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- explicitly assumes the predominant importance of the charge in the bonding region, Levine has pointed out to us that the model in fact indirectly includes the effect of nonbonding charge since it uses linear susceptibilities to determine unknown parameters. This is probably an important reason for the success of the model.
 (17) The bond additivity approximation, used in analyzing the experimental data, is independent of the bond charge model.

Spin Inversion in Triplet Diels–Alder Reactions

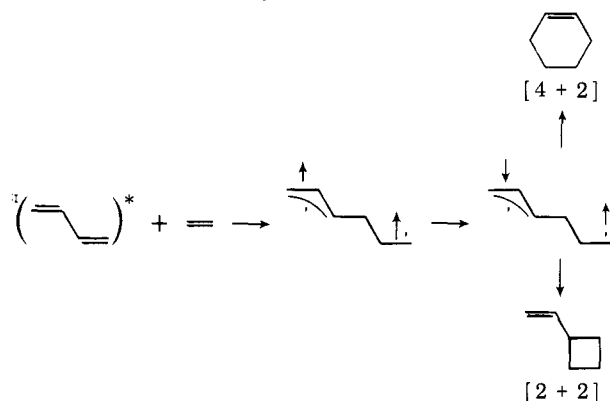
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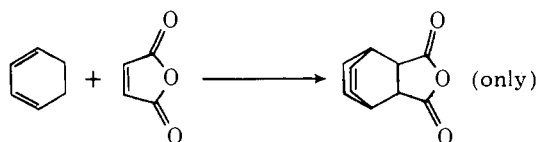
Abstract: Spin inversion in triplet $[\pi 4_s + \pi 2_s]$ complexes can be induced by stereochemically different mechanisms. Consequently, triplet Diels–Alder reactions can be 4s + 2s stereospecific, 4s + 2a (4a + 2s) stereospecific, or stereorandom. The selection of one mechanism depends on the donor–acceptor relationship and the triplet energies of the reactants. It is predicted that enhancing the donor–acceptor relationship of the reactants, i.e., increasing the reaction polarity, will increase 4s + 2s product formation relative to all other products. On the other hand, decreasing the triplet energies, at constant polarity, will result in predominant 4s + 2a product formation. Solvent polarity will have a more pronounced effect on the yield of 4s + 2s adducts. The competition of [4 + 2] and [2 + 2] cycloaddition is discussed. It is predicted that the [4 + 2]/[2 + 2] product ratio will increase as polarity increases and it will decrease as the triplet energy of one or both reaction partners decreases.

Introduction

Photosensitized cycloadditions of dienes and olefins commonly result in a mixture of [2 + 2] and [4 + 2] adducts.^{2,3} This nontoposelectivity^{4a} is usually regarded as a result of formation of triplet diradical in the early stages of the photo-reaction. It is assumed that the triplet diradical then inverts spin to yield a singlet diradical (not necessarily an intermediate) which subsequently may cyclize, giving rise to a mixture of [2 + 2] and [4 + 2] cycloadducts. This sequence of events is described schematically below.^{2,3,4b}



Interestingly, however, there are cases where the [4 + 2] adduct is the *only* product and others in which it is the *major* product of the cycloaddition.^{3b} A typical example from the work of Schenck et al.^{3b} is given below. In addition, an increase



of the [4 + 2]/[2 + 2] cycloadducts ratio roughly follows an increase in reaction polarity, defined as the inverse of $I_D - A_A$,

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where I_D is the ionization potential of the donor and A_A is the electron affinity of the acceptor.

Reformulating the experimental trends: it seems that triplet Diels–Alder reactions can indeed be efficient. This behavior, which is not compatible with orbital-symmetry predictions for singlet photoreactions, is a reminder of trends observed in thermal reactivity.⁵ It suggests the importance of yet another factor which is polarity dependent and that can differentiate between [2 + 2] and [4 + 2] cycloaddition formation.

Recently,⁶ we have derived spin inversion mechanisms for $[\pi 2_s + \pi 2_s]$ triplet complexes.^{7,8} There are several such mechanisms and each may lead to a stereochemically unique product. The relative efficiency of the mechanisms depends on reaction polarity and on the triplet energies of either reactant.^{6c} Thus, we are able to understand the occurrence of stereospecific results in some polar $2\pi + 2\pi$ triplet cycloadditions.⁹

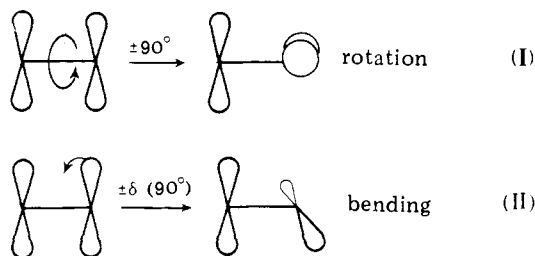
Let us now apply these ideas to $[\pi 2_s + \pi 4_s]$ triplet complexes. We will assume a certain reaction coordinate and find the spin inversion pathways resulting from it. Then we shall derive the dependence of these pathways on reaction polarity and on the triplet energies of the reactants, and compare the conclusions with available experimental data.

I. Theory

Since the theoretical background is described elsewhere⁶ only a brief summary is given here. The efficiency of spin inversion depends on the spin–orbit (SO) coupling interaction of the triplet state, T_1 , with the ground state, S_0 . The interaction is proportional to the SO coupling matrix element, $\langle T_1 | \hat{H}_{SO} | S_0 \rangle$, and inversely proportional to the energy gap separating the two states.¹⁰ Consequently, *efficient spin inversion can be induced by motions, Q_k , which maximize the SO coupling matrix element and minimize the T_1 – S_0 separation.* In order to search for such motions we utilize a strategy which is explained in a previous paper.^{6c} We use group theory to search for potentially efficient spin inversion motions (Q_k), on the basis of the equation

$$T(Q_k) = T(T_1^v) \times T(R_k) \times T(S_0) \quad (k = x, y, z) \quad (1)$$

$\Gamma(T_1^z)$ is the representation of the spatial part of T_1 . The $\Gamma(R_k)$'s are the representations of the spin wave functions which transform as the rotation vectors \mathbf{R}_k ($k = x, y, z$) in the point group of the triplet complex.¹¹ Thus, the symmetry of the spin inversion motions is given by the direct product of the representation of S_0 with those of the three components of the triplet state, T_{1x}, T_{1y}, T_{1z} , for example, $\Gamma(T_{1x}) = \Gamma(T_1^z) \times \Gamma(R_x)$.¹¹ In searching for the Q_k 's, one should keep in mind that archetypal motions which create strong SO coupling are rotation (I) and bending (II) motions.⁶ The latter can be



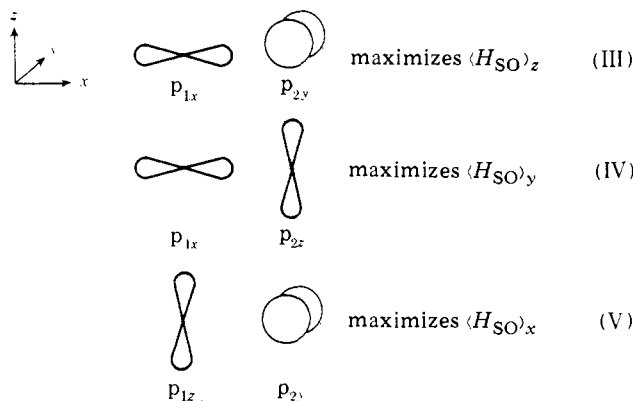
considered as partial (δ) rotations. The composite motions Q_k are based on these archetypal motions.¹²

The relative SO coupling efficiency of the mechanisms can be investigated by evaluating the MO angular momentum (\hat{l}_k) matrix elements described below, where A is the constant $e^2\hbar^2/2m^2c^2$.

$$\langle \hat{H}_{SO} \rangle_k = \frac{\pm A}{\sqrt{2}\hbar} \left\langle \text{HO} \left| \frac{\hat{l}_k}{r^3} \right| \text{LU} \right\rangle \quad \begin{cases} +k = z \\ -k = x, y \end{cases} \quad (2)$$

HO and LU are the highest occupied and lowest unoccupied delocalized MOs of the $[\pi 4_s + \pi 2_s]$ complex^{13a} expressed so that their shapes and energies as a function of the distortion Q_k can be followed. Using the LCAO expressions for the HO and the LU, the right-hand side of eq 2 can be rewritten in terms of the atomic integrals. The only significant contributions to $\langle \hat{H}_{SO} \rangle_k$ arise from two-center integrals¹⁴ over two perpendicular p atomic orbitals (AOs) on two neighboring centers.¹⁵

The specific requirements for maximizing the components of the two-center SO coupling interactions are shown pictorially below (III–V).¹⁵



The interaction terms which arise from the relationship of these AOs are defined in the right-hand sides of eq 3–5.

$$\left\langle p_{1x} \left| \frac{\hat{l}_{1z}}{r_1^3} + \frac{\hat{l}_{2z}}{r_2^3} \right| p_{2y} \right\rangle = -\frac{i\hbar}{2} \left\{ \left\langle p_{1x} \left| \frac{1}{r_1^3} + \frac{1}{r_2^3} \right| p_{2x} \right\rangle + \left\langle p_{1y} \left| \frac{1}{r_1^3} + \frac{1}{r_2^3} \right| p_{2y} \right\rangle \right\} \quad (3)$$

$$\left\langle p_{1x} \left| \frac{\hat{l}_{1y}}{r_1^3} + \frac{\hat{l}_{2y}}{r_2^3} \right| p_{2z} \right\rangle = \frac{i\hbar}{2} \left\{ \left\langle p_{1z} \left| \frac{1}{r_1^3} + \frac{1}{r_2^3} \right| p_{2z} \right\rangle + \left\langle p_{1x} \left| \frac{1}{r_1^3} + \frac{1}{r_2^3} \right| p_{2x} \right\rangle \right\} \quad (4)$$

$$\left\langle p_{1y} \left| \frac{\hat{l}_{1x}}{r_1^3} + \frac{\hat{l}_{2x}}{r_2^3} \right| p_{2z} \right\rangle = \frac{-i\hbar}{2} \left\{ \left\langle p_{1z} \left| \frac{1}{r_1^3} + \frac{1}{r_2^3} \right| p_{2z} \right\rangle + \left\langle p_{1y} \left| \frac{1}{r_1^3} + \frac{1}{r_2^3} \right| p_{2y} \right\rangle \right\} \quad (5)$$

There are two types: a σ -type interaction like $\langle p_{1x} | (1/r_1^3) + (1/r_2^3) | p_{2x} \rangle$ and π -type interactions such as $\langle p_{1y} | (1/r_1^3) + (1/r_2^3) | p_{2y} \rangle$. Hereafter, we shall use the following definitions:

$$V_{NM}^\sigma = \left\langle p_{Nx} \left| \frac{1}{r_N^3} + \frac{1}{r_M^3} \right| p_{Mx} \right\rangle \quad (6)$$

$$V_{NM}^\pi = \left\langle p_{Ny} \left| \frac{1}{r_N^3} + \frac{1}{r_M^3} \right| p_{My} \right\rangle \text{ and/or}$$

$$\left\langle p_{Mz} \left| \frac{1}{r_M^3} + \frac{1}{r_N^3} \right| p_{Nz} \right\rangle \quad (7)$$

M and N are atomic centers positioned along the x axis (see III–V). V^σ and V^π behave similarly to the corresponding atomic overlap integral such that, in general, eq 8–10 hold.

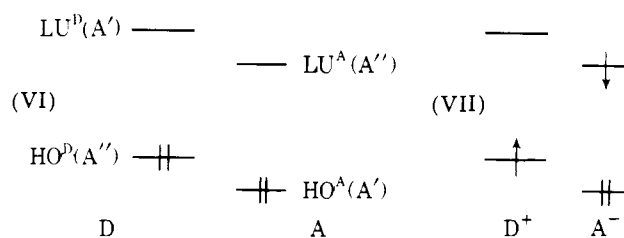
$$V_{NM}^\pi < |V_{NM}^\sigma| \quad (8)$$

$$V_{NM}^\sigma < 0 \quad (9)$$

$$V_{NM}^\pi > 0 \quad (10)$$

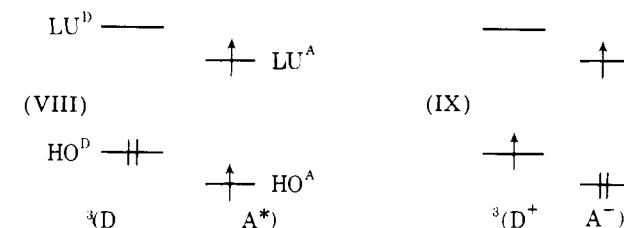
II. Potential Energy Surfaces and Mechanisms of Triplet $[\pi 4_s + \pi 2_s]$ Cycloadditions

Consider an acceptor olefin, A, and a donor diene, D, approaching one another in a $4s + 2s$ manner such that the reaction complex maintains a C_s symmetry. The one-dimensional ground (S_0) and triplet (T_1) potential energy (PE) surfaces are schematically drawn in Figure 1.^{4a,16} The symbols in parentheses indicate the state symmetries in the C_s point group. The ground surface S_0 belongs to the totally symmetric representation (A'). In a configurational sense, it arises from the mixing of the ${}^1D^+A^-$ configuration into the 1DA . These configurations are depicted below (VI and VII) where we show



only the highest occupied (HO) and the lowest unoccupied (LU) MOs of the diene (D) and the olefin (A) with their symmetries in parentheses.

The triplet surface (T_1) of a polar reaction arises from a double crossing of two surfaces having different symmetries, one belonging to A' and the other to the antisymmetric representation, A'' . $T_1(A'')$ contains a mixture of the locally excited configurations ${}^3DA^*$ (VIII) and ${}^3D^*A$. ${}^3D^+A^-$ (IX) is



the leading configuration of $T_1(A'')$.^{4a,17} When the two reactants are not a good donor-acceptor pair the ${}^3DA^* \rightarrow {}^3D^+A^-$ crossing does not materialize and the first triplet surface is $T_1(A'')$ throughout the reaction coordinate.¹⁸ This case will

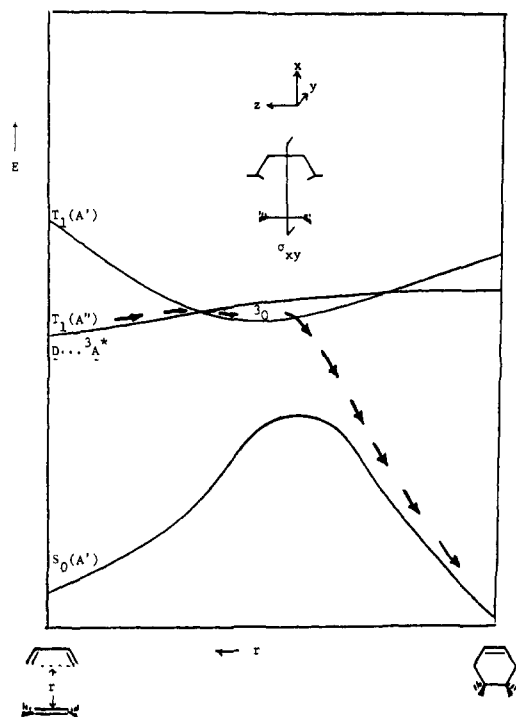
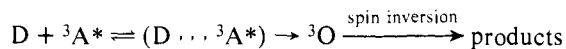


Figure 1. Schematic diagram of the potential energy surfaces for a polar $[\pi 4_s + \pi 2_s]$ cycloaddition. σ_{xy} is the plane of symmetry conserved during the reaction. The arrows indicate the course of the triplet reaction initiated by excitation of the acceptor (A). 3O is a possible intermediate described by ${}^3D^+A^-$ in a configurational sense.

not be treated and we shall focus on *polar triplet reactions in which spin inversion takes place in a $[\pi 4_s + \pi 2_s]$ complex on a $T_1(A')$ type surface.*¹⁹

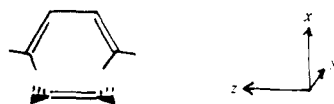
The course of a polar triplet photoreaction is described by the arrows (Figure 1). Past the $T_1(A'')$ - $T_1(A')$ crossing region an excited intermediate 3O , which lies near the minimum of the original diabatic ${}^3D^+A^-$ curve, may be formed. Further approach of the reactants leads the system to a point on $T_1(A')$ past the locus of the maximum on S_0 (i.e., the thermal transition state). There, the triplet complex inverts spin and decays to the ground surface. This sequence of events, for a reaction initiated by excitation of the acceptor A, can be summarized by the following chemical equation.¹⁹



The efficiency of spin inversion is proportional to the SO coupling interaction of $T_1(A')$ and $S_0(A')$. The ${}^3DA^* \rightarrow {}^3D^+A^-$ configuration crossing is analogous to the MO crossing discussed by Woodward and Hoffmann.⁵ As the two reactants approach one another, the two highest occupied orbitals, one antisymmetric (A'') and the other symmetric (A'), cross one another. Similar orbital crossing takes place between the two lowest vacant orbitals. The double orbital crossing may result in polar reactions in a double $T_1(A')$ - $T_1(A'')$ surface crossing which we have just expressed in a configurational sense. The configurational expression of the surface crossing will be helpful in analyzing the effect of reaction polarity on the spin inversion efficiency.

The transformation properties of the different spatial (ν) and spin wave functions¹¹ in the C_s group are given below for a donor-acceptor reactant pair.

$$\begin{aligned} \Gamma(S_0) &= A' \\ \Gamma(T_1^y) &= A' \\ \Gamma(R_x) &= A'' \\ \Gamma(R_y) &= A'' \\ \Gamma(R_z) &= A' \end{aligned}$$



Using eq 1 we obtain the symmetries of the Q_k 's ($k = x, y, z$) which can potentially promote spin inversion.

$$\Gamma(Q_z) = A' \quad (11)$$

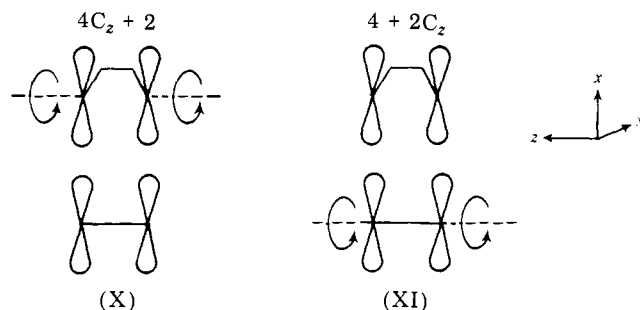
$$\Gamma(Q_x) = \Gamma(Q_y) = A'' \quad (12)$$

In the next section we search for nuclear movements which satisfy these symmetries.

III. Stereoselection Rules for Spin Inversion in Triplet $[\pi 4_s + \pi 2_s]$ Complexes

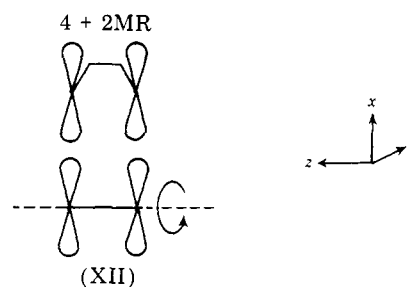
Before proceeding further, let us make clear that our focus on the stereochemical results of the spin inversion mechanisms does not imply that other factors (e.g., barriers, intermediates, etc.) are not important. It only means that we admit the complexity of the problem and choose to treat the spin inversion aspect separately. In illustrating these results we make use of p orbitals with the two lobes differently colored in order to indicate *directional changes* following distortion.

A. Stereoselection Rules (Q_z) for T_{1z} . The motion Q which promotes spin inversion in the z component of T_1 is one which contains a totally symmetric component and generates a p_x - p_y perpendicular AO relationship. Two motions which satisfy these requirements are shown below (X and XI). In both, one



of the reactants performs a conrotation (C)²⁰ about the z axis. Thus mechanism (X) is described by the nomenclature $4C_2 + 2$ to signify conrotation of the diene whereas (XI) is described by $4 + 2C_2$ to signify conrotation of the olefin.

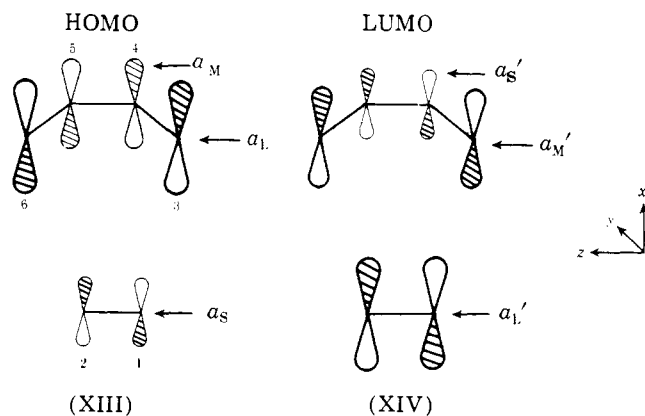
Alternatively, a single rotation of one terminus of the olefin is also acceptable.¹² This motion (XII) is designated by $4 + 2MR$ (monorotation).



Let us compare the relative SO coupling efficiency of $4 + 2C_2$ and $4 + 2MR$. The delocalized antisymmetric HO and LU of the $4 + 2$ complex past the $T_1(A')$ - $T_1(A'')$ crossing are depicted below (XIII and XIV). The subscripts L, M, and S describe the relative sizes of the coefficients (a) and signify large, medium, and small, respectively. The MOs of the complex after rotation by θ in the direction shown in (XI) are expressed in the equations

$$\begin{aligned} \text{HOMO} &= a_S(p_{1x} \cos \theta - p_{1y} \sin \theta - p_{2x} \cos \theta + p_{2y} \sin \theta) \\ &\quad + a_L(-p_{3x} + p_{6x}) \\ &\quad + a_M(-p_{4x} + p_{5x}) \quad (13) \end{aligned}$$

$$\begin{aligned} \text{LUMO} &= a'_L(p_{1x} \cos \theta - p_{1y} \sin \theta - p_{2x} \cos \theta + p_{2y} \sin \theta) \\ &\quad + a'_M(p_{3x} - p_{6x}) \\ &\quad + a'_S(p_{4x} - p_{5x}) \quad (14) \end{aligned}$$



where, for example, p_{1x} is the p_x AO on carbon 1 in (XIII).

Using these MOs and the definitions in eq 6 and 7, the z component of the SO coupling matrix element takes the form

$4 + 2C_z$:

$$\langle \hat{H}_{SO} \rangle_z = \frac{iA}{\sqrt{2}} (a_L a_L' + a_S a_M') \{V_{13}^\sigma + V_{13}^\pi\} \sin \theta \quad (15)$$

Repeating the procedure for $4 + 2MR$ leads to

$4 + 2MR$:

$$\langle H_{SO} \rangle_z = \frac{iA}{2\sqrt{2}} (a_L a_L' + a_S a_M') \{V_{13}^\sigma + V_{13}^\pi\} \sin \theta \quad (16)$$

Both expressions vary proportionally to the V_{13} terms and hence will increase as the intermolecular separation decreases. Thus, $4 + 2C_z$ and $4 + 2MR$ become more efficient as the reaction complex becomes "tighter".

The approximate geometric characteristics of the decaying species can be discovered by maximizing the angular part. Since the angular function is $\sin \theta$, it reaches maximum at $\theta = 90^\circ$,^{13b} at which angle the SO coupling expressions become

$4 + 2C_z(90^\circ)$:

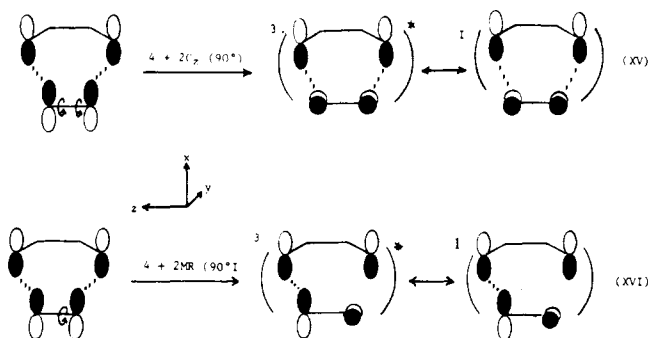
$$\langle \hat{H}_{SO} \rangle_{z, \max} = \frac{iA}{\sqrt{2}} (a_L a_L' + a_S a_M') \{V_{13}^{\sigma+\pi}\} \quad (17)$$

$4 + 2MR(90^\circ)$:

$$\langle \hat{H}_{SO} \rangle_{z, \max} = \frac{iA}{2\sqrt{2}} (a_L a_L' + a_S a_M') \{V_{13}^{\sigma+\pi}\} \quad (18)$$

$$V_{13}^{\sigma+\pi} = V_{13}^\sigma + V_{13}^\pi \quad (19)$$

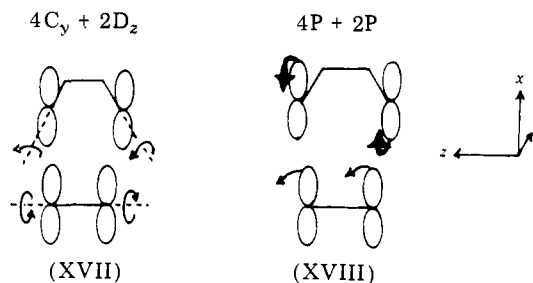
The spin inversion event is pictorially described for the two mechanisms by (XV) and (XVI). The dotted lines indicate bonds to be formed. From (XV) and (XVI) it is evident that



$4 + 2C_z(90^\circ)$ results in retention of the geometric integrity of the rotating olefin, while $4 + 2MR(90^\circ)$ leads to stereorandomization via what may be loosely termed a perpendicular diradical. Equations 17 and 18 show that $4 + 2C_z(90^\circ)$ is at

least^{13b} twice as efficient as $4 + 2MR(90^\circ)$ insofar as SO coupling is concerned.

B. Stereoselection Rules (Q_y) for T_{1y} . Spin inversion in T_{1y} requires motions which generate a p_x - p_z perpendicular AO relationship and which transform as representations containing A'' . Two mechanisms, $4C_y + 2D_z$ (XVII) and $4P + 2P$



(XVIII), meet these requirements. $4C_y + 2D_z$ describes two motions: a conrotation of the dienic termini about the y axis (C_y) and a disrotation of the olefinic termini about the z axis (D_z). $4P + 2P$ is a pyramidalization (P) mechanism.

The SO coupling matrix elements associated with each motion are derived in the usual way. The results are expressed as a function of the angles of distortion (rotation or pyramidalization), θ (in the olefin) and ϕ (in the diene).

$4C_y + 2D_z$: $\langle \hat{H}_{SO} \rangle_y$

$$= \frac{iA}{\sqrt{2}} (a_L a_L' + a_S a_M') \{V_{13}^{\sigma+\pi} - V_{16}^{\sigma+\pi}\} \sin \phi \cos \theta \quad (20)$$

$4P + 2P$: $\langle \hat{H}_{SO} \rangle_y = \frac{iA}{\sqrt{2}} (a_L a_L' + a_S a_M')$

$$\times [\{V_{13}^{\sigma+\pi} - V_{16}^{\sigma+\pi}\} \sin \theta \cos \phi + (a_S a_S' + a_M a_L') \{V_{14}^{\sigma+\pi} - V_{15}^{\sigma+\pi}\} \sin \theta] \quad (21)$$

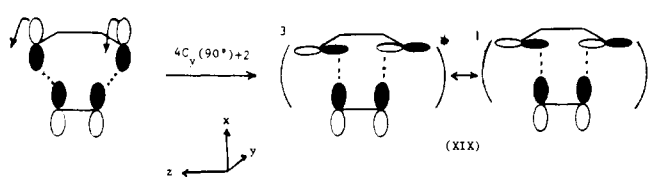
The SO coupling expressions in eq 20 and 21 vary proportionally to the intermolecular interactions of the σ and the π types defined in eq 6 and 7. Consequently, spin inversion via either mechanism takes place in "tight" complexes (short intermolecular distances) where the $V_{13}^{\sigma+\pi}$ term is maximized.

Let us now investigate the angular functions in eq 20 and 21 in order to ascertain the geometric properties of the decaying species. If the two reactants are allowed to distort independently, the SO coupling expression for $4C_y + 2D_z$ reaches maximum at $\theta = 0^\circ$ and $\phi = 90^\circ$ at which angle the mechanism becomes simply $4C_y(90^\circ) + 2$:

$4C_y(90^\circ) + 2$:

$$\langle \hat{H}_{SO} \rangle_{y, \max} = \frac{iA}{\sqrt{2}} (a_L a_L' + a_S a_M') \{V_{13}^{\sigma+\pi} - V_{16}^{\sigma+\pi}\} \quad (22)$$

On the other hand, if the two distortions are performed synchronously, a lower value is reached at $\theta = \phi = 45^\circ$. The complex (XIX) generated by $4C_y(90^\circ) + 2$ is depicted using



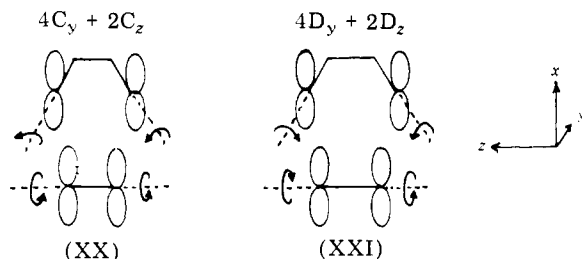
the coloring convention of the p AOs as described at the beginning of this section. The dotted lines indicate bonds to be formed. Thus $4C_y(90^\circ) + 2$ may result in inversion of the geometric integrity of the diene. Since pyramidalization motions are geometrically constrained to $\sim 19.47^\circ$ (which completes tetrahedral angles), the SO coupling matrix element in eq 21 reaches its possible maximum at $\phi = 0^\circ$ and $\theta = 19.47^\circ$,

where it becomes

$4 + 2P$:

$$\langle \hat{H}_{SO} \rangle_{y,\max} \cong \frac{iA \sin 19.47^\circ}{\sqrt{2}} (a_L a_{L'} + a_S a_{M'}) \{V_{13}^{\pi+\pi}\} \quad (23)$$

C. Stereoselection Rules (Q_x) for T_{1X} . Spin inversion in T_{1X} requires a motion which contains an antisymmetric component, A'' , and which generates a p_y - p_z perpendicular AO relationship. Two motions which meet these requirements are shown below (XX and XXI).



$4C_y + 2C_z$ is composed of a conrotation of the dienic termini about the y axis and a conrotation of the olefinic termini about the z axis. On the other hand, $4D_y + 2D_z$ consists of disrotations.²⁰

The SO coupling expressions vary proportionally to the intermolecular term, V_{13} . Consequently, spin inversion is more efficient at "tight" complexes where the short intermolecular distance leads to maximization of V_{13} .

The angular part is a function of $\sin \theta \sin \phi$ and maximum is achieved at $\theta = \phi = 90^\circ$. At these angles the SO coupling expressions become

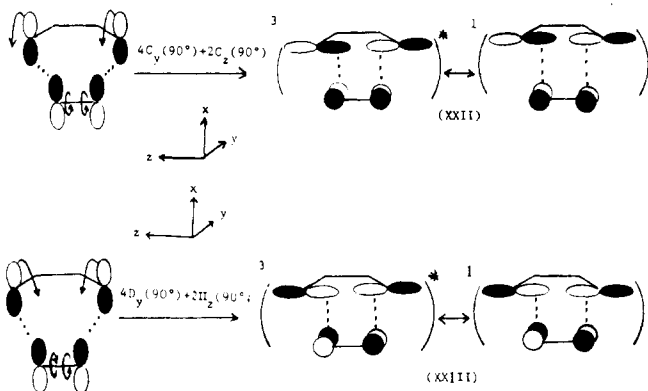
$4C_y (90^\circ) + 2C_z (90^\circ)$:

$$\langle \hat{H}_{SO} \rangle_{x,\max} = \sqrt{2}iA(a_L a_{L'} + a_S a_{M'}) \{V_{13}^\pi - V_{16}^\pi\} \quad (24)$$

$4D_y (90^\circ) + 2D_z (90^\circ)$:

$$\langle \hat{H}_{SO} \rangle_{x,\max} = \sqrt{2}iA(a_L a_{L'} + a_S a_{M'}) \{V_{13}^\pi + V_{16}^\pi\} \quad (25)$$

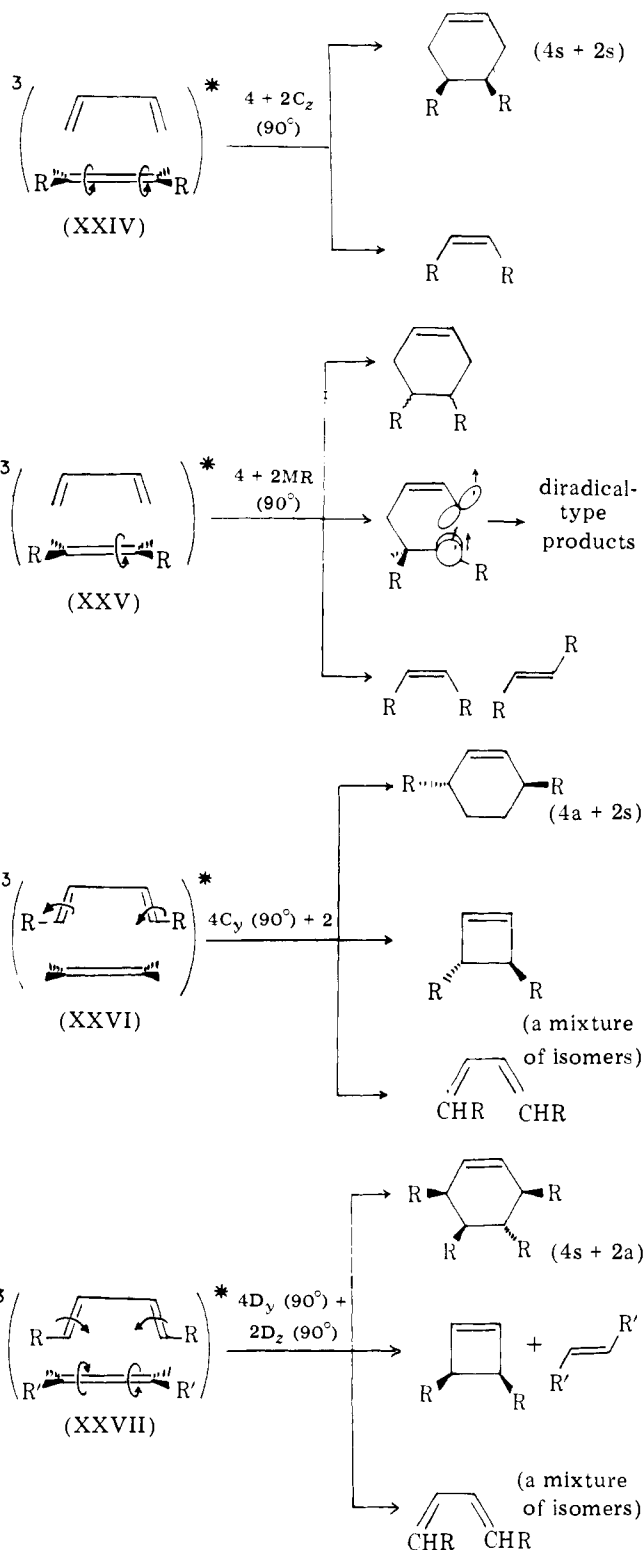
The complexes corresponding to these angular characteristics are shown in (XXII) and (XXIII) and illustrate that $4C_y (90^\circ)$



+ $2C_z (90^\circ)$ can lead to inversion of the geometric integrity of the diene, whereas $4D_y (90^\circ) + 2D_z (90^\circ)$ results in inversion of the olefin geometry.

IV. Mechanisms of Triplet $[4 + 2]$ Cycloadditions

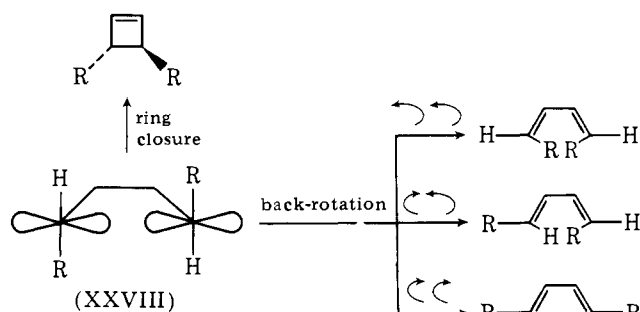
The mechanisms of triplet cycloadditions which result from spin inversion in a $[\pi 4_s + \pi 2_s]$ complex can be grouped into three classes: (1) those which result in retention of stereochemical information, (2) those which lead to a single geometric inversion, and (3) those which result in stereorandomization. Some of the mechanisms which were discussed in section III will not be mentioned here. For example, $4 + 2P$ has the smallest SO coupling matrix element and will not be considered. The selected mechanisms are shown below along



with the nomenclature that is used to describe product stereochemistry (i.e., Woodward-Hoffmann nomenclature). In each case quenching results are also shown.

These mechanisms describe the fate of the triplet $[\pi 4_s + \pi 2_s]$ complex. When $4 + 2C_z (90^\circ)$ is performed, the decaying complex may relax to 4s + 2s cycloadduct or decompose back to unchanged reactants. If $4 + 2MR (90^\circ)$ is performed, the resulting singlet species may rotate back to form a mixture of cyclohexenes or it can decompose to yield a mixture of cis and trans olefins. Alternatively, a perpendicular triplet diradical may be formed (see discussion in section V), giving rise to other products, typical of diradicals (e.g., H abstraction, polymerization). In the case of $4C_y (90^\circ) + 2$, 4a + 2s cycloadduct

may form and the quenching products may include an isomeric mixture of dienes and also a 3,4-disubstituted cyclobutene which results from the collapse of the conrotated diene as shown in (XXVIII).



Finally, when $4D_y$ (90°) + $2D_z$ (90°) is performed, $4s$ + $2a$ adduct can form together with an isomerized olefin and an isomeric mixture of dienes. In addition, a 3,4-disubstituted cyclobutene may arise from the collapse of the disrotated diene.

The picture that emerges reveals the following trends: (a) The stereochemical information obtained from the recovered reactants cannot serve as information about the stereochemical course of the cycloaddition.

Similar conclusions were obtained for [2 + 2] cycloadditions.^{6c,9f,g} (b) The cycloaddition will appear nonstereospecific if all or several of the spin inversion mechanisms occur simultaneously. Alternatively, it may be stereospecific if a single mechanism is more efficient than others.

V. Stereoselectivity of Triplet [$\pi 4_s$ + $\pi 2_s$] Cycloadditions

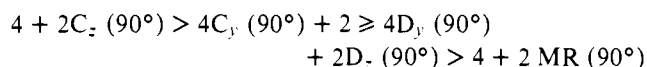
In order to reduce the complexity of the problem one must choose an idealized system in which the stereoselectivity-determining variable is the efficiency of spin inversion. Other factors such as barriers to rotation can be considered later as effects which may or may not modify the trend.

First we consider the relative magnitude of the SO coupling matrix elements in eq 17, 18, 22, 24, and 25. Using the relations

$$|V_{13}| \gg V_{16} \quad (26)$$

$$V_{13}^- + V_{16}^- < \frac{1}{2} |V_{13}^{+\pi}| \quad (27)$$

based on overlap considerations we can rank the mechanisms in the following order of decreasing efficiency:



The second factor is the relative magnitude of the T_1 - S_0 separation (ΔE) associated with each spin inversion mechanism and its variation with the electron donor-acceptor relationship of the reactants. This can be anticipated on the basis of an approximate analytical expression for ΔE as a function of the ionization potential of the donor (I_D) and the electron affinity of the acceptor (A_A).

Consider a [$\pi 4_s$ + $\pi 2_s$] complex on the triplet surface $T_1(A')$ in a region above and near the thermal transition state. In this neighborhood, the triplet wave function (in a configurational sense) is mainly ${}^3D^+A^-$ (see section II). Thus, its energy relative to the no-bond configuration 1DA (VI) becomes

$$E(T_1) \approx I_D - A_A - C - 2KS_{HL}^2 \quad K < 0 \quad (28)$$

Similarly, the ground state arises mainly from the mixing of ${}^1D^+A^-$ (VII) into 1DA (VI). In a perturbation sense, this mixing is inversely proportional to the 1DA - ${}^1D^+A^-$ energy gap expressed as $I_D - A_A - C$ ^{4a,16} and proportional to the square

of the 1DA - ${}^1D^+A^-$ matrix element which, in turn, is proportional to the HO^D - LU^A (VI) overlap integral, S_{HL} .^{4a,16,21} The ground-state energy relative to 1DA is

$$E(S_0) \approx \frac{-K^2S_{HL}^2}{I_D - A_A - C + KS_{HL}^2} \quad (29)$$

K in eq 28 and 29 is the usual proportionality constant which ties the MO matrix elements with the corresponding overlap integral,²² and C accounts for the Coulombic interaction between D^+ and A^- .^{4a,16} The $-2KS^2$ term in eq 28 denotes the repulsion due to interaction of the electrons having the same spin in ${}^3D^+A^-$ (IX), one in HO^D , the other in LU^A (VI).²³ On the other hand, the same term in eq 31 accounts for the attraction of the electrons having opposite spin in ${}^1D^+A^-$ (VII).²³

On the basis of eq 28 and 29 we can derive an approximate expression for the T_1 - S_0 energy gap. This is

$$\Delta E = E(T_1) - E(S_0) = I_D - A_A - C - KS_{HL}^2 + \frac{K^2S_{HL}^2}{I_D - A_A - C + KS_{HL}^2} \quad (30)$$

ΔE is composed of two contributions. The first ($I_D - A_A$) is an intrinsic property of the reactant pair and serves as a measure of reaction polarity. As the reactants become a better donor-acceptor pair, i.e., the reaction becomes more polar, ($I_D - A_A$) decreases and T_1 approaches S_0 . The second element in eq 30 is a function of the stereochemical course of the reaction. This information is contained in the overlap integral (S_{HL}) of the frontier MOs of the reactants, HO^D and LU^A (VI). As S_{HL} increases the T_1 - S_0 energy separation sharply increases. When $4 + 2C_z$ (90°) is performed (XV) the overlap integral S_{HL} changes proportionally to the *cosine* of the rotation angle, θ , and the T_1 - S_0 energy gap becomes

$$\Delta E(\theta) = I_D - A_A - C - K^2S_{HL}^2 \cos^2 \theta + \frac{K^2S_{HL}^2 \cos^2 \theta}{I_D - A_A - C + K^2S_{HL}^2 \cos^2 \theta} \quad (31)$$

Thus, as θ increases, S_0 rises owing to the loss of the stabilizing interaction, whereas T_1 descends because of the opposite reason. Minimization of ΔE is achieved at $\theta = 90^\circ$. At this angle S_0 becomes identical with DA (VI) and T_1 with the radical ion pair ${}^3D^+A^-$, with the result that ΔE now equals ($I_D - A_A$) less the Coulombic energy, C . This latter term increases as the intermolecular distance decreases, *creating a preference for "tight" complex geometries*. A further decrease of E can be achieved with the help of totally symmetric $C=C$ stretching motions which lower ($I_D - A_A$) leading to a touching of the two surfaces at a limiting polarity.

When $4D_y$ (90°) + $2D_z$ (90°) is performed (XXIII) symmetry is broken and the configurational manifold of $T_1(A'')$, ${}^3DA^*$ and ${}^3D^*A$, can now mix with ${}^3D^+A^-$ leading to energy depression of the triplet surface. At the same time S_0 , which is gradually losing the aromatic stability of a [$\pi 4_s$ + $\pi 2_s$] complex, rises in energy. At $\theta = 45^\circ$, when the olefin reaches a perpendicular conformation, the triplet surface lies below S_0 and they cross one another at $45^\circ < \theta < 90^\circ$. The reason for this behavior is that at $\theta = 45^\circ$ S_0 and T_1 are both generated from covalent diradical states with T_1 being usually lower.^{15,23a,b} The conclusions are the following.

(a) The triplet state T_1 is more "ionic" in the case of $4 + 2C_z$ (90°). *Consequently, $4s + 2s$ product formation will be more sensitive to solvent effect than either $4s + 2a$ or $4a + 2s$ cycloadducts formation.* The term "ionicity" refers to the relative contribution of the charge-transfer configuration (${}^3D^+A^-$) to T_1 .

(b) In moderately polar cases, $4s + 2a$ cycloadduct formation will dominate because the T_1 - S_0 separation associated with $4D_y$ (90°) + $2D_z$ (90°) is much smaller than that asso-

Table I. Stereoselectivity of Triplet [4 + 2] Cycloadditions as a Function of Polarity and Triplet Energies of the Reactants

variation type	effect on product stereoselectivity	quenching trend
increase of polarity ^a for given triplet energies	$\frac{[4s + 2a] + [4a + 2s]}{[4s + 2s]}$ decrease ^{b-d}	less isomerization (of diene and olefin)
decrease of triplet energies for a given polarity	$\frac{[4s + 2a] + [4a + 2s]}{[4s + 2s]}$ increase	increased isomerization

^a Polarity is defined by the quantity $(I_D - A_A)^{-1}$. I_D is the ionization potential of the donor and A_A is the electron affinity of the acceptor. ^b $4s + 2a$ will be favored over $4a + 2s$ throughout the polarity spectrum. ^c $4 + 2MR(90^\circ)$ will compete with efficiency decreasing as polarity increases; i.e., diradicals intervene mainly in the nonpolar end.²⁴ ^d Solvent polarity affects mainly the yield of $4s + 2s$.

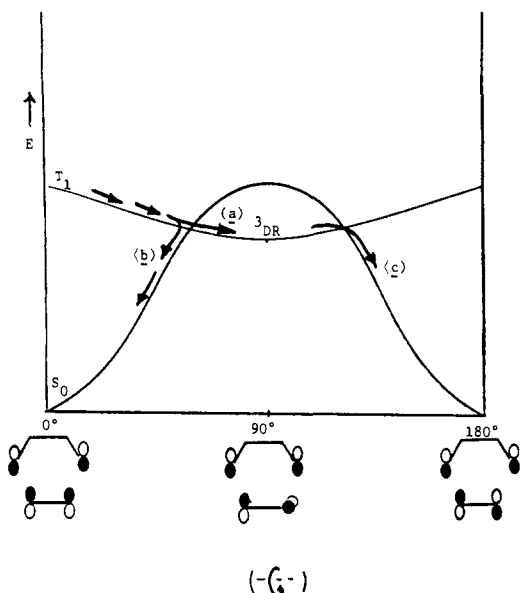


Figure 2. Schematic potential energy surfaces transformation during the monorotational mechanism, $4 + 2MR(90^\circ)$. Only T_1 and S_0 are shown. The arrows indicate the various pathways which a triplet $[\pi 4s + \pi 2s]$ complex on T_1 may choose (a) generating a perpendicular triplet diradical 3DR , (b) decaying to ground-state $[4 + 2]$ cycloadduct with retention of olefin geometry, (c) decaying to ground-state $[4 + 2]$ cycloadduct with inversion of olefin geometry. The coloring convention of the p orbitals is used to indicate stereochemical changes.

ciated with $4 + 2C_2(90^\circ)$. As the reactants are gradually made a better donor-acceptor pair the trend will change. The T_1 - S_0 gap associated with $4 + 2C_2(90^\circ)$ will shrink, reaching zero at a limiting polarity. Since $4 + 2C_2(90^\circ)$ has also the largest SO coupling matrix element, its efficiency will increase as polarity increases. Thus $4s + 2s$ product formation will become more efficient as polarity increases. This trend is reinforced by the fact that $4 + 2C_2(90^\circ)$ is energetically less expensive than $4D_y(90^\circ) + 2D_z(90^\circ)$, which may require surmounting a rotational barrier.

(c) The triplet excitation energies of the reactants will exert an opposite effect. At a given polarity, the $[4s + 2a]/[4s + 2s]$ cycloadducts ratio will increase as the triplet energies of the reactants decrease. This trend is due to the contribution of the locally excited configurations ${}^3DA^*$ and ${}^3D^*A$ to the triplet wave function associated with $4D_y(90^\circ) + 2D_z(90^\circ)$.

The competition between $4C_y(90^\circ) + 2$ and $4D_y(90^\circ) + 2D_z(90^\circ)$ can be discussed by considering the relative T_1 - S_0 energy gap associated with them. For $4D_y(90^\circ) + 2D_z(90^\circ)$ disrotation of the olefin is required. This lowers the triplet energy of the olefin and makes it also a better acceptor, and thus lowers the energy of T_1 . At the same time, S_0 rises sharply causing eventual S_0 - T_1 crossing. Consequently, the T_1 - S_0 energy gap for this mechanism will be smaller than that for $4C_y(90^\circ) + 2$, which does not require this distortion. This, together with roughly equal SO coupling matrix elements, favors $4D_y(90^\circ) + 2D_z(90^\circ)$ over $4C_y(90^\circ) + 2$.

Table II. Stereoselectivity of $2\pi + 2\pi$ Triplet Reactions

type of reaction	product stereochemistry	dominant spin inversion mechanism
very polar	$2s + 2s > 2s + 2a$	$2 + 2BP > 2 + 21D(90^\circ)$
polar	$2s + 2a > 2s + 2s$	$2 + 21D(90^\circ) > 2 + 2BP$
reactants with low triplet energies	$2s + 2s > 2s + 2a$	$2 + 2BP > 2 + 21D(90^\circ)$

At the early stage of $4 + 2MR(90^\circ)$ T_1 lies above S_0 and ultimately becomes the lowest diradical state at $\theta = 90^\circ$, crossing at $\theta < 90^\circ$. The T_1 - S_0 surfaces interrelationship is illustrated in Figure 2 as a function of the rotation angle θ . During the rotation phase, the triplet complex (on T_1) may proceed along the triplet surface, ultimately producing a perpendicular diradical (path a).²⁴ This species has to invert a spin and it is surrounded by barriers to ring closure. Hence, it may follow alternative reaction paths (e.g., polymerization, H abstraction) when the barriers are large enough and spin inversion is inefficient. Alternatively, the triplet complex can cross over to S_0 (paths b, c), giving rise to an isomeric mixture of cycloadducts. As polarity increases, the "ionic" $[\pi 4s + \pi 2s]$ complex (eq 28) is stabilized relative to the diradical resulting in shifting of the T_1 - S_0 crossing to progressively smaller θ values. This results in gradual reduction of the SO coupling matrix elements at the T_1 - S_0 crossing points (Figure 2) and, hence, in the efficiencies of paths b and c. Thus, as polarity increases, $4 + 2 - MR$ will play a lesser role in cycloadduct formation.

In summary, the polarity of the reactants strongly influences the stereoselectivity of triplet $[4 + 2]$ cycloadditions. The conclusions are summarized in Table I. In addition, it is tempting to speculate that olefins may catalyze electrocycloaddition of dienes, a well-established inefficient triplet reaction² [see (XXVI)-(XXVIII)].

VI. The [4 + 2]-[2 + 2] Competition

A triplet reaction between a diene and an olefin may result either in $[2 + 2]$ or in $[4 + 2]$ adducts. Let us now try to understand what factor(s) can make the orbital-symmetry-forbidden $[4 + 2]$ reaction as efficient as the symmetry-allowed $[2 + 2]$.²⁵

One way of dealing with this intricate problem is to superimpose the trends predicted for the various $[2 + 2]$ mechanisms (Table II)^{6c} over those predicted for the $[4 + 2]$ mechanisms (Table I). Inspection of Tables I and II reveals that the efficiency of the spin inversion mechanisms for $[2 + 2]$ and $[4 + 2]$ varies with the polarity of the reactants and with their triplet excitation energies. Thus, the $[4 + 2]/[2 + 2]$ ratio can be viewed as a function which is dependent upon these two variables. This function should be inspected in three principal regions (see Table II). The first is a region of a very high polarity. Here the main $[2 + 2]$ mechanism is $2 + 2BP$ which leads to $2s + 2s$ products, whereas the main $[4 + 2]$ mechanism is $4 + 2C_2(90^\circ)$ which leads to $4s + 2s$ adducts. Within this region, increase of polarity leads to a decrease of the SO coupling ef-

efficiency associated with $2 + 2BP$ and has an opposite effect on the efficiency of $4 + 2C_z$ (90°) (see section V). Thus, an increase of polarity (in this region) will result in an increase of the $[4s + 2s]/[2s + 2s]$ ratio.

In the moderately polar region $2 + 2ID$ (90°) (Table II) is the main $[2 + 2]$ mechanism, whereas $4 + 2C_z$ (90°) and $4D_y$ (90°) + $2D_z$ (90°) compete with each other as the main $[4 + 2]$ mechanisms. Since $4 + 2C_z$ (90°) creates strong SO coupling and is energetically less expensive than either $2 + 2ID$ (90°)²⁶ or $4D_y$ (90°) + $2C_z$ (90°), as polarity increases an increase of $4s + 2s$ adduct formation and a decrease of $2s + 2a$ and $4s + 2a$ adduct are expected.²⁶

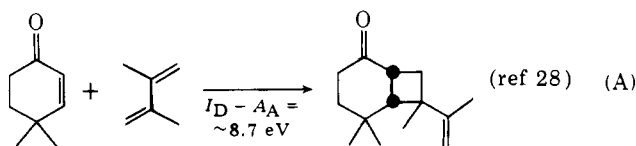
The third region is a region of low triplet excitation energies (and unspecified polarity). Here, the main $[2 + 2]$ mechanism is $2 + 2BP$, which competes successfully with $2 + 2ID$ (90°), whereas $4D_y$ (90°) + $2D_z$ (90°) is the main $[4 + 2]$ pathway. As polarity increases in this region, $4D_y$ (90°) + $2D_z$ (90°), which is required to rotate, will be suppressed²⁶ resulting in the predominance of $2 + 2BP$. At the same time, $4 + 2C_z$ (90°) starts gaining efficiency. Thus, as polarity increases (in this region), we may observe a shift from $4s + 2a$ toward $2s + 2s$ with $4s + 2s$ starting to take over as the $[4 + 2]$ mechanism.

In conclusion, as polarity increases $[4 + 2]$ adducts will be produced more efficiently. However, in order to gain more insight into this complicated problem, one must investigate the $[4 + 2]/[2 + 2]$ function systematically by varying the polarity and triplet energies of the reactants over a wide range for each reaction family (e.g., cycloaddition of dienes to cycloenones).

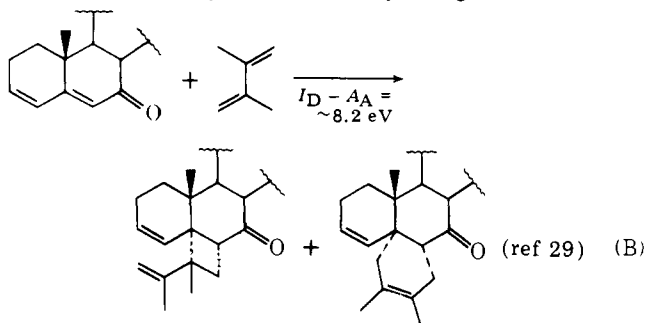
VII. Experimental Trends in Triplet $[4 + 2]$ Cycloadditions

The stereochemistry of $[4 + 2]$ cycloadditions has not been investigated systematically and our predictions in Table I cannot be compared yet with experimental evidence. Thus, we shall restrict the comparison to the $[4 + 2]/[2 + 2]$ competition.

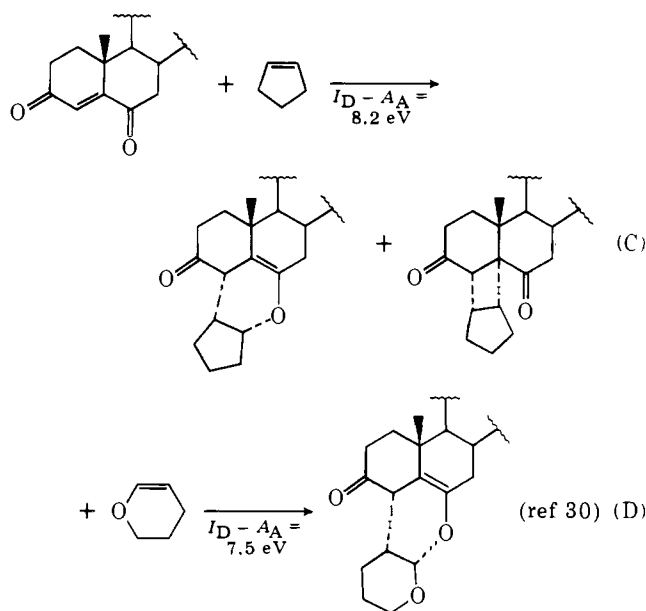
A. $[4 + 2]/[2 + 2]$ Cycloadduct Ratio. There are a few systems in which the $[4 + 2]/[2 + 2]$ cycloadducts ratio shows a trend in accord with the predictions of section VI. The photocycloadditions of cycloenones (and cyclodienones) are known to originate from a triplet state.^{9a-d} The parent system cyclohexenone and its 4,4-dimethyl derivative react with a large variety of dienes to give exclusively or mainly $2s + 2s$ cycloadducts.^{27,28} An illustrative example is given in reaction A.



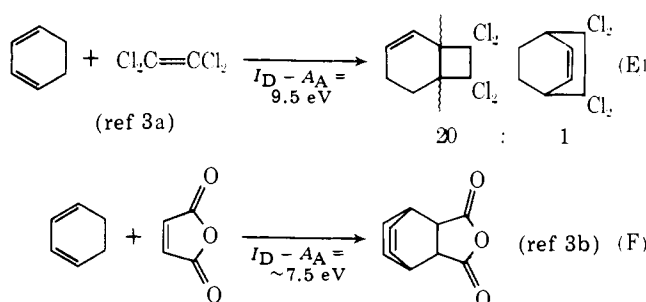
When cyclohexenone is replaced by the better acceptors, dienone and enedione, $[4 + 2]$ cycloadducts are produced and become eventually the only products of the reaction. For example, the dienone system gives a mixture of $[4 + 2]$ and $[2 + 2]$ products in its reaction with 2,3-dimethylbutadiene (reaction B). Similarly, the enedione system gives a mixture of



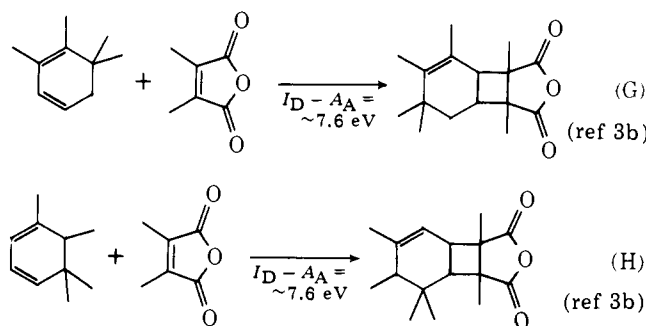
$[2 + 2]$ and $[4 + 2]$ adducts when it reacts with cyclopentene (reaction C) and only a $[4 + 2]$ adduct when it reacts with the better donor dihydropyran (reaction D).



The same trend is observed in the photosensitized reactions E and F, an increase in the amount of $[4 + 2]$ adduct as polarity increases.



Although this trend is quite general, some reactions yield mostly $[2 + 2]$ adducts despite the polar nature of the reactant pair. The exceptions which we have identified seem to be a result of steric determinants. This is illustrated in reactions G and H. In each case, $[2 + 2]$ takes place at the less hindered



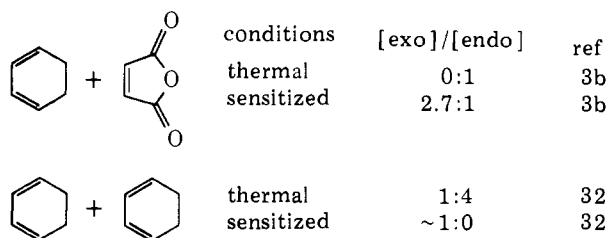
double bond of the diene, whereas the $[4 + 2]$ cycloaddition which does not have this choice is inhibited.

Note that steric effects enter the theory explicitly through the SO coupling matrix element which varies as $1/r^3$ (eq 3-5). Consequently, the less congested complex will be preferred in order to afford maximal proximity of the union centers.³¹

In conclusion, efficient $[4 + 2]$ cycloadditions are expected whenever the diene-olefin is a good donor-acceptor pair, much as in ground-state reactivity.

B. Steric Effects in $[4 + 2]$ Cycloadditions. We have already mentioned that steric factors play an important role in the

selectivity by dictating "tight" complex geometries owing to the $1/r^3$ dependence of the SO coupling matrix elements (section III). The result of this requirement (for "tight" geometries) is the amplification of steric repulsion owing to substituents on the union centers. Consequently, one expects the exo isomer to be the main result of the [4 + 2] cycloaddition.³¹ Two examples which are in accord with this prediction are given below. Others can be found in the literature.³³



Conclusions

In reactions which maintain some degree of symmetry, the three triplet levels (T_x , T_y , and T_z) have different symmetries.^{6c,8} Consequently, spin inversion can take place via stereochemically different mechanisms. The relative efficiency of the spin inversion mechanisms for the $[\pi 4_s + \pi 2_s]$ complex was found to vary with the donor-acceptor relationship and the triplet excitation energies of the reactants (Table I). These variations, if indeed important, form a basis for anticipating and designing stereospecific triplet Diels-Alder reactions.

Other features of triplet cycloadditions such as the [4 + 2]/[2 + 2] products ratio (toposelectivity)^{4a} were shown to be in accord with the choice of the most efficient spin inversion mechanism by a given reactant pair.

Experimental scrutiny of these verifiable predictions (Table I and section VI) is needed.^{34,35} "When these predictions fail the theory can be enriched by reexamination".³⁶

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- (11) The three triplet sublevels (defined over the Cartesian axes) for a system described by two singly occupied MOs, ϕ_1 and ϕ_2 , are

$$(\phi_1\phi_2 - \phi_2\phi_1) \begin{cases} \frac{1}{\sqrt{2}}(\alpha\beta + \beta\alpha) = T_z \\ \frac{1}{\sqrt{2}}(\alpha\alpha - \beta\beta) = T_x \\ \frac{i}{\sqrt{2}}(\alpha\alpha + \beta\beta) = T_y \end{cases}$$
- For the symmetry classification of these wave functions see (a) E. P. Wigner, "Group Theory and Its Applications to the Quantum Mechanics of Atomic Spectra", Academic Press, New York, 1959; (b) R. M. Hochstrasser, "Molecular Aspects of Symmetry", McGraw-Hill, New York, 1964, Chapter 9; (c) R. S. Knox and A. Gold, "Symmetry in the Solid State", W. A. Benjamin, New York, 1964; (d) S. P. McGlynn, T. Azumi, and M. Kinoshita, "The Triplet State", Prentice-Hall, Englewood Cliffs, N.J., 1969.
- (12) Among the acceptable Q_k 's are also motions which transform as reducible representations which contain an irreducible component satisfying eq 1. See ref 6c.
- (13) (a) Equation 2 is an approximation. When necessary, more configurations should be used to describe S_0 and T_1 , and additional MO matrix elements have to be evaluated. In our experience the HOMO-LUMO matrix element is usually sufficient for revealing the relative efficiency of different motions. (b) When T_1 and S_0 are described by more configurations, θ_{\max} for 4 + 2MR becomes somewhat smaller than 90°. For more details see ref 6 and 15a.
- (14) In systems like diene-olefin complex the one-center integrals vanish due to symmetry. See discussions in ref 11d and in S. R. Langhoff and C. W. Kern in "Application of Electronic Structure Theory", H. F. Schaefer III, Ed., Plenum Press, New York, 1977, p 414.
- (15) These AO relationships are due to the fact that when \hat{l}_k ($k = x, y, z$) operates on a P AO it rotates it by $\pm 90^\circ$ around the axis specified by the subscript k . Consequently, only an initially perpendicular AO pair will overlap after operation by \hat{l}_k , and give rise to nonvanishing interaction (eq 3-5). For a lucid discussion see (a) L. Salem and C. Rowland, *Angew. Chem., Int. Ed. Engl.*, **11**, 92 (1972); (b) L. Salem, *Pure Appl. Chem.*, **33**, 317 (1973).
- (16) The construction of qualitative PE surfaces of the type sketched in Figure 1 is described in (a) N. D. Epiotis and S. Shaik in "Progress in Theoretical Organic Chemistry", Vol. 2, I. G. Csizmadia, Ed., Elsevier, Amsterdam, 1977; (b) N. D. Epiotis and S. Shaik, *J. Am. Chem. Soc.*, **99**, 4936 (1977); (c) *ibid.*, **100**, 1, 8, 29 (1978); (d) N. D. Epiotis, S. Shaik, and W. Zander in "Rearrangements in Ground and Excited States", P. De Mayo, Ed., Academic Press, New York, 1979.
- (17) The configurational composition can be verified by mapping the spin-adapted determinantal wave function based on the delocalized MOs of the complex into fragment configurations. For an example of this mapping technique see ref 4a and 16.
- (18) In such a case the spin inversion mechanisms will differ from these of a polar case. For more detail see ref 6.
- (19) Even if $T_1(A^-)$ (i.e., $^3D^+A^-$) is not the lowest triplet, it may become accessible by decay from a higher singlet. The spin-inversion rules apply also to this case.
- (20) The term conrotation describes two rotational motions in the same direction, whereas disrotation describes two motions performed in opposite directions.
- (21) The rules for evaluating matrix elements between configurations are given inter alia in (a) S. P. McGlynn, L. G. Vanquickenborne, M. Kinoshita, and D. G. Carroll, "Introduction to Applied Quantum Chemistry", Holt, Rinehart and Winston, New York, 1972, pp 281-298; (b) W. G. Richards and J. A. Horsley, "Ab Initio Molecular Orbital Calculations for Chemists", Clarendon Press, Oxford, 1970.
- (22) See ref 21a, Chapter 4.
- (23) This term is analogous to $\pm 2\beta S$ which appears in the energy expression of the singlet and triplet states, respectively, in the Heitler-London treatment of H_2 . This is common to all species which can be described by a wave function which localizes two electrons on two different fragments (i.e., diradicaloids) like $^3D^+A^-$ (IX). The interaction of two electrons having the same spin (i.e., triplet) is repulsive if the electrons occupy orbitals which overlap strongly, and the reverse is true when the electrons have opposite spins. For discussions see (a) H. E. Zimmerman and G. A. Epling, *J. Am. Chem. Soc.*, **92**, 1411 (1970); (b) J. Michl, *Top. Curr. Chem.*, **46**, 1 (1974), and references cited therein; (c) K. Fukui, "Theory of Orientation and Stereoselection", Springer-Verlag, West Berlin, 1975, and references cited therein; (d) K. Fukui and K. Tanaka, *Bull. Chem. Soc. Jpn.*, **50**, 1391 (1977); (e) ref 16c,d; (f) S. Shaik, Ph.D. Dissertation, University of Washington, Seattle, Wash. 1978, Appendix I.
- (24) Formation of the diradical can be favored in nonpolar cases where it may be the global minimum of the triplet surface.^{23a-d} In this case, little or no $[\pi 4_s + \pi 2_s]$ complex will form and the diradical may be the primary photoproduct. Alternatively the diradical may result from paths which are not related to the $4s + 2s$ cycloaddition, e.g., reaction of a twisted triplet olefin with a diene (or vice versa). In each case the fate of the diradical depends on the factors considered in the text. As polarity increases, the $[\pi 4_s + \pi 2_s]$ complex is stabilized relative to the diradical and the formation of the latter will become progressively less efficient.
- (25) As polarity increases both [2 + 2] and [4 + 2] complexes resemble $^3D^+A^-$

- and orbital symmetry rules are weakened. Thus, symmetry-forbidden complexes (e.g., triplet [$\pi 4_s + \pi 2_s$]) may become as stable as symmetry-allowed ones (e.g., triplet [$\pi 2_s + \pi 2_s$]) and spin inversion may dictate the [4 + 2]/[2 + 2] competition (in polar cases). For a discussion on orbital-symmetry effects vs. polarity effects see ref 4a, Chapter 22.
- (26) In a polar case the T_1 wave function for the $2s + 2s$ complex is mainly $^3D^+A^-$; namely, the individual reactants are not in their locally excited states but are in their ionic states (D^+ and A^- , respectively). Thus, there will be a barrier for disrotation of a reactant in the $2 + 2D$ (90°) mechanism. This barrier will increase as the reactant pair is made more polar and may eventually suppress $2s + 2a$ product formation. The same conclusions apply to $4D_y$ (90°) + $2D_z$ (90°), which require disrotation of both reactants.
- (27) (a) T. S. Cantrell, *Chem. Commun.*, 1656 (1970); (b) *J. Org. Chem.*, **39**, 3063 (1974).
- (28) Reference 9c, p 224.
- (29) (a) G. R. Lenz in a private communication to S. S. Shaik and N. D. Epiotis; (b) G. R. Lenz, *Tetrahedron Lett.*, 3027 (1972); (c) *ibid.*, 2483 (1977).
- (30) (a) G. R. Lenz, *J. Chem. Soc., Chem. Commun.*, 700 (1977); (b) *J. Org. Chem.*, in press.
- (31) This trend is almost exclusive in [2 + 2] cycloadditions where almost always the anti isomer is favored over the syn. See ref 2, for example.
- (32) D. Valentine, N. J. Turro, Jr., and G. S. Hammond, *J. Am. Chem. Soc.*, **86**, 5202 (1964).
- (33) See, for example, ref 2e, p 47.
- (34) Selective photochemistry from the three triplet sublevels can test our prediction. For developments in this area see M. A. El-Sayed, *Annu. Rev. Phys. Chem.*, **26**, 235 (1975).
- (35) Different rates of reactivity were observed for the triplet sublevels of dimethyl-*s*-tetrazine by B. Dillinger, R. M. Hochstrasser, and A. B. Smith, III, *J. Am. Chem. Soc.*, **99**, 5834 (1977).
- (36) From the closing sentences of R. Hoffmann in "Aspects de la Chimie Quantique Contemporaine", R. Daubel and A. Pullman, Eds., CNRS, Paris, 1971.

Interactions of Gallium(III) with Bleomycin Antibiotics^{1a}

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Abstract: The addition of Ga(III) to an aqueous solution of bleomycin results in the observation of several new peaks in the ¹H NMR spectrum, concomitant with the reduction in intensity of several of the peaks of the antibiotic. By measuring the relative intensity of the resonance of the C₄ proton of the imidazole at various Ga(III) concentrations, we have found that the Ga(III)-bleomycin complex has a 1:1 stoichiometry. The lifetime of the Ga(III)-bleomycin complex was found to be ca. 15 s at 343 K (70 °C) from NMR transfer of magnetization and spin-lattice relaxation time measurements. On the basis of a combination of fluorescence binding studies and proton-displacement experiments, we conclude that the binding of Ga(III) to the bleomycins (A₂ and B₂) displaces a single proton from the α -amino group of the diaminopropionamide moiety of the drugs. This evidence implicates this portion of the molecule directly in metal binding.

Introduction

The clinical uses of the radioisotope gallium-67 have developed from the observation that this isotope selectively localizes in a broad range of tumors and lymphomas.^{2,3} Current applications are directed at the detection and staging of solid tumors and lymphomas⁴ as well as the use of gallium nitrate as a therapeutic agent⁵ in the treatment of human neoplasias. In our laboratories, investigations into the mechanism of gallium-67 localization have proceeded along two lines: in vitro studies of the uptake of gallium by normal and malignant cells⁶⁻¹⁰ as well as NMR investigations of the aqueous chemistry of gallium.¹¹⁻¹⁴ The present study is directed at the characterization of complexes of gallium with the bleomycin antibiotics.

The bleomycins are a family of glycopeptide antibiotics isolated from *Streptomyces verticillus* by Umezawa and co-workers.¹⁵ The revised primary structures¹⁶ of these molecules are shown in Figure 1. The various congeners of the bleomycins differ from each other in their terminal amine moiety (R group in Figure 1). Blenoxane, the commercial form of these drugs, marketed by Bristol Laboratories (Syracuse, N.Y.), contains ca. 70% bleomycin A₂ and 25% bleomycin B₂, with trace amounts of other congeners. These drugs have been employed clinically in the treatment of a wide variety of human carcinomas and lymphomas.¹⁷ In addition, these molecules have been used in tumor scanning as carriers for various radionucleotides including gallium-67.⁴ The impetus for the present study arises from the following considerations: (1) the observation that the bleomycins inhibit the uptake of gallium-67 in L1210 leukemic cells;¹⁸ (2) gallium-67 complexes of the

bleomycins have been employed as radiopharmaceuticals;⁴ (3) metal ions (especially Fe(II))¹⁹ have been proposed to play an important role in the mechanism of action of these drugs.²⁰

Previous spectroscopic investigations into the interactions of the bleomycins with polyvalent metal ions have focused on the Zn(II),²¹⁻²³ Cu(II),²⁴ and Fe(II)¹⁹ complexes. Umezawa and co-workers have proposed a square pyramidal coordination geometry for the Cu(II) complex on the basis of UV evidence²⁴ and X-ray crystallographic data²⁵ on a metabolite of these antibiotics. In contrast, Dabrowiak et al. have inferred a square-planar geometry for the Zn(II) and Cu(II) complexes from the results of ¹³C NMR studies,²³ ¹H NMR investigations, and UV difference spectra.²¹ On the basis of our previous studies on the kinetics of dissociation of the Zn(II) complex of bleomycin, we have suggested that the coordination geometry is tetrahedral.²⁶ Thus, there is still some controversy surrounding the coordination geometry around various metal ions in their complexes with bleomycin and, in fact, there probably are different geometries for different metal ions.

In the present study we have monitored the interactions of gallium(III) with the bleomycins using ¹H NMR, fluorescence spectroscopy, and potentiometric titrations. We have also determined the kinetics of dissociation of the Ga(III)-bleomycin complex from NMR transfer of magnetization and spin-lattice relaxation time (T_1) measurements. These results are compared with the results of similar experiments conducted on the Zn(II)-bleomycin complex.²⁶

Experimental Section

Blenoxane, a generous gift from Drs. W. T. Bradner and S. T. Crooke of Bristol Laboratories, was separated into its component