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Relationship between basicity and nucleophilicity

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ABSTRACT: The empirical concepts of basicity and nucleophilicity are related but not strictly proportional. Hence, the aim of this study is to help in elucidating the range where both concepts are directly proportional. To do this, the relationship between a recently introduced nucleophilicity index and the proton affinity (PA) of several families of bases has been studied. A good correlation between the PA and the nucleophilicity index using HF and HCN as electrophilic partner has been found. Our studies show that the correlation exists only when the interaction is soft–soft in character and for strong bases with weak acids. However, the relationship is not only valid for exothermic reactions as it has been previously postulated but also for endothermic reactions.

KEYWORDS: nucleophilicity index; nucleophiles; basicity; proton affinity; reactivity; HSAB principle; acid–base reaction; endothermic reactions

INTRODUCTION

A nucleophile is a Lewis base that uses an available electron pair to form a bond to its reaction partner (an electrophile). Whereas the term nucleophilic ability is normally used to describe trends in the kinetic aspects of substitution reactions, that is, a good nucleophile is one that forms fast a new bond,[1] the basicity is related in terms of the position of an equilibrium reaction with a proton or some other acid.[1] It is generally accepted that basicity is a thermodynamic concept and nucleophilicity a kinetic one. The difference is established at the moment that the current scales use kinetic data for nucleophilicity (rate constants) and thermodynamic data for basicity (proton affinities or Gibbs free energy). However, from a theoretical point of view the distinction is not so clear. Most of the argumentations used previously, especially for the density functional descriptors, are based in some energy minimization which points out to a thermodynamic argument. However, almost always the discussion is based in equations at first order of perturbation theory. Hence, it contains information of the very beginning of the reaction, at most information of the transition state, which implies only kinetic information. Therefore, it is interesting to study how good is a theoretical nucleophilicity index based on the density functional descriptors in describing the basicity of a molecule. The question to be studied can also be formulated as how far the concepts of base and nucleophile are proportional to each other.

There are several factors governing the nucleophilic ability.[2] The solvation energy of the nucleophile, the strength of the bond being formed, the size of the nucleophile, the electronegativity and the polarizability of the attacking atom may be considered as the most important factors influencing on nucleophilicity.[1] Experimentally as well as theoretically there is a good evidence of the unfeasibility of a unique nucleophilicity scale. Furthermore, the experimental scales have incorporated thermodynamics properties, kinetic rate constants,[2,3,5,6] polarizability values[3] and empirical reactivities rules.[4] The first empirical scale was proposed by Swain and Scott.[5] A two-parameter equation was found correlating the relative rates of several nucleophilic reagents with organic substrates in aqueous solution.[5] One parameter was associated to the substrate and the other one was defined as the constant of the nucleophilic species. Quantitative correlations of the relative rates were found in S_N2 reactions using methyl halides as a reference substrate.[5] Another important model of nucleophilicity/electrophilicity has included the gas phase hydrogen bonded complexes[7,8] based on the electrostatic character[9] of the hydrogen bond formed between a Lewis base B and an electrophile as HX. More recently, Mayr *et al.*[10] proposed a linear free energy relationship based on kinetic data recorded for a series of nucleophiles which presents a wide diversity in structure and bonding properties. Their empirical scales are characterized by three parameters, one parameter describing the electrophilic species and two more describing the nucleophiles.[10]

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On the other hand, the intrinsic (gas phase) basicity can be probed and quantified by the proton affinity (PA),[11,12] which is defined as the enthalpy change (ΔH) associated to the following reaction:

$$\mathrm{BH}^+ \rightleftharpoons \mathrm{B} + \mathrm{H}^+$$

This quantity plays an important role in the proton transfer reactions in organic chemistry and biochemistry in the gas phase.[13–15] In the literature, there are many experimental data of proton affinities as measure of the intrinsic basicity[15–18] and also theoretical calculations for sizeable molecules.[19–21] Even though the PA values are a thermodynamic quantity, through a comparison of the PA and nucleophilicity values may be possible to find some relationship between both quantities.

Usually a hard–hard interaction is electrostatic in nature and parameters such as electrostatic potential, binding energy and force constant may explain the nucleophilicity reactivity. Recently, our research group has discussed the nucleophilicity in terms of this kind of interaction.[22] On the other side, a soft–soft interaction can be tried as frontier orbitals controlled. This has been quantitatively expressed in different scales for both type of interactions.[22,23] Specifically, we studied several kinds of nucleophiles such as simple anions, neutral species and σ and π nucleophiles (alkenes, simple amines, phosphanes and phosphites). Their nucleophilic character was tested using Eqn (2) and the kinetic data in specific reactions being our results consistent with experimental nucleophilicity.[22,23]

We stress that it is generally accepted that the nucleophilicity ability, a concept associated to the kinetic of some reactions, should be also related to the basicity,[24] a concept associated to the thermodynamic of the reaction. Although, both concepts are not always proportional, they should be related when they are applied to a family of nucleophiles in which the donor atom remains the same.[25] Furthermore electrophilicity[26,27] is other concept treated as a kinetic quantity, which has recently been correlated with the free energy of activation, a thermodynamic quantity.[28]

The global and local molecular parameters such as Fukui function,[29] electronegativity[30] and effective polarizability,[30] have been used to correlate,[29] to predict[30] and to analyse substituent effects in nucleophilic molecules.[31,32] Recently, it has been shown that some structural parameters used as descriptors of nucleophilicity can be correlated in identity $\mathrm{S_N2}$ reactions.[33] This work has also analysed both, the kinetic and thermodynamic, concepts associated to the nucleophilicity and basicity, respectively.[33] In general, the results suggest that both quantities are directly related in strongly exothermic reactions.[33]

Experimentally has also been possible to find a relationship between basicity and nucleophilicity in aryl compounds containing *N*-anions.[34] In that work, the reaction rate is determined by the basicity of the anion and by the sensitivity of the rate constant to basicity variation in $\mathrm{S_N2}$ reactions. The Marcus equation[34] makes it possible to correlate variation of the Bronsted coefficient with the height of internal barriers.[34]

As it was mentioned above the recently proposed nucleophilicity index[22] has been a reliable descriptor of the kinetic behaviour in several substitution reactions in agreement with experimental data reported by Gronert.[35] Additionally, the new index has been tested in alkenes, amines, phosphanes and phosphites with the corresponding electrophilic partners[23] in agreement with kinetic data of Mayr and Patz.[10a]

The aim of this work is to explore further the relationship between the nucleophilicity index[22,23] and the PA, as a measure of the basicity of the system. Acid-base reactions of nucleophiles as alcohols, amines, ethers, substituted anilines, imines and diimines, which are classified as strong bases, reacting with weak acids as HF and HCN, have been first explored. It will be shown that in all cases there is a good correlation between the PA and the nucleophilicity index. Additionally the factors influencing the relationship of both properties are discussed.

THEORETICAL MODEL AND COMPUTATIONAL DETAILS

A recent model to describe the nucleophilicity concept, which takes into account the specific electrophilic substrate has been used.[22,23] A specific electrophile would accept a specific amount of charge and other electrophile a different one. In a very simple model this amount of charge will be given by the following equation:

$$N = \frac{\mu_A - \mu_B}{\eta_A + \eta_B} \tag{1}$$

where μ_A and μ_B are the chemical potential[35] of the nucleophilic and electrophilic molecule, respectively. η_A and η_B are the respective hardnesses.[36] This equation has been derived by Parr[36] from Malone's ideas.[37] This amount of charge is fixed and different for each couple of reactants. Since the amount of charge is fixed, the scenario is the grand canonical ensemble, where the potential is given using the chemical potential and the external potential as the independent variables.

The relationship used as our nucleophilicity index, ω^-, is[22]:

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

Note that the index depends not only on the nucleophilic system but also on the electrophilic species. Therefore, there is no a unique nucleophilic scale. It will vary from one electrophile to the other. But this has

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allowed studying several reactions with different electrophilic species.[23] In this work, the benchmark is an acid–base reaction.

As all other indices derived in density functional theory[36] one needs a practical scheme to calculate it. As usual, the frozen orbital and the finite differences approximations are used to obtain the respective μ and η [36] values. Therefore, the results will also depend on the quality of the respective HOMO and LUMO (one-electron) energies. Successful applications for a variety of nucleophiles have been reported.[23]

Total geometries of the molecules were optimized at MP2/6–31+G(d,p) level using the Gaussian03 package.[38] The reactivity descriptors such as chemical hardness (η),[36] chemical potential (μ),[36] were calculated using the frozen orbital and the finite difference approximations. The change of energy (ΔE) corresponding to the acid–base reaction,

$$\mathrm{B} + \mathrm{HX} \rightarrow \mathrm{BH}^{+} + \mathrm{X}^{-}$$

where B is a nucleophile and HX (HF) electrophile, was calculated at the same theory level.

RESULTS AND DISCUSSION

PA of the bases B, defined as the negative of the enthalpy change for the protonation reaction in gas phase is a quantitative measure of the gas phase basicity[11,12]:

$$\mathrm{B}_{(\mathrm{g})} + \mathrm{H}^{+}_{(\mathrm{g})} \rightarrow \mathrm{BH}^{+}_{(\mathrm{g})} \qquad (3)$$

PA is given by

$$\begin{aligned} \mathrm{PA}(\mathrm{B}) &= -\Delta H^{\mathrm{o}}_{\mathrm{f}} \\ &= \Delta H^{\mathrm{o}}_{\mathrm{f}}(\mathrm{B}) + \Delta H^{\mathrm{o}}_{\mathrm{f}}(\mathrm{H}^{+}) - \Delta H^{\mathrm{o}}_{\mathrm{f}}(\mathrm{BH}^{+}) \qquad (4) \end{aligned}$$

and may be approximated by

$$\mathrm{PA}(\mathrm{B}) = -\Delta H^{\mathrm{o}}_{\mathrm{f}} \cong \Delta E = E(\mathrm{B}) - E(\mathrm{BH}^{+}) \qquad (5)$$

where $E(\mathrm{B})$ and $E(\mathrm{BH}^{+})$ correspond to the total energies of the B bases, and the conjugated acid, BH^{+}, respectively, and ΔE is the energy change of the reaction (3) and may be associated to the PA of the base B.

Nucleophilicity (ω^{-})[22,23] is a descriptor of reactivity that allows us to have a quantitative classification of the nucleophilic nature (electron donating capacity) in front of the electrophile, and it is a relative descriptor depending on their electrophilic partner. In this work, the acid–base reaction evaluated were those where HF and HCN act as weak acid, with alcohols,[30] amines,[20b] ethers,[30] substituted anilines,[39] imines and diimines[39] and some weak bases.[18] The electronic properties and the nucleophilicity values are showed in Tables 1–6. The last column of these tables contains the available experimental PA values. PA values for substituted anilines and diimines were taken from the literature at MP2 theory level.[40] This level of theory has been already validated.[11,40] It is worth to mention here that our main interest is to study the possible correlation between PA values and the recently introduced theoretical nucleophilicity index and not to reproduce the experimental PA values. There are other quantities better suited to match the proton affinities.

For alcohol series the comparison between the experimental PA[30] and the nucleophilicity index with both electrophiles (HF and HCN) is shown in Fig. 1A.

The linear regression equations for the set of alcohols with HF and HCN are, respectively:

$$\begin{aligned} \mathrm{PA} &= 92.64\omega^{-} + 170.98 \quad (N = 11, r = 0.9774) \\ \mathrm{PA} &= 51.25\omega^{-} + 170.50 \quad (N = 11, r = 0.9817) \end{aligned}$$

A reasonable regression correlation coefficient is found for both types of interaction.

Table 1. Chemical hardness (η), chemical potential (μ), amount of charge (N), calculated nucleophilicity (ω^{-}), energy change (ΔE) and experimental proton affinity (PA) for amines[20]

Amines	η (eV)	μ (eV)	N (HF)	N (HCN)	N (HCl)	ω^{-} (HF) (kcal/mol)	ω^{-} (HCN) (kcal/mol)	ω^{-} (HCl) (kcal/mol)	ΔE (kcal/mol)	PA(exp)[20] (kcal/mol)
NH_3	0.537	−0.155	0.055	0.072	0.037	0.504	0.870	0.225	262.0	204.0
CH_3NH_2	0.465	−0.155	0.057	0.076	0.039	0.479	0.849	0.217	115.8	214.1
$CH_3CH_2NH_2$	0.467	−0.153	0.059	0.078	0.041	0.510	0.900	0.244	130.5	217.0
$(CH_3)_2CHNH_2$	0.466	−0.153	0.059	0.078	0.041	0.510	0.900	0.243	128.7	218.6
$(CH_3)_2NH$	0.449	−0.143	0.068	0.090	0.052	0.649	1.136	0.376	125.9	220.6
$(CH_3)_3CNH_2$	0.462	−0.154	0.058	0.078	0.040	0.494	0.875	0.231	126.4	220.8
$(CH_3)_3N$	0.437	−0.136	0.074	0.098	0.059	0.749	1.308	0.481	121.7	225.1
$(CH_3)CN$	0.516	−0.198	0.023	0.034	−0.003	0.089	0.182	0.001	168.3	189.2
Et_3N	0.424	−0.134	0.076	0.101	0.062	0.771	1.350	0.509	358.2	232.3
Electrophiles										
HF	0.839	−0.230								
HCN	0.580	−0.235								
HCl	0.565	−0.195								

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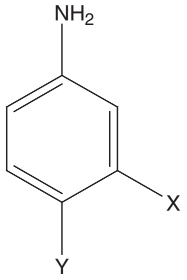
Table 2. Chemical hardness (η), chemical potential (μ), amount of charge (N), calculated nucleophilicity (ω^-), energy change (ΔE) and experimental proton affinity (PA) for alcohols[30]

Alcohols	η (eV)	μ (eV)	N (HF)	N (HCN)	N (HCl)	ω^- (HF) (kcal/mol)	ω^- (HCN) (kcal/mol)	ω^- (HCl) (kcal/mol)	ΔE (kcal/mol)	PA(exp)[30] (kcal/mol)
MeOH	0.529	−0.185	0.033	0.045	0.009	0.179	0.337	0.014	171.0	184.9
EtOH	0.517	−0.179	0.037	0.051	0.015	0.227	0.419	0.034	165.8	190.3
n-PrOH	0.519	−0.183	0.034	0.047	0.011	0.192	0.360	0.019	164.2	191.4
i-PrOH	0.520	−0.176	0.040	0.053	0.017	0.255	0.470	0.049	161.6	192.7
n-BuOH	0.510	−0.182	0.036	0.049	0.012	0.203	0.380	0.023	163.2	192.0
t-BuOH	0.507	−0.177	0.039	0.053	0.017	0.248	0.455	0.045	157.2	195.0
CHF_2CH_2OH	0.545	−0.201	0.021	0.031	−0.005	0.077	0.159	0.004	179.0	180.6
CF_3CH_2OH	0.566	−0.207	0.017	0.025	−0.010	0.049	0.110	0.019	186.9	174.9
$(CF_3)_2MeCOH$	0.588	−0.222	0.005	0.011	−0.024	0.005	0.021	0.104	192.5	172.9
$(CF_3)_2CHOH$	0.599	−0.226	0.003	0.008	−0.027	0.001	0.011	0.133	198.6	170.9
$(CF_3)_3COH$	0.612	−0.239	−0.006	0.003	−0.037	0.007	0.0001	0.268	358.2	169.0

Table 3. Chemical hardness (η), chemical potential (μ), amount of charge (N), calculated nucleophilicity (ω^-), energy change (ΔE) and experimental proton affinity (PA) for ethers[30]

Ethers	η (eV)	μ (eV)	N (HF)	N (HCN)	N (HCl)	ω^- (HF) (kcal/mol)	ω^- (HCN) (kcal/mol)	ω^- (HCl) (kcal/mol)	ΔE (kcal/mol)	PA (exp)[30] (kcal/mol)
$(C_2H_5)_2O$	0.500	−0.165	0.048	0.065	0.028	0.367	0.655	0.123	157.9	200.4
$(CH_3)_2O$	0.502	−0.167	0.047	0.062	0.026	0.343	0.614	0.105	161.7	193.1
EtOMe	0.498	−0.165	0.049	0.065	0.028	0.371	0.662	0.126	156.9	196.5
n-Pr_2O	0.495	−0.163	0.050	0.067	0.030	0.392	0.698	0.142	155.9	202.9
i-PrOEt	0.498	−0.164	0.050	0.066	0.029	0.384	0.683	0.135	150.9	203.4
n-Bu_2O	0.492	−0.163	0.050	0.067	0.030	0.391	0.696	0.141	149.9	203.9
i-Pr_2O	0.491	−0.161	0.052	0.069	0.032	0.418	0.742	0.163	138.6	206.0

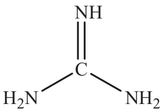
Table 4. Chemical hardness (η), chemical potential (μ), amount of charge (N), calculated nucleophilicity (ω^-), energy change (ΔE) and theoretical proton affinity (PA) of some substituted anilines[38]



X	Y	η (eV)	μ (eV)	N (HF)	N (HCN)	ω^- (HF) (kcal/mol)	ω^- (HCN) (kcal/mol)	ΔE (kcal/mol)	PA (MP2)[38] (kcal/mol)
CN	H	0.377	−0.133	0.080	0.107	0.760	1.356	162.7	198.8
H	CN	0.373	−0.133	0.080	0.107	0.753	1.347	163.0	198.5
F	H	0.376	−0.122	0.089	0.118	0.929	1.644	157.0	204.8
H	F	0.369	−0.119	0.092	0.123	0.983	1.739	155.5	206.2
OH	H	0.369	−0.115	0.095	0.127	1.053	1.857	151.2	210.4
H	OH	0.353	−0.107	0.103	0.137	1.177	2.081	150.1	211.2
NO_2	H	0.357	−0.148	0.070	0.093	0.533	0.976	163.8	197.7
H	NO_2	0.377	−0.147	0.070	0.092	0.554	1.005	164.4	197.5
CHO	H	0.370	−0.127	0.085	0.114	0.843	1.502	157.4	204.1
H	CHO	0.373	−0.128	0.084	0.112	0.831	1.479	159.6	202.3
OCH_3	H	0.359	−0.112	0.098	0.131	1.085	1.919	150.4	212.5
H	OCH_3	0.349	−0.105	0.105	0.140	1.212	2.144	148.2	213.4
H	H	0.368	−0.112	−0.098	−0.130	1.098	1.935	156.8	209.5[a]

[a] Experimental data was taken from Reference [41].

Table 5. Chemical hardness (η), chemical potential (μ), amount of charge (N), calculated nucleophilicity (ω^-), energy change (ΔE) and theoretical proton affinity (PA) of some imines and diimines[38]



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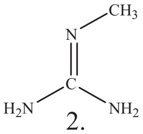

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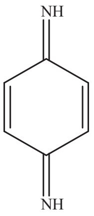

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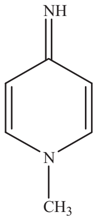

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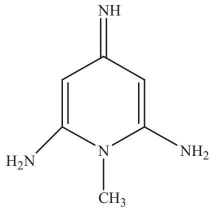

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Molecule	η (eV)	μ (eV)	N (HF)	N (HCN)	ω^- (HF) (kcal/mol)	ω^- (HCN) (kcal/mol)	ΔE (kcal/mol)	PA (MP2)[38] (kcal/mol)
1	0.423	−0.146	0.066	0.089	0.585	1.040	120.7	233.7
2	0.415	−0.140	0.072	0.095	0.671	1.187	144.1	237.2
3	0.366	−0.160	0.059	0.080	0.393	0.731	127.7	221.9
4	0.338	−0.112	0.100	0.134	1.061	1.896	94.0	257.5
5	0.327	−0.113	0.101	0.135	1.037	1.863	85.4	267.8

Similarly, the linear regression equations for the set of amines[20] with the same reference electrophiles were:

$$\mathrm{PA} = 57.64\omega^- + 185.29 \quad (N = 9, r = 0.9166)$$
$$\mathrm{PA} = 33.94\omega^- + 184.17 \quad (N = 9, r = 0.9234)$$

It may be seen as a good correlation between both quantities as it is shown in Fig. 1B.

The alkyl substituent effects in alcohols and amines are consistent with experimental and theoretical studies.[31] The observed trend has been attributed to inductive and polarization stabilization effects of alkyl groups directly bonded to the nucleophilic atom. At this point, clearly, basicity and nucleophilicity seem to be governed by the same factors affecting both properties in both families. It can be seen as a clear direct relationship between PA and the nucleophilicity (Figs 1A,B).

The linear regression equations for the set of ethers with HF and HCN are:

$$\mathrm{PA} = 177.74\omega^- + 133.15 \quad (N = 7, r = 0.9193)$$
$$\mathrm{PA} = 105.08\omega^- + 129.57 \quad (N = 7, r = 0.9172)$$

A pretty well correlation between experimental PA[30] and nucleophilicity (ω^-) is shown in Fig. 1C. It may be observed that bulky and ramified alkyl groups show a synergic effect increasing the nucleophilic character in this kind of nucleophiles. Other factors as electron withdrawing and electron releasing groups decrease and increase the nucleophilicity, respectively, as it was shown in previous works.[22,23] In the substituted anilines, it is interesting to note that in general the nucleophilicity values are higher with electron releasing groups. The basicity is also increased, that is, groups as OCH_3, OH, CHO and F, increase the electron density on nitrogen

Table 6. Chemical hardness (η), chemical potential (μ), amount of charge (N), calculated nucleophilicity (ω^-), energy change (ΔE) and experimental proton affinity (PA) of some weak bases[18]

Weak Bases	η (eV)	μ (eV)	N (HF)	N (HCN)	ω^- (HF) (kcal/mol)	ω^- (HCN) (kcal/mol)	ΔE (kcal/mol)	PA (Exp)[18] (kcal/mol)
CF_3CH_2OH	0.569	−0.212	0.013	0.020	0.029	0.072	185.1	166.4
C_2H_4	0.466	−0.141	0.068	0.090	0.675	1.173	189.5	162.6
CF_3COCl	0.563	−0.224	0.004	0.010	0.003	0.016	197.6	161.2
$(CF_3)_2CO$	0.555	−0.243	−0.010	0.007	0.016	0.010	209.0	153.8
C_2H_6	0.581	−0.196	0.024	0.033	0.103	0.203	220.6	146.9
CF_3Br	0.525	−0.202	0.021	0.030	0.072	0.151	218.7	141.3
CF_3Cl	0.588	−0.220	0.007	0.013	0.009	0.030	225.6	139.0
CH_4	0.638	−0.227	0.002	0.007	0.001	0.009	238.4	134.7

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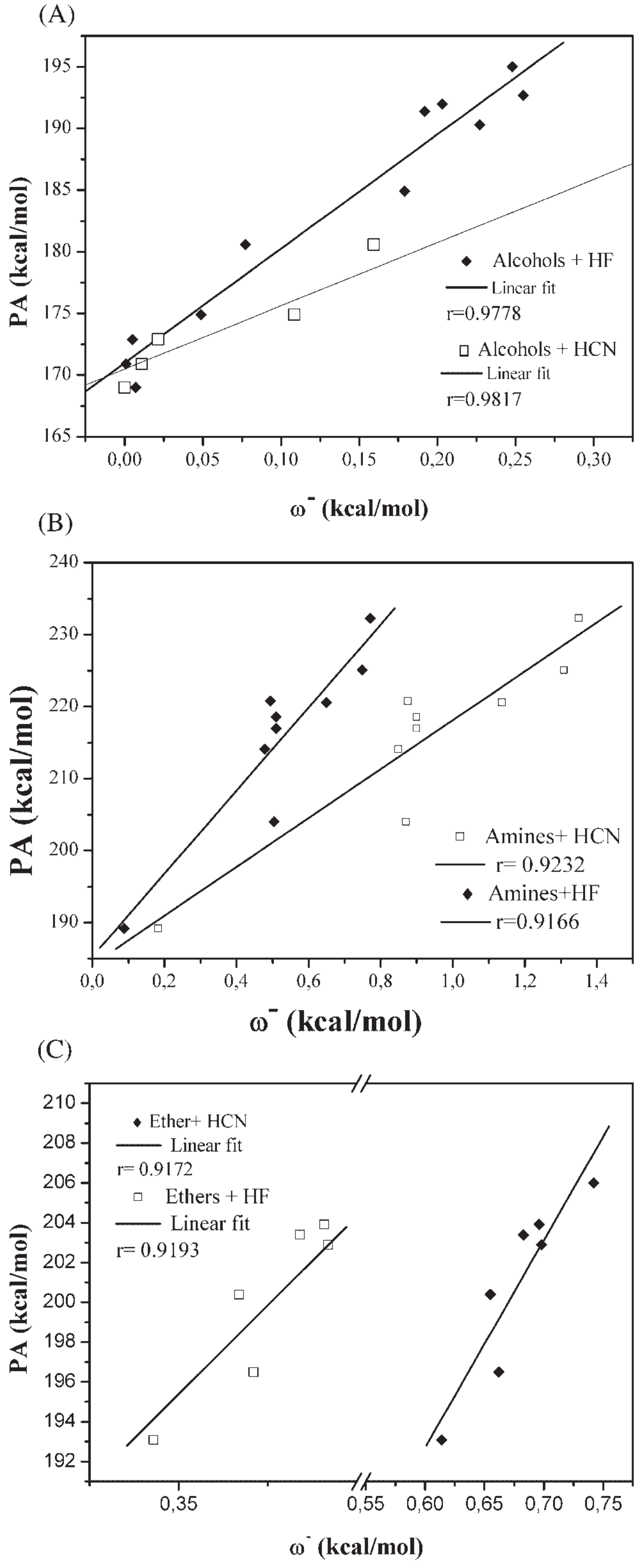

Figure 1. (A) Relationship between calculated nucleophilicity and experimental proton affinity for alcohols. (B) Relationship between calculated nucleophilicity and experimental proton affinity for amines. (C) Relationship between calculated nucleophilicity and experimental proton affinity for ethers

atom and thereby may be interpreted as a donation of the lone pair electron in acid–base reaction or another nucleophilic reactions. In contrast, electron withdrawing groups like NO_2 make aniline to be less basic and less nucleophilic than other substituted anilines, shown in Table 4 (for example when $X = NO_2$, $Y = H$, $PA = 197.7$ kcal/mol and $\omega^- = 0.976$ eV).

The linear regression analysis for the set of substituted anilines with HF and HCN are the following:

$$\mathrm{PA} = 25.55\omega^- + 181.93 \quad (N = 13,\ r = 0.9572)$$
$$\mathrm{PA} = 14.89\omega^- + 181.11 \quad (N = 13,\ r = 0.9585)$$

An excellent linear correlation between both properties is showed in these nucleophiles (Fig. 2A). Aniline molecule was included in the correlation as it was suggested by the referee. The inductive and resonance effects in aromatic amines seem to have the same effect on the nucleophilicity and basicity.

In some imines and diimines the relationship between calculated nucleophilicity and theoretical PA[20] is pretty well as evidenced by the linear regression analysis with HF and HCN:

$$\mathrm{PA} = 62.22\omega^- + 196.99 \quad (N = 5,\ r = 0.9735)$$
$$\mathrm{PA} = 35.20\omega^- + 196.34 \quad (N = 5,\ r = 0.9755)$$

The relationship between the calculated nucleophilicity (ω^-) and theoretical PA is plotted in Fig. 2B. It is evident that the calculated nucleophilicity index in superbases (imines and diimines), although structurally different, is directly related to the basicity.

In Table 6 is shown that there is no relationship in the reaction between weak bases and weak acids. In these examples a good base is not necessarily a good nucleophile. Another relevant result is displayed in Fig. 2C (numerical values are found in Tables 1–2). For nucleophiles interacting with a strong acid like HCl non-linear relationship between the calculated nucleophilicity and experimental PA is found. (Fig. 2C only report amines and alcohols). In this case, it seems that basicity and nucleophilicity are governed by different factors. The interaction has a more electrostatic character as it was proposed in Reference 11. This result follows the Hard and Soft Acids and Bases (HSAB) principle concluding that hard interactions are mainly of the electrostatic character.

Hence, the results presented here for weak–weak endothermic reactions together with those presented in Reference 33 for exothermic reactions predict a pretty good correlation between basicity (measured by the PA) and nucleophilicity for weak–weak reactions with an important energy difference between reactants and products. It means, for reactions mainly governed by thermodynamics arguments. This is surely a consequence of the use of only thermodynamics arguments in the derivation of the theoretical parameter. It can also be

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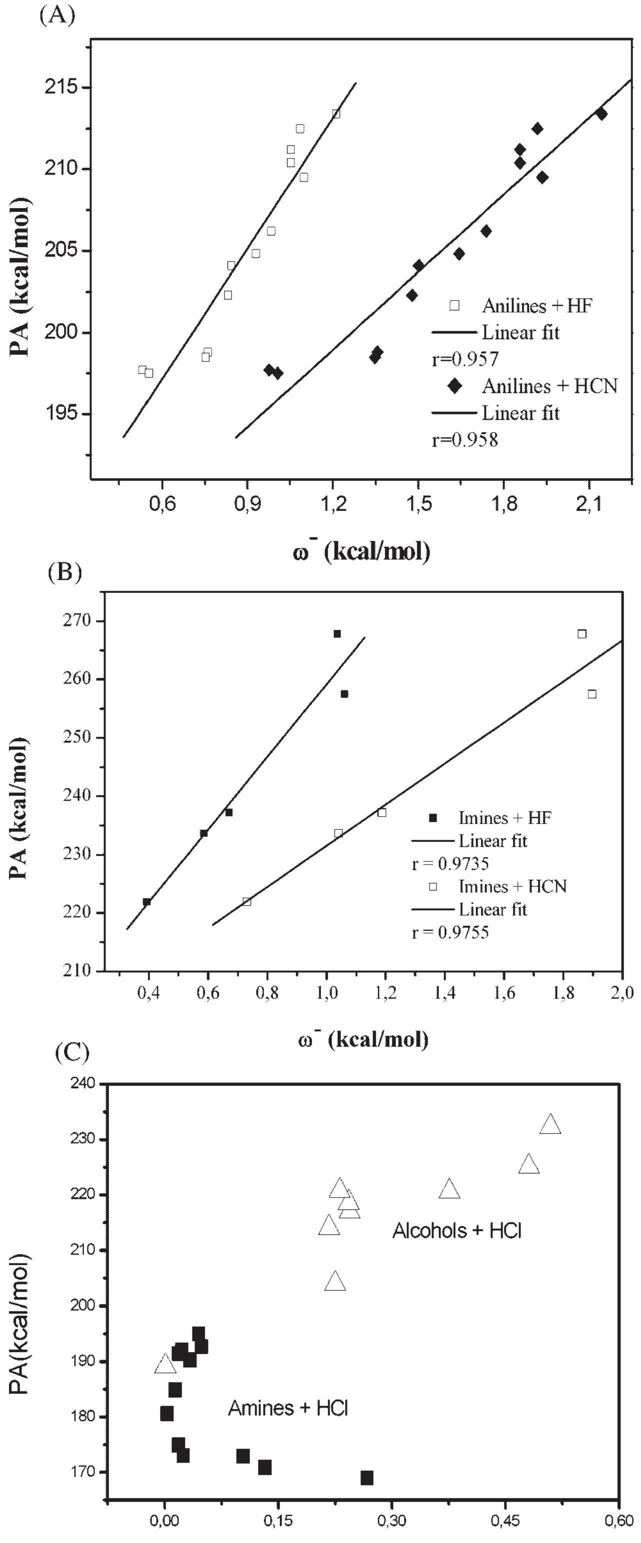

Figure 2. (A) Relationship between calculated nucleophilicity and experimental proton affinity for substituted anilines. (B) Relationship between calculated nucleophilicity and experimental proton affinity for imines and diimines. (C) Relationship between calculated nucleophilicity and experimental proton affinity for alcohols and amines with HCl as electrophile

advanced by the existence of similar relationship between electrophilicity and acidity.[28]

CONCLUSIONS

Good correlations between basicity, measured by the PA values and the recently proposed nucleophilicity index have been found. Six different kinds of nucleophiles or bases have been used as benchmark. This relationship is only observed when the families of nucleophiles are classified as strong bases and the electrophilic partner is labelled as a weak acid, like HF and HCN. Clearly in this situation, basicity and nucleophilicity are governed by inductive effects of alkyl groups, the electron-donating and electron-withdrawing groups close to the nucleophilic atom. When the acid–base reaction is between a weak base/acid pair this relationship is not observed.

It is important to emphasize that the nucleophilic and electrophilic partners (in soft–soft interactions) follows a HSAB principle. This relationship is emphasized between basicity and nucleophilicity. Finally, the relationship between nucleophilicity and basicity is limited in some families of nucleophiles to strong endothermic reactions as in this work. These results are complementary of previous works[30] predicting a good relationship in strongly exothermic reactions.

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REFERENCES

1. Carey FA, Sundberg RJ. *Advanced Organic Chemistry*, 3rd ed., Part A. Structure and Mechanisms. Plenum press: New York, 1990.
2. Edwards JO, Pearson RG. *J. Am. Chem. Soc.* 1962; **84**: 16–24.
3. (a) Edwards JO. *J. Am. Chem. Soc.* 1954; **76**: 1560–1563; (b) Edwards JO. *J. Am. Chem. Soc.* 1956; **78**: 1819–1820.
4. Pearson RG. *J. Org. Chem.* 1987; **52**: 2131–2136.
5. Swain CG, Scott CB. *J. Am. Chem. Soc.* 1953; **75**: 141–147.
6. (a) Richie CD. *Acc. Chem. Res.* 1972; **5**: 348–354; (b) Richie CD. *Can. J. Chem.* 1986; **64**: 2239–2250.
7. Legon AC, Millen DJ. *J. Am. Chem. Soc.* 1987; **109**: 356–358.
8. (a) Legon AC, Millen DJ. *Acc. Chem. Res.* 1987; **20**: 39–46; (b) Legon AC, Millen DJ. *Chem. Rev.* 1986; **86**: 635–657.
9. Buckingham AD, Fowler PW. *Can. J. Chem.* 1985; **63**: 2018–2025.
10. (a) Mayr H, Patz M. *Angew. Chem. Int. Ed Engl.* 1994; **33**: 938–957; (b) Roth M, Mayr H. *Angew. Chem. Int. Ed Engl.* 1995; **34**: 2250–2252; (c) Mayr H. *Angew. Chem. Int. Ed Engl.* 1990; **29**: 1371–1384; (d) Mayr H, Müller KH, Rau D. *Angew. Chem. Int. Ed Engl.* 1993; **32**: 1630–1632; (e) Mayr H, Ofial AR,

DOI: 10.1002/poc

Sauer J, Schmied B. *Eur. J. Org. Chem.* 2000; **11**: 2013–2020; (f) Mayr H, Ofial AR. *Tetrahedron Lett.* 1997; **38**: 3503–3506; (g) Lucius R, Mayr H. *Angew. Chem. Int. Ed Engl.* 2000; **39**: 1995–1997.

11. Lias SG, Bartmess JE, Liebman JF, Holmes JL, Levin RD, Mallard WG. *J. Phys. Chem. Ref. Data* 1988; **17** (Suppl. I): 696–698.
12. Angelleli F, Aschi M, Pepi F, DePetris G. *J. Phys. Chem.* 1995; **99**: 6551–6556.
13. Pérez P, Contreras R. *Chem. Phys. Lett.* 1998; **293**: 239–244.
14. Mó O, Yañez M, Decouzon M, Gal J-F, Maria P-Ch, Guillemin J-C. *J. Am. Chem. Soc.* 1999; **121**: 4653–4653.
15. Kaljurand I, Koppel IA, Kütt A, Room E-I, Rodima T, Koopel I, Mishima M. *J. Phys. Chem. A.* 2007; **111**: 1245–1250.
16. Raczynska ED, Decouzon M, Gal J-F, Maria P-Ch, Taft RW, Anvia F. *J. Org. Chem.* 2000; **65**: 4635–4640.
17. Brauman JI, Blair LK. *J. Am. Chem. Soc.* 1970; **92**: 5986–5992.
18. McMahon TB, Kebarle P. *J. Am. Chem. Soc.* 1985; **107**: 2612–2617.
19. Lamsabhi M, Esseffar M, Bouab W, El Messaoudi T, El Messaoudi M, Abboud JL-M, Alcami M, Yáñez M. *J. Phys. Chem. A.* 2002; **106**: 7383–7389.
20. (a) Drago RS, Cundari TR, Ferris DC. *J. Org. Chem.* 1989; **54**: 1042–1047; (b) Szulejko JE, McMahon TB. *J. Am. Chem. Soc.* 1993; **115**: 7839–7848.
21. (a) Burk P, Koppel IA, Koppel I, Leito I, Travnikova O. *Chem. Phys. Lett.* 2000; **323**: 482–489; (b) Deakyne CA. *J. Int. Mass. Spectrom.* 2003; **227**: 601–616; (c) Swart M, Bickelhaupt FM. *J. Chem. Theory. Comput.* 2006; **2**: 281–287.
22. Jaramillo P, Pérez P, Contreras R, Tiznado W, Fuentealba P. *J. Phys. Chem. A.* 2006; **110**: 8181–8187.
23. Jaramillo P, Fuentealba P, Pérez P. *Chem. Phys. Lett.* 2006; **427**: 421–427.
24. Pross A. *Theoretical and Physical Principles of Organic Reactivity.* John Wiley & Sons, Inc.: New York, 1995.
25. Bordwell FG, Cripe TA, Hughes DL. In *Nucleophilicity*, ACS Advances in Chemistry Series No. 215, Harris JM, McManus SP (eds). American Chemical Society: Washington, DC, 1987.
26. Parr RG, Szentpály L, Liu S. *J. Am. Chem. Soc.* 1999; **121**: 1922–1924.
27. Maynard AT, Huang M, Rice WG, Covel DG. *Proc. Natl. Acad. Sci. U S A.* 1998; **95**: 11578–11583.
28. Chattaraj PK, Sarkar U, Roy DR, Elango M, Parthasarathi R, Subramanian V. *Ind. J. Chem. A.* 2006; **45**: 1099–1137.
29. (a) Pérez P, Simon-Manso Y, Aizman A, Fuentealba P, Contreras R. *J. Am. Chem. Soc.* 2000; **122**: 4756–4762; (b) Weitao Y, Mortier WJ. *J. Am. Chem. Soc.* 1986; **108**: 5708–5711.
30. Gasteiger J, Hurchings MG. *J. Am. Chem. Soc.* 1984; **106**: 6489–6495.
31. Umeyama H, Morokuma K. *J. Am. Chem. Soc.* 1976; **98**: 4400–4404.
32. Arnett EM, Petro C. *J. Am. Chem. Soc.* 1976; **98**: 1468–1471.
33. (a) Uggerud E. *J. Chem. Soc. Perkin. Trans.* 1999; **2**: 1459–1463; (b) Uggerud E. *Chem. Eur. J.* 2006; **12**: 1127–1136.
34. Vlasov VM, Os'kina IA. *Russ. J. Org. Chem.* 2002; **38**: 1705–1718.
35. Gronert S. *Chem. Rev.* 2001; **101**: 329–360.
36. Parr RG, Yang W. *Density Functional Theory of Atoms and Molecules*. Oxford Science Publications: New York, 1989.
37. Malone JG. *J. Chem. Phys.* 1933; **1**: 197–199.
38. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Montgomery JA, Jr., Vreven T, Kudin KN, Burant JC, Millam JM, Iyengar SS, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani G, Rega N, Petersson GA, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox JE, Hratchian HP, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Ayala PY, Morokuma K, Voth GA, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain MC, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Burant JC, Clifford S, Ayala PY, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Gonzalez C, Pople JA. *Gaussian 03, Revision C.02*, Gaussian, Inc., Wallingford CT, 2004.
39. Maksić ZB, Kovačević B. *J. Phys. Chem. A.* 1998; **102**: 7324–7328.
40. Swart M, Bickelhaupt MF. *J. Chem. Theory Comput.* 2006; **2**: 281–287.
41. Hillebrand C, Klessinger M, Eckert-Maksić M, Maksić ZB. *J. Phys. Chem.* 1996; **100**: 9698–9702.

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