Regional Matching of Atomic Softnesses in Chemical Reactions: A Two-Reactant Charge Sensitivity Study

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A semiempirical charge sensitivity analysis in atomic resolution is used to examine the regional softness parameters within two pairs of coordinating atoms in cyclization reactions, in a search for possible softness matching rules to be used as diagnostic tools for predicting regiochemistry trends. The cycloaddition reactions of a few typical 1,3-dipoles with the phosphorus-containing dipolarophiles and substituted ethylenes are examined. Two types of the two-reactant charge response properties of strongly interacting subsystems are tested: the valence state (polarizational, P) softnesses of atoms in the polarized reactants, before the globally isoelectronic charge transfer (CT), and the in situ CT softnesses. The present analysis identifies a simple regional softness matching rule in terms of two-reactant properties, called the maximum complementarity rule, which is shown to provide a very successful predictor of regioselectivity, particularly at the P + CT level of description. It correctly indexes a relative accessibility of alternative transition states in a series of illustrative 1,3-dipolar cycloadditions. The rule is compared with the earlier regional HSAB principle, formulated in terms of quantities of the separated reactants. The physical implications of various regional softness matching principles are discussed, and the two-reactant influences on atomic FF indices are examined in some detail.

1. Introduction

A clearer understanding of main factors influencing the preferred path and kinetics of a reaction in a system of complicated reactants is of fundamental importance for chemistry. Density functional theory (DFT)[1−3] has provided a very useful framework for developing new criteria for rationalizing, predicting, and eventually understanding many aspects of chemical processes.[2,4−10] A variety of chemical concepts which are now widely used as descriptors of chemical reactivity, e.g., global electronegativity,[6] hardness or softness quantities,[9] etc., appear naturally within DFT.[2,4,5,7,8,10] For example, global electronegativity and hardness have been identified[7,10] as the first and second derivatives of the electronic energy with respect to the open system overall (average) number of electrons. The Fukui function (FF),[8] representing the relative local softness of the electron gas, measures the local (equilibrium) electron density/population displacements corresponding to the inflow of a single electron. The local softness, another important local reactivity descriptor, carries similar physical information by indexing the corresponding density/population displacements per unit shift in the system chemical potential.

All these properties represent responses to typical external potential and populational perturbations in a reactive system;[4] they change relative to the corresponding separated reactant values as a result of interaction between reactants at the current stage of their mutual approach.[4] Therefore, it is vital to include these interreactant contributions in a realistic determination of the truly two-reactant quantities, at both polarizational (P) and charge transfer (CT) levels of describing the electronic structure of alternative transition states. We intend to eventually use such response properties in an approximate diagnosis of the chemical reactivity preferences.[4,11,12] These charge couplings between reactants, usually ignored, are easily accessible within the charge sensitivity analysis (CSA).[4,12] Understanding the role played by such "environmental", two-reactant terms in determining the preferred hardness/softness matching patterns of reactants is a major goal in the theory of chemical reactivity.[4]

It remains to be seen whether such regional matching rules, should they exist, are similar to the familiar global hard and soft acids and bases (HSAB) principle,[9,10] i.e., whether the soft (S) and hard (H) fragments of one reactant align themselves in front of the S and H fragments of the other reactant, respectively. On one hand, the separated reactants approach of Chandra and Nguyen[13] seems to suggest that this indeed is the case; namely, the criterion measuring the matching between the acidic softnesses of one reactant and the basic softnesses of the other reactant for pairs of coordinating atoms puts H (S) atoms of one subsystem against H (S) atoms of the other subsystem in the transition state of lower energy. On the other hand, the charge displacement patterns from the two-reactant CSA in most cases arrange the preferred reactive complexes in such a way that the most basic (electron donating) atoms of one reactant place themselves in front of the most acidic (electron accepting) atoms of the other reactant.[4,11] This should also be expected on the basis of purely electrostatic considerations, since the electrostatic potentials reactants are matched to maximize the

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overlap between electron stabilizing and destabilizing regions of both reactants. Additional support for this expectation comes from the Laplacian distribution analysis of Bader et al.,[14] which clearly demonstrates that the electron depletion (electrophilic, acidic) centers of one reactant prefer to arrange themselves to face the electron accumulation (nucleophilic, basic) centers of the other reactant. In other words, on intuitive grounds, one would expect the atoms of one reactant exhibiting the most weakly bonded electrons to coordinate to atoms of the other reactant in which the valence electrons are the most strongly bonded. In terms of the unity normalized Fukui functions of both reactants, contrary to the regional HSAB principle,[13] this line of reasoning suggests that the atoms with the largest positive FF values of the basic reactant should be expected to prefer to coordinate to atoms with the lowest positive or the largest negative FF of the acidic reactant.

In the most commonly used finite difference approach,[2,8] the global FF values of separated reactants are determined from atomic charges of the neutral and ionic species, while a calculation of the global hardnesses requires the knowledge of their ionization potential and electron affinity. According to Parr and Yang,[2,8] the finite difference approach distinguishes the acidic and basic FF's, corresponding to the systems acting as the Lewis acid (electron acceptor) or base (electron donor), respectively. Clearly, for strongly interacting subsystems, this distinction, when based upon the separated reactant electronegativities, may be misleading,[4,11,12] since the chemical potentials of reactants depend strongly upon the geometrical and electronic structure of the reactive system as a whole. Moreover, putting such an emphasis on the donor−acceptor action of coordinating atoms, implying an appreciable CT, also seems to link the reactivity criterion too strongly to the coordination aspect of the chemical bond; it would seem more apropriate in the case of the strongly interacting subsystems, at least from the point of view of the dominating covalent component of the newly formed bonds, not to a priori prejudice any of the possible actions of reactants, thus using unbiased (average, radical) estimates of the response properties, which are more closely related to the quantities determined within the CSA.

The CSA[4] provides an alternative route of determining the electron density/population response properties directly from the canonical hardness matrix of constituent atoms. In this semiempirical modeling of the charge couplings inside and between reactants, the hardness matrix represents the symmetric tensor of the valence s-shell electron repulsion integrals, estimated via Pariser[15] and Ohno[16] interpolation formulas from the atomic ionization potential/electron affinity data.[4,17]

It was found previously that the so called one-reactant charge response criteria, although quite successful in predicting localization of an attack by a small agent, are often inadequate to generate correct reactivity conjectures concerning systems of large reactants.[4] The present CSA investigation of the optimum matching of the local softness/Fukui function quantities of coordinating atoms[4,11−13] in cyclization reactions takes into account all relevant inter- and intrareactant contributions. An attempt will be made to interpret the observed regiochemistry in various cycloaddition reactions between a 1,3-dipole (henceforth referred to as 13DP) and a phosphorus-containing dipolarophile (henceforth referred to as DPh) and between 13DP and substituted ethylenes. These cycloaddition reactions are important in synthetic organic chemistry because of their potential to form many starting materials for the syntheses of heterocycles.

2. Theory

Regional Softness Matching Criteria. In the cyclization reactions, involving two pairs of coordinating atoms, ($a-b$) and ($a'-b'$), where (a, a', ...) denote constituent atoms of the electron-accepting (acidic) reactant A and (b, b', ...) stand for atoms in the electron-donating (basic) reactant B, one is interested in the regional matching of the atomic softness (or FF) parameters of the atoms involved in two bonds being formed.[13,18] According to the classical HSAB rule, soft (hard) reactants form more stable compounds with the soft (hard) partners in the reactive system M = A−B. It has been found previously, on the basis of the finite difference atomic softnesses of isolated reactants, that a regional version of this principle also seems to hold.[13] Namely, the preferred arrangement of reactants in the lowest energy *transition state* (TS), TS*, in a series of cyclization reactions follows from the minimum principle

$$\min_{\mathrm{TS}} \Delta_{aa'}^{bb'}(\mathrm{TS}) \rightarrow \mathrm{TS}^* \tag{1}$$

of the following function of the atomic softnesses, $\{s_x^{\mathrm{X}}\}$, calculated via finite differences relevant for the A and B reactants in M:

$$\Delta_{aa'}^{bb'}(\mathrm{TS}) = (s_a^{\mathrm{A},0} - s_b^{\mathrm{B},0})^2 + (s_{a'}^{\mathrm{A},0} - s_{b'}^{\mathrm{B},0})^2 \tag{2}$$

$$s_a^{\mathrm{A},0} \equiv \left.\frac{\partial N_a^{\mathrm{A}}}{\partial \mu_{\mathrm{A}}}\right|_0 = \left.\frac{\partial N_a^{\mathrm{A}}}{\partial N_{\mathrm{A}}}\right|_0 \Big/ \left.\frac{\partial \mu_{\mathrm{A}}}{\partial N_{\mathrm{A}}}\right|_0 \equiv f_a^{\mathrm{A},0}/\eta_{\mathrm{A}}^0$$

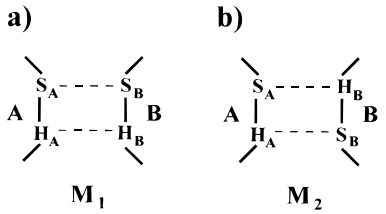
$$s_b^{\mathrm{B},0} = f_b^{\mathrm{B},0}/\eta_{\mathrm{B}}^0$$

$$\sum_{x\in \mathrm{X}} f_x^{\mathrm{X},0} = 1, \quad \mathrm{X} = \mathrm{A}, \mathrm{B} \tag{3}$$

They are approximated by the corresponding values in the limit of separated, infinitely distant reactants, $\mathrm{M}^0 = \mathrm{A}^0 + \mathrm{B}^0$. More specifically,[8] $f_a^{\mathrm{A},0} = N_a^{\mathrm{A}^-} - N_a^{\mathrm{A}^0}$, $a \in$ A, and $f_b^{\mathrm{B},0} = N_b^{\mathrm{B}^0} - N_b^{\mathrm{B}^+}$, $b \in$ B, to obtain the assumed normalization of both $\{f_a^{\mathrm{A},0}\}$ and $\{f_b^{\mathrm{B},0}\}$ to an inflow of a single electron. Here X^0, X^+, and X^- denote the neutral reactant X, its cation, and its anion, respectively; N_x^{X} stands for the electron population of an atom x in X, $\mu_{\mathrm{X}} = \partial E_{\mathrm{X}}/\partial N_{\mathrm{X}}$ denotes the chemical potential of X as a whole, measuring the gradient of the subsystem energy, E_{X}, with respect to its global number of electrons, N_{X}, while $\{f_x^{\mathrm{X},0}\}$ are the condensed atomic FF indices and η_{X}^0 is the global hardness of the isolated reactant X. In the last equation, all derivatives are calculated for the fixed external potential due to nuclei; throughout the paper, this Born−Oppenheimer approximation will not be explicitly indicated in the list of constraints. However, we wish to emphasize that the corresponding CSA derivatives for the finite separation between reactants are calculated for the modified external potential atomic indices on each reactant, which take into account the correction due to the atomic point charges of the other reactant.[4,11]

We also wish to emphasize that the softness/FF indices of eq 2 are of acidic character, since they correspond to an inflow of electrons to the system (A). The corresponding basic softness/FF indices require a change of sign, to reflect an outflow of electrons from the system (B). In other words, the quantity $\Delta_{aa'}^{bb'}(\mathrm{TS})$ of eqs 1 and 2 measures in fact the squares of the sums of the acidic softness of an atom in A and the basic softness of its coordinating partner in B. Clearly, the softness matching criterion of eq 2, using the above single-reactant

CHART 1



atomic softnesses, reaches its minimum value when the pair of coordinating atoms (of separated reactants) are of a similar hard/soft character. As shown in Chart 1a (TS* = M_1), this criterion arranges together the softer atoms, S_A and S_B, and harder atoms, H_A and H_B, of the two coordinating atoms in each reactant. Therefore, it can be indeed interpreted as the regional HSAB rule, be it limited only to the coordinating atoms.

As we have argued in the Introduction, there are physical grounds to propose the opposite criterion in the case of strongly interacting subsystems in M = A − B:

$$\max_{\mathrm{TS}} \Delta_{aa'}^{bb'}(\mathrm{TS}) \rightarrow \mathrm{TS}^* \tag{4}$$

Here M denotes the reactive system at finite separations; therefore, the softnesses of reactants in M, to be used to calculate $\Delta_{aa'}^{bb'}$(TS), have to be of a truly two-reactant character. In the next section we discuss two estimates of this response property, corresponding to the P and CT stages of a reaction, respectively. This maximum complementarity rule searches for the largest differences between softnesses of the basic and acceptor atoms of each newly formed bond, to guarantee that the easily accessible electrons of the former are strongly stabilized by the latter. As such, it selects as the preferred arrangement of coordinating atoms TS* = M_2 shown in Chart 1b. Such a matching was previously observed in the CSA charge displacement diagrams,[4,11] and it is implied by both the electrostatic and the density Laplacian distribution arguments.

Both criteria 1 and 4 distinguish between the acidic action of A and the basic action of B in M. In a case of strongly interacting subsystems, this distinction cannot be made a priori, without additional calculations of polarized reactant chemical potentials. In the CSA implementation of criterion 4, this is immaterial, since the other choice leads to the same result. However, one could propose yet another criterion, which does not attribute any A or B character to reactants:

$$\min_{\mathrm{TS}} \Gamma_{aa'}^{bb'}(\mathrm{TS}) \rightarrow \mathrm{TS}^* \tag{5}$$

Here the quantity $\Gamma_{aa'}^{bb'}$(TS) is the sum of squares of the bond softnesses s_{a-b} and $s_{a'-b'}$:

$$\Gamma_{aa'}^{bb'}(\mathrm{TS}) = (s_a^{\mathrm{A}} + s_b^{\mathrm{B}})^2 + (s_{a'}^{\mathrm{A}} + s_{b'}^{\mathrm{B}})^2 \equiv s_{a-b}{}^2 + s_{a'-b'}{}^2 \tag{6}$$

This minimum bond softness rule also emphasizes that the coordinating atoms should exhibit maximum differences in their softnesses, as does criterion 4. Indeed, should one ignore a change of atomic softnesses in a series of compared TS arrangements, it can be easily demonstrated that both criteria 4 and 5 select TS* = M_2 shown in Chart 1b as the preferred one. Let $s_{\mathrm{H}}^{\mathrm{X}}$ and $s_{\mathrm{S}}^{\mathrm{X}}$ denote the softnesses of H_X and S_X, respectively. Then the differences $\Delta_{aa'}^{bb'}(\mathrm{M}_1) - \Delta_{aa'}^{bb'}(\mathrm{M}_2)$ and $\Gamma_{aa'}^{bb'}(\mathrm{M}_1) - \Gamma_{aa'}^{bb'}(\mathrm{M}_2)$ differ only in sign:

$$\Delta_{aa'}^{bb'}(\mathrm{M}_1) - \Delta_{aa'}^{bb'}(\mathrm{M}_2) = -[\Gamma_{aa'}^{bb'}(\mathrm{M}_1) - \Gamma_{aa'}^{bb'}(\mathrm{M}_2)] = -2(s_{\mathrm{S}}^{\mathrm{A}} - s_{\mathrm{H}}^{\mathrm{A}})(s_{\mathrm{S}}^{\mathrm{B}} - s_{\mathrm{H}}^{\mathrm{B}}) \tag{7}$$

Thus, in terms of the separated reactant softnesses, the maximum complementarity and the minimum bond softness rules give the same prediction TS* = M_2. However, when one uses truly two-reactant, geometry-dependent softnesses, one should expect different predictions from both these principles in some reactions.

Two-Reactant Atomic Softnesses from CSA. As we have already remarked, at finite separations charge sensitivities change as a result of the interaction between the two complementary subsystems in M. Therefore, in order to characterize the valence states of subsystems in M more realistically, adequate two-reactant measures of the coordinating atoms' softnesses/FF are required, at both P [mutually closed reactants, $M^+ = (A^+|B^+)$] and CT [mutually open reactants, M* = (A*:B*)] stages, which correspond to the intrareactant and global chemical potential/electronegativity equalizations, respectively.[4]

At the intermediate, *polarizational stage* of charge reconstruction in transition state, in which the electrons of two reactants are characterized by different values of their equilibrium chemical potentials, $\mu_{\mathrm{A}} = (\partial E_{\mathrm{M}}/\partial N_{\mathrm{A}})_{N_{\mathrm{B}}} \neq \mu_{\mathrm{B}} = (\partial E_{\mathrm{M}}/\partial N_{\mathrm{B}})_{N_{\mathrm{A}}}$, the following valence state measure of the two-reactant atomic softness can be used to select TS*:

$$s_x^{\mathrm{X}} \approx s_x^{\mathrm{X},+} = \left(\frac{\partial N_x^{\mathrm{X}}}{\partial \mu_{\mathrm{X}}}\right)_{N_{\mathrm{Y}\neq\mathrm{X}}} = \left(\frac{\partial N_x^{\mathrm{X}}}{\partial N_{\mathrm{X}}}\right)_{N_{\mathrm{Y}}} \Big/ \left(\frac{\partial \mu_{\mathrm{X}}}{\partial N_{\mathrm{X}}}\right)_{N_{\mathrm{Y}}} \equiv f_x^{\mathrm{X,X}}/\eta_{\mathrm{X,X}} \tag{8}$$

$$\mathrm{X} = (\mathrm{A}, \mathrm{B})$$

Equation 8 defines the so-called diagonal atomic FF index in M, $f_x^{\mathrm{X,X}}$, and the diagonal condensed hardness of reactant X, $\eta_{\mathrm{X,X}}$. In contrast to the corresponding isolated reactant quantities of eqs 2 and 3, the FF and hardness parameters of the polarized reactants in M^+ (eq 8) include the effect of the displaced external potential and the interactions (hardness couplings) between the two reactants.[4,11]

At the final, charge transfer, stage with open reactants in the transition state, marked by the chemical potential/electronegativity equalization throughout M*, the two-reactant approach calls for the following in situ atomic softnesses[4,11,18] to be used in determining the preferred TS:

$$s_x^{\mathrm{X}} \approx s_x^{\mathrm{X},*} = \left(\frac{\partial N_x^{\mathrm{X}}}{\partial \mu_{\mathrm{CT}}}\right)_N = \left(\frac{\partial N_x^{\mathrm{X}}}{\partial N_{\mathrm{CT}}}\right)_N \Big/ \left(\frac{\partial \mu_{\mathrm{CT}}}{\partial N_{\mathrm{CT}}}\right)_N = f_x^{\mathrm{X,CT}}/\eta_{\mathrm{CT}} \tag{9}$$

It corresponds to the globally isoelectronic, B → A transfer of N_{CT} electrons:

$$N_{\mathrm{CT}} = \mathrm{d}N_{\mathrm{A}} \equiv N_{\mathrm{A}}^* - N_{\mathrm{A}}^+ = -\mathrm{d}N_{\mathrm{B}} \equiv -(N_{\mathrm{B}}^* - N_{\mathrm{B}}^+) > 0 \tag{10}$$

Above, the atomic CT FF[4,11] is

$$f_a^{\mathrm{A,CT}} = \frac{\partial N_a^{\mathrm{A}}}{\partial N_{\mathrm{A}}}\frac{\mathrm{d}N_{\mathrm{A}}}{\mathrm{d}N_{\mathrm{CT}}} + \frac{\partial N_a^{\mathrm{A}}}{\partial N_{\mathrm{B}}}\frac{\mathrm{d}N_{\mathrm{B}}}{\mathrm{d}N_{\mathrm{CT}}} = f_a^{\mathrm{A,A}} - f_a^{\mathrm{B,A}}, \quad \text{etc.} \tag{11}$$

the CT chemical potential difference is

$$\mu_{\mathrm{CT}} = \frac{\partial E}{\partial N_{\mathrm{CT}}} = \left(\frac{\partial E}{\partial N_{\mathrm{A}}}\right)_{\mathrm{M}^+}\frac{\mathrm{d}N_{\mathrm{A}}}{\mathrm{d}N_{\mathrm{CT}}} + \left(\frac{\partial E}{\partial N_{\mathrm{B}}}\right)_{\mathrm{M}^+}\frac{\mathrm{d}N_{\mathrm{A}}}{\mathrm{d}N_{\mathrm{CT}}} \equiv \mu_{\mathrm{A}}^+ - \mu_{\mathrm{B}}^+ \tag{12}$$

TABLE 1: Comparison between the CSA Atomic Fukui Function Indices for the Reactive Systems of Figure 1a

			TS1[a]		TS2[a]	
reaction	atom[a]	SRL	P	P + CT	P	P + CT
$H_2CNN + HCP$	C(1)	1.56	1.70	1.01	1.77	0.94
	N(2)	0.33	0.31	0.37	0.33	0.23
	P(3)	−0.16	−0.29	−0.05	−0.30	−0.17
	C(4)	1.60	1.81	1.45	1.87	1.51
$H_2CNN + CH_3CP$	C(1)	1.56	1.58	1.25	1.57	1.35
	N(2)	0.33	0.32	0.39	0.30	0.22
	P(3)	0.19	0.13	0.25	0.15	0.10
	C(4)	0.62	0.71	0.64	0.67	0.69

[a] For the numbering of atoms and the transition state structures, see Figure 1.

and, finally, the CT hardness is

$$\eta_{CT} = \frac{\partial(\mu_A - \mu_B)}{\partial N_{CT}} = \frac{\partial \mu_A}{\partial N_A}\frac{\partial N_A}{\partial N_{CT}} + \frac{\partial \mu_A}{\partial N_B}\frac{\partial N_B}{\partial N_{CT}} - \frac{\partial \mu_B}{\partial N_A}\frac{\partial N_A}{\partial N_{CT}} - \frac{\partial \mu_B}{\partial N_B}\frac{\partial N_B}{\partial N_{CT}} = \eta_{A,A} - \eta_{B,A} - \eta_{A,B} + \eta_{B,B} \quad (13)$$

As indicated in eq 11, in order to determine the CT FF of atoms in interacting subsystems, one requires both diagonal and off-diagonal blocks of the condensed FF indices of polarized reactants

$$\mathbf{f}^{(A|B)} \equiv \left\{ \mathbf{f}^{A,A} = \left(\frac{\partial \mathbf{N}_A}{\partial N_A}\right)_{N_B}, \quad \mathbf{f}^{B,A} = \left(\frac{\partial \mathbf{N}_A}{\partial N_B}\right)_{N_A}, \quad \text{etc.} \right\} \quad (14)$$

A reference to eqs 8 and 9 shows that, to evaluate the in situ atomic softnesses, one also has to determine the whole condensed hardness matrix of M in reactant resolution:

$$\boldsymbol{\eta}_{(A|B)} \equiv \left\{ \eta_{X,Y} = \frac{\partial \mu_Y}{\partial N_X} \right\}, \quad (X, Y) = (A, B) \quad (15)$$

All these properties can be calculated from the canonical hardness matrix in atomic resolution[4,11]

$$\boldsymbol{\eta} = \partial^2 E/\partial \mathbf{N}\, \partial \mathbf{N} = \partial \boldsymbol{\mu}/\partial \mathbf{N} = \{\partial \mu_j/\partial N_i \approx \gamma_{ij}\} \quad (16)$$

where the vector of atomic chemical potentials $\boldsymbol{\mu} = (\boldsymbol{\mu}_A, \boldsymbol{\mu}_B)$ groups the corresponding vectors for the two reactants, $\boldsymbol{\mu}_X = (\boldsymbol{\mu}_x, \boldsymbol{\mu}_{x'}, ...)$; similarly, $\mathbf{N} = (\mathbf{N}_A, \mathbf{N}_B)$ stands for the vector of atomic electron populations with $\mathbf{N}_X = (N_x, N_{x'}, ...)$. As indicated in eq 16, within the semiempirical (ZDO-type) parametrization of CSA, elements of the hardness matrix in atomic resolution are approximated by the corresponding Coulombic interactions between two electrons in the atomic valence s shells, $\gamma_{i,j} = \langle s_i^{val}(1)\ s_j^{val}(2)|(1/r_{i,j})|s_i^{val}(1)\ s_j^{val}(2)\rangle$, estimated empirically using the Pariser[15] and Ohno[16] formulas from the experimental ionization potential and electron affinity data.[4,17]

The valence state (polarization) and in situ (charge transfer) softness/FF parameters of reactants in M^+ will be identified in Tables 1−4 by the "P" and "P + CT" acronyms, respectively.

3. Reactions and Computational Details

In the present work, we shall apply the criteria of eqs 4 and 5 to regiochemistry of selected cycloaddition reactions involving 13DP and either DPh or substituted ethylenes (Figure 1 and Table 5). When the active fragments of a dipolarophile, $x(3)-x'(4)$, and of a 1,3-dipole, $y(1)-y'-y''(2)$, approach one another, in principle two cycloadducts, henceforth denoted as TS1 and TS2, are possible (see Figure 1): Chart 2. In the majority of cases, one of such transition states has a distinctly lower energy than the other; this results in a some degree of preference for

TABLE 2: Comparison between the CSA Atomic Fukui Function Indices for the Reactive Systems of Figure 1b

			TS1[a]		TS2[a]	
reaction	atom[a]	SRL	P	P + CT	P	P + CT
$H_2CNN + CH_2CHF$	C(1)	1.56	1.73	1.51	1.70	1.52
	N(2)	0.33	0.31	0.30	0.30	0.28
	C(3)	0.67	0.75	0.47	0.72	0.40
	C(4)	−0.17	−0.18	−0.04	−0.18	0.01
$H_2CNN + CH_2$ CHCl	C(1)	1.56	1.67	1.54	1.65	1.39
	N(2)	0.33	0.30	0.32	0.31	0.28
	C(3)	0.32	0.34	0.26	0.34	0.22
	C(4)	−0.07	−0.06	0.03	−0.07	0.10
$H_2CNN + CH_2$ $CHCH_3$	C(1)	1.56	1.63	1.53	1.54	1.42
	N(2)	0.33	0.31	0.33	0.30	0.27
	C(3)	0.18	0.19	0.18	0.19	0.13
	C(4)	0.15	0.18	0.19	0.17	0.25
$H_2CNN + CH_2$ CHCN	C(1)	1.56	1.64	1.61	1.61	1.47
	N(2)	0.33	0.30	0.30	0.31	0.30
	C(3)	0.18	0.19	0.19	0.20	0.16
	C(4)	0.07	0.07	0.09	0.07	0.16

[a] For the numbering of atoms and the transition state structures, see Figure 1.

TABLE 3: Comparison between the CSA Atomic Fukui Function Indices for the Reactive Systems of Figure 1c

			TS1[a]		TS2[a]	
reaction	atom[a]	SRL	P	P + CT	P	P + CT
HNNN + HCP	N(1)	0.53	0.56	0.51	0.57	0.68
	N(2)	0.37	0.37	0.41	0.36	0.29
	P(3)	−0.16	−0.21	−0.19	−0.19	−0.24
	C(4)	1.60	1.67	1.65	1.63	1.66
HNNN + CH_3CP	N(1)	0.53	0.56	0.56	0.57	0.74
	N(2)	0.37	0.37	0.43	0.36	0.30
	P(3)	0.19	0.16	0.17	0.16	0.09
	C(4)	0.62	0.66	0.79	0.65	0.83

[a] For the numbering of atoms and the transition state structures, see Figure 1.

TABLE 4: Comparison between the CSA Atomic Fukui Function Indices for the Reactive Systems of Figure 1d

			TS1[a]		TS2[a]	
reaction	atom[a]	SRL	P	P + CT	P	P + CT
HNNN + CH_2CHF	N(1)	0.53	0.56	0.65	0.57	0.64
	N(2)	0.37	0.36	0.38	0.36	0.37
	C(3)	0.67	0.68	0.74	0.68	0.78
	C(4)	−0.17	−0.16	−0.05	−0.16	−0.07
HNNN + CH_2CHCl	N(1)	0.53	0.56	0.68	0.59	0.66
	N(2)	0.37	0.36	0.35	0.35	0.37
	C(3)	0.32	0.31	0.36	0.32	0.44
	C(4)	−0.07	−0.05	0.12	−0.06	0.06
HNNN + CH_2CHCH_3	N(1)	0.53	0.58	0.71	0.57	0.63
	N(2)	0.37	0.35	0.34	0.36	0.40
	C(3)	0.18	0.17	0.24	0.18	0.30
	C(4)	0.15	0.17	0.34	0.17	0.29
HNNN + CH_2CHCN	N(1)	0.53	0.56	0.67	0.55	0.57
	N(2)	0.37	0.37	0.36	0.37	0.30
	C(3)	0.18	0.18	0.27	0.19	0.33
	C(4)	0.07	0.08	0.19	0.07	0.11

[a] For the numbering of atoms and the transition state structures, see Figure 1.

TABLE 5: Activation Energies (kcal/mol) and a Summary of Regioselectivity Predictions from the Maximum Complementarity (Δ) and Minimum Bond Softness (Γ) Principles, Applied at the Separated Reactants Limit (SRL), Polarizational (P), and Charge Transfer (P + CT) Levels of Description

reaction	E_{act} TS1[a]	E_{act} TS2[a]	Δ(SRL) Γ(SRL)	Δ(P)	Δ(P + CT)	Γ(P)	Γ(P + CT)
$H_2CNN + HCP$	5.86	6.92	TS1(+)	TS1(+)	TS1(+)	TS1(+)	TS1(+)
$H_2CNN + CH_3CP$	9.47	12.37	TS1(+)	TS1(+)	TS1(+)	TS1(+)	TS1(+)
$H_2CNN + CH_2CHF$	17.46	17.26	TS2(+)	TS2(+)	TS2(+)	TS2(+)	TS2(+)
$H_2CNN + CH_2CHCl$	15.84	16.96	TS2(−)	TS2(−)	TS1(+)	TS2(−)	TS2(−)
$H_2CNN + CH_2CHCH_3$	16.84	18.06	TS2(−)	TS1(+)	TS1(+)	TS2(−)	TS2(−)
$H_2CNN + CH_2CHCN$	10.81	13.48	TS2(−)	TS2(−)	TS1(+)	TS1(+)	TS2(−)
HNNN + HCP	8.77	11.12	TS1(+)	TS1(+)	TS1(+)	TS1(+)	TS1(+)
$HNNN + CH_3CP$	12.38	14.85	TS1(+)	TS1(+)	TS1(+)	TS1(+)	TS1(+)
$HNNN + CH_2CHF$	21.00	18.59	TS2(+)	TS2(+)	TS2(+)	TS2(+)	TS2(+)
$HNNN + CH_2CHCl$	20.61	19.82	TS2(+)	TS2(+)	TS2(+)	TS2(+)	TS2(+)
$HNNN + CH_2CHCH_3$	19.56	19.11	TS2(+)	TS2(+)	TS2(+)	TS2(+)	TS1(−)
$HNNN + CH_2CHCN$	17.68	<TS1[b]	TS2(+)	TS2(+)	TS2(+)	TS2(+)	TS1(−)

[a] For the transition state structures, see Figure 1. [b] The inequality following from the partially optimized DFT structure.

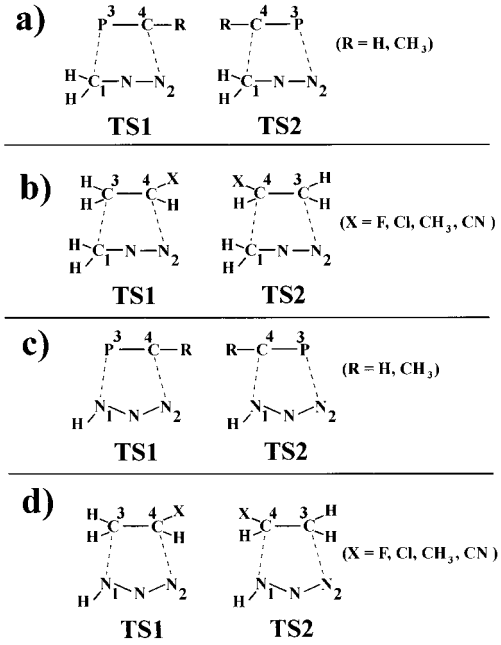
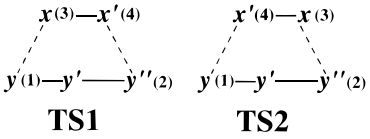


Figure 1. Schematic representation of the transition state structures together with the atom numbering scheme adopted in the present work.

CHART 2



one reaction path (regioselectivity).[19−22] For example, in the case of a cycloaddition between HCP and H_2CNN (Figure 1a), the reaction proceeds mainly through the transition state in which the carbon of the second reactant forms a bond with the phosphorus of the first reactant (TS1). Similarly, in cycloadditions of H_2CNN to a monosubstituted ethylene (Figure 1b), the preferred reaction path is through the complex in which the terminal nitrogen of the dipole is linked to the substituted carbon of the dipolarophile (TS1).[21] Houk et al.[23] applied the frontier molecular orbital perturbation theory to explain, with relative success, this observed regioselectivity in 1,3-dipolar cycloadditions. Very recently, it was demonstrated[13,24] that the observed regioselectivity trends in many such reactions follow from the regional HSAB principle of eqs 1−3, which correctly identifies the lower energy transition state when finite difference estimates of atomic softnesses of the isolated acidic and basic reactants are used.

The fully optimized equilibrium geometries and transition state structures were determined from the DFT calculations using the B3LYP functional (the Gaussian 94 program[25]); the 6-31G-(d, p) basis set was selected for constituent atoms of all structures considered. The first-order saddle-point characters of all transition state structures were verified by the frequency calculations at the same level of theory. The calculated activation energies are listed in Table 5. In the CSA calculations of the local softnesses and FF, the optimum isolated reactant geometries were kept "frozen"; the transition states were then modeled by slightly modifying the reactant mutual orientation to reproduce the optimum TS distances between two pairs of coordinating atoms of both subsystems; the angles involving newly formed bonds in such model TS structures exhibit only minor differences, of 5−10°, in comparison with the fully optimized DFT geometries. The effect of these deviations on the predicted atomic softness/FF parameters were numerically found to be negligible. To determine the atomic hardness tensor, reflecting the actual valence states of atoms in separated reactants, the Mulliken charges from the MNDO[26] (minimum valence basis set) were used to interpolate the input ionization potential/electron affinity data within the standard CSA program.[4,27]

4. Results and Discussion

Two-Reactant Fukui Functions. In Tables 1−4 we have compared various CSA estimates of the Fukui function indices of coordinating atoms in alternative transition states shown in Figure 1. The tables compare the reference values for the separated reactants limit (SRL) with the corresponding predictions at the P and P + CT levels of describing the electronic structures of the two alternative transition states.

A general inspection of these tables shows that the inclusion of the polarization of separated reactants and/or charge transfer between polarized reactants does indeed change the FF indices of coordinating atoms. Although in most cases this effect is relatively weak, some atoms are seen to be strongly affected in the TS. For example, the C(1) atom in the first reaction of Table 1 is seen to be strongly hardened according to the P + CT FF estimate, in comparison to its state in the SRL; it should be noticed that the P stage predicts a slight softening of this atom. Other cases where the interreactant couplings lead to a change of sign of the atomic FF number can be observed for

the C(4) atom (the first two reactions in Table 2 and the second reaction in Table 4). We wish to emphasize that these interaction changes of FF are accompanied by the corresponding shifts in the global softness (hardness) charge sensitivities (not reported here), which also affect the regiochemistry criteria. Therefore, it comes as no surprise that even such minor FF index variations result in different regioselectivity predictions (see Table 5), which we shall discuss in the next section.

The comparisons of Tables 1−4 also allow one to test the adequacy of the weak TS geometry dependence of response properties, which we invoked in section 2 to demonstrate approximate equivalence of the maximum complementarity and the minimum bond softness rules. Clearly, as we have already observed above, the SRL values do change at finite separations between reactants. However, a comparison between corresponding P and P + CT entries for TS1 and TS2, respectively, shows that they are very close indeed, thus a posteriori validating such an assumption. This general trend, however, does not preclude more significant changes in atomic FF values in both transition states. At the P + CT level, they can be observed, for example, for N(2) in the second reaction of Table 1, for N(1) in both reactions of Table 3, and for C(3) in the second reaction of Table 4. Therefore, one should expect that the predictions from criteria of eqs 4 and 5 may differ in some cases; this is indeed reflected by the summary of Table 5.

Regioselectivity Predictions. In Table 5, we have listed the DFT activation energies for transition states shown in Figure 1 (in columns 2 and 3). The remaining part of the table summarizes the TS* identifications from the maximum complementarity [$\Delta \equiv \Delta_{aa'}^{bb'}(\mathrm{TS})$] and minimum bond softness [$\Gamma \equiv \Gamma_{aa'}^{bb'}(\mathrm{TS})$] principles, when applied to the SRL and at the P and P + CT stages of the reactant charge cloud reorganization. We have indicated there the selected transition state, marked in parentheses by the signs + (−) to indicate the principle success (failure) in pointing out the lower energy transition state.

It follows from the energies of Table 5 that the activation energies for the two alternative transition complexes differ by less than 3 kcal/mol. As indicated in the SRL column 4, the isolated reactant softnesses give rise to 75% success in predicting TS* via both criteria (eqs 4 and 5), which give identical diagnoses. An inspection of next two columns (5, 6) for criterion 4 indicates that an inclusion of the polarization and charge transfer effect gradually improves predictions: 83% and 100% at the P and P + CT levels, respectively. Thus, the most realistic in situ measures of the coordinating atom softnesses produce, somewhat accidentally, the full agreement with qualitative trends in DFT activation energies. In other words, the two-reactant CSA response properties validate the intuitive expectation that the more electron deficient atom (relative acidic character) in one reactant prefers to coordinate to the electron richer atom (relative basic character) in the other reactant. It should be stressed that a similar conclusion follows from the CSA SRL atomic softnesses.

As far as the minimum bond softness criterion 5 is concerned, its 25% failure rate in the SRL is diminished to 17% when the valence state polarizational softnesses of coordinating atoms are used to calculate the Γ quantity of eq 6. However, this trend is dramatically reversed to 42% failure in the P + CT approximation. The performance data from columns 7 and 8 demonstrate that the approximate equivalence of criteria 4 and 5 may manifest itself by different success frequencies at various stages of electronic density reconstruction, due to a weak geometry dependence of two-reactant response properties. A relatively low success rate in the Γ(P + CT) approximation provides a clear indication that the maximum complementarity rule at the P + CT level of description should be recommended as the most adequate regioselectivity principle.

The trends exhibited by the absolute values of the quantities $\Delta_{aa'}^{bb'}(\mathrm{TS1})$ and $\Delta_{aa'}^{bb'}(\mathrm{TS2})$ [or $\Gamma_{aa'}^{bb'}(\mathrm{TS1})$ and $\Gamma_{aa'}^{bb'}(\mathrm{TS2})$] do not reflect the trends observed in the corresponding activation energies. Therefore, the Δ and Γ quantities, adequate for identifying TS*, should not be used in any semiquantitative predictions of the relative preferences of paths 1 (TS1) and 2 (TS2) in different reactions.

5. Conclusion

This work has extended a range of applications of CSA to problems of regioselectivity in organic reactions. The maximum complementarity rule, the most successful in predicting the lower energy TS, connects to the intuitive chemical ideas that an acidic site of one reactant will most likely approach the basic site of the other reactant and vice versa. This complementary matching behavior of interacting molecular systems is in general agreement with the matching principles involving other physical properties, e.g., electrostatic potentials and Laplacian distributions of the electron density. Such an arrangement has also been observed previously in the energetically preferred chemisorption structures on surfaces of transition metal oxides.[4,11]

The direct CSA modeling of the populational response properties, by correctly reproducing these physically and chemically well-founded intuitions, provides therefore a good representation of the chemical thinking about reactivity of molecules. Since the maximum complementarity rule of eq 4 is, in fact, opposite to the regional HSAB rule of eqs 1 and 2, within CSA the success of the former implies the failure of the latter in correctly identifying the lowest energy TS. We attribute the previously reported[13] apparent success of the regional HSAB rule, when applied to this reactivity problem, to the different finite difference procedures[8] used to estimate atomic FF indices of the basic and acidic reactants. We wish to stress that the alternative criteria tested in this work do not even require an a priori determination of the actual acidic/basic character of the two reactants in TS.

Within the recommended maximum complementarity rule, we have demonstrated that an inclusion of the two-reactant contributions to the atomic softnesses gradually improves the quality of predictions. Since these effects are easily accessible from the very simple CSA calculations, one may as well adopt the most realistic (P + CT)-estimates, which were shown to give an unexpectedly high rate of success.

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