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SYNTHESES OF OPTICALLY ACTIVE POLYACRYLATES

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Key Words: Lipase, Acrylate, Transesterification, Resolution, Optically Active

ABSTRACT

Different secondary alcohols were resolved by lipase catalyzed transesterification using 2,3-butanedione monoxime acrylate as acrylating agent. The results showed that the reaction rates were the fastest among reactions reported until now. The effect of solvent on the transesterification rate was studied. The enantiomeric excess (ee) and enantiomeric purity (E value) of all the acrylate monomers were determined. The synthesized optically active acrylate monomers were polymerized by free radical polymerization technique.

INTRODUCTION

Synthesis of optically active polyacrylates involves the synthesis of optically active acrylate monomers and their polymerization. The optically active acrylate monomer can be synthesized either by condensation of optically active alcohol with acrylic acid or by stereo selective acryloylation of racemic alcohols.

Resolution of alcohols by lipase catalyzed transesterification is well known [1-3]. Vinylacrylates were found to be efficient acrylating agents for lipase catalyzed synthesis of acrylates. Even though the reaction proved to be irreversible, the yield reported is quite low [4]. It was reported that acryloyl ester with a good leaving group like trihaloethanol increases the reactivity and, hence, the yield [5]. Recently,

oxime acrylate has been introduced as an acrylating agent for the resolution of racemic alcohols [6]. Since, lipase catalyzed acryloylation of secondary alcohols is much slower than primary alcohols, activated acrylates have been employed to accelerate the reaction [5]. The fast reaction rate of oxime esters towards lipase catalyzed transesterification has prompted us to use oxime acrylate as an acrylating agent for the resolution of secondary alcohols.

In the present study, different secondary alcohols containing bulky phenyl group were transesterified with 2,3-butanedione monoxime acrylate to get optically active acrylate monomers.

EXPERIMENTAL

Materials

Chemicals

2,3-Butanedione monoxime acrylate was synthesized by the condensation of 2,3-butanedione monoxime and acryloyl chloride. All the alcohols were synthe - sized by the $NaBH_4$ reduction of corresponding ketones. All the solvents used were of analytical grade.

Lipozyme IM 20 (41 Iug^{-1}), a commercially available lipase from fungus *mucor meihei* immobilized on a macroporous anion exchange resin was obtained from Novo Nordisk.

Methods of Synthesis

Synthesis of Reactants

2,3-butanedione monoxime acrylate

In a 250 ml round bottom flask, fitted with addition funnel, 2,3-butanedione monoxime (0.100 mol), triethylamine (0.105 mol) and dichloromethane (100 ml) were added. The resulting solution was cooled to 0°C and stirred. Acryloyl chloride (0.110 mol) was added dropwise over a period of half an hour and further stirred for 2 hours to ensure the reaction completion. The reaction mixture was then neutralized with dilute hydrochloric acid to remove the excess triethyl amine and then extracted in dichloromethane. The organic layer was washed repeatedly with water, separated, and the traces of water were removed by drying over anhydrous sodium sulfate. The product was recovered by evaporating the solvent. The yield was 94.2 %.

TABLE 1. Reduction of Acetophenone and Substituted Acetophenone

Reactant	Product	B.P./M.P. °C/mm of Hg	Yield (%)
Acetophenone	1-phenyl ethanol	207/760	98
p-Methoxy acetophenone	1-(4-methoxyphenyl) ethanol	126-128/12	96
p-Chloro acetophenone	1-(4-chlorophenyl) ethanol	118-119/10	96
p-Fluoro acetophenone	1-(4-fluorophenyl) ethanol	101-102	95

Synthesis of Alcohols by Reduction of Acetophenone and its Derivatives [7]

Acetophenone (0.1 mol) in methanol (200 ml) was placed in a two-necked round bottom flask fitted with a reflux condenser and stopper. The reaction of sodium borohyride ($NaBH_4$) with acetophenone being exothermic, the addition of $NaBH_4$ (0.3 mol) was controlled to avoid bumping, and was continued for a period of half an hour with vigorous stirring. The reaction mixture was further refluxed for two hours. The solvent was evaporated on rotavapor and 50 ml of dilute HCl (5N) was added. The alcohol obtained was freed from inorganic salts and water soluble impurities by extracting it in chloroform. Finally, chloroform, being more volatile (b.p. 60°C) than the newly synthesized alcohol (Table 1), was evaporated.

Derivatives of acetophenone, namely p-methoxy acetophenone, p-chloro acetophenone and p-fluoro acetophenone were similarly synthesized. The yield of all the alcohols were found to be quantitative (Table 1).

Synthesis of Optically Active Acrylate by Lipase Catalysis

A mixture of racemic alcohol (0.01 mol), 2,3-butanedione monoxime acrylate (0.005 mol) in diisopropyl ether (25 ml) was taken in 100 ml round bottom flask and stirred. Lipase (0.5 g) was added to the mixture and stirring was continued at ambient temperature (30°C). After completion of the reaction, the reaction mixture was filtered, enzyme was separated and the filtrate was concentrated and passed through a silica gel column to separate the acrylate monomer from the mixture. The enzyme was washed repeatedly with diethyl ether and stored for reuse.

TABLE 2. Lipase Catalyzed Transesterification of Alcohols

Alcohol	Acrylate	Conv. (%)	Yield (%)
1-phenyl ethanol	1-phenyl ethyl acrylate	100	46
1-(4-methoxyphenyl) ethanol	1-(4-methoxyphenyl) ethyl acrylate	100	96
1-(4-chlorophenyl) ethanol	1-(4-chlorophenyl) ethyl acrylate	100	96
1-(4-fluorophenyl) ethanol	1-(4-fluorophenyl) ethyl acrylate	100	95

For kinetic study, the reaction samples were taken periodically and the reaction was monitored by gas chromatography. The yields based on the consumption of alcohol are listed in Table 2.

Polymerization of Optically Active Acrylates

All the acrylates synthesized (Table 2) were polymerized by the following method.

A predetermined amount of acrylate (0.002 mol) and benzene (20 ml) were taken in a 50 ml two-necked round bottom flask fitted with a condenser. To prevent the inhibition of polymerization due to atmospheric oxygen the mixture was kept under nitrogen atmosphere. An accurately weighed amount of initiator, azo-bis-isobutyronitrile (0.002 g) was added to this mixture and heated to 60°C with constant stirring. The reaction was arrested by precipitating the reaction mixture in hexane. The polymer was purified by repeated precipitation in hexane. The yields obtained were in the range of 80-90%.

Determination of Specific Rotation

Specific rotation of the acrylate monomers and the polymers were measured by JASCO Digital polarimeter. A known quantity of the sample was dissolved in chloroform and the specific rotation was measured using cell of 50 mm length.

Determination of Optically Purity (ee)

The 'ee' of the products were determined by using either standard methods [8] or by chiral HPLC technique [9].

High Performance Liquid Chromatography (HPLC)

HPLC analyses were performed on Waters HPLC model 6000 A with Waters 590 pump and UV 440 detector.

Conditions

Column	DNPG (Pirkle chiral column)
Solvent	Mixture of hexane and isopropanol
Flow	1 ml to 2 ml/minute
Detector	UV at 254 nm

Infra-red Spectroscopy

Infra-red (IR) spectra were recorded on Shimadzu FTIR-4200 dual beam spectrophotometer.

Gas Chromatographic (GC) Analysis

GC analyses were performed on a Shimadzu 9 A Gas Liquid Chromatograph equipped with flame ionization detector having capabilities of oven temperature programming.

The sample to be analyzed was weighed accurately and diluted with suitable solvent, if found necessary. It was injected into a gas chromatograph under the following conditions :

Carrier gas	Nitrogen (1.5 ml/minute)	
Inlet split ratio	10:1	
Column	RSL 200	
Oven	With temperature programming	
	Initial temp.	100°C
	Initial time	3 minutes
	Rate	30°C/min.
Injector temperature	300°C	
Detector (FID) at	300°C	

Peak area data obtained from the integrator was used to estimate the amount of component of interest in the sample. The kinetic study of the optically active acrylate synthesis was done by GC.

Elemental Analysis

Elemental composition of the monomers were found by using a Carlo Erba Elemental analyzer MOD 1100.

Determination of Molecular Weight ($\overline{M}_w$)

The average molecular weight of the polyacrylates was obtained by gel

permeation chromatography.

Columns	μ-styragel (10^5, 10^4, 10^3 Å)
Solvent	Dry THF
Flow rate	1.5 ml/minute
Detector	Refractive index
Sample size	100 μl
Chart speed	0.5 cm/minute
Standards	Polystyrene

RESULTS AND DISCUSSION

Characterization

Reactants

2,3 Butanedione monoxime acrylate

Purity of 2,3-butanedione monoxime acrylate was measured by gas chroma-tography.

Infrared Spectroscopy

IR spectrum of 2,3-butanedione monoxime acrylate showed the following characteristic absorptions:

2900 cm^{-1} (broad)	1762 cm^{-1} (strong)
1708 cm^{-1} (strong)	1625 cm^{-1} (medium)
1510 cm^{-1} (weak)	1380 cm^{-1} (strong)

^1H NMR Spectroscopy

The NMR spectrum taken in $CDCl_3$ using TMS as internal standard, showed the following characteristic peaks:

δ2.1 ppm (singlet, 3H, $O=C-CH_3$)
δ2.5 ppm (singlet, 3H, $O-N=C-CH_3$)
δ5.6-6.7 ppm (complex splitting, 3H, $-CH=CH_2$)

Alcohols

The boiling point and yield of the alcohols are listed in Table 1. The purity of all the alcohols was confirmed by GC analysis. Their retention times are as follows :

1-phenyl ethanol - 3.73 minutes
1-(4-chlorophenyl)ethanol - 5.54 minutes

TABLE 3. ^1H NMR Spectral Data of Acrylate Monomers Derived from Secondary Alcohols

Acrylates	Aromatic Protons δ ppm	O-CH-Ph δ ppm	$-OCH_3$ δ ppm	$-CH_3$ δ ppm	O C-CH=CH_2 δ ppm
1-phenyl ethyl acrylate	7.30	5.80	-	1.50	5.76 to 6.53
1-(4-fluoro phenyl) ethyl acrylate	6.89 to 7.42	5.80	-	1.51	5.71 to 6.56
1-(4-chloro phenyl) ethyl acrylate	6.90 to 7.44	5.83	-	1.52	5.72 to 6.56
1-(4-methoxy-phenyl) ethyl acrylate	6.75 to 7.36	5.80	3.76	1.38	5.80 to 6.33

1-(4-fluorophenyl)ethanol - 5.40 minutes
1-(4-methoxyphenyl)ethanol - 5.85 minutes

Acrylate Monomers

The purity of the synthesized acrylate monomers was confirmed by gas chromatography.

^1H NMR Spectroscopy

The δ ppm values of the NMR spectra of the acrylates obtained from the secondary alcohols are listed in Table 3.

Elemental Analysis

The comparison of the elemental analysis of the monomers obtained with their theoretical values is presented in Table 4.

TABLE 4. Results of Elemental Analysis of Acrylate Monomers

Acrylate Monomer	Theoretical (%)			Found (%)		
	C	H	O	C	H	O
1-phenyl ethyl acrylate	75.01	6.81	18.18	75.00	6.82	18.18
1-(4-fluorophenyl) ethyl acrylate	68.04	5.60	-	68.03	5.61	-
1-(4-chlorophenyl) ethyl acrylate	62.88	5.23	-	62.86	5.24	-
1-(4-methoxyphenyl) ethyl acrylate	69.90	6.76	23.3	69.88	6.26	23.32

Polyacrylates

IR spectra of all the polyacrylates showed the following characteristic peaks:

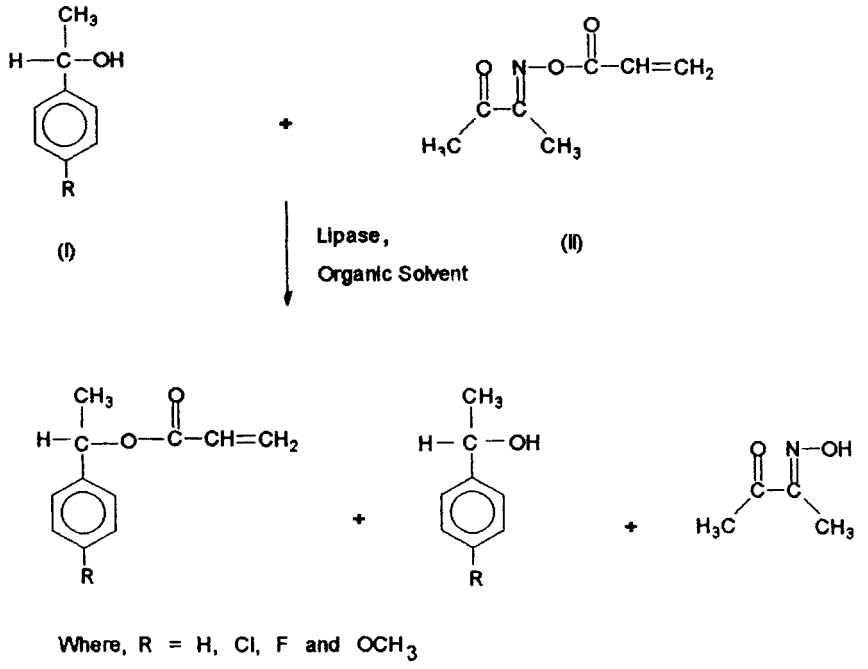
3030 cm^{-1} (broad) 2950 cm^{-1} (strong)

1740 cm^{-1} (very broad) 1600 cm^{-1} (weak)

Transesterification of Secondary Alcohols by Lipase Catalysis

It has been observed that the rate of transesterification of secondary alcohols is slow, however, it can be increased by using activated esters [10, 11]. The oxime acrylate, being the best acyl donor, [6] compared to other acrylating agent, was used as the acrylating agent for optimizing the reaction conditions in the present work (Scheme 1).

The secondary alcohol and 2,3-butanedione monoxime acrylate were taken in the stoichiometric ratio 2:1 for getting better enantiomeric purity at maximum conversion [12]. The yield and the time taken for completion of the reaction are detailed in Table 5. It is known that the transesterification of secondary alcohols with acryloyl ester is very slow. Margolin *et al.* [5] reported that even after using activated esters as acrylating agents the reaction time had reduced to only 3 days. It is clearly seen from Table 5 that the reaction time was reduced from a few days to a few hours when oxime acrylate was used as the acrylating agent. The yields of all the reactions were found to be quantitative and nearly the same.



SCHEME 1

TABLE 5. Lipase Catalyzed Transesterification of Secondary Alcohols

Substrate	Product	Reaction time (Hrs.)	Yield* (%)
1-phenyl ethanol	1-phenyl ethyl acrylate	17	46.5
1-(4-methoxyphenyl) ethanol	1-(4-methoxyphenyl) ethyl acrylate	20	46.0
1-(4-chlorophenyl) ethanol	1-(4-chlorophenyl) ethyl acrylate	13	47.0
1-(4-fluorophenyl) ethanol	1-(4-fluorophenyl) ethyl acrylate	12	47.0

*Calculated with respect to alcohol

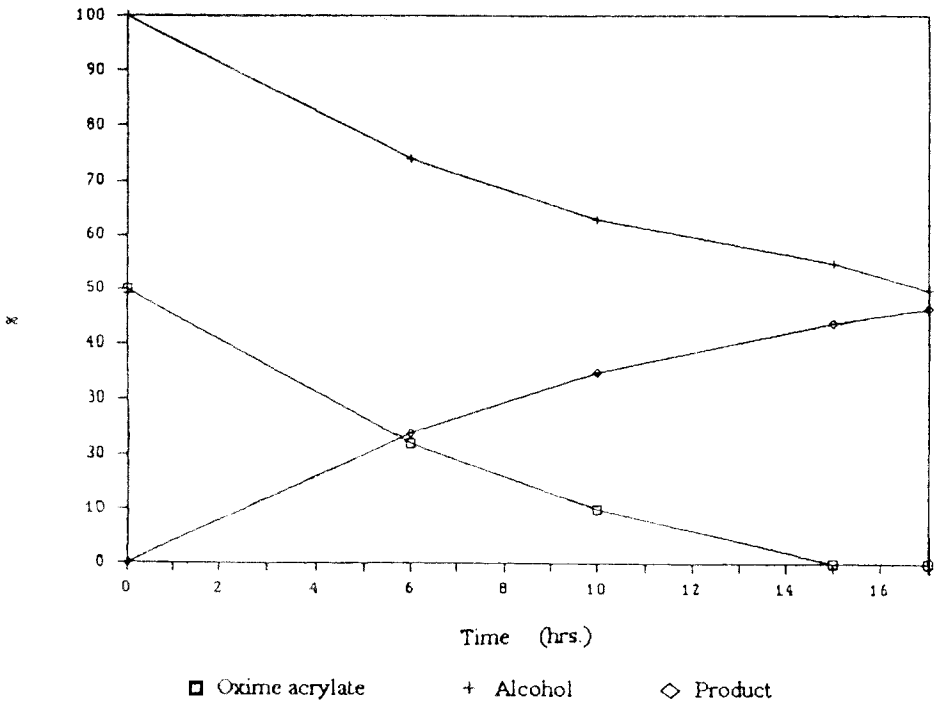


Figure 1. Kinetics of transesterification of 1-phenyl ethanol and oxime acrylate as a function of time.

Kinetics

Samples were removed from the reaction mixture of 1-phenyl ethanol and 2,3-butanedione monoxime acrylate at different time intervals and subjected to GC analysis. A plot of the change in the concentration of reactants and products with time (Figure 1), clearly shows that the reaction stopped around 50% conversion with respect to alcohol. The low conversion obtained is simply because the concentration of oxime acrylate used was only half of that of alcohol. Figure 1 also shows that the rate of consumption of oxime acrylate was the fastest and the rate of the consumption of alcohol and the rate of formation of product were almost identical.

Effect of Substitution on the Reaction Rate

Figure 2 exhibits the rate of % conversion with respect to different substituted alcohols. It is clear that, 1-(4-fluorophenyl)ethanol and 1-(4-chlorophenyl)ethanol reacted faster than 1-phenyl ethanol, whereas, 1-(4-methoxyphenyl) ethanol reacted slower than 1-phenyl ethanol. Thus, when the electron withdrawing

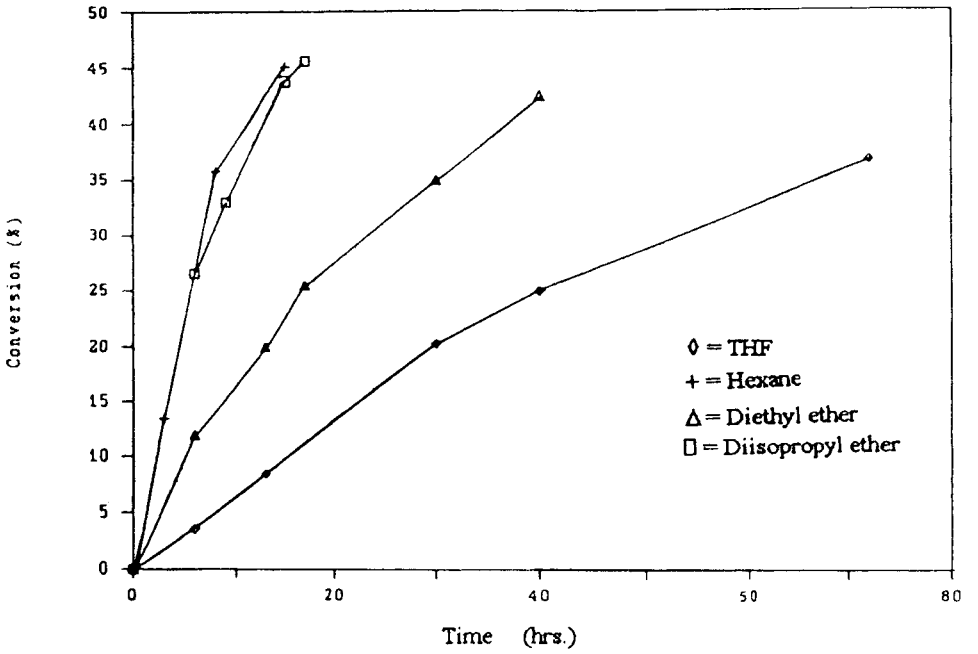


Figure 2. Comparison between the rate of transesterification of secondary alcohol.

groups like fluorine, chlorine were substituted on the para position of the phenyl ring the reactivity of 1-phenyl ethanol towards lipase catalysis increased, whereas, it decreased when an electron donating group like methoxy group was substituted. In the case of secondary alcohol, the difference in steric effect due to substituted groups was relatively less than the electronic effect because the substitution was in the para position and far away from the reaction site. These results highlight the fact that along with the steric effect the electronic effect also plays a major role in the lipase catalyzed transesterification reaction.

Effect of Solvent

In order to study the effect of solvents on lipase catalyzed transesterification reaction, a model reaction of 1-phenyl ethanol with 2,3-butanedione monoxime acrylate was carried out in different solvents. Solvents of different log P values were selected for this purpose. Figure 3 presents the plot of the rate of conversion of 1-phenyl ethanol in different solvents versus time.

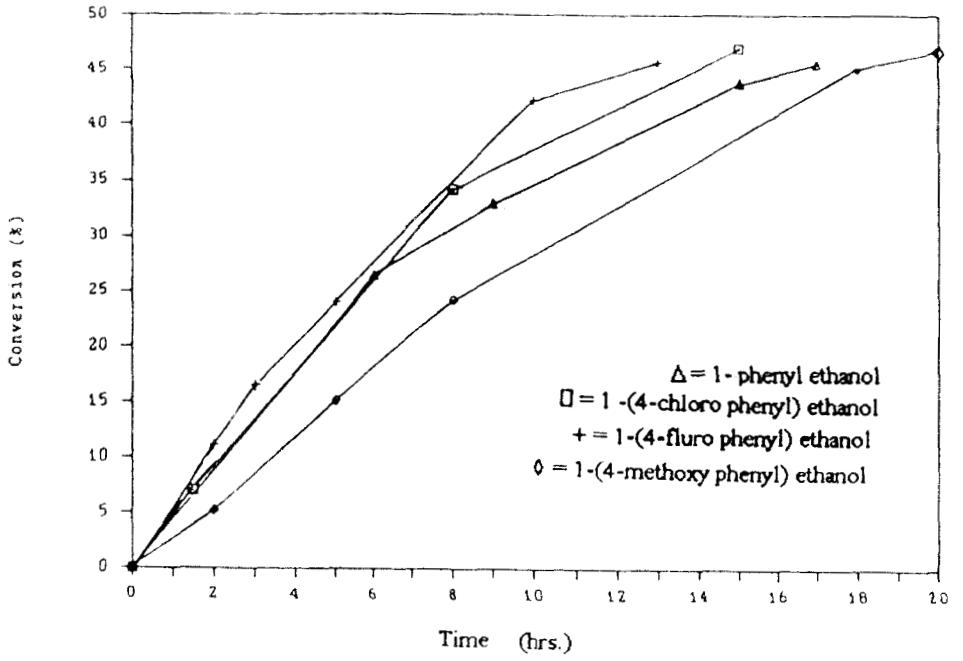


Figure 3. Effect of solvent on the lipase catalyzed transesterification of 1-phenyl ethanol.

It is worth observing that the substantial difference in hydrophobicity of solvents hexane (Log P = 3.5) and diisopropyl ether (Log P = 2.0) has not influenced the rate of reaction in presence of the solvents (Figure 4). The difference in the rate of the reaction carried out in hexane and diisopropyl ether is marginal.

As compared to hexane and diisopropyl ether, the reaction period is extremely high for THF (Log P = 0.49) and diethyl ether (0.89) which can be attributed to their relatively low Log P values. As a result, THF and diethyl ether are less hydrophobic (in other words more 'hydrophilic') than hexane and diisopropyl ether and probably affect the enzyme activity which has been reflected in the longer reaction periods.

Stereochemistry of Acrylate Monomers

All the optically active acrylate monomers which were separated from column chromatography showed +ve rotation (Table 6). The absolute configuration of 1-phenylethyl acrylate was obtained by hydrolyzing it to alcohol and comparing

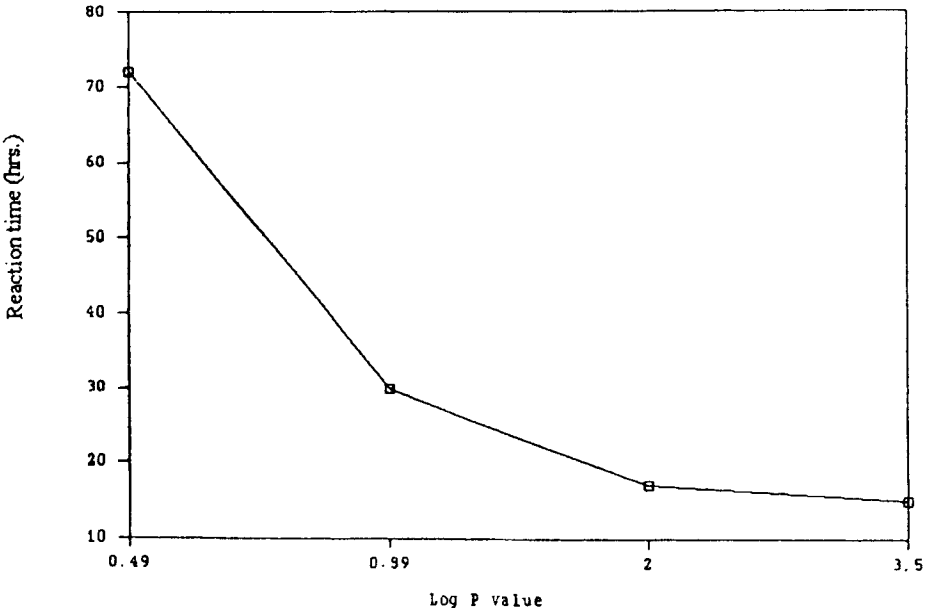


Figure 4. Effect of log P value of solvent on reaction time.

TABLE 6. Stereochemical Data of Acrylate Monomers Derived from Secondary Alcohols

Acrylates	Yield (%)	[α^{25}	'ee'	E value
1-phenyl ethyl acrylate	46.5	+72.2	88.6	38.5
1-(4-fluorophenyl) ethyl acrylate	46.0	+64.5	95.1	99.9
1-(4-chlorophenyl) ethyl acrylate	47.0	+68.8	97.7	>100
1-(4-methoxy phenyl) ethyl acrylate	47.0	+56.5	84.7	27.1

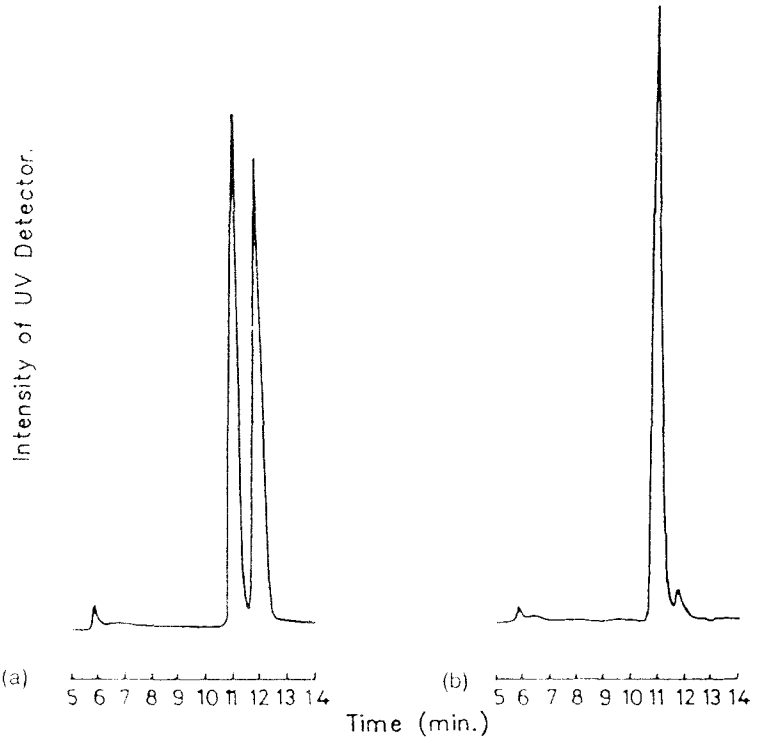


Figure 5. HPLC of (a) racemic 1-phenyl ethyl acrylate and (b) optically active 1-phenyl ethyl acrylate.

with authentic enantiomers [3]. By analogy with 1-phenyl ethyl acrylate, one can assume that the absolute configuration of all the acrylates is 'R' only. The enantiomeric excess of all the acrylate monomers was obtained by separating both the enantiomers using chiral HPLC technique [13]. Figure 5 shows the HPLC chromatogram of separated R and S isomers of both racemic and optically active 1-phenylethyl acrylate.

The enantiomeric excess (ee) of all the acrylates were calculated using the following formula [8] :

$$ee = \frac{\text{(Area of R isomer) - (Area of S isomer)}}{\text{Total area}} \times 100$$

The biochemical constant 'E value' was calculated using the formula [9],

Table 7. Polymerization of Optically Active Acrylate Monomers

Polymers	Time (Hrs.)	Conv. (%)	(M_w	(M_w/(M_n	$[\alpha]^{25}$
Poly(1-phenyl ethyl acrylate)	10.5	79	27800	2.9	+64.8
Poly[1-(4-fluoro phenyl) ethyl acrylate]	12.0	82	24200	1.8	+60.5
Poly[1-(4-chloro phenyl) ethyl acrylate]	10.0	85	32800	1.9	+63.5
Poly[1-(4-methoxy-phenyl) ethyl acrylate]	10.5	80	33200	2.2	+64.0

$$E = \frac{\ln[(1-c)\,(1 + ee(p))]}{\ln[(1-c)\,(1 - ee(p))]}$$

where, c = extent of conversion, and ee(p) = enantiomeric excess of the product fraction.

Figure 5 clearly shows that the R isomer of 1-phenylethyl acrylate moved slower than the S isomer when in DNB PG Pirkle chiral column.

The yields of all the acrylate monomers were nearly the same. From Table 6, it is clear that the 'ee' as well as the biochemical constant 'E value' obtained for p-fluoro and p-chloro derivatives of 1-phenylethyl acrylates were quite high in comparison with 1-phenylethyl acrylate. However, the p-methoxy derivative showed marginally lower 'ee' as well as 'E value'.

The order of 'ee' of the acrylate monomers is found to be 4-methoxy < 1-phenyl < 4-fluoro < 4-chloro which can be probably ascribed to the substrate selectivity of the enzyme and for some electronic factors (inductive effect).

Polymerization of Optically Active Monomers

The newly synthesized acrylate monomers were polymerized by free radical initiation technique and their optical rotation was measured (Table 7). As expected,

the polymerization was smooth and the specific rotation obtained for the polymer was slightly less than their corresponding acrylate monomers.

CONCLUSION

The results showed that the lipase catalyzed transesterification of secondary alcohols with 2,3-butanedione monoxime acrylate in diisopropyl ether solvent is the fastest among the reactions reported until now. The rate of transesterification reaction increases with the hydrophobicity of the solvent. The enantioselectivity of oxime ester is same as that of the trihaloethyl ester. However, using oxime esters as acrylating agents the conversions are much better. The importance of this work lies in its application to resolve hindered secondary alcohols where other acrylating agents are ineffective.

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