FEATURE ARTICLE

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Diels–Alder and ene reactions of singlet oxygen, nitroso compounds and triazolinediones: transition states and mechanisms from contemporary theory

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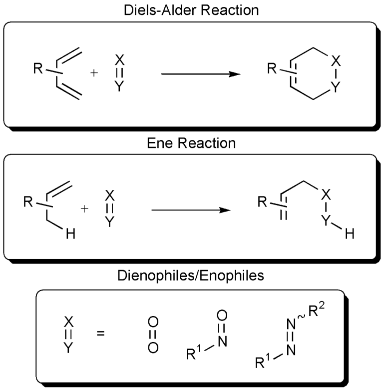
Singlet oxygen, nitroso compounds and triazolinediones have similar electronic structures: they share a low lying LUMO, making them powerful electrophiles, and a high lying HOMO, orthogonal to the LUMO and consisting of an antibonding combination of lone pairs. This bestows some nucleophilic character on these species. We describe a number of studies employing the best levels of theory currently available for systems of this size and demonstrate that the Diels–Alder and ene reactions of these three species are calculated to show subtle changes in mechanism. The calculations have been calibrated, wherever possible, by comparison to experimental observations including measured activation and reaction energies, regio- and stereoselectivities, intermediates observed either spectroscopically or by trapping, and kinetic isotope effects.

Theory predicts that the Diels–Alder reactions of singlet oxygen range from stepwise, proceeding through polarised diradical intermediates, to highly asynchronous concerted, whilst the Diels–Alder reactions of nitroso compounds and triazolinediones are generally concerted and involve highly asynchronous transition states. The ene reaction of singlet oxygen is concerted, and proceeds through one early transition state with the symmetry of a perepoxide which precedes a valley-ridge inflection where the two regioisomeric paths split. The ene reactions of nitroso compounds and triazolinediones are calculated to be stepwise involving diradical intermediates that may also cyclise to 3-membered heterocyclic intermediates, or abstract hydrogen to form the ene product.

These mechanisms are all linked by bond formation predominantly at one atom of the dienophile (or enophile). This preference arises because the orthogonal HOMO and LUMO allow these species to simultaneously react as electrophiles and nucleophiles at one atom—a property shared with carbenes. This favours asynchronicity in concerted Diels–Alder transition states and favours stepwise paths involving polarised diradicals (in which only one of the 1,1 bonds has formed) and formation of three-membered ring heterocycles (in which both 1,1 bonds have formed), although the latter are never obligatory intermediates. The stepwise mechanisms intervene whenever the polarised diradical or heterocycle is not sufficiently reactive to undergo barrierless product formation.

The hetero-ene and hetero-Diels–Alder reactions of singlet oxygen, nitroso compounds and activated diazo compounds are a broad class of reactions for which a confusing jumble of contradictory mechanistic schemes have been proposed. Here, we showcase the theoretically determined state-of-the-art in mechanisms and transition states for these reactions. A unifying mechanistic portrait of these reactions is presented.



The Diels–Alder reaction is one of the most powerful tools available for synthesis. Many examples are highly regio- and stereo-selective and effect the controlled creation of up to four sp^3 chiral centres from pro-chiral sp^2 atoms. The ene reaction—also discovered by Alder—has found less synthetic application but may allow for the controlled creation of three stereocentres in an acyclic molecule, providing a useful complement to the cyclic structures accessible through the Diels–Alder reaction.

Singlet oxygen, nitroso-alkanes and -arenes and diazo-alkanes and -arenes comprise a series of three widely studied hetero-electrophiles. The electrophilicity diminishes progressively from singlet oxygen through nitrosoalkanes to diazoalkanes as first one electronegative oxygen atom and then a second is replaced with a less electronegative nitrogen atom. The electronegativity of the diazene (or azo group) is enhanced when substituted with carbonyls and constrained to a *cis* geometry as in triazolinediones. While the presence of oxygen and nitrogen in these groups means that the reactions of these compounds generate fewer new stereocentres, new heterofunctionality can be introduced in this way.

These heterodienophiles have a low-lying π^* LUMO, the source of their powerful electrophilicity. The three heterodienophiles may also be nucleophilic as they have a high energy HOMO which is geometrically orthogonal to the LUMO. This HOMO is composed of the out of phase combination of lone pairs. The more usual π HOMO (the bonding counterpart of the

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LUMO) is frequently the SHOMO (second highest occupied molecular orbital) or even lower placed amongst the orbitals. The frontier molecular orbitals of singlet oxygen, HNO and triazolinedione are illustrated in Fig. 1. The orbitals of simple azoalkanes are similar but these compounds are feeble electrophiles in the absence of carbonyl groups. The involvement of perpendicular orbitals makes the process of bond making and bond breaking more complex, since many states are close in energy.

Because the HOMO and LUMO of singlet oxygen are both π^* orbitals, the electronic configuration is more complicated than for nitroso and azo compounds, where the HOMO–LUMO gap is small, but the HOMO and LUMO are not identical. Although the electronic populations shown in Fig. 1 are reasonable for nitroso and azo compounds, this is not the case for singlet oxygen. In terms of the orbitals shown in Fig. 1,[1] but showing only spatial components,[2] doubly degenerate $^1\pi_g$ states of O_2 may be represented as HOMO(1)HOMO(2) − LUMO(1)LUMO(2) and HOMO(1)LUMO(2) + LUMO(1)HOMO(2), where '1' and '2' refer to two electrons with opposite spins. These states are referred to as (vertical–horizontal) zwitterionic and diradical states respectively. For comparison, the triplet ground state of O_2 is represented as HOMO(1)LUMO(2), where electrons 1 and 2 have the same spin.[3]

Because of the split in degeneracy of the HOMO and LUMO of nitroso and azo compounds, the singlet states are adequately represented by HOMO(1)HOMO(2), although the admixture of LUMO(1)LUMO(2) is more significant than for molecules with a large HOMO–LUMO gap. Similarly, excited singlet and triplet states of nitroso and azo compounds are low in energy, as reflected by the intense colours of these compounds (*t*-BuNO is blue and PTAD is reddish–orange).

The difference in symmetry—$D_{\infty h}$, C_s and C_{2v}—of oxygen, nitroso compounds and triazolinediones will also affect the geometries of the transition states achievable by these reactions. A range of mechanisms may be expected, and the relative contributions of stepwise and concerted mechanisms may vary among these species. We summarize the latest experimental and theoretical mechanistic studies for these reactions.

Pericyclic reaction mechanisms

According to the Woodward–Hoffmann rules,[4] both the Diels–Alder and ene reactions are allowed to follow a concerted pathway. The concerted Diels–Alder reaction may be described as a $[{}_{\pi}4_{S} + {}_{\pi}2_{S}]$ reaction and the ene reaction as $[{}_{\pi}2_{S} + {}_{\sigma}2_{S} + {}_{\pi}2_{S}]$ (Fig. 2).

Fig. 2 Woodward–Hoffmann description of the generic Diels–Alder and ene reactions.

The parent Diels–Alder reaction between butadiene and ethylene has been concluded to proceed through a concerted synchronous transition state, **1**.[5] Synchronicity is not required by the Woodward–Hoffmann rules, and it has been shown that inclusion of dynamic electron correlation[6] tends to favour more synchronous mechanisms while nondynamical correlation favours asynchronous or stepwise transition states.[7]

In one of the first cases in which experimental kinetic isotope effects were compared to theoretical predictions, Beno, Houk and Singleton studied the reaction between isoprene and maleic anhydride, a generic Diels–Alder reaction.[8] The B3LYP/6-31G* method predicted that the reaction proceeds through slightly asynchronous transition states, **2** and **3**, with a significant preference for an *endo* rather than an *exo* approach (Fig. 3). Kinetic isotope effects predicted by B3LYP agreed extremely well with experiment.

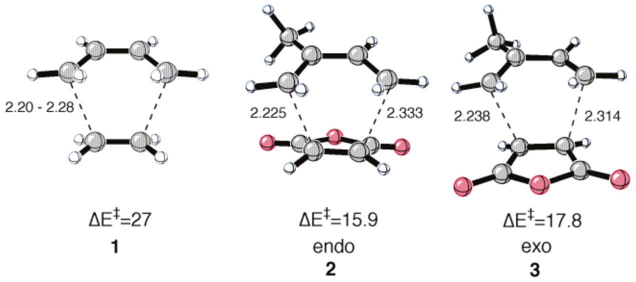


Fig. 3 The transition state for the parent Diels–Alder reaction between ethylene and butadiene (**1**) and *endo* and *exo* B3LYP/6-31G* transition states for the Diels–Alder reaction between maleic anhydride and isoprene (**2** and **3** respectively). Key bond lengths are shown in Å and activation energies are given in kcal mol^{-1}.

For the ene reaction, Singleton and Hang showed that the prototypical reaction between allyl benzene and maleic anhydride proceeds through two concerted but asynchronous transition states, **4** and **5**, that are very close in energy (Fig. 4).[9] Measured and predicted ^2H and ^{13}C isotope effects are again in good agreement.

These examples provide strong support for the validity of transition state geometries obtained by B3LYP/6-31G*.

Stepwise reaction mechanisms

For the Diels–Alder reaction, a range of stepwise paths may be proposed. These are illustrated in Scheme 1. They include routes involving diradical, zwitterionic and 3-, 4- or 5-membered ring heterocyclic intermediates. This array of paths is

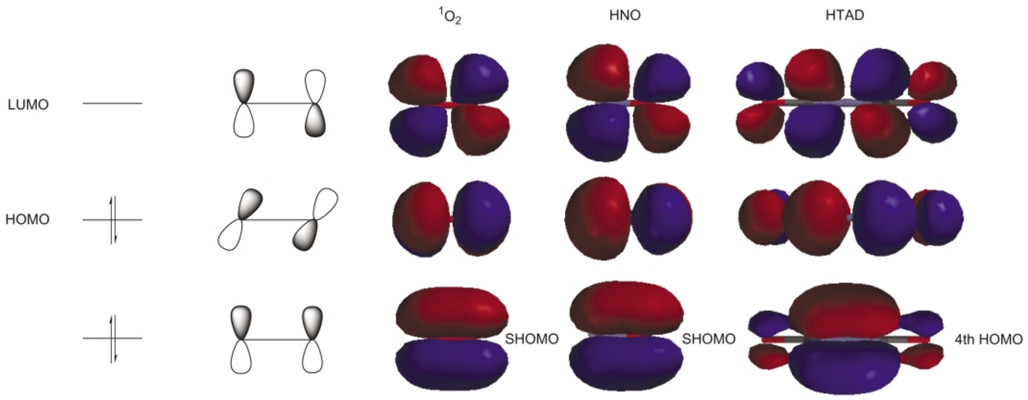
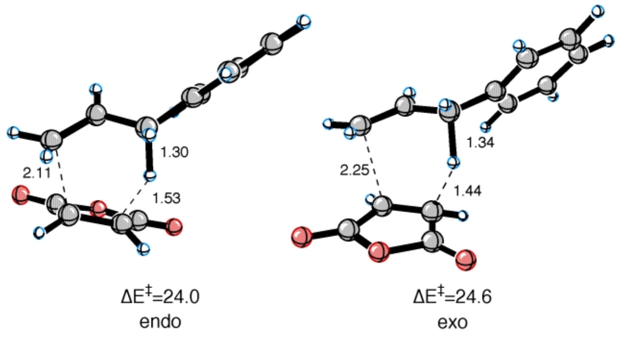


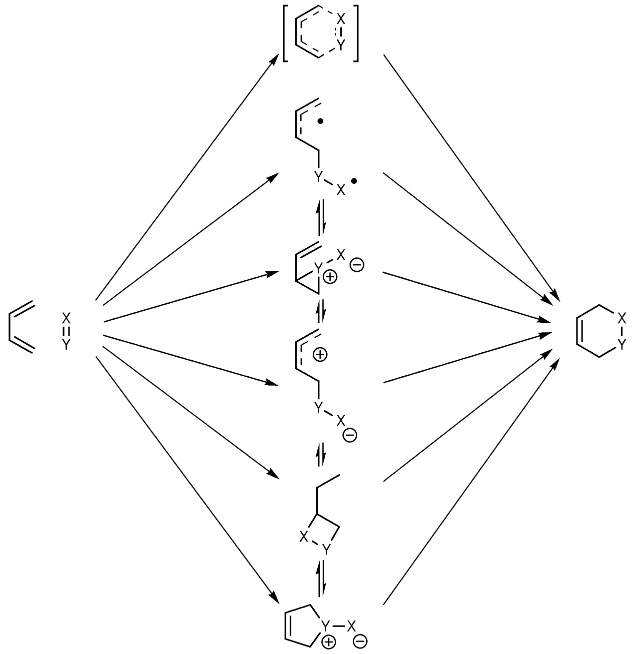
Fig. 1 The frontier molecular orbitals of singlet oxygen, HNO and triazolinedione (HTAD).



4 **5**

Fig. 4 B3LYP/6-31G* transition states for the ene reaction between maleic anhydride and allyl benzene.[10]

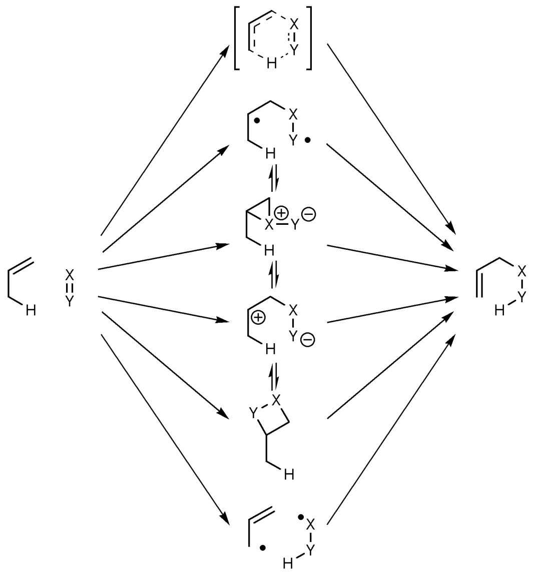
further complicated by the possible interconversion of these intermediates.



Scheme 1 Potential concerted and stepwise mechanistic pathways for the Diels–Alder reaction.

A similarly complex array of stepwise mechanisms is possible for the ene reaction (Scheme 2). An alternative mechanism in which the allylic hydrogen is first abstracted before recombination of the two resulting radicals (or anion and cation) is possible in this case, but not for the Diels–Alder reaction. The generation of such reactive species intermolecular to one another would likely lead to polymerisation and has received no theoretical attention, although a related, but radical-chain, mechanism is often employed to explain the autooxidation of fatty acids which leads to rancidity in oily foodstuffs such as butter.

A theoretical treatment that is to adequately distinguish between alternative pericyclic and stepwise transition states must include a high-level treatment of correlation energy. Post-Hartree Fock, or density functional methods are required. The description of open chain intermediates, in particular diradicals, requires a balanced treatment of non-dynamical and dynamical electron correlation. CASSCF includes non-dynamical correlation that is critical in open-shell systems, but the neglect of much dynamical correlation exaggerates the stability of diradicals. CAS methods with a second order perturbation theory correction (CAS-MP2 or CASPT2), some post-HF methods and density functional theory may be more appropriate. In principle, diradicals cannot be described by a single-configurational wavefunction and, therefore, some have questioned the validity of many of these approaches, particularly DFT.[11] Others have found that although theoretically troubling, methods such as B3LYP (DFT) reproduce experimental energetics satisfactorily for diradicals,[12] and differences with CASSCF geometries are very small.[13]



Scheme 2 Potential mechanistic pathways for the ene reaction.

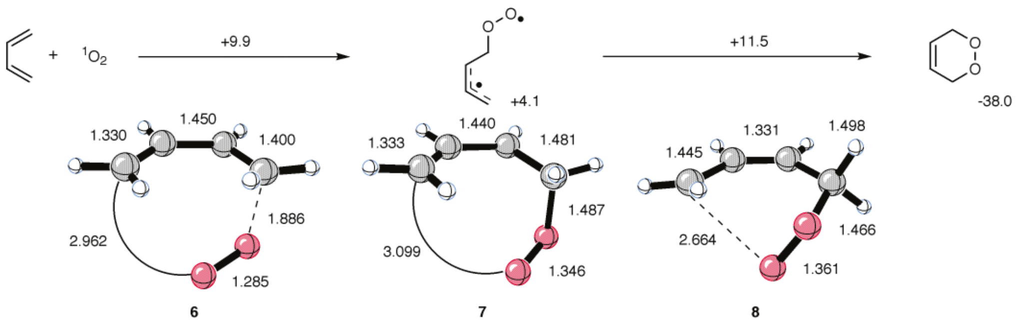
Although stepwise reactions such as many of those shown in Schemes 1 and 2 are not strictly subject to the Woodward–Hoffmann rules, we have found that orbital symmetry may in fact influence the preferred direction of cyclisation of diradicals. Even in such cases, aromatic transition states are favoured and steer stepwise reactions toward the Woodward–Hoffmann allowed products.[14]

Diels–Alder reactions of singlet oxygen

The Diels–Alder reaction between singlet oxygen and conjugated dienes is one of the general photochemical oxidations. Although these reactions had been known for many years,[15] it was some time before the active species in the reaction was identified as a singlet excited state of oxygen.[16] The Diels–Alder reaction of singlet oxygen has found much application in synthesis, for the stereo-controlled generation of two 1,4-related oxygen bearing stereocentres. This has been exemplified by the recent synthesis of some agarofuran sesquiterpenes and in Kuwajima's total synthesis of Taxol.[17]

Two recent reports with reliable levels of theory have appeared and concur that the favoured mechanism of this reaction with normal dienes is a stepwise one, passing through diradical intermediates. Bobrowski *et al.* have reported a thorough investigation of the reaction of both butadiene and benzene with singlet oxygen, employing CASSCF/6-31G* geometry optimizations and energy evaluations using a quasi-degenerate perturbation theory correction to the CASSCF energetics (MCQDPT2).[18] A range of active spaces was tested and the (10,8) active space (10 electrons in 8 orbitals), including σ, $\pi_{\pm1}$, $\pi_{\pm1}^*$ and σ^* orbitals of oxygen and π and π^* of the olefins was found to be adequate. Basis set superposition corrections were made to the energies.

The reaction with butadiene was found to be highly exothermic ($\Delta E = -38$ kcal mol^{-1}) and to occur preferentially through a singlet diradical stepwise path. The transition state, **6**, linking the reactants to the diradical, **7**, had a forming C–O distance of 1.886 Å and the O–O bond was stretched from 1.240 Å in the reactant to 1.285 Å in the transition state. A subsequent

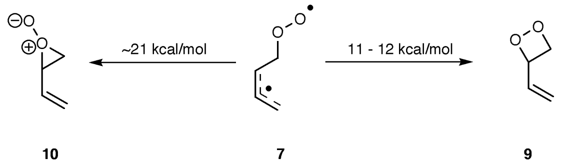


Scheme 3 CASSCF(10,8)/6-31G* optimised geometries and MCQDPT2 energetics for the Diels–Alder reaction between singlet oxygen and butadiene.[18] The energy for each species is given in kcal mol^{1} relative to reactants.

transition state, **8**, linking the diradical to the endoperoxide product was also found. The initial addition involved an activation energy of 9.9 kcal mol^{1}, leading to the diradical with an endothermicity of 4.1 kcal mol^{1}. The conversion of diradical to product, through transition state **8**, is rate limiting (Scheme 3).

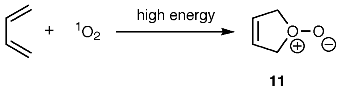
A concerted pathway could be found by constraining the system to C_S symmetry but, this structure, at 10.9 kcal mol^{1}, was a second order saddle point. The forming bond lengths are 2.085 Å in this concerted structure. This concerted path is lower than the second step of the diradical mechanism, so dynamically, paths which sample the intermediate diradical and paths which pass over the intermediate directly to the product are likely.[19]

A related study by Maranzana *et al.* found, using CASPT2/6-31G*//CASSCF/6-31G*, UB3LYP/6-31G* and UB3LYP/6-311+G(2d,2p)//UB3LYP/6-31G*, that the diradical formed between singlet oxygen and butadiene could close to a dioxetane, **9**, with a barrier of 1–12 kcal mol^{1} or to a perepoxide, **10**, with a barrier of ~21 kcal mol^{1} (Scheme 4).[20] The perepoxide, **10**, was found not to be a stable minimum with B3LYP.



Scheme 4 B3LYP energetics for alternative ring closures of diradical **7**.

A third mechanism was also considered by Bobrowski *et al.*, involving the cheletropic addition of singlet oxygen to butadiene to form a zwitterionic peroxolane, **11** (Scheme 5). This species was formed *via* both concerted and stepwise paths, but both were more than 10 kcal mol^{1} higher in energy than those already discussed.



Scheme 5 Cheletropic reaction between butadiene and singlet oxygen.

Although the authors claim that the low degree of charge transfer in the stepwise path *via* diradical **7** compared to that in the concerted transition state is consistent with the low degree of solvent sensitivity of this reaction, the charge data they provide is inconsistent with this suggestion. Mulliken charges indicated a transfer of 0.32 electrons in the concerted path and 0.21, 0.38 and 0.39 electrons in **6**, **7** and **8** respectively for the stepwise path. The diradicals have significant charge separation and should be considered as polarised diradicals.

The calculated activation barriers (10–12 kcal mol^{1}) for the stepwise path were a little higher than those observed experimentally for cyclopentadiene (3.9 kcal mol^{1}) and cyclohexadiene (5.5 kcal mol^{1}). It should be borne in mind that these cyclic dienes are constrained to an *s-cis* conformation and there will be no impediment to closure of the second bond.

Although the stepwise path might preferably proceed through reaction with the *s-trans* conformer of butadiene, the authors found that the barrier to rotation about the central C–C bond of the *s-trans* diradical (Fig. 5) was only 6.2 kcal mol^{1} whereas the barrier to dissociation of the diradical was 5.9 kcal mol^{1}. This rotation barrier is very low since normally, the rotation about a partial bond in the allyl radical has a barrier of approximately 15 kcal mol^{1}.[21] A bonding interaction takes place between the oxygen atom in the C–O bond and the adjacent carbon atom (indicated in Fig. 5), a contribution that leads to high barriers to rotation about formally single bonds in this kind of diradical,[22] discussed in detail in the section concerning the ene reactions of nitroso compounds. This same interaction also diminishes the allylic radical character of the diradical, reducing the strength of the partial π bond. Because of this low barrier, the non-stereospecific reaction of singlet oxygen with some dienes that cannot undergo the Diels–Alder reaction directly from their most stable conformation may take place *via* the *s-trans* diradical intermediate.

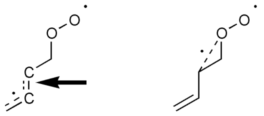
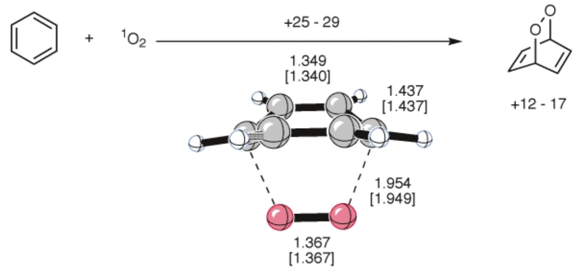


Fig. 5 C–C partial double bond (indicated in left hand structure) calculated to have a barrier to rotation of 6.2 kcal mol^{1} which is higher than the barrier to dissociation of the diradical. Contributions from structures involving significant perepoxide character (such as that on the right) lower the bond order and contribute to this low barrier. This interaction also leads to high C–O rotational barriers.

Extension of this study to the reaction of singlet oxygen with benzene showed that this reaction is calculated to follow a concerted path with a barrier of 25–29 kcal mol^{1} and endothermicity of 12–17 kcal mol^{1} (Scheme 6). Although a diradical could be located, it was very high in energy (26.7 kcal mol^{1} above reactants) and no transition state linking it to reactants could be found. The transition state for the concerted process, **12**, was synchronous and had forming bond lengths of 1.95 Å. The higher degree of solvent dependence of the reaction of singlet oxygen with aromatic dienes was considered to be consistent with these reactions following the concerted pathway, with its associated high degree of charge transfer (0.4 electrons in this case).

Sevin and McKee studied the reaction of singlet oxygen with cyclohexadiene using B3LYP/6-31G* and CASPT2/6-31G* single points on the B3LYP geometries.[23] As for butadiene, the stepwise path proceeding through **13**, **14** and **15** was lower in energy than a transition state constrained to be synchronous (Scheme 7). A preliminary van der Waals complex of diene and singlet oxygen can account for the negative activation barriers



12

Scheme 6 Concerted transition state for the reaction between benzene and singlet oxygen. Distances (in Å) are given for the CASSCF(10,8)/6-31G* structure and those for the CASSCF(12,10)/6-31G* structure are given in brackets.

of the first step. Both CASPT2 and B3LYP agree that the stepwise path is 10–11 kcal mol^{1} lower in energy than the concerted one. The authors conclude that an asynchronous concerted mechanism may operate at low temperatures due to the small to negative barrier between the diradical and products. At higher temperatures, the diradical becomes a genuine free energy minimum, because its entropy is higher than that of the transition state for ring closure, and the reaction is stepwise.

The CASPT2 reaction barrier (6.5 kcal mol^{1}) is in good agreement with that found experimentally (5.5 kcal mol^{1}). The calculated entropy of activation (−31.2 e.u.) is also in accord with that measured for the reaction with cyclopentadiene (−25.8 e.u.). Charge transfer of 0.26 electrons occurs in the stepwise diradical transition state, and the dipole moment is enhanced compared to reactants. Acceleration of the reaction by polar solvents can be rationalised.

In the light of the calculated mechanisms of the Diels–Alder reaction of nitroso compounds and triazolinediones, we note that the stepwise mechanism of the reaction with singlet oxygen represents an extreme case of a highly asynchronous mechanism, as observed in other cases. This is particularly highlighted by the uncertainty, found by Sevin and McKee, about the existence of the barrier to formation of the second C–O bond from the diradical intermediate. We also note that, as in all of the other reactions reported here, the asynchronicity arises, at least in part, from a high tendency for both the HOMO and LUMO of these compounds to be simultaneously involved in these reactions. Two independent, opposite interactions take place at one oxygen atom, making this atom electronically resemble a carbene being both electrophilic and nucleophilic. The transition states share a tendency towards 1,1 bond formation, as opposed to the simultaneous 1,2 bond formation distinctive of the synchronous, concerted transition state of the Diels–Alder reaction (*e.g.* **1**). This tendency is observed in all the cases reported here but is most pronounced for singlet oxygen.

The Diels–Alder reaction between singlet oxygen and simple open chain or cyclic dienes is calculated to proceed via a stepwise path involving a polarised diradical intermediate—the extreme case of an asynchronous mechanism. The magnitude of the second barrier is still in doubt, and is most likely negligible in some cases. The reactions with aromatic dienes are predicted to have higher barriers and to proceed through concerted mechanisms.

Diels–Alder reactions of nitroso compounds

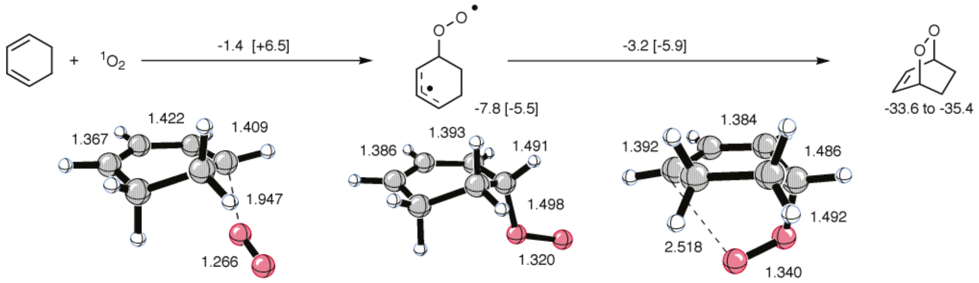
The Diels–Alder reaction of nitroso based dienophiles is a long established method of heterocycle synthesis. The reaction was first observed by Wichterle,[24] and has been found to have high stereo- and regio-selectivity which has recently been utilised in the total synthesis of the annonaceous acetogenin muricatetrocin C and of the potent analgaesic, epibatidine.[25] Our recent calculations constitute the most advanced theoretical study of this reaction to date.

B3LYP/6-31G* calculations of the reactions of a range of nitroso dienophiles with a number of differently substituted dienes examined both concerted and stepwise paths through diradicals.[26] We also explored a third possibility, involving the intermediacy of a 3-membered aziridine *N*-oxide (ANO).

Although HNO itself dimerises rapidly and forms N_2O and water, the reaction between HNO and butadiene was chosen as a simple model for this class of reactions. Two concerted transition states, **16** and **17**, were found (Scheme 8).[27] The *endo* transition state, **16**, is a remarkable 8.6 kcal mol^{1} below the *exo* transition state, **17**! With larger substituents on nitrogen (R in RNO), the *endo*–*exo* energy difference diminished only slightly. The *endo* transition state is always at least 5.9 kcal mol^{1} more stable than *exo*, and this value was for the reaction between PhNO and butadiene. The very large *endo* preference is known as the '*exo* lone pair effect'[27] since it arises from repulsions that occur when the lone pair on N in the nitroso is forced to be *endo*.

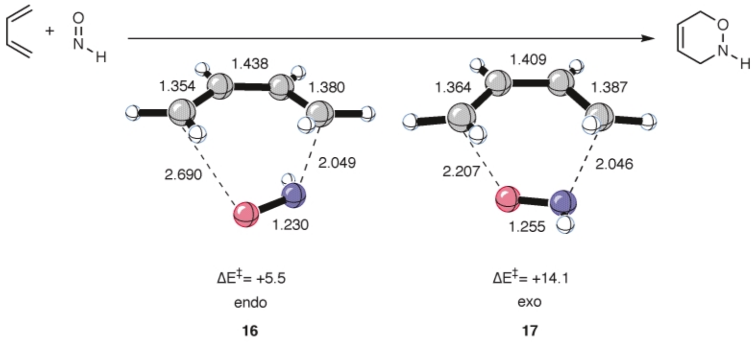
The B3LYP transition states are considerably more asynchronous than those with RHF.[27] The preferred *endo* transition state is more asynchronous than the *exo* transition state and has a C–O forming bond length of 2.690 Å and C–N distance of 2.049 Å. In the *exo* transition state, these distances are 2.207 Å and 2.046 Å, respectively. Constraining the *endo* transition state to be synchronous raised its energy by only 2.0 kcal mol^{1}. A charge transfer of 0.13 electrons from the diene to HNO in the transition state, **16**, and an increase in the dipole moment from 1.6 D (of HNO) to 2.1 D in **16** indicate that polar solvents may accelerate the reaction. The dipole moment of PhNO decreases from 3.8 D to 2.2 D in the transition state, indicating a possible decelerating effect. This variable effect of solvent polarity supports suggestions made by Kresze.[28]

A diradical, **18**, and the transition states linking it to reactants and products were also found (Scheme 9). The diradical is 1.8 kcal mol^{1} below the reactants, and the activation energy for diradical formation is 9.0 kcal mol^{1}, 3.5 kcal mol^{1} higher in

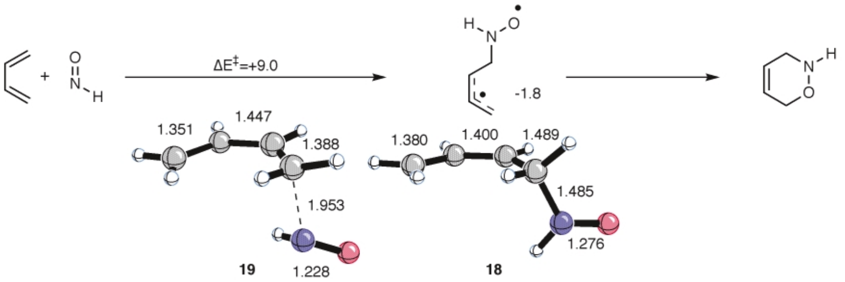


13 **14** **15**

Scheme 7 B3LYP/6-31G* diradical intermediates and transition states for the lowest energy reaction pathway between 1,3-cyclohexadiene and singlet oxygen. B3LYP/6-31G* energies are given and CASPT2/6-31G* values are alongside these in brackets. The energy for each species is given in kcal mol^{1} relative to reactants.



Scheme 8 *endo* and *exo* concerted transition states for the reaction between HNO and butadiene. Distances (in Å) are given for the B3LYP/6-31G* structures.

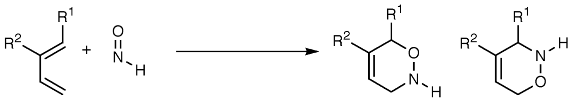


Scheme 9 An alternative diradical stepwise path for the Diels–Alder reaction between butadiene and HNO.

energy than the concerted *endo* transition state. The subsequent step, forming the C–O bond was found to have a barrier of ~ 2.7 kcal mol^{1}.

It was calculated that the diradical pathway might be favoured by small substituents R in RNO, radical stabilising substituents on the diene and in hydrogen-bonding solvents, but is unlikely to be the lowest energy path in most cases. Large barriers to rotation about the formally single bonds in the diradical give them some unusual rigidity, discussed in the context of ene reactions below. Dienes which cannot readily achieve an *s-cis* conformation may prevent the concerted reaction from occurring, but the highly reactive nitroso compounds may undergo competing reactions, such as dimerisation rather than undergo the stepwise Diels–Alder reaction through a diradical intermediate.

The reactions between HNO (or CHONO) and a variety of substituted butadienes were used to probe the effects determining regioselectivity. The predictions are in agreement with available experimental data, and are summarised in Scheme 10.



R^1	R^2	proximal	distal
CN	H	***	
Me	H	**	
OMe	H	**	
H	CN		***
H	Me	*	
H	OMe	*	

Scheme 10 Regioselectivity calculated for the Diels–Alder reaction between HNO and substituted butadienes. The number of *s indicate the degree of selectivity calculated.

In line with simple frontier molecular orbital predictions, all 1-substituted dienes prefer the proximal isomer. Electron-withdrawing substituents on the diene have a larger influence than electron-donating substituents. Substitution at the 2-position was found to be less influential. Cis-substitution at the 1-position had a variable effect depending upon whether the partially negative oxygen of the nitroso compound interacts attractively or repulsively with the substituent on the diene in the proximal transition state.

Although the diene HOMO–RNO LUMO interaction is most important, this is not the only influence on selectivity. The interaction of the RNO HOMO (an antibonding combination of the lone pairs on N and O, Fig. 1) with the diene LUMO is also important, particularly for dienes with electron-withdrawing substituents (in line with observations made by Eisenstein *et al.*).[29] Electrostatic interactions of the polar NO functional grouping, or the substituents, R, in RNO, with the substituents on the diene also play a role.

The mechanism of this reaction again reflects the tendency for the dienophiles described in this article to undergo a 1,1 bond formation. Bond formation is dominated at one atom, favouring asynchronous concerted transition states and stepwise reactions through diradicals (1,1 interaction leading only to the formation of one bond).

The Diels–Alder reactions of nitroso compounds are calculated to proceed through highly asynchronous, but nevertheless concerted transition states. A powerful exo lone pair effect ensures a strong preference for the (substituent) endo transition state. A stepwise path through a diradical intermediate may be competitive in exceptional cases. This stepwise path and the highly asynchronous nature of the concerted transition states are consistent with a preference for 1,1 bond formation of these dienophiles.

Diels–Alder reactions of triazolinediones

The discovery of the powerful dienophilic properties of PTAD in 1962 prompted a number of experimental studies that have recently been complemented with theoretical mechanistic investigations.[30]

Chen *et al.* utilized density functional theory, as implemented with the restricted B3LYP/6-31G* method to study the reaction between HTAD, **20**, and butadiene (Scheme 11).[31] It was found that the lowest energy pathway is a concerted one. As with nitroso compounds, the transition states are highly asynchronous. The *endo* transition state, **21**, was found to be the lowest in energy. As with the reactions of nitroso compounds, already discussed, the favored *endo* transition state was considerably more asynchronous than the *exo* transition state, **22**. The difference between the two forming bond lengths in the *endo* case was a massive 0.67 Å. This pathway was calculated to have a very low activation barrier of only 5.5 kcal mol^1. The *exo* transition state was 9.2 kcal mol^1 higher in energy and, whilst still asynchronous, was rather less so, with a difference in forming bond lengths of 0.38 Å. This constitutes a massive *exo* lone pair effect,[27] since both nitrogen lone pairs experience repulsive interactions with the diene π electrons in the *exo* transition state.

Constraining the transition states to a synchronous, C_S symmetric geometry exacted a penalty of 1.9 kcal mol^1 for the *endo* transition state and only 0.3 kcal mol^1 for the *exo* transition state.

Three 3-membered ring aziridine imide (AI) intermediates, and the transition states linking them to reactants were also located (Scheme 12). The lowest energy of these stepwise paths, *via* AI **24**, had a barrier of 9.3 kcal mol^1, which is 3.8 kcal mol^1 above the concerted *endo* transition state, **21**. The transition states for AI formation all involve the tilting of the plane of the triazolinedione away from a perpendicular approach and are reminiscent of those for carbene reactions, which maximise FMO interactions and avoid being forbidden by following a non-perpendicular approach. The difference in charges on the adjacent nitrogens of the azo group was greater in the stepwise transition states, **26**–**28** (0.34–0.39 with ChelpG) than in the concerted *endo* transition state, **21** (0.21), suggesting that polar solvents may permit the stepwise path to become competitive.

More recently, Singleton *et al*. used transition states at the same level of theory as just described (B3LYP/6-31G*), with the addition of a *tert*-butyl group at the 2-position of the diene, to predict kinetic isotope effects for both deuterium and ^{13}C substitution in the reaction with PTAD (Scheme 13).[32] They found two highly asynchronous concerted *endo* transition states, and a transition state constrained to be synchronous. The higher energy stepwise aziridine *N*-oxide and concerted *exo* transition states were not considered. The kinetic isotope effects predicted for a Boltzmann average of the two asynchronous concerted transition states (which differed in energy by only 0.05 kcal mol^1) were within experimental error of those observed experimentally. By contrast, the kinetic isotope effects predicted for the synchronous transition state deviate substantially from experiment.

The Diels–Alder reactions of triazolinediones are calculated to proceed through asynchronous concerted transition states, consistent with the tendency of these species to be dominated by bond formation at one end of the dienophile. As with nitroso compounds, the exo lone pair effect dictates a strong preference for reaction via an endo transition state. Kinetic isotope effects calculated for these transition states are in good accord with experimentally observed values.

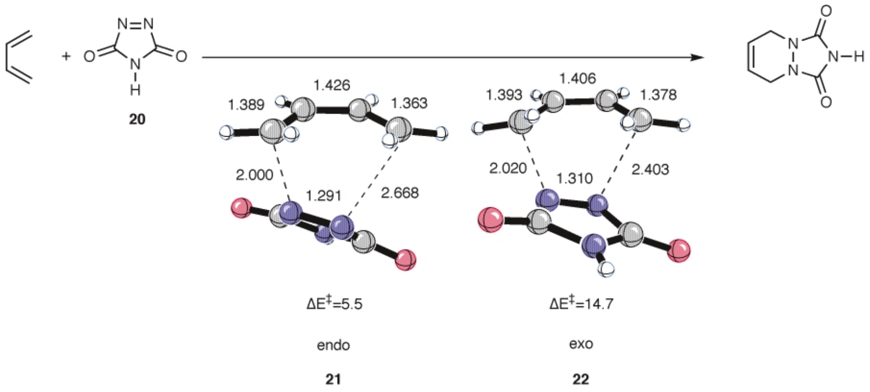
Ene reactions of singlet oxygen

Of the reactions discussed in this article, the one that has received by far the most attention is that of the ene reaction (frequently alongside studies of the [2 + 2] reaction) of singlet oxygen. The reaction was discovered early in the last century,[15] but the active oxidant was only identified as an excited singlet state of oxygen in the mid-60s by the groups of Foote and Corey.[16] This reaction, which is sometimes referred to as the Schenk reaction, has found applications in synthesis. These were reviewed recently by Prein and Adam.[33] The application of singlet oxygen ene reactions has been illustrated well by the recent synthesis of asteriscanolide by Paquette and co-workers.[34] Adam and co-workers have recently developed new methods for stereocontrol in these reactions.[35] There is a long history of quantum mechanical studies of this reaction,[36] but only recently have methods for multiconfigurational and diradical systems approached the accuracy necessary to distinguish between the many possible mechanisms.

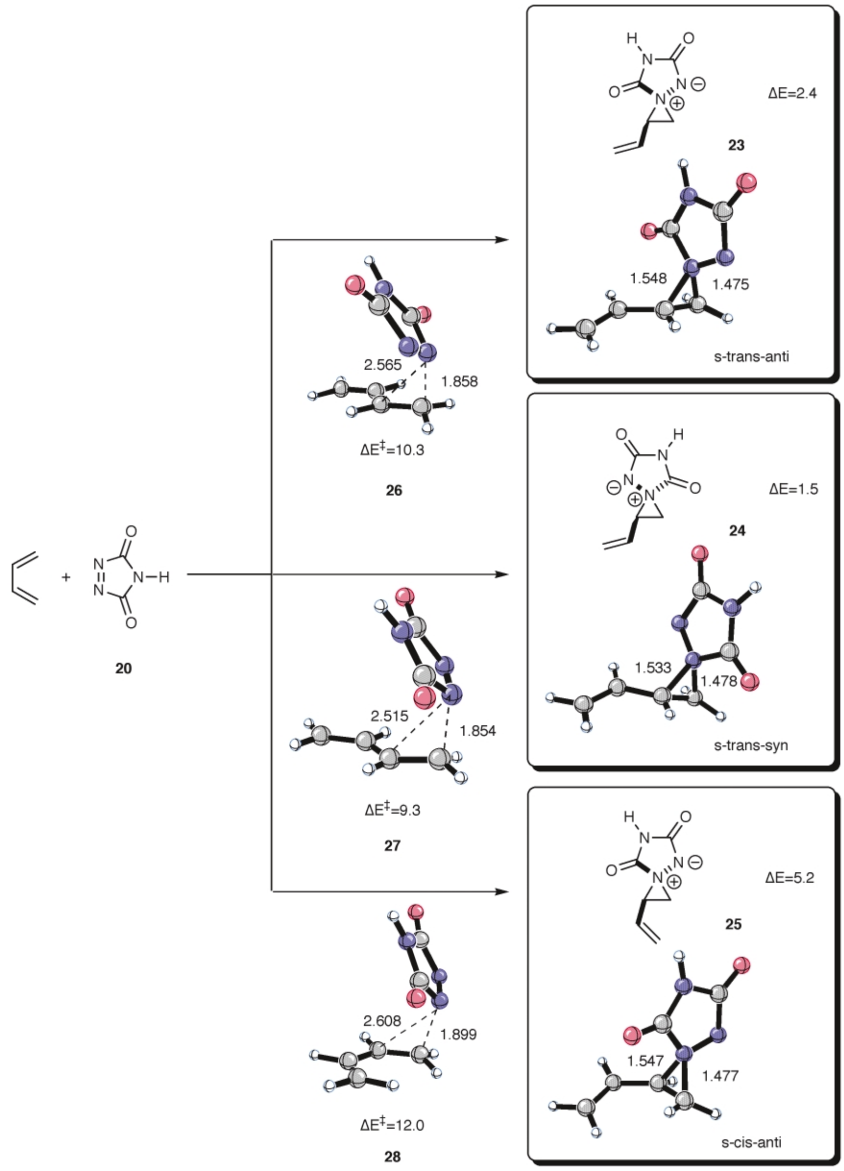
In their study of the Diels–Alder reaction between cyclohexadiene and singlet oxygen, described earlier, Sevin and McKee also found a concerted transition state for the ene reaction, **29** (Scheme 14).[23] This is higher in energy than the Diels–Alder transition state. Alternative transition states linking the diradical to a [2 + 2] oxetane product and *via* a [1,3]-hydrogen shift to a vinylic perepoxide were also located and found to be much higher in energy.

The most recent study of this reaction has been performed by Singleton, Houk, Foote *et al.*, culminating years of effort from the Houk group.[37] Deuterium isotope effects measured by Stephenson for tetramethylethylene (TME)[38] and Foote and Orfanopolous for butenes[39] and ^{13}C isotope effects for TME by Singleton[37] demonstrated that a species with the symmetry of a perepoxide must be involved in the reaction of singlet oxygen with TME. Isomers with *cis*-related CH_3 and CD_3 groups showed deuterium isotope effects of ~1.4. Isomers of TME with two *cis*-related CH_3 and two *cis*-related CD_3 groups showed an isotope effect of 1.04–1.09. This requires a mechanism in which the selectivity determining step allows selection between H-abstraction only between groups on the same side of the olefin. Several high levels of theory were employed in the initial theoretical study. Perplexingly, three different mechanisms are predicted; the results are summarised in Scheme 15.

CASSCF predicts a stepwise perepoxide mechanism, placing the perepoxide, **30**, 14.8 kcal mol^1 above reactants. A highly asymmetric transition state, **31**, leads to the perepoxide. This level of theory predicts that hydrogen abstraction, *via* **32**, is rate determining and greatly overestimates the experimental activation energy, which is near 3.2 kcal mol^1 in the gas phase.[40] The barrier is even lower (0.5 kcal mol^1) in MeOH solution.[41]



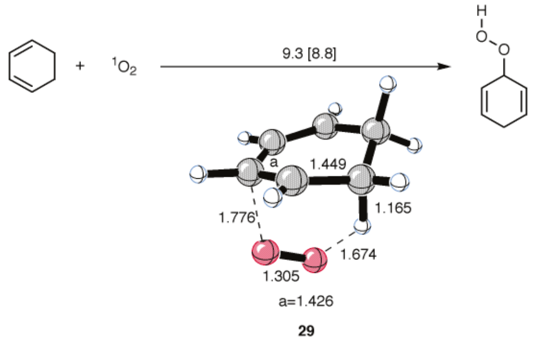
Scheme 11 B3LYP/6-31G* concerted transition states for the Diels–Alder reaction between HTAD (**20**) and butadiene.



Scheme 12 Potential aziridine imide intermediates and the transition states leading to them for the Diels–Alder reaction between HTAD (**20**) and butadiene. Distances for these B3LYP/6-31G* structures are given in Å and energetics in kcal mol^{1}. The energy for each species is given in kcal mol^{1} relative to reactants.

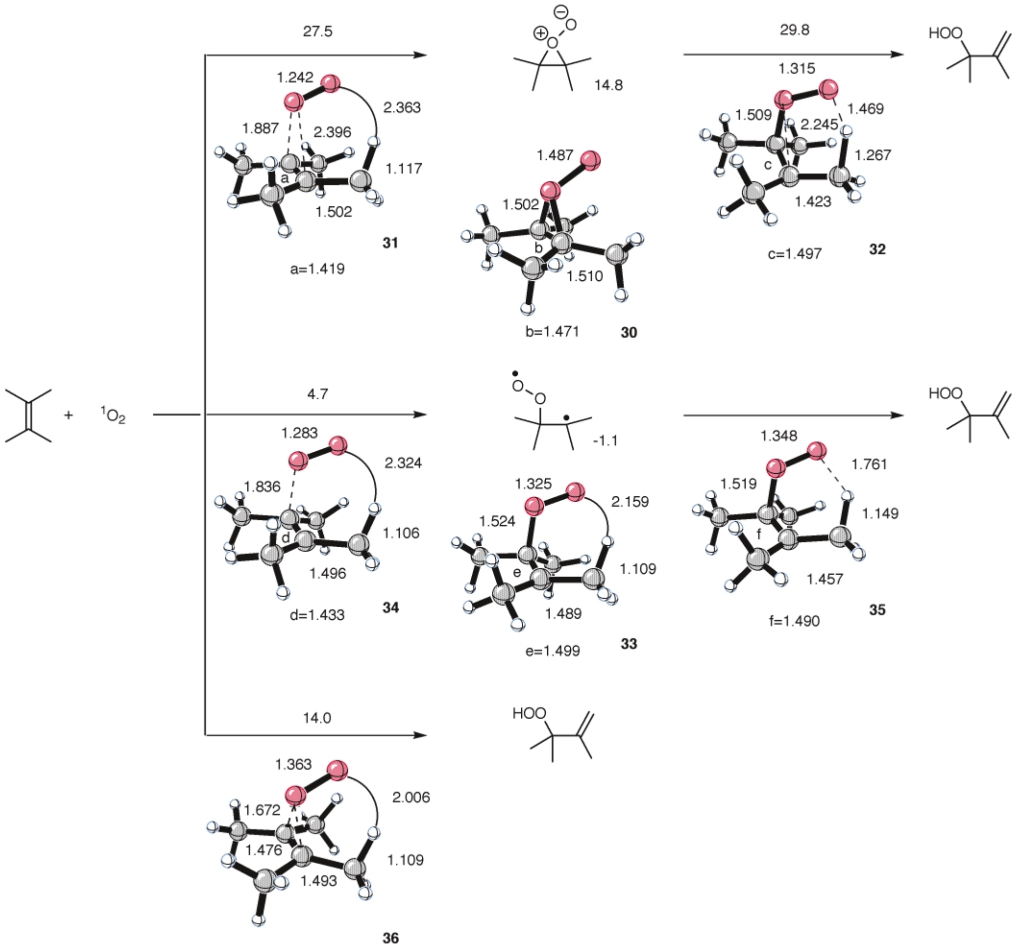
Scheme 13 The reaction of 2-*tert*-butylbutadiene with PTAD for which experimental kinetic isotope effects were obtained. The reaction of the same diene with HTAD was used to calculate theoretical isotope effects.

B3LYP makes different predictions, depending upon whether an open-shell broken symmetry, or closed-shell calculation is used. In the unrestricted calculations, a stepwise diradical mechanism is predicted. The diradical, **33**, forms *via* transition state **34**, and has two possibilities open to it (other than dissociation). It may either abstract a hydrogen with a barrier of 1.3 kcal mol^{1}, through transition state **35**, or else convert to the regioisomeric diradical through a transition state (not shown) with the symmetry of a perepoxide with a barrier of 5.4 kcal mol^{1}. When restricted B3LYP/6-31G* calculations are used, only one transition state, **36**, also having the symmetry of a perepoxide could be found. This species connects the reactants to both regioisomeric hydroperoxides, resulting from hydrogen abstraction from either terminal methyl group in the vicinity of the oxygen—this corresponds to a concerted mechanism.



Scheme 14 The B3LYP/6-31G* concerted transition state for the ene reaction between cyclohexadiene and singlet oxygen. B3LYP/6-31G* energetics are provided alongside CASPT2/6-31G* energies in brackets, both are in kcal mol^{1}.

A series of constrained B3LYP optimisations, providing better evidence about which is the lowest energy path, was performed. The structures obtained from these optimisations were used to calculate 225 single point energies at the CCSD(T)/6-31G* level. This revealed a surface that explains



Scheme 15 Three predicted mechanisms for the ene reaction between TME and singlet oxygen. The first mechanism is that predicted by CASSCF/6-31G*, the middle one by UB3LYP/6-31G* and the bottom one by RB3LYP/6-31G*. The energy for each species is given in kcal mol^{1} relative to reactants.

many of the experimental observations (Fig. 6). A transition state, like **36**, exists on the surface as does the perepoxide that it apparently leads to, although this too is a transition state. Between the transition state and the perepoxide, a valley ridge inflection intervenes, permitting the path to fall off to one side or the other while abstracting a hydrogen from either terminal methyl group. When the alkene is unsymmetrically substituted, the relative steepness of the slope on either side of the valley ridge inflection will determine the ratio of regioisomeric abstraction. Desymmetrisation might be expected ultimately to perturb the surface sufficiently that a diradical intermediate might appear as a genuine minimum. The mechanism predicted has many of the features of a stepwise mechanism through diradical intermediates and a stepwise mechanism through a perepoxide intermediate, but it does not sample either of these two possibilities.

The unusual nature of the potential energy surface for these reactions makes the application of transition state theory problematic, in particular for calculating isotope effects. A dynamics treatment will be necessary in order to explore fully the way this reaction occurs. The kinetic isotope effect for d_6-isomers of TME with a CH_3 and CD_3 group *cis* to one another is measured to be ~1.4. This ratio is also the ratio of the vibrational frequencies of the CH and CD bonds, and the rate of hydrogen abstraction on downward sloping surfaces is related to these frequencies.[42]

The description of the Diels–Alder reactions above suggested a preference for 1,1 bond formation that is most pronounced for singlet oxygen. This is also in operation in the ene reaction—the mechanism described here is synchronous in terms of 1,1 bond formation at the perepoxide-like transition state of the reaction. Introducing asymmetry would move the transition state to be more diradical-like, as observed for the two other types of ene reactions, described below.

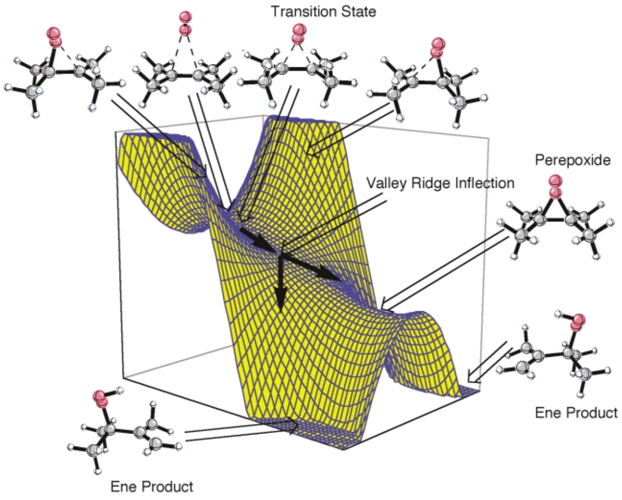


Fig. 6 A schematic representation of the potential energy surface for the reaction between singlet oxygen and TME evaluated by CCSD(T)/6-31G* single point calculations on geometries obtained by constrained optimizations using RB3LYP/6-31G*. The bold arrows indicate the motion over the surface from the symmetrical transition state which permits the reaction to bypass the perepoxide. The point at which two paths diverge towards the two regioisomeric products is the valley ridge inflection.

The ene reaction of singlet oxygen is calculated to proceed through a highly asynchronous concerted mechanism, involving regions of the potential surface with both perepoxide and polarised diradical character. Although both diradical and *perepoxide intermediates can be located on the potential energy surface, both are bypassed by way of a valley ridge inflection, and the reaction is concerted. As with its Diels–Alder reactions, the highly reactive singlet oxygen has a propensity for 1,1 bond formation, but the diradical that could thus be formed is highly reactive and gives products with no barrier.*

Ene reactions of nitroso compounds

Despite being known to undergo Diels–Alder reactions since the 1940s, nitroso compounds were not found to undergo ene reactions until 1965.[43] As with the ene reactions of triazolinediones, these reactions have been little studied until very recently. Wanner and Koomen recently studied the reactivity of 2-nitrosoadenosine as an enophile and Adam and co-workers have demonstrated the useful reactivity of nitrosoarenes with electron-poor aromatic components, including their stereoselective reaction with allylic alcohols.[44] The only theoretical publication on this reaction previous to 2001 was the PM3 study of Davies and Schiesser.[45] They showed that at that level of theory, the reaction of HNO with propene proceeded preferentially through an aziridine *N*-oxide (ANO).

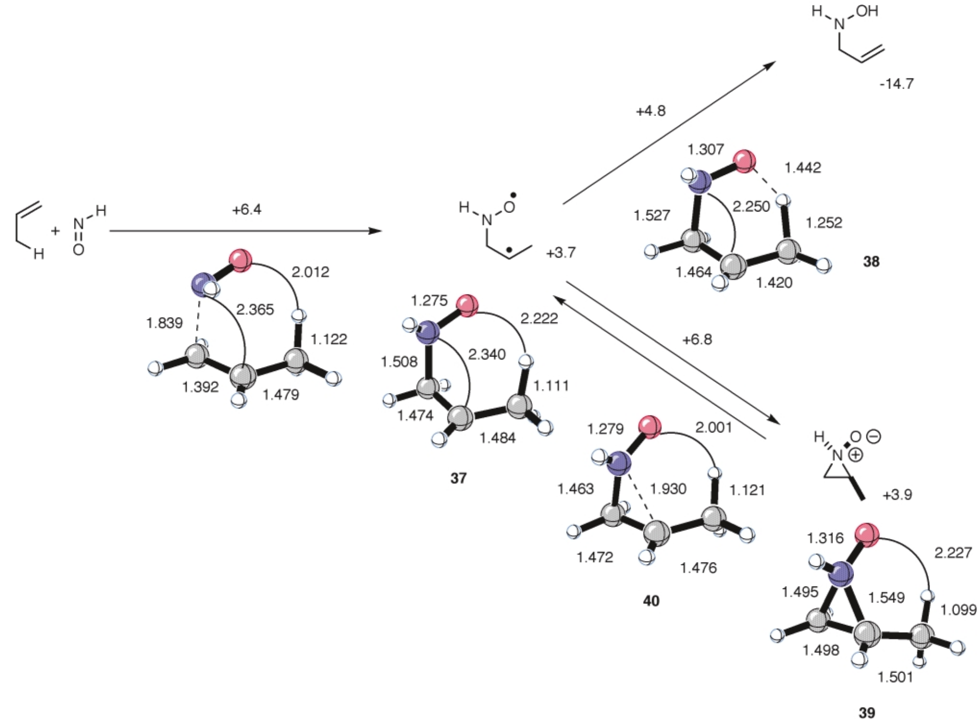
Adam *et al.* recently reported B3LYP/6-31+G* calculations on the reaction between 2-methybut-2-ene with *p*-$NO_2C_6H_4NO$.[46] They claimed that the reaction proceeds through an ANO intermediate, formed in a rate determining step from reactants which could then go on to product formation. We have recently re-examined their work and found that they had overlooked a diradical intermediate in the process.[47]

In our UB3LYP/6-31G* study of the ene reaction of nitroso compounds,[47] we found that the reaction between HNO and propene proceeds preferentially through a stepwise diradical pathway (Scheme 16), similar to that predicted for triazolinedione ene reactions.[48] For this parent reaction, it was found that HNO reacts with propene with an activation barrier of 6.4 kcal mol^{1} to form polarised diradical intermediate, **37**. Two paths are then open to this intermediate. It can either abstract an allylic hydrogen and form product, through transition state **38**, corresponding to a barrier of 1.1 kcal mol^{1}. Alternatively, a second C–N bond may form yielding the ANO **39** through transition state **40**, entailing a barrier of 3.1 kcal mol^{1}. The B3LYP/6-31G* structures were used to perform single points at QCISD(T)/6-31G** (based on restricted and unrestricted HF wavefunctions), UCCSD(T)/6-31G**, and UCCSD(T)/6-311+G**. These methods showed the same relative positions of competing transition states but predicted all transition states and intermediates to be approximately 10 kcal mol^{1} higher in energy with respect to isolated HNO and propene than with B3LYP/6-31G*. Single points with CASPT2/6-31G** however were in good agreement with B3LYP.

The diradical intermediate has high barriers to rotation (~ 4–5 kcal mol^{1}) around the formally single CN bond and the adjacent CC bond. These arise because of a CH–O hydrogen bond to the oxygen of the diradical and because of a small bonding interaction between the singly-occupied NO π^* and carbon 2p orbitals. These are nearly degenerate orbitals, as shown schematically in Fig. 7. The CASPT2 single point calculations revealed that configurations corresponding to zwitterionic [$\phi_1(1)\phi_1(2) \pm \phi_2(1)\phi_2(2)$ spatial components] and diradical [$\phi_1(1)\phi_2(2) + \phi_2(1)\phi_1(2)$] structures contribute to the electronic structure of this singlet intermediate. The zwitterionic contribution polarises the diradical in the direction of $^{-}ONHCH_2CH^{+}CH_3$; hence the moniker, 'polarised diradical' for **37** and others discussed in this article.

Other reactions involving various nitroso compounds (including *p*-$NO_2C_6H_4NO$) and alkenes were also examined. All show the same mechanism—rate limiting formation of a polarised diradical intermediate with subsequent partitioning between direct H-abstraction and closure to form an ANO.

Using MeNO we predicted the deuterium kinetic isotope effects that would be expected for the two competing pathways open to the reaction with TME and its isotopomers—direct H-abstraction or reversible cyclisation to form an ANO followed by H-abstraction. Rotation barriers are higher than those for either of these processes, and thus stereochemical integrity of the intermediate is maintained, a property originally attributed to the sole intermediacy of an ANO. Direct H-abstraction shows only a small, secondary isotope effect characteristic of the first step, for reaction of *cis*-TME-*d*$_6$, because all subsequent steps involve no possibility of choice between H or D. Cyclisation permits the molecule to choose between abstraction from one



Scheme 16 The UB3LYP/6-31G* mechanism of the reaction between HNO and butadiene. The energy for each species is given in kcal mol^{1} relative to reactants. Selected distances in Å are given alongside the structures.

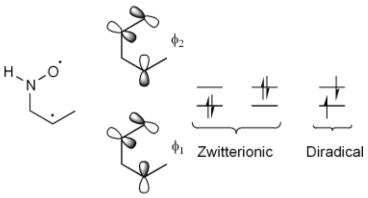
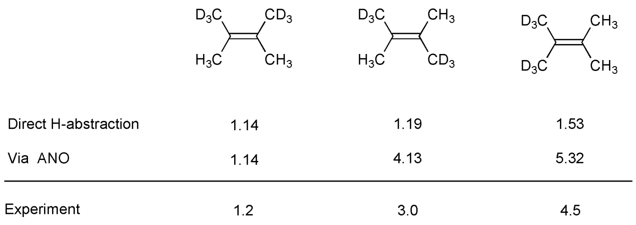


Fig. 7 The two nearly degenerate orbitals of polarised diradical **37** and the contributing electronic configurations.

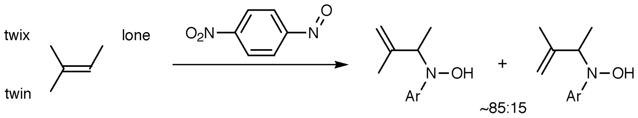
end or the other of the olefin and therefore for *trans*-TME-d_6 and *gem*-TME-d_6, large primary kinetic isotope effects arising from the final H-abstraction step are predicted. Comparison of these predicted KIEs (Fig. 8) to those measured with C_6F_5NO[49] permits the estimation of the proportion of the reactions that must proceed through the two competing processes. A difference of 0.4 kcal mol^{-1} would explain the experimental results, whereas the difference calculated by B3LYP is 0.7 kcal mol^{-1}.



Direct H-abstraction	1.14	1.19	1.53
Via ANO	1.14	4.13	5.32
Experiment	1.2	3.0	4.5

Fig. 8 Calculated and experimental kinetic isotope effects for d_6 isomers of TME, reacting with MeNO (calculated) or C_6F_5NO (experiment).

Calculations using MeNO also reproduce the regioselectivity observed experimentally in the reaction of 2-methylbut-2-ene with p-$NO_2C_6H_4NO$ (Scheme 17). The favoured position of H-abstraction is at the position called twix by Adam.[44b] Our calculations show that in both the transition state for H-abstraction and in the transition state for diradical formation, the twix regioisomer is preferred. These twix transition states are 0.6 kcal mol^{-1} and 1.0 kcal mol^{-1} lower in energy than those for the next favoured regioisomer, respectively. The second favourite predicted regioisomer is that styled twin. The experimentally observed ratio of abstraction between the twix and twin sites is ~85:15 (averaged over the reactions with two different isotopically labeled compounds) and corresponds to a difference in barrier heights of ~1 kcal mol^{-1}, which is close to our calculated value.



Scheme 17 The regioselectivity of the reaction between 2-methylbut-2-ene and p-$NO_2C_6H_4NO$.

The orthogonal 1,1 interactions characteristic of all of the reactions described in this article are highlighted in this section and are responsible for the preference for a stepwise path through polarised diradicals and for the competitive cyclisation to ANOs. The 1,1 interactions also operate in the polarised diradicals themselves, leading to significant barriers to CC and CN rotation and bestowing some ANO character on these open chain intermediates.

The ene reactions of nitroso compounds are stepwise processes that proceed through polarised diradical intermediates. These intermediates may either proceed directly to product via hydrogen abstraction or may reversibly cyclise to form aziridine N-oxide intermediates. High barriers to rotation in the polarised diradical give this mechanism some of the characteristics of a stepwise reaction involving cyclic aziridine N-oxides.

Ene reactions of triazolinediones

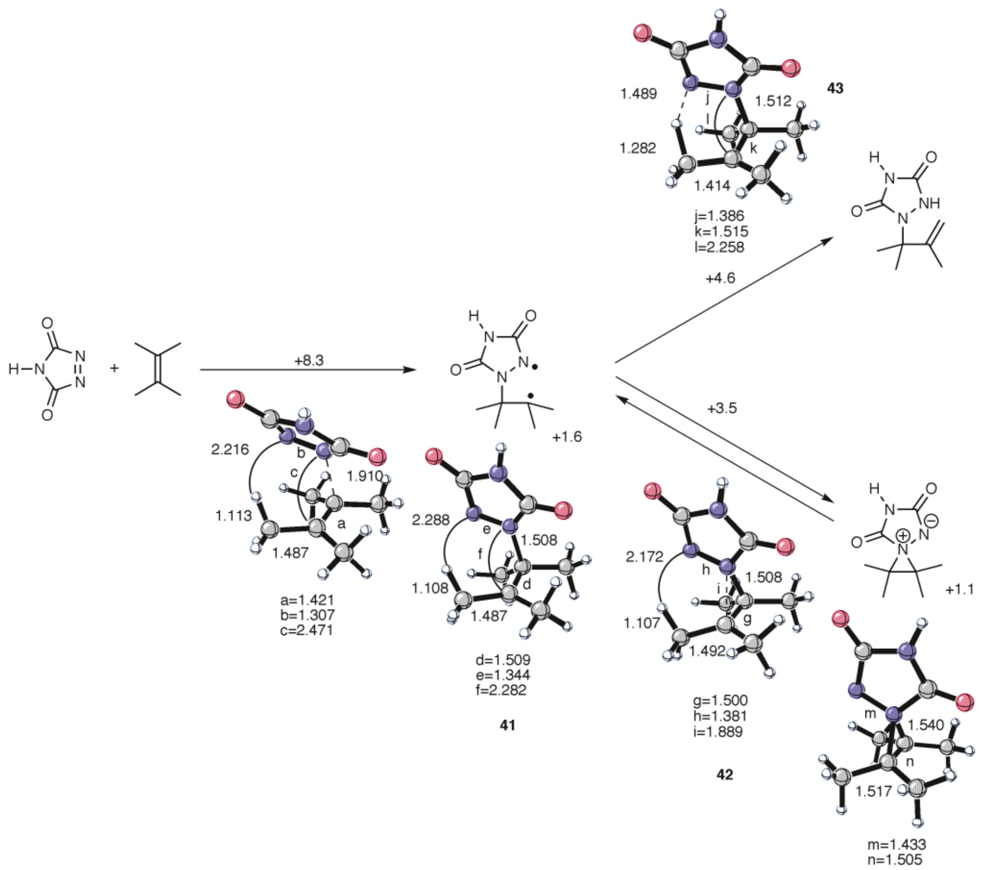
Triazolinediones were first employed to react in an ene fashion by Pirkle and Stickler in 1967.[50] Since that time, these reactions have received some attention, particularly because of the apparent similarities between the ene reactions of triazolinediones and those of singlet oxygen. Although little employed in synthesis, Adam *et al.* have recently demonstrated a relatively mild hydrolysis of the products of this ene reaction, thus permitting the reaction to be used to generate allylic amines which may find some utility.[51]

The most recent study of these ene reactions was focussed on measuring kinetic isotope effects experimentally and comparing them to those predicted by a range of theoretical methods.[48] The theoretical study employed RHF/6-31G* and B3LYP/6-31G* and located stationary points for the reaction between HTAD and isobutene, 2-methyl-2-butene and tetramethylethylene (TME). The RHF calculations, in line with the results of Chen *et al.* predicted a stepwise path through AI intermediates.[52] However, the B3LYP calculations predicted a stepwise path through a diradical such as **41** (UB3LYP) or polar (RB3LYP) intermediate: the intermediates are highly diradical in character but all except one of the four possible structures could also be optimized with RB3LYP. We prefer to style such intermediates polarised diradicals. The closed shell, more polar species were higher in energy than the unrestricted diradicals by 2–4 kcal mol^{-1}. The zwitterionic character of these structures would be increased in solution, but the 0.5 electrons transferred from the diene to the HTAD is less than that expected for a real zwitterion. CASSCF(2,2) calculations also predicted the existence of the intermediate. The transition states linking the diradical through ring closure to an AI, such as **42**, or through hydrogen abstraction to product formation, such as **43**, were also found. The reaction with TME is used to illustrate the mechanism in Scheme 18.

Whereas for TME, ring closure occurs preferentially over H-abstraction by 1.1 kcal mol^{-1}, for isobutene there is a 0.8 kcal mol^{-1} favouring of product formation over ring closure. This different degree of partitioning between the two paths (diradical going directly to product and diradical first sampling a cyclic structure before leading to product) has an influence on many of the observed reactions and dictates kinetic isotope effects, in a similar fashion to that discussed for the ene reactions of nitroso compounds.

The authors describe the AI as an ‘innocent bystander’ because although it can be formed, it cannot lead to product formation without first re-opening to a diradical. At low temperatures, when the entropic disadvantage of MeOH trapping compared to hydrogen abstraction can be overcome, the AI can be trapped. Experimental MeOH trapping experiments showed that, at the temperatures normally employed for this reaction, the amount of reactant that could be intercepted as an AI was limited, suggesting that some fraction of the reactant does not sample the AI at all, in line with theoretical prediction.[53]

The barrier to rotation about the CN bond in the diradical was investigated, because the observed isotope effects require that an open chain diradical does not allow stereochemical scrambling by rapid rotation about formally single bonds. For the diradical formed between isobutene and HTAD, the CN rotation barrier was found to be 3.9 kcal mol^{-1}, 1.0 kcal mol^{-1} higher than the hydrogen abstraction transition state; whereas for the diradical formed with TME, the barrier was 5.5 kcal mol^{-1}, 2.5 kcal mol^{-1} above the hydrogen abstraction transition state. This polarised diradical, in line with that for the ene reaction of nitroso compounds therefore has some of the properties of an AI. The rotational barriers and transition states, which reveal interesting and unusual properties of heteroatomic diradicals,



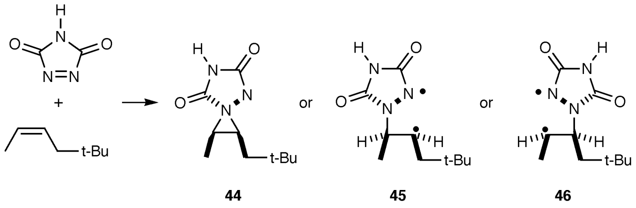
Scheme 18 The UB3LYP/6-31G* mechanism of the reaction between HTAD and TME. The energy for each species is given in kcal mol^{1} relative to reactants.

were not dealt with in a thorough manner. They merit further attention.

With a range of transition states in hand, the authors calculated H/D and $^{12}C/^{13}C$ isotope effects; these relied on an expected high barrier to rotation in the diradical. However, it was suggested that the relatively high kinetic isotope effects observed for isobutene-d_3 and *trans*-but-2-ene-d_3, arise because the rotational barrier is only slightly higher than that for hydrogen abstraction and, thus, some of the diradical does undergo rotation and can abstract H or D in the product determining step. Inter- and intra-molecular kinetic isotope effects that were calculated were generally in good agreement with those measured.

The relative reactivities of different alkenes were consistent with calculated activation barriers. For example, 2-methylbut-2-ene reacts 33 times faster than isobutene, and TME reacts 1500 times faster than isobutene; calculated activation energies are 7.9 kcal mol^{1} for TME, 10.5 kcal mol^{1} for 2-methylbut-2-ene and 11.1 kcal mol^{1} for isobutene. Regioselectivity was correctly predicted and was explained as a result of steric interactions which are more severe in a transition state from an open diradical than from an AI. Thus AI intermediate, **44**, might be expected to abstract hydrogen from either position in a rather similar way. However, the two open chain diradicals, **45** and **46**, would be very different in character and therefore lead to the high degree of selectivity observed experimentally (Scheme 19). Calculations of solvent effects, with the SCIPCM model, showed that the UB3LYP stepwise diradical mechanism should be less dependent upon the solvent than the RHF stepwise AI mechanism and was therefore more consistent with the experimentally observed weak solvent effect.

As in the other reactions already described, we observe that the propensity for 1,1 attractive interactions is in operation in this reaction leading to the preference for a stepwise path through polarised diradicals—the formation of the first bond to one atom of the enophile. The second of the 1,1 bonds may also form, competitively with H-abstraction, leading to AI intermediates. These 1,1 interactions are also likely to be significant contributors to the high rotational barriers observed in the polarised diradicals.



Scheme 19 Possible aziridine imide (**44**) and diradical (**45** and **46**) intermediates for the reaction of *cis*-5,5-dimethylhex-2-ene.

The ene reactions of triazolinediones are stepwise with obligatory diradical intermediates. These intermediates may cyclise, leading to aziridine imides but must revert to the open chain diradical in order to proceed to ene products. These polarised diradicals are rigidified by high rotational barriers about formally single bonds.

Conclusions

Modern theoretical methods have been applied to the Diels–Alder and ene reactions of singlet oxygen, nitroso compounds and triazolinediones. Despite the electronic similarity between these three electrophile types, the mechanism calculated for each reaction is, at least in detail, different from the others. The mechanisms calculated for each reaction type range from concerted reactions to stepwise reactions which involve diradical, polarised diradical and 3-membered ring zwitterionic intermediates. They are all linked by a preference for 1,1 bond formation—that is, for formation of two bonds to one atom, either N or O in these systems. The HOMO and LUMO of these compounds cause them to act as both electrophile and nucleophile simultaneously at one atom. These frontier orbital interactions lead to a preference for highly asynchronous concerted paths or stepwise paths through polarised diradicals. These interactions also influence the properties of these intermediates, causing significant rotational barriers about formally single bonds of the polarised diradical.

Acknowledgements

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