Asymmetric Reactions. III. The Asymmetric Synthesis of Methyl 2-Phenylpropionate in the Presence of Chiral Polymers

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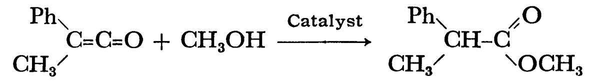
The asymmetric addition of methanol to phenylmethylketene was carried out in the presence of a chiral polymer obtained by the co-polymerization of *N*-benzyl-2-pyrrolidinylmethyl acrylate with methyl acrylate. The products obtained for the above co-polymer showed a correlation between log k_R/k_S and $1/T$ deviating from linearity, while those for poly(*N*-benzyl-2-pyrrolidinylmethyl acrylate) exhibited a linear relationship. *N*-Benzyl-2-pyrrolidinylmethyl butyrate, hexanoate, and stearate were also used as catalysts; they showed asymmetric efficiencies intermediate between those of *N*-benzyl-2-pyrrolidinylmethyl propionate and poly(*N*-benzyl-2-pyrrolidinylmethyl acrylate). The use of several high- and low-molecular-weight catalysts derived from cinchonine was similarly attempted in order to examine the polymer effect with regard to the stereoselectivity.

Several chiral polymers[1-2] derived from optically active amino alcohols have been used for the study of polymer effects in the asymmetric addition of methanol to phenylmethylketene (PMK):



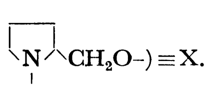
$$\mathrm{Ph(CH_3)C{=}C{=}O + CH_3OH \xrightarrow{Catalyst} Ph(CH_3)CH{-}C({=}O)OCH_3}$$

In previous papers,[1-2] poly(*N*-benzyl-2-pyrrolidinylmethylacrylate (PA) yielded optically rotational products with a sign opposite to that of products for its corresponding monomeric model compound (*N*-benzyl-2-pyrrolidinylmethyl propionate; A1).

The products obtained for PA showed a linear correlation between log k_R/k_S and $1/T$, while those for A1 exhibited only a non-linear relationship. (k_R and k_S: the rate constants for the *R* and *S*-isomers respectively).

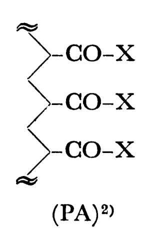
The results obtained with PA were interpreted in terms of the effect of molecular immobility;[2-3] the steric bulkiness of the back-bone of the polymer increases the degree of conformational rigidity of the molecules in the side chain.

In the present work, several *N*-benzyl-2-pyrrolidinylmethanol derivatives were used to clarify these observations more precisely.

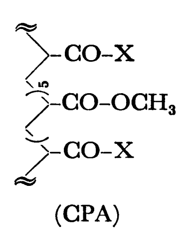


$\mathrm{CH_3(CH_2)_n{-}CO{-}X}$

A1[2]	$n = 1$
A2	$n = 2$
A3	$n = 4$
A4	$n = 16$



(PA)[2]



(CPA)

The asymmetric addition of methanol to PMK was carried out in a manner similar to that reported earlier.[1-2]

Figure 1 shows the log k_R/k_S–$1/T$ relation of the addition products obtained for the above catalysts.

A soluble co-polymer (CPA) was obtained by the co-polymerization of one molar equivalent amount of *N*-benzyl-2-pyrrolidinylmethyl acrylate with five molar equivalent amounts of methyl acrylate. The products from CPA reveal a relationship deviating somewhat from linearity (see Fig. 1). CPA decreases the degree of conformational rigidity of the molecules in the side chain in comparison with PA. The optically active molecules (X) of CPA are more mobile than those of PA because of the larger distance among the chiral pendants (X) of CPA.

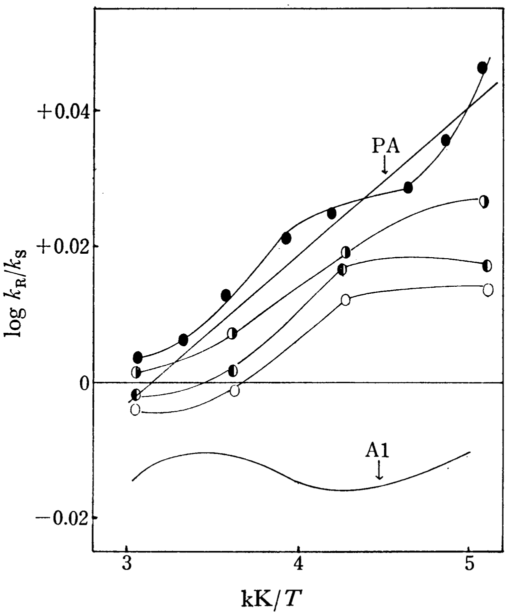


Fig. 1. Plots of log k_R/k_S against $1/T$ in case of A2 (○), A3 (◐), A4 (◑) and CPA (●).

A2, A3, and A4 were derived through the reaction of *N*-benzyl-2-pyrrolidinylmethanol with butyryl, hexanoyl, and stearoyl chloride respectively.

Figure 1 shows that the action of low-molecular-weight catalysts gradually became similar to that of polymeric catalysts with the increase in the length of the carbon chain in the acyl group.

Figure 2 indicates the plots of the optical yields of the addition products obtained for the *N*-benzyl-2-pyrrolidinylmethanol catalysts at −78 °C.

A1 gave a product with an excess of *S*-enantiomer in a 1% optical yield, and CPA yielded a product with an excess of *R*-enantiomer in the highest optical yield (5.3%).

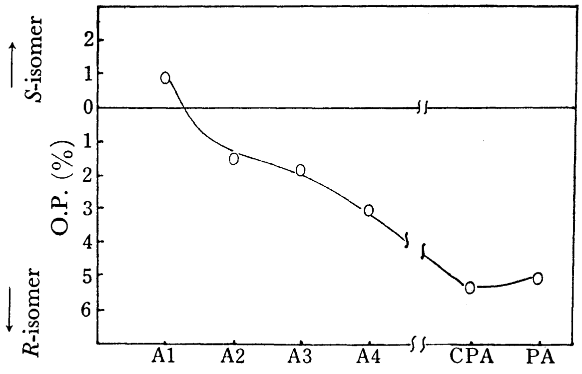
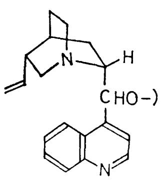
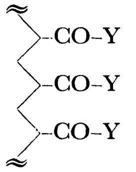


Fig. 2. The optical purities (O.P.) of the esters obtained with N-benzyl-2-pyrrolidinylmethanol catalysts at −78 °C.

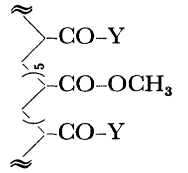
Let us also describe the use of several cinchonine catalysts in order to examine this sort of polymer effect more clearly.



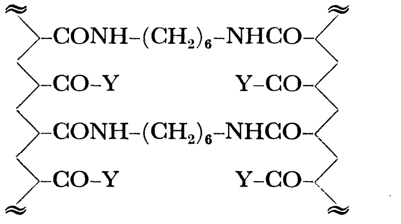
$CH_3(CH_2)_n$-CO-Y B1,2) $n=0$
B2,2) $n=1$
B3, $n=2$
B4, $n=4$
B5, $n=16$



(PB)2)



(CPB-1)



(CPB-2)2)

B3, B4, and B5 were obtained by the reaction of cinchonine with butyryl, hexanoyl, and stearoyl chloride respectively. CPB-1 (soluble co-polymer) was derived through the co-polymerization of one molar equivalent amount of o-acryloylcinchonine2) with five molar equivalent amounts of methyl acrylate. PB and CPB-2 were prepared according to the method reported previously.2)

Figure 3 shows plots of log k_R/k_S against $1/T$ in the case of the above cinchonine catalysts.

Figure 3 shows that low-molecular-weight catalysts (B3, B4, and B5) gave the addition products of an R-configuration predominantly at higher reaction temperatures, and yielded the products of an S-configuration preferentially at lower temperatures. Figure 3 also indicates that polymeric catalysts (CPB-1, PB and CPB-2) provided the addition products of an S-configuration preferably in the present range of reaction temperatures (−78 °C—+50 °C). CPB-2, in which the mobility of the chiral pendants (Y) is most strongly restricted by the cross-linking of the polymer, yielded addition products showing linear plots between log k_R/k_S and $1/T$.

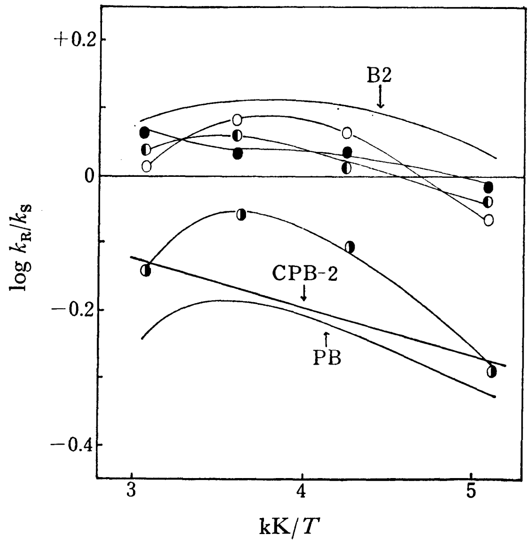


Fig. 3. Plots of log k_R/k_S against $1/T$ in case of B3 (●), B4 (◐), B5 (○) and CPB-1 (◑).

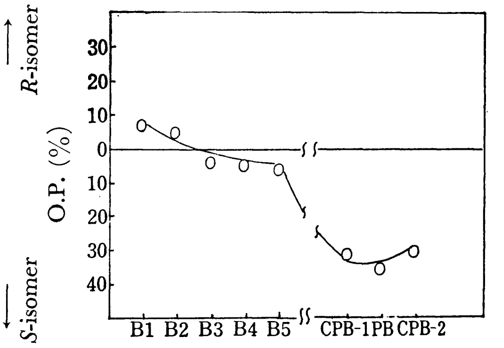


Fig. 4. The optical purities (O.P.) of the esters obtained with cinchonine catalysts at −78 °C.

Figure 4 shows the plots of the optical yields of the addition products given for cinchonine catalysts at −78 °C.

The preferable configuration of the addition products obtained for low-molecular-weight catalysts changed from R to S with an increase in the length of the carbon chain in the acyl group. Polymeric catalysts gave the addition products of an S-configuration predominantly; the maximum optical yield (35%) of the addition product was given in the case of PB.

Figures 3 and 4 reveal that cinchonine catalysts gave results similar to those obtained for N-benzyl-2-pyrrolidinylmethanol catalysts.

Experimental

N-*Benzyl-2-pyrrolidinylmethyl Butyrate (A2).* A solution of *N*-benzyl-2-pyrrolidinylmethanol (1 g), butyryl chloride (0.55 g), and triethylamine (0.53 g) in dry dichloromethane (100 ml) was stirred at room temperature. After 24 h, the solution was poured into water (100 ml). The organic layer thus separated out was washed with saturated sodium hydrogencarbonate and water, and dried over anhydrous sodium sulfate. After the removal of the solvent, the residue was distilled to give a colorless oil. Yield, 70%. Bp 180—190 °C at 2 mmHg. $[\alpha]_D^{20}=-28°$ (*c* 1.4, benzene). Found: C, 73.18; H, 8.92; N, 4.99%. Calcd for $C_{16}H_{23}NO_2$; C, 73.56; H, 8.81; N, 5.36%.

N-*Benzyl-2-pyrrolidinylmethyl Hexanoate (A3).* Yield, 80%. Bp 180—190 °C at 1 mmHg. $[\alpha]_D^{20}=-26°$ (*c* 1, benzene). Found: C, 74.81; H, 9.44; N, 4.61%. Calcd for $C_{18}H_{27}NO_2$: C, 74.74; H, 9.34; N, 4.84%.

N-*Benzyl-2-pyrrolidinylmethyl Stearate (A4).* Yield, 70%. Mp 43—45 °C. $[\alpha]_D^{15}=-19°$ (*c* 1.6, benzene). Found: C, 78.71; H, 11.50; N, 2.74%. Calcd for $C_{30}H_{51}NO_2$: C, 78.77; H, 11.15; N, 3.06%.

o-*Stearoylcinchonine (B5).* A solution of cinchonine (1.5 g), stearoyl chloride (1.6 g), and triethylamine (0.8 g) in dry benzene (100 ml) was stirred under refluxing. After 20 h, the solution was cooled to room temperature and poured into water (100 ml). The organic layer thus separated out was washed with saturated sodium hydrogencarbonate and water, and then dried over anhydrous sodium sulfate.

After the removal of the solvent, the residue was recrystallized from ether. Yield, 71%. Mp 37 °C. $[\alpha]_D^{20}=+57°$ (*c* 2, chloroform). Found: C, 79.13; H, 10.23; N, 4.83%. Calcd for $C_{37}H_{56}N_2O_2$: C, 79.28; H, 10.00; N, 5.00%.

o-Butyrylcinchonine (B3) was similarly obtained as an oily material in a 79% yield. $[\alpha]_D^{20}=+97°$ (*c* 2, chloroform).

o-Hexanoylcinchonine (B4) was also given as a syrup in a 76% yield. $[\alpha]_D^{20}=+87°$ (*c* 2, chloroform).

The TLC of B3 (B4) gave only one spot for several solvent systems and showed it to be a single material.

*Poly(*N*-benzyl-2-pyrrolidinylmethyl acrylate-methyl acrylate) (CPA).* A mixture of *N*-benzyl-2-pyrrolidinylmethyl acrylate (0.588 g) and methyl acrylate (1.03 g) containing azobisisobutyronitrile (10 mg) was polymerized without any solvents in a sealed tube at 80 °C for 24 h, and then cooled to room temperature. The product was dissolved in a small amount of dry benzene and then poured into ether. A sticky precipitate was given in an 85% yield. $[\alpha]_D^{12}=-9.7°$ (*c* 1, benzene). Mol wt 4840 (benzene).

*Poly(*o*-acryloylcinchonine-methyl acrylate) (CPB-1).* A solution of *o*-acryloylcinchonine[2] (1 g), methyl acrylate (1.2 g), and azobisisobutyronitrile (10 mg) in dry benzene (10 ml) was refluxed with stirring in an argon atmosphere. After 20 h, the solution was cooled to room temperature and poured into ether. A precipitate (CPB-1) was filtered off and washed thoroughly with ether. Yield, 70%. $[\alpha]_D^{20}=+38°$ (*c* 2, chloroform). Mol wt 12500 (dichloromethane).

The Addition of Methanol to PMK. Freshly distilled PMK (330 mg) and CPA (17 mg) were added to 25 ml of dry toluene at −78 °C in an argon atmosphere. After the addition of methanol (82 mg), the mixture was stirred at the same temperature. After 10 h, the end point of the reaction was confirmed by the absence of the yellow color of PMK. The toluene solution was then poured into dilute hydrochloric acid and filtered off. The organic layer thus separated out was washed with saturated sodium hydrogencarbonate and water, and dried over anhydrous sodium sulfate. After the removal of the solvent, the residue was distilled to give an oil in an 80% yield. $[\alpha]_D^{20}=-5.8°$ (*c* 10, toluene).

The TLC and GLC of the product showed it to be a single material. The IR and NMR spectra of the product were completely in agreement with those of authentic methyl-2-phenylpropionate. The use of other basic catalysts was similarly attempted at various reaction temperatures.

In those experiments, a Jasco IRA-1 (IR) apparatus, a JEOL-60 MC (NMR) apparatus, a Varian M920 (GLC) apparatus, a Rex-automatic polarimeter (optical rotation; 10-cm cell), and a Knauer vapor-pressure osmometer (molecular weight) were used for the measurement of the samples.

References

1) T. Yamashita, H. Yasueda, and N. Nakamura, *Chem. Lett.*, **1974**, 585.

2) T. Yamashita, H. Yasueda, Y. Miyauchi, and N. Nakamura, *Bull. Chem. Soc. Jpn.*, **50**, 1532 (1977).

3) a) H. Pracejus and G. Kohl, *Ann. Chem.*, **722**, 1 (1969). b) H. Pracejus and H. Matje, *J. Prakt. Chem.*, **24**, 195 (1964).