

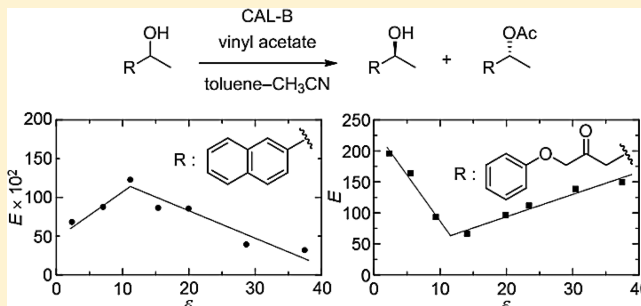
Effect of Solvent Polarity on Enantioselectivity in *Candida Antarctica* Lipase B Catalyzed Kinetic Resolution of Primary and Secondary Alcohols

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Supporting Information

ABSTRACT: The *Candida antarctica* lipase B (CAL-B) catalyzed kinetic resolution of primary and secondary alcohols via acetylation is dependent on the permittivity (ϵ) of the reaction solvent. For example, the enantiomeric ratio (E) vs ϵ plot for the acetylation of 1-(naphth-2-yl)ethanol (**1**) exhibits a convex shape, taking the maximum E value at a medium ϵ value (11.2), whereas the same plot for the acetylation of benzyl 3-hydroxybutyrate (**3**) exhibits a concave shape, taking the minimum E value at a similar ϵ value (11.6). Kinetic studies reveal that the difference in shape of the E vs ϵ plots originates from the relative reaction rate between the enantiomers with different Michaelis constants (K_m). Thus, when the enantiomer with a larger K_m value in the middle ϵ region reacts more slowly than its antipode, the ϵ dependence of E exhibits a convex shape. On the other hand, when the enantiomer reacts more quickly, it exhibits a concave shape. The E vs ϵ plot for the acetylation of 2-methoxy-2-phenylethanol (**7**) exhibits a convex shape with the maximum E value (20) at $\epsilon = 14.1$. The E value can be further improved to almost reach the efficiency required for industrial applications ($E \approx 30$) by the addition of a nitro compound.



INTRODUCTION

Enzymatic kinetic resolution is a method widely employed in the drug industry, as well as in the laboratory, to optically resolve a racemic compound by an enzyme-catalyzed reaction, taking advantage of the difference in reaction rates between the enantiomers.^{1,2} Resolution reactions have often been conducted using enzymes suspended in organic solvents in order to resolve water-insoluble compounds, suppress undesired side reactions, and shift the thermodynamic equilibrium to products.³ For example, enantiopure carbocyclic nucleosides, which are key intermediates for the synthesis of antiviral agents, were prepared by the pancreatin-catalyzed acetylation of their precursory alcohols.^{3e} Synthesis of the C16–C20 segment of an endogenous lipid mediator, resolvins E1, was achieved by the lipase-catalyzed acetylation of its precursory secondary alcohol.^{3f} Dynamic kinetic resolution, which allows us to obtain an enantiopure product quantitatively from a racemic substrate by racemizing the substrate during kinetic resolution, has also been successfully conducted in organic solvents.⁴ In the resolution reaction of alcohols, amines, and carboxylic acids via acylation or transesterification,⁵ it is often the case that the stereoselectivity varies depending on the solvent employed.⁶ In some reports, the solvent effects are correlated with the polarity or hydrophobicity of the solvents.^{7–9} These reports assert that solvents affect the enzymes or enzyme–substrate complexes by producing changes in the conformational rigidity of enzymes,⁷ invading the active site,⁸ or altering the solvation of the

transition state.⁹ On the other hand, Cainelli and co-workers pointed out the importance of solvent effects on substrate molecules. They reported that in the *Candida antarctica* lipase (CAL) catalyzed acetylation of 1-(naphth-2-yl)ethanol (**1**),¹⁰ the $\ln E$ vs $1/T$ plot (herein, E denotes the enantiomeric ratio¹¹ (eq 1)) comprises two half-segments with different slopes,

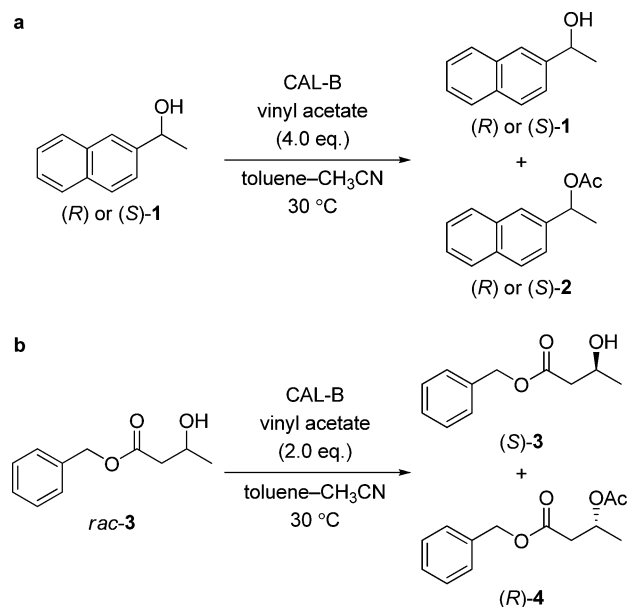
$$\begin{aligned} E &= \frac{k_{\text{cat},R}/K_{m,R}}{k_{\text{cat},S}/K_{m,S}} \\ &= \frac{\ln[1 - c(1 + ee_p)]}{\ln[1 - c(1 - ee_p)]} \\ &= \frac{\ln[(1 - c)(1 - ee_s)]}{\ln[(1 - c)(1 + ee_s)]} \\ &= \frac{v_{0,R}}{v_{0,S}} \end{aligned} \quad (1)$$

connecting at a point identified as an inversion temperature (T_{inv}). Similar observations have been made in other enzymatic and nonenzymatic reactions.¹² Variable-temperature (VT) NMR analysis of the substrate strongly suggested that the breakpoint at T_{inv} represents a transition between two different

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solute–solvent clusters, which serve as distinct supramolecules with different reactivities and enantioselectivities. During the optical resolution of racemic 1,1'-binaphthalene-2,2'-dicarboxylic acid by crystallization after conversion into diastereomeric amides with (*S*)-1-phenylethylamine, we recently found that the deposited diastereomer can be switched by the permittivity (ϵ) of the crystallization solvent,¹³ which provides an example of dielectrically controlled resolution (DCR) proposed by Sakai, Sakurai, and co-workers.^{14,15} Mechanistic studies revealed that this phenomenon was caused by ϵ -dependent changes in the aggregation state of the amide molecules in solution and the ease with which solvent molecules are incorporated into the crystals. On the basis of our findings combined with those of Cainelli's group, we reasoned that enzymatic kinetic resolution should be controllable by principles similar to those of DCR. Herein, we report that the enantioselectivity for the lipase-catalyzed kinetic resolution of primary and secondary alcohols is controllable by altering solvent polarity, using solvent permittivity as a measure (Scheme 1).

Scheme 1. CAL-B Catalyzed Acetylation of Alcohols 1 and 3



RESULTS AND DISCUSSION

Acetylation of Alcohols 1 and 3 in Mixed Solvents with Different Polarities. First, alcohol 1 was acetylated with vinyl acetate in toluene–acetonitrile using CAL-B as a catalyst (Scheme 1a). It has been reported that CAL-B maintains a rigid conformation in organic solvents¹⁶ and its acyl transfer reaction follows Michaelis–Menten kinetics: in particular, the bi-bi ping-pong mechanism.¹⁷ The polarity of the reaction solvent was varied by changing the volumetric ratio of the two components (v/v), instead of employing a series of solvents with different ϵ values. Therefore, the structural effect of the solvents, e.g. bulkiness and functional groups, on E can be reduced.¹⁸ The ϵ value of the mixed solvent, which was calculated as a weighted average of the component ϵ values,¹⁹ was employed as a measure of the polarity of the reaction system; although effects of solutes on ϵ were not taken into account, the ϵ value calculated from the solvent ϵ values should be in a linear

relationship with that of the whole system, because the initial concentrations of solutes were kept constant throughout a series of runs. The E value in the reaction of racemic alcohol *rac*-1 was too large to be accurately determined from the conversion (c) and the enantiomeric excess of either the product (ee_p) or substrate (ee_s) (eq 1). Consequently, each enantiomer was separately subjected to the acetylation, and the E value was calculated as the ratio of the initial rate of the faster reacting *R* isomer to that of the *S* isomer, $v_{0,R}/v_{0,S}$. Figure 1a

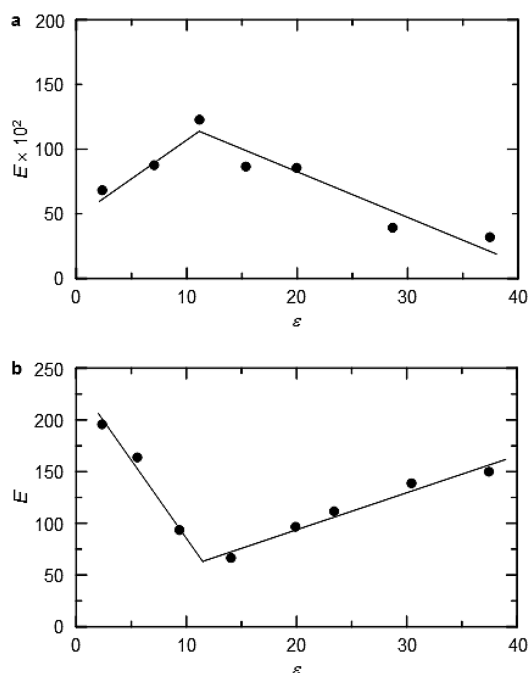


Figure 1. Dependence of enantiomeric ratio (E) on solvent permittivity (ϵ) for the CAL-B-catalyzed acetylation of (a) alcohol 1 and (b) alcohol 3.

shows the plot of E vs ϵ . Analogous to the temperature dependence of $\ln E$ reported by Cainelli (vide supra),¹⁰ the plot comprises two half-segments with different slopes, connecting at a point with a medium ϵ value ($\epsilon = 11.2$). The racemic alcohol *rac*-3 was also acetylated under similar conditions (Scheme 1b); in this case, the E value could be calculated from c and ee_p (eq 1). The E vs ϵ plot for alcohol 3 also comprises two half-segments with different slopes, connecting at a point with a medium ϵ value ($\epsilon = 11.6$) (Figure 1b). These results indicate that the enantioselectivity of enzymatic kinetic resolution may be controlled by altering the polarity of the reaction media.

Kinetic Studies and ¹H NMR Analysis. In order to clarify the origin of the ϵ dependence of the enantiomeric ratio, the two reactions were examined further. The Michaelis constants for the individual enantiomers, $K_{m,R}$ and $K_{m,S}$, were determined by Lineweaver–Burk plots in toluene–acetonitrile with different composition ratios. The K_m vs ϵ plot for alcohol 1 exhibited a convex shape, taking the maximum value at the same ϵ value as that of the node observed in the E vs ϵ plot (Figure 2a compared with Figure 1a). For most ϵ ranges, the *S* enantiomer exhibited a larger K_m value than the *R* enantiomer. The magnitude of change in K_m was also larger for the *S* enantiomer. Similar observations were made for alcohol 3, except that the K_m value and its magnitude of change were larger for the *R*

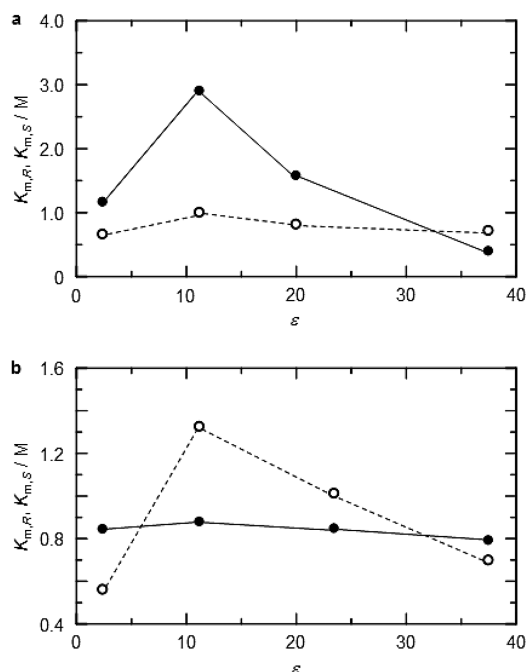


Figure 2. Dependence of Michaelis constant (K_m) on solvent permittivity (ϵ) for the acetylation of (a) alcohol **1** and (b) alcohol **3**. The solid line with $\bullet$ and broken line with $\circ$ represent Michaelis constants $K_{m,S}$ and $K_{m,R}$, respectively.

enantiomer than for the *S* enantiomer (Figure 2b). On the other hand, the ϵ -dependent change of maximum velocity, V_{max} , was very small (Figure 3). This indicates that the catalytic activity of the enzyme is almost constant regardless of the solvent polarity. Therefore, since the enantiomeric ratio (*E*) is expressed as the product of the ratio of catalytic constants, $k_{cat,R}/k_{cat,S}$, and the ratio of Michaelis constants, $K_{m,S}/K_{m,R}$, the ϵ dependence of *E* is mostly attributable to the latter quotient, the difference in the ϵ dependence of K_m between the enantiomers. The K_m vs ϵ plot for each enantiomer of alcohols **1** and **3** exhibited a convex shape (Figure 2). This indicates that, in a medium-permittivity solvent, the substrate molecules do not easily diffuse into the substrate-binding pocket of the enzyme.

We then analyzed the behavior of the alcohol molecules by ^1H NMR spectroscopy in toluene- d_8 –acetonitrile- d_3 with varying compositions. The chemical shift vs ϵ plot for the methyl protons of each racemic alcohol comprised two half-segments with different slopes, connecting at a point with a medium ϵ value (Figure 4). The ϵ values of the nodes ($\epsilon = 10.9$ and 11.3 for alcohols **1** and **3**, respectively) are in reasonable agreement with those of the nodes of the K_m vs ϵ plots (vide supra). Similar ϵ -dependent changes were observed for the other protons of alcohols **1** and **3** (Figure S1 in the Supporting Information). It is conceivable that the two half-segments in the δ vs ϵ plots correspond to different changes in the aggregation state of the alcohol molecules.

Mechanistic Considerations. With these observations in mind, a feasible mechanism for the ϵ -dependent convex change of K_m is proposed as follows (Figure 5). In a solvent with an ϵ value higher than that of the node, the alcohol molecules are less polar than the solvent and are associated with each other by hydrophobic interactions (Figure 5a). In such a solvent, the polarity of the substrate-binding pocket of the enzyme will also be lower than that of the solvent. As a result, alcohol molecules

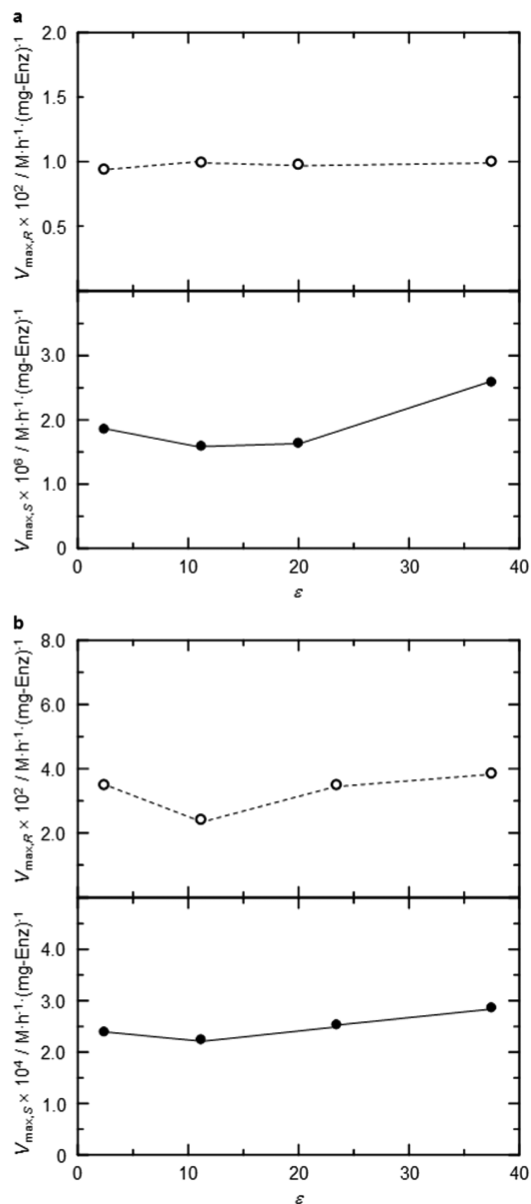


Figure 3. Dependence of maximum velocity (V_{max}) on solvent permittivity (ϵ) for the CAL-B-catalyzed acetylation of (a) alcohol **1** and (b) alcohol **3**.

are stabilized by inclusion into the pocket, which decreases the K_m value. In a solvent with an ϵ value similar to that of the node, alcohol molecules will have a polarity similar to that of the solvent and be stabilized by solvation (Figure 5b). In such a solvent, the polarity of the substrate-binding pocket will also be similar to that of the solvent. Under these conditions, the inclusion of the alcohol molecules into the pocket comes at the expense of the stabilization energy of solvation. As a result, the K_m value becomes high. In a mixed solvent with an ϵ value lower than that of the node, alcohol molecules are more polar than the solvent and are associated with each other by intermolecular hydrogen bonds (Figure 5c). In such a solvent, the polarity of the substrate-binding pocket will also be higher than that of the solvent. As a result, alcohol molecules are stabilized by inclusion into the pocket, which decreases the K_m value. As two enantiomeric substrate molecules form diastereomeric enzyme–substrate complexes, the magnitude

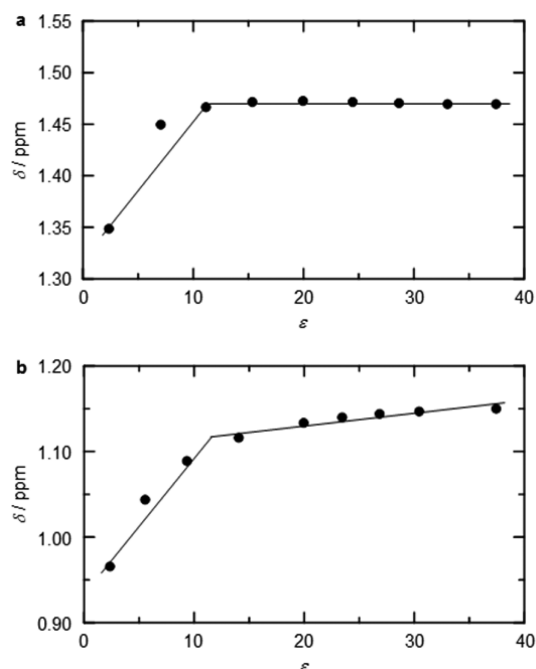


Figure 4. Changes in the chemical shifts of (a) alcohol 1 and (b) alcohol 3 depending on solvent permittivity (ϵ) for the methyl protons. Conditions: alcohol 1 (0.200 M) or alcohol 3 (0.141 M), toluene- d_8 -acetonitrile- d_3 , 30 °C.

of ϵ -dependent change in K_m may be different between the enantiomers (Figure 2).

Interestingly, the ϵ dependence of enantiomeric ratio (E) exhibited a convex shape for alcohol 1 (Figure 1a), whereas it exhibited a concave shape for alcohol 3 (Figure 1b). As shown in Figure 2, as the solvent permittivity approaches the ϵ value of the node, it becomes difficult for the enantiomer with a larger K_m value to form an enzyme–substrate complex to a greater extent than its antipode. Therefore, the reaction rate of this enantiomer is reduced by a larger magnitude in comparison to that of its antipode, as evidenced by the initial rate v_0 vs ϵ plot (Figure S2 in the Supporting Information). The relevant enantiomer is the *S* enantiomer for alcohol 1 and the *R* enantiomer for alcohol 3, while the *R* enantiomer reacts more quickly than the *S* enantiomer in both cases.²⁰ Thus, we concluded that, when the enantiomer with a larger K_m value reacts more slowly than its antipode in the middle ϵ region, the ϵ dependence of E exhibits a convex shape. On the other hand, when the enantiomer reacts more quickly, it exhibits a concave shape.

Control of Enantioselectivity in Other Kinetic Resolution Systems. The mechanistic considerations strongly suggest that CAL-B-catalyzed acetylation exhibits the maximum or minimum E value in a solvent with polarity similar to that of the substrate regardless of the substrate and solvent system employed, unless the solvent does not affect the reaction other than by solvating the substrate. We then tested the applicability of the present polarity-controlled method to other kinetic resolution systems (Scheme 2). The E vs ϵ plot for the CAL-B-catalyzed acetylation of alcohol 5 in toluene–acetonitrile exhibited a concave shape (Figure 6a). On the other hand, the acetylation of alcohol 7 conducted under the same conditions exhibited a convex shape (Figure 6b). The latter reaction was also carried out in 1,4-dioxane–acetonitrile, which exhibited a slightly different change from that observed in

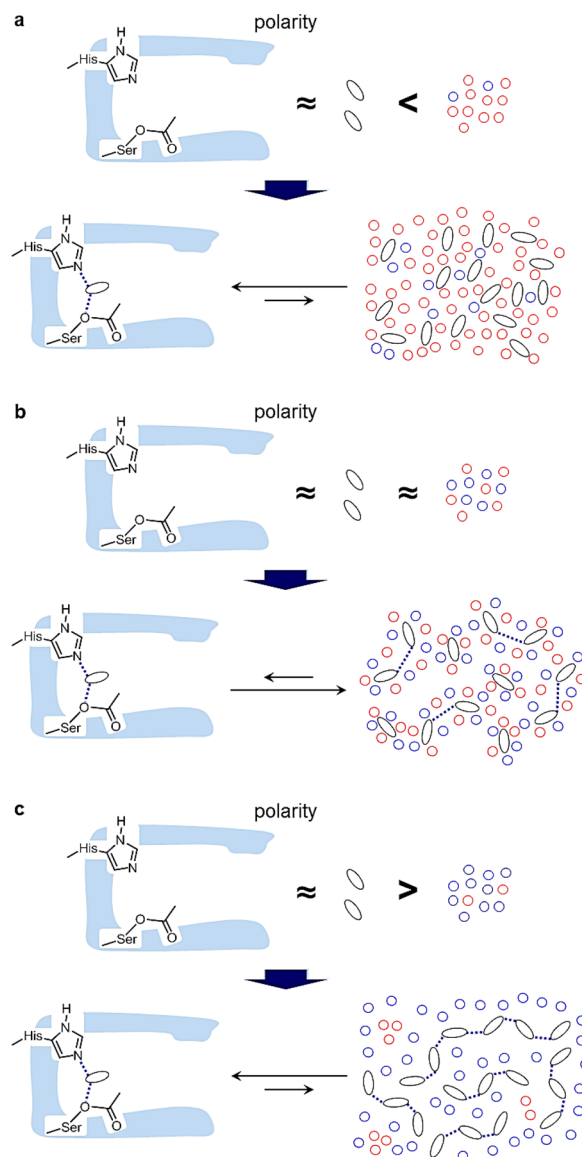


Figure 5. Feasible mechanism for the ϵ dependence of K_m : the order of the polarities of the mixed solvent, the alcohol molecule, and the substrate-binding pocket of the enzyme, the aggregation state of molecules in solution, and the ease for alcohol molecules to be included into the pocket in (a) high-, (b) medium-, and (c) low-polarity solvents. The ellipsoids and blue and red circles represent alcohol molecules and solvent molecules with low and high ϵ values, respectively. The dotted lines indicate intermolecular hydrogen bonds between alcohol molecules.

toluene–acetonitrile. This indicates that the enantiomeric ratio (E) is not solely determined by the solvent permittivity but is also affected by the structures of solvent molecules.

We reasoned that, when the E vs ϵ plot exhibits a convex shape, the resolution efficiency at the node can be improved by using an additive which increases K_m by retarding the diffusion of a substrate into the binding pocket of the enzyme. We found that nitro compounds are useful for this purpose (Table 1). Interestingly, the maximum E value (20) obtained for alcohol 7 in toluene–acetonitrile (2/1, v/v) at $\epsilon = 14.1$ (Figure 6b and entry 1 in Table 1) increased to 28 with the addition of an equimolar amount of 4-nitrophenyl *N*-hexylcarbamate (**12**) (entry 5 in Table 1); the improved E value almost reaches the efficiency required for industrial applications.^{1,2} In the ^1H NMR

Scheme 2. CAL-B-Catalyzed Acetylation of Alcohols 5 and 7

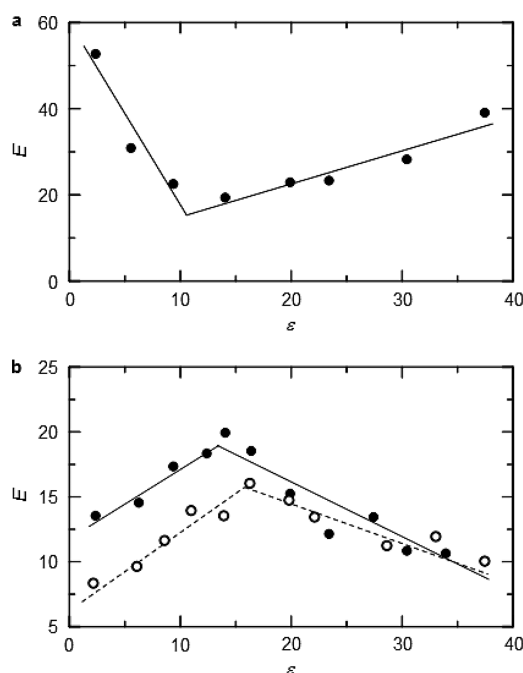
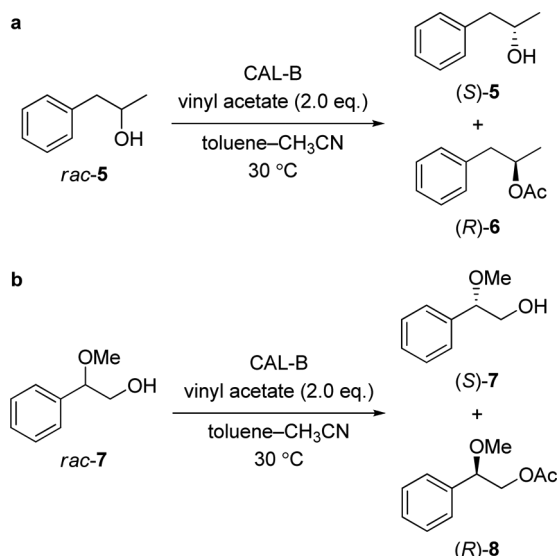


Figure 6. Dependence of enantiomeric ratio (E) on solvent permittivity (ϵ) for the acetylation of (a) alcohol 5 in toluene-acetonitrile and (b) alcohol 7 in toluene-acetonitrile (solid line with ●) and 1,4-dioxane-acetonitrile (broken line with ○).

spectrum, the hydroxy signal of alcohol 7 was shifted downfield by the addition of compound 12, suggesting the formation of intermolecular hydrogen bonds with compound 12 (Figure S3 in the Supporting Information). In addition, the initial rate (v_0) of the acetylation of alcohol 7 ($7.98 \times 10^{-4} \text{ M h}^{-1} (\text{mg-Enz})^{-1}$) was diminished ($6.03 \times 10^{-4} \text{ M h}^{-1} (\text{mg-Enz})^{-1}$) by the addition of compound 12. These observations indicate that the nitro compound serves as a hydrogen-bond acceptor and forms aggregates with the alcohol molecules, which retards the formation of an enzyme-substrate complex. This should affect the S enantiomer with a larger K_m value to a greater extent similarly to the solvent effects described above. As a result, the reaction rate of the more slowly reacting S enantiomer

Table 1. Addition Effect of Nitro Compounds in the CAL-B-Catalyzed Acetylation of Alcohol 7^a

entry	additive	conversion ^b (%)	ee _S ^c [% ee (S)]	ee _P ^b [% ee (R)]	E^d
1	none	30	37	87	20
2		37	52	88	26
3		26	31	89	23
4		29	36	89	25
5		21	24	91	28
6		19	21	91	27

^aConditions: *rac*-7 (0.700 mmol), vinyl acetate (1.40 mmol), CAL-B (10.0 mg), additive (0.700 mmol), toluene-acetonitrile (2/1, v/v; 5.0 mL), 30 °C, 4 h. ^bDetermined by GC analysis. ^cCalculated by $ee_P / (1 - c)$. ^dCalculated by $\ln[1 - c(1 + ee_P)] / \ln[1 - c(1 - ee_P)]$.

decreases to a greater extent than that of the R enantiomer to improve the E value.

CONCLUSION

In conclusion, we have shown that the enantioselectivity of enzymatic kinetic resolution may be controlled by adjusting the polarity of the reaction solvent, by using solvent permittivity as a measure. The results presented in this paper clearly indicate that the solvent permittivity is a useful parameter to optimize the conditions for enzymatic kinetic resolution.

EXPERIMENTAL SECTION

General Considerations. ¹H NMR spectra were measured with tetramethylsilane as an internal standard. *Candida antarctica* lipase B (CAL-B) powder was prepared by freeze-drying of Lipozyme CALB-L solution (Novozymes, Lot No. LCN02106, 5000 Units/g, 1.2 g mL⁻¹), after dialysis with regenerated cellulose tubing (Spectra/Por 1 dialysis tubing, MWCO 6000–8000 Da). The activity of the freeze-dried CAL-B powder was determined to be 1.9×10^5 Units g⁻¹, following the literature procedure.²¹ 1-(Naphth-2-yl)ethanol (1),²² benzyl 3-hydroxybutyrate (3),²³ 1-phenyl-2-propanol (5),²⁴ 2-methoxy-2-phenylethanol (7),²⁵ and 4-nitrophenyl *N*-hexylcarbamate (12)²⁶ were prepared according to the literature procedures. Reaction solvents and vinyl acetate were freshly distilled before use. Other reagents were used as purchased.

Preparation of 1-Nitro-4-nonylbenzene (13). To a stirred solution of nonylbenzene ($d = 0.858$; 1.0 mL, 5.71 mmol) in acetic anhydride (8.0 mL) was added 69% nitric acid ($d = 1.42$; 256 μ L, 5.71 mmol) dropwise over a period of 20 min at 0 °C, and the mixture was stirred at room temperature for 2 h. The mixture was poured onto ice-cold water and extracted with diethyl ether. The extract was washed

successively with saturated aqueous NaHCO_3 and water, dried over MgSO_4 , and evaporated. The residue was purified by column chromatography with hexane–ethyl acetate (3/1) as an eluent to give nitro compound **13** (608 mg, 43%) as a pale yellow oil: IR (neat) 2926, 2855, 1601, 1519, 1346, 1110, 854, 747, 697 cm^{-1} ; ^1H NMR (400 MHz) δ 0.86 (t, 3H, $J = 6.9$ Hz), 1.26–1.32 (m, 12H), 1.60–1.68 (m, 2H), 2.71 (t, 2H, $J = 7.7$ Hz), 7.32 (d, 2H, $J = 8.8$ Hz), 8.13 (d, 2H, $J = 8.8$ Hz); ^{13}C NMR (100 MHz) δ 14.2, 22.8, 29.3, 29.4, 29.5, 29.6, 31.1, 32.0, 36.0, 123.7, 129.3, 146.3, 151.0; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{23}\text{NNaO}_2$ ($M + \text{Na}$) $^+$ 272.1626, found 272.1621.

Typical Procedure for the Analysis of ϵ Dependence of Enantiomeric Ratio (E) for CAL-B-Catalyzed Acetylation. To a solution of alcohol (R)-**1** (344 mg, 2.00 mmol) and vinyl acetate ($d = 0.93$; 740 μL , 8.0 mmol) in toluene–acetonitrile (3/1, v/v ($\epsilon = 11.2$), 2.0 mL) in a 30 mL screw-cap vial was added CAL-B powder (15.0 mg), and the suspension was shaken at 30 $^\circ\text{C}$. A small portion (20 μL) of the mixture was taken out at 20 min intervals, quenched with 5% (w/v) aqueous trichloroacetic acid, and extracted with dichloromethane. The organic extract was dried over MgSO_4 , concentrated, and submitted to GC analysis (column, Quadrex MPS-10 (0.32 mm i.d. $\times$ 25 m); oven temperature, 150 $^\circ\text{C}$; detector, FID) to determine the conversion (c). The initial rate ($v_{0,R}$) was determined to be $4.93 \times 10^{-3} \text{ M h}^{-1} (\text{mg-Enz})^{-1}$ from the slope of the c vs t plot at $t = 0$. The acetylation of antipode (S)-**1** was carried out by the same procedure, except for the amount of CAL-B powder (30.0 mg) and the sampling interval (24 h). The c vs t plot determined the initial rate ($v_{0,S}$) to be $4.03 \times 10^{-7} \text{ M h}^{-1} (\text{mg-Enz})^{-1}$. The E value was calculated from these initial rates to be 1.22×10^4 at $\epsilon = 11.2$. The E vs ϵ plot (Figure 1) was obtained by repeating this procedure using toluene–acetonitrile mixtures with varying composition ratios as reaction solvents.

The E vs ϵ plot for each of alcohols **3**, **5**, and **7** was obtained by a procedure similar to that mentioned above. Racemic alcohol was used as a substrate, and the enantiomeric excess of the resulting ester (e_e) was determined by GC analysis (column, Restek, RT/DEXse (0.25 mm i.d. $\times$ 30 m); oven temperature, 130 $^\circ\text{C}$ for ester **4**, 95 $^\circ\text{C}$ for esters **6** and **8**; detector, FID).

The NMR spectra of compounds **2**,²⁷ **6**,²⁸ and **8**²⁹ obtained by the acetylation are essentially identical with those reported in the literature.

Compound 4: colorless oil; IR (neat) 3034, 2934, 1731, 1498, 1455, 1372, 1240, 957, 751, 698 cm^{-1} ; ^1H NMR (400 MHz) δ 1.29 (d, 3H, $J = 6.3$ Hz), 1.95 (s, 3H), 2.55 (dd, 1H, $J = 15.5$, 5.5 Hz), 2.68 (dd, 1H, $J = 15.5$, 7.7 Hz), 5.13 (d, 1H, $J = 15.0$ Hz), 5.25–5.33 (m, 1H), 7.32–7.37 (m, 5H); ^{13}C NMR (100 MHz) δ 20.0, 21.2, 41.0, 66.6, 67.4, 128.4, 128.5, 128.7, 135.9, 170.2, 170.4; HRMS (FAB) calcd for $\text{C}_{13}\text{H}_{17}\text{O}_4$ ($M + \text{H}$) $^+$ 237.1127, found 237.1126.

Typical Procedure for the Analysis of ϵ Dependence of Michaelis Constant (K_m) and Maximum Velocity ($V_{\max}$) for CAL-B-Catalyzed Acetylation. The initial rate of the acetylation of alcohol **1** was determined for each enantiomer by the same procedure as that mentioned for the analysis of the ϵ dependence of E with varying concentrations of alcohol **1** (1.0, 1.5, 2.0, and 2.5 M) in toluene–acetonitrile (3/1, v/v ($\epsilon = 11.2$)). Using the relation between the concentration of alcohol **1** and the initial rate, K_m and $V_{\max}$ were determined by Lineweaver–Burk plots. The K_m vs ϵ plot (Figure 2) and $V_{\max}$ vs ϵ plot (Figure 3) were obtained by repeating this procedure using toluene–acetonitrile mixtures with varying composition ratios as reaction solvents.

■ ASSOCIATED CONTENT

● Supporting Information

Figures and tables giving changes in the chemical shifts of alcohols **1** and **3** depending on the solvent permittivity, ϵ dependence of initial rate for the acetylation of alcohols **1** and **3**, and change in the chemical shift of alcohol **7** upon addition of nitro compound **12**, data for Figures 1–3 and 6, and ^1H and ^{13}C spectra of the compounds synthesized. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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