ELECTRONIC SUPPLEMENTARY INFORMATION

Why proton is transformed into hydride by [NiFe] hydrogenases? An intrinsic reactivity analysis based on Conceptual DFT

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Theoretical Framework

Energy and Reaction Force: A transition state (TS) is a chemical entity that exhibits one imaginary frequency and is a maximum along the intrinsic reaction coordinate (IRC = ξ).[1, 2] It connects reactants and products through the minimum potential energy surface (PES) in a one-step chemical reaction.

The reaction force, F, is defined as the negative first derivative of the total energy, E, with respect the IRC (Eqn .1):

$$F(\xi) = -\frac{dE}{d\xi} \tag{1}$$

According to the Transition State Theory[3] (TST), the energy profile of an elementary step presents three critical points: two minima, one for reactants (ξ_R) and another for products (ξ_P), and one maximum for the TS (ξ_{TS}) (see Scheme below). In addition, F exhibits two critical points: a minimum at ξ_1 and a maximum at ξ_2. Thus, three regions can be defined along the IRC: i) in the $[\xi_R, \xi_1]$ range, region associated to reactants and mainly driven by structural rearrangements; ii) in the (ξ_1, ξ_2) range, region associated to the TS and where most electron rearrangements by formation and breaking of bonds take place; and iii) in the $[\xi_2, \xi_P]$ range, region associated to products where mainly occurs structural relaxations.[4-10] Note that $\xi_R < \xi_1 < \xi_{TS} < \xi_2 < \xi_P$.

The reaction force analysis provides an energy partition of the activation barrier, $E^{\neq}$. Thus, W_1 represents the energy required for the system to be reorganized geometrically, i.e. purely structural reordering; and W_2 represents the energy demanded for the system for an electronic reorganization in order to reach the TS, i.e. purely electronic rearrangement (Eqns. 2 to 4):

$$E^{\neq} = W_1 + W_2 \tag{2}$$

$$W_1 = -\int_{\xi_R}^{\xi_1} F(\xi)d\xi > 0 = E(\xi_1) - E(\xi_R) \tag{3}$$

$$W_2 = -\int_{\xi_1}^{\xi_{TS}} F(\xi)d\xi > 0 = E(\xi_{TS}) - E(\xi_1) \tag{4}$$

Scheme 1. The solid and black line represents a generic energy profile, *E*, *vs*. the IRC. The dotted and blue line represents the reaction of force, *F*, *vs*. the IRC. The location of the stationary points of the energy and reaction force are indicated as $\xi_R/\xi_{TS}/\xi_P$ and ξ_1/ξ_2, respectively. Two vertical lines separate the reactants region (left), the TS region (center), and the products region (right).
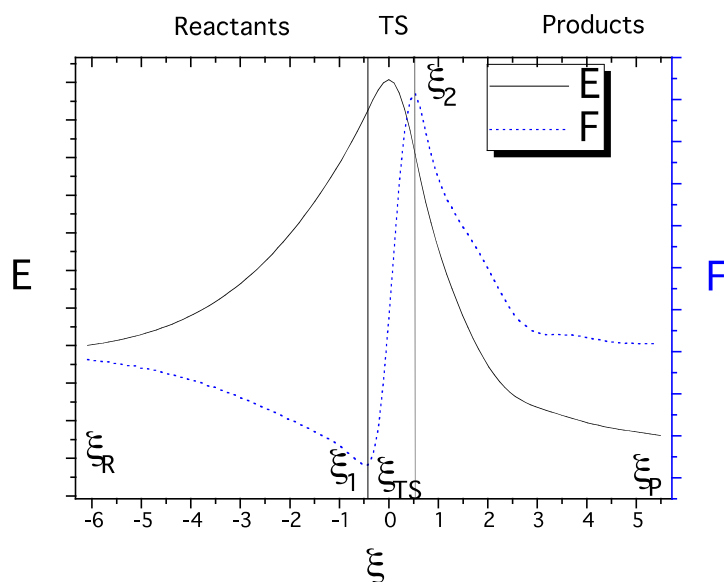
Global Chemical Properties based on Conceptual DFT: Conceptual DFT[11, 12] offers a range of useful theoretical tools allowing an analysis of the intrinsic reactivity for the chemical events occurring at electronic level, which are directly associated within physicochemical properties from both global and local nature.

Concerning the global properties, the electronic chemical potential, μ, for a system containing *N* electrons is defined as the derivative of the total energy, *E*, with respect *N* when the external potential, *v(r)*, remains constant (Eqn. 5). Considering that the number of electrons, *N*, is a discontinuous variable, the electronic chemical potential can be approximated, through the application of finite differences and the Koopmans' theorem[13] by extension of the Hartree-Fock theory, as the negative semi-sum of the first ionization potential, *I,* and the electron affinity, *A.* Also, these two parameters, *A* and *I,* can be approximated to the energy values of the highest occupied and lowest unoccupied molecular orbitals, ε_H (HOMO) and ε_H (LUMO), respectively. The electronegativity,[14] χ, is defined as the opposite of μ:

$$\mu = -\chi = \left(\frac{\partial E}{\partial N}\right)_{v(\vec{r})} \approx -\left(\frac{I+A}{2}\right) = \frac{\varepsilon_L + \varepsilon_H}{2} \tag{5}$$

By analogy between E and F, the reaction electronic flux (REF), J, can be defined as the negative first derivative of the electronic chemical potential, μ, with respect the IRC (Eqn .6):

$$J(\xi) = -\frac{d\mu}{d\xi} \tag{6}$$

While the electronic chemical potential measures the electronic activity, the interpretation of the REF results from the analogy with classical thermodynamics: positive values of J should be associated with spontaneous rearrangements of the electron density driven by bond strengthening or forming processes, and negative values of J are indicating non-spontaneous rearrangements of the electron density that are mainly driven by bond weakening or breaking processes.[15]

Furthermore, the chemical hardness,[16, 17] η, is defined as the second derivative of the total energy, E, with respect N when $v(\vec{r})$ is constant (Eqn. 7). Also, applying the finite differences approximation and the Koopmans' theorem, it can be approximated as the difference between the energy of the LUMO and HOMO. The chemical softness, S, is defined as the inverse of η:

$$\eta = S^{-1} = \left(\frac{\partial^2 E}{\partial N^2}\right)_{v(\vec{r})} \approx -(I-A) \approx \varepsilon_L - \varepsilon_H \tag{7}$$

Finally, the electrophilic power, ω, which was introduced by Parr et al.[18] by analogy with the power in classical electricity, is defined as (Eqn. 8):

$$\omega \approx \frac{\mu^2}{2\eta} \approx \frac{(I+A)^2}{8(I-A)} \approx \frac{(\varepsilon_L + \varepsilon_H)^2}{8(\varepsilon_L - \varepsilon_H)} \tag{8}$$

Local Properties. The Fukui Function: The global properties defined, so far, are useful in monitoring intrinsic changes in the molecules. However, the reactivity of such molecules resides

on the atomic centers, and consequently, the evaluation of local properties are desirable. They can be calculated from the Fukui function,[19] $f(r)$, which is defined as the second derivative of the total energy with respect N and $v(r)$ (Eqn. 9). This function complies an important property: its integration over all the space gives the unit value (Eqn. 10):

$$f(\vec{r}) = \left[\frac{\partial^2 E}{\partial N \delta v(\vec{r})} \right] \tag{9}$$

$$\int_{\Omega} f(\vec{r}) dr = 1 \tag{10}$$

Due to the discrete nature of N, two Fukui functions can be derived: the nucleophilic, $f^{+}(r)$, and the electrophilic, $f^{-}(r)$, functions. They can be approximated through the electron density of the LUMO and HOMO frontier orbitals, respectively. Both, nucleophilic and electrophilic Fukui functions can be evaluated for each atom as indicated in Eqns. 11 and 12:

$$f^{+}(\vec{r}) = \left| \phi^{L}(\vec{r}) \right|^2 = \rho^{L}(\vec{r}) \rightarrow f_k^{+} = p_k(N+1) - p_k(N) \tag{11}$$

$$f^{-}(\vec{r}) = \left| \phi^{H}(\vec{r}) \right|^2 = \rho^{H}(\vec{r}) \rightarrow f_k^{-} = p_k(N) - p_k(N-1) \tag{12}$$

where the subscript k refers to a particular atom k. Then, $p_k(N)$ is the electronic population on an atom k in the neutral molecule, $p_k(N+1)$ is the electronic population on an atom k in the radical anion molecule, and $p_k(N–1)$ is the electronic population on an atom k in the radical cation molecule.

Using the nucleophilic Fukui function and the global electrophilicity, the local electrophilicity index, ω_k for an atom k, is defined as (Eqn. 13):[20]

$$\omega_k = f_k^{+} \omega \tag{13}$$

Cartesian Coordinates of the TS

SCF Energy: –4982.17163806 a.u.

Charge, Multiplicity: –2, 2

Symmetry: C_1

```
Ni   -0.773807   -0.210286   -0.374543
Fe    1.717853   -0.189381    0.384061
C     2.968478   -0.648772    1.461908
C     2.749042   -0.542480   -1.172624
C     2.252339    1.627038    0.257117
O     3.806988   -0.981421    2.223628
N     3.391055   -0.783975   -2.133105
N     2.547086    2.768473    0.169382
*C   -4.328978   -1.951990    1.574504
C    -2.996543   -1.342679    1.207737
S    -2.905660   -0.956358   -0.578156
*C   -0.038616   -4.203418   -1.783903
C     0.851596   -2.969034   -1.521790
S     0.437543   -2.049336    0.033554
*C   -0.969644    4.256857   -2.431558
C    -0.211437    2.967265   -2.170579
S    -1.428796    1.722760   -1.558954
*C   -1.388992    2.798770    2.752265
C    -0.076545    2.137087    2.248934
S    -0.081806    0.353922    1.751922
*H   -1.021120    3.669118    3.295795
H    -2.062707    3.096617    1.924548
H    -1.949842    2.147448    3.456495
H    -4.420109   -2.135428    2.673471
H    -5.173573   -1.293639    1.272150
*H   -4.462375   -2.907216    1.066906
*H   -1.319212    4.792169   -1.548587
H    -0.334411    4.978506   -3.000688
H    -1.867032    4.066913   -3.063779
H    -1.052923   -3.923780   -2.133879
H     0.464967   -4.844418   -2.531393
*H   -0.151094   -4.795051   -0.849016
H    -0.532619    1.408937   -0.448056
H     0.370123    2.730720    1.426584
H     0.673836    2.170384    3.068229
H     0.247918    2.590440   -3.108155
H     0.606819    3.083619   -1.430458
H    -2.820334   -0.414718    1.788111
H    -2.165469   -2.030397    1.471463
H     0.830390   -2.257484   -2.369187
H     1.913593   -3.268639   -1.407837
```

*Frozen atoms.

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