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Enzymatic reactions in supercritical CO_2: carboxylation, asymmetric reduction and esterification

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Abstract

Catalytic reactions in supercritical CO_2 have been receiving increased attention during the last decade. This report reviews enzymatic reactions in supercritical CO_2 such as carboxylation of pyrrole by a decarboxylase, asymmetric reduction of ketones by an alcohol dehydrogenase and enantioselective esterification of a trifluoromethyl alcohol by a lipase.

Keywords: Supercritical CO_2; Enzyme; Decarboxylase; Alcohol dehydrogenase; Lipase; Enantioselectivity; Carboxylation; Reduction; Esterification; Chiral compounds; Trifluoromethyl alcohol

1. Introduction

1.1. Properties of supercritical CO_2

Supercritical fluids have the unique properties to present a grand opportunity to discover a range of novel chemical processes [1–6]. Among many fluids, supercritical CO_2, CO_2 above its critical point as shown in Fig. 1, has the added benefits of an environmentally benign nature, nonflammability, low toxicity, high availability and an ambient critical temperature ($T_c = 31.0\,^{\circ}C$).

Supercritical fluids differ from ordinary solvents in having both their gas-like low viscosities and high diffusivities and their liquid-like solubilizing power. Moreover, these properties are tunable by the manipulation of the pressure and temperature [7–10]. Small changes in pressure or temperature lead to significant changes in density and density-dependent solvent properties such as the dielectric constant, the solubility parameter and the partition coefficient as shown in Fig. 2 [7]. When solvent effects on the reaction are examined with supercritical fluids, it can be done without changing the kind of solvent. In addition, the solvent properties can be changed continuously by manipulating the pressure and temperature, so continuous change in a reaction can be expected.

1.2. Applications using supercritical CO_2

Various applications using supercritical CO_2 have been developed as shown in Table 1 [11–26]. For example, in the area of extraction, the use of supercritical CO_2 on an industrial scale began in 1978 [11].

1.3. Enzymatic reactions in supercritical CO_2

The first report on the enzyme catalyzed reactions in supercritical fluids was in 1985 by Randolph et al. [27], Hammond et al. [28], and Nakamura et al. [29]. Recently, the benefit of using supercritical fluids for enzymatic reactions has been demonstrated by Mori et al. [30,31] and Kamat et al. [32–35], e.g. improved reaction rates, control of selectivities by pressure, etc. Some examples of enzymatic reactions are shown in Fig. 3.

However, most of the enzymes used in supercritical fluids are hydrolytic enzymes such as lipases and proteases [38–48]. In this report, the use of decarboxylase [49] and alcohol dehydrogenase [50,51] as well as lipase [52,53] in supercritical CO_2 is reviewed.

2. Carboxylation

The development of CO_2 fixation reactions on organic molecules is one of the challenges in synthetic chemistry. An increasing number of chemical CO_2 fixation reactions

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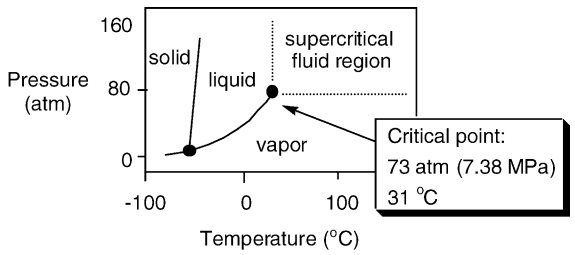


Fig. 1. Phase diagram of CO_2.

[54–61] has been reported, especially using supercritical CO_2, such as the synthesis of urethane [54], dimethyl carbonate [55], styrene carbonate [56], and methyl ethanoate [57]. On the other hand, biocatalysis is now one of the most powerful and indispensable tools for organic synthesis due to its environmental friendliness and excellent enantio-, regio- and chemoselectivities [62–66]. Some enzymatic CO_2 fixation reactions have also been reported including the central CO_2 fixation reaction in photosynthetic organisms catalyzed by ribulose-1,5-diphosphate carboxylases [67], the reduction of CO_2 to formic acid or methanol by dehydrogenases [68–72], the reductive CO_2 fixation on 2-oxoglutarate and pyruvate by isocitrate [73] or malate [74] dehydrogenases, and the CO_2 fixation on pyrrole and phenolic compounds (phenol and catechol) by decarboxylases from *Bacillus megaterium* [75–78] or *Clostridium hydroxybenzoicum* [79,80], respectively. In this chapter, it is described that cells of *B. megaterium* catalyze the reverse reaction, CO_2 fixation, in supercritical CO_2 [49]. As shown in Scheme 1, CO_2 was fixed on pyrrole (**1**) to produce pyrrole-2-carboxylate (**2**) at 10 MPa and 40 °C. The yield of the reaction in supercritical CO_2 was much higher than that at atmospheric pressure.

The cells of *B. megaterium* [76] were employed for the CO_2 fixation reaction. The reaction was conducted by adding CO_2 to 10 MPa to the mixture of (**1**), the cells, $KHCO_3$, and NH_4OAc in potassium phosphate buffer. For the reaction at atmospheric pressure (0.1 MPa), the evolved CO_2 was released to keep the pressure atmospheric. The yields of the reaction at 40 °C are listed in Table 2. The yield is much higher for the reaction in supercritical CO_2 than at atmospheric pressure (Table 2, Entries 1–4). It was also confirmed by the control experiment without the cells that the non-biocatalytic carboxylation of (**1**) did not proceed (Table 2, Entry 5). A control reaction using heat treated cells afforded no carboxylation product, either, which indicates that a biocatalyst is at work and that the carboxylation is not an unexpected process promoted by non-enzymic constituents of the cell.

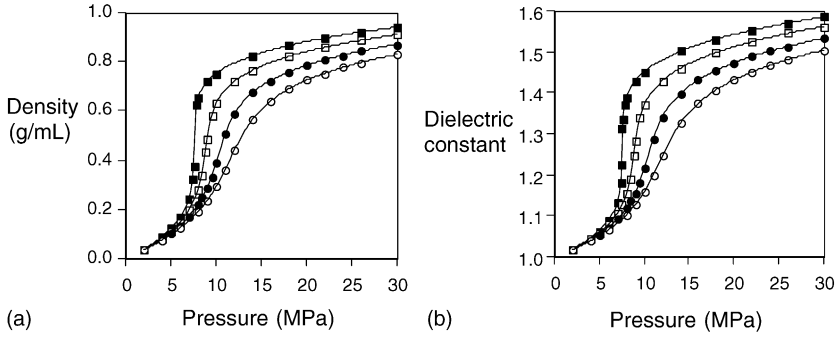


Fig. 2. Tunability of solvent properties of CO_2 by the temperature and pressure (a) density (b) dielectric constant (closed square: 32 °C, open square: 40 °C, closed circle: 50 °C, open circle: 60 °C) [7].

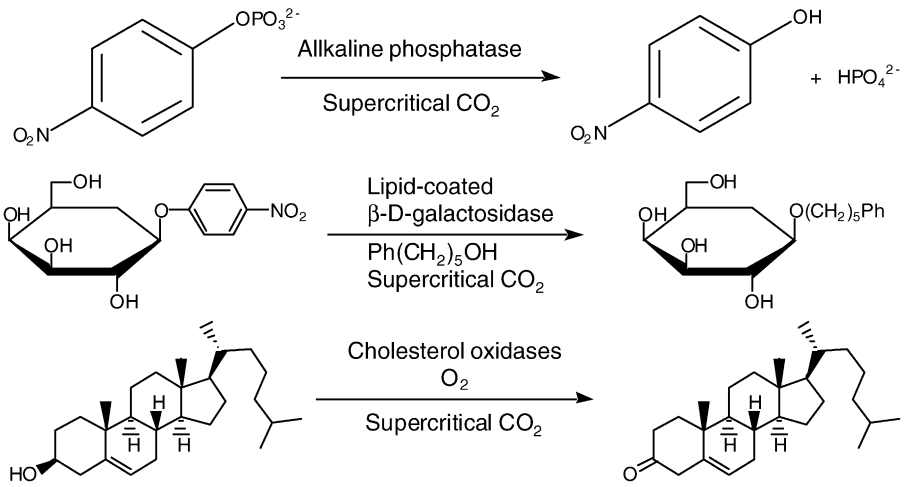
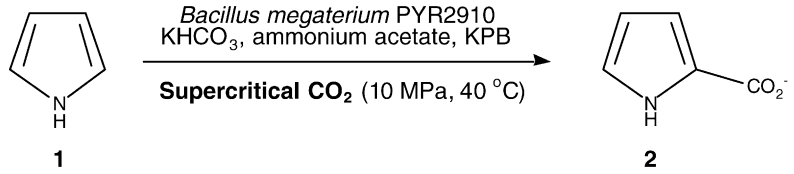


Fig. 3. Examples of enzymatic reactions in supercritical CO_2 [27,30,31,36,37].

Table 1
Applications using supercritical CO_2

Applications	Examples [Ref.]
Extraction	Extraction of caffeine from coffee beans [11], extraction of oil from corn fiber [12], extraction of compounds with pharmaceutical importance from microalgae [13], enantioseparation of chiral alcohols by complex formation and subsequent supercritical fluid extraction [14]
Chromatography	Separation of fatty acids [15], separation of enantiomers [16], supercritical fluid chromatography-mass spectrometry [17], two-dimensional supercritical fluid chromatography [18]
Reactions	Hydrogenation of supercritical CO_2 to formic acid, alkyl formates, and formamides by homogeneous catalysts [19,20], enantioselective hydrogenation of imines in supercritical CO_2 by iridium-catalyst [21], hydroformylation in supercritical CO_2 by rhodium catalysts [22], asymmetric Diels–Alder reactions in supercritical CO_2 catalyzed by rare earth complexes [23]
Other	Polymer coating/encapsulation of nanoparticles using a supercritical anti-solvent process [24], improvement of insulin absorption from intratracheally administrated dry powder prepared by a supercritical CO_2 process [25], dyeing of natural fibers from perfluoropolyether reverse micelles in supercritical CO_2 [26]



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Scheme 1. [49].

Table 2
Carboxylation of (**1**) by *Bacillus megaterium* in supercritical CO_2 [49]

Entry	Pressure (MPa)	Cells (mL)[a]	pH	Time (h)	Yield (%)[b]
1	0.1 (atmospheric)	0.5	5.5	1	7
2	0.1 (atmospheric)	0.5	5.5	3	6
3	10 (supercritical)	0.5	5.5	1	54
4	10 (supercritical)	0.5	5.5	3	55
5	10 (supercritical)	0.0	5.5	3	0
6	10 (supercritical)	1.0	5.5	3	59
7	10 (supercritical)	0.5	7.0	1	59

[a] $OD_{610} = 32$; decarboxylation activity for (**2**) = 0.024 mmol/min/mL.
[b] Yield is the percentage of (**2**) based on the starting amount of (**1**).

The time courses of the reaction at 10 MPa and at atmospheric pressure in Fig. 4 also have a higher yield for the former reaction. The reaction reached an equilibrium position within a few hours and did not proceed further. As listed in Table 2, the doubling of the quantity of cells (Entry 6) as well as the change in the initial pH value from 5.5 to 7.0 to prevent a pH decrease caused by CO_2 (Entry 7) did not have any significant effect on the equilibrium position.

The effect of pressure on the carboxylation of (**1**) was also investigated, and the result is shown in Fig. 5. The maximum yield was between 4 and 7 MPa; the yield at just above its critical pressure (7.6 MPa) is about 12 times that at atmospheric pressure (0.1 MPa). Similar pressure dependencies of the yield were also observed using an increased quantity of the cells, shorter reaction times and different temperatures (data not shown). At present, it is not clear why the increased concentration of CO_2 in the range greater than the critical pressure did not favorably shift the carboxylation equilibrium.

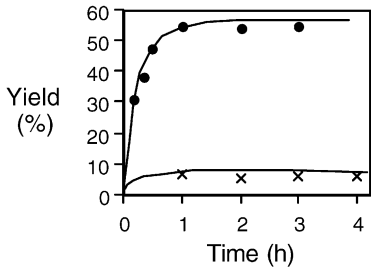


Fig. 4. Time course of carboxylation of (**1**) by *Bacillus megaterium*: (●) 10 MPa (supercritical); (×) 0.1 MPa (atmospheric) [49].

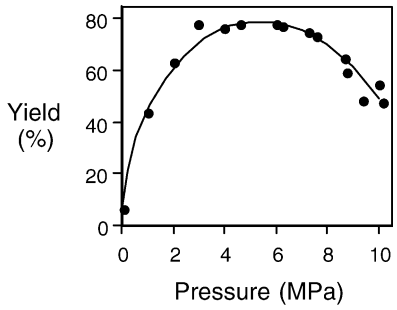
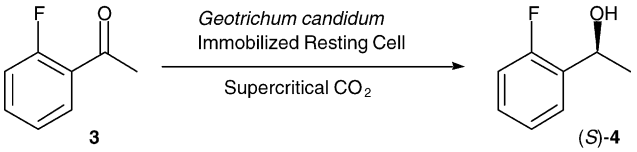


Fig. 5. Effect of pressure on carboxylation of (**1**) by *Bacillus megaterium* [49].

3. Asymmetric reduction

The resting cells of a fungus, *Geotrichum candidum* [81–83], were employed for the reduction of various ketones in supercritical CO_2 [50,51]. The advantage of alcohol dehydrogenase catalyzed reactions in supercritical CO_2 is the ease of the product isolation from CO_2. When an aqueous solvent is used, the product has to be extracted



Scheme 2. [50,51].

from the solvent, but this is unnecessary when using supercritical CO_2. The whole resting cell instead of an isolated enzyme was used for the reduction, and thus no addition of an expensive coenzyme was required. Also, the solubility of the coenzymes in supercritical CO_2 did not need to be considered. The cell was immobilized on a water-absorbing polymer [83] to spread it on the large surface of the polymer. At first, the reduction of *o*-fluoroacetophenone (**3**) in supercritical CO_2 at 10 MPa was conducted, which afforded (*S*)-1-(*o*-fluorophenyl)ethanol ((*S*)-**4**) at 81% after 12 h (Scheme 2). A control experiment to prove that the reduction did not proceed before the supercritical condition was also conducted. The time course of the reaction (Fig. 6) shows that the yield increased with the reaction time, which proved that the alcohol dehydrogenase catalyzed the reduction even in the supercritical condition.

The substrate specificity was investigated, and as listed in Table 3, the enzymatic reduction in supercritical CO_2 proceeded for various ketones. Acetophenone, acetophenone derivatives, benzyl acetone and cyclohexanone were used as substrates, and it was found that all of them were reduced by the alcohol dehydrogenase in supercritical CO_2. The effects of fluorine substitution at the *ortho*-, *para*- and α-positions of acetophenone were obvious. Compared with the unsubstituted analogue, substitution at the *ortho*- or α-position increased the yield, whereas substitution at the *para*-position decreased the yield.

The finding that the alcohol dehydrogenase is active in supercritical CO_2 is significant, but not sufficient for practical use; high enantioselectivity of the reduction is also necessary for synthetic purposes. In our case, very high enantioselectivities (>99% ee) were obtained for the reduction with the majority of the substrates tested, while slightly lower enantioselectivities (96, 97% ee) were observed for a few of them. The enantioselectivities obtained in this system are superior to or at least equal to those for most other biocatalytic and chemical systems [62–66,81–83].

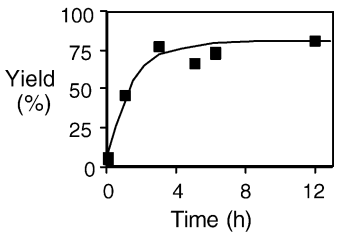


Fig. 6. Time course of reduction of (**3**) by *Geotrichum candidum* in supercritical CO_2 at 10 MPa [50].

Table 3
Reduction of various ketones by *Geotrichum candidum* in supercritical CO_2 [50]

Substrate	Yield (%)	ee (%)	Configuration
	51	>99	*S*
	81	>99	*S*
	53	>99	*S*
	11	97	*S*
	96	96	*R*
	22	>99	*S*
	61	>98	*S*
	96	–	–

The immobilized resting cell of *G. candidum* was also used as a catalyst for the reduction of ketones in a semi-continuous flow process using supercritical CO_2 [51]. With flow reactors, the addition of a substrate to the column with a catalyst yields the product and CO_2, which is a gas at ambient pressure, whereas, with the batch reactor, separation of the product from the biocatalyst is necessary after depressurization. Therefore, the flow type is superior to the batch type for achieving virtually no solvent reaction. Moreover, the size of the reactors using the flow process to generate an amount of product comparable with the corresponding batch reactors is smaller, which is particularly attractive for a supercritical fluid system [84]. This reaction using a semi-continuous flow process also resulted in a higher space-time yield than that of the corresponding batch process.

The reduction of cyclohexanone was examined first as a model reaction to test the viability of the process. The apparatus is shown in Fig. 7. The typical experiment is as follows. The immobilized cells were placed in a stainless steel reactor, and a stainless steel pipe was inserted in the bottom of the test tube. The conditions were set to 35 °C and 10 MPa. The substrate, cyclohexanone, dissolved in 2-propanol (which is necessary as a hydrogen donor) was injected through an HPLC injection valve and then the product was trapped (injection/trap 1 in Table 4). The injection of the substrates was repeated four times to assess reusability (injection/traps 2–5). The results are shown in Table 4. Cyclohexanol was obtained successfully. The biocatalyst was recycled up to four times with only a slight loss in activity.

Encouraged by this promising result, reduction of *o*-fluoroacetophenone (**3**) was conducted by the same

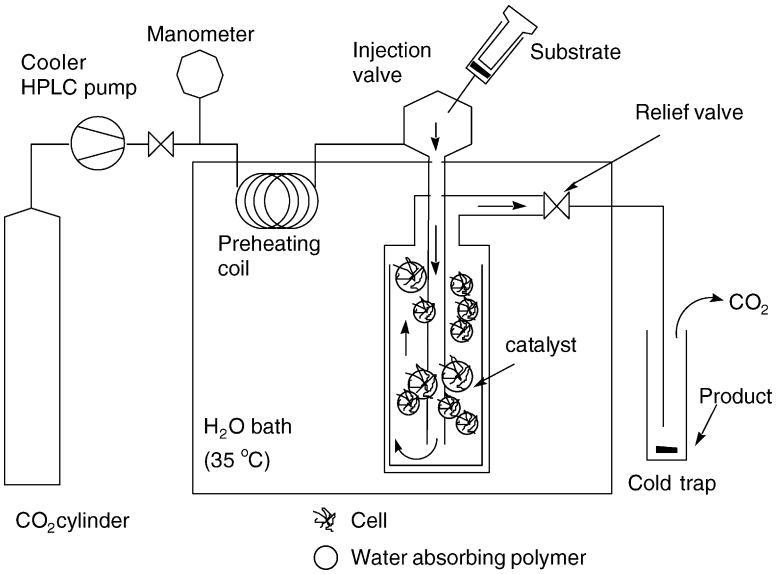


Fig. 7. Apparatus for biocatalytic reduction with flow process using supercritical CO_2 [51].

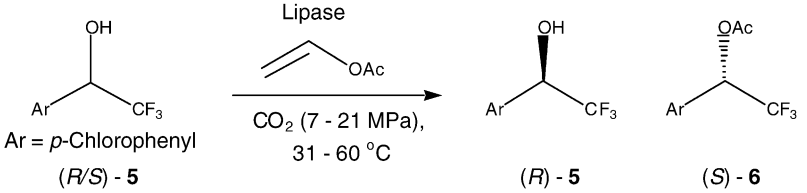
Table 4
Reduction of cyclohexanone by *Geotrichum candidum* with the semi-continuous flow process using supercritical CO_2 [51]

Injection/trap	Yield (%)
1	12
2	21
3	36
4	36
5	30

method. ((*S*)-**4**) was obtained successfully with a yield of 8%. The space-time yield of this flow system was compared with that of the corresponding batch system. That of the flow system (0.24 μmol/min) was almost twice as much as that of the corresponding batch system (0.13 μmol/min) at 35 °C and 10 MPa using a pressure-resistant vessel (Taiatsu Techno Co., Osaka, TVS-N2 type, 10 mL) for the reduction of (**3**). Therefore, the flow-type reactor is more efficient than the corresponding batch system.

4. Esterification

One of the most characteristic features of the supercritical fluid is the tunability of the properties. Our interest is to control the biocatalytic reaction in supercritical CO_2 by adjusting the pressure and temperature [52,53]. Such attempts to control enzymatic reactions have been done by using supercritical fluoroform because its polarity changes drastically with pressure and temperature [1,5,21,34,35,38,85,86]. For example, Mori et al. demonstrated the reversible control of transglycosylation by a lipid-coated β-D-galactosidase [85] and enantioselective esterification by a lipid-coated lipase [86]. Kamat et al. examined the enantioselectivity of subtilisin Carlsberg and an *Aspergillus* protease [34,35] in supercritical fluoroform. However, only a few reports on the control of biocatalytic reactions using supercritical CO_2 under various pressures and temperatures have been reported [39,40]. We have examined the enantioselective acetylation of racemic 1-(*p*-chlorophenyl)-2,2,2-trifluoroethanol ((*R/S*)-**5**) with lipases and vinyl acetate [87] in supercritical CO_2 as shown in Scheme 3 [52,53]. The fluorinated compound was chosen as a model substrate because optically pure fluorinated alcohols have received much attention for the synthesis of ferroelectric liquid crystals or bioactive compounds [88–91]. We found that the enantioselectivity of a reaction using the lipase Novozym can be controlled by adjusting the pressure and temperature of supercritical CO_2. Moreover, at constant density, the modified Eyring plot of $\ln E$ [92] against $1/T$ was found to be linear, which correlates well with results predicted by the theory of the effects of temperature on enantiochemistry [93].



Scheme 3. [52,53].

Table 5
Screening of lipases for enantioselective acetylation of ((*R/S*)-**5**) in supercritical CO_2 [53]

Lipase	Low pressure conditions (9.1 MPa)		High pressure conditions (14.5 MPa)	
	Yield (%)	E[a]	Yield (%)	E[a]
LPL (*Pseudomonas aeruginosa*)	52	12	38	16
AY (*Candida rugosa*)	8	1[b]	2	2
AH (*Pseudomonas cepacia*)	3	29	0	–
PS-D (*Pseudomonas cepacia*)	0	–	0	–
PS-C (*Pseudomonas cepacia*)	43	8	22	17
Lipozyme (*Rizomucor miehei*)	0	–	0	–
Novozym (*Candida antarctica*)	25	38	24	23

Reaction conditions: 40 °C, 4 h.
[a] Enantiomeric ratio, E value, was used to evaluate enantioselectivity. $E = (V_A/K_A)/(V_B/K_B)$ where V_A, K_A and V_B, K_B denote maximal velocities and Michaelis constants of the fast- and slow-reacting enantiomers, respectively. The (*S*)-enantiomer reacted faster than (*R*)-enantiomer.
[b] In this case, the (*R*)-enantiomer reacted slightly faster than the (*S*)-enantiomer.

First, we screened various lipases for the enantioselective acetylation of ((*R/S*)-**5**) with vinyl acetate in supercritical CO_2. The results are listed in Table 5. To evaluate the enantioselectivity of this reaction, the ratio of the specificity constants of the enantiomers, E value, was used. (*S*)-Enantiomers reacted faster than (*R*)-enantiomers, affording (*S*)-acetate ((*S*)-**6**) and the remaining (*R*)-alcohol ((*R*)-**5**) except when lipase AY was used at 9.1 MPa. The highest enantioselectivity ($E = 38$) was obtained using Novozym at 9.1 MPa. Interestingly, the enantioselectivity was significantly affected by the pressure.

The enantioselective acetylation of ((*R/S*)-**5**) with vinyl acetate in supercritical CO_2 by Novozym was investigated at 55 °C and 10 MPa. The reaction rate decreased when the yield of acetate (**6**) reached approximately 50%. The effect of pressure on the enantioselectivity was investigated by changing the reaction time from 2 to 4 h. As shown in Fig. 8, the E value changed continuously from 50 to 10 when the pressure was changed from 8 to 19 MPa, regardless of the reaction time.

The effect on enantioselectivity of changes in pressure is indeed noteworthy, although the reason is not clear at present. When the pressure of supercritical CO_2 was changed, there was no significant change in the polarity evaluated as dielectric constant (Fig. 2b) [7] and log P (at 50 °C; 1.4 at 8 MPa and 1.9 at 11 MPa) [94]. It is not clear if this small change in polarity has a large effect on this reaction. On the other hand, the density of supercritical CO_2 does change from 0.20 to 0.42 g/mL when the pressure is changed from 8 to 11 MPa at 55 °C [7,8]. Ikushima explained the high enantioselectivity of lipase in a very limited pressure range at 304.1 K as resulting from interaction between CO_2 and enzyme molecules [39,40]. We also propose that the large change in density could significantly change the interaction of CO_2 and the enzyme by the formation of carbamates from CO_2 and the free amine groups on the surface of the enzyme [38], by CO_2 adsorption on the enzyme as reported in other proteins [95] and/or by CO_2 incorporation in the substrate-binding pocket of the enzyme as reported in the incorporation of organic molecules in enzymes [96,97]. These interactions may gradually change the conformation of the enzyme in response to pressure, resulting in a continuous change in enantioselectivity.

On the contrary, the continuity of the enantioselectivity change was not observed using conventional organic solvents for the same reaction as shown in Fig. 9. Moreover, it is unclear whether the E values depended only on the polarity of the solvent, because a polarity change is inevitably accompanied by a change in the molecular structure of the

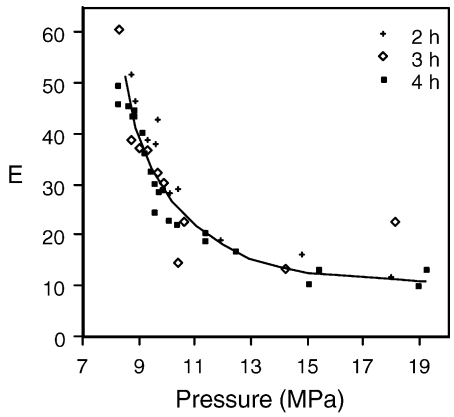


Fig. 8. Effect of pressure on enantioselectivity of acetylation of ((*R/S*)-**5**) by Novozym in supercritical CO_2 at 55 °C [52] (*E*: enantiomeric ratio described in Table 5 [92]).

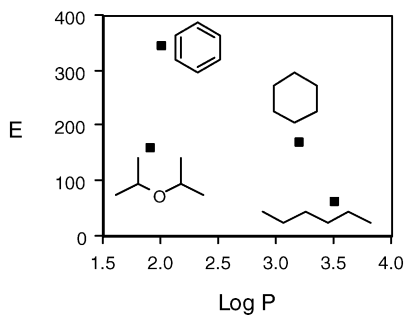


Fig. 9. Effect of organic solvent on enantioselectivity of acetylation of ((*R/S*)-**5**) by Novozym [52] (*E*: enantiomeric ratio described in Table 5 [92]).

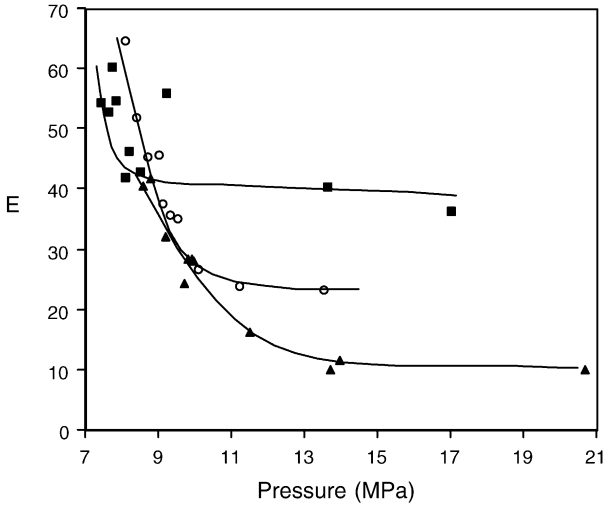


Fig. 10. Effect of pressure on enantioselectivity of acetylation of ((*R/S*)-**5**) by Novozym in supercritical CO_2 at 31 °C (square), 40 °C (circle) and 60 °C (triangle) [53] (*E*: enantiomeric ratio described in Table 5 [92]).

solvent (cyclic or acyclic) and the molecular structure of the solvent, as well as its polarity, affects the enantioselectivity of the reaction [96]. On the other hand, by using CO_2, the solvent properties can be changed simply by altering the pressure.

The effect of pressure on the enantioselective acetylation of ((*R/S*)-**5**) with vinyl acetate in supercritical CO_2 by Novozym was also investigated at 31, 40 and 60 °C (Fig. 10). As in the case at 55 °C, the (*S*)-enantiomer reacted faster than the (*R*)-enantiomer, affording ((*S*)-**6**) and unreacted ((*R*)-**5**). The *E* value changed continuously according to the pressure. This is probably due to the change in the density as in the case at 55 °C. This explanation agrees with the following observations. At lower temperature (31, 40 °C), the *E* values changed rapidly from high to low values within a small range of pressure below 10 MPa. However, at higher temperature (55, 60 °C), the *E* values changed gradually within a larger range of pressure below 14 MPa. These changes correlate well with the change in density as shown in Fig. 2a [7,8].

However, when *E* values of the same density (at different temperatures and different pressures) were compared, *E* values were affected by the temperature. The enantioselectivity is determined not only by the density but also by the temperature. In a reaction under ambient conditions, the enantioselectivity in the kinetic resolution is temperature-dependent and obeys a modified Eyring equation [93,98,99]:

$$\ln E = -\frac{\Delta\Delta H^{\ddagger}}{R}\frac{1}{T} + \frac{\Delta\Delta S^{\ddagger}}{R}$$

Therefore, with the equation, a temperature modulation of stereochemistry of enzymatic catalysis is possible. Using enzymatic reactions performed at temperatures ranging from 30 to −50 °C, Sakai et al. showed the first experimental evidence supporting the theory of the effect of temperature on stereochemistry [98,99]. Here, we examined whether the theory is applicable to the reaction in supercritical CO_2 for the first time. At a density of 0.75 g/mL (31 °C at 9.5 MPa, 35 °C at 11.2 MPa, 40 °C at 13.2 MPa, 45 °C at 15.3 MPa, 50 °C at 17.5 MPa, 55 °C at 19.6 MPa, and 60 °C at 21.8 MPa), ln *E* was plotted against 1/*T*. As shown in Fig. 11, the Eyring plot was found to be linear throughout this range and thus indicates the conformational stability of the transition state.

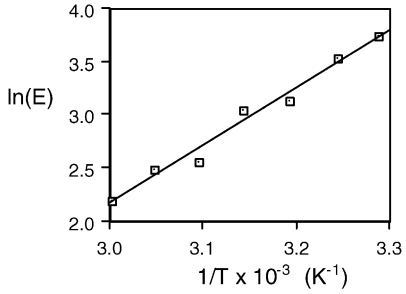


Fig. 11. Effect of temperature on enantioselectivity of acetylation of ((*R/S*)-**5**) by Novozym in supercritical CO_2 at 0.75 g/mL [53] (*E*: enantiomeric ratio described in Table 5 [92]).

The observation of variation in the enantioselectivity by changing the temperature at the same density, i.e. at the same dielectric constant [7], is in contrast to the case for the transglycosylation by a lipid-coated β-D-galactosidase [85] or the enantioselective esterification by a lipid-coated lipase [86] in supercritical fluoroform by Mori et al. In these reports, reactivities and selectivities were controlled by the dielectric constant but either solely by temperature or by pressure. This contrasting result is probably due to the difference between fluoroform and CO_2 in the magnitude of the change in dielectric constants caused by the manipulation of pressure and temperature. In our case, both the density and the temperature controlled the reaction, but in their case, the effect of temperature on the reactions was probably negligible compared to the effect of the dielectric constant.

5. Conclusion

Carboxylation by a decarboxylase, asymmetric reduction by an alcohol dehydrogenase and enantioselective esterification by a lipase in supercritical CO_2 were described in this report. This is the beginning of the investigation of novel reaction systems which are in harmony with the natural environment. We believe that it opens up new possibilities for synthesis by various kinds of enzymes with a natural, easily removable, and high-functional solvent, supercritical CO_2.

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