

Supporting Information

Enhancing Bioactivity by Transferring Active Moiety

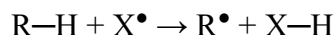
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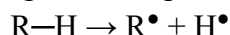
1. Thermodynamic Descriptors and Scavenging Mechanisms

Radicals can be deactivated by the R–H scavenger via the five fundamental mechanisms specified below.

HAT (*Hydrogen Atom Transfer*)



This mechanism is widely applied in processes in which the hydrogen atom is transferred from the basic compound to the reactive intermediate. The antiradical potency of a compound is related to the low bond dissociation enthalpy (BDE) of the N–H bond in amines, S–H in organosulfur compounds, O–H in polyphenols, alcohols, carboxylic acids and O=C–H in aldehydes. Hence, crucial for calculating the BDE parameter is reaction

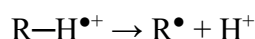
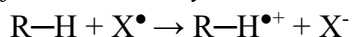


initiating the HAT process, which allows defining the BDE parameter [22]

$$\text{BDE} = H(\text{R}^\bullet) + H(\text{H}^\bullet) - H(\text{R-H}) \quad (1)$$

in which $H(\text{R}^\bullet)$, $H(\text{H}^\bullet)$ and $H(\text{R-H})$ denote enthalpies of the radical, hydrogen atom, and the neutral molecule.

SET-PT (*Single Electron Transfer Followed by Proton Transfer*)



This scenario involves the transfer of an electron from the parent compound

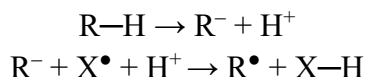


generating a cation radical $\text{R-H}^{\bullet+}$ and, in the next step, the proton transfer from the cation radical producing parent agent in the radical form $\text{R}^\bullet$. These two stages are characterized by the adiabatic ionization potential (AIP) and the proton dissociation enthalpy (PDE) calculated from the formulae [22]

$$\begin{aligned} \text{AIP} &= H(\text{R-H}^{\bullet+}) + H(\text{e}^-) - H(\text{R-H}) \\ \text{PDE} &= H(\text{R}^\bullet) + H(\text{H}^+) - H(\text{R-H}^{\bullet+}) \end{aligned} \quad (2)$$

Here, $H(\text{R-H}^{\bullet+})$, $H(\text{e}^-)$, $H(\text{H}^+)$, and $H(\text{R-H})$ represent the enthalpies of the cation, electron, proton, and the parent compound, respectively. AIP is determined using the enthalpies of the optimized cationic state and the optimized neutral molecule. The Vertical Ionization Potential (VIP) defined as the difference between the energy of the optimized neutral structure and that of the corresponding cationic system at the neutral geometry is not considered in this work.

SPLET (*Sequential Proton Loss Electron Transfer*)



The second step of the reaction above specified is initiated by the reaction



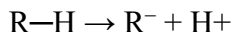
The SPLET process is therefore characterized by the proton affinity (PA) and electron transfer enthalpy (ETE) calculated according to the formulae [22]

$$\begin{aligned} \text{PA} &= H(\text{R}^-) + H(\text{H}^+) - H(\text{R-H}) \\ \text{ETE} &= H(\text{R}^\bullet) + H(\text{e}^-) - H(\text{R}^-) \end{aligned} \quad (3)$$

If the reactions specified above are not sequential and involve the concerted shift of a single electron and a single proton they are called Concerted Proton-Electron Transfer (CPET) [23]. This pathway belongs to the wide class of a Proton-Coupled Electron Transfer (PCET) [24], which involves the shift of electrons and protons from one molecule (atom) to another.

TMC (*Transition Metals Chelation*)

This mechanism is related to the chelation of the transition metal ions (especially Fe^{2+} and Cu^{2+}), which produces stable complexes that remove them from the reaction medium and contribute to the slowing down of the radical cascade reactions. Vital for this mechanism is the dissociation decay



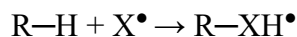
The parameter characterizing TMC in solvents is the free Gibbs acidity [25]

$$G_{\text{acidity}} = G(\text{R}^-) - G(\text{R-H}) \quad (4)$$

in which $G(\text{R}^-)$ and $G(\text{R-H})$ denote the Gibbs free energy of the anion and its parent compound, respectively. A lower value of this parameter indicates a greater ability to chelate metals and, consequently, a greater potency to slow down radical processes.

RAF (*Radical Adduct Formation*)

In this scenario, radicals are deactivated in the reaction [26]



which is characterized by the enthalpy or Gibbs free energies formation calculated for a given radical and an antioxidant considered. Hence, this pathway is characterized by the descriptor depending on the radical type. Consequently, it will not be considered here. In calculations of the BDE, PDE, AIP, ETE, PA, G_{acidity} parameters, we used the values of the electron, proton and hydrogen enthalpies in the vacuum, water, and benzene recommended by Rimarčik et al. [22].

2. Chemical Activity Descriptors

An important source of information on the reactivity of chemical compounds is the difference in the energies of the HOMO and LUMO frontier orbitals. The shape of these orbitals, as well as the energy gap (usually expressed in electron volts [eV])

$$\Delta E = E_{LUMO} - E_{HOMO} \quad (5)$$

have an impact on the chemical reactivity of compounds. A large energy difference defines a *hard* molecule that is more stable and less active, while a small energy gap defines a *soft* molecule that is less stable and more reactive. Based on the energy of the LUMO and HOMO orbitals, as well as the Koopmans' theorem [23] for the closed shell molecules, one may define the global activity descriptors [5,28,29], which model the chemical reactivity of compounds [30]. The most important descriptors are specified below.

Ionization potential

$$IP = -E_{HOMO} \quad (6)$$

It describes the minimum energy required to remove an electron from the molecule's HOMO orbital and move it to infinity. The small IP value indicates a greater tendency of the molecule to participate in the chemical reaction related to electron transfer. The best radical scavengers are endowed with low IP values.

Electron affinity

$$EA = -E_{LUMO} \quad (7)$$

It expresses the ability of a molecule to accept an electron and produce an anion. Due to the fact that radicals scavenging might act either via donating or accepting electrons, the EA descriptor is useful to characterize the capacity of a compound to accept electrons.

Chemical hardness

$$\eta \approx \frac{E_{LUMO} - E_{HOMO}}{2} \quad (8)$$

It describes a molecule with a low susceptibility to deformation or polarization of the electron cloud under the influence of external factors, e.g., reagents.

Chemical softness

$$S \approx \frac{1}{E_{LUMO} - E_{HOMO}} \quad (9)$$

The inverse of chemical hardness – the S-descriptor characterizes molecules with the high susceptibility to deformation and polarization of the electron cloud.

Chemical potential

$$\mu \approx \frac{E_{LUMO} + E_{HOMO}}{2} \quad (10)$$

Employed to describe the thermodynamic activity of substances and used, for example, in the derivation of the phase equilibrium constants.

Electronegativity

$$\chi = -\mu \approx -\frac{E_{LUMO} + E_{HOMO}}{2} = \frac{EA + IP}{2} \quad (11)$$

It characterizes a tendency to attract electrons that create the chemical bond. The common electron pair is shifted towards the atom having a high value of χ , which is accompanied by the formation of a polar or ionic bond.

Electrophilicity Index

$$\omega \approx \frac{\chi^2}{2\eta} = \frac{(E_{LUMO} + E_{HOMO})^2}{4(E_{LUMO} - E_{HOMO})} \quad (12)$$

This descriptor was introduced by Robert Parr and coworkers [31]. It measures the energy change of an electrophilic reagent (acceptor) when it is saturated with electrons provided by another reagent (donor). Higher values of ω characterize a strong electrophile, whereas a strong nucleophile is described by lower values of ω .

Electro-donating and electro-accepting power

A radical scavenger (RS) can act in two ways: either by donating electrons to, or accepting electrons from a radical (R)



Following this fact, Gázquez et al. [32] introduced new descriptors characterizing the electro-donating ω^- and electro-accepting ω^+ power of RS, defined in the following manner

$$\omega^- = \frac{(3IP + EA)^2}{16(IP - EA)} \quad \omega^+ = \frac{(IP + 3EA)^2}{16(IP - EA)} \quad (13)$$

To characterize the relative electro-accepting (donating) power of an arbitrary radical scavenger X, Martinez [5] introduced the acceptance Ra and donation Rd indexes

$$Ra = \frac{\omega_X^+}{\omega_F^+} \quad Rd = \frac{\omega_X^-}{\omega_{Na}^-} \quad (14)$$

defined by the IP and EA for the F and Na atoms. They represent a good electron acceptor (F) and a good donor (Na), respectively. In the calculations, the experimental values [5] for F: IP = 17.42282, EA = 3.4011898 [eV], and for Na: IP = 5.1391, EA = 0.547926 [eV] are employed. Ra and Rd are useful for classifying any compound X in terms of its electron donating (accepting) capacity. Hence, they can be applied to characterize the antiradical capacity of X in terms of its electro-donating (accepting) power with respect to the F and Na atoms, taken as the reference points [5].