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Thermodynamics of the lipase-catalyzed transesterification of 1-phenyl-1-alkanols and butyl acetate in organic solvents

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Abstract

The thermodynamics of the lipase-catalyzed transesterification reactions of butyl acetate and 1-phenyl-1-alkanols from C_1 to C_4 have been studied in organic solvents. Equilibrium measurements of the reactions with benzyl alcohol and (*R*)-(+)-1-phenyl ethanol were carried out in *n*-hexane, acetonitrile, 2-butanone, *tert*-butyl methyl ether, carbon tetrachloride and neat (no solvent added) at 298.15 K. The average value for the equilibrium constant and the standard molar Gibbs energy change $\Delta_r G^\circ_m$ in these solvents for the reaction with benzyl alcohol (C_1) are 0.29 and 3.1 kJ mol^{-1}, respectively; for the reaction with (*R*)-(+)-1-phenyl ethanol (C_2) the respective values are 0.11 and 5.4 kJ mol^{-1}. The difference of 2.3 kJ mol^{-1} in the values of $\Delta_r G^\circ_m$ between the C_1 and C_2 alkanols is attributed to increased steric hindrance associated with the additional methyl group in (*R*)-(+)-1-phenyl ethanol. In addition, the temperature dependence of the equilibrium constants for the reactions with C_1 and C_2 alkanols were also studied in *n*-hexane. The standard molar Gibbs energy $\Delta_r G^\circ_m$, enthalpy $\Delta_r H^\circ_m$, and entropy $\Delta_r S^\circ_m$ changes at 298.15 K have been calculated from these results. It is seen that the temperature variation of the values of the equilibrium constants is small and that the values of $\Delta_r H^\circ_m$ are zero within experimental error. The equilibrium constants for the reactions involving (*R*)-(+)-1-phenyl-1-propanol (C_3) and (*R*)-(+)-1-phenyl-1-butanol (C_4) were measured in *n*-hexane only and the values are both 0.11. The fact that the values of the equilibrium constants for the reactions involving C_2–C_4 are constant is consistent with the view that no additional steric hindrance is caused by adding more than one methylene group to the (*R*)-(+)-1-phenyl-1-alkanol reactant.

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Keywords: Benzyl alcohol; 1-Butanol; Butyl acetate; Enthalpy; Equilibrium constant; Lipase; (*R*)-(+)-1-Phenyl ethanol; (*R*)-(+)-1-Phenyl-1-propanol; (*R*)-(+)-1-Phenyl-1-butanol; Thermodynamics

1. Introduction

Enzyme-catalyzed esterification and transesterification reactions in organic media have been used for stereoselective synthesis [1–3] and resolution of racemic mixtures of industrially important compounds [3]. Lipases have been commonly used for the esterification of glycerol [4–8], for the stereoselective esterification of menthol [9,10] and ibuprofen [11], and for transesterification reactions [11–14] in organic solvents. Other significant features of biocatalysis in organic media are the enhanced availability of hydrophobic substrates and the ability to shift reaction equilibria toward the formation of products unavailable in aqueous media.

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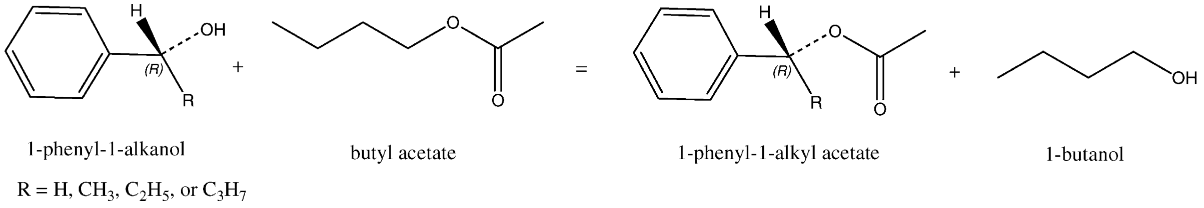

Fig. 1. Structures of the substances in reactions (1)–(4).

There are several publications dealing with the thermodynamics of enzyme-catalyzed reactions [6,8,9,12,15–18] in organic media, but there is only one study [12] involving transesterification reactions. Additionally, it was seen that there was an opportunity to investigate the steric effects of alkyl side chains on the thermodynamics of these transesterification reactions.

In this study, we have carried out equilibrium studies on the following transesterification reactions (see Fig. 1 for the structures of the substances in these reactions):

$$\text{benzyl alcohol (sln)} + \text{butyl acetate (sln)} = \text{benzyl acetate (sln)} + \text{1-butanol (sln)} \quad (1)$$

$$(R)\text{-}(+)\text{-1-phenyl ethanol (sln)} + \text{butyl acetate (sln)} = (R)\text{-}(+)\text{-1-phenyl ethyl acetate (sln)} + \text{1-butanol (sln)} \quad (2)$$

$$(R)\text{-}(+)\text{-1-phenyl-1-propanol (sln)} + \text{butyl acetate (sln)} = (R)\text{-}(+)\text{-1-phenyl-1-propyl acetate (sln)} + \text{1-butanol (sln)} \quad (3)$$

$$(R)\text{-}(+)\text{-1-phenyl-1-butanol (sln)} + \text{butyl acetate (sln)} = (R)\text{-}(+)\text{-1-phenyl-1-butyl acetate (sln)} + \text{1-butanol (sln)} \quad (4)$$

where, “sln” denotes the organic media used in this study. The equilibrium constants for reactions (1) and (2) have been measured in *n*-hexane, acetonitrile, 2-butanone, *tert*-butyl methyl ether, carbon tetrachloride, and neat (no solvent added) at 298.15 K. The equilibrium constants for reactions (1) and (2) have also been determined as a function of temperature using *n*-hexane and then used to calculate the standard molar Gibbs energy $\Delta_r G^\circ_m$, enthalpy $\Delta_r H^\circ_m$, and entropy $\Delta_r S^\circ_m$ changes for these reactions.

In addition, the equilibrium constants for reactions (3) and (4) have been measured in *n*-hexane at 298.15 K and the results then used to determine the steric effects of the alkyl side chain in (*R*)-(+)-1-phenyl-1-alkanols on the thermodynamics of these reactions. These results provide essential data needed for both the understanding of the energetics of these reactions and the practical utilization of enzyme-catalyzed reactions carried out in organic solvents. Specifically, any quantitative kinetic and mechanistic models of these reactions must be consistent with the thermodynamic parameters (the Gibbs energy and enthalpy changes) that define the difference between the initial and final states of the reacting system. Also, any practical applications (e.g. bioprocess engineering) that utilize this enzyme are benefited greatly by knowing both the extent of reaction and the energy requirements of the reaction.

2. Experimental

2.1. Materials

The substances used in this study, their Chemical Abstract Service (CAS) registry numbers, empirical formulas, molar mass, sources, and purity as determined by gas chromatography (GC) are given in Table 1.[1] A GC analysis of the solvents used in this study indicated that the mole fraction purities were >0.99. The vendor reported mole fraction chiral

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[1] Certain commercial equipment, instruments, or materials are identified in this paper to specify the experimental procedures adequately. Such identification is not intended to imply recommendation or endorsement by the National Institute of Standards and Technology, nor is it intended to imply that the materials or equipment identified are necessarily the best available for the purpose.

Table 1
Principal substances used in this study with their Chemical Abstracts Service (CAS) registry numbers, empirical formulas, molecular masses M_r, supplier[a], mole fraction purity x as stated by the vendor, and methods used to determine the mole fraction purity

Substance	CAS number	Formula	M_r	Supplier	x	Method[b]
Benzyl alcohol	100-51-6	C_7H_8O	108.14	A	0.99	GC
Benzyl acetate	140-11-4	$C_9H_{10}O_2$	150.18	Sy	0.99	GC; NMR
1-Butanol	71-36-3	$C_4H_{10}O$	74.12	A	0.99	GC
Butyl acetate	123-86-4	$C_6H_{12}O_2$	116.16	A	0.99	GC
(*R*)-(+)-1-Phenyl ethanol[c]	1517-69-7	$C_8H_{10}O$	122.17	A	0.99	GC
(*S*)-(−)-1-Phenyl ethanol[c]	1445-91-6	$C_8H_{10}O$	122.17	A	0.99	GC
(*R*)-(+)-Phenyl-1-propanol[c]	1565-74-8	$C_9H_{12}O$	136.19	A	0.99	GC
(*R*)-(+)-1-Phenyl-1-butanol[d]	22144-60-1	$C_{10}H_{14}O$	150.22	A	0.97	GC
(*R*)-(+)-1-Phenyl ethyl acetate		$C_{10}H_{12}O_2$	164.20	Sy	0.99	GC; NMR
(*S*)-(−)-1-Phenyl ethyl acetate		$C_{10}H_{12}O_2$	164.20	Sy	0.99	GC; NMR
(*R*)-(+)-1-Phenyl-1-propyl acetate		$C_{11}H_{14}O_2$	178.23	Sy	0.99	GC; NMR
(*R*)-(+)-1-Phenyl-1-butyl acetate		$C_{12}H_{16}O_2$	192.25	Sy	0.99	GC; NMR
1-Decanoic acid	334-48-5	$C_{10}H_{22}O_2$	172.27	S	0.99	GC
tert-Butyl methyl ether	1634-04-4	$C_5H_{12}O$	88.15	A	0.998	GC
Carbon tetrachloride	56-23-5	CCl_4	153.82	M	0.99	GC
n-Hexane	110-54-3	C_6H_{14}	86.18	A	0.99	GC
Acetonitrile	75-05-8	C_2H_3N	41.05	M	0.999	GC
2-Butanone	78-93-3	C_4H_8O	72.11	A	0.999	GC

[a] Sy: synthesized, A: Aldrich, S: Sigma, M: Mallinckrodt.

[b] These are the methods used by the vendors to determine the purity of these compounds except for the compounds synthesized in our laboratory. The vendor's stated purities were also confirmed by GC analysis using the methods described in Section 2.

[c] Reported mole fraction chiral purity >0.99.

[d] Reported mole fraction chiral purity >0.98.

purities of 0.998, 0.998, and 0.987, respectively, for (*R*)-(+)-1-phenyl ethanol, (*R*)-(+)-1-phenyl-1-propanol, (*R*)-(+)-1-phenyl-1-butanol. The acetates of benzyl alcohol, (*R*)-(+)-1-phenyl ethanol, (*R*)-(+)-1-phenyl-1-propanol, and (*R*)-(+)-1-phenyl-1-butanol were synthesized in our laboratory by using established procedures (CH_3COCl/pyridine/diethyl ether) [19]. The mole fraction purities of the prepared acetates were checked by NMR and also by GC using the conditions described below and were found to be >0.99. The enzyme used in this study was Chirazyme from Biocatalytics Inc., Pasadena, CA. This is a lipase (E.C. 3.1.1.3) having a broad substrate specificity and substantially high activity and that had been obtained from *Candida antartica*. The enzyme was in the form of a lyophilized powder.

2.2. Chromatography

The analysis of the substrates and products was carried out with an HP 5890 GC equipped with a flame ionization detector and a fused silica Phenomenex ZB-FFAP capillary column (30 m long and 0.53 mm i.d.). The injector and detector temperatures were 250 and 270 °C, respectively. The head pressure of the helium carrier gas was 283 kPa. The initial column temperature of 60 °C was held for 3 min and then raised to 240 °C at a rate of 20 $°C\,min^{-1}$ and held at 240 °C for 15 min. The internal standard for quantitative determination of substrates was 1-decanoic acid. Under these conditions the retention times of butyl acetate, 1-butanol, benzyl acetate, benzyl alcohol and 1-decanoic acid were, respectively, 2.65, 3.60, 8.48, 9.28 and 11.08 min for reaction (1). Similarly for reaction (2) the retention times of (*R*)-(+)-1-phenyl ethyl acetate and (*R*)-(+)-1-phenyl ethanol were 8.30 and 8.92 min; for reaction (3) the retention for times of (*R*)-(+)-1-phenyl-1-propyl acetate and (*R*)-(+)-1-phenyl-1-propanol were 8.60 and 9.25 min; and for reaction (4) the retention times of (*R*)-(+)-1-phenyl-1-butyl acetate and of (*R*)-(+)-1-phenyl-1-butanol were 8.95 and 9.75 min, respectively.

2.3. Response factor ratios

A standard solution of benzyl alcohol, benzyl acetate, 1-butanol, butyl acetate, and 1-decanoic acid was prepared gravimetrically in *n*-heptane. Using this solution the response factors (ratio of concentration to peak area) with reference to 1-decanoic acid were determined for butyl acetate, 1-butanol, benzyl acetate, and benzyl alcohol were determined and found to be 1.99 ± 0.07, 2.63 ± 0.09, 1.05 ± 0.02, and 1.26 ± 0.02, respectively. A separate standard solution of (*R*)-(+)-1-phenyl ethanol, (*R*)-(+)-1-phenyl ethyl acetate, and 1-decanoic acid in *n*-heptane was prepared to determine the response factor ratios of these substances with reference to 1-decanoic acid. These ratios were 1.25 ± 0.03 for (*R*)-(+)-1-phenyl ethanol and 1.01 ± 0.02 for (*R*)-(+)-1-phenyl ethyl acetate. Similarly, standard solutions of (*R*)-(+)-1-phenyl-1-alkanol, its acetate, and 1-decanoic acid were gravimetrically prepared in *n*-heptane to determine their response factor ratios with reference to 1-decanoic acid. The respective response factor ratios for (*R*)-(+)-1-phenyl-1-propyl acetate and (*R*)-(+)-1-phenyl-1-propanol, were 0.838 ± 0.005 and 0.995 ± 0.005; for (*R*)-(+)-1-phenyl-1-butyl acetate and (*R*)-(+)-1-phenyl-1-butanol the respective ratios were 0.901 ± 0.009 and 1.02 ± 0.01.

2.4. Equilibrium studies

The positions of equilibrium of reactions (1) and (2) were approached from both the forward and the reverse directions in *n*-hexane, acetonitrile, 2-butanone, *tert*-butyl methyl ether, carbon tetrachloride, and neat. The positions of equilibrium of reactions (3) and (4) were studied similarly but only in *n*-hexane. For both directions of reaction, ∼0.1 g of Chirazyme was added to a solution that contained the reactants (concentrations of $\sim 0.006\,\mathrm{mol\,kg^{-1}}$). This solution was then placed in a thermostatted shaker bath (±0.1 K) and allowed to equilibrate. For the neat mixture involving reaction (1), ≈0.1 g of Chirazyme was added to {0.017 g of benzyl alcohol + 10.3 g of butyl acetate (forward direction)} and to {0.008 g of 1-butanol + 0.0167 g of benzyl acetate + 10.0 g of butyl acetate (reverse direction)}. For reaction (2), ≈0.1 g of Chirazyme was added to {0.014 g of (*R*)-(+)-1-phenyl ethanol + 8.9 g of butyl acetate (forward direction)} and to {0.01 g of 1-butanol + 0.017 g of (*R*)-(+)-1-phenyl ethyl acetate + 8.8 g of butyl acetate (reverse direction)} for the neat system. The reaction mixtures were periodically analyzed by GC. All reactions were judged to be at equilibrium when the GC peak ratios of the areas of products/reactants were essentially identical from the solutions involving the forward and the reverse directions of reaction. We found that reactions (1) and (2) reached equilibrium in less than 24 h, reaction (3) required 3 days, and reaction (4) took ≈25 days. The analogous reaction with {(*S*)-(−)-1-phenyl ethanol + butyl acetate} (forward direction) and {(*S*)-(−)-1-phenyl ethyl acetate + 1-butanol} (reverse direction) was also attempted in *n*-hexane. After 43 days of equilibration, the GC peak ratios of the areas of products/reactants for the forward and reverse directions of reaction were 0.04 and 10.5, respectively. This indicates essentially no reaction from either direction. Thus, the enzyme can be considered to be stereoselective for the (*R*)-enantiomer(s) of 1-phenyl-1-alkanols.

2.5. Quantitative analysis

The procedure used to carry out the quantitative analysis of the reactants and products in the equilibrated reaction mixtures is now described. First, ≈2 ml of reaction mixture and 50–60 μl of internal standard solution (1-decanoic acid in *n*-heptane, $c = 0.12536\,\mathrm{mol\,kg^{-1}}$) were added to a vial, shaken, and tightly capped. Approximately 0.6 μl of this solution was then injected into the GC and analyzed. The concentration (expressed as $\mathrm{mol\,(kg\,sln)^{-1}}$) of each substrate involved in the reaction was determined from its chromatographic peak area, its response factor, and the peak area of the internal standard solution of known concentration. To determine the concentration of butyl acetate in the neat systems, 60 μl of reaction mixture and 60 μl of internal standard solution were added to a vial and then diluted them with 4 ml of *n*-hexane and analyzed. Other components in the reaction mixture were analyzed by the method described above. All analytical procedures were carried out gravimetrically using calibrated balances. The temperature dependence of the equilibrium constants in the reactions (1) and (2) were studied in *n*-hexane only. The equilibrium studies of the reactions (3) and (4) have also been carried out in *n*-hexane only.

3. Results and discussion

The equilibrium constants for reactions (1)–(4) are

$$K = \{c(\text{benzyl acetate}) \cdot c(\text{1-butanol})\}/\{c(\text{benzyl alcohol}) \cdot c(\text{butyl acetate})\} \quad (5)$$

$$K = \{c((R)\text{-}(+)\text{-1-phenyl ethyl acetate}) \cdot c(\text{1-butanol})\}/\{c((R)\text{-}(+)\text{-1-phenyl ethanol}) \cdot c(\text{butyl acetate})\} \quad (6)$$

$$K = \{c((R)\text{-}(+)\text{-1-phenyl-1-propyl acetate}) \cdot c(\text{1-butanol})\}/\{c((R)\text{-}(+)\text{-1-phenyl-1-propanol}) \cdot c(\text{butyl acetate})\} \quad (7)$$

$$K = \{c((R)\text{-}(+)\text{-1-phenyl-1-butyl acetate}) \cdot c(\text{1-butanol})\}/\{c((R)\text{-}(+)\text{-1-phenyl-1-butanol}) \cdot c(\text{butyl acetate})\} \quad (8)$$

In the above equations, c is the concentration in mol (kg sln)$^{-1}$. Since reactions (1)–(4) are symmetrical with regards to the reactants and products, the equilibrium constants are naturally dimensionless and are also independent of the units chosen to express concentration. The standard state for the solutes is the hypothetical ideal solution of unit concentration and the standard state of the solvent is the pure solvent. This follows the convention used in the NBS Tables of Chemical Thermodynamic Properties [20]. Because the substrates involved in these reactions are all in unionized form in the organic solvents and since their concentrations are small, we have assumed that activity coefficients are close to unity. In the case of the reaction carried out in the neat mixture, the solvent is also one of the reactants. Here, we have taken the activity of the solvent to be equal to the concentration of the solvent which was determined experimentally. Therefore, the equilibrium constants have been identified with thermodynamic equilibrium constants defined in terms of activities.

The results of the equilibrium measurements are given in Table 2. The values of the equilibrium constants K (column 8 in Table 2), obtained from the two opposite directions of reaction, were calculated from the measured concentrations of the reactants and products and are the averages of five measurements. The values of K (combined) (column 9 in Table 2) are the averages of the equilibrium constants obtained from both the forward and the reverse directions of reaction. It is important to note that, in all cases, the values of the equilibrium constants obtained from opposite directions of reaction were in agreement. This is excellent evidence that equilibrium has been reached. Also given in Table 2 are the results of the temperature dependency of the equilibrium constant for reactions (1) and (2) which were studied using n-hexane as the solvent.

The reported uncertainties in Table 2 are the random errors associated with the measurements expressed as two estimated standard deviations of the mean. These uncertainties do not include possible systematic errors in the measurements, which are now considered. The possible systematic errors are estimated to be $\pm 0.02K$ in the GC measurement of concentrations of reactants and products, $\pm 0.05K$ in the response factor ratios, and $\pm 0.01K$ due to sample impurities. These estimated errors were then combined in quadrature together with the statistical uncertainties in the measured vales of these quantities expressed as one standard deviation of the mean to obtain combined standard uncertainties [21]. These uncertainties were then multiplied by 2 to get the final uncertainties. Thus, the final uncertainty in the equilibrium constants involving benzyl alcohol is ± 0.01 or $0.035K$; for the remaining three reactions involving (R)-(+)-phenyl-1-alkyl alcohols, the uncertainties are ± 0.006 or $0.056K$.

Table 3 contains the final values of the equilibrium constants K, standard molar Gibbs energy changes $\Delta_r G_m^\circ$, and, for reactions (1) and (2) in n-hexane, standard molar enthalpy changes $\Delta_r H_m^\circ$, and standard molar entropy changes $\Delta_r S_m^\circ$ at 298.15 K for these reactions. The values of $\Delta_r H_m^\circ$ and of $\Delta_r S_m^\circ$ were calculated by using the model of Clarke and Glew [22] and the values of K that were measured at several temperatures. In calculating values of $\Delta_r H_m^\circ$ and $\Delta_r S_m^\circ$ it was assumed that the standard molar heat capacity changes $\Delta_r C_{p,m}^\circ$ for these reactions were zero. Since the values of $\Delta_r H_m^\circ$ are based on the slope of K versus temperature and since the possible systematic errors in the values of K considered above should be independent of temperature, the uncertainties in the $\Delta_r H_m^\circ$ values are based on the statistical uncertainty obtained with the model calculation.

An examination of the results in Table 3 shows that the equilibrium constants for transesterification

Table 2
Results of equilibrium measurements for the transesterifcation reactions: 1-phenyl alkanol (sln) + butyl acetate (sln) = 1-phenyl alkyl acetate (sln) + 1-butanol (sln) in organic solvents and the neat reaction mixture (no solvent added)

Solvent	Direction	T (K)	c(BzAl) × 10^3	c(ButAc) × 10^3	c(BzAc) × 10^3	c(1-butanol) × 10^3	K	K (combined)
Reaction (1): benzyl alcohol (sln) + butyl acetate (sln) = benzyl acetate (sln) + butanol (sln)								
n-Hexane	Forward	292.95	1.738	4.162	1.563	1.467	0.317 ± 0.006	0.317 ± 0.005
	Reverse	292.95	1.857	3.745	1.468	1.494	0.315 ± 0.006	
	Forward	298.15	1.102	2.212	1.093	0.687	0.308 ± 0.003	0.310 ± 0.003
	Reverse	298.15	1.669	3.745	1.566	1.242	0.311 ± 0.004	
	Forward	303.15	2.219	5.292	2.200	1.706	0.320 ± 0.005	0.317 ± 0.003
	Reverse	303.15	2.004	3.699	1.651	1.411	0.314 ± 0.002	
	Forward	308.15	2.218	5.279	2.200	1.708	0.321 ± 0.005	0.319 ± 0.003
	Reverse	308.15	2.303	3.885	1.979	1.430	0.316 ± 0.003	
No solvent (neat reaction mixture)	Forward	298.15	0.472	8395	11.98	95.84	0.290 ± 0.005	0.294 ± 0.004
	Reverse	298.15	0.384	8313	10.23	92.93	0.298 ± 0.004	
Carbon tetrachloride	Forward	298.15	2.685	3.345	1.783	1.539	0.306 ± 0.005	0.305 ± 0.003
	Reverse	298.15	4.187	6.179	2.389	3.303	0.305 ± 0.004	
Acetonitrile	Forward	298.15	6.829	3.247	1.332	4.978	0.299 ± 0.001	0.299 ± 0.002
	Reverse	298.15	5.963	3.365	1.285	4.656	0.298 ± 0.005	
tert-Butyl methyl ether	Forward	298.15	8.493	7.781	2.516	6.216	0.237 ± 0.004	0.237 ± 0.002
	Reverse	298.15	7.499	5.947	1.748	6.048	0.237 ± 0.002	
2-Butanone	Forward	298.15	9.767	2.294	0.495	12.66	0.280 ± 0.001	0.281 ± 0.002
	Reverse	298.15	9.340	2.133	0.381	14.74	0.282 ± 0.002	

Solvent	Direction	T (K)	c(PhEtOH) × 10^3	c(ButAc) × 10^3	c(PhEtAc) × 10^3	c(1-butanol) × 10^3	K	K (combined)
Reaction (2): (*R*)-(+)-1-phenyl ethanol (sln) + butyl acetate (sln) = (*R*)-(+)-1-phenyl ethyl acetate (sln) + 1-butanol (sln)								
n-Hexane	Forward	292.95	2.641	3.462	1.046	0.918	0.105 ± 0.001	0.103 ± 0.001
	Reverse	292.95	2.837	3.444	1.367	0.727	0.102 ± 0.006	
	Forward	298.15	2.640	3.373	1.038	0.926	0.108 ± 0.002	0.107 ± 0.001
	Reverse	298.15	2.797	3.444	1.359	0.756	0.107 ± 0.004	
	Forward	303.15	4.153	2.965	1.010	1.391	0.114 ± 0.001	0.114 ± 0.001
	Reverse	303.15	3.126	3.660	1.353	0.956	0.113 ± 0.001	
	Forward	308.15	3.153	3.640	1.279	0.968	0.108 ± 0.005	0.106 ± 0.005
	Reverse	308.15	3.066	3.378	1.499	0.711	0.103 ± 0.004	
No solvent (neat reaction mixture)	Forward	298.15	1.131	7925	10.43	94.20	0.110 ± 0.001	0.111 ± 0.003
	Reverse	298.15	1.084	8278	10.42	96.47	0.112 ± 0.005	
Carbon tetrachloride	Forward	298.15	4.300	4.212	1.479	1.371	0.112 ± 0.003	0.112 ± 0.003
	Reverse	298.15	1.084	8.278	1.042	0.965	0.112 ± 0.005	

Acetonitrile	Forward	298.15	7.166	3.599	0.731	4.813	0.136 ± 0.002	0.138 ± 0.001
	Reverse	298.15	8.957	4.404	0.937	5.852	0.139 ± 0.001	
tert-Butyl methyl ether	Forward	298.15	10.43	9.841	1.664	6.140	0.100 ± 0.001	0.101 ± 0.001
	Reverse	298.15	10.40	7.128	1.281	5.847	0.101 ± 0.002	
2-Butanoe	Forward	298.15	10.45	2.178	0.193	12.00	0.102 ± 0.001	0.104 ± 0.002
	Reverse	298.15	10.76	2.562	0.161	17.98	0.105 ± 0.002	

Solvent	Direction	T (K)	c(PhPrOH) × 10^3	c(ButAc) × 10^3	c(PhPrAc) × 10^3	c(1-butanol) × 10^3	K	K (combined)
Reaction (3): (*R*)-(+)-1-phenyl-1-propanol (sln) + butyl acetate (sln) = (*R*)-(+)-1-phenyl-1-propyl acetate (sln) + 1-butanol (sln)								
n-Hexane	Forward	298.15	5.737	7.653	2.619	1.744	0.104 ± 0.003	0.105 ± 0.002
	Reverse	298.15	7.037	9.206	2.522	2.723	0.106 ± 0.002	

Solvent	Direction	T (K)	c(PhBuOH) × 10^3	c(ButAc) × 10^3	c(PhBuAc) × 10^3	c(1-butanol) × 10^3	K	K (combined)
Reaction (4): (*R*)-(+)-1-phenyl-1-butanol (sln) + butyl acetate (sln) = (*R*)-(+)-1-phenyl-1-butyl acetate (sln) + 1-butanol (sln)								
n-Hexane	Forward	298.15	7.503	8.658	3.717	1.911	0.109 ± 0.003	0.111 ± 0.002
	Reverse	298.15	7.330	8.696	3.701	1.932	0.112 ± 0.003	

The concentrations c (mol (kg solvent)$^{-1}$) given in columns 4–7 are the average concentrations of the reactants and products based on either five or six measurements. The values of the equilibrium constants K (column 8) an average values calculated from the concentrations. The values of K (combined) (column 9) are the combined averages of the equilibrium constants obtained from both directions of reaction. Abbreviations used are: BzAl, benzylalcohol; BzAc, benzylacetate; ButAc, butyl acetate; PhEtOH, (*R*)-(+)-1-phenyl ethanol; PhEtAc, (*R*)-(+)-1-phenyl ethyl acetate; PhPrOH, (*R*)-(+)-1-phenyl-1-propanol; PhPrAc, (*R*)-(+)-1-phenyl-1-propyl acetate; PhBuOH, (*R*)-(+)-1-phenyl-1-butanol; and PhBuAc, (*R*)-(+)-1-phenyl-1-butyl acetate. The uncertainties are equal to two estimated standard deviations of the mean.

Table 3
Equilibrium constants K, standard molar Gibbs energy $\Delta_r G^\circ_m$, standard molar enthalpy $\Delta_r H^\circ_m$, and standard molar entropy changes $\Delta_r S^\circ_m$ at 298.15 K for the transesterification reactions of 1-phenyl-1-alkanols and butyl acetate

Reaction	Solvent	K	$\Delta_r G^\circ_m$ (kJ mol^{-1})	$\Delta_r H^\circ_m$ (kJ mol^{-1})	$\Delta_r S^\circ_m$ (J K^{-1} mol^{-1})
1	*n*-Hexane	0.315 ± 0.011	2.86 ± 0.09	0.6 ± 1.9	−(7.6 ± 6.4)
	No solvent (neat reaction mixture)	0.294 ± 0.011	3.03 ± 0.09		
	Carbon tetrachloride	0.305 ± 0.011	2.94 ± 0.09		
	Acetonitrile	0.299 ± 0.010	2.99 ± 0.08		
	2-Butanone	0.281 ± 0.010	3.15 ± 0.08		
	tert-Butyl methyl ether	0.237 ± 0.008	3.57 ± 0.08		
2	*n*-Hexane	0.111 ± 0.006	5.45 ± 0.13	2.3 ± 6.2	−(11 ± 21)
	No solvent (neat reaction mixture)	0.111 ± 0.006	5.45 ± 0.13		
	Carbon tetrachloride	0.112 ± 0.006	5.43 ± 0.13		
	Acetonitrile	0.138 ± 0.008	4.91 ± 0.14		
	2-Butanone	0.103 ± 0.006	5.63 ± 0.14		
	tert-Butyl methyl ether	0.100 ± 0.006	5.71 ± 0.14		
3	*n*-Hexane	0.105 ± 0.006	5.59 ± 0.14		
4	*n*-Hexane	0.111 ± 0.006	5.45 ± 0.13		

The basis of the uncertainties is discussed in the text (see Section 3).

reactions of benzyl alcohol and butyl acetate are in the range of 0.24–0.32, whereas for (*R*)-(+)-1-phenyl ethanol and butyl acetate the values are in the range of 0.10–0.14. The literature contains only one set of equilibrium data dealing with transesterification reactions in organic solvents [12], namely

$$\begin{aligned}&(-)\text{-menthol (sln)} + \text{dodecyl dodecanoate (sln)}\\&\quad = (-)\text{-menthyl dodecanoate (sln)}\\&\qquad + 1\text{-dodecanol (sln)}\end{aligned} \tag{9}$$

The average value of the equilibrium constant for this reaction in four organic solvents (*n*-heptane, *n*-hexane, toluene, and 2,2,4-trimethylpentane) is 0.37 which is comparable to the average value of 0.29 found in the present study for the reaction of benzyl alcohol and butyl acetate, a system without steric hindrance. Thus, the equilibrium constants for transesterification reactions are surprisingly constant as compared to the equilibrium constants of esterification reactions [8,9,17,18]. For example the equilibrium constant for the esterification reaction of (−)-menthol and 1-dodecanoic acid [9] in organic solvents varies from 3.2 in acetonitrile to 23.7 in 2,2,3-trimethyl pentane. For the reaction of 1-dodecanoic acid and 1-dodecanol [18] the equilibrium constant varies from 18 in toluene to 40 in hexane.

In our present study, the average equilibrium constants and standard molar Gibbs energy change $\Delta_r G^\circ_m$ are, respectively, 0.29 ± 0.03 and 3.09 ± 0.25 kJ mol^{-1} for reaction (1) and 0.11 ± 0.01 and 5.45 ± 0.28 kJ mol^{-1} for reaction (2) in all solvents. This difference of 0.18 in the equilibrium constant and 2.4 kJ mol^{-1} in molar Gibbs energy change, $\Delta(\Delta_r G^\circ_m)$ between reactions (1) and (2), may be attributed to the steric hindrance due to a methyl group in (*R*)-(+)-1-phenyl ethanol.

We have also examined the effect of additional methylene groups in the 1-phenyl alkanol side chain on the values of the equilibrium constants. The results for reactions (2)–(4), carried out in hexane, indicate that the values of the equilibrium constants for these reactions and their corresponding molar Gibbs energy change $\Delta_r G^\circ_m$ at 298.15 K are essentially the same, namely ≈0.11 and ≈5.5 kJ mol^{-1}, respectively. These results show that the additional methylene groups in the alkyl side chain do not increase the steric hindrance pertinent to the transesterification reactions and that the change in the standard molar Gibbs energy associated with each additional methylene group is zero beyond the first one.

In summary, the average value of the equilibrium constants for transesterification is ≈0.29 for benzyl alcohol reactions and 0.11 for (*R*)-(+)-1-phenyl ethanol reactions. The difference of 0.18 between these equilibrium constants is associated with steric hindrance caused by a methyl group in (*R*)-(+)-1-phenyl ethanol. The standard molar Gibbs energy change $\Delta_r G_m^\circ$ for each additional methylene group in reactions involving (*R*)-(+)-1-phenyl ethanol to (*R*)-(+)-1-phenyl-1-butanol is zero.

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