Influence of the Nature of the Solvent on the Enantioselectivity of Lipase-Catalyzed Transesterifications: A Comparison between the Lipases from Porcine Pancreas and *Pseudomonas Fluorescens*

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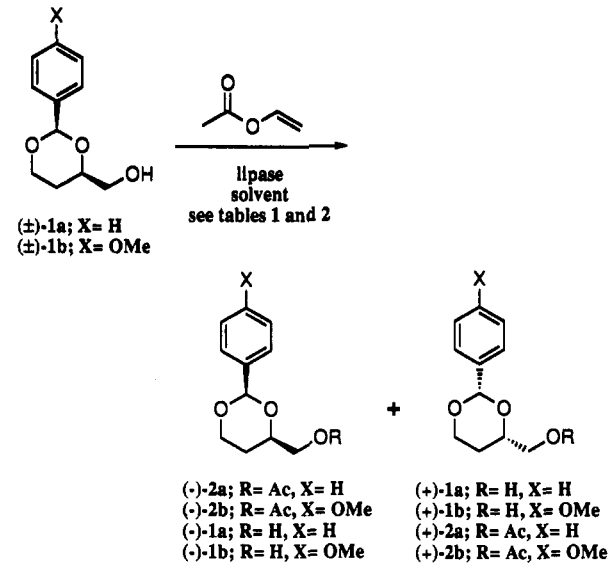
Lipases are useful catalysts to perform selective transformations on unnatural substrates. Although some chemoselective, regioselective, and diastereoselective transformations have been reported, the most valuable property is their capacity to differentiate enantiomers or enantiotopic groups in racemic or achiral substrates.[2] Although the natural function of these enzymes is to hydrolyze triesters of glycerol, they are also very efficient in catalyzing esterifications of alcohols in media with low water content.[3] The high stability of lipases in organic solvents opens the possibility to use a variety of solvents to modulate the reactivity and selectivity of lipases. Although the synthetic potential of lipases in organic solvents is considerable, the field is still in its beginnings; only scarce studies on the influence of the nature of the solvent on the selectivity of lipase-catalyzed transformations have been reported,[4] and more data are needed in order of get a clearer picture of the reaction course in organic solvents.

In connection with a program on the synthesis of chiral building blocks using biocatalysts,[5] we have had the opportunity to study the effect of the nature of the organic solvent as well as its water content on the enantioselectivity of lipase-mediated transesterification of the racemic alcohols (±)-1 using vinyl acetate as acylating agent (Scheme 1).[6] The effectiveness of the kinetic resolution has been calibrated by the value of the enantioselectivity E as defined by Sih and Wu.[7] We have found that while the enantioselectivity of the transesterification catalyzed by the lipase from porcine pancreas (PPL) is relatively insensitive to the nature of the solvent, the enantioselectivity of the transformation catalyzed by the lipase from *Pseudomonas fluorescens* (PFL) can be modulated by changes in the nature of the solvent.

Scheme 1



The results of the acetylation of (±)-1 catalyzed by PPL are indicated in Table 1. It is observed that, in all the solvents tested,[8] the (*R*,*R*)-enantiomer of the substrate (±)-**1a** is preferentially acetylated giving the acetate (−)-**2a** and the alcohol (+)-**1a** (entries 1–8, Table 1), although in low enantiomeric purities.[9] As indicated in Table 1, the value of the enantioselectivity E is relatively insensitive to the nature of the solvent. The use of water-saturated solvents has been reported to increase both the velocity and the selectivity of lipase-catalyzed transformations.[10] We have observed a slight increase in both the velocity (as indicated by the time necessary to achieve a 25% conversion, $t_{1/4}$) and the enantioselectivity of the reaction when water-saturated chloroform is used instead of dry chloroform (entries 2 and 3, Table 1). The opposite trend is observed when water-saturated diethyl ether is used instead of dry diethyl ether (entries 4 and 5). Sometimes, remote substitution in the substrate causes great differences in the selectivity of lipase-catalyzed transformations.[11] To test the influence of the structure of the substrate on the enantioselectivity, PPL has been used to catalyze the acetylation of (±)-**1b** (Scheme 1). The conditions tried (entry 9, Table 1) are the ones that have given the best result in terms of velocity and selectivity in the esterification of (±)-**1a**, but the enantioselectivity has also been modest.

The results of the acetylation of (±)-1 catalyzed by PFL (Scheme 1) are indicated in Table 2. The stereochemical

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Table 1. Results of the Porcine Pancreas Lipase-Catalyzed Acetylation of (±)-1a and (±)-1b[a]

entry	starting material	solvent[b]	$t_{1/4}$ (h)[c]	time (h)	%c[d]	alcohol, %ee (%y)[e]	ester, %ee (%y)[e]	E[f]
1	(±)-1a[g]	toluene	170	220	31	(+)-1a 23 (50)	(−)-2a 52 (30)	4.0
2	(±)-1a	$CHCl_3$		120	12	(+)-1a 6 (61)	(−)-2a 45 (11)	3.0
3	(±)-1a	wet $CHCl_3$	21	32.5	33	(+)-1a 35 (57)	(−)-2a 72 (24)	8.7
4	(±)-1a[h]	Et_2O	2.5	6.75	56	(+)-1a 54 (46)	(−)-2a 43 (45)	4.2
5	(±)-1a	wet Et_2O	35	144	31	(±)-1a 0 (59)	(±)-2a 0 (22)	1.0
6	(±)-1a	THF	4	24	66	(+)-2a 80 (21)	(−)-2a 41 (57)	5.5
7	(±)-1a	EtOAc[i]	3.5	8.75	50	(+)-2a 42 (33)	(−)-2a 42 (40)	3.6
8	(±)-1a[g]	vinyl acetate[j]	12	44.5	47	(+)-1a 37 (41)	(−)-2a 42 (44)	3.5
9	(±)-1b	wet $CHCl_3$	190	420	29	(+)-1b 26 (59)	(−)-2b 63 (25)	5.7

[a] All the reactions were carried out at room temperature. Unless otherwise indicated, 2.5 mol equiv of vinyl acetate was used. The enzyme used was porcine pancrease lipase (PPL) purchased from Sigma. The specific activity of this enzyme is 17.5 U/mg. Unless otherwise indicated, 500–600 units of PPL per mmol of (±)-1 was used. A unit corresponds to the quantity of enzyme which hydrolyzes 1 μmol of triacetin per hour at pH 7.4 (as defined in the Sigma catalogue). [b] All the solvents were of the highest quality available (water content <0.5%). "Wet solvent" means water-saturated solvent. [c] $t_{1/4}$ indicates the time at which 25% conversion was achieved as determined by ^{1}H-NMR spectroscopy. [d] The conversion degree was calculated by the expression $c = ee_s/(ee_s + ee_p)$ (ref 7). [e] %ee was determined by ^{1}H-NMR spectroscopy of either (+)-1 or (−)-2 in the presence of 0.35–0.50 mol equiv, of Eu(hfc)$_3$; all the yields refer to isolated compounds after flash chromatography. [f] Calculated according to ref 7. [g] 1000 units of PPL per mmol of (±)-1 was used. [h] 800 units of PPL per mmol of (±)-1 was used. [i] The reaction in the absence of vinyl acetate was very slow. [j] 48 mol equiv of vinyl acetate was used.

outcome of the reaction is the opposite to the reaction catalyzed by PPL: the (*S*,*S*)-enantiomers of (±)-**1a** and (±)-**1b** are preferentially esterified, giving the alcohols (−)-**1a** and (−)-**1b** and the acetates (+)-**2a** and (+)-**2b**, respectively (Scheme 1).[9] An important feature of this transformation is that the velocity and the enantioselectivity are highly dependent on both the nature of the solvent and the structure of the substrate.

The enantioselectivity of the PFL-catalyzed acetylations of (±)-**1a** (entries 1–11, Table 2) and (±)-**1b** (entries 12–16, Table 2) is from modest (E = 4.5, using chloroform as solvent for the acetylation of (±)-**1a**, entry 3) to excellent (E > 44 for the kinetic resolution of (±)-**1a** using THF as solvent, entry 9; and E > 50 for the acylation of (±)-**2a** using toluene and wet chloroform as solvents, entries 12, 15, and 16, Table 2). Some experimental results deserve comment. The acetylation is slow in dry halogenated solvents (entries 3, 5, and 14), higher amounts of PFL being necessary to reach acceptable reaction rates (entries 3 and 14). On the contrary, the reaction is quite fast in toluene and ethereal solvents (entries 1, 7, 9, and 12, Table 2). The effect of the addition of water[10] on both the velocity and the selectivity has been studied. The reaction is slightly faster and the enantioselectivity is slightly lower in wet toluene than in dry toluene for both substrates (entries 1, 2, 12, and 13). A dramatic effect is observed when wet chloroform is used instead of dry chloroform: much faster and more selective transformations are achieved when the wet solvent is used (entries 3, 4, and 14–16, Table 2). Analogous to the case of chloroform,

Table 2. Results of the *Pseudomonas fluorescens* Lipase-Catalyzed Acetylation of (±)-1a and (±)-1b[a]

entry	starting material	solvent[b]	$t_{1/4}$ (h)[c]	time (h)	%c[d]	alcohol, %ee (%y)[e]	ester, %ee (%y)[e]	E[f]
1	(±)-1a	toluene	3.5	9	54	(−)-1a 90 (35)	(+)-2a 77 (46)	23
2	(±)-1a	wet toluene	1.75	6	52	(−)-1a 81 (39)	(+)-2a 76 (49)	18
3	(±)-1a[g]	$CHCl_3$	22	72	64	(−)-1a 39 (30)	(+)-2a 71 (46)	4.5
4	(±)-1a[h]	wet $CHCl_3$	13.75	13.75	25	(−)-1a 36 (56)	(+)-2a 86 (32)	21
5	(±)-1a	CH_2Cl_2	240	504	36	(−)-1a 43 (47)	(+)-2a 78 (31)	12
6	(±)-1a	wet CH_2Cl_2	9.5	28	50	(−)-1a 70 (42)	(+)-2a 69 (46)	11
7	(±)-1a	Et_2O	3	9	48	(−)-1a 68 (36)	(+)-2a 74 (39)	13
8	(±)-1a	wet Et_2O	25	67	45	(−)-1a 59 (34)	(+)-2a 72 (38)	11
9	(±)-1a	THF	5.5	45	54	(−)-1a >97 (39)	(+)-2a 82 (48)	>44
10	(±)-1a	THF–H_2O (200:1, v/v)	12	32	49	(−)-1a 84 (41)	(+)-2a 88 (45)	42
11	(±)-1a	THF–H_2O (50:1, v/v)	69	168	25[i]	(−)-1a nd	(+)-2a nd	nd
12	(±)-1b	toluene	1.5	4.5	50	(−)-1b 91 (38)	(+)-2b 90 (40)	>50
13	(±)-1b	wet toluene	1	3.5	58	(−)-1b >98 (41)	(+)-2b 72 (47)	>30
14	(±)-1b[j]	$CHCl_3$	6.5	26	52	(−)-1b 84 (47)	(+)-2b 78 (47)	21
15	(±)-1b	wet $CHCl_3$	2.5	8	48	(−)-1b 86 (52)	(+)-2b >94 (40)	>50
16	(±)-1b	wet $CHCl_3$	2.5	20	54	(−)-1b >98 (44)	(+)-2b 83 (44)	>50

[a] All the reactions were carried out at room temperature using 2.5 mol equiv of vinyl acetate. The enzyme used was *Pseudomonas fluorescens* lipase (PFL) purchased from Fluka. The specific activity of this enzyme is 31.5 U/mg. Unless otherwise indicated, 195–240 units of PFL per mmol of (±)-1 was used. A unit corresponds to the quantity of enzyme which liberates 1 μmol of oleic acid per min at pH 8.0 and 40 °C (as defined in Fluka catalogue). [b] All the solvents were of the highest quality available (water content <0.5%). "Wet solvent" means water-saturated solvent. [c] $t_{1/4}$ indicates the time at which 25% conversion was achieved as determined by ^{1}H-NMR spectroscopy. [d] The conversion degree was calculated by the expression $c = ee_2/(ee_s + ee_p)$ (ref 7). [e] %ee was determined by ^{1}H-NMR spectroscopy of either (−)-1 or (+)-2 in the presence of 0.35–0.50 mol equiv of Eu(hfc)$_3$; all the yields refer to isolated compounds after flash chromatography. [f] Calculated according to ref 7. [g] 410 units of PFL per mmol of (±)-1 was used. [h] 120 units of PFL per mmol of (±)-1 was used. [i] The reaction stopped after *ca.* 70 h. Acetic acid was detected. The reaction products were not isolated and the conversion degree was determined by ^{1}H-NMR spectroscopy. [j] 440 units of PFL per mmol of (±)-1 was used.

there is a considerable rate increment when wet methylene chloride is used instead of dry methylene chloride, although the selectivity is nearly the same (entries 5 and 6). The opposite tendency is observed when dry diethyl ether is replaced by wet diethyl ether. The reaction is slower in the wet solvent than in the anhydrous solvent, but no appreciable change in the enantioselectivity is observed (entries 7 and 8, Table 2). The addition of a small amount of water to THF has hardly any effect on the enantioselectivity of the reaction, although the reaction is slower (entries 9 and 10). When the proportion of water in THF increases (entry 11, Table 2), the reaction is very slow; after *ca.* 70 h, the reaction does not progress anymore and acetic acid is detected in the reaction media.[12]

(12) Most likely acetic acid is formed from vinyl acetate, although the hydrolysis of **2a** cannot be ruled out. We have also observed by ^{1}H-NMR spectroscopy that the ratio **2a**:**1a** decreases slightly with time.

It is interesting to compare the results of the kinetic resolution of (±)-**1a** and (±)-**1b**: faster and more-selective reactions are obtained when the methoxy-substituted alcohol (±)-**1b** is the substrate. Although the structural dissimilarity between these two alcohols is far away from the reacting center, there is a relatively high difference in the values of the enantioselectivity *E* in the PFL-catalyzed acetylation of these two substrates, which indicates that relatively far away from the active site there is a region that has some influence on the outcome of the reaction.

Summarizing, we have shown that the velocities and the selectivities of the transesterifications catalyzed by PFL are more sensitive to the nature of the solvent than that for the transformations mediated by PPL. This property makes PFL a very versatile enzyme for the purpose of organic synthesis, because it allows highly enantioselective transformations by a simple change in the nature of the solvent. This characteristic has allowed us to prepare efficiently derivatives of both enantiomers of butane-1,2,4-triol, which are useful intermediates for the syntheses of branched-chain nucleoside analogues,[13] pheromones,[14] prostanoids,[15] and chiral auxiliaries for asymmetric synthesis.[16]

Experimental Section[17]

General Procedure for the Lipase-Catalyzed Acetylation of (±)-1a and (±)-1b. Vinyl acetate (2.5 mol equiv) was added to a mixture of (±)-**1** and PPL or PFL (the amount indicated in Table 1 or 2) in the corresponding solvent. The mixture was stirred at room temperature. The reactions were readily followed by ^{1}H-NMR. When the desired conversion degree was achieved, the mixture was diluted with CH_2Cl_2. The enzyme was filtered off and thoroughly washed with CH_2Cl_2. Evaporation of the solvents gave a crude material, which was chromatographed [hexane–EtOAc, 3:1 to 2:3] affording the ester **2** and the alcohol **1**. The analytical and spectroscopic data of compounds (−)-**1a**, (+)-**2a**, (−)-**1b**, and (+)-**2b** are indicated below.

(*R,R*)-4-(Hydroxymethyl)-2-phenyl-1,3-dioxane [(−)-1a]: >98% ee; $[\alpha]_D$ = −10.0° ($CHCl_3$, *c* = 1.18); MS *m/e* = 194 (41.7), 193 (65.1), 163 (72.5), 123 (7.8), 117 (7.2), 107 (44.7), 106 (18.4), 105 (100), 91 (47.5), 79 (75.2), 78 (24.8), 77 (68.8), 71 (47.7), 57 (35.8), 43 (24.8); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.53–7.33 (m, 5H), 5.56 (s, 1H), 4.31 (ddd, 1.3, 5.2, 11.4, 1H), 4.09–3.92 (m, 2H), 3.72–3.65 (m, 2H), 2.10 (broad s, exchange with D_2O, 1H), 2.04–1.83 (m, 1H), 1.51–1.41 (m, 1H). ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ 138.4 (s), 128.9 (d), 128.4 (2C, d), 126.1 (2C, d), 101.3 (d), 77.6 (d), 66.6 (t), 65.6 (t), 26.8 (t). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02%; H, 7.27%. Found: C, 67.78%; H, 7.60.

(*S,S*)-4-(Acetoxymethyl)-2-phenyl-1,3-dioxane [(+)-2a]: >98% ee; $[\alpha]_D$ = +27.1° ($CHCl_3$, *c* = 1.2); MS *m/e* = 236 (19.1), 235 (22.2), 193 (2.7), 176 (3.8), 163 (28.0), 114 (39.4), 105 (100), 91 (33.2), 79 (29.9), 77 (44.2), 43 (76.4); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.61–7.46 (m, 2H), 7.32 (m, 3H), 5.53 (s, 1H), 4.25–4.09 (m, 1H), 4.25–4.09 (m, 3H), 4.00 (dt, *J* = 4.0, 12.7, 1H), 2.11 (s, 3H), 2.05–1.80 (m, 1H), 1.62–1.49 (m, 1H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 171.4 (s), 138.7 (s), 129.2 (d), 128.6 (2C, d), 126.5 (2C, d), 101.5 (d), 75.1 (d), 66.8 (2C, t), 27.7 (t), 21.1 (q). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.16; H, 6.80.

(*R,R*)-4-(Hydroxymethyl)-2-(4-methoxyphenyl)-1,3-dioxane [(−)-1b]: >98% ee; $[\alpha]_D$ = −10.3° ($CHCl_3$, *c* = 1.45); MS *m/e* = 224 (17.6), 223 (27.3), 193 (27.6), 135 (100), 109 (22.4), 108 (23.8), 77 (45.1), 71 (48.6), 57 (46.5), 55 (30.5), 43 (71.5), 41 (55.2); ^{1}H-NMR (200 MHz, acetone-d_6) δ 7.39 (m, 2H), 6.90 (m, 2H), 5.49 (s, 1H), 4.25–3.90 (m, 3H), 3.79 (s, 3H), 3.59 (m, 2H), 2.86 (s, 1H), 1.78–1.69 (m, 1H), 1.57 (m, 1H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 160.5 (s), 131.3 (s), 127.8 (2C, d), 114.0 (2C, d), 101.5 (s), 77.8 (d), 66.8 (t), 66.0 (t), 55.6 (q), 27.0 (t). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27%; H, 7.19%. Found: C, 64.62%; H, 7.29%.

(*S,S*)-4-(Acetoxymethyl)-2-(4-methoxyphenyl)-1,3-dioxane [(+)-2b]: >94% ee; $[\alpha]_D$ = +26.6° ($CHCl_3$, *c* = 0.8); MS *m/e* = 266 (17.2), 265 (20.0), 193 (26.3), 152 (21.0), 135 (100), 43 (64.7); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.42 (m, 2H), 6.90 (m, 2H), 5.49 (s, 1H), 4.30 (dd, *J* = 11.5, 4.0, 1H), 4.20–4.08 (m, 3H), 3.97 (dt, *J* = 2.5, 11.8, 1H), 3.80 (s, 3H), 2.09 (s, 3H), 1.89 (m, 1H), 1.51 (m, 1H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 171.3 (s), 160.4 (s), 131.2 (s), 127.8 (2C, d), 113.9 (2C, d), 101.4 (d), 75.0 (d), 66.9 (t), 66.8 (t), 55.5 (q), 27.7 (t), 21.1 (q). Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14%; H, 6.81%. Found: C, 63.30%; H, 7.21%.

Determination of the Enantiomeric Excess of (*R,R*)-4-(Hydroxymethyl)-2-phenyl-1,3-dioxane [(−)-1a]. A typical procedure is as follows. A mixture of 4.4 mg of enantiomerically enriched (−)-**1a** (of 60% ee) and 13.6 mg (0.5 mol equiv) of Eu(hfc)$_3$ was dissolved in *ca.* 0.6 mL of $CDCl_3$. After 15–20 min, a ^{1}H-NMR spectrum was taken, showing peaks (1:4.03 ratio) at 7.095 ppm (for the minor diastereoisomer) and at 7.047 ppm (for the main diastereoisomer) for the acetalic protons.

Determination of the Enantiomeric Excess of (*S,S*)-4-(Acetoxymethyl)-2-phenyl-1,3-dioxane [(+)-2a]. A typical procedure is as follows. A mixture of 8.8 mg of enantiomerically enriched (+)-**2a** (of 78% ee) and 17.9 mg (0.4 mol equiv) of Eu(hfc)$_3$ was dissolved in *ca.* 0.6 mL of $CDCl_3$. After 15–20 min, a ^{1}H-NMR spectrum was taken, showing peaks (8.09:1 ratio) at 3.790 ppm (for the main diastereoisomer) and at 3.730 ppm (for the minor diastereoisomer) for the methyl groups.

Determination of the Enantiomeric Excess of (*R,R*)-4-(hydroxymethyl)-2-(4-methoxyphenyl)-1,3-dioxane [(−)-1b]. A typical procedure is as follows. A mixture of 3.6 mg of enantiomerically enriched (−)-**1b** (of 76% ee) and 10.6 mg (0.55 mol equiv) of Eu(hfc)$_3$ was dissolved in *ca.* 0.6 mL of $CDCl_3$. After 15–20 min, a ^{1}H-NMR spectrum was taken, showing peaks (1:7.23 ratio) at 7.053 ppm (for the minor diastereoisomer) and at 7.003 ppm (for the main diastereoisomer) for the acetalic protons.

Determination of the Enantiomeric Excess of (*S,S*)-4-(Acetoxymethyl)-2-(4-methoxyphenyl)-1,3-dioxane [(+)-2b]. A typical procedure is as follows. A mixture of 1.4 mg of enantiomerically enriched (+)-**2b** (of 84% ee) and 9.57 mg (0.5 mol equiv) of Eu(hfc)$_3$ was dissolved in *ca.* 0.6 mL of $CDCl_3$. After 15–20 min, a ^{1}H-NMR spectrum was taken, showing peaks (10.95:1 ratio) at 2.982 ppm (for the main diastereoisomer) and at 2.949 ppm (for the minor diastereoisomer) for the methyl of the acetyl groups.

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(17) See footnotes to Table 1 and 2. For a general experimental procedure, see ref 8d.