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A comparison between theoretical and experimental models of electrophilicity and nucleophilicity

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ABSTRACT

Four different theoretical models of electrophilicity and nucleophilicity has been discussed in the light of experimental available evidence for a series of 20 benzhydrylium ions taken as reference electrophilic systems and 16 primary and secondary amines as nucleophilic systems. It is shown that the theoretical scales are linearly related to the well-known experimental ones based on the electrophilicity (E) and nucleophilicity (N and s) parameters derived by Mayr from the rate constants $k_{20\ ^\circ C}$ associated to general electrophile–nucleophile combinations, $\log k_{20\ ^\circ C} = s(N + E)$.

1. Introduction

Electrophilicity and *nucleophilicity* are chemical concepts of great usefulness in the rationalization of electronic aspects of reactivity, selectivity, substituent effects, and solvent effects [1–10]. Despite these two quantities are known to depend on several factors, including the nature of substrate, the reagent, solvent, etc, that preclude the existence of unique and absolute indexes that could be applied to any chemistry situation [11–14], *relative* scales intended to categorize such reactivities have been proposed to be defined in terms of free energy relationships [11,15]. In this sense, and within an experimental perspective, Mayr et al. have emphasized that [7,9,15–31] benzhydrylium ions and quinone methides can be used as reference electrophiles [29,32,33] for characterizing a large variety of π-nucleophiles (e.g., alkenes, arenes, enol ethers, ketene acetals, enamines, allyl compounds, transition metal complexes, diazoalkanes, and delocalized carbanions), n-nucleophiles (e.g., amines, alcohols, alkoxides, phosphanes, inorganic anions, and pyridines), and σ-nucleophiles (e.g., hydrides) [19,20,22,31,34–40]. In their approximation, the rate constants have been correlated through,

$$\log k_{20^\circ C} = s(N + E) \tag{1}$$

where $k_{20^\circ C}$ is the second-order rate constant in units of $M^{-1}\ s^{-1}$, s is a nucleophile specific slope parameter, N is the nucleophilicity parameter, and E is the electrophilicity parameter. For a set of reference electrophiles, Eq. (1) defines nucleophilicity N values as the intercept of the correlation line with the abscissa, and the slopes of these correlations yield the s parameters. This last number can be indeed neglected in qualitative considerations [41]. A comprehensive list of nucleophiles and electrophiles in terms of their N and E parameters is available spanning several hundreds of order of magnitude in terms of the associated experimental rate constants. An internet database containing a compilation of published reactivity parameters has been also made available [42]. It has been shown that the derived nucleophilicity orders also holds for reactions of these nucleophiles with non-charged electrophiles such as quinone methides [43].

Several theoretical efforts have been devoted to get qualitative and quantitative insights rationalizing these central concepts. Within this perspective and from a theoretical point of view, it has been emphasized that density functional theory (DFT) provides a powerful framework for the development and exploration of a chemical reactivity theory [44–55]. The electrophilicity index ω defined by Parr et al. [56] in terms of the electronic chemical potential and the chemical hardness [44], has shown to be a fruitful tool in the light of such proposal (see for instance Refs. [57–67] for recent examples). A review covering several application and extensions of this density functional theory descriptor is also available [68]. Extensions of such kind of descriptors into the framework of spin-polarized version of DFT have been also recently explored [69–76]. Within the interests of the current work we would like to emphasize that the electrophilicity index ω have been found linearly related to Mayr's electrophilicity E parameters for a series of reference benzhydryl cations [77]. The ω index has recently been successfully applied to quantitatively categorize in a simple scale both global [78] and local [79] reactivities of diene

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and dienophile reagents participating in DA reactions, dipole and dipolarophile pairs in 1,3-dipolar cycloadditions [80] and cycloaddition reactions of substituted *captodative* ethylenes [81,82]. It has also shown that ω is an important index to get further understanding on the reactivity of singlet carbenes and its electrophilic pattern [83]. Within a continuum model of solvent effects, it has been shown that the electrophilicity power of neutral electrophilic ligands becomes enhanced but it is attenuated in charged and ionic electrophiles [84]. There have also been many important attempts to define a theoretical quantity as an intrinsic nucleophilic index. Roy et al. [85] have proposed the direct use of local DFT reactivity descriptors such as hardness and softness [44] to predict both intramolecular an intermolecular nucleophilic attacks on carbonyl compounds. In a more general strategy, the (local) philicity concept introduced by Chattaraj et al. [66] emphasizes the idea of a unique generalized index, which can be applied to electrophilic, nucleophilic, and radical reactions [63,86] by projecting the global electrophilicity [56] through the electronic Fukui functions [44]. Dual and multiphilic descriptors have also been introduced describing the reactivity and selectivity [58,87–90]. These descriptors are intended to simultaneously give the electrophilicity and nucleophilicity proclivities of a given molecular system. A nucleophilicity index derived from a perturbation model for the interaction between a nucleophile and a positive test charge was presented [91]. Such model was validated for a series of neutral nucleophiles with a known nucleophilic pattern [91]. The use of point charges to study nucleophilicity has previously received a detailed attention within the context of energy changes in a perturbative framework [47,51,92–95]. In addition, nucleophilicity and electrophilicity of active radicals have been discussed using a variety of models proposed in the literature [96]. Recently, some of us have proposed an empirical nucleophilicity index for soft–soft interactions [97]. Such index is written in terms of frontier molecular orbitals, and it has been successfully validated against experimentally available kinetic data for amines, diimines, anilines, alcohols, ethers, alkenes, and π- and n-nucleophiles [97–99]. The appealing linear correlation found between the global electrophilicity and the nucleophilicity scales suggests that these concepts are indeed inversely related along related series of simple substituted systems [96]. A simple and useful model of nucleophilicity has demonstrated its usefulness for categorizing cycloadduct reagents [81,100]. The local extension of such nucleophilicity index was recently explored in the context of predicting substituent director effects in electrophilic aromatic substitution reactions [101].

Following our ongoing interest in to gain more insights into and to extend the range of applicability of theoretical models devoted to rationalize and quantify the electrophilicity and nucleophilicity concepts [77–82,97–101], in this work we further explore the theoretical basis defining electrophilicity and nucleophilicity quantities within the density functional theory framework. Our aim is to test the suitability of simple models (as presented in Section 2) of electrophilicity and nucleophilicity that arises from a variational perturbative approximation of a given system in interaction with an appropriate donor or acceptor environment. We mostly focus on the performance of the simplest approximations to these models in comparison to the well-established experimental Mayr's parameters [7,15–17,21,29–33] of electrophilicity and nucleophilicity.

2. Theory

Let us start by examining the recent discussion presented very recently by Gázquez et al. [102] within the conceptual framework provided by DFT [45,56,68]. It has been emphasized that the development of theoretical models for intrinsic electrophilicity and nucleophilicity powers can be derived from the examination of energy changes associated to a system in interaction with a "bath" simulating a given chemical environment. At first glance the bath can be considered as a reservoir for donating/accepting a finite number of electrons to/from the system. Thus, at global level this interaction can be considered to produce a net charge transfer, ΔN, between the system and the environment, will be modulated by the difference in chemical potentials between the bath and the system, $\mu_{bath} < 0$ and $\mu^{\pm} < 0$, respectively. Given the discontinuity of the energy with respect to the number of electrons, and considering that the responses of a system to accept/donate charge should be different, Gázquez et al. [102] have stressed that both the electroaccepting (e.g., intrinsic electrophilicity) and electrodonating (e.g., intrinsic nucleophilicity) powers of a given species can be defined by minimizing the change in the grand-potential energy $\Delta\Omega^{\pm} = \Delta E^{\pm} - \mu_{bath}\Delta N$ with respect to this amount of charge transfer, ΔN. Hence, such optimum transferred charge making stationary the grand canonical potential changes is,

$$(\Delta N)^{*} = \frac{\mu_{bath} - \mu^{\pm}}{\eta^{\pm}}. \tag{2}$$

This expression emphasizes that under the validity associated to such simple system–environment interaction, the difference in the chemical potentials *between the bath and the system* is the driven force for such charge transfer process. The system's energy change, ΔE, consequently is given by,

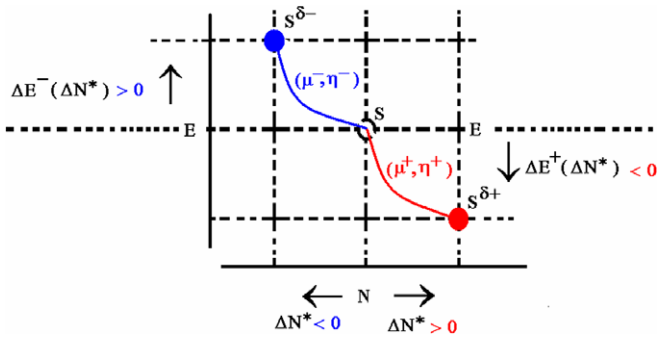
$$\Delta E^{\pm}(\Delta N^{*}) = \frac{\mu_{bath}^{2} - (\mu^{\pm})^{2}}{2\eta^{\pm}}. \tag{3}$$

Eq. (3) say implies that this energetic change is negative (e.g., $\Delta E^{+} < 0$) for a process where the system acts as an *electrophile* (i.e., by accepting charge from the bath, $\Delta N^{*} > 0$), and it is positive (e.g., $\Delta E^{-} > 0$) when the system acts as a *nucleophile* (i.e., donating charge to the bath, $\Delta N^{*} < 0$) as pictorially represented in Scheme 1. Note also that Eq. (3) incorporates the explicit dependence of the system's energy change in relation to the reaction partner, intrinsically represented at global level in terms of the bath's chemical potential. Note also in this point that Eqs. (2) and (3) are associated to a zero hardness chemical hardness, e.g., there is not resistance from the bath to charge transfer. Hence, electroaccepting/electrodonating powers have been [102] associated to the *intrinsic* system's contribution to its energy change,

$$\omega^{\pm} \equiv \frac{(\mu^{\pm})^{2}}{2\eta^{\pm}}. \tag{4}$$

The electrophilicity index first proposed by Parr et al. [56],

$$\omega \equiv \frac{\mu^{2}}{2\eta} = \frac{1}{8}\frac{(I+A)^{2}}{(I-A)} \quad \text{(Model I)} \tag{5}$$



Scheme 1. The system's chemical potential and hardness quantities are negative and positively valued (e.g., $\mu^{\pm} < 0$, $\eta^{\pm} > 0$) for both the process of charge accepting and charge donation. The electrophilic systems' response (i.e., $\Delta N^{*} < 0$), raises its energy $\Delta E^{-} > 0$, whereas the nucleophilic one (i.e., $\Delta N^{*} > 0$), lowers it $\Delta E^{+} < 0$.