Asymmetric Reactions. II. Asymmetric Synthesis of Methyl α-Phenylpropionate by Means of Chiral Polymers

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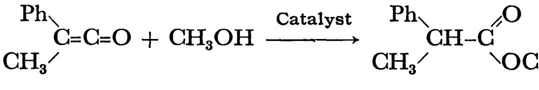
The asymmetric addition of methanol to phenylmethylketene was carried out in the presence of propionylcinchonine and poly(acryloylcinchonine). The use of poly(acryloylcinchonine) produced additional products with higher optical yields than that of propionylcinchonine. The highest optical yield (35%) was obtained with the above polymeric catalyst at −78 °C. An insoluble, cross-linked polymer obtained by the co-polymerization of acryloylcinchonine with *N*,*N'*-diacryloylhexamethylenediamine, was also used as a catalyst. The products obtained for the cross-linked polymer showed a linear correlation between log k_R/k_S and $1/T$ while those with non-cross-linked poly(acryloylcinchonine) exhibited a relationship deviating somewhat from linearity. A linear relationship was also observed using insoluble, cross-linked poly(acryloylquinine).

The use of chiral synthetic polymers for asymmetric synthesis has been attempted by several workers[1–8] because of the interest in the study of asymmetric reactions, new catalysts, enzyme models, and polymer effects.

In a previous paper,[1] the asymmetric addition of methanol to phenylmethylketene (PMK) was examined in the presence of optically-active polymers and their corresponding monomeric model compounds.



$$\mathrm{\overset{Ph}{\underset{CH_3}{>}}C{=}C{=}O + CH_3OH \xrightarrow{Catalyst} \overset{Ph}{\underset{CH_3}{>}}CH{-}C\overset{\displaystyle /\!/O}{\underset{\displaystyle \backslash OCH_3}{}}}$$

A distinct polymer effect with regard to stereoselectivity was observed with poly(*N*-benzyl-2-pyrrolidinylmethyl acrylate) (**P-1**) and poly(acryloylquinine) (**P-2**).

Figure 1 indicates the result of the addition reaction obtained with **P-1** and *N*-benzyl-2-pyrrolidinylmethyl propionate in plots of log k_R/k_S against $1/T$ [$k_R(k_S)$: the rate constant for the *R*(*S*)-isomer]. The addition products with **P-1** showed a linear relationship between log k_R/k_S and $1/T$.

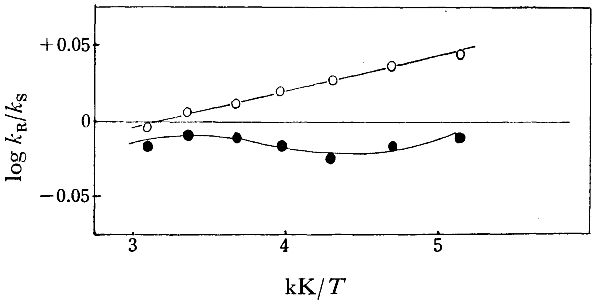


Fig. 1. Plots of log k_R/k_S against $1/T$ in case of **P-1** (—○) and *N*-benzyl-2-pyrrolidinylmethyl propionate (—●).

Pracejus and his co-workers[9] have previously reported that a linear correlation between log k_R/k_S and $1/T$ was observed with α-isocinchonine[9c] (**B**) (a cyclic ether derived from cinchonine) rather than with acetylcinchonine[9b] (**A-1**) (see Fig. 2).

Pracejus *et al.* explained their results using the effect of molecular immobility. Rotation about the carbon-carbon bond (C_8–C_9) of **B** is strongly restricted, and the conformation of **B** is more rigid than that of **A-1**.

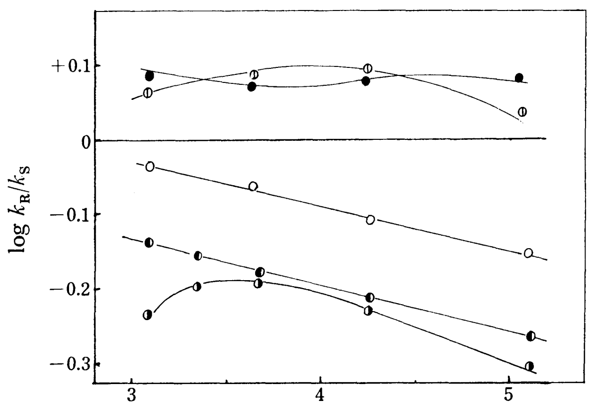
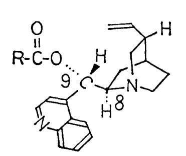
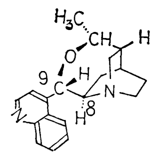


Fig. 2. Plots of log k_R/k_S against $1/T$ in case of cinchonine catalysts
A-1 —●, **A-2** —⦶, **B** —○, **P-3** —◑, **P-4** —◐.



Acylcinchonine (**A**)
A-1, CH_3
A-2, CH_2CH_3
A-3, $CH{=}CH_2$



α-Isocinchonine (**B**)

The results obtained with **P-1** are interpreted on the basis of the concept of Pracejus *et al.* The steric bulkiness of the back-bone of the polymer restricts the mobility of the side chain and increases the degree of conformational rigidity of the molecules in the side chain.

In the present work, this sort of polymer effect was examined in detail with cinchonine and quinine derivatives as catalysts. The reactions of cinchonine with acetic anhydride, propionic anhydride and acryloyl chloride was carried out in the presence of triethylamine producing **A-1**, **A-2**, and **A-3**, respectively.

Acryloylcinchonine (**A-3**) was polymerized using azobisisobutyronitrile as an initiator in dry benzene under reflux giving a polymer (**P-3**) soluble in common organic solvents.

An insoluble, cross-linked polymer (**P-4**) was obtained by the co-polymerization of **A-3** with *N*,*N*′-diacryloylhexamethylenediamine.[10] Acryloylquinine[1] was similarly co-polymerized with *N*, *N*′-diacryloylhexamethylenediamine and *N*,*N*′-diacryloyldodecamethylenediamine to give **P-5** and **P-6**, respectively. These insoluble, polymeric catalysts were easily separated from the reaction mixture by filtration.

The asymmetric addition of methanol to PMK was carried out with the above catalysts in a manner similar to that reported earlier.[1] To one equivalent amount of PMK and a small excess of methanol was added a 0.01 molar equivalent of the catalyst.

The molar equivalent amount of the polymeric catalyst was calculated on the basis of that of the monomer used in the polymerization (*e.g.*, 10 mg of **P-3** corresponds to 10 mg of **A-3**).

Table 1. The specific rotations, optical yields and configurations of the addition products

Catalyst	*T* (°C)						Conf[b)]
	−78		0		+50		
	$[\alpha]_D$	O.Y.[a)]	$[\alpha]_D$	O.Y.	$[\alpha]_D$	O.Y.	
A-2	−4.8	4.4	−10.5	9.6	−8.9	8.2	*R*
P-3	+38.1	35.0	+23.6	21.7	+29.6	27.2	*S*
P-4	+33.1	30.4	+23.3	21.4	+17.5	16.1	*S*
P-5	−16.2	14.9	−11.4	10.5	−8.4	7.7	*R*
P-6	−12.9	11.8	−11.3	10.4	−10.1	9.3	*R*

a) The O.Y. (optical yield, %) was calculated from the specific rotation of the product and that of optically pure methyl α-phenylpropionate[9a)] (*S*-form, $[\alpha]_D^{22}=+109°$, *c* 6.2, toluene). b) Configuration of the predominant isomer.

Table 1 gives the specific rotations, optical yields and configurations of the addition products obtained with cinchonine and quinine catalysts at −78, 0 and +50 °C.

Figure 2 shows the log (k_R/k_S) *vs.* $1/T$ relation of the addition products obtained for the cinchonine catalysts (**A-2**, **P-3**, and **P-4**).

The products for **P-4** (cross-linked) showed a linear relationship between log k_R/k_S and $1/T$ while those with **P-3** (non-cross-linked) showed a relation deviating from linearity.

In Figure 3 are shown plots of log k_R/k_S against $1/T$ in the case of the quinine catalysts (**P-2**, **P-5**, and **P-6**).

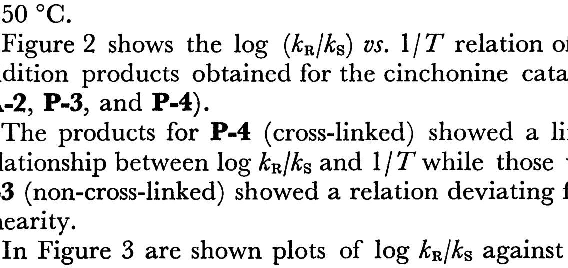


Fig. 3. Plots of log k_R/k_S against $1/T$ in case of **P-2** (—◐), **P-5** (—○), **P-6** (—●).

The products for the cross-linked polymer (**P-5** and **P-6**) showed a linear correlation between log k_R/k_S and $1/T$.

Figures 2 and 3 suggest that the cross-linking of polymers, which further restricts the mobility of the side chain, resulted in the linear relationship for the addition products of the cinchonine and quinine catalysts.

Experimental

Propionylcinchonine (A-2). A solution of cinchonine (1.5 g), propionic anhydride (0.7 g) and triethylamine (0.8 g) in dry benzene (100 ml) was stirred under refluxing. After 4 h, the solution was cooled to room temperature, and poured into water (100 ml). The organic layer separated out was washed with saturated sodium hydrogencarbonate and water, and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was recrystallized from ether. Yield, 90%. Mp 46 °C. $[\alpha]_D^{20}=+101$ ° (*c* 2, chloroform). Found: C, 75.60; H, 7.50; N, 8.15%. Calcd for $C_{22}H_{26}O_2N_2$: C, 75.42; H, 7.42; N, 8.00%. IR (cm^{-1}): 1720, 1180: NMR (ppm): 1.1, 2.4 (propionyl group proton), 5.5—6.5 (olefinic proton), 7.5, 8.1, 8.8 (quinoline ring proton).

Acryloylcinchonine (A-3). To a solution of cinchonine (3 g) and triethylamine (1.5 g) in dichloromethane (100 ml) a solution of freshly distilled acryloyl chloride (1.3 g) in dichloromethane (50 ml) at −20 °C was dropwise added with stirring. After standing overnight, the reaction mixture was poured into water (200 ml). The organic layer separated out was washed with saturated sodium hydrogencarbonate and water, and dried over anhydrous sodium sulfate.

The solution was concentrated, and subjected to chromatography on alumina (2×30 cm, 200 mesh, neutral). Elution with ethyl acetate gave **A-3** as a clear oil in a 94% yield. $[\alpha]_D^{20}=+80$ ° (*c* 2, chloroform). TLC of **A-3** gave only one spot for several solvent systems. IR (cm^{-1}): 1720, 1180, 990. NMR (ppm): 5.6—6.5 (olefinic proton), 7.5, 8.1, 8.8 (quinoline ring proton).

Poly(acryloylcinchonine) (P-3). A solution of **A-3** (1 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 (**P-3**) was filtered off and washed thoroughly with ether. Yield, 74%. $[\alpha]_D^{20}=+50$ ° (*c* 1, chloroform). Mol wt 13000 (dichloromethane).

Acryloylquinine[1] was similarly polymerized to give **P-2.**[1] Yield, 56%. $[\alpha]_D^{20}=-14$ ° (*c* 1, chloroform). Mol wt 14000 (dichloromethane).

Cross-linking Agents. 1) *N*,*N*′-diacryloylhexamethylenediamaine (**CA-1**) was prepared by the reaction of hexamethylenediamine with acryloyl chloride according to the method reported previously.[10] Mp 147 °C. Found: C, 64.45; H, 9.00; N, 12.11%. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.28; H, 8.92; N, 12.50%. IR (cm^{-1}): 3300, 1660, 1610. NMR (ppm): 5.5—6.5 (olefinic proton). 2) *N*,*N*′-Diacryloyldodecamethylenediamine (**CA-2**) was obtained similarly by the reaction of dodecamethylenediamine with acryloyl chloride. Mp 123—125 °C. Found: C, 69.90; H, 10.50; N, 8.70%. Calcd for $C_{18}H_{32}N_2O_2$: C, 70.12; H, 10.38; N, 9.09%. IR (cm^{-1}): 3300, 1665. NMR (ppm): 5.6—6.6 (olefinic proton).

Co-polymers. A solution of **A-3** (700 mg), **CA-1** (224 mg) and azobisisobutyronitrile (10 mg) in dry benzene (10 ml) was refluxed with stirring in an argon atmosphere. After 40 h, a white precipitate was filtered off and washed thoroughly with acetone, benzene, chloroform, ethanol and ethyl acetate, successively. An insoluble polymer (**P-4**) was obtained in an 80% yield. Acryloylquinine was similarly co-polymerized with **CA-1** (**CA-2**) to give **P-5** (**P-6**) in an 80—90% yield.

*Poly(*N*-benzyl-2-pyrrolidinylmethyl acrylate) (**P-1**).* *N*-Benzyl-2-pyrrolidinylmethyl acrylate[1] (2.1 g) containing azobisisobutylronitrile (21 mg) was polymerized without solvents in a sealed tube at 80 °C for 70 h and cooled to room temperature. The product was dissolved in benzene and the solution was poured into methanol. A yellow precipitate was filtered off and washed with methanol. Yield, 50%. $[\alpha]_{\rm D}^{15}=-43$ ° (*c* 1.6, benzene). Mol wt 5300 (dichloromethane).

The polymerization of *N*-benzyl-2-pyrrolidinylmethyl acrylate was not successful under the conditions described for the cases of **P-2** and **P-3**.

The co-polymerization of *N*-benzyl-2-pyrrolidinylmethyl acrylate with **CA-1** and **CA-2** was also unsuccessful and gave only polymers of **CA-1** and **CA-2**. The *N*-benzyl-2-pyrrolidinylmethyl acrylate was largely recovered. The shapes of the ORD and CD curves for **P-1** were similar to those of *N*-benzyl-2-pyrrolidinylmethyl propionate. The hydrolyzed **P-1** showed no optical activity.

These facts suggest that there was no occurrence of asymmetric induction to the main chain configuration of **P-1**.

Similar results[11] were also observed for **P-2**[11a] and **P-3**.

The Addition Reaction of Methanol with PMK. (A) Freshly distilled PMK (330 mg) and **P-5** (11 mg) were added to 25 ml of dry toluene at −78 °C in an argon atmosphere. After addition of methanol (82 mg), the mixture was stirred at the same temperature for 20 h. The end point of the reaction was confirmed by the absence of the yellow color of PMK. After the removsl of **P-5** by filtration, the toluene solution was washed with saturated sodium hydrogencarbonate and water, and dried over anhydrous sodium sulfate. The solution was evaporated to dryness under reduced pressure. The residue was distilled to give a colorless oil in a 70% yield. Bp 69—71 °C at 2 mmHg. $[\alpha]_{\rm D}^{20}=-16.2$ ° (*c* 10, toluene).

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 α-phenylpropionate. The addition of methanol to PMK was carried out similarly in the presence of other insoluble catalysts (**P-4** and **P-6**) at various reaction temperatures.

(B) Freshly distilled PMK (330 mg) and **A-2** (8 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 for 10 h. The toluene solution was poured into dilute hydrochloric acid. The organic layer separated out was washed with saturated sodium hydrogencarbonate, water, and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was distilled to give an oil in a 72% yield. $[\alpha]_{\rm D}^{20}=-4.8$ ° (*c* 10, toluene).

The structure of this oil was confirmed in the manner described in (A).

The use of other soluble catalysts was similarly attempted at various reaction temperatures.

For the measurement of the samples, a Jasco IRA-1 (IR), a Jeol-60 MC (NMR), a Varian M920 (GLC), a Jasco J-20(ORD,CD), a Rex-automatic polarimeter (specific rotation, length of sample: 10 cm) and a Knauer vapor-pressure osmometer (molecular weight) were used in this experiment.

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