}{\langle\chi\rangle_{r_0}} = \frac{1}{2}q_{\mathrm{cr}}\varphi(r_0) \qquad \text{(A7)}$$

In analogy with the definition of the electrophilicity index given in eq 5, we define the nucleophilicity index ω^- as

$$\omega^- \equiv \Delta E_{\mathrm{cr}} = -\frac{1}{2}\frac{|\varphi(r_0)|^2}{\langle\chi\rangle_{r_0}} \qquad \text{(A8)}$$

Note that ω^- corresponds to the second derivative of $\Delta E(q)$ with respect to the test charge q, at $q = 0$, thereby showing that $\langle\chi\rangle_{r_0}$ has the dimensions of a hardness quantity.

Appendix 2. Isoelectronic Model for the Calculation of $\langle\chi\rangle_{r_0}$. The electronic part of the electrostatic potential is given by

$$\Phi_{\mathrm{e}}(r) \equiv -\int \frac{\rho(r')}{|r-r'|}\,\mathrm{d}r' \qquad \text{(A9)}$$

When a test charge q is placed at r_0, the molecular density is modified and its changes can be expressed by a functional Taylor expansion

$$\Delta\rho(r) = -q\int \frac{\chi(r,r')}{|r_0-r'|}\,\mathrm{d}r' + ... \qquad \text{(A10)}$$

In consequence, the electronic electrostatic potential changes by

$$\Delta\Phi_{\mathrm{e}}(r) = -\int \frac{\Delta\rho(r')}{|r-r'|}\,\mathrm{d}r' = q\int \frac{\chi(r',r'')}{|r-r'||r_0-r''|}\,\mathrm{d}r'\,\mathrm{d}r'' + ... \qquad \text{(A11)}$$

Evaluation at $r = r_0$ leads to

$$\Delta\Phi_{\mathrm{e}}(r_0) = q\langle\chi\rangle_{r_0} + ... \qquad \text{(A12)}$$

and finally

$$\langle\chi\rangle_{r_0} = \lim_{q\to 0}\frac{\Delta\Phi_{\mathrm{e}}(r_0)}{q} = \lim_{q\to 0}\frac{\Phi'_{\mathrm{e}}(r_0) - \Phi_{\mathrm{e}}(r_0)}{q} \qquad \text{(A13)}$$

where $\Phi'_{\mathrm{e}}(r_0)$ is the electronic part of the electrostatic potential associated with the density of the molecule in the presence of a test charge q at r_0. The electrostatic potentials for the isoelectronic partners needed to evaluate the $\langle\chi\rangle_{r_0}$ quantity were computed by placing point charges with $q = (^1/_{16})$, $(^1/_8)$ at r_0. These charges allow the extrapolation to $q = 0$.

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