Anatomy of Ene and Diels–Alder Reactions between Cyclohexadienes and Azodicarboxylates

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In contrast with other (C • • • H • • • N) hydrogen transfers, the high-pressure kinetics of the ene reaction between cyclohexa-1,4-diene and diethyl azodicarboxylate show a concerted transition state. The discrepancy is assigned to the enhanced rigidity of the cyclohexadiene molecule with orthogonal hydrogen transfer to the nitrogen atom. Cyclohexa-1,3-diene reacts with diethyl azodicarboxylate according to a concerted Diels–Alder reaction.

In contrast with the Diels–Alder reaction for which mechanistic parallels have frequently been proposed,[1] the ene reaction has been much less investigated, despite its potential utility as a synthetic method.[2] The ene reaction involves a complex electronic reorganization with multiple bond-breaking and bond-forming processes. At first sight, the number of events involved should imply that they do not occur in concert. Nevertheless, Dewar favoured synchronicity in ene reactions from the consideration that one of the bond-breaking/making processes involves bonds to a common hydrogen atom, and therefore should not contribute significantly to the activation energy of the reaction.[3] This situation is peculiar to hydrogen because of its propensity to form three-centre bonds.[4] However, the mechanism of the ene reaction has been found to vary through a wide spectrum of possibilities, from pure concerted[5] to clearly stepwise processes involving zwitterions,[6] biradicals,[7] or even more complex intermediates.[8] Thus, it is clear that the mechanism must be established in each specific case.

In the laboratory, the timing of bond-making and bond-breaking in the ene reactions is difficult to investigate with unambiguous experimental tests. Mechanistic arguments are various [stereospecificity, thermodynamic parameters, kinetic isotope effects (KIE), theoretical calculations, *etc.*]. A seemingly strong method was proposed by Stephenson for ene reactions, which consisted of comparing intermolecular KIE with the intramolecular KIE obtained with *gem*-(*E*)- and -(*Z*)-2,3-dimethyl[1,1,1,3,3,3-$^2H_6$]but-2-ene.[9] An alternative method based upon the pressure dependence of the reaction rate yielded the volume of activation.[10]

Kinetic pressure investigations were made for concerted ene reactions involving (C • • • H • • • O)[11] and (O • • • H • • • O) hydrogen transfer[12] (C,O: atom from which the H-atom is abstracted, O: oxygen atom to which it is transferred). A more recent study considered the pressure effect in (C • • • H • • • N) hydrogen-transfer reactions involving diethyl azodicarboxylate (DEAD) and (*Z*)-cyclo-olefins.[13] The most interesting result was that the volume of activation $\overline{\Delta V^{\ddagger}}$ was found to be very different from the reaction volume $\overline{\Delta V}$ (at least in reactions involving cyclopentene and cyclohexene), suggesting a transition state significantly different from the product, thus supporting a stepwise mechanism (see ref. 10 for the correlation between volume profiles and mechanisms). In further work, the (C • • • H • • • N) hydrogen transfer was examined in the ene additions of DEAD with allylbenzene, α-methylstyrene and β-pinene.[14] The values of the ratio θ ($\Delta V^{\ddagger}$:$\overline{\Delta V}$) were all consistent with the formation of a biradical intermediate, thus confirming the results of the former study (see Table 3, later).

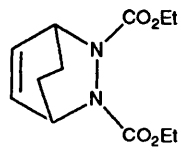
We became interested in ene reactions involving cyclohexadienes, since it has been hypothesized that the addition of DEAD to both cyclohexa-1,3- and -1,4-diene satisfies the criteria for concertedness.[15] In view of this hypothesis and our previous pressure studies on (C • • • H • • • N) hydrogen transfer, we decided to investigate the pressure effect in the reactions between DEAD and cyclohexadienes in order to find out whether concertedness applies in the ene reactions of cyclohexadienes, as well as in the [4 + 2]cycloaddition of cyclohexa-1,3-diene,

Results and Discussion

1. *Addition Reactions of DEAD with Cyclohexa*-1,3-*diene.*—For some conjugated dienes the ene reaction competes favourably with the Diels–Alder reaction provided that the dienophile is DEAD. Indeed, DEAD is known to favour the ene reaction as has been exemplified in its addition to cyclohexa-1,3-diene, which typically gives 80% ene adduct and only 20% Diels–Alder cycloadduct.[15,16]

The reason for a given addition reaction proceeding *via* either [4 + 2]cycloaddition or an ene reaction is still unsettled. Jacobson suggested steric effects or secondary orbital interaction between a π-electron-containing substituent on the enophile and the other double bond of the diene or a slight difference in orbital energies of the (*Z*)- and (*E*)-DEAD enophiles.[17]

If cyclohexa-1,3-diene is allowed to react with DEAD at 35 °C in a diluted medium (CH_2Cl_2 as solvent)—conditions required for accurate kinetic measurements—we observed the formation of only one adduct along with diethyl hydrazodicarboxylate which is always produced in varying amounts depending on conditions (mainly temperature and DEAD:diene initial ratio). The product was isolated and shown to be the Diels–Alder cycloadduct **1**, in striking contrast with former



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results.[15–18] It should be noted that, under irradiation conditions, the same result was observed, *i.e.* exclusive formation of the cycloadduct.[19] When the reaction was performed at ambient temperature in the absence of solvent, approximating

Table 1. Diels–Alder reaction between cyclohexa-1,3-diene and DEAD. Pressure effect.[a]

Pressure/MPa	$k/10^{-5}$ dm^3 mol^{-1} s^{-1}	
0.1	9.46	
19.3	12.3	$\Delta V_1^{\ddagger}$ − 38.1 cm^3 mol^{-1}
29.8	13.4	
39.4	15.9	$\Delta V_{25}^{\ddagger}$ − 36.8 cm^3 mol^{-1}
47.9	16.2	
69.2	20.1	$\overline{\Delta V}_{25}$ − 34.4 cm^3 mol^{-1}
79.1	21.7	
92.9	26.4	θ_{25} 1.07

[a] Solvent toluene, 33.1 °C.

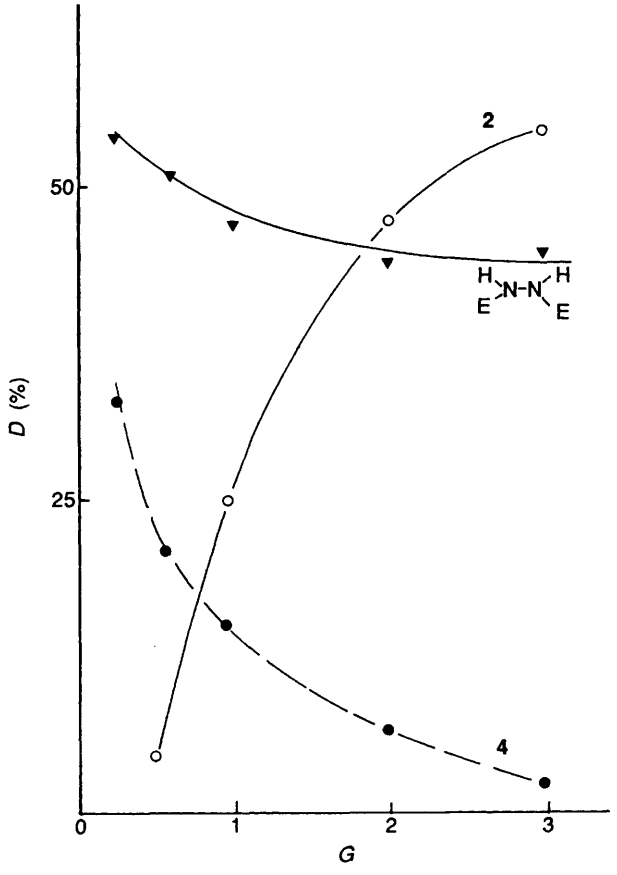


Fig. 1. Effect of diene:DEAD ratio (G) on product distribution (D) in the ene reaction of cyclohexa-1,4-diene with DEAD (80 °C; ambient pressure; 20 h). E is CO_2Et.

conditions used in the works cited,[15,16] the two expected ene and Diels–Alder adducts were produced. Thus, it is evident that in the addition of DEAD to cyclohexa-1,3-diene the chemoselectivity is extremely dependent on the experimental conditions. These facts prompted us to undertake kinetic measurements, since deviation from the initial concentration may alter the product ratio, leading to unrealistic $\Delta V^{\ddagger}$-values and, subsequently, to erroneous mechanistic conclusions. As a consequence, the pressure effect on the (DEAD + cyclohexa-1,3-diene) reaction was examined up to 100 MPa, but only under conditions leading to the formation of the 1,4-cyclo-adduct (**1**) (Table 1).*

The value of $\Delta V^{\ddagger}$ is undoubtedly similar to those characteristic of typical concerted [$\pi^4 + \pi^2$] processes.[1]

Table 2. Ene reaction between cyclohexa-1,4-diene and DEAD. Pressure effect.[a]

Pressure/MPa	$k/10^{-5}$ dm^3 mol^{-1} s^{-1}	
0.1	1.77	
8.0	2.01	
19.1	2.07	$\Delta V_1^{\ddagger}$ − 36.4 cm^3 mol^{-1}
29.8	2.49	
46.6	3.02	$\Delta V_{25}^{\ddagger}$ − 30 cm^3 mol^{-1}
70.0	3.97	
86.5	4.58	

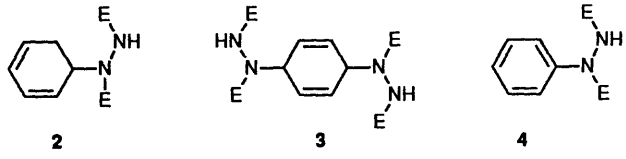
[a] Conditions: diene:DEAD (3:1), solvent toluene, T = 73.8 °C.

Table 3. DEAD ene additions to alkenes.[a]

Ene component	$-\Delta V^{\ddagger}$/cm^3 mol^{-1}	$-\overline{\Delta V}$/cm^3 mol^{-1}	θ	Ref.
Cyclohexa-1,4-diene	30.0	34.0	0.88	This work
Cyclohexene	19.7	34	0.58	13
β-Pinene	22	35.4	0.62	14
α-Methylstyrene	22	32.0	0.69	14
Allylbenzene	27.0	35.8	0.75	14

[a] Data calculated for reaction at 25 °C.

2. *Addition Reactions of DEAD with Cyclohexa-1,4-diene.*— The DEAD–cyclohexa-1,4-diene reaction has previously been studied.[15–19]† Though the 1,4-diene cannot react in a [4 + 2] manner and should be expected to yield the ene product, Franzus observed the formation of at least two products **2** and **3** (E = CO_2Et).[20]



Under our temperature conditions (70–80 °C), three products were found in the mixture, along with diethyl hydrazodicarboxylate: the mono ene adduct **2**, an aromatic product **4** derived from adduct **2**, and a heavier product which was usually formed in low yield and which was not characterized (tentatively assigned as compound **3**). The distribution of these products was largely dependent on the initial diene:DEAD ratio as shown in Fig. 1.

With an excess of DEAD with respect to cyclohexa-1,4-diene, the ene product is, within the indicated reaction time, almost entirely aromatized into compound **4**. With low DEAD:diene ratios, compound **2** was obtained selectively and, therefore, the kinetics of the ene reaction were followed under these concentration conditions (Table 2).

From these results, the volume of activation was calculated and compared with the volume data of other DEAD ene additions (Table 3).

The results in Table 3 are very informative. It appears that the mechanism of DEAD ene additions is highly dependent on the ene component. While DEAD adds to cycloalkenes[13] and to specific olefins like allylbenzene, α-methylstyrene and β-

* Cyclohexa-1,3-diene can also undergo a cyclodimerization reaction according to [4 + 2]- and [6 + 4]-ene processes, especially at high temperatures (F. G. Klärner, B. M. Dogan, O. Ermer, W. von E. Doering and M. P. Cohen, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 108). However, the low temperature employed in this work precluded the possibility of dimerization.

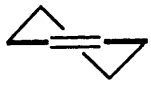


Fig. 2.

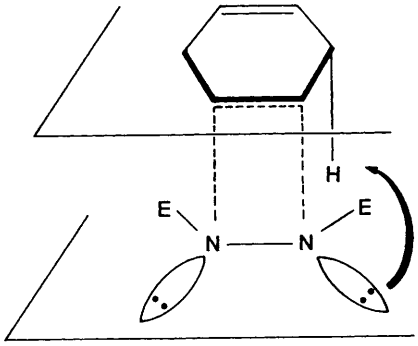


Fig. 3. Transition state in the DEAD–cyclohexa-1,4-diene ene reaction.

pinene[14] possibly by a sequential process, it has been reported to follow a concerted pathway with linear olefins[21] and tetracyanoethylene[22] though, in the latter case, other mechanisms have been proposed.[22,23]

In the present study, the $\Delta V^{\ddagger}$-values support concertedness for both the Diels–Alder cycloaddition of DEAD to cyclohexa-1,3-diene and the ene addition of DEAD to cyclohexa-1,4-diene (allylic hydrogen transfer coupled to C–N bond formation). The result for the DEAD–cyclohexa-1,4-diene reaction is rather surprising when compared with the DEAD–cyclohexene reaction.[13]

Both ene components have common features: they are unsaturated six-membered rings and the hydrogens removed are both secondary and held in rough alignment with the π-system. However, the additional double bond in cyclohexa-1,4-diene introduces enhanced rigidity in the molecule, which adopts a quasicoplanar structure. This is a highly favourable orientation for hydrogen abstraction, as exemplified by the respective ene reactivities: cyclohexa-1,4-diene reacts *ca.* 15-times faster than cyclohexene in the reaction with DEAD at 78 °C.

The orientation of the allylic hydrogen in cyclohexa-1,4-diene is such that it can be co-ordinated with the non-bonded electron pair of the nitrogen atom in DEAD. The hydrogen atom is thus transferred orthogonally. In contrast, in the case of cyclohexene, the hydrogen abstraction appears to be considerably different, probably due to the greater flexibility of the ring and the preferential conformation of cyclohexene known to be as shown in Fig. 2.

Consequently, we may depict the transition state in the DEAD–cyclohexa-1,4-diene reaction as a 'pseudopericyclic' transition state as described by Kwart[24] (see Fig. 3).

The trend is peculiar for the N=N enophile, since the C=O bond in mesoxalates abstracts the α-hydrogen from cycloalkenes in a concerted way.[14]

Whether the H-atom is transferred in an angular or linear fashion in the cyclohexa-1,4-diene reaction is not clear. Kwart proposed the terminology of 'bent transition states' for superene reactions on the basis of kinetic isotope effects.[24] However, the validity of this mechanistic criterion was recently disputed.[25] Considering the θ-value, we favour a linear transition state, since the rigidity of the transition state appears looser than previously demonstrated in (C • • • H • • • C)[14] and (C • • • H • • • O)[11] hydrogen-transfer reactions.

Conclusions.—These results indicate that a concerted transition state is preferred for the addition reactions of DEAD with the rigid *cisoid* cyclohexa-1,3-diene and the nearly planar cyclohex-1,4-diene. The results also indicate that caution must be exercised before conclusive remarks can be made for the mechanism of ene additions.

Considering the $\Delta V^{\ddagger}$ results of this study and the results gained from our pressure investigations relative to other (C • • • H • • • N) ene reactions, it should be noted that each time a parallel could be drawn between mechanisms determined at atmospheric pressure by various methods and mechanisms deduced from $\Delta V^{\ddagger}$ values, the agreement was found to be remarkably good. This is of significance for the acceptance of the volume of activation as a mechanistic criterion despite recent doubts.[26]

Experimental

^{1}H NMR spectra were obtained at 60 MHz (Perkin-Elmer R32) or 200 MHz (Bruker WP 200 SY) with $CDCl_3$ as solvent and Me_4Si as internal standard. IR spectra were recorded on a Perkin-Elmer 1310 spectrophotometer for CCl_4 solutions. Mass spectra were carried out with a LKB-9000S instrument. GC analyses were performed on a Hewlett-Packard 5700 gas chromatograph (OV 225 1% on Chromosorb WDMCS 80–100 mesh; 2 m; φ $\frac{1}{8}''$; 70–230 °C, 6 °C min^{-1}). Liquid column chromatography was carried out on a 30 × 1.5 cm column filled with silica gel Merck 230–400 mesh, and hexane–diethyl ether or hexane–ethyl acetate (1:2) as eluant systems.

Pressure kinetic measurements were made as previously described;[11] mesitylene served as internal standard. The volume of activation was determined graphically and controlled *via* the published linear relationship.[27]

Synthesis of Cycloadduct **1** *from Cyclohexa*-1,3-*diene + DEAD.*—DEAD (276 mg, 1.58 mmol) was added to a CH_2Cl_2 solution of cyclohexa-1,3-diene (126 mg, 1.58 mmol). The solution was heated at 40 °C for 24 h. Diethyl hydrazodicarboxylate precipitated upon cooling. After filtration, the adduct **1** was isolated by column chromatography as a viscous, pale yellow liquid; ν_{max} 2980, 2930, 1740, 1700 and 1615 cm^{-1}; δ_H 6.65 (t, 2 H), 4.92 (s br, 2 H), 4.27 (q, 4 H), 1.80–2.30 (m br, 4 H) and 1.27 (t, 6 H).

Reaction between Cyclohexa-1,4-*diene and DEAD.*—DEAD (94 mg, 0.54 mmol) was added to a CH_2Cl_2 solution of cyclohexa-1,4-diene (338 mg, 4.22 mmol). The solution was heated at 100 °C for 24 h. Column chromatography yielded adduct **2** as a pale yellow liquid, ν_{max} 3380, 2980, 2930, 1760 and 1715 cm^{-1}; δ_H 6.30 (s, 1 H), 5.75 (m, 4 H), 4.15 (q, 4 H), 2.50 (m br, 2 H) and 1.23 (t, 6 H); *m/z* 254, 176 and 78.

The synthesis of compound **4** was carried out by heating a CH_2Cl_2 solution of DEAD (376 mg, 2.16 mmol) and cyclohexa-1,4-diene (43 mg, 0.54 mmol) at 40 °C for 22 h. Compound **4** was obtained as a yellow oil, ν_{max} 3450, 3060, 2960, 1760 and 1740 cm^{-1}; δ_H 7.20–7.50 (m, 5 H), 6.97 (s, 1 H), 4.25 (q, 4 H) and 1.30 (t, 6 H); *m/z* 252, 180, 119, 107, 91 and 77.

Precision Density Measurements.—These were carried out as previously described,[14] yielding the following partial molar volumes in toluene (cm^3 mol^{-1}): cyclohexa-1,4-diene (98.0), DEAD (153.4), **2** (217.4); cyclohexa-1,3-diene (98.6), **1** (217.6).

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