Careful Scrutiny of the Philicity Concept

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The philicity concept [*J. Phys. Chem. A* **2003**, *107*, 4973] is put in proper perspective. In the present work we analyze different physicochemical problems using philicity. It provides satisfactory results in all such cases. We also compare the relative electro(nucleo)philicity with philicity to show that philicity is better than relative electro(nucleo)philicity when the intermolecular reactivity trends are considered and there is hardly any preference of one above the other as far as the intramolecular reactivities are concerned. On the contrary, the philicity concept has some advantages over the other concept.

Introduction

Prompted by the work of Maynard et al.,[1] the global electrophilicity index (ω) has been introduced by Parr et al.[2] as

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

where μ and η are chemical potential[3] and chemical hardness,[4] respectively. A local variant of ω has been proposed[5] via the resolution of the identity associated with the normalization of the Fukui function,[6] $f(\mathbf{r})$, as

$$\omega^{\alpha}(\vec{r}) = \omega f^{\alpha}(\vec{r}) \tag{2}$$

where $f^{\alpha}(\vec{r})$ is the Fukui function[6] associated with $\alpha = +, -$, and 0 referring to nucleophilic, electrophilic, and radical reactions, respectively. Corresponding condensed-to-atom variants may be written for the kth atomic site in a molecule as

$$\omega_k^{\alpha} = \omega f_k^{\alpha} \tag{3}$$

A special case of this general treatment is provided in refs 7 and 8. Similarly, local softnesses are defined as[9]

$$s^{\alpha}(\vec{r}) = S f^{\alpha}(\vec{r}) \tag{4}$$

$$s_k^{\alpha} = S f_k^{\alpha} \tag{5}$$

where $S = 1/2\eta$ is the global softness.[3] For a current perspective on chemical reactivity and conceptual density functional theory see refs 10 and 11.

The local softness is obtained through the decomposition of the global softness, and the former indicates that the soft−soft interactions are preferred in comparison to the hard−soft ones. On the other hand, the decomposition of global electrophilicity provides the local philicity, which is capable of showing the preference of electrophile−nucleophile interaction over electrophile−electrophile interactions. It may, however, be noted that the local philicity and the local softness will provide the same trend of reactivity if μ^2 remains more or less constant or varies more slowly than S or has a variation similar to that of S in a group of molecules because $\omega = \mu^2 S$ (see also eqs 1−5). A molecule with high global electrophilicity value would be more reactive toward that with a corresponding low value. For two such molecules the reaction would be through the atomic center having the largest ω_k^- in one molecule with the atomic center having the largest ω_k^+ of the other molecule. The electrophilic or nucleophilic power is distributed over all atomic sites in a molecule keeping the overall philicity conserved.

When an electrophile interacts with a nucleophile from a large distance, their global electrophilicities (ω) decide their behavior, viz. $\omega_{\text{electrophile}} > \omega_{\text{nucleophile}}$. The local variants, in general, remain spectators until they come very close when the most electrophilic site of electrophile will attack the most nucleophilic site of the nucleophile. It may not be true in all cases (especially when two or more strong electro(nucleo)philic centers of comparable strength are present in a molecule) that the most electrophilic site in the electrophile has a larger ω_k^+ value than that of the most electrophilic site of the nucleophile. Similarly, global and local HSAB principles may be at variance with each other in some occasions. Of course, the HSAB principle is not violated in that case and also during strong interactions between a hard and a soft species with a substantial electronegativity difference. Charge based descriptors should be used in analyzing charge-controlled hard−hard interactions[12] where the Fukui function and the related descriptors (s_k^{α},ω_k^{α}) may provide wrong reactivity trends. In this paper we try to analyze the potential of philicity in diverse types of situations. For this purpose we choose the following cases:

Locating the Transition State through the Philicity Profiles

We calculate the related quantities ($\omega_{F_a}^-$, $\omega_{F_b}^-$, $\omega_{F_a}^- + \omega_{F_b}^-$, $\omega_{F_a}^+ + \omega_{F_b}^+$, bond orders and E) associated with the bond-making and bond-breaking processes[13] along the path of the gas-phase S_N2 substitution: $F_a^- + CH_3-F_b \rightarrow F_a-CH_3 + F_b^-$ and analyze their behavior in course of the chemical reaction (along the intrinsic reaction coordinate (IRC)).

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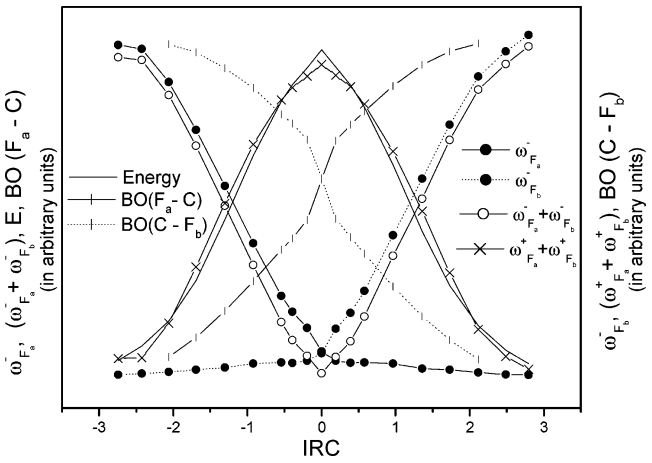

Figure 1. Profiles of philicity descriptors along the path of the gas-phase S_N2 substitution $F_a^- + CH_3-F_b \rightarrow F_a-CH_3 + F_b^-$. Also shown are the associated energy and bond order profiles.

Analyzing Toxicity through Global and Local Electrophilicities

The toxicity values ($pIGC_{50}$) of several aliphatic compounds (donor and acceptor type toxins) toward ciliated freshwater protozoa *Tetrahymena pyriformis* are correlated[14] with ω and ω_k^+/ω_k^- values. In refs 13 and 14 Mulliken charges were used in the place of the respective populations. Comparison of the electronegativity (negative of the chemical potential) values of the toxins and that of the biosystems simulated by NA bases (adenine, thymine, guanine, cytosine and uracil) and DNA base pairs (GCWC and ATH) reveals that guanine is the strongest donor and uracil is the strongest acceptor. The donor type toxins are unsaturated, α-acetylenic and amino alcohols and amines respectively whereas the acceptor type toxins are saturated alcohols, diols and halogenated alcohols, mono and diesters, carboxylic and halogenated acids, aldehydes and ketones, respectively. The joint hardness and the amount of electron transfer provide similar inferences. Other descriptors such as $\Delta_\omega^{ij} = (\omega^+_{\max(i)}$ (electrophile) $- \omega^-_{\max(j)}$ (nucleophile))^2 and condensed local temperatures and electron localization functions are being developed for this purpose in our laboratory.

Chemical Kinetics in the Light of Global and Local Electrophilicities

Inspired by the work of Maynard et al.,[1] the rates of Friedel−Crafts benzoylation reactions are correlated with global and local electrophilicities.[15] The calculated ln(RR), $RR = k_{toluene}/k_{benzene}$, is compared with the experimental ln(RR) of 7 benzoylating agents[16] for this purpose.

Comparison with Other Local Descriptors

To avoid the misconceptions created by two recent papers[17,18] claiming the superiority of the relative electro(nucleo)philicity

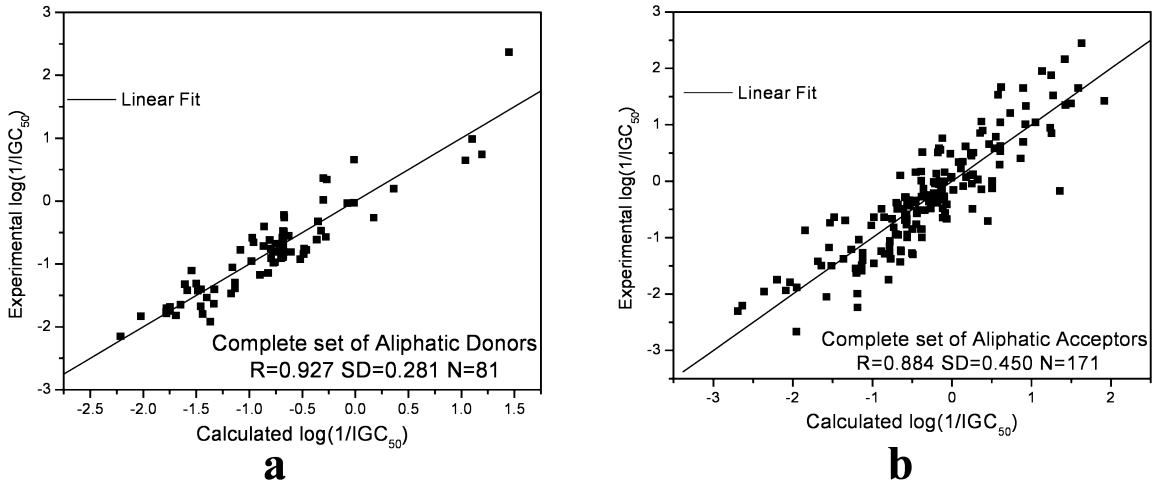

Figure 2. Experimental versus calculated $\log(IGC_{50}^{-1})$ values with the two parameter (ω, $\omega^-_{Omax}/\omega^+_{Cmax}$) regression analysis of (a) all the electron donor aliphatic compounds and (b) all the electron acceptor aliphatic compounds taken together.

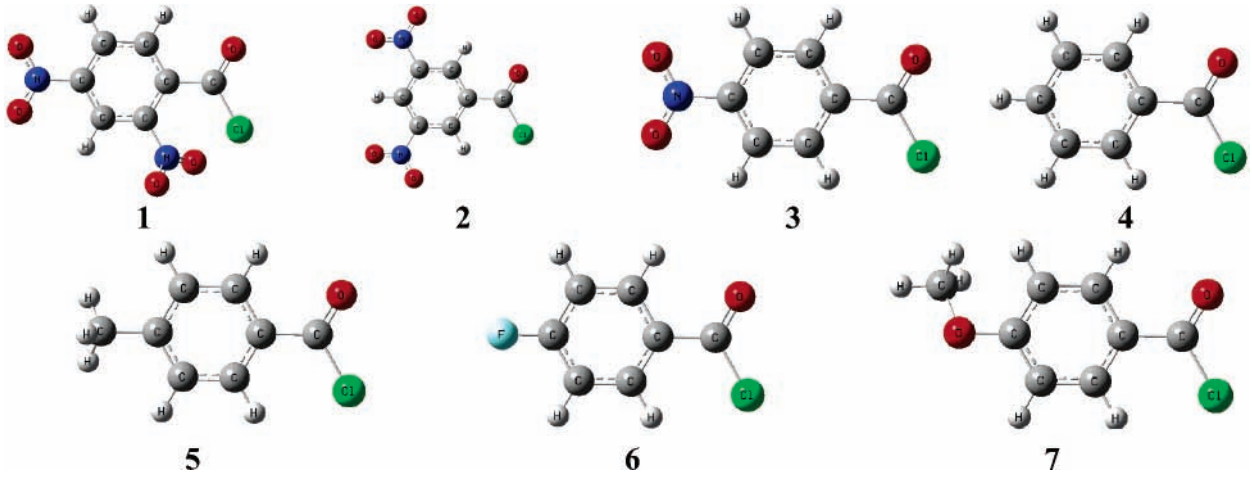

Figure 3. Optimized structures of 7 benzoylating agents involved in the Friedel−Crafts benzoylation reactions.

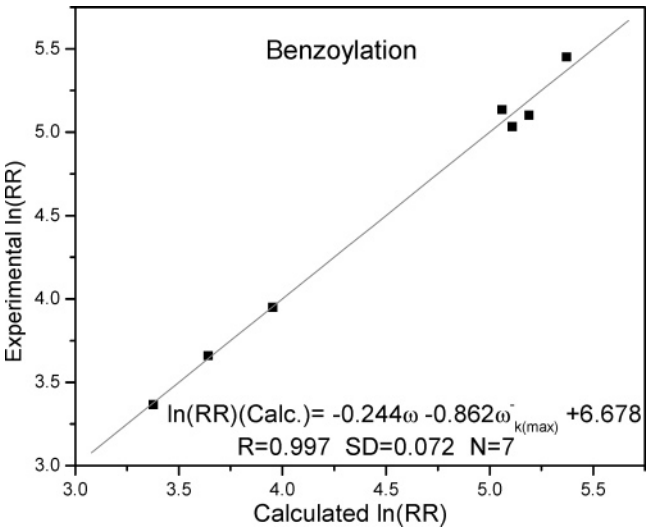

Figure 4. Experimental versus calculated rates of Friedel−Crafts benzoylation reactions.

over philicity, we also calculate those quantities for the systems studied in those references. It may be noted that many authors[19] strongly criticized the relative electro(nucleo)philicity concept including Roy himself.[20] In several publications[21−24] from the groups of Contreras, Perez, Fuentealba, Chatterjee, Toro-Labbe and others it has been argued that the relative electrophilicity is less universal than the local electrophilicity and unlike the former, the latter provides proper normalization and the former should not be trusted in the interpretation of intermolecular interactions. The philicity and the local softness are equally reliable as the Fukui function in analyzing intramolecular reactivity. However, they provide different trends during vibration, rotation, rearrangement and/or interactions with solvent/external field when ω and S also change in addition to $f(\vec{r})$. The relative electro(nucleo)philicity is identical with the corresponding relative Fukui function (which can be "analytically" shown, rather trivially) in all cases and hence does not warrant any special significance. Accordingly, it may not be a suitable intermolecular (no global information) reactivity descriptor. Moreover, it treats anions and cations at par and with no clear-cut prescription for the radical reactions. Even one of the referees has pointed out that the relative nucleophilicity concept of Roy et al. is wrong because it is taking the ratio twice. It is based on the handwaving argument of a ratio to be less sensitive toward basis set and correlation effects. On the contrary, as pointed out by one of the referees, the relative descriptors, being ratios, are more sensitive. It was originally introduced to avoid the negative values of the condensed softness[25] without other a priori justification. However, as they[26] claim that the Hirshfeld population analysis scheme will always provide nonnegative Fukui functions, albeit with a recent counterexample,[27] there is no need of the said relative quantities any more.

Connection with the Experimental Electrophilicity

We recalculate the local electrophilicities of 18 benzhydryl cations as done by Perez et al.[28] and compare them with the relative electrophilicities vis-à-vis the experimental electrophilicities provided by Mayr et al.[29]

Computational Details

All the calculations regarding gas-phase S_N2 substitution: $F_a^- + CH_3-F_b \rightarrow F_a-CH_3 + F_b^-$ is performed in the B3LYP method with the 6-311+G** basis set considering Mulliken population analysis (MPA) scheme using the Gaussian 98.[30] The geometries of aliphatic toxin molecules are minimized in the Hartree−Fock level of calculation with the 6-311G** basis set and corresponding local quantities are calculated considering natural population analysis (NPA) scheme using the Gaussian

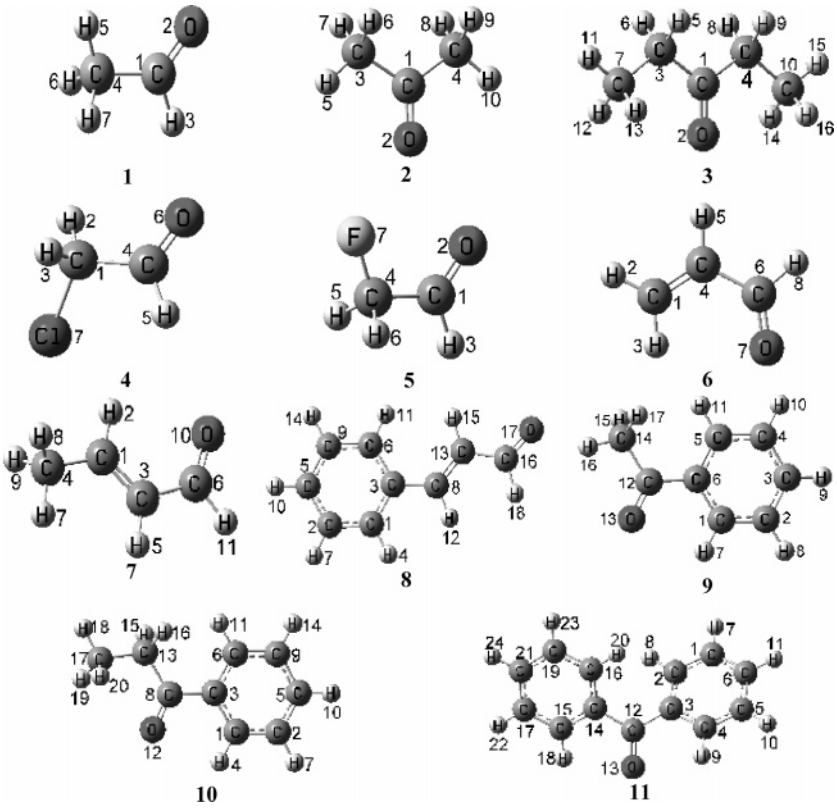

Figure 5. Optimized geometries of the 11 carbonyl compounds with atom numbering in the BLYP method with DNP basis set.

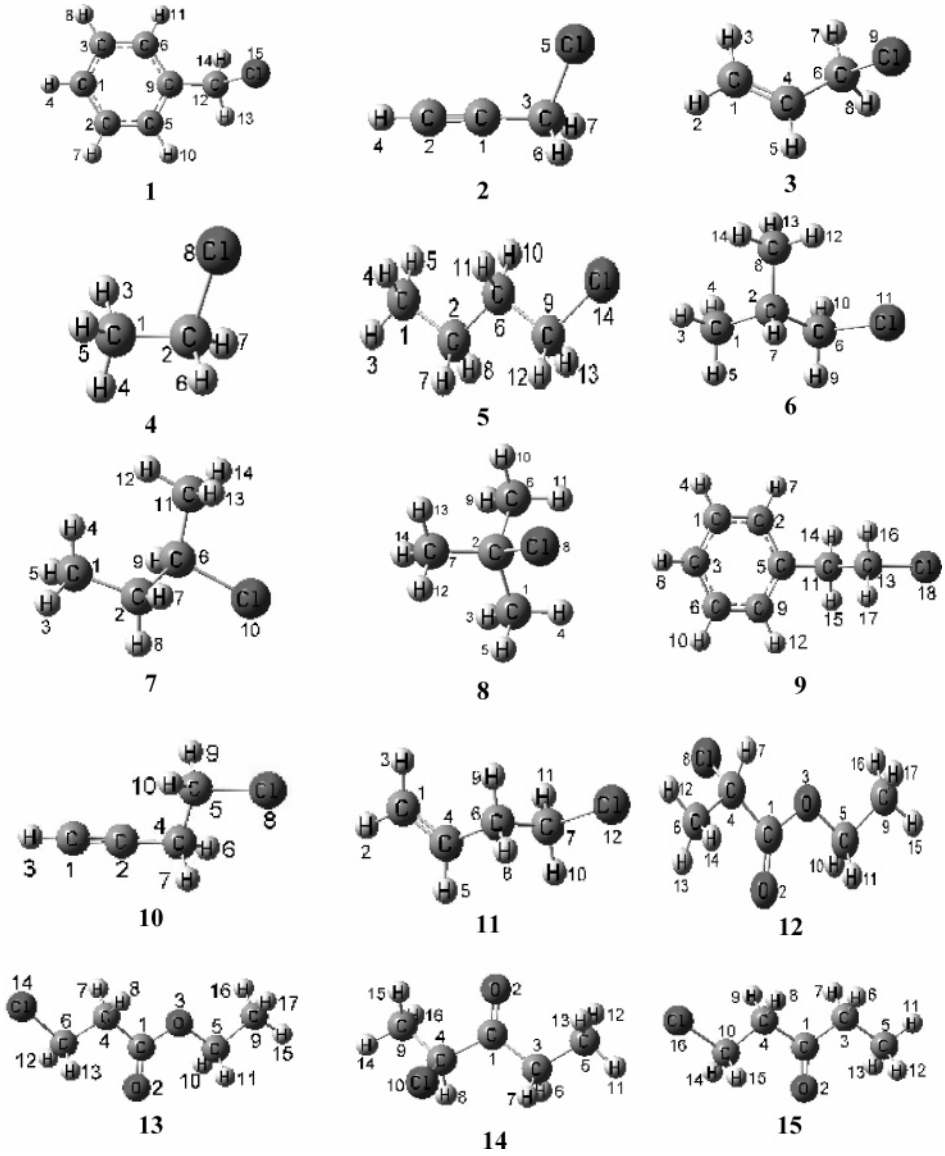

Figure 6. Optimized geometries of the 15 chloro compounds with atom numbering in the BLYP method with DNP basis set.

03.[30] Geometries of all the molecules involved in the Friedel−Crafts benzoylation reactions considered in the present study are minimized in the B3LYP level with 6-31G* basis set, and the corresponding local quantities are calculated considering Mulliken population analysis (MPA) scheme using Gaussian 98.[30]

Geometries of the same set of molecules as considered in refs 17 and 18 are initially optimized in BLYP method with the basis set 6-31G* using the Gaussian 03[30] and re-optimized in BLYP level of calculation with the basis set DNP by using DMOL[3] program.[31]

The quantitative definitions for chemical potential (μ)[3] and chemical hardness (η)[4] for an N− electron system with total energy E can respectively be given as

$$\mu = \left[\frac{\partial E}{\partial N}\right]_{v(\vec{r})} \tag{6}$$

and

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{v(\vec{r})} = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_{v(\vec{r})} \tag{7}$$

where $v(\vec{r})$ is the external potential.

Using a finite difference method the working equations for the calculation of chemical potential and chemical hardness can be given by

$$\mu = -\frac{\mathrm{IP} + \mathrm{EA}}{2} \qquad \eta = \frac{\mathrm{IP} - \mathrm{EA}}{2} \tag{8}$$

where IP and EA are ionization potential and electron affinity of the system, respectively.

If ϵ_{HOMO} and ϵ_{LUMO} are the energies of the highest occupied and lowest unoccupied molecular orbitals, respectively, then the above equations can be rewritten using Koopmans' theorem[3] as

$$\mathrm{IP} \approx -\epsilon_{\mathrm{HOMO}} \qquad \mathrm{EA} \approx -\epsilon_{\mathrm{LUMO}}$$
$$\mu = \frac{\epsilon_{\mathrm{HOMO}} + \epsilon_{\mathrm{LUMO}}}{2} \qquad \eta = \frac{\epsilon_{\mathrm{LUMO}} - \epsilon_{\mathrm{HOMO}}}{2} \tag{9a}$$

Alternatively, using the ΔSCF finite difference approach, we can calculate the IP and EA for the N-electron system as follows:

$$\mathrm{IP} \approx E(N-1) - E(N) \qquad \mathrm{EA} \approx E(N) - E(N+1) \tag{9b}$$

TABLE 1: Global and Local Descriptors of Selected Carbonyl Compounds Calculated in BLYP/DNP Method

carbonyl compounds	atomic centers	S	ω	MPA		HPA		MPA		HPA	
				s_k^+/s_k^-	ω_k^+	s_k^+/s_k^-	ω_k^+	s_k^-/s_k^+	ω_k^-	s_k^-/s_k^+	ω_k^-
1	$C_{C=O}$	2.3742	0.0593	3.8333	0.0150	1.8297	0.0176	0.2609	0.0039	0.5465	0.0096
	$O_{C=O}$			0.8270	0.0193	0.7837	0.0177	1.2092	0.0233	1.2760	0.0226
2	$C_{C=O}$	2.4115	0.0480	4.9143	0.0083	1.8630	0.0103	0.2035	0.0017	0.5368	0.0055
	$O_{C=O}$			0.5805	0.0106	0.6711	0.0114	1.7227	0.0182	1.4901	0.0170
3	$C_{C=O}$	2.5136	0.0459	3.9535	0.0078	2.0448	0.0092	0.2529	0.0020	0.4891	0.0045
	$O_{C=O}$			0.6398	0.0094	0.7306	0.0098	1.5631	0.0148	1.3687	0.0134
4	$C_{C=O}$	2.5608	0.0761	3.6949	0.0166	1.9333	0.0172	0.2706	0.0045	0.5173	0.0089
	$O_{C=O}$			0.6818	0.0148	0.8102	0.0171	1.4667	0.0218	1.2343	0.0211
	Cl			0.6228	0.0162	0.7326	0.0179	1.6056	0.0260	1.3649	0.0245
5	$C_{C=O}$	2.1590	0.0588	3.3000	0.0136	1.7946	0.0148	0.3030	0.0041	0.5572	0.0082
	$O_{C=O}$			0.6262	0.0112	0.7769	0.0137	1.5969	0.0179	1.2872	0.0176
	F			0.1658	0.0018	0.4423	0.0043	6.0323	0.0110	2.2607	0.0096
6	C_1	2.7454	0.0884	1.8462	0.0149	1.6047	0.0180	0.5417	0.0080	0.6232	0.0112
	$C_{C=O}$			2.7083	0.0115	1.3364	0.0155	0.3692	0.0042	0.7483	0.0116
	$O_{C=O}$			0.4833	0.0154	0.5273	0.0161	2.0690	0.0318	1.8965	0.0306
7	C_1	2.7452	0.0820	1.9688	0.0103	1.4246	0.0130	0.5079	0.0052	0.7020	0.0091
	$C_{C=O}$			2.5800	0.0106	1.5860	0.0139	0.3876	0.0041	0.6305	0.0088
	$O_{C=O}$			0.6761	0.0137	0.7114	0.0143	1.4790	0.0202	1.4057	0.0202
8	C_8	3.4588	0.1030	2.1379	0.0064	1.9275	0.0096	0.4677	0.0030	0.5188	0.0050
	$C_{C=O}$			2.3667	0.0073	1.3655	0.0097	0.4225	0.0031	0.7323	0.0071
	$O_{C=O}$			0.6836	0.0124	0.7401	0.0133	1.4628	0.0182	1.3511	0.0180
9	$C_{C=O}$	3.0390	0.0826	3.0303	0.0083	2.1245	0.0094	0.3300	0.0027	0.4707	0.0044
	$O_{C=O}$			0.7717	0.0117	0.8081	0.0117	1.2958	0.0152	1.2375	0.0145
10	$C_{C=O}$	2.9785	0.0742	2.5676	0.0071	0.5025	0.0073	0.3895	0.0027	0.5025	0.0037
	$O_{C=O}$			0.7184	0.0093	1.3284	0.0091	1.3920	0.0129	1.3284	0.0121
11	C_6	3.5182	0.0920	1.8462	0.0044	1.3120	0.0064	0.5417	0.0024	0.7622	0.0049
	C_{21}			1.8462	0.0044	1.3120	0.0064	0.5417	0.0024	0.7622	0.0049
	$C_{C=O}$			2.5000	0.0082	2.7070	0.0088	0.4000	0.0033	0.3694	0.0033
	$O_{C=O}$			0.8609	0.0119	0.7638	0.0108	1.1615	0.0138	1.3092	0.0141

TABLE 2: Global and Local Descriptors of Selected Chloride Compounds Calculated in BLYP/DNP Method

no.	chloride compounds	atomic centers	S	ω	MPA		HPA	
					s_k^+/s_k^-	ω_k^+	s_k^+/s_k^-	ω_k^+
1	$C_6H_5CH_2Cl$	C_{C-Cl}	2.8775	0.0677	−3.0588	0.0035	2.7645	0.0048
2	$CH{\equiv}C-CH_2Cl$	C_{C-Cl}	2.4592	0.0655	−24.200	0.0079	1.9347	0.0083
3	$CH_2{=}CH-CH_2Cl$	C_{C-Cl}	2.4928	0.0621	−1.6774	0.0032	1.9619	0.0057
4	CH_3CH_2Cl	C_{C-Cl}	2.0825	0.0466	2.4000	−0.0034	1.6918	0.0067
5	$CH_3CH_2CH_2CH_2Cl$	C_{C-Cl}	2.2002	0.0476	0.1818	−0.0002	2.0099	0.0048
6	$CH_3CH(CH_3)CH_2Cl$	C_{C-Cl}	2.1964	0.0498	0.6364	−0.0007	1.8187	0.0049
7	$CH_3CH_2CH(CH_3)Cl$	C_{C-Cl}	2.2363	0.0481	0.2195	−0.0004	1.6613	0.0045
8	$CH_3C(CH_3)_2Cl$	C_{C-Cl}	2.1800	0.0452	0.2576	−0.0008	1.6459	0.0033
9	$C_6H_5CH_2CH_2Cl$	C_{C-Cl}	2.8539	0.0590	−0.1786	0.0003	1.9745	0.0032
10	$CH{\equiv}C-CH_2CH_2Cl$	C_{C-Cl}	2.3744	0.0547	0.5806	−0.0010	2.4101	0.0055
11	$CH_2{=}CH-CH_2CH_2Cl$	C_{C-Cl}	2.4323	0.0532	−0.3704	0.0005	1.8233	0.0043
12	$CH_3CH(Cl)COOC_2H_5$	C_{C-Cl}	2.6259	0.0673	−1.8276	0.0036	1.9719	0.0057
13	$ClCH_2CH_2COOC_2H_5$	C_{C-Cl}	2.3756	0.0498	−0.2727	0.0005	1.8777	0.0031
14	$CH_3CH(Cl)COC_2H_5$	C_{C-Cl}	2.8234	0.0711	−1.1071	0.0022	1.4668	0.0050
15	$ClCH_2CH_2COC_2H_5$	C_{C-Cl}	2.6259	0.0510	0.0541	−0.0001	2.2792	0.0028

In eq 3 the condensed Fukui functions are calculated as follows:

$$f_k^+ = q_k(N+1) - q_k(N) \quad \text{for nucleophilic attack} \quad (10a)$$

$$f_k^- = q_k(N) - q_k(N-1) \quad \text{for electrophilic attack} \quad (10b)$$

$$f_k^0 = [q_k(N+1) - q_k(N-1)]/2 \quad \text{for radical attack} \quad (10c)$$

where q_k is the electronic population of atom k in a molecule. The electronic populations are calculated using both the Mulliken population analysis (MPA)[32] and Hirshfeld population analysis scheme (HPA)[33] employing BLYP level of calculation with the basis set DNP by using DMOL^3 program.[31]

The global electrophilicity (ω), chemical potential (μ) and hardness (η) are calculated by using eqs 1 and 9. The ω_k^α, s_k^α and f_k^α values are calculated by using eqs 3, 5, and 10. Also for benzhydryl cations these quantities are calculated using those equations at the BLYP/DNP level in the DMOL^3 program.[31] To check the variations within the DMOL^3 package for different occupation options and grid integrations, at the same level of theory and using the same population analysis scheme, we calculate some local and global quantities for two representative molecules, CH_3CHO and CH_3COCH_3, using Koopmans' approximation (eq 9a) and HPA charges (See Supporting Information).

Results and Discussion

Figure 1 depicts the profiles of the philicity descriptors such as $\omega_{F_a}^-$, $\omega_{F_b}^-$, $\omega_{F_a}^- + \omega_{F_b}^-$, $\omega_{F_a}^+ + \omega_{F_b}^+$ associated with the bond-making and bond-breaking processes along the path of the gas-phase S_N2 substitution: $F_a^- + CH_3{-}F_b \rightarrow F_a{-}CH_3 + F_b^-$. The profiles of $\omega_{F_a}^-$ and $\omega_{F_b}^-$ intersect at the TS, whereas $\omega_{F_a}^- + \omega_{F_b}^-$ minimizes and $\omega_{F_a}^+ + \omega_{F_b}^+$ maximizes at the TS and help in locating the TS. They provide information complimentary to that obtained from the energy and the bond order profiles. The free F_a^- is much more reactive than the bonded F_b^- to start with and the situation gets reversed as the reaction proceeds.

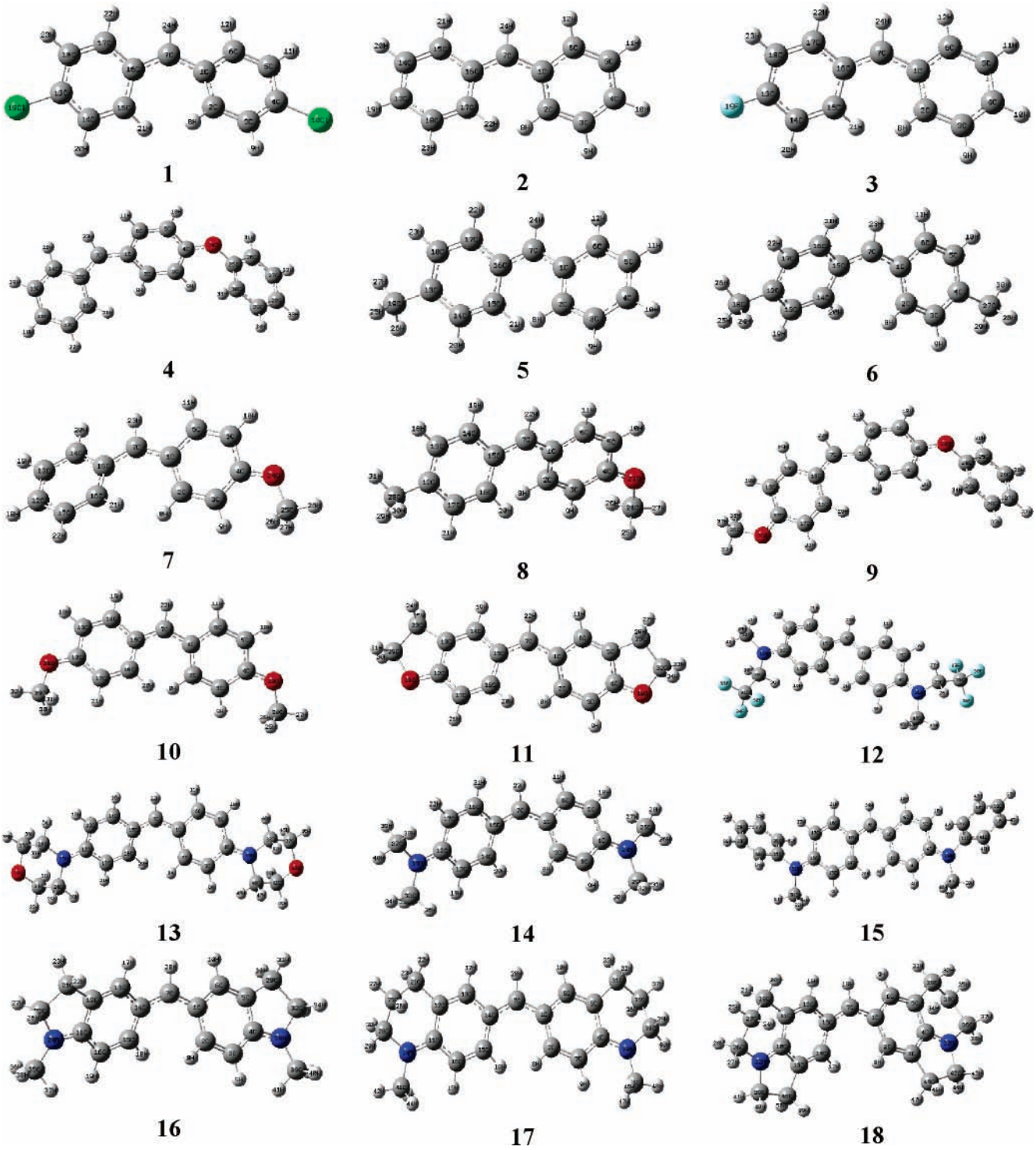

Figure 7. Optimized structures with atom numbering for the selected set of Benzhydryl Cations.

Figure 2 shows the correlations of experimental toxicity of several aliphatic donor toxins (unsaturated, α-acetylenic and amino alcohols and amines) and acceptor toxins (saturated alcohols, diols and halogenated alcohols, mono and diesters, carboxylic and halogenated acids, aldehydes and ketones) with that calculated using ω and $\omega^{-}_{\mathrm{O/Nmax}}/\omega^{+}_{\mathrm{Cmax}}$. The correlation is very good in the sense that the other such approaches use higher numbers of completely disjoint descriptors with hardly any relation to toxicity and often with poorer correlation. The present analysis puts emphasis on charge transfer between the toxin and the biosystem in analyzing the toxic behavior.

Figure 3 presents the optimized structures of the benzoylating agents[16] used in this analysis, and the correlation[15] between the experimental relative rates ($\mathrm{RR} = k_{\mathrm{toluene}}/k_{\mathrm{benzene}}$) of the associated Friedel−Crafts reactions with the corresponding theoretical rates calculated using ω and ω_k^{-} is provided in Figure 4. It is transparent that the global and local electrophilicities can successfully reproduce the rates of these reactions albeit with a possible collinearity and overfitting.

The carbonyl and chloro compounds along with the corresponding atom numbering are provided in Figures 5 and 6, respectively.

TABLE 3: Global Parameters (au) for the Selected Set of Benzhydryl Cations Obtained Using BLYP/DNP Method

molecule	I	A	η	μ	ω	S	$\Delta\omega$	ΔS	E^a
1	0.4304	0.2426	0.0939	−0.3365	0.6030	0.8292	0.1162	−0.1979	6.02
2	0.4507	0.2403	0.1052	−0.3455	0.5672	0.8815	0.0804	−0.1456	5.90
3	0.4525	0.2382	0.1071	−0.3454	0.5567	0.8982	0.0699	−0.1289	5.60
4	0.4012	0.2220	0.0896	−0.3116	0.5418	0.9228	0.0550	−0.1043	2.90
5	0.4407	0.2311	0.1048	−0.3359	0.5382	0.9290	0.0514	−0.0981	4.59
6	0.4294	0.2236	0.1029	−0.3265	0.5179	0.9655	0.0311	−0.0616	3.63
7	0.4240	0.2204	0.1018	−0.3222	0.5101	0.9802	0.0233	−0.0469	2.11
8	0.4117	0.2158	0.0979	−0.3137	0.5024	0.9953	0.0156	−0.0318	1.48
9	0.3767	0.2090	0.0839	−0.2928	0.5111	0.9782	0.0243	−0.0489	0.61
10	0.3956	0.2083	0.0936	−0.3019	0.4868	1.0271	0.0000	0.0000	0.00
11	0.3796	0.2027	0.0884	−0.2911	0.4793	1.0431	−0.0075	0.0160	−1.36
12	0.3581	0.1926	0.0828	−0.2753	0.4580	1.0916	−0.0288	0.0645	−3.85
13	0.3416	0.1846	0.0785	−0.2631	0.4409	1.1341	−0.0459	0.1070	−5.53
14	0.3428	0.1827	0.0800	−0.2628	0.4315	1.1588	−0.0553	0.1317	−7.02
15	0.3402	0.1791	0.0805	−0.2596	0.4185	1.1947	−0.0683	0.1676	−5.89
16	0.333	0.1759	0.0785	−0.2544	0.4121	1.2132	−0.0747	0.1861	−8.76
17	0.3309	0.1753	0.0778	−0.2531	0.4115	1.2150	−0.0753	0.1879	−8.22
18	0.3198	0.1678	0.0760	−0.2438	0.3912	1.2780	−0.0956	0.2509	−10.04

[a] Experimental electrophilicity values.[27]

TABLE 4: Local Parameters (au) for the Selected Set of Benzhydryl Cations Obtained Using BLYP/DNP Method

molecule	f^+	f^-	ω_C^+	ω_C^-	s_C^+	s_C^-	s_C^+/s_C^-	$\Delta\omega_C^+$	$\Delta(s_C^+/s_C^-)$
1	0.0785	0.0468	0.0473	0.0282	0.0651	0.0388	1.6774	0.0098	0.1080
2	0.0932	0.0455	0.0529	0.0258	0.0822	0.0401	2.0484	0.0154	0.4790
3	0.0929	0.0442	0.0517	0.0246	0.0834	0.0397	2.1018	0.0142	0.5324
4	0.0795	0.0396	0.0431	0.0215	0.0734	0.0365	2.0076	0.0056	0.4382
5	0.0900	0.0435	0.0484	0.0234	0.0836	0.0404	2.069	0.0109	0.4996
6	0.0863	0.0417	0.0447	0.0216	0.0833	0.0403	2.0695	0.0072	0.5001
7	0.0875	0.0457	0.0446	0.0233	0.0858	0.0448	1.9147	0.0071	0.3453
8	0.0822	0.0446	0.0413	0.0224	0.0818	0.0444	1.8430	0.0038	0.2737
9	0.0712	0.0428	0.0364	0.0219	0.0697	0.0419	1.6636	−0.0011	0.0942
10	0.0769	0.0490	0.0374	0.0239	0.0790	0.0503	1.5694	0.0000	0.0000
11	0.0725	0.0510	0.0347	0.0244	0.0756	0.0532	1.4216	−0.0028	−0.1478
12	0.0646	0.0516	0.0296	0.0236	0.0705	0.0563	1.2519	−0.0079	−0.3175
13	0.0587	0.0420	0.0259	0.0185	0.0666	0.0476	1.3976	−0.0116	−0.1718
14	0.0626	0.0534	0.0270	0.0230	0.0725	0.0619	1.1723	−0.0105	−0.3971
15	0.0549	0.0363	0.0230	0.0152	0.0656	0.0434	1.5124	−0.0145	−0.0570
16	0.0587	0.0510	0.0242	0.0210	0.0712	0.0619	1.1510	−0.0133	−0.4184
17	0.0595	0.0507	0.0245	0.0209	0.0723	0.0616	1.1736	−0.0130	−0.3958
18	0.0561	0.0503	0.0219	0.0197	0.0717	0.0643	1.1153	−0.0156	−0.4541

Table 1 presents the various global and local reactivity descriptors for the carbonyl compounds. The expected reactivity trends[17] (intermolecular electrophilicity) would be (Table 1)

(i) $CH_3CHO > CH_3COCH_3 > C_2H_5COC_2H_5$

(ii) $CH_2ClCHO > CH_2FCHO$

(iii) $CH_2 = CHCHO > CH_3CH = CHCHO > C_6H_5CH = CHCHO$

(iv) $C_6H_5COCH_3 > C_6H_5COC_2H_5 > C_6H_5COC_6H_5$

It is heartening to note (Table 1) that ω_k^+ values on $C_{C=O}$ provide correct trends in more cases in both MPA and HPA when compared to that with s_k^+/s_k^-, totally against the claim of Roy.[17]

Comparing the intramolecular nucleophilicity on these carbonyl compounds (Table 1), one observes that both ω_k^- and s_k^-/s_k^+ can properly take care of the correct trend, viz., the $O_{C=O}$ to be the strongest nucleophilic center.

Table 2 provides the global and local reactivity descriptors for the chloro compounds considered in ref 18. We analyze the same set of molecules, grouped in a similar fashion (see below), as in ref 18.

Series I:

$$C_6H_5CH_2Cl > CH{\equiv}C{-}CH_2Cl > CH_2{=}CH{-}CH_2Cl > CH_3CH_2Cl$$

It is important to note that only global ω can reproduce the correct trend and neither s_k^+/s_k^- nor ω_k^+ can reproduce the exact trend.

Series II:

$$CH_3CH_2CH_2CH_2Cl > CH_3CH\,(CH_3)CH_2Cl > CH_3CH_2CH(CH_3)Cl > CH_3C(CH_3)_2Cl$$

Global ω cannot reproduce the expected trend. The ω_k^+ reproduces the trends in both MPA and HPA but for molecule 6 whereas the order for s_k^+/s_k^- with MPA is wrong.

Series III:

$$C_6H_5CH_2Cl > C_6H_5CH_2CH_2Cl$$

Global ω reproduces the trend. The ω_k^+ values calculated using both MPA and HPA provide the correct trend whereas s_k^+/s_k^- values calculated using MPA give the wrong trend.

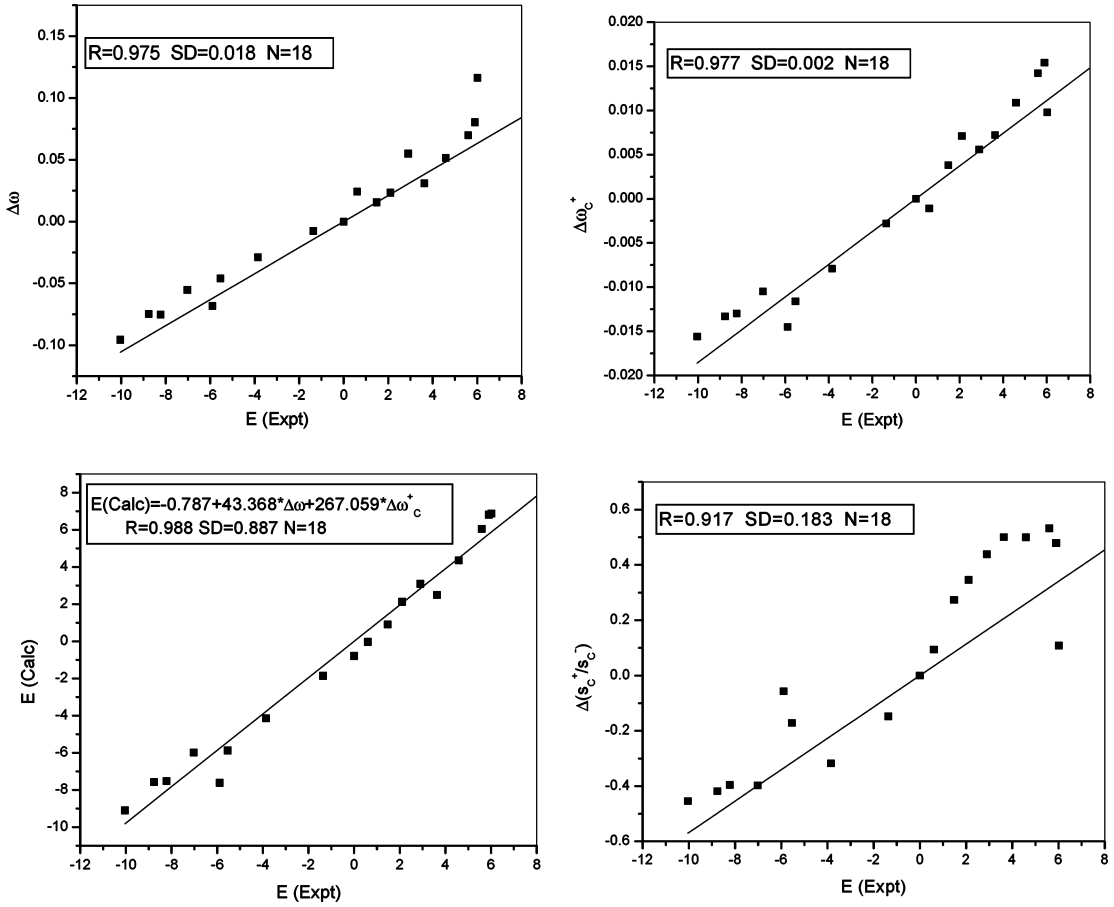

Figure 8. Calculated versus experimental electrophilicities of 18 benzhydryl cations.

Series IV:

$$CH{\equiv}C{-}CH_2Cl > CH{\equiv}C{-}CH_2CH_2Cl$$

Global ω reproduces the trend. The ω_k^+ *values calculated using both MPA and HPA provide the correct trend whereas* s_k^+/s_k^- *values calculated using both MPA and HPA provide the wrong trend.*

Series V:

$$CH_2{=}CH{-}CH_2Cl > CH_2{=}CH{-}CH_2CH_2Cl$$

Global ω reproduces the trend. The ω_k^+ *values calculated using both MPA and HPA provide the correct trend whereas* s_k^+/s_k^- *values calculated using MPA give the wrong trend.*

Series VI:

$$CH_3CH\ (Cl)\ COOC_2H_5 > ClCH_2CH_2COOC_2H_5$$

Global ω reproduces the trend. The ω_k^+ *values calculated using both MPA and HPA provide the correct trend whereas* s_k^+/s_k^- *values calculated using MPA provide the wrong trend.*

Series VII:

$$CH_3\,CH\ (Cl)COC_2H_5 > ClCH_2CH_2COC_2H_5$$

Global ω reproduces the trend. The ω_k^+ *values calculated using both MPA and HPA provide the correct trend whereas* s_k^+/s_k^- *values calculated using MPA give the wrong trend.*

It is important to point out the following to put everything in proper perspective.[34]

1. For the intramolecular reactivity, philicity, local softness and Fukui function provide the same trend and hence are equally reliable, except for some intramolecular processes where both the global and local quantities change. Relative electro(nucleo)-philicity is identical with the relative Fukui function in all cases.[34a]

2. For the intermolecular reactivity, when two molecules react, which one will act as an electrophile (nucleophile) will depend on which has a higher (lower) electrophilicity index. This global trend originates from the local behavior of the molecules or precisely the atomic sites, which are prone to electrophilic (nucleophilic) attack. During an electrophile−nucleophile interaction process, when two reactants approach each other from a large distance, they see each other's global electrophilicities without any idea about their local counterparts. The one with the larger electrophilicity will behave as an electrophile and the other as a nucleophile. The most electrophilic site of the electrophile will prefer to interact with the most nucleophilic site of the nucleophile. It may be noted that the atom with the maximum value of the local electrophilicity in the electrophile may not necessarily have a larger local electrophilicity value than that of the most electrophilic atom in the nucleophile. A similar situation will arise during the hard−soft interaction and will show that the local HSAB principle may not be always in conformity with its global counterpart. The Fukui function and all other related descriptors such as local softness and philicity may not provide reasonable trends for the hard−hard reactions where charge based descriptors are known to be more appropriate.

3. For testing the intramolecular and the intermolecular reactivities, we calculate more or less at the same level of theory

and using the same population analysis schemes, the various global and local reactivity descriptors using the same molecules chosen in refs 17 and 18, group as they did, and analyze in the same line as they did. It is clearly delineated that there is hardly any reason to consider the relative electro(nucleo)philicity to be the best. Indeed, the philicity provides a much better result in a higher number of cases. We had our results rechecked by Accelrys Inc., which confirmed their accuracy.[35]

However, they have mentioned that there would be some variation from version to version mainly because of improvement in the basis set quality and also from using different options.[35] This is confirmed through explicit calculations (Tables S1−S7).

Optimized structures of 18 benzhydryl cations are provided in Figure 7, and their global and local descriptors are presented in Tables 3 and 4, respectively. Excellent correlation between the theoretically calculated electrophilicity and its experimental counterpart is obtained (Figure 8). The importance of using both local and global quantities is highlighted.

4. The conceptual and technical problems associated with the relative electro(nucleo)philicity as pointed out by others are cited and the original papers may be checked for details.

Conclusions

Various applications of the philicity concept are presented that provide satisfactory results as well as important insights into structure, properties, kinetics, reactivity, toxicity, and reaction mechanism. Some recently reported misconceptions associated with the philicity concept are addressed. Through numerical calculations on the same set of molecules as well as through analytical reasoning it is clearly demonstrated that the philicity is a better intermolecular reactivity descriptor than the relative electro(nucleo)philicity and there is hardly any choice of one above the other when intramolecular reactivity is concerned.

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Supporting Information Available: Tables of Fukui functions, global electrophilicity indexes, and local philicities. This material is available free of charge via the Internet at http://pubs.acs.org.

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