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Chemical Pseudoexcitation and Paradoxical Orbital Interaction Effect

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Abstract: Some third-order configuration interaction (CI) perturbation energy terms for bimolecular interactions have been shown to be interpreted as representing the local excitation within one or both of the interacting molecules, induced by charge transfer (chemical pseudoexcitation). The chemical pseudoexcitation effect was more explicitly expressed by the second-order perturbation energy terms obtained on the assumption of the degeneracy of a particular transferred configuration with the original one. The following rules have been derived. (1) Some thermal reactions between strong donors and strong acceptors are endowed with some characteristics of the photochemical reactions of weaker donor–acceptor cases. (2) Some reactions normally requiring photoinduction may take place on, or may be accelerated by, a complex formation of one of the reactants with catalysts which enhances the donor–acceptor relationship. (3) Paradoxical orbital interaction, in which the HOMO–HOMO and/or the LUMO–LUMO interactions play a dominant role, is expected to govern some significant stages of a variety of reactions in place of the normal HOMO–LUMO interaction. The regioselectivity in two types of thermal 2 + 2 cycloaddition reactions between strong donors and strong acceptors, the mechanisms of thermal and photochemical reactions via charge-transfer complexes, and the mechanisms of thermal and photochemical electrophilic substitution in aromatic systems are generally discussed with some beautiful examples.

Perturbation approaches to chemical reaction mechanisms on the basis of molecular orbital (MO) method have given rise to the concept of orbital interaction. The electron delocalization due to the interaction between the "frontier" orbitals, the highest occupied (HO) MO of donor, and the lowest unoccupied (LU) MO of acceptor contributes dominantly not only to the stabilization of the interacting system but also to the intermolecular bond formation.[1-5] There may be no room for doubt about the role of the interaction between these particular orbitals in determining the stereochemical paths of various reactions which proceed through concerted or least-motion approach of reactants. This implies that the transferred configuration involving an electron shift from the HOMO of donor to the LUMO of acceptor is of a profound importance, when we describe the interaction in terms of the configuration function. Even in nonconcerted transformations composed of several distinguishable elementary processes, a certain electron configuration can be assigned to each step of the reaction. There may, however, be a number of equivocal processes which are located between the two extremes, concerted and step-by-step mechanisms. It would be a poor approximation to discuss such reactions only in terms of HOMO–LUMO interaction, namely, in terms of interaction between the transferred configuration and the original configuration. It is necessary to take the other orbital interactions into consideration, or to perform multiconfiguration interaction analysis.

The possibility of a drastic change in stereochemical path due to an electron transfer was first pointed out by one of the present authors (K.F.) in connection with a "symmetry-forbidden"[6] reaction, an electrophilic cis-1,2 addition to olefinic double bonds.[7] From a series of papers by Epiotis[8] he developed a similar idea and discussed the mechanisms of a variety of thermal and photochemical reactions. The interactions between one transferred configuration and another, between one locally excited configuration and another, and between a transferred configuration and a locally excited configuration should be studied in order to discuss such problems in a strict way. The roles of the above configuration interactions in reaction mechanisms have not been discussed in detail so far[5] while the significance of the interaction of the original electron configuration with the transferred configuration has been fully discussed together with the interaction of the original configuration with the locally excited configuration.[9]

The purpose of the present paper is to present in general a theoretical basis of the roles of the various configuration interactions not necessarily involving the zero configuration, by analyzing the second-order perturbed wave function and the third-order perturbed energy for nondegenerate systems, and the first-order perturbed wave function and the second-order perturbed energy for degenerate systems. It is also aimed to relate the concept of such configuration interactions to the reaction mechanisms, especially to the intermediary processes between the concerted and the stepwise reactions, and between the thermal and the photochemical reactions. The current topics in organic chemistry would be quoted to visualize the theoretical concept in a chemically graspable manner.

Theoretical Background

The background of the present work is found in the perturbation theory based on the concept of configuration interaction as described in our previous paper.[5] Suppose that a ground-state molecule (A) weakly interacts with a ground-state partner (B). The occupied and the unoccupied MO's of A and those of B are denoted by the letters i, j, k, and l, respectively. We use an arrow to signify an electron shift, for instance, $i \rightarrow l$ stands for the electron transfer from the ith occupied orbital of A to the lth unoccupied MO of B, and $i \rightarrow j$ means an electron promotion from the

ith occupied MO to the jth unoccupied MO within A. An electronic state of the interacting system can be represented by a linear combination of various electronic configurations. The zero-configuration function Ψ_0 is described by a single Slater determinant composed of the originally occupied MO's of the isolated molecules. The expectation value of the total Hamiltonian H with respect to Ψ_0 includes the Coulombic and the exchange interaction energies. One can describe the transferred and the locally excited configurations by using the originally unoccupied orbitals of the isolated molecules in addition.

The secular equation for weakly interacting system is given by eq. 1. Then, the approximate solution can be expanded as[10] eq 2, in which $H_{IJ} = \int \Psi_I{}^* H \Psi_J \mathrm{d}\tau$ and $S_{IJ} = \int \Psi_I{}^* \Psi_J \mathrm{d}\tau$, and where the subscripts denote the electronic configurations. The perturbed wave function is also given by eq 3. Although it is desirable to take as many electronic configurations as possible into consideration in order to discuss the details of interaction, our present purpose needs only several interaction terms in eq 2 and 3. The magnitude of each term is, as shown in our previous paper,[5] estimated by the order of MO overlap between A and B, s_{ab}, on the assumption that the off-diagonal elements of the secular eq 1 are proportional to the overlap integrals between the configurations, S_{KL}. The general relation of overlap integrals between S_{KL} and s_{ab} is given by eq 4, in which ν is the minimum number of electron shifts between A and B required to obtain the electronic configuration K from L. The energy terms not higher than $o(s_{ab}{}^4)$ can be classified as follows (the terms derived from the mathematical equivalency between A and B are not presented for brevity).

$$\begin{vmatrix} H_{00} - E & \cdots & H_{0K} - S_{0K}E & \cdots & H_{0L} - S_{0L}E & \cdots \\ \vdots & & \vdots & & \vdots & \\ H_{K0} - S_{K0}E & \cdots & H_{KK} - E & \cdots & H_{KL} - S_{KL}E & \cdots \\ \vdots & & \vdots & & \vdots & \\ H_{L0} - S_{L0}E & \cdots & H_{LK} - S_{LK}E & \cdots & H_{LL} - E & \cdots \\ \vdots & & \vdots & & \vdots & \end{vmatrix} = 0 \tag{1}$$

$$H_{00}{}' = H_{00} + \sum_{\substack{K \\ (\neq 0)}} \frac{|H_{0K} - S_{0K}H_{00}|^2}{H_{00} - H_{KK}} + \sum_{\substack{K \\ (\neq 0)}} \sum_{\substack{L \\ (\neq 0,\, K)}} \frac{(H_{0K} - S_{0K}H_{00})(H_{KL} - S_{KL}H_{00})(H_{L0} - S_{L0}H_{00})}{(H_{00} - H_{KK})(H_{00} - H_{LL})} + (\text{small terms of higher than the third order}) \tag{2}$$

$$\Psi_0{}' = \left\{1 - \sum_{\substack{K \\ (\neq 0)}} \frac{H_{K0} - S_{K0}H_{00}}{H_{00} - H_{KK}} S_{0K} - \frac{1}{2} \sum_{\substack{K \\ (\neq 0)}} \frac{|H_{0K} - S_{0K}H_{00}|^2}{(H_{00} - H_{KK})^2} \right\} \Psi_0 + \sum_{\substack{K \\ (\neq 0)}} \left\{ \frac{H_{K0} - S_{K0}H_{00}}{H_{00} - H_{KK}} + \sum_{\substack{L \\ (\neq 0,\, K)}} \frac{(H_{L0} - S_{L0}H_{00})(H_{KL} - S_{KL}H_{00})}{(H_{00} - H_{KK})(H_{00} - H_{LL})} \right\} \Psi_K + (\text{small terms of higher than the second order}) \tag{3}$$

$$S_{KL} = o(s_{ab}{}^{\nu}) \tag{4}$$

(i) One-electron transfer from A to B

$$\sum_{i}^{\substack{\mathrm{A} \\ \mathrm{occ}}} \sum_{l}^{\substack{\mathrm{B} \\ \mathrm{uno}}} \frac{|H_{0,i\to l} - S_{0,i\to l}H_{00}|^2}{H_{00} - H_{i\to l,i\to l}} \tag{5a}$$

(ii) One-electron excitation within A

$$\sum_{i}^{\substack{\mathrm{A} \\ \mathrm{occ}}} \sum_{j}^{\substack{\mathrm{A} \\ \mathrm{uno}}} \frac{|H_{0,i\to j} - S_{0,i\to j}H_{00}|^2}{H_{00} - H_{i\to j,i\to j}} \tag{5b}$$

(iii) One-electron excitation within A induced by one-electron transfer from A to B

$$\sum_{i}^{\substack{\mathrm{A} \\ \mathrm{occ}}} \sum_{j}^{\substack{\mathrm{A} \\ \mathrm{uno}}} \sum_{l}^{\substack{\mathrm{B} \\ \mathrm{uno}}} 2 \times \left\{ \frac{(H_{0,i\to l} - S_{0,i\to l}H_{00})(H_{i\to j,0} - S_{i\to j,0}H_{00})}{(H_{00} - H_{i\to l,i\to l})(H_{00} - H_{i\to j,i\to j})} \times (H_{i\to l,i\to j} - S_{i\to l,i\to j}H_{00}) \right\} \tag{5c}$$

(iv) One-electron excitation within A induced by one-electron transfer from B to A

$$\sum_{i}^{\substack{\mathrm{A} \\ \mathrm{occ}}} \sum_{j}^{\substack{\mathrm{A} \\ \mathrm{uno}}} \sum_{k}^{\substack{\mathrm{B} \\ \mathrm{occ}}} 2 \times \left\{ (H_{0,k\to j} - S_{0,k\to j}H_{00}) \times \frac{(H_{k\to j,i\to j} - S_{k\to j,i\to j}H_{00})(H_{i\to j,0} - S_{i\to j,0}H_{00})}{(H_{00} - H_{k\to j,k\to j})(H_{00} - H_{i\to j,i\to j})} \right\} \tag{5d}$$

(v) Two-electron transfer from A to B

$$\sum_{i}^{\substack{\mathrm{A} \\ \mathrm{occ}}} \sum_{i'}^{\substack{\mathrm{A} \\ \mathrm{occ}}} \sum_{l}^{\substack{\mathrm{B} \\ \mathrm{uno}}} \sum_{l'}^{\substack{\mathrm{B} \\ \mathrm{uno}}} \frac{|H_{0,(i\to l,i'\to l')} - S_{0,(i\to l,i'\to l')}H_{00}|^2}{H_{00} - H_{(i\to l,i'\to l'),(i\to l,i'\to l')}} \tag{5e}$$

(vi) Two-electron transfer from A to B induced by one-electron transfer from A to B

$$\sum_{i}^{\substack{\mathrm{A} \\ \mathrm{occ}}} \sum_{i'}^{\substack{\mathrm{A} \\ \mathrm{occ}}} \sum_{l}^{\substack{\mathrm{B} \\ \mathrm{uno}}} \sum_{l'}^{\substack{\mathrm{B} \\ \mathrm{uno}}} 2 \left\{ \frac{(H_{0,i\to l} - S_{0,i\to l}H_{00})}{H_{00} - H_{i\to l,i\to l}} \times (H_{i\to l,(i\to l,i'\to l')} - S_{i\to l,(i\to l,i'\to l')}H_{00}) \times \frac{H_{(i\to l,i'\to l'),0} - S_{(i\to l,i'\to l'),0}H_{00}}{H_{00} - H_{(i\to l,i'\to l'),(i\to l,i'\to l')}} \right\} \tag{5f}$$

(vii) Mutual electron transfer between A and B

$$\sum_{i}^{\substack{\mathrm{A} \\ \mathrm{occ}}} \sum_{j}^{\substack{\mathrm{A} \\ \mathrm{uno}}} \sum_{k}^{\substack{\mathrm{B} \\ \mathrm{occ}}} \sum_{l}^{\substack{\mathrm{B} \\ \mathrm{uno}}} \frac{|H_{0,(i\to l,k\to j)} - S_{0,(i\to l,k\to j)}H_{00}|^2}{H_{00} - H_{(i\to l,k\to j),(i\to l,k\to j)}} \tag{5g}$$

(viii) Mutual electron transfer induced by one-electron transfer from A to B

$$\sum_{i}^{\substack{\mathrm{A} \\ \mathrm{occ}}} \sum_{j}^{\substack{\mathrm{A} \\ \mathrm{uno}}} \sum_{k}^{\substack{\mathrm{B} \\ \mathrm{occ}}} \sum_{l}^{\substack{\mathrm{B} \\ \mathrm{uno}}} 2 \times \left\{ \frac{(H_{0,i\to l} - S_{0,i\to l}H_{00})(H_{i\to l,(i\to l,k\to j)} - S_{i\to l,(i\to l,k\to j)}H_{00})}{H_{00} - H_{i\to l,i\to l}} \times \frac{H_{(i\to l,k\to j),0} - S_{(i\to l,k\to j),0}H_{00}}{H_{00} - H_{(i\to l,k\to j),(i\to l,k\to j)}} \right\} \tag{5h}$$

(ix) Mutual electron transfer induced by one-electron transfer from B to A

$$\sum_{i}^{\substack{\mathrm{A} \\ \mathrm{occ}}} \sum_{j}^{\substack{\mathrm{A} \\ \mathrm{uno}}} \sum_{k}^{\substack{\mathrm{B} \\ \mathrm{occ}}} \sum_{l}^{\substack{\mathrm{B} \\ \mathrm{uno}}} 2 \times \left\{ \frac{(H_{0,k\to j} - S_{0,k\to j}H_{00})(H_{k\to j,(i\to l,k\to j)} - S_{k\to j,(i\to l,k\to j)}H_{00})}{H_{00} - H_{k\to j,k\to j}} \times \frac{H_{(i\to l,k\to j),0} - S_{(i\to l,k\to j),0}H_{00}}{H_{00} - H_{(i\to l,k\to j),(i\to l,k\to j)}} \right\} \tag{5i}$$

The configurations which mix into the ground-state function Ψ_0' directly or indirectly are similarly obtained, the order with respect to MO overlap being not higher than second order.

(i) One-electron transfer from A to B

$$\sum_{i}^{\overset{\text{A}}{\text{occ}}} \sum_{l}^{\overset{\text{B}}{\text{uno}}} \frac{H_{i\to l,0} - S_{i\to l,0}H_{00}}{H_{00} - H_{i\to l,i\to l}} \Psi_{i\to l} \tag{6a}$$

(ii) One-electron excitation within A

$$\sum_{i}^{\overset{\text{A}}{\text{occ}}} \sum_{j}^{\overset{\text{B}}{\text{uno}}} \frac{H_{i\to j,0} - S_{i\to j,0}H_{00}}{H_{00} - H_{i\to j,i\to j}} \Psi_{i\to j} \tag{6b}$$

(iii) One-electron excitation within A induced by one-electron transfer from A to B

$$\sum_{i}^{\overset{\text{A}}{\text{occ}}} \sum_{j}^{\overset{\text{B}}{\text{uno}}} \sum_{l}^{\overset{\text{B}}{\text{uno}}} \frac{(H_{i\to l,0} - S_{i\to l,0}H_{00})(H_{i\to j,i\to l} - S_{i\to j,i\to l}H_{00})}{(H_{00} - H_{i\to l,i\to l})(H_{00} - H_{i\to j,i\to j})} \Psi_{i\to j} \tag{6c}$$

(iv) One-electron excitation within A induced by one-electron transfer from B to A

$$\sum_{i}^{\overset{\text{A}}{\text{occ}}} \sum_{j}^{\overset{\text{B}}{\text{uno}}} \sum_{k}^{\overset{\text{B}}{\text{occ}}} \frac{(H_{k\to j,0} - S_{k\to j,0}H_{00})(H_{i\to j,k\to j} - S_{i\to j,k\to j}H_{00})}{(H_{00} - H_{k\to j,i\to j})(H_{00} - H_{i\to j,i\to j})} \Psi_{i\to j} \tag{6d}$$

(v) Two-electron transfer from A to B

$$\sum_{i}^{\overset{\text{A}}{\text{occ}}} \sum_{i'}^{\overset{\text{A}}{\text{occ}}} \sum_{l}^{\overset{\text{B}}{\text{uno}}} \sum_{l'}^{\overset{\text{B}}{\text{uno}}} \frac{H_{(i\to l,i'\to l'),0} - S_{(i\to l,i'\to l'),0}H_{00}}{H_{00} - H_{(i\to l,i'\to l'),(i\to l,i'\to 1')}} \Psi_{i\to l,i'\to l'} \tag{6e}$$

(vi) Two-electron transfer from A to B induced by one-electron transfer from A to B

$$\sum_{i}^{\overset{\text{A}}{\text{occ}}} \sum_{i'}^{\overset{\text{A}}{\text{occ}}} \sum_{l}^{\overset{\text{B}}{\text{uno}}} \sum_{l'}^{\overset{\text{B}}{\text{uno}}} \frac{H_{i\to l,0} - S_{i\to l,0}H_{00}}{H_{00} - H_{i\to l,i\to l}} \frac{H_{(i\to l,i'\to l'),i\to l} - S_{(i\to l,i'\to l'),i\to l}H_{00}}{H_{00} - H_{(i\to l,i'\to l'),(i\to l,i'\to l')}} \Psi_{i\to l,i'\to l'} \tag{6f}$$

(vii) Mutual electron transfer between A and B

$$\sum_{i}^{\overset{\text{A}}{\text{occ}}} \sum_{j}^{\overset{\text{A}}{\text{uno}}} \sum_{k}^{\overset{\text{B}}{\text{occ}}} \sum_{l}^{\overset{\text{B}}{\text{uno}}} \frac{H_{(i\to l,k\to j),0} - S_{(i\to l,k\to j),0}H_{00}}{H_{00} - H_{(i\to l,k\to j),(i\to l,k\to j)}} \Psi_{i\to l,k\to j} \tag{6g}$$

(viii) Mutual electron transfer induced by one-electron transfer from A to B

$$\sum_{i}^{\overset{\text{A}}{\text{occ}}} \sum_{j}^{\overset{\text{A}}{\text{uno}}} \sum_{k}^{\overset{\text{B}}{\text{occ}}} \sum_{1}^{\overset{\text{B}}{\text{uno}}} \frac{(H_{i\to 1,0} - S_{i\to l,0}H_{00})(H_{(i\to l,k\to j),i\to l} - S_{(i\to l,k\to j),i\to l}H_{00})}{(H_{00} - H_{i\to l,i\to l})(H_{00} - H_{(i\to l,k\to j),(i\to l,k\to j)})} \times \Psi_{i\to l,k\to j} \tag{6h}$$

(ix) Mutual electron transfer induced by one-electron transfer from B to A

$$\sum_{i}^{\overset{\text{A}}{\text{occ}}} \sum_{j}^{\overset{\text{A}}{\text{occ}}} \sum_{k}^{\overset{\text{B}}{\text{uno}}} \sum_{l}^{\overset{\text{B}}{\text{uno}}} \frac{(H_{k\to j,0} - S_{k\to j,0}H_{00})(H_{(i\to l,k\to j),k\to j} - S_{(i\to l,k\to j),k\to j}H_{00})}{(H_{00} - H_{k\to j,k\to j})(H_{00} - H_{(i\to l,k\to j),(i\to l,k\to j)})} \times \Psi_{i\to l,k\to j} \tag{6i}$$

The roles of one-electron transfer (eq 5a and 6a) and one-electron local excitation (eq 5b and 6b) in mechanisms of chemical reactions have been fully examined and discussed already.[5] One can say that the electron delocalization from the HOMO of donor to the LUMO of acceptor, i.e., the interaction between the transferred configuration and the zero configuration, contributes dominantly to the stabilization of the interacting system of neutral or weakly polar species. It is, however, likely that the polarization energy due to the interaction between the locally excited configuration and the zero configuration, and the Coulombic energy contained in H_{00} may play considerable roles in the interaction between charged or highly polarizable species. Let us focus our attention to the other interaction terms. The choice of the terms to be considered of importance here has been made at first by estimating the magnitude of the numerators based upon the MO overlap ($s_{ab}{}^{\nu}$). It is necessary, moreover, to select relatively significant terms among them by looking at the magnitude of the denominators. On this assumption, the terms involving two-electron transfer may be omitted, since the energy gaps between the zero configuration and the two-electron transferred configurations are usually so large as compared with the ones between the zero configuration and one-electron transferred or locally excited configurations. The terms in eq 5e–5i and 6e–6i are expected to contribute little. It may be reasonable to concentrate our attention on the terms in eq 5c, 5d, 6c, and 6d.

The third-order perturbation energy terms, eq 5c and 5d, contain a transferred configuration and a locally excited configuration. The interpretation of the configuration interaction between the two is not necessarily unequivocal. They may be interpreted as the local excitation induced by the charge transfer or as the delocalization induced by the local excitation. The ambiguity is eliminated by the absence of the terms interpreted as the charge transfer induced by the local excitation and the presence of the terms interpreted as the local excitation induced by the charge transfer in the perturbed wave function (eq 6c and 6d). The nonequivalent contributions from $\Psi_{i\to l}$ and $\Psi_{i\to j}$ (eq 6c) and that from $\Psi_{k\to j}$ and $\Psi_{i\to j}$ (eq 6d) to the second-order perturbed wave function are owing to the difference in the order between the interactions of $\Psi_{i\to l}$ and $\Psi_{i\to j}$ with Ψ_0. The order of the delocalization (former) is $o(s_{ab}{}^1)$ while the polarization (latter) is $o(s_{ab}{}^2)$. As a result, the terms in eq 5c and 6c represent the $i \to j$ local excitation within A induced by the $i \to l$ transfer from A to B. The process involves the interactions among the zero (0), the transferred $K(i \to l)$, and the locally excited $L(i \to j)$ configurations, as depicted in Figure 1a. The other mode of the $i \to j$ local excitation within A is induced by the $k \to j$ transfer from B to A, represented by eq 5d and 6d. In this case the $k \to j$ transferred configuration is involved in place of the $i \to l$ configuration (Figure 1b). One can imagine the process in which an electron transfers from i to l and then moves to j, while a hole in k, resulting from the $k \to j$ electron transfer, is filled with an electron from i.[7,8,11] Hereafter, we may call the local excitation induced by the charge transfer simply as "(chemical) pseudoexcitation".[12] A theoretical reasoning should be made for emphasizing the role of the higher-order

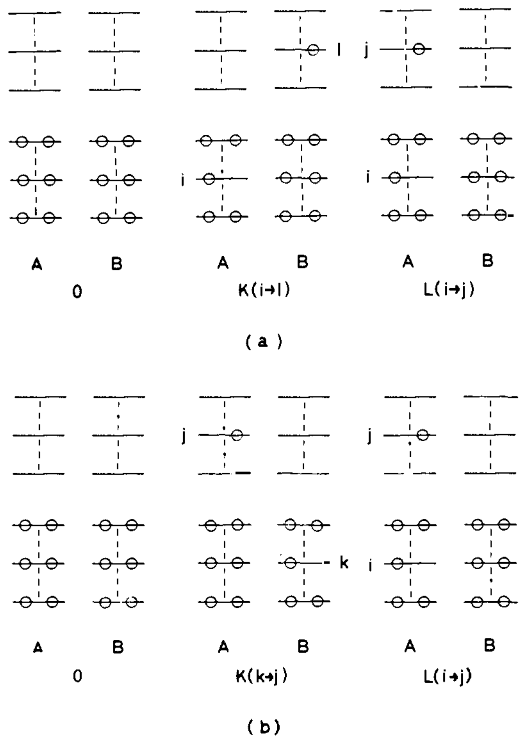


Figure 1. Pseudoexcitation within the A molecule induced by charge transfer from A to B (a) and from B to A (b).

local excitation terms (eq 5c, 5d, 6c, and 6d) rather than that of the lower-order terms (eq 5b and 6b). Both perturbation terms are of the same orders with respect to MO overlap: s_{ab}^4 in H_{00}' and s_{ab}^2 in Ψ_0'. However, the higher-order terms are likely to contribute more greatly in the case that the energy separation of the transferred configuration from the zero configuration gets smaller.

The circumstances can be grasped in much more straightforward manner if we apply the perturbation theory for the degenerate system. It can be assumed that a very strong charge transfer is represented better by the degenerate combination of the zero configuration 0 and one of the transferred configurations (D), i.e., $H_{DD} \sim H_{00}$. In such a case, the perturbed energy H_{00}' and the perturbed wave function Ψ_0' are given as follows.

$$H_{00}' = H_{00} - \left|H_{0D} - S_{0D}H_{00}\right| + \frac{1}{2}\left[\sum_{\substack{K \\ (\neq 0, D)}} \left\{ \frac{|H_{0K} - S_{0K}H_{00}|^2}{H_{00} - H_{KK}} + \frac{|H_{DK} - S_{DK}H_{00}|^2}{H_{00} - H_{KK}} \right\} - 2\sum_{\substack{K \\ (\neq 0, D)}} \left\{ \frac{(H_{0D} - S_{0D}H_{00})(H_{DK} - S_{DK}H_{00})(H_{K0} - S_{K0}H_{00})}{|H_{0D} - S_{0D}H_{00}|(H_{00} - H_{KK})} \right\} - 2\{(H_{D0} - S_{D0}H_{00})S_{0D}\} \right] + \text{(small terms of higher than the second order)} \quad (7)$$

$$\Psi_0' = \frac{1}{\sqrt{2}}\left\{1 - \frac{1}{2}\frac{(H_{D0} - S_{D0}H_{00})}{|H_{0D} - S_{0D}H_{00}|} S_{0D}\right\}\left[\Psi_0 + \frac{(H_{D0} - S_{D0}H_{00})}{|H_{0D} - S_{0D}H_{00}|}\Psi_D + \sum_{\substack{K \\ (\neq 0, D}} \left\{ \frac{H_{K0} - S_{K0}H_{00}}{H_{00} - H_{KK}} + \frac{(H_{D0} - S_{D0}H_{00})(H_{KD} - S_{KD}H_{00})}{|H_{0D} - S_{0D}H_{00}|(H_{00} - H_{KK})} \right\} \Psi_K \right] + \text{(small terms of higher than the first order)} \quad (8)$$

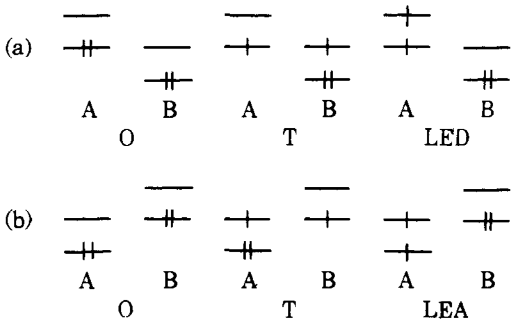


Figure 2. A simplified CI presentation of the pseudoexcitation within donor (a) and within acceptor (b).

The orders of the terms involving the degenerate transferred configuration are lower by one in the degenerate system than in the nondegenerate system. Accordingly, the pseudoexcitation would be conspicuous by way of the interaction with the electron transferred configuration (D), while the mixing-in of the locally excited configurations through the direct interaction with the zero configuration remains intact in the perturbation formulas for the degenerate system. The coefficients of the locally excited configuration Ψ_K, $(H_{D0} - S_{D0}H_{00})(H_{KD} - S_{KD}H_{00})/|H_{0D} - S_{0D}H_{00}|(H_{00} - H_{KK})$ $(o(s_{ab}^1))$, are greater than $(H_{K0} - S_{K0}H_{00})/(H_{00} - H_{KK})$ $(o(s_{ab}^2))$. The same results are also obtained from the perturbed energy (eq 7). The second-order energy $|H_{0K} - S_{0K}H_{00}|^2/(H_{00} - H_{KK})$ is $o(s_{ab}^4)$ while the energy to be compared, $(H_{0D} - S_{0D}H_{00})(H_{DK} - S_{DK}H_{00})(H_{K0} - S_{K0}H_{00})/|H_{0D} - S_{0D}H_{00}|(H_{00} - H_{KK})$, is $o(s_{ab}^3)$. In addition, a new term $|H_{DK} - S_{DK}H_{00}|^2/(H_{00} - H_{KK})$ $(o(s_{ab}^2))$ appears in the perturbed energy for the degenerate system. This term originates from the fourth-order perturbation energy in the nondegenerate system. This can be understood by noting that the transferred configuration and the zero configuration have the same amplitude in the degenerate system.

One can readily see the importance of the configurations where the electron shift involves the HOMO's and the LUMO's, since such configurations are close enough to the zero configuration in energy to make the energy gaps in the denominators the smallest. Let the pseudoexcitation be represented by a simplified CI. The particular MO's of importance are employed in the presentation. The configurations involved in the pseudoexcitation within A induced by the charge transfer from A to B are the zero configuration (0), the transferred configuration (T), where one electron is shifted from the HOMO of A to the LUMO of B, and the locally excited configuration (LED), where one electron is promoted from the HOMO of A to the LUMO of A within the donor, as depicted in Figure 2a. Similarly, the pseudoexcitation within A induced by the charge transfer from B to A is represented by the CI among 0, T and the locally excited configuration (LEA), where the electron promotion occurs from the HOMO to the LUMO within the acceptor A, as depicted in Figure 1b.

Consequently, one can reach the following conclusions.

Rule 1. Some thermal reactions between good donors and good acceptors may tend to exhibit some characteristics which are common with the photochemical reactions of weak donor-acceptor systems.

Rule 2. Some reactions normally requiring photoinduction are expected to be brought about in the absence of light source, or to be promoted, by the catalysts which enhance the donor-acceptor relation through a complex formation with one of the reactants.

An important reservation with rule 1 must be made here. Remark 1: a combination of excessively strong donor and

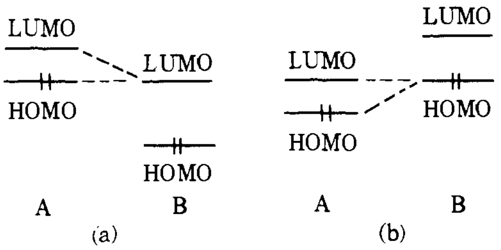


Figure 3. The key orbital interactions for the pseudoexcitation within donor (a) and for that within acceptor (b).

strong acceptor may give rise to a pair of stable cation and anion radicals, may dissociate in solution, may bind loosely, or may stay too stable to undergo the reactions expected from the pseudoexcitation effect.

This is the case with $H_{00} > H_{TT}$. The perturbed ground-state energy and wave function of such a case are given by the expansion at $E = H_{TT}$.

$$H_{TT}' = H_{TT} + \sum_{K} \frac{|H_{TK} - S_{TK}H_{TT}|^2}{KH_{TT} - H_{KK}} + \ldots \quad (9)$$

$$\Psi_T' = \Psi_T + \sum_{K} \frac{H_{KT} - S_{KT}H_{TT}}{H_{TT} - H_{KK}} \Psi_K + \ldots \quad (10)$$

The second terms in the right-hand side include those which come from the mixing-in of 0, LED, and LEA configurations. The inequality $|H_{00} - H_{TT}| < |H_{\mathrm{LED,LED}} - H_{TT}| \sim |H_{\mathrm{LEA,LEA}} - H_{TT}|$ can be assumed usually in this case and the difference in the absolute values is expected to be large as the H_{TT} is low. These mean that excessively strong charge transfer may stabilize the system mainly due to the relative increase in the contribution from the zero configuration to the ground-state wave function. The mixing-in of the zero configuration predominates over that of LED and LEA configurations to the extent to which the T configuration predominates over the other transferred configurations in the normal ground-state interaction ($H_{00} < H_{TT}$).

It is desirable and practical to reduce the CI expression at the MO level. The third energy term, eq 5c, or the pseudoexcitation $i \rightarrow j$ induced by electron transfer $i \rightarrow l$ contains the product of the overlap integrals between the configuration, $S_{0,i\rightarrow l}S_{i\rightarrow l,i\rightarrow j}S_{i\rightarrow j,0}$. The product is reduced to the form of the MO overlap product $s_{il}^2 s_{lj}^2$. The product $S_{0,k\rightarrow j}S_{k\rightarrow j,i\rightarrow j}S_{i\rightarrow j,0}$ in the pseudoexcitation term, eq 5d, is reduced to the form $s_{ki}^2 s_{ik}^2$.

Let the HOMO's and the LUMO's be i and k, and j and l, respectively. One can then see that the pseudoexcitation within A induced by the charge transfer from A to B needs the effective $(\mathrm{HOMO})_{\mathrm{A}}$-$(\mathrm{LUMO})_{\mathrm{B}}$-$(\mathrm{LUMO})_{\mathrm{A}}$ interaction (Figure 3a), and that the pseudoexcitation within A induced by the charge transfer from B to A involves the $(\mathrm{HOMO})_{\mathrm{A}}$-$(\mathrm{HOMO})_{\mathrm{B}}$-$(\mathrm{LUMO})_{\mathrm{A}}$ interaction (Figure 3b). The same conclusion can be readily drawn from the second-order terms, eq 6c and 6d, in the perturbed wave function. This is also the case with the perturbation formulas for the degenerate system.

One can reach the third rule accordingly.

Rule 3: the stereochemical course of the reaction, in which the initial HOMO-LUMO interaction directly leads to no stable species and leaves the possibility of selecting one of energetically equivalent or nearly so courses may be determined by the pseudoexcitation, namely, by the HOMO-HOMO interaction or by the LUMO-LUMO interaction.

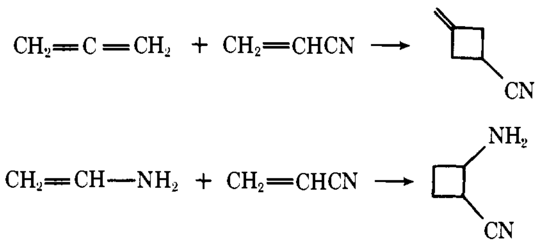
An important remark should also be made with rule 3. Remember the dynamic aspect of chemical reaction. The pseudoexcitation is induced by the charge transfer. The HOMO-LUMO interaction predominant at the early stage may lead the interacting system to one stereochemical course separated from another by a high energy barrier between them. In such a case, even if the pseudoexcitation occurs in the subsequent process appreciably, the effect is expected to be little on the reaction course, since the pseudoexcitation takes place within the framework determined by the HOMO-LUMO interaction.

Remark 2: the HOMO-HOMO interaction or the LUMO-LUMO interaction does not necessarily determine the stereochemical course of the reactions in which the pseudoexcitation occurs considerably.

A Semiempirical MO Study on Regioselectivity of Thermal 2 + 2 Cycloaddition Reactions

Concerted 2 + 2 cycloaddition reactions are a typical class of excited-state reactions.[6] The addition of electron-donating olefins to strong acceptors, $^1\Delta_g$ molecular oxygen,[13] benzyne,[14] cyano-substituted olefin,[15] azodicarboxylic ester,[16] ketene,[17] keteneimmonium cation,[18] chlorosulfonyl isocyanate,[19] and sulfur trioxide,[20] is, however, known to take place stereoselectively with the retention of the initial configuration of the olefins. These facts support the validity of rule 1. Recent theoretical investigations have suggested that thermal 2 + 2 donor-acceptor condensation reactions may be initiated by the three-centered interaction between the two p orbitals of donor and one of the p orbitals of acceptor,[21-24] followed by the rotation of the acceptor molecule to form the final four-membered ring product.[21,25] The three-centered interaction in the initiation stage was found to be governed by the normal HOMO-LUMO interaction.[23-25] The growing contribution from the transferred configuration to the ground-state wave function, resulting from the foregoing HOMO-LUMO interaction, may facilitate the rotation process through the pseudoexcitation. The interaction between the transferred configuration and the locally excited configuration allows the HOMO-HOMO and the LUMO-LUMO interaction.[25,26] It has been confirmed by a spectroscopic and kinetic study that the thermal 2 + 2 cycloaddition reactions between vinyl ethers and tetracyanoethylene consist of successive charge transfer and cycloaddition processes.[27]

Here we will attempt to investigate the possible mechanisms of the regioselectivity-determining step in the 2 + 2 cycloaddition reactions. The regioselectivity may be considered to be determined by the direction in which the atom of acceptor with the largest LUMO amplitude, constituting the transient three-membered ring at the early stage, moves preferentially. A typical reaction is the addition of allene with acrylonitrile.[28] The terminal carbon of acrylonitrile with the largest LUMO amplitude is known to be combined with the central carbon of allene with the smaller HOMO and the larger LUMO amplitudes. The combination is paradoxical in the sense that the atom of the donor with the *smaller* HOMO amplitude forms a bond with the atom of the acceptor with the largest LUMO amplitude. Similar regioselectivity was observed in the reactions of acrolein and of acrylic esters as acceptors.[28]



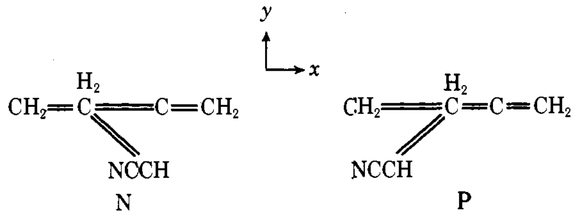


Figure 4. Arrangements of reactants with the normal (N) and the paradoxical (P) orbital interactions.

Another typical reaction is the addition of aminoethylene with acrylonitrile, a simplified model of the reactions of enamines with acrylonitrile,[29] and with propiolate esters.[30] In these cases, the cycloadducts are produced through the normal combination between the β carbon of the donor with the largest HOMO amplitude and the β carbon of the acceptor with the largest LUMO amplitude.

We analyzed atomic orbital (AO) overlap population in order to scrutinize the regioselectivity-determining step. Molecular arrangement at the relevant reaction stage is assumed to be a transient one in which the three-centered interaction geometry is just being transformed to four-membered ring product. This assumption is supposed to be reasonable according to a series of theoretical investigations on the nuclear configuration change along the reaction coordinate as cited before. Now let us compare the two modes of interactions of olefins, for instance, allene and acrylonitrile. The electrophilic center of acrylonitrile was located 1.75 Å above the middle point between the nucleophilic terminal carbon and the center of the C=C bond of allene in N-type interaction, while the carbon of acrylonitrile was placed 1.75 Å above the point halfway from the middle point of a C=C bond to the central carbon of allene in P-type interaction. The planes of the donor and the acceptor were kept parallel and acrylonitrile was rotated by 45° clockwise or counterclockwise to simulate the course of ring closing (Figure 4).

The AO overlap populations, calculated by the extended Hückel MO method,[31] are partitioned into the contributions from each pair of MO's between allene and acrylonitrile.[32] The results of the analysis of the AO overlap population between the p orbital of the electrophilic carbon of acrylonitrile and the terminal carbon of allene in the N model and between the former and the central carbon of allene in the P model are listed in Table I. A similar analysis is also made for the aminoethylene–acrylonitrile system (Table II). The orbitals having the maximum extention in the Z direction are designated by the next (N) HOMO, HOMO, LUMO, and NLUMO. The preference of P to N in the allene–acrylonitrile system, consistent with the experimental observations, is seen in the AO overlap populations, 0.157 in N and 0.175 in P. The difference is attributed mainly to the preferential contribution from the LUMO–LUMO interaction (0.103) in the P model. The dominant contribution in the N model is 0.089 owing to the HOMO–LUMO interaction. The partial AO population coming from the HOMO–HOMO interaction is not as large in both of the models. This calculation suggests that the regioselectivity of the reaction of allene with acrylonitrile is controlled for the most part by the pseudoexcitation within the donor while the pseudoexcitation within the acceptor is of minor effect. In the reaction of aminoethylene the HOMO–LUMO interaction (0.070 in N and 0.032 in P) together with the pseudoexcitation within the acceptor (0.048 in N and 0.022 in P) determines the regioselectivity while the effect of the pseudoexcitation within the donor is comparable in both models, though large (0.072 in N and 0.073 in P).

Table I. Analysis of AO Overlap Populations of Allene and Acrylonitrile[a]

	Acrylonitrile			
Allene	NHOMO	HOMO	LUMO	NLUMO
N (total AO overlap population 0.157)				
NHOMO	0.000	0.000	0.005	−0.001
HOMO	0.001	0.042	0.089	0.008
LUMO	−0.001	−0.024	0.037	0.001
NLUMO	0.000	0.000	0.000	0.000
P (total AO overlap population 0.175)				
NHOMO	0.000	0.006	0.013	0.002
HOMO	0.002	0.042	0.042	0.004
LUMO	−0.005	−0.039	0.103	0.006
NLUMO	0.000	0.000	−0.001	0.000

[a] Analysis of AO overlap population between p_z-AO on the terminal carbon of allene and p_z-AO on the terminal carbon of acrylonitrile (N) and that between p_z-AO on the central carbon of allene and p_z-AO on the terminal carbon of acrylonitrile (P).

Table II. Analysis of AO Overlap Populations of Aminoethylene and Acrylonitrile[a]

	Acrylonitrile			
Aminoethylene	NHOMO	HOMO	LUMO	NLUMO
N (total AO overlap population 0.185)				
NHOMO	0.000	0.007	0.015	0.003
HOMO	0.003	0.048	0.070	0.005
LUMO	−0.004	−0.040	0.072	0.006
P (total AO overlap population 0.147)				
NHOMO	0.001	0.017	0.032	0.004
HOMO	0.001	0.022	0.032	−0.002
LUMO	−0.002	−0.029	0.073	−0.002

[a] Analysis of AO overlap population between p_z-AO's on C_α of aminoethylene and on the terminal carbon of acrylonitrile (P) and that between the p_z-AO's on C_β of aminoethylene and on the terminal carbon of acrylonitrile.

The difference in the regioselectivity mentioned above is supposed to result from the property of the donor HOMO. The perturbation of the ethylenic π orbital due to the neighboring groups, i.e., a lone pair of electrons of the amino group and the C–H σ bond of methylene, may be different appreciably in strength. The lone-pair orbital lies so high as to produce strong polarization leading to the concentration of the HOMO electron density on the terminal carbon of aminoethylene, while the C–H bond orbital of allene is located too low to interact effectively with the ethylenic π orbital. The highly polarized HOMO of aminoethylene may cause the breaking of the three-centered structure at the relatively earlier stage of the reaction since the HOMO–LUMO interaction between the terminal carbon of acrylonitrile and the β carbon of enamine stabilizes the system (remark 2). In contrast, the three-centered structure may continue to exist longer in the approach of acrylonitrile to allene.

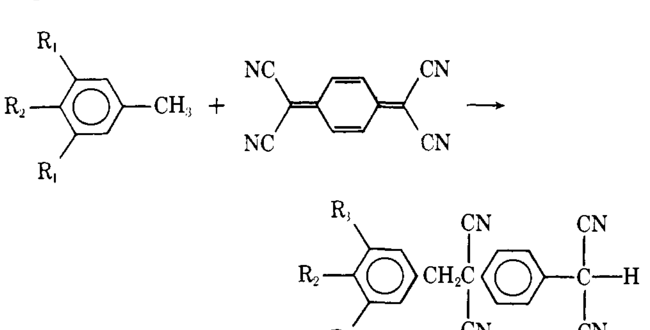
At the three-centered geometry, the HOMO–LUMO charge-transfer interaction and the pseudoexcitation within the acceptor involving the HOMO–HOMO interaction can take place sufficiently, while the pseudoexcitation within the donor involving the LUMO–LUMO interaction can hardly be of importance on account of orbital symmetry. Accordingly the pseudoexcitation within the donor is expected to control the orientation of the electrophilic center of acrylonitrile in the second stage. The effect of the orbital interaction on the regioselectivity-determining step of the allene–acrylonitrile condensation reaction is paradoxical in the sense that the LUMO, instead of the HOMO, of the donor play a significant role in governing the stereoselection even on the thermal condition.

Remark 1 must be noted again in connection with the mechanism of the thermal 2 + 2 donor-acceptor condensation reactions. A too strong charge transfer does not necessarily promote the reactions requiring the pseudoexcitation. An experimental evidence is now available. In fact it was recently reported that the rate of the thermal 2 + 2 cycloaddition reaction between vinyl ethers and tetracyanoethylene has an optimum with respect to the changes in the strength of charge-transfer interaction.[27]

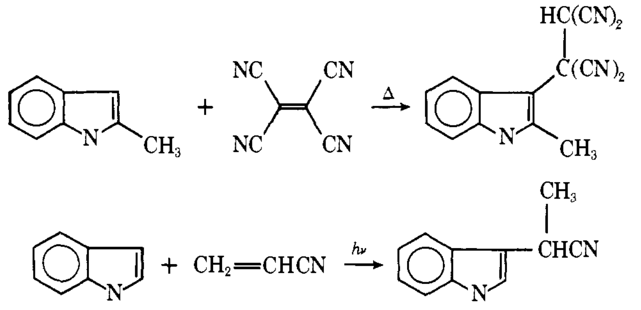
It is meaningful to compare briefly the thermal 2 + 2 cycloaddition reactions with the Diels-Alder reactions and with the 1,3-dipolar cycloaddition reaction. The regioselectivity of the concerted reactions has been understood in terms of the normal orbital interaction effect or the interaction of the HOMO of the donor with the LUMO of the acceptor; the chemical combinations usually occur between the atom of the donor with the largest HOMO amplitude and the atom of the acceptor with the largest LUMO amplitude.[33] The concerted cycloaddition reactions can be discussed generally based on the symmetry of the relevant "frontier" orbitals without invoking the significant geometry change on the course of the reaction to the final product. On the contrary, the 2 + 2 thermal cycloaddition reactions should inevitably require the sufficient mixing-in of the locally excited configurations, with the peculiar change in the relative orientation of the reactants.

Applications

The continuity between the photochemical and the thermal reactions is exemplified here. The reactions of electron-donating toluene derivatives with electron-accepting 7,7,8,8-tetracyanoquinodimethane (TCNQ) provide us with an elegant example of rule 1. The stronger donors, mesitylene (R_1 = Me, R_2 = H)[34] and *p*-methoxytoluene (R_1 = H, R_2 = OMe),[35] react only on heating with TCNQ, while in the case of the weaker donors, toluene ($R_1 = R_2$ = H) and *p*-xylene (R_1 = H, R_2 = Me), the photoirradiation is required. The addition reactions may be initiated by the charge transfer from the aromatics to TCNQ. Strong charge transfer may induce the pseudoexcitation with the electron promotion in the toluenes, presumably, from the HOMO to the σ LUMO of the benzylic C-H to be abstracted, through the LUMO of TCNQ. The LUMO-LUMO interaction (rule 3) may be of key importance in the final stage of the chemical transformation while the normal HOMO-LUMO interaction predominates in the stage of the complex formation.

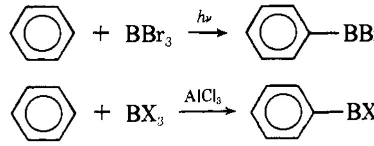


Another example, although not systematically investigated, is found in the reactions of indoles with cyanoethylenes. The reaction of tetracyanoethylene with 2-methylindole gives 2-methyl-3-tetracyanoethylindole in a quantitative yield at room temperature under no irradiation.[36] As indoles are known to form immediately a deep blue-black colored π complex with tetracyanoethylene,[37] this reaction may also take place through the charge transfer accompanied by the pseudoexcitation. A weaker acceptor, acrylonitrile, requires photoinduction to cause a similar kind of reaction, α-cyanoethylation on the 3 position of indoles.[38] On the basis of the fact that the charge-transfer band is absent in the absorption spectra and that the fluorescence of indole is effectively quenched by acrylonitrile, a mechanism of α-cyanoethylation was proposed which involves the direct excitation of indoles followed by the exciplex formation.[38] The donor-acceptor relationship between indoles and acrylonitrile may not be so remarkable as to cause appreciable pseudoexcitation. In the case of the reaction of less distinct donor-acceptor systems, benzene-pyrrole[39] and naphthalene-pyrrole,[40] the mechanism involving the direct excitation was also proposed.



A remarkable effect of $ZnCl_2$ observed in the photochemical reactions of benzene with acrylonitrile[41] should be noted here in connection with the role of catalysts in the pseudoexcitation processes (rule 2). The yield of 1,2 cycloadduct of benzene with acrylonitrile in the photochemical reaction increases more than five times in the presence of $ZnCl_2$. The increase in the yield may be attributed to the pseudoexcitation enhanced or introduced through the complex formation of acrylonitrile with $ZnCl_2$. Another example to show the significance of catalyst is the ground-state 2 + 2 cycloaddition reactions between the acetylenic compounds and the carbonyl compounds, modified by BF_3.[42] The mechanism of the thermal oxetane formation of highly electron-accepting carbonyl compounds has been fully discussed in our previous paper.[25b] The essential feature has been found to be quite similar to the singlet oxygen reactions.[24,25a] It has been recognized that a Lewis acid, BF_3, induces the 2 + 2 cycloaddition even between a weak donor and a weak acceptor.[42] This fact is completely explained by rule 2.

Electrophilic substitution reactions of aromatic compounds provide the preceding theoretical arguments with an experimental support. The substitution reactions are usually caused by strong electrophiles in the thermal conditions. Recently an aromatic substitution with a weak electrophile, boron tribromide, was reported to occur through charge-transfer complex on the photoirradiation, while no detectable reaction took place in the dark.[43] Heating the reaction system without light afforded the different products, presumably derived from the homolysis of BBr_3.[43] The photohaloboronation supports rule 1. It is further interesting that $AlCl_3$ has been reported to enable the haloboronation to take place readily on the thermal condition.[44] This can be explained by means of rule 2.



Discussion

The attempt of Epiotis[8] to give a rationale to the facility and the selectivity of the ground-state 2 + 2 cycloaddition reactions was appropriate in the sense that he proposed the significance of the transferred configuration in a strong charge-transfer interaction between the reactants. It may be worth referring to the dynamic aspects of the mechanism of the reactions appreciably involving the pseudoexcitation. The mechanism of the thermal 2 + 2 cycloaddition reaction of the strong donor-acceptor system proposed by the present authors[22] should be distinguished from the s + s and the s + a processes of Woodward and Hoffmann.[6] According to our proposed mechanism, the reaction should begin with the cyclic three-centered interaction among the two nucleophilic atoms of donor and a more electrophilic atom of the acceptor.[21-25] The other atom of the acceptor is far away from the interaction center in the initial stage of the reaction. This supposition came from the consideration of the most favorable interaction between the HOMO of the donor and the LUMO of the acceptor.[22-25,45] At the early stage, the charge transfer from the donor to the acceptor and the accompanied pseudoexcitation within the acceptor are allowed to take place, but the pseudoexcitation within the donor cannot occur because Ψ_{LED} belongs to a symmetry different from that of the other dominant configurations. Then, the wave function of this state Ψ_0' is approximately given by

$$\Psi_0' \sim C_0\Psi_0 + C_T\Psi_T + C_{\mathrm{LEA}}\Psi_{\mathrm{LEA}}$$

$$(C_0 \gtrsim C_T > C_{\mathrm{LEA}}, C_{\mathrm{LED}} = 0) \qquad (11)$$

Subsequently, the rotation of the acceptor molecule leading to the four-membered ring product makes possible the pseudoexcitation within the donor. The transient state is similarly approximated by

$$\Psi_0' \sim C_0\Psi_0 + C_T\Psi_T + C_{\mathrm{LEA}}\Psi_{\mathrm{LEA}} + C_{\mathrm{LED}}\Psi_{\mathrm{LED}}$$

$$(C_0 \sim C_T \sim C_{\mathrm{LEA}} \sim C_{\mathrm{LED}}) \qquad (12)$$

In the above case the regioselectivity may be controlled by the pseudoexcitation within the donor, or by the LUMO-LUMO interaction, which newly appears on the breaking of the three-centered structure. In another case the electronic state of the interacting system even at the beginning of the reaction can be described by eq 12, where the coefficients C_0 and C_T dominate over the others. This means that the regioselectivity is determined by the HOMO-LUMO interaction. The selection of the reaction course depends solely on whether the donor HOMO amplitude is localized mainly on one atom or delocalized uniformly between the two, as exemplified.

The significance of the three-centered geometry at the early stage is, though indirectly, supported by some experimental results. An episulfoxide, dibenzoylstilbene episulfoxide, was reported to be photochemically converted to the decomposition products, monothiobenzil and benzil, presumably via a four-membered ring intermediate, oxathietane.[46] It is interesting that the rearrangement of the episulfoxide to oxathietane requires the photoinduction while the reaction of olefins with $^1\Delta_g$ molecular oxygen to dioxetane through a perepoxide quasiintermediate[25a] takes place "thermally". This difference can be explained in terms of the difference in the electron acceptability between O_2 and SO parts (rule 1). Another evidence is provided by the fact that the partial loss of the stereochemical integrity occurs in the acceptor molecule while the stereochemistry of donor is retained.[15c] This may come from our proposal that the stereochemistry of donor is fixed by the three-centered interaction while the tailing atom of the reacting centers in the acceptor is possible to rotate at the early stage.[47]

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General Methods of Synthetic Analysis. Strategic Bond Disconnections for Bridged Polycyclic Structures

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Abstract: A general procedure has been developed for the analysis of bridged polycyclic molecular networks to identify those bond disconnections most apt to lead to synthetically accessible precursor structures. This procedure has been implemented in LHASA-10, the Harvard program for computer-assisted synthetic analysis, and it has been utilized in various ways for goal generation to guide antithetic operations. Examples are given to illustrate the use of the strategic bond method, its limitations, and possible refinement. An evaluation of the method based upon a comparison with current synthetic practice is presented. The techniques and strategies described herein are also relevant to human problem solving.

The strategy devised by a synthetic chemist for the construction of a complicated molecule is usually related specifically to particular aspects of the structure in question or to particular "key" chemical reactions which seem unusually suitable for the synthesis. Until recently[1] there has not been much concern for the development of more general strategies of synthesis which could be applied to a *wide range* of problems. Such strategies are operative at a higher level in the sense that they can assist in finding the "*ad hoc*" strategies which are restricted or tailored to an individual problem. One of the objectives of our project to devise a program for computer-assisted synthetic analysis has been the development of well-defined, *general* synthetic strategies[1a] and their testing to determine scope, power, and possible utility in the pedagogy and practice of synthetic chemistry.

Whether a problem-solving strategy is aimed at reducing the time and effort required to find a plausible solution or at the discovery of an unusually simple and effective solution, it may be characterized in terms of its position in a hierarchical collection of strategies, its objectives, its relationship to other strategies, its scope, its power, and its utility. Strategies for use in synthetic analysis by chemists may take the form of definite procedures or more flexible "guidelines". (In the extreme, the human intellect must even be capable of using subtle strategies of which it is not even consciously aware.) An example of a strict procedural (or algorithmic) strategy is the choice[1b] of a rigorously antithetic[1a] (retrosynthetic) mode of synthetic analysis.[2] An example of a more flexibly used strategy is the recognition of the merit of "convergence" [3] in a synthesis and the use of this as a "guideline" in the analysis of a particular problem. In this case the objective of the strategy is clear but, since the means of achieving that objective are not delineated, the application of the strategy is pragmatic.

The Harvard program for computer-assisted synthetic analysis (LHASA-10) is highly interactive and allows virtually unlimited input and decision making by the chemist-