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Effect of pressure on sterically hindered reactions with late transition states

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ABSTRACT: The effect of high pressure is examined in two types of sterically congested reactions presenting late transition states: isopolar Diels–Alder cycloadditions of isoprene and quinones of various steric environment and conjugate additions of *tert*-butylamine and acrylic compounds. In the Diels–Alder cycloadditions, pressure has no enhanced kinetic sensitivity in sterically demanding reactions compared with unhindered ones. This is due to the structural closeness of the transition state and product. At variance, in the conjugate addition of amines, the effect of pressure is magnified with increasing steric congestion at the reaction centres. This is ascribed to enhanced electrostriction with removal of steric hindrance to ionization. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: steric hindrance; pressure; transition state; Diels–Alder reaction; Michael reactions

INTRODUCTION AND THEORY

Steric hindrance is an old and wide concept encompassing the effect of bulkiness of reactants and the steric accessibility of reaction centres on reagent approach. The effect of steric hindrance on reaction rates is well established, although quantitative aspects may still need refining. The major contributions to the quantification of these effects are due to early workers,[1] and more recent contributions refined the concept.[2] Among the various routes explored for the analysis of steric perturbations, it was proposed to consider activation parameters as indicators of steric congestion (see Refs 10 and 18–20 quoted in our previous review paper[3]). In this respect, the reaction volume and the activation volume are certainly the most convincing quantities as they are related to the size of the substituents, the spacing of the reactants and the modification of the virtual volume of the activated complex.

At the time when pressure was considered an interesting physical parameter in organic synthesis, it was soon recognized that, in some condensations, sterically congested reactions were more accelerated by pressure than would be expected from comparison with similar reactions free of steric hindrance.[4] This enhanced sensitivity to pressure was quantified later via the activation volume.[3,5]

We started some time ago a programme directed towards high-pressure synthesis of hindered functionalized compounds using Knoevenagel,[6] Passerini,[7] Strecker[8] and Stetter[9] reactions and cyanoalkylations[10] and miscellaneous reactions.[11] In all these processes we observed that the reactant bulkiness may severely influence the reactivity under pressure in the sense that greater steric hindrance induced an enhanced pressure kinetic response, confirming the results of the earlier and sparse related literature.[12] However, in contrast, sterically hindered Baeyer–Villiger oxidations of ketones did not conform to this kinetic scheme.[13]

The aim of the this work was to clarify the relationship between pressure and steric hindrance in specific reactions with late transition states.

Steric effects can be described by the Hammond postulate.[14] This popular concept states that for a single reaction step, the geometry of the transition state resembles the side to which it is closer in energy. This means that, as an example, the transition state of an endothermic one-step reaction will be more product-like than that for an exothermic similar reaction.

Space filling by substituents of gradual higher bulkiness slows the reaction and induces higher energy requirements. In other words, a steric perturbation in reactions of the same family is associated with a change in the position of the transition state. Its location is best defined by the nuclear positions on the reaction coordinate. From this point of view, the only, although indirectly, measurable activation quantity is the activation volume ΔV^*, which can be determined from a kinetic study as a function of pressure:

$$\Delta V^* = -RT(\partial \ln k/\partial P)_T \qquad (1)$$

ΔV^* results basically from two volume changes: molecular reorganization (ΔV_s^*) and interactions of reactants and activated complex with the medium (ΔV_ε^*):

$$\Delta V^* = \Delta V_s^* + \Delta V_\varepsilon^* \qquad (2)$$

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ΔV^*_s is the structural term and ΔV^*_ε the electrostriction term (rigorously considered, ΔV^* may also contain viscosity contributions, which are certainly negligible in the pressure range used for the present kinetic determinations).

Taking into account this version of the Hammond postulate, this should mean that when the transition state of similar reactions is structurally very close to the final state, an increase in steric constraints should not induce a magnified kinetic pressure effect compared with the normal effect expected for this type of reaction. However, this is true in so far as the volume shrinkage due to the application of pressure is the only consequence of bond reorganization: the geometric volume change resulting from bond breaking and forming. For polar reactions with late transition states, one may wonder whether the additional activation volume term ΔV^*_ε can be affected by steric effects.

As candidate reactions, we chose the Diels–Alder reaction of dienes with quinones and the conjugate addition of amines to acrylic compounds, both being characterized by late transition states. In our context, the lateness of a transition state is meant as the closeness of transition state and product in terms of volume, e.g. the nuclei of the activated complex are already near their final positions.

In [4 + 2] cycloadditions with normal electron demand (reaction of electron-donating dienes with electron-withdrawing dienophiles), the lateness of the transition state has been amply demonstrated in several ways, convincingly by pressure kinetics.[15] In these reactions, the values of $\theta = \Delta V^*/\Delta V_R$ lie between 0.8 and 1.0 (ΔV_R = reaction volume based on partial molar volumes). If the reactants have a low polarity, the transition and the ground states are nearly isopolar ($\Delta V^*_\varepsilon \approx 0$).

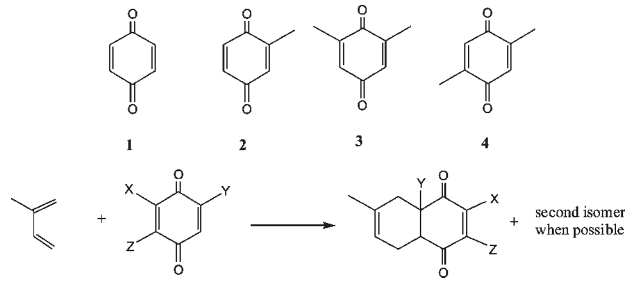
The Michael-like conjugate addition of amines to acrylic derivatives leading to β-amino compounds was shown to be strongly accelerated by pressure, pointing to a late and tight transition state.[16] In these reactions, $\theta = \Delta V^*_s/\Delta V_R \approx 1$ and ΔV^*_ε can take significant values depending on the medium.

Accordingly, we determined ΔV* values from the pressure effect on rate constants in the Diels–Alder reaction of isoprene and quinones with variable steric environment and the conjugate addition of *tert*-butylamine and acrylic compounds of increasing steric complexity.

RESULTS

Diels–Alder reaction of isoprene and quinones

The [4 + 2] cycloaddition of 1,3-dienes and quinones was studied a long time ago.[17] For our purpose, we chose four diversely substituted 1,4-quinones, **1**–**4** (Scheme 1). We investigated the kinetic solvent effect, the pressure effect and the temperature effect on the second-order rate constant in their reactions with isoprene.



Scheme 1

Table 1. Solvent effect in the Diels–Alder reactions of isoprene with quinones **1**–**3**[a]

		$10^6\,k$ (dm^3 mol^{-1} s^{-1})		
Solvent	δ^{2b}	**1**	**2**	**3**
Ethyl acetate	83	6.53	—	0.16
Tetrahydrofuran	83	4.58	—	—
Chloroform	86	—	0.87	0.36
Dichloromethane	104	—	0.52	—
Ethanol	161	14.58	2.23	0.81

[a] T = (303.3 K for reactions involving **1** and **2** and 312.8 K for those using **3**.

[b] Cohesion energy density.

According to Table 1, the solvent effect is small, showing an amplification ratio of 2–5 from low-polarity solvents to ethanol. Visibly, the reactions are quasi-isopolar despite the relative polarity of quinones. This implies weakly polarized transition states justifying the assumption $\Delta V^* = \Delta V^*_s$, although ΔV^*_ε might take a small value. As expected, the fastest reactions involve the quinones having at least one unsubstituted double bond (**1** and **2**) whereas **3** and **4** react more slowly by a factor of 10–15.

The pressure coefficient of reaction rates (Table 2) yields the activation volume (Table 3). All ΔV^* values were homogenized for $T = 298$ K with the aid of El'yanov's relationship.[18] The results underscore the remarkable uniformity of ΔV^* values, which are all in the range -32 to $-38\,\text{cm}^3\,\text{mol}^{-1}$. These are typical of normal electron demand Diels–Alder reactions. The reaction volume ΔV_R based on partial molar volumes of reactants and adduct also takes similar values so that θ is very close to unity.

Three conclusions can be drawn from these results:

1. Interestingly, the ΔV^* values do not vary within uncertainty limits according to the medium and, accordingly, are free of any electrostatic term.
2. The fact that θ is very close to unity demonstrates the extreme lateness of the transition state for these cycloadditions, pointing to a concerted mechanism, although the structures of the transition states are certainly not symmetrical with respect to the lengths of the two newly forming σ-bonds.
3. Finally, θ is independent of the steric requirements in the transition state. As suggested by a referee, the

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Table 2. Pressure effect on the Diels–Alder reactions of isoprene with quinones in different solvents[a]

	$10^6\,k$ (dm^3 mol^{-1} s^{-1})						
Pressure (MPa)	**1** (ethanol)	**2** (ethanol)	**2** (chloroform)	**3** (ethanol)	**3** (chloroform)	**4** (ethanol)	**4** (chloroform)
0.1	14.6	22.3	8.7	1.57	0.69	1.05	0.56
15	—	—	—	2.05	0.96	—	—
18	18.9	29.7	—	—	—	—	—
22	21.4	—	—	—	—	—	—
24	—	—	11.8	—	—	1.44	0.78
30	—	35.9	—	—	—	—	—
35	—	—	14.6	—	—	—	—
50	31.3	40.2	18.2	3.29	1.72	1.82	1.16
60	34.8	44.0	21.7	—	—	—	—
75	35.2	—	25.7	5.50	2.02	2.42	1.38
100	—	—	—	—	—	2.98	2.05

[a] T = 303.3 K for reactions involving **1** and **2**, 312.8 K for those using **3** and 314.2 K with **4** as the dienophile.

Table 3. Activation and reaction volumes of the Diels–Alder reactions of isoprene with quinones in different solvents[a]

Parameter	**1** (ethanol)	**2** (ethanol)	**2** (chloroform)	**3** (ethanol)	**3** (chloroform)	**4** (ethanol)	**4** (chloroform)
ΔV^*_{298} ($\pm$2.0 cm^3 mol^{-1})	−37.2	−35.2	−37.2	−38.1	−35.6	−32.3	−35.3
ΔV_R (at 298 K) ($\pm$1.5 cm^{3}mol^{-1})	nd	−37.4	−36.5	−35.4	nd	nd	−36.5
θ ($\pm$0.10)[b]	—	0.94	1.02	1.08	—	—	0.97

[a] nd, Not determined.
[b] $\theta = \Delta V^*/\Delta V_R$.

effect of steric hindrance on the fictive volume of the transition state caused by the higher degree of substitution on the concerted C atoms is compensated by the effect of longer partial bonds. Quantum chemical calculations could probably provide conclusive information on the steric effects reported here.

These conclusions are corroborated by the other activation quantities determined from a thermodynamic study. Inspection of the E, ΔS^*, ΔG^* values in Table 4 shows little change in the four quinone reactions. In particular, there is no enthalpic penalty in the most sterically hindered reactions. The ΔS^* values are highly negative, especially for the cycloadditions involving **3** and **4**. They are in accord with highly ordered transition-state complexes, confirming the concertedness of the mechanism.

From this study, it is concluded that hindered isopolar and concerted Diels–Alder reactions are no more endothermic than those of their unhindered analogues. Steric hindrance is manifested only in reduced rate constants for the dimethylbenzoquinone reactions. The results endorse our initial hypothesis based on the Hammond postulate, that in sterically hindered isopolar reactions with late transition states the pressure effect is the normal effect expected for unhindered reactions, with similar activation volumes.

Conjugate additions of *tert*-butylamine with acrylic esters and nitriles

The conjugate addition of amines to ethylenic compounds activated by electron-attracting groups consists in a nucleophilic attack taking place at the β-position of the olefinic double bond resembling the Michael reaction. The reaction mechanism has been investigated in a previous study.[16] The rate-determining step is nucleophilic attack on the activated double bond of the acrylic reactant with complete development of zwitterionic-like species which undergo rapid proton transfer (Scheme 2).[16,19]

The reaction is extremely sensitive to the steric accessibility of the reaction centres. In particular, α- and

Table 4. Activation parameters of the Diels–Alder reactions of isoprene with quinones in different solvents

Parameter	**1** (ethanol)	**2** (ethanol)	**2** (chloroform)	**3** (ethanol)	**3** (chloroform)	**4** (ethanol)	**4** (chloroform)
E ($\pm$2.5 kJ mol^{-1})	67.1	66.2	68.1	69.5	70.9	64.4	68.1
Ln A ($\pm$1.2)	15.3	15.2	15.4	13.5	12.9	10.3	12.3
ΔS^* ($\pm$9 J mol^{-1} K^{-1})	−118	−118	−117	−133	−137	−159	−143
ΔG^*_{298} ($\pm$10 kJ mol^{-1})	100	101.5	100.5	106.5	109	109	108

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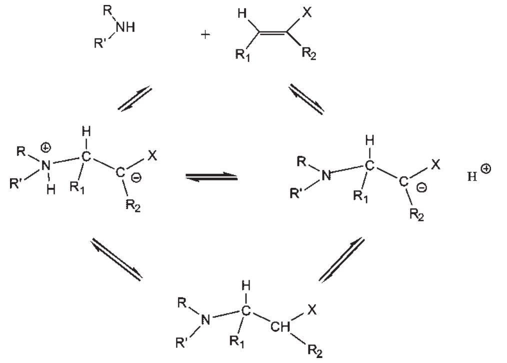

Scheme 2

Table 5. Kinetics of the addition of *tert*-butylamine to acrylic compounds at ambient pressure[a]

T (K)	X	Solvent	$k_0:k_X$	
			Crotonic	Methacrylic
308.9	$COOCH_3$	Acetonitrile	230	815
318.0	CN	Ethanol	880	1495

[a] k_0 = rate constant of the corresponding reaction involving the unhindered acrylic compound ($R_1 = R_2 = H$).

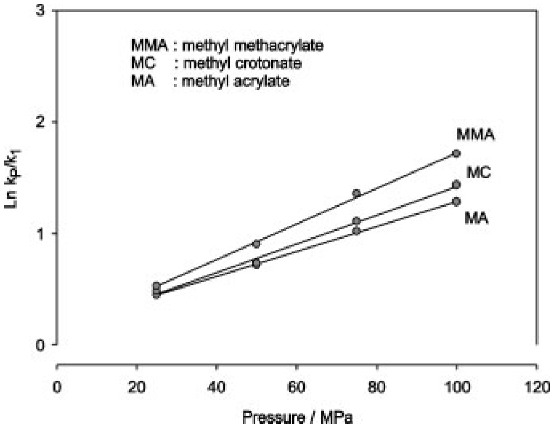

Figure 1. Pressure effect on relative rate constants in the addition of *tert*-butylamine to methyl acrylates (CH_3CN, 308.9 K)

β-methyl groups decrease the reactivity owing to a combination of electronic and, mainly, steric effects. Table 5 reports some results. Interestingly, independent of the nature of X, crotonic derivatives react faster than methacrylic compounds.

The pressure effect was examined in the addition reactions of *tert*-butylamine to unsaturated esters and nitriles. The kinetic behaviour of three unsaturated methyl esters is portrayed in Fig. 1. Clearly, the kinetic sensitivity to pressure is higher for the reactions involving methyl methacrylate and methyl crotonate. From the k values, the overall activation volumes can be deduced (Table 6).

In contrast with the above quinone Diels–Alder reactions, comparison of ΔV^* and ΔV_R values shows that the overall activation volume is much lower than the reaction volume; it follows, therefore, that Eqn (2) is applicable. This indicates that electrostriction is the dominant determining factor in high-pressure kinetics. Electrostriction interactions depend from the evidence on steric constraints imposed by R_1 and R_2 as ΔV^* becomes more negative (lower ΔV^* values) with restricted access to the α and β reaction centres in the acrylic compound. Such a result can be interpreted as a pressure removal of steric hindrance to ionization.[10] In other words, in the conjugate additions considered in this work, the pressure effect on steric hindrance is not manifested, or only slightly, in ΔV_s^* owing to the lateness of transition states, but is an integral part of ΔV_ε^*.

For the methacrylic ester, the methyl group destabilizes the anionic part of the dipolar transition state even if its steric effect is small. For the crotonate, the methyl substituent has a strong steric effect and a weak electronic effect. The stronger pressure kinetic enhancement for the methacrylate Michel reaction is due to enhanced pressure stimulation of the formation of ionic species. In this case, pressure compensates for the destabilizing effect of the methyl group on the anionic part of the dipole in the transition state.

The high negative ΔV^* values listed in Table 6 are also in line with the ΔH^* and ΔS^* values determined for two of these reactions.

At variance, it should be emphasized that the steric environment in the amine is much less crucial for the pressure kinetics with ΔV^* values between −48 and $-53\,cm^3\,mol^{-1}$ (Table 7). This is probably due to a high degree of C—N bond formation in the transition state and, simply, is in harmony with a late transition state.

The ΔV^* values listed in Table 6 can differ from those determined for the traditional base-catalysed Michael reaction. In a previous study, we examined the addition

Table 6. Activation parameters of *tert*-butylamine conjugate additions (homogeneized for $T = 298$ K)

X	R_1	R_2	Medium	ΔV^{*a}	ΔV_R^b	ΔH^{*c}	ΔS^{*d}
$COOCH_3$	H	H	CH_3CN	−39	−25.5	29.3	−176
$COOCH_3$	CH_3	H	CH_3CN	−43	−25.4	35.1	−217
$COOCH_3$	H	CH_3	CH_3CN	−50	−26.5	nd	nd
CN	H	H	CH_3OH	−35	−29.1	nd	nd
CN	H	CH_3	C_2H_5OH	−57	−28.6	nd	nd

[a] ± 3–$5\,cm^3\,mol^{-1}$.
[b] $\pm 1.5\,cm^3\,mol^{-1}$.
[c] $\pm 2.5\,kJ\,mol^{-1}$.
[d] $\pm 10\,J\,mol^{-1}\,K^{-1}$.

Table 7. Activation volumes in the addition of amines to methyl methacrylate (308.9 K, solvent acetonitrile)

R	R′	$-\Delta V^*$ ($\pm$3–5 cm^{3}mol^{-1})
Pr	H	48
*i*Pr	H	50
Bu	H	49
*i*Bu	H	53
t-Bu	H	53
Pr	Pr	51

of nitromethane to two differently crowded vinyl ketones catalysed by tetrabutylammonium fluoride.[20] The formation of the carbanion in this reaction does not require pressure assistance ($\Delta V^*_\varepsilon \approx 0$). Since $\Delta V^* \approx \Delta V_R$, steric effects do not induce a stronger pressure acceleration and should not be reflected in ΔV^* values. This is in fact the case since $\Delta V^*/\Delta V^*_R$ is close to unity for the Michael reactions involving either the unhindered methyl vinyl ketone or the highly congested mesityl oxide.[20] In the latter reaction, steric hindrance is evidenced only in the considerable slowing of the rate.

EXPERIMENTAL

Kinetic determinations. Isoprene, acrylic esters and nitriles were distilled before use. Other reagents were used as received. Kinetic measurements were performed as follows. Weighed reagents and internal standard (1,2,3-trimethoxybenzene or bibenzyl, depending on the reaction) were introduced in flexible PTFE tubes. After completing the residual volume with the solvent, the tube was closed and introduced into the thermostated ($\pm$0.1 °C) high-pressure vessel. After reaction, the solvents were removed *in vacuo*. The residue was then analysed by ^{1}H NMR (300 MHz). The kinetic data were reproducible to better than 5%. Activation volumes were determined in two ways: (i) from the initial slope of the smoothed log k values against pressure and (ii) from derivatization of the polynomial ($\log k = a + bP + cP^2$).

Determination of reaction volumes. Precision density measurements permit the apparent molar volume, Φ_V, to be determined according to the known equation

$$\Phi_V = M_w/d_0 - (1000/C)(d - d_0)/d_0 \qquad (3)$$

where M_w is the molecular weight of the solute and C its molar concentration and d and d_0 are the densities of the solution and the solvent, respectively. Extrapolation of Φ_V to zero concentration gives the value of the partial molar volume. Density measurements were performed at 25.0 °C in the corresponding solvent with a digital densimeter (Parr DMA 602).

CONCLUSION

This study shows that for sterically hindered reactions featuring late transition states the dependence of the pressure effect on the magnitude of steric congestion varies with the reaction type. It is small or non-existent as long as the volume of activation is a one-component structural expression. If steric hindrance to solvation or ionization is likely to intervene, the pressure kinetic acceleration is magnified with increasing steric congestion at the reaction centres. The pressure effect on sterically hindered reactions can, therefore, be clearly described by the Hammond postulate, expressed as follows: the more endothermic activated complex should involve more contraction along the reaction coordinate provided that there is some space for the transition state to progress toward the final state and, if occurring, stronger electrostriction owing to the corresponding higher polarization of the reactive species.

In addition, the clear predominance of electrostrictive and steric effects in the conjugate addition reactions is of high value for synthetic purposes. Activation volumes of -50, -60, -70 cm^3 mol^{-1} (values at 298 K) relate to rate amplification ratios of about 60, 130 and 300, respectively, at 300 MPa.

REFERENCES

1. Charton M. *Top. Curr. Chem.* 1983; **114**: 57–91; Gallo R. *Prog. Phys. Org. Chem.* 1983; **14**: 115–163; Hansch C, Leo A, Taft RW. *Chem. Rev.* 1991; **91**: 165–195.
2. Isizawa J, Sakakibara K, Hiroto M. *Bull. Chem. Soc. Jpn.* 1996; **69**: 1003–1015.
3. Jenner G. *J. Chem. Soc., Faraday Trans. 1* 1985; **81**: 2437–2460.
4. Gonikberg MG, Zhulin VM, El'yanov BS. *The Physics and Chemistry of High Pressure.* Society of Chemical Industry: London, 1963; 212–218.
5. Kiselev VD, Konovalov AI, Asano T, Kashaeva EA, Iskhakova GG, Shibab MS, Medvedeva MD. *J. Phys. Org. Chem.* 2001; **14**: 636–643.
6. Jenner G. *Tetrahedron Lett.* 2001; **42**: 243–245.
7. Jenner G. *Tetrahedron Lett.* 2002; **43**: 1235–1238.
8. Jenner G, Ben Salem R, Kim JC, Matsumoto K. *Tetrahedron Lett.* 2003; **44**: 447–449.
9. Jenner G. *High Press. Res.* in press.
10. Jenner G. *Tetrahedron* 2002; **58**: 4311–4317.
11. Jenner G. *High Press. Res.* 2002; **22**: 511–514.
12. Jenner G. *High Press. Res.* 1992; **11**: 21–32.
13. Jenner G. *Tetrahedron Lett.* 2001; **42**: 8969–8971.
14. le Noble WJ, Asano T. *J. Am. Chem. Soc.* 1975; **97**: 1778–1781.
15. Jenner G. In *Organic High Pressure Chemistry*, le Noble WJ (ed). Elsevier: Amsterdam, 1988; 143–203.
16. Jenner G. *New J. Chem.* 1995; **19**: 243–245.
17. Onishenko AS. *Diene Synthesis.* Israel Program for Scientific Translations: Jerusalem, 1964; 85–273.
18. El'yanov BS, Vasylvitskaya EM. *Rev. Phys. Chem. Jpn.* 1980; **50**: 169–184.
19. Shenhav H, Rapoport Z, Patai S. *J. Chem. Soc. B* 1970; 469–476; Rappoport Z, Peled P. *J. Am. Chem. Soc.* 1979; **101**: 2682–2693.
20. Jenner G. *New J. Chem.* 1999; **23**: 525–529.

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