Acidity of *meta*- and *para*-substituted aromatic acids: a conceptual DFT study†

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Quantum chemical computations with full geometry optimization at the B3LYP/6-31G(d) level in aqueous phase at 298 K are performed to calculate a set of molecular properties for 45 aromatic organic acids such as benzoic acid, phenol, cinnamic acid, benzohydroxamic acid, anilinium ion and their *meta*- and *para*-substituted derivatives. In a separate set of calculations the 6-31 + G(d) basis set is employed for substituted benzoic and cinnamic acids as representative test cases, to test the effect of diffuse functions. Molecular descriptors such as ionization potential, electron affinity, hardness, chemical potential, global electrophilicity and free energy of deprotonation of these acids are computed. The local descriptors such as Fukui functions and group philicity (ω_g^+) are calculated with Mulliken Population Analysis (MPA) and Hirschfeld Population Analysis (HPA) schemes. These aromatic acids are reacted with a strong base, OH^-. The computed Gibbs free energy of deprotonation, the fractional number of electrons transferred, ΔN and electrophilicity based charge transfer index (ECT) in acid–base reaction with a strong base, OH^-, ω_g^+ and group charges are correlated with the experimental pK_a values of these acids. It is found that this approach is particularly effective in discussing trends of changes in acidity of intimately related molecules. The effect of substituents on these descriptors is also studied. These parameters are correlated with experimental Hammett substituent constants (σ). The ECT, fractional number of electron transfer (ΔN) and group charge correlate strongly with pK_a and σ in separate groups of aromatic acids. Minimum energy, maximum hardness and minimum electrophilicity principles are tested for the acid–base reactions.

Introduction

Aromatic acids are very important compounds used as raw materials for agrochemicals, pharmaceuticals, varnishes and other specialty materials. Density functional theory[1–4] based descriptors may be useful in the prediction of acidity (pK_a) of molecules. The knowledge of pK_a is helpful in understanding the biological activity of an aromatic acid. Ionization potential (I), electron affinity (A), electronegativity (χ), chemical hardness (η) and chemical potential (μ) are known as global reactivity descriptors. Parr *et al.*[5] have defined a new descriptor to quantify the global electrophilic power of the molecule as electrophilicity index (ω), which provides a quantitative classification of the global electrophilic nature of a molecule within a relative scale.

The work done on aromatic acids is limited to pK_a prediction based on a quantitative structure-property relationship (QSPR). A descriptive and interpretable model has been developed based on QSPR and by using a multiple linear regression approach and quantum chemical descriptors for determination of the acidity constants of some aromatic acid derivatives. These are related to theoretical descriptors, the partial charges at each atom in $O^{\delta-}$–$H^{\delta+}$ bond and the changing of bond length in O–H molecular structures.[6]

Quantitative structure property relationships (QSPR) for the pK_a of phenols, carboxylic acids and alcohols have been developed from descriptors derived from semi-empirical molecular orbital theory as has been discussed by Citra.[7]

Substituent effects on the physical properties and pK_a of phenol have been studied using density functional theory calculations.[8] Substituents alter the physical properties of phenol such as the C–O and O–H bond lengths, the C–O–H bond angle, and the energy barrier to rotation about the C–O bond, and also influence the hydroxyl-group pK_a. Except for the rotational barrier, Hammett σ constants have shown strong correlation with these property changes. Several quantum chemical parameters, including the natural charge on the phenolic hydrogen and the natural charge on the phenoxide oxygen, the HF/6-311G (d,p) HOMO energy, and the proton-transfer energy have outperformed the empirical Hammett constants in modeling changes in the pK_a.

An artificial neural network has been presented for the prediction of the acidity constants (pK_a) of various benzoic acids and phenols with diverse chemical structures using a nonlinear quantitative structure–property relationship. Habibi-Yangjeh *et al.*[9] have used six different molecular descriptors for predicting pK_a.

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Thermodynamic data[10] of proton dissociation of 75 organic acids belonging to four classes (protonated amines, aliphatic carboxylic acids, benzoic acids, phenols) have been processed by multivariate chemometric techniques in the aqueous medium, at 25 °C and $I = 0$ mol dm^{-3}. The variables consist of conventional thermodynamic quantities (Gibbs function, enthalpy, entropy) and of partial components of these quantities (internal and external, electrostatic and non-electrostatic components). The Hammett σ constants have also been considered.

Namazian and Halvani[11] have calculated Gibbs free energies and pK_a values of a large number of carboxylic acids in aqueous phase by employing DFT method. Linear correlations have been reported[12] on the calculated deprotonation Gibbs free energy changes and experimental pK_a values (aqueous) for a series of 21 carbon acids. Parthasarathi *et al.*[13] have predicted pK_a of carboxylic acids, substituted phenols, anilines, phosphoric acid and alcohols using group philicity. Gupta *et al.*[14] have used the fractional electron transfer and the associated energy change for the reaction of 58 acids with trimethyl amine, as the possible descriptors for the Lewis acidity.

Magill *et al.*[15] have predicted the aqueous pK_a values for the three different hydrogen atoms in the imidazolium cation by employing complete basis set CBS-QB3 in conjunction with the conductor-like polarized continuum (CPCM) method. The pK_a values of phenols[16] have also been predicted employing the same method and the basis set. da Silva *et al.*[17] have used the frontier effective-for-reaction MOs in order to obtain a correlation between the acidity and molecular orbital energies for a collection of conjugate bases of carboxylic acids, phenols, and alcohols. Quantum topological molecular similarity descriptors[18] have been used for estimation of pK_a values of aliphatic carboxylic acids, anilines and phenols. It has been reported that the minimum average local ionization energy[19] on the molecular surface produces good pK_a values of anilines. Polycyanated hydrocarbons and related compounds have been found to be extremely powerful Brönsted acids.[20]

In the present study we use ionization potential (I), electron affinity (A), electronegativity (χ), chemical hardness (η), chemical potential (μ), global electrophilicity (ω) and Gibbs free energy of deprotonation (ΔG) as molecular descriptors of aromatic acids. We compute the fractional number of electrons transferred (ΔN) and associated energy change (ΔE), Gibbs free energy change (ΔG) and the electrophilicity based charge transfer (ECT) for the reactions of these acids with OH$^-$. The correlation of ΔN, ΔE, ΔG, ECT, $\omega_g{}^+$ and group charge with the aqueous pK_a[21] values of acids and Hammett substituent constants[22] (σ) are studied. It is found that this approach is particularly effective in discussing trends of changes in acidity of intimately related molecules. A stable configuration or a favourable process is often associated with the minimum energy, the maximum hardness[23] and the minimum electrophilicity[24] values. Minimum energy, maximum hardness and minimum electrophilicity principles are tested for the acid–base reactions. It may, however, be noted that a minimum Gibbs free energy condition (rather than the minimum energy criterion) may provide better insight into the spontaneity of a process. In fact in some cases steric, entropic and solvent effects may play a decisive role.

Theoretical background

Chemical potential[25] (μ) and electronegativity (χ)[26] could be written in terms of the partial derivative of the system's energy with respect to the number of electrons at a fixed external potential $\nu(r)$ as follows:

$$\mu = -\chi = -\left(\frac{\partial E}{\partial N}\right)_{\nu(\vec{r})} \tag{1}$$

The hardness (η) of that system is defined as[27]

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

The working formulae in DFT for calculating chemical potential (μ), electronegativity (χ) and hardness (η) are as follows:

$$\mu = -\chi \approx -(I + A)/2 \tag{3}$$

$$\eta \approx (I - A)/2 \tag{4}$$

The ionization energy (I) and electron affinity (A) can be replaced by the HOMO and LUMO energies, respectively, using Koopmans' theorem[28] yielding

$$\mu = -\chi \approx \left(\frac{E_{\mathrm{HOMO}} + E_{\mathrm{LUMO}}}{2}\right) \tag{5}$$

$$\eta \approx \left(\frac{E_{\mathrm{LUMO}} - E_{\mathrm{HOMO}}}{2}\right) \tag{6}$$

The deprotonation reaction for an aromatic acid in the aqueous phase can be represented by

$$\mathrm{ArH\ (aq) + H_2O\ (aq) = Ar^-\ (aq) + H_3O^+\ (aq)}$$

where Ar = aryl group.

For this reaction,

Table 1 List of aromatic acid molecules under study

No.	Molecule	No.	Molecule
1	*p*-Nitrobenzoic acid	23	*m*-*tert*-Butylphenol
2	*m*-Nitrobenzoic acid	24	*p*-Methoxyphenol
3	*p*-CHO-benzoic acid	25	*p*-*tert*-Butylphenol
4	*m*-CHO-benzoic acid	26	*p*-Cresol
5	*m*-Hydroxybenzoic acid	27	*m*-Chloro-*trans*-cinnamic acid
6	*m*-Methoxybenzoic acid	28	*p*-Chloro-*trans*-cinnamic acid
7	Benzoic acid	29	*trans*-Cinnamic acid
8	*m*-Methylbenzoic acid	30	*m*-Methylcinnamic acid
9	*p*-Methylbenzoic acid	31	*p*-Methylcinnamic acid
10	*p*-Hydroxybenzoic acid	32	*p*-Cyanobenzohydroxamic acid
11	*p*-Methoxybenzoic acid	33	*p*-Nitrobenzohydroxamic acid
12	*p*-Nitrophenol	34	*p*-Chlorobenzohydroxamic acid
13	*m*-Nitrophenol	35	*p*-Fluorobenzohydroxamic acid
14	*m*-Chlorophenol	36	Benzohydroxamic acid
15	*m*-Fluorophenol	37	*p*-Nitroanilinium ion
16	Resorcinol	38	*m*-Nitroanilinium ion
17	*p*-Chlorophenol	39	*m*-Chloroanilinium ion
18	*m*-Methoxyphenol	40	*m*-Fluoroanilinium ion
19	Hydroquinone	41	*p*-Chloroanilinium ion
20	*p*-Fluorophenol	42	*p*-Fluoroanilinium ion
21	Phenol	43	*m*-Methylanilinium ion
22	*m*-Cresol	44	Anilinium ion
		45	*p*-Methylanilinium ion

Table 2 Experimental pK_a, Hammett sigma constant (σ), electronegativity (χ), chemical hardness (η), ΔG(deprot.), group electrophilicity (ω_g^+) and group charge of the aromatic acids in aqueous phase at 298 K

						ω_g^+		Group charge	
No.	Exptl. pK_a[a]	σ	χ/eV	η/eV	ΔG(deprot.)/eV	MPA	HPA	MPA	HPA
1	3.41	0.778	5.3298	2.3892	2.3322	1.1117	1.0641	−0.0780	−0.0603
2	3.47	0.71	5.2628	2.5171	2.3464	0.6712	0.5997	−0.0760	−0.0558
3	3.77	0.42	4.8345	2.4496	2.4211	1.1116	1.0782	−0.0950	−0.0770
4	3.84	0.35	4.6490	2.5851	2.4428	0.7483	0.6981	−0.0960	−0.0772
5	4.06	0.12	3.8070	2.4658	2.5702	1.0720	1.0542	−0.1350	−0.1126
6	4.1	0.115	3.8105	2.4516	2.5711	1.0492	1.0286	−0.1400	−0.1147
7	4.19	0	4.2122	2.8711	2.5855	1.1186	1.0938	−0.1300	−0.1137
8	4.25	−0.069	4.0638	2.7395	2.5696	1.0640	1.046	−0.1360	−0.1164
9	4.37	−0.17	4.1305	2.8135	2.4402	1.0127	1.0005	−0.1060	−0.1286
10	4.48	−0.37	3.7231	2.6443	2.6503	0.9690	0.9477	−0.1520	−0.1331
11	4.50	−0.268	3.7313	2.6149	2.6409	0.9384	0.9200	−0.1530	−0.1342
12	7.15	1.27	4.5672	2.1893	2.2742	0.4669	0.4716	−0.2010	0.0017
13	8.36	0.71	4.5845	2.0218	2.9268	0.3638	0.3534	−0.2140	−0.0085
14	9.12	0.373	3.3157	2.9557	2.7555	0.1562	0.1506	−0.2210	−0.0193
15	9.29	0.337	3.1374	3.0349	2.8510	0.1524	0.1492	−0.2280	−0.0238
16	9.32	0.12	2.8282	2.9923	2.9836	0.1270	0.1256	−0.2370	−0.0316
17	9.41	0.227	3.2321	2.8539	2.8099	0.1537	0.1482	−0.2250	−0.0237
18	9.65	0.115	2.8765	2.9851	3.0007	0.1247	0.1206	−0.2380	−0.0325
19	9.80	−0.37	2.7396	2.6724	3.1052	0.1208	0.1166	−0.2470	−0.0410
20	9.89	0.062	3.1158	2.8200	2.9582	0.1532	0.1446	−0.2360	−0.0311
21	9.99	0	2.9818	2.9894	3.0153	0.1324	0.1279	−0.2380	−0.0339
22	10.09	−0.069	2.9516	2.9576	3.1252	0.1237	0.1193	−0.2430	−0.0353
23	10.12	−0.1	2.9403	2.9618	3.1038	0.1182	0.1124	−0.2420	−0.0358
24	10.21	−0.268	2.7530	2.6779	3.0961	0.1174	0.1132	−0.2460	−0.0405
25	10.23	−0.2	2.8704	2.9109	3.0647	0.1160	0.1104	−0.2420	−0.0353
26	10.30	−0.17	2.8784	2.8950	3.1244	0.1231	0.1173	−0.2410	−0.0369
27	4.29	0.373	4.4182	2.3062	2.3794	1.0411	1.0623	−0.0610	−0.1206
28	4.41	0.227	4.3273	2.2460	2.4045	1.0088	1.0296	−0.0650	−0.1251
29	4.44	0	4.2350	2.2998	2.4490	1.0021	1.0177	−0.0760	−0.1330
30	4.44	−0.069	4.1108	2.2654	2.6849	0.9809	0.9884	−0.1120	−0.1357
31	4.56	−0.17	4.0452	2.2303	2.6770	0.9611	0.9722	−0.1140	−0.1380
32	0.66	0.66	4.5887	2.5888	2.7994	1.1265	1.1184	−0.0610	−0.0275
33	8.12	0.778	5.0438	2.1982	3.6291	1.1052	1.0763	−0.0490	−0.0324
34	8.7	0.327	4.1331	2.7682	2.8964	1.1293	1.1200	−0.0990	−0.0676
35	8.81	0.062	3.9916	2.8488	2.9529	1.1186	1.1102	−0.1030	−0.0769
36	8.91	0	4.0476	2.8411	3.0252	1.1850	1.1706	−0.1080	−0.0939
37	1.02	1.27	5.7990	2.6233	0.5878	0.7114	0.7051	0.5300	0.6682
38	2.46	0.71	5.8323	2.6501	0.7181	0.5840	0.5262	0.5300	0.6724
39	3.52	0.373	4.5662	3.0599	0.8786	0.6712	0.6508	0.5020	0.6486
40	3.59	0.337	4.5584	3.1083	0.9098	0.6618	0.6417	0.5140	0.6514
41	3.98	0.227	4.5754	3.0842	0.9179	0.6618	0.6346	0.5000	0.6449
42	4.65	0.062	4.5084	3.2062	1.0226	0.6086	0.5706	0.5110	0.6485
43	4.72	−0.069	4.3245	3.1721	1.0645	0.6013	0.5807	0.4990	0.6377
44	4.87	0	4.4775	3.3042	1.0664	0.6341	0.6128	0.5040	0.6418
45	5.1	−0.17	4.3067	3.2324	1.1013	0.6110	0.5881	0.4980	0.6367

[a] Taken from ref. 21.

$$\Delta G(\text{deprot.}) = G[\text{Ar}^- \text{(aq)}] + G[\text{H}_3\text{O}^+ \text{(aq)}] - G[\text{ArH (aq)}] - G[\text{H}_2\text{O (aq)}]$$

$$\Delta G^0 = -2.303RT\log(K_a/[\text{H}_2\text{O}]) \qquad (7)$$

where ΔG^0 is the free energy change for the dissociation reaction[11] at 298 K with standard state corresponding to a concentration of 1 mol L^{-1} and [H_2O] = 55.56 mol L^{-1}.

Hammett[22] proposed a formula to represent the effect of a substituent in *m*- and *p*-positions of the benzene ring upon the rate or equilibrium constant of a reaction in which the reacting group is in a side-chain attached to the ring.

$$\log K = \log K^0 + \rho\sigma \qquad (8)$$

where σ is a substituent constant; ρ is a reaction constant dependent upon the reaction, medium and temperature. Since equilibrium constant, K is related to ΔG, σ is also related to ΔG.

The reaction of an aromatic acid with OH^- can be represented by

$$\text{ArH (aq)} + \text{OH}^- \text{(aq)} = \text{Ar}^- \text{(aq)} + \text{H}_2\text{O (aq)}$$

For this reaction,

$$\Delta G(\text{neut.}) = G[\text{Ar}^- \text{(aq)}] + G[\text{H}_2\text{O}] - G[\text{ArH (aq)}] - G[\text{OH}^- \text{(aq)}] \qquad (9)$$

If two systems, A and B, are brought together, electrons flow from that of lower χ to that of higher χ, until the potentials become equal. As a first approximation, the (fractional) number of electrons transferred for the generalized acid–base reaction:

Table 3 Fractional number of electrons transferred (ΔN), electrophilicity based charge transfer (ECT), associated energy change (ΔE), ΔG(neutralization), change in hardness ($\Delta\eta$) and change in electrophilicity ($\Delta\omega$) for the reactions of the aromatic acids with OH^- in aqueous phase at 298 K

No.	ΔN	ECT	ΔE/eV	ΔG(neut.)/eV	$\Delta\eta$/eV	$\Delta\omega$/eV
1	0.5898	2.7172	−2.0916	−2.8906	0.5218	−0.7330
2	0.5721	2.5773	−2.0095	−2.8763	0.4065	−0.1362
3	0.5432	2.4601	−1.7917	−2.8016	0.8022	−1.4039
4	0.5164	2.2848	−1.6554	−2.7799	0.6972	−0.6529
5	0.4574	2.0304	−1.2736	−2.6525	1.5250	−1.5460
6	0.4587	2.0407	−1.2782	−2.6516	1.5265	−1.6113
7	0.4600	1.9536	−1.3742	−2.6372	1.1166	−1.5422
8	0.4579	1.9699	−1.3338	−2.6531	1.2322	−1.5041
9	0.4578	1.9545	−1.3488	−2.7825	1.1814	−1.4860
10	0.4376	1.8945	−1.2003	−2.5724	1.4600	−1.0470
11	0.4404	1.9134	−1.2096	−2.5818	1.4597	−1.0974
12	0.5445	2.5726	−1.7233	−2.9485	0.9929	−1.8117
13	0.5622	2.7539	−1.7841	−2.2959	0.6730	−1.4711
14	0.3860	1.6082	−0.9799	−2.4672	0.9303	−0.9721
15	0.3680	1.5203	−0.9015	−2.3717	0.9446	−0.8781
16	0.3470	1.4316	−0.7964	−2.2391	1.0121	−0.6901
17	0.3856	1.6190	−0.9629	−2.4128	0.9613	−0.9610
18	0.3510	1.4501	−0.8141	−2.2220	0.9870	−0.7189
19	0.3576	1.5116	−0.8049	−2.1176	0.9816	−0.7374
20	0.3786	1.5913	−0.9234	−2.2645	0.9142	−0.9394
21	0.3587	1.4839	−0.8510	−2.2074	0.9013	−0.8062
22	0.3582	1.4844	−0.8442	−2.0975	0.8930	−0.7901
23	0.3571	1.4792	−0.8396	−2.1189	0.8910	−0.7884
24	0.3583	1.5145	−0.8090	−2.1266	0.9985	−0.7389
25	0.3545	1.4725	−0.8212	−2.1580	0.9281	−0.7541
26	0.3560	1.4807	−0.8261	−2.0983	0.9322	−0.7708
27	0.5212	2.4023	−1.6107	−2.8434	1.1185	−1.6194
28	0.5188	2.4131	−1.5797	−2.8182	1.1819	−1.5867
29	0.5063	2.3279	−1.5182	−2.7738	1.2107	−1.6147
30	0.4987	2.3011	−1.4645	−2.5378	1.2510	−1.4646
31	0.4961	2.3002	−1.4406	−2.5457	1.3047	−1.4569
32	0.5112	2.2590	−1.6234	−2.4233	0.0269	−1.2505
33	0.5846	2.7810	−1.9895	−1.5936	0.5472	−0.3993
34	0.4612	1.9795	−1.3596	−3.3263	0.1978	−1.5561
35	0.4446	1.8876	−1.2790	−2.2698	0.2355	−1.5579
36	0.4494	1.9111	−1.3055	−2.1975	0.2107	−1.6418
37	0.6053	2.6970	−2.2884	−4.6349	0.7725	−1.6369
38	0.6054	2.6872	−2.2988	−4.5046	0.5470	−0.9090
39	0.4735	1.9787	−1.4983	−4.3441	1.1419	−1.3860
40	0.4695	1.9530	−1.4838	−4.3129	1.1806	−1.5544
41	0.4725	1.9699	−1.4972	−4.3048	1.0393	−1.3923
42	0.4591	1.8926	−1.4396	−4.2001	0.8849	−1.2565
43	0.4479	1.8497	−1.3631	−4.1582	1.0766	−1.3207
44	0.4504	1.8415	−1.4052	−4.1563	0.9427	−1.3535
45	0.4427	1.8188	−1.3432	−4.1214	0.9460	−1.2316

$A + {:}B \rightarrow A{:}B$ is given by[28]

$$\Delta N = \frac{(\chi_A - \chi_B)}{2(\eta_A + \eta_B)} \qquad (10)$$

The energy lowering due to electron transfer to a system of lower chemical potential is given by[26]

$$\Delta E = -\frac{(\chi_A - \chi_B)^2}{4(\eta_A + \eta_B)} \qquad (11)$$

If $\Delta N < 0$, A is a donor and B is an acceptor.

If $\Delta N > 0$, the case is just the reverse.

Parr *et al.*[5] 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

$$\omega = \mu^2/2\eta \qquad (12)$$

The maximum electronic charge the electrophile may accept from the environment is given by

$$(\Delta N)_{\max} = -\mu/\eta \qquad (13)$$

If we consider two systems A and B approaching each other, the amount of charge transfer can be written in terms of electrophilicity, that is, electrophilicity based charge transfer (ECT), is given by [29]

$$\mathrm{ECT} = (\Delta N_{\max})_A - (\Delta N_{\max})_B \qquad (14)$$

If ECT < 0, A is a donor and B is an acceptor;

If ECT > 0, the case is the reverse.

It is tacitly assumed that the electrophilicity effect dominates over the electronegativity effect.

The Fukui function (FF) is defined as the derivative of the electron density $\rho(\vec{r})$ with respect to the total number of electrons N in the system, at constant external potential $\nu(\vec{r})$ acting on an electron due to all the nuclei in the system[1]

$$f(\vec{r}) = [\delta\mu/\delta\nu(\vec{r})]_N = [\partial\rho(\vec{r})/\partial N]_{\nu(\vec{r})} \qquad (15)$$

where μ is the chemical potential of the system.

The generalized concept of philicity has been proposed by Chattaraj *et al.*[30] A local quantity called philicity (ω_k^α) associated with a site k in a molecule with the aid of the corresponding condensed-to-atom Fukui function (f_k^α)[31] has been defined as

$$\omega_k^\alpha = \omega \cdot f_k^\alpha \qquad (16)$$

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".[32] This is a very useful concept in unraveling the reactivity of various molecular systems. It can be expressed as

$$\omega_g^\alpha = \sum_{k=1}^{n} \omega_k^\alpha \qquad (17)$$

where n is the number of atoms coordinated to the reactive atom, where ω_k^α is the local philicity of the atom k, and ω_g^α is the group philicity obtained by adding the local philicity values of the nearby bonded atoms.

Methods

The geometries of all the selected series of molecules (45) and their conjugate bases are optimized at B3LYP/6-31G(d) level in the aqueous phase at 298 K using GAUSSIAN 03 package.[33] The same computation is also carried out employing 6-31+G(d) basis set for substituted benzoic acids and cinnamic acids. The ionization potential, electron affinity, electro negativity, hardness, chemical potential and global electrophilicity are computed employing Koopmans' theorem.[28] The molecules are optimized in the framework of a self consistent reaction field polarized continuum model. The number of imaginary vibrational frequencies is found to be zero in all cases implying

Table 4 Correlation coefficient (R), standard deviation (SD), intercept (c) and slope (m) of different plots for different sets of organic acids

Aromatic acids		ΔG(deprot.) *vs.* pK_a	ΔG(neut.) *vs.* pK_a	ECT *vs.* pK_a	ΔN *vs.* pK_a	ω_g^+ *vs.* pK_a	Group charge (HPA) *vs.* pK_a
Benzoic acids (n = 11)	R	0.8656	0.8656	0.9642	0.9601	0.3160	0.9806
	SD	0.0599	0.0599	0.0826	0.0163	0.1629	0.0060
	c	1.4523	−3.7704	5.2192	1.0583	0.4054	−0.0756
	m	0.2609	0.2609	−0.7564	−0.1406	0.1366	0.2034
Phenols (n = 15)	R	0.8994	0.8994	0.8437	0.8631	0.9306	0.9513
	SD	0.0996	0.0996	0.2286	0.0357	0.0394	0.0038
	c	0.7134	−4.5094	5.5789	1.0531	1.2566	0.1006
	m	0.2343	0.2343	−0.4108	−0.0698	−0.1145	−0.0136
trans-Cinnamic acids (n = 5)	R	0.7502	0.7502	0.7456	0.8457	0.9354	0.8981
	SD	0.1146	0.1146	0.0423	0.0070	0.0144	0.0037
	c	−2.6574	−7.8801	4.2325	0.9525	2.5338	0.1735
	m	1.1690	1.1690	−0.4254	−0.1003	−0.3432	−0.0687
Benzohydroxamic acids (n = 5)	R	0.5102	0.5102	0.9212	0.9405	0.0832	0.6882
	SD	0.3261	0.3261	0.1687	0.0232	0.0388	0.0241
	c	7.1649	7.1649	10.6398	1.8508	1.1136	−0.0207
	m	−0.4795	−0.4795	−0.9902	−0.1590	0.0008	−0.0055
Anilinium ions (n = 9)	R	0.9928	0.9928	0.9220	0.9205	0.4491	0.9015
	SD	0.0220	0.0220	0.1464	0.0273	0.0503	0.0058
	c	0.4314	−4.7913	3.0030	0.6625	0.6794	0.6822
	m	0.1293	0.1293	−0.2459	−0.0453	−0.0178	−0.0085

that all the structures presented here correspond to the minima on the potential energy surface. The fractional number of electrons transferred (ΔN), energy change (ΔE), ΔG, ECT, $\Delta\eta$ and $\Delta\omega$ for the reaction of these acids with OH^- are computed. Fukui functions and group charge are calculated with the Mulliken Population Analysis[34] (MPA) and Hirschfeld Population Analysis[35] (HPA) schemes employing the BLYP/DND method using DMOL3 package.[36]

Results and discussion

Table 1 presents a list of aromatic acid molecules under study. Table 2 lists experimental pK_a values, computed electronegativity (χ), chemical hardness (η), ΔG(deprot.), and group electrophilicity (ω_g^+) of the aromatic acids in the aqueous phase at 298 K. The groups considered for group philicity and group charge computations are functional groups of the respective acids.

Table 5 Correlation coefficient (R), standard deviation (SD), intercept (c) and slope (m) of different plots for different sets of organic acids.

Aromatic acids		ΔG(deprot.) *vs.* σ	ECT *vs.* σ	ΔN *vs.* σ	ω_g^+ *vs.* σ	Group charge (HPA) *vs.* σ
Benzoic acids (n = 11)	R	0.8688	0.9603	0.9558	0.3087	0.9749
	SD	0.0593	0.0869	0.0171	0.1634	0.0068
	c	2.5446	2.0535	0.4697	0.9762	−0.1131
	m	−0.2599	0.7477	0.1390	−0.1325	0.0746
Phenols (n = 15)	R	0.9068	0.8231	0.8502	0.9116	0.9842
	SD	0.0961	0.2419	0.0372	0.0442	0.0022
	c	3.0107	1.5557	0.3695	0.1348	−0.0323
	m	−0.4744	0.8046	0.1380	0.2252	0.0282
trans-Cinnamic acids (n = 5)	R	0.8711	0.9415	0.9795	0.9668	0.9985
	SD	0.0851	0.0214	0.0027	0.0104	0.0005
	c	2.5614	2.3322	0.5046	1.0030	−0.1329
	m	−0.5870	0.2323	0.0502	0.1534	0.0330
Benzohydroxamic acid (n = 5)	R	0.4586	0.8916	0.9131	0.7237	0.9685
	SD	0.3369	0.1964	0.0278	0.0269	0.0083
	c	2.9025	1.8120	0.4336	1.1448	−0.0889
	m	0.4328	0.9625	0.1550	−0.0702	0.0801
Anilinium ions (n = 9)	R	0.9878	0.9154	0.9151	0.4729	0.9008
	SD	0.0287	0.1522	0.0282	0.0496	0.0058
	c	1.0338	1.8577	0.4514	0.5954	0.6424
	m	−0.3786	0.7186	0.1326	0.0552	0.0251

Table 6 Correlation coefficient (R), standard deviation (SD), intercept (c) and slope (m) of different plots for different sets of organic acids (related descriptors are computed using B3LYP/6-31 + G(d) level of theory.)

Aromatic acids		ΔG(deprot.) *vs.* pK_a	ΔG(neut.) *vs.* pK_a	ECT *vs.* pK_a	ΔN *vs.* pK_a	ω_g^+ *vs.* pK_a	Group charge (HPA) *vs.* pK_a
Benzoic acids	R	0.5422	0.5422	0.9620	0.9498	0.3980	0.9811
(n = 11)	SD	0.1536	0.1536	0.0918	0.0177	0.1884	0.0060
	c	1.4337	−2.4706	4.8516	0.8372	0.3462	0.2042
	m	0.2497	0.2497	−0.8149	−0.1354	0.2058	−0.0762
trans-Cinnamic acids	R	0.7726	0.7728	0.8056	0.8976	0.9016	0.8727
(n = 5)	SD	0.0924	0.0924	0.0384	0.0062	0.0234	0.0037
	c	−2.0864	−5.9928	3.8469	0.7996	3.1814	0.1312
	m	1.0117	1.0120	−0.4706	−0.1141	−0.4388	−0.0560

Table 7 Correlation coefficient (R), standard deviation (SD), intercept (c) and slope (m) of different plots for different sets of organic acids (related descriptors are computed using B3LYP/6-31 + G(d) level of theory)

Aromatic acids		ΔG(deprot.) *vs.* σ	ECT *vs.* σ	ΔN *vs.* σ	ω_g^+ *vs.* σ	Group charge (HPA) *vs.* σ
Benzoic acids	R	0.5426	0.9572	0.9439	0.3896	0.9758
(n = 11)	SD	0.1536	0.0974	0.0186	0.1892	0.0067
	c	2.4790	1.4412	0.2705	1.2074	−0.1144
	m	−0.2480	0.8048	0.1336	−0.2000	0.0752
trans-Cinnamic acids	R	0.8858	0.9655	0.9682	0.8721	0.9901
(n = 5)	SD	0.0675	0.0169	0.0035	0.0264	0.0011
	c	2.4293	1.7452	0.2907	1.2248	−0.1363
	m	−0.5016	0.2439	0.0532	0.1836	0.0294

These aromatic acids are reacted with a strong base, OH^-. Corresponding change in energy, ΔE and fractional number of electrons transferred, ΔN are computed. Table 3 lists fractional number of electrons transferred (ΔN), energy change (ΔE), ECT, ΔG(neut.), change in hardness ($\Delta\eta$) and change in electrophilicity ($\Delta\omega$) for the reactions of the aromatic acids with OH^- in aqueous phase at 298 K. It may be noted that both ΔE and ΔG values are negative for all the 45 cases studied.

ΔG (deprot.), ΔG (neut.), ECT, ΔN and ω_g^+ are plotted against experimental pK_a (from ref. 21) and substituent constant, σ for different groups of aromatic acids using linear regression method. The correlation coefficients (R), standard deviations (SD), intercepts (c) and slopes (m) of the linear plots are listed serially in Tables 4 and 5 respectively. Electrophilicity based charge transfer index (ECT), fractional number of electron transfer (ΔN) and group charge are strongly correlated with pK_a values in most of the separate groups of aromatic acids (Table 4). Also, ECT, ΔN and group charge are strongly correlated with σ in all separate groups of aromatic acids (Table 5).

Since the diffuse functions generally produce better results for anions[37] all the above descriptors are computed for substituted benzoic acids and cinnamic acids employing B3LYP/6-31 + G(d) level of theory to test the effect of diffuse function on the descriptors. Substituted benzoic acids and cinnamic acids are chosen as representative test cases for this purpose. Tables 6 and 7 list the correlation coefficients of these descriptors with pK_a and σ.

No significant change in the correlation is found in most of the cases. The pK_a values for different sets of molecules may be estimated reasonably well in terms of ΔN or ECT. As ΔN or ECT increases pK_a decreases in all cases (slopes are negative). However, the experimental pK_a values do not correlate well with any of the DFT descriptors when all the 45 acids are considered. This may be due to the fact that the structure of the molecule greatly influences the proton donating or electron accepting ability. The compounds with grossly different structures are not expected to follow the same QSAR-model. Table 8 presents the regression equations for two and three parameter models. The sign of the ΔN-coefficient remains same (negative) in most cases whereas that of the ECT-coefficient depends on whether the ΔN term overestimates or underestimates the pK_a value. There is a marginal improvement in correlation by adding the local quantity ω_g^+ as the third descriptor.

The experimental pK_a values for all 45 acids belonging to five different sets of acids are plotted against their pK_a values estimated (Table 8) in terms of (ΔN, ECT) (Fig. 1) and (ΔN, ECT, ω_g^+) (Fig. 2). Eqn (18a) and (18b) provide linear correlations between the experimental and calculated pK_a values. The correlations between the experimental and the calculated pK_a through two- and three parameter models for the complete set of 45 molecules from five different sets are as follows:

Two-parameter model (ΔN, ECT):

$$\mathrm{p}K_a\ (\text{calc.}) = 0.1081 + 0.9825 \cdot \mathrm{p}K_a\ (\text{exptl.}) \tag{18a}$$

$$R = 0.9912,\ \mathrm{SD} = 0.3825,\ N = 45$$

Three-parameter model (ΔN, ECT, ω_g^+):

$$\mathrm{p}K_a\ (\text{calc.}) = 0.0654 + 0.9894 \cdot \mathrm{p}K_a\ (\text{exptl}) \tag{18b}$$

$$R = 0.9947,\ \mathrm{SD} = 0.2986,\ N = 45$$

Table 8 Two- (ΔN, ECT) and three- (ΔN, ECT, ω_g^+) parameter regression models for different sets of aromatic acids for estimating their pK_a values

Molecules	Regression eqn for pK_a (calc.)	R	SD	N
Benzoic acids				
Two parameter	$pK_a = -0.84\cdot\Delta N - 1.07\cdot\text{ECT} + 6.77$	0.9643	0.1014	11
Three parameter	$pK_a = -0.52\cdot\Delta N - 1.13\cdot\text{ECT} + 0.04\cdot\omega_g^+ + 6.69$	0.9644	0.1013	11
Two parameter[b]	$pK_a = -1.30\cdot\Delta N - 0.92\cdot\text{ECT} + 5.85$	0.9627	0.1034	11
Three parameter[b]	$pK_a = -1.42\cdot\Delta N - 0.92\cdot\text{ECT} - 0.11\cdot\omega_g^+ + 6.01$	0.9642	0.1015	11
Phenols				
Two parameter	$pK_a = -69.95\cdot\Delta N + 9.86\cdot\text{ECT} + 20.27$	0.9114	0.3282	15
Three parameter	$pK_a = -29.92\cdot\Delta N + 5.27\cdot\text{ECT} - 8.52\cdot\omega_g^+ + 13.78$	0.9473	0.2656	15
trans-Cinnamic acids				
Two parameter	$pK_a = -23.96\cdot\Delta N + 3.57\cdot\text{ECT} + 8.22$	0.9397	0.0357	5
Three parameter	$pK_a = 14.97\cdot\Delta N - 1.44\cdot\text{ECT} - 5.19\cdot\omega_g^+ + 5.48$	0.9469	0.0338	5
Two parameter[b]	$pK_a = -11.76\cdot\Delta N + 1.07\cdot\text{ECT} + 6.00$	0.9163	0.0408	5
Three parameter[b]	$pK_a = -17.32\cdot\Delta N + 1.73\cdot\text{ECT} + 0.72\cdot\omega_g^+ + 5.56$	0.9168	0.0407	5
Benzohydroxamic acids				
Two parameter	$pK_a = -968.33\cdot\Delta N + 149.80\cdot\text{ECT} + 157.61$	0.9746	0.9019	5
Three parameter	$pK_a = -980.45\cdot\Delta N + 152.34\cdot\text{ECT} + 9.75\cdot\omega_g^+ + 147.14$	0.9766	0.8690	5
Anilinium ions				
Two parameter	$pK_a = 68.36\cdot\Delta N - 16.07\cdot\text{ECT} + 3.52$	0.9246	0.4995	9
Three parameter	$pK_a = 1.59\cdot\Delta N - 3.61\cdot\text{ECT} - 8.89\cdot\omega_g^+ + 15.92$	0.9866	0.2284	9

[b] Related descriptors are computed at B3LYP/6-31+G(d) level of theory.

The correlations are good with R values of 0.9912 and 0.9960, respectively for the two- (ΔN, ECT) and three- (ΔN, ECT, ω_g^+) parameter models. It is worth mentioning that in both the plots, the slope is close to unity and the intercept is close to zero, as expected.

The natural direction of a chemical reaction is towards a state of minimum electrophilicity. This fact may be called Minimum Electrophilicity Principle. To be precise, during molecular vibrations, internal rotations and chemical reactions any configuration/conformation/molecular structure associated with the maximum values of the chemical potential and the hardness will correspond to a minimum electrophilicity condition which is often related to the stability of the system or spontaneity of the associated process.[24] Similarly, the natural direction of a chemical reaction is towards a state of minimum energy, known as Minimum Energy Principle. The ΔE values for the reactions of the aromatic acids with OH^- are always negative and hence the reactions are expected to be favorable. The $\Delta\eta$ values for these reactions are always positive satisfying the Maximum Hardness Principle (MHP). The Minimum Electrophilicity Principle (MEP) is also

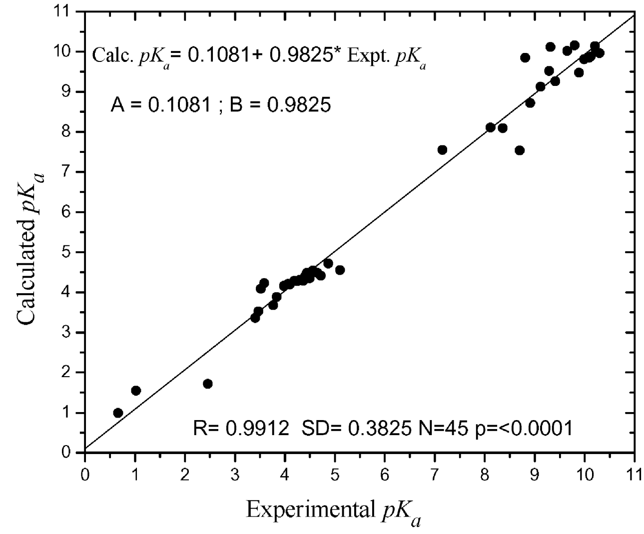

Fig. 1 Relationship between the experimental and predicted pK_a values with electrophilicity based charge transfer index (ECT) and fractional number of electron transfer (ΔN) of the aromatic acids.

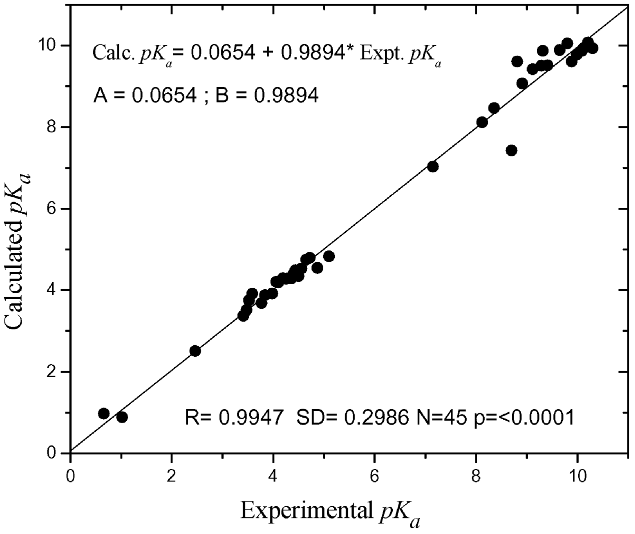

Fig. 2 Relationship between the experimental and predicted pK_a values with fractional number of electron transfer (ΔN), electrophilicity based charge transfer index (ECT) and group philicity (ω_g^+) of the aromatic acids.

satisfied in all 45 cases. A similar behaviour was observed[38,39] for the acid–base reactions of a set of inorganic molecules.

Conclusions

Electrophilicity based charge transfer (ECT) index, fractional number of electrons transferred (ΔN) and group charge separately correlate reasonably well with pK_a values in most of the groups of aromatic acids containing adequate number of molecules. They also correlate favorably with σ values in all the groups of aromatic acids. If ECT and ΔN are considered as indices of Lewis acidity, there is a relatively worse correlation between Brönsted acidity (pK_a) and Lewis acidity in general, when acids of different structures are considered. However, the situation improves drastically when acids of similar structures are considered. The ΔE values for the reactions of the aromatic acids with OH^- are always negative. The $\Delta\eta$ values for these reactions are always positive satisfying the Maximum Hardness Principle (MHP). Minimum Electrophilicity Principle (MEP) is satisfied in all cases when 6-31G(d) basis set is used.

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