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Letter

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Elimination vs Substitution Reaction. A Dichotomy between Brønsted–Lowry and Lewis Basicity

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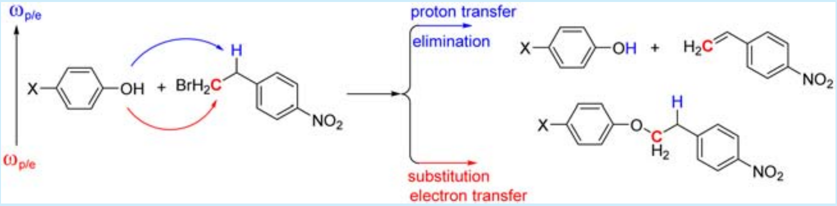
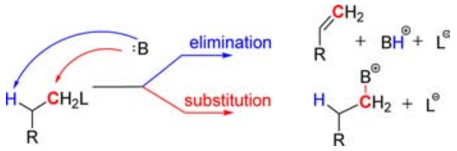
Ⓢ *Supporting Information*



ABSTRACT: The Brønsted–Lowry and Lewis basicity dichotomy in the elimination vs substitution reaction competition is analyzed in terms of a novel Brønsted–Lowry–Lewis basicity $\omega_{p/e}$. This new index unifies the dichotomy and explains the competition between elimination and substitution mechanisms of alkyl centers with *para*-substituted phenols.

A fundamental question in organic chemistry, still unresolved, is how to determine whether elimination (E) or substitution (S_N) reactions are favored (Scheme 1).[1]

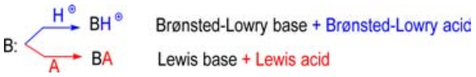
Scheme 1



In the elimination reaction E2, the species B acts as a Brønsted–Lowry base to remove a proton (deprotonation), while in the nucleophilic substitution reaction S_N2 the Lewis base B (nucleophile) attacks the carbon atom of the alkyl center (electron pair donation). The E2 and S_N2 reactions compete with each other depending on the balance deprotonation/electron pair donation of the base/nucleophile.[2] The dichotomy of the base to behave as a Brønsted–Lowry base or as a Lewis base modulates the E2 and S_N2 competition, and it occurs because the reactive site of the base is an unshared electron pair (Scheme 2).[1] To unify the dichotomy one has to understand the E2/S_N2 competition.

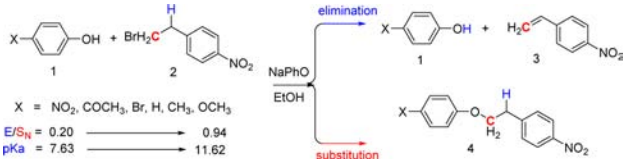
Several authors have suggested that the acid/base Brønsted–Lowry theory is a special case of the acid/base Lewis theory because the proton transfer is the structural result of electron-pair displacement.[3] However, the natural way to describe the acid/base Brønsted–Lowry properties should be in terms of the proton transfer, and the acid/base Lewis properties in terms of the electron transfer. In this letter, we introduce a unified acid/base Brønsted–Lowry–Lewis proposal[4] to analyze the competition between elimination and substitution reactions. The new Brønsted–Lowry–Lewis acidity $\omega_{e/p}$ and basicity $\omega_{p/e}$ indexes are defined in terms of electronic[5,6] (electronegativity χ_e, chemical hardness η, and electrophilicity ω_e) and protonic[4,7,8] (protofelicity χ_p, protonic hardness Π, and protophilicity ω_p) properties.[9] Specifically, $\omega_{e/p} = \omega_e/\omega_p$, and $\omega_{p/e} = \omega_p/\omega_e$. In this paper, we use for the first time the $\omega_{e/p}$ and $\omega_{p/e}$ indexes to explain the influence of the Brønsted–Lowry–Lewis acidity/basicity of a set of *para*-substituted phenols **1** on the ratio of elimination/substitution rates upon reaction with *p*-nitrophenethyl bromide **2** obtained by Hudson and Klopman (Scheme 3).[10]

Scheme 2



The main point here is that if the E2 and S_N2 reactions compete with each other depending on the balance deprotonation/electron pair donation of the base/nucleophile, and the Brønsted–Lowry–Lewis basicity $\omega_{p/e}$ measures the

Scheme 3



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combined capacity of the molecule to attract protons (ω_p) and to release electrons (ω_e^{-1}), then $\omega_{p/e}$ explains and unifies the dichotomy of **1** to remove a proton (Brønsted−Lowry base) and to attack the carbon atom of the alkyl center (Lewis base) of **2**. A linear free energy relationship[11] between the ratio E/S_N of rates and $\omega_{p/e}$ values then confirms the Hudson and Klopman experimental observations.

The systematic study of Hudson and Klopman showed that the elimination products were obtained in lower yield than substitution products and that the percentage of elimination increased steadily with the pK_a of **1** (Scheme 3). Table 1 shows the experimental values for the ratio of elimination/substitution rates obtained by Hudson and Klopman. The change in those rates depends essentially on the structure of the *para*-substituted phenol. A correlation between the ratio of rates E/S_N and equilibrium pK_a data confirmed the experimental observation: $E/S_N = -1.406 + 0.197\text{p}K_a$ ($R = 0.951$).[12]

Table 1. Calculated χ_e, χ_p, η, and Π Values for *Para*-Substituted Phenols 1 XC$_6$H$_4$OH (Values in eV, Calculated at the B3LYP/6-31+G(d,p) Level of Theory) and Experimental Ratio of Rates E/S_N and pK_a Values (They Have No Units)

−X	E/S_N[a]	pK_a[a]	χ_e[b]	χ_p[b]	η[b]	Π[b]
−OCH$_3$	0.94	11.52	3.36	11.47	4.33	3.55
−CH$_3$	0.93	11.67	3.55	11.45	4.57	3.60
−H	0.86	11.28	3.68	11.36	4.78	3.63
−Br	0.52	10.50	3.81	11.11	4.50	3.55
−COCH$_3$	0.30	9.21	4.28	10.92	4.40	3.42
−-NO$_2$	0.20	7.63	5.02	10.51	4.28	3.40

[a]Values were obtained from ref 10. [b]Values for OCH$_3$, CH$_3$, H and NO$_2$ were obtained from ref 4.

According to the Hudson and Klopman proposal that the change in the rates of substitution and elimination depends fundamentally on the structure of the *para*-substituted phenol, we have carried out density functional molecular orbital calculations at the B3LYP/6-31+G(d,p) level of theory using Gaussian 09[13] for a set of *para*-substituted phenols **1** (X = NO$_2$, COCH$_3$, Br, H, CH$_3$, and OCH$_3$) and their protonated and deprotonated species. The anionic and cationic species were calculated at the same level of theory using the geometry of their corresponding neutral *para*-substituted phenols.[14]

The electronic (χ_e and η) and protonic (χ_p and Π) indexes measure the energy change with respect to a change in the number of electrons and protons, respectively. Using a finite difference approximation for the electronic derivatives, χ_e and η can be written in terms of the ionization potential I and electronic affinity A: $\chi_p = (I + A)/2$ and $\eta = (I - A)/2$. The protonic derivatives χ_p and Π can be written in terms of the gas-phase acidity GA and basicity GB: $\chi_p = (\text{GA} + \text{GB})/2$ and $\Pi = (\text{GA} - \text{GB})/2$. In Table 1, we observe that phenols with electron-releasing substituents (upper rows of Table 1) have lower electronegativity χ_e and higher protofelicity χ_p values than phenols with electron-withdrawing substituents (lower rows of Table 1). Electron-releasing substituents make the phenols good Brønsted−Lowry bases. When χ_e increases, χ_p decreases ($\chi_p = 13.524{-}0.6043\chi_e$, $R^2 = 0.968$). Phenols with strong electron-releasing substituents or with strong electron-withdrawing substituents have the smallest resistance to changes in the number of electrons (η) and protons (Π) in the set, making those phenols more reactive than the H-phenol.

The ω_e and ω_p indexes ($\omega_e = \chi_e^2/2\eta$ and $\omega_p = \chi_p^2/2\Pi$) measure the energy change of a Lewis acid and a Bronsted−Lowry base as they are saturated with electrons and protons, respectively.[4,6] Therefore, ω_e^{-1} and ω_p measure the capacity of the Lewis base to release electrons and the capacity of the Bronsted−Lowry base to attract protons, respectively. Table 2 shows that the values of ω_p are much higher than the values of ω_e^{-1}. This suggests that the *para*-substituted phenols are more likely to accept protons (Brønsted−Lowry basicity) than to donate electrons (Lewis basicity). However, the relative change between the maximum and minimum values of ω_e^{-1} in the group of substituted phenols of Table 2, $[\omega_e^{-1}(\text{max}) - \omega_e^{-1}(\text{min})]/\omega_e^{-1}(\text{max}) = 0.56$, is larger than the corresponding change of 0.12 for ω_p. This indicates that the capacity of phenols to donate electrons (Lewis basicity) is more sensitive to the specific substituent than their capacity to accept protons (Brønsted−Lowry basicity). Phenols with electron-releasing substituents have higher ω_p and ω_e^{-1} values than phenols with electron-withdrawing substituents. Then, electron-releasing substituents make the phenols better Brønsted−Lowry and Lewis bases than phenols with electron-withdrawing substituents. The relationship $\omega_p = 14.915 + 4.3478\omega_e^{-1}$ ($R^2 = 0.830$) confirms the proposal.

Table 2. Calculated Values of ω_e, ω_e^{-1}, ω_p, $\omega_{p/e}$, and $\omega_{e/p}$ for *Para*-Substituted Phenols XC$_6$H$_4$OH (Values in eV, Calculated at the B3LYP/6-31+G(d,p) Level of Theory)

−X	ω_e[a]	ω_e^{-1}	ω_p[a]	$\omega_{p/e}$	$\omega_{e/p}$
−OCH$_3$	1.30	0.769	18.53	14.25	0.070
−CH$_3$	1.38	0.724	18.21	13.20	0.076
−H	1.42	0.704	17.78	12.52	0.080
−Br	1.48	0.675	17.38	11.74	0.085
−COCH$_3$	2.06	0.485	17.43	8.46	0.118
−NO$_2$	2.95	0.338	16.24	5.51	0.182

[a]Values for OCH$_3$, CH$_3$, H, and NO$_2$ were obtained from ref 4.

The Brønsted−Lowry−Lewis basicity $\omega_{p/e} = \omega_p\omega_e^{-1}$ measures the combined capacity of the molecule to attract protons (ω_p) and to release electrons (ω_e^{-1}). As we can observe from Table 2, phenols with electron-releasing substituents have higher Brønsted−Lowry−Lewis basicity $\omega_{p/e}$ and lower acidity $\omega_{e/p}$ values than phenols with electron-withdrawing substituents. The linear correlation between Ln(E/S_N) and the basicity $\omega_{p/e}$ presented in Figure 1, $\text{Ln}(E/S_N) = -2.7439 + 0.1935\omega_{p/e}$ ($R^2 = 0.9554$), shows that the E/S_N ratio increases when $\omega_{p/e}$ increases.

From this analysis, we conclude that (i) the large values of ω_p, in comparison to ω_e^{-1}, indicate that the phenols are more susceptible to behave like Brønsted−Lowry bases than as Lewis bases and (ii) the sensitivity to specific substituents is much higher in the capacity of phenols to be Lewis bases than Brønsted−Lowry bases. These conclusions have been confirmed by the analysis of the experimental results of Hudson and Klopman provided 50 years ago. In those experiments, the Brønsted catalysis law described the changes in rate constants, k_E and k_{SN} with the pK_a of the phenol. For elimination, $\log k_E = \alpha_E\text{p}K_a + C_1$, and for substitution, $\log k_{SN} = \alpha_S\text{p}K_a + C_2$. On the other hand, the elimination products were obtained in lower yield than substitution products.[15]

Therefore, the Brønsted−Lowry−Lewis basicity $\omega_{p/e}$ index reflects the susceptibility and capacity of the base to attract protons and to release electrons. This capacity is correlated

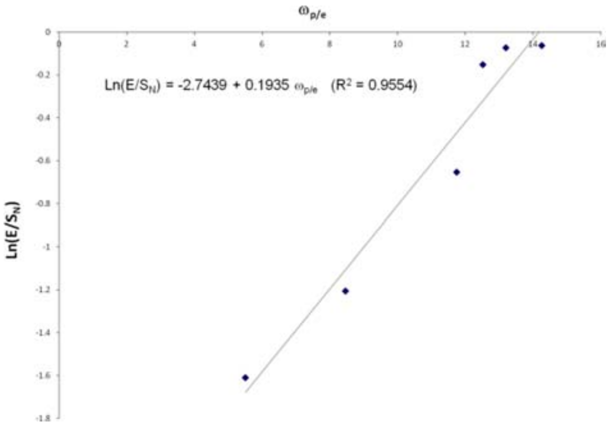

Figure 1. Linear correlation between $\mathrm{Ln}(E/S_N)$ values and the Brønsted–Lowry–Lewis basicity index $\omega_{p/e}$.

with the dichotomy of the base to remove a proton (Brønsted–Lowry base) and to attack the carbon atom of the alkyl center (Lewis base). The unification of the dichotomy leads to an understanding of the competition between the E2 and S_N2 reaction paths.

The results obtained in this work open the possibility of analyzing several S_N2 and E2 reactions in terms of the electronic and protonic indexes, for example: (a) $NCCH_2CH_2Cl$ with OH^- and SH^-, (b) alkyl nitrates ($CH_3CH_2ONO_2$) with NH_2^- and SH^-, and (c) dianion of $HSO_3C_6H_4CCC_6H_4CO_2H$ with one tetraalkylammonium counterion R_4N^+.[16] An interesting system is the reaction NADH + A^+ = AH + NAD^+. Important questions remain concerning the detailed mechanism: the reaction can proceed via (a) concerted H^- transfer, (b) separate transfer of H^+ and 2e−, or (c) even stepwise $H^\bullet$ and e− transfer. A desire for deeper mechanistic understanding motivates future research.[17]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Cartesian coordinates, electronic energies, zero-point energies, and thermochemical data for fully optimized geometries of *para*-substituted phenols **1** are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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