Intermolecular reactivity through the generalized philicity concept

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Abstract

In the light of the generalized philicity concept, intermolecular reactivity of some selected systems is analyzed and the concept of group philicity (ω_g) has been proposed. It can be found that DFT offers the possibility to calculate important functional group properties from the first principles in a non-empirical way. Unified philicity clearly predicts the exact reactivity trends for all the selected systems. In conjunction with the electrophilicity, ω_g^+ offers direct availability of charge distributions of molecular systems in a more pronounced way than the relative electrophilicity/nucleophilicity and the group softness and might be of importance in reactivity studies.
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1. Introduction

Conceptual density functional theory (DFT) has been widely used to understand the chemical reactivity and site selectivity of the molecular systems [1–27]. Chemical potential, global hardness, global softness, electronegativity and electrophilicity are the global reactivity descriptors, highly successful in predicting global chemical reactivity trends. Fukui function (FF) and local softness are extensively applied to probe the local reactivity and site selectivity. The formal definitions of all these descriptors and working equations for their computation have been clearly described [1–4]. Various applications of both the global and the local reactivity descriptors in the context of chemical reactivity and site selectivity have been reviewed in detail [3,4].

Concept of electrophilicity (ω) was introduced by Parr et al. [5] as a global reactivity index similar to the chemical hardness and chemical potential. This new re-

activity index measures the stabilization in energy when the system acquires an additional electronic charge ΔN from the environment. The electrophilicity is defined as

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

In Eq. (1), $\mu \approx -(I + A)/2$ and $\eta \approx (I-A)/2$ are the electronic chemical potential and the chemical hardness of the ground state of atoms and molecules, respectively, approximated in terms of the vertical ionization potential (I) and electron affinity (A). The electrophilicity is a descriptor of reactivity that allows a quantitative classification of the global electrophilic nature of a molecule within a relative scale [5].

In addition to the knowledge of global softness (S) [6], different local softnesses [8] used to describe the reactivity of atoms in molecule can be defined as

$$S_k^\alpha = S f_k^\alpha, \tag{2}$$

where ($\alpha = +, -$ and 0) represents local softness quantities describing nucleophilic, electrophilic and radical attacks, respectively. Based on local softness, relative nucleophilicity (sk^-/sk^+) and relative electrophilicity (sk^+/sk^-) indices have also been defined and their

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usefulness to predict reactive sites has also been addressed [14]. It has been established that the quantum chemical model selected to derive wave function, population scheme used to obtain the partial charges and basis set employed in the molecular orbital calculations are important parameters, which significantly influence the FF values [7–19].

Geerlings and co-workers [10–13] have made systematic studies to understand the intermolecular reactivity with the aid of various local reactivity descriptors and their variants in the cases of active functional groups. It was found that the local softness is inadequate to provide the correct intermolecular reactivity trends and hence, the power of group softness [10,11] as a local reactivity descriptor has been highlighted [18]. The group softness is defined as

$$S_g = \sum_{k=1}^{n} S_k. \tag{3}$$

Recently, the generalized concept of philicity has been proposed by Chattaraj et al. [20]. It contains almost all information about hitherto known different global and local reactivity and selectivity descriptors, in addition to the information regarding electrophilic/nucleophilic power of a given atomic site in a molecule. It is possible to define a local quantity called philicity associated with a site k in a molecule with the help of the corresponding condensed-to-atom variants FF f_k^α, as

$$\omega_k^\alpha = \omega f_k^\alpha, \tag{4}$$

where ($\alpha = +, -$ and 0) represents local philic quantities describing nucleophilic, electrophilic and radical attacks. Eq. (4) predicts that the most electrophilic site in a molecule is the one providing the maximum value of ω_k^+. 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 at the atomic site(s) that is prone to electrophilic (nucleophilic) attack. Chattaraj et al. [20] established a generalized treatment of both global and local electrophilicity, as well as nucleophilicity. Recently, the usefulness of electrophilicity index in elucidating the toxicity of benzidine and polychlorinated biphenyls has been assessed in detail [21,22,24]. It has also been shown that the philicity is a reliable descriptor for both intermolecular [25–27] and intramolecular [23,26,27] reactivity, including single as well as multiple reactivity centers. For a critical analysis of the reliability of the philicity as a descriptor of intermolecular and intramolecular reactivity, see [26].

In the exploration of new reactivity descriptors to probe the reactivity of chemical systems, a new philicity-based descriptor using group approach has been defined. In the present work, we have emphasized the usefulness of the unified philicity concept and the group philicity (ω_g) to predict the intermolecular reactivity trends in various carbonyl compounds.

2. Group concepts in chemical reactivity

The use of group concepts in unraveling reactivity of various molecular systems is well known. The concept of grouping the reactivity descriptors like electronegativity of the functional atoms by Korchowiec and Nalewajski [9] and the group softness concept using the summation of the softnesses by Geerlings and co-workers [10,11] is known to be important. The use of group softness in understanding the intermolecular reactivity of various carbonyl compounds has also been demonstrated [18]. In order to obtain proper reactivity trends in these molecular systems, Pal and co-workers [18] have defined group softness (Eq. (3)) as the sum of softness over a group of relevant atoms. It is known that the differences in the strength of acidity among the group of molecules arise from the variations in geometry, substitutions of one atom by another atom, etc. Since group softness contains information about changes in the electron density at a particular site as well as the relevant neighboring atoms, it could explain intermolecular reactivity trends [10,11]. The effectiveness of electrophilicity and the unified philicity in exploring the chemical reactivity and site selectivity has recently been established [21–27]. The success of group-based approach in probing the chemical reactivity has led us to define a new group philicity descriptor.

3. Group philicity

The condensed philicity summed over a group of relevant atoms is defined as the 'group philicity'. It can be expressed as

$$\omega_g^\alpha = \sum_{k=1}^{n} \omega_k^\alpha, \tag{5}$$

where n is the number of atoms coordinated to the reactive atom, ω_k^α is the local electrophilicity of the atom k, and ω_g^α is the group philicity obtained by adding the local philicity of the nearby bonded atoms, ($\alpha = +, -$ and 0) represents nucleophilic, electrophilic and radical attacks, respectively. In the present study, we have used the nucleophilic group electrophilicity index (ω_g^+) for the selected systems to compare the chemical reactivity trends.

4. Computational details

The geometries of HCHO, CH$_3$CHO, CH$_3$COCH$_3$, and C$_2$H$_5$COC$_2$H$_5$ are optimized by HF/6-31G* using the GAUSSIAN 98 package [28]. Various reactivity and

selectivity descriptors such as chemical hardness, chemical potential, softness, electrophilicity and the appropriate local quantities employing Mulliken population analysis (MPA) and Hirshfeld population analysis (HPA) schemes are calculated. The HPA scheme (stockholder partitioning scheme) [29] as implemented in the DMOL^3 package has been used to calculate local quantities employing BLYP/DND method [30]. For a system of N electrons, independent calculations have been made using the population schemes on $N-1$, N and $N+1$-electronic systems with the same molecular geometry to get the charges $q_k(N-1)$, $q_k(N)$ and $q_k(N+1)$ for all atoms k and the corresponding FF values viz., f_k^+, f_k^- and f_k^0 were obtained. Using the standard working equations, both the global and local reactivity descriptors have been used to compute the group philicity as defined in Eq. (5).

5. Results and discussion

In this study, a series of carbonyl compounds have been selected to probe the usefulness of the unified philicity and the group philicity in comparison with the group softness and the relative electrophilicity. Due to

bipolar nature of C=O bond, both nucleophilic and electrophilic attacks are possible at C and O sites. It is expected that the rate of nucleophilic addition on the carbonyl compound be reduced by electron donating alkyl groups and enhanced by electron withdrawing ones [31,32]. The expected order for the possible nucleophilic addition reaction on carbon is $H_2CO > RCHO > RR'CO$, where R and R' are alkyl groups. In order to identify the possible site for nucleophilic addition, the local reactivity descriptors describing the nucleophilic attack at the carbon site have been used here to probe the intermolecular reactivity trends.

Series of carbonyl compounds considered for the present investigation and their calculated global molecular properties are shown in Table 1. The calculated local reactivity descriptors for these molecules are presented in Table 2. It is evident that f_k^+, s_k^+ and sk^+/sk^- values calculated from the MPA scheme could not explain the exact intermolecular reactivity trends in these compounds. Variations in the electron density around the reactive atom due to the changes in the geometry of the molecular system are not effectively reproduced by the MPA scheme. However, the same local quantities calculated from the HPA scheme provided the expected reactivity trends. It is clear from the

Table 1
Calculated global reactivity descriptors of the selected molecules

	Chemical hardness	Chemical potential	Electrophilicity	Softness
HF/6-31G (eV)*				
HCHO	7.914	−3.945	0.983	0.063
CH$_3$CHO	7.932	−3.498	0.772	0.063
CH$_3$COCH$_3$	7.831	−3.242	0.671	0.064
C$_2$H$_5$COC$_2$H$_5$	7.768	−3.115	0.625	0.064
C$_6$H$_5$CHO	5.884	−3.552	1.072	0.085
p-MeOC$_6$H$_4$CHO	5.715	−3.047	0.812	0.087
CH$_2$=CHCHO	6.602	−4.025	1.227	0.076
CH$_3$CH=CHCHO	6.481	−3.673	1.041	0.077
C$_6$H$_5$=CHCHO	5.210	−3.410	1.116	0.096
CH$_3$COCl	8.035	−4.228	1.112	0.062
CH$_3$COOCH$_3$	8.704	−3.335	0.639	0.057
BLYP/DND (eV)				
HCHO	1.942	−4.260	4.673	0.258
CH$_3$CHO	2.096	−3.791	3.425	0.238
CH$_3$COCH$_3$	2.133	−3.456	2.800	0.234
C$_2$H$_5$COC$_2$H$_5$	2.151	−3.367	2.635	0.233
C$_6$H$_5$CHO	1.643	−4.253	5.505	0.304
p-MeOC$_6$H$_4$CHO	1.709	−3.936	4.533	0.293
CH$_2$=CHCHO	1.545	−4.413	6.303	0.324
CH$_3$CH=CHCHO	1.593	−4.132	5.359	0.314
C$_6$H$_5$=CHCHO	1.383	−4.338	6.803	0.362
CH$_3$COCl	2.507	−4.525	4.084	0.199
CH$_3$COOCH$_3$	2.862	−3.378	1.993	0.175

Table 2
Calculated local molecular reactivity descriptors on the carbonyl carbon atoms of some selected compounds

	f_k^+	s_k^+	Group softness	s_k^+/s_k^-	ω_k^+	ω_g^+
Mulliken population analysis						
HCHO	0.303	0.019	0.063	0.577	0.298	0.983
CH_3CHO	0.287	0.018	0.040	0.590	0.222	0.493
CH_3COCH_3	0.246	0.016	0.021	0.557	0.165	0.221
$C_2H_5COC_2H_5$	0.251	0.016	0.019	0.563	0.157	0.186
C_6H_5CHO	0.156	0.013	0.040	0.366	0.168	0.501
p-$MeOC_6H_4CHO$	0.141	0.012	0.039	0.345	0.115	0.366
$CH_2{=}CHCHO$	0.152	0.012	0.038	0.358	0.186	0.615
$CH_3CH{=}CHCHO$	0.155	0.012	0.038	0.367	0.161	0.508
$C_6H_5{=}CHCHO$	0.096	0.009	0.021	0.248	0.107	0.243
CH_3COCl	0.033	0.002	0.046	0.164	0.037	0.823
CH_3COOCH_3	0.303	0.017	0.028	0.546	0.194	0.316
Hirshfeld population analysis						
HCHO	0.397	0.102	0.258	0.170	1.856	4.673
CH_3CHO	0.300	0.072	0.185	0.129	1.027	2.654
CH_3COCH_3	0.211	0.049	0.137	0.109	0.590	1.630
$C_2H_5COC_2H_5$	0.135	0.031	0.089	0.090	0.355	1.010
C_6H_5CHO	0.142	0.043	0.127	0.080	0.783	2.303
p-$MeOC_6H_4CHO$	0.142	0.042	0.119	0.070	0.642	1.847
$CH_2{=}CHCHO$	0.206	0.067	0.158	0.154	1.300	3.075
$CH_3CH{=}CHCHO$	0.174	0.055	0.170	0.111	0.933	2.902
$C_6H_5{=}CHCHO$	0.108	0.039	0.132	0.083	0.733	2.490
CH_3COCl	0.233	0.047	0.159	0.076	0.952	3.246
CH_3COOCH_3	0.129	0.023	0.072	0.079	0.258	0.818

analysis that the bottleneck in understanding the chemical reactivity and site selectivity with the help of DFT-based descriptors mainly arise from the level of treatment, choice of basis set and the use of appropriate population analysis scheme. Several research workers have explained the usefulness of HPA scheme in determining local quantities in the recent past [17,21–24].

In order to explore the predictive ability of group philicity, the local electrophilicity of the first group of nearly coordinated three atoms has been added to the local electrophilicity of the carbonyl carbon of carbonyl compounds so as to obtain the group electrophilicity index (ω_g^+) values. It is interesting to note that both local philicity (ω_k^+) and group philicity (ω_g^+) calculated from MPA and HPA schemes yield an appropriate reactivity trend as HCHO > CH_3 CHO > CH_3COCH3 > $C_2H_5COC_2H_5$. It is interesting to note that irrespective of the population schemes used in the calculation, both ω_k^+ and ω_g^+ quantitatively provide the meaningful reactivity trends.

Reactivity trends of C_6H_5CHO, p-$MeOC_6H_4CHO$ systems have been analyzed with the help of group softness [18]. Although the differences in the local softness indices derived from MPA scheme are very small, a rea-

sonable difference between the two systems can be obtained with the help of local philicity and group philicity values. It is evident from the reactivity descriptors that the reactivity of these two systems follows the order C_6H_5CHO > p-$MeOC_6H_4CHO$.

Krishnamurti et al. have also chosen $CH_2{=}CHCHO$, $CH_3CH{=}CHCHO$ and C_6H_5 $CH{=}CHCHO$ molecular systems to probe the intermolecular reactivity trends using group softness [18]. From the values of group softness, they have predicted the expected acidity trends as $CH_2{=}CHCHO$ > $CH_3CH{=}CHCHO$ > $C_6H_5CH{=}CH$ CHO. A similar trend has been achievable from the condensed philicity and the group philicity values shown in Table 2. For a given series of chemical compounds, a sizeable difference in the values of local philicity and the group philicity between two molecules can be noted from the results. This difference helped to make unambiguous ordering of the reactivity trend with the help of the local philicity and the group philicity. This observation clearly demonstrates that the electrophilicity-derived quantities are better descriptors of intermolecular reactivity trends than the group softness (Table 2), which does not clearly reproduce the correct reactivity trend for this set of molecules even using the HPA

scheme. Since global electrophilicity of two different molecules is different, the best sites of two different molecules for a given reaction can be explained only in terms of the philicity and not by the FF. Hence, electrophilicity-based local quantities are better descriptors of intermolecular chemical reactivity. Similar, reactivity trend has also been studied for CH_3COCl and CH_3COOCH_3 systems and it has been observed that the condensed philicity and the group philicity values calculated from the HPA scheme yield the expected reactivity trend as $CH_3COCl > CH_3COOCH_3$. In addition, the calculation on the relative electrophilicity/nucleophilicity has also been made. The results on relative electrophilicity/nucleophilicity obtained from the MPA scheme fail to predict the exact intermolecular reactivity trends. However, this quantity calculated with the HPA scheme yields an appropriate ordering in the reactivity for all systems considered in this present investigation except for this set of molecules. It is evident from the results that the major factor, which influences the exact reactivity trend, is the choice of the population analysis scheme. Since HPA scheme is inherently superior to MPA scheme from the point of view of the partitioning of the electron density, the local quantities derived from the HPA scheme clearly distinguish the reactivity of two different sites in two different molecules. Both ω_k^+ and ω_g^+ provide exact reactivity trends for all the systems obtained using HPA scheme. Even the MPA scheme results for ω_k^+ and ω_g^+ for all the systems are in accordance with expected reactivity trends except in the case of CH_3COCl and CH_3COOCH_3 systems. The results presented in this investigation have shown that philicity and group philicity predict unambiguous ordering of the reactivity trend in a series of molecules in a more effective manner than the other local reactivity descriptors and may provide a better insight while dealing with reactivity and selectivity of various chemical systems. These descriptors have wider application in the area of drug design and in developing a new QSPR/QSAR.

6. Summary

Philicity values calculated using the HPA/MPA scheme provide appropriate intermolecular reactivity trends for several sets of molecules. A new chemical reactivity descriptor, namely the group philicity, has been defined based on group approach in the light of the unified philicity. The global electrophilicity index contains more information about electrophilic attack when compared to the global softness and as a consequence the local ω_k^+ has added information than the corresponding s_k^+ in providing the corresponding intermolecular reactivity trends. The usefulness of these descriptors in explaining the reactivity trends in carbonyl compounds

has been studied and the reactivity trends have also been compared with those obtained from other local quantities, including the relative electrophilicity and the group softness. Group philicity values derived from both MPA and HPA schemes have provided the expected reactivity trends in all sets of molecules considered for evaluation. Hence, philicity and group philicity can be used as better chemical reactivity descriptors when compared to all other local reactivity descriptors.

References

[1] R.G. Parr, W. Yang, Density Functional Theory of Atoms and Molecules, Oxford University Press, Oxford, 1989.
[2] R.G. Pearson, Chemical Hardness – Applications from Molecules to Solids, VCH-Wiley, Weinheim, 1997.
[3] H. Chermette, J. Comp. Chem. 20 (1999) 129.
[4] P. Geerlings, F. De Proft, W. Langenaeker, Chem. Rev. 103 (2003) 1793.
[5] R.G. Parr, L.V. Szentpaly, S. Liu, J. Am. Chem. Soc. 121 (1999) 1922.
[6] W. Yang, R.G. Parr, Proc. Natl. Acad. Sci. USA 82 (1985) 6723.
[7] W. Yang, W.J. Mortier, J. Am. Chem. Soc. 108 (1986) 5708.
[8] C. Lee, W. Yang, R.G. Parr, J. Mol. Struct. (Theochem) 163 (1988) 305.
[9] J. Korchowiec, R.F. Nalewajski, Int. J. Quantum Chem. 44 (1992) 1027.
[10] F. De Proft, W. Langenaeker, P. Geerlings, J. Phys. Chem. 97 (1993) 1826.
[11] F. De Proft, K. Choho, S. Amira, P. Geerlings, J. Phys. Chem. 98 (1994) 5227.
[12] W. Langenaeker, F. De Proft, P. Geerlings, J. Mol. Struct. (Theochem) 362 (1996) 175.
[13] F. De Proft, M.L.J. Martin, P. Geerlings, Chem. Phys. Lett. 256 (1996) 400.
[14] R.K. Roy, S. Krishnamurti, P. Geerlings, S. Pal, J. Phys. Chem. A 102 (1998) 3746.
[15] R.R. Contreras, P. Fuentealba, M. Galván, P. Pérez, Chem. Phys. Lett. 304 (1999) 405.
[16] R.K. Roy, S. Pal, K. Hirao, J. Chem. Phys. 110 (1999) 8236.
[17] R.K. Roy, S. Pal, K. Hirao, J. Chem. Phys. 117 (2000) 1372.
[18] S. Krishnamurti, S. Pal, J. Phys. Chem. A 104 (2000) 7639.
[19] P. Thanikaivelan, J. Padmanabhan, V. Subramanian, T. Ramasami, Theor. Chem. Acc. 107 (2002) 326.
[20] P.K. Chattaraj, B. Maiti, U. Sarkar, J. Phys. Chem. A 107 (2003) 4973.
[21] R. Parthasarathi, J. Padmanabhan, V. Subramanian, U. Sarkar, B. Maiti, P.K. Chattaraj, Internet Electron. J. Mol. Des. 2 (2003) 798.
[22] R. Parthasarathi, J. Padmanabhan, V. Subramanian, B. Maiti, P.K. Chattaraj, J. Phys. Chem. A 107 (2003) 10346.

[23] L. Meneses, W. Tiznado, R.R. Contreras, P. Fuentealba, Chem. Phys. Lett. 383 (2004) 181.

[24] R. Parthasarathi, J. Padmanabhan, V. Subramanian, B. Maiti, P.K. Chattaraj, Curr. Sci. 86 (2004) 535.

[25] R.K. Roy, J. Phys. Chem. A 108 (2004) 4934.

[26] P.K. Chattaraj, U. Sarkar, Internet Electron. J. Mol. Des., Proceedings of the IECMD (in press).

[27] P.K. Chattaraj, U. Sarkar, R. Parthasarathi, V. Subramanian, Int. J. Quant. Chem., Proceedings of the DFT conference held at Brussels, Belgium (in press).

[28] M.J. Frisch et al., GAUSSIAN 98, Revision A.5, Gaussian Inc., Pittsburgh, PA, 1998.

[29] F.L. Hirshfeld, Theor. Chim. Acta 44 (1977) 129.

[30] DMOL^3, Accelrys, Inc. San Diego, CA.

[31] J. March, Advanced Organic Chemistry: Reactions, Mechanisms and Structure, Wiley, New York, 1998.

[32] F.A. Carey, R.J. Sundberg, Advanced Organic Chemistry, Part A: Structure and Mechanisms, fourth edn., Kluwer Academic/ Plenum Publishers, New York, 2000.