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THE TRANSITION STATE OF DIELS–ALDER REACTIONS

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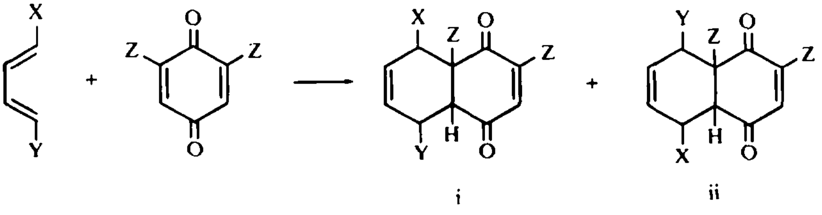
Abstract—The kinetic studies of Diel–Alder reactions of 1.4-unsymmetrically disubstituted dienes with 2.6-dimethylbenzoquinone suggest that the transition state is asymmetric for the cases examined. A rationalization is presented for the mechanism involving a concerted process in which one of the σ bonds proceeds in advance of the second one.

THE Diels–Alder reaction is a symmetry allowed process involving six electrons.[1] However, the exact temporal sequence of the changes in covalency within the activated complex remains to be determined. The characteristic Diels–Alder orientation rules are generally regarded as a manifestation of an unsymmetrical transition state in which the formation of one σ bond might proceed entirely or partially in advance of the second one.[2, 3]

Several of the proposed mechanisms assume the existence of discreet intermediates prior to the formation of the second single bond.[3, 6] The criticisms of these two step mechanisms are sufficiently documented and well-known.[2, 3]

It has been firmly established, however, that the reaction proceeds through a geometrically highly oriented transition state. The high negative entropies of activation and the operation of the cis-endo addition principle are convincing testimonies to this effect.[4] The insensitivity of rates to extramolecular circumstances might be attributed to the tight transition state. All these facts lend support to the essentially concerted formation of the two σ bonds. Recently Dewar has shown that the transition state of the diene addition is definitely cyclic albeit unsymmetrical for the cases studied.[5] The possibility of unequal σ bond formation was previously examined by the secondary isotope method which, however, did not lead to conclusive results.[7, 8, 5] Charton examined a series of rate data for the reactions of 2.3-unsymmetrically disubstituted dienes with unsymmetrically disubstituted dienes and concluded that the transition state of Diels–Alder reaction is symmetrical.[9] It has been pointed out recently that the method of analysis adopted in this paper might be unsatisfactory.[5] Recently one of us initiated a novel method of investigating the transition state of the Diels–Alder



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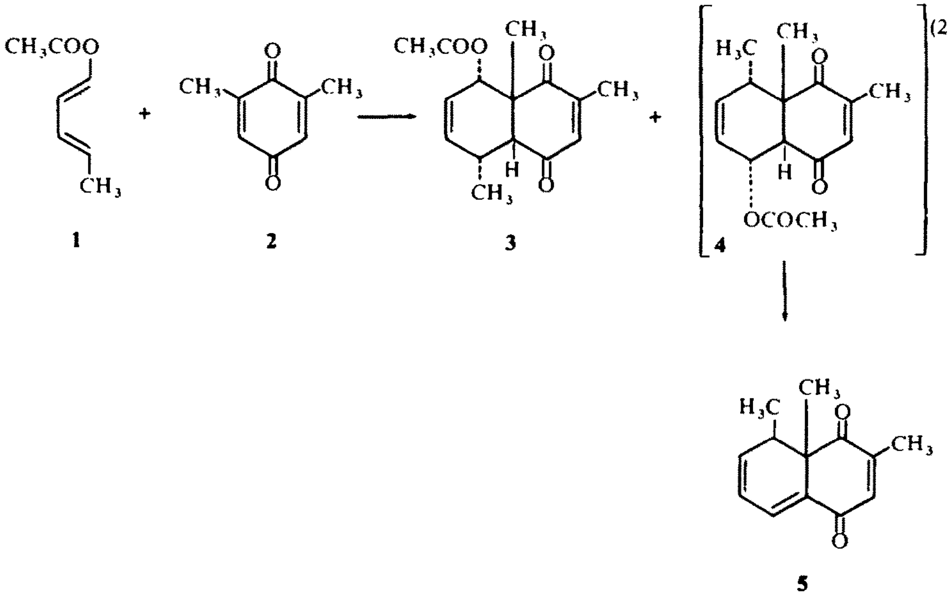
reaction by studying the additions of 1.4-unsymmetrically disubstituted dienes with 2.6-disubstituted benzoquinones (Eq 1).[10] Such an approach offers an efficient variation of electronic distribution concentrated at the four centers of the two incipient σ bonds (Eq 1).[11]

It is known that in the presence of a terminal substituent in the diene a substituent at positions 2 or 3 has no influence on the ratio of the two possible adducts.[2,3] It was therefore concluded that our main attention should be devoted to the effect of terminal substituents in the diene.[11] The determination of these competitive ortho directing influences[10] as defined in Eq 1 and their kinetic evaluation should provide a deeper insight into the transition state of Diels–Alder reactions.

The present paper investigates the kinetics of two such additions (Eq 2 and 3).



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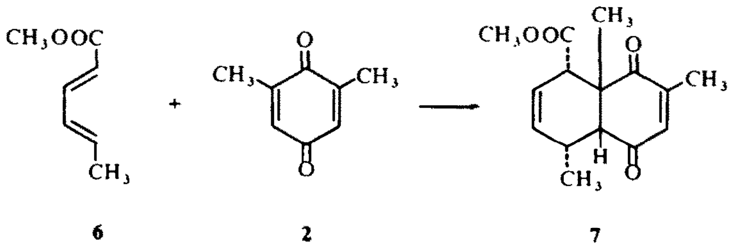


(3)

RESULTS

Preliminary experiments established that the reaction of 1-acetoxy-1.3-pentadiene (**1**) with 2.6-dimethylbenzoquinone is first order in diene and quinone towards the formation of both adducts: **3** and **4**. Thus the following rate equations were used:

$$\frac{d[\text{adduct } 3]}{dt} = k_3\,[\text{diene } 1]\,[\text{quinone } 2]$$

$$\frac{d[\text{adduct } 4]}{dt} = k_4\,[\text{diene } 1]\,[\text{quinone } 2]$$

It is noted that adducts **3** and **4** formed from two competitive reactions. The rate constants k_3 and k_4 were calculated from the initial rates of formation of adducts **3** and **4**. It is assumed that the rate of formation of adduct **4** can be measured in terms of the elimination product **5**. Since adduct **4** was not detected in the reaction mixture at any temperature it is assumed that the elimination **4** → **5** is fast. Such an elimination leading to compound **5** deserves some comment. An abundance of Diels–Alder reactions are known which are followed by elimination leading to aromatic products.[3] The stability of an extensively conjugated system of double bonds should be a driving force in this reaction. It can be assumed that the *cis* adduct **4** isomerizes to the corresponding *trans* fused system in which the elements of acetic acid are *cis* to each other. Since the primarily formed Diels–Alder adduct **3** isomerizes to **3a** a similar isomerization for **4** is conceivable which is then followed by the thermal elimination of acetic acid leading to **5**.

As expected[14] it was found that compounds **3** and **5** did not undergo the reverse Diels–Alder reaction under our experimental conditions.

The initial rates were obtained by plotting rates at different time intervals as given in Table I which were then extrapolated to 0 time. Knowing the initial concentrations of diene 1 and dienophile 2 the rate constants k_3 and k_4 were calculated at 168·8° as follows:

$$k_3 = 5{\cdot}8 \times 10^{-5}\ \text{l}\,\text{m}^{-1}\,\text{sec}^{-1}$$

$$k_4 = 5{\cdot}1 \times 10^{-5}\ \text{l}\,\text{m}^{-1}\,\text{sec}^{-1}$$

In order to obtain initial rates, the integral method being employed here is preferred over the differential method as has been shown in a recent paper.[13] It is noted that the rate obtained by both methods will approach the same value when t → 0 because of the following mathematical relationship:

$$\frac{dx}{dt} = \underset{\Delta t \to 0}{\text{Limit}} \frac{\Delta x}{\Delta t}$$

TABLE I. RATE OF FORMATION OF ADDUCTS 3 AND 4 AT DIFFERENT TIME INTERVALS AT 168·8°.

t (hr)	[adduct 3]/t × 10^6 mole l^{-1} sec^{-1}	[adduct 4]/t × 10^6 mole l^{-1} sec^{-1}
0·5	2·00	1·75
0·75	1·87	1·62
1·0	1·72	1·50
1·25	1·58	1·35
1·5	1·43	1·20
2·0	1·12	0·92
2·5	0·84	0·71

In the reaction of methyl sorbate (**6**) with 2.6-dimethylbenzoquinone (**2**). preliminary results also showed that this reaction is first order both in diene and dienophile. The following rate law was used to compute k_7.

$$\frac{d[\text{adduct } \mathbf{7}]}{dt} = k_7 \, [\text{diene } \mathbf{6}] \, [\text{dienophile } \mathbf{2}]$$

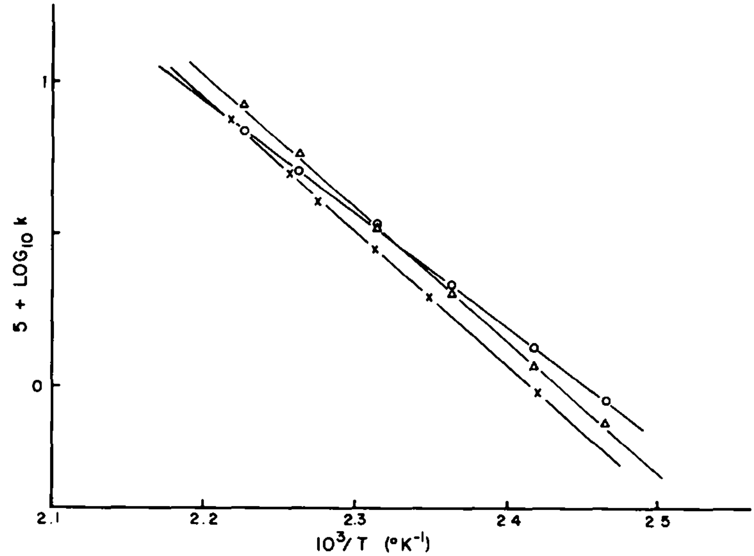


FIG 1. Arrhenius plot for the formation of adducts 3, 4, and 7: △ = adduct 3: ○ = adduct 4: × = adduct 7

This reaction (Eq 3) was also found irreversible under the conditions of the forward reaction. The temperature dependence of k_3 and k_4 is given in Table II and that of k_7 is tabulated in Table III. The Arrhenius plot of these rate constants is given in Fig I. Least squares treatment on the data in Tables II and III gave the following Arrhenius parameters:

$$k_3 = 10^{6\cdot54 \pm 0\cdot42} \exp(-21\cdot75 \pm 0\cdot82/RT) \, l \, \text{mole}^{-1} \, \text{sec}^{-1}$$
$$k_4 = 10^{4\cdot79 \pm 0\cdot10} \exp(-18\cdot33 \pm 0\cdot63/RT) \, l \, \text{mole}^{-1} \, \text{sec}^{-1}$$
$$k_7 = 10^{6\cdot52 \pm 0\cdot51} \exp(-21\cdot91 \pm 1\cdot01/RT) \, l \, \text{mole}^{-1} \, \text{sec}^{-1}$$

TABLE II. VARIATION OF k_3 AND k_4 AS A FUNCTION OF TEMPERATURE.

°C	1/K° 10^3	k_3 l m^{-1} sec^{-1}	log k_3	k_4 l m^{-1} sec^{-1}	log k_4
132·8	2·463	$7\cdot59 \times 10^{-6}$	−5·1198	$8\cdot92 \times 10^{-6}$	−5·0496
140·4	2·418	$1\cdot17 \times 10^{-5}$	−4·9318	$1\cdot34 \times 10^{-5}$	−4·8729
150·0	2·363	$2\cdot00 \times 10^{-5}$	−4·6990	$2\cdot14 \times 10^{-5}$	−4·6696
159·2	2·313	$3\cdot32 \times 10^{-5}$	−4·4789	$3\cdot38 \times 10^{-5}$	−4·4711
168·8	2·263	$5\cdot80 \times 10^{-5}$	−4·2366	$5\cdot10 \times 10^{-5}$	−4·2924
176·0	2·226	$8\cdot44 \times 10^{-5}$	−4·0737	$6\cdot92 \times 10^{-5}$	−4·1599

TABLE III. VARIATION OF k_7 AS A FUNCTION OF TEMPERATURE.

°C	$1/K° \, 10^3$	$k_7 \, l\,m^{-1}\,sec^{-1}$	$\log k_7$
140·0	2·420	$9·55 \times 10^{-6}$	−5·0200
152·5	2·349	$1·96 \times 10^{-5}$	−4·7077
159·0	2·314	$2·80 \times 10^{-5}$	−4·5528
166·4	2·275	$4·04 \times 10^{-5}$	−4·3936
170·0	2·257	$5·05 \times 10^{-5}$	−4·2967
178·0	2·217	$7·40 \times 10^{-5}$	−4·1308

DISCUSSION

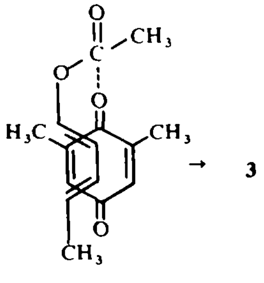
The approach of investigation expressed by Eq 1 is a deliberate attempt to induce and detect an unsymmetrical transition state in the Diels–Alder reaction. The three substituents in Eqs 2 and 3 (—CH_3. —$OCOCH_3$. —$COOCH_3$) are very different in their electronic properties but they are as close to one another as possible in steric requirements. The conspicuously different results of Eqs 2 and 3 can therefore hardly be attributed to steric causes.

Whereas the addition of 1-acetoxy-1.3-pentadiene (**1**) led to the formation of both possible adducts **3** and **4** at comparable rates. the addition of methyl sorbate **6** furnished only one of the two possible adducts: **7**. The alternatively oriented adduct: **8** was not detected, even in traces. The entropies[5] and energies of activation for the formation of adducts **3**. **4**. and **7** are listed in Table IV.

TABLE IV.

Adducts	Activation energy kcal $mole^{-1}$	Entropies of activation e.u.
3	21·75 ± 0·82	−29·36 ± 1·92
4	18·33 ± 0·63	−37·32 ± 0·48
7	21·91 ± 1·01	−29·44 ± 2·33

The abundantly documented operation of the *endo-cis* addition principle and the large negative entropy values presuppose **9**. **10**. **11**. and **12** pretransitional orientations prior to the formation of adducts **3**. **4**. **7**. and **8** respectively.



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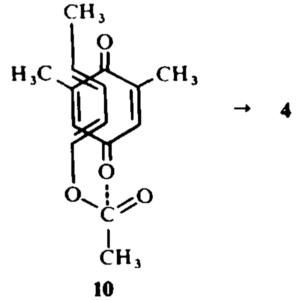

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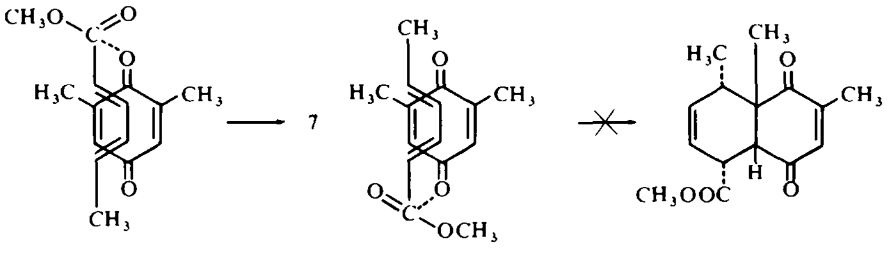
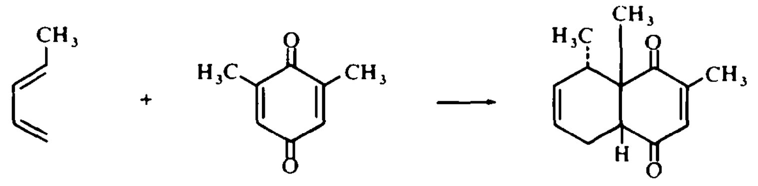


11 **12** **8**

First of all it is recognized that molecular alignment **12** does not lead to a successful transition state whereas **9**, **10**, and **11** all result in the formation of the corresponding adducts **3**, **4**, and **7**. This could be attributed to the repulsion of the two approaching Me groups, which might arise in orientation **12**. This assumption should, however, be discarded immediately since molecular alignment **10** gives rise to adduct **4**. Furthermore the addition of piperylene **13** to quinone **2** leads to the exclusive formation of **14**.[16]



13 **2** **14**

Clearly the failure of the transition state which follows alignment **12** might be attributed to the carbomethoxy group insofar as the latter is approaching the less hindered C atom of quinone **2**. This is corroborated by the fact that alignment **11** leads to a successful transition state.

Assuming the nearly concerted overlap of six orbitals, these observations and the kinetic parameters in Table IV allow us to suggest the following mechanistic aspects for the Diels–Alder reaction. (i) Out of the two σ bonds being formed in the transition state the bonding of the less hindered carbon atom in the dienophile with the correspondingly aligned center in the diene proceeds in advance of the second one. (ii) The electronic movement appears to be initiated from the diene towards the less hindered carbon atom of the dienophile, provided that a sufficient electron density is present in the diene at that center.

Since, in alignment **12**, the carbomethoxy group depletes the electronic density at the adjacent carbon atom, adduct **8** does not form. Whereas in alignments **9**, **10**, and **11** the methyl and acetoxy groups are sufficiently electron donating substituents for the initiation of the electronic process. In agreement with this the activation energy for the formation of adduct **4** is lowered by **3** kcals than for compound **3**, which reflects the better electron donating ability of an acetoxy group compared to a methyl. On the other hand the activation energies for the formation of **3** and **7** are practically identical since in alignments **9** and **11** the substituents involved at the site of the more advanced σ bond are identical.

Correspondingly the very different electronegativities of an acetoxy group in **1** and the carbomethoxy group in **6** at the other terminal substituent of the diene do not appear to influence the energy of activation.

The significantly more negative entropy of activation leading to **4** as compared to **3** and **7** indicates the operation of strong dipole interactions in orientation **10** (dashed line) between the acetoxy and the carbonyl group. While this kind of interaction must help to lower the activation energy. it also imposes restrictions on the motion of especially the acetyl group leading to a highly negative entropy of activation. Such a dipole interaction presupposes a geometry in the transition state which can accommodate the interacting groups. In orientations **9** and **11** the corresponding interactions (dashed lines) are interfered with by the methyl group of 2.6-dimethylbenzoquinone **2**.

It remains to be explained why 1-substituted dienes with substituted benzoquinones[17] and other unsymmetrical dienophiles lead predominantly to the *ortho* oriented adducts (i) rather than to the meta compound[3] (ii) (Eq 1 : Y = H).

If X is electron withdrawing (e.g., COOR, —COH) then the more developed σ bond at the less hindered reaction center of the dienophile will be preferentially formed with the participation of the unsubstituted terminal of the diene because of higher electron density.

On the other hand if X = alkyl. Y = H then the electron donating ability of this group is not much better than at the other terminal of the diene carrying only H. Therefore the primary overlap between the unsubstituted reaction centers is considerably facilitated merely on steric grounds.

In summary our results appear to indicate that the Diels-Alder addition is a concerted process in which the first σ bond develops in advance to the other between those centers at which the overlap of orbitals is the least hindered sterically. Furthermore it is preferably initiated by that terminal of the diene which possesses the higher electron density. From the entropies of activation there is good evidence for the existence of secondary forces.

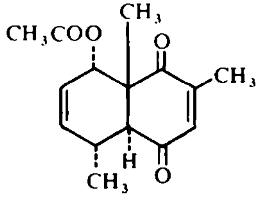
It is recognized that the conclusions drawn in this paper require corroboration by further examples. Such work is in progress in our laboratory.

EXPERIMENTAL

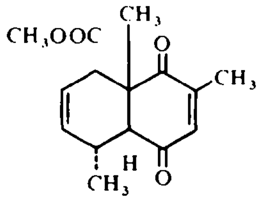
(a) *The kinetics of* 1-*acetoxy*-1.3-*pentadiene* (**1**) *with* 2.6-*dimethylbenzoquinone* (**2**). Diene **1** was prepared as described.[10] The quinone **2** was purchased from Aldrich Chemical Company. The kinetical runs were carried out by placing 1/2 ml of the stock soln into a thick wall tube. The samples were degassed, sealed under reduced pressure and suspended in a constant temp oil bath regulated to $\pm 0{\cdot}1^\circ$. It was also found that the effect of a small amount of O_2 present in the sample was insignificant.

The sealed tubes were removed at the appropriate time and immediately chilled in ice water. The concentrations of adduct **3** and elimination product **5** were determined by gas chromatographic analysis.** Besides the starting materials. solvent and products no other components were detected on the chromatogram. The calibrations were based on adduct **3a** and the elimination product **5** using toluene as an internal standard.

**Gas chromatographic conditions: the samples were analyzed on a Victoreen 4000 series GLC unit with a thermal conductivity detector. The recorder used was a Fisher 100 series 1 mv recorder. A six-foot column. 1/8 inch in diameter. packed with 4% SE and 6% QF-1 coated on 60–80 mesh chromosorb W (HMDS treated).



3a



7a

It was recognized in the preliminary experiments that the retention time of the crystalline adduct **3a** is slightly different from that of the primarily formed adduct **3**. The mixture on the preparative scale was subjected to column chromatography on alumina.[10] Since in structure **3a** there is only one readily isomerizable center it is assumed tentatively that the primarily formed compound **3** isomerized to the *trans* fused adduct **3a**. This was confirmed by passing a sample of **3** through alumina and taking subsequently its chromatogram. The peak corresponding to **3** disappeared completely and only the signal of **3a** appeared on the chromatogram. Our attempts to isolate the primary adduct **3** by preparative gas chromatography were futile because of the ready isomerization of **3** to **3a** on the surface of a fluoropak-silicon oil column. The previously reported stereochemical assignment of the compound isolated after the alumina treatment[10] should therefore be modified to the *trans* ring junction. It was found that the mixtures of *trans*-fused adduct **3a** and **3** have the same sensitivity towards the thermal conductivity cell. The initial concentrations of diene **1** and quinone **2** were $1{\cdot}70 \times 10^{-1}$ mole/litre and $2{\cdot}33 \times 10^{-1}$ mole/litre respectively in benzene. (Stock soln). Since the formation of compound **4** was followed by the elimination of a molecule of AcOH, the effect of added AcOH on the reaction rate was examined. Our experiments showed that the kinetics remained essentially the same when the stock soln was made up in 10% AcOH 90% benzene. A sufficient mass balance (better than 95%) was obtained using known samples of **1**. **2**. **3a** and **5**.

(b) *The reaction of methyl sorbate* **6** *with* 2.6-*dimethylbenzoquinone* (**2**). The *trans. trans* methyl sorbate **6** was prepared as described.[12] The initial concentrations of diene **6** and 2.6-dimethylbenzoquinone were $2{\cdot}49 \times 10^{-1}$ mole/litre and $2{\cdot}54 \times 10^{-1}$ mole/litre respectively in benzene. The procedure followed in studying this reaction was identical with that of the first reaction. The rate of the reaction was followed by determining the concentration of the only product: **7**.

Since the primarily formed **7** could be converted quantitatively to **7a** by passing its soln through a column of alumina it is assumed that **7a** is a stereoisomer of **7**. Since there are two isomerizable centers in **7** we are unable to assign the stereochemistry of **7a**. The detector responses for **7** and **7a** were identical. Consequently the calibration was based on the crystalline **7a** using toluene as the internal standard.

Besides the starting materials. benzene and the product **7** no other components were indicated on the chromatogram. A good mass balance was obtained (95% or better) using known samples of **2.6** and **7a**.

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