pK_a Prediction Using Group Philicity

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Acid−base dissociation constants (pK_a values) are important in understanding the chemical, environmental and toxicological properties of molecules. Though various methods have been developed to predict pK_a by experimental and theoretical models, prediction of pK_a is still complicated. Hence, a new approach for predicting pK_a using the group philicity concept has been attempted. Presence of known functional groups in a molecule is utilized as the most important indicator to predict pK_a. The power of this descriptor in describing pK_a for the series of carboxylic acids, various substituted phenols, anilines, phosphoric acids, and alcohols is probed. Results reveal that the group electrophilicity is suitable for effectively predicting the pK_a values.

Introduction

Acid−base dissociation constant (pK_a value) is a measure of the strength of an acid or a base. Chemical properties of molecules mainly depend on its ionization behavior. It governs the form of the substance which in turn determines its behavior and transport. In the world of chemoinformatics, there is an immense interest in developing new and better models for pK_a prediction. Various research groups were focusing on the new approaches using molecular modeling and statistical methods to predict pK_a values, because of its relevance to physicochemical properties, chemical synthesis, pharmacodynamics/kinetics, drug design, mammalian toxicology and environmental issues.[1] Li and Cui[2] have developed a new approach to pK_a prediction using a hybrid quantum mechanical/molecular mechanical potential and the free energy perturbation technique.

Numerous studies and various approaches have been used in the calculation of pK_a and relationship between pK_a and a variety of pharmacological properties are also reported.[1−5] pK_a values can also be calculated using formalisms from statistical thermodynamics. [6−9] Fragment-based methods are well-known and are available in commercial programs but they are limited in scope.[10] Efficient software packages have been implemented to predict the values. However, due to their fragment based approach, they are inadequate when fragments present in a molecule under study are absent in the database. Such pK_a prediction only depends on the compounds very similar to those available in the training set. In the present study, we have chosen to model the pK_a of the following well-known classes of compounds: carboxylic acids, phenols, anilines, phosphoric acids, and alcohols. Modeling the pK_a of carboxylic acids using semiempirical methods, workers in the field attempted quantum chemical analyses of the dissociation constants and comparative molecular field analyses.[11−13] However, these approaches are computationally expensive and they involve diverse structures and complexity. Ab initio approaches have also been extended to model the pK_a for a set of phenols using various quantum chemical parameters.[14]

Density functional theory based descriptors have found immense use in the prediction of reactivity of atoms and molecules as well as site selectivity.[15−18] Chemical hardness (η), chemical potential (μ), polarizability (α), and softness are known as global reactivity descriptors. The Fukui function (FF) and local softness are called local reactivity descriptors. Parr et al.[19] have defined a new descriptor to quantify the global electrophilic power of the molecule as electrophilicity index (ω), which defines a quantitative classification of the global electrophilic nature of a molecule within a relative scale. Recently, Chattaraj et al.[20] have proposed more powerful descriptors of reactivity and site selectivity. Subsequently, attempts have been made to probe the power of electrophilicity and other global quantities in the QSAR parlance.[21] The usefulness of electrophilicity index in unraveling the toxicity of polychlorinated biphenyls and benzidine has been analyzed.[22] Usefulness of electrophilicity in describing the biological activity and toxicity prediction has also been established.[23]

According to the Brønsted−Lowry classifications, acids are proton donors, and a stronger acid is characterized by a smaller pK_a value whereas the Lewis acids are defined in terms of their capability to accept a pair of electrons so that the electrophilicity may be a measure of their strengths.[24] A connection between these two quantities becomes natural within the context of a generalized acid−base framework. Although, electrophilicity is considered to be a kinetic quantity (electron affinity being its thermodynamic counterpart which, however, does not correlate well in all cases with pK_a)[25a] it has been shown that it possesses enough thermodynamic information.[25b,c] Recently, our group has proposed the group philicity[26] in the light of generalized philicity concept and in the present study we have utilized the group philicity as a descriptor to predict the pK_a of a series of carboxylic acids, various substituted phenols, anilines, phosphoric acids, and alcohols.

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Theoretical Background

The conceptual density functional theory provides rigorous theoretical basis for various descriptors of global and local reactivity. Both global and local reactivity descriptors and various electronic structure principles have been applied in numerous situations to understand the chemical reactivity and site selectivity.[15−23] The definitions of various descriptors and their usefulness in elucidation of structure−reactivity correlations have been elegantly highlighted in the recent reviews.[17,18] Parr et al. [19] have introduced the global electrophilicity index (ω) as a measure of energy lowering due to maximal electron flow between donor and acceptor in terms of chemical potential and hardness as

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

In eq 1 $\mu \approx -(I + A)/2$ and $\eta \approx (I - A)/2$ are the chemical potential and the chemical hardness, respectively, approximated in terms of the vertical ionization potential (I) and electron affinity (A).

Recently, the generalized concept of philicity was proposed.[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 aid of the corresponding condensed-to-atom Fukui function (f_k^α),[15,17−22] as

$$\omega_k^\alpha = \omega f_k^\alpha \tag{2}$$

where $\alpha = +, -$, and 0 represents local philic quantities describing nucleophilic, electrophilic, and radical attacks.

The condensed philicity summed over a group of relevant atoms is defined as the "group philicity".[26] It can be expressed as

$$\omega_g^\alpha = \sum_{k=1}^{n} \omega f_k^\alpha \tag{3}$$

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, $\alpha = +, -, 0$ represents nucleophilic, electrophilic and radical attacks, respectively. In the present study we have used the nucleophilic group philicity index (ω_g^+) for the selected systems to compare their chemical reactivity trends.

Computational Details

The geometries of all the selected series of molecules are optimized at HF/6-31G* level using the GAUSSIAN 98 package.[27] Various reactivity and selectivity descriptors such as chemical hardness, chemical potential, electrophilicity and the appropriate local quantities employing Hirshfeld population analysis (HPA)[28] scheme are calculated. The HPA scheme (Stockholder partitioning scheme) as implemented in the DMOL^3 package[29] has been used to calculate local quantities employing BLYP/DND method. 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 are obtained. Using the standard working equations, both the global and local reactivity descriptors have been used to compute group philicity as defined in eq 3. One parameter regression analysis is performed using a least-squares error estimation method to calculate the pK_a values.[30]

Results and Discussion

pK_a demonstrates the proton donating capacity of a molecule whereas electrophilicity is a descriptor of reactivity that allows a quantitative classification of the global electrophilic nature (electron accepting capacity) of a molecule within a relative scale. When two molecules react, one that has a higher (lower) electrophilicity index will act as an electrophile (nucleophile). This reactivity index measures the stabilization in energy when the system acquires an additional electronic charge ΔN from the environment. Principally, reactivity of a molecule is based on primary, secondary and tertiary types of atoms in a molecule. The primary atom type is based on the atoms, the group, and its valence. Secondary atoms access the effects of nearby formal charges and tertiary atoms determine the charge states that are allowed for each atom in a molecule. In line with the above arguments, the electrophilicity (of a whole molecule, which determines the molecular reactivity), the local philicity (which identifies the particular reactive site of a molecule), and the group philicity (which provides the effects of nearby atoms, thereby explaining inter- and intramolecular reactivity trends) are used to predict the pK_a of the series of organic molecules.

It is well-known from the structure−activity studies that development of QSAR involves the use of a variety of descriptors such as shape, size, and electronic, thermodynamic, and quantum chemical properties etc. Since many descriptors are available, development and selection of appropriate descriptors in describing a selected property becomes a herculean task. In this context, the approach with limited number of descriptors in the development of QSAR is very important. The density functional based descriptors offer a powerful solution to this problem. Since the pK_a values of the series of homologous compounds are dependent on the changes in the functional group, the application of group philicity concept in the prediction of the pK_a value has been envisaged in this study.

For the prediction of the pK_a values, a series of carboxylic acids are chosen as model systems (Table 1). Since only the (O═C)-O−H fragment is common to all the molecules, we restrict the group philicity calculation to those atoms. The calculated pK_a values obtained using group philicity (ω_g^+) of substituted carboxylic acids are presented in Table 1 along with the experimental pK_a values.[31] The group philicity describing the local nucleophilic attack (ω_g^+) has been used here to develop a QSAR. A linear regression analysis is performed with group philicity as independent variable and experimental pK_a value as dependent variable for the series of carboxylic acids. The calculated linear relationship is

$$\mathrm{p}K_a = -4.51\omega_g^+ + 7.4$$
$$N = 31, \quad r = -0.86, \quad \mathrm{SD} = 0.12 \tag{4}$$

The relationship between the experimental pK_a values of substituted carboxylic acids with group philicity index (ω_g^+) is plotted in Figure 1. The inverse relationship between group philicity and experimental pK_a values is evident from the correlation coefficient ($r = -0.86$). This suggests the fact that group philicity can be used as a possible descriptor in the prediction of pK_a.

TABLE 1: Group Philicity Index of Substituted Carboxylic Acids with Experimental and Calculated pK_a Values

compounds	group philicity (ω_g^+)	exptl pK_a[a]	calcd pK_a
pivalic acid	0.612	5.05	4.58
propionic acid	0.661	4.87	4.35
isobutyric acid	0.618	4.86	4.55
valeric acid	0.653	4.86	4.39
butyric acid	0.65	4.82	4.41
isovaleric acid	0.664	4.78	4.34
acetic acid	0.694	4.76	4.2
4-bromobutyric acid	0.713	4.58	4.12
4-chlorobutyric acid	0.709	4.52	4.13
isocrotonic acid	0.946	4.41	3.04
glutaric acid	0.718	4.35	4.09
vinylacetic acid	0.537	4.34	4.93
succinic acid	0.828	4.2	3.58
3-bromopropionic acid	0.713	3.99	4.12
lactic acid	0.713	3.86	4.12
glycolic acid	0.699	3.83	4.18
2-hydroxybutyric acid	0.74	3.68	3.99
mercaptoacetic acid	0.532	3.67	4.95
formic acid	0.812	3.55	3.66
2-bromopropionic acid	1.13	2.97	2.19
bromoacetic acid	0.77	2.9	3.85
2-chloropropionic acid	1.053	2.88	2.55
2-chlorobutyric acid	1.024	2.84	2.68
malonic acid	0.851	2.83	3.48
chloroacetic acid	0.813	2.82	3.65
fluoroacetic acid	0.871	2.59	3.39
2-bromobutyric acid	1.121	2.55	2.23
cyanoacetic acid	1.036	2.45	2.63
dichloroacetic acid	1.298	1.26	1.42
difluroacetic acid	1.141	1.24	2.14
trichloroacetic acid	1.389	0.63	1

[a] Experimental data as in ref 31.

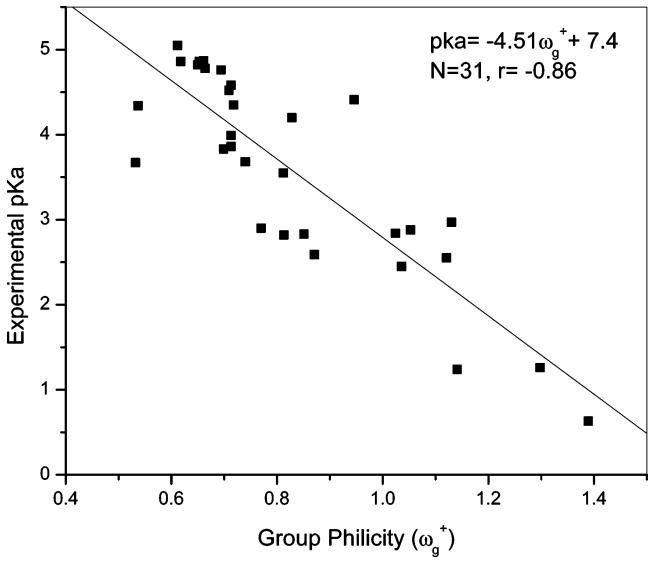

Figure 1. Relationship between the experimental pK_a values of substituted carboxylic acids with group philicity index.

The calculated group philicity (ω_g^+) and experimental [31] and computed pK_a values of the selected set of substituted phenols are given in Table 2. In the phenolic series, the important functional groups of atoms (OH) are utilized to calculate the group philicity (ω_g^+). The plot between experimental pK_a values and group philicity is shown in Figure 2. The linear regression equation is

$$pK_a = -6.08\omega_g^+ + 10.5$$
$$N = 9, \quad r = -0.88, \quad SD = 0.63 \qquad (5)$$

TABLE 2: Group Philicity Index of Substituted Phenols with Experimental and Calculated pK_a Values

compound	group philicity (ω_g^+)	exptl pK_a[a]	calcd pK_a
o-methylphenol	0.11	10.3	9.85
o-chlorophenol	0.15	8.6	9.59
o-nitrophenol	0.53	7.2	7.30
m-nitrophenol	0.49	8.4	7.55
p-methoxyphenol	0.11	10.2	9.85
p-methylphenol	0.12	10.3	9.79
p-chlorophenol	0.15	9.4	9.56
p-nitrophenol	0.44	7.2	7.85
p-hydroxyphenol	0.12	9.8	9.8

[a] Experimental data as in ref 31.

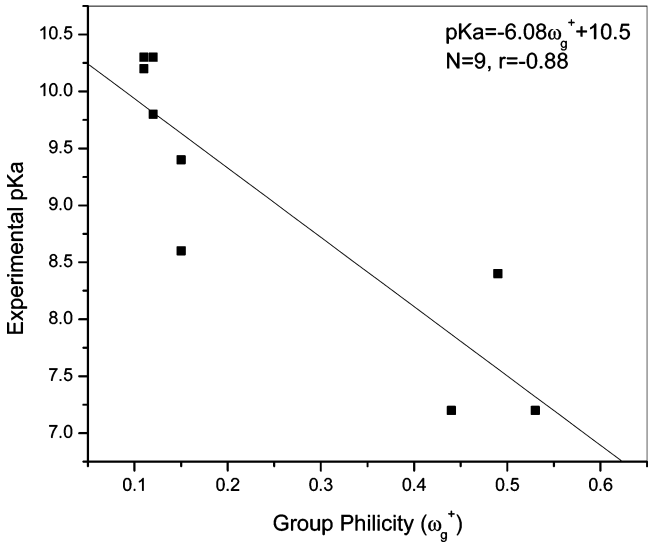

Figure 2. Relationship between the experimental pK_a values of substituted phenols with group philicity index.

The linear fit provides a correlation coefficient, $r = -0.88$ indicating once again the inverse relationship between the group philicity and pK_a values.

To verify the relationship between pK_a vs group philicity for diverse sets of functional groups, analysis has been extended to series of substituted anilines (NH_2),[14] phosphoric acids (PO_4),[32] and alcohols (OH).[1,13] The linear regression equation for the combined set of substituted anilines (NH_2) and phosphoric acids (PO_4) is

$$pK_a = -50.59\omega_g^+ + 6.24$$
$$N = 14, \quad r = -0.85, \quad SD = 0.48 \qquad (6)$$

Similarly, the linear regression equation for the set of alcohols is

$$pK_a = -30.43\omega_g^+ + 23.62$$
$$N = 9, \quad r = -0.91, \quad SD = 0.73 \qquad (7)$$

The computed group philicity and experimental pK_a values along with predicted pK_a values calculated using the functional group of the respective series (in parentheses as mentioned above) have been presented in Table 3. The linear regression analysis with correlation coefficient(r), providing the relationship between the proposed models for combined set of anilines and phosphoric acids (Figure 3) and alcohols (Figure 4) have been shown. From the results it is clear that the present model reliably predicts pK_a values.

TABLE 3: Group Philicity Index of Substituted Anilines,[a] Phosphoric Acids,[b] and Alcohols[c] with Experimental and Calculated pK_a Values

compounds	group philicity (ω_g^+)	exptl pK_a*	calcd pK_a
m-bromoaniline	0.049	3.51	3.75
m-fluoroaniline	0.045	3.59	3.95
m-hydroxyaniline	0.034	4.17	4.50
m-methylaniline	0.032	4.69	4.64
m-methoxyaniline	0.030	4.20	4.70
p-aminoaniline	0.023	6.08	5.09
p-braniline	0.045	3.91	3.97
p-hydroxyaniline	0.031	5.50	4.67
p-methylaniline	0.030	5.12	4.72
phosphoric acid monophenyl ester	0.008	5.83	5.83
phosphoric acid mono-(4-chlorophenyl ester)	0.009	5.84	5.78
phosphoric acid mono-(4-bromophenyl)	0.009	5.44	5.79
p-nitrophenyl phosphate	0.021	5.20	5.18
phosphotyrosine	0.004	5.55	6.04
2-butanol	0.194	17.6	17.7
1,2-ethanediol	0.346	13.6	13.1
1,2-propanediol	0.297	14.9	14.6
1,3- propanediol	0.282	15.1	15.0
1,4-butanediol	0.257	15.1	15.8
ethanol	0.263	15.9	15.6
propanol	0.239	16.2	16.4
tert-butyl alcohol	0.181	19.2	18.1
2-methoxyethanol	0.248	14.8	16.1

[a] Experimental data as in ref 14. [b] Experimental data as in ref 32. [c] Experimental data as in refs 1 and 13.

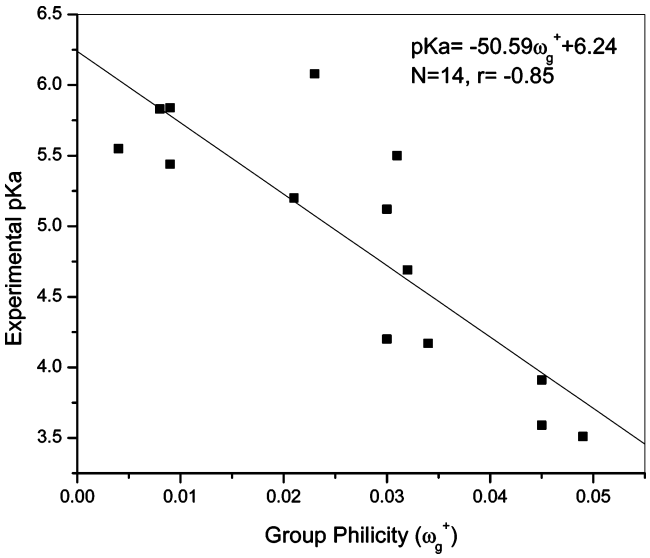

Figure 3. Relationship between the experimental pK_a values and group philicity index of substituted anilines and phosphoric acids.

To analyze the importance of group philicity (ω_g^+) in the heterogeneous molecular systems, both linear and second-order regression analyses have been carried out. It is evident from the linear regression analysis for all the molecules taken together, that there is no good linear relation (unlike the individual sets) between the pK_a values and the group philicity (ω_g^+). Polynomial second order analysis for all the 63 molecules provides a low correlation. To improve the quality of the polynomial regression, we choose to remove some of the compounds as outliers as followed in the standard QSAR methods. Best polynomial fit with high correlation coefficient ($R = 0.97$) has been achieved when we reduced the set of molecules from 63 to 43. Individually but not collectively all the selected sets correlate linearly with group philicity. Figure 5 clearly shows

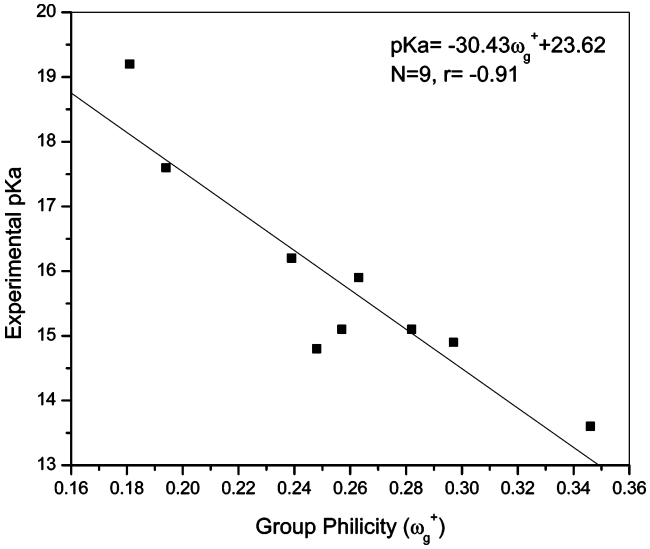

Figure 4. Relationship between the experimental pK_a values and group philicity index of alcohols.

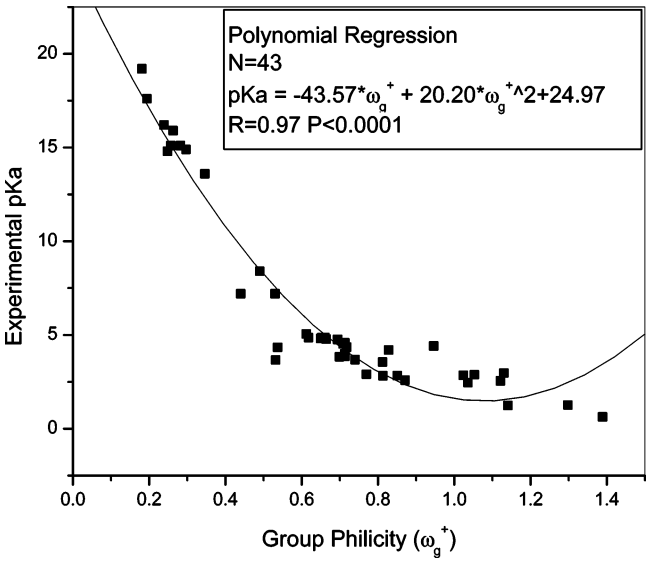

Figure 5. Polynomial second-order regression analysis of experimental pK_a values and group philicity index of series of carboxylic acids, various substituted phenols, anilines, phosphoric acids, and alcohols, excluding low-group philicity value species.

the second order relationship between the experimental pK_a values and the calculated group philicity. The second order polynomial fit (Figure 5) gives strong support that group philicity can effectively predict pK_a values for diverse classes of small molecules. The molecules appearing in the left-hand side of the plot are weak acids (both Lewis and Brønsted senses) whereas those in the right are strong acids both in the Brønsted and Lewis senses. This analysis clearly distinguishes the various functional groups in the training set considered in this study. As suggested by an anonymous reviewer, the hyperbolic relationship between experimental pK_a and ω_g^+ has also been attempted by plotting pK_a vs $1/\omega_g^+$, and it is shown in Figure 6. The straight line passing through origin confirms the hyperbolic (rectangular) nature of the relationship between pK_a and ω_g^+ for a heterogeneous set of compounds.

Finally, Figure 7 depicts the predicted (calculated with separate regression for individual sets) vs experimental pK_a values for all 63 compounds with an excellent correlation. It is heartening to note that the line passes through the origin (0,0) and its slope is close to unity.

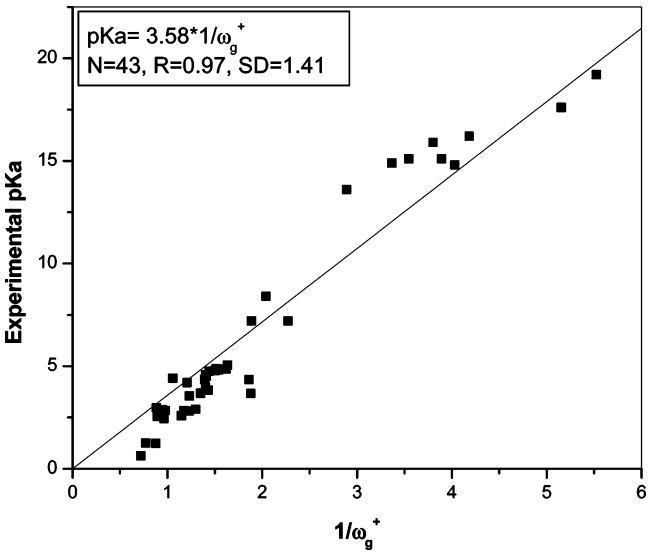

Figure 6. Linear fit of experimental pK_a values and reciprocal of group philicity index for the series of carboxylic acids, various substituted phenols, anilines, phosphoric acids, and alcohols, excluding low-group philicity value species as outliers.

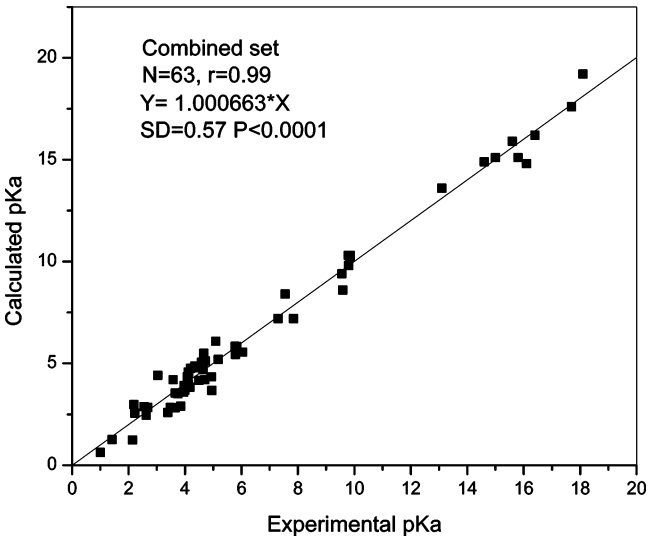

Figure 7. Relationship between the experimental pK_a values with predicted pK_a values using group philicity index of all the selected molecules.

Conclusion

Conceptual density functional theory has helped in many ways to relate the structure of molecules and their reactivity. Prompted by the success of density functional descriptors in the QSAR applications, an attempt has been made to develop SAR for the prediction of pK_a values of various compounds viz., carboxylic acids, various substituted phenols, anilines, phosphoric acids and alcohols. An inverse linear relationship between group philicity (ω_g^+) and experimental pK_a values has been observed. In addition, the polynomial analyses of these quantities reveal that group philicity (ω_g^+) can be used to describe the pK_a of different compounds with different functional groups apart from homologous species. Also, the hyperbolic relationship between experimental pK_a and ω_g^+ has also been attempted by plotting pK_a vs $1/\omega_g^+$. The straight line passing through the origin confirms the hyperbolic (rectangular) nature of the relationship between pK_a and ω_g^+ for a heterogeneous set of compounds. Results provide a reasonably good correlation with a single parameter and, hence, reveal the fact that group philicity can act as a suitable descriptor in the prediction of pK_a values.

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