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EFFECT OF SOLVENT STRUCTURE ON ENANTIOSELECTIVITY OF LIPASE-CATALYZED TRANSESTERIFICATION

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Summary: Enantioselectivity in transesterification of a secondary alcohol under lipase-catalysis is largely affected by the solvent used. Two groups of solvents, cyclic and acyclic, show different feature on enantioselectivity.

The potential of lipases as stereoselective acylation catalysts in an organic solvent is of considerable interest in the field of organic synthesis.[1] Although a solvent usually plays an important part in organic reactions,[2] selection of the solvent for a biocatalytic reaction has not attracted much attention by chemists in this field. The effect of solvent on stereoselectivity of biocatalytic reaction is not easily understandable at present. Several contradicted results have been reported: Klibanov *et al.* showed that enantioselectivity of the subtilisin-catalyzed transesterification with amino acids decreases in order of the increase in hydrophobicity of the solvent.[3] Wong *et al.* reported that the enantioselectivity in the transesterification of glycerol acetonide is not affected by the nature of the solvent.[4] Recently, Dordick *et al.* reported that a solvent of suitable hydrophobicity gives a maximum enantioselectivity in the esterification of α-hydroxyacids.[5] The last report prompted us to publish our brand-new results on the solvent effect in kinetic resolution of 1-nitro-2-propanol (**1**). Chiral nitro alcohols are useful chiral building blocks in the synthesis of natural products.[6]

The transesterification of **1** with vinyl acetate in hexane[7] in the presence of a lipase from *Pseudomonas* sp. (Amano AK) gave the (+)-1-nitro-2-acetoxypropane ((+)-**2**) along with unreacted (+)-**1**.[8] The enantiomeric ratio (*E* value,[9] 16.2) was calculated from the enantiomeric excess (e.e.) in the product (63.0%) and that in the starting material (95.7%), which was not sufficiently large. The unsatisfactory selectivity was, however, improved when THF was employed as the solvent (*E* = 47.7). Being encouraged with this result, we examined the effect of solvents on *E* values. Fig. 1 shows a plot of the *E* value against log P (hydrophobicity parameter: the logarithm of the partition coefficient of a solvent between octanol and water[10]). A large log P is associated by a large hydrophobic character. At the first

glance, the plot seems to be scattered. However, when the solvents are divided into two groups, cyclic and acyclic, both of the solvent groups afford smooth curves, respectively, showing different characteristics toward the lipase-catalyzed transesterifications. From these two curves, some features of lipase-catalyzed transesterifications in organic solvents are recognized: (i) the stereoselectivity of the reaction in a series of cyclic solvents is more sensitive than that of acyclic solvents, and (ii) the curve for the cyclic solvent group has a maximum at the position of THF (log P ≈ 0.5), whereas the curve for the acyclic group does not exert a sharp maximum. Rather it seems to be flat with the solvents having log P value larger than 0. Then, *E* values for the cyclic and acyclic groups becomes similar at the solvents with log P larger than 2.5. Contrary to the *E* value, the rate of transesterification increases with the increase in log P and there is no difference between the two groups, which means that the rate of the reaction is affected only by the polarity of the solvent with no influence from its structure or the molecular shape. The effect of solvent-polarity on the reaction rate is oftenly observed in enzymatic reactions.[1c,11] The phenomenon can be interpreted that hydrophilic solvents may denature enzymes by penetrating into the hydrophobic core of proteins or by stripping off the essential water from the enzyme.[1c]

Although the mechanism of solvent effect on the stereochemistry is entirely unknown at present, it is suggestive that a biocatalytic reaction in a bulky solvent is reported to give a high enantioselectivity.[11] In the present reaction, bulky *t*-butyl methyl ether gives a relatively high *E* value (36.9), too. When we assume the unknown log P to be 1.9 for *t*-butyl methyl ether (the value for isopentyl methyl ether[12]), the plot for this acyclic solvent falls on the curve for cyclic solvents. Thus, the stereochemistry of the present reaction seems to be influenced by a local solvent-enzyme interaction at the close vicinity of the active site instead of the change in the bulk conformation of the enzyme.

Based on the present results, we would like to propose a useful guide for the choice of an solvent in lipase-catalyzed reactions: in order to obtain high selectivity, *a cyclic solvent is recommended*. A suitable cyclic solvent may result in satisfactory enantioselectivity in esterification. To test our proposal, another lipase was examined, and found that transesterification of **1** by Amano PS (from *Pseudomonas* sp.) gave the similar result, although the maximum *E* value was observed with benzene. To examine the scope and limitation of our proposal, other lipase-catalyzed reactions are now being tested with a variety of substrates and lipases.

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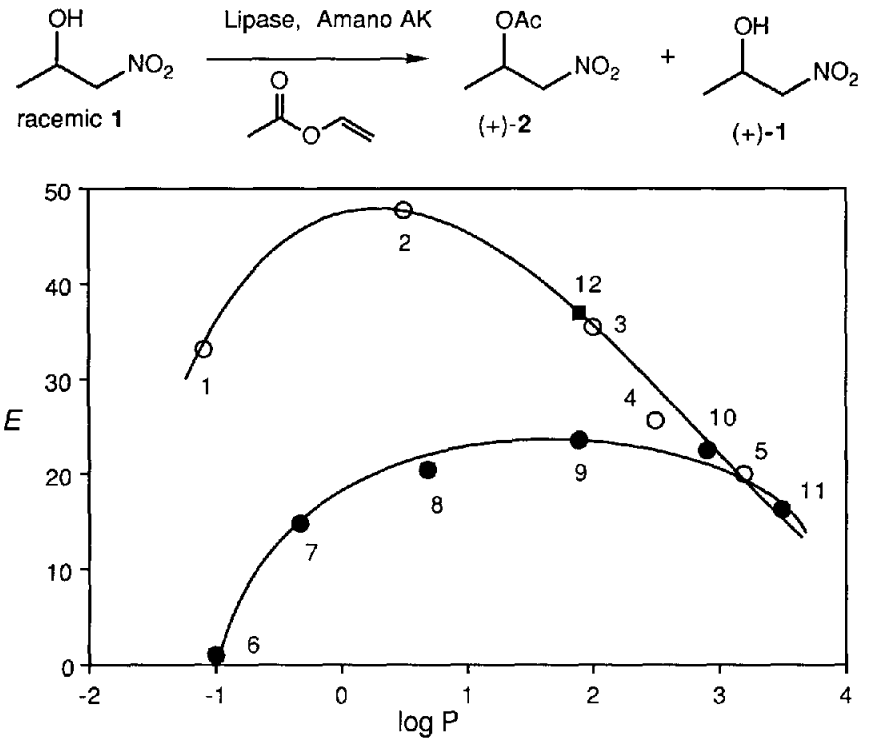

Solvents: 1, dioxane; 2, THF; 3, benzene; 4, toluene; 5, cyclohexane; 6, DMF; 7, acetonitrile; 8, ethyl acetate; 9, diisopropyl ether; 10, dibutyl ether; 11, hexane; and 12, *t*-butyl methyl ether.

○ : cyclic solvents, ● : acyclic solvents.

Fig. 1. Relationship of *E* vs. log P in the transesterification.

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7. Water in the solvent used was removed by refluxing the solvent with benzophenone ketyl before the distillation.
8. A mixture of **1** (2.86mmol), vinyl acetate (17.4mmol) and a lipase, Amano AK, (200mg) in hexane (5 mL) was stirred for 5 h at 30 °C. The resulting mixture was filtered and the filtrate was concentrated. The residue was subjected to column chlomatography on silica gel with dichloromethane as an eluent ginving 43.3 % of **2** and 28.3 % of recovered **1**. The e.e. of the product ((+)-**2**) was determined to be 63 % by the ^{1}H NMR analysis using Eu(hfc)$_3$ as a chiral shift reagent. The recovered **1** which exerted a positive optical rotation was chemically converted with AcCl/pyridine into (-)-**2**, and its e.e. was determined to be 95.7% by the ^{1}H NMR analysis.
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