the ground state to the transition state. Enzymes must therefore single out for chemical recognition those few features of a substrate that do change. We have considered the generation of hydrates I and II at the active sites of deaminases as analogues of the process by which the enzyme generates intermediates in substrate hydrolysis. In these compounds, a tetrahedrally oriented hydroxyl group is an obvious feature that distinguishes these compounds from the aromatic starting materials. Evidently one or a few polar interactions involving this group, arising fleetingly in the transition state, are capable of generating a large part of the added binding affinity that is needed to explain the rate enhancement (ca. 10^{12}-fold)[28] that an enzyme of this kind produces.

Extreme levels of binding discrimination should be feasible for proteins other than enzymes, and it is of interest to consider whether there is likely to have been selective pressure for their emergence in nonenzymatic processes. For example, it should be physically possible for antibodies to develop very high affinities for antigens; indeed, prospects are encouraging that this can be accomplished by chemical or genetically induced modification of monoclonal antibodies. In experimental animals, however, few antibodies have been reported with affinities corresponding to dissociation constants of less than 10^{-10} M. This appears natural if one considers that, in an immunized individual, concentrations of circulating antibodies are typically 10^{-8} M or higher, and that these antibodies should be sufficient to "titrate" any ligand with a dissociation constant much lower than 10^{-8} M. Because removal of the antigen is already so efficient, a complex with a dissociation constant of 10^{-11} M probably offers little selective advantage over a complex with a dissociation constant of 10^{-10} M.

It is also of interest to consider the range of binding affinities that is likely to be useful in proteins that serve a regulatory function. In controlling the activity of an allosteric enzyme, for example, it is presumably necessary that ligand binding take place reversibly on a biological time scale, allowing the ligand to be bound and released at a sufficient rate to respond to changing conditions. A regulatory complex with a dissociation constant of 10^{-13} M, because of its slow rate of ligand release, would require hours to arrive at binding equilibrium and would therefore appear unsuitable for regulation over short periods of time.[29] Enzyme–substrate complexes escape this difficulty, because the binding forces that fleetingly stabilize the transition state are not yet present in the enzyme–substrate complex and are no longer present in the enzyme–product complex. With the exergonic, monomolecular collapse of $ES^{\ddagger}$ to EP, bonds that were critical for transition-state stabilization vanish, removing what would otherwise be formidable kinetic barriers to the entry of substrates and the egress of products.[30]

We are grateful to Walda Jones Powell, Lloyd Frick, and Charles Yang for their experimental and theoretical contributions to this work. Work in this laboratory was supported by NIH Grant No. GM-18325.

(28) Frick, L.; Mac Neela, J. P.; Wolfenden, R. *Bioorg. Chem.* 1987, *15*, 100.

(29) To respond to ligand concentrations changing in this range, such a "receptor" protein would itself presumably need to be present at extremely low concentrations in order to avoid removing virtually all the regulating ligand from solution.

(30) It is sometimes suggested that an enzyme could act by combining with an activated form of the substrate, which might approach the transition state in structure, rather than with the substrate in the ground state. However, any enzyme can be considered to approach the point of greatest usefulness if, among other characteristics, its second-order rate constant for product formation, k_{cat}/K_m, approaches the limit imposed by the rate at which the most abundant of the enzyme and the substrate encounter each other in solution. That criterion cannot be met by reactions between species that are not fairly populous, simply because encounter is too infrequent. From the large second-order rate constants (k_{cat}/K_m) that have been recorded for many enzyme reactions, it seems clear that mass transfer tends to occur as a result of productive combination of an enzyme with its substrate in forms that are not chemically activated to any great extent. Evidently activation must occur in synchrony with the development of strong binding forces, which relax later as products are formed and released.[6]

The Overlap Component of the Stereoelectronic Factor. Remote Control of Stereogenicity Transfer through the Anisotropic Influence of a Ring

JEROME A. BERSON

Department of Chemistry, Yale University, New Haven, Connecticut 06511

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In a more innocent time, before the theory of orbital symmetry conservation, organic chemists frequently invoked the "stereoelectronic factor" in explicating and predicting reactions.[1a-c] By definition,[1b] the stereoelectronic factor causes reactions to "proceed best when certain spatial relationships pertain between electrons involved in the bonds formed or broken". These

Jerome A. Berson was born in Sanford, FL, in 1924. He received degrees from the City College of New York (B.S.) and Columbia University (M.A. and Ph.D. with W. von E. Doering), and he did postdoctoral research at Harvard University (with R. B. Woodward). An academic since 1950, he taught successively at the University of Southern California and the University of Wisconsin and is now Irénée du Pont Professor of Chemistry at Yale University. He and his collaborators focus their research on the mechanisms of organic reactions and the synthesis of molecules designed to test theoretical concepts.

(1) Several good examples are described by Eliel: Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; (a) p 139; (b) p 227; (c) pp 241–243. (d) In fact, the two ideas sometimes are not readily separable. For example, the preference for a linear rather than an angular S_N2 transition state can be explained as an orbital symmetry effect.[1e] (e) Salem, L. *Electrons in Chemical Reactions*; Wiley-Interscience: New York, 1982; p 164 and references cited therein.

0001-4842/91/0124-0215$02.50/0

"certain spatial relationships" are *mutual orientations of reaction sites*, such as collinearity of the three atoms involved in the S_N2 displacement, or near coplanarity of the four ligands on the developing double bond in olefin-forming vicinal eliminations. We venture to suggest, however, that it would be proper to generalize the term "stereoelectronic effect" to include not only this mutual orientation or *orbital overlap requirement* but also the *orbital symmetry factor*.[1d]

At the Sheffield symposium in 1966,[2] Woodward recounted the events that led him and Hoffmann to the formulation[3] of the orbital symmetry conservation rules. The main outlines of the story are well-known, but one feature of it is particularly relevant here. At one stage in the projected synthesis of vitamin B_{12}, the plan called for the construction of a key intermediate by the stereospecific cyclization of a complicated but stereochemically well defined triene to a cyclohexadiene. Woodward and his colleagues were confident from inspection of molecular models that "minimization of angle strain and π-uncoupling"[2] (in other words, the orbital overlap factor) would favor cyclization by only one of the two possible pathways, namely, the one we today would call conrotatory. The reaction in fact was found to be highly stereospecific, but contrary to prediction, actually took the disrotatory path instead. To explain the apparent contradiction (and a number of other facts), it became necessary to recognize a new stereoelectronic controlling force, which Woodward and Hoffmann called the conservation of orbital symmetry. Among the several benefits of reading (or rereading) that lecture is the perception of being present at a cusp of history. One realizes how much has changed in the way organic chemists think, for here was Woodward, who was himself already engaged in founding the orbital symmetry theory, recollecting his immediately prior invocation of just the kind of orbital overlap reasoning then popular in the field. The new insights brought to light an effect powerful enough to overwhelm the overlap component of the stereoelectronic factor. No wonder that the older ideas of orbital overlap fell into the shadows!

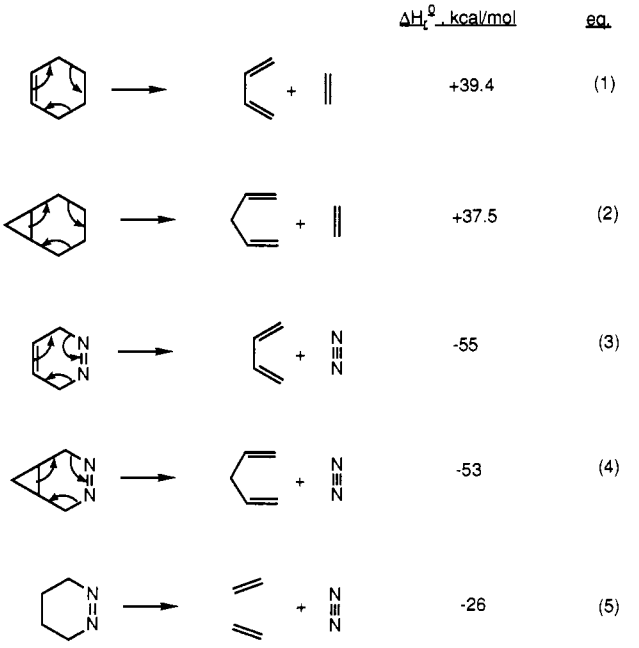
Moreover, the seed of the most effective tests of the new theory already had been planted in the 1966 lecture. By chance (or perhaps, in a sense, by necessity), the orbital symmetry thinking grew out of a conflict between experiment and the predictions of older, incomplete, intuitive ideas of stereoelectronic effects. It was natural to seek further confirmations of the orbital symmetry concepts by constructing experiments in which the orbital symmetry effect was placed *in opposition* to either steric or overlap effects. One hoped that, in this way, the phenomena specifically caused by orbital symmetry factors could be isolated and dramatized.

Nevertheless, the older ideas of orbital overlap never really had been examined fully. They were eclipsed in the dust storm kicked up by a herd of chemists jostling each other and scuffling for working space on the orbital symmetry problem. What now is beginning to emerge from several laboratories is the thought that in order

(2) Woodward, R. B. In *Aromaticity*, Special Publication No. 21; The Chemical Society: London, 1967; p 217.

(3) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970 and references cited therein.

Scheme I



to evaluate the strength of the overlap component of the stereoelectronic effect, it will be necessary to design experiments in which competing pathways in the test system are all orbital symmetry allowed, but some are preferred because of better overlap. Our contributions to this research have explored the consequences of the replacement of a double bond of a simple model system by an alicyclic[4] ring. Such a structural change will cause one of two orbital symmetry allowed reaction pathways of the derived homologue to enjoy better overlap.

Overlap in Cycloreversions. Stereochemistry of the Thermal Reverse Homo-Diels–Alder Reaction.[5,6] The usual reverse Diels–Alder reaction is a fragmentation of a cyclohexane to give a 1,3-diene and an alkene (Scheme I, eq 1). The unsubstituted version of this process is endothermic by about 39 kcal/mol. Unless special strain or product stability effects are present, therefore, the reaction is slow. This difficulty also is present in the reverse homo-Diels–Alder with an alkene dienophile (Scheme I, eq 2).

However, the corresponding fragmentations (Scheme I, eq 3) of 3,6-dihydropyridazines, diaza analogues of cyclohexenes, and of their homologues (Scheme I, eq 4) occur much more rapidly because the formation of the very stable fragment N_2 makes the reaction more than 90 kcal/mol more exothermic than that of eq 1.[7,8] The absence of ring-closure products and the extraordinary rate enhancements[5,6,9] associated with the di-

(4) In principle, a heterocyclic unit also could function in this way, although we know of no such examples.

(5) (a) Berson, J. A.; Olin, S. S. *J. Am. Chem. Soc.* **1969**, *91*, 777; (b) *J. Am. Chem. Soc.* **1970**, *92*, 1086. (b) Berson, J. A.; Petrillo, E. W., Jr.; Bickart, P. *J. Am. Chem. Soc.* **1974**, *96*, 636.

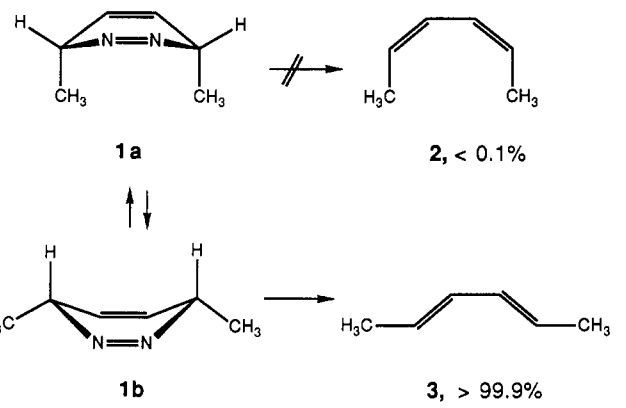
(6) Berson, J. A.; Olin, S. S.; Petrillo, E. W., Jr.; Bickart, P. *Tetrahedron* **1974**, *30*, 1639.

(7) The estimate given elsewhere[6] was based upon an earlier value of the heat of formation of azomethane. The present one uses a more recent determination.[8]

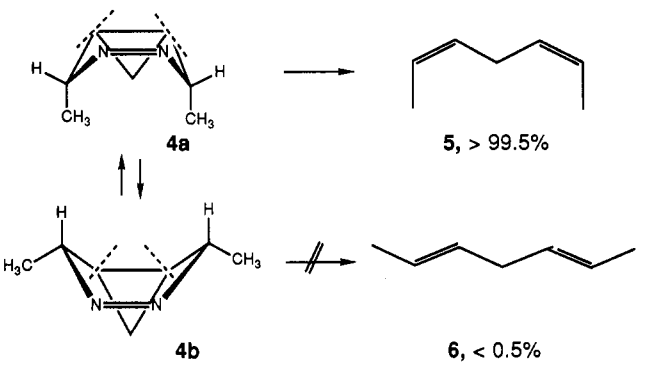
(8) Engel, P. S.; Montgomery, R. L.; Mansson, M.; Leckonby, R. A.; Foyt, H. L.; Rossini, F. D. *J. Chem. Thermodyn.* **1978**, *10*, 205.

(9) For kinetic studies of some related cases, see: (a) Allred, E. L.; Hinshaw, J. C. *J. Chem. Soc. D* **1969**, 1021. (b) Allred, E. L.; Hinshaw, J. C. *Tetrahedron Lett.* **1972**, 387. (c) Allred, E. L.; Hinshaw, J. C.; Johnson, A. L. *J. Am. Chem. Soc.* **1969**, *91*, 3383. (d) Allred, E. L.; Voorhees, K. J. *J. Am. Chem. Soc.* **1973**, *95*, 620.

Scheme II



Scheme III



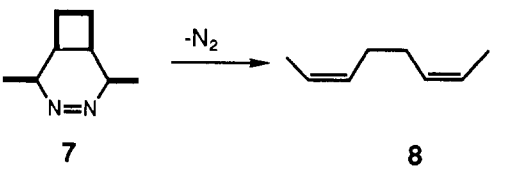
hydropyridazines, whose fragmentations are many orders of magnitude faster than those of tetrahydrahydropyridazines (e.g., Scheme I, eq 5), are consistent with concerted mechanisms for the reactions of eqs 1–4.

Appropriately placed substituents, as in the *cis*-3,6-dimethyl-3,6-dihydropyridazine (**1**) (Scheme II), bring out the fact that these fragmentations really have two orbital symmetry allowed pathways of decomposition, which are indistinguishable in the unsubstituted case. Formally, these may be represented as passing over transition states resembling conformations **1a** and **1b**. In the unsubstituted case (with hydrogens instead of CH_3 groups), the two pathways are equienergetic, but in the dimethyl case, the "flagpole" substituents in **1a** strongly interfere with each other and destabilize that transition state relative to the transition state from **1b**, where the methyl groups occupy "bowsprit" positions and the steric interference is minimized. Indeed, the sole product (Scheme II) of the fragmentation of **1** is the *E,E* diene **3**.[5,6] Here the steric factor is so large that one of the two orbital symmetry allowed pathways is preferred by a factor of >1000.

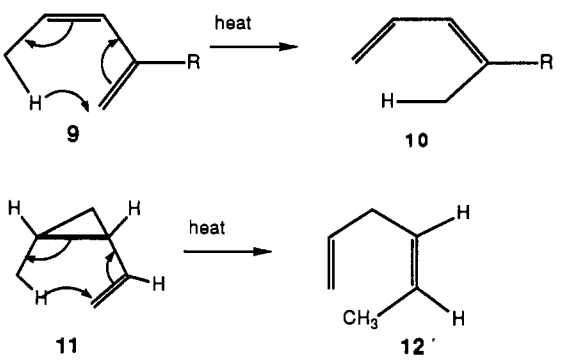
We now bring the overlap effect into play by replacing the C=C double bond of the dihydropyridazine **1** with a cyclopropane ring (Scheme III).[5] To test its strength, we place it in opposition to the steric effect in the syn bicyclic diazene **4**. Because of the gauche interaction of the "flagpole" methyls with the cyclopropane methylene group in **4a**, the preference for the uncrowded transition state (from **4b**) should be even larger than in the monocyclic case **1** and should lead to

(10) (a) Parziale, P. A.; Berson, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 1650. (b) Parziale, P. A.; Berson, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 4595. (c) Getty, S. J.; Berson, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 1652. (d) Getty, S. J.; Berson, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 4607.

Scheme IV



Scheme V



the *E,E* diene **6** if steric control were dominant. In fact, however, the only observed product (>200:1) is the *Z,Z* diene **5**. Some influence must be at work in the **4a** transition state that *reverses* the normal steric preference by a factor of >200 000. We proposed[5,6] that this powerful effect has its origin in the superior orbital overlap in the **4a** transition state, where the breaking C–N bonds are properly aligned with the canted orbital axes (dashed lines, Scheme III, **4a**) of the breaking cyclopropane ring bond. In the rival **4b** transition state, overlap is unsatisfactory because in projection, the axes of the orbitals involved are essentially perpendicular. Synthetically, the cyclopropane has compelled the choice of one pathway and controlled the stereochemical course of reaction at the sites of the two newly formed C=C double bonds.

This type of stereospecificity is not limited to cyclopropanes. We also have found[5,6] similar behavior with cyclobutanes (Scheme IV). Although the cycloreversion is much slower in this case, the diazene **7** with the *syn*-cyclobutane ring gives exclusively the *Z,Z* diene **8**, again with a stereospecificity too high to measure.

Overlap in Sigmatropic Rearrangements. Stereochemistry of the Intramolecular Reverse Ene Reaction. In principle, the overlap effect expressed in the above cycloreversions and generated by the anisotropic influence of a ring should apply also to other types of concerted pericyclic reactions. One now expects that, in general, replacement of a double bond by a ring will cause one of two orbital symmetry allowed pathways to be favored. On this hypothesis, we have begun a search for such selectivity in sigmatropic rearrangements. The first cases[10] we have studied are the intramolecular reverse ene reactions (homodienyl hydrogen shifts) in *cis*-2-alkyl-1-alkenylcyclopropanes and the analogous *cis*-2-alkyl-1-alkenylcyclobutanes. These systems generalized as **11** → **12** (Scheme V)[11–15] may be

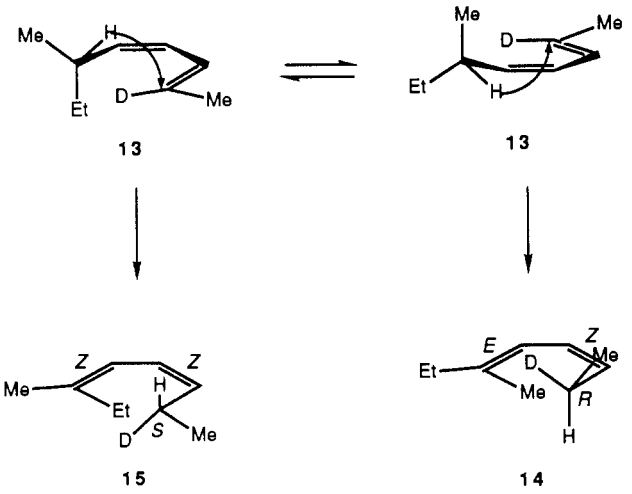
(11) (a) Ellis, R. J.; Frey, H. M. *J. Chem. Soc.* **1964**, 4770. (b) Frey, H. M.; Pope, B. M. *J. Chem. Soc. A* **1966**, 1701. (c) Ellis, R. J.; Frey, H. M. *Proc. Chem. Soc., London* **1964**, 221. (d) Ellis, R. J.; Frey, H. M. *J. Chem. Soc.* **1964**, 5578.

(12) (a) Roth, W. R.; König, J. *Justus Liebigs Ann. Chem.* **1965**, *688*, 28. (b) Roth, W. R.; König, J. *Justus Liebigs Ann. Chem.* **1966**, *699*, 24.

(13) Glass, D. S.; Boikess, R. S.; Winstein, S. *Tetrahedron Lett.* **1966**, 999.

(14) (a) Daub, J. P.; Berson, J. A. *Tetrahedron Lett.* **1984**, *25*, 4463. (b) Parziale, P. A. Ph.D. Thesis, Yale University, New Haven, CT, 1990.

Scheme VI



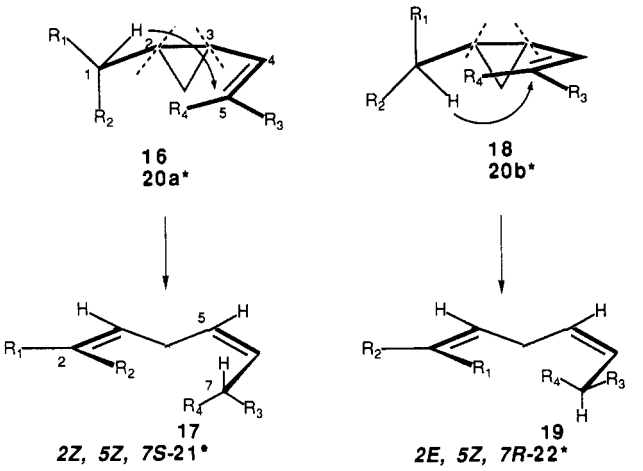
thought of as derived from the dienyl [1,5]-sigmatropic hydrogen shift[16] **9** → **10** (Scheme V) by replacement of the central double bond with a ring.

As a standard of comparison, the stereochemistry of the thermal dienyl [1,5]-sigmatropic hydrogen shift of (6*S*)-(2*E*,4*Z*)-6-methyl-2,4-octadiene-2-*d* (**13**, Scheme VI), elucidated by Roth and co-workers,[17] is instructive. As predicted by orbital symmetry, the reaction is suprafacial, giving only two products: (7*R*)-(3*E*,5*Z*)- and (7*S*)-(3*Z*,5*Z*)-octa-3,5-dienes-7-*d*, **14** and **15**, respectively. The electron distribution above and below the plane of the reactant diene **13** is essentially isotropic (it would be exactly so were it not for the stereogenic center). If the substituents were free of differential steric demands, one therefore would expect that **14** and **15** would be formed in equal amounts. Actually, product **14** is slightly favored (by 1.5:1), probably because of the slightly smaller steric demand of methyl vs ethyl.

Scheme V indicates what has been known about the stereochemistry of the homodienyl shift reaction, namely, that the substituents must be cis for the concerted process to occur and that the new double bond attached to the terminus of migration is always formed cis.[11,12] The latter preference has been estimated experimentally[14] to be at least 12 kcal/mol and calculated by ab initio theoretical methods[18] to be 17 kcal/mol.

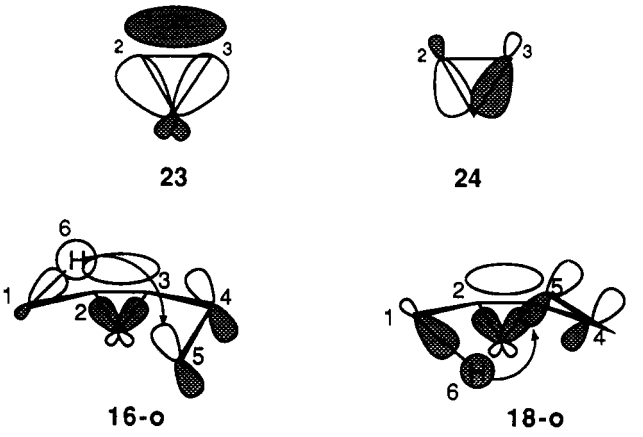
As Scheme VII shows, the homodienyl shift, like its dienyl counterpart, has two allowed suprafacial pathways (**16** → **17** and **18** → **19**), both of which produce the necessary cis configuration of the acceptor-derived double bond. However, a new stereoelectronic factor is introduced, because with respect to the space above and below the mean plane of the reacting carbon atoms (C_1–C_5, sigmatropic numbering), the electron distribution now is *anisotropic*, for reasons similar to those brought out in the homo-Diels–Alder cycloreversions of Scheme III. Analogously, orbital overlap in a transition state derived from **16** should be better than in one from **18**. Although they provided no direct experimental evidence, Glass, Boikess, and Winstein[13] seem to have been the first to recognize this stereoelectronic requirement of the homodienyl hydrogen shift,

Scheme VII[a]



[a] (*) $R_1 = CH_3$, $R_2 = CD_3$, $R_3 = CH_3$, $R_4 = D$.

Scheme VIII



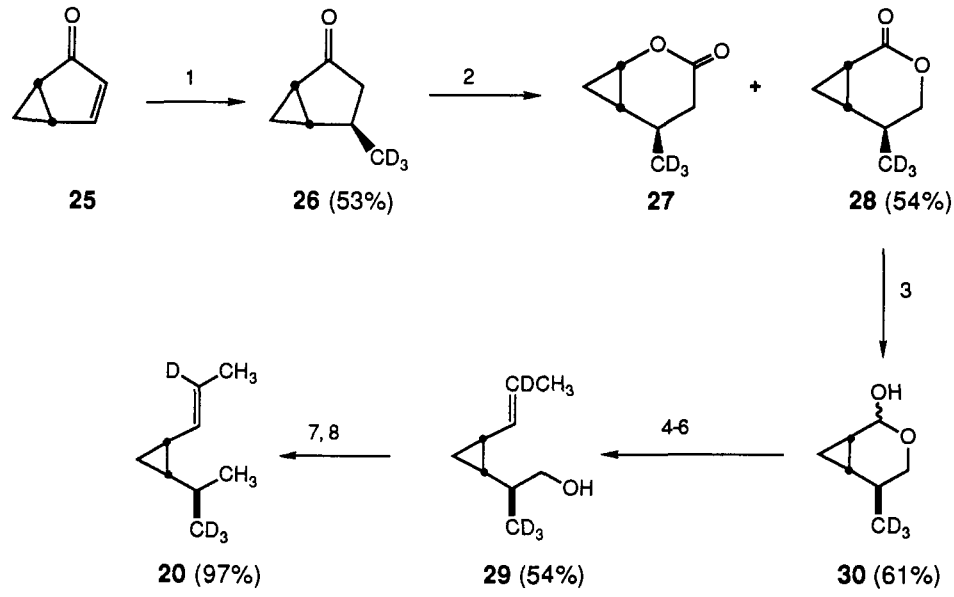
which they formulated in the comment "models indicate that this conformation (*i.e.* **16**) is the most favorable for overlap of the developing p-orbitals derived from the cyclopropane ring bond with the olefinic group and also the developing p-orbital derived from the C–H bond".

The idea of overlap outlined in the early work[13] relied merely upon the presumed directions of the cyclopropane orbital axes, but an analysis[10] of the actual orbital shapes and phase properties offers some new explicative and predictive advantages. The analysis predicts the same stereospecificity as the earlier one[13] and differs from it mainly in the identification of the actual orbital correlations. The key orbitals are the degenerate 3E′ highest occupied molecular orbitals (HOMOs) of cyclopropane, shown schematically as **23** and **24** (Scheme VIII).[19] It is the symmetric component **23** that correlates with a bonding π-orbital of the product, whereas the antisymmetric component **24** correlates with a bonding σ-orbital. The C–H σ-orbital of the reactant correlates with a C–H σ-orbital of the product. These phase properties imply that *overlap* of the other reacting orbitals with the symmetric component **23** will be an important influence on the geometry of the transition state.

Structure **16-o** (Scheme VIII) shows that the C–H bond orbital is aligned for good overlap with the sym-

(15) Review: Gajewski, J. J. *Hydrocarbon Thermal Isomerizations*: Academic Press: New York, 1981; p 186.
(16) (a) Wolinsky, J.; Chollar, B.; Baird, M. B. *J. Am. Chem. Soc.* **1962**, *84*, 2775. (b) Review: ref 15, p 106.
(17) Roth, W. R.; König, J.; Stein, K. *Chem. Ber.* **1970**, *103*, 426.
(18) Loncharich, R. J.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 2089.
(19) See: (a) Jorgensen, W. L.; Salem, L. *The Organic Chemist's Book of Orbitals*; Academic Press: New York, 1973; p 154. (b) Honegger, E.; Heilbronner, E.; Schmelzer, A. *Nouv. J. Chim.* **1982**, *6*, 519.

Scheme IX[a]



[a] Methods: (1) $(CD_3)_2CuLi$; (2) *m*-chloroperbenzoic acid; (3) $(i\text{-Bu})_2AlH$; (4) $CH_3CD{=}PPh_3$; (5) MeOD; (6) D_2O; (7) MsCl; (8) LAH; (9) GC separation. Yields represent isolated chromatographed product in the optically active series.

metric ring orbital when the migrant hydrogen is pointed toward the outside of the ring. Likewise, the best overlap of the acceptor double bond π-orbital (made up of the p-orbitals shown) with the ring orbital occurs in **16-o**, where the double bond adopts a position that makes its π-orbital nodal plane fit into the nodal notch between the lobes of the ring orbital. On the other hand, overlap of the relevant orbitals in structure **18-o** is unsatisfactory, since the C–H σ-orbital lies in the nodal notch, and the double-bond π-orbital presents its nodal plane to the outside lobe of the ring orbital. Note that both geometries correspond to suprafacial pathways and that both produce the characteristic 5*Z* double-bond stereochemistry.

It is true, of course, that in the transition state, the geometries **16** and **18** and the orbitals involved will be distorted from those of the ground state, but we follow the usual assumption[20-23] that orbital phase properties tend to persist along the reaction coordinate of a symmetry allowed reaction.

Thus, pathway **16** → **17** should be favored over pathway **18** → **19**, even though both are formally allowed by orbital symmetry.

Experimental Design. The Alkylalkenylcyclopropane Rearrangement. The rearrangement of *cis*-2(*S*)-[2(*S*)-propyl-*1*-d_3]-1(*S*)-[1(*E*)-propenyl-*2*-*d*]-cyclopropane (**20**) (Scheme VII) provides a test of this analysis.[10a,b] The molecule has the cis configuration of the side-chain substituents necessary for the concerted reverse ene reaction. Making the two substituents at the donor site differ only in isotopic content minimizes any steric bias to the configuration of the donor-derived double bond in the product. Similarly, the product owes its chirality to an isotopic distinction, so that the configuration at the newly created stereogenic center cannot be appreciably influenced by a simple steric preference at that site.

If the rearrangement occurred from conformation **20a** analogous to the predicted pathway **16** → **17** of Scheme VII, the product would be 2-methylocta-2(*Z*),5(*Z*)-diene-*1*-d_3-*7*(*S*)-*d* (**21**), whereas if it occurred from **20b**, analogous to the supposedly less favorable pathway **18** → **19**, the diastereomeric 2*E*,5*Z*-7*R* species **22** would be formed. Which pathway predominates would be revealed by determinations of the configurations of the product's double bonds and by correlation of the configurations of the stereogenic centers of the reactant and product.

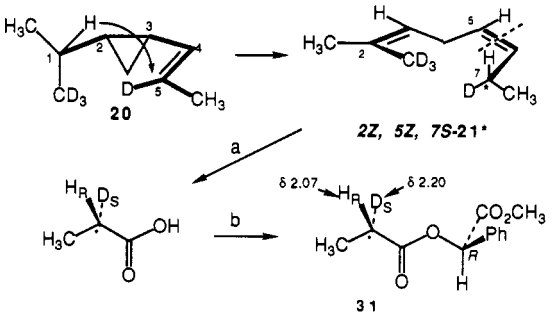
As would be expected by analogy with the earlier research,[11-15,17] the only product observed (0.1% detection limit) in the pyrolysis of racemic unlabeled **20** was the 5*Z* diene. The kinetic activation parameters, determined by measurements of the (cleanly first-order) rates of disappearance of **20** over the temperature range 183.0–247.9 °C, E_a = 35.5 kcal/mol and log A = 12.1 (A in s^{-1}), agreed well with those for pyrolysis of the closely related substance 1-propenyl-2,2-dimethylcyclopropane determined[14a] in earlier work.

Scheme IX shows the synthesis of the appropriate reactant **20** with all of the stereogenicity[24] and isotopic content incorporated. The absolute configurations of all three stereogenic carbons of **20** then were established by stereochemical correlation of the bicyclic enone **25** to the known[25] configurational reference 3-methylcyclopentanone.

Pyrolysis of Optically Active, Isotopically Labeled 20 and Stereochemical Analysis of the Product Diene 21. The >99.9% stereospecific 5*Z* configuration of the product diene **21** already observed in the pyrolysis of the unlabeled substrate **20** occurred again in the product of the labeled series. The configuration at the donor-derived double bond (C_2–C_3) was determined by ^1H NMR spectroscopy to be *Z* (>99.2%).

(20) Reference 2, p 10.
(21) Longuet-Higgins, H. C.; Abrahamson, E. W. *J. Am. Chem. Soc.* **1965**, *87*, 2045.
(22) Zimmerman, H. E. *Acc. Chem. Res.* **1972**, *5*, 393.
(23) Fukui, K. *Acc. Chem. Res.* **1971**, *4*, 57.
(24) Enantiomeric purity established by enantiospecific capillary gas chromatographic analysis of a derivative of **25** by the method of Schurig and Weber: Schurig, V.; Weber, R. *J. Chromatogr.* **1981**, *217*, 51.
(25) Eisenbraun, E. J.; McElvain, S. M. *J. Am. Chem. Soc.* **1955**, *77*, 3383.

Table I.
Percent Stereospecificity in the Transformation 20 → 21



(a) RuO_4. (b) (*R*)-PhCH(OH)CO_2CH_3, DCC.

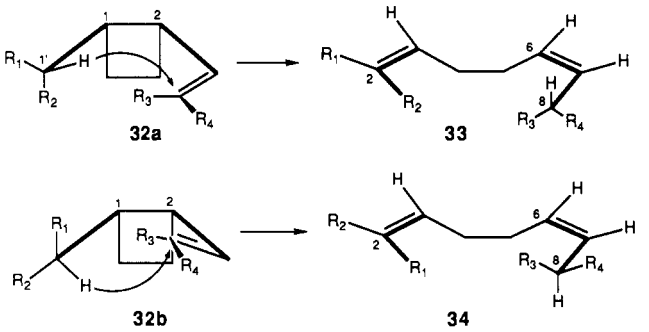
method	reactant (20)	product (21)	stereospecificity
^{2}H NMR	ee 86.7 ± 1.8; 87.3 ± 2.4	ee 86.1 ± 3.7; 83.8 ± 5.2	ee 99 ± 5
^{1}H NMR	ee 82.0 ± 1.8; 82.5 ± 2.4	ee 80.9 ± 0.7	ee 99 ± 4
^{1}H NMR	2(*S*)-propyl-*1*-d_3 99.5 ± 0.5	2*Z* 99.2 ± 0.3	2*Z* 99.7 ± 0.6
GC		5*Z* >99.9	5*Z* >99.9

These results imply that, if the hydrogen migration is suprafacial, the overlap-favored pathway dominates (Scheme VII, **20a** → **21**). A direct proof of suprafaciality was obtained by oxidative degradation of the product diene **21**-*7-d* to propanoic acid-*2-d* (Table I), which was converted to the (*R*)-methyl mandelate ester **31** with enantiomerically homogeneous methyl mandelate. It was known[26] that the *pro-R* and *pro-S* protons of the propanoyl group of this ester could be distinguished by NMR spectroscopy. In the unlabeled series, the H_S and H_R resonances occur at δ 2.20 and 2.07, respectively. ^{2}H and ^{1}H NMR analyses of the **31** obtained from the degradation of the pyrolysis product diene **21** showed resonances at the D_S and H_R chemical shift positions corresponding to 99 ± 5% and 99 ± 4%, respectively, of those maximally available from the reactant hydrocarbon **20**. The stereospecificity at each of the three stereogenic sites of the product **20** thus is essentially complete.

A comparison of the results of the dienyl and homodienyl hydrogen shift reactions (**13** vs **20**) thus shows that replacement of the central double bond of a 1,3-diene (C_2–C_3 of the sigmatropic system) with a cyclopropane ring converts a molecule that is nearly indiscriminate in its choice between two suprafacial pathways to one that is, within experimental error, totally stereospecific in the sense predicted by the orbital overlap effect. With respect to the C_2–C_3 nodal plane, it is the change from an isotropic electron distribution in the diene to an anisotropic one in the homodiene that causes the dramatic switch in stereospecificity.

Experimental Design. The Alkylalkenylcyclobutane Rearrangement.[10c,d,27] Like the HOMOs of cyclopropane, the HOMOs of cyclobutane consist of one component symmetric and the other antisymmetric with respect to a plane C_s between C_1 and C_2.[28-31] Formally, therefore, the correlation diagrams for the

Scheme X



reverse ene hydrogen shift reactions of the cyclobutane and cyclopropane systems will be similar. Only the symmetric HOMO of the reactant can correlate with a bonding π-orbital of the diene product, and the C_s-symmetric HOMO may be said to control the stereochemistry of the reaction. Analogy to the cyclopropane case would predict that, for the concerted rearrangement of *cis*-2-alkyl-1-alkenylcyclobutanes, the stereoelectronically preferred transition-state geometry should be that generated from conformation **32a** rather than **32b** (Scheme X), and the predominant reverse ene product should be diene **33** rather than **34**.

Several obstacles make the execution of this plan more difficult than in the cyclopropane system. First, the reverse ene reactions of *cis*-1-alkenyl-2-alkylcyclobutanes are much slower than those of their cyclopropane counterparts.[10c,d,27,32] As a result, at 243 °C, for example, fragmentation (34%), epimerization (32%), and carbon sigmatropic rearrangement (10%), reactions not seen in the corresponding cyclopropane system, now all compete with the reverse ene reaction (24%) of the cyclobutane, whose product is the depository of the desired stereochemical information but now is formed in only a minor amount.

Second, since the primary product of the reverse ene reaction is a 1,5-diene, one might expect secondary Cope rearrangement to consume it or, if the rearrangement

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(27) (a) An earlier approach from this laboratory is described elsewhere: Jordan, L. M. Ph.D. Dissertation, Yale University, 1974. (b) Reviewed by Gajewski: Gajewski, J. J. In *Hydrocarbon Thermal Isomerizations*; Academic Press: New York, 1981; p 178.
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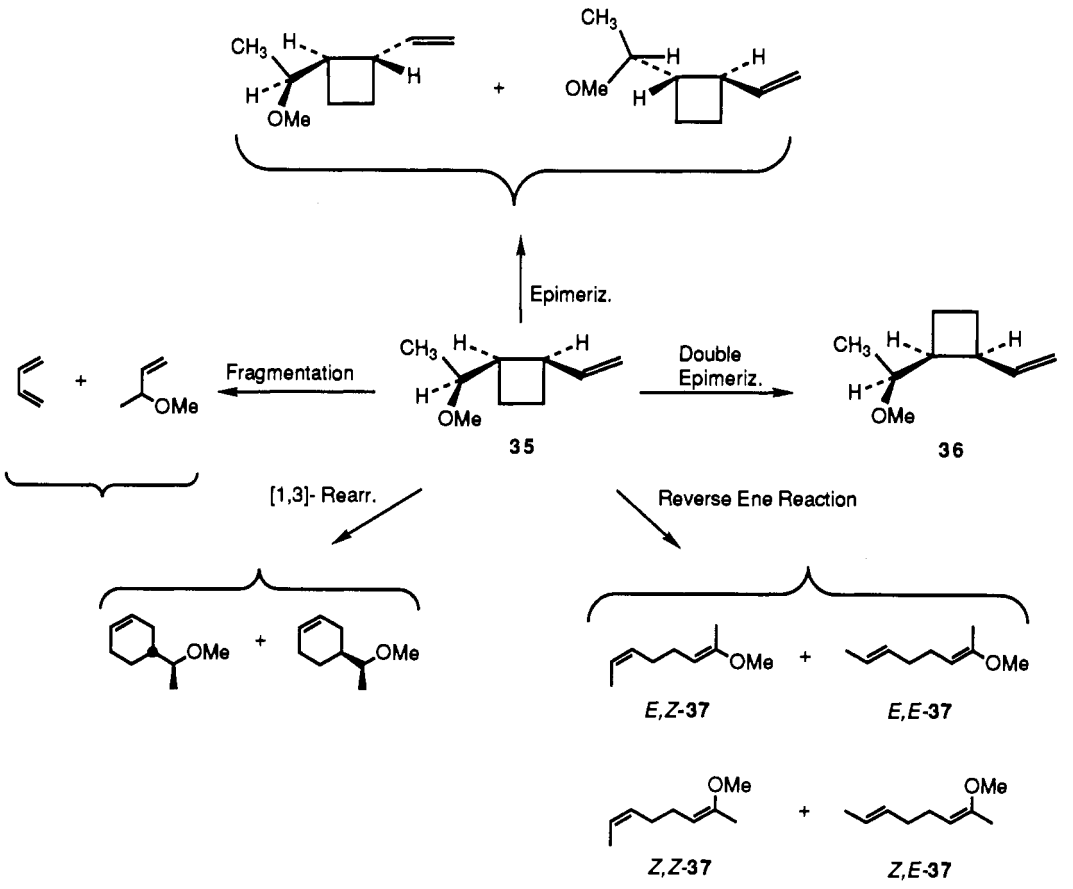
Scheme XI



is reversible, to alter it stereochemically. In fact, prior studies[27] already had found such a stereochemical disturbance in a related case. For reasons given elsewhere,[10c,d] the use of a methoxy group as R_1 or R_2 was expected to and did provide a suitable solution to this problem.

Although the full definition of the stereochemistry of the reverse ene reaction requires a reactant with specified configuration at three carbon atom stereocenters and one double bond (Scheme X), a less complete labeling pattern in which the reactant's double bond terminates in the stereochemically uninformative CH_2 group (Scheme X, $R_3 = R_4 = H$) also can yield valuable partial solutions with significant savings in synthetic and analytical effort. Accordingly, we have conducted experiments in two series of reactants, one a racemic, partially labeled case ($R_1 = CH_3$, $R_2 = OCH_3$, and vice versa; $R_3 = R_4 = H$), and the other an enantiomerically enriched, fully labeled case ($R_1 = OCH_3$, $R_2 = CH_3$, $R_3 = D$, $R_4 = CH_3$).

Products and Kinetics in the Partially Labeled Series. Scheme XI shows the products obtained in the pyrolysis of the partially labeled cyclobutane **35**. A corresponding study (not depicted here) was carried out on the diastereomer **36**, whose behavior matched that of **35** closely. This confirmed our hypothesis that the effect of the methoxy group would be independent of its configuration and hence that it would act here as an essentially inert stereochemical marker. From the temperature dependences of the overall rate of disappearance of the reactant **35** and the product distributions, the activation parameters for the individual pathways could be determined. These are given in Table II. Although the analytical uncertainties limit the accuracy of the data, the activation energy and preexponential term for the reverse ene reaction do seem to be lower than those of the other three competing pathways (fragmentation, epimerization, and [1,3]-sigmatropic rearrangement). This finding is at least consistent with a difference in mechanism for the two sets of reactions: a concerted pathway for the reverse ene reaction and stepwise biradical processes for some or all of the others.

Table II.
Activation Parameters for Major Rearrangement Pathways of 35

process	E_a, kcal/mol	log A (A in s^{-1})	$\Delta S^{\ddagger}$, gibbs/mol
fragmentation	50.6 ± 2.6	15.5 ± 1.1	9.4 ± 4.9
epimerization	48.4 ● 2.4	14.5 ± 1.0	4.6 ± 4.5
[1,3]-rearrangement	48.2 ± 2.7	14.0 ± 1.1	2.3 ± 5.1
reverse ene	42.4 ± 2.3	11.9 ± 1.0	−7.2 ± 4.3

As Scheme XI shows, the double epimerization at the ring stereogenic centers causes diastereomeric interconversion of reactants **35** and **36**. Since the rates of reverse ene reaction in the pyrolyses of the two diastereomers are comparable, it must be the case that some of the product in the pyrolysis of **35** actually arises from **36**, and vice versa. Therefore, the actual product distributions in the reverse ene reactions of mechanistic interest here must be corrected for the concurrent double epimerization. When this was done (by a procedure described elsewhere[10c,d]), it was possible to show that the mechanistically significant ratio of product 2(*E*),6(*Z*)-**37** to 2(*Z*),6(*Z*)-**37** formed *directly from reactant* **35** is >220:1, and the ratio of product 2(*Z*),6-

(*Z*)-**37** to 2(*E*),6(*Z*)-**37** formed directly from reactant **36** is >35:1.

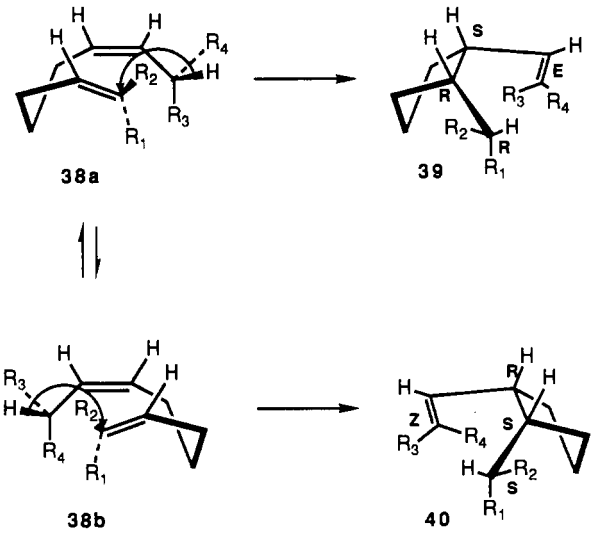
In these partially labeled systems, the product configuration at the origin of migration and at the double bond adjacent to the terminus of migration are unambiguously defined. The results strongly imply the transition-state stereochemistry associated with the reaction **32a** → **33** of Scheme X. Only if the hydrogen shift took an unexpectedly antarafacial course could the interpretation be in jeopardy. This remote possibility is experimentally made untenable by an independent study of a fully labeled, enantiomerically enriched reactant (1*R*,2*R*,1′*S*)-1-(1-methoxyethyl)-2-[1(*E*)-propenyl-2-*d*]cyclobutane (Scheme X, **32**, R_1 = OMe, R_2 = CH_3, R_3 = D, R_4 = CH_3). The hydrogen shift accounts for only 6% of the total product in this case, which makes a quantitative determination of the efficiency of stereogenicity transfer to the newly created center at the terminus of migration difficult, but the degradation of the deuterated diene **33** (R_1 = OMe, R_2 = CH_3, R_3 = D, R_4 = CH_3) to (*S*)-propanoic acid-2-*d* by the same method used in the cyclopropane series shows that the hydrogen shift is at least 81% stereospecifically suprafacial.

Thus, despite the small energetic benefit, the reverse ene reaction in both diastereomeric cyclobutanes **35** and **36** and in the fully labeled case **32** (R_1 = OMe, R_2 = CH_3, R_3 = D, R_4 = CH_3) is highly stereospecific in the sense predicted by overlap control. Since the stereospecificities in these rearrangements are all so high as to be "off scale", it is not yet possible to tell whether the transfer of stereogenicity in the cyclopropane is more efficient than that in the cyclobutanes.

Prospects. Can Overlap Control of the Intramolecular Ene Reaction Persist in Larger Rings? As already has been mentioned, the symmetry properties of the canonical HOMOs of cyclopropane (**23** and **24**, Scheme VIII) also are found in cyclobutane. In fact, the pattern of two nominal σ_{CC} orbitals, one symmetric and one antisymmetric to the C_σ plane, is characteristic of the HOMOs of all of the simple alicyclic rings. In the case of cyclopentane in the envelope conformation, for example, the corresponding two such (nominal) HOMOs are found, with the symmetric component being lower in energy by only about 4.5 kcal/mol (at the MINDO/2 level of theory).[35] Would orbital overlap effects similar to those we observe in cyclopropane and cyclobutane also be present in cyclopentanes? One counterargument is that, for an increasing number of carbon atoms in the ring, the amount of bending in the ring bonds would become negligible and the concentration of electron density outside the ring quickly would fall off, hence diminishing the preference of the migrant hydrogen to stay to the outside. However, the electron distribution still would be anisotropic, because a nodal surface *inside* the ring would persist, just as in cyclopropane.

A second deterrent to the study of the cyclopentane case is a practical matter: Because of the decreased ring strain in cyclopentane, the *reverse* ene reaction, *cis*-1-alkenyl-2-alkylcyclopentane → acyclic 1,6-diene, would become contrathermodynamic in simple cases. This suggests that the study of the stereochemistry of the *forward* intramolecular ene reaction would be fruitful. Scheme XII shows the outlines of such an experiment, which is now under way.[36] Because the reactant **38** is acyclic, *two* overlap-favored pathways become available, one leading to **39**, which has the *E* configuration of the double bond at the migration origin, and the other to **40**, which has the *Z* configuration. The configurations at all three stereogenic carbon centers of **39** and **40** are enantiomeric. It should be obvious that orbital overlap effects in the intramolecular ene reaction can operate sometimes to reinforce and sometimes to oppose the more conventional steric effects usually employed[37-42] as means of stereocontrol in synthesis.

Scheme XII



Conclusions. Orbital overlap effects now have been observed to control the stereochemistry and rate of a range of pericyclic reactions. The effect can be overwhelming, in some instances at least 2×10^5 times as strong as a countervailing >1000:1 steric effect. Further mechanistic investigation should define the limits of stereocontrol by the anisotropic electron distribution of a breaking or forming ring. The implications of these phenomena for the design of extremely efficient stereogenicity transfer reactions of synthetic value remain to be explored.

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