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Asymmetric Cyclization of Propylene Chlorohydrins Catalyzed by an Optically Active Cobalt(salen) Type Complex

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By using an optically active cobalt complex, *N,N′*-disalicylidene-(1*R*,2*R*)-1,2-cyclohexanediaminatocobalt(II), as a catalyst, optically active methyloxirane was synthesized by the asymmetric elimination of hydrogen chloride with a base from racemic propylene chlorohydrins. The highest optical purity of methyloxirane so far obtained was 35%, observed when 2-chloro-1-propanol and potassium carbonate were used as substrate and base, respectively. The optical rotations of the products and of the unchanged substrates indicate that (*S*)-1-chloro-2-propanol reacted selectively to produce (*S*)-methyloxirane, whereas in the case of 2-chloro-1-propanol, the (*R*)-isomer was preferentially cyclized to give (*S*)-methyloxirane with inversion of the asymmetric carbon. The physicochemical data of the circular dichroism and absorption spectra indicated a complexation of the optically active cobalt(II) species with potassium carbonate, either the (*R*)- or (*S*)-substrate interacting selectively with the Co^*/K_2CO_3 complex formed, followed by cyclization of the substrate.

There has been considerable interest in the reactivities of the square-planar, tetradentate Schiff base complexes of cobalt, such as cobaloxime and Co(salen) in connection with coenzyme B_{12}.[1,2] The reactions of low-spin complexes of cobalt(I) and cobalt(II) with organic halides are of some biochemical importance and constitute a versatile preparative method for organocobalt compounds. Schrauzer has presented evidence indicating that the reaction of vitamin B_{12s} with alkyl halide follows an S_N2 mechanism,[3] involving powerfully nucleophilic cobalt(I) species. On the other hand, Halpern *et al.* reported that the cobalt(II) complexes such as pentacyanocobaltate(II) and cobaltoxime(II) react with organic halides by a free radical mechanism.[4]

We recently reported the synthesis of an optically active cobalt complex, *N,N′*-disalicylidene-(1*R*,2*R*)-1,2-cyclohexanediaminatocobalt(II), $Co(II)(sal)_2$(*R*-CHXDA), and asymmetric reactions using the Co^I complexes, reduced derivatives of $Co(II)(sal)_2$(*R*-CHXDA).[5] In continuation of our studies,[6–8] we report here the synthesis of optically active methyloxirane by asymmetric cyclization of propylene chlorohydrins in the presence of the $Co(II)(sal)_2$(*R*-CHXDA) complex, a reaction which presumably involves an interaction between the cobalt species and C–Cl bond of the substrate prior to cyclization.

Experimental

Measurements. Absorption spectra were measured with a Shimadzu automatic recording spectrophotometer Model MPS-50L, and CD spectra with a JASCO Model J-20 spectrometer. Optical rotations were observed with a Perkin-Elmer Polarimeter Model 241. GLC analyses were carried out with a Hitachi Model K-53 Gas Chromatograph equipped with a column containing PEG. Thermogravimetry (TG) and differential thermal analyses(DTA) were made using a Rigaku-denki Model TG-DTA instrument.

Preparation of $Co(II)(sal)_2$*(*R-*CHXDA).* Reagents were purified by standard methods.[9] The $Co(II)(sal)_2$-(*R*-CHXDA) complex was prepared by a method described previously. *N,N′*-Disalicylidene-(1*R*,2*R*)-1,2-cyclohexanediamine, prepared by the reaction of (1*R*,2*R*)-1,2-cyclohexanediamine and two molar equivalents of salicylaldehyde, was allowed to react with anhydrous cobalt acetate in 1-propanol at 60 °C for 1 h with stirring to give $Co(II)(sal)_2$-(*R*-CHXDA) as an orange-red powder.[5]

Preparation of Propylene Chlorohydrin. 1-Chloro-2-propanol was prepared by modifying the procedure of Stewart and Vanderwerf.[10] Into a 2-L flask fitted with reflux condenser, stirrer, and dropping funnel was added 1L of dry ether and 50 g(1.28 mol) of $LiAlH_4$. After the mixture was cooled, 330 g(3.6 mol) of chloroacetone was added over a period of 6 h with stirring. The reaction mixture was stirred for 1 h before decomposition of the excess hydride with water. The ether layer was dried over magnesium sulfate, and 1-chloro-2-propanol was obtained by fractional distillation; bp 50.5 °C/30 mmHg, yield 55%. 2-Chloro-1-propanol was prepared by an analogous procedure involving the reduction of α-chloropropionic acid with $LiAlH_4$; bp 53 °C/29 mmHg, yield 35%.

Thermal Analyses of Potassium Carbonate and $Co(II)(sal)_2$*-(*R-*CHXDA).* The TG and DTA curves of commercial potassium carbonate, $Co(II)(sal)_2$(*R*-CHXDA), and a mixture of the carbonate and Co^{II} complex are shown in Fig. 1. The results indicate that reagent grade potassium carbonate contains a small amount of water and that it can be completely dried by heating at 130—150 °C. The $Co(II)(sal)_2$-(*R*-CHXDA) complex does not decompose on heating with carbonate up to 200 °C, as was also confirmed by infrared studies.

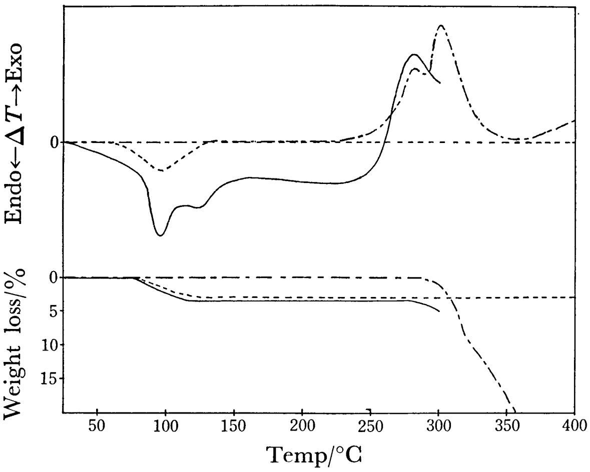


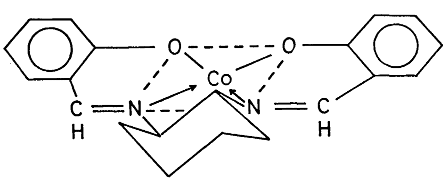
Fig. 1. TG and DTA curves for the systems of Co*(II)/K_2CO_3 (——), K_2CO_3 (----), and Co*(II) (—–—).

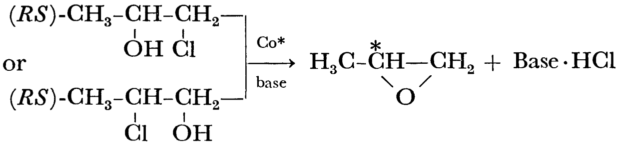
Asymmetric Cyclization of Propylene Chlorohydrins. Into a 50 ml-flask was charged 0.1895 g(0.5 mmol) of Co(II)-$(\mathrm{sal})_2$(*R*-CHXDA) and 8.292 g(60 mmol) of potassium carbonate. The mixture was dried at 130—150 °C for 3 h *in vacuo*. The experiment with hydrous K_2CO_3 did not require this period of heating. After cooling, 40 ml of solvent was added under dry nitrogen. A 120 mmol of 1-chloro-2-propanol or 2-chloro-1-propanol was added to the suspended solution and the reaction mixture was stirred at 25 °C. After an appropriate reaction time, the methyloxirane formed and the unconverted substrate were analyzed by gas chromatography. The optical rotations of the methyloxirane and propylene chlorohydrins recovered by fractional distillation were measured.

The optical purities (*e.e.*) of methyloxirane were evaluated from the optically pure methyloxirane, $[\alpha_0]_D = +12.53°$ (neat).[11] The expected optical purities ($e.e._{\mathrm{calcd}}$) of methyloxirane in Tables 1 and 2 were evaluated from the optical purities of the recovered substrates; $e.e._{\mathrm{calcd}} = [\alpha]/[\alpha_0]\{(100-\mathrm{conv.})/\mathrm{conv.}\} \times 100$. $[\alpha_0]_D = -19.19°$ (*c* 5.17 $CHCl_3$)[12] and $[\alpha_0]_D = -6.544°$ (neat) (calculated by, $[\alpha_0](\mathrm{neat}) = [\alpha_0](CHCl_3) \cdot [\alpha](\mathrm{neat})/[\alpha](CHCl_3)$) for pure (*R*)-1-chloro-2-propanol. $[\alpha_0]_D = +17.39°$(neat)[13] for pure (*S*)-2-chloro-1-propanol.

Results and Discussion

The complex, *N*,*N*′-disalicylidene-(1*R*,2*R*)-1,2-cyclohexanediaminatocobalt(II), has been established as low-spin square-planar complex (μ_{eff} 2.41 B.M.) having a λ-conformation of the central chelate ring.[5] By using the Co(II)$(\mathrm{sal})_2$(*R*-CHXDA) complex as a catalyst, asymmetric cyclization of 1-chloro-2-propanol or of 2-chloro-1-propanol was examined, according to the following principle. Namely, optically active methyloxirane may be obtained when either (*R*)- or (*S*)-substrate selectively interacts with the optically active cobalt species, followed by the elimination of hydrogen chloride from the selected substrate with a base.





The results with $[\mathrm{Co(III)(sal)_2}(R\text{-CHXDA})]^+I^-$ reported previously,[8] and subsequent experiments using a variety of bases, revealed that the combination of Co(II)$(\mathrm{sal})_2$(*R*-CHXDA) with potassium carbonate was most effective for this asymmetric reaction.

Asymmetric Cyclization. The reactions of 1-chloro-2-propanol and of 2-chloro-1-propanol with potassium carbonate were carried out in the presence of catalytic amounts of Co(II)$(\mathrm{sal})_2$(*R*-CHXDA) in several solvents. To make comparison with these reactions, analogous experiments without the $\mathrm{Co^{II}}$ complex were performed under similar conditions. Potassium carbonate is hygroscopic, and thus a small amount of H_2O (or OH^-) contained in it may affect the asymmetric reaction by functioning as a solvating agent for K_2CO_3 and/or axial base for the $\mathrm{Co^{II}}$ complex. Thermal analyses (see Experimental) showed that commercial

Table 1. Synthesis of methyloxirane (Me-oxir) by the asymmetric cyclization of 1-chloro-2-propanol (1-Cl-PrOH)

Base	Solvent[a]	Co*(II)[b]	Time / day	Conv.[c] / %	Me-oxir[d] / 1-Cl-2-PrOH %	Me-oxir		1-Cl-2-PrOH	
						$[\alpha]_D^{20}$ [e] / °	*e.e.*[f] / %	$[\alpha]_D^{20}$ [g] / °	$e.e._{\mathrm{calcd}}$[h] / %
Hydrous K_2CO_3	Diox	yes	5	17.2	69	−3.05	24.3	−0.26	19.2
	Diox	—	5	6.7	23	—	—	—	—
	Diox/H_2O	yes	5	11.1	47	−2.96	23.6	−0.18	—
	PrOH	yes	5	47.8	80	−1.68	13.4	−0.98	16.3
	PrOH	—	5	47.0	77	—	—	—	—
	DCE	yes	5	42.5	86	−2.70	21.5	−1.26	25.9
	DCE	—	5	18.4	82	—	—	—	—
	CH_2Cl_2	yes	5	47.7	87	−1.14[i]	18.3	−1.15	19.3
	CH_2Cl_2	—	5	23.1	88	—	—	—	—
	PhCl	yes	5	43.1	85	−2.22	17.7	−2.85[j]	—
Dry K_2CO_3	Diox	yes	5	16.4	82	−2.83	22.6	−0.33	25.9
	PrOH	yes	5	28.2	96	−0.90	7.2	−0.25	9.7
	DCE	yes	5	47.7	87	−0.79	6.3	−1.11	18.5

a) Diox: dioxane, PrOH: 1-propanol, DCE: 1,2-dichloroethane, PhCl: chlorobenzene, Diox/H_2O: 40/1(v/v). b) Co(II)$(\mathrm{sal})_2$(*R*-CHXDA). c) Conversion of 1-Cl-2-PrOH. d) Me-oxir formed/1-Cl-2-PrOH converted (mol/mol) ×100. e) Specific rotation of Me-oxir formed. f) Optical purity of Me-oxir formed; $[\alpha]_D = +12.53°$ (Ref. 11) for pure (*R*)-Me-oxir. g) Specific rotation of non-reacted 1-Cl-2-PrOH recovered. h) Optical purity of Me-oxir, evaluated from the optical purity of non-reacted 1-Cl-2-PrOH; $e.e._{\mathrm{calcd}} = [\alpha]/[\alpha_0]\{(100-\mathrm{conv.})/\mathrm{conv.}\} \times 100$; $[\alpha_0]_D = -19.19°$ (*c* 5.17 $CHCl_3$) (Ref. 12), $-6.544°$ (neat) [calcd, $[\alpha_0](\mathrm{neat}) = [\alpha_0](CHCl_3) \cdot [\alpha](\mathrm{neat})/[\alpha](CHCl_3)$] or pure (*R*)-1-Cl-2-PrOH. i) Measured in CH_2Cl_2 soln. j) Measured in PhCl/*m*-xylene soln.

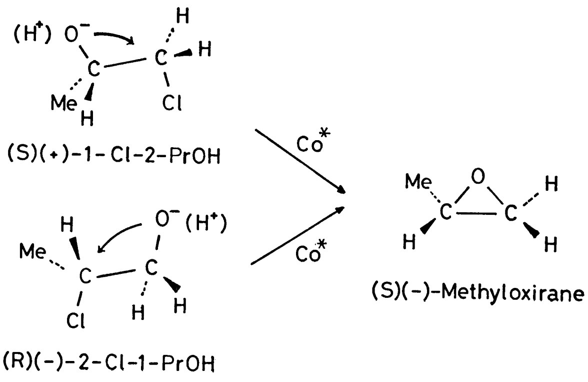
Table 2. Synthesis of methyloxirane (Me-oxir) by the asymmetric cyclization of 2-chloro-1-propanol (2-Cl-1-PrOH)

Base	Solvent$^{a)}$	Co*(II)$^{b)}$	Time day	Conv.$^{c)}$ %	Me-oxir$^{d)}$ / 2-Cl-1-PrOH %	Me-oxir		2-Cl-1-PrOH	
						$[\alpha]^{20}_D$ $^{e)}$ °	e.e.$^{f)}$ %	$[\alpha]^{20}_D$ $^{g)}$ °	e.e.$_{calcd}$$^{h)}$ %
Hydrous K_2CO_3	Diox	yes	15	9.9	62	−4.44	35.4	+0.27$^{i)}$	—
	Diox	—	6	2.6	66	—	—	—	—
	PrOH	yes	5	39.7	83	−0.26	2.1	+0.22	1.9
	PrOH	—	5	33.9	87	—	—	—	—
	DCE	yes	4	20.3	77	−1.23	9.8	+0.75	16.7
	DCE	—	4	43.4	25	—	—	—	—
Dry K_2CO_3	Diox	yes	4	8.8	84	−4.39	35.0	+0.64	38.3
	Diox	—	4	trace	—	—	—	—	—
	PrOH	yes	5	41.9	87	−1.92	15.3	+1.71	13.6
	PrOH	—	5	35.5	75	—	—	—	—
	DCE	yes	5	40.3	88	−3.34	26.7	+3.25	27.7
	DCE	—	5	17.8	82	—	—	—	—

a)—h) As in Table 1. $[\alpha]^{25}_D=17.39°$ (neat) (Ref. 13) for pure (*S*)-2-Cl-1-PrOH. i) Measured in Diox/*m*-xylene soln.

potassium carbonate contained about 2.7% water (*i.e.*, 0.213 mol of H_2O per mol of K_2CO_3) and that the carbonate was completely dried by heating at 130—150 °C *in vacuo*. We used both dry potassium carbonate (dry K_2CO_3) and commercial carbonate (hydrous K_2CO_3) as bases for the cyclization reactions.

The results with 1-chloro-2-propanol and 2-chloro-1-propanol are summarized in Tables 1 and 2, respectively. All the asymmetric reactions gave (*S*)(−)-methyloxirane. The highest optical purity was 35.4% ($[\alpha]_D=-4.44°$), when the cyclization of 2-chloro-1-propanol was carried out in a dioxane solution. The highest *e.e.* value from 1-chloro-2-propanol was 24.3%, which was observed in the reaction with hydrous K_2CO_3 in dioxane as well. The unchanged 1-chloro-2-propanol recovered showed (−) optical rotation, while the unchanged 2-chloro-1-propanol gave (+) rotation. These facts suggest that (*S*)-L-(+)-1-chloro-2-propanol is selectively bound to the optically active cobalt complex and converted to (*S*)-L-(−)-methyloxirane where no reaction is involved at the asymmetric center. They also suggest that the cyclization reaction of (*R*)-D-(−)-2-chloro-1-propanol to (*S*)-L-(−)-methyloxirane involves an inversion of configuration at the asymmetric carbon. The stereochemistry of the oxirane formation from halohydrin can be explained by assuming a mechanism in which cyclization takes place by a backside attack of the alcoholate anion formed initially by the action of a base, at the carbon atom bearing the leaving halogen atom.[14] This S_N2 ring-formation is considered to hold mainly for the above kinetic resolution reactions.



All the reactions using dry K_2CO_3 resulted in higher conversions of the reacted substrates to methyloxirane, as compared to the corresponding reactions with hydrous K_2CO_3. The ratios of methyloxirane formed to reacted 1-chloro-2-propanol or 2-chloro-1-propanol in Tables 1 and 2 are higher than 80%, implying that side reactions such as polymerization are considerably suppressed. This behavior is also demonstrated by the data in dioxane in Table 1; the ratios are 82, 69, and 47% for dry K_2CO_3 (Diox), hydrous K_2CO_3 (Diox), and hydrous K_2CO_3(Diox–H_2O), respectively. On the other hand, there is a tendency that, in regard to asymmetric selectivity, use of dry K_2CO_3, instead of hydrous K_2CO_3, causes decrease in selectivity in the reactions with 1-chloro-2-propanol, while methyloxirane having higher optical activities is obtained from 2-chloro-1-propanol.

The solvent effects were found to be complicated, as might be expected, since the solvents used have functional groups and heterogeneity of the reaction system is changeable according to the nature of solvent. The reaction in dioxane resulted in the best asymmetric selectivity, although the conversion was poor. In 1-propanol, a satisfactory yield of methyloxirane was obtained but the selectivity was disappointing. The results in 1,2-dichloroethane solvents are of interest; especially in the reaction of 2-chloro-1-propanol with dry K_2CO_3, a fairly high selectivity (*e.e.* 26.7%) was observed in spite of a high conversion (40.3% based on initial substrate and 80.6% on K_2CO_3). A similar result was obtained for the 1-chloro-2-propanol/hydrous K_2CO_3 system.

It is considered that, as for cyclization in the presence of Co(II)(sal)$_2$(*R*-CHXDA), the reaction proceeds by two parallel pathways, with respective cobalt*-catalyzed and non-Co*-catalyzed mechanisms, as given by Eqs. 1 and 2.

$$\text{substrate} + K_2CO_3 \xrightarrow{\text{Co*}} \text{methyloxirane*} \tag{1}$$

$$\text{substrate} + K_2CO_3 \longrightarrow \text{methyloxirane} \tag{2}$$

The data with dry K_2CO_3 in Table 2, which were the most reproducible, indicated that the highly asymmetric selectivity was achieved in dioxane because the Co*-catalyzed reaction (Eq. 1) took place almost exclusively. The reaction in 1-propanol, a highly polar solvent, involved to a considerable extent the non-Co*-catalyzed pathway (Eq. 2) in addition to Eq. 1, producing methyloxirane with low optical purity. The *e.e.* values of methyloxirane formed in the three solvents decrease in this order: dioxane>1,2-dichloroethane>1-propanol; this is consistent with the presumed order of the extents of Eq. 1 involved in the asymmetric reactions.

Mechanism of Asymmetric Cyclization. In order to obtain insight into the mechanism of the asymmetric cyclization of propylene chlorohydrins, the reaction systems were investigated by absorption and circular dichroism (CD) spectroscopy. The absorption spectrum of the Co(II)(sal)$_2$(*R*-CHXDA) complex itself and that of a binary system of Co(II)(sal)$_2$(*R*-CHXDA) and dry K_2CO_3 are shown in Fig. 2. The spectrum of the latter is very similar to that of the Co^{II} complex itself and is completely different from those of such Co^I complexes as Li$^+$[Co(I)(sal)$_2$(*R*-CHXDA)]$^-$ [5] and Na$^+$[Co(I)(salen)]$^-$.[15] This indicates that the cobalt species in the Co(II)(sal)$_2$(*R*-CHXDA)/K_2CO_3 system is not reduced to Co^I, but remains as the Co^{II} state.

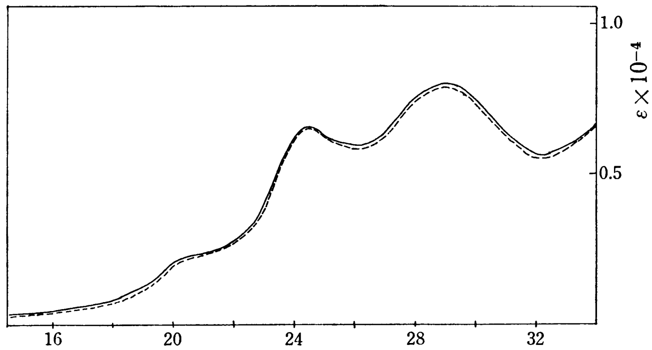


Fig. 2. The absorption spectra of Co*(II) (——) and of Co*(II)/K_2CO_3 (----) in dioxane.

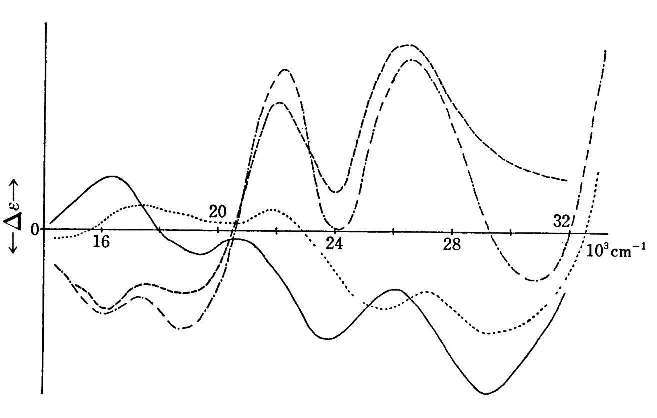


Fig. 3. The CD spectra for the systems of Co*(II) (——), Co*(II)/K_2CO_3 (----), Co*(II)/K_2CO_3/1-Cl-2-PrOH (—·—·), and Co*(II)/K_2CO_3/2-Cl-1-PrOH (······). Measured as dioxane solutions saturated with the Co* species.

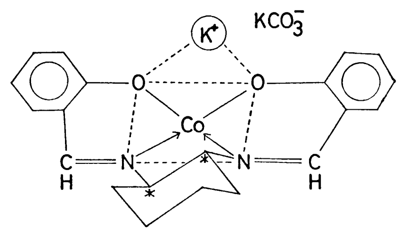
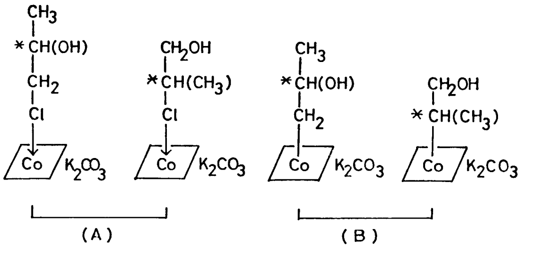


Fig. 4. A possible structure of Co*(II)/K_2CO_3 complex.

The CD spectra of Co(II)(sal)$_2$(*R*-CHXDA) itself and systems of Co^{II}/K_2CO_3, Co^{II}/K_2CO_3/1-chloro-2-propanol, and Co^{II}/K_2CO_3/2-chloro-1-propanol are depicted in Fig. 3. A marked spectral difference is observed between the Co^{II}/K_2CO_3 system and the Co^{II} complex itself, which indicates the formation of a complex between the Co(II)(sal)$_2$(*R*-CHXDA) and K_2CO_3 by combination of a potassium atom of K_2CO_3 with the two phenolic oxygens (Fig. 4), as suggested by related systems.[16]

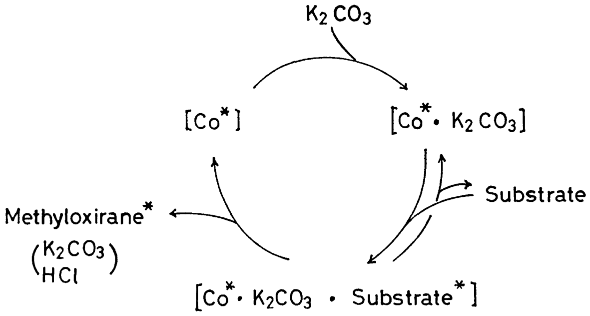
Little change occurred in the CD spectrum when 1-chloro-2-propanol was added to the Co^{II}/K_2CO_3 system, whereas a drastic change was observed in the case of 2-chloro-1-propanol, as shown in Fig. 3. The CD spectral data for the Co^{II}/K_2CO_3/propylene chlorohydrin systems suggest the formation of new chiral complexes such as (A) and/or (B).[4]



The large CD spectral change for the system of 2-chloro-1-propanol can be interpreted in terms of large chiral and steric effects of the asymmetric moiety, ClC*H(CH$_3$)CH$_2$OH or –C*H(CH$_3$)CH$_2$OH, on the chiral circumstance around the central cobalt atom, compared with the case of 1-chloro-2-propanol system. The complexes of type (B) are considered to be rearranged to ketone or aldehyde under basic conditions; the formation of methyloxirane from the (B)-complexes seems unlikely.[5,17]

On the basis of the results so far obtained, this kinetic resolution type reaction which gives rise to optically active methyloxirane from 1-chloro-2-propanol or 2-chloro-1-propanol is considered to proceed by the mechanism depicted in Scheme 1; the selection of (*R*)- or (*S*)-substrate would take place at the stage of coordination of the substrate onto the chiral cobalt complex.

Further investigations are now in progress.



Scheme 1.

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