

Kinetic effects in water and ethylene glycol. Application to high pressure organic synthesis

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The kinetic effect of various Diels–Alder and Michael reactions is studied in water and ethylene glycol *vs.* organic solvents. The rate enhancement is considerable in water, much less in ethylene glycol. It is proposed that strong solvophobic interactions operate in water whereas the kinetic results in glycol are best explained by hydrogen bonding and polarity effects. From a synthetic point of view, use of the properties of water (hydrophobic interactions) or ethylene glycol (ionogenic medium) associated with the kinetic effect of high pressure may constitute an interesting multiactivation method to increase chemical reactivity. Examples of triactivation (high pressure catalytic Diels–Alder reactions in ethylene glycol) are given.

In our quest to optimize the chemical yield of organic reactions, we turned to multiactivation modes involving high pressure as the basic parameter.¹ In earlier papers we described the combined effect of lanthanide catalysis and high pressure.² We report herein the effect of pressure on organic reactions carried out in aqueous solution and in water-like media with the aim of utilizing their solvophobic properties as driving forces for synthetic purposes (physicochemical activation).

Despite its common use water is a peculiar liquid under ambient and around ambient conditions (0–90  C, 0–200 MPa). The liquid state is characterized by extended hydrogen bonding. This physical singularity has been exploited in chemical reactions by Breslow³ and since water has become a popular medium to enhance, sometimes considerably, the rate constant of many organic reactions.⁴ The kinetic effect of water is ascribed to several causes (often associated or inter-related), which basically are: (i) enforced hydrophobic interactions,⁵ (ii) hydrogen bonding to carbonyl and nitrile bonds when available^{6,7} and (iii) electrostatic interactions.^{8,9}

Hydrophobic interactions result from the associative effect forcing the organic molecules together to minimize the water–hydrocarbon interfacial area. The reduction of the solvent accessible surface area as part of the activation process contributes to the reduction of the Gibbs energy of activation.⁷ The relative insolubility of the substrates conditions the magnitude of the hydrophobic interactions. Any factor, such as addition of additives or application of pressure, that may influence these interactions leads to an alteration in the rate through salting-in or salting-out effects. As the aqueous reaction proceeds *via* the tiny amount of dissolved reactants, it would mean that the chemical yield is strongly dependent on their solubility. In addition, the hydration sphere must also accommodate the product as long as it forms during the reaction. This leads to important limitations to the use of water as a medium in synthetic organic chemistry. It is therefore desirable to look for other media that might also be capable of favoring molecular aggregation while allowing better miscibility of organic liquids or solubilization of solid reactants. Such media are sometimes called “water-like” and include some diols and formamide. Ethylene glycol and formamide

are both polar solvents and strongly self-associate by hydrogen bonding.¹⁰ They possess sufficient cohesive force to promote association of solvophobic molecules, however to a lesser extent than water does.

On the other hand, we investigated in a former study the kinetic effect of pressure on Michael and Diels–Alder reactions in aqueous solution.¹¹ It was observed that the rate constant of aqueous reactions was less sensitive to pressure as compared to the rate constant determined in hydrocarbon solvents. The result, though complex, was ascribed to a detrimental effect of pressure on hydrophobic interactions. However, the values of the activation volume were found negative enough in such a way that it could be interesting to consider a possible combination of pressure activation and hydrophobic effects to stimulate the reactivity of sluggish molecules.

The purpose of this paper is to report (i) the comparative kinetic effect of water and ethylene glycol in selected reactions and (ii) the combined synthetic effect of pressure and solvophobic interactions exerted by these media in some reactions that do not proceed at normal pressure in hydrocarbon solvents.

Results and discussion

Kinetic behavior in water and diols

The rate of a bimolecular reaction depends on the specific rate constant and the concentration of reactants, that is their solubility if the reaction is carried out in water. As an example, Fig. 1 portrays the variation of the yield *vs.* concentration of reactants in an aqueous Michael-like reaction (conjugate addition of *tert*-butylamine to methacrylonitrile).

For high values of *w* (corresponding to diluted aqueous solutions of methacrylonitrile), the medium is homogeneous or pseudo-homogeneous and the yields of the Michael adduct are low. Best results are obtained at the saturation limit. The yield at constant reaction time obviously depends on the amount of hydrophobic surface that becomes accessible in the transition state. As shown in Fig. 1, increasing the concentration of reactants beyond the saturation limits (low *w* values)

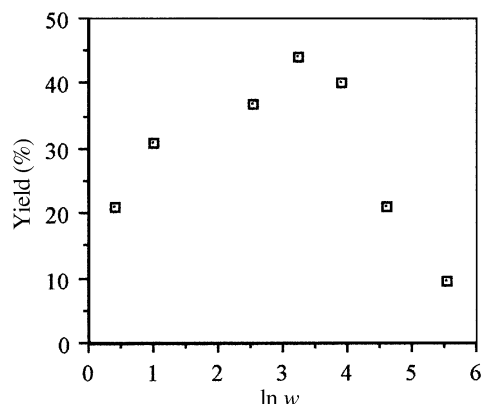


Fig. 1 Addition of *tert*-butylamine to methacrylonitrile in water (0.1 MPa, 50 °C, 24 h, $V_{\text{amine}} : V_{\text{nitrile}} = 1.5$, total volume: 3.5 mL). Yield of β -aminonitrile (based on methacrylonitrile) as a function of w (volume of water to volume of methacrylonitrile).

lowers the overall yield. Such limitation prompted us to investigate organic reactions in diols and formamide. The medium effect on yields (Table 1) was studied in the Diels–Alder reaction of isoprene and toluquinone shown in Scheme 1 (the two other possible regioisomers were not formed). From the results of Table 1, it is clear that water, formamide, ethylene glycol and other diols are perfectly suitable for this cycloaddition, as surmised. Glycerol is an exception; the lower yield is due to a very poor solubilization of the quinone. This is also the case of water; however, hydrophobic aggregation of reactants is much higher in water than in glycerol. The result

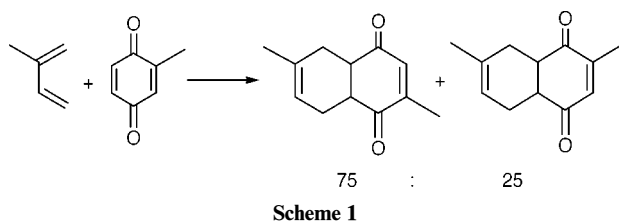


Table 1 Medium effect in the [4 + 2] cycloaddition of toluquinone (TQ) to isoprene^a

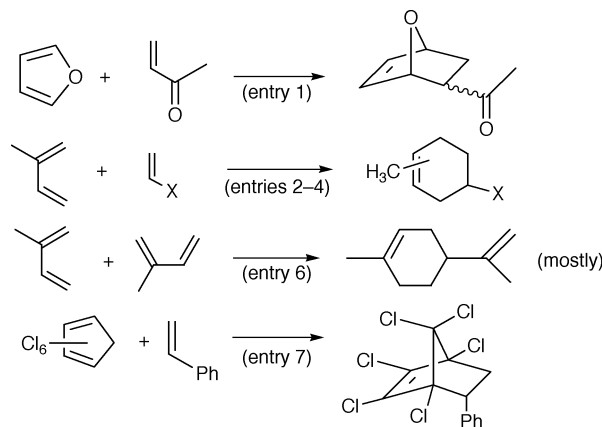
Medium	TQ/M	Isoprene/M	Yield ^b /%
Acetone	0.5	1.0	0
Methanol	0.5	1.0	1
Ethylene glycol	0.5	1.0	24
1,3-Propanediol	0.5	1.0	29
Glycerol	0.5	1.0	5
Formamide	0.5	1.0	21
Water	0.1	0.2	37
Water	0.2	0.4	28

^a P (0.1 MPa), T (22.0 °C), reaction time (2 h). ^b Based on initial TQ.

conforms to the behavior shown in Fig. 1; the yields in aqueous solution decrease with increasing concentration of reactants beyond saturation. Whereas under such conditions as shown in Table 1 there is no or little reaction in acetone and methanol, the adducts are formed in 20–30% yield in diols and formamide. These results are apparently related to solvophobic interactions. It is difficult to invoke a mere electrostatic or polarity origin since the reaction proceeds slowly in methanol compared to the yields obtained in diols, even though these alcohols have similar values for the cohesive energy density (208 for methanol and 213 for ethylene glycol). Hydrogen bonding between the two carbonyl bonds of toluquinone and water or diols is probably a major cause of the enhanced reactivity.¹²

To get a better idea of the effect of water and ethylene glycol, we followed the kinetics of several Diels–Alder reactions, with normal electronic demand, with the diene bearing successively a keto, ester and cyano group, with neutral (dimerization of isoprene) and inverse (HCCP + styrene) electronic demand (Table 2, Scheme 2).

The data listed in Table 2 indicate that the rate enhancement is very variable in ethylene glycol as well as in aqueous solutions. In glycol the highest values for the kinetic ratio k_s/k_{ref} are found in Diels–Alder reactions of unsaturated carbonyl compounds (entries 1, 2, 5). In cycloadditions involving styrene or acrylic compounds (methyl acrylate, acrylonitrile) the rate enhancement is two or three times lower (entries 3, 4, 7). However, the enhancement of the rates is only one order of magnitude at best when comparing the rate constants in the chloroalkane and the diol respectively. This is hardly compatible with solvophobic interactions as the actual cause of rate acceleration. It is better explained by simple polarity effects and hydrogen bonding between the hydroxyl groups of ethylene glycol and the carbonyl group of the ketone or quinone in their cycloaddition with furan or isoprene. In a previous paper we examined the solvent dependence of the rate constant in the dimerization of isoprene (entry 6).¹³ Under the same con-



Scheme 2

Table 2 Kinetics of Diels–Alder reactions in water and ethylene glycol^a

Entry	Reaction ^b	T/°C	$k/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$			Ratio k_s/k_{ref} ^c	
			CH_2Cl_2	Glycol	Water	Glycol	Water
1	Furan + MVK	30.1	0.8×10^{-7}	1.2×10^{-6}	5.22×10^{-5}	15	650
2	Isoprene + MVK	41.2	1.2×10^{-7}	1.32×10^{-6}	6.91×10^{-5}	11	575
3	Isoprene + MA	62.0	7.6×10^{-7d}	3.8×10^{-6}	7.72×10^{-4}	5	1015
4	Isoprene + AN	65.5	2.3×10^{-7}	1.2×10^{-6}	1.7×10^{-5}	5	75
5	Isoprene + TQ	30.1	3.4×10^{-5}	4.5×10^{-4}	1.68×10^{-2}	13	495
6	Isoprene (dimerization) ^e	83.0	1.3×10^{-7d}	9.2×10^{-7}	1.5×10^{-4}	7	1150
7	HCCP + styrene	50.4	2.1×10^{-6}	1.7×10^{-5}	2.5×10^{-3}	8	1200

^a At ambient pressure. Concentration of reactants in water was 10^{-3} M. ^b MVK (methyl vinyl ketone), MA (methyl acrylate), AN (acrylonitrile), TQ (toluquinone) HCCP (hexachlorocyclopentadiene). ^c k_s , k_{ref} : rate constant in glycol or water and CH_2Cl_2 (reference), respectively. ^d Chloroform was the solvent. ^e Pressure (20 MPa).

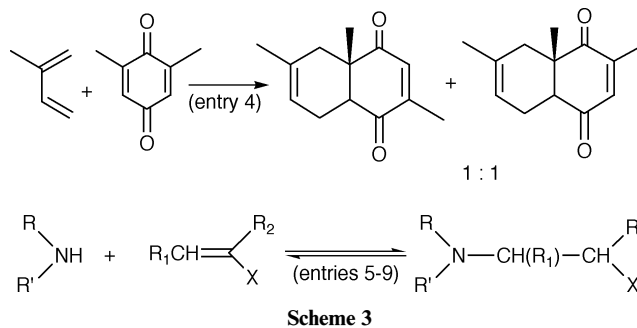
ditions the value of this rate constant in ethylene glycol perfectly correlates with the k values determined in other polar and nonpolar solvents according to the theory of regular solutions: $9.2 \times 10^{-7} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ in glycol ($E_T = 56.3$, $\delta^2 = 213$) and $10.8 \times 10^{-7} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ in formamide ($E_T = 56.6$, $\delta^2 = 369$).

The kinetic ratios in water *vs.* chloroalkanes of the Diels–Alder reactions involving isoprene are much higher, in agreement with the results reported for the corresponding cyclopentadiene [4 + 2] cycloadditions.¹⁴ In this case hydrophobic interactions are obviously the major reason for the kinetic alterations. The highest values are observed for the least hydrophilic molecules (HCCP, styrene, methyl acrylate) (entries 3, 7). When ketones are involved electric polarization with enhanced solvation of a more polar transition state than the initial state must also be considered.⁸

To distinguish hydrophobic effects from other effects it is common practice to use additives that increase or decrease hydrocarbon solubility.¹⁵ It is well known that lithium halides have a salting-out effect in aqueous solution whereas lithium perchlorate or urea increase this solubility. However, in ethylene glycol as solvent, it was shown that LiClO_4 produced a salting-out effect.¹⁶ Our results are listed in Table 3. With the exception of the rate decrease observed in the furan reaction in aqueous LiCl solution, the relative rate constants determined in water are indicative of hydrophobic interactions. The k values are higher in LiCl solutions and lower in LiClO_4 solutions. However, the kinetic trends are rather erratic if ethylene glycol is used as the solvent.

High pressure synthesis in water

Considering the rate enhancements reported in Table 2, we were prompted to investigate the efficiency of multiactivation, considered as the combination of pressure and solvophobic activation. However, from the synthetic point of view, it is evident that high reactant concentrations are desired. This means heterogeneous conditions, which also prevail when



Scheme 3

pressure is used as a synthetic parameter in aqueous reactions. With the given reactant concentrations, the results obtained for bimolecular reactions such as Diels–Alder cycloadditions and Michael reactions are shown in Table 4 (Scheme 3).

The following observations are in order:

(i) From a general point of view, Table 4 clearly shows that water promotes Diels–Alder and Michael reactions in agreement with the literature results. Notable exceptions are disclosed in entries 8 and 9 where the addition of amines to acrylic esters operates in acetonitrile but not in water. The reason was discussed in a former paper and unambiguously ascribed to the prevalence of the reverse reaction.¹⁶

(ii) The modest Diels–Alder reactivity of furan was not solved until the late 1970s when Dauben and Krabbenhoft reported an efficient high pressure route permitting use of less reactive dienophiles.¹⁷ Furan does not add to MVK at ambient pressure in hydrocarbon solvents (entry 1). Interestingly, water promotes the cycloaddition even at atmospheric pressure. Increasing pressure to 300 MPa leads to an excellent yield. For comparison, the same yield is obtained in dichloromethane only at pressures in excess of 1000 MPa.¹⁸

(iii) As expected pressure has a positive effect in bringing some aqueous reactions to completion at 300 MPa whereas the reactivity is zero in organic solvents. In entries 8 and 9, the absence of reactivity persists even at 300 MPa, meaning that

Table 3 Salt effect upon the relative rate constants of Diels–Alder reactions in water and in ethylene glycol^a

Reaction ^b	Water			Ethylene glycol	
	No additive	3 M LiCl	3 M LiClO ₄	No additive	3 M LiClO ₄
Furan + MVK	1	0.88	0.93	—	—
Isoprene + MVK	1	1.10	0.87	1	1.18
Isoprene + MA	1	1.40	0.71	1	0.90
HCCP + styrene	1	1.10	0.75	1	1.09

^a See conditions of Table 2. ^b MVK (methyl vinyl ketone), MA (methyl acrylate), HCCP (hexachlorocyclopentadiene).

Table 4 High pressure synthesis in aqueous solution^a

Entry	Reaction ^b	C ^c /M	T/°C	t/h	Yield/%	
					0.1 MPa	300 MPa ^d
1	Furan + MVK	1.20	30	16	27	87(0)
2	Isoprene + PBQ	0.92	20	5	21	82(0)
3	Isoprene + TQ	0.98	20	5	15	65(0)
4	Isoprene + DMBQ	0.88	20	24	12	47(0)
5	CCN + Bu ^t NH ₂	1.25	30	24	6	45(0)
6	CCN + Pr ⁱ (Me)NH	1.25	30	24	50	100(0)
7	MCN + Pr ₂ NH	1.20	50	24	19	95(2)
8	MMA + Pr ⁱ ₃ NH	1.10	50	24	0	0(23)
9	MMA + Bu ^t NH ₂	0.95	30	24	0	0(11)

^a No reaction in organic solvents (chloroform for entry 1, acetone for entries 2–4, acetonitrile for entries 5–9) at the same T and P of (0.1 MPa).

^b MVK (methyl vinyl ketone), PBQ (*p*-benzoquinone), MMA (methyl methacrylate) DMBQ (2,6-dimethylbenzoquinone), CCN (crotononitrile), MCN (methacrylonitrile), TQ (toluquinone). ^c Total concentration of reactants (reactants in equimolar amounts), in water (3.5 mL). ^d In parentheses yield obtained under the same conditions in the organic solvents listed in footnote (a).

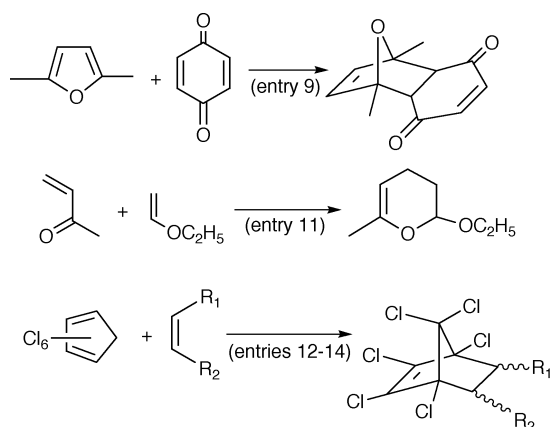
pressure is unable to shift the equilibrium toward the amino-ester in water.

As a provisional conclusion, operation in water under pressure can be a powerful means to drive organic synthesis. It can be viewed as a combination of physical activation (pressure) and physicochemical activation (hydrophobic stabilization of the transition state). This is probably true for Diels–Alder reactions. However, there may be another reason for the speeding up of the Michael-like reactions reported in Table 4. This type of reaction involves zwitterions whose generation is strongly promoted by highly polar media.¹⁹ Another comment is concerned with the general pressure effect in aqueous solution. As evoked in the introduction, the activation volume relative to homogeneous aqueous reactions ($\Delta V_{\text{water}}^\ddagger$) was invariably found to be higher than the activation volume relative to the corresponding reactions carried out in less polar organic solvents (ΔV_s^\ddagger).¹¹ This means a lower pressure dependence of the rate constant in water and reveals the limits of the pressure multiactivation process. An outstanding example is the Diels–Alder reaction of hexachlorocyclopentadiene and styrene described in a previous paper.¹¹

High pressure synthesis in ethylene glycol

Ethylene glycol, which possesses an extensive hydrogen bonding network, may also be used at high pressure. However, in this case, at variance with aqueous reactions, the solution is usually homogeneous. The results are listed in Table 5 (Scheme 4).

In the conjugate addition of amines to acrylic nitriles pres



Scheme 4

Table 5 High pressure addition reactions in ethylene glycol^a

Entry	Reaction ^b	T/°C	Yield/%	
			0.1 MPa	300 MPa
1	MMA + Pr ⁱ NH	50	3	2
2	MMA + Bu ⁱ NH ₂	30	22	26
3	CCN + Bu ⁱ NH ₂	30	5	21
4	CCN + Pr ⁱ (Me)NH	30	26	67
5	MCN + Bu ⁱ NH ₂	50	8	51
6	MCN + Pr ₂ NH	30	17	100
7	Isoprene + TQ	30	24	85
8	Furan + MVK	30	18	86
9	DMFu + PBQ	20	14	59
10	DMFu + TQ	20	0	6
11	MVK + EVE	30	0	28
12	HCCP + 3,3-dimethyl-1-butene	80	0	2
13	HCCP + 2-pentene	80	n.d.	11
14	HCCP + 4-methyl-1-pentene	80	20	29

^a Concentration of reactants (0.5–0.6 mmol each), volume of glycol (3 mL).

^b MMA (methyl methacrylate), CCN (crotononitrile), MCN (methacrylonitrile), TQ (toluquinone), MVK (methyl vinyl ketone), DMFu (2,5-dimethylfuran), PBQ (*p*-benzoquinone), EVE (ethyl vinyl ether), HCCP (hexachlorocyclopentadiene).

sure is a fairly sensitive parameter. The yields obtained in the diol at 300 MPa are comparable to those obtained in aqueous solution. However, in harmony with the results of Table 4, ethylene glycol is a dissociating medium promoting generation of zwitterions in the same way as water does. The Michael reaction between amines and acrylic esters is sluggish in ethylene glycol. The yield is not enhanced by pressure, suggesting again predominant reverse reactions. We checked this reversal in entry 1. The β -aminoester synthesized in acetonitrile at 300 MPa from methyl methacrylate and diisopropylamine was dissolved in ethylene glycol and exposed to a 300 MPa pressure. After 24 h at 50 °C, 65% reversal was observed.

There was no retro-Diels–Alder reactions in entries 7–14. Entry 8 deserves particular interest since furans are very reluctant to enter into [4 + 2] cycloadditions unless highly reactive dienophiles are involved. Thus, methyl vinyl ketone does not add to furan under ambient pressure in ether, chlorinated solvents, acetonitrile or methanol. An 18% yield is observed in ethylene glycol. Formamide produces a comparable yield (Table 6). Interestingly, the *endo* : *exo* ratio (61 : 39) is not altered in water, ethylene glycol and formamide, whereas it varies with the polarity of the medium.⁸ This would give support to the existence of enforced hydrophobic interactions.

The yields in Table 6 are quite fair at 300 MPa, making the method synthetically useful. In comparison, a yield of 90% was reached only above 1000 MPa in ether or dichloromethane.¹⁸ Similar results relative to pressure acceleration in ethylene glycol are obtained in entries 9 and 10 in Table 5. However, the additional methyl group in toluquinone imposes severe steric hindrance leading to low yields at 300 MPa. The hetero-Diels–Alder reaction (entry 11) is significantly promoted by pressure in ethylene glycol. Lastly, Diels–Alder reactions with inverse electronic demand involving HCCP (entries 12–14) give low yields of adducts at 300 MPa in ethylene glycol.

Some of these results (Table 5) contrast with those obtained in aqueous solutions (Table 4) while others show similarities:

(i) For normal electronic demand Diels–Alder reactions carried out in ethylene glycol (entries 7–11 in Table 5), the yield ratio is modified in nearly comparable proportion as in water when pressure is varied from ambient to 300 MPa. However, the inverse electronic demand reactions (entries 12–14) are less sensitive to pressure.

(ii) The conjugate addition of amines to acrylic compounds proceeds in the same way in both media.

A possible explanation may be offered with the involvement of polarity and hydrogen bond donating effects. Polarity effects are strongly manifested in Michael reactions, either in water or diol solution. Enforced hydrophobic effects would accelerate the rate of normal electronic demand Diels–Alder reactions in aqueous solution and to a much lesser degree in ethylene glycol in accordance with the comments relative to Table 2. Hydrogen bonding and polarity effects would also affect these reactions (for a more detailed insight see our previous paper¹¹).

The rather modest results obtained in the Diels–Alder reac-

Table 6 Solvent effect in the cycloaddition of methyl vinyl ketone (MVK) and furan^a

Medium	δ^2	Yield/%		% <i>endo</i> product	
		0.1 MPa	300 MPa	0.1 MPa	300 MPa
Dichloromethane	104	0	17	—	74
Methanol	208	0	18	—	52
Ethylene glycol	213	18	86	60	61
Formamide	369	23	97	62	62
Water	547	23	87	60	61

^a T (30 °C), t (16 h).

Table 7 Lanthanide catalysis in water-like media at high pressure^a

Reaction ^b	T/°C	Solvent	Catalyst	Yield/%
MVK + EVE	30	Chloroform	None	12
		Glycol	None	28
		Glycol	Yb(OTf) ₃	100
Crotonaldehyde + EVE	60	Chloroform	None	3
		Glycol	None	40
		Glycol	Yb(OTf) ₃	100
DMFu + TQ	20	Dichloromethane	None	0
		Glycol	None	6
		Glycol	Yb(OTf) ₃	26

^a *P* (300 MPa), *t* (24 h). The catalytic experiments were carried out with ytterbium triflate (2.5% molar). ^b MVK (methyl vinyl ketone), EVE (ethyl vinyl ether), DMFu (2,5-dimethylfuran), TQ (toluquinone).

tions listed in Table 5 prompted us to associate chemical activation *via* Lewis acid catalysis. Organic lanthanide compounds as mild Lewis acid catalysts are particularly suitable in hetero cycloadditions involving substrates possessing carbonyl groups.² Table 7 reports the notable improvements obtained when conducting the experiments in ethylene glycol under 300 MPa in the presence of ytterbium triflate. However, the generality of such a triactivation process is limited.²⁰

Conclusions

The results reported in this paper point to the rather complex effect of water in organic reactions. From a synthetic point of view, it is related to the amount of hydrophobic interactions—in relation with reactant solubilities—and to the magnitude of the activation volume.⁹ Combination of pressure and hydrophobic activation may be an interesting method to increase the reactivity of reluctant molecules.

Substitution of ethylene glycol for water leads in some cases to interesting results. For isopolar reactions such as Diels–Alder reactions, use of ethylene glycol as a medium is beneficial only if carbonyl groups are involved, presumably *via* hydrogen bonding and polarity effects rather than through pure solvophobic interactions. In fact, our results show that such interactions do not exist or at the best, very moderate.

The results shown in this paper should give full adherence to high pressure as a synthetic parameter, possibly combined with additional activation methods. The multiactivation procedure can efficiently complement other synthetic strategies as clearly demonstrated in the cycloaddition of furan.

Experimental

Ambient and high pressure runs are carried out as follows. A 3.5 mL flexible PTFE tube is filled up with 1,2,3-trimethoxybenzene (standard) and substrates as required. The

volume of the tube is adjusted with water, ethylene glycol or the organic solvent as required. The tube is shaken for about one minute and then introduced in the pressure vessel thermostated at the given temperature. In the case of pressure runs, pressure is gradually generated by an oil driven intensifier up to 300 MPa. Reaction pressure is then released and the solution transferred into a separating funnel. The organic layer is collected by two successive extractions with diethyl ether and dried. After usual removal of the solvent the crude residue is directly analyzed by ¹H NMR (200 MHz, CDCl₃) and the yield determined from relative intensities of characteristic protons *vs.* methoxy groups of the internal standard. Kinetic measurements are carried out as thoroughly described previously.¹¹

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