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PAPER

The nucleophilicity *N* index in organic chemistry†

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The nucleophilicity *N* index (*J. Org. Chem.* **2008**, *73*, 4615), the inverse of the electrophilicity, $\frac{1}{\omega}$, and the recently proposed inverse of the electrodonating power, $\frac{1}{\omega^-}$, (*J. Org. Chem.* **2010**, *75*, 4957) have been checked toward (i) a series of single 5-substituted indoles for which rate constants are available, (ii) a series of *para*-substituted phenols, and for (iii) a series of 2,5-disubstituted bicyclic[2.2.1]hepta-2,5-dienes which display concurrently electrophilic and nucleophilic behaviors. While all considered indices account well for the nucleophilic behavior of organic molecules having a single substitution, the nucleophilicity *N* index works better for more complex molecules. Unlike, the inverse of the electrophilicity, $\frac{1}{\omega}$, ($R^2 = 0.71$), and the inverse of the electrodonating power, $\frac{1}{\omega^-}$ ($R^2 = 0.83$), a very good correlation of the nucleophilicity *N* index of twelve 2-substituted-6-methoxy-bicyclic[2.2.1]hepta-2,5-dienes *versus* the activation energy associated with the nucleophilic attack on 1,1-dicyanoethylene is found ($R^2 = 0.99$). This comparative study allows to assert that the nucleophilicity *N* index is a measure of the nucleophilicity of complex organic molecules displaying concurrently electrophilic and nucleophilic behaviors.

Introduction

Regarding the electronic behavior of breaking- and forming-bonds along a chemical reaction, organic reactions can be classified as non-polar and polar reactions. While non-polar reactions take place through species with some radical character, polar reactions take place through zwitterionic ones. Most organic molecules having polarized functional groups present polar reactivity, which is characterized by nucleophilic/electrophilic interactions. Therefore, it is desirable to have simple models of reactivity indices able to predict the nucleophilic and electrophilic behavior of organic molecules.

Since the introduction of nucleophile and electrophile concepts in the nineteen-thirties,[1] many efforts have been made to construct nucleophilicity/electrophilicity scales. Swain-Scott[2] and Edwards[3] proposed the first nucleophilicity scale through a linear free energy relationship based on rate constants for S_N2 reactions. Nucleophilicity has usually been understood as dependent on several factors. Indeed, Bunnett in 1963 presented a study identifying 17 factors that must to be considered in a quantitative description of nucleophilicity.[4] Electronic factors on the nucleophilic-electrophilic interactions were also emphasized by Pearson *et al.*[5] applying the principle of hard and soft acids and bases (HSAB). Considering this background, Ritchie's *constant selectivity relationship* attracted much attention because it was determined that a particular nucleophilic system can be characterized by only one constant parameter, N_+, which is independent of the nature of the electrophile.[6] Even though both nucleophilicity and electrophilicity are known to depend on several factors, it is desirable to establish absolute nucleophilicity and electrophilicity scales.

In that sense, Mayr and Patz proposed nucleophilicity/electrophilicity scales[7] based on the rate constants for a large list of nucleophile/electrophile combination reactions. Mayr and co-workers found that the kinetic rate constants of nucleophiles and electrophiles obey the relationship $\log k = s(E + N)$, where electrophiles are characterized by the E parameter and nucleophiles are characterized by two parameters, N and s.[7] On this basis, these authors developed experimental electrophilicity and nucleophilicity scales for a great diversity of organic and organometallic compounds.[8]

Moreover, theoretical quantitative scales have become a desirable tool in the rationalization of the reactivity of chemical species, as well as in the global reactivity, selectivity and their variations induced by field effects arising from chemical substitution or due to conformational changes. Global and local reactivity indices defined within the conceptual Density Functional Theory (DFT)[9] have shown to be powerful means in the study of reactivity

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† Electronic supplementary information (ESI) available: Tables with nucleophilicity (*N*), inverse of the electrophilicity (*N′*) and Roy's nucleophilicity (*N″*) of substituted unsaturated bicyclic systems and alkenes **11–16**. Table with total energies of reagents and TSs associated with the nucleophilic attacks of twelve substituted methoxy bicyclo[2.2.1]hepta-2,5-dienes **10-IIIa-l** on dicyanoethylene. B3LYP/6-31G* computed total energies, unique frequency imaginary, and cartesian coordinates of TSs associated with the nucleophilic attacks of twelve substituted methoxy bicyclo[2.2.1]hepta-2,5-dienes **10-IIIa-l** on dicyanoethylene. See DOI: 10.1039/c1ob05856h

and regioselectivity in polar reactions. In this context, the electrophilicity ω index first studied by Maynard[10] and later revisited on physical basis by Parr *et al.*[11] has shown to be a useful theoretical tool to predict the electrophilic behavior of organic molecules. A comprehensive review and an update on such a descriptor is available in the literature.[12] Chattaraj *et al.*[13] stressed the usefulness of a generalized version of the electrophilicity called *philicity* and which is aimed at the successful description of electrophilic, nucleophilic and radical reactions[12,14] Extensions of such descriptors into the framework of spin-polarized version of DFT have been recently explored.[15] A local electrophilicity or site (k) electrophilicity, ω_k, was defined using the Fukui function for a nucleophilic attack $f^+{}_k$, namely, $\omega_k = \omega f^+{}_k$[16] thereby showing that the maximum electrophilicity power in a molecule will be developed at the site where $f^+{}_k$ displays its maximum value, *i.e.* at the active site (k) of the electrophile.

An exhaustive study on the electrophilicity index of reagents involved in cycloaddition reactions allowed to establish a unique electrophilicity scale.[17] This scale permits the classification of organic molecules as strong, $\omega > 1.5$ eV, moderate, $0.8 < \omega < 1.5$ eV, and marginal electrophiles, $\omega < 0.8$ eV.[17] On the other hand, a good correlation between the inverse of the electrophilicity ($\frac{1}{\omega}$) and the nucleophilicity was found in these electrophilicity scales of organic molecules having a single electron-withdrawing (EW) or electron-releasing (ER) substitution. Thus, molecules located at the bottom of the electrophilicity scale, such as vinyl ethers and vinyl amines, which are classified as marginal electrophiles, correspond with good nucleophiles.[17]

However, when the molecule bears more than one functional group with opposite electronic demand, its nucleophilic character cannot be straightforwardly associated with the inverse of the electrophilicity. This is true for captodative (CD) ethylenes, which can behave as good electrophiles and good nucleophiles (see Chart 1).[18] Therefore, it would be desirable to have a different descriptor available to give further information about the nucleophilicity pattern of reactivity. In this sense, we have recently proposed the simplest approach relating the nucleophilicity with the highest occupied molecular orbital (HOMO) energy obtained within the Kohn–Sham scheme.[19] Hence, we introduced the nucleophilicity N index, namely[18]

$$N = E_{HOMO(Nu)}(eV) - E_{HOMO(TCE)}(eV), \tag{1}$$

where tetracyanoethylene (TCE) was taken as reference. In this scale, the nucleophilicity index for TCE is $N = 0.0$ eV, presenting the lowest HOMO energy in a long series of organic molecules already considered. This choice allowed us conveniently to handle a nucleophilicity scale of positive values. The capacity of the N index describing the nucleophilic behavior of organic molecules was tested in the context of the analysis of the nucleophilic behavior of a series of CD ethylenes.[18] The nucleophilicity N index is related to the solution nucleophilicity index proposed as a first attempt of a quantitative scale from solution phase ionization potentials (I_S); $\omega^- = I_S$.[20]

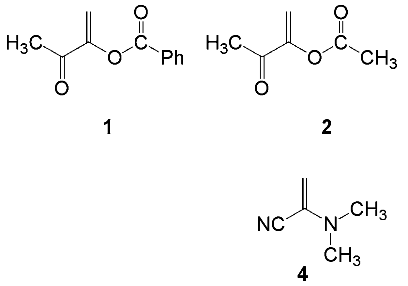


Chart 1

A subsequent study using a broader series of substituted alkenes, substituted aromatic compounds and simple nucleophilic molecules supported and validated the usefulness of the nucleophilicity N index in the nucleophilicity model.[21] This latter study established the classification of organic molecules as strong, $N > 3.00$ eV, moderate, $2.00 \text{ eV} < N < 3.00$ eV, and marginal nucleophiles, $N < 2.00$ eV.[21] It is noteworthy that this global reactivity descriptor has been extended to a condensed-to-atoms nucleophilicity version, *i.e.* N_k index, where k is a given atom of the nucleophilic system.[22] This condensed form has been used to account for the usefulness and predictive character in the director effects on electrophilic aromatic substitutions (EAS).[22]

Recently, Gázquez *et al.*[23] have defined the electroaccepting (eqn (2)), ω^+, and electrodonating (eqn (3)), ω^-, powers as,

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

$$\omega^- = \frac{I^2}{2(I-A)}, \tag{3}$$

where ω^+ is the measure of the propensity of a given system to accept charge and ω^- represents the propensity to donate charge. It is important to note here that a greater ω^+ value corresponds to a better capability of accepting charge, whereas a smaller value of ω^+ of a system makes it a better electron donor.

Then, in order to equalize with the general notion that "more is better", very recently, Roy *et al.*[24] have proposed the nucleophilicity index, N'', as the inverse of the electrodonating ω^- power.[23] In addition, since the nucleophilicity index obtained as $\frac{1}{\omega^-}$ was below 1, the authors have lately defined the nucleophilicity N'' index as[25]

$$N'' = \frac{1}{\omega^-} \times 10. \tag{4}$$

The inverse of the electrophilicity power, denoted as N', the nucleophilicity N index, and the nucleophilicity index N'' were checked towards 69 most commonly used arenes and heteroarenes.[24] Roy *et al.* suggested that the N'' values obtained *via* eqn (4) correlated better with experimental observations than those from eqn (1) and the inverse of the electrophilicity power, N'. However, note that most of these 69 commonly used arenes and heteroarenes have a simple substitution, presenting an expected nucleophilic behavior.[24]

Nevertheless, a preliminary analysis of Roy's nucleophilicity N'' indices obtained for a short series the CD ethylenes studied in ref. 18, which experimentally showed electrophilic and nucleophilic behaviors, evidenced that the nucleophilicity N'' of amino derivatives **4** and **6** are clearly underestimated (see Table 1). Note that the value of the nucleophilicity index of CD ethylene **6**, $N = 3.60$ eV, is higher than those of CD ethylene **1**, $N = 2.12$ eV, and **3**, $N = 2.15$ eV, which is in clear agreement with the stronger ER character of the NMe_2 group than the OCOPh one. This behavior has neither been

Table 1 Electrophilicity (ω) and nucleophilicity (N), inverse of the electrophilicity (N') and Roy's nucleophilicity (N'') values of some captodative ethylenes (see Chart 1)

	A	D	ω (eV)	N (eV)	N' (eV)	N'' (eV)
5	NO	$PhOCH_3$	3.00	3.26	0.33	1.81
6	NO	NMe_2	2.89	3.60	0.35	1.89
1	COMe	OCOPh	1.85	2.12	0.54	2.13
3	COOMe	OCOPh	1.73	2.15	0.58	2.20
2	COMe	OCOMe	1.72	2.15	0.58	2.21
4	CN	NMe_2	0.98	3.46	1.02	2.92
	H	NMe_2	0.21	4.28	4.70	5.45

considered by the inverse of the electrophilicity, N', nor by Roy's nucleophilicity index, N'' (see Table 1). It may be observed from Fig. 1 that there is no correlation between N'' and N values. Note that CD ethylene **4** participates as a good nucleophile in polar [2 + 2] cycloaddition reactions (see Scheme 1).[26]

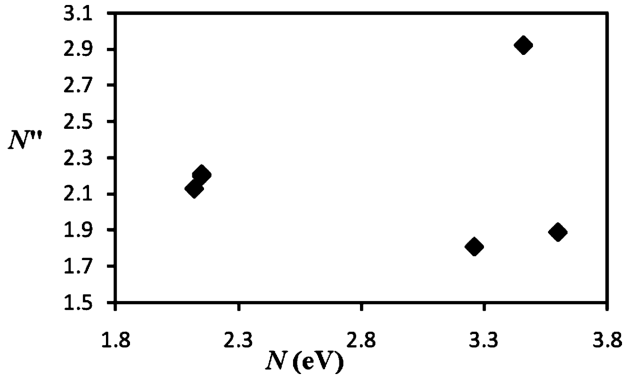
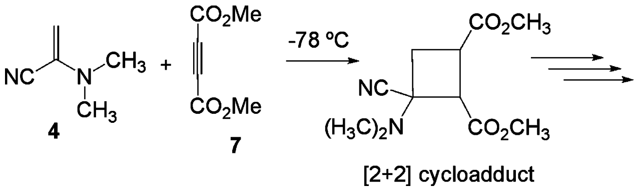


Fig. 1 Comparison between N'' (eqn (4)) and N nucleophilicity index (eqn (1)) for the series of CD ethylenes given in Table 1. See the text for details.



Scheme 1

In view of these preliminary results, we have performed a comparative analysis of the results obtained using the nucleophilicity N index, eqn (1), with those values obtained by the inverse of the electrophilicity power, N', and those obtained by eqn (4), N'. For this purpose, three series of organic molecules have been studied: i) a series of single 5-substituted indoles, for which experimental rate constants,[27] nucleophilicity values[27] and experimental oxidation potentials[28] are available; ii) a series of *para*-substituted phenols studied by Roy *et al.*[20] and iii) a series of bicyclo[2.2.1]hepta-2,5-diene (BCHD) molecules possessing simultaneously both ER and EW substitutions.

Computational methods

All calculations were carried out with the Gaussian 03 suite of programs.[29] DFT calculations were carried out using the B3LYP[30] exchange–correlation functionals, together with the standard 6-31G(d) basis set.[31] The optimizations were carried out using the Berny analytical gradient optimization method.[32] The stationary points were characterized by frequency calculations in order to verify that TSs have one and only one imaginary frequency.

Results and discussion

1. Comparative analysis of the nucleophilicity indices N, N' and N'' with experimental data for a series of 5-substituted indoles 8

To discuss the models shown in the Introduction section concerning the nucleophilicity index, a series of 5-substituted indoles for which experimental data are available was first selected (see Chart 2). Table 2 depicts the N, N' and N'' nucleophilicity values, Ln k for the interaction of these indoles with a series of benzhydryl cations as a set of reference electrophiles,[27] experimental Mayr's nucleophilicity values,[27] and oxidation potentials (E_p) measured by linear sweep voltammetry (LSV).[28]

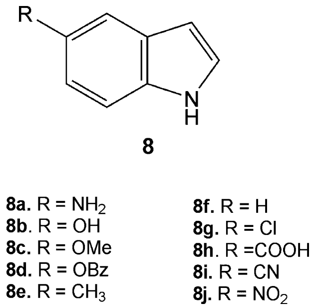


Chart 2

It can be seen that the N values obtained using eqn (1) correlate well with the corresponding experimental Mayr's rate constants[27] (Fig. 2, diamond series), for which the R^2 regression coefficient is 0.98. On the other hand, the inverse of the electrophilicity powers, N', Roy's nucleophilicity values, N'', also correlate well with Ln k (R^2 = 0.98, triangle series and R^2 = 0.95, asterisk series). If the comparison is now done between the values obtained using three nucleophilicity models with Mayr's nucleophilicity[27] (see Fig. 3), the regression coefficient remains unchanged in three graphs (R^2 = 0.98, R^2 = 0.97 and R^2 = 0.95, respectively). A final comparison of nucleophilicity N values with that the inverse of the electrophilicity powers, N', and Roy's N'' values, shows a reasonable agreement (R^2 = 0.93 and R^2 = 0.94, respectively, see Fig. 4). Thus, it is expected that any model of nucleophilicity can be used to represent this property when the molecule has a simple substitution.

Table 2 Nucleophilicity (N), inverse of the electrophilicity power (N'), Roy's nucleophilicity (N'') values, experimental Mayr's nucleophilicity [27],Ln k [27] and the peak oxidation potentials (E_p in V) [28] for a series of 5-substituted indoles **8a–j** (see Chart 2)

	N (eV)	N' (eV)	N'' (eV)	N (exp)	Ln k	E_p(V)
8a	4.29	1.70	4.18	7.22	5.46	0.56
8b	3.93	1.44	3.77	6.44	3.5	0.74
8c	3.91	1.51	3.82	6.22	3.04	0.83
8d	4.02	1.45	3.82	—	—	0.90
8e	3.77	1.49	3.74	6.00	2.37	0.94
8f	3.72	1.43	3.66	5.55	0.83	1.10
8g	3.39	1.10	3.21	4.42	−1.61	1.30
8h	3.33	0.90	2.96	3.97	−2.75	1.45
8i	3.03	0.83	2.78	2.83	−5.65	1.64
8j	2.93	0.51	2.20	—	—	1.70

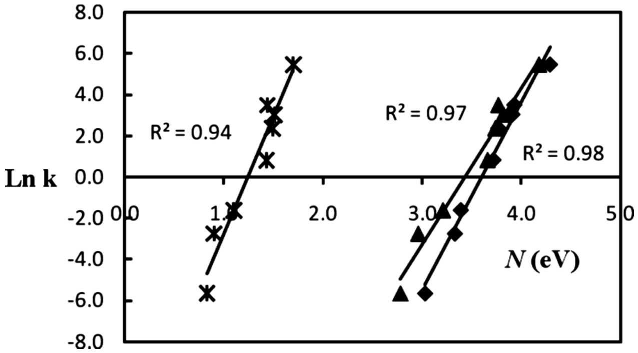


Fig. 2 Plot of experimental Ln k and the calculated gas-phase nucleophilicity index (in eV) for a series of 5-substituted indoles obtained from eqn (1) (diamond series), from the inverse of electrophilicity (asterisk series) and from eqn (4) (triangle series).

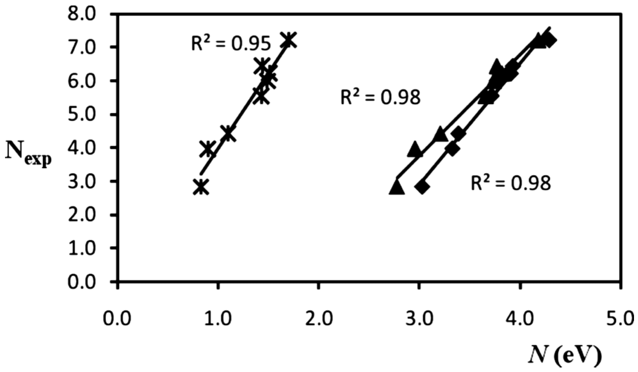


Fig. 3 Plot of experimental nucleophilicity values (N_{exp}) and the calculated gas-phase nucleophilicity index (in eV) for a series of 5-substituted indoles obtained from eqn (1) (diamond series), from the inverse of electrophilicity (asterisk series) and from eqn (4) (triangle series).

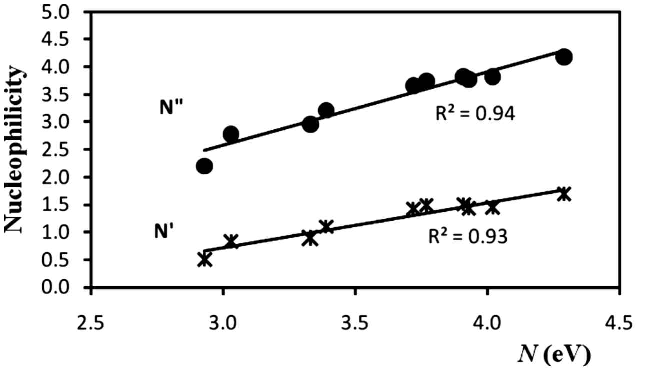


Fig. 4 Relationship between calculated gas-phase nucleophilicity N values (in eV) and those obtained from eqn (4) (circle series) and from the inverse of electrophilicity (asterisk series).

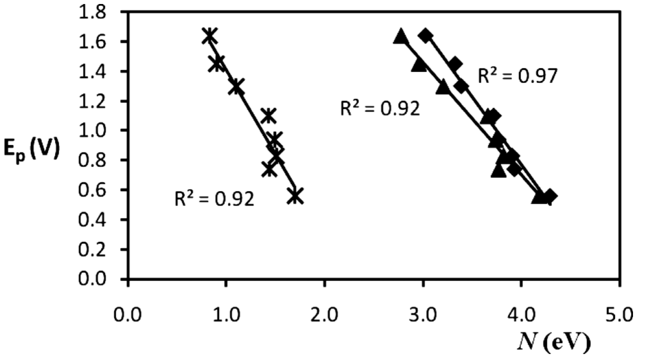


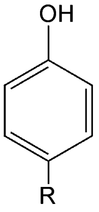
Fig. 5 Plot of experimental redox potential (Ep) in Volts and the calculated gas-phase nucleophilicity index (in eV) for a series of 5-substituted indoles obtained from eqn (1) (diamond series), from the inverse of electrophilicity (asterisk series) and from eqn (4) (triangle series).

On the other hand, it can be observed from Fig. 5, that the three nucleophilicity models correlate well with experimentally available E_p values[28] (R^2 = 0.97 for the N nucleophilicity model, $R^2 = 0.92$ for the inverse of the electrophilicity model, and $R^2 = 0.92$ for Roy's nucleophilicity model). Hence, it is worth emphasizing here that when a single effect is present in a molecule, the three nucleophilicity models provide a suitable response of such an effect. However, the nucleophilicity N index effectively reflects this property when a second substituent group with inverse electronic demand is introduced into a molecule, as it was shown in the CD ethylene series.[18] Yet, the inverse of the electrophilicity powers, N' and Roy's N'' indices may not be suitable to discuss nucleophilicity with regard to these complex organic molecules, as we will show hereafter.

2. Comparative analysis of the nucleophilicity indices N, N' *and* N'' for a series of *para*-substituted phenols 9

Recently, we have shown that the nucleophilicity N index is an effective tool to analyze the reactivity of the monosubstituted aromatic compounds towards EAS reactions.[22] The presence of a second group in the aromatic system can change the EAS reactivity to modify the nucleophilic character of the corresponding compound. Thus, it is expected that the presence of a second ER group, *e.g.* NH_2, OMe or Me, activates the aromatic system towards an EAS reaction, whereas the presence of a second EW group, *e.g.* NO_2, CN or Cl, deactivates it.

Monosubstituted phenols are an important group of compounds with EAS reactivity. In order to prove the response of these nucleophilicity indices towards a second ER or EW substitution on the aromatic ring, seven *para*-substituted phenols were studied (see Chart 3). The nucleophilicity N, N' and N'' values of the *para*-substituted phenols are given in Table 3.



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9a. R = NH_2
9b. R = OMe
9c. R = OH
9d. R = Me
9e. R = Cl
9f. R = CN
9j. R = NO_2

Chart 3

The nucleophilicity index of phenol is $N = 3.16$ eV (see ref. 22). As expected, the presence of a second ER group on the aromatic ring increases the nucleophilicity of the corresponding monosubstituted phenol, whereas the inclusion of an EW group decreases it. The decrease of the nucleophilic character of the *para*-substituted phenol series, given by the nucleophilicity N index, is consistent with the expected decrease of the ER character of the substituent R (NH_2 > OMe > OH > Me) and the increase of the EW character of the substituent R (Cl < CN < NO_2).

A similar trend is observed analyzing the nucleophilicity N' and N'' indices given in Table 3. In order to compare the results obtained using the three nucleophilicity models, a graphical representation of the nucleophilicity N' and N'' values *versus* nucleophilicity N values was made (see Fig. 6). Good correlations are also obtained for the N' and N'' models, $R^2 = 0.97$ for N' and $R^2 = 0.98$ for N'', indicating that the three models are able to establish the nucleophilic behavior of the *para*-substituted phenols.

Interestingly, although the disubstituted benzenes **9e–g** have two groups of opposite electron-demand, their electronic effects are balanced, and consequently, the increase of the EW character of the second group forces the decrease of the nucleophilic character of phenol. Therefore, the combining effect of the two groups on benzene is well established by the three-nucleophilicity models.

Table 3 Nucleophilicity (N), inverse of the electrodonating power (N'), Roy's nucleophilicity (N'') of *para*-substituted phenols **9a–g** (see Chart 3)

	N (eV)	N' (eV)	N' (eV)
9a	4.13	1.73	4.11
9b	3.78	1.50	3.75
9c	3.70	1.42	3.64
9d	3.38	1.45	3.53
9e	3.03	1.08	3.06
9f	2.52	0.75	2.53
9g	2.20	0.45	1.96

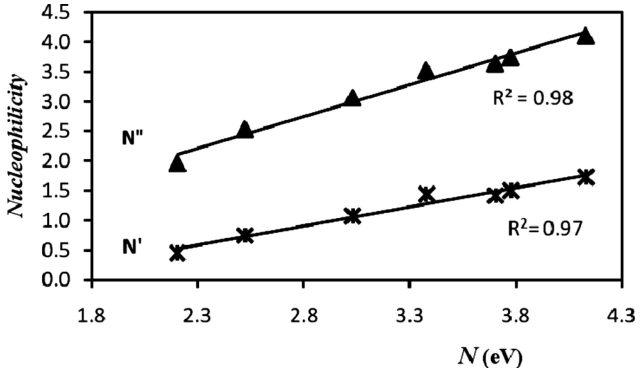

Fig. 6 Relationship between calculated gas-phase nucleophilicity N values (in eV) for a series of *para*-substituted phenols obtained from eqn (4) (triangle series) and those obtained from the inverse of electrophilicity (asterisk series). See the text for details.

3. Comparative analysis of the nucleophilicity indices N, N' and N'' for a series of 2,5-disubstituted bicyclic[2.2.1]hepta-2,5-dienes displaying both electrophilic and nucleophilic behaviors

In the previous sections, we have shown that the inverse of the electrophilicity powers, N', and Roy's nucleophilicity index, N'', for a series of single 5-substituted indoles and monosubstituted phenols correlate well with the proposed nucleophilicity N index. The three models account for the nucleophilic behavior of molecules with an increased ER substitution, CH_3 < OH < OMe < NH_2, or with an increased electron-withdrawing substitution NO_2 < CHO < CN < Cl. However, as anticipated in the Introduction, the N' and N'' indices fail in the CD series displaying electrophilic and nucleophilic behaviors. In order to test the feasibility of the three indices to predict the nucleophilicity of complex organic molecules, the corresponding values for a series of sixteen 2,5-disubstituted BCHDs having electrophilic and nucleophilic behavior have been calculated as computational models (see Chart 4).

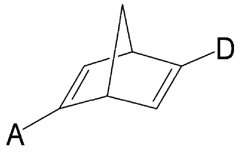

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Chart 4

Bicyclo[2.2.1]hepta-2,5-diene (**11**) has two non-conjugated C–C double bonds. Concurrent substitution of each C–C double bond by an ER and an EW group should transfer electrophilic and nucleophilic behavior to the molecule. Two modes of disubstitution are feasible: 1,5- and 1,6-disubstitution. For this comparative study the former was selected in order to minimize intramolecular electronic interactions. Therefore, four groups of increased EW behavior, CN < COMe < CHO < NO_2, and four groups of increased ER behavior Me < OMe < OH < NH_2, were chosen. Combination of these groups afforded sixteen 1,5-disubstituted BCHDs, which are presented in order of decreasing electrophilicity ω values in Table 4. Nitro derivatives are located at the top of

Table 4 Electrophilicity (*ω*), nucleophilicity (*N*), inverse of the electrodonating power (*N′*), Roy's nucleophilicity (*N″*) of substituted unsaturated bicyclic systems **10**

	A	D	*ω* (eV)	*N* (eV)	*N′* (eV)	*N″* (eV)
10-IIa	NO_2	OH	2.47	3.06	0.40	1.98
10-IIIa	NO_2	OMe	2.41	3.13	0.42	2.02
10-IVa	NO_2	Me	2.34	2.57	0.43	1.97
10-Ia	NO_2	NH_2	2.27	3.53	0.44	2.15
10-IIIb	CHO	OMe	1.66	3.39	0.60	2.49
10-IIb	CHO	OH	1.65	3.32	0.61	2.48
10-IVb	CHO	Me	1.65	2.92	0.61	2.39
10-IIc	COMe	OH	1.53	3.49	0.65	2.61
10-Ib	CHO	NH_2	1.51	3.81	0.66	2.71
10-IVc	COMe	Me	1.50	3.04	0.67	2.53
10-IId	CN	OH	1.50	3.17	0.67	2.56
10-IIIc	COMe	OMe	1.49	3.52	0.67	2.65
10-IVd	CN	Me	1.47	2.74	0.68	2.48
10-IIId	CN	OMe	1.45	3.26	0.69	2.62
10-Ic	COMe	NH_2	1.35	3.93	0.74	2.89
10-Id	CN	NH_2	1.30	3.63	0.77	2.85

Table 4 in clear agreement with the high EW character of the NO_2 group, while aldehydes are positioned at the top of carbonyl derivatives. Finally, methyl ketones and cyan derivatives are mixed at the bottom of the table.

An expected order is found when ordering this series by decreasing nucleophilicity *N* values (see columns 1, 2 and 3 in Table S1 in ESI†). Amino compounds, with nucleophilicity *N* values in the $3.53 < N < 3.93$ eV range, are located at the top of the table. They are classified as strong nucleophiles within the nucleophilic scale.[21] On the other hand, the methyl compounds, with nucleophilicity values lower than 3.04 eV, are located at the bottom of the scale. They are classified as moderate nucleophiles within the nucleophilic scale. In the middle of the table, hydroxy and methoxy compounds are mixed as a consequence of their closer ER character.

On the other hand, when the BCHD series is ordered by *N′* or *N″* indices, poor correlations are found (see columns 4 to 9 in Table S1 in the ESI†). Note that in this case the order of the BCHD series is controlled by the EW groups; the molecules present an inverse order than that obtained in Table 4, ordered by the electrophilicity *ω* index.

A plot of the inverse of the electrophilicity power, *N′*, and Roy's nucleophilicity index, *N″*, *versus* the nucleophilicity *N* index of the sixteen disubstituted BCHDs is shown in Fig. 7a and b. Unlike for 5-substituted indoles and *para*-substituted phenols, a poor correlation is found, indicating that both models fail to predict the nucleophilic behavior of these molecules.

In order to test these indices with respect to kinetic data, we calculated the activation energy barriers associated with the nucleophilic attacks of twelve 2-substituted-5-methoxy BCHDs of increased electrophilicity towards the electron-deficient 1,2-dicyanoethylene, used to test the nucleophilic behavior of organic molecules.[18,33] The transition structures associated with the nucleophilic attacks of the nucleophilically activated 6 position of the twelve BCHDs on the β conjugate position of 1,2-dicyanoethylene were optimized at the B3LYP/6-31G* level (see Chart 5). The geometries and the cartesian coordinates of the TSs are given in the ESI.† The nucleophilicity *N* index, inverse of the electrophilicity power, *N′*, and Roy's nucleophilicity index, *N″*, of the twelve bicyclic systems and the corresponding activation energy barriers are given in Table 5. These data are presented in order of increased nucleophilicity *N* values.

BCHD **11** has a high nucleophilicity value, $N = 3.22$ eV, compared with cyclohexene, $N = 2.77$ eV (see Table S2 in the ESI†). Two structural behaviors of BCHD **11** may be responsible for the increase of nucleophilicity: i) the strain associated with the bicyclic system, and ii) the proximity of the two C–C double bonds. On the other hand, bicyclo[2.2.1]heptene has a nucleophilicity

Table 5 Activation energies ($\Delta E^{\neq}$) associated with the nucleophilic attracts of substituted insaturated bicyclic systems to dicyanoethylene, and nucleophilicity (*N*), inverse of the electrodonating power (*N′*), Roy's nucleophilicity (*N″*) values of the twelve methoxy bicyclic systems

	A	$\Delta E^{\neq}$ (kcal mol^{-1})	*N* (eV)	*N′* (eV)	*N″* (eV)
10-IIIe	$CHO\text{-}BF_3$	10.61	2.70	0.30	1.64
10-IIIf	$CHO\text{-}BH_3$	9.79	2.90	0.34	1.78
10-IIIa	NO_2	8.54	3.13	0.42	2.02
10-IIIg	$COCF_3$	7.98	3.22	0.46	2.14
10-IIId	CN	8.12	3.26	0.69	2.62
10-IIIh	CFO	7.82	3.26	0.57	2.40
10-IIIb	CHO	6.93	3.39	0.60	2.49
10-IIIi	CF3	6.74	3.45	1.03	3.15
10-IIIc	COMe	6.21	3.52	0.67	2.65
10-IIIj	COOMe	5.95	3.56	0.77	2.84
10-IIIk	$CONH_2$	5.63	3.56	0.83	2.93
10-IIIl	H	4.26	3.87	1.66	3.92

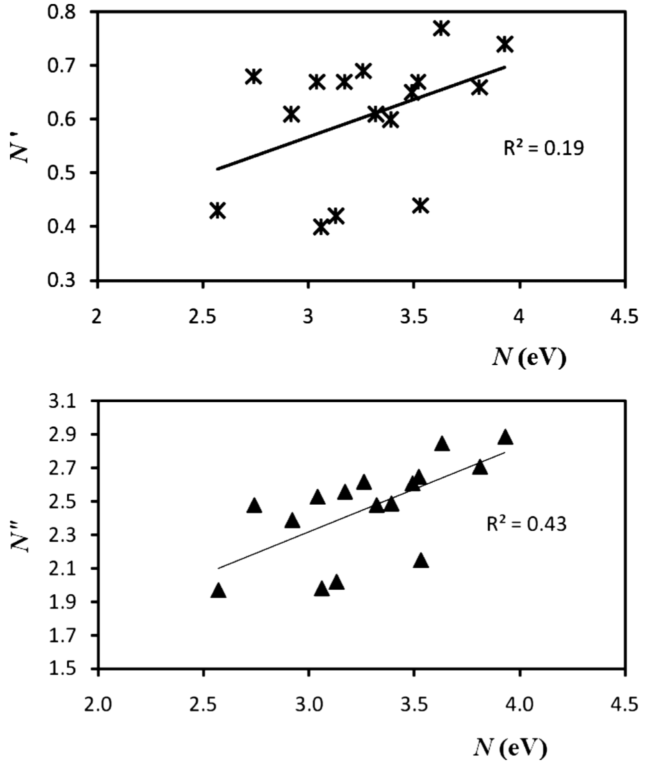
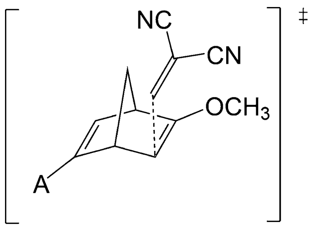


Fig. 7 **(a)** Relationship between calculated gas-phase nucleophilicity *N* values (in eV) for a series of substituted bicyclics with nucleophilicity values obtained from the inverse of electrophilicity. See the text for details. **(b)** Relationship between calculated gas-phase nucleophilicity *N* values (in eV) for a series of substituted bicyclics with nucleophilicity values obtained from eqn (4). See the text for details.



TS-10-III

Chart 5

index of $N = 2.84$ eV, which is slightly higher than that for cyclohexene. Therefore, the electronic repulsion between both π systems is the responsible factor for the high nucleophilic character of these BCHDs. On the other hand, compound **10-IIIl** has a nucleophilicity value of $N = 3.87$ eV, which is larger than that for BCHD **11** and for methyl vinyl ether, $N = 3.17$ eV. 2-Substituted BCHDs present a nucleophilicity value in the $2.7 < N < 3.5$ eV range. As expected, the nucleophilicity *N* index decreases with the increase of the EW character of the 2-substituent. Thus, while Lewis acid - aldehyde complexes **10-IIIe** and **10-IIIf** are located at the top of the series, the two carboxylate derivatives complexes **10-IIIj** and **10-IIIk** are at the bottom. Interestingly and correctly, on going to the bottom of the table the activation energy barrier decreases with the increase of the nucleophilicity *N* power (see Table 5).

When the relative energies associated with the nucleophilic attacks are plotted *versus* the nucleophilicity *N* index (see Fig. 8a), a very good correlation is found ($R^2 = 0.99$), *i.e.* the nucleophilicity *N* index computed at the ground state of the molecule is able to predict the activation energies involved in these polar nucleophilic/electrophilic interactions. It is interesting to note that the nucleophilicity *N* index accounts for a global property of the molecule that includes intramolecular electronic interactions owing to the presence of two C–C double bonds substituted with opposite electron-demanding groups and the strain associated with the bicyclic system. As demonstrated, both

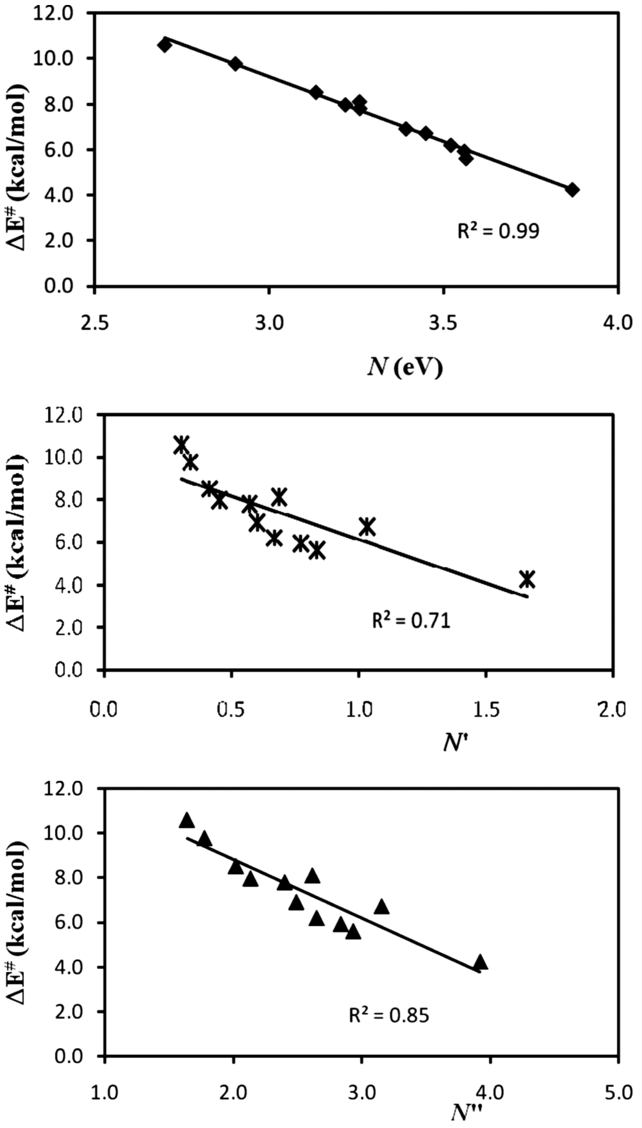


Fig. 8 **(a)** Plot of the activation energies ($\Delta E^{\#}$, in kcal mol^{-1}) associated with the nucleophilic attacks of twelve substituted methoxy bicyclo[2.2.1]hepta-2,5-dienes **10-IIIa-l** on dicyanoethylene *versus* the nucleophilicity *N* index. **(b)** Plot of the activation energies ($\Delta E^{\#}$, in kcal mol^{-1}) associated with the nucleophilic attacks of twelve substituted methoxy bicyclo[2.2.1]hepta-2,5-dienes **10-IIIa-l** on dicyanoethylene *versus* the nucleophilicity *N'* index. **(c)** Plot of the activation energies ($\Delta E^{\#}$, in kcal mol^{-1}) associated with the nucleophilic attacks of twelve substituted methoxy bicyclo[2.2.1]hepta-2,5-dienes **10-IIIa-l** on dicyanoethylene *versus* the nucleophilicity *N''* index.

behaviors should be evidenced in the reactivity of these molecules in polar reactions,

Finally, when the relative activation energies are plotted *versus* the inverse of the electrophilicity power, N', and Roy's nucleophilicity index, N'', (see Fig. 8b and 8c), poor correlations are found ($R^2 = 0.71$ and $R^2 = 0.85$ respectively), showing a lower ability of these indices to predict the nucleophilic behavior of complex organic molecules. It is interesting to note that although these deviations are not too large, the inability to display the nucleophilicity of these molecules correctly may produce changes in the relative positions on a nucleophilicity scale (see Table S1 in the ESI†).

Conclusions

The nucleophilicity N index, the inverse of the electrophilicity power, N', and Roy's nucleophilicity index, N'', for a series of 5-substituted indoles, *para*-substituted phenols and 2,5-disubstituted bicyclic[2.2.1]hepta-2,5-dienes displaying electrophilic and nucleophilic behaviors have been correlated *versus* kinetic data available. For 5-substituted indoles containing a single substitution and *para*-substituted phenols, the three indices show a very good correlation with regard to experimental data. However, for more complex molecules having C–C double bonds substituted by EW and ER groups, which transfer electrophilic/nucleophilic behavior to the molecule, different results are obtained. While the activation energies associated with the nucleophilic attack of these species on 1,1-dicyanoethylene present a very good correlation *versus* the nucleophilicity N index, the inverse of the electrophilicity power, N', and Roy's nucleophilicity index, N'', manifest inferior correlations with the global reactivity expected. This comparative study allows to assert that the nucleophilicity N index is a measure of the nucleophilicity of simple molecules and complex organic molecules displaying concurrently electrophilic and nucleophilic behaviors.

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