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

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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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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]

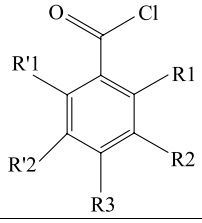
In this article we present a theoretical model to quantitatively describe the substrate selectivity in terms of the global electrophilicity of the benzylating and acylating reagents involved in the Friedel–Crafts EAS reactions, using a global electrophilicity index.[21,22] We rank, within a unique absolute 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

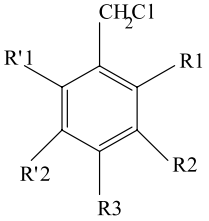
The concept of electrophilicity viewed as a reactivity index was introduced by Maynard et al. to study the reaction of the human inmunodeficiency virus type 1 (HIV-1) nucleocapsid protein p7 (NCp7) with a variety of electrophilic agents.[21] It was reformulated by Parr et al.[22] using a second order 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.

All the structures included in this study are shown in Chart 1. They were optimized at the B3LYP level of theory using the Gaussian98 package of programs.[27] Several basis set, including 6-31G*, 6-311G** and 6-311++G** were used in order to test the stability of the reactivity index with respect to the basis set. The values of the electronic chemical potential and the chemical hardness were obtained from the expressions $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx \varepsilon_L + \varepsilon_H$, in terms of the one electron energies of the HOMO and LUMO frontier molecular orbitals, ε_H and ε_L, respectively.[28] With these quantities at hand, the global electrophilicity at the ground state of molecules was obtained using Eq. (1).

3. Results and discussion

The global electrophilicity patterns of the substituting acylating (**A**) and benzylating (**B**) agents, commonly used in Friedel–Crafts reactions are ranked in Chart 2. Acylating agents display global electrophilicity values located at the top of the scale, within the range [2.0–4.0] eV. Benzylating agents on the other hand display lower electrophilicity values within the range [1.0–2.0] eV. In both cases it is possible to rationalize the electrophilic activating/deactivating effects promoted by substituent group in these molecules. For instance, if we start from the unsubstituted reference compound **A4** ($\omega = 2.50$ eV), substitution at R3 by

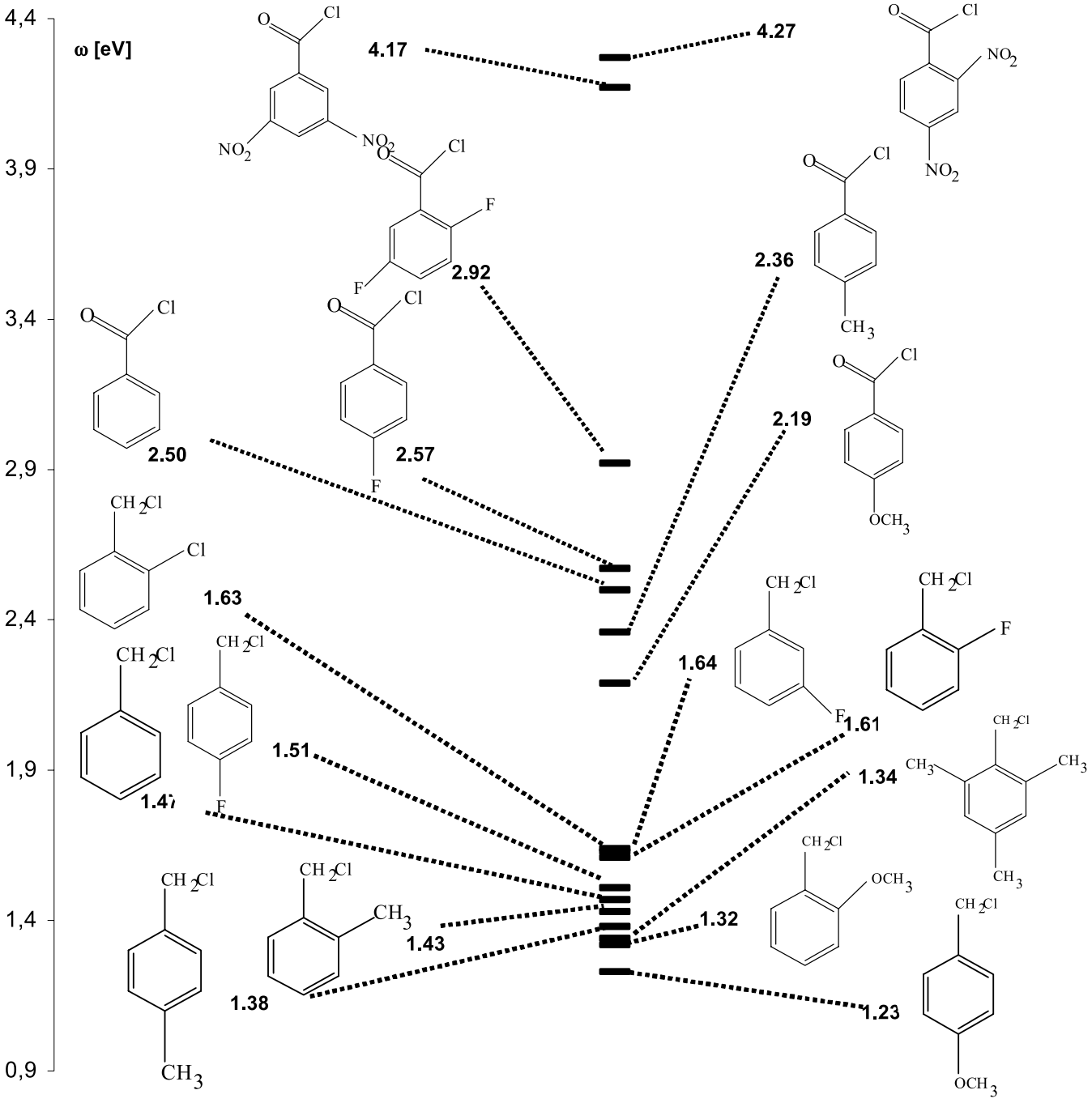


Chart 2. Theoretical scale of global electrophilicity for the acylating (**A**) and benzylating (**B**) agent series involved in Friedel–Crafts reactions considered in this work.

Table 1. Global electrophilicity values (in eV units) obtained from different basis set at the B3LYP level of theory for the ground state (ω) of acylating (**A**) and benzylating (**B**) agents[a]

Compound	(ω), Basis set			$\ln(k_T/k_B)$
	6-31G*	6-311G**	6-311++G**	
A1	3.77	3.97	4.27	3.37
A2	3.64	3.86	4.17	3.66
A3	2.45	2.75	2.92	4.57
A4	2.14	2.37	2.50	5.03
A5	2.03	2.25	2.36	5.10
A6	2.18	2.43	2.57	5.14
A7	1.84	2.05	2.19	5.45
B1	1.35	1.57	1.63	1.53
B2	1.31	1.54	1.64	1.53
B3	1.29	1.52	1.61	1.57
B4	1.20	1.40	1.47	1.84
B5	1.21	1.42	1.51	2.16
B6	1.16	1.36	1.43	2.95
B7	1.12	1.31	1.38	3.66
B8	1.10	1.28	1.34	3.67
B9	1.04	1.24	1.32	4.10
B10	0.97	1.15	1.23	4.57

[a] Experimental substrate selectivity index $\ln(k_T/k_B)$ from Ref. 10.

the weak electron releasing $-CH_3$ group results in an electrophilic deactivation in compound **A5** ($\omega = 2.36$ eV). Substitution at the same position with the stronger electron releasing $-OCH_3$ group results in an even higher electrophilic deactivation in compound **A7** ($\omega = 2.19$ eV). Substitutions with electron withdrawing groups show, as expected, electrophilic activation. For instance, with reference to compound **A4**, substitution at R3 with fluorine causes a slight activation of about 0.07 eV in compound **A6**, whereas substitution with two fluorine atoms at R1 and R2′ in compound **A3** results in an even higher electrophilic activation of about 0.42 eV within the ω scale. Note, however, that the most efficient activation with reference to compound **A4** is achieved by $-NO_2$ substitution at (R1, R3) and (R2, R2′) in compounds **A1** ($\omega = 4.27$ eV) and **A2** ($\omega = 4.17$ eV), respectively.

For the series of benzylating agents, a similar picture is obtained, yet the effect of the substituting groups is largely lower than that obtained for the acylating agent series. For instance, starting from the reference compound **B4** ($\omega = 1.47$ eV), substitution at R1 with chlorine and fluorine atoms results in a moderate electrophilic activation in compounds **B1** ($\omega = 1.63$ eV) and **B3** ($\omega = 1.61$ eV). Note that substitution with fluorine at R2 in compound **B2** ($\omega = 1.64$ eV) has a similar activating effect. Electrophilic deactivation promoted by electron releasing groups is also moderate. Substitution at R1 or R3 by a $-CH_3$ group causes a marginal deactivation in compounds **B6** ($\omega = 1.43$ eV) and **B7** ($\omega = 1.38$ eV), respectively. Multiple substitutions with $-CH_3$ groups at positions R1, R1′ and R3 in compound **B8** ($\omega = 1.34$ eV) do not show any additional deactivating effects. Note however that, as expected, a single substitution by the stronger electron releasing $-OCH_3$ group at position R1 or R3 in compounds **B9** ($\omega = 1.32$ eV) and **B10** ($\omega = 1.23$ eV), respectively, results in a slightly higher electrophilic deactivation. In summary, while chemical substitution by EW and ER groups dramatically affects the electrophilic pattern of the acylating agents, this effect is markedly smaller in the series of benzylating agents. This result may be traced to an additional resonance effect promoted by the conjugated carbonyl group in the acyl series, making substituent effects more efficient than that observed for the series B, where this resonance effects is not present. Table 1 shows the global electrophilicity values for the whole series of acylating and benzylating agents at several levels of theory for the GS of the substituting agents. Note that the global electrophilicity index is computationally very stable with respect to the basis set change.

The usefulness of a reactivity scale has been clearly described and illustrated by Mayr et al.[29–31] A reactivity scale should be able of answering fundamental questions about reaction feasibility; intramolecular selectivity and other important aspects of reactivity.[29–31] Within the present approach, and for the particular cases where the activated species are very close in structure to reactants, we intend to illustrate the usefulness of the validated scale of electrophilicity to quantitatively account for the substrate selectivity observed in the acylation and benzylation

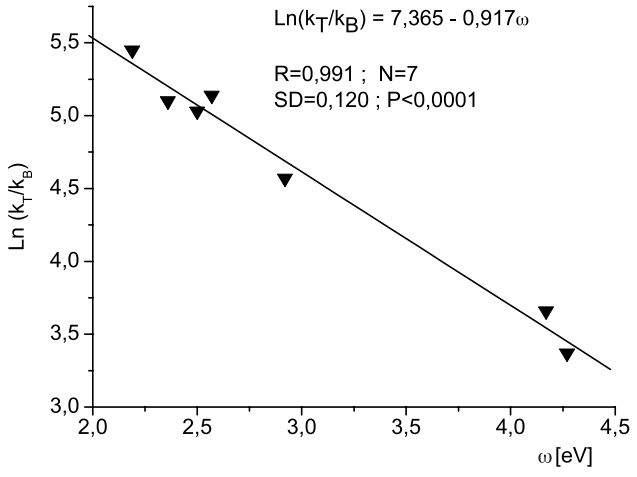


Figure 1. Comparison between the experimental substrate selectivity index $\ln(k_T/k_B)$ and the global electrophilicity evaluated at the ground state structure for the acylating agent series. Electrophilicicty values from B3LYP/6-311++G** calculations. R is the regression coefficient; N is the number of points in the regression; SD is the standard deviation and P is the probability that the observed relationship was randomly obtained.

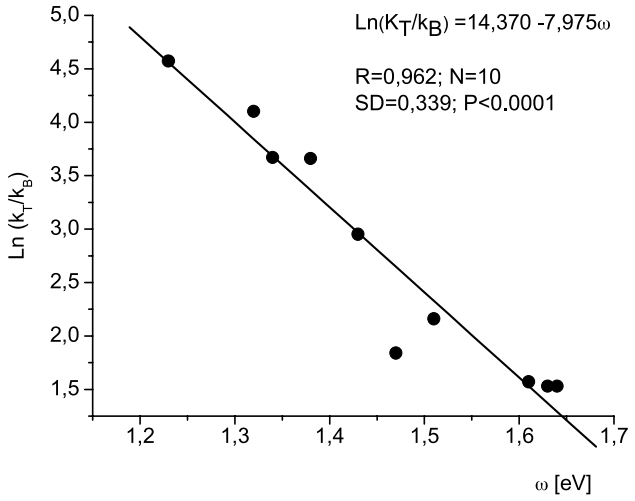


Figure 2. Comparison between the experimental substrate selectivity index $\ln(k_T/k_B)$ and the global electrophilicity evaluated at the ground state structure for the benzylating agent series. Electrophilicicty values from B3LYP/6-311++G** calculations. R is the regression coefficient; N is the number of points in the regression; SD is the standard deviation and P is the probability that the observed relationship was randomly obtained.

reaction of aromatic compounds. First of all we observe in Figures 1 and 2, that the relationship between k_T/k_B ratio and global electrophilicity index shows a negative slope. This is because strongly electrophilic reagents leads to low substrate selectivity in the form of low k_T/k_B rate coefficient ratios.[10] We compare in Figure 1 the experimental substrate selectivity described by the k_T/k_B ratio and the global electrophilicity index for the series of acylating agents evaluated at the B3LYP/6-311++G** level. The experimental data are available from literature.[10] The resulting regression equation is:

$$\mathrm{Ln}(k_T/k_B) = 7.365 - 0.917\omega \quad (R = 0.991) \qquad (2)$$

In order to test the quality of the linear relationship obtained for this series, two new compounds **A8** (R3 = NO_2) and **A9** (R1 = CH_3, R3 = CH_3, R1′ = CH_3) not included in the regression shown in Figure 1 were selected from Olah's data base to test the predictive power of the model.[10] This empirical equation predicts for compound **A8**, for which $\omega = 3.96$ eV, a value $\ln(k_T/k_B) = 3.73$, which is in excellent agreement with the experimental value $\ln(k_T/k_B) = 3.95$. Compound **A9** on the other hand, which has an electrophilicity value $\omega = 1.86$ eV yields a predicted $\ln(k_T/k_B) = 5.66$, which is again in excellent agreement with the experimental value $\ln(k_T/k_B) = 5.28$.[10]

The comparison between the $\ln(k_T/k_B)$ index and the global electrophilicity at the ground state of benzylating agents evaluated at the B3LYP/6-311++G** level is displayed in Figure 2. The comparison yields the following regression equation:

$$\mathrm{Ln}(k_T/k_B) = 14.379 - 7.975\omega \quad (R = 0.959) \qquad (3)$$

This empirical equation was tested for compounds **B11** (R3 = Cl) and **B12** (R1 = OCH_3, R2 = CH_3, R3 = OCH_3, R2′ = CH_3 and R1′ = OCH_3) not included in the regression shown in Figure 2. Compound **B11** for which $\omega = 1.62$ eV, yields a value $\ln(k_T/k_B) = 1.45$, which is to be compared to the experimental one $\ln(k_T/k_B) = 1.82$.[10] Compound **B12** on the other hand, for which we evaluated a global electrophilicity $\omega = 1.26$ eV yields a $\ln(k_T/k_B)$ value of 4.32, which is to be compared to the experimental one $\ln(k_T/k_B) = 4.91$.[10] The predictions for the benzylating agent series are not as accurate as those for the acylating agent series, a result probably traced to the low global electrophilicity value evaluated for the activated reference compound **B4**, which show a significant deviation from linearity. This result may be probably improved going beyond the ground state of reactants, by using an activated structure closer to the transition state

These comparisons may be somehow questionable in the sense that the choice of molecules to perform the comparison is completely arbitrary. In order to make a

Table 2. Statistical data for different correlations between global electrophilicity index evaluated at the ground state (ω) and the experimental substrate selectivity index $\ln(k_T/k_B)$[a]

Line	Compounds included in the correlation	Constant	Slope	*R*	*N*	Predicted, $\ln(k_T/k_B)$
1	**A2**,**A3**,**A4**,**A5**,**A6**,**A8**,**A9**	6.8084	−0.7340	0.980	7	**A1**: 3.67 (3.37), **A7**: 5.20 (5.45)
2	**A1**,**A3**,**A4**,**A5**,**A7**,**A8**,**A9**	7.1932	−0.8168	0.977	7	**A2**: 3.79 (3.66), **A6**: 5.09 (5.14)
3	**A1**,**A2**,**A4**,**A6**,**A7**,**A8**,**A9**	7.0966	−0.8270	0.972	7	**A3**: 4.68 (4.57), **A5**: 5.14 (5.10)
4	**A2**,**A3**,**A4**,**A5**,**A6**,**A7**,**A8**	7.1548	−0.8313	0.986	7	**A1**: 3.60 (3.37), **A9**: 5.61 (5.28)
5	**A1**,**A2**,**A3**,**A4**,**A5**,**A6**,**A9**	7.0178	−0.8220	0.982	7	**A7**: 5.22 (5.41), **A8**: 3.76 (3.95)
6	**B2**,**B3**,**B4**,**B5**,**B6**,**B7**,**B8**,**B9**,**B11**,**B12**	15.1760	−8.4740	0.950	10	**B1**: 1.36 (1.53), **B10**: 4.75 (4.57)
7	**B1**,**B3**,**B4**,**B5**,**B6**,**B7**,**B8**,**B10**,**B11**,**B12**	14.8679	−8.2872	0.956	10	**B2**: 1.28 (1,53), **B9**: 3.93 (4.10)
8	**B1**,**B2**,**B4**,**B5**,**B6**,**B7**,**B9**,**B10**,**B11**,**B12**	14.8528	−8.2442	0.957	10	**B3**: 1.58 (1.57), **B8**: 3.80 (3.67)
9	**B1**,**B2**,**B3**,**B4**,**B6**,**B8**,**B9**,**B10**,**B11**,**B12**	14.5906	−8.0698	0.963	10	**B5**: 2.40 (2.16), **B7**: 3.45 (3.66)
10	**B1**,**B2**,**B3**,**B5**,**B7**,**B8**,**B9**,**B10**,**B11**,**B12**	14.7875	−8.1399	0.987	10	**B4**: 2.82 (1.84), **B6**: 3.15 (2.95)

[a] In the last column the experimental substrate selectivity index $\ln(k_T/k_B)$ is given in parentheses for comparisons.

meaningful conclusion about the relationship between electrophilicity of the substituting agents and the experimental substrate selectivity index, it is necessary to perform additional comparisons with several sets of molecules randomly selected. The result is summarized in Table 2. It may be seen that in general there exist a true linear relationship between both variables. Hence the predictive power of the generated linear relationships may become accurate to within 10% and less, thereby showing the usefulness of the present reactivity scale. There remains however some improvements that can be made by explicitly introducing the catalyst, and evaluating the global electrophilicity of molecules at a more realistic stage of the reaction, namely the Wheland complex or even at the transition state.

4. Concluding remarks

The global electrophilicity of benzylating and acylating agents participating in Friedel–Crafts electrophilic aromatic substitution reactions has been ranked within a unique absolute scale using the global electrophilicity index. The theoretical scale correctly accounts for the electrophilic activation/deactivation effects promoted by electron withdrawing and electron releasing substituents in these molecules. The comparison between global electrophilicity and the experimental relative rate coefficients ($k_{\text{Toluene}}/k_{\text{Benzene}}$) shows a quantitative linear relationship. The values of relative rate coefficients predicted from the knowledge of the global electrophilicity index may be accurate to within 10% and less.

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