Reduction of Epoxides (8 and 9). A solution of **8** or **9** (50 mg) in 1% aqueous $NaBH_4$ (5 mL) was kept at room temperature for 1 day. After neutralization of the solution by addition of dilute HCl, the mixture was chromatographed by a reversed-phase column with an elution of water to give pure **11** (42 mg, 83%) or **12** (47 mg, 93%). Physical data of these compounds are as follows.

11: ^{13}C NMR (22.5 MHz, D_2O, characteristic absorptions) δ 54.1, 57.9, 63.2 65.0, 65.5, 96.9, 98.4, 98.6, 102.3, 102.9; FABMS m/z 1119 ($M + H^+$); R_f value on TLC 0.05.

12: ^{13}C NMR (22.5 MHz, D_2O, characteristic absorptions) δ 54.0, 57.9, 62.9, 63.2, 65.0, 65.5, 96.9, 98.4, 98.6, 102.9; FABMS m/z 957 ($M + H^+$); R_f value on TLC 0.05.

Acetylation of 11 and 12. A solution of **11** or **12** (5 mg) and acetic anhydride (0.25 mL) in pyridine (0.25 mL) was allowed to stand at room temperature for 4 h and concentrated by evaporation of volatile materials together with a stream of nitrogen. After dry chloroform (0.5 mL) was added to the residue, the evaporation was repeated. This procedure was carried out 2 more times. The crude products were purified by reversed-phase HPLC with a gradient elution from 50% aqueous CH_3CN to 80% aqueous CH_3CN to give pure **14** (4.2 mg, 37%) and **15** (5.3 mg, 49%). They were analyzed by FDMS and EIMS spectra. The EIMS spectral fragmentations observed are shown in Figure 3. FDMS m/z **14**: 1981 ($M + Na^+$); **15**: 1693 ($M + Na^+$).

Acknowledgment. Thanks are due to Dr. Nobuyuki Nakamura (Japan Maise Products Co. Ltd.) for the generous gift of β-cyclodextrin and to Dr. Hiroyuki Sugimoto (Wakunaga Pharmaceutical Co. Ltd.) for ^1H NMR (270-MHz) measurements.

Asymmetric Synthesis. Metal Complex Mediated Synthesis of Chiral Glycine by Enantioselective Proton Exchange

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Abstract: The complex [Co((*S*,*S*)-proam)(picgly)]$^+$, a species containing a chiral tridentate triamine ligand, (*S*,*S*)-proam, and a tridentate ligand incorporating a glycine residue, picgly, has been prepared. The α-protons of the coordinated glycine residue exchange at different rates in basic D_2O solutions. The difference in rate was found to be 7.8:1 in favor of the *pro-S* proton at pD 11.2 at 25 °C with a $NaHCO_3/Na_2CO_3$ buffer. It is proposed that the origins of this enantiosection arise from both steric and hydrogen-bonding effects as inferred from the determined crystal structure of the complex. A kinetic analysis of the exchange process shows that the system is essentially that of an asymmetric synthesis ($CH_2 \rightarrow CHD$) followed by a reinforced kinetic resolution ($CHD \rightarrow CD_2$). As such, the optical purity of the chiral glycine (NH_2CHDCO_2H) continuously increases with the extent of reaction. This was confirmed. It is suggested that the present kinetic relationships are representative of the majority of asymmetric syntheses involving enantiotopic atoms or groups, and it follows that, for such systems, quoting an enantiomeric excess has meaning only when the extent of reaction is specified.

The remarkable ability of enzymes to react selectively with the enantiotopic hydrogen atoms of a methylene group[1] has so far proved difficult to reproduce synthetically. Thus, in relation to the present work, we note that the *pro-S* hydrogen atom of glycine is preferentially exchanged by serine hydroxymethyltransferase in the presence of pyridoxyl phosphate and tetrahydrofolic acid.[2] In deuterated water chiral glycine (NH_2CHDCO_2H) is obtained in the absence of formaldehyde by this enzymatic reaction. Since the discovery that the methylene protons of an amino acid coordinated to a transition-metal complex were exchanged under basic aqueous conditions, there have been a number of attempts to reproduce the selectivities of the enzymatic reactions.[3] The more notable of these attempts were described by Golding and Sargeson,[4] who studied the relative exchange rates of the *pro-S* and *pro-R* glycine protons of the chiral complex bis(ethylenediamine)(*N*-benzylglycinato)cobalt(III), $[Co(en)_2(N\text{-bzgly})]^{2+}$. They observed a selectivity of about 4:1 in a Na_2PO_4/D_2O buffer at pD 10.5, and they attributed this selectivity to the preferred chirality of the nitrogen atom substituents of the coordinated *N*-bzgly ligand induced by the chiral disposition of the two en chelate rings. Curiously, subsequent work showed that the replacement of the benzyl group in $[Co(en)_2(N\text{-bzgly})]^{2+}$ by either 2-methylbenzyl or 1-methylenenaphthyl gave systems which showed no selectivity in the exchange of the methylene glycine protons.[5] A more recent report by Belokon[6] using the bis(3-methylsalicyaldimo)(glycinato)cobalt(III) complex described the preferential exchange of the methylene protons of the coordinated glycine group.

This paper describes a different approach to the selective exchange of the methylene protons of a coordinated glycine ligand. We also demonstrate how the kinetics of exchange can be employed to produce chiral glycine to any degree of chiral purity. The system chosen is [Co((*S*,*S*)-proam)(picgly)]$^+$, a cobalt(III) complex consisting of two tridentate ligands, one of which contains the glycine residue.

Strategy and Synthesis. A coordinated glycinate molecule is devoid of puckering, and hence its enantiotopic methylene protons lie above and below the mean molecular plane. Exchange of these protons by hydroxide ions presumably involves a transition-state geometry consisting of a linear carbon–hydrogen–oxygen aggregate.

In order to distinguish the two methylene protons, a chiral auxiliary is required which protects one or other of the coordinated glycinate methylene protons from attack by hydroxide ions or which, in some way, directs hydroxide ion attack preferentially to one or other of these protons. The chiral auxiliary preferably should possess a C_2 axis in order to avoid isomeric ambiguity in an octahedral complex.

With these considerations in mind, we prepared the chiral auxiliary, (*S*,*S*)-proam, a tridentate ligand derived from (*S*)-

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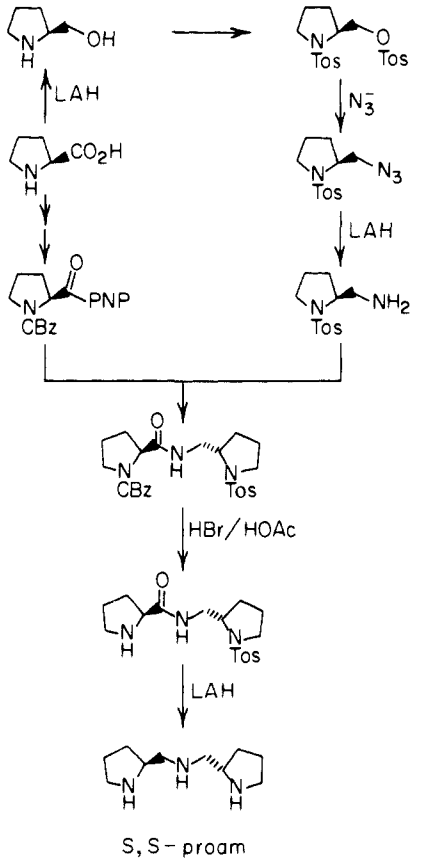

Figure 1. An outline of the synthesis of (*S*,*S*)-proam from (*S*)-proline; CBZ = carbobenzyloxy, PNP = *p*-nitrophenol, Tos = *p*-tosyl.

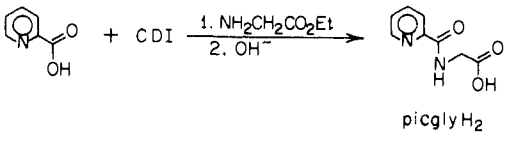

Figure 2. An outline of the synthesis of picglyH_2; CDI = *N*,*N*'-carbonyldiimidazole.

proline by the sequence of reactions outlined in Figure 1. The synthesis proved to be uneventful, somewhat cumbersome, but it is relatively efficient. This ligand was efficiently coordinated to cobalt(III) by the reaction with $[Co(CO_3)_3]^{3-}$ in the presence of HCl. A water-insoluble complex, [Co((*S*,*S*)-proam)Cl_3], is produced, and it was used as the starting material for subsequent reactions.

In order to avoid isomeric complexity, we chose to incorporate the glycine moiety into the tridentate chelate, *N*-(2-picolinoyl)-glycine (picglyH_2). This ligand was obtained by the condensation of 2-picolinic acid, activated by *N*,*N*'-carbonyldiimidazole (CDI), and ethyl glycinate, followed by base hydrolysis (Figure 2).

The desired complex [Co((*S*,*S*)-proam)(picgly)]Cl was prepared by the reaction of [Co((*S*,*S*)-proam)Cl_3] and picglyH_2 in the presence of triethylamine in dry dimethylformamide solution. The product is an orange crystalline solid which is very soluble in water and is stable indefinitely in basic solutions (pH < 14).

Crystal Structure. The absolute crystal structure of [Co((*S*,*S*)-proam)(picgly)]Cl·$2H_2O$ was determined, and the structure is shown in Figure 3. The bond lengths and angles are unexceptional, but we note that the structure shown in Figure 3 represents one of the possible geometrical isomers of the complex. This isomerism[7] arises from the orientation of the hydrogen atom coordinated to the central nitrogen atom (N4) of the proam ligand. The hydrogen atom can point either at the pyridine ring, as in the shown structure, or at the carboxylate group of the picgly ligand. In basic solutions, where N–H proton exchange is rapid,

(7) Keene, F. R.; Searle, G. H. *Inorg. Chem.* **1972**, *11*, 148.

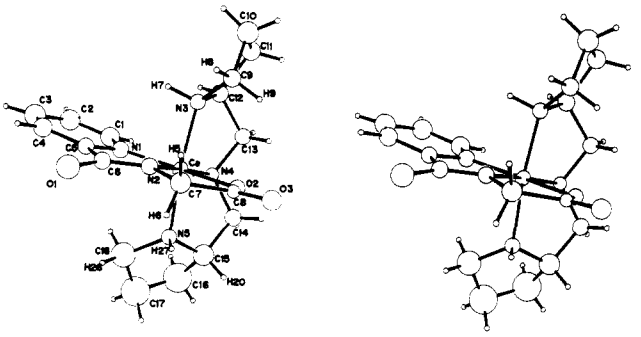

Figure 3. Stereoscopic view of [Co((*S*,*S*)-proam)(picgly)]$^+$ showing the environments of the diastereotopic glycine protons H5 and H6. Selected bond distances and bond angles are Co–O(2) = 1.908 (8) Å, Co–N(1) = 1.93 (1) Å, Co–N(2) = 1.879 (8) Å, Co–N(3) = 1.958 (9) Å, Co–N(4) = 1.951 (8) Å, Co–N(5) = 1.96 (1) Å, O(2)–Co–N(1) = 168.0 (4)°, N(2)–Co–N(4) = 175.5 (4°), and N(3)–Co–N(5) = 172.0 (4)°.

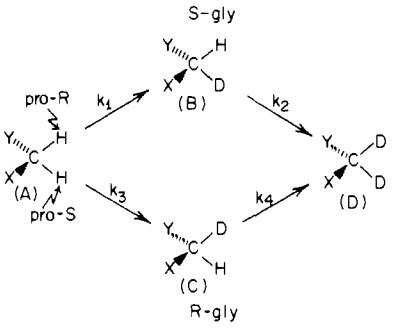

Figure 4. A kinetic scheme for the exchange of the (diasterotopic) methylene protons with deuterium.

we would expect that these isomers would be capable of facile interconversion through inversion about the N4 nitrogen atom of proam.[8] The two isomers result in somewhat different orientations of the two pyrrolidine rings with respect to the glycine methylene protons. Molecular models suggest, however, that the preferred isomer is likely to be the one shown in Figure 3, and we shall assume this to be the case here.

The *pro-R* (H5) and *pro-S* (H6) methylene protons of the glycine ligand occupy different structural environments, particularly with respect to the pyrrolidine rings. Although the differences are not great and depend on the particular conformation adopted by the pyrrolidine rings, the *pro-R* (H5) proton lies in the more hindered half of the molecule; the top pyrrolidine ring (as shown in Figure 3) is inclined toward the *pro-R* proton whereas the bottom pyrrolidine ring is inclined away from the *pro-S* proton. We note, however, that the contact distance between the *pro-S* (H6) proton and the amine hydrogen atom of the bottom pyrrolidine ring (H27) is 2.67 Å. This arrangement allows an hydroxide ion to hydrogen bond to the H27 proton and be within bonding distance to the *pro-S* proton, a situation which does not exist for the *pro-R* proton. Such hydrogen bonding would lead to an increase in the local concentration of hydroxide about the *pro-S* proton as compared to its *pro-R* counterpart. Thus we expect that steric hindrance and the hydrogen-bond directing effect will both contribute to the preferential rate of abstraction of the *pro-S* proton. This proved to be the case under the conditions we now describe.

Differential Proton Exchange Rates. The exchange of the glycine methylene protons of [Co((*S*,*S*)-proam)(picgly)]Cl was carried out at 25 °C in D_2O in a $Na_2CO_3/NaDCO_3$ buffer adjusted to pD 11.2. The progress of the reaction was monitored by ^1H NMR spectroscopy at 200 MHz.

In principle, the exchange process consists of a series of parallel consecutive reversible exchange reactions, but we have contrived the conditions so that each of the steps is essentially irreversible.

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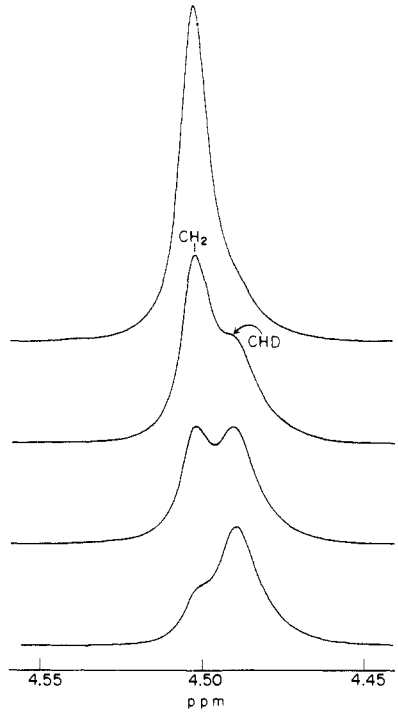

Figure 5. Glycine methylene proton ^{1}H NMR signals of [Co((*S*,*S*)-proam)(picgly)]Cl in D_2O solution containing a $NaHCO_3/Na_2CO_3$ buffer at pD 11.2 and 25 °C as proton exchange occurs with time.

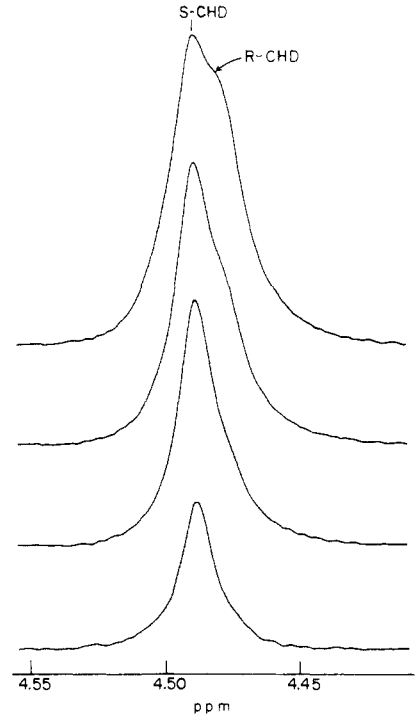

Figure 6. Glycine half-deuterated methylene proton ^{1}H NMR signals of [Co((*S*,*S*)-proam)(picgly)]Cl in D_2O solution containing a $NaHCO_3/Na_2CO_3$ buffer at pD 11.2 and 25 °C as proton exchange occurs.

Thus by use of the complex where the NH protons have been replaced by ND, the exchange of the methylene protons in 99.996% D_2O was found to be essentially irreversible. In this way the scheme shown in Figure 4 becomes representative of the exchange process. A typical 200-MHz ^{1}H NMR time-interval trace for the exchange $CH_2 \rightarrow CD_2$ is shown in Figure 5. It will be noted that as the original downfield signal (CH_2, which occurs as a sharp singlet even at 400 MHz) decreases in intensity, a (broader) higher-field signal (CDH) appears. Eventually the CH_2 signal completely disappears, leaving the higher-field signal, which then also goes to zero intensity. The area of the lower-field signal (A_{CH_2}) at any time was obtained by computer deconvolution of the curves. A plot of ln A_{CH_2} vs. time gave a straight line of slope $k_1 + k_3$ (Figure 4). After the CH_2 signal had disappeared, a similar plot for the higher-field signal (ln A_{CDH} vs. time) also gave a straight line of slope k_2 because, as we confirm presently, after the CH_2 signal has disappeared, only the (*S*)-CDH isomer remains.

In order to obtain the value of k_4 and to confirm that k_2 was correctly determined by the above method, we prepared a sample of [Co((*S*,*S*)-proam)(pic-[^{2}H$_1$]-(*R*,*S*)-gly)]Cl, a species which is a mixture of equal amounts of the half-deuterated (*R*)- and (*S*)-glycine enantiomers. Figure 6 shows the decay of the two ^{1}H NMR signals (*R*)- and (*S*)-CDH with time. The total signal area ($A_{(R)\text{-CDH}+(S)\text{-CDH}}$) was measured, and a plot of ln ($A_{(R)\text{-CDH}+(S)\text{-CDH}}$) vs. time gave a curve typical of two parallel reactions. After appropriate manipulation, this plot gave the value of the constants k_2 and k_4, and the value of k_2 was the same as previously determined.

Kinetic Analysis. The constants $k_1 + k_3$, k_2, and k_4 have been determined directly from the kinetics, but we also required the individual values of k_1 and k_3. It will be noted that although both k_1 and k_4 involve exchange of a *pro-S* proton and that both k_3 and k_2 refer to *pro-R* proton exchange (Figure 4), k_1 and k_4 are not equal, nor are k_3 and k_2, because of secondary isotope effects. If, however, we assume that the secondary isotope effects will be the same in the two cases, then we may write $k_1 = \beta k_4$ and $k_3 = \beta k_2$, and hence we may determine the individual values of k_1 and k_3 from these relationships and from the determined values of $k_1 + k_3$, k_2, and k_4. The rate constants at 25 °C and pD 11.2 were found to be $k_1 + k_3 = (1.16 \pm 0.03) \times 10^{-3}$ s^{-1}, $k_2 = (9.08 \pm 0.12) \times 10^{-5}$ s^{-1}, and $k_4 = (7.08 \pm 0.08) \times 10^{-4}$ s^{-1}; hence from the secondary isotope assumption, $k_1 = 1.03 \times 10^{-3}$ s^{-1} and $k_3 = 1.32 \times 10^{-4}$ s^{-1}.[9]

Thus the rate of exchange of the *pro-S* proton is 7.8 times faster than that of the *pro-R* proton. This, however, does not imply that the (*S*)- and (*R*)-glycines are generally produced in this ratio because of the simultaneous operation of the k_2 and k_4 paths.

The kinetic proportions of the species, A, B, C, and D shown in Figure 4 can be determined for any time as follows.

$$-\frac{d[A]}{dt} = (k_1 + k_3)[A] \quad (1)$$

$$[A] = [A]_0 e^{-(k_1+k_3)t} \quad (1a)$$

$$\frac{d[B]}{dt} = k_1[A] - k_2[B] \quad (2)$$

$$\frac{d[C]}{dt} = k_3[A] - k_4[C] \quad (3)$$

Combining (1a) and (2):

$$\frac{d[B]}{dt} = k_1[A]_0 e^{-(k_1+k_3)t} - k_2[B] \quad (4)$$

Integration (by the factor method):

$$[B] = \frac{k_1[A]_0}{k_2 - (k_1 + k_3)}(e^{-(k_1+k_3)t} - e^{-k_2 t}) \quad (5)$$

Similarly for C:

$$[C] = \frac{k_3[A]_0}{k_4 - (k_1 + k_3)}(e^{-(k_1+k_3)t} - e^{-k_2 t}) \quad (6)$$

And D is

$$[D] = [A]_0 - ([A] + [B] + [C]) \quad (7)$$

Equations 5–7 allows us to calculate the concentrations of A, B, C, and D for any time during the exchange reaction. Thus

(9) These rate constants imply a secondary isotope effect of 1.45 which is large but not unknown for these types of reaction. See: *Methods Enzymol.* **1980**, *64*, 108–109. We are grateful to A. J. Kresge for drawing our attention to these data.

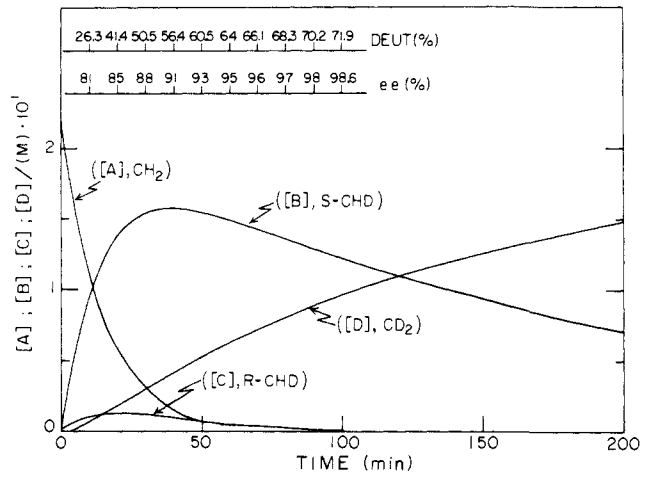

Figure 7. Calculated concentrations of the various glycine species (Figure 4) with time by use of the four rate constants (k_1, k_2, k_3, k_4) found for the exchange of the glycine methylene protons of [Co((*S*,*S*)-proam)(picgly)]Cl under the present conditions. Deut(%) = the total percent deuteration of all of the species = the percent loss of methylene protons.

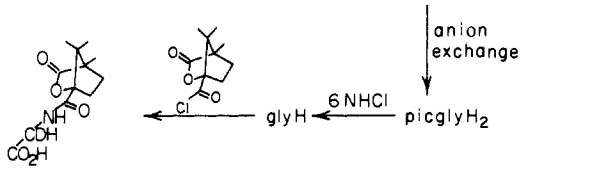

Figure 8. An outline of the isolation of chiral glycine from [Co((*S*,*S*)-proam)(picgly)]$^+$ and the formation of its camphanoyl derivative.

using the rate constants and eq 5–7 we show a plot of the time-dependent concentrations of the four species in Figure 7.

It will be noted that as the concentration of A decreases, the concentration of the *S* enantiomer (B) increases much more rapidly than that of the *R* enantiomer (C) and, as time goes on, the ratio *S*:*R* increases. Thus the enantiomer excess (ee) is 88% at 50.5% *total* deuteration (i.e., when the methylene proton signal has decreased 50.5% in intensity), and at 72% deuteration essentially pure (*S*)-glycine is obtained. Provided we are prepared to sacrifice chemical yield, we can obtain (*S*)-glycine to any degree of optical purity.

Assay of Chiral Glycine. In order to confirm the above kinetic analysis the proportions of the various species were assayed. The complex [Co((*S*,*S*)-proam)(picgly)]$^+$ was allowed to exchange its methylene glycine protons under the present conditions. After 63% of total deuteration, the reaction was quenched to pH 7 and the deuterated glycine was converted to the amide derivative of (−)-(1*S*,4*R*)-ω-camphanic acid by the method outlined in Figure 8. This camphanic acid derivative gives a large splitting of the diastereotopic methylene protons of glycine, and the enantiomers of the half-deuterated glycine have been assigned.[10,11] The NH-decoupled 200-MHz ^{1}H NMR spectrum of the camphanic acid derivatives is shown in Figure 9 for the glycine methylene protons. We find from integration of the signals that the ratio of CH_2:(*R*)-CDH:(*S*)-CDH is 1.2:1:19, respectively, and the predicted ratios are 1.2:1:35, correspondingly. Given the fact that ratios are involved and that there was considerable error in the determined values of the small signals (CH_2 and (*R*)-CDH) and also the fact that the somewhat harsh conditions used for the hydrolysis of picglyH_2 caused ~4% exchange of the methylene protons with H_2O, the found and calculated ratios are well within experimental error.

Generality of the Kinetic Relationships. So far the majority of asymmetric syntheses have been carried out on prochiral

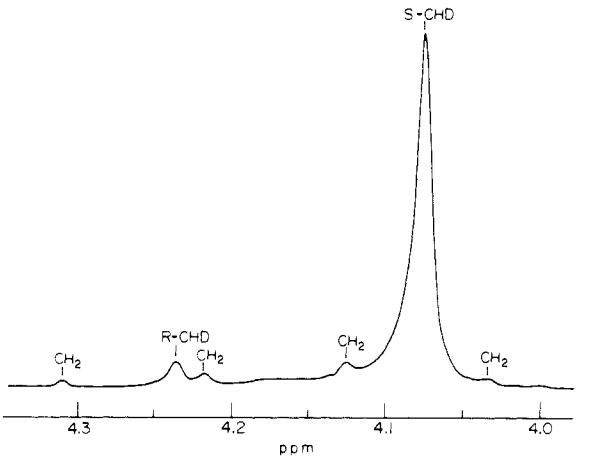

Figure 9. NH-decoupled ^{1}H NMR spectrum in $CDCl_3$ at 200 MHz of the glycine methylene region of the glycine amide of (1*S*,4*R*)-ω-camphanic acid after 63% of total deuterium exchange.

substrates with enantiotopic faces such as olefins, ketones, and aldehydes. Although many enzymatic reactions discriminate enantiotopic groups or atoms to produce chiral products, few purely synthetic systems of this kind have appeared. The present system is an example of enantiotopic atom discrimination, and the derived kinetic relationships described here will apply to a majority of asymmetric syntheses involving enantioselective group or atom reactions.

Consider the scheme in Figure 4 but replace H by Z (CXYZZ) and D by L (CXYZL). We now have an enantioselective reaction where the enantiotopic groups or atoms (Z) are replaced by L. The chiral products, CXYZL, will be produced at different rates via k_1 and k_3, and were the reaction to stop at this stage, the enantiomer ratio would be only determined by these two rate constants. In general, k_1, k_3, k_2, and k_4 will be comparable in magnitude, and moreover, whatever discriminating features of the enantioselective reaction make $k_1 > k_3$, for example, will also make $k_4 > k_2$. These relationships apply to the present methylene exchange reaction, and their generality becomes obvious if one considers the example of diester hydrolysis (Z = CO_2R). Thus eq 1–7 apply generally to enantioselective reactions of enantiotopic groups or atoms. It follows that for these types of reactions, optical yields have precise meaning only when the extent of reaction is specified.

The scheme in Figure 4 is in essence an asymmetric synthesis (k_1, k_3) followed by a kinetic resolution (k_2, k_4) and differs from the latter only to the extent that the usual kinetic resolution begins with an equal ratio of enantiomers. In this respect the scheme is not new; the principles described have been periodically applied in various guises over the last 80 years.[12–21] The present derivation was explicitly recognized by Sih,[22] who applied it to hydrolytic enzymes. Our purpose in discussing this general system is to illustrate and emphasize that, unlike the cases of the enantiotopic face substrates, asymmetric synthesis involving enantiotopic groups or atoms is a time-dependent phenomenon where the optical yields

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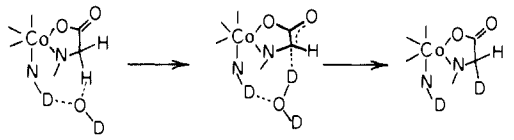

Figure 10. Suggested mechanism of proton exchange involving hydroxide hydrogen bonding to a NH proton of the (*S*,*S*)-proam ligand (Figure 3).

will increase with the extent of reaction.

Mechanism of Exchange. The accepted mechanism for the exchange of the methylene protons of a coordinated amino acid involves an OH^- abstracting a proton to leave a fleeting planar or nearly planar stabilized carbanion which is then rapidly reprotonated by a water molecule. There is considerable evidence for this mechanism,[23,24] and we invoke it in our interpretation of the enantioselection observed for the [Co((*S*,*S*)-proam)(picgly)]$^+$ complex.

As we pointed out earlier, the *pro-S* glycine methylene proton of [Co((*S*,*S*)-proam)(picgly)]$^+$ is somewhat less sterically hindered than the *pro-R* proton, and also the *pro-S* proton has a NH proton positioned to form a hydrogen bond with the OH^- so that, in this arrangement, the OH^- ion is within contact distance of the *pro-S* proton. The proposed origin of the enantioselection is depicted in Figure 10 for the preferred (*pro-S*) proton abstraction. We note that microscopic reversibility demands that the proton that is more readily abstracted is also the proton that is more readily replaced at the planar intermediate; that is, the carbanion is more readily reprotonated from the "bottom side" (Figure 10). It is possible that a path involving carbonate ion abstraction exists, but we have not pursued this question.

Experimental Section

Preparation of (*S*,*S*)-proam. (*S*)-*N*,*O*-Bis(*p*-toluenesulfonyl)-2-(hydroxymethyl)pyrrolidine. *p*-Toluenesulfonyl chloride (240 g) was added gradually to dry pyridine (530 mL) which was stirred in an ice bath. A solution of (*S*)-proline (57.7 g) in dry pyridine (65 mL) was added dropwise to the mixture, and the resultant mixture was then stirred for 12 h. The deep red-brown reaction mixture was cooled to 0 °C, and a slurry of HCl (12.3 M, 500 mL) in crushed ice (500 mL) was added to it. A red oil separated, and the supernatant liquid was decanted from it. Ethanol (250 mL) was added to the red oil, and the mixture was heated gently on a steam bath whereupon the oil crystallized. The slurry of crystals was cooled, and the crystals were collected, washed with ethanol followed by hexane, and air-dried. The crude material (220 g) was recrystallized from boiling ethanol (750 mL) to give the product as a mixture of transparent prisms and opaque needles: 200 g, 86%; mp 93–94 °C; α^{25}_D −115.5° (*c* 0.9, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.2–2.1 (m, 4 H, CH_2CH_2), 2.43 (s, 3 H, OTs), 2.48 (s, 3 H, NTs), 2.8–4.4 (m, 5 H, NCH_2 and OCH_2CH), 7.08–7.4 (m, 4 H, OTs), 7.36–7.9 (m, 4 H, NTs). Anal. Calcd for $C_{19}H_{23}NO_5S_2$: C, 55.7; H, 5.7; N, 3.4; S, 15.7. Found: C, 55.4; H, 5.5; N, 3.5; S, 15.5.

(*S*)-2-(Azidomethyl)-*N*-(*p*-toluenesulfonyl)pyrrolidine (Caution). A mixture of the bis tosylate (240 g) and sodium azide (88 g) in diethylene glycol (1 L) was stirred and heated at 100 °C (1 h). The clear, yellow solution was cooled to ca. 80 °C and transferred into a large beaker; then it was diluted slowly with iced water (1250 mL). The resulting slurry of white crystals was filtered, and the solid was washed thoroughly with water (1.5 L). The crude material (156 g) was dissolved in hot ethanol (1 L), and water (750 mL) was added gradually to the hot solution. Upon cooling, the solution deposited large white needles of the azide. The mixture was cooled (12 h) at 4 °C and filtered, and the solid was washed with cold 50% aqueous ethanol and then dried: 117 g, 78%; mp 82–83 °C; α^{25}_D −113.5° (*c* 1.2, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.2–2.0 (m, 4 H, CH_2CH_2), 2.43 (s, 3 H, NTs), 2.85–3.95 (m, 5 H, NCH_2 and OCH_2CH), 7.1–7.75 (m, 4 H, NTs). Anal. Calcd for $C_{12}H_{16}N_4O_2S$: C, 51.4; H, 5.8; N, 20.0; S, 11.4. Found: C, 51.4; H, 5.7; N, 19.9; S, 11.5.

(*S*)-2-(Aminomethyl)-*N*-(*p*-toluenesulfonyl)pyrrolidine. The azide (117 g) was added in small portions to a stirred suspension of LAH (26 g) in dry diethyl ether (2 L). The yellow mixture was stirred (0.25 h), then cooled in an ice bath, and hydrolyzed by the successive addition of water (26 mL), 12% NaOH (26 mL), and water (78 mL). The white slurry was filtered and the aluminate cake extracted with hot THF (2 × 200 mL). The combined filtrate and extracts were evaporated to a milky oil, which was then redissolved in benzene and again evaporated. The clear, pale yellow oil was stirred with a mixture of hexane (400 mL) and dry diethyl ether (30 mL) until it crystallized. The solid was filtered, washed with a mixture of diethyl ether (100 mL) and hexane (400 mL), then with hexane, and was dried in a vacuum desiccator. The hygroscopic white solid could not be recrystallized and was used as obtained for the next step: 90 g, 85%; ^1H NMR ($CDCl_3$) δ 1.1–2.0 (m, 4 H, CH_2CH_2), 1.33 (s, 2 H, NH_2), 2.4 (s, 3 H, NTs), 2.72–2.91 (m, 2 H, NH_2CH_2), 3.05–3.97 (m, 3 H, CH_2NCH), 7.15–7.85 (m, 4 H, NTs).

(*S*)-2-((*N*-(*S*)-Prolylamino)methyl)-*N*-(*p*-toluenesulfonyl)pyrrolidine. A solution of triethylamine (35.3 g) in dichloromethane (100 mL) was added dropwise over 2 h to an ice-cooled solution of *N*-(carbobenzyloxy)-L-proline *p*-nitrophenyl ester (129 g) and (*S*)-2-(aminomethyl)-*N*-(*p*-toluenesulfonyl)pyrrolidine (89 g). The cooling bath was removed and the yellow mixture was stirred for another 0.5 h. The mixture was washed with water (500 mL), then with 0.75 M HCl (500 mL), and then with three cycles of the following sequence of washings: water (200 mL), 0.5 M NaOH (200 mL), 0.75 M HCl (200 mL), and water (200 mL). The dichloromethane solution was dried ($MgSO_4$) and was evaporated to give the CBZ-protected compound as a yellow gum. A solution of hydrogen bromide (73 g) in acetic acid (400 mL) was added to the yellow gum, and the mixture was stirred (12 h). Dry diethyl ether (700 mL) was added to the orange solution, and the mixture was stirred vigorously until crystals formed. The slurry was filtered, and the solid was washed thoroughly with dry diethyl ether and then with hexane. The dried hydrobromide salt was dissolved in water (500 mL) containing 15.4 M NH_4OH (75 mL), and the free base was extracted from the yellow mixture with dichloromethane (2 × 250 mL). The combined extracts were washed with 1 M NH_4OH (4 × 250 mL) and then with water (250 mL) and were dried (Na_2SO_4) and evaporated. The oily residue was redissolved in benzene (300 mL) and was evaporated on a rotary evaporator, such that as much as possible of the solvent was removed. The colorless oily product crystallized spontaneously upon standing at room temperature; 110 g, 90%. A small sample of this amide was recrystallized from benzene by the addition of hexane and gave colorless needles: mp 96 °C; α^{25}_D −118° (*c* 0.97, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.08–2.3 (m, 8 H, CH_2CH_2), 2.2 (s, 1 H, amine NH), 2.4 (s, 3 H, NTs), 2.8–4.0 (m, 8 H, $CH_2N(Ts)CHCH_2N$ and $CHNCH_2$), 7.2–7.85 (m, 4 H, NTs), 8.0 (brm, 1 H, amide NH). Anal. Calcd for $C_{17}H_{25}N_3O_3S$: C, 59.0; H, 7.2; N, 12.0; S, 9.1. Found: C, 58.7; H, 7.3; N, 11.9; S, 9.2.

(*S*,*S*)-Bis(2-pyrrolidinylmethyl)amine ((*S*,*S*)-proam). The amide (109 g) was dissolved in dry THF (700 mL) by warming, and the solution was added dropwise to a slurry of LAH (49 g) in THF (1 L) which was stirred mechanically in an ice bath. The green mixture was heated under reflux (48 h), during which it became almost colorless. After the conventional hydrolysis with water (49 mL), 12% NaOH (49 mL), and then more water (147 mL), the thick mixture was heated (4 h) and was then suction-filtered through a broad Büchner funnel. The aluminate cake was reextracted with hot THF (2 × 1 L), and the combined filtrates were evaporated. Traces of water were removed from the yellow, oily residue by azeotroping it with benzene (4 × 300 mL). The first attempt to distill the oil under high vacuum was defeated by the deposition of a large amount of aluminate material, accompanied by some gas evolution, when the temperature of the still pot reached ca. 130 °C. The mixture was held at this temperature until the precipitation of solid seemed to be complete. The mixture was then cooled and extracted with hot THF (100 mL). The filtered THF extract was evaporated and the residue was distilled. The distillate, collected at bp 90–100 °C (1 mm), was redistilled to give the triamine, 40 g, bp 80 °C (1 mm), which codistilled with a small amount of unidentified white, waxy material. This material, although not completely pure, was sufficient for the preparation of the complexes.

Preparation of picglyH$_2$. *N*-(2-Picolinoyl)glycine Ethyl Ester. *N*,*N*′-Carbonyldiimidazole (21.17 g) was added to a suspension of a picolinic acid (16.1 g) in dry THF (175 mL), and the mixture was stirred (1 h) until gas evolution ceased. A solution of glycine ethyl ester (13.5 g) in THF (45 mL) was then added, and the solution was stirred (12 h), filtered, and then was evaporated. Traces of THF were removed from the residue by adding benzene and reevaporating the solution. The residue was dissolved in benzene (300 mL) and extracted with water (4 × 25 mL) to remove the imidazole byproduct. The benzene solution was dried ($MgSO_4$) and evaporated to a colorless oil which then crystallized: 22.3 g, 82%; ^1H NMR ($CDCl_3$) δ 1.3 (t, 3 H, J = 7.5 Hz, CH_2CH_3), 4.28 (q, 2 H, J = 7.5 Hz, CH_2CH_3), 4.28 (d, 2 H, NCH_2), 7.22–8.6 (m, 4 H, C_5H_4N), 8.55 (br s, 1 H, NH).

***N*-(2-Picolinoyl)glycine.** A suspension of the ethyl ester (22.3 g) in water (40 mL) was heated at 80 °C and stirred vigorously as 1 equiv of NaOH (104.9 mL of 1.024 M) was added dropwise over 1.5 h. The clear

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solution was stirred a further 0.5 h at 80 °C and then overnight at room temperature. The filtered solution was treated with 1 equiv of HCl (12.3 M, 8.74 mL), whereupon a white precipitate formed. The mixture was cooled and filtered, and the white solid was washed with cold water and dried. Another crop of crystals was obtained by concentrating and cooling the filtrate. The combined crops (18.6 g) were recrystallized from hot water (60 mL) to give the product as large colorless prisms: 17.6 g, 91%; mp 167–168 °C [lit.[25] 164–165 °C]; ^{1}H NMR (d_6-Me_2SO) δ 3.98 (d, 2 H, J = 6 Hz, NCH_2), 7.4–8.68 (m, 4 H, C_5H_4N), 8.9 (br m, 1 H, NH).

Preparation of Complexes. [Co((*S*,*S*)-proam)Cl$_3$]. Hydrochloric acid (12.3 M, 10.8 mL) was added to a cooled solution of proam (8 g) in water (8 mL). This solution was added to a suspension of $Na_3[Co(CO_3)_3]\cdot 3H_2O$[26] (15.8 g) in water (80 mL), and the mixture was heated on a steam bath (10 min). The purple-brown mixture was filtered through a broad pad of Celite and washed through with water. The purple filtrate was concentrated on a rotary evaporator to a volume of ca. 40 mL, then it was treated with HCl (12.3 M, 12 mL), and the mixture was allowed to stand (12 h) at room temperature. The brown crystals that precipitated were filtered, washed with water and acetone, and then dried; 11.9 g, 78%. Anal. Calcd for $C_{10}H_{21}Cl_3CoN_3$: C, 34.5; H, 6.1; N, 12.1; Cl, 30.5. Found: C, 34.2; H, 6.1; N, 12.3; Cl, 30.8.

[Co((*S*,*S*)-proam)(picgly)]Cl. [Co((*S*,*S*)-proam)Cl$_3$] (0.92 g) and picglyH$_2$ (0.48 g) were suspended and stirred in dry DMF (5.5 mL) as the temperature of the mixture was raised to 80 °C. Then triethylamine (0.56 mL; 1.5 equiv) was added, and the temperature was maintained at 80 °C. After 5 min, a further 0.56 mL of triethylamine was added and the mixture was stirred at 80 °C for 40 min. During this time the starting materials dissolved and the product deposited as orange crystals. The mixture was allowed to cool slowly to 25 °C, and the solid was collected, washed thoroughly with DMF and then with acetone, and finally with pentane. The orange solid was taken up in methanol (5 mL) and was precipitated by the slow addition of acetone with cooling. The complex crystallized with one molecule of acetone which was removed under high vacuum at 50 °C; 0.92 g, 76%. Anal. Calcd for $C_{18}H_{27}N_5O_3ClCo$: C, 47.4; H, 6.0; N, 15.4; Cl, 7.8. Found: C, 47.3; H, 5.9; N, 15.3; Cl, 7.7.

[^{2}H$_1$]-Glycine Complex of [Co((*S*,*S*)-proam)(picgly)]Cl. The half-deuterated glycine methyl ester was prepared according to the method of Lehn[27] and was coupled to picolinic acid by the method described here for the ethyl ester. In order to avoid proton exchange, the *N*-(2-picolinoyl)[^{2}H$_1$]glycine methyl ester was hydrolyzed with 1.2 equiv of a 0.5 N aqueous solution of NaOH at 25 °C for 24 h. No α-proton exchange occurred, and the half-deuterated picglyH$_2$ was reacted with [Co((*S*,*S*)-proam)Cl$_3$] by the method just described. The product was found to contain over 98% pure racemic glycine.

Kinetics. A typical procedure for the kinetic runs was as follows. [Co((*S*,*S*)-proam)(picgly)]Cl (0.125 g) was dissolved in D_2O (2 mL; 99.8 atom %) containing DSS (5 mg) and $NaHCO_3$ (3.75 mg; 99%). The solution was allowed to stand at 25 °C for 15 min in a closed flask to allow the NH protons to fully exchange. The solution was then lyophilized, and the dry residue was taken up in D_2O (1 mL; 99.996 atom %). After standing for 15 min, the solution was lyophilized and the residue was taken up in D_2O (1.25 mL; 99.996 atom %) in an NMR tube; the ratio of NH deuterated complex to H_2O was now 12:1. After the solution was thermally equilibrated at 25 °C, Na_2CO_3 (21.25 mg; 99.999%) was added to it to raise the pD to 11.2. The exchange of the methylene protons of the glycine residue was monitored by the disappearance of the (methylene) signals at δ ~4 by using a varian XL 200-MHz NMR spectrometer. The areas of these signals were normalized to the downfield pyridine proton signals. At the completion of the exchange, the pD was checked. After computer deconvolution of the peaks for the initial exchange, plots of ln (area) vs. time gave excellent straight lines for three half-lives of reaction for all exchange reactions. At the end of the exchange, the amount of ^{1}H incorporation into the complex was negligible, establishing that essentially irreversible exchange conditions prevailed.

Preparation of Chiral Glycine. The α-glycine protons of [Co((*S*,*S*)-proam)(picgly)]Cl (0.5 g) were allowed to exchange under the same conditions described for the kinetic runs. After 63% total deuteration, the reaction was quenched to pD 7 by the addition of DCl and then H_2S was bubbled through the solution for 15 min. The black precipitate was filtered through Celite and was washed thoroughly with water. The volume of the filtrate was reduced in vacuo to 5 mL, and the solution was loaded onto an anion exchange column (Dowex 2-X8, 20 mL, OH^- form). The (*S*,*S*)-proam was first washed off with water (200 mL), and then the picglyH$_2$ was eluted with HCl (10%, 100 mL). The volume of the acidic solution containing picglyH$_2$ was concentrated until it was 6 N in HCl, and the picglyH$_2$ was hydrolyzed by refluxing this solution for 8 h. This solution was then cooled and neutralized with NaOH, and to it was slowly added simultaneously (1*S*,4*R*)-ω-camphanoyl chloride (120 mg) in ether (2 mL) and an aqueous solution of 2 N NaOH with vigorous stirring and with ice cooling at such a rate that the pH of the reaction mixture remained between 7 and 8. After the addition was complete, the reaction mixture was made basic (NaOH) to pH 9 and the water layer was extracted with ether. The water layer was then acidified to pH 3 and extracted with chloroform. The chloroform layer was dried (Na_2SO_4), filtered, and evaporated, leaving the desired camphanoyl glycinate and the camphanic acid; the latter does not interefere with the NMR assay of the α-glycine protons (Figure 9).

Crystal Structure. Crystals of [Co((*S*,*S*)-proam)(picgly)]Cl·2H$_2$O were obtained from methanol/acetone as thin red plates. Precession photographs were used to check crystal quality, which was generally poor. Eventually a suitable crystal was found, and further work on an Enraf-Nonius CAD4 diffractometer using graphite-monochromatized Mo Kα radiation (λ = 0.71069 Å) gave the crystal data summarized in the supplementary material. The absolute configuration was determined.

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Registry No. (*S*,*S*)-proam, 100702-16-7; picglyH$_2$, 5616-29-5; Co[(*S*,*S*)-proam]Cl$_3$, 100702-17-8; [Co((*S*,*S*)-roam)(picgly)]Cl, 100702-18-9; [^{2}H$_1$]-glycine complex of [Co((*S*,*S*)-proam)(picgly)]Cl, 100763-06-2; (*S*)-prolinol, 23356-96-9; *p*-toluenesulfonyl chloride, 98-59-9; (*S*)-*N*,*O*-bis(*p*-toluenesulfonyl)-2-(hydroxymethyl)pyrrolidine, 52682-03-8; (*S*)-2-(azidomethyl)-*N*-(*p*-toluenesulfonyl)pyrrolidine, 100702-11-2; (*S*)-2-(aminomethyl)-*N*-(*p*-toluenesulfonyl)pyrrolidine, 100702-12-3; *N*-(carbobenzyloxy)-L-proline *p*-nitrophenyl ester, 3304-59-4; (*S*)-2-[(*N*-((*S*)-*N*-benzyloxycarbonylprolyl)amino)methyl]-*N*-(*p*-toluenesulfonyl)pyrrolidine, 100702-13-4; (*S*)-2-[(*N*-((*S*)-*N*-benzyloxycarbonylprolyl)amino)methyl]-*N*-(*p*-toluenesulfonyl)pyrrolidine hydrobromide, 100702-14-5; (*S*)-2-[(*N*-(*S*)-prolylamino)methyl]-*N*-(*p*-toluenesulfonyl)pyrrolidine, 100702-15-6; picolinic acid, 98-98-6; glycine ethyl ester, 459-73-4; *N*-(2-picolinoyl)glycine ethyl ester, 39484-31-6.

Supplementary Material Available: Tables listing crystal data, bond lengths, and bond angles and a figure showing crystal packing details (6 pages). Ordering information is given on any current masthead page.

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