
7 Reaction mechanisms

Part (ii) Pericyclic reactions

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1 Introduction

Research into the mechanisms of pericyclic reactions continues at a rapid pace. Many of the studies described below address the factors which influence whether a reaction will proceed *via* concerted rearrangement or will follow a stepwise alternative. Numerous papers published this year report high-level computational studies undertaken to explain unusual regiochemistry or stereochemistry determined by experiment. Heteroatomic versions of pericyclic rearrangements also have attracted much attention.

The existence of secondary orbital interactions in pericyclic reactions was questioned by García, Mayoral and Salvatella.¹ Several examples were reinterpreted, using other factors such as solvent effects, steric interactions, hydrogen bonds and electrostatic forces to account for stereoselectivity previously explained by secondary orbital interactions. The authors center their discussion on the *endo:exo* selectivity in the Diels–Alder reaction.

Kläerner and Wurche reviewed the effects of pressure on organic reactions, including pericyclic reactions.² Pressure effects are thought to arise from differences in packing coefficients between reactants and transition states, and pericyclic activation volumes tend to be negative due to the highly organized transition states. Swiss and Firestone question whether accurate activation volumes are obtained by measuring the pressure dependence of reaction rates.³ They point to a second factor, solvent viscosity, which can also affect reaction rates. For example, Diels–Alder reactions, 1,3-dipolar cycloadditions and Claisen rearrangements are accelerated in solvents with increasing viscosity; thus, the activation volumes previously determined must be corrected for the pressure-induced change in solvent viscosity, and as such the changes in volumes become less negative. This correction can be as great as 61%.

Two books which include discussions of pericyclic reactions were published. Ansari, Qureshi and Qureshi authored a book titled *Electrocyclic Reactions: From*

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*Fundamentals to Research.*⁴ Williams contributed *Concerted Organic and Bio-organic Mechanisms*.⁵

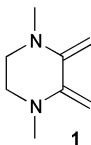
2 Cycloaddition reactions

Ponti uses density functional theory (DFT) to predict the regioselectivity of cycloaddition reactions.⁶ The author develops a quantitative measure of the relative stability and importance of individual atom–atom interactions. This uniform figure of merit was obtained from the atomic grand potential variation. The predictions made using this approach are equivalent to the commonly used but less rigorously derived local softness matching criteria.

Diels–Alder reactions

The concerted *versus* stepwise Diels–Alder cycloaddition of butadiene and ethylene were compared by Sakai.⁷ High-level CAS calculations correctly reproduce the experimental reaction energy, but provide a barrier for concerted cycloaddition of 41–47 kcal mol^{−1}, significantly larger than the experimental value of 27.5 kcal mol^{−1}; these differences may be due to dynamical effects. Configuration interaction/localized molecular orbital CASSCF calculations along the intrinsic reaction coordinate reveal the concerted transition state to be aromatic. The transition state for the concerted reaction is 2.7 kcal mol^{−1} lower than the first transition state for the stepwise alternative which produces the *anti* biradical. The *anti* biradical undergoes bond rotation followed by barrierless ring closure.

Kniep, Boese and Sustmann studied the Diels–Alder cycloaddition of electron-rich diamino diene **1** with alkenes of various electrophilicities.⁸ Cycloaddition occurs

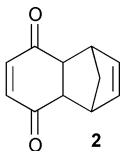


readily, and retention of alkene configuration is observed with (*E*)- and (*Z*)-1,2-dicyanoethene, indicative of a concerted process. Stereoselectivity is lost in cycloadditions of **1** with dimethyl dicyanofumarate and dimethyl dicyanomaleate, which occur *via* a zwitterionic intermediate. Stepwise addition of tetracyanoethylene yields a cyclopentene derivative in addition to the formal Diels–Alder adduct. Differences in reactivity are due to the relative electrophilicity of the alkene, compared to the nucleophilicity of the diene.

Diels–Alder cycloaddition of *s-trans*-butadiene with ethylene, yielding *trans*-cyclohexene, was investigated by Johnson *et al.*⁹ A variety of computational methods reveal that concerted cycloaddition can occur *via* a C₂-symmetric transition state which is 43 kcal mol^{−1} above reactants and about 17 kcal mol^{−1} higher in energy than the transition state for a conventional Diels–Alder reaction. The magnetic properties calculated for the *s-trans* transition state are consistent with an aromatic structure. Stepwise reaction of *s-trans*-butadiene has an activation energy of 32–35 kcal mol^{−1}.

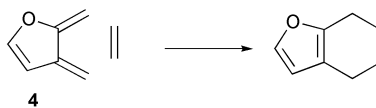
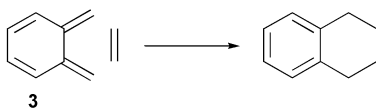
The energetics of the retro-Diels–Alder reaction of *cis*-cyclohexene suggest that *cis*–*trans* isomerization may occur competitively with concerted cycloreversion, a reaction which could conceivably occur from *trans*-cyclohexene.

Pool and White studied the structures of retro-Diels–Alder reactants.¹⁰ Specifically, they looked at crystal structures of bicyclic cyclohexenes in which the ring is held in a boat-like conformation, pre-aligned for the cycloreversion. The retro-Diels–Alder substrates exhibited elongation of the C–C σ bonds, compared to the saturated analogs. The greatest elongation was observed in **2**, which is known to undergo retro-Diels–Alder reaction at room temperature, due to ground-state destabilization.

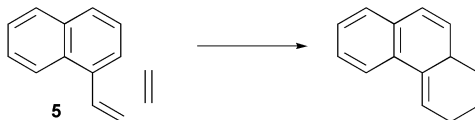


Geerlings and co-workers studied Diels–Alder reactions in which the substituent either gains or loses aromaticity.¹¹ For example, reaction of non-aromatic *o*-quinodimethane **3** or furanoquinodimethane **4** with ethylene yields an aromatic product, while 1-vinylnaphthalene **5** loses aromaticity upon reaction (Scheme 1). Calculations (B3LYP/6-31G*) show that reactions in the first category occur with lower activation energies and higher exothermicities than the parent reaction of

gain in aromaticity: fast, favorable reaction



loss of aromaticity: slow, less favorable reaction



intermediate situation



Scheme 1

butadiene and ethylene, and that these reactions proceed through early transition states. In compounds like **5**, the net loss of aromaticity deactivates cycloaddition compared to the reaction of butadiene and ethylene, and in reactions of compounds such as benzo[*c*]furan **6**, the compromises between aromaticity gains and losses are revealed both structurally and energetically. Nucleus independent chemical shifts and magnetic susceptibility exaltations were also calculated for these reactions.

Hetero Diels–Alder reactions. Numerous studies on heteroatomic variants of the Diels–Alder reaction were published. For example, Mayr and co-workers determined reaction rates for the aza Diels–Alder cycloaddition of $\text{Me}_2\text{N}^+=\text{CH}_2$ with a variety of dienes.¹² The reaction with cyclopentadiene is believed to occur through a concerted mechanism, since the rate of reaction is 10^4 times greater than expected for the stepwise alternative. The reactions with methyl-substituted butadienes are not significantly faster than predicted for a stepwise reaction, and if concerted would be highly asynchronous. All reactions proceeded with high regio- and stereoselectivity.

Bobrowski, Liwo *et al.* studied the [4 + 2] addition of singlet oxygen to buta-1,3-diene and benzene.¹³ Butadiene undergoes a stepwise reaction with a 10 kcal mol^{-1} barrier to form a linear biradical intermediate, which lies 4 kcal mol^{-1} above reactants. Benzene reacts *via* a concerted pathway. The authors suggest that these reactivity differences are due to the conformation of the peroxide unit; the concerted reaction requires a *syn* structure, which is unfavorable to attain in the reaction with butadiene.

Stereo- and regioselectivity. A large number of computational studies were performed to better understand stereo- and regioselectivities observed experimentally. For example, Calvo-Losada and Suárez investigated the *endo:exo* selectivity in the cycloaddition of furan and maleic anhydride;¹⁴ experiments do not agree on the relative energies of the two cycloaddition modes. The calculated gas-phase free energies of activation either show the *endo* transition state to be favored by 0.6 kcal mol^{-1} (MP4/6-311+G(3df,2p)) or find isoenergetic transition states (B3LYP/6-311+G(3df,2p)//B3LYP/6-31G*). The two transition states have very similar bonding and electronic structures, but only the *endo* transition state was found to have both a ring and cage critical point using Bader's theory of atoms in molecules, indicative of π – π secondary contacts. The authors also compared the transition state energies obtained in acetonitrile solution and found that solvation stabilizes the *exo* transition state more than the *endo* transition state.

Effects of reaction medium. The environment in which a Diels–Alder reaction occurs can have a large influence on the reaction. Otto and Engberts reviewed Diels–Alder reactions in water.¹⁵ Also, Kong and Evanseck report a DFT study on the aqueous Diels–Alder reaction of butadiene and acrolein.¹⁶ The inclusion of explicit water molecules causes polarization of the transition states, and stabilizes them more than the reactants. In the most favorable *endo-s-cis* transition state, hydrogen bonding accounts for half of the rate acceleration. Macroscopic solvent effects, obtained using the polarizable continuum model, are responsible for the other 50%, specifically through enforced hydrophobic interactions and antihydrophobic cosolvent effects. An analysis of Mulliken overlap reveals that three different types of secondary orbital

interactions are needed to fully explain the $2.4 \text{ kcal mol}^{-1}$ bias towards the *endo* cycloaddition mode. The results all support Alder's hypothesis of maximum accumulation of unsaturation.

The role of solvent in the *endo-s-cis* Diels–Alder cycloaddition of cyclopentadiene and methyl vinyl ketone was studied by Hammes-Schiffer and co-workers.¹⁷ The minimum energy path was calculated for the gas-phase reaction as well as with two water molecules. Dynamic effects were included using a reaction path Hamiltonian, which includes vibrational motion orthogonal to the minimum energy path. Hydrogen bonding of the two water molecules to the oxygen is stronger at the transition state than at the reactant, and lowers the free energy of activation by $5.2 \text{ kcal mol}^{-1}$. The water molecules also lead to a more dissociative and polar transition state. The transmission coefficient in the presence of water was slightly lower than without water. For this Diels–Alder reaction, the dynamical solvent effects are small.

Reactions conducted in a confined space have been observed to promote Diels–Alder cycloaddition. For example, Sanders and co-workers prepared two metallo-porphyrin hosts which accelerate the reaction of 4-pyridyl butadiene with 3-nitrosopyridine by factors of 65 and 840.¹⁸ The product binds tightly to the host and induces structural changes, as determined by X-ray crystallographic analysis of the product-bound and unbound host. The desolvation of host and guests may also contribute to the rate accelerations observed.

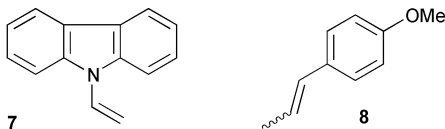
Lewis-acid catalysis. Lewis acids are commonly used to accelerate Diels–Alder reactions and increase regio- and stereoselectivity, though the origins of these effects are still under debate. Previous calculations suggest that a BF_3 -catalyzed $[4 + 2]$ cycloaddition may occur using two electrons from butadiene with four electrons from acrolein, followed by Claisen rearrangement to the normal Diels–Alder product. Yamabe and Minato extended this study by calculating the reaction of butadiene and acrolein in the presence of BCl_3 , AlCl_3 , SnCl_4 , and other Lewis acids, with and without one dimethyl ether solvent molecule.¹⁹ The AlCl_3 -catalyzed reaction was studied thoroughly, and conventional Diels–Alder cycloaddition is preferred by 12 kcal mol^{-1} over an alternative stepwise pathway (B3LYP/6-311+G(2d,p) SCRF//B3LYP/6-31G* SCRF). The concerted pathway has a very flat potential energy surface up to the late transition state, which is only $0.8 \text{ kcal mol}^{-1}$ above reactants. The stepwise pathway occurs *via* a zwitterionic intermediate that closes to a vinyl dihydrofuran, which then undergoes Claisen rearrangement to the conventional Diels–Alder adduct. Inclusion of one dimethyl ether molecule does not greatly change the structures along the reaction coordinate, and the aluminium–oxygen distance remains constant throughout. However, the energy of activation increases by 5 kcal mol^{-1} . Using the harder BCl_3 catalyst, solvation effects are smaller, consistent with a large boron–oxygen distance. The authors conclude that the preferred *endo* mode of cycloaddition is due to secondary orbital interactions.

Avalos, Babiano *et al.* calculated the BF_3 -catalyzed cycloaddition of furan with methyl vinyl ketone at the B3LYP/6-31G* level of theory.²⁰ Four transition states were considered, both for the catalyzed and uncatalyzed reactions, with the dienophile *s-cis* versus *s-trans*, and *endo* versus *exo*. All cycloadditions are concerted and asynchronous, with the BF_3 -catalyzed reactions being more asynchronous and occurring with a lower activation energy. The most favorable reaction is catalyzed,

with *endo* approach of reactants and methyl vinyl ketone in the *s-cis* conformation, and has a late transition state. In this structure, secondary interactions between the diene and dienophile are maximized, leading to stabilization. The interaction of BF_3 and the dienophile was found to be less important.

Radical cation Diels–Alder reactions. The gas-phase cycloaddition of buta-1,3-diene radical cation and acetylene was studied using FT-ICR mass spectrometry by Bouchoux and co-workers.²¹ The reaction products are all C_6H_7^+ ions: protonated benzene and two protonated forms of fulvene. These products are obtained following stepwise cycloaddition to cyclohexa-1,4-diene radical cation. Calculations (UMP2/6-311+G(d,p)//UMP2/6-31G(d)) were also performed and are consistent with experiment. Note that the product of reaction of buta-1,3-diene radical cation with ethylene is the cyclopentenyl cation instead of the Diels–Alder adduct.

Bauld and co-workers published several papers on radical cation Diels–Alder cycloadditions. They are interested in determining the cross-over point between stepwise and concerted reactions. Cycloadditions of the radical cation of *N*-vinylcarbazole **7** and cyclopentadiene or cyclohexadiene are stepwise based on deuterium labeling studies, and occur through a relatively long-lived distonic radical cation intermediate.²² The electron-donating nitrogen substituent stabilizes the intermediate carbocation and hence the stepwise pathway. A preference for *endo* cycloaddition was observed. No cyclobutane adducts were produced, despite the known ability of **7** to undergo neutral/radical cation cyclodimerization. Also, the



cycloadditions of the radical cations of *cis*- and *trans*-anetholes **8** with cyclopentadiene were studied; the methoxy group is expected to stabilize the radical cation intermediate less than the nitrogen group in **7**.²³ Reaction of the *cis* isomer gives similar amounts of all four stereoisomeric products, indicative of a stepwise reaction. The *trans* isomer gives exclusively *trans* cycloaddition adducts; ring closure from the radical cation intermediate is thus 1000 times faster than bond rotation, possibly due to the steric effect of the methyl group. Alternatively, the high selectivity could be explained by a concerted cycloaddition, though it would be unusual for *cis* and *trans* isomers to exhibit such different reactivity. The authors explore this point further using deuterium-labeled 4-vinylanisole to address the steric role of the *trans* methyl group.²⁴ This radical cation cycloaddition occurs by a stepwise mechanism, suggesting that the reaction of *trans*-**8** follows the same pathway. The authors conclude that high stereoselectivity does not necessarily indicate that a reaction is concerted.

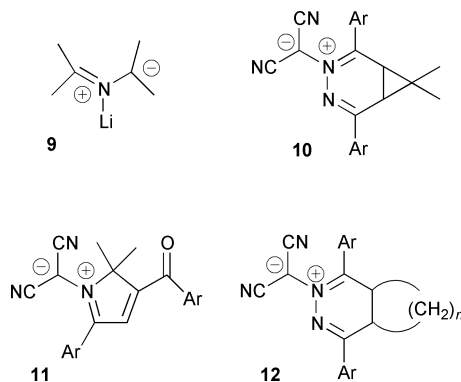
1,3-Dipolar cycloadditions

Due to the synthetic utility of 1,3-dipolar cycloadditions, there is great interest in understanding the variables which influence the reaction mechanism. A large number of studies were performed to investigate whether a reaction is stepwise or concerted,

as well as to determine reaction rates, regioselectivities and stereoselectivities. A few representative papers are discussed in this section.

Vivanco *et al.* studied the [3 + 2] cycloaddition of azomethine ylides **9** to electron-poor nitroalkenes.²⁵ *N*-Metalation of the ylide leads to a stepwise reaction. The zwitterionic intermediate can be observed by NMR and was also found computationally. Reaction of *N*-unsubstituted azomethine ylides with nitroalkenes may be stepwise or concerted, depending on the extent to which substituents stabilize the zwitterionic intermediate. The authors present an analysis based on second-order perturbation theory to predict whether a variety of cycloadditions will occur in a concerted or stepwise fashion.

Cycloaddition reaction rates for addition of stable azomethine ylides **10–12** to dipolarophiles were determined by Sauer and co-workers.²⁶ Some dipolarophiles had



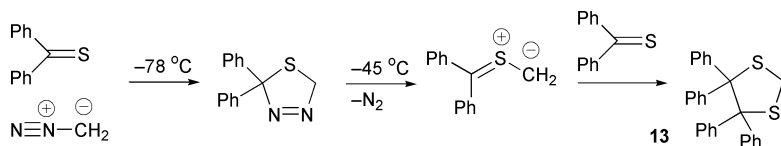
bond angle strain, others were electron poor, and others electron rich. Most reactions are controlled by HOMO_{dipolarophile}–LUMO_{dipole} interactions. The reaction rates were not greatly affected by solvent, and Hammett analysis revealed that the reaction constants ρ were small, both indicative of concerted cycloaddition.

Domingo reported the results of calculations of the inverse electron demand cycloaddition of nitrones $R_2C=N^+R-O^-$ with vinyl ethers.²⁷ Calculations at the B3LYP/6-31G* level reveal that gas-phase cycloaddition is concerted but asynchronous, and the *ortho* regiochemistry is more favorable than *meta*. The *endo*:*exo* product ratio is dependent on steric interactions. Lewis acids increase the asynchronicity of the reaction and lower the activation enthalpy for *ortho* but not *meta* cycloaddition. The effects of solvent were included using the polarizable continuum model, and lead to even greater asynchronicity. With catalysts and solvent included, the reaction is best described as proceeding by a two-phase concerted reaction mechanism in which nucleophilic attack by the alkene on the nitrone is followed by cyclization, rather than as pericyclic.

The cycloadditions of nitrone to ethene, cyclobutadiene and benzocyclobutadiene were calculated by Di Valentin *et al.*²⁸ For ethene and benzocyclobutadiene, concerted cycloaddition is greatly preferred over the stepwise diradical reaction mechanism. The high-energy antiaromatic nature of cyclobutadiene increases the likelihood of stepwise reaction, making it competitive with the concerted process; this is the first example which may follow the diradical mechanism proposed by Firestone.

Cycloaddition rates for the reaction of ozone with alkenes were measured at room temperature by Marston and co-workers.²⁹ The alkenes include methylene cycloalkanes, chlorinated alkenes and monoterpenes, which are important in atmospheric chemistry. The reaction rates were analyzed in terms of frontier orbital theory, and some deviations in the expected relationship between HOMO–LUMO gap and activation energy were observed. This scatter was attributed to unsymmetrical electron density distributions in the alkene HOMOs.

Huisgen *et al.* determined the mechanism of the Schönberg reaction for the formation of 1,3-dithiolanes **13** from thioketones and diazomethane (Scheme 2).³⁰ At $-78\text{ }^{\circ}\text{C}$, diazomethane and thiobenzophenone condense in a 1:1 ratio without the evolution of nitrogen. This 1,3-dipolar cycloaddition is followed by a cycloreversion with loss of nitrogen at $-45\text{ }^{\circ}\text{C}$. The *S*-methylide thus formed and a second equivalent of thioketone undergo cycloaddition to yield **13**, or can form a thioepoxide by electrocyclic ring closure.



Scheme 2

[2 + 2] Cycloadditions

Ma and Wong calculated the [2 + 2] cycloadditions of ethene with ketene, thioketene and selenoketene.³¹ Additions to the C=C *versus* C=X moieties of $\text{H}_2\text{C}=\text{C}=\text{X}$ were compared at the G2(MP2) level of theory. All attempts to locate zwitterionic intermediates were unsuccessful. The transition state for concerted addition to the C=C bond is highly asynchronous in all cases, with the difference in bond lengths roughly 0.66 Å. Addition to the C=X bond is also highly asynchronous, with C–C bonding further progressed than C–X bonding. Cyclobutanone is both the kinetic and thermodynamic product of reaction of ketene. The barriers for the two modes of addition to selenoketene are nearly the same, and the selenoether product is more stable due to decreased strain. This decrease in product strain from X = O to S to Se is also reflected in lower activation energies for the heteroketenes. The activation energies are also influenced by the shift in electron density in the (hetero)ketene HOMOs.

The rate constants for [2 + 2] cycloaddition between diethyl azodicarboxylate and ethyl vinyl ether were obtained in a variety of solvents at 30 °C by Gholami and Yangjeh.³² In this reaction, the activated complex is more polar than the reactants, leading to rate acceleration in solvents with a high solvent polarity/polarizability (π^*) parameter. The solvent's ability to donate hydrogen bonds, as represented by the solvent α parameter, was equally important, as determined by a dual-parameter correlation analysis. In aqueous methanol and dioxane solutions, the reaction rate had higher correlation with the solvent solvophobicity parameter Sp than the solvent E_{T}^{N} value. This indicates that the solvent effects are also due to a decrease in the hydrophobic surface area at the transition state.

Cycloaddition of singlet oxygen to an electron-rich alkene leads to a 1,2-dioxetane. The diradical *versus* peroxirane mechanisms for the [2 + 2] addition of oxygen to ethene, methyl vinyl ether, and butadiene were calculated (B3LYP and CAS-PT2/CAS-MCSCF) by Tonachini and co-workers.³³ The peroxirane intermediate forms only from the diradical; however, the diradical is more likely to ring close to the 1,2-dioxetane product. Even if the peroxirane were formed, the barrier to the formation of product is large, thus the peroxirane is unlikely to be involved in the reaction.

Photochemical reactions. Wilsey *et al.* calculated the ground and excited state ($\pi\pi^*$ T₁) surfaces for the [2 + 2] photocycloaddition of acrolein to ethene to better understand the factors which influence product regioselectivity.³⁴ The CASSCF/6-31G* calculations reveal that reaction begins with formation of a triplet biradical, which can adopt numerous conformations. The ratio of α to β attack depends on the relative energies of the transition states on the triplet surface, with β attack being favored by 3–4 kcal mol⁻¹. After intersystem crossing, ring closure occurs on the ground-state surface. *gauche* Biradicals are more likely to form cyclobutane, while *anti* biradicals are more likely to revert to reactants. The importance of the carbonyl group and the role of $n\pi^*$ surfaces were also explored. β -Attack leading to a 1,6-biradical is slightly less favored than reaction on the $\pi\pi^*$ surface; in other systems with structural constraints, this mode of addition may be important.

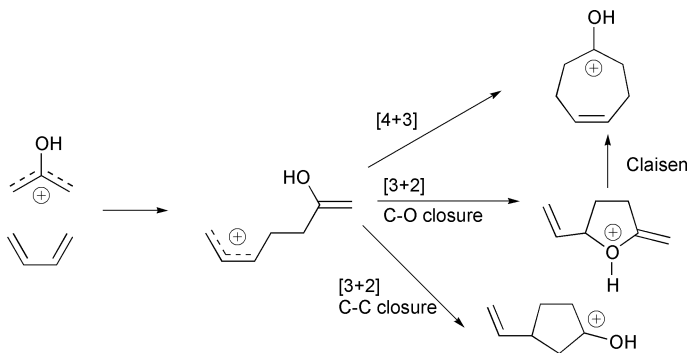
The photochemistry of penta-1,4-diene was studied computationally (UB3LYP/6-31G* and CASSCF/6-31G*) by Wilsey.³⁵ Intramolecular [2 + 2] cycloaddition was compared to vinylcyclopropane formation. The [2 + 2] cycloaddition may occur in two different ways, to give the 'parallel' cyclobutane product or the 'cross' bicyclobutane product. It is known that odd-numbered dienes penta-1,4-diene and hepta-1,6-diene give predominantly the 'parallel' products, while even-numbered hexa-1,5-diene gives mostly the 'cross' product, despite an apparent conflict with Baldwin's rules. The calculated results are in good agreement with experiment. All reactions proceed through cyclic biradicals formed on the triplet surface, and the initial bond formation event is influenced by biradical stability, geometry of the transition structure, and orbital interactions through bonds.

Radical cation [2 + 2] cycloaddition. Bauld and Gao reinvestigated the cyclodimerization of *N*-vinylcarbazole **7**.³⁶ Isotopic labeling studies reveal that the radical cation/neutral cycloaddition occurs through a distonic radical cation intermediate. The *gauche* conformation of this intermediate is more stable than the *anti* conformer, due to stronger electrostatic attractions between the radical and cation termini. The stepwise nature of this reaction is in contrast to other stereospecific radical cation cyclodimerizations, in which substituents are less able to stabilize the intermediate.

Other cycloadditions

The cycloaddition of oxyallyl cations to buta-1,3-diene was studied by Cramer and Barrows.³⁷ Calculations at the MP2/6-31G* level of theory were performed for

concerted $[4 + 3]$ and $[3 + 2]$ cycloadditions as well as stepwise alternatives (Scheme 3). Hydroxyallyl cation undergoes preferential stepwise cycloaddition, primarily due to the high electrophilicity of the dienophile compared to the electrofugacity of the diene. This difference is smaller for lithium and sodium oxyallyl cations, and here reaction proceeds *via* concerted but asynchronous $[3 + 2]$ cycloaddition to the 3*H*-dihydrofuran, which can undergo subsequent Claisen rearrangement to the formal $[4 + 3]$ product.



Scheme 3

3 Electrocyclic reactions

Arnold and Carpenter carried out calculations on ring opening of cyclopropyl radical and cation to allyl radical and cation, respectively, using high-level methods with various treatments of electron correlation.³⁸ Cyclopropyl cation is a transition state with no barrier to ring opening. The cyclopropyl radical undergoes forbidden disrotatory ring opening, with a barrier of 90 kJ mol^{-1} . The results agree with most experimental data and the results from different computational methods are compared.

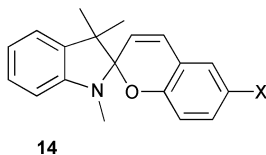
Contreras and co-workers studied the electrocyclic ring closure of butadiene to cyclobutene to evaluate whether it obeys Pearson's maximum hardness principle and the principle of minimum polarizability.³⁹ *Ab initio* and DFT calculations reveal that the transition state for allowed conrotatory ring closure is lower in energy, harder and less polarizable than that for the disrotatory pathway, and that the transition states for both reaction pathways are softer and more polarizable than either the reactant or product. These results are in accord with both principles.

The photochemical ring opening of cyclobutene to butadiene is allowed *via* a disrotatory process, but this prediction has not yet been unambiguously confirmed by experimental studies. Ben-Nun and Martínez studied the reaction using *ab initio* molecular dynamics.⁴⁰ Disrotatory rotation begins within $\sim 15 \text{ fs}$ of electronic excitation and no evidence of conrotatory motion was found. The authors discuss normal modes of the reaction and suggest experiments which could more clearly reveal a disrotatory reaction.

The photochemical reactions of butadiene were explored computationally by Sakai.⁴¹ The CASSCF calculations reveal a pronounced difference in the reactivity of the *s-cis* conformer compared to the *s-trans* conformer, due to dynamic effects. Both reaction coordinates involve decay through a conical intersection, followed by reaction on the ground-state surface. The *s-cis* conformer forms predominantly cyclobutene, while the *s-trans* isomer is more likely to yield butadiene and bicyclobutane.

Sakai investigated the electrocyclic ring closure of *o*-xylylene to benzocyclobutene *via* both disrotation and conrotation.⁴² CAS calculations show that the allowed conrotatory pathway has an energy of activation of 35–37 kcal mol^{−1} and is more favorable than the disrotatory reaction by only 7–8 kcal mol^{−1}. The benzene π system is just starting to form at the transition state for conrotation; in contrast, it is nearly complete at the transition state for disrotation, leading to the small energy difference between the two pathways.

Thermal racemization of **14** was found by Lemieux and co-workers to occur by two pathways.⁴³ In cyclohexane solution, racemization is slow, and Hammett analysis reveals that the isomerization occurs *via* six-electron electrocyclic ring opening followed by reclosure. Racemization in acetonitrile is faster, and Hammett analysis is consistent with a polar mechanism.



Two studies were published describing electrocyclic reactions in annulenes. Oth and Gilles studied the thermal rearrangement of [18]annulene by scanning microcalorimetry.⁴⁴ The annulene rearranges to three isomeric tetracyclic intermediates through a series of three electrocyclic ring closures, then stepwise dissociation gives benzene and a benzannulated cyclooctatriene, which undergoes two [1,5]-hydrogen migrations. Numerical simulation of the thermograms provides reaction enthalpies and activation parameters. Rzepa and co-workers calculated the tricyclization reactions of aromatic [10]-, [14]- and [18]annulenes compared to formally antiaromatic [16]annulene.⁴⁵ Due to delocalization, only one Kekulé resonance structure is observed for the [10]- and [14]annulenes, which undergo simultaneous bis-ring closure, formally either tandem electrocyclic ring closures or a Diels–Alder cycloaddition. The delocalized [18]annulene undergoes two sequential rather than concurrent electrocyclic ring closures. Antiaromatic [16]annulene has two bond-shift isomers due to the localization of π electrons. One isomer undergoes two sequential electrocyclic ring closures. The other conformer was found to be Möbius aromatic, though no transition states for rearrangement were located.

Reactions of radical cations

Due to the flat potential energy surface for the ring opening reaction of cyclobutene radical cation, the effects of substituents can be significant. Swinarski and Wiest

carried out calculations of reactions of C3-substituted cyclobutene radical cation at the B3LYP/6-31G* level of theory.⁴⁶ Electron donating and withdrawing groups were investigated. The energies of the product butadiene radical cations are highly influenced by the substituent electronic properties, and the substituent steric requirements govern the relative stability of the *E* versus *Z* products. The concerted mechanism follows the lowest-energy pathway for each reaction examined. The reaction of cyclopropyl carbinyl radical cation was also studied. It was found that this radical cation lies in a shallow energy well and has a nonclassical structure when there are electron-donating groups on the cyclopropyl ring.

4 Sigmatropic rearrangements

Birladeanu presents an historical review of the determination of the mechanism of the Wagner–Meerwein rearrangement.⁴⁷ Two reviews were published on the ene reaction of singlet oxygen with alkenes. Stratakis and Orfanopoulos focus on regiochemical issues,⁴⁸ while Clennan reviews mechanistic and synthetic features of the reaction.⁴⁹

Cope rearrangements

Sakai studied the Cope rearrangement of hexa-1,5-diene using configuration interaction/localized molecular orbital/CASSCF computational methodology.⁵⁰ The loose chair, loose boat and Dewar-type transition structures were compared. The loose chair transition state has an aromatic electronic state, while the loose boat is not aromatic; previous calculations suggested that both of these structures were aromatic. However, distortion of the boat, for example as in semibullvalenes, may lead to an aromatic structure. The Dewar-type transition state leads to a 1,4-diyl intermediate, and has high diradical character.

Staroverov and Davidson describe a computational evaluation of the diradical character of the Cope transition region.⁵¹ They define the ‘density of effectively unpaired electrons’ which reveals the amount of radical character in molecules, including singlets. Using B3LYP/6-31G* geometries with C_{2h} symmetry, CASSCF wave functions were calculated. With an interallyl distance of 1.54 Å, as in the 1,4-diyl intermediate, radical character is high and localized on C2 and C5. At the Cope transition state, unpaired electron density is low and distributed relatively evenly over all carbons in the molecule, as expected for an aromatic structure. At high interallyl separation, the radical character increases and the electron distribution is similar to allyl radicals. The number of effectively unpaired electrons is at a minimum near the highly aromatic Cope transition state.

Doering and co-workers report an experimental study on the rearrangements of 1,3,4,6-tetraphenylhexa-1,5-dienes.⁵² The racemic (*E,E*) stereoisomer and *meso* (*E,E*) stereoisomer interconvert rapidly at 100 °C; this stereoisomerization is not possible from a normal Cope rearrangement. At 100 °C, $\Delta H^\ddagger = 30.7 \text{ kcal mol}^{-1}$ and $\Delta S^\ddagger = 2.1 \text{ eu}$ (1 eu = $4.184 \text{ J K}^{-1} \text{ mol}^{-1}$). The entropy of activation is unusual, being much more positive than the concerted rearrangement of hexa-1,5-diene (−13.8 eu) yet not so

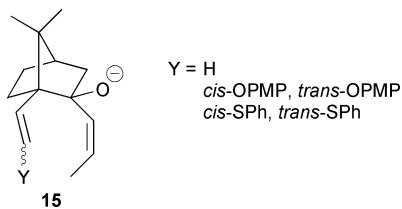
large as predicted for dissociation to free radicals. A free radical was observed by EPR on heating the *meso* compound, and simulations were consistent with it being 1,3-diphenylallyl. However, radical traps did not affect the rate of interconversion of the racemic and *meso* isomers, and crossover experiments reveal that some but not all of the rearrangement occurs *via* radical intermediates. The activation volume for the interconversion was positive, consistent with a dissociative reaction, yet the magnitude was not as large as expected for the formation of free radicals. The authors conclude that the rearrangement occurs toward the homolytic–colligative region of the mechanistic continuum, *via* a radical pair confined in a solvent cage. In addition, the racemic compound was resolved, and racemization occurs at 40 °C through what is believed to be a normal Cope rearrangement, based on the activation entropy and volume.

In a computational study, Borden and co-workers compare Cope rearrangement of hexa-1,5-dienes with up to four phenyl substituents, using B3LYP/6-31G* methodology.⁵³ In question is the previously described non-additive effect of multiple substituents on the activation enthalpy. Multiple substituents can interact either cooperatively or competitively, depending on whether they stabilize the same or different diradical resonance structures of the transition state. The observation that the calculated activation enthalpies are in good accord with experimental results is given as evidence that the calculated geometries are also correct. The interallylic bond lengths of the Cope transition states are greatly affected by the position and number of phenyl groups, with bond orders varying from 0.94 for the 2,5-diphenyl compound, to a bond order of 0.06 for the 1,3,4,6-tetraphenyl compound. The pyramidalization of the terminal carbons in the allyl fragments is also highly influenced by substituents. When multiple substituents stabilize the same diradical intermediate, each added substituent further perturbs the geometry towards the diradical, and each individual substituent can exert a greater stabilizing effect than it could alone; this explains the cooperative effect. When multiple substituents stabilize different diradical intermediates, the geometry is a compromise, and individual substituents have less of a stabilizing effect. The authors also investigated the rearrangement of 2,5-diphenylhexa-1,5-diene, and conclude that this rearrangement goes through a diyl intermediate which lies in a very shallow energy well.

Staroverov and Davidson also carried out calculations on cooperative *versus* competitive cyano substituent effects on Cope rearrangement transition states.⁵⁴ The authors use isodesmic reactions to evaluate substituent effects on two isolated allyl radicals, *versus* two interacting allyl radicals held at various distances. With cyano substituents at the 2 and 5 positions, the minimum energy point occurs with a short interallyl distance, since the cyano groups stabilize the 1,4-diyl structure. With cyano groups at positions 1, 3, 4 and 6, the lowest energy point occurs with a large interallyl distance, as cyano groups in these positions will stabilize the bis-allyl structure. With cyano groups at positions 1, 3 and 5 conflict arises, and the structure and energy at the energy minimum are the average of the other two cases; the structure is a compromise yet all substituents are stabilizing, albeit less than previously due to the compromise in geometry. The radical characters of the cyano-substituted transition states and diradical intermediates were evaluated, and are very similar to the parent hexa-1,5-diene for a given interallyl distance. The authors conclude that the substituents themselves do not perturb the radical character of a structure, but rather distort the

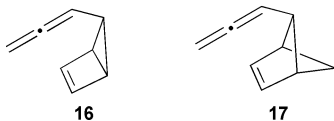
geometry to afford maximum stabilization. A comparison of computational methods was also performed. For the parent hexa-1,5-diene UB3LYP calculations find a spurious shallow minimum with an interallyl distance of 1.65 Å. The authors conclude that (U)BPW91 methodology gives the best results, and, based on these calculations, all but the 2,5-dicyano compound are believed to undergo concerted Cope rearrangement.

Paquette, Houk and co-workers measured reaction rates for the oxyanionic Cope rearrangement of **15** with either C6 sulfur or oxygen substituents.^{55,56} The *cis* and *trans* C6 *p*-methoxyphenoxy derivatives rearrange with similar rates compared to the parent, while *cis* and *trans* C6 phenylthio substitution accelerates rearrangement by 10^3 . Previous calculations support a stepwise rearrangement for sulfur but not oxygen derivatives, due to the greater stabilizing effect of sulfur on the intermediates formed by dissociation. The sulfur derivatives of **15** give products consistent with concerted

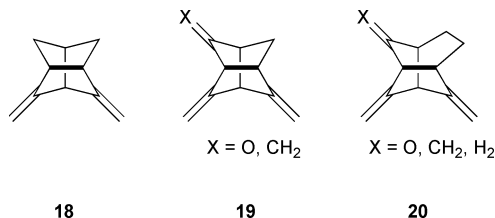


rearrangement, but the close proximity of the dissociated fragments may favor recombination to give exclusively the formal Cope product. Calculations reveal that the gas-phase rearrangement of the parent **15** proceeds *via* heterolytic bond dissociation. With the inclusion of tetrahydrofuran solvent, dissociation is less favorable. With the effects of solvation, the heterolytic dissociation of the sulfur derivative is calculated to occur without a barrier.

Examples of the first fully concerted allenyl Cope rearrangement were calculated ((8,8)CASSCF/6-31G*) by Duncan and Spong.⁵⁷ Previous calculations and experiments reveal that rearrangement of hepta-1,2,6-triene occurs by both concerted and stepwise rearrangement. By distorting the structure of the hepta-1,2,6-triene unit as in **16** and **17**, a concerted Cope rearrangement was determined to occur exclusively, due partially to high strain in the putative 1,4-diyl intermediate. In addition, the stronger $sp-sp^2$ σ bond which forms in the allenyl Cope rearrangement is thought to promote concerted rearrangement, since the vinyl analogues of allenyl compounds **16** and **17** were found to rearrange *via* a stepwise mechanism.



Gleiter and co-workers studied strained substrates **18**, **19** and **20** in search of a stepwise Cope rearrangement.⁵⁸ The rigid geometry of these substrates is expected to inhibit electron delocalization at the transition state for the concerted Cope rearrangement; previous gas-phase studies by Roth find that **18** rearranges by a



stepwise mechanism. In the solvent toluene the rearrangement of **19** was found to occur with the lowest activation energy: $27.0 \text{ kcal mol}^{-1}$ for $\text{X} = \text{O}$ and $26.3 \text{ kcal mol}^{-1}$ for $\text{X} = \text{CH}_2$. The results of trapping experiments and the observation of positive entropies of activation are consistent with the stepwise reaction mechanism. High-level calculations on **18**, **19** ($\text{X} = \text{CH}_2$) and **20** ($\text{X} = \text{H}_2$) find concerted and stepwise rearrangement to occur with similar activation energies, and for **18** and **20**, the stepwise reaction is slightly more favorable than concerted.

Bergman cyclizations and related reactions

Shaik and co-workers present a valence bond study of the Bergman cyclization of hex-3-ene-1,5-diyne to *p*-benzynes.⁵⁹ Only three configurations, using three in-plane molecular orbitals, are needed to give results similar to previous high level CASSCF(6,6) and CASPT2 studies. The out-of-plane π electrons play a secondary role, and the lowest-energy π configuration in the reactant develops without a barrier into the product. As such, the reaction can be thought of as an in-plane $[2 + 2]$ cycloaddition, in which through-bond coupling of the biradical to the σ system makes the reaction allowed. The dominant diyne configuration of the reactant is unimportant in the product, and the dominant biradical configuration of the product contributes little to the reactant. The transition state occurs at the avoided crossing of these two configurations. The geometry of the transition state is 80% product-like, while electronically, it is 70% reactant-like. Also, π resonance at the transition state is small, but σ -aromaticity is high, thus substituents interacting with the σ -framework should exert the greatest influence on the activation energy.

Linear free energy relationships were determined for the Bergman cyclization of 4-substituted-1,2-diethynylbenzenes by Russell and co-workers.⁶⁰ The authors analyzed these data using the σ_m and σ_p parameters developed for polar reactions, and the σ_{ji} and σ_{mp} parameters developed for radical systems. Also, a two parameter regression was performed using the Swain–Lupton field and resonance parameters. The σ_m parameter has the highest correlation to the rate data, with $\rho = 0.65$ and an intercept of 0. The Swain–Lupton analysis gave $0.662F + 0.227R$; it is reasonable that the inductive effect is more important than resonance since the radicals formed are orthogonal to the π system. These findings are consistent with previous studies, in which electron-deficient alkenes undergo accelerated rearrangement.

Electronic effects on competing cyclization pathways of hepta-1,2,4-trien-6-yne were explored by Wenthold and Lipton.⁶¹ Calculations at the B3LYP/6-31G* level of theory were performed to compare Myers–Saito C2–C7 cyclization *versus* Schmittel

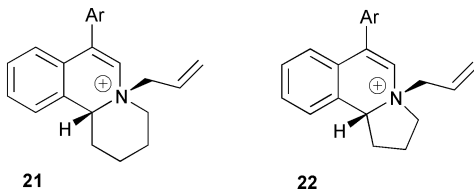
C2–C6 cyclization. The Myers–Saito biradical product is more stable than the Schmittle biradical, and is also obtained *via* a lower energy pathway. Benzannulation was found to increase the likelihood of Schmittle cyclization, in accord with experiment.

Claisen and 3-aza-Cope rearrangements

The role of solvent in Claisen rearrangement of allyl vinyl ether was studied by Hammes-Schiffer and co-workers.¹⁷ The minimum energy path was calculated for the gas-phase reaction as well as with two water molecules. Dynamical effects were included using a reaction path Hamiltonian, which includes vibrational motion orthogonal to the minimum energy path. Hydrogen bonding of the two water molecules to the oxygen is stronger at the transition state than at the reactant, and lowers the free energy of activation by 6 kcal mol^{−1}. The water molecules also lead to a more dissociative and polar transition state. The transmission coefficients with and without water molecules were calculated to be nearly 1. For the Claisen rearrangement, the dynamical solvent effects are small.

Two hybrid quantum mechanical/molecular mechanical studies relevant to the Claisen rearrangement of chorismate to prephenate were published. Martí *et al.* investigated the conformational equilibria of chorismate in the gas phase and in the solvated enzyme.⁶² New conformers of chorismate were located. Differences in the enzyme deformation energies for the various chorismate conformers are responsible for the stabilization of the reactive conformer, rather than differences in enzyme–substrate interactions. Hillier and co-workers carried out calculations on the enzymatic rearrangement of chorismate to prephenate, using methodology which allows for geometric relaxation in both the QM and MM regions during the reaction.⁶³ In the enzyme, the activation energy is 1.4 kcal mol^{−1}, compared to 29.1 kcal mol^{−1} in the gas phase. This is consistent with previous studies which suggest that the enzymatic rate-determining step is not Claisen rearrangement, but rather dissociation of product from the enzyme. The transition state of the enzyme-catalyzed Claisen rearrangement is early, with a C–O bond distance of 1.98 Å, compared to 2.20 Å in the gas phase. The smaller activation energy and greater exothermicity of the enzymatic reaction compared to the gas-phase rearrangement are believed to arise from stabilizing interactions between carboxylate groups and the ether oxygen of the substrate, and the nearby arginine residues in the enzyme, which increase as the structure changes from reactant to product.

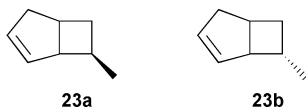
McComsey and Maryanoff studied the 3-aza-Cope rearrangement of *N*-allyl enammonium salts **21** and **22**.⁶⁴ The rearrangement of **21** occurs cleanly at 23 °C with exclusive *suprafacial* allyl transfer from nitrogen to carbon, suggesting a concerted rearrangement. Rearrangement of **22** requires higher temperature, and while the *suprafacial* product predominates, a small percentage of the *antarafacial* product was observed, presumably formed by a competing, dissociative reaction. Deuterium labeling studies are consistent with rearrangement of **22** occurring primarily *via* a concerted [3,3] process. The differences in reactivity of **21** and **22** are explained by the closer proximity of the alkene termini in **21**.



[1,3] Sigmatropic rearrangements

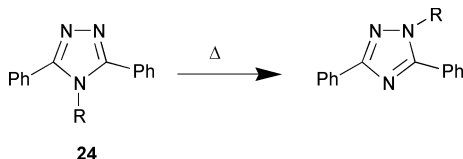
Photochemical [1,3] hydrogen migrations involve a conical intersection, as determined by CASSCF/6-31G* calculations by Wilsey and Houk.⁶⁵ Rearrangement of propene, cyclohexene and cyclohexa-1,4-diene were studied, and, at the H/allyl conical intersection, the allylic unit is planar, and the migrating hydrogen interacts most strongly with the central carbon. The four quasi-unpaired electrons can recombine several ways, to give the reactant alkene, the [1,3] hydrogen shift product, trimethylene diradical, or dissociated radicals. The energies of the conical intersections are 80–125 kcal mol⁻¹ above the reactants and 30–35 kcal mol⁻¹ above dissociated radicals. Alkyl/allyl conical intersections were located for cyclohexene, cyclohexa-1,4-diene, and norbornadiene. The H/allyl and alkyl/allyl conical intersections for cyclohexene have similar energies, but the H/allyl conical intersection for cyclohexadiene is 16 kcal mol⁻¹ below the alkyl/allyl.

Leber and co-workers studied the gas-phase thermal rearrangement of **23** to norbornene, in order to determine the extent to which rearrangement proceeds through the *suprafacial*, *inversion* pathway allowed by orbital symmetry.⁶⁶ Due to geometrical constraints, only *suprafacial* migration is possible. A number of previous studies on related bicyclo[3.2.0]heptenes show that other reactions occur competitively with the allowed [1,3] shift, giving the *suprafacial*, *retention* product as well as fragmentation to cyclopentadiene and ethylene. The *si/sr* ratio for the [1,3] rearrangement of **23a** was determined to be 7, while that for **23b** is 1/≥38. These results are consistent with the predictions of previous dynamics calculations. In addition, the temperature dependence on the *si/sr* ratio for **23a** was found to be negligible, thus the two products are unlikely to arise from competing pathways. Fragmentation of **23a** is rare (<1%) which is consistent with concerted [1,3] rearrangement, though with an apparent relaxation of the orbital symmetry rules.



Rearrangement of 4-alkyl-1,2,4-triazoles **24** (Scheme 4) could occur through a concerted [1,3] rearrangement. Gautun and Carlsen performed crossover experiments which reveal that rearrangement is not concerted.^{67,68} Instead, a nucleophilic displacement reaction yields a triazolium triazole ion pair intermediate which goes on to give products.

The circumambulatory rearrangement of cyclopropenes is formally a [1,3] process. Minkin *et al.* calculated the rearrangement of 3-formylcyclopropene at the MP2(fc)/

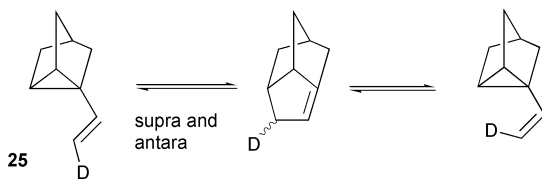


Scheme 4

6-31G** level of theory.⁶⁹ Rearrangement involves a bicyclo[1.1.0]butane oxide-like zwitterionic intermediate, which is 42.6 kcal mol⁻¹ above the reactant, and also leads to the formation of Dewar furan (cyclobutadiene oxide). A concerted reaction, involving inversion of the tetrahedral carbon, occurs through a carbene-like transition state (+51.8 kcal mol⁻¹) formed *via* C–C bond breaking. Protonation of the formyl group leads to facile circumambulation, through a hydroxycyclopropenylcarbinyl cation intermediate.

Vinylcyclopropane rearrangements. The major products of the rearrangement of vinylcyclopropane to cyclopentene are those expected from concerted rearrangement. However, the formation of all four stereoisomeric products and the energy of activation suggest the involvement of a non-equilibrated diradical intermediate. Alkyl substitution at one of the methylene carbons or the terminal vinyl carbon is known to increase the formation of the allowed *suprafacial*, *inversion* product. Nendel *et al.* calculated the rearrangement of vinylcyclopropane and a variety of derivatives using CASSCF(4,4)/6-31G**/UB3LYP/6-31G* methodology.⁷⁰ The parent vinylcyclopropane and the 4-*tert*-butyl, 5-methyl, and 2,5-dimethyl derivatives all undergo concerted rearrangement; however, the transition state is a diradical without cyclic conjugation, preceded by a wide energetic plateau. Reactive species all proceed through the same transition state, but those which previously deviated from the concerted pathway, to energetically-accessible diradical intermediates, give rise to other stereoisomers. Alkyl substituents destabilize the side reactions which lead to stereochemical scrambling, though substitution has little effect on the energy of activation for concerted rearrangement. Calculated secondary kinetic isotope effects are in agreement with experimental values. Stereoisomerization of the vinylcyclopropanes was also discussed. In addition, the authors describe calculations involving methoxy, amino, and fluorine substituents. These electronically-active groups lower the activation energy substantially when positioned to stabilize a forming radical center, and cause a shift to an earlier reaction transition state.

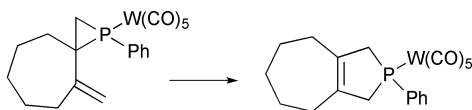
Baldwin and Dunmire studied the ‘no reaction’ reaction of 1-vinylnortricyclene **25** to tricyclo[4.2.1.0^{3,7}]non-3-ene (Scheme 5).⁷¹ This study indirectly confirms that



Scheme 5

vinylcyclopropane rearrangement of **25** does occur. Formation of the high-energy, non-observable product would be followed by a rapid return to reactant. Based on the knowledge that vinylcyclopropane rearrangements proceed with both *suprafacial* and *antarafacial* participation of the allylic group, the authors prepared *E*-1-*d* **25**. Gas-phase thermolysis of **25** leads to equilibration of the *E*-1-*d* and *Z*-1-*d* isomers, and analysis is consistent with the intermediacy of the tricyclononene, rather than direct alkene isomerization or surface-catalyzed isomerization.

Lammertsma, Bickelhaupt and co-workers investigated the thermal rearrangement of 2-vinylphosphirane to 3-phospholene (Scheme 6).⁷² The enthalpy of activation is 125 kJ mol^{-1} and the entropy of activation is $-1 \text{ J K}^{-1} \text{ mol}^{-1}$, consistent with reaction *via* a biradical pathway. In the presence of copper chloride, rearrangement is accelerated, with an activation enthalpy of 80.2 kJ mol^{-1} and activation entropy of $-100 \text{ J K}^{-1} \text{ mol}^{-1}$. These data suggest that the copper(I)-catalyzed rearrangement follows a concerted path.

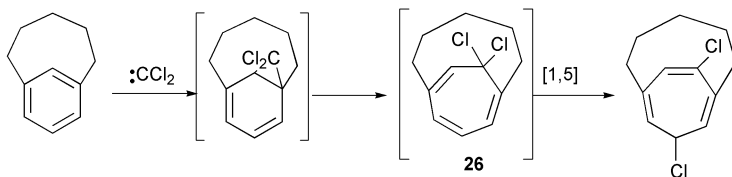


Scheme 6

[1,5] Sigmatropic rearrangements

Electronic and steric effects on [1,5] hydrogen shifts in (3*Z*)-penta-1,3-diene, substituted derivatives and hetero-analogs, were calculated by Saettel and Wiest at the B3LYP/6-31G* level of theory.⁷³ The energy of activation for the rearrangement of the parent is $32.9 \text{ kcal mol}^{-1}$ from the *s-cis* conformer of pentadiene, in good agreement with experiment and other computational studies. Electron donating substituents stabilize the aromatic transition state while electron withdrawing groups are destabilizing. It was noted that a consideration of both the σ and π substituent effects was required to explain these results, and that the 1,5-difluoro substitution destabilizes the transition state by a steric effect.

Bickelhaupt and co-workers report a concerted [1,5] chlorine migration in strained cycloheptatriene derivative **26** (Scheme 7).⁷⁴ The authors rule out other possible mechanisms by which the norcaradiene could generate **26**, such as dissociation to a tropylium cation followed by recombination. Subsequent isomerization of **26**,



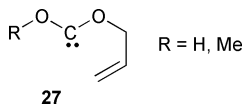
Scheme 7

however, is believed to occur *via* a slow dissociation/recombination pathway. Calculations (HF/3-21G and B3LYP/6-31G*) support these conclusions, as well as reveal the importance of the pentamethylene tether in lowering the activation energy of [1,5] chlorine migration to 70.5 kJ mol⁻¹.

[2,3] Sigmatropic rearrangements

Fokin *et al.* studied the [2,3] rearrangement of allyl sulfinyl carbanions, a key step in the reaction of ketones with CH₃SOCH₂⁻ in DMSO, to give primarily γ -unsaturated thiols.⁷⁵ A computational analysis of this rearrangement at the B3LYP/6-31+G* level of theory finds that rearrangement of the bare anion is exothermic by 26–29 kcal mol⁻¹, with a barrier of 0.3–5 kcal mol⁻¹. Rearrangement is concerted and moderately synchronous, as is the case for other [2,3] rearrangements. Inclusion of a lithium counterion increases the activation energy by 21–23 kcal mol⁻¹ but does not significantly affect the geometry. The aromaticity of the transition structures was supported by nucleus-independent chemical shifts and diamagnetic susceptibility exaltations.

Reid and Warkentin found that allyloxy(methoxy)carbenes **27** rearrange *via* homolysis–recoupling, in contrast to other bishetero carbenes which are known to undergo [2,3] rearrangement.⁷⁶ High-level calculations on carbene **27** (R = H) find an activation energy for [2,3] rearrangement of 21–25 kcal mol⁻¹ and an early transition state. The energy required to cause homolytic dissociation of the singlet carbene is less than or about the same as the barrier to [2,3] rearrangement, depending on the level of theory. The barrier for [1,2] allyl migration was found to be twice as high as that for [2,3] rearrangement.



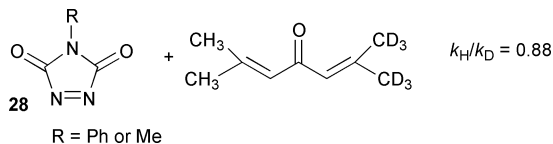
Ene reactions

Singleton and Hang measured ¹³C and ²H kinetic isotope effects for the ene reaction of formaldehyde with 2-methylbut-2-ene catalyzed by diethylaluminium chloride.⁷⁷ The reactive methyl group has $k_{12C}/k_{13C} = 1.006$ – 1.009 . A deuterium isotope effect of $k_H/k_D = 1.22$ is observed for the migrating hydrogen, which is a combination of primary and secondary isotope effects. The authors conclude that this catalyzed ene reaction occurs through reversible formation of a carbocation intermediate, followed by rate-determining proton transfer. However, small changes in the Lewis acid, enophile or reaction conditions may alter the rate-determining step.

Singleton and Hang also determined isotope effects for the selenium dioxide-mediated allylic hydroxylation of alkenes, which is known to proceed through an ene reaction followed by a [2,3] sigmatropic shift.⁷⁸ In question were the nature of the ene reaction, and the identity of the selenium oxidant. The isotope effects do not distinguish three potential mechanisms: concerted ene reaction of SeO₂, an ene

reaction of the corresponding selenous ester, or stepwise rearrangement *via* rapid addition of HSeO_2 followed by rate-determining proton transfer. The results of calculations provide support for a concerted ene reaction of SeO_2 as the major pathway for this rearrangement reaction.

The ene reaction of triazolidinedione **28** with (*R,R*)-*cis*-hex-3-ene-2,5- d_2 was found by Orfanopoulos and co-workers to be a stereospecific *suprafacial* reaction.⁷⁹ This finding, as well as analysis of kinetic isotope effects, supports the intermediacy of an aziridinium imide intermediate rather than a biradical or dipolar intermediate. Isotope effects were also determined for the ene reaction of triazolidinedione **28** with a conjugated enone (Scheme 8).⁸⁰ The inverse secondary kinetic isotope effect is again consistent with rate-determining formation of an aziridinium imide intermediate, and varies little with solvent. The authors allow that other substrates may exhibit different behavior.

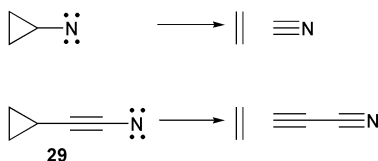


Scheme 8

5 Coarctate and pseudopericyclic reactions

Pseudopericyclic and coarctate orbital topologies are alternative modes for concerted reactions. Coarctate reactions occur when two bonds are made or broken on the same atom. Pseudopericyclic reactions are characterized by a planar transition state involving an in-plane lone pair, and are not bound by the rules of orbital symmetry.

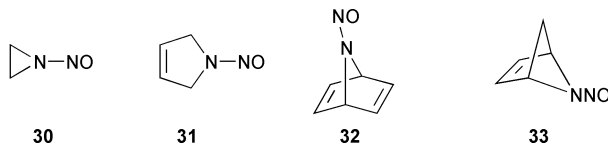
Herges and co-workers discuss the homology of coarctate reactions.⁸¹ Homologues for polar and pericyclic reactions are obtained *via* addition of a double bond. Analysis of coarctate reactions reveals that here addition of a triple bond is necessary, as both π bonds are used in the fragmentation (Scheme 9). This prediction was confirmed experimentally; decomposition of **29** yields ethene and cyanoacetylene.



Scheme 9

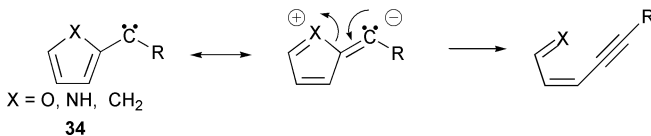
The cheletropic decomposition of cyclic nitrosamines, a coarctate reaction, was studied by Shustov and Rauk.⁸² The decomposition of nitrosoaziridine **30** was studied in heptane and methanol. Calculations of this decomposition in the gas phase at the B3LYP/6-311++G(3df,2pd) level showed good agreement with experiment. Previous studies suggest that decomposition proceeds *via* a forbidden pathway. In addition, the

cycloreversions of nitrosamines **31** and **32**, known to have high thermal stability, and **33** were also explored computationally. Two questions were addressed in this study. First, the ease of adopting the antiperiplanar conformation about the N–N bond, thought to be necessary for cycloreversion, was explored. Also, the role of ring strain was studied using isodesmic reactions. Rotation of the N–N bond in compounds **31–33** costs at least 16 kcal mol^{−1}, and extrusion of nitrous oxide occurs *via* an asynchronous process in which the ring nitrogen is planar. In contrast, **30** has an N–N rotational barrier of <9 kcal mol^{−1} and elimination occurs *via* a low-energy synperiplanar transition state, which is unusual due to the unique properties of the three-membered ring. The barriers for cheletropic fragmentation for **31**, **32** and **33** are 58, 18 and



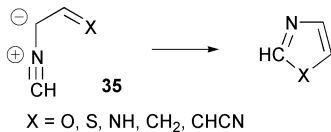
12 kcal mol^{−1}, respectively, and the calculated strain energies are 0, 39 and 52 kcal mol^{−1}. These data are consistent with strain being the major factor in determining the thermal stability of nitrosoamines.

Birney compared coarctate and pseudopericyclic modes for the facile electrocyclic ring opening of singlet 2-furylcarbene **34**.⁸³ Herges had used this rearrangement as an example of an allowed coarctate reaction, assuming the vacant orbital on the carbene was included but not the lone pair. However, previous calculations found the transition state for rearrangement to be planar, in conflict with the coarctate reaction. Inspection of a resonance structure of **34** reveals a potential in-plane process, expected to have a



low energy barrier for pseudopericyclic product formation. Calculations of **34** and related molecules at the B3LYP/6-31G(d,p) and G2(MP2) levels of theory reveal that **34** (X = O, NH) rearranges *via* a pseudopericyclic and not coarctate process. In contrast **34** (X = CH₂) undergoes an eight electron, Möbius, conrotatory coarctate rearrangement, with a high barrier to rearrangement.

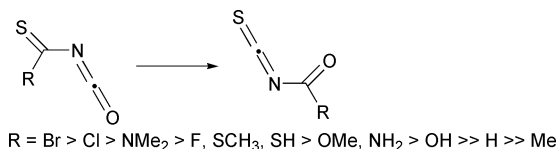
Fabian, Kappe and Bakulev present a similar comparison of the cyclization modes of ylides **35** and related molecules.⁸⁴ Calculations, performed at the MP4(SDTQ)/6-311+G**//MP2/6-311+G** and B3LYP/6-311+G** levels of theory, again reveal



differences in reactivity when X is a heteroatom *versus* X = CHR. Pseudopericyclic reactivity is observed in the heteroatom cases, with small activation energies, while

pericyclic electrocyclozation is found with $X = \text{CHR}$. These results are consistent with experimental findings that the hetero-ylides undergo rapid intramolecular cyclizations, while the other ylides are more likely to undergo bimolecular 1,3-dipolar cycloaddition reactions.

Acetylketenes are known to undergo $[4 + 2]$ cycloaddition in preference to $[2 + 2]$ cycloaddition. Experimental and computational studies by Shumway *et al.* using chiral aldehydes and ketones as the dienophile reveal a preference for the Felkin-Anh diastereomer.⁸⁵ The authors present evidence that this selectivity is possible if reaction occurs through a concerted pseudopericyclic cycloaddition, but not a Diels–Alder reaction.



Scheme 10

Koch and Wentrup studied the rearrangement of thioacyl isocyanate to acyl isothiocyanate (Scheme 10) using G2(MP2,SVP) and B3LYP/6-31G* computational methods.⁸⁶ This pseudopericyclic 1,3-rearrangement occurs readily due to the orthogonal orbitals in the cumulated π system. The geometry of the transition state is planar, involving C–N–C and the migrating group. Activation energies range from 75–285 kJ mol^{−1}, and the two theoretical methods give very similar results, excluding the halogens. The calculated migratory aptitudes agree with the order determined experimentally. The energy of the lone pair involved in migration is highly correlated with the activation energy.

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