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Empirical scale of nucleophilicity for substituted pyridines

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Abstract

Two classical tools, the intermolecular stretching force constants of H-bonded complexes and the molecular electrostatic potential are used to propose a nucleophilicity index evaluated for a series of pyridines. The model is validated against kinetic data recorded for the aminolysis of *S*-methyl 2,4-dinitrophenyl thiocarbonate.

1. Introduction

Since the introduction of the electrophilicity and nucleophilicity concepts to describe the electron-deficient (electrophile) and electron-rich (nucleophile) species [1,2], respectively; there has been a growing interest in classifying atoms and molecules within empirical scales of electrophilicity and nucleophilicity [3–8]. The availability of experimental scales of electrophilicity/nucleophilicity provides useful clues for the rationalization of chemical reactivity. They provide for instance quantitative criteria to decide whether or not a given electrophile–nucleophile combination reaction will take place [6,7]. On the other hand, theoretical scales of electrophilicity/nucleophilicity [8,9] are highly desirable, as they can be used to rationalize the mechanistic aspects of a chemical reaction, intermolecular and intramolecular selectivity, and their variations induced by chemical substitution, solvation and other field effects [7]. While the electrophilicity concept has been variationally defined as the stabilization in energy when the electron acceptor binds an additional electronic charge from an environment viewed as a sea of electrons [10], the quantitative definition of a theoretical nucleophilicity index is more difficult. The reason lies in the fact that when atomic or molecular systems lose electronic charge their total energy increases, so that the curvature of the total energy versus the number of electrons plot is of opposite sign, therefore a variational calculation such as the one introduced by Parr et al. to define the electrophilicity index no longer applies.

Experimental attempts to define nucleophilicity numbers for neutral and charged electron donors have been reported [5,11–15]. The major efforts have been devoted to define universal kinetic scales of nucleophilicity, incorporating thermodynamics (pK_a), polarizability values [12,13], and empirical reactivity rules, like the hard and soft acid and bases (HSAB) principle [14]. More recently, Mayr et al. persuasively argued in favor of universal electrophilicity/nucleophilicity scales based on kinetic data recorded for a series of nucleophiles presenting a wide diversity in structure and bonding properties in different solvents [6,7,16].

Among the different approaches in the literature, two deserve particular attention since they will constitute the starting point of our model. The first one is the spectroscopic scale of nucleophilicity/electrophilicity proposed by Legon and Millen [3,4]. It is based on the hypothesis that the intermolecular stretching force constant obtained from the rotational or vibrational spectra of an interacting B$\cdots$HX complex (X = F, Cl) can be used as a measure of the strength of the interaction between a nucleophile and

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an electrophile, thereby leading to limiting gas phase nucleophilicity/electrophilicity scales. For any B···HX complex at a given geometry, the strength of the interaction will depend on the magnitude of the nucleophilicity at the reaction site of the electron donor and the electrophilicity of the electron accepting end of the HX probe. This observation suggests that the nucleophilicity (N) can be assigned to each nucleophile with respect to the electrophilicity (E) of HX. The strength of the hydrogen bond, as measured by hydrogen-bond stretching force constants (k_σ) for the B···HX complex, is then given by [3,4]:

$$k_\sigma = cNE \tag{1}$$

where c is a constant of proportionality.

On the other hand, the minimum values of the molecular electrostatic potential have been widely proposed as a measure of the basicity of a large number of electron donors. For instance, Politzer et al. demonstrated that the minimum values of the electrostatic potentials could be used to quantitatively correlate the hydrogen bond ability of primary amines, alkyl ethers, and molecules containing double-bonded oxygen [17–19]. These authors have stressed the fact that, on the basis of the electrostatic potential alone, it is very difficult to describe nucleophilicity because the minimum values of the $V(r)$ quantity of any free neutral atom is positive everywhere, increasing to a maximum at the nucleus [18]. Gadre et al. have used the minimum values of the electrostatic potential to account for a series of experimental results, including the regioselectivity observed in the electrophilic additions to alkenes (i.e) the Markoknikov's selectivity rule) [20], patterns of cation binding sites [21] and energetics for molecular systems in several macromolecular conformers [22] or solvation effects on nucleic acid [23]. Other attempts to theoretically define the nucleophilicity concept based on global and local ionization energies have been proposed. Within this model, the best electron donor would be the one that minimizes the destabilization energy resulting upon releasing one electron to the environment [9].

In this work, we present an empirical approach leading to a tentative definition of a nucleophilicity index that combines these two classical tools previously used to identify the nucleophilic sites of Lewis bases. They are on one hand, the Legon and Millen [3,4] spectroscopic model and the classical molecular electrostatic potential (MEP) method [17–19]. The model is validated against kinetic data recorded for the aminolysis of *S*-methyl 2,4-dinitrophenyl thiocarbonate [24].

2. The model and computational details

In our model, we start with the optimization of the minimum energy structure of the B···HX complexes. For simplicity, we have taken X = F. We then performed a frequency calculation that yields the frequency, v_σ, associated with the intermolecular stretching between B and HF. The associated force constants, k_σ, are obtained from the frequency values using the classical expression for the harmonic oscillator, by using a reduced mass $\mu = m_B m_{HF}/m_B + m_{HF}$. The k_σ values alone provide a first appraisal about the nucleophilic strength of the electron donor B, according to the Legon and Millen model [3,4]. We stress here that we are not using Eq. (1) to evaluate the nucleophilicity index, and therefore we do not need to assign any value to the E and c parameters in Eq. (1). We next drop the HF probe and evaluate the electrostatic potential $V_{r(\mathrm{H})}$ at the site where the electrophilic H atom of the probe HF was placed in the minimum energy B···HF structure. This $V_{r(\mathrm{H})}$ is our empirical index of nucleophilicity. Following a prescription given in the literature [25,26], B3LYP/6-31 + G(d, p) calculations were performed to obtain the intermolecular stretching frequencies that yield the k_σ values. The molecular electrostatic potentials at $V_{r(\mathrm{H})}$, were evaluated at the same level of theory. All the calculations were performed using the GAUSSIAN 98 package of programs [27].

3. Results and discussion

Table 1 summarizes the series of eight pyridines for which kinetic data for substitution reactions with thiocarbonate are available from the literature [24]. Included in Table 1 are the electrostatic potential at $r_{(\mathrm{H})}$, the minimum value of the MEP, intermolecular stretching frequencies, the associated force constants, nucleophilic rate coefficients [24] and the available substituent Hammett constants [28,29]. If we take the intermolecular force constants as a first approach to the nucleophilic strength of pyridines, it may be seen that the $V_{r(\mathrm{H})}$ index compares better than $V_{r(\mathrm{min})}$ with respect to k_σ.

Fig. 1 shows the result of the comparison between $V_{r(\mathrm{H})}$ and k_σ for the series of pyridines. Even though the comparison is fairly quantitative (regression coefficient, $R = 0.967$) it seems that both quantities assesses well the electrostatic aspects of the B···HF interaction. This result is not surprising as Legon and Millen already suggested that because the electrostatic contribution is the dominant term in the partition of the hydrogen bonding energy, the local interaction between the net charge on the proton acceptor atom and the net charge on the hydrogen-bonding proton drives the intermolecular interaction [3,4,30–33].

In order to validate the nucleophilicity index $V_{r(\mathrm{H})}$ against experimental kinetic data, we have taken the rate coefficients for the pyridinolysis of *S*-methyl 2,4-dinitrophenyl thiocarbonate, reported by Castro et al. [24] involving **5** out of the **8** pyridines compiled in Table 1. The comparison between the nucleophilicity index $V_{r(\mathrm{H})}$ and the experimental rate coefficients is shown in Fig. 2. It may be seen that the comparison is significant (regression coefficient, $R = 0.998$). Note that the range of variation of the nucleophilic rate coefficients covers approximately four orders of magnitude. The resulting regression equation