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Kinetic effect of pressure on Michael and Diels–Alder reactions in aqueous solutions

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ABSTRACT: The kinetic pressure effect on some Michael-like and [4 + 2] cycloadditions in aqueous solution was studied. This effect is complex and variable, in contrast to the pressure dependence of rate constants in organic solvents. In order to determine the origin of this kinetic behavior, systematic solvent studies were made. As a general observation, for a given reaction, the pressure effect is weaker in water than in hydrocarbon solvents. For Michael reactions, the smaller effect is certainly due, at least in part, to the reduction in the volume of electrostriction. For Diels–Alder reactions, pressure alters the intensity of hydrophobic interactions. In the cycloaddition of isoprene with methyl vinyl ketone, the solvent dependence of the volume of activation suggests operation of electrostatic effects in conjunction with hydrophobic interactions and hydrogen bonding effects when the reaction is carried out in water. It is concluded that in aqueous Diels–Alder reactions the pressure effect is dependent on both solvophobic and polarity parameters, the weight of each being dependent on the reaction partners involved. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: pressure; kinetic effect; Michael reactions; Diels–Alder reactions; cycloaddition; aqueous solutions

INTRODUCTION

The importance of the solvent with respect to the course of organic reactions is well established. One of the first systematic studies of solvent effects on the rates of chemical reactions is due to Menshutkin, who determined rate constants for the addition of ethyl iodide to triethylamine.[1] This is a typical example of an ionogenic reaction in which the stability of the transition state is highly sensitive to the nature of the solvent. The solvent–solute interactions are acompanied by a volume shrinkage known as electrostriction, which is detected and quantified by means of high-pressure kinetics.[2] However, in addition to polar effects, reaction rates may also be affected by the medium in other ways. For example, hydrophobic interactions were shown to exert a strong influence on reactions involving water-immiscible organic compounds in aqueous solutions.[3]

In the last decade, numerous studies have revealed that water is able to induce dramatic rate accelerations in reactions such as Diels–Alder cycloadditions,[3,4] benzoin condensation,[5] Claisen rearrangements,[6] Mukaiyama aldol reactions,[7] Michael reactions,[8] Baylis–Hillman reactions[9] and 1,3-dipolar cycloaddition.[10] The origin of the kinetic effect has been debated. Most of the factors have been identified but their relative contributions are often not well known.[3,11–16]

Various factors were suggested and taken into account, e.g. hydrogen bonding, polarity, enforced hydrophobic interactions and micellar catalysis. An earlier suggestion considered the high cohesion energy density of water corresponding to an applied hydrostatic pressure of about 2000 MPa.[17] The cohesive energy density of water is so high that the water effect has been tentatively compared with the pressure effect, with the argument that water would act like a compressive medium retaining solvent ordering.[18] A comparable situation would occur with other highly polar media such as $LiClO_4$–diethyl ether solutions which develop in addition high internal pressures. However, no real correlation between pressure and solvents of high cohesive energy or internal pressure could be established.[19]

The most recent views consider that the acceleration is due to two main factors: hydrogen bonding effects and enforced hydrophobic interactions between the reactants.[20] The rate acceleration of reactions in aqueous solution versus those carried out in traditional organic solvents is certainly related to the peculiar interaction between water and the activated complex. Owing to their low solubility in water, organic molecules aggregate in such a way that the water–hydrocarbon interfacial area is reduced. Such interactions can involve volume changes which are potentially revealed by pressure studies.[21] In this respect, we felt that these investigations may provide

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

Medium	δ^2	T (K)	k_1 (dm^3 mol^{-1} s^{-1})[a]	$\Delta V^{\neq}$ (cm^3 mol^{-1})
Diethyl ether	55	317.2	1.50×10^{-6}	-55
Chloroform	86	317.2	1.60×10^{-6}	-54
Acetonitrile	141	317.2	1.63×10^{-6}	-56
Methanol	208	300.7	6.15×10^{-5}	-35
Ethylene glycol	213	300.7	8.68×10^{-5}	-33
Formamide	369	300.7	16.5×10^{-5}	-21
Water	547	300.7	82×10^{-5}	-25

[a] Second-order rate constant at ambient pressure.

useful information on the nature of the effect causing the rate acceleration.

RESULTS

Two types of reactions were examined in aqueous solution and in organic solvents. To ensure a homogeneous solution of organic molecules in water, the kinetics in aqueous solution were followed in PTFE tubes of large volume (15 ml). The concentration of substrates was chosen low enough that no visual separation or turbidity occurred after mixing them with water. The kinetics were followed in the 0.1–100 MPa range with low reagent concentrations compatible with their solubility in water, allowing the determination of homogeneous rate constants k (see Experimental section). The volume of activation ($\Delta V^{\neq}$) was deduced graphically from plotted ln k values against pressure and mathematically via El'yanov's procedure.[22] It was compared with the values obtained by solving of the quadratic equation $\ln k = \ln k_0 + bP + cP^2$.

The pressure effect was investigated for Michael-like reactions and Diels–Alder cycloadditions.

Michael-like reactions

The conjugate addition of amines α, β-ethylenic derivatives (Scheme 1) is highly sensitive to pressure.[23]

Scheme 1

The reaction between acrylonitrile and *tert*-butylamine has been studied in several organic solvents of increasing polarity (represented by their cohesive energy density, δ^2) and in aqueous solution. The results are listed in Table 1. It was necessary to adopt a slightly higher temperature (317.2 K) for the reactions carried out in the least polar solvents in order to obtain measurable k values. Examination of the kinetic values at atmospheric pressure shows that the reaction is hardly modified by the polarity of the solvent in diethyl ether, chloroform or acetonitrile. However, in the most polar media, the rate constant is significantly accelerated. This is clearly evidenced in Fig. 1, showing the kinetic discontinuity in the δ^2 range 140–160. However, the polarity of the solvent seems not to be the determining parameter as the difference in cohesion energy density between acetonitrile and methanol is relatively small.

The $\Delta V^{\neq}$ values also reflect this sharp dichotomy between the two groups of solvents. The activation volume is nearly constant in diethyl ether, chloroform, acetonitrile (*ca* -55 cm^3 mol^{-1}) whereas much higher values are determined in the most polar media. In alcohols $\Delta V^{\neq} \approx -35$ cm^3 mol^{-1} whereas in formamide and water the $\Delta V^{\neq}$ values reach -25 to -21 cm^3 mol^{-1}, meaning a net lowering of the reaction sensitivity to pressure.

How these results can be interpreted?

The reaction mechanism was investigated in a previous study.[24] The rate-determining step is a nucleophilic attack on the activated double bond of the nitrile with complete development of a zwitterionic-like species (Scheme 2) which undergoes rapid proton transfer.

The activation volume of such reactions is a composite

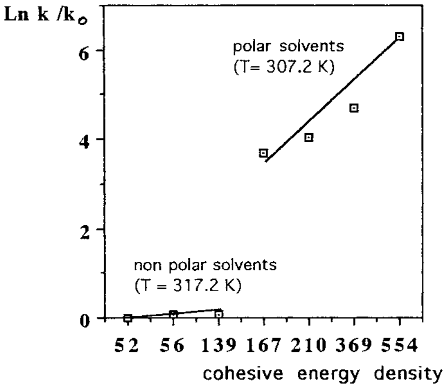

Figure 1. Effect of cohesive energy density of the medium on the kinetic ratio in the conjugate addition of *tert*-butylamine to acrylonitrile at ambient pressure (k_0 = rate constant in dichloromethane)

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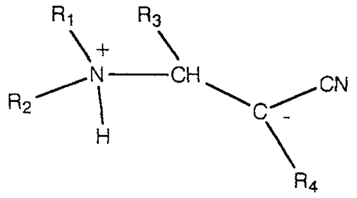

Scheme 2

quantity. When steric contributions can be neglected, the activation volume is written as

$$\Delta V^{\neq} = \Delta V^{\neq}{}_0 + \Delta V^{\neq}{}_e \qquad (1)$$

$\Delta V^{\neq}{}_0$ is the standard activation term, e.g. the variation in volume due to changes in the nuclear positions of the reactants during the formation of the transition state; $\Delta V^{\neq}{}_e$ is the volume effect generated from changes in solute–solvent interactions during the process. In the present case it refers to the formation of zwitterions. $\Delta V^{\neq}{}_0$ should approach $-20\ \mathrm{cm^3\ mol^{-1}}$ as a result of N—C bond formation in a late transition state.[24]

$\Delta V^{\neq}{}_e$ is the electrostriction component. The charge build-up is difficult in the less polar solvents, explaining the low *k* values at ambient pressure. However, pressure is known to assist the formation of zwitterions when feasible in low polar solvents. The Drude–Nernst equation:

$$V_e = (-q^2/2r\epsilon)(\partial \ln\epsilon/\partial P)$$

Where ε = dielectric constant, indicates that in such media the ionic forces operate over long distances with a fairly significant V_e. In highly polar solvents, the introduction of an ionic charge cannot magnify the pressure effect that much further. It is therefore not surprising that $|\Delta V^{\neq}{}_e|$ diminishes and eventually may vanish in such polar media as formamide and water. This was shown by Lees *et al.*,[25] indicating that the easy solvation of ions by formamide involves the oxygen atom for cations and the amino group for anions, i.e. mainly electrostatic interactions without the need for pressure assistance.

Although no extensive solvent studies have been made, the above results can be applied to analogous Michael reactions as for the conjugate addition of piperidine to methacrylonitrile. The determination of $\Delta V^{\neq}$ at 323.2 K led to similar values for the activation volume: $-50\ \mathrm{cm^3\ mol^{-1}}$ in chloroform and $-26\ \mathrm{cm^3\ mol^{-1}}$ in water.

Apart from these structural and electrostatic contributions, in aqueous media there are additional terms which are difficult to distinguish in the above reactions since $\Delta V^{\neq}{}_e$ cannot be calculated with reasonable accuracy. For this reason we turned to Diels–Alder reactions.

Diels–Alder reactions

The Diels–Alder cycloaddition is the prototypical example of a reaction showing a relative solvent insensitivity. In contrast, Diels–Alder reactions are fairly sensitive to pressure. The dependence is reflected in the volume of activation, $\Delta V^{\neq}$ (-25 to $-40\ \mathrm{cm^3\ mol^{-1}}$ at ambient temperature[26]). Solvent effects on $\Delta V^{\neq}$ values were previously investigated in [4 + 2] cycloadditions and were generally found to be fairly constant, indicating that the transition and initial states are nearly isopolar.[27] To our knowledge, the pressure effect in aqueous Diels–Alder reactions has not yet been reported except in a recent paper describing the condensation of anthracene-9-methanol and *N*-ethylmaleimide[28] and in a study emanating from our laboratory.[29]

The pressure kinetics of several Diels–Alder reactions were studied in CH_2Cl_2 and H_2O. The cycloadditions considered were normal electron demand cycloadditions (entries 1–4 and 6) and one inverse electron demand reaction (entry 5). Most of them have been investigated previously under pressure in our laboratory.[30] The water effect on *k* values is reflected in the *k* water: *k* dichloromethane ratios listed in Table 2. Clearly, there is a significant kinetic effect of water. The volume data are collected in Table 3, including the reaction (entry 6) reported in Ref. 28

Figure 2 shows an example of the pressure effect on the rate constant in CH_2Cl_2 and water (entry 5). It clearly shows a lower pressure dependence of *k* when the reaction is carried out in aqueous solution.

Table 2. Effect of the medium on *k* values in Diels–Alder reactions[a]

Entry	Reaction[b]	*T* (K)	$10^7\ k$ (dm^3 mol^{-1} s^{-1}) CH_2Cl_2	H_2O	Ratio
1	Cyclohexa-1,3-diene + MVK	313.2	1.6	1400	875
2	Isoprene + MVK	313.7	1.2	691	576
3	Furan + MVK	303.8	0.8	522	653
4	Isoprene + methyl acrylate	335.3	7.6	772	1020
5	HCCP + styrene	313.7	21	2500	1190

[a] At atmospheric pressure
[b] MVK = methyl vinyl ketone; HCCP = perchlorocyclopentadiene.

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Table 3. Effect of the medium on the activation volume in Diels–Alder reactions

Entry	Reaction[a]	T (K)	$\Delta V^{\neq}$ (cm^3 mol^{-1})[b]			θ[c]
			CH_2Cl_2	CH_3OH	H_2O	
1	Cyclohexa-1,3-diene + MVK	313.2	−38.0	−35.4	−32.0	0.84
2	Isoprene + MVK	313.7	−39.5	−35.0	−33.8	0.86
3	Furan + MVK	303.8	−32.4	nd	−28.5	0.88
4	Isoprene + methyl acrylate	335.3	−38.7	−38.5	−36.7	0.95
5	HCCP + styrene	313.7	−35.4[d]	−33.2	−28.0	0.79
6	AM + *N*-ethylmaleimide	318.2	−28.6[e]	−31.4[e]	−36.0	1.26

[a] AM = anthracene-9-methanol.
[b] Precision can be estimated to ±1.0 cm^3 mol^{-1}
[c] $\theta = \Delta V^{\neq}(\text{water})/\Delta V^{\neq}(CH_2Cl_2)$ (± 0.06).
[d] An earlier determination of $\Delta V^{\neq}$ (−38.5 cm^3 mol^{-1}) was made at 353.2 K in decane[30c].
[e] In heptane (−28.6 cm^3 mol^{-1}) and *n*-butanol (−31.4 cm^3 mol^{-1}).[28]

According to these results, it is evident that the volume of activation is dependent on the nature of the medium. Perceptible variations in $\Delta V^{\neq}$ are observed for most reactions on changing the medium from dichloromethane to water ($\theta < 1$). Except in reactions described in entries 4 and 6, $|\Delta V^{\neq}|$ decreases when the organic solvent is replaced by water. Our results prompted us to carry out a more detailed solvent and pressure study involving the cycloaddition of MVK to isoprene (entry 2), for which the volume of activation was clearly solvent dependent. The solvent study was made in order to establish a possible correlation between water and organic solvents with a large polarity difference. The polarity scale chosen was the cohesive energy density, δ^2, which is the energy associated with the different types of molecular interactions (dispersion forces, polar interactions, hydrogen bonding). The theory of regular solutions[31] predicts a linear correlation between rate constants and δ^2. When k_1 values are plotted as ln k/k_0 (k_0 is the rate constant of the standard reaction carried out in dichloromethane at ambient pressure) against δ^2, a linear plot is observed including water ($\delta^2 = 554$ and $\ln k_{water}/k_0 = 6.37$) (Fig. 3).

The pressure dependence of the rate constants on δ^2 was examined for this reaction in the same solvents and yielded the corresponding values for the volume of activation shown in Fig. 4. Again, a straight line is observed with values ranging from −41.5 to −32.6 cm^3 mol^{-1} when the reaction is carried out in bulk and in ethylene glycol, respectively. These values certainly reflect an additional electrostatic term $\Delta V^{\neq}_e$ (see Discussion) that, in contrast to most Diels–Alder reactions, cannot be neglected in the cycloaddition of MVK and isoprene, since it represents nearly 20–25% of the overall value of $\Delta V^{\neq}$. However, in aqueous solution, the volume of activation is close to −34 cm^3 mol^{-1}, a value which visibly does not follow the general trend. Extrapolation of the linear relationship valid in organic solvents would lead to a less negative value (Fig. 4). This result may reflect the particular properties of water considered as a medium for Diels–Alder reactions, although no anomaly could be detected in the rate diagram in Fig. 3.

DISCUSSION

Taken *ex abrupto*, the values of the volumes of activation

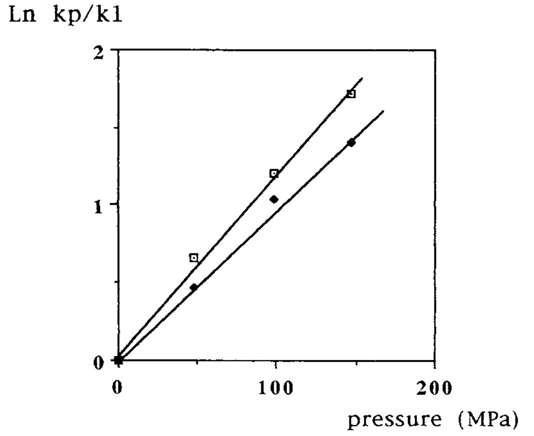

Figure 2. Effect of pressure on the relative rate constant of the Diels–Alder reaction between styrene and perchlorocyclopentadiene. ⊡: Dichloromethane, ◆: Water

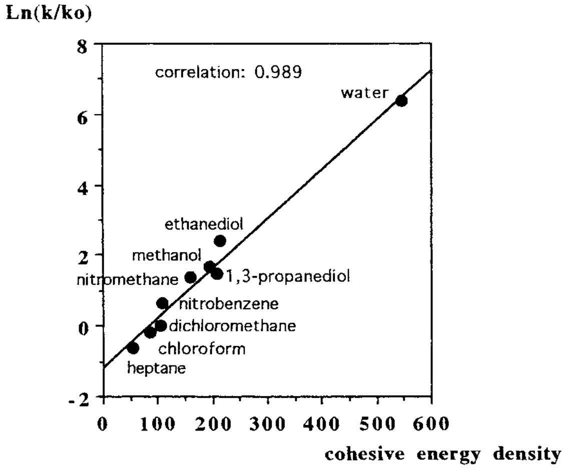

Figure 3. Application of the theory of regular solutions to the cycloaddition of methyl vinyl ketone to isoprene ($T = 313.7$ K) (k_0 = rate constant in dichloromethane)

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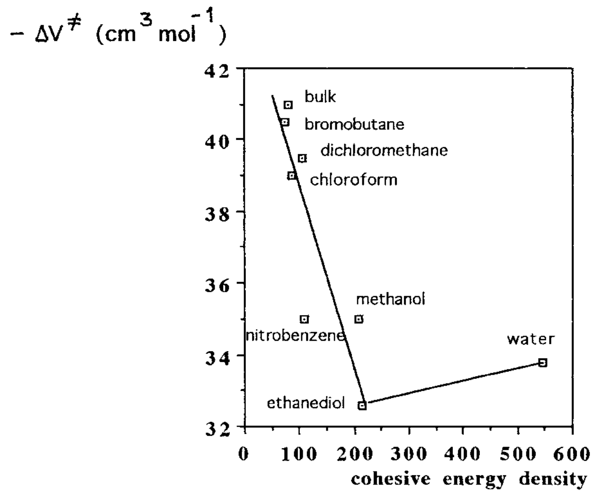

Figure 4. Solvent effect on the volume of activation in the cycloaddition of methyl vinyl ketone to isoprene (T= 313.7 K)

Table 4. Activation parameters in the Diels–Alder reaction between HCCP and styrene

Medium	E (kJ mol^{-1})	LnA	$\Delta S^{\neq}$ (J mol^{-1} K^{-1})
Water	67.4	16.81	−243
Dichloromethane	69.5	12.19	−331

obtained for the Diels–Alder reaction between isoprene and MVK in water and alcohols are not immediately interpretable. The results could suggest either a slightly weaker concertedness of the pericyclic process or specific interactions of the transition state with the medium such as a charge-transfer complex or hydrogen bonding or other effects. Concerning the first hypothesis, it seems unlikely that the nature of the medium causes a change in the mechanism which was established as archetypical of a normal Diels–Alder reaction, although synchronicity of formation of the two bonds may differ[32] as inferred by recent calculations showing that the asynchronicity can be made larger by an appropriate solvent effect, particularly water.[33] It can be envisaged that the partial molar volume of reactants and product in water are also altered in such a way that the $\Delta V^{\neq}:\overline{\Delta V}$ ratio is virtually unaffected ($\overline{\Delta V}$ = reaction volume based on partial molar volumes of reactants and product; $\overline{\Delta V}$ can be affected by mere structural parameters[34]) when compared with volume values determined in organic solvents. In fact, volume changes are to be expected when hydrocarbons are transferred from a non-polar medium into aqueous solution.[35]

The second hypothesis (specific interactions) is certainly not only plausible but also ascertained insofar as water considerably accelerates the rate of Diels–Alder reactions (Table 2). The origin of this special kinetic effect might be attributed to several reasons: (a) enforced hydrophobic interactions which induces a marked destabilization of the reactants; (b) specific solvation of polar transition states; and (c) hydrogen bond stabilization of the activated complex We now consider these points.

(a) Enforced hydrophobic interactions imply their participation as an integral part of the activation process.[36] The associative effect that reduces the water–hydrocarbon interfacial area is accompanied by a decrease in the volume of the reactants along the reaction coordinate in such way that pressure certainly influences this solvent-accessible surface during the activation process. For the reactions reported in this work, the $\Delta V^{\neq}$ values (entries 1, 2, 3 and 5) are indicative of a lower pressure enhancement in water opposed to the kinetic effect in conventional organic solvents of low polarity. Accordingly, in these reactions, hydrophobic interactions would at first sight be less efficient under pressure. This view would be in accordance with the reported values of the entropy of activation for aqueous Diels–Alder reactions: $\Delta S^{\neq}$ is less negative in water than in organic solvents.[37] A less negative $\Delta V^{\neq}$ value corresponds also to a less ordered transition state. To vindicate this point of view, we determined the activation energy and the activation entropy of the cycloaddition of styrene to HCCP (entry 5 in Table 3) (Table 4). Comparison of the respective values shows that whereas E was little affected, operation in water produced a change of ln A and $\Delta S^{\neq}$.

(b) In a previous paper,[29] it was shown that for furan cycloaddition (entry 3) the stereoselectivity was dependent on the polarity of the medium: the *endo* selectivity decreased with increasing polarity except in water, which favoured the most compact *endo* transition state. The result was rationalized by considering simultaneously hydrophobic interactions and polarity effects. According to this evidence, polar effects must be taken into account as revealed by variations in the volume of activation according to solvent polarity (Fig. 4). In the Diels–Alder reaction of isoprene with methyl vinyl ketone, $\Delta\Delta V^{\neq}$ is about 8 cm^3 mol^{-1} when the solvent is changed from dichloromethane to diols, well beyond data uncertainties, indicating that the transition state is more polar than the reactants. This phenomenon has not gone unobserved.[38–41] It may be compared with the transition state in pericyclic reactions such as $[4+2]$ cycloadditions;[38] as an example, in the Diels–Alder reaction of isoprene and maleic anhydride, $\Delta\Delta V^{\neq} \approx -7$ cm^3 mol^{-1} with a change of solvent from dichloromethane to nitrobenzene.[39] Concerning the aqueous Diels–Alder reactions involving methyl vinyl ketone (entries 1–3), electrostatic forces in this highly polar medium operate over short distances compared with those developed in non-polar solvents. Consequently, the volume $\Delta V_e^{\neq}$ must be small in water.[42] In other words, the absolute value of the

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activation volume is highest in apolar solvents, as indeed is observed experimentally. This reasoning agrees with the conclusions emanating from computational studies relative to the aqueous Diels–Alder reaction of cyclopentadiene with methyl vinyl ketone,[15,43] a closely related reaction to the cycloaddition described in entry 2 and the Claisen rearrangement of allyl vinyl ether.[16] Therefore, on an electrostatic basis, the highest (i.e. the least negative) $\Delta V_e^{\neq}$ and, consequently $\Delta V^{\neq}$ values should be observed in water.

(c) As this is not exactly the case, another effect should be taken into account. Water molecules may be considered as a continuous hydrogen-bonded network undergoing topological rearrangement resulting in a fluctuating system which is affected by physico-chemical and physical parameters, e.g. pressure. In an earlier paper, we suggested that hydrogen bonding is likely to intervene in aqueous Diels–Alder reactions involving MVK.[29] Taking into account hydrophobic and electrostatic effects, we suggest the following expression for $\Delta V^{\neq}$:

$$\Delta V^{\neq} = \Delta V_0^{\neq} + \Delta V_e^{\neq} + \Delta V_\Phi^{\neq} \qquad (2)$$

The quantity $\Delta V_\Phi^{\neq}$ relies on the specific volume changes associated with the interactions between water and the activated complex. In fact, based upon physico-chemical[14] and theoretical studies,[43,44] we propose it to be a combination of enforced hydrophobic interactions $\Delta V^{\neq}_{hi}$ and hydrogen bond effects $\Delta V^{\neq}_H$:

$$\Delta V_\Phi^{\neq} = \Delta V_{hi}^{\neq} + \Delta V_H^{\neq} \qquad (3)$$

The volume contribution to $\Delta V_\Phi^{\neq}$ due to hydrophobic effects is difficult to evaluate, but in a fact pressure has a detrimental effect on such interactions, meaning that $\Delta V_{hi}^{\neq} > 0$. On the other hand, hydrogen bond stabilization of polarizable activated complexes appears to be an important parameter in the hydrophobic acceleration of the rate of aqueous Diels–Alder reactions involving unsaturated carbonyl compounds.[45–47] Hydrogen bond formation is intuitively promoted by pressure. In fact, it is accompanied by slight negative volume changes due to shortening of the interatomic distances.[48] According to such reasoning, the experimental overall $\Delta V^{\neq}$ values obtained in aqueous cycloadditions involving MVK (entries 1–3) and the apparent discrepancy in Fig. 4 are now more understandable. $\Delta V_\Phi^{\neq}$ is thought to be negative with $|\Delta V_H^{\neq}| > |\Delta V_{hi}^{\neq}|$.

For the reaction in entry 4, the apparent insensitivity of $\Delta V^{\neq}$ to the medium may rely on hydrophobic and electrostatic effects equally matched.[49] In entry 5, perchlorocyclopentadiene and styrene are two apolar substrates which will interact in water according to enforced pairwise hydrophobic interactions.[14] In this reaction, $\Delta V_H^{\neq}$ and $\Delta V_e^{\neq}$ would be close to zero and the volume associated with pure hydrophobic effects ($\Delta V_{hi}^{\neq}$) would amount to $+7\,\mathrm{cm^3\,mol^{-1}}$. This value should be treated with caution as the $\Delta V^{\neq}$ terms in Eqn. (2) are approximate values (except $\Delta V_0^{\neq}$) and as the hydrogen bonding network of water probably does not fluctuate monotonously with pressure.[50] In contrast to our $\Delta V^{\neq}$ values in Table 2, the results in Ref. 25 show an opposite trend as the rate is more pressure dependent in water than in organic solvents. The authors proposed an increased solvation of the transition state. Although the θ value (1.26) is significant, an alternative partial explanation could be provided by considering enforced hydrogen bonding between the two carbonyl bonds of maleimide with water and the diene (anthracene-9-methanol) resulting in a large $\Delta V_H^{\neq}$ value.

CONCLUSIONS

The volume of activation of Diels–Alder reactions with normal electron demand may be dependent on the solvent although concertedness is preserved

The effect of pressure on organic reactions in aqueous solutions is complex. In the reactions studied in this work, the acceleration effect of pressure is lower in water than in organic solvents. In the aqueous cycloaddition of methyl vinyl ketone to isoprene, the kinetic effect is dependent not only on hydrophobic interactions of the substrates with water but also on the existence of hydrogen bonding and increased polarization of the transition state. As a general conclusion, the relative contribution of solvophobic and polarity parameters to the rate expression is obviously dependent on the nature of the reaction partners. These contributions are particularly reflected in the pressure dependence of the rate constant. As an example, the $\Delta\Delta V^{\neq}$ difference in the Diels–Alder reaction of HCCP and styrene (two unsaturated hydrocarbons) performed in dichloromethane and water, respectively, rather points to predominant hydrophobic interactions. As shown in this paper, volume contributions arising from structural, solvation and hydrophobic modifications during the progression of the reaction from the initial to transition state act in divergent ways, making the prediction of the pressure effect and the interpretation delicate. However, an aqueous medium should be considered for future high-pressure syntheses in the light of new concepts relating to hydrophobic effects.[51] We are pursuing the possible ramifications of such specific water interactions by means of high-pressure kinetics.

Experimental. Dienes and dienophiles were distilled prior to use. Experiments involving styrene were conducted in the presence of pyrogallol. Reactions in aqueous media were run with deionized water.

High-pressure experiments were carried out in flexible PTFE tubes of large volume (15 ml). A stock solution of

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weighed dienophile and internal standard was prepared and kept at -5 °C. In order to obtain homogeneous values of rate constants, the concentration of substrates was chosen low enough (about 10^{-3} mol dm^{-3} or less) so as no visual turbidity or demixing occurred after mixing 60 µl of the stock solution with water. The PTFE tube was filled with 60 µl of the stock solution and the corresponding diene. After completing the residual volume with water, the tube was closed and vigorously shaken for about 30s. before introduction into the thermostated (±0.1 °C) high-pressure vessel. The reaction times were usually not less than 15 h. After depressurization, the tube was removed from the vessel. Analysis was performed by gas–liquid chromatography (Girdel 300, 7% PPE on Chromosorb G AW DMCS; internal standards were mesitylene or diglyme according to reaction) and/or high-resolution ^{1}H NMR (all kinetic runs were at least duplicated). In the first case, dichloromethane (2 ml) was added to the aqueous solution. After shaking, the organic layer was isolated and analyzed. In the case of spectroscopic analysis, the organic layer was carefully collected by successive extractions with dichloromethane. After drying of the solution over magnesium sulfate, dichloromethane was removed in vacuo. The residue was then analyzed (1,2,3-trimethoxybenzene was the internal standard). The kinetic data were reproducible to better than 2–3%.

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