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Protophilicity index and protofelicity equalization principle: new measures of Brønsted-Lowry-Lewis acid–base interactions

Francisco Méndez · Julio A. Alonso · Arlette Richaud

Abstract The simultaneous contributions of proton and electron transfer to the Brønsted-Lowry and Lewis acid–base properties of a set of p-substituted phenols are reported in this work. As a result of the analysis, a novel protophilicity index considered as the second-order energy change of a Brønsted-Lowry base as it is saturated with protons, a combined Brønsted-Lowry-Lewis acidity index (with a corresponding basicity index), and a protofelicity equalization principle (a parallel of the electronegativity equalization principle) are presented.

Introduction

Several chemical reactions begin with steps that involve reagent protonation (deprotonation) or electron pair acceptance (donation). Specifically, in the fundamental chemical addition, elimination and substitution reactions, the Brønsted-Lowry $AH^{(+)}+B \rightarrow A+BH^{(+)}$, and Lewis $A + :B \rightarrow A:B$ acid–base interactions are the most important proton and electron carrying paths, respectively [1]. Therefore, the strengths of the Brønsted-Lowry and Lewis acids ($AH^{(+)}$ and A), and bases (B and :B), have been discussed extensively in the literature [2, 3]. In particular, the Brønsted-Lowry and Lewis acid–base interactions have been studied in terms of electronic reactivity indexes obtained from density functional theory (DFT) [4–8]. Those indexes are the chemical potential μ_e (the negative of the electronegativity χ_e); the chemical hardness η (the resistance to a change in the number of electrons, often measured by the gap between the energies of the highest occupied and the lowest unoccupied molecular orbitals); and the electrophilicity index ω_e (the second-order energy change of an electrophile as it is saturated with electrons). However, although Brønsted-Lowry acid–base interactions should be studied in terms of protonic reactivity indexes, since the proton is the constant reference acid for all Brønsted-Lowry bases, they are rarely discussed in these terms [9–17], although the DFT protonic reactivity indexes protofelicity χ_p (the first-order energy change with respect to the number of protons) and proton hardness Π (the resistance to a change in the number of protons) have been defined previously by Lohr [17] and justified by Parr and Ayers [18]. Therefore, both ingredients—electronic and protonic—are needed to describe acid–base interactions [19–24]. Using DFT and the hard and soft acid and bases (HSAB) principle [25–28], we have previously derived equations to achieve a quantitative description for the effect of a substituent X on the Brønsted-Lowry acidity and reactivity of p-substituted phenols XC_6H_4OH in terms of electronic indexes [29–31]. With this in mind, we introduce a protophilicity index ω_p—the second-order energy change of a Brønsted-Lowry base as it is saturated with protons. We also propose a combined Brønsted-Lowry-Lewis acidity index $\omega_{e/p}$ (and the corresponding basicity index $\omega_{p/e}$) exploring the simultaneous contributions of proton and electron transfer to the Brønsted-Lowry and Lewis acid–base properties of the p-substituted phenols. We also use a protofelicity equalization principle (a parallel of the electronegativity equalization principle). Concepts similar to protofelicity and proton hardness have been extended to atomic addition in homogeneous clusters [32] and have been applied to understand the mass spectra of clusters grown by gas phase techniques [33].

F. Méndez (✉) · A. Richaud
Departamento de Química, División de Ciencias Básicas e Ingeniería, Universidad Autónoma Metropolitana-Iztapalapa, A.P. 55-534, México, DF 09340, Mexico
e-mail: fm@xanum.uam.mx

A. Richaud
e-mail: cbi204382812@xanum.uam.mx

J. A. Alonso
Departamento de Física Teórica, Atómica y Óptica, Universidad de Valladolid, 47011 Valladolid, Spain
e-mail: jaalonso@tta.uva.es

Electronic and protonic reactivity indexes

The extension of chemical potential μ_e and chemical hardness η_e to the proton transfer reactions is immediate. The responses of the energy of the system $E[N_e, N_p]$ to changes in the number of electrons N_e and protons N_p can be expressed, following the non-Born-Oppenheimer general formalism of Capitani, Nalewajsky and Parr [34], in a two-variable Taylor series:

$$E\big[N_e + \Delta N_e, N_p + \Delta N_p\big] = E\big[N_e, N_p\big] + \mu_e\, \Delta N_e$$
$$+\, \mu_p\, \Delta N_p + \frac{1}{2}\eta\big(\Delta N_e\big)^2$$
$$+\frac{1}{2}\Pi\big(\Delta N_p\big)^2$$
$$+\, \beta \Delta N_e\, \Delta N_p + \ldots \qquad (1)$$

where the first and second derivatives give the electronegativity, hardness, protofelicity and proton hardness [4, 17, 18, 23, 35–39]

$$\mu_e = \partial E / \partial N_e = -\chi_e \qquad (2)$$

$$\eta = \partial^2 E / \partial N_e^2 \qquad (3)$$

$$\mu_p = \partial E / \partial N_p = -\chi_p \qquad (4)$$

$$\Pi = \partial^2 E / \partial N_p^2 \qquad (5)$$

and the cross term response,

$$\beta = \frac{\partial^2 E}{\partial N_e \partial N_p} \qquad (6)$$

These derivatives can be evaluated by finite differences, leading to:

$$\mu_e \approx \frac{1}{2}\big(E\big[N_e + 1, N_p\big] - E\big[N_e - 1, N_p\big]\big) = -\frac{IP + EA}{2} \qquad (7)$$

$$\eta \approx \frac{1}{2}\big(E\big[N_e + 1, N_p\big] - 2E\big[N_e, N_p\big] + E\big[N_e - 1, N_p\big]\big)$$
$$= \frac{IP - EA}{2} \qquad (8)$$

$$\mu_p \approx \frac{1}{2}\big(E\big[N_e, N_p + 1\big] - E\big[N_e, N_p - 1\big]\big) = -\frac{PDE + PA}{2} \qquad (9)$$

$$\Pi \approx \frac{1}{2}\big(E\big[N_e, N_p + 1\big] - 2E\big[N_e, N_p\big] + E\big[N_e, N_p - 1\big]\big)$$
$$= \frac{PDE - PA}{2} \qquad (10)$$

where IP is the ionization potential, AE is the electron affinity, PDE is the proton detachment energy and PA is the proton affinity. Finally,

$$\beta = \frac{\partial \mu_p}{\partial N_e} = \frac{\partial \mu_e}{\partial N_p} \approx \frac{\mu_e[N_p + 1] - \mu_e[N_p - 1]}{2} \approx \frac{1}{4}\big(E\big[N_e + 1, N_p + 1\big] - E\big[N_e + 1, N_p - 1\big] - E\big[N_e - 1, N_p + 1\big] + E\big[N_e - 1, N_p - 1\big]\big) \qquad (11)$$

because

$$\mu_e\big[N_p + 1\big] \approx \frac{1}{2}\big(E\big[N_e + 1, N_p + 1\big] - E\big[N_e - 1, N_p + 1\big]\big) \quad (12)$$

and

$$\mu_e\big[N_p - 1\big] \approx \frac{1}{2}\big(E\big[N_e + 1, N_p - 1\big] - E\big[N_e - 1, N_p - 1\big]\big). \qquad (13)$$

Therefore, the electronic (μ_e, η) and protonic (μ_p, Π) coefficients control the change of the energy for electron-transfer and proton-transfer reactions respectively, and the cross coefficient β controls the change of the energy with respect to the simultaneous electron transfer and protonation of the molecule.

Methodology and computational details

Figure 1 shows the proton and electron carrying paths for the neutral *p*-substituted phenols (N_e, N_p) involving their corresponding anionic (N_e+1, N_p), cationic (N_e-1, N_p), protonated (N_e, N_p+1), deprotonated (N_e, N_p-1), anionic-protonated (N_e+1, N_p+1), anionic-deprotonated (N_e+1, N_p-1), cationic-protonated (N_e-1, N_p+1) and cationic-deprotonated (N_e-1, N_p-1) species. The changes of the

Fig. 1 Proton and electron carrying paths for the neutral *p*-substituted phenols [N_e, N_p]
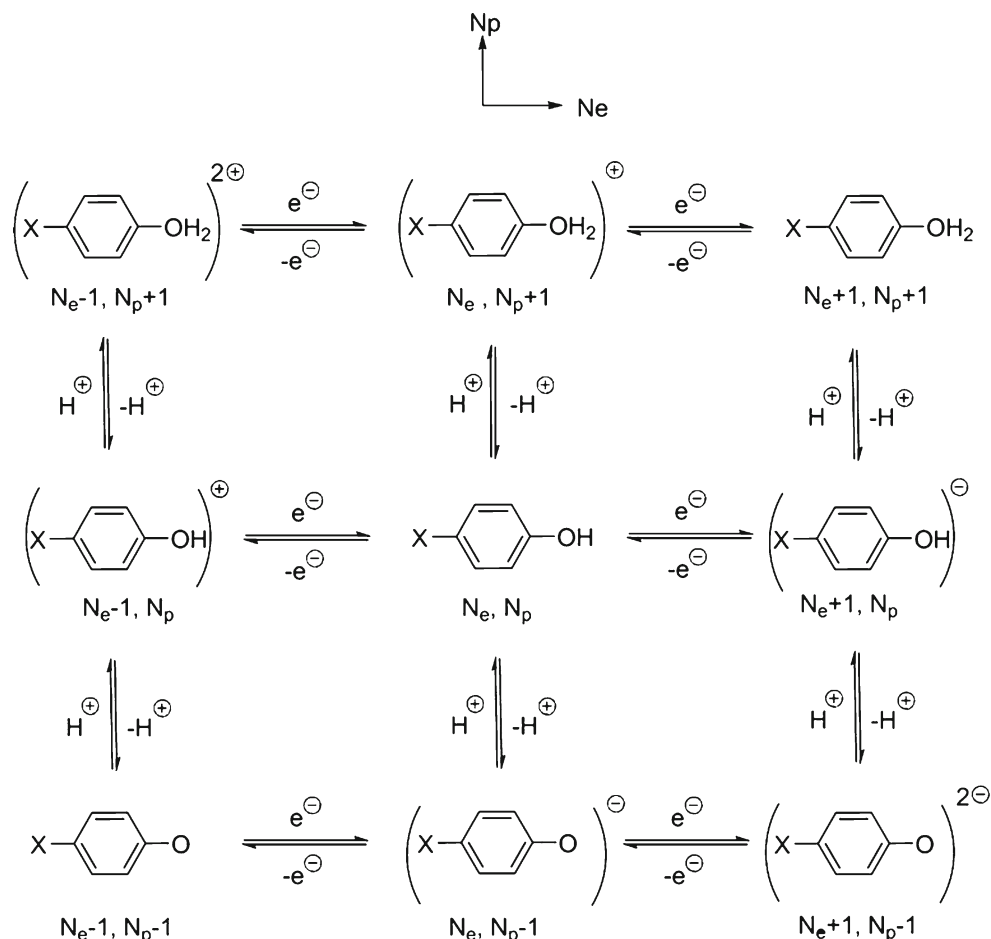
energy in the N_e axis and the N_p axis are related with the power of the system to attract electrons and protons, respectively. On the other hand, η and Π give the resistance to changes in N_e and N_p, respectively.

The ground-state structures of the neutral *p*-substituted phenols and their protonated and deprotonated species were optimized using the B3LYP [40] version of DFT and 6-31+G(d,p) basis sets, as implemented in the GAUSSIAN03 package [41]. The anionic and cationic species were calculated at the geometry of their corresponding neutral *p*-substituted phenols and protonated and deprotonated species. DFT investigations of thermodynamic properties at a similar level of theory have been shown to perform well, providing invaluable insight into aspects of gas phase acidity and bond dissociation energy [29–31, 42]. Using a finite difference approximation for the derivatives of the energy with respect to the number of protons, μ_p and Π can be written in terms of the proton detachment energy PDE and the proton affinity PA [see Eqs. (9) and (10)]. However, we use Gibbs free energy differences ΔG^{o}_{298} as the measures of gas-phase acidity GA and basicity GB, instead of PDE and PA. Then,

$$\mu_p \approx -\frac{GA + GB}{2} \approx -\chi_p \qquad (14)$$

and

$$\Pi \approx \frac{GA - GB}{2}. \qquad (15)$$

Gibbs free energies were obtained from calculations for the most stable conformer of each compound. The Gibbs free energy of the proton in the gas phase, -6.26 kcal mol^{-1}, was obtained considering the translational energy of the proton using statistical thermodynamics relations [31]. Frequency calculations were carried out without any symmetry constraints to confirm that the structures correspond to energy minima.

Results and discussion

The calculated gas phase χ_e, χ_p, η, Π and β values for neutral *p*-substituted phenols are presented in Table 1. χ_e and χ_p reflect the substituent effect, with NH$_2$ (electron-releasing substituent) and NO$_2$ (electron-withdrawing substituent) placed at the two extremes. Phenols with electron-releasing substituents have lower χ_e and higher χ_p values than phenols with electron-withdrawing substituents. Therefore, electron-releasing substituents make the phenols

Table 1 Calculated gas-phase χ_e, χ_p, η, Π, β of p-substituted phenols XC_6H_4OH (−X is the substituent). ΔNe and ΔNp are the electron transfer and proton transfer in reactions (16) and (17) of the text. All values are in eV, except ΔN_e and ΔN_p that are given in au. χ_e and η were obtained from [31]

-X	χ_e	χ_p	η	Π	β	ΔN_e	ΔN_p
-NH$_2$	3.18	11.62	4.19	3.53	−4.46	−0.028	0.018
-OCH$_3$	3.36	11.47	4.33	3.55	−4.62	−0.018	0.008
-OH	3.51	11.43	4.40	3.60	−4.85	−0.009	0.005
-CH$_3$	3.55	11.45	4.57	3.60	−4.88	−0.007	0.006
-t-Bu	3.57	11.44	4.43	3.55	−4.61	−0.006	0.006
-i-Pr	3.58	11.44	4.46	3.56	−4.68	−0.005	0.005
-CH$_2$CH$_3$	3.59	11.43	4.48	3.57	−4.76	−0.005	0.005
-H	3.68	11.36	4.78	3.63	−5.22	0.000	0.000
-Cl	3.77	11.12	4.63	3.57	−4.86	0.005	−0.016
-F	3.82	11.21	4.71	3.64	−5.16	0.007	−0.010
-CO$_2$CH$_3$	4.11	10.98	4.52	3.43	−4.61	0.023	−0.027
-CF$_3$	4.18	10.86	4.84	3.52	−5.05	0.026	−0.035
-CO$_2$H	4.25	10.89	4.54	3.44	−4.75	0.031	−0.033
-CN	4.29	10.70	4.62	3.49	−4.87	0.032	−0.046
-CHO	4.44	10.79	4.42	3.43	−4.77	0.041	−0.040
-NO$_2$	5.02	10.51	4.28	3.40	−4.75	0.074	−0.060

better Brønsted-Lowry bases than Lewis acids. The correlation obtained from the data in Table 1, $\chi_p = 13.827 - 0.687\,\chi_e$ ($R^2 = 0.94$), confirms the proposal.

A plot of Π versus η_e in Fig. 2 separates the neutral p-substituted phenols with electron-withdrawing groups (high χ_e) and electron-releasing groups (low χ_e), dots and diamond symbols, respectively. The range of values of η is similar in both groups (4.28–4.84 eV and 4.19–4.78 eV, respectively), but the values of Π are different: 3.40–3.52 eV in the first group, and 3.53–3.64 eV in the second. That is, the range of variation in the electronic hardness, a measure of the resistance to a change in the number of electrons, is similar in the two groups, but the range of protonic hardness, a measure of the resistance to a change in the number of protons, is different in the two groups. Phenols with strong electron-releasing substituents (those
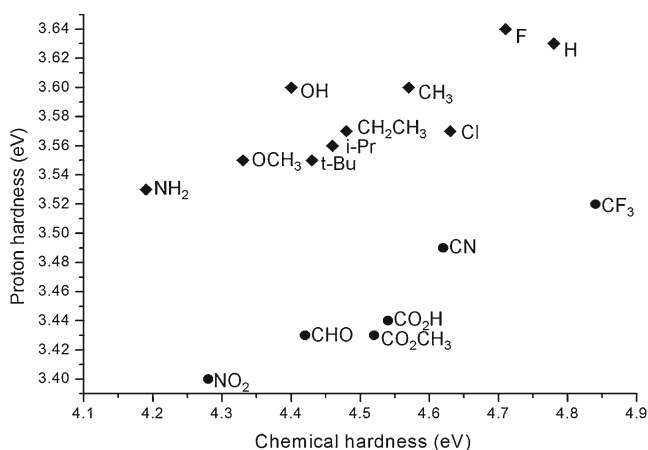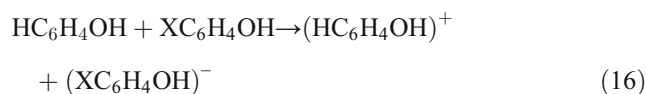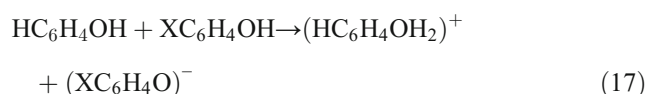
on the bottom-left part of the group of diamonds in Fig. 2) or strong electron-withdrawing substituents (those on the bottom-left part of the group of dots) have lower Π and η values compared to other p-substituted phenols of their respective groups, making these phenols more reactive.

While Brønsted-Lowry acidity/basicity is mostly electrostatic (pure proton transfer), in any real system (i.e., any system with a reaction partner; any solvated system) there is an electron transfer term also (the Lewis acidity/basicity). The cross index β coupling the two effects controls the changes of the energy with respect to simultaneous electron and proton transfer. A clear trend is not evident in the values of β, but one can observe that β is less negative for phenols with strong electron-releasing or strong electron-withdrawing substituents.

Relative electron-transfer ΔN_e and proton-transfer ΔN_p of the p-substituted phenols XC_6H_4OH with respect to HC_6H_4OH itself, that is, for the reactions:

$$HC_6H_4OH + XC_6H_4OH \rightarrow (HC_6H_4OH)^+$$
$$+ (XC_6H_4OH)^- \quad (16)$$

and

$$HC_6H_4OH + XC_6H_4OH \rightarrow (HC_6H_4OH_2)^+$$
$$+ (XC_6H_4O)^- \quad (17)$$

have been calculated. Using the number N_p of protons as a variable, a parallel of the electronegativity equalization principle [43, 44]:

Fig. 2 Proton hardness versus chemical hardness for p-substituted phenols XC_6H_4OH. X is the substituent

$$\Delta N_e = \frac{\chi_e(XC_6H_4OH) - \chi_e(HC_6H_4OH)}{2(\eta(XC_6H_4OH) + \eta(HC_6H_4OH))} \quad (18)$$

can be established, the protofelicity equalization principle [17, 18].

$$\Delta N_p = \frac{\chi_p(XC_6H_4OH) - \chi_p(HC_6H_4OH)}{2\left(\Pi\left(XC_6H_4OH\right) + \Pi\left(HC_6H_4OH\right)\right)}. \quad (19)$$

The results for ΔN_e and ΔN_p calculated in this way are given in Table 1 and Fig. 3. Positive ΔN_e and ΔN_p values indicate electron and proton transfer, respectively, from HC_6H_4OH to XC_6H_4OH. Electrons flow from species of low electronegativity to species of high electronegativity, and protons flow from species of low protofelicity to species of high protofelicity. Just as the electronegativity equalization principle requires the ability to transfer fractions of electrons (ergo, a continuum of electron number, as allowed in DFT), a protofelicity equalization principle requires a continuous proton density, as defined through statistical mechanics or through non-Bon-Oppenheimer DFT [34].

With HC_6H_4OH as the reference molecule, the electron transfer from HC_6H_4OH to XC_6H_4OH increases as the XC_6H_4OH species becomes more electron-poor: $N_e = -0.028$ (X=NH$_2$)<−0.007 (X=CH$_3$)<0.041 (X=CHO)<0.074 (X=NO$_2$). The proton transfer from HC_6H_4OH to C_6H_4OH increases as XC_6H_4OH becomes more electron-rich: $\Delta N_p = -0.060$ (X=NO$_2$)<−0.040 (X=CHO)<0.008 (X=OCH$_3$)<0.018 (X=NH$_2$). All the electron and proton transfer values are small in these reactions, and there is an excellent correlation: $\Delta N_p = -0.005 - 0.881\Delta N_e$ (R^2=0.93).

Table 2 reports the electrophilicity index ω_e of the neutral p-substituted phenols. ω_e measures the second-order change ΔE of the energy of a Lewis acid (electrophile) as it is saturated with electrons, maintaining a constant number of protons [5]. The change in energy associated to a small uptake of electronic charge is favorable at the beginning; that is, the energy is lowered until saturation is reached.
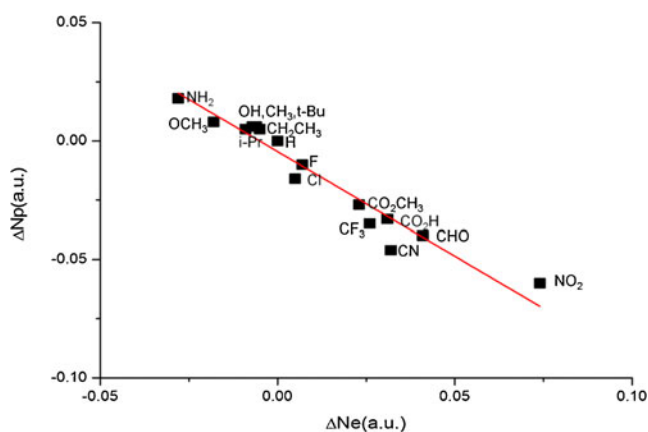

Fig. 3 Electron-transfer ΔN_e and proton-transfer ΔN_p for the reactions $HC_6H_4OH + XC_6H_4OH \rightarrow [HC_6H_4OH]^+ + [XC_6H_4OH]^-$, and $HC_6H_4OH + XC_6H_4OH \rightarrow [HC_6H_4OH_2]^+ + [XC_6H_4O]^-$, respectively. The ΔN_e and ΔN_p values are in au

Table 2 Calculated gas-phase electrophilicity index ω_e, protophilicity index ω_p, and Brønsted-Lowry-Lewis basicity $\omega_{p/e}$ and acidity $\omega_{e/p}$ indexes for p-substituted phenols XC_6H_4OH (X is the substituent). Also, experimental values of the gas-phase acidity $\Delta G°_{gas}$ and the absolute aqueous-acidity pKa. The values of ω_e and ω_p are given in eV, and $\Delta G°_{gas}$ in eV mol^{-1}. pKa, $\omega_{e/p}$ and $\omega_{p/e}$ have no units. $\Delta G°_{gas}$ and pKa values were obtained from references 2, 3, 45 and 46

-X	ω_e	ω_p	$\omega_{p/e}$	$\omega_{e/p}$	$\Delta G°_{gas}$	pKa
-NH$_2$	1.21	19.13	15.810	0.063	15.02	10.3
-OCH$_3$	1.30	18.53	14.254	0.070	14.93	10.21
-OH	1.40	18.15	12.964	0.077	14.93	9.96
-CH$_3$	1.38	18.21	13.196	0.076	14.92	10.14
-t-Bu	1.44	18.43	12.799	0.078	14.85	10.39
-i-Pr	1.43	18.38	12.853	0.078	14.88	—
-CH$_2$CH$_3$	1.44	18.30	12.708	0.079	14.90	—
-H	1.42	17.78	12.521	0.080	14.87	9.98
-Cl	1.53	17.32	11.320	0.088	14.62	9.38
-F	1.55	17.26	11.135	0.090	14.77	9.95
-CO$_2$CH$_3$	1.86	17.57	9.446	0.106	14.37	—
-CF$_3$	1.80	16.75	9.306	0.107	14.36	—
-CO$_2$H	1.99	17.24	8.663	0.115	14.45	9.40
-CN	1.99	16.40	8.241	0.121	14.15	7.95
-CHO	2.23	16.97	7.610	0.131	14.19	7.62
-NO$_2$	2.95	16.24	5.505	0.182	13.97	7.15

Beyond that point, further flow of electronic charge raises the energy. Starting with the second-order Taylor series for the energy given in Eq. (1), saturation of electrons, maintaining N_p constant, occurs when $\partial E/\partial N_e = 0$. Then, one obtains [5]:

$$\omega_e = \frac{\chi_e^2}{2\eta}. \quad (20)$$

In a similar way, we can define a new basicity index, the protophilicity ω_p, which measures the second-order energy change of a Brønsted-Lowry base as it is saturated with protons, maintaining constant the number of electrons N_e. Saturation occurs when $\partial E/\partial N_p = 0$. Then, Eq. (1) leads to

$$\omega_p = \frac{\chi_p^2}{2\Pi}. \quad (21)$$

From Table 2, we observe that the values of ω_p are much higher than the values of ω_e. This indicates that the p-substituted phenols are more susceptible to changes in the number of protons than to changes in the number of electrons (the same feature can be appreciated by comparing χ_p and χ_e in Table 1). However, the relative change between the maximum and minimum values of ω_e in the series of substituted phenols of Table 2, $[\omega_e(max) - \omega_e(min)]/\omega_e(max) = 0.59$, is larger than the corresponding change, of 0.15, for ω_p.

Due to a cancellation of effects in Eq. (20), ω_e is related to EA, showing a good linear correlation, EA$=-2.454+1.077\omega_e$ ($R^2=0.97$). In a similar way, ω_p and GB show a good linear correlation, GB$=1.606+0.341\omega_p$ ($R^2=0.98$). The neutral p-substituted phenols with strong electron-releasing substituents have higher ω_p and lower ω_e values, and will be better Brønsted-Lowry bases and worse Lewis acids than the neutral p-substituted phenols with strong electron-withdrawing substituents. As a consequence, phenols with electron-withdrawing substituents are better Brønsted-Lowry acids than phenols with electron-releasing substituents.

The Brønsted-Lowry assumption (a strong acid is a weak base and a weak acid is a strong base) is confirmed by the correlation obtained between ω_p and the experimental absolute gas phase acidity ΔG^o_{gas}, whose values for the neutral p-substituted phenols [2] are shown in Table 2. Namely, $\Delta G^o_{gas}=8.109+0.370\omega_p$ ($R^2=0.83$). That is, ΔG^o_{gas} increases (the Brønsted-Lowry acidity decreases) when ω_p increases. The same trend is found by analyzing the experimental values of the absolute aqueous acidity pKa [45, 46], given in Table 2. That is, pKa increases (the Brønsted-Lowry acidity decreases) when ω_p increases. However, the linear correlation obtained, pKa$=-10.272+1.114\omega_p$ ($R^2=0.75$), is less accurate.

Finally we propose a new basicity index $\omega_{p/e}$

$$\omega_{p/e} = \frac{\omega_p}{\omega_e} = \frac{\eta\,\chi_p^2}{\Pi\,\chi_e^2} \qquad (22)$$

that we interpret in the following way: ω_p is a measure of the capacity of the molecule to "attract" protons, and $1/\omega_e$ is a measure of its capacity to "release" electrons. So, both factors ω_p and $1/\omega_e$ contribute to the basicity and $\omega_{p/e}$ is a global measure of the basicity of the system. Table 2 shows the $\omega_{p/e}$ values for p-substituted phenols; high $\omega_{p/e}$ values correspond to strong bases and low $\omega_{p/e}$ values to weak bases. The inverse of $\omega_{p/e}$ can be interpreted as an acidity index

$$\omega_{e/p} = \frac{\omega_e}{\omega_p} = \frac{\Pi\,\chi_e^2}{\eta\,\chi_p^2} \qquad (23)$$

because ω_e is a measure of the capacity of the molecule to "attract" electrons, and $1/\omega_p$ is a measure of its capacity to "release" protons. Table 2 shows that high $\omega_{e/p}$ values correspond to phenols with electron-withdrawing substituents and they are better acids than phenols with electron-releasing substituents. Evidently, $(\omega_{p/e})(\omega_{e/p})=1$. The new $\omega_{p/e}$ and $\omega_{e/p}$ indexes explore the simultaneous contribution of ω_p and ω_e to the Brønsted-Lowry and Lewis acid–base properties and they should be useful in the study of the fundamental chemical addition, elimination and substitution reactions.

Conclusions

A protophilicity index ω_p (the second-order energy change of a Brønsted-Lowry base as it is saturated with protons), a combined Brønsted-Lowry-Lewis acidity index $\omega_{e/p}$ (and the corresponding $\omega_{p/e}$ basicity index), and a protofelicity equalization principle were proposed and used to explore the simultaneous contributions of proton and electron transfer to the Brønsted-Lowry and Lewis acid–base properties of a set of p-substituted phenols. Phenols with strong electron-releasing substituents are proton acceptors, and they behave as Brønsted-Lowry bases. Substitution by strong electron-withdrawing species changes the properties of the phenols in the direction of making them electron acceptors, behaving as Lewis acids. Experimental work [2, 3, 45, 46] supports the theoretical proposals.

Cartesian coordinates of the p-substituted phenols studied in this work are provided in the Online Resource link.

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