

AN ENE REACTION WITH A POLAR TRANSITION STATE AS ASCERTAINED FROM SOLVENT EFFECTS

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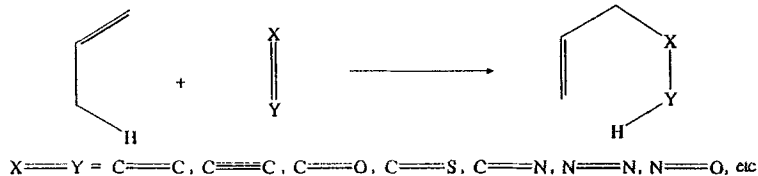
A kinetic study is reported for the ene reaction between methyl acrylate as the enophile and β -pinene, with aluminium chloride as catalyst, in a series of solvents varying in polarity. These experiments point to a transition state having pronounced zwitterionic character, in line with earlier suggestions in the literature. An unexpected and significant change of the rate constant with the initial concentrations is also found.

INTRODUCTION

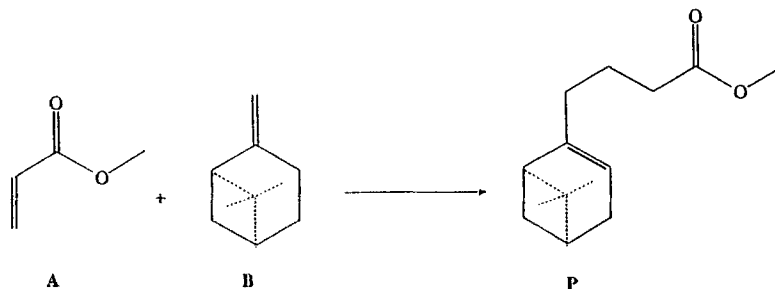
The ene reaction¹ forms a new carbon–carbon bond between the partners. Hence its importance for synthetic organic chemistry, together with other ‘bread-and-butter’ classics such as the Michael and Grignard additions, the aldol (Borodine) and Claisen condensations, and the Diels–Alder cycloaddition. Indeed the ene reaction is a close relative of the Diels–Alder. They are isoelectronic. They differ in that the ene reaction typically has higher activation energies and thus in practice often demands elevated reaction temperatures, in the absence of activation or a catalyst. The former is provided whenever the enophile is a good electron

acceptor (Scheme 1). Complexation of the enophile by Lewis acids lowers its LUMO and thus narrows the gap between the frontier orbitals.² Indeed Lewis acids catalyse the ene reaction.³ The mechanism of the ene reaction has been studied both theoretically⁴ and experimentally.⁵ An unresolved issue is that of the zwitterionic character of the transition state; this has been suggested from consideration of secondary deuterium isotope effects.^{6,7}

We have opted to study the addition of methyl acrylate (A), an enophile activated by the electron-withdrawing ester group, onto β -pinene (B), a rather reactive olefin for the ene reaction (Scheme 2).



Scheme 1



Scheme 2

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EXPERIMENTAL

β -Pinene and methyl acrylate (Aldrich) are distilled under an inert atmosphere (nitrogen) prior to use. Aluminium chloride (Aldrich 99.99%) is stored and handled in a dry box under nitrogen. Benzene (SDS) is dried by distillation over sodium/benzophenone. The chlorinated solvents (Prolabo) are dried by distillation over P_2O_5 . Deuterated benzene (CEA, 99.6%) is used without further purification. The NMR runs are performed (1H) with a Bruker 400 MHz spectrometer thermostated at 300 K. The gas chromatographic determinations are performed by sampling the reaction mixture with a syringe (after a filtration on silicagel to remove the catalyst) and injecting into a Varian 3300 gas chromatograph equipped with a Chrompack CP-Sil 5CB apolar capillary column (length 25 m, diameter 0.25 mm) and using an internal *n*-tridecane reference.

NMR measurements. The sample tubes are prepared entirely inside a dry box. Two deuteriobenzene solutions are prepared. The first consists of methyl acrylate 2.5 or 5 M together with 0.1 equivalent of aluminium chloride. The second consists of β -pinene, also 2.5 or 5 M depending on the desired molar ratio. Equal volumes from each solution are mixed at time zero in the 5 mm outer diameter NMR tube.

Kinetics as a function of the solvent. In a two-necked flask (50 mL) surrounded by a constant temperature (25 °C) oil bath, fitted with an argon inert atmosphere inlet and with a magnetic stirring bar, aluminium chloride (1 mmol), the *n*-tridecane internal standard (0.5 g) and the solvent (10 mL) are thoroughly mixed.

Methyl acrylate (12 mmol) is then added with a syringe and then in like manner ($t = 0$) β -pinene (10 mmol). Samplings of aliquots from the reaction mixture are regularly performed and injected in the gas chromatograph as the reaction proceeds.

RESULTS

Kinetic order of the reaction

The expectation is for the studied reaction to be first order in alkene (β -pinene) and in acrylate-Lewis acid

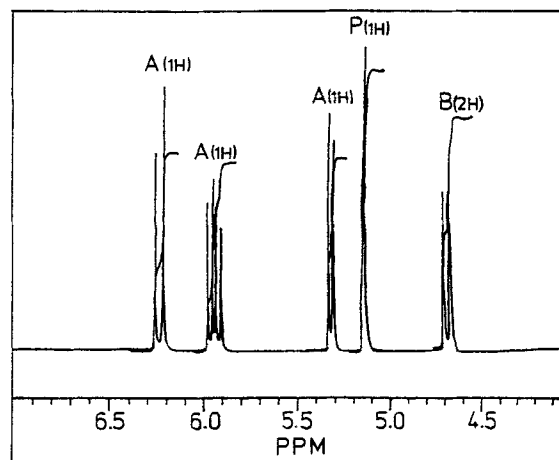


Figure 1. 1H NMR of the reaction mixture in C_6D_6 in the range δ 4.0–7.0 used to monitor the kinetics

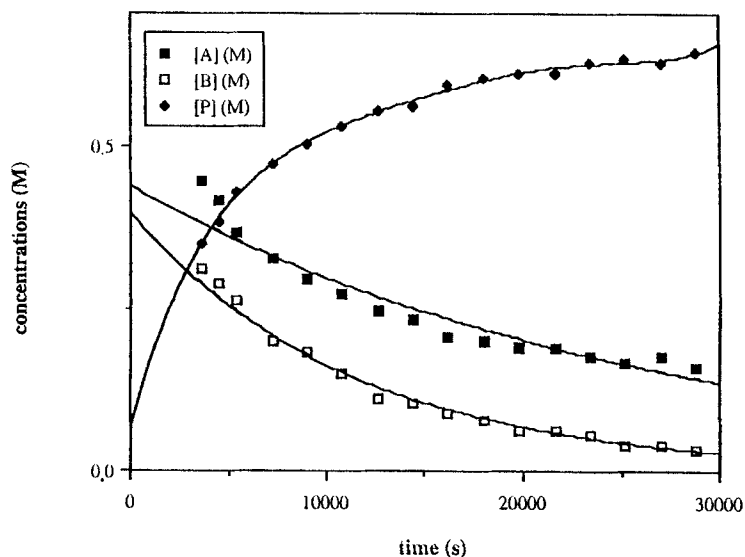


Figure 2. Representative plot of the time evolution of the concentrations of the reactants and the adduct as determined by NMR

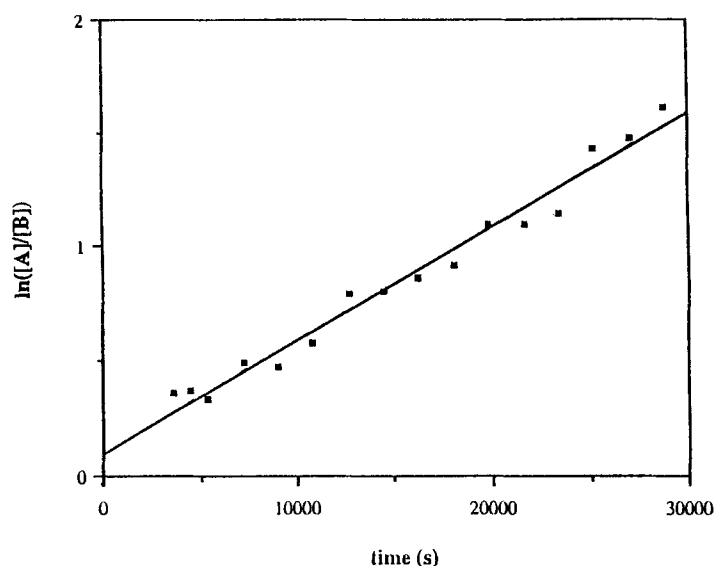


Figure 3. Linear regression of the data to first-order kinetics with respect to each of the reactants

Table 1. Kinetic results in benzene-*d*₆. The *k_a* are the rate constants for disappearance of the reactants

Run	A + B	$\ln [A]/[B] = f(t)$	$[A_0]/[B_0]$	$[A_0]$ (M)	$[B_0]$ (M)	$k(10^{-4} \text{ l mol}^{-1} \text{ s}^{-1})$	$k_d(A)(10^{-4} \text{ s}^{-1})$	$k_d(B)(10^{-4} \text{ s}^{-1})$
1	1 + 1	$0.1294 + 4.638 \times 10^{-5}t$	1.138	1.25	1.098	3.0 ± 0.25	0.39 ± 0.05	0.85 ± 0.05
2	2 + 1	$0.8075 + 2.390 \times 10^{-4}t$	2.242	2.50	1.115	1.7 ± 0.06	^a	2.7 ± 0.1
3	1 + 2	$-0.3500 - 3.723 \times 10^{-5}t$	0.705	1.25	1.774	0.7 ± 0.08	0.95 ± 0.05	^a

^a The disappearance of the reactants is not exponential when they are in excess.

complex. The *a priori* difficulty is that methyl acrylate, the ene adduct and the other components (e.g. β -pinene undergoing Lewis acid-catalysed polymerization), all compete for the Lewis acid. Hence, meaningful kinetic studies are difficult. A necessary premise, unfulfilled in earlier studies,⁶ is the determination of the experimental order for the reaction. Examination of the proton magnetic resonance spectrum for mixtures of the reactants in benzene-*d*₆ shows that a rather narrow spectral window displays sharp resonances (Figure 1), which are very convenient for following the advancement of the reaction. Accordingly, we opted to monitor kinetics by NMR, even though such a procedure is not very accurate – concentrations are determined through integrated intensities only to $ca \pm 2\%$.

The two reactants, methyl acrylate (**A**) and β -pinene (**B**), show concentrations that decay exponentially with time (Figure 2). Postulating that the rate law is of order two, integration gives:

$$\ln \frac{[A]}{[B]} = \ln \frac{[A_0]}{[B_0]} - ([B_0] - [A_0])kt \quad (1)$$

Measurement of $\ln[A]/[B]$ versus time shows (Figure 3) that the rate law conforms with the expectation of first order in each of the reactants. However, one peculiarity should be noted – the apparent rate constant is slightly greater if the β -pinene rather than the acrylate concentration is monitored. This feature can be noted in Figure 2. The straight lines in Figure 3-type plots provide the results in Table 1, including the *effective* $[A_0]$ and $[B_0]$ concentrations at time $t = 0$, assuming that methyl acrylate does not undergo secondary reaction. The instant depletion in β -pinene as soon as it comes into contact with the catalyst is presumably due to polymerization. This explains why the concentration $[B_0]$ extrapolated back to the initial time (Figure 3) is significantly less than the original analytical concentration $[B]$.

Solvent effects

Gas chromatography (GC) is an alternative means for following the reaction kinetics. It provides values more precise than NMR, in good qualitative agreement with the NMR results. Using an internal standard, the

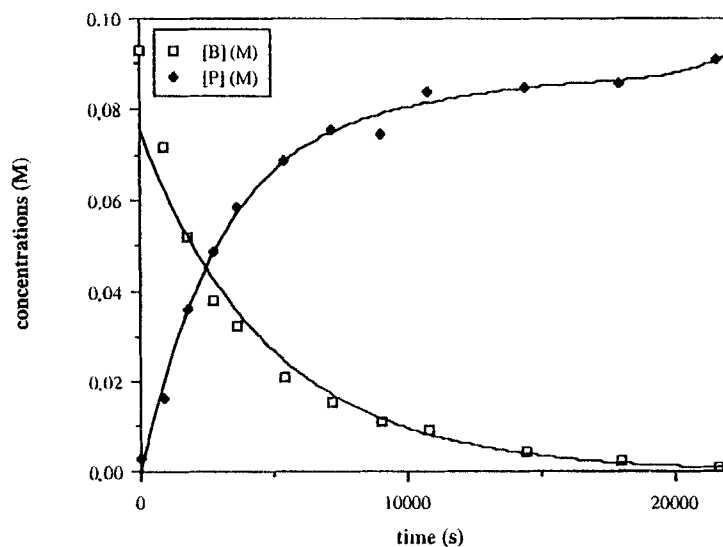
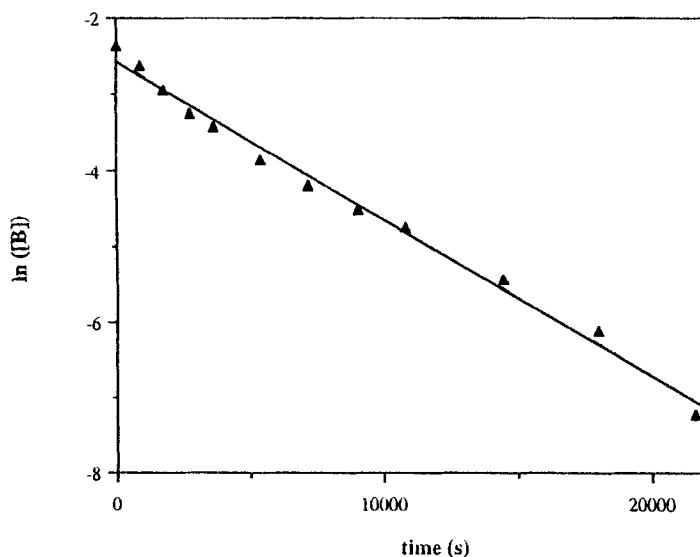


Figure 4. Same as Figure 2 as observed by GC (see text)

disappearance of the bicyclic olefin and the appearance of the adduct is monitored (with the column used the retention time of acrylate is such as to merge its peak with those of the solvents chosen). A typical plot of such results is shown (Figure 4). Because of the difference in the concentrations the rate constants do not match those from the NMR study. We could measure the rate constant for disappearance of β -pinene as a function of the nature of the solvent or binary solvent mixture. One of the resulting plots is

shown (Figure 5). These rate constants appear in Figure 6 as a function of the dielectric constants ϵ for the solvents used. Clearly there is a correlation. One does not need to have recourse to a more elaborate function. With one obvious discrepancy (that of 1,2,4-trichlorobenzene), the rate constants depend linearly on the dielectric constant ϵ^8 (Figure 6).

As in many other experimental situations, the bulk dielectric constant is too crude a parameter. More than the dielectric constant of the solvent has to be

Figure 5. Exponential decay of the β -pinene concentration with time as monitored by GC

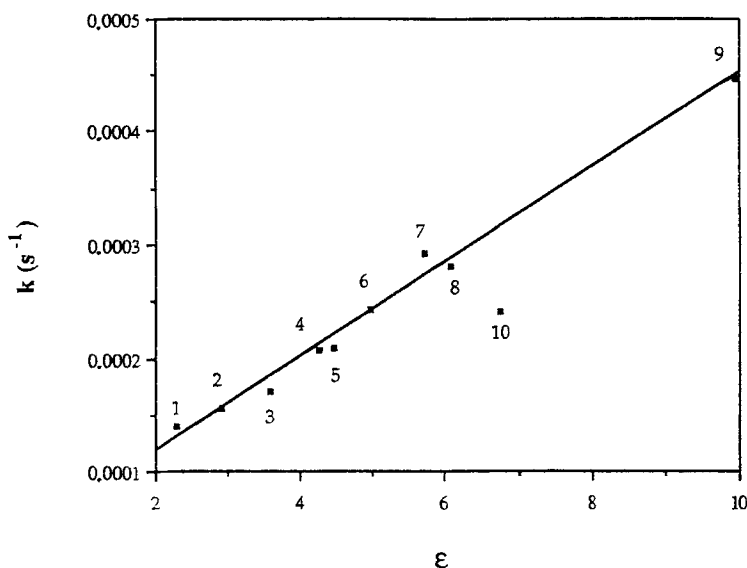


Figure 6. Solvent effects (bulk dielectric constant ϵ) on the rate constant. The reaction is accelerated by more polar solvents. (1) benzene, (2) benzene: chlorobenzene, 80:20, (3) benzene: chlorobenzene, 60:40; (4) benzene: chlorobenzene 40:60; (5) *o*-chlorobenzene; (6) benzene: chlorobenzene 20:80; (7) chlorobenzene; (8) *p*-chlorobenzene; (9) *o*-dichlorobenzene, (10) 1,2,4-trichlorobenzene (ϵ of mixtures determined by D. Decroocq⁸)

considered. Specific effects can be expected and do indeed occur. Dichloromethane has a dielectric constant of 9.08, but, unlike benzene, does not form a weak complex with AlCl_3 ⁹ so that the reaction, and the competing polymerization of the alkene, are faster in dichloromethane (see below). The increase in rate with solvent change, as measured empirically by the dielectric constant, may also be argued to result from decreased basicity of the solvent with introduction of chlorine atoms, which facilitates binding of the Lewis acid to the acrylate (since it is less tied-up by solvent molecules). However, the 1,2,4-trichlorobenzene result does not agree with such a picture.

All these reactions in the various solvents of Figure 6 have similar high selectivities (75–80%) in the ene product. These values for selectivity, it should be noted, pertain to the reactions with a molar ratio of methyl acrylate to β -pinene of 1:2, i.e. to the study of solvent effects on rates. Such a result is independent, thus, of those listed in Table 1. The competing side-reactions are predominantly the oligomerization of β -pinene, already alluded to; this is also the likely cause for the small discrepancy in the rates of disappearance of the two reactants.

DISCUSSION

Snider and Ron^{6a} have measured the secondary deuterium isotope effects,⁷ both intra- and inter-molecular, in the ene additions between methylene-

cyclohexane and 2,3-dimethyl-but-2-ene, on the one hand, and methyl propiolate, diethyl oxomalonate and formaldehyde, on the other. These reactions were catalysed by Lewis acids.^{6a} They reported a mechanism neither concerted nor uniform with these different reaction partners. They proposed that the rate-determining step, depending on the reaction partners, was formation of (a) a three-membered ring devoid of the rigidity characteristic of epoxides or other three-membered rings, (b) a pair of zwitterions in fast equilibrium or (c) a π complex between the olefin and the enophile–Lewis acid complex.^{6a}

Song^{6b} and Beak have made the same kind of studies on carbonyl enophiles, to investigate the mechanism of ene reactions catalysed or not by Lewis acids. They concluded that the variations of mechanism for ene reactions can be analysed in terms of competitive partitioning of a geometrically defined reaction intermediate (dissociation to starting material, product formation and equilibration between its different isomers). Variations in these steps can occur with changes in enophile, catalyst or substrate.

Our results, with solvent effects ranging over a factor of 3 (Figure 6), are consistent with the proposal of a transition state having zwitterionic character as depicted in these two detailed studies.⁶ This transition state would be followed by the neutralization of both charges with the attendant hydrogen shifts; unfortunately the sequence of events cannot yet be described more precisely. The solvent effects measured in this

study are reminiscent of those in Diels–Alder reaction. For instance, a study by Jung and Gervay¹⁰ has demonstrated intervention of a strong Coulombic component in the cycloaddition of a fumaric-type diester to a furan.

Another feature of our results is the rather surprising changes in the rate constant (Table 1). In the search for an explanation, we wondered if the reaction might be endowed with a radical character. Accordingly, we ran the identical methyl acrylate– β -pinene addition in a 1:1 benzene:bromotrichloromethane mixture; so that transient free radicals present would be trapped by bromination.¹¹ This experiment, just like the reaction run in methylene chloride,¹² gave numerous side-reactions of isomerization and oligomerization of β -pinene and the ene adduct was obtained in medium yield only. However, an NMR spectrum of the reaction mixture failed to show any brominated product. Hence, one may rule out a radical character for the reaction.

The observed rate constant k decreases markedly as soon as the stoichiometry of the reactants deviates from 1:1 (Table 1). We do not have a convincing explanation for these effects. One can rule out the effect of the basicity of the ene adduct. If it is a stronger Lewis base than methyl acrylate, the aluminum chloride will selectively complex to it, resulting in a decrease in rate after 10% reaction – this was not observed. A second explanation would be coexistence of an uncatalysed reaction with the catalysed one. The uncatalysed component would stem from inactivation of the aluminium chloride Lewis acid at the catalytic level used (0.1 equivalent) by attachment to either or both reaction partners. If this were the case, one would expect the rate constant to drop further when methyl acrylate is in excess, contrary to the observations (Table 1).

Another factor that might explain the strange concentration behaviour is if the *local* concentration in the reactants differed from the *mean* concentrations. Such a phenomenon is conceivable if for instance dipole–dipole interactions led to clustering of the highly polar methyl acrylate solute within the low dielectric benzene solvent. Such self-association would decrease the effective concentration of the enophile, relative to its actual, analytic concentration. Thus the apparent rate constant would be lowered.

A fourth possible explanation for the marked changes in the rate ‘constant’ is that β -pinene is very much prone to oligomerization. This polymerization of the olefin is found experimentally to be highly depen-

dent on the monomer concentration. It would likewise deplete the reaction mixture in enophile, thus again decreasing the apparent rate constant for the ene reaction. We believe this factor to be a likely cause for the observations.

A last possible explanation is that of a switch in the reaction mechanism. We might be dealing with a phenomenon similar to that observed by Mayr and Pock¹³ in the Lewis acid-catalysed addition of diarylcarbenium ions to conjugated olefins: in competition experiments, their relative rate constant in one case increased by one order of magnitude when the ratio of the trapping olefins was decreased by a factor 15.

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