# Role of the Medium in High Pressure Organic Reactions. A Review

G. Jenner*

*Laboratoire de Piézochimie Organique (UMR CNRS 7509), 1 rue Blaise Pascal, Université Louis Pasteur, 67008 Strasbourg, France*

**Abstract:** As a thermodynamical parameter, pressure modifies the physical and physicochemical properties of liquids considered as media for organic synthesis. In a first part, the review details the effect of pressure on solubility, freezing point, and viscosity. The second paragraph examines the pressure effects on solute-medium interactions associated with volume changes.

There are two main pressure-sensitive interactions: electrostatic and solvophobic interactions.

i) Considering electrostrictive effects, the pressure rate acceleration is highest in apolar media. This is illuminated by many examples taken from unimolecular reactions, [4+2] and [2+2] cycloadditions, Michael reactions, Menshutkin quaternisations, Morita-Baylis-Hillman additions.

ii) Pressure reduces the magnitude of solvophobic (hydrophobic, fluorophobic), interactions meaning less pressure sensitivity of reaction rates.

In the last part, future high pressure media are outlined i.e. supercritical fluids and ionic liquids. However, the results reported to date do not permit to draw a clear conclusion.

High pressure synthetic applications are described in the light of the above emphasized effects. The results presented in the review should allow a judicious choice of the right medium for a rational design of a liquid phase organic synthesis under pressure.

**Keywords:** Pressure, medium effects, electrostriction, solvophobic interactions, ionic liquids.

## 1. INTRODUCTION

The creation of new molecules by new chemical routes and new activation processes highlights the power of organic chemistry, often combining art and science. Among physical activation modes, high pressure chemistry has been confirmed as a prominent synthetic method in organic synthesis where volume changes are concerned [1]. The fundamental effect of pressure in a chemical reaction is expressed by the volume of activation $\Delta V^*$ obtained from a kinetic study at various pressures and is given by the relationship of Evans and Polanyi in the transition state theory (Eq. 1):

$$\partial \operatorname{Ln} k / \partial P = - \Delta V^* / RT \qquad (1)$$

Obviously, organic synthesis under high pressure has a sense only if $\Delta V^*$ is negative and if its absolute magnitude is sufficiently large ($\Delta V^* < -15$ cm$^3$mol$^{-1}$). There are many books reporting high pressure effects on organic reactions [2-6]. The method is simple, innocuous, respecting the stability of the reactants and products. As a physical parameter, pressure influences thermodynamic and kinetic parameters, whence the problem of the medium in high pressure chemistry must be addressed.

The importance of the medium in organic reactions has been a major scientific issue ever. The traditional and basic role of a solvent is the solubilization of the organic reactants to form a homogeneous solution. However, a heterogeneous medium can also have determining effects, particularly from a kinetic point of view. For the rational design of a liquid phase reaction in terms of yield and selectivity, the selection of the optimum solvent system is of prime importance.

Solvents must be chemically inert toward the substrates involved in the reaction. They influence its course, however, through various physicochemical parameters (polarity, hydrogen bonding capacity, solvophobicity, viscosity.) [7]. Even, they can behave as catalysts. At last, in the light of recent environmental regulations, the solvent should be non-toxic, non-flammable, non-volatile, reusable etc.

The choice of solvent is even more crucial and complex for reactions under high pressure, since pressure can affect deeply some inherent properties, modifying the outcome of reactions (yield and selectivity). The present report gives a survey of the effect of pressure on the main physicochemical properties of the solvent and reviews the medium effect in high pressure reactions with special emphasis on reactions sensitive to electrostriction and solvophobic effects.

In addition to pressure induced modifications of the physical properties of the solvent, pressure can also deeply act on reaction rates, depending on the nature of the transition state through specific solvent-pressure interactions. This occurs when the formation of the transition state involves volume changes related to the nature of the medium.

The volume of activation $\Delta V^*$ is a reflection of all volume changes $\Delta V_i^*$ that may occur during the progression

*Address correspondence to this author at the Laboratoire de Piézochimie Organique (UMR CNRS 7509), 1 rue Blaise Pascal, Université Louis Pasteur, 67008 Strasbourg, France; Tel: (33) 0388416815; E-mail: jenner@chimie.u-strasbg.fr

of the reaction from ground to transition state and within the transition state (Eq. 2):

$$\Delta V^* = \sum \Delta V_i^* \qquad (2)$$

$\Delta V^*$ results basically from two main volume effects: molecular reorganization ($\Delta V_S^*$) and interactions of the reactants and activated complex with the medium ($\Delta V_m^*$) (Eq. 3):

$$\Delta V^* = \Delta V_S^* + \Delta V_m^* \qquad (3)$$

It is clear that the solvent effect will be reflected in $\Delta V_m^*$. If $\Delta V_m^*$ is zero, the reaction is said isopolar throughout, meaning that transition and ground state are both isopolar. If, however, $\Delta V^* \neq \Delta V_S^*$, the medium is certainly playing a kinetic role, which can be overwhelming in the kinetic pressure coefficient.

Equation 3 represents the general case based on transition state theory. However, it is pertinent to wonder whether the concept still holds for reactions carried out in highly viscous media. In such conditions $\Delta V^*$ should accommodate dynamic effects related to pressure induced changes of transport properties, such as self-diffusion and viscosity. Viscosity influences reaction rates and must be taken into account either at very high pressures for common organic solvents or at lower pressures for highly viscous media. When the friction between solute and solvent molecules takes significant importance, the viscosity part may well be predominant in such a way that $\Delta V^*$ takes following expression(Eq. 4) [8]:

$$\Delta V^* = RT \, (\partial \operatorname{Ln} \eta \, / \, \partial P)_T + \text{additional terms} \qquad (4)$$

Without diving into the exposition of theories which are out of context in this review, it suffices to evoke the simplest model to describe the dynamics of reactions in solution, e.g. Kramers model [9, 10]. With the basic assumption that the chemical transformation and the rearrangement of the solvent molecules in the solvation shell are concerted, the reaction can be described by one reaction coordinate [11, 12]. Sumi suggested to include a rate constant $k_f$ for the fluctuation-limited solvent rearrangement [13] so as(Eq. 5):

$$\frac{1}{k_{obs}} = \frac{1}{k_{TST}} + \frac{1}{k_f} \qquad (5)$$

$k_{TST}$ being the normal rate constant expected from transition state theory. Thus, equation 1 should acknowledge $k = k_{obs}$

## 2. EFFECT OF PRESSURE ON PHYSICO-CHEMICAL PROPERTIES OF THE MEDIUM

The action of an external parameter on the medium is not innocent. Pressure necessarily, influences the properties in many ways. The most evident observation is the reduction of volume by compression. The compressibility decreases with pressure and increases with temperature. However, it has no effect on rate constants.

### 2.1. Solubility

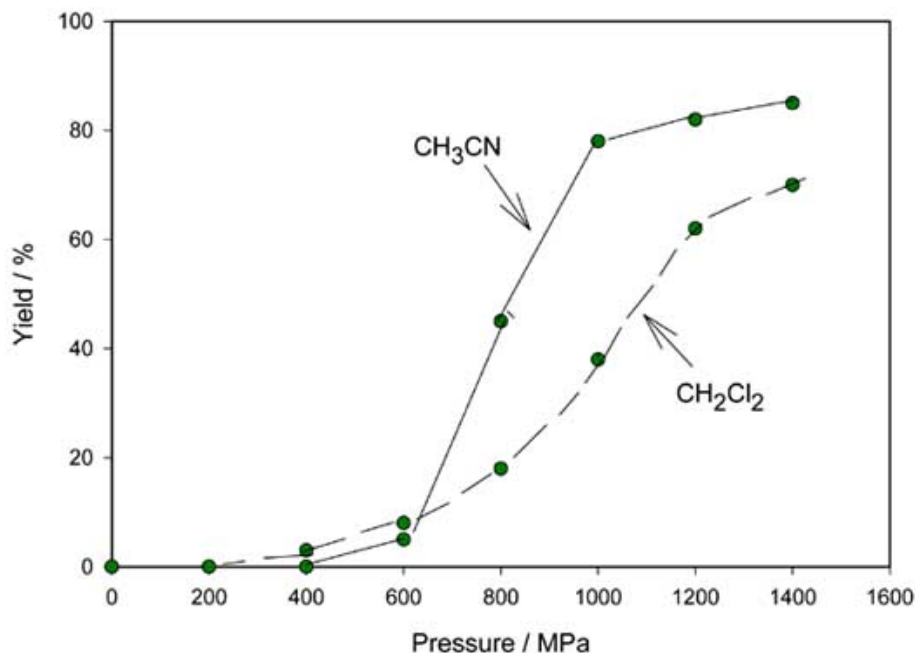Pressure increases the solubility of solids and miscibility of liquids whatever the medium. This can be important as it
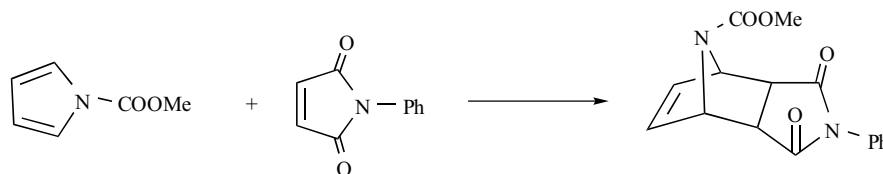


**Fig. (1).** Effect of pressure on the pyrrol Diels-Alder reaction in two solvents (Scheme 1).



**Scheme 1.**

is prone to influence the homogeneity of the medium. There is a representative example of the Diels-Alder reaction of a pyrrol with *N*-phenyl maleimide (Scheme 1) showing an extra acceleration of reaction rate in a given pressure range due to specific solvent effects (Fig. **1**) [14, 15]. In this reaction, the solvent effect cannot be correlated with polarity or viscosity. The authors proposed that the initially formed donor-acceptor complex between diene and dienophile is separated from the solvent in the range where the solvent freezes, increasing thereby, its effective concentration.

## 2.2. Melting Point

Even more important is the effect of pressure on melting points. With rare exceptions (water for example), melting points are depressed under pressure and the melting point graph has a positive slope. From a practical point of view, it is necessary to know if the reaction medium is susceptible to solidify in a pressure experiment. There are illustrative instances in the literature highlighting the importance of this effect. Thus, in the Henry addition of nitromethane to 2-butanone, the nitroalcohol yield at 750 MPa is 60% when the ketone serves as solvent, but only 9% under identical conditions with nitromethane as the medium due to the solidification of the nitro compound [16]. Similarly, the yield of the thiabicyclo[2.2.1]heptene adduct obtained in the cycloaddition of thiophene and maleic anhydride at 1500 MPa and 100°C is 47% in dichloromethane and only 6% in benzene (freezing point: 33.4°C at 100 Mpa) [17].

Most common solvents are solid at room temperature under a pressure as high as 1000 MPa. The melting curve is defined by the Clausius-Clapeyron equation:

$$dP / dT = \Delta H_f / T_o \, \Delta V \qquad (6)$$

$\Delta H_f$ : latent heat of fusion, $\Delta V$: change in volume on melting,

$T_o$: melting temperature at 0.1 MPa

A cursory, yet satisfactory, estimation of the solidification point can be made from application of Eq. 7 proposed by Simon and Glatzel [18].

$$P / \alpha = (T_P/T_c)^\beta - 1 \qquad (7)$$

$\alpha$, $\beta$: constants, $T_c$: critical temperature

Useful calculated melting points are listed in Table 1 for common solvents. From these data it is clear that in experiments carried out at high pressures (> 500 MPa), only solvents of low polarity – with the notable exception of methanol and ethanol- can be used, albeit obviously concentrated solutions modify $T_p$.

## 2.3. Viscosity

Another parameter, which is deeply affected by pressure, is viscosity. Pressure increases the viscosity of all liquids in an exponential way (Eq. 8).

$$\eta = \eta_o \exp (\gamma P) \text{ where } \gamma \text{ is the pressure coefficient} \qquad (8)$$

**Table 1.    Effect of Pressure on the Melting Points T_p of Solvents**

| Solvent | $\alpha$ / MPa | $\beta$ | $T_c$ / K | $T_P$ / °C | |
|---------|------|------|------|-----------|-----------|
| | | | | **0.1 MPa** | **500 MPa** |
| Acetonitrile | 525 | 2.06 | 229.3 | - 43.9 | 44.1 |
| Ethanol | 1060 | 1.61 | 155.9 | - 117.3 | - 75.0 |
| Dichloromethane | 1059 | 1.495 | 176.5 | - 96.7 | - 44.6 |
| Chloroform | 833 | 1.52 | 209.7 | - 63.5 | 12.5 |
| Carbon tetrachloride | 292 | 2.12 | 250.6 | - 22.6 | 128.1 |
| Dioxan | 730 | 3.3 | 284.5 | - 0.2 | 46.5 |
| Ethyl acetate | 760 | 2.2 | 189.6 | - 83.6 | - 34.6 |
| Chlorobenzene | 498 | 2.42 | 227.7 | - 45.5 | 30.3 |
| Nitrobenzene | 610 | 1.93 | 278.8 | 5.6 | 107.0 |
| *p*-Xylene | 464 | 1.76 | 286.5 | 13.2 | 160.9 |
| Formamide | 1070 | 2.7 | 275.7 | 2.5 | 201.5 |
| *tert*-Butanol | 129 | 5.6 | 298.7 | 25.5 | 123.1 |
| Diethyl ether | $\sigma$ [a] = 7.32 | | 157.2 | - 116.0 | - 40.0 |
| Nitromethane | $\sigma$ [a] = 7.15 | | 244.6 | - 28.6 | 45.4 |
| Methanol | $\sigma$ [a] = 16.3 | | 175.4 | - 117.3 | - 76.0 |

[a] $\alpha$ and $\beta$ were not determined. $\sigma$ represents the slope of the melting curve measured in  MPa K$^{-1}$

Viscosities of liquids at room temperature in the 0.1-1000 MPa range, generally, have pressure coefficients $\partial \text{Ln}\,\eta / \partial P$ between $0.8 \times 10^{-3}$ and $4 \times 10^{-3}$ MPa$^{-1}$.

At very high pressures viscosity can be so high that diffusion processes become rate-limiting, meaning that bimolecular rate constants, which are normally increased by pressure in the transition state theory, may decrease. An illustrative example is portrayed by the termination step of radical polymerization, which is actually retarded by pressure yielding polymers of higher molecular weight. Other examples have been reported in the literature, such as the displacement of bromide ion from ethyl bromide by alkoxide ions in alcohols (Fig. **2**). This reaction is first accelerated in the low pressure range, then is slowed down when pressure exceeds 2000 MPa (Fig. **2**) [19]. See also Fig. **4** in this paper.

More recent examples include Z/E isomerization of substituted azobenzenes, nitroazobenzenes and anilines [20]. Table 2 shows the pressure dependence of the rate constant for the isomerization of 4-(dimethylamino)-4'-nitroazo-benzene in a viscous silicon oil KF-54® at 25°C ($\eta_0 = 0.441$ p, $\gamma = 27.0$ GPa$^{-1}$) (Scheme 2) [21].

**Table 2. Effect of Pressure on the Isomerisation of 4-(Dimethylamino)-4'-Nitroazobenzene in KF-54 ®**

| P / MPa | $k_{obs}$ (s$^{-1}$) | $k_{TST}$ (s$^{-1}$) |
|---|---|---|
| 0.1 | 0.0154 | |
| 60 | 0.0217 | |
| 150 | 0.0337 | |
| 300 | 0.0651 | |
| 330 | 0.0714 | 0.0744 |
| 390 | 0.0748 | 0.0957 |
| 420 | 0.0613 | 0.1085 |
| 450 | 0.0402 | 0.1818 |

The rate constant due to the reaction itself ($k_{TST}$) increases normally with pressure. However, around 300 MPa, $k_{TST}$ becomes different of $k_{obs}$. Beyond that pressure,
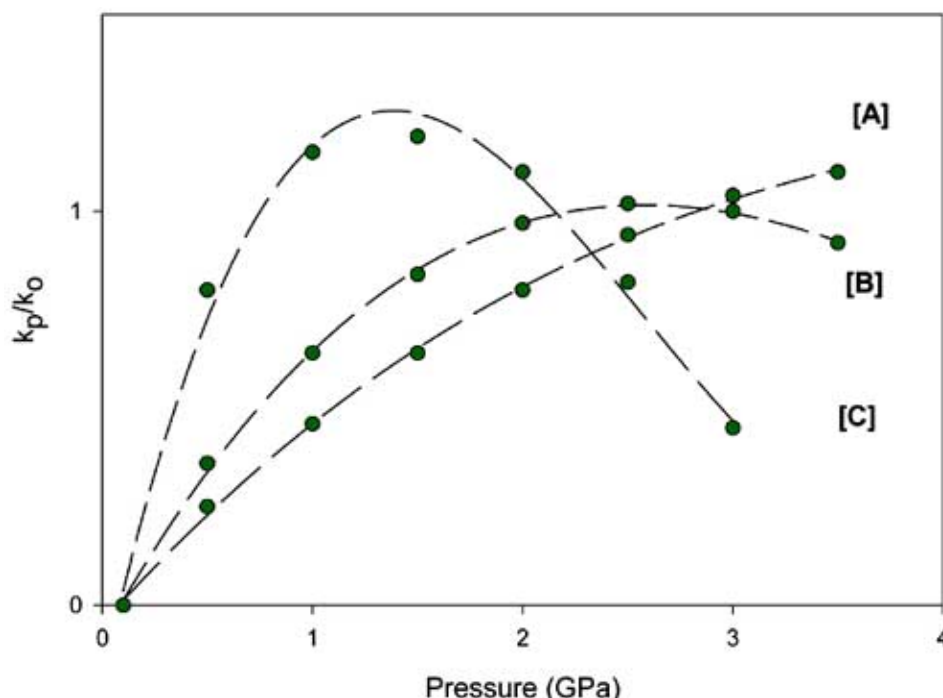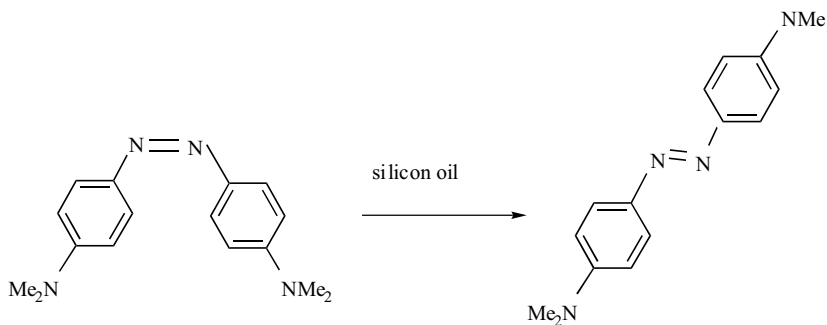


**Fig. (2).** Effect of pressure on rate constant ratio $k_p/k_0$ in reactions between $C_2H_5Br$ and alkoxide ions ($k_0$ is the value at ambient pressure). [A]: $CH_3O^-$ in methanol, [B]: $(CH_3)_2CHCH_2O^-$ in isopropanol, [C]: eugenoxide ion in a 1:1 eugenol-isopropanol mixture.



**Scheme 2.**

the reaction is retarded as $k_{obs}$ decreases, meaning predominance of viscosity effects (Eq. 5).

The present high pressure viscosity effects are in line with the vibrational activation theory stating that increasing viscosity of the solvent promotes bond making reactions. For very high viscous liquids, however, reactants in bimolecular reactions cannot locate each other due to diffusional effects. The problem has been emphasized by Firestone in examining Claisen rearrangements and Diels-Alder reactions either in apolar hydrocarbons or in glymes of increasing viscosity [22]. In both series the rate constants increase with higher viscosity like pressure. In a following paper, the authors could not confirm completely the results, but found a correlation between the rate constant and the density of solvent in such way that bond-making processes are accelerated by increased solvent density and viscosity [23]. As pressure affects both density and viscosity of the solvent, it is clear that all these factors are interrelated and influence not only kinetics but also selectivity, for example regioselectivity as shown in the [2+2] cycloaddition of styrene and 1,1-difluoroallene [24, 25]. However, Firestone's conclusions have been recently put into question [26] although, criticisms have been replied by the authors [27].

## 2.4. Miscellaneous Effects

Pressure causes changes in dielectric constant according to the description in terms of the Owen-Brinkley empirical equation (Eq. 9).

$$\varepsilon_o / \varepsilon_p = 1 - A \, Ln \, [(B+P) / (B+1)] \qquad (9)$$

where A and B are characteristic parameters for a liquid and the subscripts denote values at ambient and pressure P. The dielectric constant increases with pressure, the changes however, are small, but not unimportant. They determine the magnitude of electrostriction induced by the solvent in the vicinity of charged species (vide infra). Likewise, pressure increases the solvatochromic constant $E_T$-value, which is a measure of solvent polarity [28].

Other physical properties of solvents are also affected by pressure, such as refractive index, thermal conductivity, electrical conductivity, specific heat, surface tension. For a general overview of these phenomena, comprehensive books and reviews may be consulted [29].

A last remark will concern the thermodynamic concept of internal pressure $P_i$, which has been sometimes used abusively by correlating $P_i$ with mechanical external pressure. The internal pressure is the resultant of attractive and repulsive intermolecular forces in a liquid securing its cohesion (Eq. 10) [30]:

$$P_i = T(\partial P/\partial T)_V - P = \delta^2/n \quad (\delta^2\text{:cohesive energy density}) \qquad (10)$$

The denominator n is related to the intermolecular bond energy due to hydrogen bonds, dipole-dipole interactions etc. For non-polar liquids, n is close to unity. $P_i$-values may be high and are generally correlated with the polarity of the liquid: $P_i$ = 250 MPa for n-heptane and 2270 MPa for water. However, it was demonstrated that the internal pressure of the medium cannot be compared to applied external pressure [31]. $P_i$ is a physical property of the medium like $\varepsilon$, $E_T$, $\delta^2$.

## 3. EFFECT OF PRESSURE ON SOLUTE-MEDIUM INTERACTIONS CONNECTED WITH VOLUME EFFECTS

The reaction volume depends on three basic terms: the volume of the Van der Waals spheres, the voids around them and the volume change of the medium in the process of shell formation around the solute. The last contribution depends on solute-medium and medium-medium interactions. The same considerations hold for the activation volume.

Solute-medium interactions are usually detected through kinetic solvent effects. Hildebrand's theory is applicable to regular solutions (reactions with no ionic intermediates). It correlates rate constants with cohesive energy density $\delta^2$ or its square root, the solubility parameter $\delta$. For a bimolecular reaction, Eq. 11 applies:

$$A + B \dashrightarrow C$$
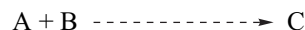
$$Ln \, (k_x / k_{ref}) = (1 / RT) \, [V_A(\delta_A - \delta_m)^2 + V_B \, (\delta_B - \delta_m)^2 - V_C(\delta_C - \delta_m)^2] \qquad (11)$$

V: molar volume

$\delta_A, \delta_B, \delta_C, \delta_m$: solubility parameter of A, B, C and medium

A typical example is shown in the cycloaddition of methyl vinyl ketone to isoprene (Fig. **3**)

Tables 3 and 4 illustrate respectively the solvent and the pressure effect on an apolar reaction (homo-Diels-Alder cycloadditions of norbornadiene) (Scheme 3) [33] and on a ionogenic reaction (conjugate addition of *tert*-butylamine to acrylonitrile) (Scheme 4) [32].
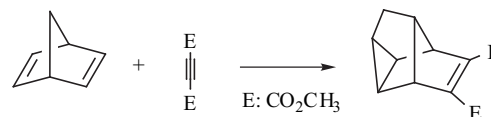
**Scheme 3.**
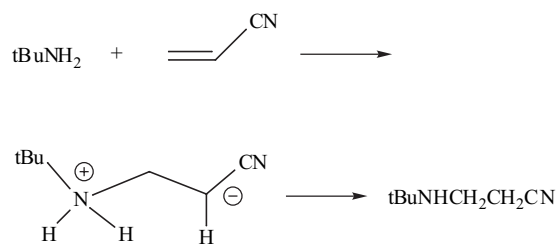
**Scheme 4.**

In the first case, the kinetic alteration is modest whereas the rate constant and the activation volume are both significantly affected in the ionogenic reaction. Coming back to Eq. 3, rate acceleration by pressure is diversely influenced by the solvent: $\Delta V_m^*$ is low or around 0 in the homo-Diels-Alder reactions, but can take considerable values in the conjugate addition, particularly in weakly polar solvents.

From the standpoint of $\Delta V_m^*$, there are two main contributions detailed hereafter: electrostriction and solvophobic interactions with the corresponding activation volumes leading to Eq. 12:

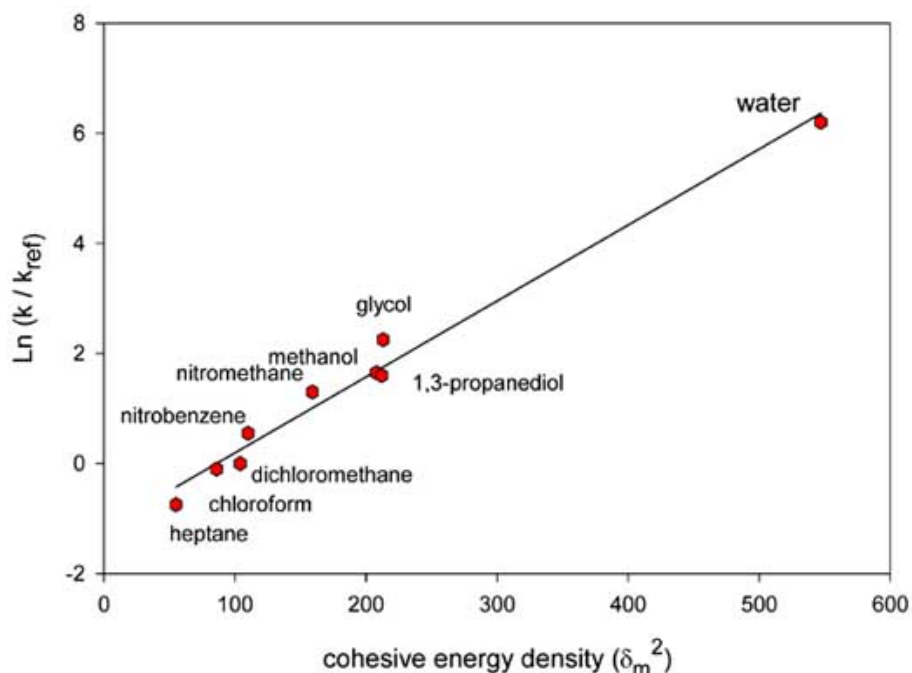$$\Delta V_m^* = \Delta V_\varepsilon^* + \Delta V_\varphi^* \qquad (12)$$

**Fig. (3)**. Application of Eq. 11 to the cycloaddition of methyl vinyl ketone to isoprene (dichloromethane is the reference solvent) [32].

**Table 3.    Homo-Diels-Alder Reaction Between Norbornadiene and DMAD or TCNE (Scheme 3) ($\Delta V_{25}$*: Volume of Activation at 25°C in cm$^3$mol$^{-1}$)**

| Solvent | $\delta^2$ | (reaction with DMAD) | | (reaction with TCNE) | |
|---|---|---|---|---|---|
| | | $k / k_{ref}$ | $- \Delta V_{25}^{*}$ | $k / k_{ref}$ | $- \Delta V_{25}^{*}$ |
| ether | 55 | 1 | - | 1 | - |
| toluene | 79 | - | - | 1.2 | 28.1 |
| benzene | 85 | 3.6 | 31.5 | 1.3 | - |
| acetone | 96 | 2.8 | - | 1.9 | - |
| dichloromethane | 104 | 4.1 | - | 3.1 | - |
| acetonitrile | 141 | 2.9 | - | 4.5 | 30.8 |

**Table 4.    Solvent and Pressure Effect on the Conjugate Addition Between Acrylonitrile and *Tert*-Butylamine (Scheme 4)**

| solvent | $\delta^2$ | $k / k_{ref}$ | $\Delta V^*$ (cm$^3$mol$^{-1}$) |
|---|---|---|---|
| ether | 55 | 1 | - 55 |
| chloroform | 86 | 1.1 | - 54 |
| acetonitrile | 141 | 1.2 | - 56 |
| methanol | 208 | 41 | - 35 |
| glycol | 213 | 58 | - 33 |
| formamide | 369 | 110 | - 21 |
| water | 547 | 550 | - 25 |

## 3.1. Electrostriction

   $\Delta V_\varepsilon$* in Eq. 12 represents the volume effects arising from changes in polarity during the formation of the transition state. Charge building-up during the reaction increases the strength of the interactions between reactants and solvent so that strong electrostatic forces tend to attract solvent molecules close around the charge. The resulting decrease in overall volume is called electrostriction. An estimation of the electrostrictive volume $V_e$ can be made by

using the Drude-Nernst equation (Eq. 13) or the equation proposed by Born and Kirkwood (Eq. 14).

$$V_e = ( - q^2 / 2 \, r \, \varepsilon ) \, ( \partial \, \text{Ln} \, \varepsilon / \partial \, P ) \qquad (13)$$

$$V_e = ( - \mu^2 / r^3 ) \, (2\varepsilon + 1) / (\partial \, \varepsilon / \partial \, P ) \qquad (14)$$

q is the charge, r the radius of the ion immersed in a solvent of dielectric constant $\varepsilon$ and $\mu$ the dipole moment. The medium dependence is given by $\partial \, \text{Ln} \, \varepsilon / \partial \, P$ (Eq. 13) or $\partial \, \varepsilon / \partial \, P$ (Eq. 14).

The derivative is largest in non-polar media and so is the volume decrease. This is easily understandable as in highly polar solvents, the introduction of an ionic charge cannot magnify the pressure effect that much further whereas in low polar media, ionic forces operate over long distances [34].

It follows that in ionogenic reactions $\Delta V_\varepsilon^*$ can vary in large proportions depending on the polarity of the medium. This is well illuminated by the example shown in Table 4 where $\Delta V_S^*$ is about $- 25$ cm$^3$mol$^{-1}$ so that $\Delta V_\varepsilon^*$ would vary from 0 to $- 30$ cm$^3$mol$^{-1}$. An interesting example of an ionogenic decomposition has been reported in the thermolysis of $\beta$-lactones (Scheme 5) [35]. Instead to be retarded by pressure, this reaction is in fact promoted meaning the involvement of a zwitterionic intermediate. Pressure assists its formation so that $\Delta V_\varepsilon^*$ takes a very negative value.
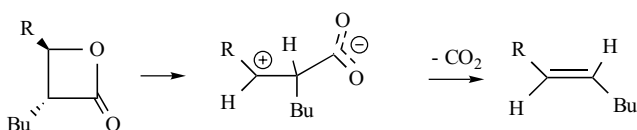
**Scheme 5.**

$$\Delta V^* = \Delta V_S^* \, (> 0) + \Delta V_\varepsilon^* \, (< 0) = - 28 \text{ cm}^3\text{mol}^{-1} \text{ (in dimethyl sulfoxide) at } 60°C$$

$$- 30 \text{ cm}^3\text{mol}^{-1} \text{ (in ethanol) at } 60°C$$

The case is not unique. The volumes of activation in the [2+2] cycloaddition of tetracyanoethylene to $\alpha$-methylstyrene are respectively $- 27$ cm$^3$mol$^{-1}$ for the forward reaction and $- 3.3$ cm$^3$mol$^{-1}$ for its reverse in chloroform [36]. The reaction involves a charge transfer complex both in the forward and in the reverse reaction.

The effect of pressure on ionogenic reactions has been investigated many times. This review reports representative examples.

### 3.1.1. Unimolecular Reactions

The pressure effect on thermal isomerizations of azobenzenes has been extensively studied by Asano's group (Scheme 6). It was possible to determine by pressure kinetics which mechanistic pathway is followed. In fact, $\Delta V^*$ was found to be dependent on the medium: at 40°C, $\Delta V^*$-values range from $- 3.0$ cm$^3$mol$^{-1}$ in hexane to $- 27.2$ cm$^3$mol$^{-1}$ in methanol, suggesting predominance of the rotational isomerization pathway, which must proceed via a highly dipolar transition state [37]. The argument was, however, contested by another group favoring the inversion mechanism [38, 39].

The thermal conversion of 6-nitrospiropyrans is retarded by pressure pointing to a biradical transition state (Scheme 7) [38]. $\Delta V^*$-values are $+ 10$ cm$^3$mol$^{-1}$ in non polar solvents and $+ 20$ cm$^3$mol$^{-1}$ in polar media. The difference was ascribed to reduced polarity of the transition state vs initial state ($\Delta V_\varepsilon^* > 0$).
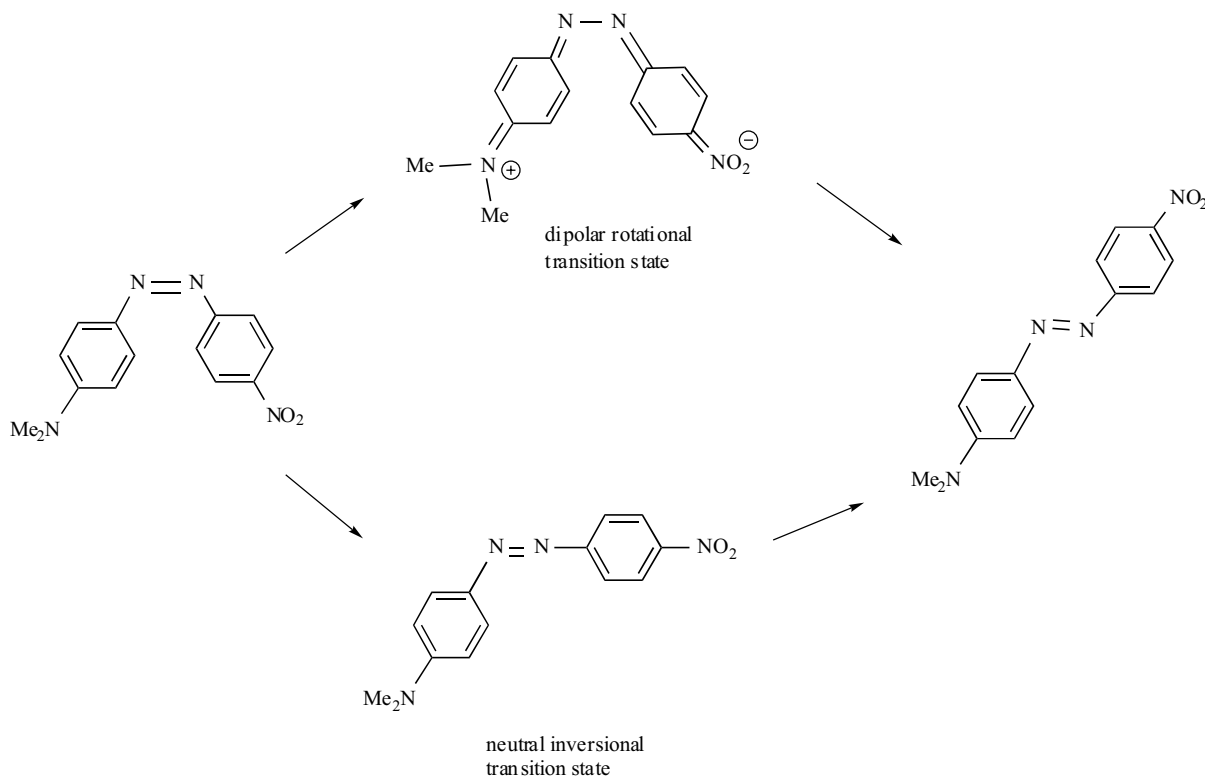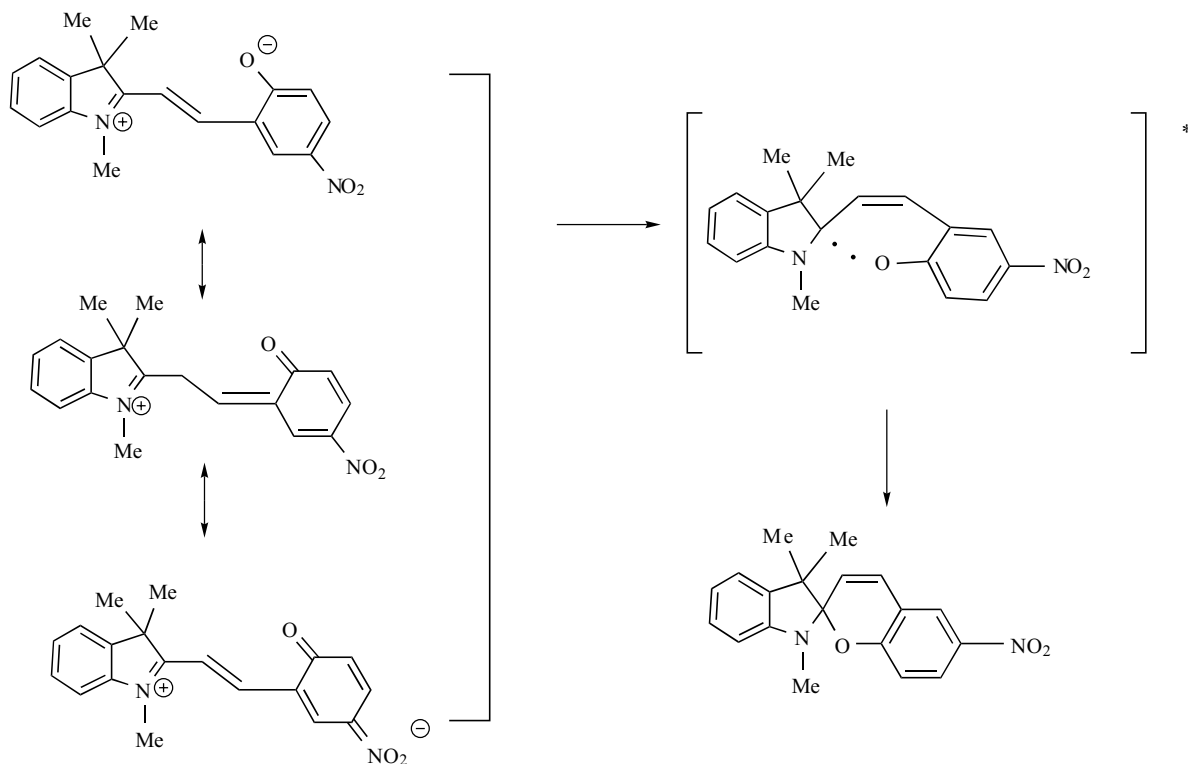
**Scheme 6.**

**Scheme 7.**

### 3.1.2. Diels-Alder Reactions and Related Cycloadditions

Although the Diels-Alder reaction and the [3+2] dipolar cycloaddition cannot be considered as ionogenic reactions, they may involve polar transition states depending on the reaction partners. In the normal electron demand [4+2] cycloaddition of 1,3-methoxy-1,3-butadiene to maleic anhydride $\theta = \Delta V^* / \Delta V_R$ ($\Delta V_R$: reaction volume) is 0.99 in acetonitrile, but 1.66 in dichloromethane, a weakly polar solvent reflecting the occurrence of electrostriction [40]. The isopolarity of Diels-Alder reactions was also questioned in the [4+2] cycloaddition of tropone with maleic anhydride and norbornene [41]. The reactions show $\Delta V^*$ variations when they are carried out in isopropylbenzene or *N,N*-dimethylformamide (Table 5). This was ascribed to the large dipole moment and resonance of tropone whereas the transition and the final states do not experience resonance and, accordingly, are less polar than the initial state, leading to less negative activation volumes in polar media.

In the same way, the pressure sensitivity of the $[\pi^6 + \pi^4]$ cycloaddition of tropone with 2,3-dimethylbutadiene [42] and 1,3-cyclohexadiene [43] (Scheme 8) is altered upon the change of the solvent. In the last reaction $\Delta V^*$ is $- 32.6$ cm$^3$mol$^{-1}$ in dimethylformamide and $- 37.6$ cm$^3$ mol$^{-1}$ in cumene. Visibly, in all these reactions involving tropone, $\Delta V_\varepsilon^*$ is a positive quantity.

**Table 5.    Effect of Pressure on Diels-Alder Reactions of Tropone**

| Dienophile | Solvent | $\Delta V^*$ (cm$^3$mol$^{-1}$) | $\Delta V_R^*$ (cm$^3$mol$^{-1}$) | $\theta$ |
|---|---|---|---|---|
| maleic anhydride | isopropylbenzene | - 21.4 | nd | nd |
| maleic anhydride | dimethylformamide | - 16.8 | - 25.5 | 0.66 |
| norbornene | isopropylbenzene | - 30.0 | - 33.5 | 0.90 |
| norbornene | dimethylformamide | - 27.8 | - 32.1 | 0.87 |
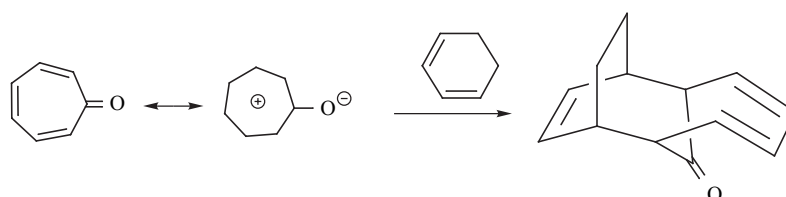


**Scheme 8.**
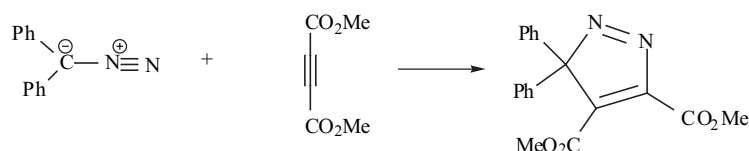
**Scheme 9.**

**Table 6.** Solvent Dependence of the Pressure Accelerated [2+3] Dipolar Cycloaddition of Diphenyldiazomethane and an Acetylenic Diester

| solvent | $\delta^2$ | $\Delta V^*$ (cm$^3$mol$^{-1}$) | $\Delta V_R^*$ (cm$^3$mol$^{-1}$) | $\theta$ |
|---|---|---|---|---|
| n-hexane | 53 | - 24 | - 34.9 | 0.69 |
| toluene | 79 | - 23 | - 26.8 | 0.86 |
| chlorobenzene | 90 | - 18 | - 26.4 | 0.68 |
| acetonitrile | 141 | - 15.5 | - 27.8 | 0.56 |

The same holds true for the [3+2] cycloadditions with dipolar character in the transition state [44]. Notable variations of $\Delta V^*$-values were observed in the 1,3-dipolar cycloaddition of diphenyldiazomethane to dimethylacetylene dicarboxylate (Table 6, Scheme 9) [45]. In this reaction, however, $\Delta V^*$ is likely a complex quantity as the volume of activation may contain a volum term originating only partly from electrostatic interactions. Swieton suggested that the solvation of the transition state occurs with reorientation in the solvation shell of the acetylenic diester, in line with the displacement of solvent molecules from the center of the cyclic compound during the reaction.

Apart from electrostatic interactions, $\Delta V^*$ may also vary in such cycloadditions for other reasons. In the Diels-Alder reaction of 1,4-diphenyl-2,3-butadiene and tetracyanoethylene, the dependence of $\Delta V^*$ on the solvent was ascribed to the π-donating character of aromatic solvents vs n-π and n-n interactions between n-donor solvents and the reagents [46].
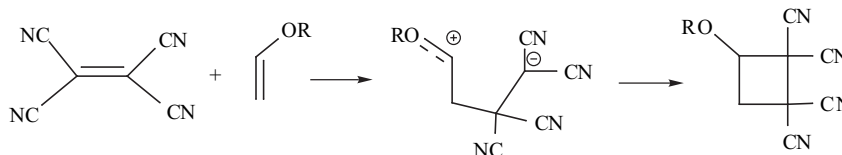
### 3.1.3. [2+2] Cycloadditions

[2+2] Cycloadditions are rarely concerted processes. Very often, they involve a zwitterionic intermediate. An illustrative example cited in all high pressure textbooks refers to the cycloaddition of tetracyanoethylene to enol ethers (Scheme 10) [47]. The volume of activation is strongly dependent on the solvent (Table 7). This was confirmed in a further study with various dihydropyrans and enol ethers [48].

Contrastingly, in the [2+2] cycloaddition of diphenylketen to n-butyl vinyl ether the dependence of $\Delta V^*$ on $\delta^2$ is small (- 28 cm$^3$mol$^{-1}$ in hexane, - 29 cm$^3$mol$^{-1}$ in CH$_2$Cl$_2$, - 32 cm$^3$mol$^{-1}$ in CCl$_4$, excluding the formation of an ionic intermediate and supporting a concerted mechanism [49].

The solvent may influence the chemoselectivity of [2+2] cycloadditions. In the high pressure reaction of ketene acetals with acroleine, the preferential formation of cyclobutanes in a polar solvent suggests that the transition state is more polar than the reaction leading to oxetanes (Scheme 11, Table 8) [50, 51]. The formation of dihydropyrans results from a [4+2] cycloaddition via a less polar transition state whereas oxetanes and cyclobutanes are formed via [2+2] cycloadditions involving polar intermediates.

From a synthetic point of view, use of solvents of low polarity (particularly toluene) in high pressure [2+2]



**Scheme 10.**

**Table 7.** Solvent Effect on the Pressure Accelerated [2+2] Cycloaddition of Tetracyanoethylene and n-Butyl Vinyl Ether

| solvent | $\delta^2$ | $\Delta V^*$ (cm$^3$mol$^{-1}$) | $\Delta V_\epsilon^*$ (cm$^3$mol$^{-1}$) (calculated) |
|---|---|---|---|
| carbon tetrachloride | 74 | - 50 | - 32 |
| benzene | 84 | - 43 | - 20 |
| acetone | 96 | - 35 | - 11 |
| dichloromethane | 104 | - 37 | - 18 |
| acetonitrile | 141 | - 29 | - 5 |

**Table 8.** **Chemoselectivity in High Pressure (1200MPa) Reactions of Enol Ethers with Acroleine**

| R$_1$ | R$_2$ | Solvent | % Conversion | Selectivity (%) | | |
|---|---|---|---|---|---|---|
| | | | | oxetane | pyran | cyclobutane |
| H | Me | acetonitrile | 100 | 0 | 35 | 65 |
| H | Me | hexane | 100 | 0 | 80 | 20 |
| OMe | OMe | acetonitrile | 70 | 10 | 10 | 80 |
| OMe | OMe | hexane | 35 | 30 | 30 | 40 |
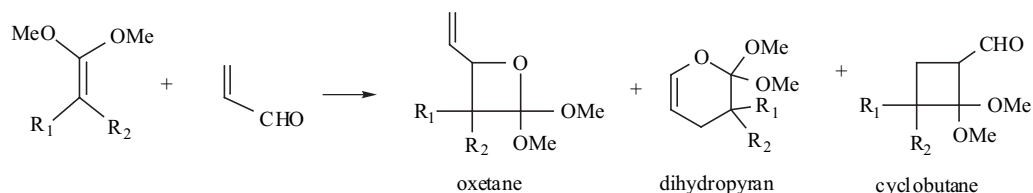


**Scheme 11.**

cycloadditions has permitted the synthesis of unprecedented very interesting β-lactams from sugars [52-55].

### 3.1.4. Menshutkin and Related Reactions

It designates the reaction of alkyl halides with tertiary amines. The reaction has been abundantly studied under pressure for steric and electrostatic reasons [56, 57]. The volume of activation, in all cases, is solvent dependent since the transition state involves strongly polar centers. Table 9 presents the results for reactions A-C portrayed in Scheme 12 [58-60].

Again it is clear that large electrostrictive effects are operating and are highest in solvents of low polarity. This becomes crystal clear for example in reaction D when it is
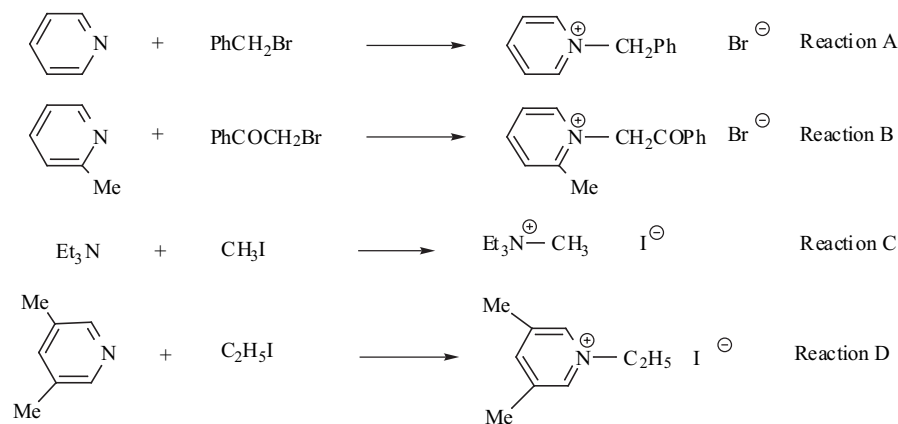


**Scheme 12.**

**Table 9.** **Solvent Effect on Pressure Accelerated Menshutkin Reactions**

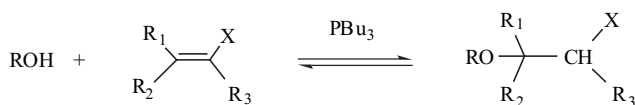| Solvent | δ$^2$ | - ΔV* (cm$^3$mol$^{-1}$) | | |
|---|---|---|---|---|
| | | A [58] | B [59] | C [60] |
| hexane | 53 | nd | nd | 45.4 |
| toluene | 79 | 39.1 | 30.2 | nd |
| benzene | 84 | 35.3 | nd | 40.1 |
| chlorobenzene | 90 | 29.1 | 26.7 | nd |
| bromobenzene | 92 | 24.9 | 26.3 | nd |
| acetone | 96 | 34.9 | 30.2 | 38.1 |
| nitrobenzene | 110 | nd | 21.1 | nd |
| methanol | 208 | 27.2 | nd | nd |

**Table 10.   Effect of Nitrobenzene on the Volume of Activation in the Menshutkin Reaction D**

| | Mole fraction of nitrobenzene (%) | | | | | |
|---|---|---|---|---|---|---|
| | **0** | **0.2** | **0.4** | **0.6** | **0.8** | **1.0** |
| $\Delta V^*$ ($cm^3mol^{-1}$) (experimental) | - 40.1 | - 38.8 | - 35.6 | - 32.0 | - 25.9 | - 22.1 |
| $\Delta V_\varepsilon^*$ ($cm^3mol^{-1}$) (estimated) | - 22.1 | - 20.8 | - 17.6 | - 14.0 | - 7.9 | - 4.1 |

carried out in benzene-nitrobenzene mixtures with progressive increased fraction of nitrobenzene (Table 10) [61]. $\Delta V_\varepsilon^*$ decreases noticeably with higher concentration in nitrobenzene. It should be added that earlier $\Delta V_\varepsilon^*$ estimations have been updated with a better precision [62].

### 3.1.5. Michael and Related Reactions

Together with the Diels-Alder cycloaddition, the Michael reaction is recognized as the most useful bond forming reaction in organic synthesis. The mechanism of the base-catalyzed version involves the facile formation of the carbanion in the initial stage. The transition state in the rate determining step – the nucleophilic attack on the β position of the acceptor – does not involve change of ionic charges. Accordingly, there is no additional electrostriction. This was exemplified in the pressure kinetic study of the Michael $Bu_4NF$ –catalyzed addition of nitromethane to methyl vinyl ketone for which the volume of activation was determined as $- 21$ $cm^3mol^{-1}$ , corresponding approximately to the reaction volume [63].



**Scheme 13.**
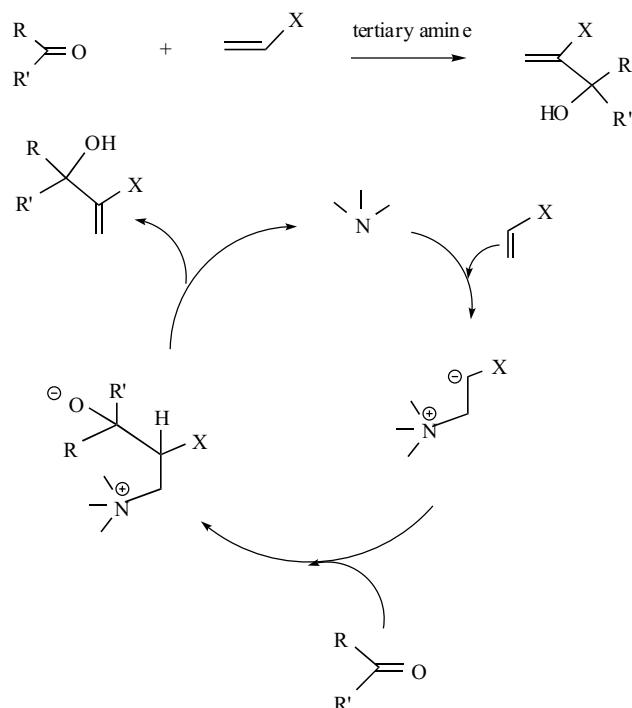


**Scheme 14.**

**Table 11.   Solvent Effect in the Pressure Accelerated Addition of 1-Propanol to Crotononitrile (Catalyst: Tri-n-Butylphosphine)**

| Solvent | $\delta^2$ | $10^6 k$ ($s^{-1}$) | $\Delta V^*$ ($cm^3mol^{-1}$) |
|---|---|---|---|
| tetrahydrofuran | 83 | 0.92 | - 46 |
| dichloromethane | 104 | 1.47 | - 46 |
| acetonitrile | 141 | 4.02 | - 50 |
| 1-propanol (reactant) | 142 | 18 | - 56 |
| formamide | 369 | 17 | - 53 |

The situation is drastically different in the phosphine-catalyzed nucleophilic addition of alcohols to acrylic compounds (Scheme 13). In the corresponding reaction of alcohols to acrylic nitriles, the $\Delta V^*$-values range from $- 40$ to $-75$ $cm^3mol^{-1}$ [64]. These astonishing negative values are considerably lower than those determined in the former Michael reaction [63] and, obviously, must accommodate electrostriction effects arising from ionogenesis leading to highly dipolar transition states. However, at variance with the solvent effect in Menshutkin reactions, the $\Delta V^*$-values do not vary so much with the polarity of the medium (Table 11). Although, there is an increase of rate constant with $\delta^2$, it is much less than the rate variation in ionogenic zwitterionic processes. This would mean that the electrostriction volume term $\Delta V_\varepsilon^*$ is important and relatively constant with a value around $- 25$ to $- 30$ $cm^3mol^{-1}$. We suggest that the result is connected with the presence of n-propanol in all runs, which is one of the reactants, thereby, conferring sufficient polarity to the medium even if it is mixed with non polar solvents.

Although alcohols are not water-like solvents, their hydrogen bonding network is of interest in high pressure asymmetric synthesis. A remarkable solvent effect was detected in the very high pressure (1400 MPa) conjugate addition of diphenylaminomethane to chiral π-stacked crotonates [65, 66]. Optically active β-aminoesters were formed in high yields (up to 93 %) and diastereoselectivity (up to 98 %) when methanol was the solvent. The results were ascribed to the pressure promoted formation of hydrogen bonds between alcohols and the carbonyl bond in crotonates.

### 3.1.6. Morita-Baylis-Hillman Reactions

These reactions are highly pressure dependent with $\Delta V^*$-values around $- 80$ $cm^3mol^{-1}$ referring to a multistep process involving zwitterions [67] as confirmed by mechanistic studies congruent with a third-order reaction (Scheme 14) [68]. The reaction is, therefore, necessarily affected by the medium and electrostriction is a major factor. The solvent
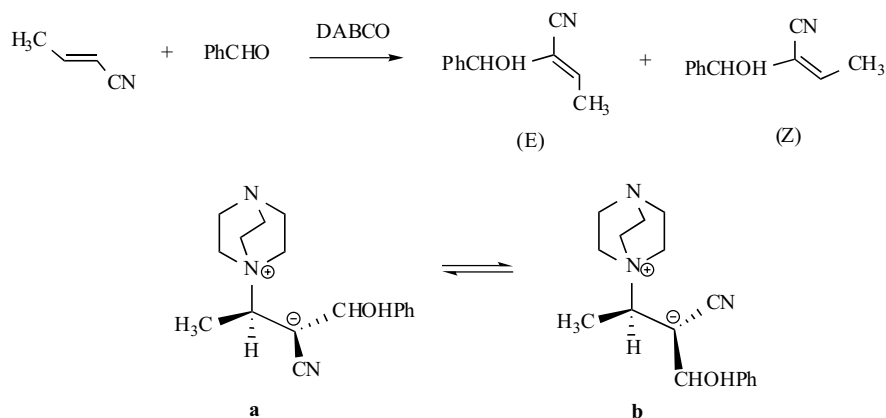
**Scheme 15.**

effect, however, cannot be fully ascribed to polarity factors, but also depends on hydrogen bond donor acidity and hydrogen bond acceptor basicity [69].

The medium has also an effect on the regioselectivity in the high pressure Morita-Baylis-Hillman addition of benzaldehyde to crotononitrile (Scheme 15) [70]. The E/Z ratio is strongly dependent on the solvent polarity. Polar solvents stabilize better the zwitterionic rotamers **a** and **b** leading to predominant formation of the E isomer.

## 3.2. Effect of Pressure on Solvophobic Interactions

The medium can stabilize the initial and the transition state differently through specific interactions. Accordingly, the activation energy is modified and so is the reaction rate. In the same way, the volume parameter may be changed as well if solvation occurs. This is reflected in the activation volume component $\Delta V_m^*$ with volume effects due to medium-solute interactions which have no electrostatic origin. The corresponding volume change is $\Delta V_\varphi^*$ defined in Eq. 12.

### 3.2.1. Effect of Pressure on Aqueous Reactions

It has been reported since two decades that reactions characterized by negative activation volumes are accelerated in aqueous solution at atmospheric pressure in the same way as under pressure [71, 72]. The induced rate acceleration can be considerable. As an example, an amplification factor of up to $10^6$ has been reported in a catalyzed Diels-Alder reaction carried out in water in the presence of micelles [73]. The origin of this kinetic change has been ascribed to several factors: high cohesive energy density of water ($\delta^2 = 554$ cal cm$^{-3}$), hydrogen bonding, enforced hydrophobic interactions, electrostatic interactions [74].

The rate acceleration of reactions in water vs reactions carried out in pure organic solvents is obviously related to the peculiar interaction between water and the activated complex. Due to their low solubility in water resulting from unfavorable entropy, organic molecules are forced to aggregate in order to minimize the water-hydrocarbon interfacial area [75]. This associative effect generates hydrophobic interactions, which can involve volume changes both in initial and transition state. A reaction proceeds via the small amount of dissolved reactants in water. If they are

completely insoluble, no hydrophobic interactions can develop and, consequently, no reaction is possible. At the opposite, if the compounds are fully soluble in water, hydrophobic effects are reduced to a minimum and the only kinetic effect of water is manifested through its polarity. A limited solubility of reactants in aqueous solution is therefore, a necessary condition. The chemical outcome of an organic synthesis performed in water depends on the effective concentration of reactants, which addresses the problem of heterogeneity. In addition, the hydration sphere must accommodate the product for as long as it forms during the progression of the reaction.

Solvophobic interactions involve small to fair volume changes which can be detected through pressure studies. Only a limited number of organic reactions in aqueous media have been investigated under pressure. There is a result shown in Table 4 reporting an experiment in water (conjugate addition of *tert*-butylamine) [32]. In this reaction however, as a zwitterionic intermediate is generated in the highly polar medium, it is difficult to attribute the kinetic alteration as well as the corresponding $\Delta V^*$ to hydrophobic interactions. It is more probably, a result of electrostriction $\Delta V_\varepsilon^*$.

The case of aqueous Diels-Alder reactions could be more convincing since $\Delta V_\varepsilon^*$ is normally low. An extensive study reported the effect of pressure on the kinetics of various Diels-Alder cycloadditions in water [32]. The corresponding $\Delta V^*$-values are listed in Table 12. A cursory comparison of $\Delta V^*$-values in $CH_2Cl_2$ and in water solution, respectively (the two extremes in Table 12 considered from the standpoint of polarity) indicates that the variations are not negligible, except in entry 4. The general trend is that aqueous Diels-Alder reactions become less pressure sensitive. A deeper dissection of each reaction reveals interesting features. Reactions described in entries 1-3 all involve methyl vinyl ketone, a polarizable molecule. They are, therefore, faced with electrostatic interactions although moderately in such way that $\Delta V^*$ should contain $\Delta V_\varepsilon^*$. As water is the highest polar medium used in the above reactions, $\Delta V_\varepsilon^*$ is minimal. In addition, the carbonyl bond in the dienophile develops hydrogen bonds with water molecules. It results that hydrophobic acceleration is due to hydrogen bonding stabilization by water of the activated complex. The pressure kinetics of such aqueous Diels-Alder reactions plays a confirmatory role in the rate enhancement

**Table 12. Effect of the Medium on ΔV*-Values in Diels-Alder Reactions[a]**

| Entry | Reaction | T(°C) | $-\Delta V^*$ (cm$^3$mol$^{-1}$) | | | |
|---|---|---|---|---|---|---|
| | | | $CH_2Cl_2$ | $CH_3OH$ | $(CH_2OH)_2$ | $H_2O$ |
| 1 | Isoprene + MVK | 40.5 | 39.5 | 35.0 | 32.5 | 33.9 |
| 2 | 1,3-Cyclohexadiene + MVK | 40.0 | 38.0 | 35.4 | nd | 32.0 |
| 3 | Furan+ MVK | 30.5 | 32.4 | nd | nd | 28.5 |
| 4 | Isoprene + methyl acrylate | 62.1 | 38.7 | 38.5 | nd | 36.7 |
| 5 | HCCP + styrene | 50.4 | 35.4 | 33.2 | nd | 28.0 |

[a] MVK (methyl vinyl ketone), HCCP (hexachlorocyclopentadiene)

by hydrogen bonding with a corresponding extra volume of activation called $\Delta V_H^*$ of about – 4 cm$^3$mol$^{-1}$ [76]. The fact that the ΔV*-values are higher (e.g. less negative) when water is the medium suggests that, despite the negative $\Delta V_\varepsilon^*$ and $\Delta V_H^*$, pressure exerts a salting-in effect, thereby, reducing the magnitude of hydrophobic interactions [77]. This is clearly apparent in the HCCP-styrene cycloaddition (entry 5) for which electrostriction (two apolar molecules are involved) and hydrogen bonding are non existent. The corresponding volume of activation increases by 7.4 cm$^3$mol$^{-1}$ when the medium is changed from dichloromethane to water. In the acrylate reaction (entry 4) ΔV*-values are seemingly constant, probably related to equally matched hydrophobic and electrostatic effects.

Taking into account all these volume terms, Eq. 12 can be expanded into Eq. 15:

$$\Delta V_m^* = \Delta V_\varepsilon^* + \Delta V_\varphi^* \qquad (12)$$

$$\Delta V_\varphi^* = \Delta V_H^* + \Delta V_{hi}^* \qquad (15)$$

$\Delta V_H^*$ : volume of activation related to formation of hydrogen bonds

$\Delta V_{hi}^*$: volume of activation related to enforced hydrophobic interactions [78].

With these volume components the ΔV*-values listed in Table 12 can now be interpreted. In reactions (entries 1-3), $\Delta V_\varphi^* < 0$ meaning that $|\Delta V_H^*| > |\Delta V_{hi}^*|$, whereas in

reaction (entry 5), $\Delta V_H^* \sim 0$ so that $\Delta V_\varphi^* \sim \Delta V_{hi}^* > 0$. Of course, due to the concerted nature of the [4+2] cycloaddition, the structural term $\Delta V_S^*$ is negative. It should be added that water can also affect the stereoselectivity. Water is an *endo*-orienting medium, as demonstrated in the Diels-Alder reaction of furan and methyl vinyl ketone at 300 MPa [79].

From a synthetic point of view, combination of high pressure and hydrophobic activation could be a powerful preparative way. Obviously, the reactants must resist the action of water and be present in high concentrations leading to heterogeneous media. It is clear that the reduced pressure acceleration effect in water compared to the kinetic effect observed in organic solvents is largely compensated by the considerable rate enhancement due to hydrophobic interactions. As illuminating examples, the rate constant ratios of the reactions listed in Table 12 at ambient pressure are respectively 575 (entry 1) and 1200 (entry 5) [80]. The synthetic advantage of the biactivation method is portrayed in Table 13. Two types of reactions are considered: Diels-Alder reactions (entries 1-4) and Michael-like reactions (entries 5-7).

### 3.2.2. Effect of Pressure on Reactions in Water-Like Solvents

Other media are also capable of favoring molecular aggregation. They are often called "water-like", although the

**Table 13. High Pressure Synthesis in Aqueous Media**

| Entry | Reaction | T(°C) | Time (h) | Yield (%) | |
|---|---|---|---|---|---|
| | | | | 0.1 MPa | 300 MPa |
| 1 | Isoprene + *p*-benzoquinone | 20.0 | 5 | 21 | 82 |
| 2 | Isoprene + toluquinone | 20.0 | 2 | 37 | 95 |
| 3 | Isoprene + 2,6-DMBQ[a] | 20.0 | 24 | 12 | 47 |
| 4 | Furan+ MVK[a] | 30.0 | 16 | 27 | 87 |
| 4 | Crotononitrile + *tert*-butylamine | 30.0 | 24 | 6 | 45 |
| 5 | Crotononitrile + iPr(Me)NH | 30.0 | 24 | 50 | 100 |
| 6 | Crotononitrile + iPr$_2$NH | 50.0 | 24 | 19 | 95 |

[a] DMBQ (dimethylbenzoquinone), MVK (methyl vinyl ketone)

denomination might appear exaggerated. Diols, particularly ethylene glycol, and formamide are both fairly polar liquids and strongly self-associated by hydrogen bonding. Their cohesive energy density is high enough to promote association of solvophobic molecules. However, it is evident that the magnitude of solvophobic interactions is less as compared to water. This is due to a reduction of the squeezing out ability of non polar solutes from solution. This has been observed in Diels-Alder reactions involving dienophiles having a carbonyl bond for which the rate enhancement was only one order of magnitude when ethylene glycol was used in place of dichloromethane, while the rate constant ratio was about $10^3$ in the case of water [80]. The rate increase in glycol is probably essentially due to polarity effects and hydrogen bonding between the hydroxyl groups of the diol and the carbonyl bond of the dienophile. From the standpoint of pressure kinetics, $\Delta V_\varphi^*$ should be relatively low compared to $\Delta V_\varepsilon^*$.

Similar results have also been observed in the high pressure Morita-Baylis-Hillman reaction of acrylonitrile and acetaldehyde [81]. Use of 1,2-diols were more effective than monoalcohols of similar cohesive energy density. The effect of diols was ascribed to a specific solvation effect by hydrogen bonding.

High pressure organic synthesis in ethylene glycol is related with the amount of effective solvophobic and electrostatic interactions and to the magnitude of the activation volume. The method can be interesting for Diels-Alder reactions as well as for conjugate additions of amines (Table 14) [80].

### 3.2.3. Effect of Pressure on Fluorophobic Interactions

In hydrophobic media the kinetic acceleration is generally the result of several factors (enforced hydrophobic interactions, hydrogen bonding, electrostatic interactions .) as outlined in 3.2.1. In most cases, it is difficult to distinguish which effect is the main determining parameter. In recent years, fluorophobic acceleration has been observed in the Diels-Alder reaction of 9-hydroxymethylanthracene and *N*-ethylmaleimide [82]. In analogy with the role of hydrophobic interactions, the rate enhancement in perfluorohydrocarbons is ascribed to the stabilizing interactions between the activated complex and the fluorous medium. These media show also poor miscibility and solvating power toward most organic compounds. They have a low dielectric constant and solubility parameter excluding occurrence of polarity effects as well as hydrogen bonding. In addition, considering their chemical inertness and lack of toxicity, they appear as promising media for organic reactions.

They are also unique as they may develop solvophobic interactions, which make them markedly different of the

**Table 14. High Pressure Synthesis in Ethylene Glycol**

| Reaction | T(°C) | Time (h) | Yield (%) | |
|---|---|---|---|---|
| | | | 0.1 MPa | 300 MPa[b] |
| Isoprene + toluquinone | 20.0 | 2 | 24 | 85 (2) |
| 2,5-Dimethylfuran + *p*-benzoquinone | 20.0 | 24 | 14 | 59 (0) |
| 2,5-Dimethylfuran + toluquinone | 20.0 | 24 | 0 | 6 (0) |
| Ethyl vinyl ether + MVK[a] | 20.0 | 24 | 0 | 28 (0) |
| Furan+ MVK[a] | 30.0 | 16 | 20 | 86 (0) |
| Furan + acrylonitrile | 30.0 | 60 | 4 | 80 (0) |
| Furan + crotonaldehyde | 30.0 | 60 | 0 | 35 (0) |
| Crotononitrile + *tert*-butylamine | 30.0 | 24 | 5 | 21 (0) |
| Methacrylonitrile + *tert*-butylamine | 50.0 | 24 | 8 | 51 (0) |
| Methacrylonitrile + $Pr_2NH$ | 50.0 | 24 | 17 | 100 (2) |

[a] MVK (methyl vinyl ketone)

[b] In parentheses: yield obtained under identical conditions in acetonitrile at 300 MPa

**Table 15. Esterification of Hindered Acids and Alcohols in Fluorous Media[a]**

| Reaction | Yield (%) | | |
|---|---|---|---|
| | $C_6F_{14}$ | FC-77® | n-hexane |
| Cyclohexanecarboxylic acid + 2-propanol | 65 | 52 | 19 |
| Cyclohexanecarboxylic acid + neopentanol | 84 | 65 | 40 |
| Isobutyric acid + neopentanol | 48 | 22 | 12 |

[a] Catalyst (diphenylammonium triflate 10% mol), 80°C, 0.1 MPa, 24h

corresponding hydrogenated compounds (alcanes) of similar polarity. This was shown in esterification reactions. The ester yield was low in n-hexane and improved in fluorous media (Table 15) [83].

A recent paper emanating from our laboratory considered the pressure effect on organic reactions carried out in perfluorohexane [84]. In order to verify whether fluorophobic interactions were operating, the solvent effect was investigated in the Diels-Alder reaction between toluquinone and isoprene and in the conjugate addition of *tert*-butylamine to acrylonitrile (Table 16).

**Table 16.** **Solvent Effect on the Rate Constant Ratio at Ambient Pressure[a]**

| Solvent | $\delta^2$ | [4+2] cycloaddition | Conjugate addition |
|---|---|---|---|
| $C_6F_{14}$ | 35 | 3.0 | 11.1 |
| $CHCl_3$ | 86 | 1.0 | 1.0 |
| $C_2H_5OH$ | 161 | 2.6 | - |
| $CH_3OH$ | 208 | - | 3.8 |
| $HCONH_2$ | 369 | 71 | 103 |
| $H_2O$ | 547 | 1460 | 683 |

[a] T (30.3°C for the Diels-Alder reaction and 44.0°C for the Michael-like addition). Chloroform is the reference solvent

**Table 17.** **Effect of the Medium on ΔV\*-Values in Organic Reactions[a]**

| Medium | $\Delta V^*$ (cm$^3$mol$^{-1}$) | | |
|---|---|---|---|
| | reaction I | reaction II | reaction III |
| $C_6F_{14}$ | - 27 | - 32 | - 65 |
| $CHCl_3$ | - 39 | - 35 | - 55 |
| $C_2H_5OH$ | - 36 | nd | nd |
| $CH_3OH$ | nd | - 33 | - 35 |
| $HCONH_2$ | - 33 | nd | - 23 |
| $H_2O$ | nd | - 28 | - 25 |

[a] I (Toluquinone + isoprene, 30.2°C), II (HCCP + styrene, 50.0°C), III (*tert*-butylamine + acrylonitrile, 44.0°C)

From Table 16 it is clear that fluorophobic rate acceleration occurs in both reactions since the rate constant ratio is 3.0 in the [4+2] cycloaddition and 11.1 in the Michael-like addition despite the lower $\delta^2$-value for $C_6F_{14}$. This ratio is even higher than it is in the polar alcohols, methanol and ethanol. The pressure kinetics of both reactions and one additional cycloaddition leads to the activation volume values shown in Table 17 [84].

The ΔV\*-variations according to the medium are in line with those listed in Table 12. The two Diels-Alder reactions exhibit a maximum in the ΔV\*-diagram. For both reactions, fluorophobic interactions take seemingly some importance leading to $\Delta V_\varphi^* > 0$, thereby increasing ΔV\*. In this case, $\Delta V_\varphi^*$ stems entirely from solvophobic interactions, e.g. $\Delta V_\varphi^* = \Delta V_{hi}^*$. No maximum is observed in the ΔV\*-

diagram for the Michael-like addition. As this reaction involves a strongly dipolar transition state, electrostriction is highest in $C_6F_{14}$, contributing mainly to the high negative value of $\Delta V^*$(- 65 cm$^3$mol$^{-1}$). However, the overall $\Delta V^*$-value must certainly include also $\Delta V_\varphi^*$, since according to Table 16 the rate constant is higher by one order of magnitude in $C_6F_{14}$ than in $CHCl_3$.

**Table 18.** **High Pressure Diels-Alder Synthesis (300 MPa) of Furan Adducts in Perfluorohexane**

| Reaction | Medium | Yield (%) |
|---|---|---|
| Furan + methyl vinyl ketone | $CHCl_3$ | 17 |
| | $C_6F_{14}$ | 40 |
| 2-Methylfuran + methyl vinyl ketone | $CHCl_3$ | 16[a] |
| | $C_6F_{14}$ | 32 |
| Furan + methyl acrylate[b] | $CHCl_3$ | 30 |
| | $C_6F_{14}$ | 57 |
| 2-Methylfuran + methyl acrylate[b] | $CHCl_3$ | 30 |
| | $C_6F_{14}$ | 60 |
| Furan + methacrylonitrile[b] | $CHCl_3$ | 6 |
| | $C_6F_{14}$ | 31 |
| Furan + phenyl vinyl sulfone[b] | $CHCl_3$ | 6 |
| | $C_6F_{14}$ | 26 |

[a] In $CHCl_3$ there is partitioning between Michael-like and Diels-Alder processes

[b] In the presence of $ZnI_2$ (20% molar)

Some high pressure syntheses can benefit of fluorophobic activation despite the reduced sensitivity to pressure in fluorous media (ΔV\*-values are increased) [84]. The biactivation protocol was found to be particularly adapted to the synthesis of 7-oxabicyclo[2.2.1]heptane derivatives from the Diels-Alder reaction between furans and dienophiles (Table 18). Such adducts are notoriously difficult to prepare due to the reluctance of furan to undergo [4+2] cycloaddition with less reactive dienophiles and the thermal fragility of adducts. High pressure coupled with fluorophobic activation and, occasionally, catalysis ($ZnI_2$) is a powerful mean to give access to such adducts in acceptable yields. In all reactions listed in Table 18, there is a marked yield improvement when the reaction is carried out in perfluorohexane.

## 4. FUTURE HIGH PRESSURE MEDIA

New media for organic reactions have emerged in recent years. They include supercritical media and ionic liquids. Their rapid development is mostly due to the environmental considerations as they respond to the principles of green chemistry [85]. However, the extension of their use to high pressure reactions remains to be investigated.

### 4.1. Supercritical Fluids

Such fluids are confirmed as valuable media for organic synthesis [86, 87]. The most suitable media having easily accessible supercritical points are fluoroform (5 MPa,

25.9°C) and carbon dioxide (7.4 MPa, 31.1°C). The latter (scCO$_2$) is obviously the cheapest and is, therefore, the preferred supercritical fluid. Such media have properties intermediate between gas and liquid. Their solubilizing power towards organic compounds is high. scCO$_2$ is the medium of choice in the pharmaceutical industry, since drugs must be exempt of any trace of solvent.

The few high pressure studies reported to date were done under modest pressures (20-100 MPa). The rate of the Diels-Alder reaction between *p*-benzoquinone and 1,3-cyclopentadiene was increased in scCO$_2$ compared to the rate determined in diethyl ether whereas the volume of activation was similar (-35 cm$^3$mol$^{-1}$) [88]. A rate enhancement was also observed in the esterification of phtalic anhydride with methanol in scCO$_2$ [89]. The synthesis of dimethyl carbonate was found to be promoted in scCO$_2$ at 90-100 MPa [90].

## 4.2. Ionic Liquids

Ionic liquids are organic liquids consisting only of ions. Their use as substituting reaction media is relatively recent due to their prominent properties (good dissolution for organic compounds, high thermal stability, no vapour pressure.) [91, 92]. Many reactions were shown to proceed cleanly and efficiently under ambient conditions. The most appropriate ionic liquids are dialkylimidazolium salts. Their possible use as high pressure media must take into account the criteria exposed above in paragraph 2, particularly freezing point, viscosity, and solubility. These physical properties can be deeply affected by pressure. To our knowledge, only our laboratory has initiated a few, yet unpublished, high pressure studies in this area. They are reported hereafter.

### 4.2.1. Diels-Alder Reactions

The pressure effect in the cycloaddition of 2,6-dimethylbenzoquinone (DMBQ) to isoprene does not show anomalies despite the polar transition state (Table 19). The result is at variance with those reported in the cycloaddition of 1,4-naphthoquinone and dimethylbutadiene [93]. Ionic liquids have the same effect as any other organic solvent in the inverse electron demand Diels-Alder reaction between hexachlorocyclopentadiene (HCCP) and styrene. This is confirmed by the $\Delta V^*$-values (Table 20).

**Table 19.   Comparative Medium Effect in [4+2] Cycloadditions at 50 MPa**

| Medium | E$_T$ | Rate constant ratio | |
|---|---|---|---|
| | | DMBQ+isoprene (30°C) | styrene+HCCP (50°C) |
| CH$_2$Cl$_2$ | 41.1 | 1.0[a] | 1.1 |
| CHCl$_3$ | 39.1 | 1.1 | 1.0[a] |
| C$_2$H$_5$OH | 51.9 | 2.1 | 0.9 |
| [bmim]BF$_4$ | 52-53[b] | 2.8 | nd |
| [bmim]PF$_6$ | 52-53[b] | nd | 1.1 |

[a] Reference

[b] Estimated

Other reactions which were found to proceed more efficiently in ionic liquids were examined under pressure and the yields compared to those obtained in our laboratory in conventional organic media.
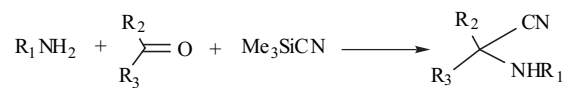
**Table 20.   Volumes of Activation in the Cycloaddition of HCCP and Styrene (50°C)**

| Medium | CH$_2$Cl$_2$ | CH$_3$OH | (CH$_2$OH)$_2$ | [bmim]PF$_6$ | H$_2$O |
|---|---|---|---|---|---|
| 10$^6$k (dm$^3$mol$^{-1}$s$^{-1}$)[a] | 2.1 | | 17 | 2.22 | 2500 |
| - $\Delta V^*$ (cm$^3$mol$^{-1}$) | 35.4 | 33.2 | nd | 36.0 | 28.0 |

[a] Rate constant at 0.1 MPa

### 4.2.2. Strecker Reactions

The three-component Strecker reaction coupling an aldehyde, an amine and trimethylsilyl cyanide affords excellent yields of α-aminonitriles in [bmim]BF$_4$ or [bmim]PF$_6$ at ambient pressure (Scheme 16) [94]. The reaction is, however, sluggish if ketones are substituted for aldehydes. In fact, we observed that operation in [bmim]PF$_6$ has a detrimental effect, even at 300 MPa, on the yield compared to our previous results [95] (Table 21).

$$R_1NH_2 \; + \; \underset{R_3}{\overset{R_2}{>}}=O \; + \; Me_3SiCN \longrightarrow \underset{R_3}{\overset{R_2}{>}}\!\!\underset{NHR_1}{\overset{CN}{<}}$$

**Scheme 16.**

**Table 21.   Effect of the Medium in Strecker Reactions**

| R$_1$ | R$_2$ | R$_3$ | Medium | Pressure (MPa) | Yield % |
|---|---|---|---|---|---|
| Ph | Me | Me | acetone | 0.1 | 11[a] |
| | | | [bmim]BF$_4$ | 0.1 | 2[a] |
| Ph | Me | Me | acetone | 300 | 49[a] |
| | | | [bmim]BF$_4$ | 300 | 5[a] |
| Ph | Me | nBu | 2-hexanone | 300 | 32[a] |
| | | | [bmim]BF$_4$ | 300 | 5[a] |
| PhCH$_2$ | Me | nPr | toluene | 0.1 | 34[b] |
| | | | [bmim]BF$_4$ | 0.1 | 16[b] |
| PhCH$_2$ | Me | nPr | toluene | 300 | 71[b] |
| | | | [bmim]BF$_4$ | 300 | 53[b] |

[a] 30°C, 16h

[b] 50°C, 24h

### 4.2.3. Knoevenagel Condensations

The reaction between aldehydes and methylene active compounds in ionic liquids leads to functionalized ethylenics with improved yields [96]. We previously examined the condensation of ketones with ethyl cyanoacetate under pressure choosing the reacting ketones as solvents (Scheme 17) [97]. Transposed in [bmim]PF$_6$, the Knoevenagel reaction proceeds, clearly, much less efficiently (Table 22).

$$\underset{R_2}{\overset{R_1}{>}}=O \; + \; H_2C\underset{COOC_2H_5}{\overset{CN}{<}} \xrightarrow{\text{piperidine}} \underset{R_2}{\overset{R_1}{>}}=\!\!\underset{COOC_2H_5}{\overset{CN}{<}}$$
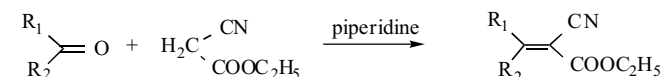
**Scheme 17.**

**Table 22.** **Effect of the Medium in Knoevenagel Condensations (23°C, 2h)**

| Ketone | Medium | Pressure (MPa) | Yield % |
|---|---|---|---|
| Acetone | acetone | 0.1 | 38 |
| | [bmim]BF$_4$ | 0.1 | 10 |
| Acetone | acetone | 300 | 59 |
| | [bmim]BF$_4$ | 300 | 18 |
| 2-Butanone | butanone | 0.1 | 28 |
| | [bmim]BF$_4$ | 0.1 | 7 |
| 2-Butanone | butanone | 300 | 99 |
| | [bmim]BF$_4$ | 300 | 13 |
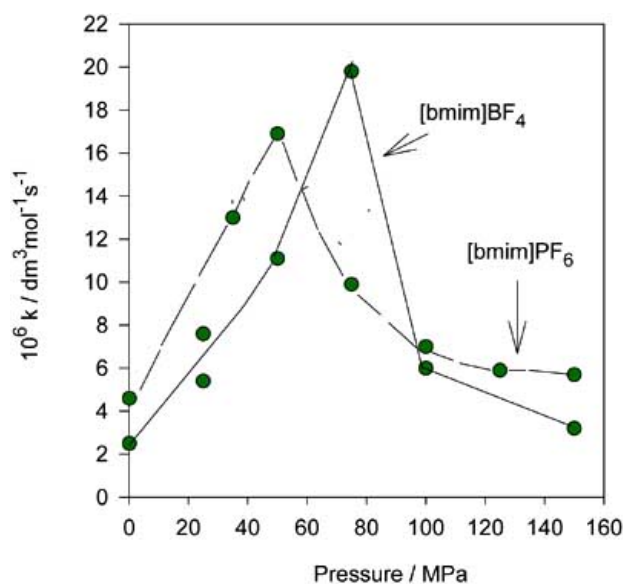


**Fig. (4).** Effect of pressure on the rate constant of the conjugate addition of *tert*-butylamine to acrylonitrile in two ionic liquids (45°C).

Considering the above results, one may wonder whether the lower yields could be ascribed to pressure-induced freezing of the ionic liquid at 300 MPa or increased viscosity, thereby restricting molecular motion. In order to clarify this point, the kinetics of the conjugate addition of *tert*-butylamine to acrylonitrile (Scheme 4) was followed in two ionic liquids in the pressure range 0.1-150 MPa (Fig. **4**). Both graphs show a maximum: at 50 MPa in [bmim]PF$_6$ and 75 MPa in [bmim]BF$_4$. This may be related to diffusion-controlled reactions due to exponential increase in viscosity under pressure (at 45°C and ambient pressure, the value of η is 140 cP for [bmim]PF$_6$ and 50 cP for [bmim]BF$_4$ [98]. Although these high pressure studies are in a very early stage, the above results cast doubt about the utility of ionic liquids for conducting high pressure reactions. At ambient pressure ionic liquids can influence the outcome in some cases, but this is not general. In fact, caution should be given when considering their apparent inertness. Imidazolium salts

were found to react with substrates in Morita-Baylis-Hillman reactions [99]. A possible promising development could consist in associating the remarkable properties of ionic liquids and supercritical fluids under pressure. A recent paper reports on the exceptional solubility of [bmim]PF$_6$ with polar organic compounds in scCO$_2$ [100].

## 5. CONCLUSION

Pressure activation of organic reactions may be a prominent synthetic strategy, particularly when traditional methods have reached their limits. A crucial parameter for the success of high pressure synthesis is the reaction medium. In order to gain a comprehensive picture of the role of the medium it is necessary to examine its melting and viscosity behavior under pressure and, according to the reaction under consideration, make appropriate selection depending on electrostriction occurrence and solvophobic properties.

Novel high pressure media may concentrate on supercritical fluids and ionic liquids. In the latter case however, their possible use as pressure media impinges on the increased viscosity favoring diffusion-controlled processes, thereby, reducing reaction rates.

## REFERENCES

[1] Ruloff, R.; Saudan, C.; Merbach, A.; Klärner, F.G. *High Pressure Chemistry*, van Eldik, R.; Klärner, F.G., Eds; Wiley: Weinheim, **2002**, pp. 348-368.
[2] *High Pressure Chemistry*, van Eldik, R.; Klärner, F.G., Eds, Wiley: Weinheim, **2002**.
[3] *Chemistry under Extreme and Non-classic Conditions*, van Eldik, R.; Hubbard, C.D. Eds; John Wiley & Sons: New York, **1997**.
[4] Acheson, R.M.; Matsumoto, K. *Organic Synthesis at High Pressure,* John Wiley & Sons: New York, **1991**.
[5] *High Pressure Chemical Synthesis*, Jurczak, J.; Baranowski, B. Eds; Elsevier Science B.V., Amsterdam, **1989**.
[6] *Organic High Pressure Chemistry*, le Noble, W.J. Ed., Elsevier Science B.V., Amsterdam, **1988**.
[7] Cativiela, C.; Garcia, J.I.; Mayoral, J.A.; Salvatella, L. *Chem. Soc. Rev.*, **1996**, 209.
[8] Troe, J. *High Pressure Chemistry,* Kelm, H. Ed., D. Reidel Publ.: Dordrecht, **1978**, pp.489-520.
[9] Kramers, H.A. *Physica*, **1940**, *7*, 284.
[10] Grote, R.F.; Hynes, J.T. *J. Chem. Phys.*, **1980**, *73*, 2715.
[11] Asano, T. *Pure Appl. Chem.*, **1999**, *71*, 1691.
[12] Goto, Y.; Takahashi, T.; Ohga, Y.; Asano, T.; Hildebrand, M.; Weinberg, N. *Phys. Chem. Chem. Phys.*, **2003**, *5*, 1825.
[13] Sumi, H. *J. Phys. Chem.*, **1991**, *95*, 3334.
[14] Aben, R.W.; Keijsers, J.A.; Scheeren, J.W. *High Press. Res.*, **1991**, *7*, 569.
[15] Keijsers, J.A.; Bouwmeesters, J.G.; Gout, A.G.; Kruse, C.G.; Scheeren, J.W. *High Press. Res.*, **1991**, *7*, 123.
[16] Jenner, G. *New J. Chem.*, **1999**, *23*, 525.
[17] Kotsuki, H.; Kitagawa, S.; Nishizawa, H.; Tokoroyama, T. *J. Org. Chem.*, **1978**, *43*, 1471.
[18] Babb, S. *Rev. Mod. Phys.*, **1963**, *35*, 400.
[19] Kelm, H.; Palmer, D. *High Pressure Chemistry,* Kelm, H. Ed.; D.Reidel Publ.: Dordrecht, **1978**, pp.281-309.
[20] Asano, T.; Furuta, H.; Sumi J. *J. Am. Chem. Soc.* **1994**, *116*, 5545.
[21] Shuto, A.; Takahashi, T.; Ohga, Y.; Asano, T.; Saito, H.; Matsuo, K.; Lüdemann, H.D. *Naturforsch.* **2000**, *55a*, 616.
[22] Firestone, R.A.; Vitale, M.A. *J. Org. Chem.*, **1981**, *46*, 2160.
[23] Firestone, R.A.; Saffar, S.G. *J. Org. Chem.*, **1983**, *48*, 4783.
[24] Dolbier, W.R.; Seabury, M.J. *J. Org. Chem.,* **1990**, *55*, 711.
[25] Dolbier, W.R.; Weaver, S.L. *J. Am. Chem. Soc.,* **1987**, *109*, 4393.
[26] le Noble, W.J.; Asano, T. *J. Phys. Chem. A*, **2001**, *105*, 3128.
[27] Firestone, R.A.; Swiss, K.A. *J. Phys. Chem. A*, **2001**, *105*, 3430.

[28]    Tamura, K.; Imoto, T. *Bull. Chem. Soc. Jpn.*, **1975**, *48*, 369.

[29]    Isaacs, N.S. *Liquid Phase High Pressure Chemistry,* John Wiley & Sons: New York, **1981**.

[30]    Dack, M.R. *Chem. Soc. Rev.,* **1975**, *4*, 211.

[31]    Jenner, G.; Ben Salem, R. *Tetrahedron*, **1997**, *53*, 4637.

[32]    Jenner, G. *J. Phys. Org. Chem*., **1999**, *12*, 619.

[33]    Jenner, G.; Papadopoulos, M. *Tetrahedron Lett.,* **1982**, *23*, 4333.

[34]    le Noble, W.J., *High Pressure Chemistry,* Kelm, H. Ed.; D.Reidel Publ.: Dordrecht, **1978** pp.325-343.

[35]    Isaacs, N.S.; Laila, A.H. *Tetrahedron Lett.,* **1983**, *24*, 2897.

[36]    Tsuzuki, H.; Uosaki, Y.; Nakahara, M.; Sasaki, M. *Bull. Chem. Soc. Jpn*., **1982**, *55*, 1348.

[37]    Asano, T.; Okada, T. *J. Org. Chem.,* **1984**, *49*, 4387.

[38]    Nishimura, N.; Kosako, S.; Sueishi, Y. *Bull. Chem. Soc. Jpn*., **1984**, *57*, 1617.

[39]    Sueishi, Y.; Ohcho, M.; Nishimura, N. *Bull. Chem. Soc. Jpn.*, **1985**, *58*, 2608.

[40]    Jenner, G. *Organic High Pressure Chemistry*, le Noble, W.J. Ed.; Elsevier Science B.V.: Amsterdam **1987**, pp. 143-203.

[41]    Takeshita, H.; Sugiyama, S.; Hatsui, T. *Bull. Chem. Soc. Jpn*., **1985**, *58*, 2490.

[42]    Sugiyama, S.; Takeshita, H. *Bull. Chem. Soc. Jpn*., **1987**, *60*, 977.

[43]    Takeshita, H.; Sugiyama, S.; Hatsui, T. *J. Chem. Soc., Perkin Trans. II*, **1986**, 1491.

[44]    Isaacs, N.S.; Rannala, E. *J. Chem. Soc. Perkin Trans. II*, **1975**, 1555.

[45]    Swieton, G.; von Jouanne, J.; Kelm, H. *J. Org. Chem*., **1983**, *48*, 1035.

[46]    Kiselev, V.D.; Konovalov, A.I.; Asano, T.; Kashaeva, E.A.; Iskhakova, G.G.; Shihab, M.S.; Medvedeva, M.D. *J. Phys. Org. Chem*., **2001**, *14*, 636.

[47]    Fleischmann, F.K.; Kelm H. *Tetrahedron Lett*., **1973**, 3773.

[48]    von Jouanne, J.; Kelm, H.; Huisgen, R. *J. Am. Chem. Soc*., **1979**, *101*, 151.

[49]    Swieton, G.; von Jouanne, J.; Kelm, H.; Huisgen, R. *J. Chem. Soc. Perkin Trans. II*, **1983**, 37.

[50]    Aben, R.W.; Scheeren, H.W. *Tetrahedron Lett*., **1985**, *26*, 1889.

[51]    Aben, R.W.; Limburg, E.P.; Scheeren, H.W. *High Press. Res*., **1992**, *11*, 167.

[52]    Chmielewski, M.; Kaluza, Z.; Belzecki, C.; Sawanski, P.; Jurczak J. *Tetrahedron Lett*., **1984**, *25*, 4797.

[53]    Chmielewski, M.; Kaluza, Z.; Belzecki, C.; Sawanski, P.; Jurczak, J.; Adamowicz, H. *Tetrahedron*, **1985**, *41*, 2441.

[54]    Chmielewski, M.; Kaluza, Z.; Mostowicz, D.; Baranowska, E.; Jacobsen, J.P.; Salanski, P., Jurczak, J. *Tetrahedron*, **1987**, *43*, 4555.

[55]    Chmielewski, M.; Kaluza, Z.; Sawanski, P.; Jurczak, J. *High Press. Res*., **1992**, *11*, 171.

[56]    le Noble, W.J.; Ogo, Y. *Tetrahedron,* **1970**, *26*, 4119.

[57]    le Noble, W.J.; Asano, T. *J. Am. Chem. Soc*., **1975**, *97*, 1778.

[58]    Kondo, Y.; Ohnishi, M.; Tokura, N.; *Bull. Chem. Soc. Jpn.,* **1972**, *45*, 3579.

[59]    Heydtmann, H.; Schmidt, A.P.; Hartmann, H. *Ber. Bunsenges. Phys. Chem*., **1966**, *70*, 444.

[60]    Brauer, H. D.; Kelm, H. *Zeitsch. Phys. Chem. NF*, **1971**, *76*, 98.

[61]    Tamura, K.; Ogo, Y.; Imoto, T. *Bull. Chem. Soc. Jpn.,* **1973**, *46*, 2988.

[62]    Forster, W.; Laird, R.M. *J. Chem. Soc. Perkin Trans. 2*, **1991**, 1033.

[63]    Jenner, G. *New J. Chem*., **1999**, *23*, 525.

[64]    Jenner, G. *Tetrahedron*, **2002**, *58*, 4311.

[65]    Dumas, F.; Mezrhab, B.; d'Angelo, J. *J. Org. Chem.,* **1996**, *61*, 2293.

[66]    Dumas, F.; Fressigne, C.; Langlet, J.; Glessner-Prettre, C. *J. Org. Chem.,* **1999**, *64*, 4725.

[67]    Hill, J.S.; Isaacs, N.S. *Tetrahedron Lett*., **1986**, *27*, 5007.

[68]    Bode, M.L.; Kaye, P.T. *Tetrahedron Lett*., **1991**, *32*, 5611.

[69]    Isaacs, N.S.; Hill, J.S.; Castelijns, M.; Corvers, A. *Physica*, **1986**, *139*, 717.

[70]    van Rozendaal, E.L.; Voss, B.M.; Scheeren, H.W. *Tetrahedron*, **1993**, *49*, 6931.

[71]    Rideout, D.C.; Breslow, R. *J. Am. Chem. Soc*., **1980**, *102*, 7816.

[72]    Ribe, S.; Wipf, P. *Chem. Comm*., **2001**, 299.

[73]    Otto, S.; Engberts, J.B.; Kwak, J.C. *J. Am. Chem. Soc*., **1998**, *120*, 9515.

[74]    Blokzijl, W.; Engberts, J.B. *Angew. Chem. Int. Ed*., **1993**, *32*, 1545.

[75]    Engberts, J.B.; Blandamer, M.J. *J. Chem. Soc., Chem. Comm*., **2001**, 1701.

[76]    Jenner, G.; Ben Salem, R. *Rev. High Press. Sci. Techn*., **1998**, *7*, 1265.

[77]    Jenner, G. High Pressure Chemistry (van Eldik, R.; Klärner, F.G. Ed.); Wiley, Weinheim, **2002**, p.305-347.

[78]    For a better understanding of these interactions, see: Blokzijl, W.; Blandamer, M.J.; Engberts, J.B. *J. Am. Chem. Soc*., **1991**, *113*, 4241.

[79]    Jenner, G. *Tetrahedron Lett.,* **1994**, *35*, 1189.

[80]    Jenner, G.; Ben Salem, R. *New J. Chem*., **2000**, *24*, 203.

[81]    Hill, J.S.; Isaacs, N.S. *J. Phys. Org. Chem*., **1990**, *3*, 285.

[82]    Myers, K.; Kumar, K. *J. Am. Chem. Soc*., **2000**, *122,* 12025.

[83]    Gacem, B.; Jenner, G. *Tetrahedron Lett*., **2003**, *44*, 1391.

[84]    Jenner, G.; Gacem, B. *J. Phys. Org. Chem*., **2003**, *16*, 265.

[85]    Anastas, P.T.; Kirchhoff, M.M. *Acc. Chem. Res*., **2002**, *35*, 687.

[86]    Oakes, R.S.; Clifford, A.A.; Rayner, C.M. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 917.

[87]    Leitner, W. *Acc. Chem. Res*., **2002**, *35*, 746.

[88]    Isaacs, N.S.; Keating, N. *J. Chem. Soc., Chem. Comm*., **1992**, 876.

[89]    Ellington, J.B.; Brennecke, J.B. *Chem. Comm*., **1993**, 1094.

[90]    Isaacs, N.S.; O'Sullivan, B. *Tetrahedron*, **1999**, *55*, 11949.

[91]    Welton, T. *Chem. Rev*., **1999**, *99*, 2071.

[92]    Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed*., **2000**, *39*, 3772.

[93]    Song, C.E.; Shim, W.H.; Roh, E.J.; Lee, S.; Choi, J.H. *J. Chem. Soc., Chem. Comm*., **2001**, 1122.

[94]    Yadav, J.S.; Reddy, B.V.; Eschwaraiah, B.; Srinivas, M.; Vishnumurthy, P. *New J. Chem*., **2003**, *27*, 462.

[95]    Jenner, G.; Ben Salem, R.; Kim, J.C.; Matsumoto, K. *Tetrahedron Lett*., **2003**, *44*, 447.

[96]    Su, C.; Chen, Z.C.; Zheng, Q.G. *Synthesis*, **2003**, 555.

[97]    Jenner, G. *Tetrahedron Lett*., **2001**, *42*, 243.

[98]    Taken from a leaflet of Acros Organics (Ionic Liquids Handbook 2002).

[99]    Aggarwal, V.K.; Emme, I.; Mereu, A. *J. Chem. Soc., Chem. Comm*., **2002**, 1612.

[100]  Weize, W.; Zhang, J.; Han, B.; Chen, J.; Liu, Z.; He, J.; LI, W. *Chem. Comm.*, **2003**, 1412.