Volumes of Activation for Catalysed Diels–Alder Reactions

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The Diels–Alder reactions between isoprene and *N*-phenylmaleimide catalysed by Lewis acids, in particular by aluminium chloride and by lithium perchlorate, have volumes of activation more negative than does the uncatalysed reaction. That between anthracene-9-methanol and *N*-ethylmaleimide is faster in water than in organic solvents, and has a slightly more negative volume of activation in the aqueous than in the organic medium. The significance of these measurements is discussed.

In recent years, catalysis of Diels–Alder reactions has become increasingly important in extending the range of synthetic applications.[1–3] Lewis acids in particular are widely used to accelerate cycloadditions, and the consensus of opinion regarding the mechanism of such catalysis is one of the electrophile coordinating to a substituent group of the dienophile, thereby bringing about a lowering of the energy of the LUMO which it provides.[4] A pre-equilibrium association between dienophile and catalyst, such as aluminium chloride, would then preface the cycloaddition (Scheme 1). Such a two-stage reaction would be characterised by a rate expression of the type of eqn. (1), and the volume of activation by eqn. (2). It would be predicted that $\Delta V(k_1)$ would be negative both on account of the association between the reagents and also due to some expected ionic character of the complex which would be accompanied by solvent electrostriction. The magnitude of $\Delta V^{\ddagger}(k_2)$ would be within the normal range of -30 to -35 cm^3 mol^{-1} if the cycloaddition remains concerted, although the value could be less negative if the catalysed reaction became a two-step process. It seems likely that the value of $\Delta V^{\ddagger}_{\text{obs}}$ would be more negative than that for an uncatalysed reaction, although to date no values have been reported. In a similar manner, catalysis by lithium perchlorate[5] may be due to the lithium ion acting as an electrophilic species, the perchlorate counter ion being chosen to afford a salt soluble in diethyl ether. Here, the situation is complicated since lithium perchlorate exists in ether solution as an anion pair and complexation with the imide oxygen will involve disruption of this pair and its solvation shell to an unknown extent. A further equilibrium, eqn. (3), might need to be considered which would be associated with a negative volume change (*i.e.* pressure favours free ions over ion pairs).[6] The value of $\Delta V^{\ddagger}_{\text{obs}}$ might then be even more negative than that for the aluminium chloride-catalysed reaction.

$$\text{Dienophile} + \text{Lewis acid} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{Complex}$$

$$\text{Complex} + \text{Diene} \xrightarrow{k_2} \text{Product}$$

Scheme 1

$$k_{\text{obs}} = k_1 k_2 \qquad (1)$$

$$\Delta V^{\ddagger}_{\text{obs}} = \Delta V(k_1) + \Delta V^{\ddagger}(k_2) \qquad (2)$$

$$(\text{Li}^+\text{ClO}_4^-)_{\text{ion pair}} \longrightarrow \text{Li}^+ + \text{ClO}_4^- \text{ (free ions)} \qquad (3)$$

Another area of catalysis recently explored, for example by Grieco and co-workers[7–10] and by Breslow and co-workers,[11–13] is the use of water as a solvent. Promotion of the Diels–Alder reaction by an aqueous medium can result in rate accelerations as much as 6000-fold.[14] However, this increase in rate is assumed to arise from an effect other than electrophilic catalysis and a wide variety of explanations have been offered. These include hydrophobic interactions[15–18] implying that, due to the tendency of water towards self-association by hydrogen bonding, hydrophobic molecules such as our Diels–Alder components tend to be forced to aggregate, and hence local high concentrations of these reagents occur with accompanying increase in rate. Micellar catalysis has been raised as a further possibility, which is akin to hydrophobic properties. Hydrophobic association is usually accompanied by a small volume decrease so would be increased by pressure. Catalysis by hydrogen bonding has been invoked, as have other recognised solvent properties. A further interpretation may also be considered. Liquids possess 'internal pressure', P_i, normally defined using the ratio of thermal expansivity, α, to adiabatic compressibility, β [eqn. (4)],[19] and is of the order of a few kbar† for organic liquids. It is a matter of conjecture as to what extent this property coincides in its effects on solutes with that of applied external pressure, since there is no internal pressure free medium available for comparison. If such a correspondence exists, liquid solvents in part facilitate Diels–Alder reactions by virtue of internal pressure. In this case, water would be an especially powerful solvent since its internal pressure is of the order of 17 kbar,[20] although this value is contentious.‡ It must be mentioned that most preparative examples are carried out under at least partially heterogeneous conditions, with reagents only slightly dissolved, since solubilities of the organic reagents are normally low. Consequently, few truly homogeneous values of rate constants have been reported. Second order rate constants reported for reactions using cyclopentadiene do not include concentrations employed, and it might be supposed

$$P_i = -T\alpha/\beta \qquad (4)$$

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† 1 bar = 10^5 Pa.

‡ The high value quoted for P_i for water is based on the opinion that water is anomalous[21] and its internal pressure better represented by the van der Waals pressure correction term, a/V^2, for which $a = 5.5$ dm^6 mol^{-2} bar^{-1} and the molar volume $V = 0.018$ dm^3 from which $P_i = 17\,000$ bar. It is the authors' opinion that the effect of internal pressure on reaction rates is at present unclear.

that such a hydrophobic species does not readily form a truly homogeneous aqueous solution, but would prefer to exist in micelles. The system chosen for study here has greater water solubility than others used and greater than that used in Lewis acid catalysis to ensure that conditions are homogeneous throughout. Recently, Engberts *et al.*[22] have rejected all these explanations as a result of measurements of thermodynamic transference parameters for diene, dienophile and product, and conclude that hydrophobic acceleration is due to destabilisation of the reagents in addition to hydrogen-bonding stabilisation of the transition state. Any prediction of the effects of pressure on aqueous systems are therefore difficult to make.

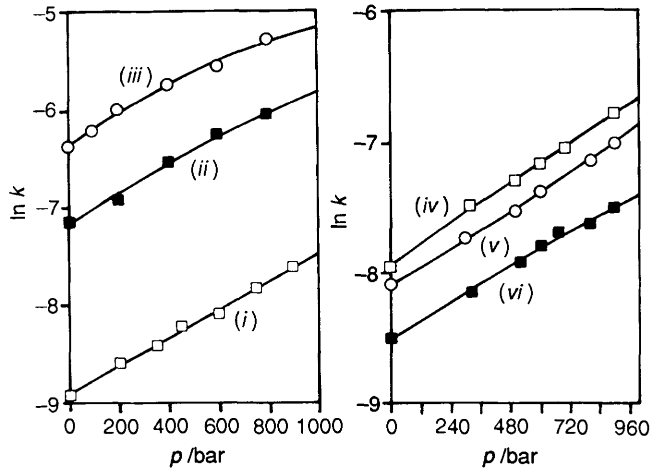
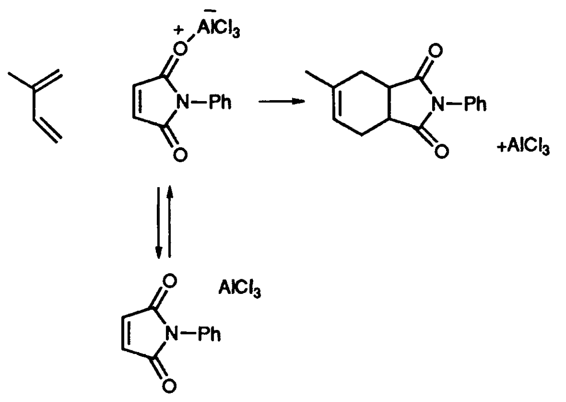


Fig. 1 Plots of ln k_{obs} against pressure. Numbers refer to the reactions as numbered in the text.



Scheme 2

Table 1 Initial concentrations of reagents and catalyst for reactions (*i*)–(*iii*)

Reaction	[Isoprene]/ mol dm^{-3}	[*N*-Phenylmaleimide]/ mol dm^{-3}	Catalyst (conc./ mol dm^{-3})
(*i*)	2.5	2.886×10^{-2}	None
(*ii*)	0.45	0.029	$AlCl_3$ (0.06)
(*iii*)	0.45	0.032	$LiClO_4$ (2.25)

Experimental

Mixtures of reagents in the concentrations specified in Tables 1 and 2 were placed in a Spectrocil spectrometer cuvette of 1 cm pathlength so as to fill it completely. The cuvette was fitted with a stopper in which a small mercury reservoir was located and connected to the interior by a capillary. This was then placed in a stainless steel pressure vessel equipped with two sapphire windows and filled with ethanol. The vessel fitted into the spectrometer so that the beam passed through the windows and the cuvette within. Pressure was applied by means of a hand pump delivering ethanol to the top of the pressure vessel and reactions were followed in the usual way by observation of the change of absorption with time. First order rate constants were computed by means of the Guggenheim method. Volumes of activation were determined by a computed least squares quadratic fit of values of ln *k* against pressure, *p*, eqn. (1), from which $\Delta V^{\ddagger}$ was obtained using eqns. (5) and (6).[12]

$$\Delta V^{\ddagger} = -RT \times \mathrm{d}\ln k/\mathrm{d}p \qquad (5)$$

$$\ln k = A + Bp + Cp^2;\ \Delta V^{\ddagger} = B \qquad (6)$$

Results

The results for reactions (*i*)–(*iii*) between isoprene and *N*-phenylmaleimide in diethyl ether at 30 °C, monitored at 390 nm, are summarised in Table 3. The analogous data for reactions (*iv*)–(*vi*) between anthracene-9-methanol and *N*-ethylmaleimide (no catalyst) at 45 °C are summarised in Table 4.

Discussion

Catalysis by aluminium chloride is very effective, the ratio of k_2 for catalysed and uncatalysed reactions being 35. Lithium perchlorate is even more effective and the ratio is now around 70. Volumes of activation for the catalysed reactions are also considerably more negative than is that for the uncatalysed, by about 6 and 10 cm^3 mol^{-1}, respectively, which is in accordance with predictions assuming a prior association between the catalyst and one or other of the reagents, presumably the dienophile (*e.g.* Scheme 2). That the volume of activation is more negative for lithium salt catalysis is also explained by the hypothesis that ion-pair separation by pressure makes the catalyst even more potent. However, recent calculations by Schleyer and Jiao[23] point to the possibility of a different mode of action of the lithium ion in a simulation of a catalysed reaction between furan and ethene. High level MO calculations indicate a preference of the lithium ion to coordinate normal to the π-system of furan with 150 kJ mol^{-1} exothermicity and thereby reduce the activation energy for the cycloaddition from 84 to 44 kJ mol^{-1}. This mode of coordination appears to be more favourable than that to the unshared pair of the furan oxygen which implies the mechanism could apply to a pure hydrocarbon diene. If this is the mechanism for catalysis with our reagents, the volume of activation is still understandable by the arguments presented above.

These observations have considerable significance for synthetic applications. A simplistic calculation using eqn. (1) and assuming linearity over the pressure range suggests that the

Table 2 Initial concentrations of reagents, solvent and spectroscopic monitoring wavelength for reactions (*iv*)–(*vi*)

Reaction	[Anthracene-9-methanol]/ mol dm^{-3}	[*N*-Ethylmaleimide]/ mol dm^{-3}	Solvent	λ/nm
(*iv*)	3×10^{-5}	1.65×10^{-3}	Water	363
(*v*)	1.5×10^{-4}	3.0×10^{-2}	Butan-1-ol	385
(*vi*)	1.5×10^{-4}	3.5×10^{-2}	Heptane	383

Table 3 Results of reactions (*i*)–(*iii*)

	Reaction (*i*)			Reaction (*ii*)			Reaction (*iii*)		
	p/bar	$10^4 k_1$/s	ln k_{rel}	p/bar	$10^4 k_1$/s	ln k_{rel}	p/bar	$10^4 k_1$/s	ln k_{rel}
	1	1.34	0	1	0.786	0	1	1.68	0
	200	1.85	0.322	200	0.990	0.23	100	2.02	0.184
	350	2.21	0.500	400	1.47	0.63	200	2.51	0.401
	450	2.70	0.701	600	1.95	0.91	400	3.25	0.66
	600	3.08	0.832	800	2.38	1.11	600	3.93	0.85
	750	3.99	1.09				800	5.10	1.11
	900	4.96	1.31						
k_2(1 bar)/mol^{-1} dm^3 s^{-1}	5.36×10^{-5}			175×10^{-5}			373×10^{-5}		
ln k	$-8.908 + 0.001\,47p - 10^{-5}p^2$			$-7.179 + 0.001\,70p - 10^{-5}p^2$			$-6.376 + 0.001\,85p - 10^{-5}p^2$		
$\Delta V^{\ddagger}$/cm^3 mol^{-1}	-36.1			-41.7			-45.4		

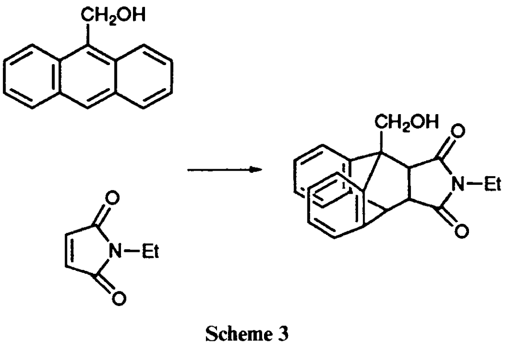
Table 4 Results of reactions (*iv*)–(*vi*)

	Reaction (*iv*)			Reaction (*v*)			Reaction (*vi*)		
	p/bar	$10^4 k_1$/s	ln k_{rel}	p/bar	$10^4 k_1$/s	ln k_{rel}	p/bar	$10^4 k_1$/s	ln k_{rel}
	1	3.50	0	1	2.03	0	1	3.05	0
	320	5.64	0.477	320	2.86	0.345	300	4.36	0.358
	500	6.90	0.679	520	3.64	0.583	500	5.38	0.564
	600	7.84	0.807	600	4.08	0.698	600	6.30	0.726
	700	8.82	0.924	670	4.52	0.797	800	8.07	0.974
	900	11.7	1.210	800	4.86	0.872	900	9.18	1.102
				900	5.51	0.988			
k_2/mol^{-1} dm^3 s^{-1}	212×10^{-3}			6.77×10^{-3}			8.71×10^{-3}		
ln k	$-7.949 + 0.001\,40p + 10^{-5}p^2$			$-8.512 + 0.001\,22p + 10^{-5}p^2$					
$\Delta V^{\ddagger}$/cm^3 mol^{-1}	-36.0			-31.4			-28.6^a		

[a] ΔV(ethanol) = 22.4 cm^3 mol^{-1}.

largest rate acceleration would result from a combination of high pressure and a Lewis acid, such as aluminium chloride, or especially lithium perchlorate. Rate accelerations at 10 kbar as compared with 1 bar, uncorrected for curvature of the ln k–p relationship give values of 1.8×10^6 for the uncatalysed, 21×10^6 for the aluminium chloride catalysed and 110×10^6 for the lithium perchlorate catalysed reactions. While these figures are greatly exaggerated when compared with actual experimental rate accelerations at this pressure, they serve to indicate that one might expect a further rate increment of around 10-fold and 60-fold, respectively, if catalysts are used in conjunction with pressure. The values obtained do not support a changeover to a two-step cycloaddition.

The reaction between anthracene-9-methanol and *N*-ethylmaleimide (Scheme 3) has previously been examined by Rideout and Breslow[24] at atmospheric pressure. Their values of k_2 (in mol^{-1} dm^3 s^{-1}) for the reaction in isooctane, 8.0×10^{-3}, and in water, 226×10^{-3}, compare well with our values in hexane, 8.7×10^{-3} and in water, 212×10^{-3}, and we also note a slight decrease in the more polar solvent, butan-1-ol. The volume of reaction is considerably less negative, giving a value of $\theta = \Delta V^{\ddagger}/\Delta V = 0.71$ (in butan-1-ol and ethanol, respectively) denoting a very compact transition state. The rate enhancement in water is thus a factor of 25 or so. The volume of activation in hexane, which we can take as being uncatalysed, is on the low side of the range for Diels–Alder reactions, but others are known which have comparable values. The volume of activation in water is somewhat more negative and this difference, about 8 cm^3 mol^{-1}, may reflect a contribution from pressure favouring increased solvation of the transition state.



Scheme 3

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