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THE ROLE OF HIGH PRESSURE METHODS IN ORGANIC CHEMISTRY

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CONTENTS

It is not the purpose of this article to review in detail the many areas of chemistry which have been investigated at elevated pressures – there are many excellent reviews on this topic already in print(1-5) – but rather to give a critical appraisal of those areas where high pressure methodology is likely to remain a valuable or even necessary tool for research and even to become a technique for industrial production.

By high pressures we mean the region between 1 and 20 kbar (0.1 – 2 MPa) and mainly in liquid systems in which pressure is actively applied in order to influence a reaction rate and not merely to contain liquids above their normal boiling points. Two objectives for this type of work may be discriminated, the measurement of the pressure coefficient of a reaction rate (usually in the range 0-2 kbar), in order to obtain mechanistic information, and secondly, the use of much higher pressures (3-20 kbar) to force difficult reactions for preparative purposes.

1. The Physical Basis of Pressure Effects on Chemical Reactions

The chemical potential,μ_i,and partial molar volume,$\bar{V}$, of a solute are related by the
expression (1)

$$\partial \mu_i / \partial p = \triangle \bar{V}_i \qquad\qquad 1$$

and consequently for the equilibrium; A + B $\rightleftharpoons$ C + D:

$$\triangle \bar{V} = \Sigma \bar{V}_{prod} - \Sigma \bar{V}_{rgts} = -RT\ \partial \ln K/\partial p \qquad\qquad 2$$

where $\triangle \bar{V}$ is the difference in partial molar volumes between products and reagents, i.e.
the volume change for the conversion of reagents into products in dilute solution. This
simply states that an equilibrium (chemical or otherwise) responds to pressure by a change
in volume.

Using the transition state approximation of Evans and Polanyi (6) which permits equilibrium
formalism to be applied to rate processes (and writing V for $\bar{V}$), we can arrive at the
analogous expression,3:

$$V^* - \Sigma V_{rgts} = -\triangle V^* = -RT\ \partial \ln k/\partial p \qquad\qquad 3$$

in which $\triangle V^*$ is the volume of activation, the volume change on converting reagents into the
transition state. It is this latter quantity which characterises the rate behaviour of a
reaction under conditions of applied pressure. In fact, since the partial molar volumes of
reagents may be individually measured from the densities of their solutions, it is possible
to evaluate that of the transition state, V^* , one of its few absolute properties to be
accessible. The relationship expressed in eq.2 is subject to checking since $\triangle V$ may be
obtained by three independent methods. First from eq.2 by the measurement of the effect of
pressure on K, second by the application of dilatometry to the reaction and thirdly by the
separate measurement and algebraic summation of partial molar volumes of reagents and
products. That these approaches agree reasonably well lends credibility to the results
obtained from pressure experiments.

A plot of ln k against p according to eq.2 does not give a straight line but invariably
curves towards the pressure axis owing to differences in compressibility between reagents
and transition state, Fig.1A. The listed values of activation volumes are normally made at
the intercept p->0 but predictions of rates at elevated pressures based upon a value of $\triangle V^*$
may therefore be considerably in error, Fig.1B.

There are numerous analytical functions, the simplest being a quadratic, to express rate

behaviour over a wider pressure range which are chosen to give a best fit to the data, e.g. eq.4

$$\ln k = A + Bp + Cp^2 \; ; \quad \text{whence} \quad \triangle V^* = BRT \qquad \qquad 4$$

2. Mechanistic Information from Volumes of Activation

The volume occupied by a solute molecule in solution and expressed by the measureable partial molar volume, is a complex quantity and comprises several components. This is apparent from the fact that values of V for certain ionic solutes can actually be negative,
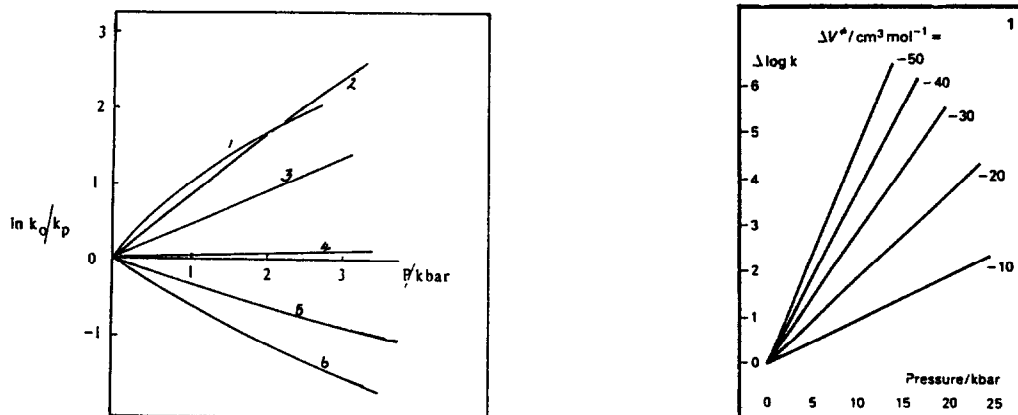

Fig 1A, Typical rate-pressure plots· (1) dimerization of cyclopentadiene, (2) nitration of benzene, (3) nitration of toluene, 0°,(4) hydrolysis of s-trioxan, (5) rearrangement of N-chloroacetanilide, (6) hydrolysis of $Co(NH_3)_5OSO_3^+$ by OH^-.
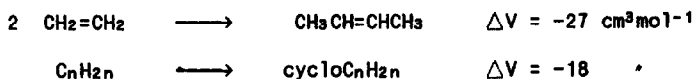
Fig.1B; The relationship between maximum rate acceleration and pressure for five different values of the activation volume, $\triangle V^*$

Table 1. Many workers differentiate three components of V (7):

$$V = V_0 + V_e + V_v \qquad \qquad 5$$

where V_0 is its 'hard-sphere' or intrinsic volume (determined by van der Waals radii of the atoms) and is amenable to computation by additivity rules of high precision, V_e is the volume change due to solvation (electrostrictive volume) and V_v the 'void volume', that concerned with intermolecular space and occupied by the molecule during the course of thermal vibration of the molecule as a whole (its 'Brownian motion'). Additivity rules may be used with reasonable precision within certain series of compounds to compute V (8) .If

two neutral molecules come together to form a bond (in the absence of ionic charge formation) a reduction in the net hard sphere volume occurs and a reduction in the void volume can also be expected since the two fragments no longer have independent thermal motion. Association of molecules in general and also cyclisation,is accompanied by a reduction in volume and is favoured by pressure. Conversely, fission of a neutral molecule into neutral fragments is associated with an increase in volume and is resisted by pressure. This can be illustrated by the volume changes accompanying the following hypothetical reactions (8);

$$2 \quad CH_2=CH_2 \quad \longrightarrow \quad CH_3CH=CHCH_3 \quad \triangle V = -27 \ cm^3mol^{-1}$$

$$C_nH_{2n} \quad \longleftrightarrow \quad cycloC_nH_{2n} \quad \triangle V = -18 \quad .$$

The same principles hold when solvation, a loose association between solvent molecules and charged or dipolar centres is present . The accompanying reduction in volume , $\triangle V_e$ ('electrostriction') can be very large and is solvent- and temperature-dependent. For an ion of charge,q, and radius,r, it is related to the dielectric constant of the solvent,D, by the Drude-Nernst equation, eq.6 :

$$V_e \ = \ \frac{Nq^2}{2rD} \ \frac{\partial \ln D}{\partial p} \qquad\qquad 6$$

and an analogous expression can be deduced for a dipolar solute. The q^2 term points to a strongly increasing volume reduction with charge as can be seen from partial molar volumes of individual ions, Table 1.

Table 1

Partial Molar Volumes of Some Ions, V/cm³mol⁻¹ (4)

Li^+	−6.18	OH^-	−9.34	OAc^-	35.2
K^+	3.7	Cl^-	12.5	ClO_4^-	38.8
Ca^{++}	−23.1	I^-	30.9	$SO_4^=$	8.7
Al^{+++}	−47.5	OPh^-	63.4	AsO_4^{3-}	−20.9

Partial Molar Volumes of a Highly Dipolar Molecule, Diphenylsydnone

solvent	V/cm³mol⁻¹	solvent	V/cm³mol⁻¹
acetone	111	nitromethane	123
ethyl acetate	116	methanol	119
cyclohexanone	120	dimethylformamide	125
benzonitrile	120	acetonitrile	121

The appearance of D in the denominator of eq.5 means that V_θ is greatest in solvents of low dielectric constant. This apparent anomaly is a reflection of the less rapid falloff of electric field with distance from the ion in a solvent of low dielectric constant than in one of high. In hexane, for example, although individual solvent molecules are affected by the electric field of the ion less strongly than are ethanol molecules, the attractive force extends to a greater volume of the surrounding medium. While it is not easy to measure ionic volumes in organic solvents, values are given in Table 1 for a very dipolar solute, phenylsydnone, which show a marked solvent dependence but no clear correspondence with recognized polarity scales (9).The effect of solvent on pressure effects may be seen from the values of $\triangle V^*$ for a typical ionogenic process such as the Menshutkin reaction which become increasingly more negative the less polar the solvent, Table 2.

<div align="center">Table 2</div>

<div align="center">**Effect of Solvent on Volumes of Activation for a Menshutkin Reaction** (4)</div>

<div align="center">Et₃N + EtI ---> Et₄N⁺ I⁻</div>

solvent	$\triangle V^*/cm^3 mol^{-1}$
aq.dioxan	-13
MeOH	-38
PhNO₂	-30
Me₂C=O	-54
PhH	-50
hexane	-58

It may be expected that the range of volume changes, $\triangle V^*$ and $\wedge V$ observed would run continuously from extremely positive to extremely negative values in the wide range of reactions and equilibria available to the experimenter and that these values contain mechanistic information. In practise the range for reactions lies between about +20 and -70 cm^3mol^{-1}, Fig.1A. For reactions it is commonly the practise to determine both $\triangle V^*$ and the volume of reaction, $\wedge V$. Together, these values map the 'volume profile' of the process akin to the more familiar 'free energy profile', Fig.2 . The degree of bond-making or -breaking and the extent of solvation change or charge development at the transition state in relation to that at the reaction- and product-state may then be assessed.
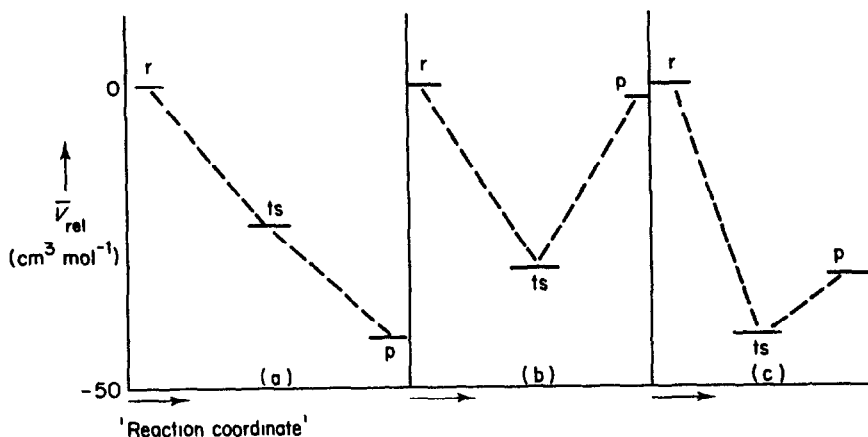
Fig.2;Volume Profiles for: a, Menshutkin reaction,b, aliphatic

electrophilic displacement; c, Diels-Alder reaction

3 Techniques of High Pressure Kinetic Measurements

Many excellent reviews and designs of equipment have been published (12) and it is not the

place of this article to duplicate these. It is true to say that any physical measurements

which can be made under normal pressures can be carried out at high pressures. Techniques

well established for high pressure adaptation include spectroscopy of all types,

conductance, X-ray and neutron diffraction, stopped-flow, p-jump and T-jump methods, even

polarography and the glass electrode. Windows of single crystal sapphire can be used to

pressures in excess of 20 kbar and diamond (in the diamond anvil cell) to beyond 1 Mbar.

Steels are available which will contain bulk samples well above 20 kbar and materials such

as tungsten carbide are suitable for pressurisation of solids to 500+ kbar. All these

considerations, of course, depend on appropriate design of the equipment which is,

naturally, costly especially if exceptionally high pressures are to be used. However, no

more than ordinary workshop facilities are required for making equipment for use up to 2-3

kbar.

4 The Interpretation of Volumes of Activation

Three reviews of data (2,11) show that estimates of $\triangle V^*$ have been made on at least 2000

reactions of widely differing types so the pressure/rate characteristics of almost all

simple organic reactions have been established. However,the question may be asked, when is

it appropriate to use values of $\triangle V^*$ for mechanistic investigation   The following account

selects examples from which, in some cases, mechanistic inferences may be confidently drawn

and others for which this is a difficult matter. In all cases the question posed is the

differentiation between two or more mechanistic possibilities and the experimenter is on

the soundest ground if expectations in the values of $\triangle V^*$ for two mechanisms would be of

opposite sign rather than merely of different magnitude.

4.1. The Diels-Alder Reaction and other Cycloadditions.

A consideration of pressure effects on various types of cycloaddition reaction will

illustrate the ambiguity of interpretation which sometimes arises and the additional

information which may afford clarification of mechanism.

Volumes of activation for some 150 Diels-Alder reactions studied - a favourite reaction

for high pressure work - lie in the range -35 +/- 5 cm^{3}mol^{-1} and are similar to volumes of

reaction, Table 3. This is consistent with a transition state which has much the same

volume properties as the product cyclohexene and could be interpreted as consistent with a

single-step cycloaddition with a tight transition state and well-developed bonding or, in

principle, a two-step ionic reaction, some electrostriction contributing to the value due

to the formation of one bond. The latter interpretation can be ruled out on the grounds

that, in many cases $\wedge V^*$ is almost independent of solvent as are rates of reaction. Some

diene reactions ,however, are somewhat susceptible to solvent change, that between maleic

anhydride and 1-methoxybutadiene must be associated with an especially polar transition

state, values of $\triangle V^*$ varying from -32 in acetonitrile to -54 in dimethyl carbonate while

volumes of activation for isoprene and maleic anhydride in the same solvents are -37 and -

39 cm^{3}mol^{-1}, respectively . In many though not all cases, the volume of activation is

actually more negative than the volume of reaction ($\theta > 1$ where $\theta = \triangle V^*/\triangle V$) and this

effect has been confirmed by the finding of a retro-Diels-Alder reaction with a negative

volume of activation (21). Values of $\theta < 1$ denote a transition state more compact than

product and this is usually inferred to be due to the "secondary orbital interactions"

originally proposed by Woodward,(22). A similar range of values is observed both for

"normal" and "inverse demand" examples; the latter, mainly cycloadditions of perchloro-

cyclopentadiene to alkenes measured by Jenner (23), tend to have $\theta < 1$. Intramolecular

cycloadditions would be expected to have a somewhat smaller volume change than

intermolecular examples since less translational freedom is lost This was found to be the

case for the substituted furan, example 5, Table 3 (20).

Other types of cycloadditions have been examined, Table 4 but large negative volumes of

activation are the rule. Ene reactions of dimethyl mesoxalate and alkenes (which occur at

relatively low temperature for such processes) have $\triangle V^* = -27$ to -31 cm^{3}mol^{-1} (24) and a

rather wider range of values (-33 to -45) is observed for (2+2) cycloadditions, for example

Table 3

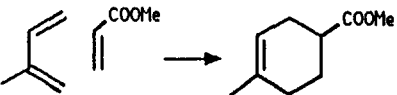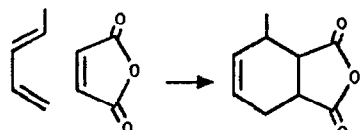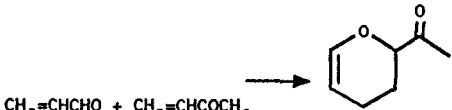Volumes of Activation and Reaction for Diels-Alder
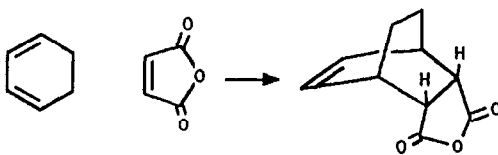
and other Cycloadditions
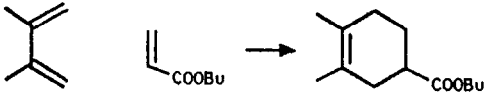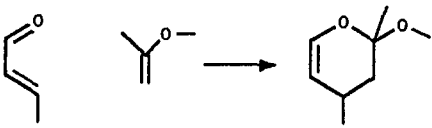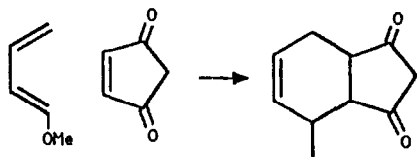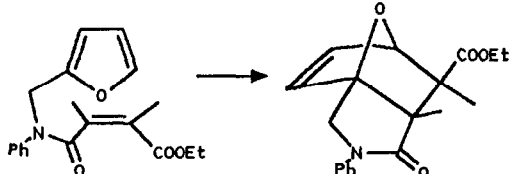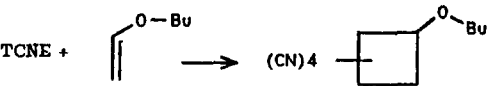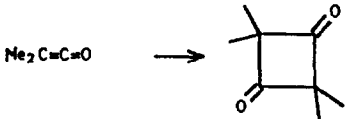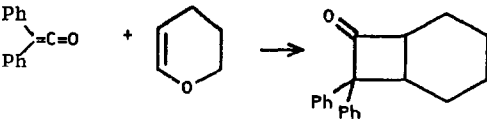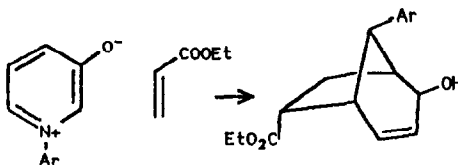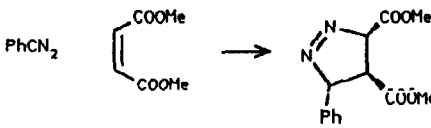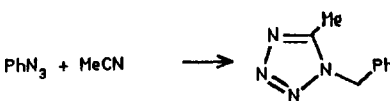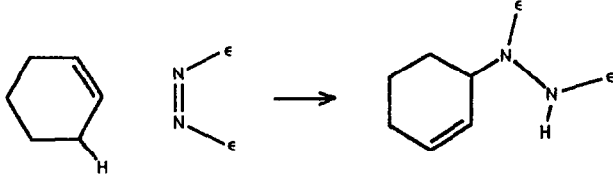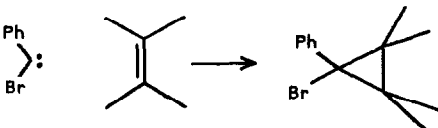
		ΔV^*	ΔV	Ref
1		(BuBr) -30.8	-36.9	12
2		(MeCN) -33 5 (CCl$_4$) -37 6 (Pr$^i_2$O) -40.7	-31.9	13
3	CH$_2$=CHCHO + CH$_2$=CHCOCH$_3$	(C$_7$H$_{16}$) -36.5	-31.9	14
4		-37	-30	15
5		-28.7		16
6		-43		17
7		-37.0	-36 4	18
8		MeCN -32 0 MeNO$_2$ -43 0 CH$_2$(OMe)$_2$ -53 BuCl -45.4 CH$_2$ClCH$_2$Cl -44	-32.4 -28.2 -32 2 -35 5 -30.4	19
9		-29	-31	20

Table 4

Volumes of Activation and Reaction for Miscellaneous Cycloadditions

#	Reaction	Solvent	$\Delta V^{\neq}$	ΔV
1	TCNE + vinyl butyl ether → (CN)4 cyclobutane	CH_2Cl_2	-34	-29
		MeCN	-23	
		CCl_4	-44	
2	$Me_2C=C=O$ → dimethyl cyclobutanedione			-30
3	$Ph_2C=C=O$ + dihydropyran → bicyclic ketone			-43
4	N-Ar pyridinium-3-olate + acrylate → bridged product		-36	-37
5	$PhCN_2$ + dimethyl maleate → pyrazoline		-23	-24
6	PhN_3 + MeCN → tetrazole			-20
7	cyclohexene + azo compound → hydrazide		-25	-34
8	Ph,Br carbene + alkene → cyclopropane			-13

those between tetracyanoethylene and vinyl ethers . Here, other evidence notably high

sensitivity of both rates and activation volumes to solvent point to a two-step dipolar

mechanism. In fact Kelm has estimated the individual values of $\triangle V_v$ and $\triangle V_\bullet$ as -10 and -35

cm^3mol^{-1}, (25) respectively for this reaction . Clearly caution must be enjoined when using

volumes of activation as criteria for concertedness. Much smaller volumes of activation are

reported for (2+2) cycloadditions of carbenes to alkenes (27) which fall within the range -

12 to -20 cm^3mol^{-1}. This presumably reflects the early transition states expected for such

reactive species.

Cycloadditions between alkenes and such 1,3-dipolar reagents as diphenyldiazomethane or

azido compounds, on the other hand,e.g 5 and 6, Table 4, have somewhat low volumes of

activation , $\triangle V^* =$ -20 to - 30 cm^3mol^{-1} (26). It might be attractive to ascribe this to

the decrease in solvation of the dipolar reagent which accompanies cycloaddition but

against this interpretation is the value for cycloaddition to the pyridinium betaine,entry

4 ,Table 4 , which should show an even greater effect of this type but has $\triangle V^* = -36$ (30) .

The likely reason for the rather low volumes of activation for dipolar cycloadditions is

that of an earlier transition state and less completely formed bonding than in the Diels-

Alder reaction.

The complementary effects of bond formation and fission and of electrostriction frequently

lead to difficulties in interpretation and the necessity to invoke all available evidence

to arrive at a satisfactory mechanism. Among retro-cycloadditions, of which rather few have

been examined under pressure, the fission of the β-lactone,3 , provides an interesting

example.

Three possible mechanisms might be considered; (a) concerted retro-(2+2) which would be

symmetry forbidden, (b) two-step diradical or (c) two-step dipolar. Both (a) and (b) would
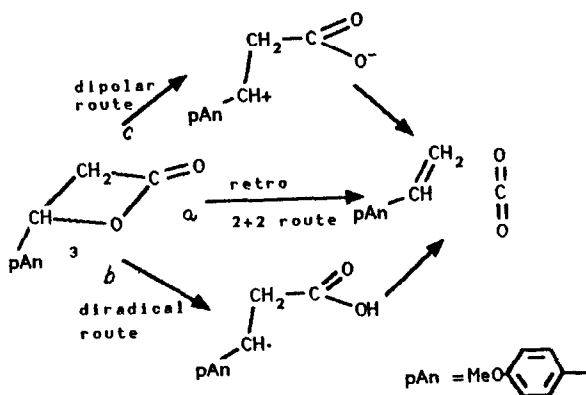
be associated with positive volumes of activation ascribable to neutral bond breaking but (c) alone could account for the experimental result found to be $\Delta V^* = -28$ cm^{3}mol^{-1} (31) and can only be due to an ionic transition state. Of course, this compound is admirably set up to be able to stabilise both positive and negative charge so one would not expect the same pressure effect for all lactone decompositions.
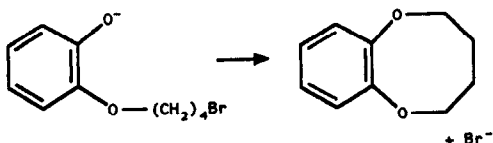

4.2 Solvolytic Reactions.

The range of mechanisms available for solvolytic reactions, one of the most highly documented in organic chemistry, run from pure S$_N$2 to the classical S$_N$1 via a whole range of possible mixed and merged mechanisms and ion-pair intermediates (32). Mechanism is highly sensitive to substrate structure and to the solvent. Table 5 includes representative values of ΔV^* from around 100 data pertaining to neutral substrates from which there is seen no clear distinction between mechanistic types.

The reason is that, while the intrinsic volume change for the associative S$_N$2 process should be negative and that for the dissociative S$_N$1 positive, transition states for both are highly dipolar and charge pair generation dominates the pressure effect so that bond making and breaking becomes only a minor contribution. Furthermore, solvation effects are very complex and desolvation of ions is believed to be an important initial stage in reactions of ionic nucleophiles. This has the consequence of making volumes of activation vary widely with both solvent and temperature; values generally become more negative as the temperature is raised and solvent becomes less polar. Even the counterion plays a part. Displacements by Cl$^-$ from LiCl are accompanied by a rather low value of ΔV^* compared with I$^-$ from KI since the former is extensively ion-paired (40).Whalley has demonstrated an interesting way in which to remove the electrostrictive effect, namely by measuring the volume of activation at extremely high pressures (up to 80 kbar) at which liquid compressibilities are very small The results are dramatic; the prototype S$_N$2 reaction of methyl iodide with glycerol continues to show a negative value of ΔV^* while that for tert-butyl chloride is negative at 'low' pressures but becomes positive above 20 kbar in keeping with a dissociative mechanism (43). The alcoholysis of isopropyl bromide behaves similarly, the inflection point being at 40 kbar ,Fig.3. One can presumably exclude the possibility that the high pressures have engendered a change in mechanism since this would surely be towards a process which increased rather than decreased the rate . Extreme high pressure kinetic measurements to isolate 'incompressible' contributions to ΔV^* look to be a very promising technique but probably limited to conductance measurements for technical reasons.

Table 5

Volumes of Activation for Some Aliphatic Substitutions

	solvent,temp/°C	$\Delta V^*/cm^3mol^{-1}$	ref
solvolyses			
$PhCH_2Cl + H_2O \longrightarrow PhCH_2OH + HCl$	water, 0	+5	32
	10	-10	
	40	-8.9	
	aqueous-organic	-10 to -20	
$isoPrBr + H_2O \longrightarrow isoPrOH + HBr$	water, 25	-8.8	33
$tertBuCl + H_2O \longrightarrow tertBuOH + HCl$	aq. acetone, 25	-16	34
	MeOH, 30	-25	35
$PhCMe_2CCl + H_2O \longrightarrow PhCMe_2OH + HCl$	aq. acetone, 25	-12	36
(m- and p-X-) "		-10 to -20	
$isoPrOTos + HCOOH \longrightarrow isoPrOCOH + TosOH$	HCOOH	-14.7	37
" + MeOH $\longrightarrow$ isoPrOMe + TosOH	MeOH	-18.9	
$2-AdONos + H_2O \longrightarrow 2-AdOH$	aq. acetone	-20.6	38
2-endonorbornyl-ONos + $H_2O \longrightarrow$ 2-endonorbornylOH	"	-21.0	39
S$_N$2 Displacements and Quaternizations			
$PrCl + K^+I^- \longrightarrow PrI + K^+Cl^-$	acetone, 30	-6	40
$PrI + Li^+Cl^- \longrightarrow PrCl + Li^+I^-$	"	-22	
$tertBuS^+Me_2 + H_2O \longrightarrow tertBuOH + Me_2S$	water, 30	+9.9	41
$Et_3N + EtI \longrightarrow Et_4N^+ I^-$	see Table		
pyridine + EtI $\longrightarrow$ Etpyridinium iodide	benzene, 40	-34	42
pyridine + MeI $\longrightarrow$ Mepyridinium iodide	acetone	-22	
2,6-ditertbutylpyridine + EtI	"	-50	
Intramolecular Displacements			
$HO(CH_2)_4Cl \longrightarrow$ tetrahydrofuran + HCl	H_2O, 40	-5.8	11
	MeOH, 40	-20	11

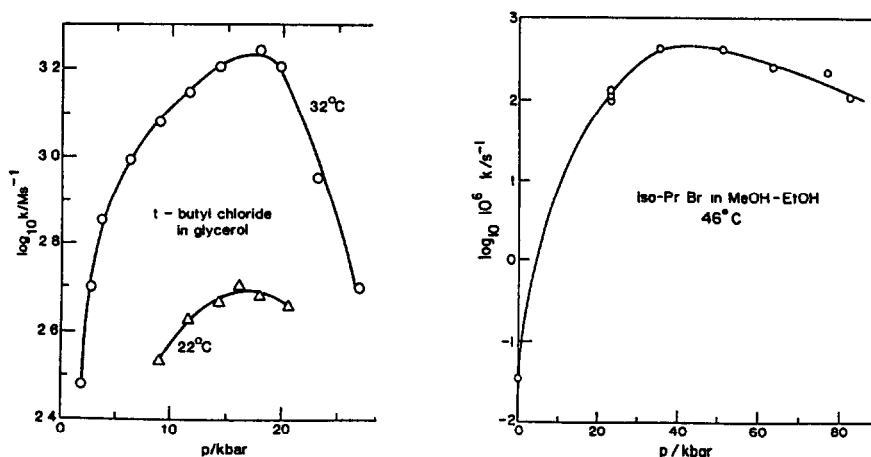
MeOH, 32   0

Fig.3: Rate-Pressure Plots for Some Solvolytic Reactions (43).

4.3 Ionogenic Displacements

In contrast to neutral S_N reactions, those involving the formation of ionic products are typically highly pressure sensitive.

One of the most fundamental is the dissociation of neutral acids or bases in water and other media. Aqueous equilibrium volumes of dissociation lie in the range -10 to -30 $cm^3 mol^{-1}$, Table 6, and are increasingly negative the higher the temperature.

Table 6

Volumes of Ionisation of Weak Acids and Bases in Water (4, 11)

acid	$\triangle V^* / cm^3 mol^{-1}$	acid	$\triangle V^* / cm^3 mol^{-1}$
water	-22.07	$CH_3 COOH$	-11.6
PhCOOH	-10.9	$(CH_2)(COOH)_2$	-12.8 (K_1)
PhOH (aq)	-28.4		-13.6 (K_2)
PhOH (in MeOH)	-39	$H_2 CO_3$	-27
$MeNH_3 +$	+2.4	$PhNH_3 +$	+4.3
base		base	
$MeNH_2$	-26.3	$Me_3 N$	-27
		$Et_3 N$ (in MeOH)	-48
$PhNH_2$	-26	pyridine	-27

Dissociation Volumes of Ion-Pairs

$NaSO_4^- \longrightarrow Na^+ + SO_4^=$	-5.4
$KI \longrightarrow K^+ + I^-$ (acetone)	-23
$CoBr_2 \longrightarrow Co^{++} + 2 Br^-$ (acetone)	-109

This means that dissociation will increase, pKₐ values decreasing by between about 0.2 and 0.4 units per kbar applied pressure at the p->0 limit. The effect of pressure on ionisation will be even greater in non-aqueous solvents though few data are available to support this. By contrast, charge-conserving proton transfer equilibria e.g.:

$$MeNH_3^+ \; + \; H_2O \; \longrightarrow \; MeNH_2 \; + \; H_3O^+ \; ; \; \triangle V^* = +2.4 \; cm^3 mol^{-1}$$

are little affected by pressure, and this type of process includes many acid-catalysed reactions in water. Clearly, we see here the dominating role of electrostriction in the volume changes observed. The dissociation of ion-pairs into free ions is also accompanied by an increase in solvation and a negative volume change especially in non-aqueous medium. Certain hydrogen transfers (proton ,hydride ion or hydrogen atom) are believed to partake of quantum mechanical tunnelling resulting in enhanced rates and abnormally high primary kinetic isotope effects. Pressure has been shown in numerous examples to cause the reduction of the isotope effect and reduce the tunnelling contribution presumably by increasing solvation and the effective mass of the hydrogen during transfer but this affords an additional criterion of tunnelling,Fig.4 (3,44).
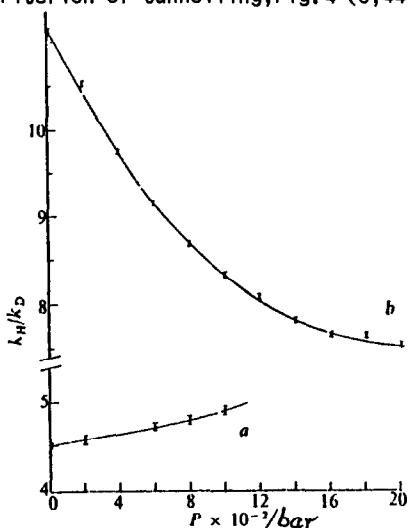

Fig 4   Effect of pressure on kinetic isotope effects.

(a) Diphenyldiazomethane and benzoic acid

(b) tunnelling reaction between leuco-crystal violet

and chloranil

Menshutkin reactions, the quaternization of tertiary amines, phosphines and sulphides have been thoroughly studied and volumes of activation found to be large and negative but

extremely variable, from -10 to as much as -60 cm^3mol^{-1}, Tables 2,5. These values must be considered the result of a negative contribution from $\triangle V_v^*$ for association between the reagents with a very variable transition state and also a major addition of a negative $\triangle V_e^*$ as shown by the strong dependence of the pressure effect on the solvent .

In general, the volumes of the transition states lie intermediate with volumes of reaction the value of θ giving information concerning the location of the transition state on the reaction coordinate. Displacements of this type with sterically hindered amines have higher activation energies and are less exothermic than those of less hindered examples and in consequence would be expected to have later transition states according to the Hammond postulate. Charges should therefore be more completely developed and transition states more 'product-like' and, in consequence, more solvated in sterically difficult reactions. This is born out by an examination of volumes of activation and values of θ for quaternisations of a series of 2- and 2,5- substituted pyridines which become increasingly negative with the size of the substituents (42). The table shows other examples of ionogenic reactions which have similar volumes of activation and for similar reasons.

The converse reaction, ion-neutralisation has been less studied. One would expect the release of electrostricted solvent to be the dominant feature and the positive value of $\triangle V_e$ to be offset somewhat by a smaller negative $\triangle V_v$ resulting from association. This interpretation holds for anionic S_N displacements of positive leaving groups such as ammonium or sulphonium ions, Table 5, (41) but insufficient data are available to judge whether an estimate of the position of the transition state could be made although the small magnitude of $\triangle V^*$ suggests an early transition state and little relaxation of solvation. What should be a simpler example of this type of reaction, the direct combination of cationic dyes such as crystal violet and malachite green with a wide variety of nucleophilic anions, in fact turns out to be more complex. These reactions actually show negative volumes of activation though positive volumes of reaction (45).

$$Ar_3C^+ \ + \ Nu:^- \ \longrightarrow \ Ar_3C-Nu \ : \ \triangle V^* = -4 \ to \ -15: \ \triangle V = +10 \ to \ +30$$
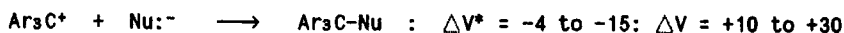
The reason for this surprising behaviour has not been definitely established but conformational equilibria involved in the activation process are possibly implicated. However, the high pressure studies on this system have uniquely highlighted unexpected details of behaviour. The importance of electrostriction as compared to bond formation or fission in determining overall volume changes is seen in the behaviour of τ-amino halides

which fragment on hydrolysis yet still show substantially negative volumes of activation (46).

e.g.   Me2N-CH2-CH2-CHMe-Cl $\longrightarrow$ Me2N$^+$=CH2 + CH2=CHMe + Cl$^-$; $\triangle$V* = -18

4.4 Carbonyl Additions and Displacements

Neutral additions and substitutions of carbonyl compounds such as ester hydrolysis and ketone additions, being associative, tend to be quite strongly accelerated by pressure though, in nonaqueous and mixed solvents, values of $\triangle$V* can be very variable and so are difficult to interpret, Table 7. Uncatalysed esterifications of carboxylic acids and hydrolyses of esters can have $\triangle$V* as large as -30 cm^{3}mol^{-1} but values are much smaller for acid-catalysed processes. This is because in the former case, the pre-equilibrium protonation is ionogenic while in the latter is charge conservative. In aqueous-organic mixed solvents, volumes of activation, presumably in parallel with entropies, vary in a complex and non-systematic manner with solvent composition. One mechanistic criterion afforded by pressure studies deserves mention, an example in which two competing mechanisms are characterised by volume changes of opposite sign (49). The common hydrolytic route for carboxylic esters (the B$_{Ac}$2 mechanism) is mildly accelerated by pressure, $\wedge$V* = -10 to -20 cm^{3}mol^{-1} and this is found to be the case for hydrolyses of m-hydroxy and p-methoxybenzoates. The unusual eliminative hydrolysis of esters (E1cb) which is the preferred route for esters such as p-hydroxybenzoates around pH 9, is characterised by a positive volume of activation since the slow step is the fragmentation, Fig.5 .
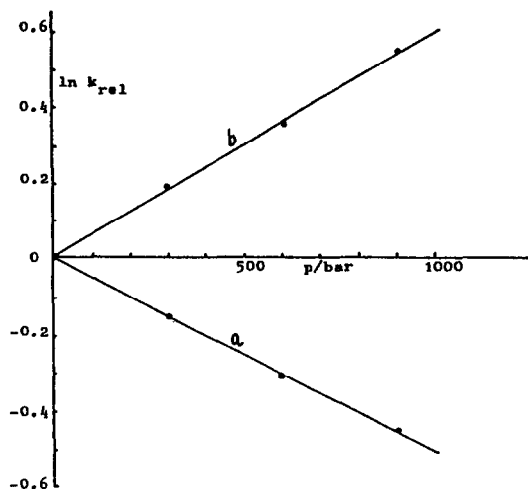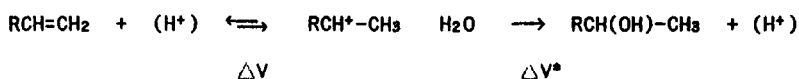

E1cb mechanism ΔV^* positive

B$_{Ac}$2 mechanism ; ΔV^* negative
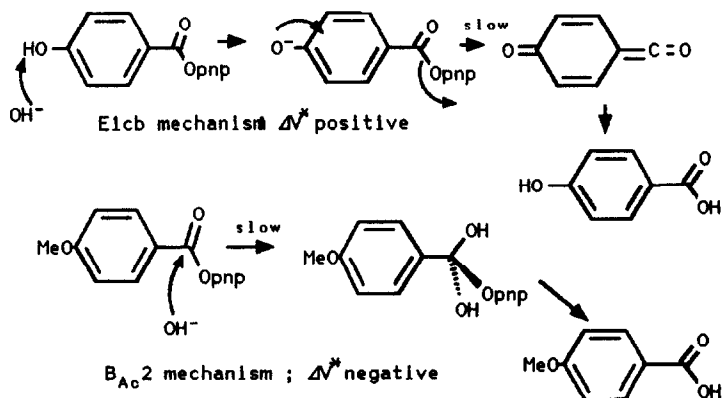
Fig 5: Rate-pressure profiles for the alkaline

hydrolysis of p-nitrophenyl esters of

(a) p-hydroxybenzoic (b) p-methoxybenzoic acids

4.5 Additions and Substitutions at π-Systems.

Electrophilic additions to alkenes would be expected to be accelerated by pressure and this
is observed in a moderate way in the case of acid-catalysed hydration (50). The mechanism
involves the intermediate carbocation and the volume of activation is the sum of volume
changes for the two steps;

$$RCH=CH_2 \ + \ (H^+) \ \rightleftharpoons \ RCH^+-CH_3 \quad H_2O \ \longrightarrow \ RCH(OH)-CH_3 \ + \ (H^+)$$

$$\Delta V \qquad\qquad\qquad \Delta V^*$$

$$\Delta V_{obs} = \ \Delta V + \Delta V^* \ = \ -15 \text{ to } -20 \text{ cm}^3\text{mol}^{-1}$$

These are both likely to be negative, the first since a π-bond which is rather bulky is
converted to a σ-bond and the second since bond formation is involved and no change in
charge. Michael additions, for example of thiols to α,β-unsaturated ketones, show a similar
pressure dependence;

$$\Delta V^* = -19 \text{ cm}^3\text{mol}^{-1}$$
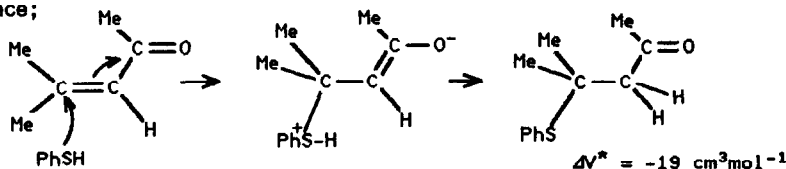
The considerable magnitude of ΔV^* reflects the dipolar transition state in this addition .
Aromatic compounds typically undergo substitution reactions via benzenium ion intermediates
whose formation is usually rate-determining. The rate of addition of a neutral electrophile
to an aromatic ring should be increased by pressure but few data are available since
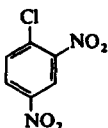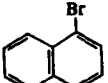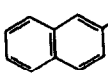kinetics are often complex and difficult to interpret. The apparent volumes of activation
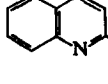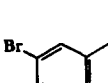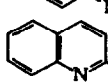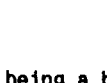
for nitration (nitric acid in acetic acid) under first and zero order conditions are around

-25 and -10 cm^{3}mol^{-1} respectively which gives information concerning the generation of NO$_2^+$

rather than on the substitution step (51). The modest pressure acceleration of a Friedel-

Crafts benzoylation ($\triangle V^* = -11$) is probably a measure of the addition of a charged

electrophile to the benzene ring (52). Nucleophilic displacements have been more

extensively examined and displacements of halide from activated aromatic molecules by

alkoxide have $\triangle V^*$ in the range -10 to -25 while displacements by amines, which are

ionogenic processes are even greater, $\triangle V^*$ from -20 to -60, Table 7 (54 - 56).

Vinyl polymerisations.

Several steps in radical polymerisation reactions consist of the addition of a radical to

the alkene monomer. These include initiation, propagation and chain transfers. Typically

each is accompanied by a reduction in volume associated with bond formation, Table 8.

Termination however is retarded by pressure, the volume of activation being related to that

for viscous flow of the monomer. Evidently, despite termination either by dimerisation or

Table 7

Volumes of Activation for Nucleophilic Aromatic Displacements

		Solvent	T (°C)	ΔV^* (cm^3 mol^{-1})
Cl NO$_2$ NO$_2$	nBuNH$_2$ t-BuNH$_2$	EtOH	35	-25 -35
Br	Piperidine	Piperidine 60%H$_2$O, Piperidine	188 188	-57 -39
	OMe$^-$	MeOH	174	-23
Br	Piperidine	Piperidine 60% aq. piperidine	189 186	-68 -44
	MeO$^-$	MeOH	174	-30
Br	Piperidine	Piperidine 60%H$_2$O Piperidine	27 0 22 43	-25 -23 -19 -20
	MeO$^-$	MeOH	0 50	-10 -15
Br	Piperidine	Piperidine 60%H$_2$O Piperidine	184 184	-69 -45
Cl	Piperidine	Piperidine 60%H$_2$O piperidine Cyclohexane	51 51 105	-33 -23 -41
	MeO$^-$	MeOH	60	-14

by disproportionation being a bimolecular associative process, the rate of this process

depends upon diffusion. Dissociation of initiator peroxides or azo compounds into radicals

is also inhibited by pressure as expected for a dissociative reaction.

Table 8 (57-60)

Volumes of Activation for Reactions Associated with Radical

Polymerisation components

initiator decomposition	$\Delta V^*/cm^3mol^{-1}$	chain transfer	$\Delta V^*/cm^3mol^{-1}$
tert.butyl perpivalate	+0.3	styrene with CCl_4	-19
di-tert.butyl peroxide	+13	vinyl acetate with CCl_4	-19
azoisobutyronitrile	+3.8	termination	
propagations		methyl methacrylate	+25
methyl methacrylate	-19	styrene	+13
vinyl acetate	-24	butyl acrylate	+21
styrene	-18	ethylene	+7
ethylene	-25		

Dimerisation ;	2 Ph$_3$C	0	2 triphenylimidazolyl	0

High pressures should therefore permit more facile polymerisation of difficult monomers and

also promote greater chain lengths. It is certainly true that many acrylates polymerise

spontaneously when subjected to pressure and this property may be an undesirable side

reaction in attempting to accomplish difficult Diels-Alder reactions with these as

dienophiles. The reaction between, for instance, α-pyrone and ethyl acrylate at 10 kbar

gives a poor yield of the adduct and mainly poly(ethyl acrylate) . At the same time it

seems that radical reactions may show additional complexity due to the importance of

diffusion rates. The one-bond homolysis of peroxides such as di-tert.butyl peroxide are

moderately large and positive (+ 12 to +20 cm^3mol^{-1}) whereas those homolyses which involve

simultaneous two-bond fission such as azo compounds and di-tert.butyl peroxypivatate , are

almost independent of pressure (0 to +4) . The reason appears to be that the former are

reversible within the solvent cage and the rate which is being measured is that for cage

escape. Homolytic bond fission is accompanied by a very small volume change indeed. This

is substantiated by volume changes for the dimerisation of stable radicals, essentially

zero.

$$\Delta V^* = +12$$

$$\Delta V^* = +1$$

DIMER

$$\Delta V^* \sim 0$$
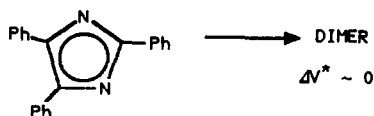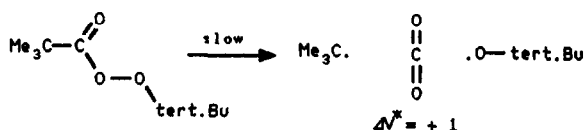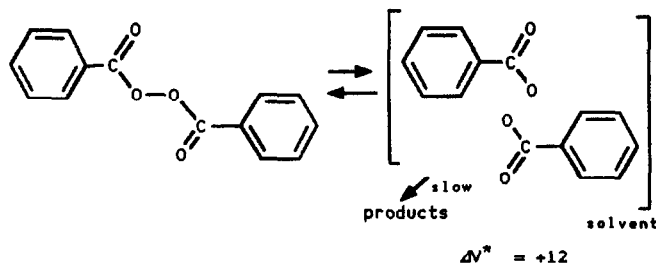
5 Synthesis at High Pressure (61)

The major application for high pressure technology in the laboratory is in synthesis, particularly in the organic field, and this is becoming a routine technique at the disposal of synthetic chemists. Naturally, the field of applications is limited to those reactions which show large, negative volumes of activation. The advantage which is usually sought is a large increase in rate which can make a reaction occur in a reasonable time or at a lower than normal temperature or even make it at all possible. Therefore an acceleration of at least 10^3-fold is required to justify the expense and inconvenience of high pressure methodology. This in turn points to reactions with $\triangle V^*$ at least as negative as > -30 cm^3mol^1 and pressures between 10-20 kbar may be used to achieve these ends. Pressures below 10 kbar will certainly suffice for reactions with very large volumes of activation but, because of the logarithmic nature of the relationship,1, raising the pressure has a rapidly increasing effect on rate. For instance, the yield of adduct from isoprene and menthyl fumarate rises from 69% at 4.5 kbar to 81% at 5.9 kbar and 100% at 7 kbar. To go above 20 kbar is not usually necessary for even very refractory reactions since, apart from technical considerations, solvent viscosities increase rapidly and limit rates by diffusion control. Indeed, it is necessary to choose solvents carefully since pressure will eventually cause crystallisation of many media provided thay have a freezing point which is not too low in temperature and a reduction in volume on freezing. If this happens, equipment may be damaged and reactions will not usually benefit from being conducted in the solid state. Some freezing pressures at 25° of common solvents are listed in Table 9.

Table 9

Freezing Pressures (kbar) for Common Solvents at 25°

cyclohexane	0.355	the following solvents do not
benzene	0.72	freeze <20 bar
chloroform	5.5	ethanol, methanol, hexane
carbon tetrachloride	1.46	dichloromethane, ether ,acetone
acetic acid	0.39	
dioxan	1.2	

The other application for the use of high pressure conditions may be to increase selectivity among alternative products; both regio- and stereo selectivities will change with pressure if there is a difference in activation volumes, $\triangle\triangle V^*$, between the different pathways. Preparative apparatus for containment of these very large forces, is necessarily rather bulky and needs to be designed and built by specialists but offers no great difficulties in operation by the chemist. Samples,for instance, may be handled in flexible containers of ptfe to isolate reactants from the vessel and the pressurising medium, usually a phthalate oil, and quantities on the scale of hundreds of grams may be pressurised. It should, however, be mentioned that pressurisation of large quantities of certain substances can be disastrous. Acrylic monomers may be induced to polymerise explosively on pressure being applied and some quaternisation reactions can proceed with violence leading to carbon and gaseous products. Where such undesirable effects are possible, slow pressurisation avoiding adiabatic heating is essential. Below are discussed some notable examples where high pressure techniques have proved essential.
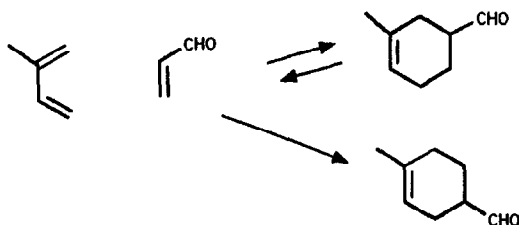
a. Diels-Alder Reactions

One of the earliest and best known high pressure synthesis is Dauben's method for cantharidine,(62) . Although it looks as if a Diels-Alder reaction using dimethylmaleic anhydride will provide a simple route, this fails even under high pressure. Dauben's solution was to use the sulphide derivative, high pressure to facilitate the reaction (although it can be carried out inefficiently at 1 bar) and a reduction-desulphurisation step to complete the synthesis.

This route compares very favourably with the more conventional but 30-odd-step synthesis of Stork (63). Table 10 lists several examples out of many Diels-Alder reactions for which high pressure methods provide the only satisfactory route to products.
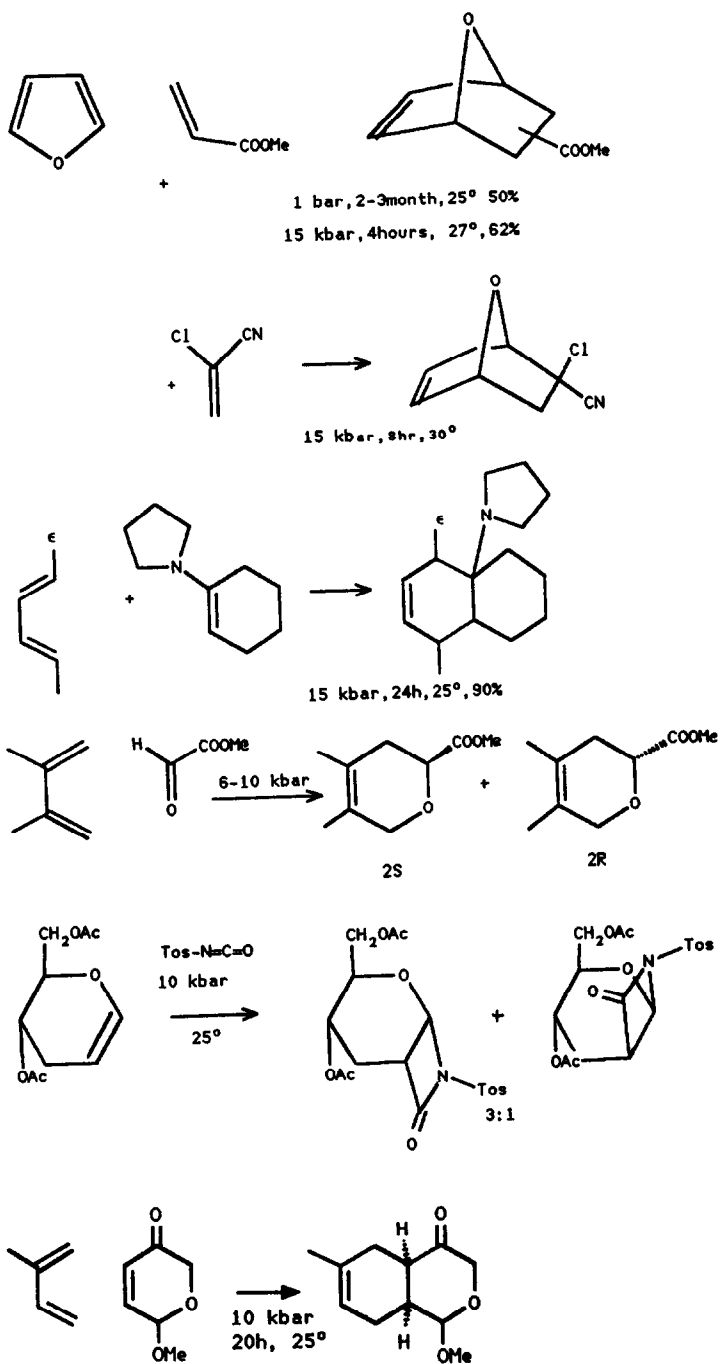
cantharidin
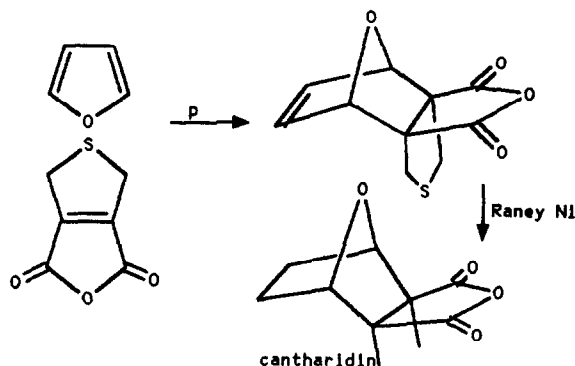
At atmospheric pressure, some cycloadditions fail since they are reversible and reach a low equilibrium yield which cannot be improved by raising the temperature. Pressure, on the other hand, favours the forward reaction and disfavours the reverse leading frequently to high yields. Cycloadditions to furans as dienes including the intramolecular cases, are good examples of this strategy. In some such reactions, the adducts spontaneously dissociate within hours in which case they must be kept at low temperature or rapidly hydrogenated after removal from the high pressure environment. It is a fortunate circumstance that rapid depressurisation from 10 kbar produces adiabatic cooling which can drop the sample temperature to below 0° and help to preserve it. The oxabicycloheptane products are valuable intermediates for further elaboration of various synthetic targets. Regio- and stereo-specificities may be affected by pressure but because of the similarities between transition states for different products, $\Lambda\Delta V^*$ is normally quite small, <5 cm^3mol^{-1} However, pressure could have the effect of changing thermodynamic into kinetic control by inhibiting the retro reaction in which case large changes in specificity could result. In many instances the endo isomer is favoured which is normally the kinetically-controlled product. In the reaction between isoprene and acrolein, for example, the mixture of regioisomers obtained at 1 bar (20°, 7 months') becomes pure 1-methyl-4-formylcyclohexene at 12 kbar, (20°, 16 hours) which probably points to a change to more kinetic product (64).

Enantiomeric excess in chiral syntheses may be increased or decreased by pressure but usually the effect is quite small. Many examples of chiral high pressure Diels-Alder

Table 10

Some Successful High Pressure Cycloadditions

1 bar, 2-3month, 25° 50%

15 kbar, 4hours, 27°, 62%

15 kbar, 8hr, 30°

15 kbar, 24h, 25°, 90%

6-10 kbar

2S   2R


Tos-N=C=O

10 kbar

25°

3:1

10 kbar
20h, 25°

reactions exist, however, such as the following (65); phenylmenthyl or, better, α-naphthylmenthyl is an efficient chiral directing group

(M = menthyl, PhM = phenylmenthyl, A-NaM = α-naphthylmenthyl)



R = M ; 10% ee
R = PhM; 50% ee
R = A-NaM; 90% ee
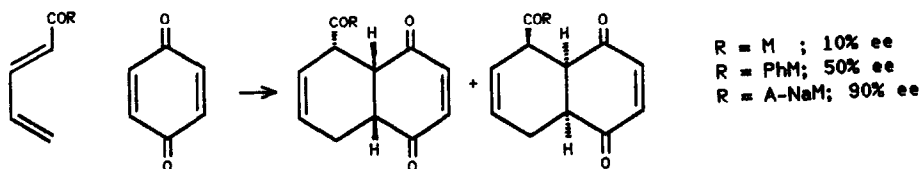
High pressure has been successfully applied in obtaining cycloadducts from very unreactive systems. Pyrroles will react at 12+ kbar provided the nitrogen is acylated in order to reduce aromaticity (66).
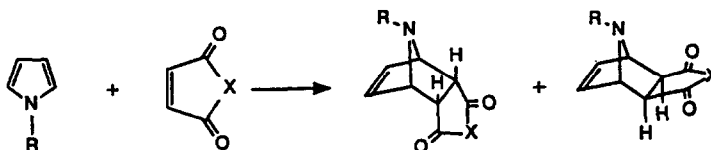

R	X		t/°C	t/h	P/Kbar	%	
COPh	N-Ph	Benzene	25	60	11	80	0/1
COPh	O	CHCl₃	24	160	11	25	0/1
COPh	O	EtOAc	25	300	12	20	1/0
COPh	N-Me	CH₂Cl₂	30	65	12	77	6/1

One example of thiophene as a diene (with maleic anhydride, at 15 kbar, 100°,) has been reported (67).

Naphthalene will add maleic anhydride at 10 kbar and 100° (68) and α-pyrones and -pyridones will also act as dienes at 10-15 kbar (69).


5 kbar, 55°, 12h, 92%
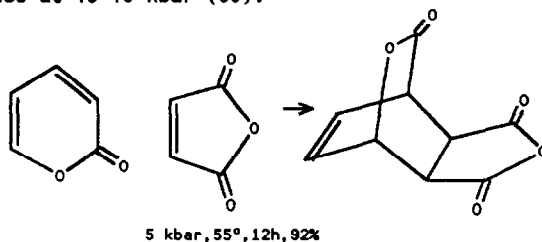
Homo-Diels-Alder reactions such as 5 become possible at 10 kbar leading to polycyclic products (70).

DMAD, 10 kbar
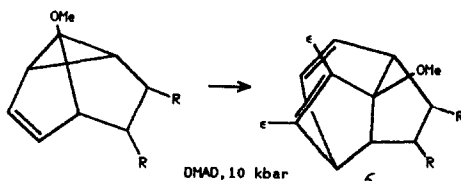
High pressures are needed for efficient imino-Diels-Alder synthesis, for example, from

triethyl azomethinetricarboxylate   ,(71):
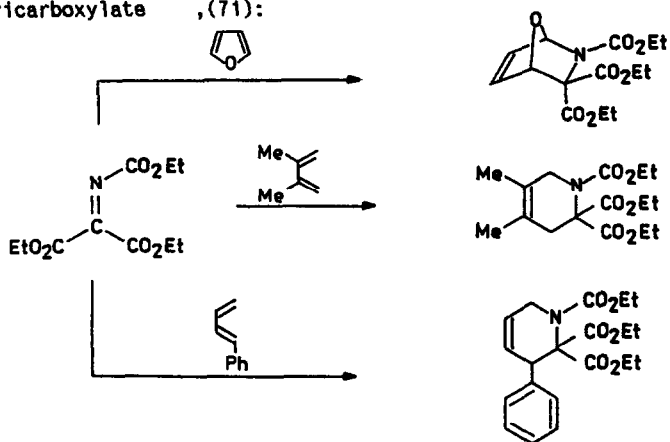
The recent synthesis by Stoddart of the interesting 'belt' compounds below required a

succession of Diels-Alder reactions, finally an intramolecular coupling .The 2-3% yield at

1 bar was improved to 30-35% at 10kbar (72).
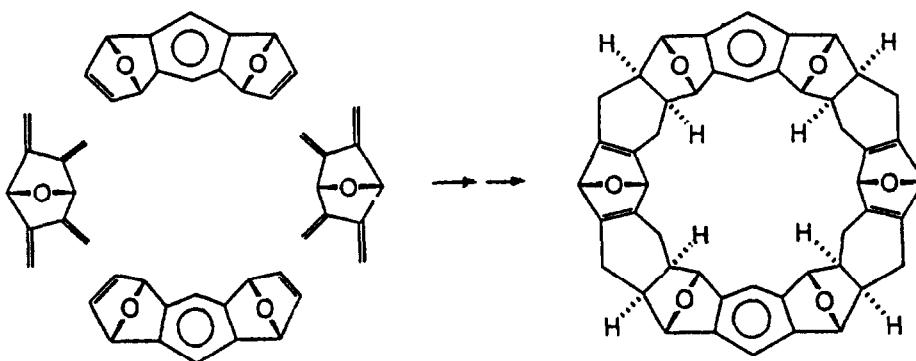
b. Other Cycloadditions

The high pressure addition of ketene acetals to aldehydes and ketones to give oxetans has

been established by Scheeren (73) as a general synthetic procedure, there being no reaction

discernable at 1 bar except when Lewis acid catalysed.

X = H, Cl, Me, OMe
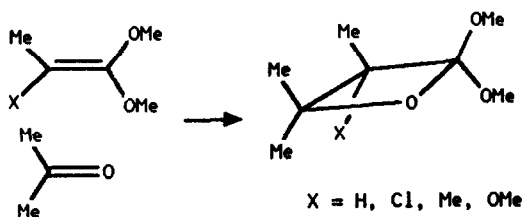
Analogous reactions with electron-poor cyclopropanes and with imines in place of the

carbonyl component also at 12 kbar, provide versatile syntheses of cyclopentanes   and

azetidines   respectively (74,75).
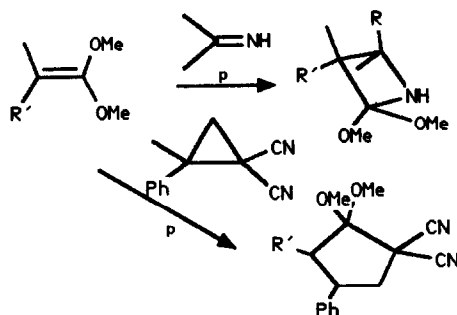
In the field of dipolar cycloadditions, reactions of nitrones with vinyl ethers and with

allylic esters have been employed at 12 kbar in the synthesis of isoxazolidines,   (76)
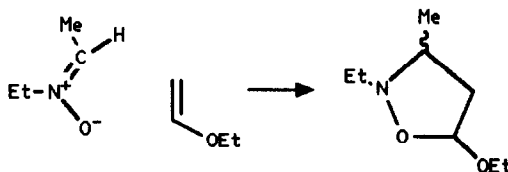
Cycloadditions of arylsulphonyl azides to give triazolines are of interest in that these

products may undergo spontaneous rearrangement and ring-contraction thus giving an entry

into cyclopentanes (77),
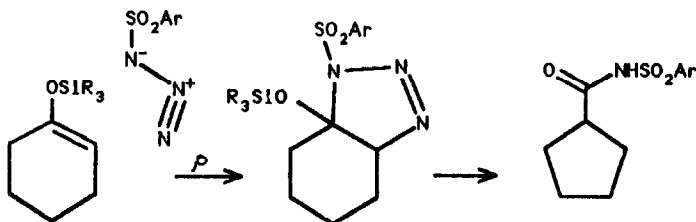
Trimerisation to the symmetrical triazine is the result of pressurising nitriles at 6-7

kbar ,100-150°. The solvent is important suggesting a very polar transition state, the

addition of methanol for instance can raise the yield of triphenyltriazine from

benzonitrile from 6 to 82% and takes part in the reaction, the mechanism of which is as

follows (78)

$$PhC\equiv N + ROH \underset{k_2}{\overset{k_1}{\rightleftharpoons}} PhC\!\!\begin{array}{c}NH\\OR\end{array}$$

$$2\ PhC\!\!\begin{array}{c}NH\\OR\end{array}\ \underset{slow}{\overset{k_3}{\longrightarrow}}\ PhC\!\!\begin{array}{c}OR\\\|\\=N\end{array}\!\!-C\!\!\begin{array}{c}NH\\Ph\end{array}\ +\ ROH$$

79

$$PhC\!\!\begin{array}{c}OR\\\|\\=N\end{array}\!\!-C\!\!\begin{array}{c}NH\\Ph\end{array}\ +\ PhC\!\!\begin{array}{c}NH\\OR\end{array}\ \underset{fast}{\overset{k_4}{\longrightarrow}}\ \text{(triazine)}\ +\ 2ROH$$
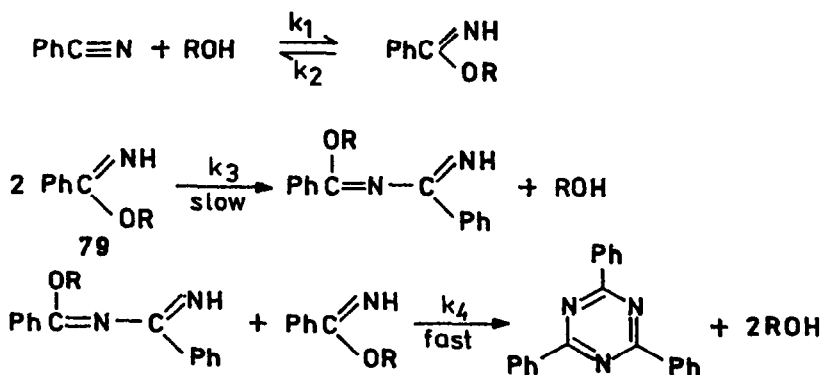
Phthalocyanines can be formed rapidly and at lower than normal temperatures at 10 kbar;

$$M^{2+} + 4\ \text{(benzene-1,2-dicarbonitrile)} \longrightarrow \text{(metal phthalocyanine)}$$
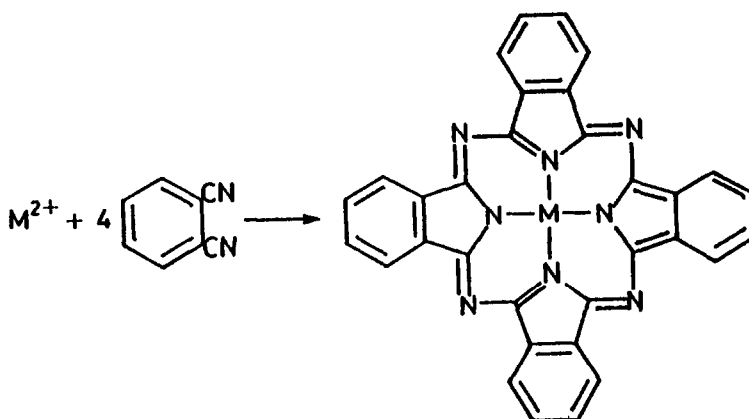
M = Cu, Co, Ni, Mn, Zn, Mo, La, UO_2, H, Pb, Zr,
Rb, Pb, Sr.

b. Quaternisations

The large volume of electrostriction which accompanies ionic charge separation makes

pressure a valuable ally for difficult Menshutkin reactions such as the N-methylation of

2,6-lutidine, or even 2,6-di-t.butylpyridine, (79).

The greater the amount of steric hindrance to be overcome, the more negative is the volume of activation. This is presumably since the transition state becomes later along the reaction coordinate and the degree of charge separation at the transition state greater. It is possible under high pressure conditions to form bis-quaternary salts from the normally rather unreactive dichloromethane,(80) :

$$CH_2Cl_2 + R_3N \ (10 \ kbar) \longrightarrow R_3N^+-CH_2-^+NR_3 \quad 2Cl^-$$

The most important example,though,is in the synthesis of cryptands, the macrocyclic metal-complexating agents. Both the initial cyclisation and the introduction of the third bridge are most effectively accomplished at pressures of at least 10 kbar. Many examples of this type of compound have been made readily available from the results of Jurczak and coworkers (81);
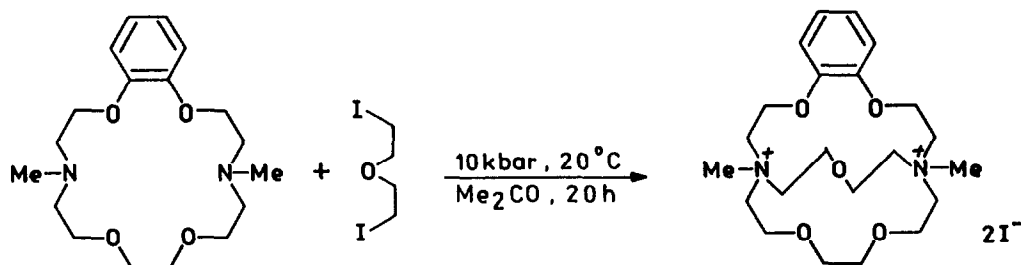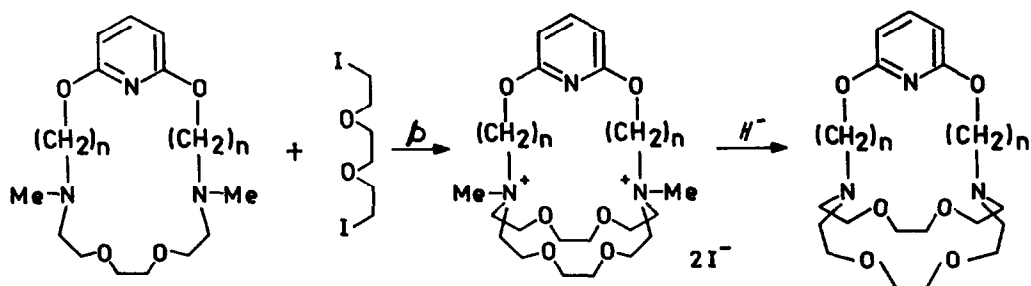
Examples embodying sugar residues have also been synthesised and provide chiral cavities for complexation of guest molecules.
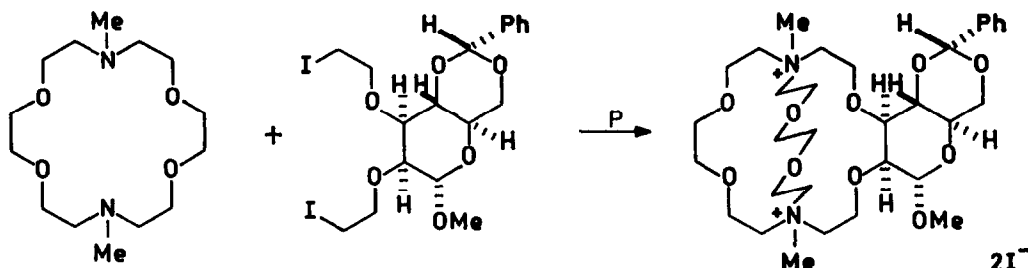
Phosphonium and sulphonium salts similarly are formed under pressure at accelerated rates, for example;

$$2 \ Ph_3P \ + \ CH_2Cl_2 \ (9 \ kbar) \longrightarrow \ Ph_3P^+-CH_2-P^+Ph_3 \ 2Cl^-$$

$$MeBr \ + \ Me_2S=O \ (9 \ kbar) \longrightarrow \ Me_2S^+-OMe \ Br^-$$
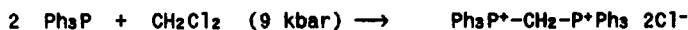
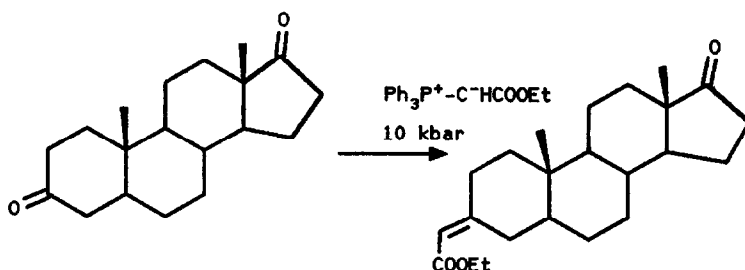This reaction is of obvious use in the synthesis of Wittig reagents and their sulphur analogues for the synthesis of alkenes and of thiiranes. Furthermore, the actual Wittig reactions between phosphoranes and carbonyl compounds are greatly facilitated by pressure; the following example will only occur at 10 kbar which overcomes steric hindrance (82):

c. Miscellaneous Reactions

An interesting application of high pressures has been found in the hydroboration of ketones and aldehydes using 'Alpine Borane' to generate a chiral alcohol . Sterically hindered carbonyl compounds give poor enantiomeric excess since hydroboration may occur from the competing reaction with 9-borabicyclo[3,3,1]nonane (9-BBN) which is achiral and which is formed by the thermal dissociation of Alpine Borane. Under high pressure conditions, this dissociation is suppressed and the hydroboration of the ketone is accelerated (83).
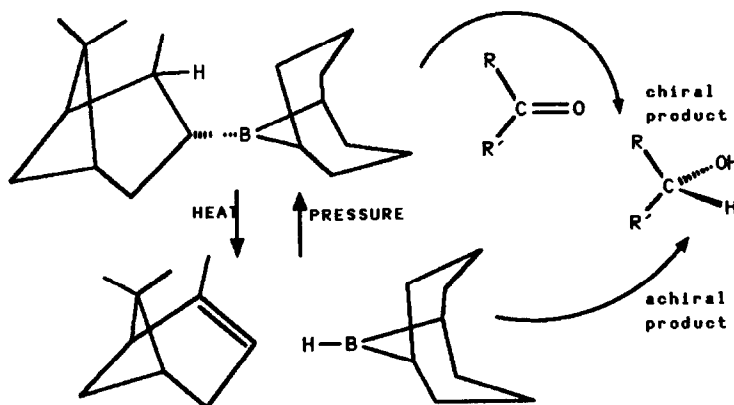
The yield and enantiomeric excess for reduction of pinacolone, for instance, is raised from a few percent to at least 95% .

Michael reactions frequently benefit from high pressure although their response seems somewhat variable. The addition of acetone to acrylonitrile catalysed by primary amines, taking 4h at 180 ° at 1 bar for 80% yield can be accomplished at 12 kbar in 5-10 minutes (84).
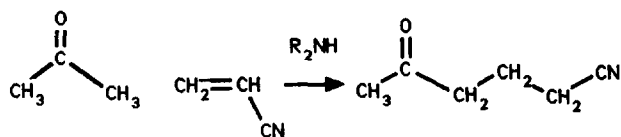
Similarly, the Michael addition of acrylonitrile to testosterone can only conveniently be carried out at ca.10 kbar (85).

CH₃NO₂, DBU, 9kbar, 6 days
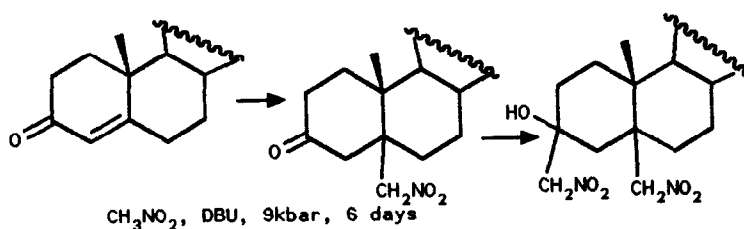
The addition of amines to β-naphthylmenthyl crotonate at 10kbar was found by D'Angelo to lead to products containing up to 99% enantiomeric excess at the new chiral centre (86).
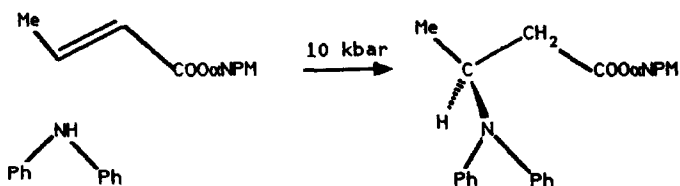
Multi-Step Reactions

Perhaps the greatest response of reaction rate to pressure is to be found in those reactions which partake of a series of steps each of which has a negative volume of activation, the last being rate-determining. In such cases the observed volume of activation is the sum of those for each step (or their volumes of reaction) and can be very

large and negative. The well-studied 'α-substitutions' (Bayliss-Hillman reaction) of acrylic esters and nitrile are a case in point with $\Delta V^{\ddagger}_{obs}$ = -70 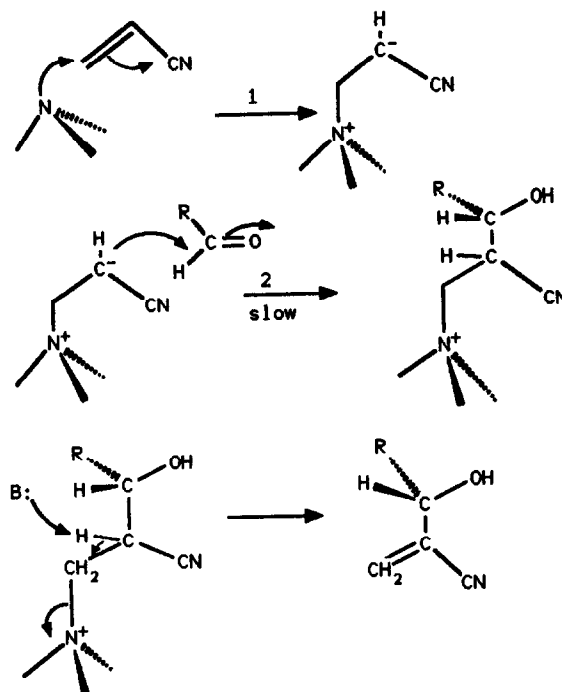cm^{3}mol^{-1}. A reaction taking 4-5 days at 1 bar can be accomplished in 10 min at a pressure no more than 5 kbar (87). There are many more complex reactions of industrial importance which would respond as favourably to pressure awaiting exploitation.

Future Prospects

In addition to the reaction types discussed there is great scope for the synthesis of otherwise inaccessible polymers and copolymers formed by both radical and ionic routes and of enhancement of the properties such as increased molecular weight, of known polymers. An almost unexplored field of high pressure chemistry lies in the reactions of organometallic compounds and in catalysis in the liquid phase, both homogeneous and heterogeneous. The scope of the technique is limited only by the imagination . High pressure techniques for

laboratory use have an assured future role in research but whether such processes will ever become commercially important ("a consummation devoutly to be wished" !) will depend upon there being a reaction of large, negative volume of activation and of sufficient economic importance to justify the cost and development of the equipment. Nonetheless, pumps operating at 5kbar or above are commercially available and could be used in a continuous flow reactor, an example of which is at present operating in the Author's laboratory. . There would be no need for large capacity pressure vessels for a length of tubing of suitable material and strength would suffice. Such equipment is at present in the experimental stage but preliminary results suggest that industry would do well to keep this prospect in view. In conclusion applications to the food industries must be mentioned. High pressure will kill microorganisms, coagulate protein and denature enzymes. 'Cold boiled' eggs and pasteurised milk or fruit juice of superior flavour may be produced at room temperature and a few kbar pressure for example. Research into food processing by pressure is actively being pursued especially in Japan and is likely to take its place as the first commercial application.

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