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CO_2-expanded bio-based liquids as novel solvents for enantioselective biocatalysis

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ABSTRACT

For the first time, CO_2-expanded bio-based liquids were reported as novel and sustainable solvents for biocatalysis. Herein, it was found that by expansion with CO_2, 2-methyltetrahydrofuran (MeTHF), and other bio-based liquids, which were not favorable solvents for immobilized *Candida antarctica* lipase B (Novozym 435) catalyzed transesterification, were tuned into excellent reaction media. Especially, for the kinetic resolution of challenging bulky secondary substrates such as *rac*-1-adamantylethanol, the lipase displayed very high activity with excellent enantioselectivity (E value > 200) in CO_2-expanded MeTHF (MeTHF concentration 10% v/v, 6 MPa), whereas there was almost no activity observed in conventional organic solvents.

1. Introduction

Solvents play a key role in the chemical industry. They are often the major component which constitutes up to 80% of the total volume of chemicals used in a process.[1] As a consequence, most of the waste generation in organic synthesis, especially in pharmaceutical industries, comes from the use of solvents.[2] The pressing eco-environmental urge to develop sustainable processes have raised the interest in the search for new alternatives for traditional solvents. The concept of a green solvent started with the well-known 12 principles of green chemistry proposed by P. Anastas and J. Warner[3]; and the term was later clarified into 12 criteria by Y. Gu and F. Jérôme.[4] A guideline of solvent selection from common to less classical solvents has been elaborated and ranked based on a simple combination of regulations.[5]

As an alternative solvent, pressurized carbon dioxide as liquid and supercritical phases has attracted great attention because of its greenness, lack of reactivity, low viscosity, high diffusivity, and ease of recovery of the reaction products.[6] However, despite of all these interesting advantages, pressurized carbon dioxide presents a drawback that hinders its utilization in many industrial applications; given its low polarity, pressurized carbon dioxide scarcely dissolves polar or high molecular-weight organic compounds.[7]

Adding an organic co-solvent (1–2% mass) can assist the solubility of pressurized carbon dioxide media.[8] For enhanced the solubility, the co-solvent can be introduced in greater amount until the saturated point, and the co-solvent may separate into another phase and the system becomes biphasic.[8] If CO_2 dissolves in this phase and the phase expands as a result of CO_2 dissolution, it is called a CO_2-expanded liquid (CXL).[7a,9] CXLs inherit the advantages of pressurized CO_2 and of traditional solvents in an optimal fashion that pressurized CO_2 enhances the transport properties by increasing diffusivity and by decreasing viscosity of the component solvent, while this component solvent improves the solubility power of the pressurized CO_2. Moreover, fire suppression capability of CO_2 is another great merit of CXLs. However, another liquid is needed when CXLs are used and this is usually a petroleum-sourced volatile organic compound, which is depletable, and often harmful to the environment.

Recently some attention has been drawn to the use of bio-derived solvents, which are renewable sources to replace petroleum-sourced solvents.[4,10] Bio-derived solvents provide clear environmentally advantages, such as sustainable production, better biodegradability and lower toxicity. For example, 2-methyltetrahydrofuran (MeTHF), which can be derived from renewable resources (e.g., furfural or levulinic

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acid), has been employed as an emerging alternative solvent for several organic synthesis[11] including some biocatalysis processes.[12] The concept of combination of $scCO_2$ and a non-volatile bio-based liquid as a *biphasic* system was raised by Medina-Gonzalez et al.[8] and recently highlighted by Abou-Shehada,[9a] however, to the best of our knowledge, no report on CXL using a bio-based liquid as *homogenous* medium for any reaction has yet been communicated. This study is the first attempt to utilize a CO_2-expanded bio-based liquid as a new class of sustainable, efficient solvent for enzymatic reaction.

2. Results and discussion

We started our study with measuring the volumetric expansion of MeTHF by varying CO_2 pressure at 20 °C. The visual measurement was performed with 1.0 mL MeTHF magnetically stirred in an 11 mL autoclave equipped with sapphire-glass windows (Supplementary Fig. S1). The volume increased rapidly as soon as the pressure reached 5.3 MPa (Supplementary Fig. S2). This expansion is very much similar to that of THF, where the solubility of CO_2 is explained by the intermolecular interactions of CO_2 in solution.[13]

The behavior of *Candida antarctica* lipase B (CAL-B, Novozym 435®) catalyzed kinetic resolution of *rac*-1-phenylethanol **1a** was performed in CO_2-expanded MeTHF under different pressure of CO_2 (Fig. 1). There was a clear increased activity towards higher system pressure. With a same amount of MeTHF, the higher pressures up to 4 MPa, which cause higher composition of CO_2, resulted in higher conversions. Moreover, it should be noticed that even though there was a ten-time expansion of system volume from 5 MPa to 6 MPa (Supplementary Fig. S2), which accordingly decreased substrate concentration, only a slightly lower conversion was witnessed (17.5% conversion at 5 MPa, 16.8% conversion at 6 MPa). The lipase was retained its excellent enantioselectivity in all media (*E*-value > 200). The higher conversion at higher composition of CO_2 could be explained by (1) improved transport properties, (2) a more favorable hydrophobicity of the solvent systems, and (3) reduced solvent inhibition caused by polar MeTHF molecules.

(1) The transport properties of CO_2-expanded MeOH, in term of diffusivity and viscosity, which are improved as more CO_2 dissolves in the solution. For example, the diffusion of benzene was reported to increase by over 300% on replacing pure methanol with 90% CO_2 at 40 °C and 15 MPa.[14] On the other hand, the viscosity decreases about 75% from pure methanol to CXL methanol at 25 °C and 5.7 MPa.[15]

(2) Another important factor should be considered is that the low hydrophobicity of MeTHF (*log* P = 1.0), which is not very preferable for the lipase-catalyzed transesterification,[6c,16] was increased by the dissociation of the non-polar CO_2 molecules. The lipase was suspected to be less active in hydrophilic solvents, and higher esterification rates were obtained with more hydrophobic solvents because hydrophilic solvents have tendency to strip off the essential water from enzymes.[17] We cited here again the case of CO_2-expanded MeOH to show tunability of this system. By measuring the dielectric constant, Roskar et al. has shown the polarity of CO_2-expanded methanol dropped with the increase of CO_2 pressure.[18] On the other hand, Wyatt et al. have observed changes of Kamlet-Tarf parameters[19] of the mixed CO_2/methanol solvent,[20] and found that the basicity (β) and the dipolarity/polarizability (π^*) dropped dramatically in the near critical area.[20] Sih et al. reported decreases in molar volume (V_m) with the increases of CO_2 pressure.[15] It should be notice that *log* P was defined by Kamlet et al. as[21]:

$$log\ P = 0.24 - 3.38\beta + 0.0266V_m - 0.96\pi^*$$

Put all these together, we calculated that *log* P of methanol/CO_2 solution at 35 °C increases from −0.54 at 0.1 MPa to 0.29 at 7.5 MPa.

(3) A possible reason contributed to higher activity observed in solvent systems with higher CO_2 compositions (0 MPa–4 MPa) is that polar solvent molecules (MeTHF) can intensively interact with the enzyme[22] and compete with the substrate to bind to the active site.[23] However, it is noticed that this solvent-inhibition effect of MeTHF is only significant when the MeTHF is used at bulk volume. When MeTHF was used at low concentrations (up to 5 times equivalent to substrate concentration), the effect was negligible (Supplementary Table S1).

We further performed the reaction in other CO_2-expanded bio-based liquids (Fig. 2). Organic carbonates, which can be considered as non-VOC-producing solvents,[24] were used as a partner solvent with pressurized CO_2. The volumetric expansion of diethylene carbonate was very alike to that of MeTHF and MeOH, (Supplementary Fig. S2). According to Jessop and Subramaniam,

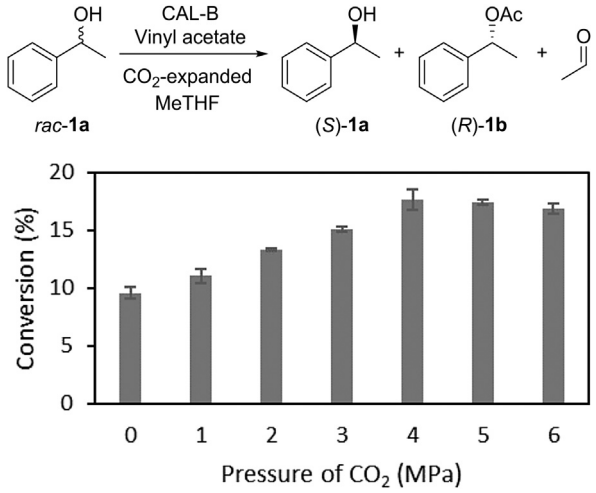

Fig. 1. Effect of CO_2 pressure on CAL-B-catalyzed transesterification of *rac*-1-phenylethanol 1a in CO_2-expanded MeTHF. Reaction conditions: 0.20 mmol 1a, 0.53 mmol vinyl acetate, 5.0 mg Novozym 435®, 1.0 mL MeTHF, 0–6 MPa of CO_2, 20 °C, 1 h. Enantiomeric excess of the corresponding acetate 1b was excellent (ee > 99%) in all media.

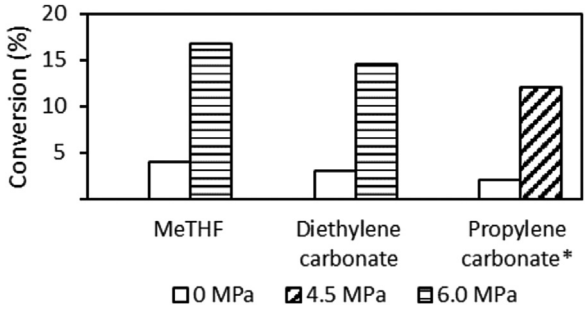

Fig. 2. CAL-B-catalyzed transesterification of *rac*-1-phenylethanol 1a in different CO_2-expanded bio-based systems and in sole bio-based liquids. Reaction conditions: 0.20 mmol 1a, 0.53 mmol vinyl acetate, 5 mg Novozym 435, 10 mL sole bio-based liquid (0 MPa of CO_2) or 10 mL CO_2-expanded bio-based systems (with initial 1 mL bio-based liquid), 20 °C, 1 h. *Reaction volume 2 mL.