Evans, *Chemtech*, 560 (1973); J. Manassen in "Catalysis Progress in Research", F. Basolo and R. L. Burwell, Jr., Ed., Plenum Press, New York, N.Y., 1973, p 117; J. C. Bailar, *Catal. Rev.*, **10**, 17 (1974); Z. M. Michalska and D. E. Webster, *Platinum Met. Rev.*, **18**, 65 (1974); C. Leznoff, *Chem. Soc. Rev.*, **3**, 65 (1974); E. Cernia and M. Graziani, *J. Appl. Polym. Sci.*, **18**, 2725 (1974); Z. M. Michalska and D. E. Webster, *Chemtech*, 117 (1975); J. Manassen in "Catalysis, Heterogeneous and Homogeneous", B. Delmon and G. Jannes, Ed., American Elsevier, New York, N.Y., 1975, p 293; G. Jannes, *ibid.*, p 83; S. L. Davydova and N. A. Plate, *Coord. Chem. Rev.*, **16**, 195 (1975).

(11) J. Manassen, *Isr. J. Chem. Suppl. Proc. Isr. Chem. Soc.*, **8**, 5p (1970); J. Manassen, *Platinum Met. Rev.*, **15**, 142 (1971).

(12) R. H. Grubbs, C. Gibbons, L. C. Kroll, W. D. Bonds, Jr., and C. H. Brubaker, Jr., *J. Am. Chem. Soc.*, **95**, 2373 (1973); W. D. Bonds, Jr., C. H. Brubaker, Jr., E. S. Chandrasekaran, C. Gibbons, R. H. Grubbs, and L. C. Kroll, *ibid.*, **97**, 2128 (1975).

(13) H. Bruner and J. C. Bailar, Jr., *Inorg. Chem.*, **12**, 1465 (1973).

(14) R. G. Muratova, R. Z. Khairullina, S. V. Shulyndin, B. E. Ivanov, and R. I. Ismailov, *Kinet. Katal.*, **15**, 137 (1974); *Kinet. Catal. (Engl. Transl.)*, **15**, 115 (1974).

(15) R. H. Grubbs, L. C. Kroll, and E. M. Sweet, *J. Macromol. Sci., Chem.*, **7**, 1047 (1973).

(16) K. Kaneda, M. Terasawa, T. Imanaka, and S. Teranishi, *Chem. Lett.*, 1005 (1975); K. Kaneda, T. Uchiyama, M. Terasawa, T. Imanaka, and S. Teranishi,

ibid., 449 (1976).

(17) R. H. Grubbs, and L. C. Kroll, *J. Am. Chem. Soc.*, **93**, 3062 (1971).

(18) M. Capka, P. Svoboda, M. Cerny, and J. Hetflejs, *Tetrahedron Lett.*, 4787 (1971).

(19) W. Dumont, J. C. Poulin, T. P. Dang, and H. B. Kagan, *J. Am. Chem. Soc.*, **95**, 8295 (1973).

(20) G. Strukul, M. Bonivento, M. Graziani, E. Cernia, and N. Palladino, *Inorg. Chim. Acta*, **12**, 15 (1975).

(21) E. Bayer and V. Schurig, *Chemtech*, 212 (1976).

(22) B. Bodganovic, *Angew. Chem.*, **85**, 1018 (1973); *Angew. Chem., Int. Ed. Engl.*, **12**, 954 (1973).

(23) J. D. Morrison, W. F. Massler, and M. K. Neuberg, *Adv. Catal.*, **25**, 81 (1976).

(24) W. J. Dale, L. Starr, and C. W. Strobel, *J. Org. Chem.*, **26**, 2225 (1961).

(25) H. B. Kagan and T. P. Dang, *J. Am. Chem. Soc.*, **94**, 6429 (1972).

(26) S. M. Birnbaum, L. Levintow, R. B. Kingsley, and J. P. Greenstein, *J. Biol. Chem.*, **194**, 455 (1952).

(27) S. P. Bakshi and E. E. Turner, *J. Chem. Soc.*, 171 (1961).

(28) P. W. Feit, *J. Med. Chem.*, **7**, 14 (1964).

(29) K. Issleib and D. W. Muller, *Chem. Ber.*, **92**, 3175 (1959).

(30) R. M. Herbst and D. Shemin, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 1.

(31) H. S. Raper, *J. Chem. Soc.*, **123**, 2557 (1923).

(32) R. Cramer, *Inorg. Chem.*, **1**, 722 (1962).

Transition Metal Catalyzed Asymmetric Organic Syntheses via Polymer-Attached Optically Active Phosphine Ligands. Synthesis of *R* Amino Acids by Hydrogenation with a Polymer Catalyst Containing Optically Active Alcohol Sites

T. Masuda and J. K. Stille*[1]

Contribution from the Department of Chemistry, University of Iowa, Iowa City, Iowa 52242. Received June 13, 1977

Abstract: The radical copolymerization of methyl vinyl ketone, 2-*p*-styryl-4,5-bis(tosyloxymethyl)-1,3-dioxolane (4), and *p*-divinylbenzene (2%) gave cross-linked resins (5) containing 9:1 and 14:1 ratios of methyl vinyl ketone to 4 in the polymer. Asymmetric reduction (hydrosilylation) of the ketone groups in 5 with catalysts (3) formed from the reaction of μ-dichloro-tetraethylenedirhodium(I) and both (+)- and (−)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP) gave a polymer (6) bearing either *S* or *R* secondary alcohol groups, respectively. The reaction of 6 with sodium diphenylphosphide afforded a polymer (7) containing the (−)-2,3-*O*-benzal-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane ligand and either *R* or *S* pendent alcohol functions. Exchange of Rh(I) onto the polymer-attached ligand provided a catalyst that hydrogenated α-acetamidoacrylic acid, α-acetamidocinnamic acids, and atropic acid in alcohol (solvent) to the corresponding *R* amino acids or hydratropic acid of the same absolute configuration and the same optical yield as can be obtained with the analogous homogeneous catalyst, DIOP-Rh(I). Hydrogenations of α-acetamidoacrylic acid in tetrahydrofuran, however, gave widely different optical yields of amino acid, depending on the configuration of the pendent alcohol group, suggesting that the alcohol plays a role in the transition state leading to the generation of the asymmetric center. The catalyst can be removed by filtration and reused with no loss of optical purity in the product on subsequent hydrogenations.

Introduction

In the previous paper,[2] we described the syntheses of a polar cross-linked polymer containing an optically active 4,5-bis-(diphenylphosphinomethyl)-1,3-dioxolane ligand, on which rhodium(I) was exchanged. This catalyst hydrogenated α-*N*-acylaminoacrylic acid to the corresponding amino acid derivatives having the same optical yields and absolute configurations as could be obtained with the homogeneous catalyst analogue, chloro[2,3-*o*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane]rhodium(I), Cl(DIOP)Rh(I). The advantage of the cross-linked polymer-attached catalyst over the homogeneous Cl(DIOP)Rh(I) catalyst is that it can be removed from the reaction by filtration and reused. A necessary requirement of such a catalyst for the hydrogenation of α-*N*-acylaminoacrylic acid, however, is that the polymer swells in the polar solvents required for dissolution of the substrates, thereby allowing access to the catalyst sites.

The ability of this polar polymer to swell in alcohol was achieved by the introduction of hydroxyethyl methacrylate units in the main chain. These units have the disadvantage, however, that they could be expected to undergo hydrolysis and alcoholysis on continued use. It was of interest, therefore, to introduce more stable, polar units into the polymer backbone of a DIOP-bearing polymer. Thus, the copolymerization of 2-*p*-styryl-4,5-bis(tosyloxymethyl)-1,3-dioxolane (4) with methyl vinyl ketone was of interest for a number of reasons. The polar character of the resulting copolymer could be expected to provide a suitable catalyst matrix for the hydrogenation of α-*N*-acylaminoacrylic acids. The ketone function could be reduced to a secondary alcohol, another suitably polar group, and under the appropriate conditions could be asymmetrically reduced to an alcohol of either configuration. Both ketone and secondary alcohol groups would be relatively stable under the reaction conditions.

© 1978 American Chemical Society

The role of polymer in providing "cooperative effects" in enzymes and in certain other polymer-attached reagents is well documented,[3] but similar observations in polymer-bound transition metal catalysts have not been reported. The introduction into the polymer matrix of a second optically active site that does not directly participate in the asymmetric hydrogenation is of interest because it allows the observation of the effect of polymer environment on asymmetric synthesis. It has been demonstrated[4] that solvent is involved in the transition state leading to the generation of the asymmetric center in the reduction of N-acyl-α-aminostyrene with the Cl(DIOP)Rh(I) catalyst. Changing the solvent from ethanol to benzene not only affects the rates and optical yields, but most remarkably results in reversal in the absolute configuration of the product. The polar environment on the polymer surrounding the catalyst, especially an asymmetric polar environment, could be expected to have an effect on the optical yield. An asymmetric synergism from these ancillary polymer-bound groups could give the polymeric catalyst an important optical yield advantage over the homogeneous species.

Results and Discussion

To ascertain the optimum conditions for the asymmetric reduction of the carbonyl group in a copolymer of 2-p-styryl-4,5-bis(tosyloxymethyl)-1,3-dioxolane (4) and methyl vinyl ketone, the homogeneous asymmetric reduction of poly(methyl vinyl ketone) was evaluated. The reaction of ketones with alkyl- or arylsilanes to yield a silyl ether is catalyzed by Wilkinson's catalysts under mild conditions,[5] and decomposition of the hydrosilylation product yields an alcohol. When the rhodium catalyst contains optically active phosphines, optically active alcohols can be obtained; with catalysts bearing the DIOP ligand optical yields as high as 60–80% can be achieved.[6]

Asymmetric Reduction of Poly(methyl vinyl ketone). The hydrosilylation of atactic poly(methyl vinyl ketone) (1) with diphenylsilane and α-naphthylphenylsilane in the presence of a catalyst (3) prepared in situ from μ-dichloro-tetraethylenedirhodium(I) and (−)-DIOP, followed by hydrolysis, gave the optically active poly(3-buten-1-ol) (2). Whereas 1 swells, but is insoluble in ethanol, 2 is soluble. Higher optical yields
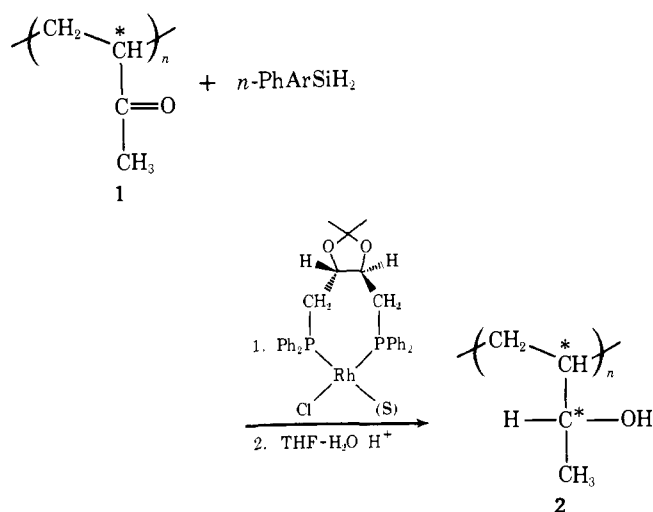
were obtained at lower reaction temperatures and in tetrahydrofuran rather than dioxane (Table I). α-Naphthylphenylsilane gave higher optical yields than diphenylsilane, although longer reaction times were necessary with α-naphthylphenylsilane.

The optical purity of the product could not be determined by use of chiral shift reagents since solvents for the polymer were not suitable solvents for utilization of the reagent. (−)-DIOP should produce the R alcohol,[8] however, so that selection

Table I. Asymmetric Reduction of Poly(methyl vinyl ketone) via Hydrosilylation[a]

Silane	Solvent	Temp, °C	Time, h	% convn[c]	$[\alpha]_D$[d]
Ph$_2$SiH$_2$[b]	Dioxane	50	48	61.5	+31.3
Ph$_2$SiH$_2$	Dioxane	50	48	94	+29.8
Ph$_2$SiH$_2$	Dioxane	25	48	96.5	+39.4
Ph$_2$SiH$_2$	THF	25	48	92	+47.4
Ph$_2$SiH$_2$	THF	0	120	81.5	+59.0
(C$_{10}$H$_7$)PhSiH$_2$	Dioxane	25	48	82.5	+44.9
(C$_{10}$H$_7$)PhSiH$_2$	Dioxane	25	120	97	+49.0
(C$_{10}$H$_7$)PhSiH$_2$	THF	25	120	88	+68.1

[a] Catalyst $\frac{1}{2}$Rh$_2$(C$_2$H$_4$)$_4$Cl$_2$; (−)-DIOP. Ketone/Rh = 100, silane/ketone = 1.02. [b] Ketone/Rh = 40; silane/ketone = 0.55. [c] Obtained by intensity measurements in the IR spectra at 1710 (C=O) and 3400 cm^{-1} (OH). [d] Polymer containing asymmetric secondary alcohol groups (c 1, C$_2$H$_5$OH).

of the proper chiral phosphine ligand for the hydrosilylation of the methyl vinyl ketone copolymer will allow the introduction of either R or S chirality at the secondary alcohol sites. Since the poly(methyl vinyl ketone) (1) obtained from free-radical polymerization is atactic, random asymmetry is introduced adjacent to the carbonyl function. This asymmetry could not be expected to have an effect on the asymmetric reduction of ketone sites along the polymer backbone, except near the polymer chain ends.[9] However, in a copolymer containing 4, the asymmetric backbone carbons could have an appreciable influence on both the absolute configuration and the optical yield of the secondary alcohol.

Synthesis of Asymmetric Polymer Attached Catalyst. Copolymerization of methyl vinyl ketone with 2-p-styryl-4,5-bis(tosyloxymethyl-1,3-dioxolane) (4) (9:1 and 14:1) by radical initiation in the presence of 2% p-divinylbenzene produced copolymer 5 in 95–100% conversion (Scheme I). The distribution of 4 in the copolymer should be almost random, though slightly alternating, judging from the reactivity ratios for styrene (r_1 = 0.29) and methyl vinyl ketone (r_2 = 0.35),[10] since
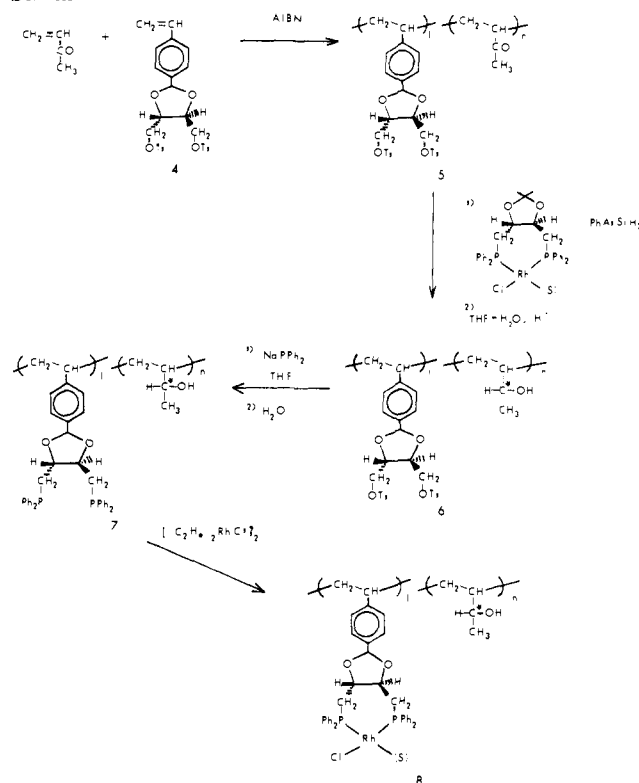
Scheme I

Table II. Asymmetric Reduction of **5**[a]

Polymer 6 (n)		Silane	Configuration		% convn
			DIOP catalyst	Alcohol	
a	9	Ph$_2$SiH$_2$	–	R	87
b	9	Ph$_2$SiH$_2$	+	S	83
c	9	(α-C$_{10}$H$_7$)PhSiH$_2$	–	R	70
d	9	(α-C$_{10}$H$_7$)PhSiH$_2$	+	S	71
e	14	Ph$_2$SiH$_2$	–	R	76
f	14	Ph$_2$SiH$_2$	+	S	62

[a] Hydrosilylations were carried out in THF at 25 °C for 3 days (Ph$_2$SiH$_2$) or 7 days [(α-C$_{10}$H$_7$)PhSiH$_2$] under nitrogen with DIOP: Rh = 1 and C=O:Rh = 50.

Table III. Phosphination Polymer **6** to **7**[a]

Polymer 6	Polymer 7 (alcohol)	% P	% S	% convn to –PPh$_2$
a	R	4.41	0.60	87
b	S	3.50	0.41	69
c	R	5.13	<0.10	~100
d	S	5.43	<0.10	~100
e	R	3.00	0.50	76.5
f	S	3.12	0.40	80

[a] NaPPh$_2$/(OTs + OH) = 1.2. Dioxane/THF = 1, 25 °C, 3 days.

monomer **4** has been shown to behave like styrene in free-radical copolymerizations.[2] Hydrosilylation of **5** was effected in THF with either (+)- or (−)-DIOP catalyst (**3**) and diarylsilane, but as in the case of reduction of poly(methyl vinyl ketone) (**1**), complete conversion to secondary alcohol could not be achieved, even with long reaction times (Table II). Phosphination of **6** gave polymer **7**, containing both optically active phosphine ligand sites and either *R* or *S* ancillary alcohol groups. With a ratio of sodium diphenylphosphide to the sum of tosyl and hydroxyl groups of 1.2, complete conversion of tosyl groups to diphenylphosphide could be obtained (Table III). The rhodium-containing catalyst (**8**) was prepared in the reaction solvent just prior to the hydrogenation by reaction of the phosphine containing polymer **7** with μ-dichlorotetraethylenedirhodium(I).

Asymmetric Hydrogenations. The asymmetric hydrogenation of α-acetamidoacrylic acid with **3** was first carried out to determine the effect of solvent on the optical yield and hydrogenation rates (Table IV). In ethanol, the rates and optical yield correspond to those reported.[4] However, in THF slower rates and low optical yields are observed; the addition of ethanol to THF improves both the rates and optical yields.

The asymmetric hydrogenation of α-*N*-acylaminoacrylic acids (**9**) with various polymer catalysts (**8**) was carried out under a variety of reaction conditions to afford the amino acid derivatives **10** (Table V). In alcohol solvents, the high optical

RCH=C(CO$_2$H)(NHAc) $\xrightarrow{\text{H}_2, \, 8}$ RCH$_2$—CH(CO$_2$H)(NHAc)

9   **10**

R

a H
b Ph
c HO—⟨◯⟩—
d AcO—⟨◯⟩—
        CH$_3$O
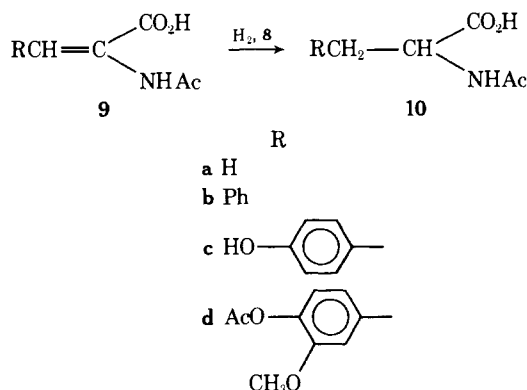
Table IV. Asymmetric Hydrogenation of α-Acetamidoacrylic Acid with **3**[a]

Solvent (mL)	Conversion, % (time, h)	ee, %
C$_6$H$_6$/EtOH (5/10)	100 (2)	70.0, 71.5
THF (15)	88.5 (24)	6.9
THF/EtOH (15/0.3)	100 (24)	48.2
THF/EtOH (5/10)	100 (2)	74.8

[a] 5 mmol of α-*N*-acylaminoacrylic acid, 1 atm H$_2$, 25°C, 0.05 mmol of [Rh(C$_2$H$_4$)$_2$Cl]$_2$, 0.11 mmol of DIOP.

yields obtained with polymer-attached catalyst **8** are comparable to those obtained with the homogeneous hydrogenation catalysts and the same absolute configurations of the product were also observed. Following hydrogenation, the polymer-bound catalyst could be removed by filtration and reused without loss of optical yields in successive hydrogenations and without appreciable loss in rates, provided that air was excluded from the polymer catalyst. When alcohol was present in the solvent, the optically active alcohol function on the polymer had no effect on the optical yield. As in the case of the soluble catalyst (**3**) (Table IV), hydrogenations in THF not only reduced the rates but lowered the optical yield. In THF, the optical yields were not diminished to 7% as in the case of **3**, probably as a result of the availability of some of the alcohol functions on the polymer. *Involvement of these ancillary alcohol sites in the transition state leading to the generation of the asymmetric center in the product is evident from the fact that a 15% difference in optical yield is obtained with otherwise identical catalysts containing the opposite chirality at the alcohol site.* The presence of large amounts of solvent alcohol washes out this effect. Unfortunately, higher optical yields in THF, where only polymer-attached chiral alcohol is available, were not obtained. This could be due to the inability of some alcohol sites to have enough mobility to become involved in the reaction.

Experimental Section

α-**Naphthylphenylsilane.** To a well-stirred mixture of 12.2 g (0.50 g-atom) of magnesium and 200 mL of tetrahydrofuran at 25 °C under nitrogen was added 103.5 g (0.50 mol) of α-naphthyl bromide. The mixture was heated under reflux for 1 h and cooled. The mixture was added to a solution of 106 g (0.50 mol) of phenyltrichlorosilane in 200 mL of tetryhydrofuran at 25 °C. Upon completion of the addition, the solution was heated to reflux for 1 h. A solution of 14.2 g (0.375 mol) of lithium aluminum hydride in 100 mL of ether was added dropwise at 25 °C to the mixture, and the solution was stirred overnight. Ethyl acetate (22 g, 0.25 mol) was added to decompose the remaining lithium aluminum hydride, followed by 300 mL of a saturated solution of sodium sulfate. The ether layer was separated and the water layer was extracted with three 100-mL portions of ether. The extracts were combined, washed with water, and dried over anhydrous magnesium sulfate. After evaporation of ether, naphthalene, which was formed as a by-product, was removed by sublimation. Distillation of the residue provided 59.2 g (50.0%) of the pure product: bp 118 °C (0.05 mm); ^{1}H NMR (CDCl$_3$) δ 8.1–7.1 (m, 12 H), 5.2 (s, 2 H).

Acrylic and Cinnamic Acids. α-Acetamidoacrylic acid (**9a**) was obtained from Aldrich Chemical Co. Atropic acid, mp 108–109 °C (lit.[15] 106–107 °C), α-acetamidocinnamic acid (**9b**), mp 190–192 °C (lit.[16] 191–192 °C), *p*-hydroxy-α-acetamidocinnamic acid (**9c**), mp 210–211 °C (lit.[17] 203–205 °C), and *p*-acetoxy-*m*-methoxy-α-acetamidocinnamic acid (**9d**), mp 146 °C (lit.[17] 146–148 °C), were prepared by known procedures.

Poly(methyl vinyl ketone) (1). The polymerization of 8.64 g (0.123 mol) of methyl vinyl ketone initiated by 0.167 mg of azobisisobutyronitrile was carried out in 30 mL of ethyl acetate at 60 °C for 24 h under nitrogen. The reaction mixture was poured into 300 mL of Skelly B and washed by stirring overnight. The Skelly B was decanted and the polymer obtained was dried under reduced pressure to yield 8.37 g (96.9%) of polymer **1**; this was stored in the dark at 0 °C. This

Table V. Asymmetric Hydrogenations of α-N-Acylaminoacrylic Acids (9) with Polymer Catalyst 8[a]

Catalyst (CHOH confign)		Substrate	Solvent (mL)	Time, h	% convn[b]	% ee[c]	Config
8b	(S)	9a	C6H6/EtOH (4/8)	2	100	76	R
			C6H6/EtOH (4/8)	2[d]	100	78	R
			C6H6/EtOH (4/8)	2.25[d]	100	76	R
			C6H6/EtOH (4/8)	2.5[d]	100	74	R
8a	(R)	9a	C6H6/EtOH (4/8)	2	100	75	R
		9b	C6H6/EtOH (6/12)	24	70	83 (81)	R
		9c	C6H6/EtOH (6/12)	24	100	70.6 (80)	R
		9d	C6H6/EtOH (6/12)	24	100	78.5 (83)	R
		Atropic acid	C6H6/EtOH (6/12)	24	100	58.9 (63)	S
8c	(R)	9a	C6H6/EtOH (4/8)	2	100	77	R
8d	(S)		C6H6/EtOH (4/8)	2	100	77	R
8a	(R)	9a	THF (12)	24	28	40	R
8c	(R)		THF (12)		32	40	R
	(R)		THF (12)		38	39	R
8b	(S)	9a	THF (12)	24	22	24	R
8d	(S)		THF (12)		29	28	R
	(S)		THF (12)		38	24	R
8e	(R)	9a	C6H6/EtOH (4/8)	2	100	77	R
8f	(S)		C6H6/EtOH (4/8)	2	100	78	R

[a] An amount of polymer 7 containing 0.412 mequiv of phosphorus was treated with 20 mg of [RhCl(C2H4)2]2 to give a P/Rh ratio of 4; 5.14 mmol of substrate (olefin/Rh = 50) was hydrogenated at 25 °C under 1 atm H2. [b] Determined by ^{1}H NMR. [c] Optical yields were calculated with respect to the following values of optically pure compounds: N-acetyl-(R)-alanine, $[\alpha]_D$ + 66.5° (c 2, H2O);[11] N-acetyl-(S)-phenylalanine, $[\alpha]_D^{26}$ +46.0° (c 1, EtOH);[12] N-acetyl-(R)-tyrosine, $[\alpha]_D$ −48.3° (H2O);[13] 3-methoxy-4-acetoxy-N-acetyl-L-phenylalanine, $[\alpha]_D^{22}$ −22.0° (c 1, acetone);[12] (S)-hydratropic acid, $[\alpha]_D^{25}$ +76.3° (c 1.6, CHCl3).[14] The values in parentheses are those obtained by Kagan et al. with soluble rhodium DIOP catalyst 3. [d] Successive hydrogenations with the same sample of catalyst that had been removed from the reaction solution by filtration.

polymer was soluble in chloroform, methylene chloride, nitrobenzene, THF, and dioxane, but insoluble in alcohols, benzene, and water. ^{13}C NMR (CDCl3) 29.47 (CH3), 32.88 (CH2), 48.08 (CH), 210.55 ppm (CO).

Poly(3-buten-1-ol) (2). Hydrosilylations of poly(methyl vinyl ketone) (1) were carried out by the following general procedure. A mixture of 58.3 mg (0.15 mmol) of μ-dichlorotetraethylenedirhodium(1),[18] 150 mg (0.30 mmol) of (−)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane, (−)-DIOP,[13] and 10 mL of tetrahydrofuran was aged for 30 min at ambient temperature under nitrogen. The reaction was started by adding the catalyst solution to a mixture of 2.1 g (30 mmol) of poly(methyl vinyl ketone), 5.64 g (30.6 mmol) of diphenylsilane,[19] and 25 mL of tetrahydrofuran at ambient temperature under nitrogen. After a reaction time of 48 h, 5 mL of 10% aqueous solution of concentrated hydrochloric acid was added. The solution was stirred for 2 h and then neutralized by 10% aqueous solution (ca. 5 mL) of concentrated ammonium hydroxide solution. The volatile materials were removed under reduced pressure. The remaining materials were dissolved in 20 mL of tetrahydrofuran, and the solution was filtered and dried. The product was purified by reprecipitating a tetrahydrofuran solution into benzene and by washing with Skelly B, yield 1.97 g (91.0%), conversion of C=O to CHOH, 92% (Table 1). In the case of α-naphthylphenylsilane the reactions were run for 120 h.

The polymers were soluble in alcohols, tetrahydrofuran, and dioxane, but insoluble in chloroform, methylene chloride, nitrobenzene, benzene, and water: ^{13}C NMR (CH3OD) 18.91 (CH3), 32.36 (CH2), 40.41 (CH), 69.30 ppm (CHOH).

Copolymerization of 2-p-Styryl-4,5-bis(tosyloxymethyl)-1,3-dioxolane with Methyl Vinyl Ketone. Polymer 5. The copolymerization of 5.45 g (10 mmol) of 2-p-styryl-4,5-bis(tosyloxymethyl)-1,3-dioxolane,[2] 6.31 g (90 mmol) of methyl vinyl ketone, and 0.52 g (2.0 mmol) of p-divinylbenzene in 40 mL of benzene was initiated by 0.136 g (1 mmol) of azobisisobutyronitrile. The polymerization was carried out at 60 °C for 24 h under nitrogen. The reaction mixture was poured into 300 mL of Skelly B and stirred overnight. The Skelly B was decanted and the polymer was dried under reduced pressure to yield 12 g (100%) of copolymer 5.

Hydrosilylation of Copolymer 5. Synthesis of Copolymer 6. Hydrosilylations of copolymer 5 were carried out by the following general procedure. A mixture of 77.8 mg (0.20 mmol) of μ-dichloro-tetraethylenedirhodium(1),[18] 200 mg (0.40 mmol) of (−)-DIOP,[13]

and 25 mL of tetrahydrofuran was aged for 30 min at ambient temperature under nitrogen. The reaction was started by adding the catalyst solution to a mixture of 2.61 g (20 mmol with respect to the methyl vinyl ketone unit) of copolymer 5 [(−)-ditosyl/C=O, 1/9], 3.87 g (21 mmol) of diphenylsilane,[19] and 50 mL of tetrahydrofuran at ambient temperature under nitrogen. After a reaction time of 72 h, 5 mL of a 10% aqueous solution of concentrated hydrochloric acid was added. The solution was stirred for 2 h and then neutralized by 10% aqueous solution (ca. 5 mL) of concentrated ammonium hydroxide solution. The volatile materials were removed under reduced pressure. The remaining materials were dissolved or swollen in 30 mL of methanol and the solution was filtered. The swollen polymer gel was washed in the filter successively with three 30-mL portions of methanol, three 30-mL portions of water, three 30-mL portions of methanol, and three 30-mL portions of ether. The product was dried under reduced pressure to yield 2.05 g (77.4%), conversion of C=O to CHOH 87%. Similar reductions were carried out with 5, (+)-DIOP, and α-naphthylphenylsilane (Table 11). In the case of α-naphthylphenylsilane, the reaction was run for 168 h.

Phosphination of Copolymer 6. Synthesis of Copolymer 7. The phosphinations of copolymers 6 were carried out by the following general procedure. A mixture of 2.75 g (120 mmol) of sodium and 50 mL of dioxane was heated at reflux with efficient mechanical stirring under a stream of nitrogen. After the sodium was converted to melted beads, 6.63 g (30 mmol) of chlorodiphenylphosphine was added dropwise over a period of 15 min. The mixture was maintained at reflux with stirring for an additional 7 h and then diluted with 50 mL of THF at ambient temperature. To this mixture was added 2.73 g (25 mequiv of OH and OTs) of copolymer 6 under a stream of nitrogen, and the mixture was stirred for 72 h. Then the reaction mixture was poured into 60 mL of methanol to decompose the excess sodium and then 100 mL of water was added. The reaction mixture was filtered and the polymer gel was washed successively on the filter with two 40-mL portions of methanol, three 60-mL portions of water, three 40-mL portions of methanol, and three 40-mL portions of ether. The polymeric product, 7, was dried under reduced pressure to yield 2.45 g (87.1%), conversion of OTs to PPh2 87.3%.

Asymmetric Hydrogenations. Hydrogenations of α-acetamidoacrylic acid (9a) with the homogeneous catalyst [(−)-DIOPRhClS][13] (3) (Table IV) and α-N-acylaminoacrylic acids or atropic acid by polymer-attached catalysts (8) (Table V) were carried out by the following general procedure. A mixture of 20 mg (0.051 mmol, 0.10

mequiv of Rh) of μ-dichlorotetraethylenedirhodium(I) and 288 mg (0.412 mequiv) of polymer **7** was placed in a Schlenk tube and the vessel was freed from oxygen by alternately evacuating and charging with dry and deoxygenated nitrogen. Benzene (4 mL) was added, the mixture was stirred for 10 min, and 8 mL of ethanol was added. The mixture was stirred at ambient temperature for 24 h under a stream of nitrogen to afford a light brown polymer-attached Rh catalyst **8**. Following the addition of 665 mg (5.15 mmol) of α-acetamidoacrylic acid under nitrogen, the reaction mixture was charged with hydrogen by alternately evacuating and then filling with hydrogen. The uptake of hydrogen was measured with a graduated cylinder connected to the reaction vessel, and the hydrogenation was run under 1 atm at 25 °C. The uptake of hydrogen ceased in 2 h. The polymer catalyst was filtered, the solvents were evaporated from the filtrate, and the residue was dried under reduced pressure. Conversion was measured by ^{1}H NMR and optical yield was determined by use of a polarimeter with reference to the value for the authentic sample, conversion 100%, optical yield 75.0%.

In the recyclization reaction, polymer filtration and all other procedures for the reaction were performed under nitrogen or hydrogen, and exposure to oxygen was strictly precluded.

References and Notes

(1) Department of Chemistry, Colorado State University, Fort Collins, Colo. 80523.
(2) N. Takaishi, H. Imai, C. A. Bertelo, and J. K. Stille, *J. Am. Chem. Soc.*, preceding paper in this issue.
(3) C. G. Overberger and K. N. Sannes, *Angew. Chem., Int. Ed. Engl.*, **13**, 99 (1974).
(4) H. B. Kagan, N. Langlois, and T. P. Dang, *J. Organomet. Chem.*, **90**, 353 (1975).
(5) See, for example, I. Ojima, M. Nihonyanagi, T. Kogure, M. Kumagai, S. Horiuchi, and K. Nakatsugawa, *J. Organomet. Chem.*, **94**, 449 (1975), and references cited therein.
(6) W. Dumont, J. C. Poulin, T. P. Dang, and H. B. Kagan, *J. Am. Chem. Soc.*, **95**, 8295 (1973); J. C. Paulin, W. Dumont, T. P. Dang, and H. B. Kagan, *C. R. Acad. Sci., Ser. C*, **277**, 41 (1973).
(7) I. Ojima, T. Kogure, and Y. Nagai, *Tetrahedron Lett.*, 1889 (1974); I. Ojima, M. Kumagai, and Y. Nagai, Abstracts, 23rd Symposium on Organometallic Chemistry, Tokyo, Japan, Oct 6–8, 1975, p 34.
(8) R. Glaser, *Tetrahedron Lett.*, 2127 (1975).
(9) M. Goodman, A. Abe, and Y.-L. Fan, *Macromol. Rev.*, **1**, 1 (1967).
(10) J. Brandrup and E. H. Immergut, "Polymer Handbook", 2nd ed, Wiley, New York, N.Y., 1975.
(11) S. M. Birnbaum, L. Levintow, R. B. Kingsley, and J. P. Greenstein, *J. Biol. Chem.*, **194**, 455 (1952).
(12) T. P. Dang, J. C. Poulin, and H. B. Kagan, *J. Organomet. Chem.*, **91**, 105 (1975).
(13) H. B. Kagan and T. P. Dang, *J. Am. Chem. Soc.*, **94**, 6429 (1972).
(14) S. P. Bakshi and E. E. Turner, *J. Chem. Soc.*, 171 (1961).
(15) H. S. Raper, *J. Chem. Soc.*, **123**, 2557 (1923).
(16) R. M. Herbst and D. Shemin, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 1.
(17) H. D. Dakin, *J. Biol. Chem.*, **82**, 439 (1929).
(18) R. Cramer, *Inorg. Chem.*, **1**, 722 (1962); *Inorg. Synth.*, **15**, 14 (1974).
(19) R. A. Benkeser, H. Landesman, and D. J. Foster, *J. Am. Chem. Soc.*, **74**, 648 (1952).

Measurement of Hydrogen Exchange at the Tryptophan Residues of a Protein by Stopped-Flow and Ultraviolet Spectroscopy

Mamoru Nakanishi,[1a] **Hitomi Nakamura,**[1a] **Akiko Y. Hirakawa,**[1a] **Masamichi Tsuboi,**[*1a] **Toshihiko Nagamura,**[1b] **and Yutaka Saijo**[1b]

Contribution from the Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo, Japan, and Union Giken Co., Ltd., Osaka, Japan. Received March 23, 1977

Abstract: A time-dependent change in the ultraviolet absorbance at 290 nm of the indole ring of tryptophan has been observed, using a stopped-flow spectrophotometer, when tryptophan was rapidly transferred from water into deuterium oxide–water solution. From this experiment, the rate constant of the hydrogen–deuterium exchange reaction of the tryptophan NH group has been determined at various pH values and at several temperatures. Stopped-flow ultraviolet spectroscopy has also been used for an examination of hydrogen exchange kinetics of the tryptophan residues of hen egg-white lysozyme. Three of the six tryptophan residues of this protein molecule were deuterated in 50 min at pH 5.5 and 22 °C. These three residues are probably Trp-62, Trp-63, and Trp-123. When *N*-acetylglucosamine was present the deuteration rates were markedly lower.

Since we have accumulated knowledge on the hydrogen exchange reactions of the main-chain NH groups of several proteins,[2-5] including hen egg-white lysozyme,[2,3] it is now desirable to extend such knowledge to the side chains. It has been shown that hydrogen–deuterium exchange reactions at the tryptophan residues in a protein can be examined by proton magnetic resonance measurement[6] and also by Raman spectroscopic measurement.[7] In this paper, we demonstrate that this can be done by stopped-flow ultraviolet spectroscopy, similarly to Cross's method for a few nucleosides.[8,9] This method has a few advantages in comparison with the other two. First, it can be applied to a fast exchange reaction which takes place in a few milliseconds. It is applicable to a high molecular weight protein, whereas the proton magnetic resonance method would not be. An ultraviolet absorption measurement, in addition, allows us to reach a sufficient signal-to-noise ratio with a relatively small amount of sample. We have applied this method to hen egg-white lysozyme, and the hydrogen-exchange kinetics of relatively labile tryptophan residues were examined both in the native, free state and in the inhibitor–enzyme complex.

Experimental Section

L-Tryptophan was purchased from Wako Pure Chemical Industries, Ltd., and six times recrystallized hen egg-white lysozyme was obtained from Seikagaku Kogyo Co., Ltd. The sample of human lysozyme used was kindly provided by Professor K. Hamaguchi, Osaka University. Deuterium oxide (99.75 atom %) was purchased from Merck.

The hydrogen and/or deuterium ion concentrations of the solution (H_2O, D_2O, or $H_2O + D_2O$) were measured with a Toa Dempa pH