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Isotope effects and the distinction between synchronous, asynchronous, and stepwise Diels–Alder reactions

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Dedicated to Professor Barry M. Trost and his inspiring enthusiasm for chemistry on the occasion of his 60th birthday

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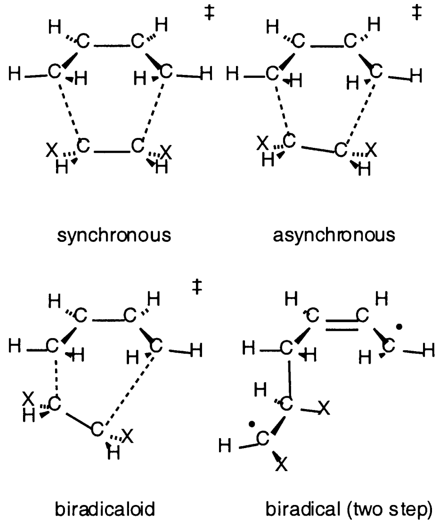
Abstract—A variety of symmetrical or nearly symmetrical Diels–Alder reactions are studied by a combination of experimental isotope effects, theoretical calculations, and rate observations. Becke3LYP calculations predicted highly asynchronous transition structures for Diels–Alder reactions of bis(boryl)acetylenes, dialkyl acetylenedicarboxylates, triazolinediones, and dialkyl maleates. Rate observations and kinetic isotope effects are consistent with these predictions, though the experimental support for the calculated structures is notably ambiguous in some cases. A concerted mechanism is supported for the retro-Diels–Alder reaction of norbornene. Overall, Diels–Alder reactions appear to be only very weakly biased toward synchronous transition states. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

It is widely accepted that most Diels–Alder reactions occur by concerted mechanisms, and the common understanding of the facility of Diels–Alder reactions centers on the idea of an aromatic transition state with synchronous formation of the two new carbon–carbon bonds. In the past there has been some controversy over these ideas, with highly asynchronous 'biradicaloid' transition states or stepwise mechanisms being favored at times by some groups.[1] However, the view that Diels–Alder reactions intrinsically prefer synchronous transition states has prevailed in later studies. Reactions of unsymmetrical dienes or dienophiles necessarily involve unsymmetrical transition states, but Diels–Alder reactions of symmetrical addends are thought to usually involve synchronous or nearly synchronous C–C bond formation. The evidence for this proposition has come mainly from ab initio calculations,[2–4] substituent effects on the rate,[5] and deuterium kinetic isotope effects (KIEs).[6]

Recently the argument over the nature of Diels–Alder reactions was briefly rekindled by Zewail and coworkers' femtosecond time-resolved observation of an intermediate in the retro-Diels–Alder reaction of norbornene.[7] Notably this intermediate's short lifetime was thought to allow a stereospecific stepwise mechanism.[8] Nevertheless, calculations predict a synchronous concerted transition state for this reaction,[9] and Zewail and Houk have found that the femtosecond norbornene observations are consistent with reactions on the excited-state energy surface.[10]



We have been intrigued by calculations predicting highly asynchronous transition states for some Diels–Alder reactions,[11–13] and we present here our studies of several symmetrical or nearly symmetrical Diels–Alder reactions. A key tool in these investigations is the comparison of experimental and theoretically predicted ^{2}H and ^{13}C KIEs. In several studies we have recently shown that high-level

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Keywords: Diels–Alder reaction; isotope effect; asynchronous transition state.

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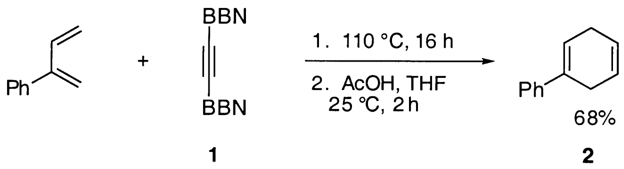
calculations can lead to excellent predictions of heavy-atom KIEs and reasonably good predictions of deuterium KIEs for reactions not involving hydrogen transfer, *provided* that the calculated transition structure more or less accurately reflects reality.[14] In this way KIEs can be used to provide an experimental basis for calculated transition state geometries. In the first application of this tool with the prototypical 'nearly symmetrical' Diels–Alder reaction of isoprene with maleic anhydride, a near-perfect prediction of the complete set of experimental KIEs was possible from the Becke3LYP-calculated transition structure.[15] This observation provided strong support for a nearly synchronous transition state, as well as supporting the applicability of Becke3LYP calculations to other Diels–Alder reactions. In this paper, we experimentally and calculationally probe a variety of reactions to distinguish synchronous versus asynchronous versus stepwise pathways. We find that none of the mechanistic probes used was consistently convincing by itself. Overall, however, the expected preference for synchroneity with symmetrical addends appears readily countered by a number of factors. The results have implications toward our general understanding of Diels–Alder reactions.

2. Results and discussion

2.1. Bis(9-borabicyclo[3.3.1]nonyl)acetylene

Our interest in unsymmetrical Diels–Alder reactions involving symmetrical dienophiles was initiated by an unusual observation with a 'doubly activated' dienophile. We have previously found that mono-dialkylboryl acetylenes were moderately reactive but successful dienophiles,[16] and bis(9-borabicyclo[3.3.1]nonyl)acetylene (**1**) was of interest owing to its expected higher reactivity. The neat reaction of bis(tributylstannyl)acetylene with two equivalents of 9-bromo-9-BBN was found to afford **1** rapidly at −78°C. Although **1** could not be isolated, support for its formation comes from the ^1H NMR observation of almost quantitative formation of Bu_3SnBr, the observation of BBN-group peaks similar to other BBN-alkynes,[16,17] and the subsequent reactivity of the solution. This convenient generation of **1** from commercially available materials provides an effective dienophile—reaction with simple acyclic dienes occurs at 110°C and good yields of 1,4-cyclohexadienes are obtained after deboronation of the presumed Diels–Alder adducts with acetic acid (Eqs. (1)–(3)).



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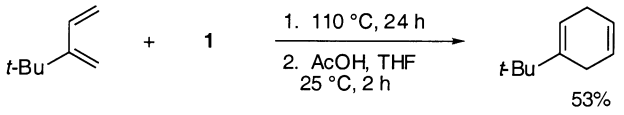

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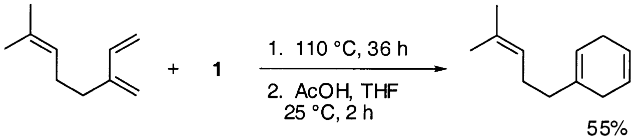


(3)

Surprisingly, however, **1** was *less reactive* than a mono-activated acetylenic borane. For example, a competition between **1** and a mono-BBN-activated dienophile[16] for reaction with butadiene had k_{rel} (bis/mono)=0.16 at 130°C. For symmetrical or nearly synchronous cycloaddition transition states, it might be expected that a second activating group would provide similar activation to the first.[1c,5] While lesser activation by the second activating group has usually been observed,[18] the observation that a single boryl group is highly activating while a second boryl group is deactivating is highly unusual.[19] This suggested that Diels–Alder reactions of **1** do not proceed by a symmetrical transition state.

Density function theory calculations support this idea (Fig. 1). Becke3LYP calculations with a $6\text{-}31G^*$ basis set predict a highly unsymmetrical transition structure (**3**) for the reaction of 1,3-butadiene with the parent bis(boryl)-acetylene. The symmetrical structure **4**, found by forcing C_s symmetry, is a second-order saddle point exhibiting two imaginary frequencies, and **4** is predicted to be 6.5 kcal/mol higher in energy than **3**. In concert with the experimental observation, the barrier for reaction of bis(boryl)acetylene is predicted to be higher than for

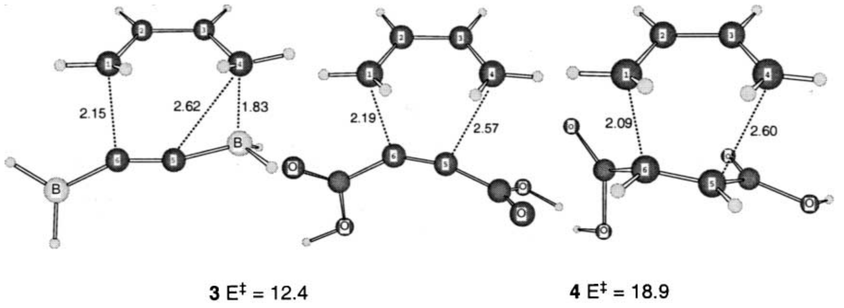


Figure 1. The calculated unsymmetrical transition structure (**3**) and symmetrical second-order saddle point (**4**) for the Diels–Alder reaction of 1,3-butadiene with bis(boryl)acetylene. Relative energies versus starting materials (including zpe) are given in kcal/mol.

reaction of the mono-activated $HCCBH_2$ (transition structure not shown) by 3.4 kcal/mol.[20]

Structure **3** is a [4 atom+3 atom] transition structure as previously predicted for Diels–Alder reactions of both vinylboranes and acetylenic boranes.[16,21] The intimate involvement of the boron atom in the transition state for boron-activated Diels–Alder reactions has been explained on an FMO basis—the LUMO of a vinyl- or alkynylborane has a large coefficient on the boron atom for interaction with the diene HOMO. The HOMO–LUMO overlap is also geometrically highly favorable as the distance between C1 and C4 on a 1,3-diene is comparable to the distance between the boron atom and terminal alkynyl carbon on an acetylenic borane. However, a [4+3] cycloaddition cannot be consummated, as it does not lead to a stable product. After the transition state, IRC analysis has the C4–C5 bond distance decreasing rapidly. This transforms the [4+3] transition structure into the stable [4 atom+2 atom] cycloadduct.

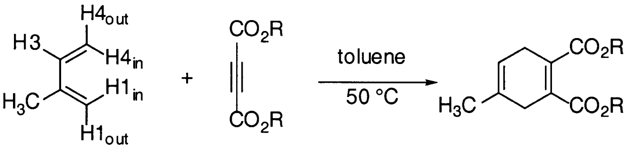
The alternative structure **4** could be described as a [4 atom+4 atom] transition structure as C1 and C4 of the diene are nearly as closely associated with the boron atoms as with the alkynyl carbons to which they would ultimately bond. Such a [4+4] structure might be expected from FMO theory because the LUMO of a planar bis(boryl)acetylene has larger coefficients on the boron atoms than on carbon.[22] However, the geometry for HOMO–LUMO overlap would not be favorable—the p orbitals for the two boron atoms cannot overlap well with the p orbitals of C1 and C4 at the same time. Instead, the second boryl group twists 90° from the first to have its empty p orbital conjugated with the second π bond of the alkyne. This rationalizes the lower reactivity of **1** compared to a monoborylalkyne.

2.2. Dialkyl acetylenedicarboxylates

The Diels–Alder reactions of **1** have the appearance of being a 'special case,' and carbonyl-activated dienophiles would not be expected to behave similarly. It was therefore surprising to note the recent calculational prediction by Morokuma and coworkers of a highly unsymmetrical transition structure for the reaction of acetylenedicarboxylic acid with cyclopentadiene.[13] We set out to assay the synchroneity of Diels–Alder reactions of carbonyl-activated alkynes in detail.

As with **1**, rate observations provided a starting point. Dimethyl acetylenedicarboxylate is notably less reactive than dimethyl fumarate, the former requiring prolonged heating with dienes that react at room temperature with the latter. To study the effect of having one activating substituent versus two in carbonyl-activated acetylenes, competition reactions were carried out with mono- and bis-activated dienophiles in their Diels–Alder reactions with butadiene. For dimethyl acetylenedicarboxylate/methyl propiolate, k_{rel} (bis/mono)=13 (100°C), while for 3-hexyn-2,5-dione/3-butyn-2-one, k_{rel} (bis/mono)=20 (25°C). The second carbonyl in each case certainly has much less activating effect than the first one did. This does not fit with expectations at the extreme of purely synchronous transition states.[1c] However, the pattern here is typical of other Diels–Alder reactions,[18] and no clear interpretation of the synchroneity of the transition state is possible from these data alone.[23]

We next probed the synchroneity of these reactions with kinetic isotope effects. Because a symmetrical Diels–Alder reaction necessarily exhibits symmetrical isotope effects due to averaging, a 'moderately unsymmetrical' Diels–Alder reaction (see Ref. 6 for a discussion of this strategy) was required. The reaction of diethyl or dimethyl acetylenedicarboxylate (**6**, R=Me or Et) with isoprene (**5**) was chosen for study (Eq. (4)).[6] Isotope effects for the uncatalyzed reaction of isoprene with **6** were determined combinatorially at natural abundance by NMR methodology.[24] Reactions of isoprene on a 0.5-mol scale in toluene at 50°C were taken to 84±2% and 83±2% conversion using limiting diethyl acetylenedicarboxylate and 75±3% conversion using dimethyl acetylenedicarboxylate. The unreacted isoprene, recovered by successive crude and fractional distillations, was analyzed by ^{13}C and ^{2}H NMR along with a standard sample of the isoprene not subjected to the reaction conditions. The changes in ^{13}C and ^{2}H composition were then calculated using the methyl group as an internal standard with the assumption that its isotopic composition does not change during the reaction. From the changes in isotopic composition the isotope effects were calculated as previously described.[24]



5 6 R = Me or Et 7

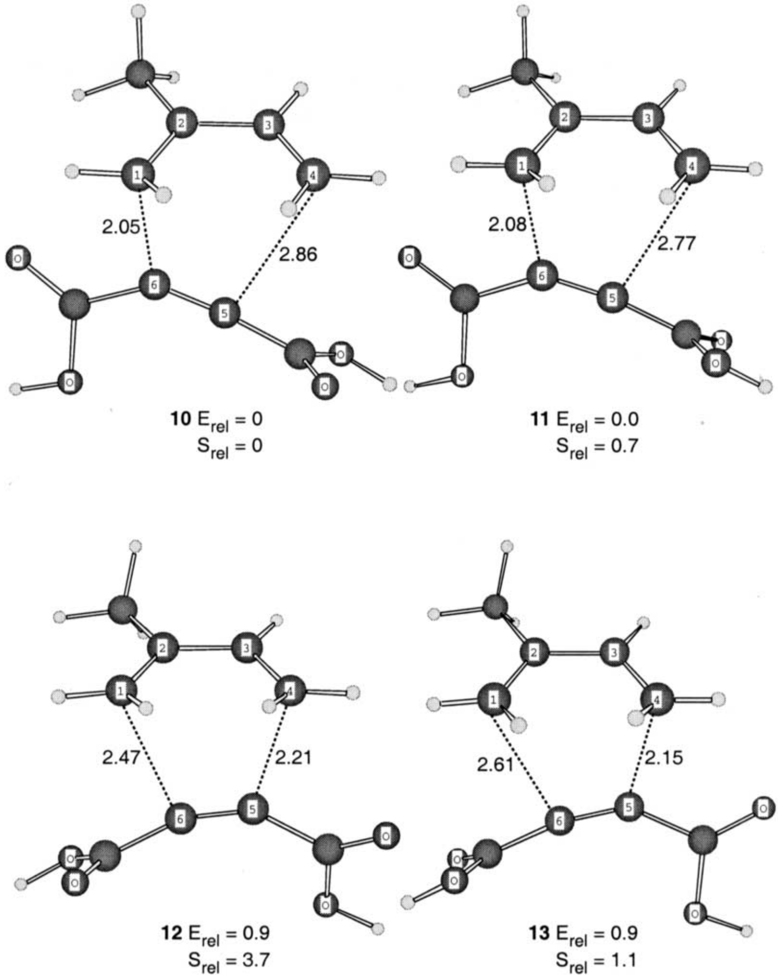
(4)

The results are summarized in Table 1. The ^{13}C KIE at C1 is larger than that observed at C4, and the inverse ^{2}H KIEs observed for $H1_{in}$ and $H1_{out}$ are more pronounced than those for $H4_{in}$ and $H4_{out}$. However, the differences in 1-position versus 4-position isotope effects are similar to those

Table 1. Experimental isotope effects ($k_{^{12}C}/k_{^{13}C}$ or k_H/k_D, 50°C) for the Diels–Alder reaction of isoprene with **6**

	Experiment[a]		
	1	2	3
C1	1.023 (3)	1.021 (2)	1.020 (3)
C2	1.000 (2)	1.000 (3)	1.001 (2)
C3	1.000 (1)	0.999 (2)	0.999 (2)
C4	1.016 (3)	1.016 (2)	1.014 (2)
$H1_{in}$	0.936 (10)	0.935 (11)	
$H1_{out}$	0.955 (4)	0.963 (3)	
H3	0.988 (7)	0.992 (5)	
$H4_{in}$	0.967 (6)	0.968 (9)	
$H4_{out}$	0.980 (6)	0.983 (6)	

[a] Experiments 1, 2 and 3 were taken to 84±2%, 83±2%, and 75±3% conversion, respectively. Experiments 1 and 2 used diethyl acetylenedicarboxylate while experiment 3 used dimethyl acetylenedicarboxylate. Deuterium isotope effects were not measured for experiment 3.



10 $E_{rel} = 0$ $S_{rel} = 0$

11 $E_{rel} = 0.0$ $S_{rel} = 0.7$

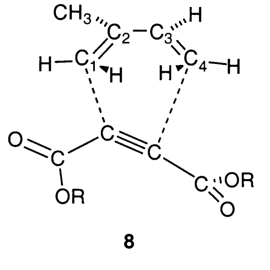
12 $E_{rel} = 0.9$ $S_{rel} = 3.7$

13 $E_{rel} = 0.9$ $S_{rel} = 1.1$

Figure 2. Transition structures for the Diels–Alder reaction of acetylenedicarboxylic acid with isoprene. Relative energies versus **10** (Becke3LYP/6-31G*+zpe) are given in kcal/mol and estimated relative entropies (25°C) are in e.u.

observed in the reaction of isoprene with maleic anhydride,[24] a reaction concluded to involve a nearly synchronous transition state.[15] The isotope effects are indicative of greater bond formation to C1 than C4 at the transition state, but they also qualitatively suggest relatively modest asynchroneity in the formation of the two new C–C bonds.

This interpretation must be tempered by a more careful consideration of the isotope effects expected if a highly asynchronous transition state is preferred for these reactions. In such a case, two transition states may contribute to the observed isotope effects—one in which bond formation to C1 is advanced over that to C4 (e.g. **8**) and one in which bond formation to C4 is advanced (e.g. **9**).



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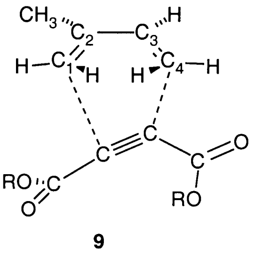


9

The predominance of structures such as **8** with greater bond formation to C1 of isoprene was a key assumption in a previous study.[6] However, if **9** contributes significantly the observed isotope effects will not reflect the asynchroneity of the reaction.

In order to quantitatively interpret the isotope effects, theoretical calculations were carried out on the model reaction of acetylenedicarboxylic acid with isoprene. The four transition structures **10**–**13** were found for this reaction in Becke3LYP calculations with a 6-31G* basis set (Fig. 2). Each is highly unsymmetrical, and the transition structures arise from two pairs of regioisomerically unsymmetrical structures where the carbonyl adjacent to the longer of the two forming C–C bonds may be directed either *endo* or *exo*. The structures **10** and **11** with more advanced bonding to C1 of isoprene are predicted to be enthalpically favored, but entropy estimates at 25°C based on the unscaled vibrational frequencies favor the regioisomerically opposite transition structures **12** and **13**.

KIEs were predicted for each of the transition structures **10**–**13** by the method of Bigeleisen and Mayer[25] from the scaled theoretical vibrational frequencies,[26] and tunneling corrections were applied using the one-dimensional infinite

Table 2. Theoretically predicted isotope effects ($k^{12}C/k^{13}C$ or k_H/k_D, 50°C) for the Diels–Alder reaction of isoprene with acetylenedicarboxylic acid

	10	**11**	**12**	**13**	Weighted average for **10–13**[a]
C1	1.030	1.029	1.015	1.008	1.022
C2	1.003	1.003	1.004	1.001	1.003
C3	1.001	1.000	1.003	1.001	1.001
C4	1.004	1.006	1.023	1.025	1.013
$H1_{in}$	0.901	0.908	0.953	0.970	0.928
$H1_{out}$	0.900	0.906	0.991	1.001	0.944
H3	0.965	0.964	0.987	0.993	0.975
$H4_{in}$	0.965	0.965	0.938	0.936	0.953
$H4_{out}$	1.003	1.000	0.940	0.920	0.972

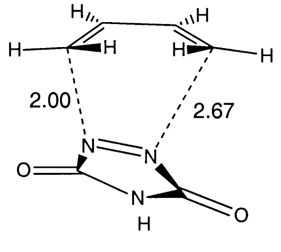
parabolic barrier model.[27] The results are shown in Table 2. The asynchroneity of C–C bond formation in **10–13** is reflected in predicted isotope effects for the individual structures—even the relatively synchronous structure **12** is predicted to exhibit a substantial difference in KIEs at C1 and C4. Because **10–13** are comparable in energy, each should contribute to the observed KIEs. Unsurprisingly, then, none of the sets of KIEs for the individual structures compare well with experiment. Table 2 shows that a much better prediction of the experimental KIEs comes from a Boltzmann-weighted average of the KIEs predicted for **10–13** based on the energies and entropies of Fig. 2. In this case the predicted carbon KIEs are in good agreement with experiment, while the weighted KIEs underpredict the observed deuterium KIEs by 1–2%. The tendency to underpredict experimental deuterium KIEs has been previously observed with the Claisen rearrangement, one possible explanation being an underprediction of tunneling by the one-dimensional tunneling correction employed.[14d]

In considering the weighted predicted KIEs it should be noted that the predictions would change substantially with small changes in the relative energies or entropies of **10–13**, and these relative energies and entropies are not reliable to such a degree. A change in the weighting could make the prediction better (for example, a small increase in contribution from **13** would bring the predicted ^{13}C KIEs into essentially perfect alignment with experiment) or worse. The possibility of fortuity in the agreement of predicted and experimental KIEs should thus be recognized. The general possibility for multiple contributing transition states limits the certainty of conclusions based on the isotope effects for Diels–Alder reactions. Nonetheless, the experimental isotope effects are certainly *consistent* with the highly asynchronous theoretical structures.

It is important to note that the calculational support for a highly asynchronous transition state is very weak by itself. For the reaction of 1,3-butadiene with acetylenedicarboxylic acid, BeckeLYP/6-31G* calculations do predict highly asynchronous transition structures (not shown, but very similar to **10** and **11**). However, a synchronous second-order saddle point obtained by enforcing C_s symmetry is only 0.1 kcal/mol higher in energy. Such a small energy difference is in no way reliable. This low difference in predicted barriers for asynchronous versus synchronous pathways also highlights the difficulty of interpreting rate ratios for mono- versus bis-activated dienophiles. The calculations predict a 1.0 kcal/mol lower barrier for the reaction of 1,3-butadiene with acetylenedicarboxylic acid than with propiolic acid, in good agreement with the relative rate observations above with dimethyl acetylenedicarboxylate/methyl propiolate. However, this cannot be taken as favoring an asynchronous over a synchronous transition state, as the barrier for formation of the synchronous structure (only 0.1 kcal different) fits just as well with experiment.

2.3. Triazolinediones

1,2,4-Triazoline-3,5-diones (TADs) are highly reactive dienophiles.[28] In a study of the Diels–Alder reaction of 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) with isomeric 2,4-hexadienes, Jensen and Foote observed a lack of stereospecificity with the *Z*,*Z* isomer. In addition, when the reactions were carried out in methanol with either the *Z*,*Z* or *Z*,*E* isomers, products indicative of intermediate trapping were observed. No trapping was observed for the *E*,*E* isomer. It was concluded that the *Z*,*Z* and *Z*,*E* isomers react by stepwise mechanisms involving aziridinium imides, while it could not be decided whether dienes that more readily obtain an *s-cis* conformation involve stepwise or concerted processes. Recent calculations by Houk and Foote have predicted that the concerted mechanism should be favored when the *s-cis* conformation is not sterically precluded.[12] However, the best transition structure found in Becke3LYP/6-31G* calculations for the reaction of the parent TAD with 1,3-butadiene was **14**. This highly unsymmetrical and asynchronous transition structure was predicted to be favored by only 1.1 kcal/mol over the second-order saddle point **15** obtained by forcing C_s symmetry. The asynchroneity of **14** was analogous with asynchroneity previously predicted for the Diels–Alder reaction of butadiene with *cis*-diazene.[11]



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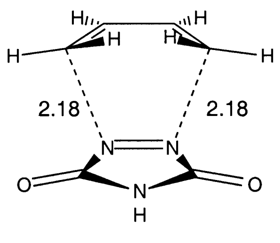

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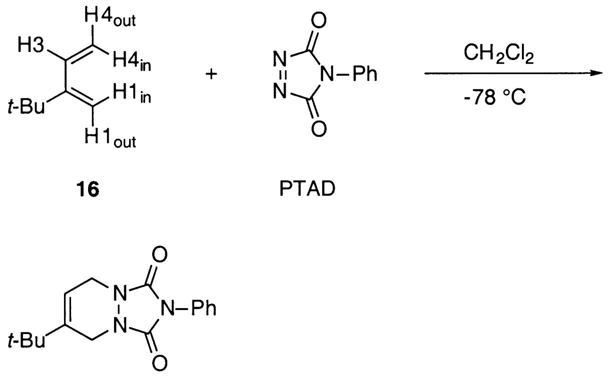
Because TADs are also highly reactive in ene reactions, a diene lacking allylic hydrogens, 2-*t*-butyl-1,3-butadiene (**16**), was chosen for the study of the isotope effects in TAD Diels–Alder reactions. Reactions of **16** with PTAD in CH_2Cl_2 at −78°C afforded the Diels–Alder adduct **17** quantitatively. The unreacted **16** from reactions taken to 71±3% and 70±3% conversion was recovered by vacuum transfer followed by fractional distillation and analyzed compared to a standard sample (vide supra) using the methyl groups as the internal standard for the NMR integrations.

Table 3. Experimental and theoretically predicted isotope effects ($k^{12}C/k^{13}C$ or k_H/k_D, −78°C) for the Diels–Alder reaction of 2-*t*-butyl-1,3-butadiene with PTAD

	Experimental[a]		Predicted		Best-fit average[b]	
	1	2	**18**	**19**		**15**
C1	1.023 (4)	1.025 (3)	1.043	1.006	1.025	1.028
C2	1.007 (4)	1.003 (3)	1.009	1.002	1.005	1.002
C3	1.001 (3)	1.001 (3)	1.000	1.004	1.001	1.002
C4	1.022 (3)	1.021 (3)	1.007	1.0045	1.023	1.028
$H1_{in}$	0.88 (2)	0.89 (2)	0.807	0.929	0.862	0.805
$H1_{out}$	0.95 (2)	0.95 (2)	0.863	1.013	0.931	0.906
H3	0.96 (1)	0.98 (1)	0.939	0.937	0.938	0.952
$H4_{in}$	0.86 (1)	0.88 (1)	0.921	0.775	0.855	0.805
$H4_{out}$	0.92 (1)	0.94 (2)	1.016	0.821	0.928	0.906

[a] Experiments 1 and 2 were taken to 71±3% and 70±3% conversion, respectively.

[b] Based on a 55:45 mixture of **18** and **19**.

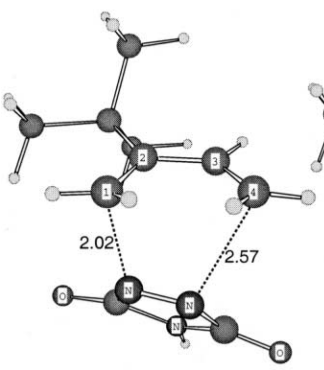


16 PTAD

17

The isotope effects obtained in this way are summarized in Table 3. The most striking observation in the reaction of **16** with PTAD is the similarity of the 1-position and 4-position isotope effects, with the $H1_{in}$ and $H1_{out}$ KIEs differing very little from those observed for $H4_{in}$ and $H4_{out}$. Qualitatively these results suggest very little asynchroneity in this reaction.

Theoretical calculations suggest a very different interpretation of the isotope effects. The transition structures **18** and **19** were obtained in Becke3LYP calculations with a 6-31G* basis set.[29] Each exhibits very asynchronous C–C bond formation. Interestingly, **18** and **19** are very nearly equal in energy (within 0.05 kcal/mol at the Becke3LYP/6-31G* level). The isotope effects predicted for these structures are given in Table 3. Each structure by itself would be predicted to exhibit quite differing 1-position and 4-position isotope effects, but a mixture of the two provides a very good prediction of the experimental isotope effects. A best-fit weighting of 55% of the predicted KIEs for **18** with 45% of those for **19** gives ^{13}C KIEs that are within experimental error of those observed and ^{2}H KIEs that are in very reasonable agreement with the experimental values (with a continued tendency, as discussed above, to slightly underpredict the experimental ^{2}H values).



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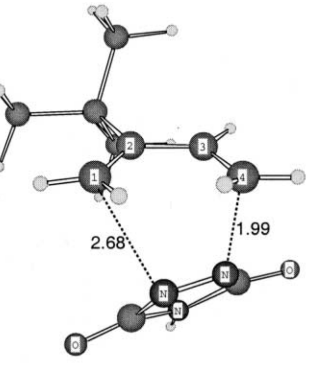

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Instead of a mixture of highly unsymmetrical transition structures, could a single nearly symmetrical transition structure account for the observed isotope effects? To address this question, we have calculated isotope effects for the Houk and Foote second-order saddle point **15**. The predicted isotope effects for **15** are necessarily symmetrical but their magnitudes show substantial differences with experiment. The C1/C4 KIEs predicted for **15** are a bit high at 1.028, and the predicted $H1_{out}/H4_{out}$ KIEs at 0.906 are 2–4% low, but the most striking difference is observed with $H1_{in}/H4_{in}$, in which the prediction for **15** is 6–9% below the experimentally observed values. Although the experimental 1-position and 4-position isotope effects in the reaction of PTAD with **16** are very similar, we conclude that they best support a mixture of highly asynchronous transition states in this reaction.

2.4. Dialkyl maleates

An intriguing observation in Diels–Alder reactions is the great reactivity difference between dialkyl fumarates and dialkyl maleates. The former react at room temperature with simple acyclic dienes while the latter require prolonged heating at ≈100°C. This observation of greater reactivity in *trans*-1,2-disubstituted alkenes over the corresponding *cis* isomers is a normal observation in concerted cycloadditions.[30] However, a factor in this trend when there is an activating carbonyl group on the alkene is that the carbonyl group can be sterically inhibited from the ideal conformation for activation. For this reason the reactivity difference between *trans* and *cis* isomers is greater for carbonyl-activated dienophiles than for those where conformational inhibition of activation is not applicable. For example, *cis*- and *trans*-dicyanoethylene are nearly equally reactive in Diels–Alder reactions.[31] It was therefore of interest whether dialkyl maleates adopt a synchronous Diels–Alder transition state with both carboxylates activating the cycloaddition equally or instead prefer to activate the transition state with a single carboxylate, allowing the other to rotate into a sterically unencumbered position.

Theoretical study of the reaction of 1,3-butadiene with maleic acid was complicated by the possibility for involvement of a large number of structures, depending on whether the transition state was *endo* or *exo* and the relative

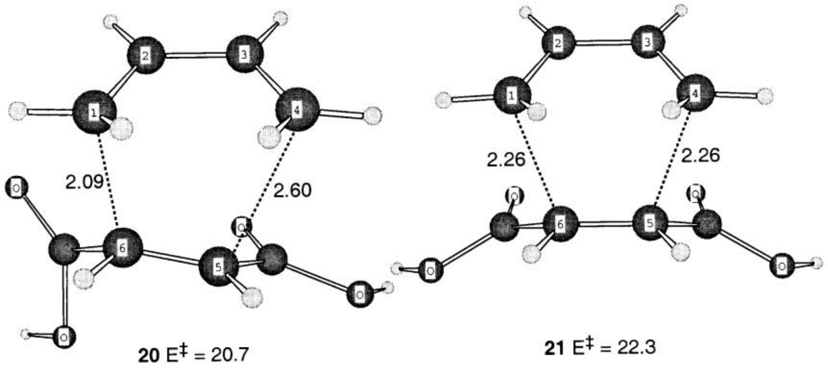


Figure 3. The best calculated unsymmetrical transition structure (**20**) and symmetrical second-order saddle point (**21**) for the Diels–Alder reaction of 1,3-butadiene with maleic acid. Relative energies versus starting materials (including zpe) are given in kcal/mol.

orientation of the carbonyl and hydroxyl groups for each acid group. These possibilities were systematically investigated in RHF 6-31G*/3-21G calculations and a total of 10 transition structures or second-order saddle points were found. Of these the lower-energy unsymmetrical and C_s-symmetric structures were reoptimized in Becke3LYP/6-31G* calculations.

The highly unsymmetrical *endo* transition structure **20** (Fig. 3) is predicted to be lowest in energy for this reaction. Carbon–carbon bond formation in this structure is highly asynchronous, with a 0.55 Å difference between the length of the two forming bonds. Notably, only one of the carboxyl groups is oriented to activate the cycloaddition, the other being turned away from aligning its π orbitals with the shorter of the two forming bonds. The best synchronous structure (**21**), a second-order saddle point obtained by forcing C_s symmetry, is predicted to be 1.6 kcal/mol higher in energy.

Isotope effects were determined for the reaction of dimethyl maleate with isoprene in xylenes at 80–100°C.[32] The unreacted isoprene from reactions taken to 98.0±0.2% and 94±1% conversion was recovered by vacuum transfer followed by fractional distillation and analyzed compared to a standard sample (vide supra) using the methyl group as the internal standard for the NMR integrations.

The resulting KIEs (Table 4) closely resemble those found above with acetylenedicarboxylates. As such, their qualitative interpretation is similar—the KIEs suggest relatively modest asynchroneity in the formation of the two new C–C bonds.

Once again, however, it is important to consider the possible contribution of two regioisomeric highly asynchronous transition states to the observed KIEs. To do this, the two transition structures **22** and **23**, corresponding to **20** with the addition of a methyl group in either of two possible positions, were calculated for the reaction of isoprene with maleic acid (Fig. 4). Structure **22** with advanced bonding to C1 would be expected to be favored, and it is, but by a predicted amount of only 0.3 kcal/mol. It would thus be expected that both isomers would contribute to the observed isotope effects.

The calculated isotope effects for **22** and **23** are shown in Table 4, along with a weighted average predicted from a Boltzmann distribution of the two using the calculated energy difference. The isotope effects predicted for **22** and **23** individually do not resemble the observed values. However, the Boltzmann weighted average of the two provides a very good prediction of the observed KIEs: all of the ^{13}C KIEs and three of the five ^{2}H KIEs are predicted within experimental error, and the other two ^{2}H KIEs are slightly underpredicted (as discussed above). Considering the differences between the gas-phase calculated reaction and the solution-phase experimental reaction, as well as the likely contribution of *exo* transition states to the observed KIEs, the values predicted for **22**+**23** agree

Table 4. Experimental and theoretically predicted isotope effects ($k_{^{12}C}/k_{^{13}C}$ or k_H/k_D, 100°C) for the Diels–Alder reaction of isoprene with dimethyl maleate

	Experimental[a]		Predicted for		Weighted average[b]	Predicted for
	1	2	**22**	**23**		**21**
C1	1.021 (2)	1.021 (4)	1.028	1.010	1.020	1.018
C2	1.006 (7)	1.004 (2)	1.003	1.002	1.003	1.002
C3	1.003 (3)	1.003 (4)	1.001	1.002	1.001	1.002
C4	1.017 (5)	1.018 (3)	1.009	1.028	1.016	1.018
$H1_{in}$	0.945 (10)	0.954 (8)	0.937	0.982	0.955	0.937
$H1_{out}$	0.975 (8)	0.980 (11)	0.938	1.008	0.966	0.969
H3	0.999 (8)	0.995 (7)	0.978	0.991	0.983	0.982
$H4_{in}$	0.952 (5)	0.960 (6)	0.975	0.933	0.958	0.937
$H4_{out}$	0.978 (5)	0.988 (9)	1.005	0.945	0.980	0.969

[a] Experiments 1 and 2 were taken to 98.0±0.2% and 94±1% conversion, respectively.

[b] A 59.3:40.7 weighting, based on a Boltzmann distribution of predicted isotope effects for **22** and **23**.

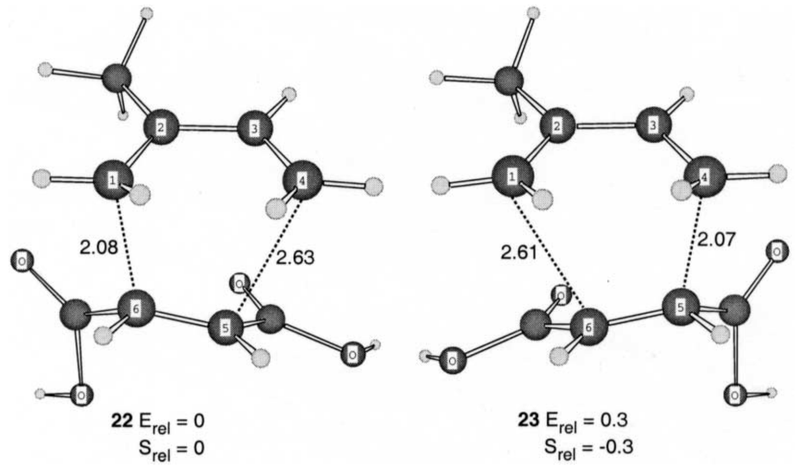


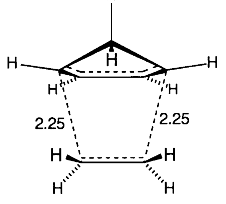
Figure 4. Transition structures for the Diels–Alder reaction of maleic acid with isoprene. Relative energies (Becke3LYP/6-31G*+zpe) are given in kcal/mol and estimated relative entropies (25°C) are in e.u.

quite well with the experimental values. Clearly, the observed KIEs are consistent with the predicted highly asynchronous transition states.

Unfortunately, the KIEs are also well consistent with a nearly synchronous transition state. This can be seen from the predicted KIEs for the symmetrical structure **21** in Table 4. These KIEs do not match as well with the observed KIEs as the weighted average from **22**+**23**. Even a small amount of asynchroneity, however, would make most of the isotope effects expected for a nearly synchronous transition state closely resemble the experimental values. Due to the use of isoprene experimentally instead of 1,3-butadiene in **21**, some asynchroneity must be expected. For this reaction, isotope effects would appear to be a very dull tool for distinguishing a synchronous from a highly asynchronous transition state.

2.5. Retro-Diels–Alder reaction of norbornene

Zewail and coworkers' femtosecond time-resolved observation of an intermediate in the retro-Diels–Alder reaction of norbornene[7] has reawakened interest in the question of a concerted versus stepwise mechanism in simple unactivated Diels–Alder reactions. Houk and coworkers have studied both concerted and stepwise mechanisms for this reaction in (U)B3LYP calculations. On the concerted pathway is the synchronous transition state **24**. The stepwise pathway involves sequential transition states **25** and **26** for breaking the σ bonds of norbornene, with a biradical intermediate in between. The (U)B3LYP/6-31G* calculations favor the concerted pathway by over 12 kcal/mol.



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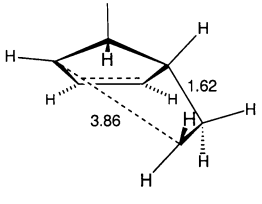

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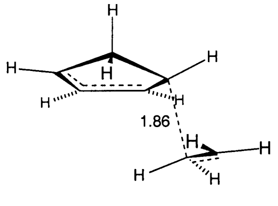

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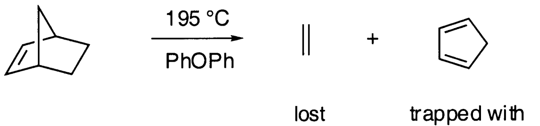
To address the question of concerted versus stepwise mechanisms for this reaction experimentally, we attempted to determine the KIEs for the retro-Diels–Alder reaction of norbornene. This proved to be especially experimentally challenging, and was successful only indirectly.



(5)

The decomposition of norbornene into ethylene and cyclopentadiene (Eq. (5)) proceeds slowly over the course of several days at 195°C. In order to accomplish the reaction practically on a large scale at atmospheric pressure, the vapor pressure of the reaction was lowered by dissolution of the norbornene at 0.25 M in diphenyl ether. Under these conditions the product cyclopentadiene reacts with norbornene to form a Diels–Alder adduct. To allow the loss of the cyclopentadiene from the reaction while minimizing loss of norbornene, the condenser for the refluxed reaction was kept at ≈45°C. In addition maleic anhydride was added to the reaction mixture to trap the cyclopentadiene as it formed.[33] Nevertheless, a significant amount of the cyclopentadiene adduct with norbornene was formed. Because of the side reaction and the uncertainty in the effective conversion,[34] the olefinic carbons and hydrogens of norbornene were ignored and the actual KIEs for the retro-Diels–Alder reaction were not calculable. Nevertheless, it was possible to evaluate the predicted KIEs for the concerted and stepwise mechanisms by comparing them with the changes in isotopic composition during the reaction.

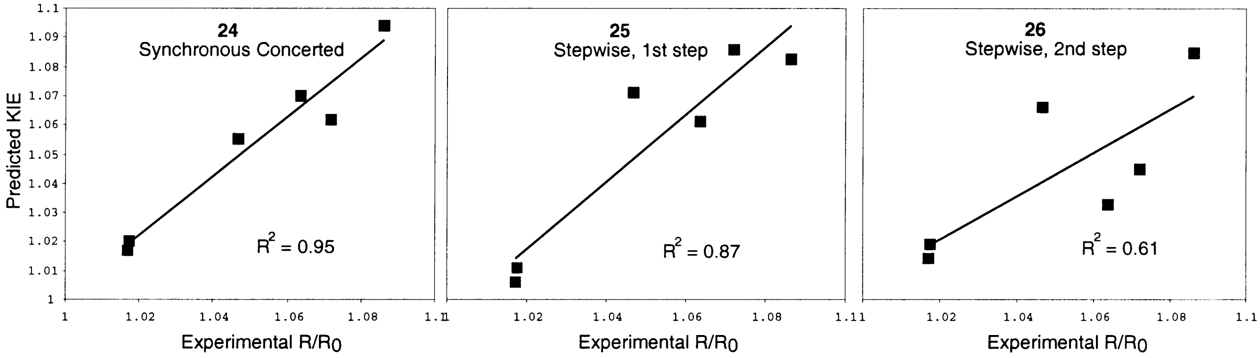


Figure 5. Graphs of experimental R/R_0 values for the retro-Diels–Alder reaction of norbornene versus KIEs predicted for transition structures **24**, **25**, and **26** (from left to right).

Reactions of norbornene on an ≈1 mol scale were taken to 78% total conversion (retro-Diels–Alder+cyclopentadiene adduct+loss of norbornene), and the unreacted norbornene was recovered by a flash distillation followed by fractional distillation at atmospheric pressure in a solids-distillation apparatus. The relative changes in isotopic composition (R/R_0 values, calculated as the ratio of ^{2}H or ^{13}C in recovered norbornene compared to original norbornene) were then determined by NMR using the C7 carbon and H_{anti} on C7 as standards for comparison.

The R/R_0 values are compared graphically with the predicted isotope effects in Fig. 5. Ideally, these plots should be straight lines going through the origin of the graph at (1,1). The predicted isotope effects for the synchronous concerted transition structure **24** correlate very well with the R/R_0 values; with uncertainties in the R/R_0 values of $\approx \pm 0.003$ for ^{13}C and ± 0.02 for ^{2}H every point falls within experimental error of the best fit line with $R^2=0.95$. In contrast, the predicted isotope effects for the stepwise transition structures **25** and **26** do not correlate as well, and the best-fit lines pass farther from (1,1). The experimental observations thus support a concerted transition state.

3. Conclusions

The Becke3LYP calculations predict unsymmetrical, highly asynchronous transition structures for the Diels–Alder reactions of bis(boryl)acetylenes, dialkyl acetylenedicarboxylates, triazolinediones, and dialkyl maleates. The predicted preference for an asynchronous transition state is substantial for bis(boryl)acetylenes, and this is the strongest theoretical case. Supported by the unique observation that the 'doubly-activated' dienophiles are less reactive than mono(boryl)acetylenes, it seems highly likely that an asynchronous transition state is involved in reality. In the other reactions, the theoretical preference for asynchronous over synchronous is less pronounced, ranging from 0.1 to 1.6 kcal/mol. This margin is less certain. The ^{13}C and ^{2}H isotope effects are in each case consistent with the asynchronous transition states, but they only really significantly disfavor a synchronous transition state with triazolinediones. Like other mechanistic probes, isotope effects have a limited resolution—it appears they can distinguish concerted from stepwise cycloadditions (as with the retro-Diels–Alder reaction of norbornene) but they might not distinguish similar transition states.

Despite the uncertainties for the individual mechanisms, there is no sign of a substantial intrinsic bias for synchroneity in Diels–Alder reactions. When any factor disfavors a synchronous transition state, for example a possible steric interaction of oxygens in **21**, asynchronous distortion of the transition state occurs readily. This is not really surprising, because transition states are inherently highly flexible. At the extreme of a stepwise Diels–Alder reaction, the energy is at most only a few kcal/mol higher than the concerted process. One of the most important classes of Diels–Alder reactions, Lewis acid-catalyzed reactions, involves extremely asynchronous transition states that could hardly be called 'aromatic'.[35] The effect of aromaticity on the Diels–Alder transition state is not an overriding factor in determining transition state geometry.

4. Experimental

4.1. Data for compounds

4.1.1. Diels–Alder reactions of bis(9-borabicyclo[3.3.1]-nonyl)acetylene (1). Example procedure. To 1.34 g (6.7 mmol) of 9-bromo-9-BBN (prepared by concentration under vacuum of a commercial solution in CH_2Cl_2) in a pressure tube at −78°C was added dropwise 1.87 g (3.1 mmol) of bis(tributylstannyl)acetylene. The resulting mixture was warmed to 25°C, and 208 mg (1.60 mmol) of 2-phenylbutadiene was added. The pressure tube was then heated to 100°C for 16 h. After cooling to 25°C, 5 mL of THF and 3 mL (3.15 g, 52 mmol) of glacial acetic acid were added and the mixture was stirred at 25°C for 2 h. The mixture was then partitioned between 50 mL of saturated aqueous $NaHCO_3$ and 30 mL of hexanes. The aqueous layer was extracted with two 30 mL portions of hexanes, and the combined hexane layers were rinsed with saturated aqueous KF and dried (Na_2SO_4). The solvent was removed on a rotary evaporator and the residue was chromatographed on a short silica gel column using hexanes as eluent to afford 169 mg (68%) of the known[36] 1-phenyl-1,4-cyclohexadiene (**2**) (contaminated with trace amounts of biphenyl): ^{1}H NMR ($CDCl_3$) δ 7.60–7.20 (m, 5 H), 6.20 (br s, 1 H), 5.85 (m, 2 H), 3.15 (m, 2 H), 2.95 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 141.8, 133.9, 128.4, 127.0, 125.0, 124.5, 123.8, 121.8, 27.8, 27.1.

Analogous procedures employing 2-*tert*-butyl-1,3-butadiene and myrcene with differing reaction times (see Eqs. (1)–(3)) afforded the known 1-*tert*-butyl-1,4-cyclohexadiene[37] and 1-(4-methyl-3-pentenyl)-1,4-cyclohexadiene,[38] respectively, in 53 and 55% yields.

4.1.2. Diels–Alder reactions of dialkyl acetylenedicarboxylates. Example procedure. A mixture of 34.03 g (0.5 mol) of isoprene, 71.9 g (0.42 mmol) of diethyl acetylenedicarboxylate, and 200 mL of toluene was heated to 50±5°C with stirring under N_2. Aliquots were periodically removed and the progress of the reaction was analyzed by ^{1}H NMR based on the ratio of the isoprene to the product cyclohexadiene. After 289 h the conversion was 84±2%. A vacuum transfer of ≈20 mL of volatiles on a water aspirator followed by two successive fractional distillations afforded 3.4 g of isoprene with no detectable impurities by ^{1}H or ^{13}C NMR.

4.1.3. Diels–Alder reaction of 2-*t*-butyl-1,3-butadiene with PTAD. Example procedure. A mixture of 26.3 g (0.150 mol) of freshly prepared[39] PTAD in 550 mL of CH_2Cl_2 was added slowly to a mixture of 22.0 g (0.200 mol) of 2-*tert*-butyl-1,3-butadiene, 8.10 g (0.055 mol) of 1,2-dichlorobenzene (used as GC internal standard), and 110 mL of CH_2Cl_2 in a dry ice–acetone bath. After 2 h the reaction was found to be 71.3±1.0% complete by GC. Vacuum transfer of the volatiles from the reaction mixture using a water aspirator followed by fractional distillation afforded 3.8 g of recovered 2-*tert*-butyl-1,3-butadiene (bp 101–102°C, >98% pure by GC).

4.1.4. Diels–Alder reaction of isoprene with dimethyl maleate. Example procedure. A mixture of 338.9 g (4.98 mol) of isoprene, 736.1 g (5.11 mol) of dimethyl maleate, 1000 mL of xylenes, and 2.00 mL of *n*-heptane (internal standard) was heated under a dry-ice condenser to 80–100°C[32] for 10 d, at which time GC analysis of an aliquot showed the conversion to be 98.0±0.2%. Vacuum transfer of ≈70 mL of volatiles from the reaction mixture using a water aspirator followed by fractional distillation afforded 3.9 g of isoprene with no observable impurities by ^{1}H or ^{13}C NMR.

4.1.5. Retro-Diels–Alder reaction of norbornene. Example procedure. A mixture of 82.9 g (0.88 mol) of norbornene, 4 kg of diphenyl ether, 50 g (0.51 mol) of maleic anhydride, and 3.6 g of diglyme was heated to 195±5°C under a positive pressure of argon in a 5 L flask equipped with a reflux condenser at 45±2°C. Aliquots were periodically removed and the progress of the reaction was analyzed by ^{1}H NMR based on the ratio of the norbornene to the internal standard diglyme. After 192 h the conversion was 78±2%. An initial distillate of 30 mL collected under a water aspirator was redistilled twice to afford 10 g of norbornene which showed no detectable impurities by ^{1}H or ^{13}C NMR.

4.2. NMR measurements

For each reaction the NMR spectra of the samples of recovered isoprene, 2-*t*-butyl-1,3-butadiene, or norbornene were compared with standard material from the same synthetic lot as used in the reaction. The NMR samples of standard and recovered material were in each case prepared identically. Both ^{13}C and ^{2}H NMR spectra were taken on neat samples. A T_1 determination by the inversion-recovery method was carried out on each NMR sample.

The ^{13}C spectra were recorded at 100.58 MHz with inverse gated decoupling. Isoprene, 2-*t*-butyl-1,3-butadiene, and norbornene spectra used 120, 240, and 120 s delays, respectively, between calibrated pulses, with acquisition times of 3.5, 10.5, and 3.9 s, respectively, collecting 158 336, 524 288, and 158 720 points, respectively, in each case zero-filled to 512 K before Fourier transformation. The ^{2}H spectra for isoprene, 2-*t*-butyl-1,3-butadiene, and norbornene were recorded at 61.395 MHz, using acquisition times of 7, 6.98, and 2.276 s and additional delays of 0, 8, and 0 s between acquisitions. ^{13}C integrations were determined numerically using a constant region for each peak that was ≈5 times the peak width at half height distance on either side of the peak. ^{2}H integrations were determined using a deconvolution program to determine the area of integration under partially overlapping peaks. A zeroth order baseline correction was generally applied, but in no case was a first-order (tilt) correction applied. From the relative integrations the isotope effects were calculated as previously described.[24]

4.3. Calculational procedures

The structures reported here were obtained with Gaussian 98[40] using the Becke3LYP[41] hybrid HF–DFT method with the 6-31G* basis set.[42] Vibrational frequency analyses were carried out on all stationary points. The energies obtained for **3**, **4**, **10**, **11**, **12**, **13**, **18**, **19**, **20**, **21**, **22** and **23** were, including zpe, −284.085421, −421.725170, −649.569011, −649.569010, −649.567547, −649.567585, −704.462371, −704.462686, −611.511281, −611.508767, −650.802797, and −650.802351, respectively. A file containing the complete geometries and energies for all calculated structures is available from the corresponding author on request.

Acknowledgements

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References

1. (a) Dewar, M. J. S.; Olivella, S.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1986**, *108*, 5771. (b) Dewar, M. J. S.; Pierini, A. B. *J. Am. Chem. Soc.* **1984**, *106*, 203. (c) Dewar, M. J. S.; Olivella, S.; Rzepa, H. S. *J. Am. Chem. Soc.* **1978**, *100*, 5650. (d) Telan, L. A.; Firestone, R. A. *Tetrahedron* **1999**, *55*, 14269.
2. (a) Loncharich, R. J.; Brown, F. K.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 1129. (b) Birney, D. M.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 4127.
3. (a) Bernardi, F.; Bottoni, A.; Field, M. J.; Guest, M. F.; Hillier, I. H.; Robb, M. A.; Venturini, A. *J. Am. Chem. Soc.* **1988**, *110*, 3050. (b) Bach, R. D.; McDouall, J. J. W.; Schlegel, H. B. *J. Org. Chem.* **1989**, *54*, 2931. (c) Houk, K. N.; Lin, Y.-T.;

Brown, F. K. *J. Am. Chem. Soc.* **1986**, *108*, 554. (d). Houk, K. N.; Loncharich, R. J.; Blake, J. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 9172. (e). Houk, K. N.; Gonzalez, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81. (f). Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 7478. (g). Goldstein, E.; Beno, B.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 6036.

4. Sakai, S. *J. Phys. Chem. A* **2000**, *104*, 922.
5. Hancock, R. A.; Wood, Jr., B. F. *J. Chem. Soc., Chem. Commun.* **1988**, 351.
6. Gajewski, J. J.; Peterson, K. B.; Kagel, J. R.; Huang, Y. C. J. *J. Am. Chem. Soc.* **1989**, *111*, 9078.
7. Horn, B. A.; Herek, J. L.; Zewail, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 8755.
8. For a countering view, see: Hrovat, D. A.; Fang, S.; Borden, W. T.; Carpenter, B. K. *J. Am. Chem. Soc.* **1997**, *119*, 5253.
9. Beno, B. R.; Wilsey, S.; Houk, K. N. *J. Am. Chem. Soc.* **1999**, *121*, 4816–4826.
10. Wilsey, S.; Houk, K. N.; Zewail, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 5772.
11. McCarrick, M. A.; Wu, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *58*, 3330.
12. Chen, J. S.; Houk, K. N.; Foote, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 12303.
13. Froese, R. D. J.; Coxon, J. M.; West, S. C.; Morokuma, K. *J. Org. Chem.* **1997**, *62*, 6991.
14. (a) Singleton, D. A.; Merrigan, S. R.; Liu, J.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 3385–3386. (b) DelMonte, A. J.; Haller, J.; Houk, K. N.; Sharpless, K. B.; Singleton, D. A.; Straßner, T.; Thomas, A. A. *J. Am. Chem. Soc.* **1997**, *119*, 9907–9908. (c) Keating, A. E.; Merrigan, S. R.; Singleton, D. A.; Houk, K. N. *J. Am. Chem. Soc.* **1999**, *121*, 3933. (d) Meyer, M. P.; DelMonte, A. J.; Singleton, D. A. *J. Am. Chem. Soc.* **1999**, *121*, 10865. (e) Singleton, D. A.; Hang, C. *J. Am. Chem. Soc.* **1999**, *121*, 11885. (f) Singleton, D. A.; Hang, C. *J. Org. Chem.* **2000**, *65*, 895.
15. Beno, B. R.; Houk, K. N.; Singleton, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 9984–9985.
16. Singleton, D. A.; Leung, S.-W. *J. Org. Chem.* **1992**, *57*, 4796.
17. Leung, S.-W.; Singleton, D. A. *J. Org. Chem.* **1997**, *62*, 1955–1960.
18. Ketone, ester, and nitrile substituents activate ethylene by a factor of $\approx 10^5$, while a second such substituent accelerates reactions by ≈ 10–10^2. See Refs. 1c and 5.
19. The steric effect of the BBN group does not appear to be significantly deactivating, as the bis(dimethylboryl)acetylene was found to be much less reactive than **1**.
20. MP2/6-31G* calculations identically predict an unsymmetrical transition structure similar to **3**, favored over the symmetrical **4** by 2.6 kcal/mol. In the MP2 calculation the barrier for reaction of bis(boryl)acetylene is 2.2 kcal/mol higher than for reaction of $HCCBH_2$.
21. Singleton, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 6563.
22. Based on RHF/3-21G outer coefficients of 0.39 for B versus 0.18 for C. In the ground-state conformation for bis(boryl)-acetylene the BH_2 groups are twisted by 90° from each other.
23. There is a general problem in many kinds of studies that have interpreted the symmetry of transition states from the rates of reaction of mono- and doubly-activated compounds. The problem is that a mono-activated reaction (e.g. the Diels–Alder reaction of butadiene with methyl propiolate) necessarily involves an unsymmetrical transition state. Thus, whether or not the transition state for a doubly-activated reaction is symmetrical, from the differing geometry of the mono- and doubly-activated transition states one cannot strictly expect the second substituent to have the same activating effect as the first. Only in extreme cases is the interpretation clear.
24. Singleton, D. A.; Thomas, A. A. *J. Am. Chem. Soc.* **1995**, *117*, 9357.
25. (a) Bigeleisen, J.; Mayer, M. G. *J. Chem. Phys.* **1947**, *15*, 261. (b) Wolfsberg, M. *Acc. Chem. Res.* **1972**, *5*, 225.
26. The calculations used the program QUIVER (Saunders, M.; Laidig, K. E.; Wolfsberg, M. *J. Am. Chem. Soc.* **1989**, *111*, 8989) with Becke3LYP frequencies scaled by 0.9614 (Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502).
27. Bell, R. P. In *The Tunnel Effect in Chemistry*; Chapman and Hall: London, 1980; pp. 60–63.
28. Gillis, B. T.; Hagarty, J. D. *J. Org. Chem.* **1967**, *32*, 330.
29. *exo* Transition structures were predicted by Houk and Foote to be much higher in energy (see Ref. 12) and were not considered here.
30. Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633.
31. Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779.
32. Early in the reaction the temperature was limited by the boiling point of the reaction mixture. As isoprene reacted, the boiling point rose and was limited at 100°C for the later stages of the reaction. Because later stages of the reaction weigh most heavily in the isotopic fractionation process (see Ref. 24 and refs therein), the observed KIEs are best considered as measured at ≈100°C.
33. This reaction with maleic anhydride was not expected to be reversible (see: Tobia, D.; Harrison, R.; Phillips, B.; White, T. L.; DiMare, M.; Rickborn, B. *J. Org. Chem.* **1993**, *58*, 6701) but based on the ineffectiveness of the trapping this assumption may not have been correct.
34. In principle this could be allowed for by adjusting the % conversion used to calculated isotope effects; for example, using a nominal % conversion of 61% for the second reaction above brings all of the isotope effects found for that reaction within experimental error of those predicted for the concerted reaction. However, such an adjustment is arbitrary and unnecessary for the purpose of comparing the calculated KIEs for the differing pathways with experiment.
35. Singleton, D. A.; Merrigan, S. R.; Thomas, A. A. *Tetrahedron Lett.* **1999**, *40*, 639–642.
36. Grisdale, P. J.; Regan, T. H.; Doty, J. C.; Figueras, J.; Williams, J. L. R. *J. Org. Chem.* **1968**, *33*, 1116.
37. Singleton, D. A.; Martinez, J. P. *Tetrahedron Lett.* **1991**, *32*, 7365.
38. Ono, N.; Kamimura, A.; Kaji, A. *J. Org. Chem.* **1988**, *53*, 251.
39. Adams, C. E.; Aguilar, D.; Hertel, S.; Knight, W. H.; Paterson, J. *Synth. Commun.* **1988**, *18*, 2225.
40. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, Jr., R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.;

Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98, Revision A.6*; Gaussian: Pittsburgh, PA, 1998.

41. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. For reviews of density-functional methods, see: (c) Ziegler, T. *Chem. Rev.* **1991**. (d) In *Density Functional Methods in Chemistry*; Labanowski, J., Andzelm, J., Eds.; Springer: Berlin, 1991. (e) Parr, R. G.; Yang, Y. *Density-Functional Theory of Atoms and Molecules*; Oxford University: New York, 1989.

42. Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; 1986; Wiley: New York, 1986.