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Definition of a Nucleophilicity Scale

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This work deals with exploring some empirical scales of nucleophilicity. We have started evaluating the experimental indices of nucleophilicity proposed by Legon and Millen on the basis of the measure of the force constants derived from vibrational frequencies using a probe dipole H−X (X = F,CN). The correlation among some theoretical parameters with this experimental scale has been evaluated. The theoretical parameters have been chosen as the minimum of the electrostatic potential $V_{\min}$, the binding energy (BE) between the nucleophile and the H−X dipole, and the electrostatic potential measured at the position of the hydrogen atom V_H when the complex nucleophile and dipole H−X is in the equilibrium geometry. All of them present good correlations with the experimental nucleophilicity scale. In addition, the BEs of the nucleophiles with two other Lewis acids (one hard, BF_3, and the other soft, BH_3) have been evaluated. The results suggest that the Legon and Millen nucleophilicity scale and the electrostatic potential derived scales can describe in good approximation the reactivity order of the nucleophiles only when the interactions with a probe electrophile is of the hard−hard type. For a covalent interaction that is orbital controlled, a new nucleophilicity index using information of the frontier orbitals of both, the nucleophile and the electrophile has been proposed.

1. Introduction

The terms associated with electron deficient (electrophile) and electron rich (nucleophile) species were introduced in the beginnings of the 1930s.[1] From that time, there have been several attempts to classify organic molecules within empirical scales of electrophilicity and nucleophilicity. The first attempt to quantify nucleophilic reactivity was proposed by Swain and Scott[2] through the following linear free energy relationship:

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

where k is the rate constant for the S_N2 reaction of a substrate with a particular nucleophile at 25° C, k_0 is the corresponding rate constant with a standard nucleophile (water), n is the intrinsic nucleophilicity for a particular nucleophile, and s represents the sensitivity parameter (normally <1), measuring the sensitivity of the substrate to variations in the nucleophile system. Later, Edwards[3] proposed a more general four parameter equation, which related the rate constants with different properties of the nucleophile such as basicity, polarizability and oxidation potential. Pearson[4] preferred to use the principle of hard and soft acids and bases (HSAB) to explain these nucleophile−electrophile interactions. Ritchie[5] found that in reactions of carbocations and diazonium ions with nucleophiles, a particular nucleophilic system could be characterized by one constant parameter N_+, which is independent of the nature of the electrophile.

Mayr et al.[6] proposed a new linear free energy relationship, demonstrating that one parameter for electrophiles (E) and two parameters for nucleophiles (N and s) are sufficient to describe quantitatively the reaction rates of a large variety of electrophile-nucleophile combinations, namely,

$$\log k = s(N + \mathrm{E}) \tag{2}$$

where s is a nucleophile specific slope parameter and N and E are the nucleophilicity and electrophilicity parameters, respectively.[6] These authors proved that eq 2 seems to be applicable for a wide variety of electrophile-nucleophile combinations.[7]

Other important model of nucleophilicity and electrophilicity has been the experimental scale proposed by Legon and Millen[8] for hydrogen bonded complexes (B−HX), where B is a Lewis base and HX is a molecule of electrophilic character. The nucleophilicity model is based in the angular geometry of the B−HX dimers[9] and the electrostatic model of the hydrogen bond.[10] In particular, at equilibrium the HX molecule lies along the axis of a nonbonding electron pair on B. That is, the B−HX hydrogen bond has been interpreted as the electrophilic site of HX (H atom) seeking the most nucleophilic site of B systems.[8] Additionally, from a large number of hydrogen bonded dimers studied by rotational spectroscopy,[11] it has been possible to enunciate some simple electrostatic rules for predicting the angular geometries of dimers. The vibrational spectroscopy has provided the low-frequency hydrogen bond stretching modes for many B−HX dimers.[11] The model considers the strength of the hydrogen bond, as measured by k_σ, given by[8]

$$k_\sigma = cN\mathrm{E} \tag{3}$$

where c is a constant of proporcionality, N is the nucleophilicity value of B, and E is the electrophilicity value of HX.

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TABLE 1: Calculated Parameters and Experimental Data of B−HF Dimers

B	υ_σ,[a] cm^{-1}	υ_σ,[b] cm^{-1}	υ_σ,[c] cm^{-1}	k_σ,[d] N/m	k_σ,[e] N/m	N[f]	V_H, kcal/mol	V_min, kcal/mol	BE, kcal/mol	BE (BSSE), kcal/mol
N_2	110.8	105.1	115.8	8.4	5.5	2.2	−5.63	−7.13	−2.51	−1.87
CO	124.9	118.7	130.6	10.7	8.5	3.4	−8.16	−14.31	−3.69	−3.09
PH_3	144.0	131.8	148.2	15.4	10.9	4.4	−23.95	−28.71	−5.94	−4.43
H_2S	141.4	131.1	143.7	14.8	12.0	4.8	−20.94	−27.19	−5.47	−4.08
HCN	166.7	167.3	171.9	18.8	18.2	7.3	−33.68	−43.21	−7.50	−6.64
CH_3CN	167.4	168.1	172.6	22.2	20.1	8.1	−41.98	−52.49	−9.08	−8.11
H_2O	219.2	223.5	233.7	26.8	24.9	10.0	−43.27	−58.93	−9.77	−8.05
NH_3	272.6	264.0	272.6	40.3	28.8	11.5	−63.22	−79.54	−14.40	−12.15

[a] Low-frequency stretching (υ_σ) values calculated at the MP2/6-31+G(d,p) level of theory. [b] Low-frequency stretching (υ_σ) values calculated at the MP2/6-311++G(d,p) level of theory. [c] Low-frequency stretching (υ_σ) values calculated at the QCISD/6-31+G(d,p) level of theory. [d] Stretching force constants, k_σ, values calculated at the MP2/6-31+G(d,p) level of theory. [e] Experimental k_σ values taken from ref 8. [f] Experimental nucleophilicity values taken from ref 8.

From a theoretical point of view, there have been many attempts to define a nucleophilicity index. The local version of the HSAB principle is one posibility,[12] Roy et al.[13] have proposed a local relative nucleophilicity index that is intramolecular in nature. Additionally, Chattaraj and Maiti[14] have proposed the concept of philicity. They stressed the point that a particular molecular site may undergo more likely an electrophilic attack or another site undergoes a nucleophilic attack. Contreras et al.[15] have proposed a relationship between nucleophilicity and solution phase ionization potentials. The authors presented an approach of the first-order energy changes associated to the variational definition of electrophilicity when the system donates one electron to the environment. It seems that there is a consensus that electrophilicity and nucleophilicity are not in a mathematical sense the inverse of each other. Some years ago, Parr et al.,[16] on the basis of a work of Maynard et al.,[17] derived an electrophilicity index that has been proven to be very reliable. However, any attempts to obtain a similar nucleophilicity index have failed. One of the reasons may lie in the theoretical difficulties in defining a local hardness,[18] a quantity that should be related to the nucleophilicity. Another reason may be the more important role the electrophilic partner plays. Different electrophilic molecules are able to receive different amount of charge. Therefore, the nucleophilic system, as a donor of charge, may be good in front of some electrophile but worse in front of another one.

In this work, we will study hard−hard interactions in the B−HX hydrogen bonding system (where B is a base Lewis and HX is a dipole), using the hydrogen bond stretching force constants, k_σ, the molecular electrostatic potential and binding energy (vide infra). A new index based on the first-order energy changes due to changes in the electron number is proposed. The benchmark S_N2 reaction for the last model is $X^- + CH_3Y$ (where X^- is a soft nucleophile and CH_3Y is an electrophile). The proposed empirical scales are compared with experimental data.

2. Empirical Model

The B−HX hydrogen bonded complexes were used as a benchmark to find the stretching force constants, k_σ, through the theoretical vibrational low-frequency stretching,[11] $\upsilon_\sigma = (2\pi)^{-1}(k_\sigma/\mu)^{1/2}$, at the harmonic approximation. As the bond length of the HX species is maintained constant, the force constant k_σ in these systems can be interpreted as a measure of the nucleophilicity of B following the Legon and Millen's model[8] ($k_\sigma = N$). The molecules of N_2, CO, PH_3, H_2S, HCN, CH_3CN, H_2O, NH_3, representing the B systems bound to HF and HCN (HX) as dipole models, have been used to applied the Legon an Millen model[8] using the theoretical calculated force constants. Next the molecular electrostatic potential (MEP)[19] at the electrophilic site of HX, V_H, has been used to postulate a nucleophilicity scale. Such a scale has been recently applied to rank the nucleophilicity of a series of substituted pyridines.[20]

On the other hand, the BEs have been used to describe the electrostatic character of the hydrogen bonded systems using the Morokuma et al. energy decomposition.[21] These authors found that the electrostatic energy contribution is dominant over polarization, exchange repulsion and charge-transfer energies. For this reason, it is possible to use the binding energy as a nucleophilicity scale.

The minimum of the electrostatic potential, V_min, was calculated in B nucleophiles. This tool has also been used to analyze the reactivity of different systems containing π-region of several substituted ethylenes,[22] as reactivity index in hydrogen bonding,[23] substituent effects in doubly substituted benzenes,[24] solvent effects,[25] complementarity and similarity (encompassing host−guest interactions[26] and structure activity relationships[27]).

On the other hand, weakly bound molecules exhibit another type of bonding characterized by van der Waals and covalent interactions. They include donor−aceptor pairs that may be bound with BH_3 and BF_3 as electrophile systems.[28] These types of complexes were also studied to have a nucleophilicity scale for weak interactions, similar to those with electrostatic interactions in B−HX dimers.

Calculations to evaluate properties of isolated molecules, hydrogen bonded complexes and binding energies were carried out at the MP2 level of theory, with 6-31+G(d,p) and 6-311++(d,p) basis sets. The species were optimized by building their geometries following Guillespie's rules[8] and the correct symmetry reported in the literature.[11] Vibrational frequencies confirmed that the structures correspond to true minima having no imaginary frecuencies. Those results were confirmed at a higher level of theory using the QCISD method.

The molecular electrostatic potential (MEP) denoted by $V(r)$, at the point r due to a molecular system with nuclear charges $\{Z_\mathrm{A}\}$ located at $\{R_\mathrm{A}\}$ and electron density $\rho(r)$ is expressed as

$$V(r) = \sum_{\mathrm{A}}^{N} \frac{Z_\mathrm{A}}{r - Z_\mathrm{A}} - \int \frac{\rho(r')\,\mathrm{d}^3 r'}{|r - r'|} \qquad (4)$$

where N is the total number of nuclei in the molecule.

The molecular electrostatic potential at the sites of the dipole (V_H) were calculated using a ghost atom at this site using the Gaussian98 program.[29] These values may be considered as intrinsic properties of the B molecule and not of the hydrogen bonded complexes B−HX. Calculated BEs were corrected through the basis set superposition error (BSSE) method. Anions

TABLE 2: Calculated Parameters and Experimental Data of B−HCN Dimers

B	υ_σ,[a] cm^{-1}	k_σ,[b] N/m	k_σ,[c] N/m	N[d]	V_H, kcal/mol	V_{min}, kcal/mol	BE, kcal/mol	BE (BSSE), kcal/mol
N_2	74.5	4.5	2.3	2.2	−3.87	−7.13	−1.61	−1.10
CO	81.9	5.4	3.3	3.4	−4.57	−14.31	−2.17	−1.59
PH_3	93.4	7.7	4.3	4.4	−16.56	−28.71	−3.58	−2.23
H_2S	96.7	8.3	4.7	4.8	−15.24	−27.19	−3.52	−1.99
HCN	119.3	11.3	8.1	7.3	−25.80	−43.21	−4.91	−4.23
CH_3CN	116.2	13.0	9.8	8.1	−32.39	−52.49	−5.97	−5.27
H_2O	158.2	15.9	11.1	10.0	−32.39	−58.93	−6.48	−4.92
NH_3	166.9	17.2	12.2	11.5	−41.92	−79.54	−7.78	−5.97

[a] Low-frequency stretching (υ_σ) values calculated at the MP2/6-31+G(d,p) level of theory. [b] Stretching force constants, k_σ, values calculated at the MP2/6-31+G(d,p) level of theory. [c] Experimental k_σ values taken from ref 8. [d] Experimental nucleophilicity values taken from ref 8.

and CH_3Y system (Y = Cl, Br and CO_2CF_3) properties were calculated at the same level of theory mentioned above. The reactivity indices were calculated using the HOMO and LUMO orbital energies at the Hartree−Fock level.

3. Results and Discussion

a. Geometry and Binding Energy. The optimized linear geometries for HCN−HF, HCN−HCN, OC−HF, OC−HCN, N_2−HF and N_2−HCN dimers are in agreement with the Legon and Millen's predicted rules.[8] NH_3−HF, NH_3−HCN, PH_3−HF, PH_3−HCN, CH_3CN−HF and CH_3CN−HCN complexes showed C_{3v} symmetry, according with the experimental results.[9] The L-shaped geometries observed for H_2S−HF and H_2S−HCN were also computational obtained.[9] The H_2O−HF equilibrium angular geometry presents a C_s symmetry in agreement with other computational[30] and experimental results.[31] To obtain the experimental symmetry for H_2O−HF, the angle H−O−H was frozen to the experimental value (104.5°) and the calculated structure does not present imaginary frequency.

The predicted and experimental parameters for the B−HF dimers are depicted in Table 1. Results for B−HCN dimers are presented in Table 2. The values of the binding energy for the B−HX dimers are listed in descending order of energy, for both series of complexes. In Tables 1 and 2, both values are presented, with and without BSSE correction. Note that the uncorrected binding energy values in both series are lower than the corrected ones. The calculated binding energies are in good agreement with the experimental ones in the cases where the later are known; for example, the experimental BEs for CH_3CN−HF are −8.2[32] and −7.1 kcal/mol[33] for HCN−HF dimers. Figure 1a displays the correlation between the calculated, corrected and uncorrected, binding energies for B−HCN and the experimental nucleophilicity values of the B series reported by Legon and Millen.[8] It may be seen that, in general, a good correlation is obtained between both quantities.

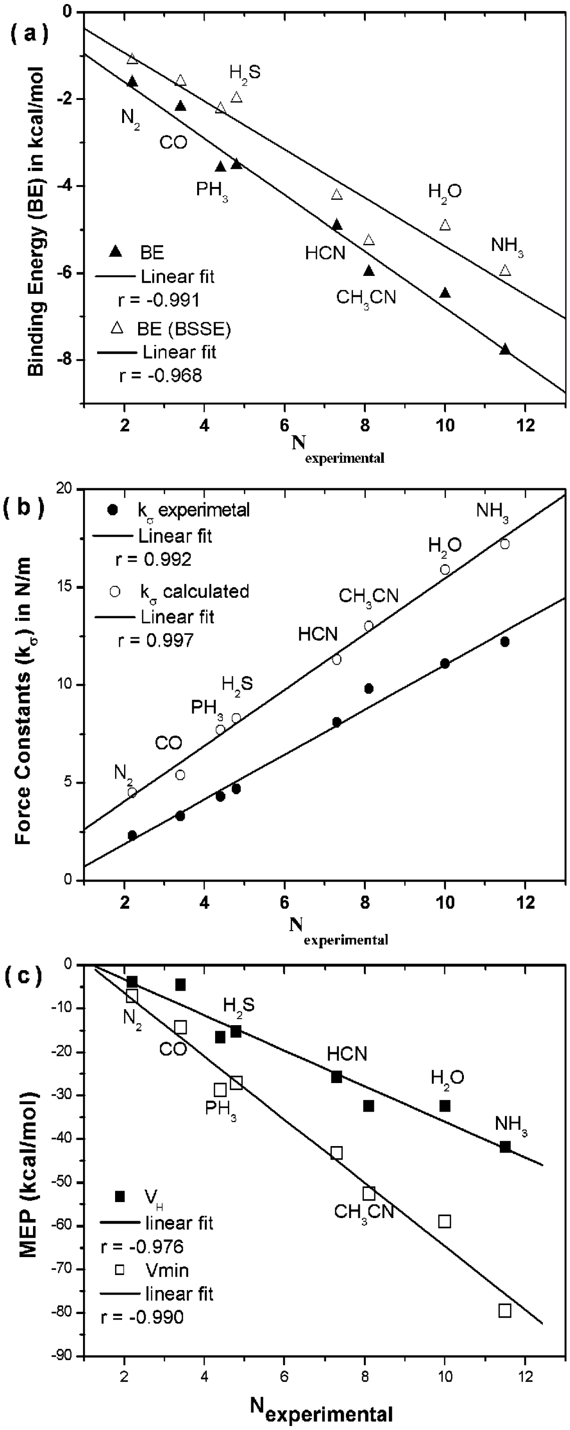

Figure 1. (a) Comparison between binding energy (kcal/mol) with and without BSSE and the experimental nucleophilicity,[8] for hydrogen bonded B−HCN systems. (b) Comparison between force constants (k_σ) (N/m) and the experimental nucleophilicity,[8] for hydrogen bonded B−HCN systems. (c) Comparison between MEP (kcal/mol), including V_{min} and V_H, and the experimental nucleophilicity,[8] for hydrogen bonded B−HCN systems. See the text for details.

b. Harmonic Vibrational Frequencies. For these complexes, the important frequency corresponds to the lowest one. The observed vibrational frequency[11] for the CH_3CN−HF dimer is υ_σ =168 ± 3 cm^{-1}, and the predicted values are 167.4 and 168.1 cm^{-1} (see Table 1) at MP2/6-31+G(d,p) and MP2/6-311++(d,p), respectively. For HCN−HF, the experimental frequency[11] is 155 ± 10 cm^{-1}, and the calculated values are 166.7 and 167.3 cm^{-1} at the same levels of theory. The QCISD/6-31+g(d,p) level of theory has been used to asses the quality of the calculated vibrational frequencies. As one can see on Table 1, the latter values are slightly greater than the ones calculated at the MP2 level of theory. With the calculated stretching frequencies at hand, it is possible to obtain the force constants (k_σ), to have an estimation of the nucleophilicity of B for the studied systems. These values are also reported in Table 1 and 2. It can be seen that the predicted values of k_σ are in reasonable agreement, with the experimental ones being always a little higher. The only exception is NH_3−HF where the deviation with respect to experimental value is significant.

Nevertheless, a plot of the force constants vs the experimental nucleophilicity for B−HCN systems yields a good linear correlation (see Figure 1b, r = 0.992 for k_σ experimental and r

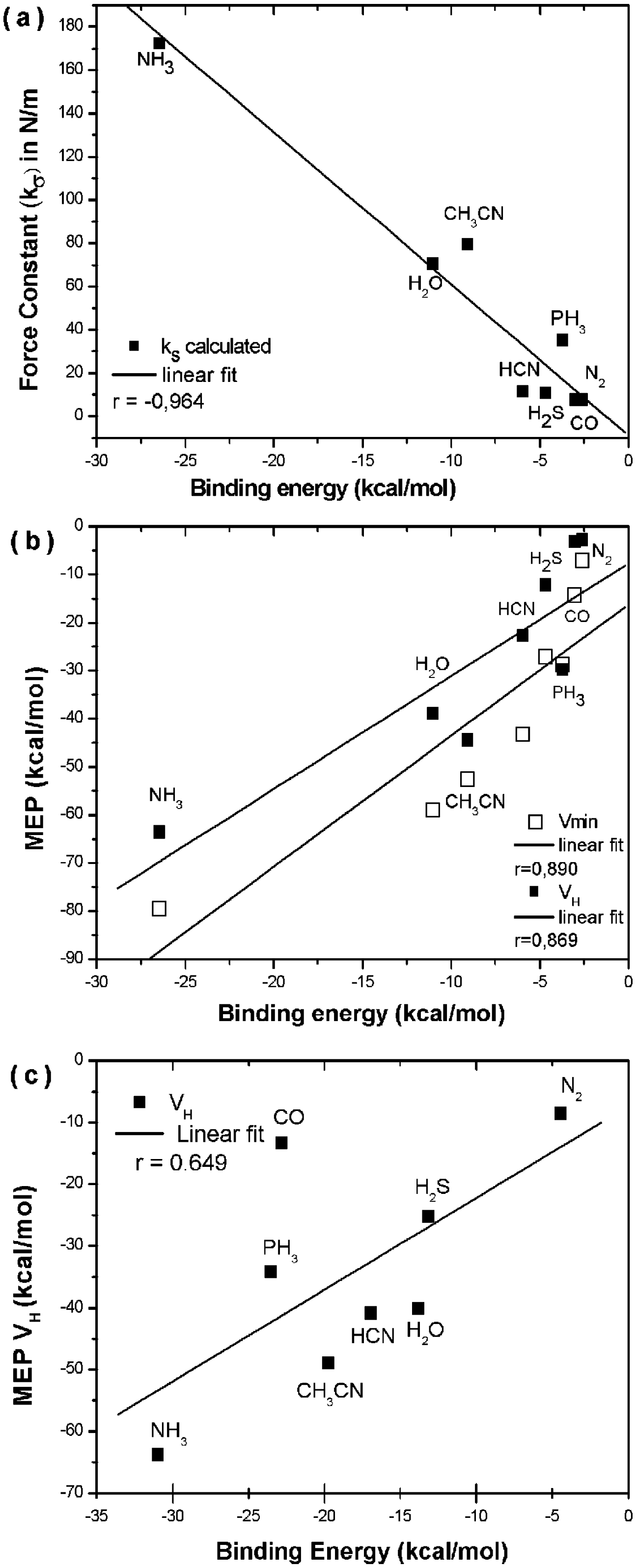

Figure 2. (a) Comparison between force constants (k_σ) (N/m) and binding energy (kcal/mol) for B$-$BF$_3$ systems. (b) Comparison between MEP (kcal/mol) and binding energy (kcal/mol) for B$-$BF$_3$ systems. (c) Comparison between MEP (kcal/mol), including $V_{\min}$ and V_H, and binding energy (kcal/mol) for B$-$BH$_3$ systems. See the text for details.

$= 0.997$ for calculated values). On the other hand, a plot of the force constants vs binding energies for the donor$-$aceptor B$-$BF$_3$ systems, do not show a good correlation, as one can see in Figure 2a ($r = 0.964$). The more covalent type of interaction of B$-$BF$_3$ could be responsible for this fact and, in those cases, the proposed empirical model of nucleophilicity scale may not be appropriate to represent this type of interaction.

c. Molecular Electrostatic Potential. The minimum value of the MEP ($V_{\min}$) has been used in the past to characterize hydrogen bonds.[23] In this work, the $V_{\min}$ has also been used as a possible measurement of nucleophilicity. The values for the series of molecules are depicted in Tables 1 and 2. One can see that $V_{\min}$ correlates fairly well with both the calculated and experimental force constants, justifying the electrostatic character in these B$-$HX hydrogen bonded systems. Then, the electrostatic potential at the position of the hydrogen atom, V_H, has also been calculated and shown in Tables 1 and 2. In Figure 1c, both, $V_{\min}$ and V_H have been plotted against the experimental nucleophilicity[8] scale for the same series of molecules. It is interesting to observe that both quantities correlate very well with the experimental values. Hence, both quantities seem to be good candidates to quantify nucleophilicity for systems with markedly electrostatic interactions.

d. Empirical Nucleophilicity Model. To test further the range of applicability of the scale of nucleophilicity based on the force constants or the electrostatic potential, two molecules have been used as the dipole. They are the BF$_3$ and BH$_3$ molecules. The former is a hard electrophile whereas the latter is a soft electrophile. Hence for these molecules there are no experimental data in the Legon$-$Millen scale,[8] the binding energy of the B$-$HCN complexes has been used as a good measurement of nucleophilicity. This is corroborated by the correlation of Figure 1a. For B$-$BF$_3$, in Figure 2a one can see the correlation of the calculated force constants and the binding energy and in Figure 2b the correlation of the $V_{\min}$ and V_H with the binding energy. In the three cases, one observes a reasonable correlation ($r = 0.890-0.869$), which is, however, poorer than the one obtained with the harder HF and HCN molecules. Going next to the soft BH$_3$ system, one finds that not one of the used parameters correlates with the binding energies, as can be seen in Figure 2c ($r = 0.649$). The molecular electrostatic potential and the force constants cannot describe the trends in binding of these complexes. It is clear that a soft$-$soft interaction is not controlled by charges and, therefore, the electrostatic potential does not seem to be a reasonable choice. A soft$-$soft interaction is orbital controlled and the relationship of this special force constant with the creation of a covalent bond is not clear.

In this work, we propose a new empirical model that takes into account the specific electrophilic substrate. A specific electrophile would accept a specific amount of charge and another electrophile a different one. In a very simple model, this amount of charge transfer will be given by the following equation

$$N = \frac{\mu_A - \mu_B}{\eta_A + \eta_B} \tag{5}$$

where μ_A and μ_B are the chemical potentials of the nucleophilic and electrophilic molecules, respectively. η_A and η_B are the respective hardnesses. This equation has been derived by Parr[34] from Malone's ideas,[35] and the factor of 2 has been omitted for convenience according to the currently accepted definition of the hardness without the factor of one-half. This amount of transferred charge is fixed and different for each couple of reactants. Because the amount of charge is fixed, the scenery is the grand canonical ensemble, where the independent variables are the chemical potential and the external potential:

TABLE 3: Calculated Properties for Nucleophiles and Electrophiles[a]

nucleophile	E_{HOMO} (au)	E_{LUMO} (au)	η (au)	μ (au)
CN^-	−0.188	0.248	0.436	0.030
HCC^-	−0.124	0.221	0.345	0.049
CF_3^-	−0.155	0.265	0.420	0.055
CH_3S^-	−0.081	0.211	0.292	0.065
H_2NS^-	−0.073	0.228	0.301	0.078
$CH_2CHCH_2^-$	−0.034	0.215	0.249	0.090
$CH_3SCH_2^-$	−0.024	0.206	0.230	0.091
CH_3O^-	−0.101	0.244	0.346	0.071
NH_2^-	−0.046	0.338	0.383	0.146
HO^-	−0.104	0.419	0.523	0.157
Cl^-	−0.150	0.302	0.452	0.076
HS^-	−0.094	0.261	0.355	0.083
F^-	−0.178	0.533	0.711	0.177
Br^-	−0.140	0.251	0.390	0.055
electrophile	**E_{HOMO} (au)**	**E_{LUMO} (au)**	**η (au)**	**μ (au)**
CH_3Cl	−0.436	0.078	0.515	−0.179
CH_3Br	−0.401	0.056	0.457	−0.173
$CH_3CO_2CF_3$	−0.499	0.067	0.566	−0.216

[a] η is hardness and μ chemical potential.

TABLE 4: Theoretical Nucleophilicity Values, ω^-, and Experimental Efficiency[36] for Nucleophiles in $X^- + CH_3Cl$ Reaction

nucleophile	efficiency (exp)	N	N^2	ω^- (eV)
CN^-	0.0005[c]	−0.220	0.048	0.287
HCC^-	0.0620[a]	−0.265	0.070	0.329
CF_3^-	0.0350[a]	−0.250	0.063	0.357
CH_3S^-	0.0650[a]	−0.302	0.091	0.362
H_2NS^-	0.0850[a]	−0.315	0.099	0.406
$CH_2CHCH_2^-$	0.1700[a]	−0.352	0.124	0.421
$CH_3SCH_2^-$	0.1900[a]	−0.362	0.131	0.411
CH_3O^-	0.2500[c]	−0.291	0.085	0.398
NH_2^-	0.6300[a]	−0.362	0.131	0.683
HO^-	0.8400[b]	−0.324	0.105	0.747

[a] Efficiency values taken from ref 36a. [b] Efficiency values taken from ref 36b. [c] Efficiency values taken from ref 36c.

TABLE 5: Theoretical Nucleophilicity Values, ω^-, and Experimental Efficiency[36] for Nucleophiles in the $X^- + CH_3Br$ Reaction

nucleophile	efficiency (exp)	N	N^2	ω^- (eV)
CN^-	0.010[a]	−0.228	0.052	0.307
CH_3S^-	0.091[b]	−0.317	0.101	0.400
CH_3O^-	0.400[b]	−0.304	0.093	0.436
H_2NS^-	0.350[a]	−0.331	0.109	0.448
Cl^-	0.007[a]	−0.274	0.075	0.461
HS^-	0.170[a]	−0.316	0.100	0.481
HO^-	0.95[a]	−0.337	0.113	0.808
F^-	0.880[a]	−0.300	0.090	0.870

[a] Efficiency values taken from ref 36b. [b] Efficiency values taken from ref 36c.

TABLE 6: Theoretical Nucleophilicity Values, ω^-, and Experimental Efficiency[36] for Nucleophiles in the $X^- + CH_3CO_2CF_3$ Reaction

nucleophile	efficiency (exp)[a]	N	N^2	ω^- (eV)
CN^-	0.010	−0.246	0.060	0.358
CH_3S^-	0.250	−0.327	0.107	0.424
Br^-	0.003	−0.284	0.080	0.427
Cl^-	0.021	−0.286	0.082	0.505
HO^-	0.470	−0.342	0.117	0.835
F^-	0.390	−0.308	0.095	0.917

[a] Efficiency values taken from ref 36c.

$$d\Omega = -N\,d\mu + \int \rho(r)\,d\upsilon(r)\,dr \tag{6}$$

Therefore, assuming the external potential is fixed (one is interested in the transfer of charge), it is possible to expand the potential until second order:

$$\Delta\Omega = -N\Delta\mu - \frac{1}{2}S\Delta\mu^2 \tag{7}$$

and look for the chemical potential variation that minimizes the variation in Ω. The result is

$$\Delta\mu = -N\eta \tag{8}$$

which should be inserted in eq 7 to obtain

$$\Delta\Omega = \frac{1}{2}N^2\eta \tag{9}$$

Now one should use eq 5 to obtain the value of N. It is proposed that this expression can be used as a good indicator of the nucleophilic character of a series of molecules against a particular electrophile. Note that if one follows the arguments of Maynard et al.,[17] for an electrophilicity scale one can consider an electron sea of zero chemical potential and hardness. Then the number of electrons according to eq 5 is $N = -\mu/\eta$, and putting it into eq 9, one recovers the original electrophilicity index.

Hence, it is proposed to use as the nucleophilicity index the following expression

$$\omega^- = \frac{1}{2}\frac{(\mu_A - \mu_B)^2}{(\eta_A + \eta_B)^2}\eta_A \tag{10}$$

Note that the proposed index depends on the electrophilic system and, therefore, there is not a unique nucleophilic scale. It will vary from one electrophile to another. Notice that opposed to the electrophilicity index,[16] which is absolute, this one is relative. As for all other indices derived in density functional theory, one needs a practical scheme to calculate it. As usual, the frozen orbital and the finite difference approximations are used to obtain the respective μ and η.[34] Therefore, the results will also depend on the quality of the respective HOMO and LUMO.

The proposed empirical nucleophilicity index was evaluated in anions that can participate as nucleophiles in S_N2 substitution reactions. Tables 3−6 show the electronic properties for some nucleophiles and the electrophiles CH_3Y (Y = Cl, Br and CO_2CF_3), in the nucleophile−CH_3Y interaction. The second column of Tables 4−6 contains the experimental efficiency values in the gas phase, allowing us to study the intrinsic reactivity of the reaction in the absence of solvation effects. Efficiency[36] is defined as the ratio of the observed rate constants to the estimated collision rate constants. The last one is based on the physical properties of the reaction partners and varies considerably with changes in the dipole, polarizability and mass of the substrate. Hence, efficiency values contain information about both reagents (nucleophile and electrophile).

The comparisons between the efficiency values[36] and the nucleophilicity index of eq 10 are shown in Figure 3a−3c for anions−CH_3Y. It may be seen that parts a and b of Figure 3 show good correlation between both quantities ($r = 0.980$ and $r = 0.923$), so the nucleophilicity depends on the electrophilic nature, as shown in these figures. The plot between efficiency[36] and ω^- using $CH_3CO_2CF_3$ as electrophile shows a poorer correlation (Figure 3c, $r = 0.851$). However, it is possible to find some trends in the nucleophilic character of the three studied systems. For instance, the nucleophilicity order given

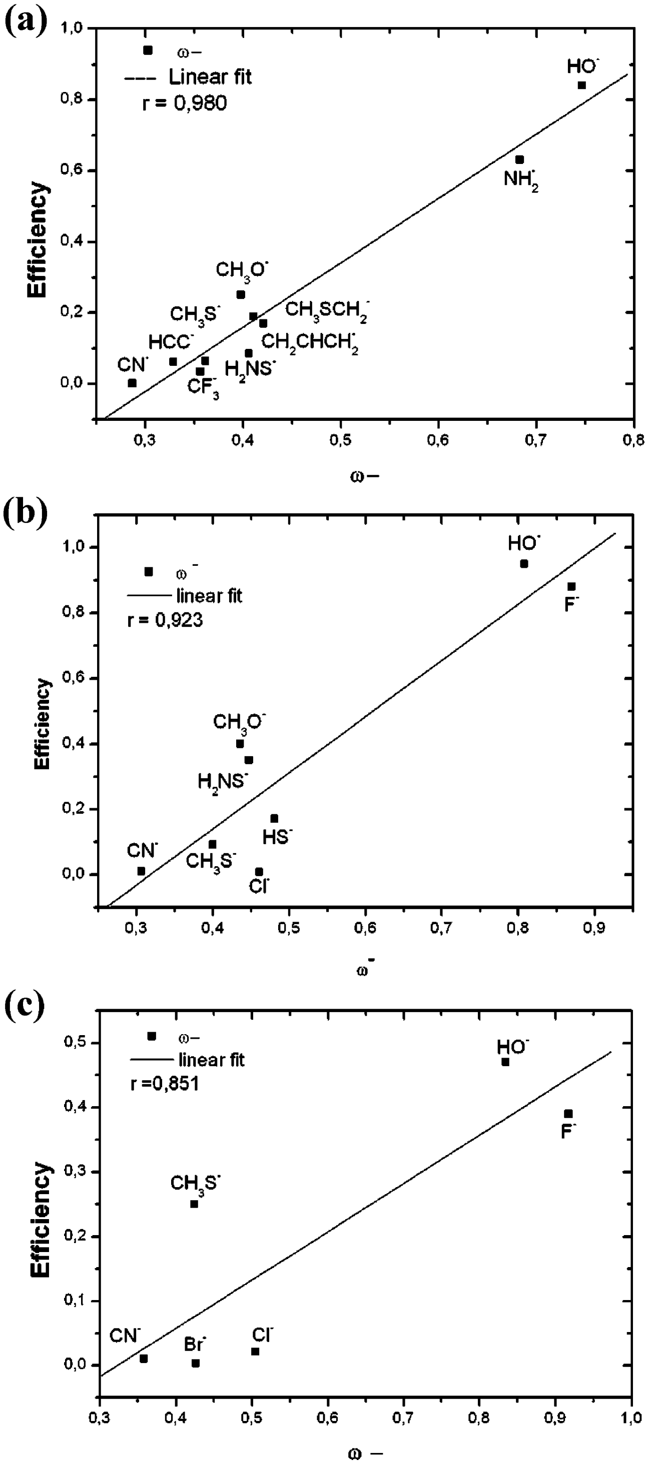

Figure 3. (a) Comparison between calculated nucleophilicity (ω^-, in eV) and experimental efficiency[36] for anions in the $X^- + CH_3Cl$ reaction. (b) Comparison between calculated nucleophilicity (ω^-, in eV) and experimental efficiency[36] for anions in the $X^- + CH_3Br$ reaction. (c) Comparison between calculated nucleophilicity (ω^-, in eV) and experimental efficiency[36] for the anions in the $X^- + CH_3CO_2CF_3$ reaction.

by ω^- is $CN^- < CH_3S^- < CH_3O^- \approx H_2NS^- < HO^-$ for the electrophiles CH_3Cl and CH_3Br, in agreement with experimental data.[36] The halide anions present an order of nucleophilicity $Br^- < Cl^- < F^-$ for $CH_3CO_2CF_3$ according to experimental data.[36c]

To test the predictive power of the model and the quality of the linear relationship between the experimental efficiency and ω^- (calculated nucleophilicity), eight of ten nucleophiles included in the regression were selected as a training set of molecules. The empirical equation for a first regression was efficiency = $1.8957\omega^- - 0.5952$ ($r = 0.977$) predicting an efficiency value for NH_2^- ($\omega^- = 0.683$ eV) of 0.6986 and for $CH_3SCH_2^-$ ($\omega^- = 0.411$ eV) of 0.1829, which are in excellent agreement with the experimental values of 0.6300[36] and 0.1900,[36] respectively. Selecting other set of eight nucleophiles, the regression is efficiency = $1.6452\omega^- - 0.5002$ ($r = 0.964$), predicting an efficiency value for OH^- ($\omega^- = 0.747$ eV) of 0.7288 and for $CH_2CHCH_2^-$ ($\omega^- = 0.421$ eV) of 0.1924, which are consistent with the experimental efficiencies of 0.8400[36] and 0.1700,[36] respectively. Although these comparisons were arbitrarily chosen, they allow us to validate the predictive character of the proposed nucleophilicity model.

4. Concluding Remarks

A simple model to develop an empirical nucleophilicity scale based on the stretching force constants of the vibrational spectrum was presented. The B−HX (X = F, CN) dimers have been the benchmark to test the model of Legon and Millen.[8] Good linear correlations between theoretical and experimental values of stretching force constant have been observed. The molecular electrostatic potential (MEP) and binding energy (BE) have been useful tools to probe the nucleophilic character in systems characterized by electrostatic interactions. The model was illustrated for a set of molecules such as N_2, CO, PH_3, H_2S, HCN, CH_3CN, H_2O and NH_3. An excellent linear correlation between the molecular electrostatic potential at the nucleophilic site and the binding energy with experimental nucleophilicity values were found. Therefore, the force constants of the stretching mode, V_{min}, V_H, and the binding energy have been found as excellent descriptors for electrostatic interactions. Finally, for a covalent interaction another empirical nucleophilicity index was proposed. This model contains information about the frontier orbitals of the nucleophile and the partner electrophile. This index showed good correlations with experimental values of nucleophilicities in systems vastly studied in S_N2 substitution reactions in the gas phase. The comparison found between the calculated nucleophilicities and the experimental data showed the dependence of the nucleophilicity scale with the reaction partner.

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