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LETTERS

DFT-Based Regioselectivity Criteria for Cycloaddition Reactions

Alessandro Ponti[†]

Centro per lo Studio sulle Relazioni tra Struttura e Reattività Chimica, Consiglio Nazionale delle Ricerche, via C. Golgi 19, I-20133 Milano, Italy

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Local softness and the local HSAB principle, as defined within DFT, have attracted considerable interest since they can be used to predict regioselectivity from the electronic properties of the isolated reactants only. This approach proved successful in predicting the regioselectivity of several cycloaddition reactions. However, the employed prediction criteria are only loosely derived from the local HSAB. In this paper the atomic grand potential variation is introduced as a quantitative measure of the stabilization induced by bond-forming interactions. Using this as a uniform figure of merit, regioselectivity criteria are obtained for two widespread reaction classes. By expressing the criteria in terms of the local softnesses, it is shown when they agree with the criteria used in the literature, thus ensuring the validity of this approach to regioselectivity prediction on a rigorous theoretical basis.

I. Introduction

It has recently been found that many important concepts useful to understand chemical reactivity appear in a natural way within the framework of the density functional theory (DFT).[1−3] Among them, global and local softness have attracted considerable interest as intermolecular reactivity indices. In particular, local softness is well suited to compare reactivity at different sites within one molecule, especially in conjunction with the hard and soft acids and bases (HSAB) principle,[4] which found a convenient theoretical framework in the DFT[5−7] too. This principle states that the most favorable interaction results when the reactants have equal softness. Local softness and the HSAB principle thus provide a way to predict the favored product on the basis of the electronic properties of the isolated reactants, without the need of transition state properties. This approach proved successful in predicting the regioselectivity of several cycloaddition reactions,[7−14] a class of reaction important for the synthesis of heterocycles. However, the employed prediction criteria are only loosely derived from the local HSAB principle. The goal of this paper is to introduce an uniform figure of merit by which atom−atom interactions can be ranked, to derive regioselectivity criteria based on this quantity and, finally, to show that the criteria used in the cited studies can be deduced from the presently obtained ones.

II. Background

Adopting an atoms-in-molecule viewpoint, where atoms are open subsystems freely exchanging energy and electrons, the natural thermodynamic quantity is the grand potential[1]

$$\Omega = E - N\mu \tag{1}$$

where E is the energy, N is the number of electrons, and μ is the electron chemical potential. The grand potential obeys the following differential expression for the change of one ground state to another

$$\mathrm{d}\Omega = -N\,\mathrm{d}\mu + \int \rho(\mathbf{r})\,\mathrm{d}v(\mathbf{r})\,\mathrm{d}\mathbf{r} \tag{2}$$

where $\rho(\mathbf{r})$ is the electron density and $v(\mathbf{r})$ is the external

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[†] Fax: +39 02 70 638 129. E-mail: ponti@csrsc.mi.cnr.it.

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potential. Several chemical concepts may be derived from eq 2 in the form of partial derivatives.[3] The softness S of a species is

$$S = \left(\frac{\partial^2 \Omega}{\partial \mu^2}\right)_{v(\mathbf{r})} = \left(\frac{\partial N}{\partial \mu}\right)_{v(\mathbf{r})} \qquad (3)$$

which can be safely taken as nonnegative.[1] Another important quantity is the local softness

$$s(\mathbf{r}) = \left[\frac{\partial}{\partial \mu}\left(\frac{\partial \Omega}{\partial v(\mathbf{r})}\right)_{\mu}\right]_{v(\mathbf{r})} = \left(\frac{\partial \rho(\mathbf{r})}{\partial \mu}\right)_{v(\mathbf{r})} \qquad (4)$$

which measures how sensitive the electron density at point **r** is to a change of electron chemical potential. The global softness S contains information on the reactivity of the molecule as a whole; the local softness $s(\mathbf{r})$ measures the relative site reactivity within the molecule. Both are intermolecular reactivity indexes which can be considered as well-grounded generalizations of the successful empirical concepts of hardness and softness.[4,15] Local softness is also related to the theory of the frontier molecular orbitals[16] via the Fukui functions.[17] From our atoms-in-molecule viewpoint, chemical bonds are considered as linking atoms, so we use local softness condensed to individual atoms[18] and indicate them as s_{A_i}, where A_i denotes atom i in molecule A.

A proof of the HSAB principle[4] based on DFT has been given.[5] Consider the reaction between molecules A and B to give AB. The mutual interaction of the reactants results in two changes, which can be taken as happening in succession. First, a charge transfer at constant external potential produces a common chemical potential between A and B, then a charge reshuffling at constant chemical potential redistributes charge within the whole system. Let $\Delta\Omega_A$ and $\Delta\Omega_B$ indicate the change in grand potential of molecules A and B due to the interaction. The argument is that $\Delta\Omega_A$ and $\Delta\Omega_B$ separately prefer to be as negative as possible once it is assumed that the charge redistribution is unimportant with respect to the charge transfer. Separate minimization of $\Delta\Omega_A$ and $\Delta\Omega_B$ with respect to S_A and S_B, respectively (the other quantities being constant), implies the equalities

$$(\Delta\Omega_A)_{\min} = (\Delta\Omega_B)_{\min} \qquad (5)$$

$$S_A = S_B \qquad (6)$$

The latter is the usual expression of the HSAB principle: "hard likes hard and soft likes soft". However, the pivot of the argument is that the most favored reaction has $\Delta\Omega_A$ and $\Delta\Omega_B$ as negative as possible. We call this the principle of separate minimization of grand potential (SMGP), which is logically more powerful than the HSAB principle (6).

Adopting an atom-in-molecule viewpoint, the local version of the HSAB principle has been demonstrated following the same line of reasoning.[6,7] Now the interaction between two molecules A and B takes place through atom i of A and atom k of B. In this case, neglecting the charge reshuffling term, the separate minimization of the atomic grand potentials $\Delta\Omega_{A_i}$ and $\Delta\Omega_{B_k}$ leads to the equalities

$$(\Delta\Omega_{A_i})_{\min} = (\Delta\Omega_{B_k})_{\min} \qquad (7)$$

$$s_{A_i} = s_{B_k} \qquad (8)$$

The equalities (5)−(8) apply to the ideal situation where the softnesses exactly match and provide maximum stabilization. However, it is not obvious how these equalities can be used in predicting the favored reaction pathway in a real situation where no pair of interacting atoms has matching softnesses or where more than one atom−atom interaction is present. In other words, a figure of merit is needed by which different interactions may be ranked.

III. Regioselectivity Criteria

In this section, a quantitative measure of the stabilization induced by an atom−atom bond-forming interaction is introduced assuming that (1) the most favorable situation is indicated by the SMGP and that (2) the charge reshuffling term can be neglected with respect to the charge-transfer term. The second assumption has already been justified;[7] it is especially reasonable in the present case of regioselectivity prediction for cycloaddition reactions where the relative energy of transition states is paralleled by the relative energy of the correspondent weakly interacting complexes forming in the early stage of the reaction.[19] This grand potential stabilization is then exploited to obtain regioselectivity criteria for two reaction types in terms of local softnesses. In this last step we assume that the local softnesses are positive. This might appear arbitrary, but it is based on the fact that the overwhelming majority of local softness values, computed by DFT[8−14,20] and by Hartree−Fock[7,21,22] methods, are positive.

The grand potential change of atom A_i upon interaction with atom B_k is[7]

$$\Delta\Omega_{i(k)} = -C\frac{s_{A_i} s_{B_k}^2}{(s_{A_i} + s_{B_k})^2}, \quad C = \frac{1}{2}(\mu_A - \mu_B)^2 \geq 0 \qquad (9)$$

and represents the stabilization induced by the charge transfer between A and B. It is always negative because of the assumed positivity of local softness. The increase $\Delta\Omega_{k(i)}$ of the grand potential of B_k upon interaction with A_i with respect to the ideal case can be similarly obtained. Hence, the interaction between A_i and B_k is stabilized by the amount[23]

$$\Delta\Omega_i^k = \Delta\Omega_{i(k)} + \Delta\Omega_{k(i)} = -C\frac{s_{A_i} s_{B_k}}{s_{A_i} + s_{B_k}} \qquad (10)$$

according to which different bond-forming interactions can be ranked. The smaller (in algebraic sense) is $\Delta\Omega_i^k$, and the most favored is the formation of the A_i−B_k bond with respect to the other bonds. Equation 10 is the pivot of the following discussion where quantitative regioselectivity criteria based on the SMGP principle are obtained for two widespread reaction classes.

First, we consider reactions which proceed through a single bond-forming interaction. The bond may form between several atoms A_i ($i = 1, 2, ..., M$) of molecule A and several atoms B_k ($k = 1, 2, ..., N$) of molecule B. The preferred reaction pathway corresponds to the largest stabilization; that is, the regioselectivity criterion is

$$\min_{i,k}\,(\Delta\Omega_i^k) \qquad (11)$$

In the special case $M = 1$, $N = 2$, the regioselectivity criterion may be so expressed: formation of bond A_1−B_1 is favored when

$$\Delta\Omega_1^1 < \Delta\Omega_1^2 \qquad (12)$$

By writing

$$\Delta\Omega_1^1 - \Delta\Omega_1^2 = C\, s_{A_1}^2 \frac{s_{B_2} - s_{B_1}}{(s_{A_1} + s_{B_1})(s_{A_1} + s_{B_2})} \tag{13}$$

eq 12 translates into

$$s_{B_2} < s_{B_1} \tag{14}$$

since local softnesses are assumed positive and $C \geq 0$. The region of the (s_{B_1}, s_{B_2}) plane where eq 14 is satisfied is hatched in Figure 1. It is noteworthy that inequality (14) is independent of s_{A_1}. This implies that, in the $M = 1$, $N = 2$ case, the most favored bond corresponds to the softest atom in molecule B and not to the atom pair with the closest softnesses. A chemical explanation for this behavior might be envisaged as follows. The charge transfer between the reactant molecules can be written as[7]

$$\Delta N_{1(k)} = -\Delta N_{k(1)} = (\mu_B - \mu_A)\left(\frac{1}{s_{A_1}} + \frac{1}{s_{B_k}}\right)^{-1}, \quad k = 1,2 \tag{15}$$

so that the largest charge transfer is obtained for the softest atom between B_1 and B_2, A_1 being fixed. Since the grand potential stabilization is proportional to the square of the charge transfer, the most favored bond corresponds to the softest atom in molecule B.

Consider now the cycloaddition reaction between reactants A and B ($M = N = 2$) that can proceed through two reaction paths differing by the relative orientation of the reactants, as shown in Scheme 1. In this case, two bond-forming interactions are present and the total stabilization is

$$\Delta\Omega_{ij}^{kl} = \Delta\Omega_i^k + \Delta\Omega_j^l \tag{16}$$

Of course, pathway I is preferred over II when

$$\Delta\Omega_{12}^{12} < \Delta\Omega_{12}^{21} \tag{17}$$

Inserting eqs 10 and 16 into eq 17, and using the assumption of positive local softnesses, we can write

$$\Delta\Omega_{12}^{12} - \Delta\Omega_{12}^{21} = CPQ \tag{18}$$

where

$$Q = (s_{A_1} - s_{A_2})(s_{B_2} - s_{B_1}) \tag{19}$$

$$P = \frac{s_{A_2}s_{B_1}s_{B_2} + s_{A_1}s_{B_1}s_{B_2} + s_{A_1}s_{A_2}s_{B_2} + s_{A_1}s_{A_2}s_{B_1}}{(s_{A_1} + s_{B_1})(s_{A_1} + s_{B_2})(s_{A_2} + s_{B_1})(s_{A_2} + s_{B_2})} \tag{20}$$

Since P is positive within our assumptions and $C \geq 0$, the regioselectivity is defined by the sign of the remarkably simple expression (19). We have thus seen how the criterion of maximum decrease in grand potential, which is obviously independent of the reaction type, takes on different analytical forms for different reaction classes when it is expressed in terms of the local softnesses. It should be noted that only these latter expressions depend on the assumption of positive local softness, the more general criteria (12) and (17) do not.

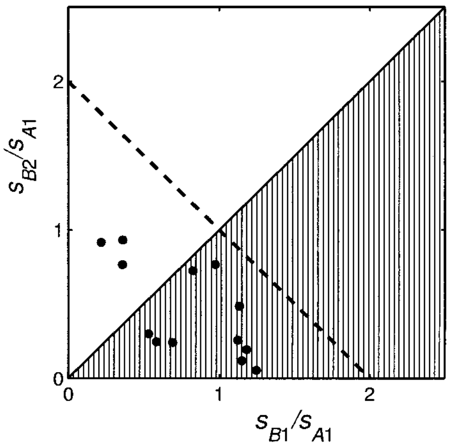
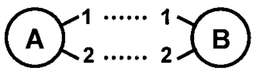


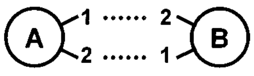
Figure 1. Schematic representation of the SMGP regioselectivity criterion eq 14. The formation of the A_1-B_1 bond is favored over A_1-B_2 in the hatched region where $s_{B_2} < s_{B_1}$. To the right of the dashed line $s_{B_1} + s_{B_2} = 2s_{A_1}$, the SMGP criterion results in opposite predictions with respect to the LSM criterion eq 21. The dots represent the local softness values for the cycloaddition reactions studied in refs 8 and 9

SCHEME 1: Schematic Representation of the Two Relative Orientations of the Reactants in a Cycloaddition Reaction

Pathway I



Pathway II



IV. Comparison with Previous Criteria

We begin with briefly recalling the previous results. The cycloaddition of hydrogen isocyanide HNC to several simple dipolarophiles[8,9] can be regarded as an example of a reaction proceeding through a single bond-forming interaction with $M = 1$ and $N = 2$. The most favorable interaction has been correctly predicted by a local softness matching (LSM) criterion, which can be expressed as: formation of bond A_1-B_1 is favored when

$$|s_{A_1} - s_{B_1}| < |s_{A_1} - s_{B_2}| \tag{21}$$

This successful criterion looks like a quite natural consequence of the local HSAB principle (8), as the figure of merit is the "distance" from the optimal case of matching local softnesses. However, as we shall shortly see, it cannot be generalized to cycloaddition reactions with two bond-forming interactions.

The regioselectivity of cycloaddition reactions with two bond-forming interactions (Scheme 1) has been rather extensively studied by means of the local HSAB principle.[7,10−14] In these studies, successful prediction of the regioselectivity has been obtained by a LSM square-sum criterion which can be so expressed: pathway I is preferred over pathway II when

$$(s_{A_1} - s_{B_1})^2 + (s_{A_2} - s_{B_2})^2 < (s_{A_1} - s_{B_2})^2 + (s_{A_2} - s_{B_1})^2 \tag{22}$$

This criterion, just like criterion (21), can be justified only a posteriori by its success. Indeed, one could devise many other LSM criteria for $M = N = 2$ cycloadditions that cannot be a priori assessed, e.g.

$$\Delta s_{12}^{12}(n) - \Delta s_{12}^{21}(n) < 0 \tag{23}$$

where

$$\Delta s_{ij}^{kl}(n) = (|s_{A_i} - s_{B_k}|^n + |s_{A_j} - s_{B_l}|^n)^{1/n}, \quad n = \pm 1, \pm 2, ... \qquad (24)$$

The choice of n is arbitrary since one does not know in advance how local softness differences should be combined. The arithmetic mean ($n = 1$) and the harmonic mean ($n = -1$) are not less (nor more) reasonable than the rms mean ($n = 2$), equivalent to the above criterion (22). Indeed, different n values may lead to different conclusions about the regioselectivity as several examples taken from the literature show. In the cycloaddition of H_2SiPH to HNNN to give an hetero-triazane or to H_2COO to give an hetero-dioxolane,[11] the correct regioselectivity (silicon attacks the hydrogen-bearing nitrogen atom or the terminal oxygen atom, respectively) is predicted when $n = 2$, whereas taking $n = -1$ gives the opposite result and taking $n = 1$ results in no regioselectivity. Other examples of uneven predictions are the addition of several (di)enes to formaldehyde to give substituted oxetanes[10] (see cited reference for regioselectivities) and that of acrylonitrile to the simple azides HNNN and H_3CNNN to give cyano-substituted triazole (regioselectivity favors the 4-cyano adduct over the 5-cyano one)[14].

The appropriate value of exponent n in LSM criteria therefore depends on the reaction type and can be determined only a posteriori. One might then argue against the validity of such regioselectivity predictions since n could be chosen to match predictions with actual regioselectivity. However, this is not the case since the successful LSM criteria (21) and (22) can be derived from the SMGP principle. In the case of single-bond forming reactions, the LSM criterion (21) is equivalent to the SMGP criterion (14) as long as $s_{B_1} + s_{B_2} < 2\, s_{A_1}$ (see Figure 1). Otherwise, they result in opposite predictions. Unfortunately, none of the reactions studied in refs 8 and 9 falls in these nonequivalence region, so the two criteria cannot be contrasted. As for $M = N = 2$ cycloaddition reactions, the complete equivalence of the SMGP and LSM criteria is easily demonstrated by showing that the left-hand members of eqs 22 and 17 have the same sign. Indeed, one can write

$$\begin{aligned}(s_{A_1} - s_{B_1})^2 + (s_{A_2} - s_{B_2})^2 - (s_{A_1} - s_{B_2})^2 - (s_{A_2} - s_{B_1})^2 &= 2(s_{A_1} - s_{A_2})(s_{B_2} - s_{B_1}) \\ &= 2Q \qquad (25)\end{aligned}$$

as needed. Hence, we have shown that the SMGP principle defines the appropriate n value for different reaction types.

V. Conclusions

In the framework of density functional theory we have used the atomic grand potential variation as a figure of merit measuring how much a generic bond-forming interaction is stabilized. Using this figure of merit, regioselectivity criteria have been deduced for two reaction types, including the important class of cycloadditions (criteria for other reaction types can be easily obtained). By expressing the developed criteria as a function of the local softnesses, we have also shown that they are (partially or completely) equivalent to the LSM criteria used in the literature, thus ensuring the validity of this approach to regioselectivity prediction on a rigorous theoretical basis. Moreover, the obtained criteria provide a uniform measure of the stabilization so that a correlation of $\Delta\Omega$ values with differences of activation energies could be expected, a point that may deserve further investigation.

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