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Review Commentary

High-pressure mechanistic delineation based on activation volumes

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ABSTRACT: High-pressure kinetics is a useful tool for the determination and the assessment of mechanisms in organic chemistry. The volume of activation ΔV^* deduced from these kinetic measurements is an indicator of the position of the transition state. In addition, if accurately determined, ΔV^* permits the detection of fine mechanistic effects such as alteration of mechanism according to substrates within the same reaction type, operation of secondary orbital interactions in Diels–Alder cycloadditions, angular hydrogen transfer in ene reactions, etc. Copyright © 2001 John Wiley & Sons, Ltd.

KEYWORDS: mechanism; kinetics; pressure; activation volume

INTRODUCTION

Thermodynamics applied to chemical reactions yields useful thermodynamic quantities such as ΔG (change in free energy of the chemical system), ΔH (change in enthalpy or heat of the reaction) and ΔS (change in entropy). These quantities refer to the starting and ending states of the system. However, they do not provide information either about the rate at which the reaction proceeds or the different events occurring when the reaction progresses from initial substrates to final products. In other words, the reaction mechanism cannot be deduced from the determination of ΔG, ΔH and ΔS.

It is evident that the knowledge of the way in which molecules are transformed into other molecules is of overwhelming importance from both theoretical and practical standpoints. Mechanistic processes are usually investigated in different ways, e.g. stereochemical outcome, kinetic isotope effects, general kinetics (reaction order). Reaction kinetics is essential for the location of transition states and detection of intermediates.

The transition state theory describes the pathways followed by the molecules as energy profiles which show maxima for the different transition states characterizing each step of a given reaction. In a multistep reaction each event must proceed through an unstable transition state followed by an intermediate and the slowest step is rate determining (RDS). The energy required to overcome the barrier (corresponding to the transition state) is the activation energy ΔG^*:

$$\Delta G^* = \Delta H^* - T\Delta S^* \qquad (1)$$

(ΔG^*, ΔH^* and ΔS^* are activation quantities, e.g. kinetic parameters).

As already stated above, one of the most useful criteria for the assessment of a mechanism is the location of transition states along the reaction coordinate (Fig. 1).

The simple case is one-step reactions such as the concerted Diels–Alder cycloaddition of methyl acrylate to isoprene (no intermediate). Figure 2 pictures the energy and the volume profile of the cycloaddition. In terms of partial molar volumes, reaction volume ΔV_R (volume difference between products and substrates) and ΔV^* (volume difference between transition state and substrates) have following values at 21 °C in 1-bromobutane:[1]

$$\Delta V_R = V_P - V_R = -36.9 \text{ cm}^3 \text{ mol}^{-1}$$
$$\Delta V^* = V^* - V_R = -31.5 \text{ cm}^3 \text{ mol}^{-1}$$

Comparison between ΔV_R and ΔV^* shows that both values are relatively close, apparently meaning that the structure of the transition state resembles that of the product.

ΔV^* is called the activation volume. It results from

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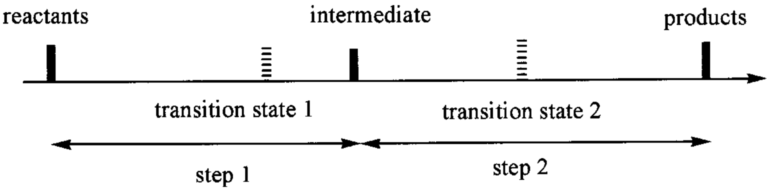


Figure 1. Linear profile of a chemical reaction

Eqn. (2) and is determined from Eqn. (3):

$$\Delta V^* = (\partial \Delta G^* / \partial P)_T \qquad (2)$$

As

$$k = \exp(-\Delta G^*/RT)$$

ΔV^* becomes

$$\Delta V^* = -RT(\partial \ln k / \partial P)_T \qquad (3)$$

Accurate measurements of the kinetic constant k at different pressures (generally in the pressure range 0–150 MPa) lead to a curve $k = f(P)$ whose initial slope gives $(\Delta V^*)_{P \to 0}$. As integration of Eqn. (3) is not possible, ΔV^* is calculated via mathematical approximations which were found to give sufficient confidence.[2]

However, ΔV^* does not result exclusively from volume modifications induced by bond transformations. It embodies all volume changes ΔV_i^* occurring during the progression of the reaction from initial to transition state and within the transition state:[3]

$$\Delta V^* = \Sigma \Delta V_i^* \qquad (4)$$

When the medium effect is small, Eqn. (4) is a one-component expression relating only to the structural activation volume term (ΔV_S^*) representing the geometric balance of bond formation and bond cleavage. However, in ionogenic reactions or, simply, when the transition state is more polar than the reactants, Eqn. (4) must acknowledge an environmental volume term (ΔV_m^*) representing the volume change resulting from solute–solvent interactions. ΔV_m^* is, consequently, solvent dependent. The pressure effect in the conjugate addition of *tert*-butylamine to acrylonitrile is a representative recent example (Table 1).[4]

$$\textit{tert} - \mathrm{BuNH_2} + \mathrm{CH_2} = \mathrm{CHCN} \rightarrow \textit{tert} - \mathrm{BuNHCH_2CH_2CN}$$

In this reaction, $\Delta V_S^* \approx -20\ \mathrm{cm^3\,mol^{-1}}$ and the additional ΔV_m^* refers to electrostriction. ΔV_m^* gives an

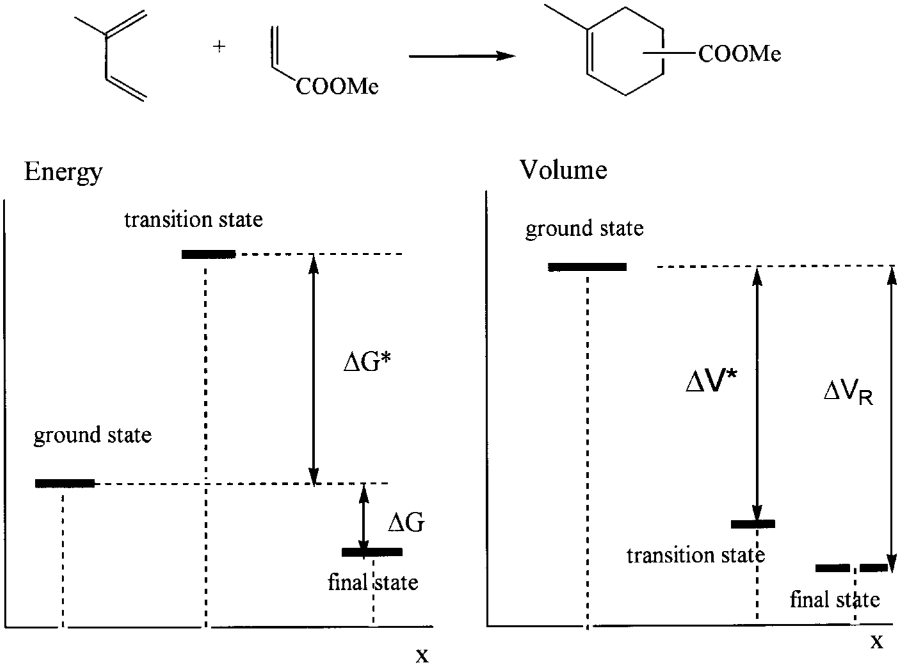
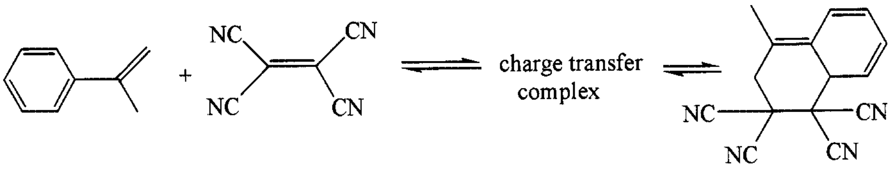


Figure 2. Energy and volume profile of the Diels–Alder addition of methyl acrylate to isoprene

Table 1. Kinetic effect of medium and pressure in the addition of *tert*-butylamine to acrylonitrile

Medium	δ^2	ΔV^* ($\mathrm{cm^3\,mol^{-1}}$)	ΔV_m^* ($\mathrm{cm^3\,mol^{-1}}$)[a]
Diethylether	55	−55	−35
Chloroform	86	−54	−35
Acetonitrile	141	−56	−35
Methanol	208	−35	−15
Ethylene glycol	213	−33	−13
Formamide	369	−21	~0
Water	547	−25	−5 to 0

[a] Estimated.



Scheme 1. Cycloaddition of tetracyanoethylene to α-methylstyrene

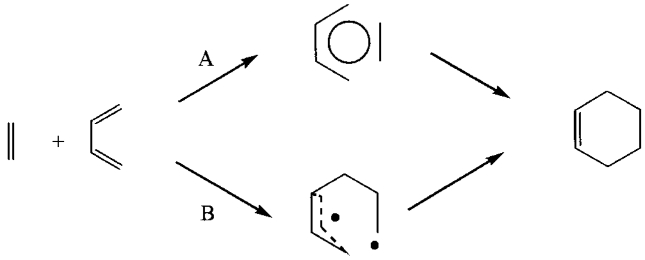
indication of the charge distribution within the transition state. Activation volume changes ΔV_m^* are smallest in very polar media, already highly electrostricted, and largest in low-polarity solvents.

As a consequence, ΔV^* may be negative in bond-breaking processes having strong dipolar character, even independently of the medium. This is due to the fact that $|\Delta V_\mathrm{m}^*|$ may be higher than $|\Delta V_\mathrm{S}^*|$. In the reaction depicted in Scheme 1, the respective ΔV^* values are $-27.0\,\mathrm{cm^3\,mol^{-1}}$ for the forward reaction and $-3.3\,\mathrm{cm^3\,mol^{-1}}$ for its reverse in chloroalkanes as solvents.[5]

Other volume effects in Eqn. (4) may stem from steric[6] and solvophobic effects.[4] An important remark concerns viscosity effects. It is generally agreed that transition state theory may be invalid in highly viscous media where diffusion processes play an important part. Since pressure increases the viscosity coefficient exponentially, such effects apparently must be taken into account. As an illustrative example, in the *Z–E* isomerization of 4-(dimethylamino)-4′-nitroazobenzene, the rate constant initially increases with pressure, then decreases at higher pressures when the medium is a viscous silicone oil.[7] However, as mentioned above, the quasi-totality of kinetic data available until now were measured only in the lower pressure range in solvents of low or reasonable viscosity (even simple glycols are suitable). This gives excellent credit to the validity of transition state theory throughout this review.

Coming back to Eqn. (4), only the structural term ΔV_S^* can be used for mechanistic delineation. This underlines that to give a structural content to the activation volume, it is necessary to examine carefully the possible occurrence of medium and, incidentally, steric effects. What credit can be granted to ΔV_S^* as a mechanistic criterion? Is ΔV_S^* really representative of the position of the transition state? A molecular volume V is composed of the volume actually occupied by the molecule, which is the van der Waals volume V_w, and the void space necessary for thermal expansion and molecular motions. The ratio between V_w and V is defined as the packing coefficient χ ($\chi = V_\mathrm{w}/V$) which applies also to the structure of the transition state ($\chi^* = V_\mathrm{w}^*/V^*$). A practical example is outlined in the elemental Diels–Alder reaction of ethylene and 1,3-butadiene. The two limiting mechanisms are A (one-step mechanism) and B (two-step mechanism with a diradical as intermediate) (Scheme 2). The volumes are listed in Table 2.[8]

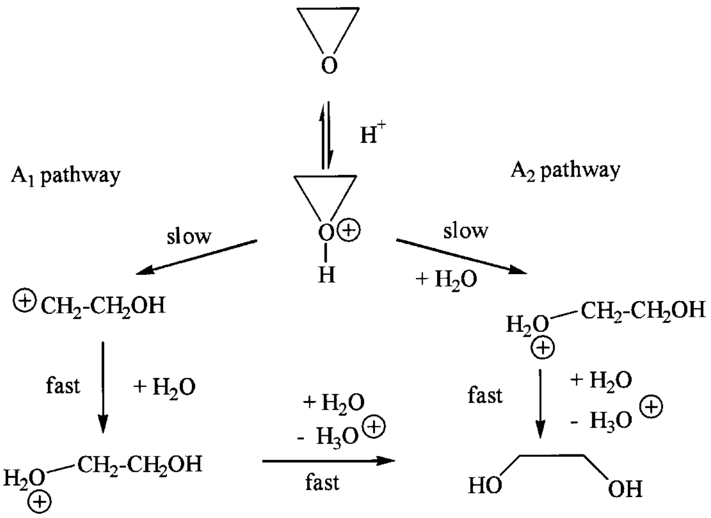
It can be observed that the van der Waals volumes of the concerted transition state (CTS) and biradical are similar. This means that the knowledge of V_w is not useful since it does not permit dichotomy between pathways A and B. At variance, the packing coefficients are different



Scheme 2. Possible pathways in the [4 + 2] cycloaddition of ethylene to butadiene

Table 2. Calculation of volumes in the Diels–Alder reaction between ethylene and 1,3-butadiene

	V ($\mathrm{cm^3\,mol^{-1}}$) (molecular volume)	V_w ($\mathrm{cm^3\,mol^{-1}}$) (van der Waals volumes)[9]	χ
Ethylene	59.9	25.5	0.4257
Butadiene	83.2	44.8	0.5385
Concerted TS (CTS)	109.1	63.8	0.5829
Diradical TS (DTS)	120.4	65.3	0.5436
Biradical	118.7	64.4	0.5424
Cyclohexene	101.4	59.1	0.5829



Scheme 3. Acid-catalyzed hydrolysis of epoxides

whereas those relative to the pericyclic transition state (CTS) and the cyclic product are exactly the same: $\chi_{\mathrm{CTS}}{}^* \neq \chi_{\mathrm{diradical}}$ or $\chi_{\mathrm{DTS}}{}^*$ but $\chi_{\mathrm{CTS}}{}^* = \chi_{\mathrm{cyclohexene}}$. $\chi_{\mathrm{DTS}}{}^* < \chi_{\mathrm{CTS}}{}^*$ demonstrates that the concerted transition state is more compact than the acyclic one.[9] Therefore, on the basis of packing coefficients, it is possible to discrimate between pathways A and B. In order to locate the transition state, we define $\theta = \Delta V^*/\Delta V$ (when $\Delta V^* \approx \Delta V_S{}^*$). This means that if θ is close to unity, the transition state resembles the product structurally. For example, in the reaction depicted in Scheme 2, from the volume values listed in Table 2, θ takes the calculated values 0.82 (CTS), 0.54 (DTS) and 0.59 (biradical).

In conclusion, molecular volumes and, hence, reaction volumes and activation volumes give full confidence in the criterion to assess the position of the transition state of the rate-determining step in an organic reaction despite recent polemical papers contesting its usefulness.[10]

MECHANISTIC DETERMINATIONS

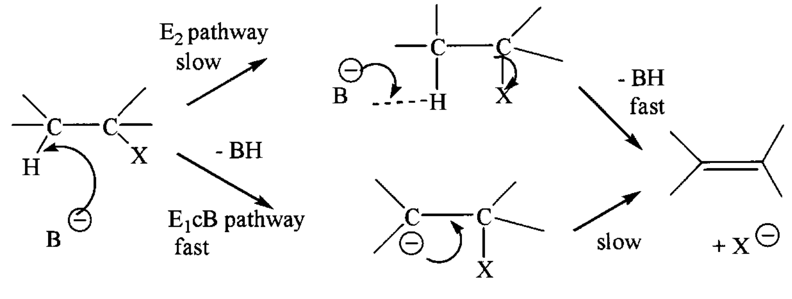
Delineation via the sign of ΔV^*

The easiest way to discriminate between mechanisms is the sign of ΔV^*. Such a procedure can be utilized when two possible mechanisms characterize rate-determining steps which are affected in opposite ways by application of pressure, e.g. one would be accelerated ($\Delta V^* < 0$) and the other decelerated ($\Delta V^* > 0$). Illustrative examples are provided by the acid-catalyzed hydrolysis of epoxides and base-catalyzed elimination reactions.

In the acid-catalyzed hydrolysis of epoxides, two mechanistic possibilities may be envisaged (A_1 and A_2) (Scheme 3).[11]

The A_1 pathway involves free carbenium ions whereas the rate-determining step in the A_2 pathway is hydrolysis affording solvated carbenium ions. The pressure effect predicts a positive value of ΔV^* for the A_1 mechanism (unimolecular decomposition) and a negative value for the A_2 mechanism (bimolecular reaction). The experimental determination of the activation volume leads to negative values: at 0°C, $\Delta V^* = -6$, -8.4 and $-9.2\ \mathrm{cm^3\,mol^{-1}}$ for the hydrolyses of ethylene oxide, propylene oxide and isobutylene oxide, respectively.[11] Consequently, the reaction proceeds according to the A_2 mechanism.

The same criterion was applied to the determination of the mechanism of some elimination reactions. In basic media they proceed via E_1, E_2 and E_1cB pathways. The



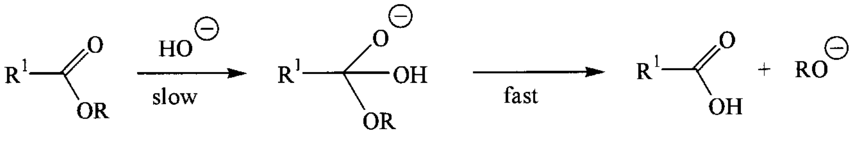
Scheme 4. Base-catalyzed elimination reactions

Table 3. Activation volumes of elimination reactions in basic media

Substrate	ΔV^* (cm^3 mol^{-1})	Mechanism
2-Bromobutane	−10	E_2
1-Chloro-2-phenylethane	−12	E_2
cis-*β*-Bromostyrene	−6	E_2
Diacetone alcohol	+6	E_1cB
Mandelonitrile	+12	E_1cB
Chloroform	+16	E_1cB

last is an E_1-type elimination with the formation of a carbanion as intermediate (Scheme 4). Pressure kinetics are expected to differ according to the mechanism. E_2 reactions feature negative activation volumes (B—H bond formation and C—X partial bond cleavage occur concertedly). E_1cB mechanisms display positive ΔV^* values as a result of the volume increase from C—X bond cleavage and no volume variation in the equilibrium involving proton transfer.[12] The mechanistic results are listed in Table 3.

Even subtle mechanistic differences can be detected via the sign of ΔV^*. This is highlighted, for instance, in the base-catalyzed hydrolysis of acetates and benzoates which usually follow the $B_{AC}2$ mechanism (base-catalyzed acyl cleavage with a tetrahedral intermediate) (Scheme 5). The pressure effect was measured in the kinetics of some ester hydrolyses (Table 4).[13]



Scheme 5. Base-catalyzed hydrolysis of esters (R^1 = Me, Ph)

Table 4. Activation volumes of hydrolyses of some esters

Ester[a]	ΔV^* (cm^3 mol^{-1})	Mechanism
o-Nitrophenyl acetate	−9	$B_{AC}2$
p-Nitrophenyl acetate	−20	$B_{AC}2$
DNP *p*-methoxybenzoate	−19	$B_{AC}2$
DNP *m*-hyroxybenzoate	−15	$B_{AC}2$
DNP *p*-hydroxybenzoate	+16	E_1cB

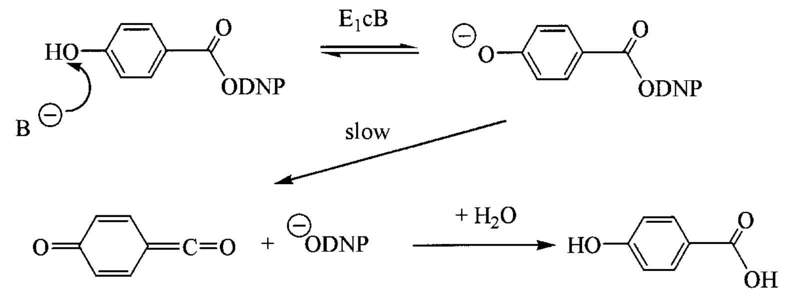
[a] DNP = 2,4-dinitrophenyl.

Whereas the $B_{AC}2$ mechanism is obeyed in most reactions, the hydrolysis of 2,4-dinitrophenyl *p*-hydroxybenzoate is decelerated by pressure and, accordingly, supports a E_1cB mechanism (Scheme 6).

Mechanistic delineation via the magnitude of Δ*V**

However, in most cases, only the absolute value of ΔV^* is susceptible to operate mechanistic discrimination.

Pericyclic reactions. Pericyclicity is a very general concept. It designates processes in which all bond events take place in concert by reorganization of electrons trough a multicenter cyclic transition state. From a mechanistic point of view, such reactions are concerted



Scheme 6. Mechanism of hydrolysis of 2,4-dinitrophenyl *p*-hydroxybenzoate

Table 5. Solvent and pressure effect in pericyclic addition reactions

Solvent effect	ΔV^*	Mechanism	Transition state
Strong	Variable, depending on solvent	Sequential	Zwitterionic
Weak	Moderately negative	Sequential	Biradical
Weak	Very negative	Concerted	Cyclic

Table 6. Effect of pressure in normal electron demand Diels–Alder reactions

Diene[a]	Dienophile	Solvent effect	θ^b
Isoprene	Methyl acrylate	Weak	0.85
Isoprene	Acrylonitrile	Weak	0.96
Isoprene	Methyl vinyl ketone	Moderate	1.02
DMB	*n*-Butyl acrylate	Weak	0.89
MOB	Maleic anhydride	Fairly strong	0.99 (in MeCN)
MOB	Maleic anhydride	Fairly strong	1.66 (in CH_2Cl_2)

[a] DMB = 2,3-dimethyl-1,3-butadiene; MOB = 1-methoxy-1,3-butadiene.
[b] θ Values ($\theta = \Delta V^*/\Delta V$) are standardized to 20–25 °C.

one-step processes. Non-concertedness implies stepwise pathways with formation of an intermediate. Intermediates are essentially of two types: zwitterions which are highly polar intermediates and biradicals. Their detection can be operated simply via kinetic studies taking into account the solvent effect on one side and the pressure effect on the other side on the rate constant (Table 5).

The magnitude of the activation volume, even, allows refinement of mechanistic details (see below).

Cycloadditions. The [4 + 2] cycloaddition is a prototypical high-pressure reaction. It has been extensively studied under pressure.[14] The effect of pressure on the kinetics of normal, neutral, inverse electron demand cycloadditions has been reviewed.[1] Selected data are listed in Tables 6, 7 and 9.

The solvent dependence for most reactions listed in Table 6 is small and θ values are close to unity. The reactions are one-step processes. However, reactions involving polar substrates are characterized by fairly polar transition states. This is clearly visible in the MOB–maleic anhydride cycloaddition: θ can be >1 in a weakly polar solvent (CH_2Cl_2) whereas it is ~1 in a more polar solvent (MeCN). These results reflect the occurrence of electrostriction (ΔV_m*).

Table 7. Effect of pressure in neutral electron demand Diels–Alder reactions

Diene/dienophile	Solvent effect	θ
Isoprene	Weak	0.88
DMB	Weak	0.72
Chloroprene	Weak	~1[a]
Chloroprene	Weak	<0.8[b]

[a] With respect to the formation of [4 + 2] cycloadducts.
[b] With respect to the formation of [2 + 2] cycloadducts.

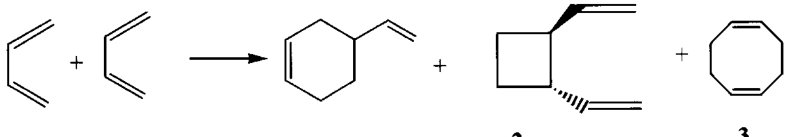
The dimerization of 1,3-butadiene has been investigated in some detail (Scheme 7, Table 8).[9]

Tables 7 and 8 raise interesting comments. The [4 + 2] dimerization of isoprene is unquestionably concerted. However, θ is lower in the corresponding dimethylbutadiene reaction, although only the [4 + 2] cycloadduct is observed. This indicates a weakening of concertedness, possibly ascribed to steric hindrance and the possibility of mixed (one-and two-step) mechanisms.[15] Such a situation is clearly established in the cyclodimerization of chloroprene and butadiene (Scheme 7) in which two or more products are formed, the formation of each being differently affected by pressure. It can be rationalized only as a competition of pericyclic concerted Diels–Alder reaction with stepwise [2 + 2] and [4 + 2] or [4 + 4] cycloadditions.

In the perchlorocyclopentadiene Diels–Alder reactions, θ can take values in a large range from 0.6 to 1.0, suggesting various mechanistic possibilities from concerted transition states to stepwise processes with a biradical as intermediate since the smallness of solvent kinetic effects excludes ionic species.[1,16] The gradual shifting of the concerted mechanism to the diradical pathway with increasing ring size of cycloalkenes may be explained by the increase in the ring constraints which

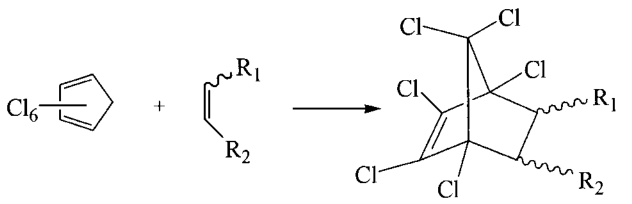
Table 8. Activation volumes in butadiene dimerization

Formation of	ΔV_{25}* ($cm^3\ mol^{-1}$)	θ_{25}
1	−26.5	0.79
2	−14.4	0.59
3	−23.5	0.54



1 **2** **3**

Scheme 7. Dimerization of 1,3-butadiene



Scheme 8. Diels–Alder reactions of hexachlorocyclopentadiene

Table 9. Effect of pressure in the inverse electron demand reactions of perchlorocyclopentadiene (Scheme 8)

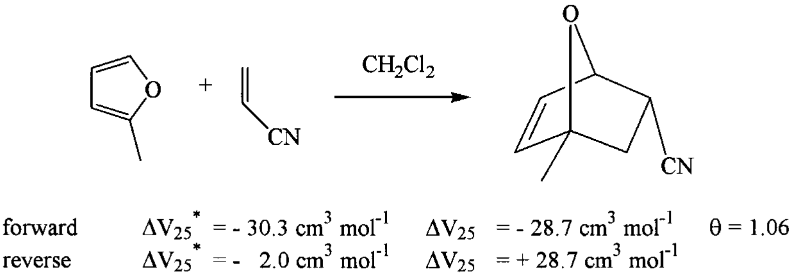
R_1	R_2	θ	ΔS^* ($J\ mol^{-1}\ K^{-1}$)
H	Pr	0.84	–
H	iPr	0.92	–
H	Ph	1.03	–
Me	Pr	0.95	–
—$(CH_2)_3$—		1.05	−205
—$(CH_2)_4$—		0.97	−213
—$(CH_2)_6$—		0.75	−130
—$(CH_2)_8$—		0.64	−138

would force the reaction to proceed through a looser symmetrical transition state. Potential diradical intermediates may also be stabilized by the chlorine atoms. The θ values are corroborated by ΔS^* values (see Table 9). Low θ values indicate a less rigid transition state with less ordering.

Additional information can be gained from the knowledge of ΔV^* and ΔV_R in Diels–Alder reactions.

(i) In some Diels–Alder reactions, it has been observed that $\theta > 1$, even if the solvent effect is weak or negligible. This would mean that the volume profile exhibits a minimum or, in other words, that the transition state is more compact than the product. A representative example is furan cycloaddition (Scheme 9).[17]
Albeit the importance of secondary orbital interactions for the explanation of the *endo* preference in Diels–Alder reactions is controversially discussed,[18] the result ($\theta > 1$) could be rationalized by extra stabilization of the *endo* transition state by secondary orbital stabilization. A different conclusion was drawn from the finding that the retro-Diels–Alder reaction of the *exo*-dimethylfulvene-*N*-phenylmaleic imide adduct shows a negative activation volume whereas the activation volume of the cleavage of the corresponding *exo*-adduct is positive.[18] However, as the cycloadducts bear a maleic anhydride or maleimide moiety, ΔV^* obviously must accommodate polarity effects (ΔV_m^*) as shown in [4 + 2] cycloadditions (Table 6).

(ii) It has also been observed in Diels–Alder reactions involving acetylenic substrates that both ΔV^* and ΔV are more negative than the corresponding values in reactions involving ethylenic dienophiles.[19] The reason has been ascribed to the rigidity of the acetylenic linear structure. In this case, the θ values do not show great differences whatever acetylenic or ethylenic dienophiles are opposed to a diene. Accordingly, concertedness is fully preserved (Table 10).



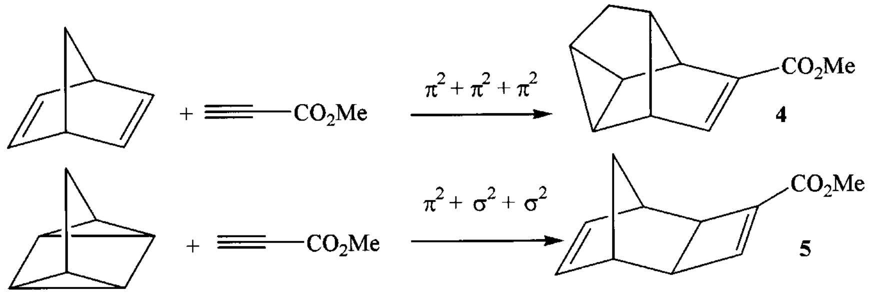
forward $\Delta V_{25}^* = -30.3\ cm^3\ mol^{-1}$ $\Delta V_{25} = -28.7\ cm^3\ mol^{-1}$ $\theta = 1.06$
reverse $\Delta V_{25}^* = -\ 2.0\ cm^3\ mol^{-1}$ $\Delta V_{25} = +28.7\ cm^3\ mol^{-1}$

Scheme 9. Volumes in the Diels–Alder reaction of 2-methylfuran and acrylonitrile

Table 10. Activation volumes in cycloadditions involving acetylenic dienophiles

Reaction[a]	ΔV_{25}^* ($cm^3\ mol^{-1}$)	ΔV_{25} ($cm^3\ mol^{-1}$)	θ_{25}
Cyclopentadiene + methyl acrylate	−28.3	−33.5	0.84
Cyclopentadiene + DMAD	−32.2	−36.1	0.89
Isoprene + methyl acrylate	−31.5	−37.0	0.85
Isoprene + methyl propiolate	−34.6	−39.5	0.88
DMB + methyl acrylate	−28.3	−34.7	0.82
DMB + DMAD	−34.1	−38.8	0.88

[a] DMAD = dimethylacetylene dicarboxylate; DMB = 2,3-dimethyl-1,3-butadiene.



Scheme 10. Homo-Diels–Alder and bishomodiene reactions

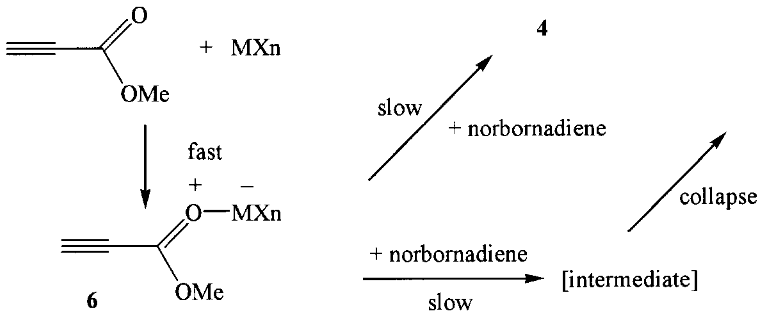
Table 11. Activation volumes in homo-Diels–Alder and bishomodiene reactions

Process (Scheme 10)	Product	Solvent	ΔV_{25}* (cm^3 mol^{-1})	θ_{25}
$(\pi^2 + \pi^2 + \pi^2)$	**4**	Benzene	−31.5	0.89
$(\pi^2 + \sigma^2 + \sigma^2)$	**5**	Chloroform	−33.8	0.87

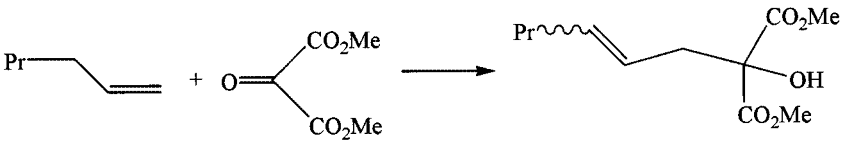
Related pericyclic reactions. Related reactions embody homo-Diels–Alder $(\pi^2 + \pi^2 + \pi^2)$ and bishomodiene $(\pi^2 + \sigma^2 + \sigma^2)$ cycloadditions (Scheme 10). The solvent effect is weak. Table 11 portrays the pressure effect.[1] These reactions are perfectly concerted according to the θ values.

A nice example of the demonstration of ΔV* as mechanistic argument is provided by the catalyzed cycloaddition reactions between norbornadiene and methyl propiolate, where both adducts **4** and **5** are produced. The calculated activation volumes for the catalyzed homo-Diels–Alder and [2 + 2] processes are −33.0 and −20.5 cm^3 mol^{-1}, respectively. The ΔV* difference reveals a change in mechanism: the concertedness of the catalyzed homo-Diels–Alder reaction $(\theta = 0.92)$ is preserved whereas adduct **5** is formed according to a stepwise [2 + 2] process $(\theta = 0.53)$ (Scheme 11).[20] There is no polarity effect as the rate-determining step is the addition of the diene to the complex **6** yielding an intermediate. This means that ΔV* is a measure of only ΔV_S*, supporting the above mechanistic conclusion.

Ene reactions. Ene reactions may be paralleled with Diels–Alder cycloadditions as they involve cyclic transition states. However, owing to lack of symmetry, the mechanism must be established in each specific case.[1] Scheme 12 presents the addition of dimethyl ketomalonate (DMKM) to 1-hexene. This is an ene reaction involving (C—H—O) hydrogen transfer.[21]



Scheme 11. Mechanism of the catalyzed addition of methyl propiolate to norbornadiene



Scheme 12. Ene reaction involving an alkene and DMKM

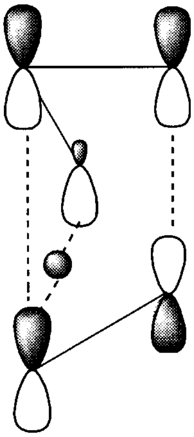
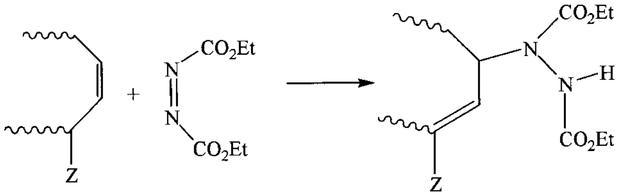


Figure 3. Angular H-abstraction in (C—H—O) ene reactions

The reaction is insensitive to solvent effects. Pressure kinetics leads to the volume values $\Delta V^* = -28.4\,\mathrm{cm^3\,mol^{-1}}$ and $\Delta V = -27.0\,\mathrm{cm^3\,mol^{-1}}$. The θ value (1.05) is >1 and, obviously, reflects a very tight transition state, even more compact than the product. However, unlike Diels–Alder reactions also experiencing highly rigid transition states (see above), in the present case, the ΔV^* data must be interpreted differently. The compactness of the activated complex may be explained by an angular hydrogen abstraction. Figure 3 pictures a possible geometry for such a transfer.

There are many examples of ene reactions for which θ >1 (Table 12). The concerted angular mechanism is also postulated for the (C—H—C) hydrogen transfer. In the ene reaction of β-pinene with DMAD, it is interesting to note that, again, the ΔV^* value is made more negative owing to the rigidity of DMAD. However, in the (O—H—O) hydrogen transfer reaction between acetone and DEKM, θ <1, the mechanism is concerted, however, the hydrogen transfer is a likely linear process.[22]

The activation volume can be a means to detect a change of mechanism in ene reactions between alkenes and diethyl azodicarboxylate (DEAD) (Scheme 13, Table 13).[23] It is clear that these reactions occur mostly stepwise and involve presumably biradical species.



Scheme 13. Ene addition of DEAD to alkenes

Table 13. Ene reactions involving (C—H—N) hydrogen transfer[1,23]

Alkene	ΔV_{25}* ($\mathrm{cm^3\,mol^{-1}}$)	θ_{25}
Cyclopentene	−23.1	0.68
Cyclohexene	−19.7	0.58
Cyclooctene	−26.9	0.79
Allylbenzene	−20	0.56
α-Methylstyrene	−23	0.69
β-Pinene	−16	0.45

A striking dichotomy in six-membered cycloalkene ene reactions could be evidenced through the activation volume.[24] Whereas θ is 0.58 in the addition of DEAD to cyclohexene (Table 13) it is 0.88 (with $\Delta V_{25}^* = -30\,\mathrm{cm^3\,mol^{-1}}$) in the corresponding ene reaction of 1,4-cyclohexadiene, suggesting a concerted hydrogen transfer process. The reason may be due to the enhanced rigidity of 1,4-cyclohexadiene (additional double bond) which adopts a quasi-coplanar structure like the product (Scheme 14). In this scheme the allylic hydrogen is transferred orthogonally (θ <1 but close to unity).

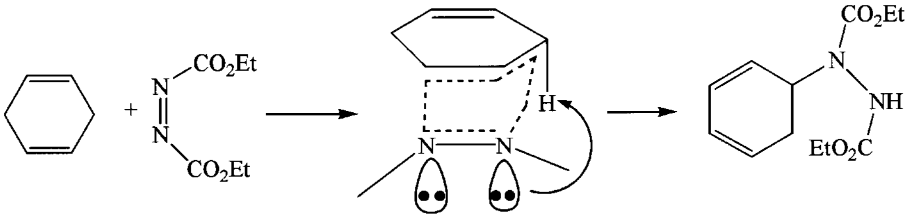
Finally, the mechanism of the thermal decomposition of allylic sulfinyl acids (desulfination) could be shown to proceed according to a concerted retro-ene reaction ($\Delta V^* = -5.5\,\mathrm{cm^3\,mol^{-1}}$) (Scheme 15).[25]

Cheletropic reactions. These reactions encompass fragmentation reactions of type as shown in Scheme 16. The volume profile of a reverse cheletropic process has been determined by high-pressure kinetics.[26] The volumes found were $\Delta V^* = -35.0\,\mathrm{cm^3\,mol^{-1}}$ and $\Delta V = -33.0\,\mathrm{cm^3\,mol^{-1}}$ with $\theta = 1.06$. It was concluded that a concerted pericyclic mechanism applies, involving a

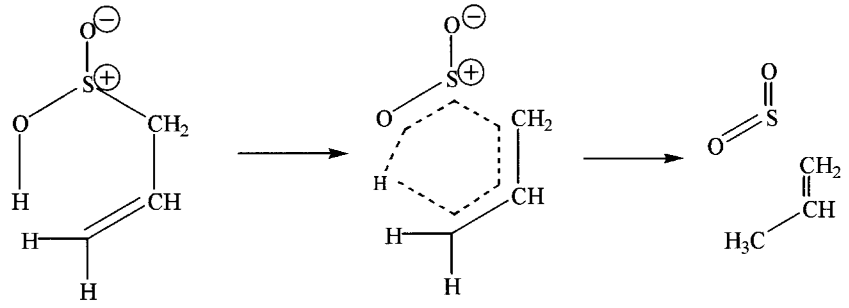
Table 12. Ene reactions involving different types of hydrogen transfer[1,22,23]

Reaction[a]	Hydrogen transfer	ΔV_{25}* ($\mathrm{cm^3\,mol^{-1}}$)	θ_{25}
2-Ethyl-1-butene + DMKM[b]	C—H—O	−32.8	1.05
2-Ethyl-1-butene + DMKM[c]	C—H—O	−34.9	1.12
2,4,4-Trimethyl-1-pentene + DMKM	C—H—O	−32.0	1.04
β-Pinene + DMKM	C—H—O	−31.3	1.06
β-Pinene + DMAD	C—H—C	−39.6	1.12
Acetone + DEKM	O—H—O	−30.0	0.88

[a] Solvent is CCl_4 or CH_2Cl_2. DMKM, DEKM = dimethyl and diethyl ketomalonate.
[b] Yielding *Z*-isomer.
[c] Yielding *E*-isomer.



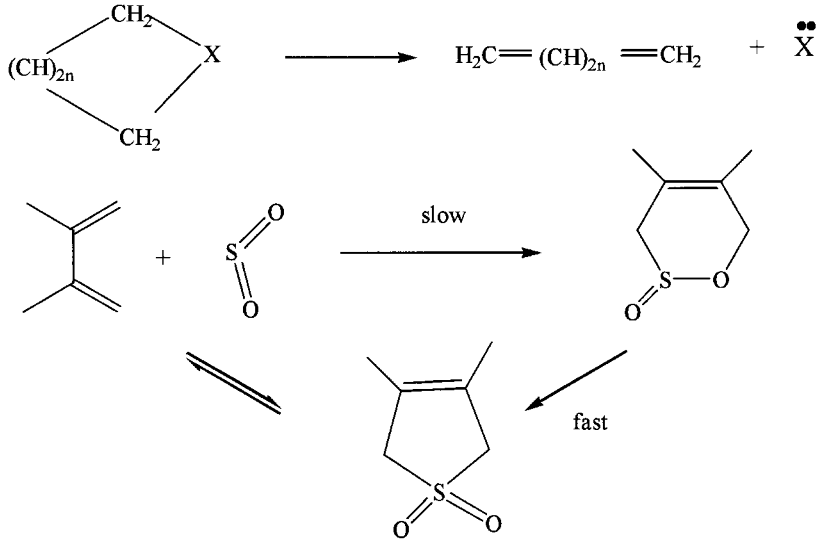
Scheme 14. Ene reaction and transition state with DEAD and 1,4-cyclohexadiene



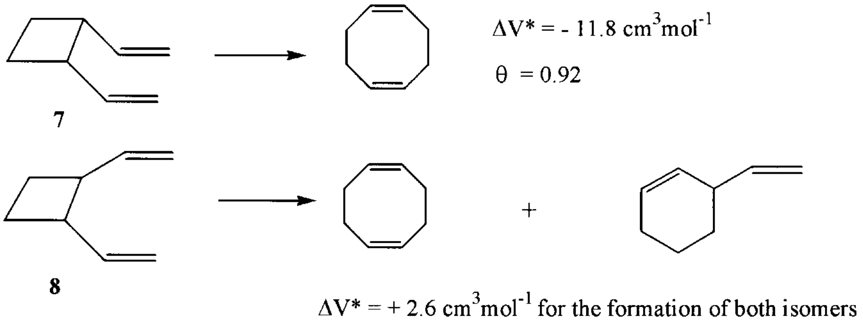
Scheme 15. Pericyclic transition state in the desulfination of allylic sulfinyl acids

highly ordered transition state with bond reorganization almost complete. The possibility of a mechanism consisting of a slow $[4+2]$ cycloaddition with rapid rearrangement of the resulting sulphenolactone was also evoked. Both mechanistic pathways are compatible with the ΔV^* and θ values.

Sigmatropic rearrangements. These reactions consist of intramolecular migration of a σ-bond. Most sigmatropic shifts experience concertedness, meaning that the shifting occurs through a cyclic transition state. Pressure kinetic studies corroborate this view in all respects. For example, in [3,3] sigmatropic shifts (Claisen, Cope) there is simultaneous bond breaking and bond formation. From a strict volume standpoint, such reactions should be little sensitive to pressure since the reaction volume is around zero. In fact, activation volumes have values ranging between -10 and $-18\,\text{cm}^3\,\text{mol}^{-1}$.[1] The negative sign refers to pericyclicity (high molecular ordering in the transition state). This is confirmed by large negative activation entropies and insensitivity of rate constants to solvents. In the same way, [1,9] and [1,5] sigmatropic shifts show comparable activation volumes and proceed, therefore, according to a concerted mechanism.[27]



Scheme 16. Mechanism of the formation of 3,4-dimethylsulfolene

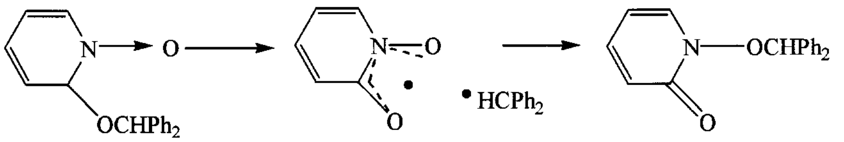


$\Delta V^* = -11.8\ cm^3mol^{-1}$

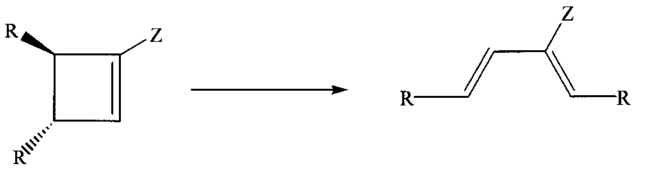
$\theta = 0.92$

$\Delta V^* = +2.6\ cm^3mol^{-1}$ for the formation of both isomers

Scheme 17. Rearrangement of *cis*- and *trans*-1,2-divinylcyclobutanes



Scheme 18. Radical intermediate in the [1,4] shift of a 2-alkoxypyridine-*N*-oxide



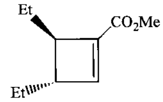
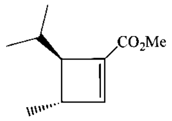
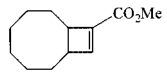
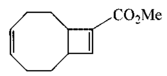
Scheme 19. Conrotatory opening of cyclobutenes

However, some [3,3] shifts may be stepwise as shown in the Cope rearrangement of *cis*- and *trans*-1,2-divinylcyclobutanes (Scheme 17).[28] The reaction involving the *cis*-isomer **7** is accelerated by pressure (concerted mechanism) whereas the corresponding rearrangement of the *trans*-isomer **8** is slowed. The reason is that the second process requires initial cleavage of the C-1—C-2 bond before undergoing rearrangement (stepwise mechanism).

A radical intermediate was postulated in a [1,4] shift in 2-alkoxypyridine-*N*-oxides. A positive value for ΔV^* (+ 10 cm^3 mol^{-1}) was obtained when R is CHPh$_2$ (Scheme 18).[29] The assumed radical is stabilized by the two phenyl groups.

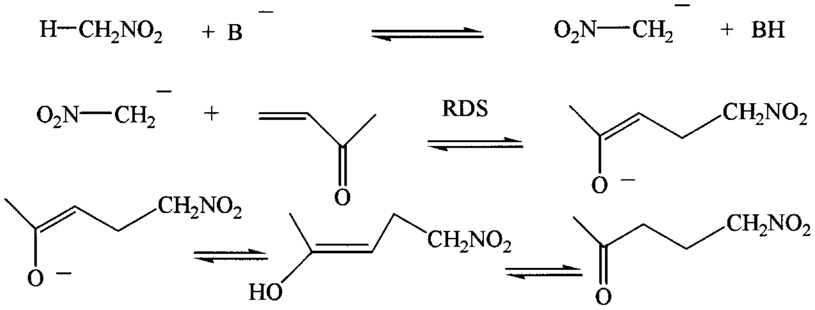
Electrocyclic reactions. The best example is represented by the conrotatory opening of cyclobutenes (Scheme 19). The pericyclicity of the reaction is testified by the clean stereochemistry. During the process strain is released and a σ-bond is cleaved. The geometric balance of these events results in a positive reaction volume (about +2 cm^3 mol^{-1}) and so also should be ΔV^* (intuitively, pressure should retard bond breaking). In fact, in such electrocyclic reactions, it was found that the conrotatory opening of cyclobutenes is promoted by pressure (Table 14).[30]

Table 14. Kinetic pressure effect in the conrotatory opening of cyclobutenes

Alkene	ΔV_{25}^* (cm^3 mol^{-1})
	−2.2
	−2.4
	−3.2
	−3.5

It is suggested that such concerted processes require a strict orbital topology fixing the direction of twisting of the cyclobutane ring. In other words, the conrotatory opening of cyclobutenes involves a very compact transition state before opening of the σ framework.

Michael reactions. The kinetic pressure effect was measured in the Michael addition of nitromethane to methyl vinyl ketone (Scheme 20).[31] In the base-catalyzed reaction the activation volume refers to the rate-determining step (−19.7 cm^3 mol^{-1}). Despite the formation of charged species (enolate), ΔV_m^* is negligible (pressure has no or little effect on the formation of



Scheme 20. Michael addition of nitromethane to methyl vinyl ketone

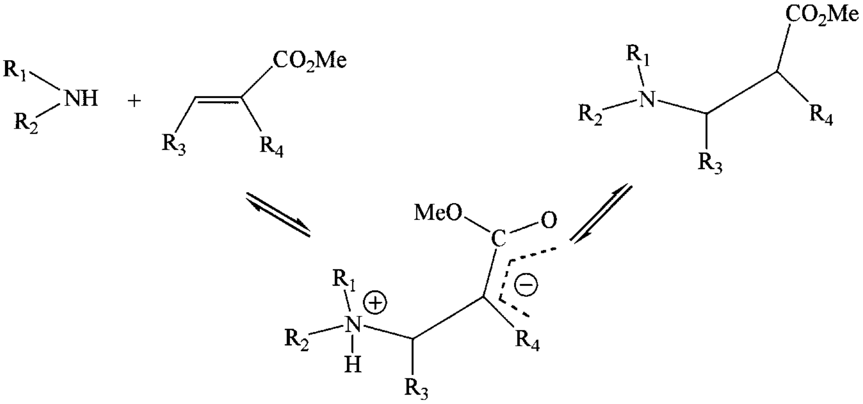
Table 15. Nitroaldol reactions[a]

Ketone	Nitroalkane	ΔV_{25}* ($cm^3\ mol^{-1}$)	ΔV_{25} ($cm^3\ mol^{-1}$)
Cyclopentanone	Nitromethane	−20.5	−22.5
Acetone	Nitromethane	−21.8	−24.3
3-Pentanone	Nitromethane	−20.8	nd
Acetone	Nitroethane	−24.8	nd

[a] Solvent, tetrahydrofuran; base, $Bu_4NF \cdot 3H_2O$.

Table 16. Addition of *tert*-butylamine to α,β-unsaturated esters

Acrylic ester	ΔV* ($cm^3\ mol^{-1}$)	ΔV ($cm^3\ mol^{-1}$)	ΔS* ($kJ\ K^{-1}\ mol^{-1}$)
Methyl acrylate	−42	−25.5	−176
Methyl crotonate	−45	−25.4	−217
Methyl methacrylate	−53	−26.5	−163



Scheme 21. Addition of *tert*-butylamine to unsaturated α,β-unsaturated esters

enolate, which is easily generated at ambient pressure). However, since such a reaction is reversible, the observed ΔV* should acknowledge the activation volume of the retro-Michael reaction. In fact, this volume amounts to zero. Since the reaction volume is $\Delta V_R = -20.8\ cm^3\ mol^{-1}$, $\theta = 0.95$ and the Michael addition is characterized by a late transition state.

The parent base-catalyzed nitroaldol reaction between ketones and nitroalkanes proceeds in the same way (Table 15). Although a similar conclusion is reached for the Michael-like reaction between amines and α,β-ethylenic esters, there is a notable difference since considerable electrostriction (generating a magnified ΔV_m*) occurs in the transition state owing to the formation of zwitterions strongly promoted by pressure (Scheme 21, Table 16).[32]

The very negative values for ΔV^* acknowledge $\Delta V_m{}^*$ and support a late transition state. This is in line with ΔS^* values and is based on the following reasoning. In an early transition state, the negative charge is delocalized over the entire molecule including the substituents (Scheme 21). According to the Drude–Nernst equation related to electrostriction, in this case, $\Delta V_m{}^*$ and hence ΔV^* should be different for a mono- and a diacrylic ester. However, this does not occur. When the ester is dimethyl maleate, $\Delta V^* = -45\ \mathrm{cm}^3\ \mathrm{mol}^{-1}$ compared with $\Delta V^* = -42\ \mathrm{cm}^3\ \mathrm{mol}^{-1}$ for the corresponding methyl acrylate addition (Table 15). The ΔV^* values are similar and support a transition state in which the formation of the C—N bond is completed, forcing the negative charge to a position remote from the substituent.

CONCLUSION

Based on the many examples highlighted in this review, the volume of activation ΔV^* may be a straightforward criterion to assess mechanistic details in organic reactions through its sign and absolute value. The actual significance of ΔV^* is of mechanistic value when the following precautions are taken:

- precise determination of rate constants versus pressure;
- decomposition of ΔV^* into volume terms reflecting all volume contributions arising during the progression of the reaction from initial to transition state (structural, steric, environmental, e.g. electrostriction and solvophobicity, etc.);
- comparison of ΔV^* with the reaction volume in order to locate the transition state along the reaction coordinate.

Taking into account these necessary requirements, pressure kinetic studies can play a remarkable confirmatory role in mechanistic delineation.

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