Journal of Molecular Structure: THEOCHEM 895 (2009) 86–91

Contents lists available at ScienceDirect

Journal of Molecular Structure: THEOCHEM

journal homepage: www.elsevier.com/locate/theochem

A condensed-to-atom nucleophilicity index. An application to the director effects on the electrophilic aromatic substitutions

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ARTICLE INFO

Article history:
Received 1 October 2008
Received in revised form 13 October 2008
Accepted 14 October 2008
Available online 21 October 2008

Keywords:
Nucleophilicity
Electrophilicity
Electrophilic aromatic substitution
Condensed to atoms nucleophilicity
Density functional theory

ABSTRACT

The local nucleophilicity of simple substituted aromatic systems is shown to be described on a quantitative basis by using a condensed-to-atoms nucleophilicity index. This quantity constitutes an extension of the global nucleophilicity descriptor, N introduced for reagents in cycloaddition reactions and other organic molecules [Journal of Organic Chemistry 73 (2008) 4615–4624; Journal of Molecular Structure (THEOCHEM) 865 (2008) 68–72]. The local projection N_k is performed on the basis of the normalization condition of the Fukui functions. It is shown that such a simple index provides useful clues about the director effects of the substituents on the electrophilic aromatic substitution (EAS) reactions of aromatic compounds. A discussion of the general frame of validity for the condensed-to-atoms model is presented.

1. Introduction

Density-functional theory (DFT) constitutes a fruitful framework for the exploration of a conceptual chemical reactivity theory [1,2]. A complete mathematical hierarchy of global, local and non local descriptors can be properly associated with chemical responses of a molecular system under external perturbations [1,3,4]. Within this approximation to the reactivity problem, the characterization of both global and local patterns of electrophilic and nucleophilic reactivities is central in chemistry [5–16]. Electrophilicity and nucleophilicity constitute measures of the "potentiality" of species reacting as electron acceptor or electron donor, respectively, under definite conditions of reaction, including media, temperature, nature of reagents, etc. [15,17–21]. From a theoretical point of view, and within the conceptual framework of DFT [3], the global aspects (like the chemical potential, μ [3] and hardness, η [3]) of these reactivities are related to thermodynamic stability and reactivity, whereas their local counterparts can be related to the (regio)selectivity of chemical reactivity [3]. The electronic *local* reactivity descriptors play a relevant role in these considerations, being a measuring of the regional (global) susceptibilities of the system to global (local) perturbations [3,12,13,22–25]. The well-known Fukui function $f(\mathbf{r})$ is a key quantity to describe local susceptibilities [3]. $f(\mathbf{r})$ describes how the chemical potential μ changes due to local perturbations in the external potential $v(\mathbf{r})$ at constant number of electrons, N, $f(\mathbf{r}) = [\delta\mu/\delta v(\mathbf{r})]_N$. Equivalently, this quantity can be understood as the response in the electron-density to changes in N at external potential held constant, $f(\mathbf{r}) = [\partial\rho(\mathbf{r})/\partial N]_{v(\mathbf{r})}$ [3].

There has been a growing interest in to classify the species within empirical nucleophilicity/electrophilicity scales [26–28] since the introduction of the nucleophilicity and electrophilicity concepts in the 30s' [29]. While the electrophilicity concept has been variationally associated to the energy stabilization that occurs when a given system acquires an additional electronic charge from a perfectly donor environment, $\omega = \mu^2/2\eta$ [15], an unique and quantitative definition of a theoretical nucleophilicity index has been more difficult to establish. Linear free energy relationships were proposed by Swain and Scott [26], Edwards [27,30] and Ritchie [31] characterizing the nucleophile for three and four parameters including the basicity and redox potentials [27], polarizability [27,30], the HSAB principle [32]. The hydrogen bond stretching force constants for several B–HX dimers [33] and the minimum values of the molecular electrostatic potential (MEP) [34] at the electrophilic site of HX in interaction with a nucleophile [35] has been also proposed to sense the nucleophilicity. On the other hand, Pal et al. [23] introduced a local relative nucleophilicity index by including the local softness for intra and intermolecular reactivity. A local philicity quantity, $\omega_k^{\pm} = \omega f_k^{\pm}$, by using the nucleophilic f_k^- and electrophilic f_k^+ Fukui functions [3] was proposed by Chattaraj et al. [19] to characterize the most electrophilic and nucleophilic site in the study of the regioselectivity [36]. A variational procedure in a grand potential ensemble to sense the

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doi:10.1016/j.theochem.2008.10.014

response of the system to accept or receive charge from or to an environment has also been recently discussed [37]. An empirical nucleophilicity index for soft–soft interactions, which includes explicitly the electronic properties of the electrophiles has been recently introduced [35]. Relative nucleophilicity values have been estimated from the solution phase ionization potentials for neutral and charged electron donors [38]. It is worth to mention that for long time Politzer et al. [39–43] have performed relationships between ionization energy and other molecular properties like the electrostatic potentials [44], Fukui function [45], polarizabilities, [46,47] in a great variety chemical systems [41,42,48,49]. From the experimental point of view, Mayr et al. [50] have proposed successfully nucleophilicity/electrophilicity scales based on the rate constants for wide nucleophile/electrophile combination reactions [50–55].

On the other hand, Domingo's group has studied intensively the mechanism of polar cycloaddition reactions, including Diels-Alder and 1,3-dipolar cycloaddition reactions [17,18,56,57]. The mechanism of these cycloaddition reactions is characterized by a nucleophilic/electrophilic interaction instead of the well established pericyclic concerted model. Regioselectivity of these polar reactions has been well explained identifying the more electrophilic center through the local electrophilicity, ω_k [17] and the nucleophilic center using the nucleophilic Fukui function, f_k^-, for the two reactant molecules [17,18,56,57]. Whereas the ω_k index allows us explain not only regioselectivity but also local activation/deactivation between different molecules, the normalized f_k^- only affords intramolecular reactivity and not relative activation/deactivation between different nucleophiles. Thus, it will be very useful to have a local descriptor able to account for the nucleophilic local activation/deactivation for related molecules.

It is worth to mention that a serious candidate for a theoretical nucleophilicity model has been the inverse of the Parr's electrophilicity ω model [58]. However, in several studies involving organic compounds it was shown that this relationship did not work [18,56,59]. Within this context and seeking simple formalism to know the nucleophilic patterns of reactivity, we have introduced and tested an empirical nucleophilicity index based on the gas-phase ionization potential [59,60]. The model was successfully applied rationalizing the nucleophilicity behavior of captodative ethylenes reacting in cycloaddition reactions [59]. It was also tested on several substituted alkenes, aromatic systems and simple nucleophilic molecules [60].

In this work, we extend the nucleophilicity model at the selectivity regime by using the nucleophilic Fukui function, f_k^-, as a suitable local projector. In order to test this simple approximation, the substituent director effects on the electrophilic aromatic substitution (EAS) reactions of some aromatic compounds are analyzed. It is well known that the rate-determining step of an EAS is the nucleophilic attack to aromatic ring. Therefore, the increase of the electron-density on the aromatic ring increases its nucleophilicity. While the ER substitution increases the reaction rate, the EW substitution decreases it. Not only the reaction rate is modified, but also the ratio of reaction products, *ortho*, *meta* or *para*, depends on the electronic nature of the substituents. In general, while ER groups are *ortho* and *para* directors, EW groups are *meta* directors (see later). There are mainly two electronic effects that modify the electron-density on the aromatic ring: the *inductive* and the *resonance effect* (see Chart 1). The first one is mainly due to the electronegativity difference between the substituent atom attached to the aromatic C(sp^2) carbon leading to a donation or retrodonation of electron-density through a σ bond. For instance, the C(sp^3) carbon of the methyl group is lesser electronegative than the aromatic C(sp^2) carbon, then the C(sp^3)–C(sp^2) σ bond is polarized towards the aromatic carbon (see Chart 1). This fact that increases slightly the electron-density of the aromatic ring is called as +I. On the other hand, a $-$I effect is produced by a NH_3^+ group due to the larger electronegative character of the positively charged nitrogen atom (see Chart 1).

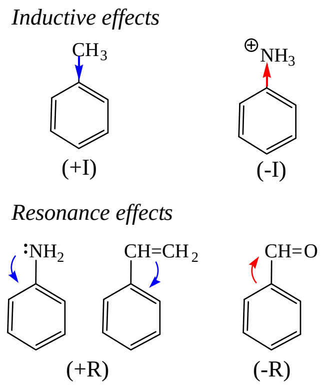

Chart 1.

The other substituent effect is the known resonance effect which can modify the electron-density of the aromatic ring. If the atom attached to benzene has a lone pair (N, O or halogen) or it is a sp^2 carbon belonging to ethylene, —CH=CR$_2$, they can delocalize electron-density on the aromatic ring along the electrophilic attack. This stabilizing effect diminishes the electron-density on the substituent and it is called as +R. On the other hand, if the atom attached to benzene is bonded by a double bond to a more electronegative atom, —C=O or —N=O, they have a strong EW effect that diminishes the electron-density on the aromatic ring. This resonance effect that increases the electron-density of the substituent is called as —R and they are extended to all conjugated aromatic system.

All functional groups exhibit inductive and resonance effects in more or less extension. In general, the resonance effect predominates over the inductive effect and only the latter is considered when the resonance effects are not relevant. In some cases, these effects have opposite sign. Thus, the halogens have a +R effect by the delocalization of the lone pairs on the aromatic ring, and a $-$I effect because the halogen is more electronegative than the carbon (see later).

The *ortho*, *para* and/or *meta* director effects (or activation/deactivation) developed by electron-releasing (ER) and electron-withdrawing (EW) groups will be discussed on the basis of a simple local nucleophilicity descriptor. We would like to emphasize in this point that a rigorous site-activation/deactivation model requires changes in both local and global quantities [61–63]. This is naturally assessed within a nonlocal scheme of chemical reactivity which can be correctly incorporated through approximations to the linear response functions of density $\chi(\mathbf{r},\mathbf{r}')$, of the Fukui functions $f(\mathbf{r},\mathbf{r}')$ [61–63] or higher order terms of density response $f^{(n)}(\mathbf{r},\mathbf{r}')$ [64]. Such type of site (activation/deactivation) models yield to model equations where a first term assess local activation at the site, and a second term takes into account the global change of the whole system [61–64]. In the present work, we focus on simpler model approximations intended to still provide useful practical reactivity information within a perturbative approximation [1,2,15,65].

2. Local nucleophilicity. Model equations

The global nucleophilicity model (N) recently introduced [38,59], based on the relationship $N = -\text{IP}$, where IP is the gas-phase (intrinsic) ionization potentials can be straightforwardly extended in order to describe the local nucleophilicity. Following