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The Cause of the Rate Acceleration by Diethyl Ether Solutions of Lithium Perchlorate (LPDE) in Organic Reactions. Application to High Pressure Synthesis.

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Abstract : Kinetic studies of isoprene cyclodimerization show that the accelerating effect caused by LPDE (solution of lithium perchlorate in diethyl ether) in some organic reactions cannot be ascribed to internal pressure of LPDE. The kinetic effect is essentially due to catalysis through Li^+. Additional arguments are provided by comparison of yields obtained in LPDE (0.1 MPa) and in organic solvents (under pressure) for Diels-Alder reactions of various electronic types. Combination of high pressure and LPDE catalysis is revealed as an excellent multiactivation process to achieve difficult syntheses, but only for [4+2] cycloadditions. © 1997 Elsevier Science Ltd.

Introduction

Pressure activation of organic reactions is a longstanding physical method to increase reactivity[1]. Those reactions undergoing major volume changes from the initial state to the formation of products are the most influenced. Number of difficult syntheses could be achieved in this way[2]. The high pressure synthesis of cantharidin is one prominent example. The simple combination of furan and 2,5-dihydrothiophene-3,4-dicarboxylic anhydride affords quantitatively under 1500 MPa within 6 h the Diels-Alder adduct which can be converted in the subsequent step into cantharidin in 63 % yield. At atmospheric pressure only a few percent are obtained after considerable reaction times[3].

However, in recent years it was found that the same cycloaddition readily occured at ambient pressure in 5M lithium perchlorate diethyl ether solution (LPDE) yielding the adduct in comparable yield (70 %)[4]. The LPDE speeding up of the reaction rate was initially rationalized by Grieco on the basis of the so called high internal pressure generated by the solubilization of LP in DE. The hypothesis was apparently comforted by the subsequent studies reporting successful syntheses in LPDE solutions consisting of Diels-Alder[5], aldol[6], ene[7], Michael[8], Mannich[9] reactions, sigmatropic rearrangements [10] and [2+2] cycloadditions [11].

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Soon after the publication of Grieco's paper, the cause of the rate acceleration was reassessed and ascribed to Lewis acid catalysis by the cation Li^+ [12]. In the following years most authors agreed upon this suggestion even Grieco himself [13] until 1994 when the concept of internal pressure again emerged in association with the activation volume of the reaction under consideration [14]. Another comparative study considered the LPDE rate enhancement in Diels-Alder and ene reactions and concluded that both factors (internal pressure and Li^+ catalysis) must contribute to the activation by LPDE [15]. Due to the increasing popularity of the use of LPDE as a mean to stimulate the lethargy of numerous reactions, we wish to report our own observations in this field in order to examine critically whether there is a real correlation between applied hydrostatic pressure and the putative internal pressure of the medium.

Position of the problem

The internal pressure is a thermodynamic concept resulting from the existence of attractive and repulsive intermolecular forces in a liquid securing its cohesion [16]. These forces create a cohesion pressure which can be high (100-2000 MPa). The thermodynamic relationship associated to the cohesion pressure are written as[17]:

$$(\partial U / \partial V)_T = T(\partial P/\partial T)_V - P = P_i$$

$$(\Delta U_{vap} / V) = \delta^2 = n P_i$$

with ΔU_{vap} (energy of vaporization) and V (molar volume), P_i is the internal pressure and δ^2 the cohesive energy density

For non polar liquids, n is close to unity[18]. The difference $\delta^2 - P_i$ is related to the intermolecular bond energy due to hydrogen bonds, dipole-dipole interactions... The magnitude of the internal pressure for some media retaining solvent ordering is so high that it is tempting to speculate on a correlation of P_i with mechanical external pressure. In fact, earlier studies were contradictory: whereas Ouellette et al. found an effect of internal pressure on conformational equilibria[19], another study failed to detect any correlation of the rate data for free-radical reactions with internal pressure[20]. However, the P_i - values considered in these studies were much smaller than those developped by LPDE solutions. Kumar apparently found a correlation between P_i of perchlorate solutions and the rate constant k for some Diels-Alder reactions by taking into account the corresponding activation volumes $\Delta V^{\neq}$ [14]. The reported values were all calculated by means of the general expression in the transition state theory :

$$\frac{\partial \operatorname{Ln} k}{\partial P} = -\frac{\Delta V^{\neq}}{RT}$$

P normally means effective external pressure, whereas Kumar used the expression with P equivalent to internal pressure. This calculation procedure cannot be easily endorsed, since the physical background associating $\Delta V^{\neq}$ and P_i is unclear, the more than the medium is not only characterized by P_i, but also by other properties such as dielectric constant, cohesive energy density and hence hydrogen bonding capacity even if some of the solvent properties may be interrelated. It is therefore not surprising that many $\Delta V^{\neq}$ - values calculated in this way look unrealistic, if they are compared to $\Delta V^{\neq}$ - values determined in the normal way by the dependence of the rate constant on external pressure. There is no known example of a Diels-Alder reaction with $\Delta V^{\neq}$ - values higher than - 18 $cm^3.mol^{-1}$ [21]. Instead, the values reported by Kumar are :

- 11.2 $cm^3.mol^{-1}$ (cyclopentadiene + methyl maleic anhydride)
- 4.3 $cm^3.mol^{-1}$ (trans,trans-1,4-diphenylbutadiene + 4-phenyl-1,2,4-triazoline-3,5-dione)
- 1.0 (!) $cm^3.mol^{-1}$ (1,3-diphenylisobenzofuran + styrene).

On the other hand, the $\Delta V^{\neq}$ - value calculated (via P_i) for the isomerization reaction of 1-phenyl allyl chloride to cinnamyl chloride was given as - 80.3 $cm^3.mol^{-1}$, an astonishing value for a unimolecular reaction even if it is assumed that the reaction involves charge build-up. The lowest value for such a reaction that can be found in the literature concerns the isomerization of some azobenzenes (- 30.8 $cm^3.mol^{-1}$) [22].

In the other work cited in the introduction[15], on the basis of rate data for the Diels-Alder reaction of 2,3-dimethylbutadiene and 4-bromonitrosobenzene carried out in LPDE, the authors concluded that part of the rate acceleration should be ascribed to increase of internal pressure. Such conclusion underlines the difficulty to detect clearly whether internal pressure or Lewis acid catalysis or any other factor is responsible for the observed rate enhancement, particularly when the rate acceleration is small. In all other papers[4-13], the LPDE promoting effect on the reaction yield was so high that the concept of LPDE internal pressure may be seriously questioned. As we are using the pressure parameter as a tool in organic chemistry over several decades, we have been moved to consider this perplexing question.

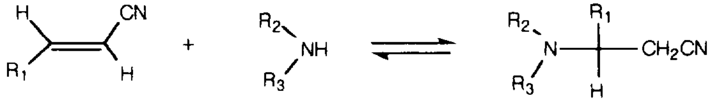
Results

The Michael-type conjugate addition of amines to α,β-unsaturated nitriles in LPDE solution was studied in a first step in order to check the possible correlation between LPDE internal pressure and external hydrostatic pressure. We therefore, carried out two series of experiments in LPDE at atmospheric pressure on one side and in chloroform under hydrostatic pressure corresponding in principle to the calculated P_i of x M LPDE (Table 1).

Table 1. Effect of LPDE in the addition of amines to nitriles[a]

LPDE	P_i (MPa)	Yield (%)	P_{ext} (MPa)	Yield(%)
R_1 = H R_2 = iPr R_3 = iPr (reaction A)				
1 M	400	21	300	20
2 M	760	55	700	95
3 M	1100	69	900	100
R_1 = Me R_2 = iPr R_3 = Me (reaction B)				
1 M	400	6	300	7
2 M	760	4	700	73
3 M	1100	5	900	99

[a] Reactions in LPDE solution were run at atmospheric pressure. Temperature was 50°C for reaction A and 30°C for reaction B (24 h). The solvent in reactions under hydrostatic pressure was diethyl ether. The values of P_i were taken from ref. 14



For both reactions, the yields were comparable at low P_i (1 M LPDE) and P_{ext} (300 MPa). However, it looks quite fortuitous, since reactions A and B defined as in Table 1 go to completion with an increase of applied external pressure whereas increasing the molar concentration of LP in DE led either to low increase in yield in reaction A or let the yield in reaction B unaffected. In fact, in both reactions, we observed reverse reactions when keeping the resulting aminonitrile (in A and B) in 1 M LPDE solution for one day, but not in ether. This may be due to the polar character of LPDE shifting the equilibrium towards reactants[23] as previously highlighted in the synthesis of β-amino compounds[24]. As a provisional conclusion, the examples listed in Table 1 are ambiguous.

In order to bring, hopefully, some clarification, we have selected a cycloaddition reaction which can be considered as insensitive to Lewis acid catalysis (no functional group on the substrates). We investigated the high pressure kinetics of the cyclodimerization of isoprene two decades ago[25] and found activation volumes ranging from - 35 to - 41 cm^3.mol^{-1} between 40 and 70°C. For the present purpose, we followed the kinetics in different solvents of various polarities defined by their E_T- (solvatochromic parameter) and δ^2-values (Table 2). We first checked the absence of any catalytic effect of a Lewis acid in the dimerization. In fact, ZnBr$_2$ caused a slight depressive effect on the rate constant. In further experiments, we varied the solvent from diethyl ether to formamide. The kinetic results are listed in Table 2 according to the E_T- and δ^2-values of the medium.

Table 2. Cyclodimerization of isoprene. Effect of the medium on the reaction rate[a]

Medium	E_T	δ^2	10^7 k (dm^3.M^{-1}s^{-1})
Diethyl ether	34.6	52	1.23
Diethyl ether[b]	-	-	1.02
Dichloromethane	41.1	104	1.30
Acetonitrile	46.0	139	1.47
Nitromethane	46.3	159	2.00
Ethanol	51.9	168	2.16
1M LPDE	52.8[c]	?	5.82
2MLPDE	53.9[c]	?	9.10
3M LPDE	56.0[c]	?	9.08
N-methylformamide	54.1	259	7.20
Formamide	56.6	369	10.8

[a] T(83.0°C), P (20 MPa)

[b] This reaction was carried out in the presence of ZnBr$_2$ (catalyst : isoprene = 1:16)

[c] Determined by interpolation from the data of ref. 26

Plotting Ln k against E_T led to erratic points (essentially for diethyl ether and ethanol which showed substantial deviations, but not for LPDE solutions) (Fig. 1a). There is a better correlation between Ln k and cohesion energy density (Fig. 1b), however the k-values obtained in LPDE solutions could not be plotted because of the unavailability of the corresponding δ^2-values. The correlation line obtained (Fig. 1b) would mean that the reaction follows, though not in a strict way, Hildebrand's theory of regular solutions[17]. Apparently, the rate enhancement in LPDE solutions is due to increase of polarity of the medium. The cyclodimerization is a neutral electron demand Diels-Alder reaction. As expected, the increase of the rate constant with increasing polarity of the medium is modest (about one order of magnitude from the least polar solvent to formamide). If the internal pressure of LPDE solutions would act as does true hydrostatic pressure, the rate acceleration should be much higher (Table 3). This casts doubts on the role of P_i acting like hydrostatic pressure as the cause of the rate acceleration.

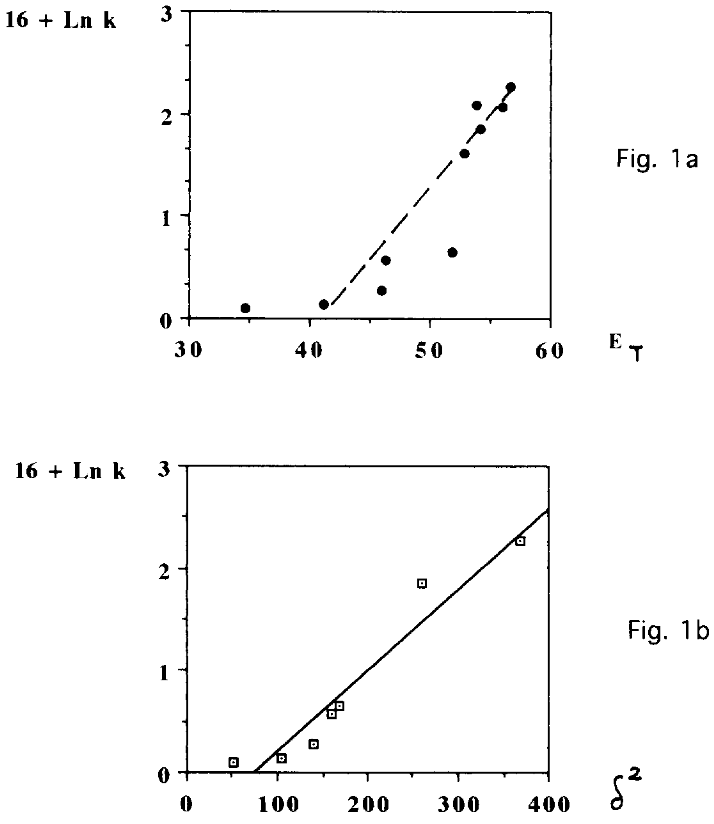


Fig. 1. Solvent effect in the cyclodimerization of isoprene (83.0°C, 20 MPa)

Table 3. Comparison of the rate enhancement in the cyclodimerization of isoprene via pseudo-internal and applied external pressure

LPDE (x)	P_i (MPa) [a]	$k_x : k_o$ [b]	$P_{external}$ (MPa)	$k_p : k_o$ [c]
1 M	400	4.7	350	20.5
2 M	760	7.4	750	55
3 M	1100	7.4	900	138

[a] All LPDE experiments were run at 83.0°C and 20 MPa.
[b] k_o is the value in diethyl ether at 20 MPa
[c] Taken from ref. 25 at 70.0°C

In a further step, we examined the reactivity of Diels-Alder reactions with normal and inverse electronic demand in LPDE solutions vs reactions in organic solvents (Table 4).

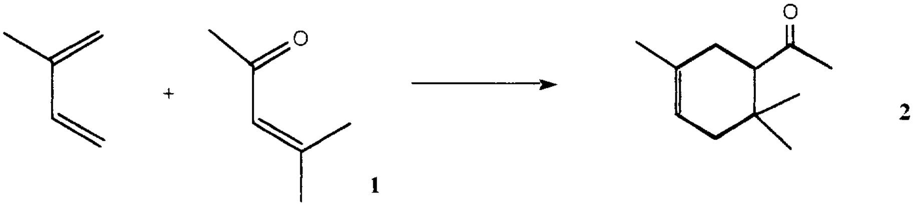
Table 4. Effect of LPDE on yields in Diels-Alder reactions

Entry	Reaction	Electronic type	T(°C)/t(h)	Yields (%) Medium organic solvent			1M LPDE
					0.1	300 MPa	0.1 MPa
1	dimerization of isoprene	neutral	83.0/24	diethyl ether	2 %	30 %	9 %
2	isoprene + benzoquinone[a]	normal	20.0 / 5	acetone	3 %	32 %	69 %
3	isoprene + toluquinone[a]	normal	20.0 / 5	acetone	2 %	29 %	89 %
4	isoprene + DMBQ [a]	normal	20.0 /24	acetone	0 %	8 %	19 %
5	HCCP [a] + styrene	inverse	33.0 / 8	diethyl ether	3 %	-	2.6 %
				formamide	6.3 %	-	3.6 %[b]

[a] DMBQ (2,6-dimethylbenzoquinone). All quinones are *para* isomers
HCCP (hexachlorocyclopentadiene)
[b] yield obtained in 3M LPDE solution

A normal electronic demand Diels-Alder reaction involves a pair of electron complementary partners, the diene bearing electron-releasing groups and the dienophile possessing electron-withdrawing substituents. As inferred by the results of Table 4, such type of reactions is remarkably promoted in LPDE solutions in agreement with the results of the literature[4,12,15]. The yields of the three quinone reactions are even higher in 1 M LPDE solution than those obtained in acetone at 300 MPa, in striking contrast with the results of the cyclodimerization of isoprene. The cause for this rate enhancement must obviously be ascribed to Lewis acid catalysis by Li^+ giving rise to specific solute-Li^+ interactions, as previously emphasized by Desimoni's group[27]. A recent study showed that the Lewis acidity of Li^+ is moderated by complexation to diethyl ether and the perchlorate anion[28], hence LPDE has weaker catalytic activity than compounds such as $BF_3 \cdot Et_2O$, $AlCl_3$.

Cycloaddition of mesityl oxide **1** to isoprene is also relevant of such electronic type. Owing to the steric hindrance imposed by the *gem*-methyl groups and in spite of the activating keto group, cyclodimerization of isoprene is the dominant reaction[29]. We reacted a mixture of isoprene (15 mmol) and mesityl oxide (4 mmol) at 100°C under a pressure of 20 MPa in two separate experiments differing by the nature of the medium. In both cases, adduct **2** is formed together with cyclodimers of isoprene. In CCl_4 the yields of dimers and adduct **2** were 14.7 and 27.5 % respectively; in LPDE 3M solution, 19.3 and 52 %, meaning a higher promoting effect of LPDE on the reaction of isoprene and **1**. This is also an indication of a catalytic effect of LPDE, though weaker than the effect reflected in entries 2-4 in Table 4.



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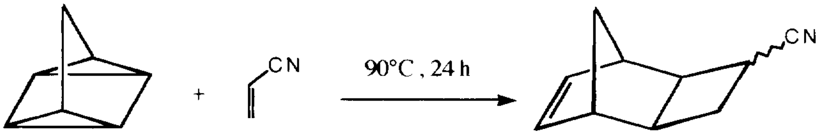
The cycloaddition of HCCP and styrene (entry 5) is a Diels-Alder reaction with inverse electronic demand. This is an interesting case since no alteration in yield occurred when switching from diethyl ether to 1 M LPDE. The reaction is relatively inert to the polarity of the medium as the yield was only doubled in formamide solution vs reaction in ether. HCCP and styrene do not bear any functional group and therefore, the reaction is unsensitive to LPDE, in the hypothesis of catalysis by LPDE. The result can be paralleled with the unability of LPDE to promote the reaction of diphenylisobenzofuran with styrene which is also a cycloaddition with inverse electron demand[14]. Such reactions are governed by the HOMO(dienophile) - LUMO(diene) separation. Generally, for these reactions, there is an increase of $\Delta E = E_{LUMO} - E_{HOMO}$ reflected by a lower reactivity making more plausible the hypothesis of a competing stepwise process[30]. In such a case, $\Delta V^{\neq}$ should be higher than the corresponding $\Delta V^{\neq}$ in a normal Diels-Alder reaction. However, this is not the case. Pericyclicity is preserved as $\Delta V^{\neq}$ for the reaction (entry 5) is $-31\ cm^3.mol^{-1}$ [31], thereby invalidating the value of $-1\ cm^3.mol^{-1}$ determined for the above isobenzofuran cycloaddition on the basis of P_i -values[14].

That the effect of LPDE is essentially due to a Lewis acid catalysis can be demonstrated in another way. The $[\pi^2 + \sigma^2 + \sigma^2]$ cycloaddition of acrylonitrile to quadricyclane[32] afforded the tricyclic adduct **3** in 29 % yield in 1 M LPDE (at 0.1 MPa) whereas the same reaction carried out at 300 MPa in $CHCl_3$ led almost quantitatively to the cycloadduct. A closer examination showed that quadricyclane in 1 M LPDE solution underwent isomerization to the much less reactive norbornadiene in 11 % yield. It is well known that this valence isomerization is promoted by Lewis acids[33].



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Application to organic synthesis

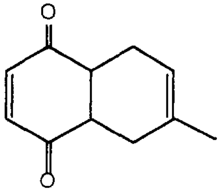
Lewis acid catalysis was reported to be effective in the Diels-Alder reaction between isoprene and N-phenylmaleimide whose kinetics was investigated in LPDE solution under pressure[34]. The reaction was found to exhibit a more negative activation volume ($\Delta\Delta V^{\neq} = 10\ cm^3.mol^{-1}$) than the uncatalyzed reaction. Such result was rationalized on the basis of some amount of electrostriction arising from ion pair separation ($Li^+ClO_4^-$) (tight ion pair) → $Li^+ + ClO_4^-$ (loose ion pair or even free ions) and subsequent catalysis by the lithium cation which would coordinate to the diene. If this is true, the catalytic properties of LPDE combined with high pressure should make difficult reactions amenable to reactivity. We have already demonstrated the advantages of this multiactivation method (lanthanide catalysis + high pressure) in the synthesis of dihydropyrans[35]. We therefore, investigated different high pressure reactions run in LPDE solutions (Table 5).

Table 5. High pressure syntheses in LPDE solutions (reaction time: 1 day)

Entry	Reaction	Medium	T(°C)	Yield (%) 0.1 MPa	Yield (%) 300 MPa	Products
2	isoprene + benzoquinone	acetone	20	3	32	**4**
		1M LPDE	20	69	100	**4**
4	isoprene + DMBQ	acetone	20	0	8	**5** + **6**
		1M LPDE	20	19	68	**5** + **6**
6	cycloheptatriene + acrylonitrile	CH_2Cl_2	80	0	0	-
		2.5 M LPDE	80	0	11	**7**
7	furan + methyl vinyl keton	$(C_2H_5)_2O$	20	0	17[b]	**8**
		3M LPDE	20	4	83[b]	**8**
8	norbornadiene + DMAD[a]	$CHCl_3$	80	18	61	**9**
		3M LPDE	80	30	82	**9**
9	1-hexene + DEKM[a]	$CHCl_3$	80	0	14	**10**
		2.5M LPDE	80	40	58	**10**
10	DMF[a] + DEKM[a]	CH_2Cl_2	25	0	100[c]	**11**
		3M LPDE	25	39	37	**11**

[a] DEKM (diethylketomalonate), DMAD (dimethylacetylene dicarboxylate), DMF (2,5-dimethylfuran)
[b] Reaction time (16 h)
[c] At 850 MPa

The Diels-Alder adduct (entry 2) was obtained in quantitative yield when the substrates were reacted in 1 M LPDE under 300 MPa. Also in entry 4, despite the severe steric hindrance imposed by the α-methyl groups in DMBQ, the adduct was formed in 60 % yield under the same conditions, whereas the system showed no reactivity at ambient pressure in acetone solution. It should be pointed out that the multiactivation method used here is a very efficient one since, even in water which is known to be a medium of choice for quinone cycloadditions through hydrophobic interactions[36], only 4 % adduct was formed after 8 days[37]. Interestingly, the regioisomer ratio was not affected by LPDE (**5** + **6** = 53:47) compared to 55:45 in benzene at 0.1 MPa [37].



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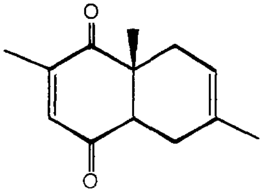

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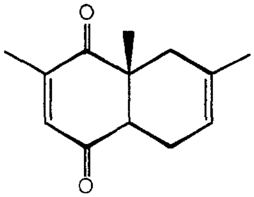

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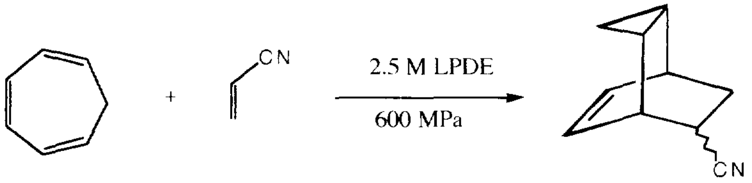
A more resistant reaction was the norcaradiene [4+2] addition between cycloheptatriene and acrylonitrile. Even LPDE was unable to catalyze this reaction at 0.1 MPa. However, a 11% yield of **7** could be obtained by exposing the substrates to 300 MPa in LPDE solution. An increase in pressure to 600 MPa led quantitatively to the desired norcaradiene cycloadduct (endo:exo = 1:1) according to :



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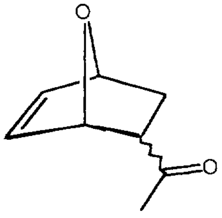
In the same way, a 83 % yield of the corresponding 7-oxabicyclic[2.2.1] system **8** (entry 7) was obtained in 3 M LPDE solution by reacting furan and methyl vinyl ketone at 300 MPa. The homo-Diels-Alder affording **9** (entry 8) was influenced only slightly in LPDE at constant pressure despite the two activating ester groups of DMAD. The ene addition (entry 9) was remarkably promoted by LPDE, the adduct **10** being produced in 40 % yield vs 0 % at ambient pressure. However, raising the pressure to 300 MPa led to a modest yield increase only.



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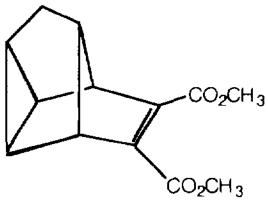

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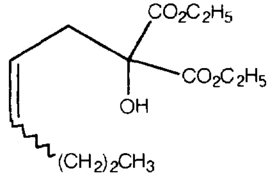

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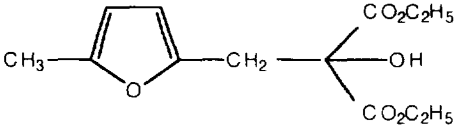
The situation was even more puzzling in the addition of DEKM to DMF (entry 10). This reaction with controversial mechanism was shown to occur only under high pressure[38]. In recent years, we could demonstrate by labeling experiments that the mechanistic pathway is essentially a complex acid-catalyzed electrophilic process[39]. If LPDE acts as a Lewis acid, the process should be accelerated. This was clearly the case: at 0.1 MPa adduct **11** was obtained in 39 % yield in LPDE solution to be compared to the lack of reaction in organic solvents. However, the LPDE catalyzed reaction seemingly did not respond to pressure at variance with the pressure assisted reaction in CH_2Cl_2 which yielded quantitatively adduct **11**, a compound of potential synthetic value[40]. A partial explanation can be provided by the mechanism we proposed earlier[39]. In the electrophilic attack of DEKM at C-2 in DMF, there must be considerable volume shrinkage due to electrostriction (charge build-up). This occurs in CH_2Cl_2, but not in LPDE, in which the charge is generated through Li^+ before application of pressure. However, the rate determining step being assumed to be a sigmatropic shift of the oxymalonate residue, a positive pressure effect, though lower than in organic solvents, should be observed even in LPDE solution.



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Conclusion

Whereas application of hydrostatic pressure leads to substantial and predictable rate enhancement in addition reactions, the effect of LPDE solutions is essentially fluctuating. The present study demonstrates that the putative internal pressure P_i of the medium cannot, by no means, be compared to applied external pressure. P_i may be included in the frame of normal solvent properties such as ε, E_T, δ (solubility parameter)...However, LPDE is a special medium due to the presence of Li^+ acting as a Lewis acid to coordinate suitable functional groups in the substrate if any. Reactions which are sensitive to such type of catalysis are prone to be remarkably promoted so that combination of high pressure and LPDE catalysis can be a mean to orchestrate difficult syntheses. However, as shown in Table 5, the effect of pressure on reactions carried out in LPDE is not evident in all cases. Such observation reveals the limits of the use of LPDE in synthetic organic strategies.

Experimental part

All substrates were commercially available. Isoprene, styrene, cycloheptatriene, dimethylfuran, acrylonitrile, 1-hexene, norbornadiene, methyl vinyl ketone were distilled prior to use. Lithium perchlorate, trihydrate was heated to 160°C until constant weight. Anhydrous diethyl ether was added and adjusted by weighing to the desired concentration.

A typical high pressure run was as follows. A flexible PTFE tube (1 cm^3) was filled up with 1,2,3-trimethoxybenzene (standard), a small amount of pyrogallol (polymerization inhibitor) and substrates (about 2 mmol). Then the organic solvent or LPDE solution was added. The tube was placed in the high pressure vessel and compressed. After reaction, pressure was released and the solution transferred into a flask containing water (in the case of LPDE experiments). After usual work-up the organic layer was washed with brine, extracted with dichloromethane and dried. The reactions were selective enough that the yield could be directly determined by ^1H NMR (200 MHz, $CDCl_3$) from relative intensities of characteristic protons (depending on reaction) vs methoxy groups or aromatic protons of the internal standard. Runs at 100°C (addition of mesityl oxide to isoprene) were performed in thick-walled stainless steel tubes consisting of a cylinder and a piston fitted with a Viton® O-ring, the extrusion of the piston due to reaction temperature was prevented with the help of a stopping screw. The isolated crude mixture was filtered through silicagel before NMR analysis. The same procedure was used in order to remove polymers in entry 8.

All adducts were known products including **11** which was described earlier[38].

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