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Relationship between the electrophilicity of substituting agents and substrate selectivity in Friedel–Crafts reactions

L. Meneses,[a,*] P. Fuentealba[b] and R. Contreras[a]

[a]*Departamento de Química, Facultad de Ciencias, Universidad de Chile, Las Palmeras 3425, Casilla 653 Santiago, Chile*
[b]*Departamento de Física, Facultad de Ciencias, Universidad de Chile, Casilla 653 Santiago, Chile*

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Abstract—The global electrophilicity index evaluated at the ground state of benzylating and acylating agents shows a quantitative linear relationship with the experimental substrate selectivity index evaluated for a series of Friedel–Crafts reactions. The theoretical scale correctly accounts for the electrophilic activation/deactivation effects promoted by electron withdrawing and electron releasing substituents in these molecules. The predicted substrate selectivity values estimated from the knowledge of the electrophilicity index may become accurate to within 10% and less.

1. Introduction

Electrophilic aromatic substitution (EAS) reaction is one of the archetypal polar processes in organic chemistry.[1–3] The accepted two step mechanism involves the formation of an ionic intermediate, the benzenium ion,[4–6] where the attacking electrophile forms a σ bond with the substrate (also named the σ complex). Extensive studies reported by Brown showed a linear relationship between the relative stability of the σ complex and relative rates for a significant number of electrophilic substitution reactions,[7] yet there was not evidence showing that the transition states were closely related to this intermediate complex.[8] An alternative two-step mechanism involves Dewar's π-complex, where the interaction of an electrophile with the aromatic substrate forms a first weak reagent–substrate complex (outer complex) which is in equilibrium with a second structure two-electron three-center complex (π-complex). The formed complex is indeed a bridged tetracoordinated carbonium ion (benzonium ion).[9] However, studies by Olah point out to a mechanism characterized by an early formation of the π-complex, followed by the formation of the σ complex, that accounts for the low substrate but high positional selectivities observed in EAS reactions.[10,11] Furthermore, they proved that transition states of these reactions were not rigidly fixed, always resembling the Wheland intermediates, but they could frequently represent a much earlier stage of the reaction that could even corresponds in structure to the starting aromatics.[12,13] The mechanism of EAS reactions has been recently revisited by Esteves et al.[14] Based on experimental and computational results, these authors have introduced a unified mechanism involving three separate intermediates on the potential energy surface of the reaction.

One of the factors determining the reactivity in EAS processes is the electrophilicity of the attacking group. For instance, it has been shown that substituents may affect the substrate selectivity as measured by the $k_{\text{Toluene}}/k_{\text{Benzene}}$ (k_T/k_B, hereafter) ratio. Thus, while electron-donating substituent located at position *ortho* and *para* with respect to the benzylic centre, increase the k_T/k_B ratio, electron-withdrawing substituents decrease it.[12,13] On the other hand, the acylation of toluene and benzene clearly proved the importance of substituents on the electrophilicity of the substituting agent, which was reflected by high k_T/k_B ratios. The effect of the nucleophilicity of the aromatic substrate was observed to cause similar effects;[15] so that with increasingly more basic aromatics, even relatively weak electrophiles resulted in early transition states resembling more starting materials than intermediates.[12,13,15] This result opens an interesting alternative to look at the substrate selectivity in EAS reactions using static reactivity models developed around the ground states of reactants.

The second relevant aspect in the EAS reactions is the activating effect promoted by Lewis acid (LA) catalysts. This is still an active area of research, and several works

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* Corresponding author. Tel.: +56 2 678 7261; fax: +56 2 271 3888; e-mail: loremen@ciq.uchile.cl

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describing a wide variety of catalysts have been recently reported.[16–19]A recent study by Sefkow and Buchs reports on the uncatalyzed Friedel–Craft alkylation of aromatic compounds through reactive benzyl cations, that are generated by thermal decomposition of aryl-benzyl-sulfamoylcarbamates.[20]

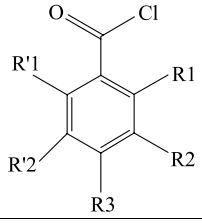
In this article we present a theoretical model to quantitatively describe the substrate selectivity in terms of the global electrophilicity of the benzylating and acylating reagents involved in the Friedel–Crafts EAS reactions, using a global electrophilicity index.[21,22] We rank, within a unique absolute scale, the global electrophilicity of a series of (10) benzylating and (7) acylating reagents. The usefulness of the theoretical scale is illustrated for the rationalization of substituent effects on the electrophilic activation/deactivation reagents and to predict the experimental substrate selectivity described by the k_T/k_B ratios of related systems.

2. Model and computational details

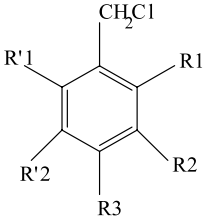
The concept of electrophilicity viewed as a reactivity index was introduced by Maynard et al. to study the reaction of the human inmunodeficiency virus type 1 (HIV-1) nucleocapsid protein p7 (NCp7) with a variety of electrophilic agents.[21] It was reformulated by Parr et al.[22] using a second order expansion of the electronic energy with respect to the charge transfer ΔN at fixed geometry. Since electrophiles are species that stabilize upon receiving an additional amount of electronic charge from the environment, there exist a minimum of energy for a particular ΔN^* value. Using this simple idea Parr et al. performed a variational calculation that led to the definition of the global electrophilicity index as $\omega = -\Delta E(\Delta N^*)$, which may be recast into the more familiar form:[21]

$$\omega = \frac{\mu^2}{2\eta} \tag{1}$$

in terms of the electronic chemical potential μ and the chemical hardness η. The ω index establishes an absolute scale of electrophilicity in the sense that the hierarchy of electrophilicity is built up from the electronic structure of molecules, independent of the nucleophilic partner, which is replaced by an unspecified environment viewed as a sea of electrons.[21] It has been successfully used to describe reactivity in different organic systems. For instance, the global electrophilicity values obtained from ω have been used to rank the electrophilicity of reagents participating in Diels–Alder and 1,3-dipolar cycloadditions reactions.[23,24] It was also found that the difference in electrophilicity for the diene/dienophile pair determined the nature of the reaction mechanism (non-polar or polar character of the process), thereby reinforcing the reliability of the ω index as a kinetic descriptor of reactivity.[23] This index is almost insensitive to solvent effects in neutral electrophiles, thus gas phase calculations suffice to establish the electrophilic power of molecules.[25] More recently, we have shown that the intrinsic electronic contribution to the substituent σ_p Hammett constants, $\sigma_e(\omega)$, can be estimated from the ω index calculated for a series of substituted ethylenes.[26] We found that electron-withdrawing substitution increased the electrophilicity power of ethylene, and that the corresponding $\sigma_e(\omega)$ values were consistently predicted as positive numbers. Our aim in this work is to illustrate how the electrophilicity index performs to quantitatively account for the observed substrate selectivity in Friedel–Craft benzylation and acylation.

General structure Acylating agents		R1	R'1	R2	R'2	R3
	1	NO_2	H	H	H	NO_2
	2	H	H	NO_2	NO_2	H
	3	F	H	H	F	H
	4	H	H	H	H	H
	5	H	H	H	H	CH_3
	6	H	H	H	H	F
	7	H	H	H	H	OCH_3

A

General structure Benzilating agents		R1	R'1	R2	R'2	R3
	1	Cl	H	H	H	H
	2	H	H	F	H	H
	3	F	H	H	H	H
	4	H	H	H	H	H
	5	H	H	H	H	F
	6	CH_3	H	H	H	H
	7	H	H	H	H	CH_3
	8	CH_3	CH_3	H	H	CH_3
	9	OCH_3	H	H	H	H
	10	H	H	H	H	OCH_3

B

Chart 1. General structure of acylating (**A**) and benzylating (**B**) agents involved in Friedel–Crafts reactions considered in this work.