Theoretical Revisit of Regioselectivities of Diels−Alder Reactions: Orbital-Based Reevaluation of Multicentered Reactivity in Terms of Reactive Hybrid Orbitals

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When reactions proceed under kinetic control, stereoselectivities are determined from energetic properties of the transition state (TS). Orbital interaction at the TS plays a significant role in determining reactivity and selectivity, because it is directly related to lowering of the activation barrier. However, the orbital interaction at the TS cannot be represented only in terms of the frontier orbitals at the reactant state. A reactive hybrid orbital (RHO) that is localized at the reaction site is used to represent the orbital around the relevant TS in terms of a combination of the canonical molecular orbitals (MOs). This representation can make comparison of reactivities and selectivities among molecules of different sizes feasible. In this paper, the regioselectivities of Diels−Alder cycloaddition reactions of a monosubstituted butadiene and a dienophile (a monosubstituted ethylene) are investigated in terms of several parameters such as reactivity index and stabilization index, which are obtained on the basis of the newly developed multicentered version of the RHO method. These values can also be compared with the corresponding parameters defined on the basis of the frontier orbitals. Predictions of the regioselectivities based on the RHOs are consistent with experimental observations, while those based on the frontier orbitals are unreliable. This is because the RHO is superior to the frontier orbital as a descriptor of the orbital participating in orbital interactions around the TS.

Introduction

In general, the feasibility of a reaction under kinetic control is determined by the magnitude of the activation energy.[1] According to orbital interaction theory, an interacting system is stabilized by electron delocalization or charge transfer from occupied orbitals of a molecule to unoccupied orbitals of the other molecule, arising from their orbital overlaps.[2] This orbital interaction at the transition state (TS) is especially important in the course of a chemical reaction, since it can be assumed to be directly related to lowering of the activation barrier.

The frontier orbitals are believed to play dominant roles in this interaction. However, in a large molecule, many orbitals are involved in the orbital interaction and the molecular orbitals (MOs) other than the frontier orbitals contribute significantly, because one-electron orbitals become close in energy to each other. Therefore, consideration of only the frontier orbitals[2,3] is apparently insufficient to analyze chemoselectivity, stereoselectivity, and regioselectivity, though it might be valid for a small, simple model molecule. Thus, it is important to effectively incorporate other MOs into the theory, so that it can be applied to molecules of experimentally practical size and complexity. In this context, the superdelocalizability-like index can serve as the reactivity index in comparing the reactivities of different molecules, while the frontier electron density becomes the reactivity index in comparing the reactivities of the different positions of a given molecule.[4,5]

The stereo- and regioselectivity of Diels−Alder reactions have been widely studied because of the synthetic value of these reactions. A theoretical prediction of regioselectivity is of fundamental importance. In fact, several theoretical approaches have been applied to the rationalization of regioselectivity in Diels−Alder reactions. Of all the approaches, the most important and well-known is the frontier orbital theory.[6−14] For example, Anh et al. studied the magnitude of the second-order stabilization energy arising from the overlap of frontier orbitals of approximately 100 examples, using the simple Hückel approximation.[9] On the basis of the calculated stabilization energies, which are larger for preferred regioselectivity, they concluded that agreement of calculations with experimental results was excellent. However, Alston et al. analyzed the LCAO-MO coefficients of frontier orbitals at the CNDO/2 level, and pointed out that there were numerous discrepancies between predictions based on the frontier orbital amplitudes of the primary interaction sites and observed regioselectivities.[10−12] They emphasized the importance of the secondary orbital interactions in determining regioselectivity. Hehre et al. performed MO calculations on several substituted dienes at the RHF/3-21G(*) level and obtained the frontier orbital coefficients.[14] They found that the frontier orbital coefficients misinterpreted the regioselectivities, in some cases. Instead they proposed the reactivity model based on quantum-chemically calculated electrostatic and hydride potentials, and suggested that this approach was superior to the frontier orbital theory.

Criteria based on the density functional theory (DFT) such as local softness have also been utilized frequently, especially in recent years.[15,16] Although the electron-density-based approaches (conceptual DFT) connect theory and some experimentally useful concepts such as hard and soft acids and bases (HSAB),[17,18] they, as well as electrostatic models,[14] are not so closely related to mutual matching of orbital phases between a reactant and a reagent, which is another important determinant

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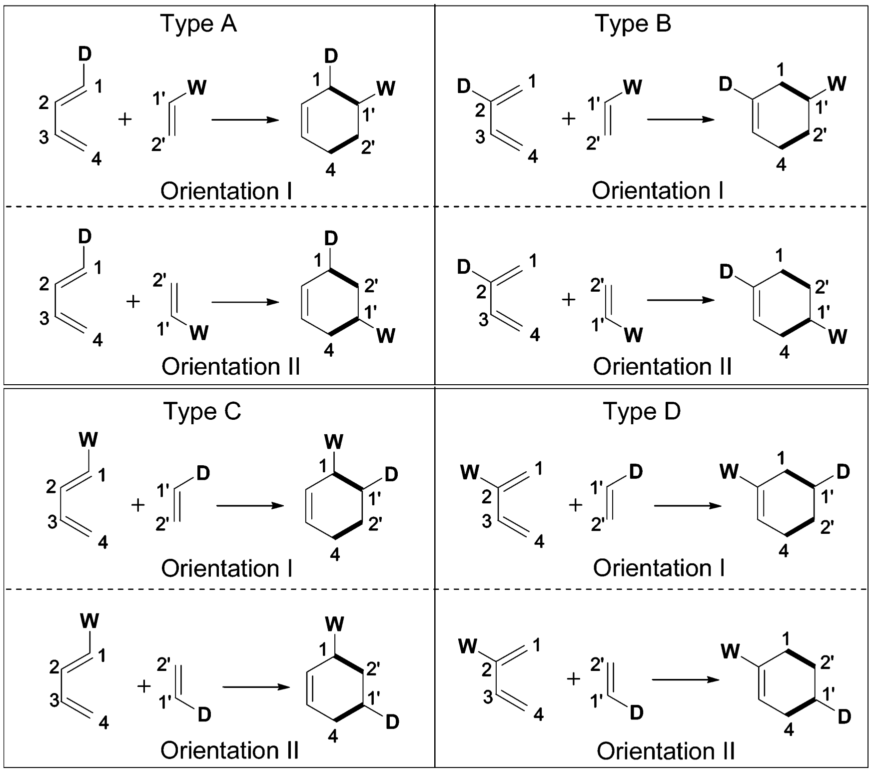
SCHEME 1: Combinations and Regioselectivites in Diels−Alder Reactions between Monosubstituted Diene and Dienophile[a]



[a] D = electron-donating group; W = electron-withdrawing group.

of reactivity.[19,20] Thus, although the frontier orbital theory can be criticized as oversimplified, an orbital-based treatment, which retains orbital-phase relations, is essential to the study of the stereoselectivities of multicentered reactions. Because the superdelocalizability is a better descriptor of reactivity as mentioned above, ideally none of the MOs should be neglected, which would, however, result in cumbersomeness. In contrast, a frontier-orbital-based index, e.g., frontier density, has the advantage of representing reactivity in terms of a single orbital, which is thus easy to analyze. A concept of reactive orbital, particularly the recently proposed reactive hybrid orbital (RHO),[21] can provide a single orbital that is localized at the reaction site.

One of the major purposes of this study is to apply the RHO method to the regioselectivities of multicentered Diels−Alder reactions. Because the original RHO method was designed for analysis of a single-centered reaction, here we extend the theoretical formalism so that multicentered reactions can be analyzed. It is also meaningful to recalculate the frontier orbitals for the Diels−Alder system (dienes and dienophiles) at a higher level, and to compare the predictive performance of the RHOs with that of the frontier orbitals, using the diene and dienophile models shown below.

R_1 = H, 1-CH_3, 1-Ph, 1-OCH_3, 1-CH=CH_2, 1-CN, 2-CH_3, 2-Ph, 2-OCH_3, 2-CH=CH_2, 2-CN, 2-Cl

R_2 = H, CH_3, Ph, OCH_3, CH=CH_2, CN

Regioselectivities of the simple Diels−Alder reactions of monosubstituted butadiene and monosubstituted ethylene (dienophile) can be classified as types A−D, shown in Scheme 1, depending on the positions of an electron-donating substituent D (D = CH_3, Ph, OCH_3, CH=CH_2) and an electron-withdrawing substituent W (W = CN).[22,23]

In each type of cyclization, there are two regioisomers of cyclization (orientations I and II). Types A and B are the simplest cases of normal-electron-demand Diels−Alder cycloadditions, while types C and D are the simplest cases of inverse-electron-demand Diels−Alder cycloadditions. The latter has recently become increasingly important, both theoretically[24,25] and experimentally.[26,27] Experimentally, in the cases of 1-substituted dienes (types A and C), ortho cyclization is favored rather than meta cyclization (i.e., orientation I, rather than orientation II), while in the cases of 2-substituted dienes (types B and D), para cyclization is favored over meta cyclization (i.e, orientation II, rather than orientation I).

Herein, regioselectivities of Diels−Alder cycloaddition reactions of a monosubstituted butadiene and a dienophile (a monosubstituted ethylene) are investigated especially in terms of several parameters such as orbital density, reactivity index, and stabilization index, which are obtained on the basis of RHOs. These values can also be compared with the corresponding parameters defined on the basis of the frontier orbitals. The predictions based on the RHOs are consistent with the experimental and calculated regioselectivities, while those based on the frontier orbitals sometimes fail. We suggest that the RHOs are superior to the frontier orbitals in the predictive perfomance of regioselectivity, because they represent the orbitals participating in orbital interactions around the TS.

Calculations

Geometry optimizations were performed at the B3LYP/6-31G** level with a suite of Gaussian 98 programs.[28] Vibrational frequency analyses were also performed to confirm that the obtained structures correspond to energy minima or saddle points. The RHO analyses were carried out within the RHF/6-31G** MO space, using the geometries optimized at the B3LYP/6-31G** level.[29] The RHO program, which reads MO coefficients and energies of canonical MOs from a Gaussian fort.7 file and performs an RHO calculation, was developed originally.[21] An initial guess, which is necessary for an RHO calculation, could be the HOMO or LUMO in small molecules. However, in larger molecules, this simple initial-guess strategy did not work well. In such a case, a reactive orbital generated by the method of Kurita et al. was used as a good initial guess.[30] As a rule, each RHO calculation finished within a few seconds.

Orbital drawings were carried out with MOLEKEL 4.2, [31] using a contour value of 0.055. To avoid conformational complexity and to reduce the number of possible combinations of a diene and a dienophile, we use only the cyano group (CN) as a representative electron-withdrawing group throughout this paper. Only s-cis conformers of the dienes were calculated and in the calculation of activation energy, and only endo addition was taken into account in locating a TS structure.

Results and Discussion

Evaluation of Reactivity of Each Atom of the Reaction Center of Multicentered Reactions. (*a*) *Analysis Based on RHOs.* In the previous study, we defined reactivity indices ρ_{oc} for a nucleophilic site and ρ_{unoc} for an electrophilic site, respectively.[21] These values are superdelocalizability-like indices for a single orbital, RHO, which were obtained by consideration of the balance between orbital density at a reaction site and orbital energy.[32] By maximizing these values, RHOs were obtained for a single reaction center. To extend this method to multicentered reactions, let us assume that the total reactivity of a molecule as an electron donor or an electron acceptor would be represented by the sum of the reactivity of each reaction center k (see eqs 1−8). Total reactivities of molecule X as an electron donor or as an electron acceptor were defined respectively by

$$\rho_{\mathrm{oc}}(\mathrm{X}) = \sum_k \rho^k_{\mathrm{oc}}(\mathrm{X}) \tag{1}$$

$$\rho_{\mathrm{unoc}}(\mathrm{X}) = \sum_k \rho^k_{\mathrm{unoc}}(\mathrm{X}) \tag{2}$$

with

$$\rho^k_{\mathrm{oc}}(\mathrm{X}) = -f^k_{\mathrm{oc}}(\mathrm{X})/\lambda_{\mathrm{oc}}(\mathrm{X}) \tag{3}$$

$$\rho^k_{\mathrm{unoc}}(\mathrm{X}) = f^k_{\mathrm{unoc}}(\mathrm{X})/\lambda_{\mathrm{unoc}}(\mathrm{X}) \tag{4}$$

$$f^k_{\mathrm{oc}}(\mathrm{X}) = \langle\phi_{\mathrm{oc}}(\mathrm{X})|\phi^k_{\mathrm{oc}}(\mathrm{X})\rangle \tag{5}$$

$$f^k_{\mathrm{unoc}}(\mathrm{X}) = \langle\phi_{\mathrm{unoc}}(\mathrm{X})|\phi^k_{\mathrm{unoc}}(\mathrm{X})\rangle \tag{6}$$

$$\lambda_{\mathrm{oc}}(\mathrm{X}) = (\sum_i^{\mathrm{oc}} d_i^{\,2}\epsilon_i(\mathrm{X}))/(\sum_i^{\mathrm{oc}} d_i^{\,2}) \tag{7}$$

$$\lambda_{\mathrm{unoc}}(\mathrm{X}) = (\sum_j^{\mathrm{unoc}} d_j^{\,2}\epsilon_j(\mathrm{X}))/(\sum_j^{\mathrm{unoc}} d_j^{\,2}) \tag{8}$$

where $\epsilon_i(\mathrm{X})$ and $\epsilon_j(\mathrm{X})$ are the energy levels of occupied MOs and unoccupied MOs of molecule X, respectively. The parameters $\rho^k_{\mathrm{oc}}(\mathrm{X})$ and $\rho^k_{\mathrm{unoc}}(\mathrm{X})$ are local reactivity indices of electron-donating or electron-accepting abilities, respectively, and $f^k_{\mathrm{oc}}(\mathrm{X})$ and $f^k_{\mathrm{unoc}}(\mathrm{X})$ are the magnitudes of amplitudes of occupied or unoccupied RHOs for the atom at the k-position. Values of $\lambda_{\mathrm{oc}}(\mathrm{X})$ and $\lambda_{\mathrm{unoc}}(\mathrm{X})$ are energy levels of occupied or unoccupied RHOs, respectively. We also assumed that cycloaddition reactions proceed in a concerted fashion, which is the basis for the above-mentioned assumption. This concertedness of the Diels−Alder reactions of butadiene and ethylene is supported by experimental and theoretical studies.[33]

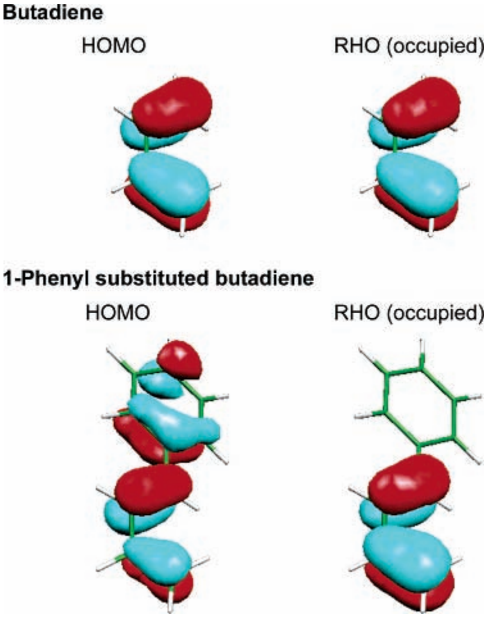


Figure 1. The HOMOs (left) and occupied RHOs (right) of butadiene and 1-pheny-substituted butadiene.

It should be noted that $f^k_{\mathrm{oc}}(\mathrm{X})$ and $f^k_{\mathrm{unoc}}(\mathrm{X})$, calculated by means of eqs 5 and 6, have forms equivalent to the Fukui functions based on frontier orbitals. This point will be explained later. Therefore, we can regard the $f^k_{\mathrm{oc}}(\mathrm{X})$ and $f^k_{\mathrm{unoc}}(\mathrm{X})$ terms as the Fukui functions based on the RHOs, which thus allow us to make fair comparisons of indices based on RHOs and frontier orbitals. The RHOs can be obtained by optimizing numerically the coefficients d_i in eq 7 or d_j in eq 8 so that ρ_{oc} or ρ_{unoc} is maximized, [34] respectively. As a result, the occupied and unoccupied RHOs can be represented by the following equations with the coefficients (d_i or d_j) optimized above.

$$\phi_{\mathrm{oc}}(\mathrm{X}) = (\sum_i^{\mathrm{oc}} d_i\psi_i(\mathrm{X}))/(\sum_i^{\mathrm{oc}} d_i^{\,2})^{1/2} \tag{9}$$

$$\phi_{\mathrm{unoc}}(\mathrm{X}) = (\sum_j^{\mathrm{unoc}} d_j\psi_j(\mathrm{X}))/(\sum_j^{\mathrm{unoc}} d_j^{\,2})^{1/2} \tag{10}$$

where $\psi_i(\mathrm{X})$ and $\psi_j(\mathrm{X})$ are canonical occupied MOs and unoccupied MOs of molecule X, respectively. Using these orbitals and the Fock operator F, λ_{oc} and λ_{unoc} are also expressed in terms of $\langle\phi_{\mathrm{oc}}|F|\phi_{\mathrm{oc}}\rangle$ and $\langle\phi_{\mathrm{unoc}}|F|\phi_{\mathrm{unoc}}\rangle$, respectively.

The HOMOs and occupied RHOs of butadiene and 1-phenyl-substituted butadiene, ((*E*)-buta-1,3-dienyl)benzene, are shown in Figure 1. In the case of butadiene, the smallest unsubstituted diene, the HOMO and the RHO show consistent distributions of orbital amplitudes. On the other hand, the HOMO of 1-phenyl-substituted butadiene has orbital amplitudes both on the diene moiety and on the phenyl ring. The orbital amplitude at the C_1 position is slightly larger than that at the C_4 position. The distribution of the RHO of 1-phenyl-substituted butadiene, however, is localized almost exclusively on the diene moiety

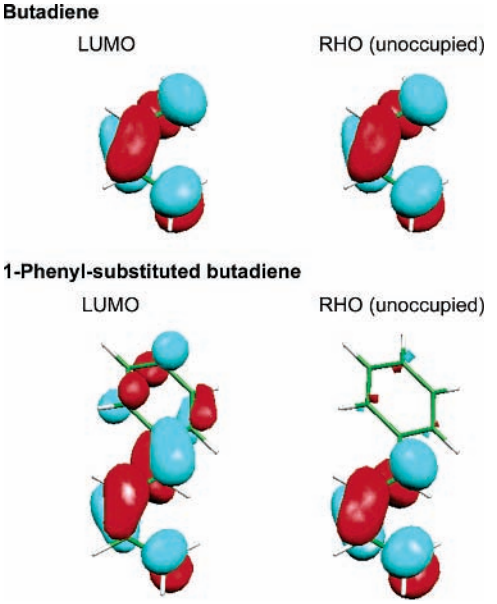


Figure 2. The LUMOs (left) and unoccupied RHOs (right) of butadiene and 1-pheny-substituted butadiene.

TABLE 1: Summary of Calculated Values Based on the Occupied RHOs at the RHF/6-31G//B3LYP/6-31G** Level**

(A) Diene

substituent R_1	λ_{oc}[a]	1-position		4-position	
		f_{oc}^1	ρ_{oc}^1	f_{oc}^4	ρ_{oc}^4
H	−0.3227	0.3132	0.9703	0.3132	0.9703
1- CH_3	−0.3160	0.2778	0.8791	0.3382	1.0704
1-Ph	−0.3158	0.2794	0.8849	0.3356	1.0630
1-OCH_3	−0.3159	0.2091	0.6619	0.3899	1.2345
1-CH═CH_2	−0.3150	0.2741	0.8701	0.3373	1.0710
1-CN	−0.3586	0.3558	0.9923	0.2764	0.7708
2-Me	−0.3203	0.3458	1.0797	0.2802	0.8749
2-Ph	−0.3208	0.3360	1.0474	0.2763	0.8612
2-OCH_3	−0.3170	0.4394	1.3861	0.2175	0.6862
2-CH═CH_2	−0.3223	0.3359	1.0420	0.2694	0.8359
2-CN	−0.3554	0.2639	0.7425	0.3262	0.9176
2-Cl	−0.3443	0.3206	0.9311	0.2870	0.8335

(B) Dienophile

substituent R_2	λ_{oc}[a]	1-position		2-position	
		f_{oc}^1	ρ_{oc}^1	f_{oc}^2	ρ_{oc}^2
H	−0.3716	0.4977	1.3394	0.4977	1.3394
1-CN	−0.4160	0.5138	1.2351	0.4496	1.0807
1-CH_3	−0.3591	0.4737	1.3189	0.5184	1.4435
1-Ph	−0.3570	0.4464	1.2505	0.5118	1.4338
1-OCH_3	−0.3568	0.3971	1.1130	0.5801	1.6260
1-CH═CH_2	−0.3582	0.4435	1.2381	0.5114	1.4276

[a] In hartrees.

TABLE 2: Summary of Calculated Values Based on the Unoccupied RHOs at the RHF/6-31G//B3LYP/6-31G** Level**

(A) Diene

substituent R_1	λ_{unoc}[a]	1-position		4-position	
		f_{unoc}^1	ρ_{unoc}^1	f_{unoc}^4	ρ_{unoc}^4
H	0.1286	0.3125	2.4295	0.3125	2.4295
1-CH_3	0.1366	0.3272	2.3963	0.3068	2.2464
1-Ph	0.1051	0.2772	2.6365	0.2870	2.7298
1-OCH_3	0.1499	0.3591	2.3952	0.2933	1.9558
1-CH═CH_2	0.1068	0.2735	2.5609	0.3019	2.8261
1-CN	0.0689	0.2391	3.4673	0.3087	4.4769
2-CH_3	0.1383	0.2876	2.0801	0.3274	2.3683
2-Ph	0.1226	0.3267	2.6648	0.2670	2.1779
2-OCH_3	0.1349	0.2154	1.5963	0.3791	2.8093
2-CH═CH_2	0.1245	0.3408	2.7379	0.2486	1.9968
2-CN	0.0806	0.4047	5.0204	0.2159	2.6784
2-Cl	0.1125	0.3079	2.7362	0.3152	2.8005

(B) Dienophile

substituent R_2	λ_{unoc}[a]	1-position		2-position	
		f_{unoc}^1	ρ_{unoc}^1	f_{unoc}^2	ρ_{unoc}^2
H	0.1799	0.4979	2.7676	0.4979	2.7675
1-CN	0.1018	0.3594	3.5298	0.5332	5.2375
1-CH_3	0.1863	0.5014	2.6914	0.4838	2.5972
1-Ph	0.1408	0.3877	2.7539	0.4612	3.2763
1-OCH_3	0.2061	0.5363	2.6027	0.4254	2.0642
1-CH═CH_2	0.1521	0.4078	2.6816	0.4796	3.1540

[a] In hartrees.

in a manner similar to those of butadiene. This reflects the fact that these two molecules, different in size and structure, undergo the same kind of reaction. Also, this suggests that, in a large molecule, not only the HOMO but also other MOs participate in the interaction. These considerations should also be valid in the case of an unoccupied orbital of the diene, which is responsible for the acceptance of electrons from the dienophile (Figure 2). Although the LUMO and the unoccupied RHO are essentially the same in butadiene, they are considerably different from each other in 1-phenyl-substituted butadiene. In Tables 1 and 2, the calculated occupied and unoccupied RHO-related parameters defined above are summarized, respectively.

In the frontier orbital theory, the interaction of a set of MOs, i.e., the HOMO (diene)-LUMO (dienophile) interaction, is usually chosen to predict the regioselectivity of normal Diels−Alder reactions, that is, reactions of a diene bearing an electron-donating group and a dienophile bearing an electron-withdrawing group. In the case of inverse-electron-demand Diels−Alder reactions, i.e., reactions of a diene substituted with an electron-withdrawing group and a dienophile substituted with an electron-donating group, a different combination, the LUMO (diene)-HOMO (dienophile) interaction, is considered. This is based on the fact that the energy differences of these pairs are smaller than those of other combinations. In this context, we can consider that the combination of the occupied RHOs of dienes and unoccupied RHOs of dienophiles in the normal-electron-demand Diels−Alder reactions is relevant, while in the inverse-electron-demand Diels−Alder reactions, the combination of unoccupied RHOs of dienes and occupied RHOs of dienophiles is relevant. We calculated the *f* values (f_{oc} or f_{unoc}) of substituted butadienes and substituted ethylenes on the basis of the RHO method. It is generally accepted in the frontier orbital theory that the interaction of the two larger atomic orbital components of the respective terminal atoms of a diene and a dienophile is predominant, i.e., large−large/small−small interactions are favored.[14] We found that the calculated magnitude of the f_{oc} and f_{unoc} values correctly predicted the combination of the reaction terminals, i.e., the observed regioselectivities, in all cases (types A−D) of butadienes substituted with an electron donor or an electron acceptor at the C_1 or C_2 position, respectively. In acrylonitrile (Table 2B), the f_{unoc} value for the C_2 position is larger than that of the C_1 position; thus, the f_{oc} value of the C_4 position in a diene bearing an electron-donating group at the C_1 position should be larger than that of the C_1 position, while the f_{oc} value of the C_1 position in a diene bearing an electron-donating group at the C_2 position should be larger than that of the C_4 position. These trends were actually observed for normal Diels−Alder reactions (Table 1A).[35] On the other hand, in dienophiles bearing electron-donating groups, the f_{oc} value is larger at the C_2 position. The f_{unoc} value of 1-cyano-substituted butadiene is larger at the C_4 position, predicting the ortho product (Table 2A). The f_{unoc} value of 2-cyano-substituted butadiene is larger at the C_1 position, predicting the para adduct (Table 2A). It should also be noted that, unlike other substituents, the cyano substituent (CN) lowers the energy levels of the occupied and unoccupied RHOs of a diene and a dienophile.

(*b*) *Analysis Based on Frontier Orbitals.* Descriptors based on frontier orbitals are defined similarly. If the structures of the relevant molecules are highly distorted from planarity, and outer functions are included in the basis set, it is difficult to compare AO coefficients at reaction sites straightforwardly. In the present case, the optimized structures of the dienes were not planar, but are to some extent twisted with respect to the central C−C bond. While the work by Hehre et al. utilized the HOMO coefficients of the outer p-functions as the index of the frontier orbitals,[14] this is ambiguous and it is not self-evident which coefficient in a split valence basis set should be used for comparison in these cases. On the other hand, the Fukui function measures a value corresponding to the HOMO (or LUMO) density unambiguously. Therefore, in this study, we used regional frontier-orbital-based Fukui functions, which were recently proposed by Contreras et al.[36] In this method, the Fukui function on atom k in molecule X is calculated by

$$f_k^{\alpha}(\mathrm{X}) = \sum_{\mu \in k}^{\mathrm{AO}} \{ |c_{\nu\alpha}|^2 + \sum_{\nu \neq \mu}^{\mathrm{AO}} c_{\mu\alpha} c_{\nu\alpha} S_{\mu\nu} \} \qquad (11)$$

where “AO” means that the summation is over all the designated AOs, $c_{\mu\alpha}$ denotes the LCAO coefficient of AO μ in the HOMO ($\alpha = -$) or the LUMO ($\alpha = +$), and $S_{\mu\nu}$ is an element of the AO overlap integral matrix that represents the overlap integral between AOs μ and ν.[37] The Fukui functions, in which − and + are superscripts, are used to distinguish electron-donating and electron-accepting abilities, respectively. As a simple descriptor for evaluating reactivity only in terms of a frontier orbital, the quantities $r_k^-(X)$ and $r_k^+(X)$ were defined here, which is similar to the one-term approximation to superdelocalizability with respect to the frontier orbitals (see eqs 12 and 13):[32]

$$r_k^{-}(\mathrm{X}) = -f_k^{-}(\mathrm{X})/\epsilon_{\mathrm{HOMO}}(\mathrm{X}) \qquad (12)$$

$$r_k^{+}(\mathrm{X}) = f_k^{+}(\mathrm{X})/\epsilon_{\mathrm{LUMO}}(\mathrm{X}) \qquad (13)$$

where $\epsilon_{\mathrm{HOMO}}(\mathrm{X})$ and $\epsilon_{\mathrm{LUMO}}(\mathrm{X})$ are the energy levels of the HOMO and LUMO of molecule X, respectively. Indices $r_k^-(\mathrm{X})$ and $r_k^+(\mathrm{X})$ can evaluate the electron-donating and electron-accepting abilities at the reaction site k, respectively. In Tables 3 and 4, we summarize these reactivity indices ($r_k^-(\mathrm{X})$ and $r_k^+(\mathrm{X})$) together with the Fukui function values ($f_k^-(\mathrm{X})$ and $f_k^+(\mathrm{X})$) based on the frontier orbitals.

TABLE 3: Summary of Calculated Values Based on the HOMOs at the RHF/6-31G//B3LYP/6-31G** Level**[a]

(A) Diene

substituent R_1	ϵ_{HOMO}[b]	1-position f_1^-	1-position r_1^-	4-position f_4^-	4-position r_4^-
H	−0.3225	0.3124	0.9688	0.3124	0.9688
1-CH_3	−0.3106	0.2872	0.9248	0.2927	0.9425
1-Ph	−0.2808	0.1472	0.5241	0.1466	0.5220
1-OCH_3	−0.3011	0.2149	0.7138	0.2797	0.9288
1-$CH{=}CH_2$	−0.2895	0.1959	0.6766	0.1959	0.6767
1-CN	−0.3455	0.2806	0.8122	0.2547	0.7372
2-CH_3	−0.3192	0.3567	1.1176	0.2624	0.8219
2-Ph	−0.2988	0.2580	0.8636	0.0816	0.2732
2-OCH_3	−0.3147	0.4444	1.4123	0.1948	0.6190
2-$CH{=}CH_2$	−0.3087	0.3476	1.1260	0.1630	0.5280
2-CN	−0.3522	0.2856	0.8109	0.2779	0.7890
2-Cl	−0.3406	0.3359	0.9862	0.2408	0.7069

(B) Dienophile

substituent R_2	ϵ_{HOMO}[b]	1-position f_1^-	1-position r_1^-	2-position f_2^-	2-position r_2^-
H	−0.3716	0.4977	1.3393	0.4978	1.3394
1-CN	−0.3915	0.3243	0.8284	0.3567	0.9113
1-CH_3	−0.3522	0.4234	1.2023	0.4988	1.4165
1-Ph	−0.2984	0.1275	0.4273	0.2339	0.7838
1-OCH_3	−0.3394	0.2744	0.8085	0.5314	1.5657
1-$CH{=}CH_2$	−0.3168	0.1695	0.5350	0.3283	1.0362

[a] Superscript (−) indicates parameters related to electron-donating ability (see eq 12). [b] In hartrees.

TABLE 4: Summary of Calculated Values Based on the LUMOs at the RHF/6-31G//B3LYP/6-31G** Level**[a]

(A) Diene

substituent R_1	ϵ_{LUMO}[b]	1-position f_1^+	1-position r_1^+	4-position f_4^+	4-position r_4^+
H	0.1267	0.3036	2.3962	0.3036	2.3962
1-CH_3	0.1321	0.2888	2.1856	0.3008	2.2768
1-Ph	0.0867	0.1678	1.9364	0.1532	1.7674
1-OCH_3	0.1430	0.2913	2.0374	0.3104	2.1714
1-$CH{=}CH_2$	0.0947	0.1993	2.1037	0.2107	2.2243
1-CN	0.0645	0.2251	3.4881	0.2436	3.7759
2-CH_3	0.1348	0.2739	2.0326	0.3123	2.3170
2-Ph	0.1073	0.2655	2.4742	0.0953	0.8879
2-OCH_3	0.1318	0.2119	1.6081	0.3588	2.7223
2-$CH{=}CH_2$	0.1144	0.3348	2.9263	0.1678	1.4667
2-CN	0.0782	0.4028	5.1530	0.1750	2.2380
2-Cl	0.1107	0.2938	2.6551	0.3070	2.7743

(B) Dienophile

substituent R_2	ϵ_{LUMO}[b]	1-position f_1^+	1-position r_1^+	2-position f_2^+	2-position r_2^+
H	0.1793	0.4946	2.7580	0.4946	2.7578
1-CN	0.0945	0.2735	2.8950	0.4692	4.9657
1-CH_3	0.1775	0.4195	2.3633	0.4345	2.4482
1-Ph	0.1067	0.1275	1.1953	0.2353	2.2063
1-OCH_3	0.2045	0.5236	2.5604	0.4198	2.0532
1-$CH{=}CH_2$	0.1263	0.1811	1.4339	0.3151	2.4953

[a] Superscript (+) indicates parameters related to electron-accepting ability (see eq 13). [b] In hartrees.

As we have already discussed above, the orbital distributions of the HOMO and the RHO of butadiene are similar (Figure 1). We can also see numerically that the Fukui functions and the reactivity indices of the RHOs for butadiene, which is comprised of only a reaction unit of the smallest size, are almost identical in magnitude to those of the frontier orbitals (Tables 1−4). Experimentally, it is known that a cycloaddition reaction of a 1-substituted diene bearing an electron-donating substituent with a dienophile bearing an electron-withdrawing substituent (type A) yields the ortho adduct.[22,23] Theoretical calculations of activation energies at the B3LYP/6-31G** level were consistent with the selectivity (Table 5). This selectivity coincides with the preference of large−large/small−small interaction, i.e., the C_4 carbon atom of the 1-substituted diene, the terminal atom with the largest Fukui function and reactivity index values, interacts with the C_2 carbon atom of acrylonitrile, which has the largest values of both LUMO and unoccupied RHO distributions. However, in the case of 1-phenyl-substituted butadiene, the Fukui function and the reactivity index based on the HOMO showed slightly larger values at C_1 than at C_4, while the index based on the occupied RHO correctly reproduced the different reactivities. Also, in 1-vinyl-substituted butadiene, where position 1 means the 3 position of 1,3,5-hexatriene, the

TABLE 5: Calculated Total Energies and Activation Energies at the B3LYP/6-31G Level**

substituent		energy[a]				activation energy [b]
diene	dienophile	diene	dienophile	TS	orientation	
H	1-CN	−155.996 051	−170.836 242	−326.805 147	−	17.0
1-Me	1-CN	−195.318 778	−170.836 242	−366.128 317	ortho	16.8
				−366.125 530	meta	18.5
1-Ph	1-CN	−387.064 449	−170.836 242	−557.875 627	ortho	15.7
				−557.869 882	meta	19.3
1-OCH$_3$	1-CN	−270.524 200	−170.836 242	−441.337 087	ortho	14.7
				−441.328 704	meta	19.9
1-CH=CH$_2$	1-CN	−233.405 594	−170.836 242	−404.214 600	ortho	17.1
				−404.209 172	meta	20.5
2-Me	1-CN	−195.317 624	−170.836 242	−366.126 134	meta	17.4
				−366.126 296	para	17.3
2-Ph	1-CN	−387.059 881	−170.836 242	−557.868 035	meta	17.6
				−557.869 272	para	16.8
2-OCH$_3$	1-CN	−270.525 275	−170.836 242	−441.331 763	meta	18.7
				−441.332 675	para	18.1
2-CH=CH$_2$	1-CN	−233.400 475	−170.836 242	−404.206 884	meta	18.7
				−404.209 898	para	16.8
2-Cl	1-CN	−615.591 888	−170.836 242	−786.397 470	meta	19.2
				−786.400 068	para	17.6
1-CN	H	−248.240 674	−78.593 808	−326.805 369	−	18.3
1-CN	1-Me	−248.240 674	−117.916 549	−366.125 285	ortho	20.0
				−366.122 924	meta	21.5
1-CN	1-Ph	−248.240 674	−309.660 909	−557.873 789	ortho	17.4
				−557.867 248	meta	21.5
1-CN	1-OMe	−248.240 674	−193.122 851	−441.327 210	ortho	22.8
				−441.322 250	meta	25.9
1-CN	1-CH=CH$_2$	−248.240 674	−156.001 668	−404.212 203	ortho	18.9
				−404.205 628	meta	23.0
2-CN	H	−248.236 275	−78.593 808	−326.804 625	−	16.0
2-CN	1-Me	−248.236 275	−117.916 549	−366.122 343	meta	19.1
				−366.123 452	para	18.4
2-CN	1-Ph	−248.236 275	−309.660 909	−557.866 512	meta	19.2
				−557.871 978	para	15.8
2-CN	1-OMe	−248.236 275	−193.122 851	−441.321 869	meta	23.4
				−441.328 935	para	18.9
2-CN	1-CH=CH$_2$	−248.236 275	−156.001 668	−404.205 479	meta	20.4
				−404.209 598	para	17.8

[a] In hartrees. [b] In kcal/mol.

TABLE 6: Comparison of Observed Regioselectivity in Normal-Electron-Demand Diels−Alder Reactions and Theories

substituent	exptl regioselectivity [a]	frontier orbital		reactivity model[c]	RHO (this study)[d]
		Hehre's study[b]	this study		
1-Me	ortho (I)	none	ortho	ortho	ortho
1-Ph	ortho (I)	meta[e]	none (meta) [f]	ortho	ortho
1-OCH$_3$	ortho (I)	ortho	ortho	ortho	ortho
1-CH=CH$_2$	ortho (I)	none	none	meta	ortho
2-Me	para (II)	para	para	para	para
2-Ph	para (II)	para	para	meta	para
2-OCH$_3$	para (II)	para	para	para	para
2−Cl	para (II)	para	para	none	para

[a] The mode illustrated in Scheme 1 is also shown in parentheses. [b] RHF/3-21G(*)//RHF/3-21G(*). See ref 14. [c] See ref 14. [d] In terms of reactivity index, stabilization index, and local softness. [e] 1-Ph was modeled by a perpendicular 1-CH=CH$_2$ substituent. [f] The frontier orbital showed almost equal distributions at the C$_1$ and C$_4$ positions, but the *f* value of C$_1$ was slightly larger (Table 3).

coefficients of the HOMO suggested that the reactivities at C$_1$ and C$_4$ are approximately equal, whereas the reactivity index based on the occupied RHO indicated that C$_4$ is more reactive than C$_1$. For the 2-substituted butadienes, the HOMOs and occupied RHOs predicted the same reaction site selectivity (para selectivity), in agreement with experiment. These predictions based on the frontier orbitals were consistent with those obtained previously on the basis of the orbital coefficient at the RHF/3-21G(*) level by Hehre et al.[14] This shows the results of orbital analyses are not so sensitive to the basis set used, at least within the present Diels−Alder case.[38] In the cases of the inverse-electron-demand Diels−Alder reactions, both RHOs and frontier orbitals gave correct prediction of regioselectivities by considering the unoccupied orbitals of dienes and the occupied orbitals of dienophiles (Tables 1−4).

We then compared the available predictions of normal-electron-demand Diels−Alder reactions by several theoretical models (Table 6). Experimentally, the 1-substituted and 2-substituted dienes show ortho and para regiochemical preferences, respectively. Frontier orbital models failed in the cases of 1-phenyl- and 1-vinyl-substituted dienes, and the reactivity model by Hehre et al. made incorrect predictions in the cases of 1-vinyl-, 2-phenyl-, and 2-chlorobutadienes. Only the RHO model showed the complete agreement with experiment.

TABLE 7: Absolute Values of LCMO Coefficients of Occupied RHOs of Butadiene and 1-Pheny-Substituted Butadiene for the Highest Five Occupied MOs Calculated at the RHF/6-31G//B3LYP/6-31G** and (B3LYP//B3LYP in Parentheses) Levels**

	H	1-Ph
HOMO	0.9996 (0.9995)	0.7766 (0.8271)
HOMO-1	0.0000 (0.0000)	0.0036 (0.0111)
HOMO-2	0.0188 (0.0207)	0.6172 (0.5463)
HOMO-3	0.0000 (0.0000)	0.0309 (0.0426)
HOMO-4	0.0000 (0.0000)	0.0062 (0.0036)

Our focus in this paper is on the delocalized property of frontier orbitals, which is common to canonical MOs.[39] As shown in Table 7, in 1-phenyl-substituted butadiene, the HOMO-2 also plays a very important role in the interaction, because it shows the distribution over the diene moiety as the HOMO does. Despite the problem of Kohn−Sham orbitals,[29] we tentatively calculated RHOs also at the B3LYP//B3LYP level (Table 7). The results obtained at the HF//B3LYP and B3LYP//B3LYP levels were essentially the same, that is, the HOMO-2 is also important. Therefore, the main reason for the failure of frontier orbitals at least in analyzing orbital interactions is ascribed not to the neglect of correlation effects but to the neglect of MOs other than the frontier orbitals. The present method treated the latter effect. It should also be noted that electron-correlated methods do not localize canonical orbitals.

Stabilization by Orbital Interaction between the RHOs of the Reagents. To examine an orbital interacting system such as the TS, we here introduce a stabilization index (see eqs 14−16) that is similar to the perturbation representation of charge-transfer stabilization energy.[40−43] In the case of a [4+2] cycloaddition reaction, two possible regioisomers, i.e., orientations I and II, are possible (Scheme 1). The transition state is stabilized by delocalization of electrons through orbital interactions between the RHOs, i.e., two combinations of oc (A) → unoc (B) and unoc (A) ← oc (B) for the orientation *P*, which can be defined by the stabilization index $R_{\mathrm{RHO}}(P)$ (eqs 14−16, where A indicates the diene and B indicates the dienophile):

$$R_{\mathrm{RHO}}(P) = R_{\mathrm{RHO}}^{\mathrm{AB}}(P) + R_{\mathrm{RHO}}^{\mathrm{BA}}(P) \tag{14}$$

with

$$R_{\mathrm{RHO}}^{\mathrm{AB}}(P) = \sum_{k,l}^{\mathrm{all}} \frac{f_{\mathrm{oc}}^{k}(\mathrm{A}) f_{\mathrm{unoc}}^{l}(\mathrm{B})}{\lambda_{\mathrm{unoc}}(\mathrm{B}) - \lambda_{\mathrm{oc}}(\mathrm{A})} \tag{15}$$

$$R_{\mathrm{RHO}}^{\mathrm{BA}}(P) = \sum_{k,l}^{\mathrm{all}} \frac{f_{oc}^{k}(\mathrm{B}) f_{\mathrm{unoc}}^{l}(\mathrm{A})}{\lambda_{\mathrm{unoc}}(\mathrm{A}) - \lambda_{\mathrm{oc}}(\mathrm{B})} \tag{16}$$

where $R_{\mathrm{RHO}}^{\mathrm{AB}}$ and $R_{\mathrm{RHO}}^{\mathrm{BA}}$ are indices for electron delocalizations from A to B and from B to A, respectively, and "all" means that the summation is over all the interacting $k-l$ atom combinations between A and B in each regioisomer (orientation *P*). For instance, $(k, l) = (1, 1')$ and $(4, 2')$ in orientation I (Scheme 1). In defining these indices, we assumed that the interaction integrals between AOs[44] can be considered to be equal within the same kind of reactions. A larger value of index R_{RHO} means that the interaction orientation is more favorable than the other. The stabilization indices based on the RHOs of several monosubstituted dienes and a dienophile are summarized in Table 8. Basically, the stabilization indices showed the same trend in regioselectivity as those based on the RHO properties of each reagent, as shown in Tables 1 and 2. That is, in the reactions of 1-substituted and 2-substituted butadienes, ortho and para cycloadducts were predicted to be more favorable, respectively, than the other possible cycloadducts. The RHOs for the orbital interaction in one direction (i.e., $R_{\mathrm{RHO}}^{\mathrm{AB}}$ or $R_{\mathrm{RHO}}^{\mathrm{BA}}$) correctly predicted the regioisomer in all cases (Table 8). When electron delocalizations in both directions are considered (i.e., R_{RHO}), the prediction of the regiochemistry is comparable except in the cases of the dienophiles bearing 1-phenyl and 1-vinyl substituents.[45] This analysis also allows us to compare approximately the relative importance of these two-directional orbital interactions, oc (A) → unoc (B) and unoc (A) ← oc (B). That is, in the normal combination of an electron-rich diene (A) and an electron-poor dienophile (B), $R_{\mathrm{RHO}}^{\mathrm{AB}}$ is larger than $R_{\mathrm{RHO}}^{\mathrm{BA}}$, and in the inverse-electron-demand combination of an electron-poor diene (A) and an electron-rich dienophile (B), $R_{\mathrm{RHO}}^{\mathrm{BA}}$ is larger than $R_{\mathrm{RHO}}^{\mathrm{AB}}$. In the reaction between 2-chlorobutadiene and acrylonitrile, where both of the substituents are electron-withdrawing groups in terms of the Hammett constant, the electron delocalization from the diene to the dienophile is slightly larger than that from the dienophile to the diene.

TABLE 8: Comparison of Stabilization Index Obtained on the Basis of the RHO Method

substituent[a]		stabilization index[b]			
diene	dienophile	$R_{\mathrm{RHO}}^{\mathrm{AB}}$	$R_{\mathrm{RHO}}^{\mathrm{BA}}$	R_{RHO}	orientation[c]
H	1-CN	0.6584	0.5528	1.2112	–
1-Me	1-CN	**0.6706**	**0.5539**	**1.2244**	**ortho**
		0.6454	0.5515	1.1969	meta
1-Ph	1-CN	**0.6691**	0.5209	**1.1900**	**ortho**
		0.6457	**0.5221**	1.1678	meta
1-OCH$_3$	1-CN	**0.6777**	**0.5590**	**1.2367**	**ortho**
		0.6024	0.5515	1.1540	meta
1-CH═CH$_2$	1-CN	**0.6679**	0.5284	**1.1963**	**ortho**
		0.6415	**0.5319**	1.1734	meta
2-Me	1-CN	0.6484	0.5322	1.1806	meta
		0.6754	**0.5368**	**1.2122**	**para**
2-Ph	1-CN	0.6343	**0.5346**	1.1689	meta
		0.6589	0.5275	**1.1863**	**para**
2-OCH$_3$	1-CN	0.6540	0.5102	1.1642	meta
		0.7461	**0.5293**	**1.2754**	**para**
2-CH═CH$_2$	1-CN	0.6233	**0.5308**	1.1541	meta
		0.6505	0.5198	**1.1704**	**para**
2-Cl	1-CN	0.6013	0.5674	1.1687	meta
		0.6144	**0.5683**	**1.1827**	**para**
1-CN	H	0.5846	0.6188	1.2034	–
1-CN	1-Me	**0.5729**	**0.6383**	**1.2112**	**ortho**
		0.5703	0.6310	1.2013	meta
1-CN	1-Ph	0.5315	**0.6215**	1.1530	ortho
		0.5432	0.6108	**1.1540**	**meta**
1-CN	1-OMe	**0.5462**	**0.6436**	**1.1898**	**ortho**
		0.5306	0.6137	1.1443	meta
1-CN	1-CH═CH$_2$	0.5437	**0.6177**	1.1615	**ortho**
		0.5549	0.6067	**1.1616**	meta
2-CN	H	0.5488	0.6831	1.2319	–
2-CN	1-Me	0.5355	0.6905	1.2260	meta
		0.5376	**0.7097**	**1.2473**	**para**
2-CN	1-Ph	**0.5093**	0.6654	1.1747	meta
		0.5001	**0.6937**	**1.1937**	**para**
2-CN	1-OMe	0.4991	0.6538	1.1530	meta
		0.5114	**0.7328**	**1.2443**	**para**
2-CN	1-CH═CH$_2$	**0.5203**	0.6607	1.1809	meta
		0.5115	**0.6899**	**1.2013**	**para**

[a] When a cyano group is attached to the diene (A) and the dienophile (B), electron delocalization from A to B (represented by $R_{\mathrm{RHO}}^{\mathrm{AB}}$) and from B to A (represented by $R_{\mathrm{RHO}}^{\mathrm{BA}}$) are the major contributors of stabilization, respectively. [b] Larger values are indicated in bold. [c] Experimentally favorable orientations are indicated in bold.

As an index for evaluating the strength of delocalization stabilization through the frontier orbitals, we also defined a

TABLE 9: Comparison of Stabilization Index Obtained on the Basis of Frontier Orbitals

substituent [a]		stabilization index[b]			
diene	dienophile	$R_{\mathrm{FO}}^{\mathrm{AB}}$	$R_{\mathrm{FO}}^{\mathrm{BA}}$	R_{FO}	orientation[c]
H	1-CN	0.5565	0.3990	0.9556	−
1-Me	1-CN	**0.5330**	**0.3838**	**0.9168**	**ortho**
		0.5303	0.3831	0.9134	meta
1-Ph	1-CN	0.2905	0.2281	0.5186	**ortho**
		0.2908	**0.2291**	**0.5199**	meta
1-OCH$_3$	1-CN	**0.4803**	**0.3840**	**0.8643**	**ortho**
		0.4483	0.3828	0.8311	meta
1-CH═CH$_2$	1-CN	0.3789	**0.2876**	0.6665	**ortho**
		0.3789	0.2868	**0.6657**	meta
2-Me	1-CN	0.5335	**0.3805**	0.9140	meta
		0.5781	0.3781	**0.9562**	**para**
2-Ph	1-CN	0.2768	0.2408	0.5176	meta
		0.3646	**0.2518**	**0.6164**	**para**
2-OCH$_3$	1-CN	0.5205	0.3760	0.8964	meta
		0.6399	**0.3669**	**1.0067**	**para**
2-CH═CH$_2$	1-CN	0.4255	0.3329	0.7584	meta
		0.5151	**0.3436**	**0.8587**	**para**
2-Cl	1-CN	0.4708	**0.4079**	0.8787	meta
		0.5136	0.4070	**0.9206**	**para**
1-CN	H	0.5045	0.5349	1.0393	−
1-CN	1-Me	0.4367	**0.5204**	**0.9570**	**ortho**
		0.4374	0.5170	0.9544	meta
1-CN	1-Ph	0.2117	**0.2361**	0.4477	ortho
		0.2178	0.2306	**0.4485**	meta
1-CN	1-OMe	**0.4615**	**0.4734**	**0.9349**	**ortho**
		0.4567	0.4616	0.9183	meta
1-CN	1-CH═CH$_2$	0.2778	**0.3098**	**0.5876**	**ortho**
		0.2852	0.3021	0.5872	meta
2-CN	H	0.5243	0.6394	1.1637	−
2-CN	1-Me	0.4541	0.5992	1.0533	meta
		0.4543	**0.6391**	**1.0934**	**para**
2-CN	1-Ph	0.2219	0.2450	0.4669	meta
		0.2237	**0.3094**	**0.5331**	**para**
2-CN	1-OMe	**0.4782**	0.4874	0.9655	meta
		0.4767	**0.6276**	**1.1043**	**para**
2-CN	1-CH═CH$_2$	0.2911	0.3183	0.6094	meta
		0.2932	**0.4099**	**0.7031**	**para**

[a] When a cyano group is attached to the diene (A) and the dienophile (B), electron delocalization from A to B (represented by $R_{\mathrm{RHO}}^{\mathrm{AB}}$) and from B to A (represented by $R_{\mathrm{RHO}}^{\mathrm{BA}}$) are the major contributors of stabilization, respectively. [b] Larger values are indicated in bold. [c] Experimentally favorable orientations are indicated in bold.

stabilization index $R_{\mathrm{FO}}(P)$ using the Fukui functions and orbital energies (eqs 17−19):

$$R_{\mathrm{FO}}(P) = R_{\mathrm{FO}}^{\mathrm{AB}}(P) + R_{\mathrm{FO}}^{\mathrm{BA}}(P) \qquad (17)$$

with

$$R_{\mathrm{FO}}^{\mathrm{AB}}(P) = \sum_{k,l}^{\mathrm{all}} \frac{f_k^{-}(\mathrm{A}) f_l^{+}(\mathrm{B})}{\epsilon_{\mathrm{LUMO}}(\mathrm{B}) - \epsilon_{\mathrm{HOMO}}(\mathrm{A})} \qquad (18)$$

$$R_{\mathrm{FO}}^{\mathrm{BA}}(P) = \sum_{k,l}^{\mathrm{all}} \frac{f_k^{-}(\mathrm{B}) f_l^{+}(\mathrm{A})}{\epsilon_{\mathrm{LUMO}}(\mathrm{A}) - \epsilon_{\mathrm{HOMO}}(\mathrm{B})} \qquad (19)$$

The stabilization indices based on the frontier orbitals for several monosubstituted dienes and a dienophile are summarized in Table 9. In the approximation where only the A-to-B or B-to-A delocalization was considered ($R_{\mathrm{FO}}^{\mathrm{AB}}$ or $R_{\mathrm{FO}}^{\mathrm{BA}}$), the frontier orbital approach failed to predict the regioselectivities of 1-phenyl- and 1-vinyl-substituted butadienes.[46] This inconsistency was not removed in the frontier orbital theory, even if the other interaction is taken into account.

Conclusion

We extended the RHO method to the multicentered version. Regioselectivities in the Diels−Alder reactions were studied by this method and also by frontier orbital theory for comparison. For detailed analyses, we utilized the orbital density, reactivity index, and stabilization index values for these orbitals. These values were compared with the experimentally known regioselectivity. It has been shown that the frontier orbital theory sometimes fails to correctly predict regioselectivity in Diels−Alder reactions, and this was reproduced here at a higher level of calculation. In contrast, the predictions based on the RHO method were consistent with the observed regioselectivity. The present results suggested that RHOs better represent the orbital interaction around the TS than frontier orbitals. Despite the general acceptance of the frontier orbital theory, it has not necessarily been clear whether reactivity depends only on one orbital (frontier control) or many.[47] Our analysis supports the idea that reactivity is described generally in terms of some relevant canonical orbitals.

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Supporting Information Available: Tables showing the comparison of stabilizaton index obtained on the basis of the RHOs and frontier orbitals, calculated total energies and activation energies at the B3LYP/6-31G** level, and LCMO coefficients of occupied RHOs of butadiene and 1-phenylbutadiene for the hightest five MOs calculated at RHF/6-31G**//B3LYP/6-31G* and B3LYP//B3LYP. This material is available free of charge via the Internet at http://pubs.acs.org.

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(37) Because the quantity in eq 3 can also be written as

$$f_k^{\alpha}(\mathrm{X}) = \langle \psi_{\alpha}(\mathrm{X}) | \psi_{\alpha}^{k}(\mathrm{X}) \rangle \tag{R1}$$

where $\psi_{\alpha}(\mathrm{X})$ is a frontier orbital ($\alpha = -$: HOMO; $\alpha = +$: LUMO) and $\psi_{\alpha}^{k}(\mathrm{X})$ is the AO components at atom k of $\psi_{\alpha}(\mathrm{X})$ in molecule X, we calculated the Fukui functions in this study on the basis of the coefficients of the HOMO or the LUMO, which is a linear combination of MOs (LCMO); function $\psi_{\alpha}^{k}(\mathrm{X})$ is represented in LCMO as

$$\psi_{\alpha}^{k}(\mathrm{X}) = \chi\mathbf{C}' = \psi\mathbf{C}^{-1}\mathbf{C}' \tag{R2}$$

where χ and ψ are row vectors representing the AOs and MOs, respectively, **C** is the matrix of LCAO-MO coefficients, and **C′** is a column vector containing the LCAO coefficients of $\psi_{\alpha}^{k}(\mathrm{X})$. Note that all the elements in **C′** corresponding to AOs in atoms other than k are zero. Since the MOs are orthogonal to one another, the quantity in eq R1 is equal to the LCMO coefficient of the frontier orbital.

(38) Thus, DFT-based reactivity indices, e.g., the local softness of a nucleophilic center, which is often described with the HOMO-LUMO approximation and is often applied to multicentered reactions, may be better described in the RHO sense not rigorously but intuitively as

$$s_{\mathrm{oc}}^{k} = \frac{f_{\mathrm{oc}}^{k}(\mathrm{X})}{\lambda_{\mathrm{unoc}}(\mathrm{X}) - \lambda_{\mathrm{oc}}(\mathrm{X})} \tag{R3}$$

(39) See, for example: Jensen, F. *Introduction to Computational Chemistry*; J. Wiley & Sons: New York, 1999; p 227.

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(42) Strictly speaking, for the interaction between Hartree−Fock MOs, stabilization of total energy as a result of charge transfer in terms of the perturbation form should be represented not by orbital energies but by wave function-based configuration energies (see ref 43). However, the latter energies cannot be calculated for an isolated state. In addition, orbital energies have historically often been utilized to compare reactivities. Thus, we utilize orbital energies as a simple measure.

(43) Fukui, H.; Fujimoto, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1989.

(44) Reference 38, p 345.

(45) This would be because of the limitation of those procedures which aimed to reproduce the orbitals around TS in terms of combination of orbitals at the reactant state.

(46) This is because important lower lying MOs are not taken into account (Table 7).

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