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Use of Liquid 1,1,1,2-Tetrafluoroethane as Solvent Media for Enzyme-Catalyzed Ring-Opening Polymerization of Lactones

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Over the past two decades, compressed CO_2, especially in its supercritical state ($scCO_2$), has been extensively investigated as a solvent media in a wide range of materials synthesis and processing following the criteria of "green chemistry".[1,2] The use of this inorganic compressed fluid (CF) has commercial interest, although the relatively high cost of the pressurized equipment required has partially restricted its extended application. More recently, 1,1,1,2-tetrafluoroethane, commercially known as R-134a, has been proposed because it requires a relatively low pressure to become liquid (<2 MPa, RT) with adequate physical and chemical properties for materials syntheses and processing.[3−6] In addition, it is a nontoxic and nonflammable fluid and, like CO_2, does not deplete the ozone layer, and it is generally recognized as safe (GRAS).[5−7] The viscosity of liquid R-134a is 0.21 cP at 25 °C, which is very close to that of $scCO_2$ (0.1 at 200 bar and 33 °C). Its surface tension is 8.7 dyn/cm, which is far from the values for common organic solvents (17−73 dyn/cm).[5] Liquid R-134a is a polar fluid, with a dipole moment DM = 2.05 and a dielectric constant ϵ = 9.5 kHz, similar to that of dichloromethane (9.08 MHz), which can enhance the solubility of polar compounds.[5] According to that, the higher solubility of the polymer growing chains in this media, particularly polar ones as compared to the nonpolar $scCO_2$, might retard their precipitation. Enzymatic polymerization of polar polymers has always been challenging due to deactivation of the biocatalyst in polar and/or hydrophilic conventional organic solvent media. The addition of small volumes of water in the hydrophilic media can address this inconvenience; however, difficulties in reaction control and generally poor results are often encountered, especially in poly-transesterifications or poliamidations.[7] Herein, we demonstrate for the first time the effectiveness of pure liquid R-134a media for enzyme-catalyzed polymer synthesis. The ROP of ϵ-caprolactone (ϵ-CL) with Novozym-435 was chosen as the model system to study the enzymatic activity in this polar media (Figure 1).

The enzyme-catalyzed ROP of the cyclic ϵ-CL monomer has been extensively studied during the past 20 years, especially in bulk, to yield low molecular weight (M_w) polymers and relatively high polydispersity index (PDI) values, on the order of 3400−8500 g mol^{-1} and 2.1−2.5, respectively.[8−13] A considerable improvement has been reported using Novozym-435 biocatalyst in toluene, which resulted in polymer yields up to 86%, with a maximum M_w of 44 800 g mol^{-1}

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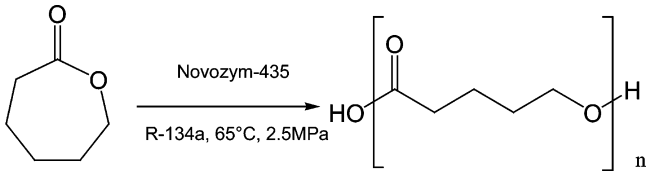

Figure 1. Reaction scheme for the enzyme-catalyzed ROP of ϵ-CL in liquid R-134a.

Table 1. Results Obtained for the Enzyme-Catalyzed ROP of ϵ-CL in Liquid R-134a

entry	press. (MPa)	temp (°C)	t (h)	polymer yield (%)	$M_w \times 10^{-3}$ (g mol^{-1})	PDI
1	2.5	65	12	67.5	37.1	1.7
2	2.5	65	24	95.0	35.6	1.6
3	2.5	65	48	75.0	37.6	1.7
4	2.5	65	72	74.7	34.1	1.8
5	2.5	55	24	54.3	33.0	1.7
6	2.5	75	24	64.4	36.1	1.6
7	5.0	65	24	94.2	34.7	1.8
8 (blank)[a]	2.5	65	12	0		

[a] Blank was carried out by using steam-sterilized enzyme.

and a PDI of 1.7.[14] Takamoto et al.[15] reported for the first time the lipase ROP of ϵ-CL using supercritical CO_2 ($scCO_2$) as solvent media with up to a maximum number-average molar mass (M_n) of 9600 g mol^{-1}. Recently, Howdle et al.[16] reported improved molecular weights (M_n = 37 000 g mol^{-1}) in the ROP of ϵ-CL in $scCO_2$ using the biocatalyst Novozym-435, with up to 98% polymer yield. The operational pressures ranged from 8 to 22 MPa, and the optimum reaction temperature was 65 °C. Alternatively, the ionic liquids are other important type of "green solvents" for synthesis manly due to their reduced vapor pressure. Takamoto et al. reported in 2002 the enzymatic ROP of ϵ-CL in ionic liquids.[17] However, the highest M_w attained was 4200 g/mol after 3 days of reaction. Other authors have pointed out the limited solubility of the poly-ϵ-CL product in ionic liquid as responsible for the inconvenient characteristics of the obtained polymer compared to toluene media, or others, in this type of enzymatic ROP.[18]

The present communication reports the successful lipase-catalyzed ROP of ϵ-CL using liquid R-134a at only 2.5 MPa. The operational parameters and the results obtained in these experiments are shown in Table 1.

The GPC/SEC (THF) analysis of the synthesized PCL samples, for entries 1−4 in Table 1, is shown in Figure 2. The maximum M_w attained in this initial study was 37 600 g mol^{-1} with a PDI of 1.7. The polymer yield was up to 95%.

The experiment of entry 8 in Table 1 for thermally inactivated enzyme demonstrates that no conversion was obtained in the absence of enzymatic activity. Experiments carried out at 55 and 75 °C for 24 h (entries 5 and 6 in Table 1) resulted in lower yields compared to those at 65 °C. This indicates that 65 °C is the optimum temperature for enzyme activity in this media, similar to previous reports for toluene or $scCO_2$.[8,16] The experiment of entry 7 in Table 1 carried out at 5 MPa and 65 °C shows no significant variations compared to that at 2.5 MPa (entry 2 in Table 1), which demonstrates that the use of compressed R-134a in its liquid state results in similar polymer characteristics at both operational pressures. Therefore, best

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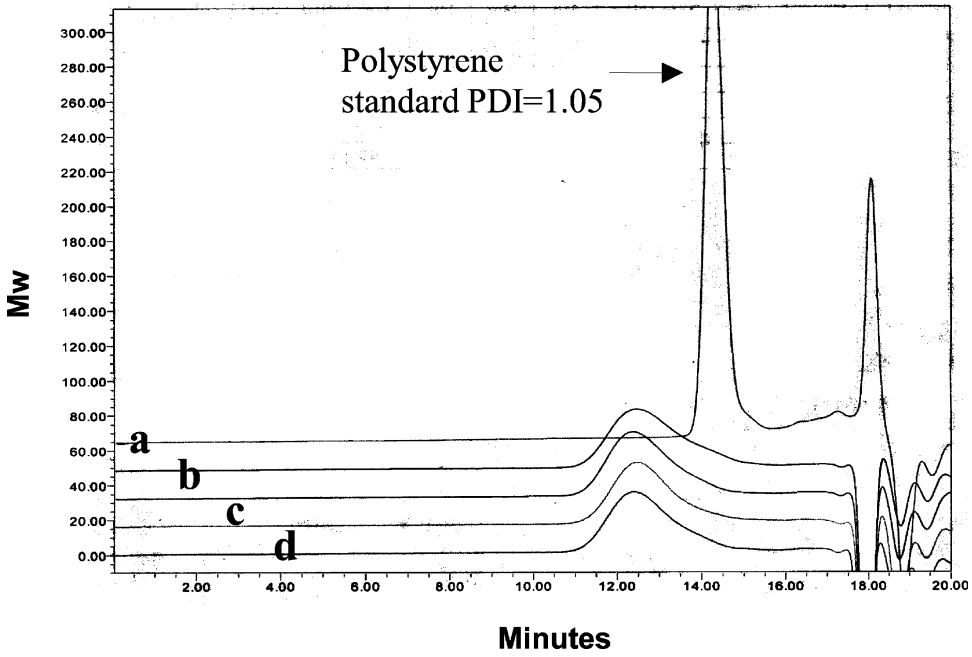

Figure 2. GPC analyses of polymer samples from entries 1−4 in Table 1.

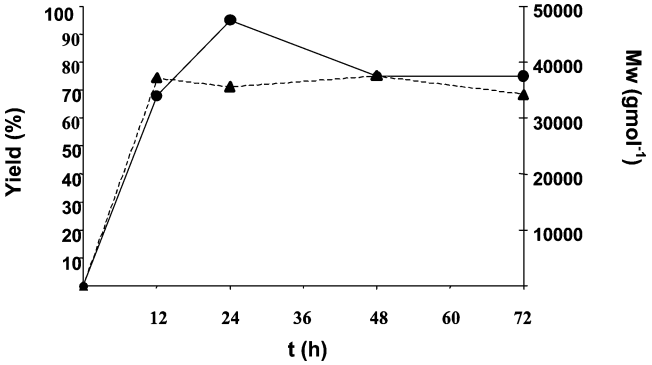

Figure 3. Yield−time and M_w−time relationships [● (yield, %), ▲ (M_w, g mol^{-1})] for the lipase-catalyzed ROP of ϵ-CL in liquid R-134a from experiments 1−4 in Table 1.

results were obtained in liquid R-134a with a 10-fold less working pressure than that with $scCO_2$.

Figure 3 shows the time−conversion and time−M_w relationships for the experiments from entries 1−4 (Table 1). As can be observed, the maximum yield was attained after 24 h. A decrease in polymer yield was observed at longer reaction times, but no significant variations were detected in M_w values of the polymers obtained.

The operational procedure used in these experiments is summarized as follows. A known concentration of ϵ-CL was loaded into a 50 mL stainless steel reactor equipped with a magnetic stirrer followed by the addition of Novozym-435 beads. The reactor was pressurized to final working pressure of 2.5 ± 0.2 MPa and maintained at constant temperature of 65 ± 1 °C, unless otherwise indicated. Depressurization of the reactor to atmospheric pressure at the end of each experiment proceeded easily after cooling the reactor in a conventional freezer (−5 °C) for a period no longer than 30 min. With such procedure, there is no risk of plugging by the plasticized polymer throughout piping and valves as earlier reported during depressurization of $scCO_2$.[14]

The enzyme was separated by filtration after dissolving the reactants and products in an adequate solvent, and the polymers were purified by precipitation in cold methanol.

Research is currently in progress to optimize and understand this reaction system as well as the enzymatic syntheses of other polymers of interest in liquid R-134a.

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