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**Asymmetric Induction Due to Chiral Crystal Environment
in Cobaloxime Complexes**

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1998

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The present study was achieved under the supervision of Prof. Yuji Ohashi
at Tokyo Insititute of Technology.

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Chapter 1

Introduction

1-1 Molecular Chirality

Chirality is attractive for scientists, especially in the field of physics, chemistry, biology and crystallography. The study on chirality is an interdisciplinary research. An interesting instance for the chirality can be found in "*The Ambidextrous Universe*" [1] which is a masterpiece in a science book. Professor V. Prelog, who won the Nobel prize for chemistry in 1975, gave a lecture on "*Chirality in Chemistry*" at Stockholm [2]. Many objects of our three-dimensional perceptual world are not only chiral and appear in nature in two versions as a chiral object and its mirror image. Most of organic compounds are dissymmetric molecule but natural products having the asymmetric carbon atom are enormous. The fact is probably originated from that the natural products had their origins in a living system. Early chemists considered that all the organic compounds cannot be produced without organism. However organic chemists nowadays synthesized not only organic compounds but also chiral molecules. Asymmetric induction involves the formation of chiral molecule. Molecular chirality arouses the chemical curiosity from theoretical and experimental view points, and the control and design of the chiral molecules awake our scientific interest. Notably the vast majority of biologically active molecule are chiral and their

chirality is essential to their function. Recently the importance of optically active compounds for pharmaceutical usages has increased more and more. I believe, the chemical insight should be instructive to understanding of a variety of problems concerning the molecular chirality.

1-2 Generation of Chirality

Chiral molecule cannot be generated without asymmetric physical origins or chiral chemical reagents. Although we do not know how chiral molecule has generated in universe [3][4], nowadays a variety of chiral generation can be observed in different situations. The method of the molecular chirality generation should be divided roughly into three classes: (1) optical resolution, (2) asymmetric transformation and (3) asymmetric induction.

At first, the works on optical resolution and asymmetric transformation will be described briefly, and then the works on asymmetric induction will be described.

Optical Resolution

The molecule may be chiral only if it does not possess an axial of improper symmetry operation **Sn**. However we need to be aware that the chiral molecule may be generated if one conformation can be maintained when the rotational energy is sufficiently large. To take a simple example, *n*-butane or biphenyl can even become a chiral molecule if the rotational freedom is frozen. As is well-known, both 1,1'-biphenyl and 1,1'-binaphthyl have interconvertible enantiomers with moderately hindered rotation, while 2,2'- and 6,6'-substituted biphenyl and 1,1'-bi-2-naphthol are apparently chiral. Although it is known that achiral 1,1'-binaphthyl were forced to crystallize spontaneously as optically active crystals [5][6]. The optically active crystallization from racemic substances is attractive from the view point of chiral generation without the help of the optically active reagents. The formation of organic crystal with non-centrosymmetry was carried out to be

related to the molecular conformation [7]. For instance, unsymmetrically substituted tolans (diphenylacetylene derivative) with moderate dipole moments are likely to adopt nonplanar, chiral conformations in the solid state and noncentrosymmetric space groups [7]. This study is utilized for the formation of a in chiral crystal for achiral molecules in order to obtain the absolute asymmetric induction.

The optically active hosts in host-guest inclusion complexes are useful for the efficient optical resolution of various racemic compounds. Toda et al. have utilized the molecular recognition by this method. For example, when a solution of compound **1** (Scheme 1) and an equimolar amount of *rac*-1-carbomethoxy-2,2-dimethylethylene oxide **2** in ether was kept, 2 : 1 inclusion crystal of compound **1** and **2** was obtained [8]. After purification, the complex was heated to give compound **2** of 93%ee in 32% yield. It is very difficult to prepare a trisubstituted ethylene oxide of high optical purity by asymmetric epoxidation of olefins. Such optical resolution method is especially valuable.

Asymmetric Transformation

The asymmetric transformation indicates optical enrichment from racemic crystals in chiral crystal environment. A good example for the asymmetric transformation was reported by Ohashi et al. that when the racemic crystal of the (1-cyanoethyl)(pyperidine)cobaloxime with the chiral space group is photoirradiated, a very interesting phenomenon was observed [9]. This racemic crystal consists of the crystallographically independent molecules A and B in the asymmetric unit, but the chemical substance is the same to each other. The crystal structures before and after photoirradiation are similar except that the reactive group in molecule B has a disordered racemates, although there is only **R** configuration before irradiation, the racemic reactive group appeared after irradiation. The ratio of **R** and **S** configuration become 70 : 30 in a whole crystal. It is obvious that chirality can be generated only by photoirradiation, if the molecular is packed

unsymmetrically in the chiral crystal, even though it is racemic crystal.

Asymmetric Induction

The solid state reaction is strongly influenced by the crystal structure. The chiral crystal environment or the optically active host compound is useful for enantioselective reaction of a prochiral guest compound. In particular, the absolute asymmetric induction would be observed if the achiral molecule forms the optically active crystal.

An ever-increasing number of asymmetric inductions in literature indicate that the photochemical reactions carried out in chiral crystal environment can lead to enantiomerically enriched products in high optical yields. Recently, the work on solid state reactions were reviewed by many scientists. Desiraju et al. gave a review on "*The Reactivity of Organic Solids*" [10], Ohashi gave a review on "*Reactivity in Molecular Crystals*" [11][12], Gavezzotti and Simonetta gave a review on "*Crystal Chemistry in Organic Solid*" [13], Dunitz gave a review on "*Phase Change and Chemical Reactions in Molecular Crystals*" [14] and Ramamurthy and Venkatesan gave a review on "*Photochemical Reactions of Organic Crystals*" [15]. In these reviews, it was said that the topochemical principle [16][17][18], that the reaction in the solid state proceed with a minimum of the atomic or molecular movement, has contributed to the organic solid state reaction. In fact, most of reactions in molecular crystal proceed topochemically. The topochemical reaction was studied extensively, for example photochemical [2+2] cycloaddition of alkenes. The reactivity are governed by the molecular geometry in the crystal structure. A slight modification of the chemical structure give rise to influence the topochemical behavior. If the asymmetric product is produced from the achiral reactant in chiral crystal environment, the reaction is known as an absolute asymmetric reaction, which means the asymmetry is deduced only by the physical origin without any chemical reagent. Kaupp gave a review on "*Absolute Asymmetric Reactions*" [19].

The X-ray structure determination plays an important role in the field of the

solid state reaction. In specially, X-ray analyses before and after reaction are the most powerful method for understanding the mechanism of the solid state reaction. In this section, the role of chiral crystal environment in unimolecular, bimolecular and host-guest inclusion complex will be described.

Unimolecular example

The reaction of the chiral crystal of achiral *N,N*-diisopropylbenzoylformamide **3** are well-known example of photocyclization to the optically active β -lactam **4** derivative of high optical purity in good chemical yield [20]. The X-ray structures both reactant and product crystals were determined in order to explain why achiral molecule form the chiral crystal and why enantioselective photocyclization proceeds so efficiently [21]. It was revealed that *N,N*-diisopropylbenzoylformamide **3** take a skewed conformation in chiral crystal and the absolute configuration of product was determined by the orientation of the carbonyl oxygen in the reaction site.

Sakamoto et al. also studied that the absolute asymmetric inductions of various *N*-(α,β -unsaturated carbonyl)benzoylformamides in both the solid and solution states. Such absolute asymmetric inductions are interesting in relation to the origin of the optically active compounds in universe.

Scheffer et al. have studied that di- π -methane photorearrangement with high enantiomeric yield in chiral crystal environment [22]. The compound **5** crystallized in the chiral space group $P2_12_12_1$ and the photoirradiation of **5** gave the compound **6** in high enantiomer excess in contrast to those in solutions in which only racemic photoproducts was given. Recently, the absolute steric course of an enantioselective single crystal-to-single crystal photorearrangement was studied [23]. Achiral dibenzobarrelene acids crystallized as chiral crystals by salt formation with chiral amines. Photolysis of these salts in the solid state gave photoproducts in high enantiomer excess. In solutions only racemic photoproducts were obtained.

This results was explained the absolute steric course of the di- π -methane reaction and the structural features characteristics that control the enantioselectivity [24]. The enantiomer excesses rang from 30 to 68% depending on the optically active sulfonic acid employed [25]. The asymmetric influence by the chiral crystal lattice may have variable effects on reaction enantioselectivity [26].

Bimolecular example

The topochemical reactions of *trans*-cinnamic acid in the crystalline state are well-known examples of [2+2] photodimerization [16] [17] [18] and such reactions are the typical example on the bimolecular reactions.

There are very few chiral crystals that are composed of two achiral compounds, except for charge-transfer complex. These crystals offer the intermolecular solid state reaction, in contrast to described above.

Koshima et al. have studied how the chirality in a two-component molecular crystal is generated and absolute asymmetric photodecarboxylating condensation is occurs. For example, a chiral two-component molecular crystal ($P2_12_12_1$) composed of acridine **7** and diphenylacetic acid **8**, which are achiral molecule, was prepared spontaneously and it was photoirradiated. An absolute asymmetric reaction was achieved in 33-39%ee by a photodecarboxylating condensation [27].

Example of inclusion complex

Toda et al. carried out extensively the solid-state asymmetric induction, such as pinacol rearrangement, Baeyer-Villiger oxidation, Grignard reaction, Witting-Hornar reaction, Aldol condensation and host-guest inclusion complex reaction with higher optical yield than those in the solution state. Here the the works on the host-guest inclusion complexes will be introduced briefly. It is known that molecules move from crystal to crystal under appropriate conditions [28]. Toda et al. reported that the mixing of powdered chiral host and achiral guest compound in the solid state gave inclusion

complex crystals in which the guest molecules are arranged in a chiral form. For example, the crystal (d 50-100 mm) of the inclusion complex of **1** and **9** was obtained just by mixing in the solid state. Photoirradiation of this inclusion complex in water suspension gave **1** of 99%ee in 48% yield.

Temperature Dependence in solid state reaction

It is found that the rate of most chemical reactions increase as the temperature is raised, but the asymmetric yield of most chemical reactions decreases as the temperature is raised. An empirical observation was explained by the combination of the Arrhenius equation and activation Gibbs energy.

The relationship between reaction rate of the racemization and the cavity volume in cobaloxime complexes was reported [29]. In addition, the temperature dependence of the racemization in cobaloxime complex was studied. This temperature dependence explained that the cavity volume around the reaction group increased when the temperature is raised, regardless the density of the crystal [29].

1-3 Cobaloxime in Chemistry

Cobaloxime is famous as a model compound of a Vitamin B₁₂ coenzyme, similar to another organocobalt derivatives of B₁₂ model compounds [30]. Cobaloxime complexes can form a variety of alkylcobaloxime complex such as methyl-, cyano-, cyanoethyl-, cyanopropyl-, methoxycarbonyl-ethyl- and di(methoxycarbonyl)ethyl complexes. In addition, cobaloxime complexes can be coordinated by a various base ligands implying the optically active compounds.

Photochemical reactions of cobaloxime complexes have been studied extensively. Similar to many corrinoids, the most striking feature of cobaloxime complexes is the cobalt-carbon bond. Hodgkin and co-workers

have discovered this unique organometallic bond in adenosylcobalamin [30]. Cobaloxime complexes occur chemical reaction such as photolysis, isomerization, racemization, epimerization and reduction. The reaction of alkylcobaloximes primary involve fission of the cobalt-carbon bond homolitycally. The ESR spectra results in the homolytical cleavage of cobalt-carbon bond on exposure to visible light in alkylcobaloxime complex [31][32][33][34][35] and X-ray analysis results in the cobalt-carbon bond cleavage in crystalline state reaction of the 1-cyanoethylcobaloxime complex [36][37]. The structure and reactivity of cobaloxime will be described in this section.

1-3-1 Structure

The structural feature of cobaloxime complexes is summarized in (1) plannality of the cobaloxime plane, (2) conformation of the reaction group and (3) anomalous trans-influences. In this categories, the most important one in the structure-reactivity correlation is the conformation of reactive group.

Cobaloxime complex consists of an alkyl group **R** on the side and a neutral base **B** on the other side of the so-called cobaloxime plane formed by the two dimethylglyoxime ligands ($\text{RCo}(\text{DH})_2\text{B}$). An idealized cobaloxime plane formed by 17 non-hydrogen atoms shows D_{2h} point group symmetry. In real, the D_{2h} symmetry of an idealized cobaloxime plane is reduced and characterized by out-of-plane deformation, such as bending, tilt or propeller, in crystal structure. Although the out-of-plane deformation has no influence on the reactivity of cobaloxime complex because the extent of the deformation is small.

In crystal, the 2-cyanoethyl group takes a perpendicular conformation or a parallel conformation to the cobaloxime plane, as shown in Figure 1-1. The averaged dihedral angles, defined as Co-C-C-CN angle, of their two conformations are 175.75° in perpendicular conformation and 83.41° in parallel conformation, respectively, when the related structures are retrieved

from the Cambridge Structure Database (1997). Difference in conformation of the 2-cyanoethyl group shows important effect on the solid-state photoisomerization, and the effect it will be described later in detail.

Anomalous trans-influence of cobaloxime was reported by Bürgi et al. In a series of $\text{RCo}(\text{DH})_2\text{B}$ complexes, the Co-R and Co-B bond distances have a correlative in which the two distances lengthen or shorten simultaneously but to different extent. This anomalous trans-influence is discussed comparing the characteristics of the axial ligands **R** and B, and discussed in terms of a simple Hückel molecular orbital model. No significant correlation has been found between the out-of-plane deformations and changes in the axial Co-C and Co-N distance. Bürgi et al. has described in this literature as follows; it is very likely that exploiting the anomalous trans-influence in the cobaloxime complex contributes significantly to the high rate of carbon radical formation, because this may well be one contribution towards an accelerated Co-C bond cleavage. This is contrary to the usual behavior in which lengthening of one bond is accompanied by shortening of the bond in the trans position or vice versa.

Similar analysis for 2-cyanoethylcobaloxime complex was carried out to retrieving from Cambridge Structure Database (1997) and Co-R distance was scatter-plotted to the Co-B distance as shown in Figure 1-2. Figure 1-2 shows the anomalous trans-influence of 2-cyanoethylcobaloxime complexes.

1-3-2 Reactivity

The reactivity of cobaloxime complexes is observed mainly in isomerization and racemization on exposure to visible light in the solid state. The reactivity has a good correlation with the crystal and molecular structure.

Isomerization

The 2-cyanoethyl cobaloxime complex is found to be photoisomerized to the 1-cyanoethyl group in the solid state, as shown in Figure 1-3. First observation was reported by Ohgo et al. that the KBr disk of 2-

cyanoethyl(pyridine)cobaloxime complex was isomerized unexpectedly to 1-cyanoethyl complex by sun-light [38]. The reaction proceeds only in the solid state, and the reverse reaction has not been observed. Notably this reaction accompanies the rearrangement of Co-C bond and produces the optically active carbon atom in the cyanoethyl group. Extensive studies have been carried out and it was examined the relation between the crystal structure and the reactivity [39][40][41][42]. As a result, three factors were found to effect the reaction rate [43]; (1) conformation of the reactive group, (2) hydrogen bond with the reactive group and (3) cavity volume around the reactive group. The reaction rates of a series of 2-cyanoethyl cobaloxime complexes with different axial ligands are listed with conformations of the reactive group in Table 1-1. The reason why the reaction rate of the parallel conformer is greater than that of perpendicular one was explained by the topochemical factors. Namely, the photoproducted 1-cyanoethyl group is geometrically resemble to the parallel conformer than the perpendicular conformer.

The hydrogen bond with the reactive group also affects the reaction rate. For example, the X-ray crystal structures of the 2-cyanoethyl cobaloxime coordinated by aniline, 3-aminopyridine [44] and phenylalaninol [45] as axial ligands revealed to take parallel and perpendicular conformers with hydrogen bond. The reaction rates obtained from changes in IR spectra were greater than those of related compounds of parallel conformer and smaller than those of related compounds of perpendicular conformer. The hydrogen bonds should be responsible for the greater and smaller reaction rates of the parallel and perpendicular conformer, respectively.

If the former two factors are the same, the reaction rates depends on the cavity volume for the reactive group [46]. The definition of the reaction cavity is shown in Figure 1-4. For example, the 2-cyanoethyl cobaloxime complexes coordinated by 3-methyl-, 3-chloro- and 3-bromopyridines were photoisomerized with retention of the single-crystal form. The reaction rates were estimated from the changes of unit-cell dimensions and from the

change of the IR spectra [47]. Table 1-1 shows the reaction rate with the cavity volume for the reaction group. The reaction rate depends on the volumes of the reaction cavity [12]. The mixed crystal of 2-cyanoethyl(3-methylpyridine)cobaloxime complex with 1-cyanoethyl complex is isomorphous to the 2-cyanoethyl complex crystal and the reaction rate is much faster than that of the 2-cyanoethyl complex crystal due to the greater cavity [48]. The reaction rates of four different crystal forms of the (2-cyanoethyl)(triphenylphosphine)cobaloxime complex depend on their cavity volumes [46].

The 2-cyanoethylcobaloxime complex coordinated by 3-methyl- and 4-methylpyridine are photoisomerized with retention of the single crystal form. The X-ray crystal structures before and after photoirradiation was determined and revealed the ratio of **R**- and **S**-configuration in different population. The reason why such different degrees of asymmetry were generated in the produced 1-cyanoethyl groups was explained by the difference in shape of the reaction cavities [49].

When several complex crystals with chiral space groups were photoirradiated in the solid state, the diastereomerically enriched products was obtained due to the chiral crystal environment. For example, a high optical yield was obtained using (**R**)-2-amino-2-phenylethanol as an axial ligand base [50]. The shape of the reaction cavity of the reactive group suggested that the configuration of produced 1-cyanoethyl group was in accord with the asymmetric environment for the reaction group.

Recently, it was reported that (3-cyanopropyl) (phenylethylamine) cobaloxime is photoisomerized to 1-cyanopropylcobaloxime in 100% of reaction yield with high diastereomer excess. The crystal structure of 2-cyanopropyl cobaloxime complex is similar to that of 2-cyanoethyl cobaloxime complex.

Racemization

Chiral alkylcobaloxime crystal is found to be photoracemized without degradation of the single crystal form [51][52]. Ohashi et al. reported that the

structures of [(**R**)-1-cyanoethyl] [(**S**)- α -methylbenzylamine]cobaloxime [2x][3x] were obtained at the initial, intermediate, and final stages of the change. The electron density map at every stage proves that the (**R**)-1-cyanoethyl group gradually changed to the disordered racemates so that the complex revealed in epimerization. The reaction rates of racemization are different cobaloxime complexes although they are almost the same in solution. Extensive studies on the racemization have been carried out and it was examined the relation between crystal structure and the reactivity. As a result, the reaction rate of the racemization depend on the cavity volume for the reaction group regardless of the chemical properties of the axial ligands. In the case of 1-cyanoethyl cobaloxime, the reaction rate is mainly controlled by the cavity volume for the reactive group [12] In crystalline state racemization of cobaloxime complexes, the reaction rate and the reaction cavity depend linearly on temperature [29]. The change of the unit cell dimensions did not reveal the true rate when the cavity was large enough. The Arrhenius plot indicated that the activation energy for the crystalline-state racemization is 5-9 kJ mol⁻¹.

Epimerization

When the diastereomerically alkylcobaloxime coordinated by a chiral base ligand was photoirradiated in crystal, it is expected the asymmetrically racemization of cyanoethyl group due to the chiral crystal environment. This reaction so-called epimerization is similar to the photoirradiation of 2-cyanoethyl cobaloxime complex in the point of asymmetric induction due to chiral crystal environment.

Reaction in Solution

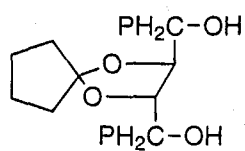
In solution, the photoreactivity of the 2-cyanoethylcobaloxime complexes is different from that in solid state. The ¹H NMR spectrum in CDCl₃ solution after photoirradiation results in the reaction that the photoisomerization of

the 2-cyanoethylcobaloxime complex does not occur in solution since the reaction shown in below occurs rapidly and H₂ is expelled out of the solution system [12].

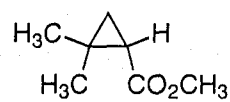


1-4 Purposes and Scope of Present Study

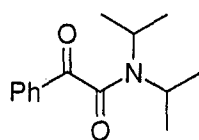
More than a decade have already passed since the solid state reaction without solvents have been studied in cobaloxime complexes. This study is of relevance to the theme in solid-state organic reactions and asymmetric reactions, as well as organometallic chemistry, notably biochemical rearrangements promoted by coenzyme B₁₂. Extensive study concerning the solid state reaction of cobaloxime has been carried out. The combination of the solid state chemistry and X-ray crystallography has proved to be invaluable for structure-reactivity correlation studies. The motivation of the present study on asymmetric induction is the chemical curiosity, that is the scope of chiral induction due to the chiral crystal environment and investigation what stereoselective reaction in the crystal structure is governed mainly. In the present study, the mechanism of the asymmetric induction in 2-cyanoethylcobaloxime will be demonstrated from a viewpoint of the combination of crystal structure, reactivity and molecular simulation.



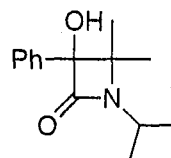
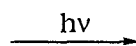
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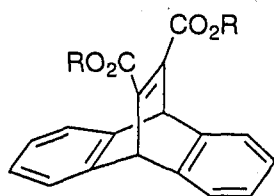
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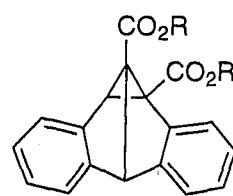
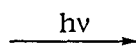
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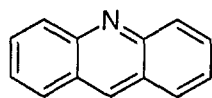
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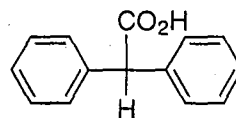
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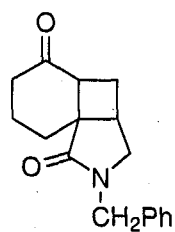
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Scheme 1

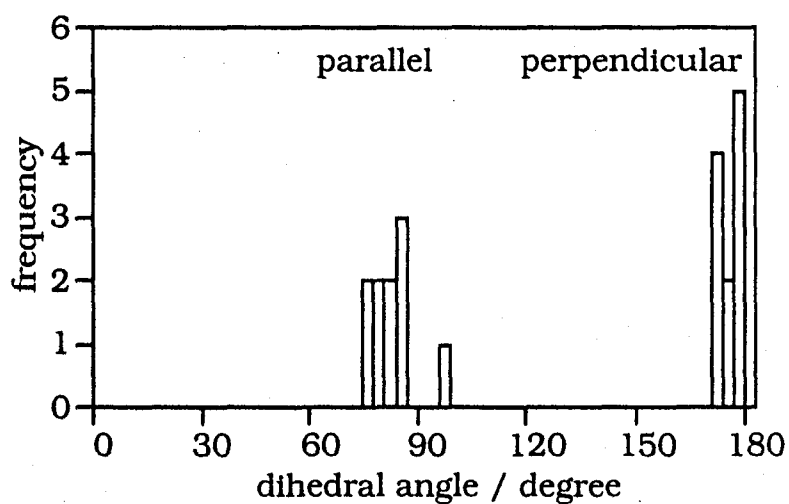
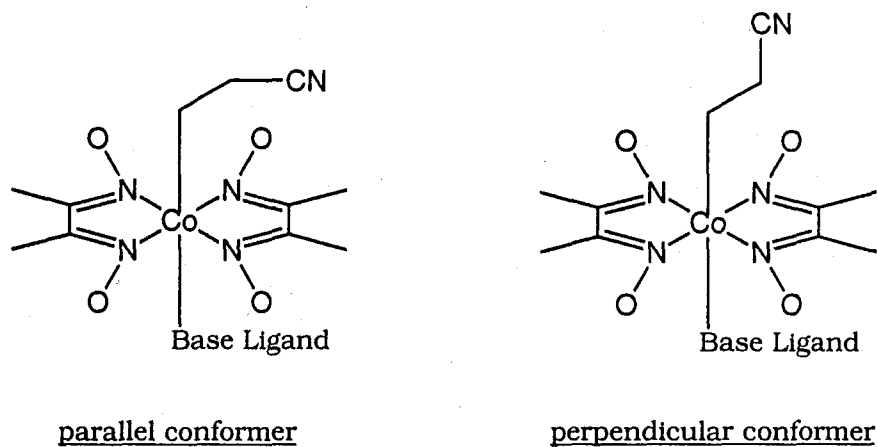


Figure 1-1 Difference in the conformation of the 2-cyanoethyl group : a parallel (top left) and a perpendicular conformation (top right), and the statical distribution (bottom) of the parallel and perpendicular conformation of the 2-cyanoethyl group to retrieving from the Cambridge Structure Database (1997), where the dihedral angle was defined as Co-C-C-CN angle.

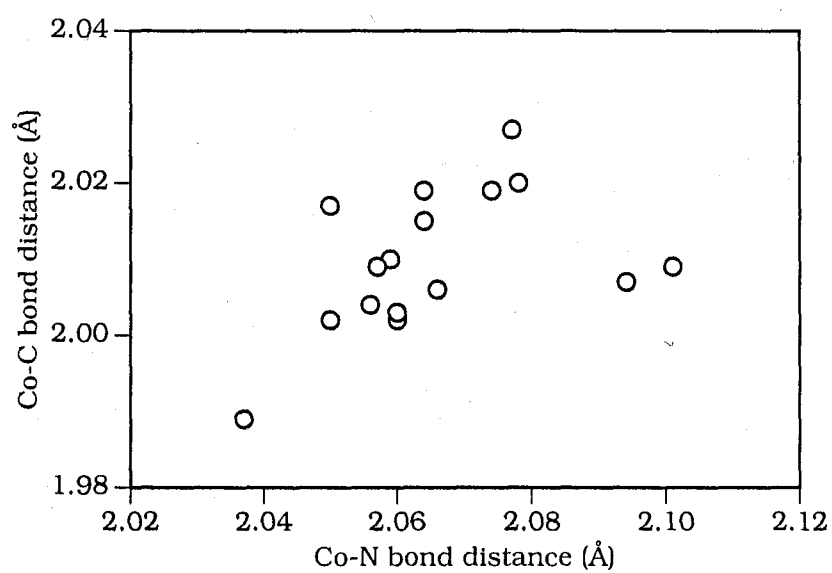


Figure 1-2 Anomalous trans influence of the 2-cyanoethyl cobaloxime complexes to retrieving from the Cambridge Structure Database (1997)

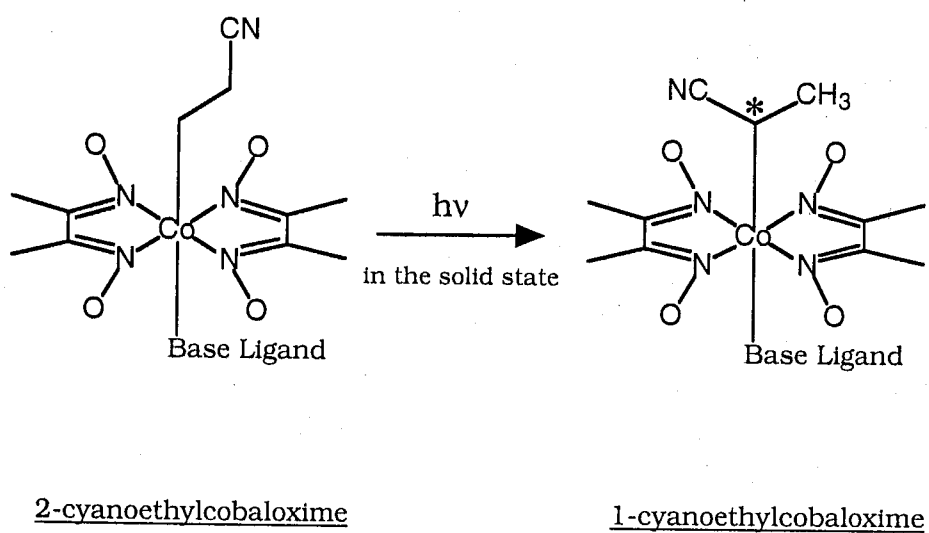


Figure 1-3 Schematic description of the photoisomerization for the 2-cyanoethyl cobaloxime complex in the solid state. This reaction proceeds only in the solid state, and the reverse reaction has not been observed. Notably the photoreaction accompanies the rearrangement of Co-C bond and the produced 1-cyanoethyl group has a chiral carbon atom bonded to the cobalt atom.

Table 1-1 Relation between cavity volume and rate constant (k) in 2-cyanoethyl cobaloxime complexes

Base ligand	Cavity volume ($\text{\AA}^3$)	k ($\times 10^4 \text{ s}^{-1}$)	Conformation
pip	10.3	-	Perpendicular
3cpy	12.2	0.8	Perpendicular
4apy	15.0	1.1	Perpendicular
3epy	13.1	1.4	Parallel
4epy	14.0	1.6	Parallel
3apy	10.1	3.2	Parallel
1abz	15.0	4.2	Parallel

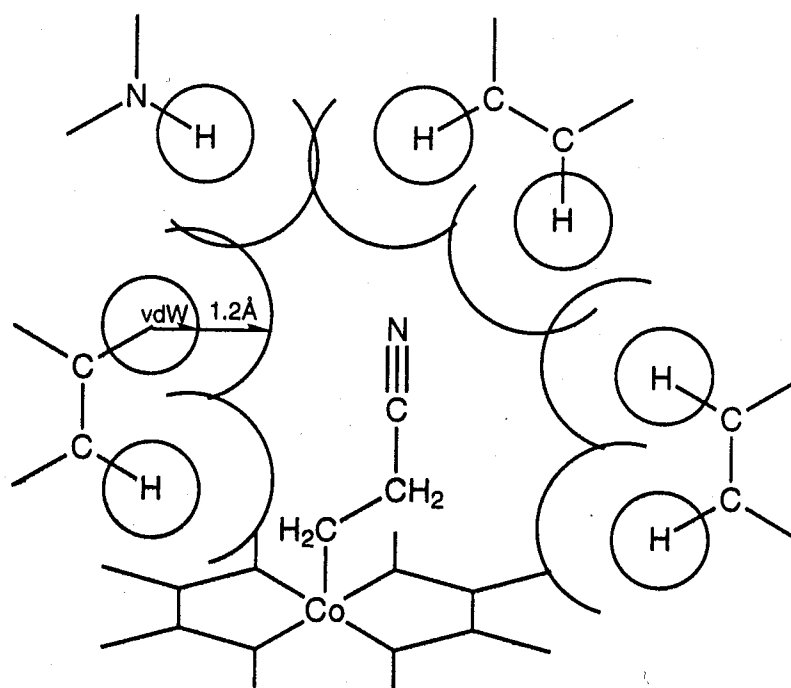


Figure 1-4 Definition of the reaction cavity. A section of one part of the cavity limited by a concave surface of the spheres from the surroundings atoms. The radius of each sphere is taken to be 1.2 Å greater than the van der Waals radius of any atoms ; provided that was used following ;
H : 1.20, C : 1.70, N : 1.55 and O : 1.52 Å as van der Waals radius [53].

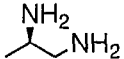
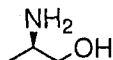
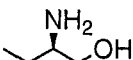
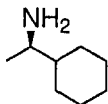
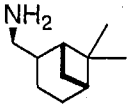
1		sec-butylamine
2		1,2-diaminopropane
3		2-amino-1-propanol
4		2-amino-1-butanol
5		1-cyclohexylethylamine
6		cis-myrtanylamine
7		pyrrolidine

Figure 1-5 Base ligands examined in the present study.

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Chapter 2

Solid-State Asymmetric Induction of *sec*-Butylamine Cobaloxime

It has been found that the 2-cyanoethyl cobaloxime complex was isomerized to the 1-cyanoethyl cobaloxime complex on exposure to visible light in the solid state [1]. This photoreaction proceeds only in the solid state, and the reverse reaction has not been observed. Notably the photoreaction accompanies the rearrangement of Co-C bond and the produced 1-cyanoethyl group has a chiral carbon atom bonded to the cobalt atom. This gave an idea that the asymmetric induction would be observed if the photoisomerization proceeded in the chiral crystal environment. The cobaloxime complex coordinated with the chiral amine derivatives as an axial base ligand will be crystallized with the chiral space group. In the present study, the 2-cyanoethyl cobaloxime complex coordinated with *sec*-butylamine as a chiral amine derivative was investigated for its crystal structure, diastereoselectivity and the packing energy, since *sec*-butylamine is the simplest chiral amine derivative and the two equivalent experiments may be performed independently using (*R*)- and (*S*)-isomers. However, a serious criticism was offered to concerning the above observation, since the produced 1-cyanoethyl group should be racemized or epimerized on exposure to a xenon lamp. Since many examples of crystalline-state photoracemization were observed for the 1-cyanoethyl group of the cobaloxime complexes [2]. It was thought that the epimerization of the 1-

cyanoethyl cobaloxime complex coordinated with *sec*-butylamine should be necessary to propose the crystal structure - diastereoselectivity.

2-1 Structure Determination

Experimental

A complex of 2-cyanoethyl (**S**)-*sec*-butylamine cobaloxime and its enantiomer were prepared in a way similar to that reported previously [3]. Orange crystals suitable for an X-ray structure analysis were obtained from acetone-hexane solution. The X-ray data were collected on a Rigaku AFC7S diffractometer. MoK α radiation monochromated with graphite was used. The structure was solved by the Patterson method with the program SAPI91 [4], and refined with the program SHELXL93 [5]. In the process of the refinement, the 2-cyanoethyl group was found to have three disordered conformations around the Co-C bond. The bond distances and the torsion angles around the C-C bond of the disordered 2-cyanoethyl groups were restrained to have fixed values in the further refinement cycles. All of the hydrogen atoms were calculated geometrically and refined with a riding model. Non-hydrogen atoms were refined with the anisotropic temperature factors, except for the disordered atoms, which were refined isotropically. The absolute configuration was determined to coincide with that of the *sec*-butylamine, which was consistent with that obtained from the Flack χ parameter in the refinement. The atomic-scattering factors were taken from International Tables for Crystallography [6]. The crystal data and experimental details are given in Table 2-1. The final atomic coordinates with the equivalent isotropic temperature factors for non-hydrogen atoms are given in Table 2-2.

Crystal and Molecular Structure

The crystal structure viewed along the c-axis is shown in Figure 2-1. An

ORTEP drawing [7] of the molecular structure with the numbering of atoms is shown in Figure 2-2. The 2-cyanoethyl group takes a perpendicular conformation to the cobaloxime plane, and has disordered conformations (A, B and C) around the Co-C bond. The occupancy factors of A, B and C are 0.48, 0.34 and 0.18, respectively. The disordered 2-cyanoethyl group contacts with the chiral *sec*-butylamine ligands of neighboring molecules, which causes a chiral environment around the 2-cyanoethyl group. The 2-cyanoethyl groups along the b-axis loosely contact with each other. This brings about a fairly large cavity for the 2-cyanoethyl group. The 2-cyanoethyl group makes no hydrogen bond with the neighboring molecules. In order to examine the reason why the occupancy factors of A, B and C are different, the packing energy of the 2-cyanoethyl group around the Co-C bond was calculated in the crystalline lattice using the program Cerius² [8] with the Universal Force Field parameter set [9]. The calculated conformer of the 2-cyanoethyl group having the lowest packing energy is in good agreement with the observed X-ray structure within 0.3° of the Co-C bond rotation (torsion angle). The packing-energy profile of the 2-cyanoethyl group rotating about the Co-C bond by 5° is shown in Figure 2-3, in which the torsion angle and packing energy indicate the deviations from the most stable conformer, A. The wide range of the bottom profile well explains the disordered conformers and their occupancy factors.

2-2 Photoisomerization

KBr disk that contained ca. 1 wt.% of the 2-cyanoethyl *sec*-butylamine cobaloxime complex was exposed to a xenon lamp at room temperature. The IR spectra obtained is shown in Figure 2-4. The absorption was assigned to the stretching vibration mode of the cyano group, ν_{CN} in the 2-cyanoethyl group, at 2241 cm^{-1} . The peak decreased with the irradiation time and ν_{CN} of the 1-cyanoethyl complex appeared at 2202 cm^{-1} , and increased.

2-3 Diastereoselectivity

Experimental

Crystals scattered onto a Petri dish were irradiated with a xenon lamp equipped with UV cut-off filter (TOSHIBA Y-46) at 300 K, as shown in Figure 2-5. After irradiation, an HPLC analysis of the crystals was carried out using the chiral stationary phase in order to determine the diastereoselectivity. The HPLC system used was a HITACHI L-7000 series system equipped with a CHIRALPAK-AD column (ϕ 4.6mm $\times$ 250 mm : 10 mm, Daisel Chem., Inc.) maintained at 300 K and with a Model L-7420 UV-Vis absorbance detector monitored at 242 nm. The mobile phase consisted of hexane with 10% v/v ethanol , and its flow rate was 1.0 ml min⁻¹. Quantification was performed by integrating the peak area using an internal standard, benzyl alcohol. No leading or tailing around the peaks corresponding to (*R*)- and (*S*)-1-cyanoethyl complexes was observed in the chromatogram. This indicates that the produced 1-cyanoethyl group was not inverted to the opposite configuration when it migrated in the chiral stationary phase of HPLC. The retention time of the (*R*)-1-cyanoethyl and (*S*)-1-cyanoethyl complexes was measured at 10.11 and 13.67 min, respectively. These two peaks were perfectly divided.

Diastereomer Excess and Conversion Rate

Table 2-3 shows the diastereomer excess and reaction yield of the produced 1-cyanoethyl cobaloxime complex with the irradiation time. The reason why the value of diastereomer excess gradually increased with the irradiation time from 16 to 256 min is probably due to the fact that isomerization would occur from the surface of the crystal, where the lattice control may be looser than that in the inner part of the crystal. The diastereomer excess converged to 27% after 256 min, as shown in Figure 2-6. The conversion rates of the 2-

cyanoethyl group to the (**R**)-1-cyanoethyl and (**S**)-1-cyanoethyl groups are shown in Figure 2-7. The conversion rates during the early stages (less than 256 min) seem to be explained by first-order kinetics. The rate constants were calculated to be 1.17×10^{-5} and $0.59 \times 10^{-5} \text{ s}^{-1}$ for the (**R**)- and (**S**)-1-cyanoethyl groups, respectively. These results strongly suggest that the epimerization of the complex or the racemization of the 1-cyanoethyl group does not occur during the process of photoisomerization. Moreover, the (**R**)-1-cyanoethyl group is preferentially produced when (**S**)-*sec*-butylamine is used as an axial base ligand. For its enantiomer, similar results were obtained consistently.

Cavity Shape of the 2-cyanoethyl group

In order to explain the reason why the (**R**)-isomer is produced when the (**S**)-*sec*-butylamine is used, the reaction cavity for the 2-cyanoethyl group in the initial crystal structure was drawn, and its volume was calculated in the same way as previously reported [3]. Figure 2-8 shows the reaction cavities for the three disordered conformers. In a calculation of the cavities, all of the conformations were included in the neighboring 2-cyanoethyl groups because a cavity with a similar shape and volume was obtained, even if any one of the three conformers was fixed to those of the neighboring 2-cyanoethyl groups. To examine the asymmetric shape, the cavity was divided into two parts by the average plane comprising the C-C-C-N atoms of the 2-cyanoethyl group. The volumes of the two parts were also calculated, and are given in Figure 2-8, in which the C-C-N moiety of each conformer is drawn so as to occupy the same position to each other.

For conformers A and B, the left part of the cavity is significantly greater than the right part. Since the CN group has a greater volume than the CH₃ group, it is favorable that the CN and CH₃ groups occupy the greater and smaller parts of the reaction cavity, respectively, after conversion to the 1-cyanoethyl group. This explains the reason why the (**R**)-1-cyanoethyl group

is preferentially produced from the (**S**)-*sec*-butylamine complex after isomerization.

For conformer C, on the other hand, the right part is significantly greater than the left part. From conformer C, a 1-cyanoethyl group with the opposite configuration would be produced. This may be a reason why this complex showed a low optical yield.

Table 2-1 Crystal Data and Experimental Details

Crystal data

Chemical formula	[Co(C ₄ H ₇ N ₂ O ₂) ₂ (C ₃ H ₄ N)(C ₄ H ₁₁ N)]
Formula weight	416.37
Cell system	Monoclinic
Space group	C2
<i>a</i> /Å	15.656(2)
<i>b</i> /Å	11.699(2)
<i>c</i> /Å	11.553(1)
β /°	96.979(9)
<i>V</i> /Å ³	2100.5(5)
<i>Z</i>	4
<i>D_x</i> /Mg m ⁻³	1.317
<i>F</i> (000)	880
Radiation type	Mo K α
Wavelength/Å	0.71073
No. of reflections for cell parameters	25
θ range/°	10-15
μ /mm ⁻¹	0.847
Temperature/K	296
Crystal form	Prismatic
Crystal size/mm	0.2 x 0.2 x 0.2
Crystal color	Orange

Data collection

Diffractometer	AFC-7R
Data collection method	ω -2 θ
Scan rate/° min ⁻¹	8
Absorption correction	Ψ scan
No. of measured reflections	2630
No. of independent reflections	2539
No. of observed reflections	1678
Criterion for observed reflections	$I > 2 \sigma(I)$
$\theta_{\max}$ /°	27.48
Range of <i>h, k, l</i>	$0 \leq h \leq 20$ $0 \leq k \leq 15$ $-15 \leq l \leq 14$
No. of standard reflections	3
Frequency of standard reflections	Every 100 reflections
Intensity decay /%	0.2

Refinement

Refinement on	F^2
$R [I > 2\sigma(I)]$	0.0521
$\omega R(I)$	0.1267
<i>S</i>	1.158
No. of reflections used in refinement ($I > 0$)	2226
No. of parameters used	247
H-atom treatment	Calculated
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.7561P)^2 + 0.1912P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max}$	0.0149
$\Delta\rho_{\max}/e\text{\AA}^{-3}$	0.380
$\Delta\rho_{\min}/e\text{\AA}^{-3}$	-0.607
Extinction correction	None
Flack χ parameter	-0.002(5)

Table 2-2Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)

atom	x	y	z	U_{eq}^a
Co1	0.34914(5)	0.5036(2)	0.79642(6)	0.035
O1	0.3220(6)	0.6106(7)	0.5774(9)	0.058
O2	0.3711(6)	0.6079(8)	1.0185(9)	0.056
O3	0.3726(6)	0.3965(9)	1.021(1)	0.061
O4	0.3209(6)	0.3999(8)	0.5704(8)	0.062
N1	0.3353(6)	0.6290(8)	0.6924(8)	0.041
N2	0.3587(6)	0.6275(8)	0.9028(9)	0.040
N3	0.3608(6)	0.382(1)	0.9024(9)	0.053
N4	0.3347(6)	0.386(1)	0.686(1)	0.047
N5A	0.0067(8)	0.477(2)	0.794(2)	0.064
N5B	0.0008(9)	0.479(2)	0.731(3)	0.064
N5C	0.007(2)	0.516(6)	0.762(6)	0.064
N6	0.4810(3)	0.505(1)	0.7945(3)	0.042
C1	0.3390(9)	0.727(1)	0.738(2)	0.051
C2	0.354(1)	0.731(1)	0.863(1)	0.063
C3	0.3532(8)	0.2816(9)	0.858(1)	0.042
C4	0.339(1)	0.280(1)	0.727(1)	0.051
C5	0.3312(8)	0.8314(9)	0.658(1)	0.059
C6	0.3576(8)	0.838(1)	0.927(1)	0.061
C7	0.361(1)	0.179(1)	0.938(2)	0.115
C8	0.325(1)	0.173(1)	0.659(2)	0.099
C9	0.2232(3)	0.517(1)	0.8018(5)	0.048
C10A	0.1588(6)	0.442(2)	0.730(2)	0.059
C10B	0.1607(6)	0.493(4)	0.692(1)	0.059
C10C	0.159(1)	0.551(6)	0.698(3)	0.059
C11A	0.0725(6)	0.459(2)	0.765(2)	0.067
C11B	0.0730(6)	0.488(3)	0.722(2)	0.067
C11C	0.0714(8)	0.530(6)	0.723(3)	0.067
C12	0.5234(4)	0.512(1)	0.6875(5)	0.054
C13	0.5510(8)	0.639(1)	0.677(1)	0.086
C14	0.5992(7)	0.437(1)	0.6883(8)	0.070
C15	0.5762(9)	0.314(1)	0.685(1)	0.101

a) $U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$

occupancy factors A:0.48(2) ; B:0.34(3) ; C:0.18(3)

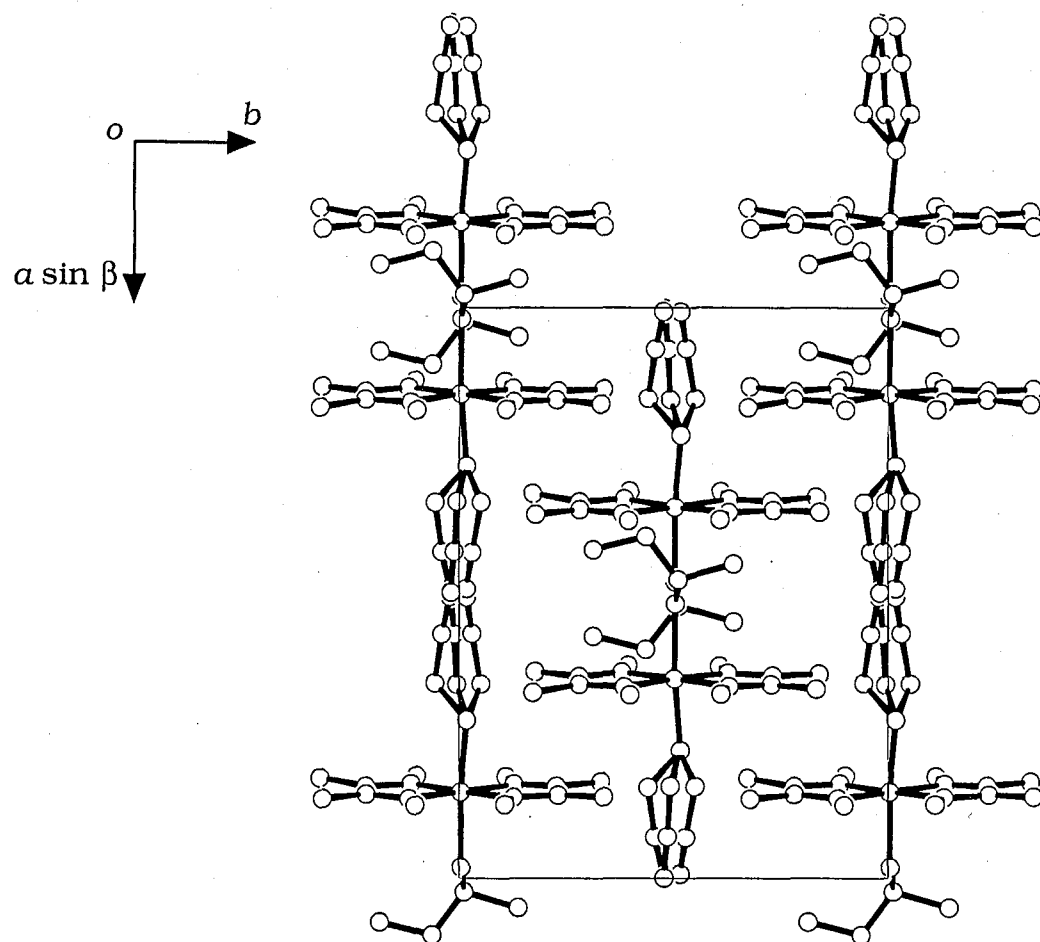


Figure 2-1 The crystal structure of the 2-cyanoethyl (S)-sec-butylamine cobaloxime

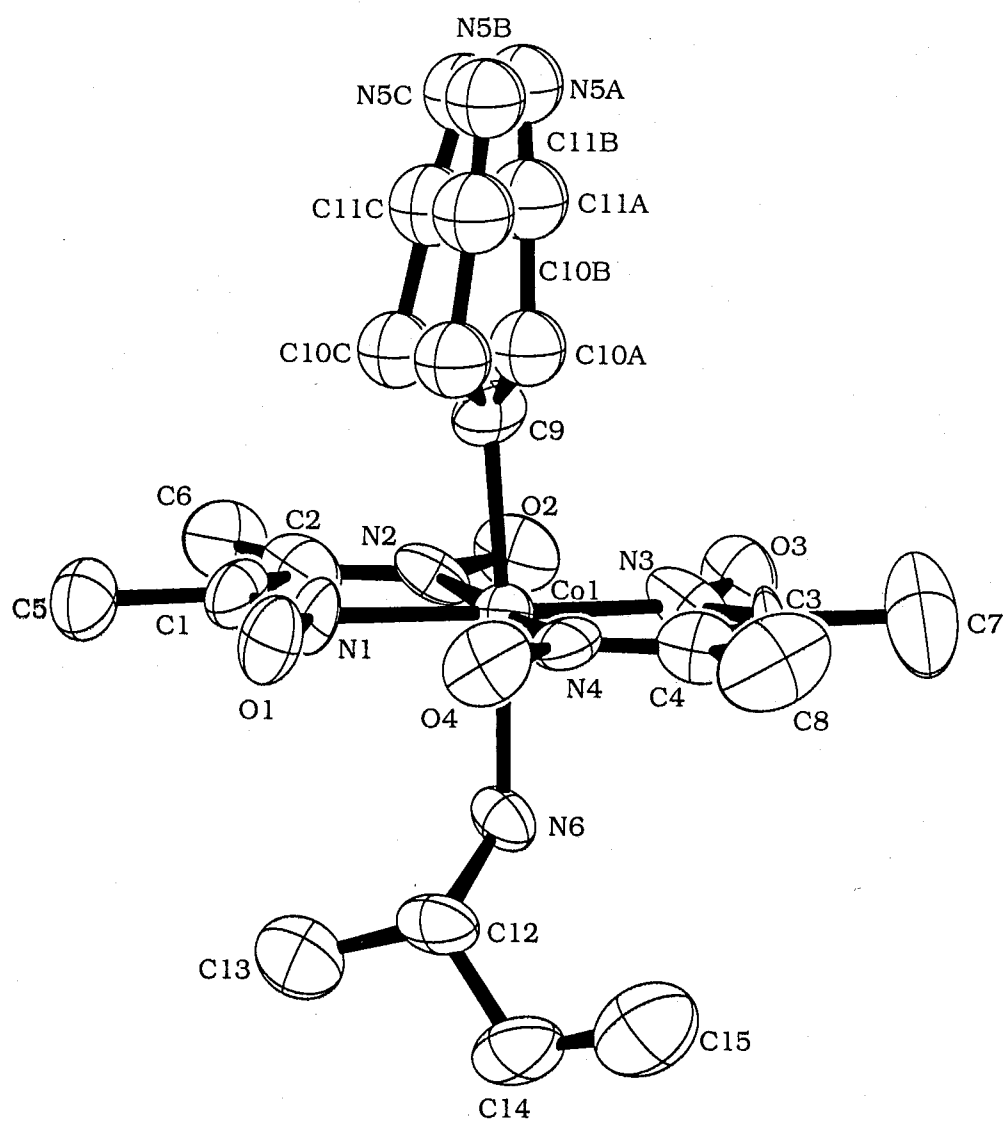


Figure 2-2 ORTEP drawing of the molecule with the numbering of the atoms. The thermal ellipsoids are 50 % level. The 2-cyanoethyl group has three disordered conformations.

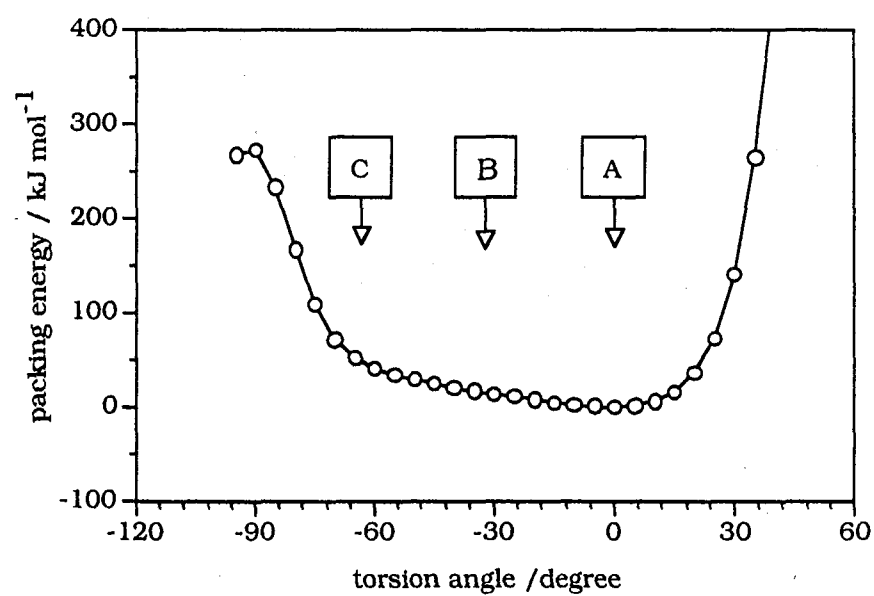


Figure 2-3 Packing energy variation of the 2-cyanoethyl group with the rotation angle around the Co-C bond. The energy was calculated in a constant interval of 5°. The values of the energy and angles are deviations from the most stable conformer, A.

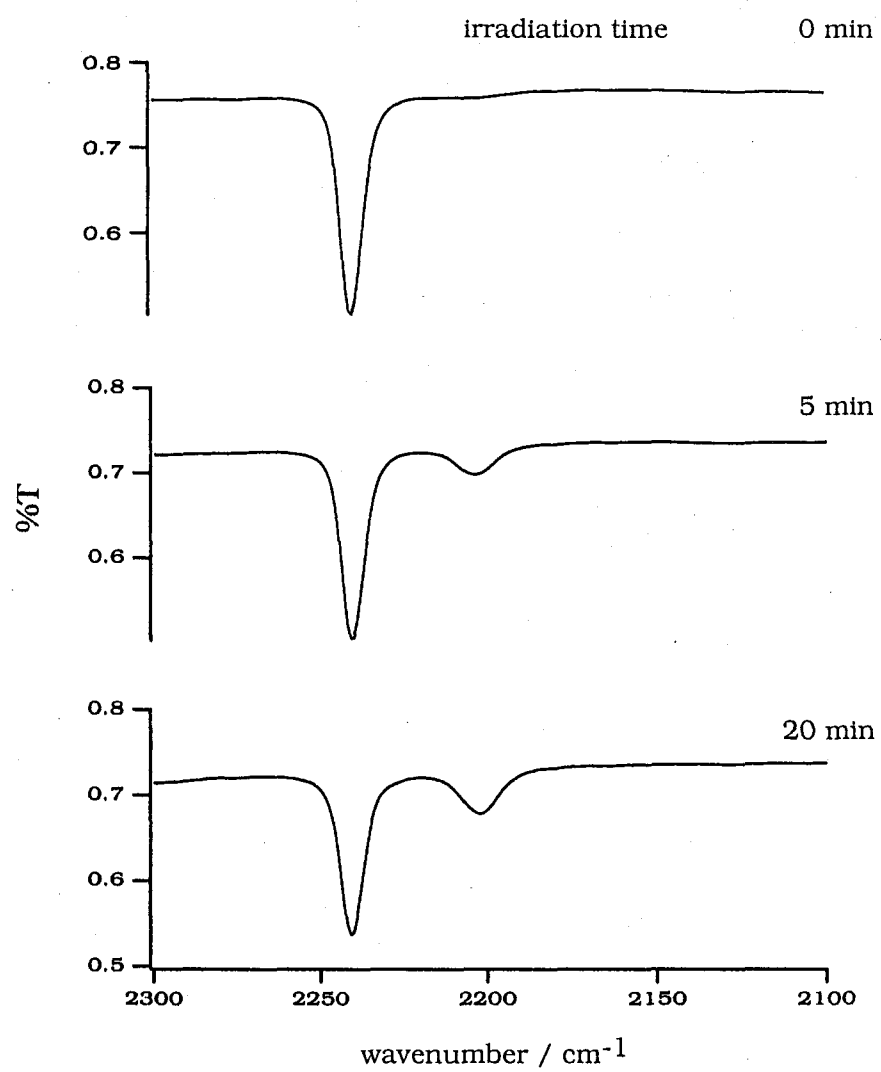


Figure 2-4 The change of IR spectra in (2-cyanoethyl)(*sec*-butylamien) cobaloxime complex

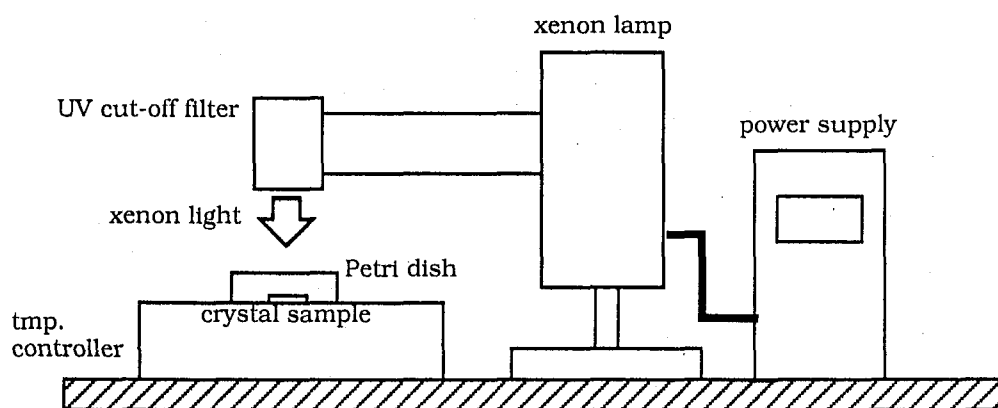


Figure 2-5 Arrangement of the sample crystals scattered onto a Petri dish, xenon lamp with UV cut-off filter and the temperature controller.

Table 2-3 The diastereoselectivity in the solid-state photoisomerization of (2-cyanoethyl)[(**S**)-sec-butylamine] cobaloxime

Irradiation time (min)	Reaction yield (%)	Major configuration	Diastereomer excess (%)
8	2.1	R	22.2
16	3.7	R	20.8
32	8.9	R	21.5
64	12.5	R	23.3
128	19.2	R	25.6
256	35.3	R	27.5
480	46.3	R	27.0

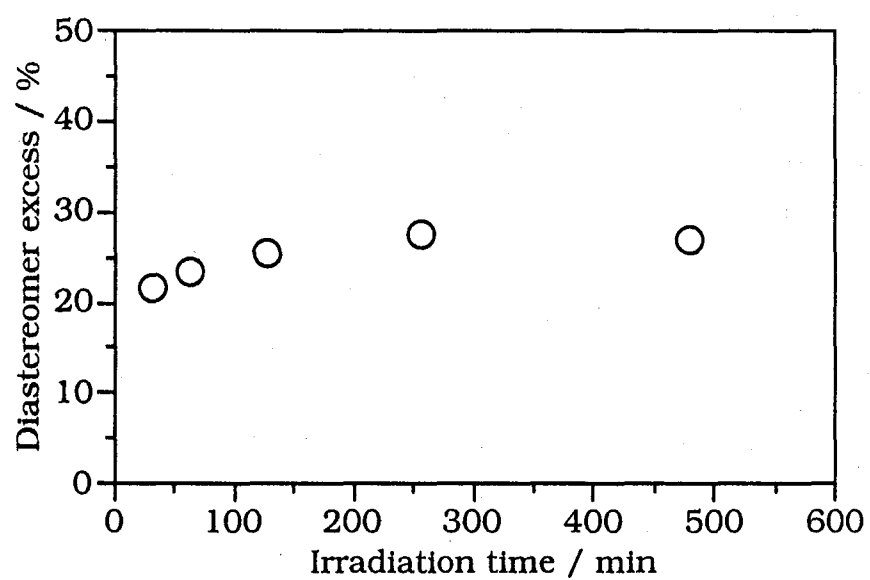


Figure 2-6 The diastereomer excess of 2-cyanoethyl cobaloxime complex coordinated with (*S*)-*sec*-butylamine at 300 K. The diastereomer excess converged to 27% after the irradiation time was 256 min.

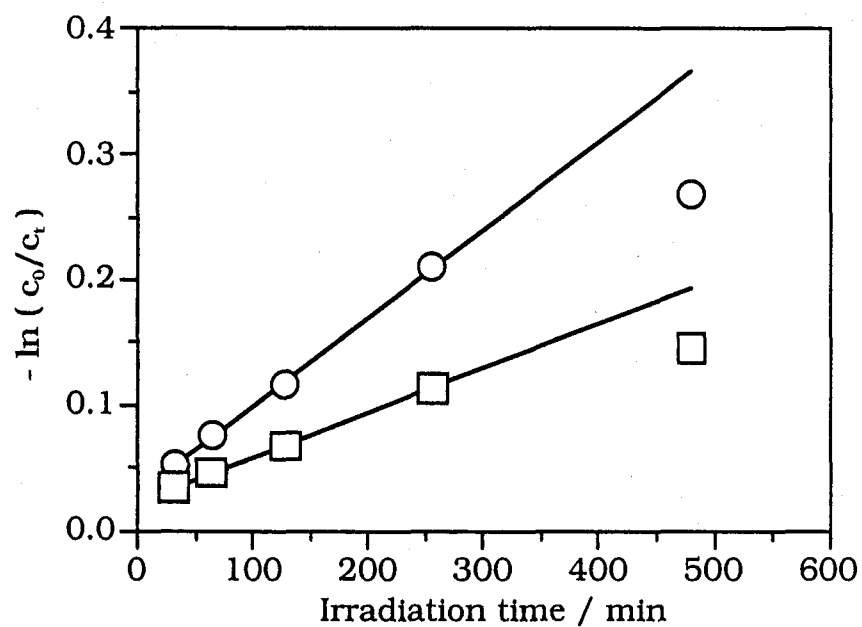


Figure 2-7 Conversion of the 2-cyanoethyl group to the (*R*)- and (*S*)-1-cyanoethyl groups with the irradiation time. In the irradiation time to 256 min, the conversions are expressed by first-order kinetics, which are drawn in solid lines. The rate constants are 1.17×10^{-5} and $0.59 \times 10^{-5} \text{ s}^{-1}$ for the (*R*)- and (*S*)-1-cyanoethyl group. The values of c_0 and c_t indicate the amounts of 1-cyanoethyl complex at the irradiation time, 0 and t , respectively.

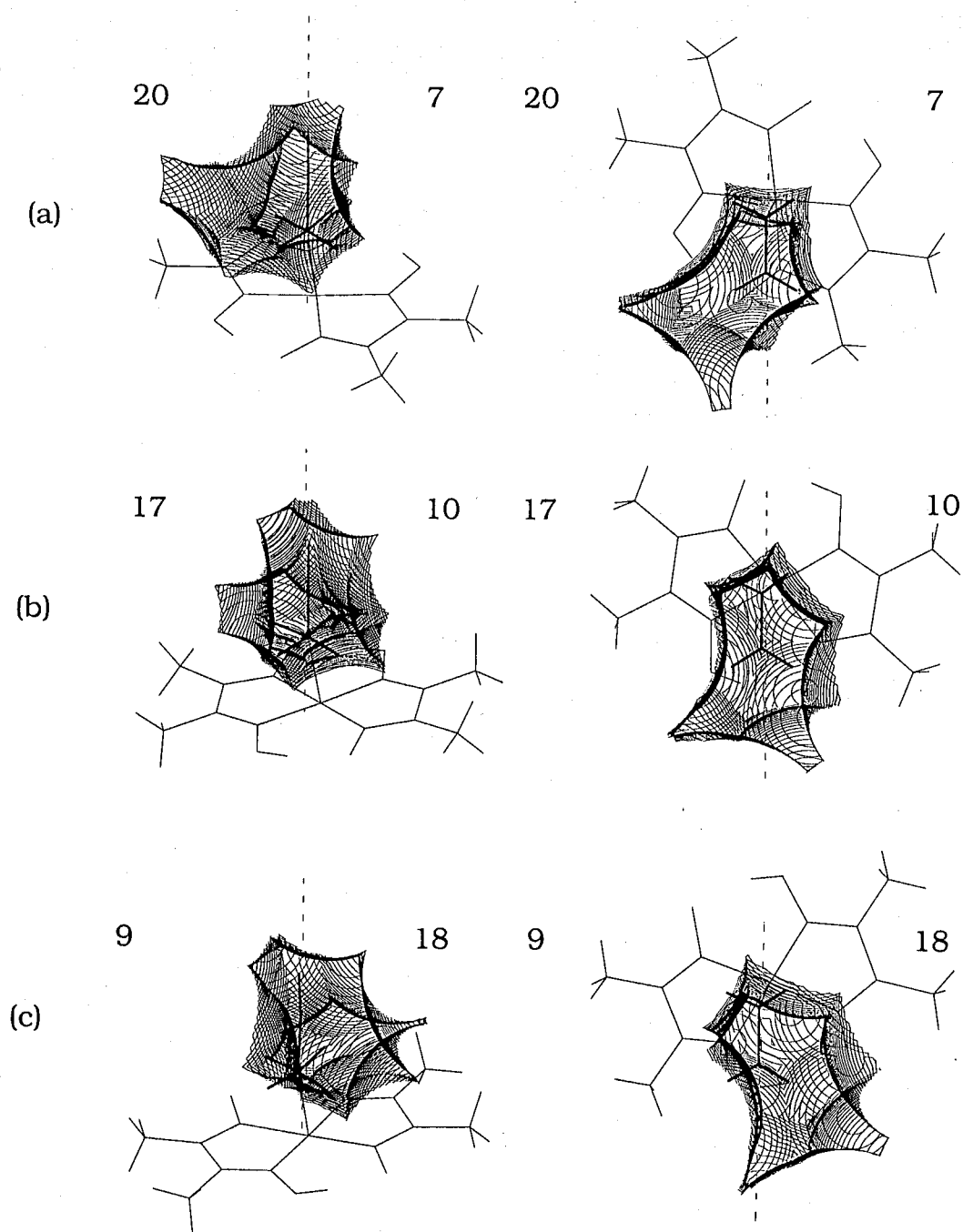


Figure 2-8 Reaction cavity for the 2-cyanoethyl group, viewed along the central C-C bond of the group (left) and viewed along the normal to the cobaloxime plane (right); (a) conformer A, (b) conformer B, and (c) conformer C. The contours are drawn at an interval of 0.1 $\text{\AA}$. Each cavity is divided into two parts by the average plane composed on the C-C-C-N bond. The cavity volumes ($\text{\AA}^3$) of left and right halves are also given.

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Chapter 3

Crystalline-State Reaction of *sec*-Butylamine Cobaloxime

Although the crystal structure determination before and after reaction is a very powerful method for the study of the structure-reactivity correlation, all of the solid state reaction can not proceed with retention of the single crystal form. Recently it has been reported that the 2-cyanoethyl cobaloxime complexes coordinated with 3-methylpyridine and 4-methylpyridine, which has a parallel conformation of the 2-cyanoethyl group to the cobaloxime plane, were photoirradiated to the 1-cyanoethyl derivatives on exposure to visible light with retention of the single crystal form [1]. The X-ray crystal structure of the 3-methylpyridine complex after photoirradiation was revealed that the ratio of the **R** and **S** configurations of the produced 1-cyanoethyl group in one site was 4 : 7, but the 1-cyanoethyl group produced only the **R** configuration in one site of the 4-methylpyridine complex. The difference in shape of the reaction cavities for the initial 1-cyanoethyl group of two complex crystals well explains the reason why such different degrees of asymmetry were generated in the produced 1-cyanoethyl group.

In chapter 2, it was revealed that 2-cyanoethyl cobaloxime complex has produced preferentially to the (**R**)-1-cyanoethyl cobaloxime complex on exposure to visible light in the solid state when (**S**)-*sec*-butylamine was used as an axial ligand base. In this chapter, the crystalline-state reaction of the

2-cyanoethyl cobaloxime complex coordinated with *sec*-butylamine as an axial base ligand will be described.

3-1 Structure Determination After Photoirradiation

Experimental

A complex of 2-cyanoethyl (**R**)-*sec*-butylamine cobaloxime and its enantiomer were prepared in a way similar to that reported previously [2]. Orange crystals were obtained from acetone-hexane solution. Crystals scattered onto a Petri dish were irradiated with a xenon lamp for 16 hours at 300 K. After photoirradiation, the X-ray data were collected on a Rigaku AFC7R diffractometer. MoK α radiation monochromated with graphite was used. The structure was solved by the Patterson method with the program SAPI91 [3], and refined with the program SHELXL97 [4]. In the process of the refinement, the 2-cyanoethyl group was found to have disordered conformations around the Co-C bond similar to the crystal structure before photoirradiation. Moreover, the produced (**S**)-1-cyanoethyl group was also appeared around Co-C bond. The bond distances and the torsion angles around the C-C bond of the disordered structure were restrained to have fixed values in the further refinement cycles. All of the hydrogen atoms were calculated geometrically and refined with a riding model. Non-hydrogen atoms were refined with the anisotropic temperature factors, except for the disordered atoms, which were refined isotropically. The absolute configuration was determined to coincide with that of the *sec*-butylamine, which was consistent with that obtained from the Flack χ parameter in the refinement. The atomic-scattering factors were taken from International Tables for Crystallography [5]. The crystal data and experimental details are given in Table 3-1. The final atomic coordinates with the equivalent isotropic temperature factors for non-hydrogen atoms are given in Table 3-2.

Crystal and Molecular Structure After photoirradiation

The crystal structure viewed along the c-axis and the molecular structure with the numbering of atoms after photoirradiation was shown in Figure 3-1 and 3-2, respectively. Figure 3-3 shows the X-ray structure of the only (**S**)-1-cyanoethyl cobaloxime produced by the crystalline state photoisomerization. The crystal structure before and after photoirradiation were essentially the same structure, except for the atom appeared around the disordered 2-cyanoethyl group, which were assigned to the atoms of the produced (**S**)-1-cyanoethyl group. The 2-cyanoethyl group has disordered conformations around the Co-C bond. The conformations of the 2-cyanoethyl group is approximately the same before and after photoirradiation. Moreover the (**S**)-1-cyanoethyl group was appeared. The occupancy factors of A, B in reactant group are 0.47 and 0.40 and C in product group is 0.13, respectively. The (**R**)-1-cyanoethyl group was not found, so that the (**S**)-1-cyanoethyl cobaloxime complex was main products by the photoisomerization when (**R**)-*sec*-butylamine was used as an axial ligand base. This results is in agreement with the solid-state asymmetric induction in chapter 2. This reason why (**S**)-1-cyanoethyl cobaloxime complex was produced preferentially is explained by the chiral crystal environment, especially around the reaction group. The C9C carbon atom, which was bonded to the cobalt atom, in the produced 1-cyanoethyl group was deviated from initial position in the 2-cyanoethyl group to the closely different position. The angle of C9C-Co1-N6 is 170°. The reason was probably due to the relaxation of C10C-C9C-C11C angle. The CH₃ group of the produced 1-cyanoethyl group was lied to the top of the cobaloxime plane. The conformation of the produced 1-cyanoethyl group was governed by the asymmetric crystal environment but the conformation does not prefer in the crystal structure, since the conformation of the 1-cyanoethyl group is rarely observed to retrieving from the Cambridge Structure Database (1997).

Reaction Cavity After Photoirradiation

In order to explain the reason why the (**S**)-1-cyanoethyl group is produced when the (**R**)-*sec*-butylamine is used, the reaction cavity for the cyanoethyl group before and after photoirradiation viewed along the Co-C bond was drawn as shown in Figure 3-4. The reaction cavity after photoirradiation has similar shape to the reaction cavity before photoirradiation. The produced 1-cyanoethyl group was included into the asymmetric reaction cavity together with the reactive 2-cyanoethyl group. Moreover the larger cyano group occupies the greater volume of reaction cavity divided into two parts by the average plane comprising the C-C-CN atom of the 2-cyanoethyl group. The observed conformation clearly indicates that the diastereocontrol was strongly depended on the asymmetric shape of the reaction cavity for the 2-cyanoethyl group. This result on the crystalline-state reaction suggest that the 2-cyanoethyl group was isomerized to the 1-cyanoethyl group by the advantage of the steric hindrance in the asymmetric reaction cavity.

3-2 Packing Energy Calculation

The molecular simulation provides the link between the crystal and molecular structure and its packing energy in the crystal structure. The information given from the molecular simulation is useful to be not taken from the X-ray structure analysis. Therefore the combination of X-ray structure determination and molecular simulation is very powerful method. In order to examine the above discussion more quantitatively, the conformation and configuration of the produced 1-cyanoethyl group after irradiation were calculated by the molecular-mechanics method using the program Cerius² [6] with the Universal Force Field (UFF) [7] parameter set. The UFF parameter set is applicable to organometallic compounds [7][8]. The initial model in molecular mechanics calculation was constructed on the basis of the observed X-ray crystal structure. At first, the initial model was

calculated to assign to the point charge on the current atom using the charge equilibration method [9]. The energy of the analyzed crystal structure was minimized with the rigid-body model. In this calculation, the 2-cyanoethyl group was treated as a disordered conformation similar to the results of the observed structure. It was confirmed that the different population in the disordered 2-cyanoethyl group in the neighboring molecules was not effected quietly to the following results. Energy minimization was carried out by the conjugate-gradient method, at the end of which the value of the root-mean-square energy derivative of the atomic coordinates was less than 0.42 kJ mol^{-1} . The conformation of the (**S**)-1-cyanoethyl group was altered at a constant interval of 30° around the Co-C bond, and the model structure was minimized geometrically with the fixed unit-cell dimension. Figure 3-5(a) shows the structure of the (**R**)-1-cyanoethyl group with the lowest energy. The same calculation was performed for the (**R**)-1-cyanoethyl group as shown in Figure 3-5(b). The lowest energy was higher by $10.33 \text{ kJ mol}^{-1}$ than that for the (**S**)-1-cyanoethyl group. Although the energy difference is too high, based on the diastereomer excess, this result is in good agreement with the observed configuration by X-ray analysis of the crystalline-state reaction. Notably, it was noted that the locations of CN and CH_3 group was surprisingly similar to the conformation obtained from X-ray structure in the crystalline-state reaction. The reaction cavity of the calculated 1-cyanoethyl group for the 2-cyanoethyl group was drawn in the same way as previously reported [2] as shown in Figure 3-6. The comparison of the cavity shape between the X-ray observed and the calculated reaction cavity was understood the similarity of the preferred conformation and configuration in the crystal structure. This results suggest that the optimized structure with lowest energy is fairly certain to the experimental fact.

Table 3-1 Crystal Data and Experimental Details**Crystal data**

Chemical formula	[Co(C ₄ H ₇ N ₂ O ₂) ₂ (C ₃ H ₄ N)(C ₄ H ₁₁ N)]
Formula weight	416.37
Cell system	Monoclinic
Space group	C2
<i>a</i> /Å	15.583(5)
<i>b</i> /Å	11.717(8)
<i>c</i> /Å	11.583(4)
β /°	97.08(3)
<i>V</i> /Å ³	2099(2)
<i>Z</i>	4
<i>D_x</i> /Mg m ⁻³	1.318
<i>F</i> (000)	880
Radiation type	Mo K α
Wavelength/Å	0.71073
No. of reflections for cell parameters	25
θ range/°	10-15
μ /mm ⁻¹	0.847
Temperature/K	296
Crystal form	Prismatic
Crystal size/mm	0.3 x 0.2 x 0.2
Crystal color	Orange

Data collection

Diffractometer	AFC-7R
Data collection method	ω -2 θ
Scan rate/° min ⁻¹	8
Absorption correction	Ψ scan
No. of measured reflections	2623
No. of independent reflections	2532
No. of observed reflections	1678
Criterion for observed reflections	$I > 2 \sigma(I)$
$\theta_{\max}$ /°	27.51
Range of <i>h, k, l</i>	$0 \leq h \leq 20$ $0 \leq k \leq 15$ $-14 \leq l \leq 15$
No. of standard reflections	3
Frequency of standard reflections	Every 100 reflections
Intensity decay /%	0.2

Refinement

Refinement on	<i>F</i> ²
$R [I > 2\sigma(I)]$	0.0546
$wR(I)$	0.1666
<i>S</i>	1.074
No. of reflections used in refinement ($I > 0$)	2226
No. of parameters used	246
H-atom treatment	Calculated
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0661P)^2 + 6.26P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max}$	0.017
$\Delta\rho_{\max}/e\text{\AA}^{-3}$	0.636
$\Delta\rho_{\min}/e\text{\AA}^{-3}$	-0.357
Extinction correction	None
Flack χ parameter	-0.04(6)

Table 3-2Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)

atom	x	y	z	U_{eq}^a
Co1	0.34915(5)	0.508(1)	0.79564(7)	0.0398
O1	0.3690(8)	0.404(1)	1.015(1)	0.077
O2	0.3219(8)	0.405(1)	0.573(1)	0.075
O3	0.3212(6)	0.616(1)	0.5746(7)	0.056
O4	0.3726(6)	0.614(1)	1.0202(8)	0.055
N1	0.3589(7)	0.383(1)	0.897(1)	0.043
N2	0.3377(8)	0.394(1)	0.6868(9)	0.050
N3	0.3341(6)	0.637(1)	0.692(1)	0.042
N4	0.3602(7)	0.627(1)	0.907(1)	0.048
N5A	0.0076(9)	0.535(2)	0.789(2)	0.067
N5B	0.004(1)	0.525(2)	0.738(2)	0.067
N5C	0.128(3)	0.454(4)	0.566(4)	0.067
N6	0.4816(3)	0.509(2)	0.7957(4)	0.0434
C1	0.353(1)	0.281(2)	0.859(2)	0.073
C2	0.340(1)	0.287(2)	0.728(1)	0.055
C3	0.3379(9)	0.733(1)	0.735(2)	0.062
C4	0.3540(8)	0.731(1)	0.859(1)	0.039
C5	0.355(1)	0.173(1)	0.936(2)	0.086
C6	0.3289(9)	0.186(2)	0.658(2)	0.079
C7	0.330(1)	0.843(2)	0.661(2)	0.097
C8	0.3661(1)	0.829(1)	0.928(2)	0.080
C9A	0.2222(3)	0.495(2)	0.8106(7)	0.040
C9B	0.2222(3)	0.495(2)	0.8106(7)	0.040
C9C	0.2193(7)	0.499(5)	0.765(4)	0.040
C10A	0.0756(1)	0.546(2)	0.767(2)	0.061
C10B	0.1643(9)	0.531(2)	0.699(1)	0.058
C10C	0.173(5)	0.615(6)	0.761(7)	0.058
C11A	0.0725(6)	0.459(2)	0.765(2)	0.067
C11B	0.073(1)	0.529(2)	0.716(2)	0.061
C11C	0.168(2)	0.474(2)	0.652(4)	0.061
C12	0.5242(5)	0.505(2)	0.6877(6)	0.062
C13	0.6006(8)	0.576(2)	0.689(1)	0.073
C14	0.578(1)	0.695(2)	0.685(2)	0.114
C15	0.5507(9)	0.376(2)	0.675(1)	0.092

a) $U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$

occupancy factors A:0.47(2) ; B:0.40(2) ; C:0.13(1)

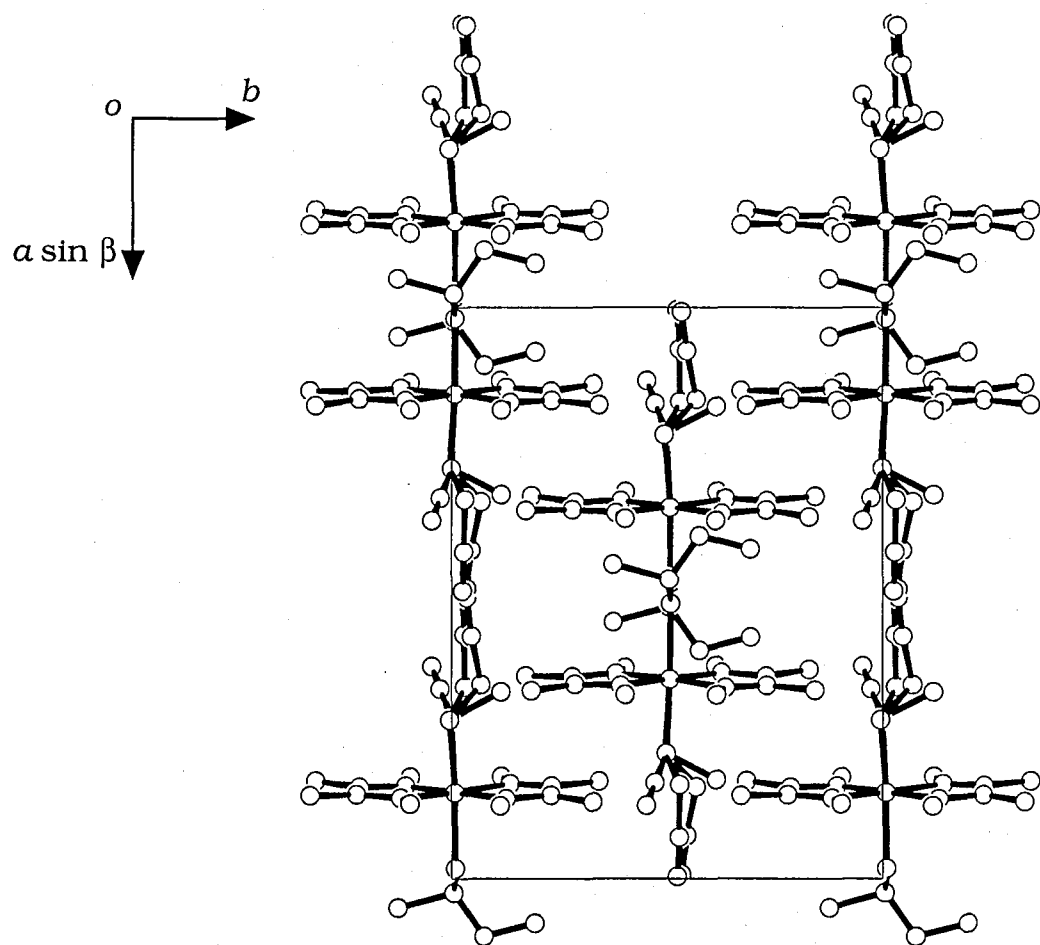


Figure 3-1 The crystal structure of (2-cyanoethyl)[(R)-sec-butylamine]cobaloxime complex after photoirradiation.

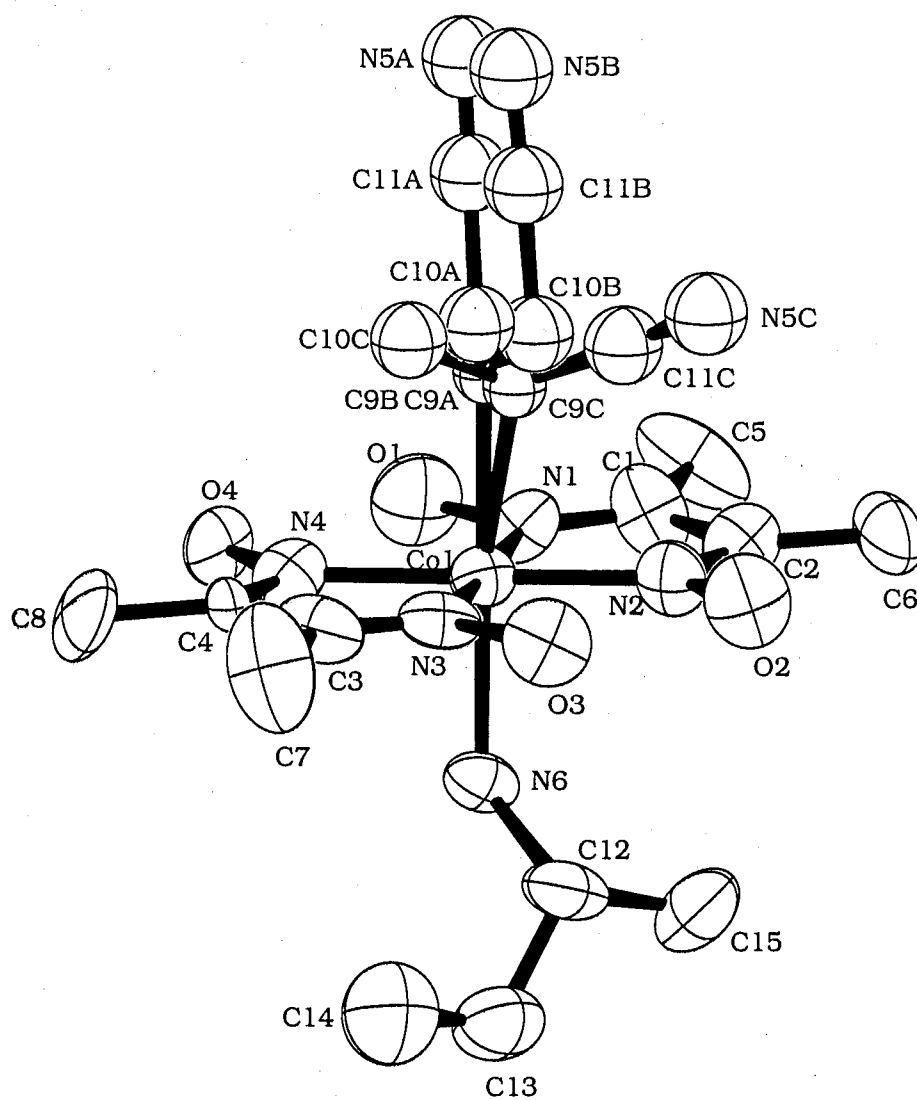


Figure 3-2 The molecule structure of (2-cyanoethyl)[(R)-sec-butylamine]cobaloxime complex after photoirradiation with the numbering of the atoms. The thermal ellipsoids are 50 % level.

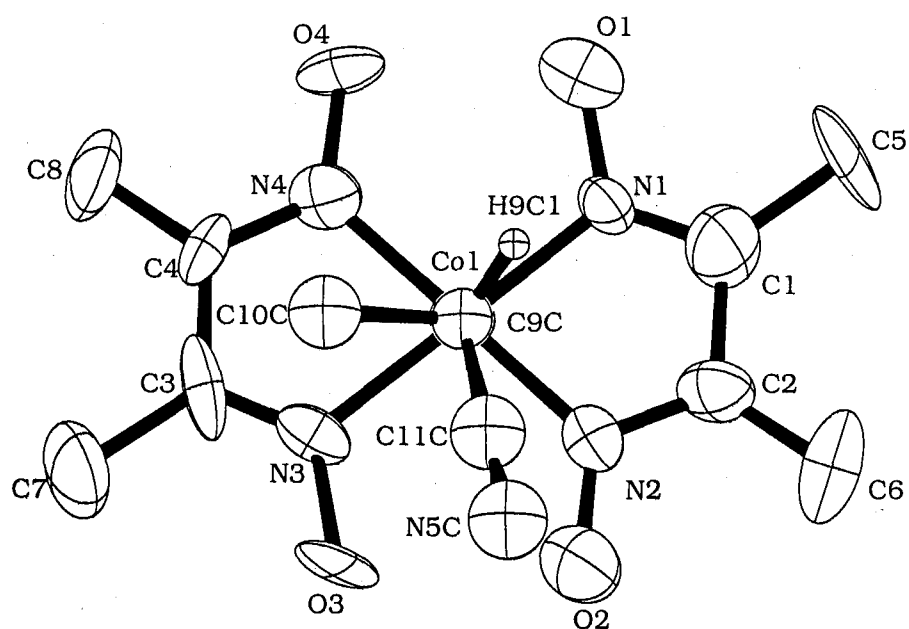
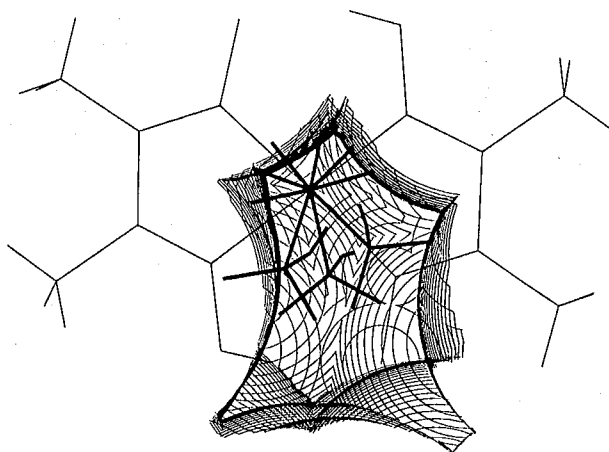


Figure 3-3 The structure of the produced (*S*)-1-cyanoethyl group in (2-cyanoethyl)[(*R*)-*sec*-butylamine]cobaloxime. Only (*S*)-1-cyanoethyl group was drawing. The thermal ellipsoids are 50 % level.

(a) before photoirradiation



(b) after photoirradiation

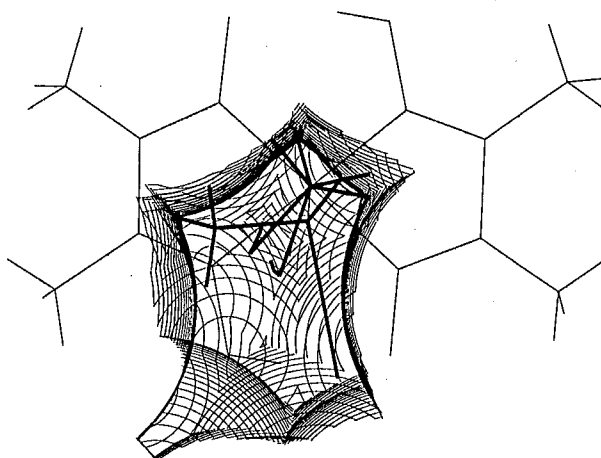
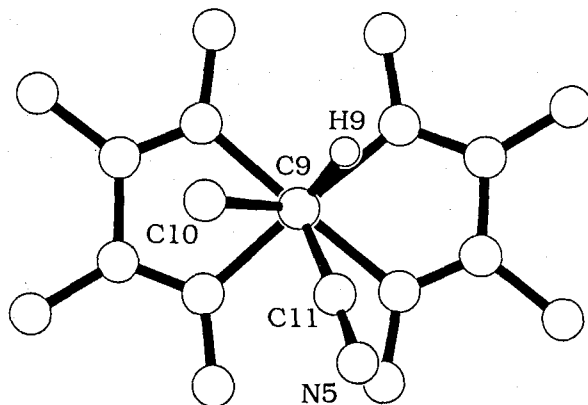
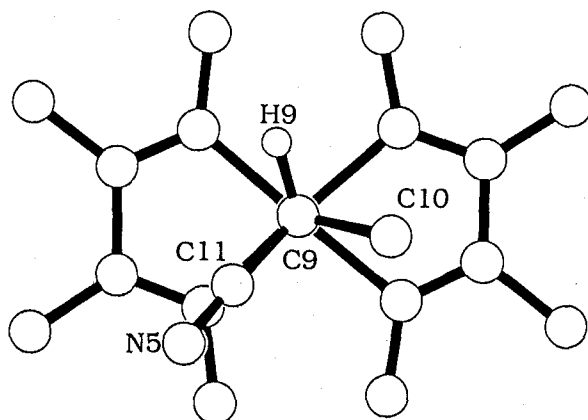


Figure 3-4 The cavity shapes of the observed X-ray structure before (a) and after photoirradiation (b).



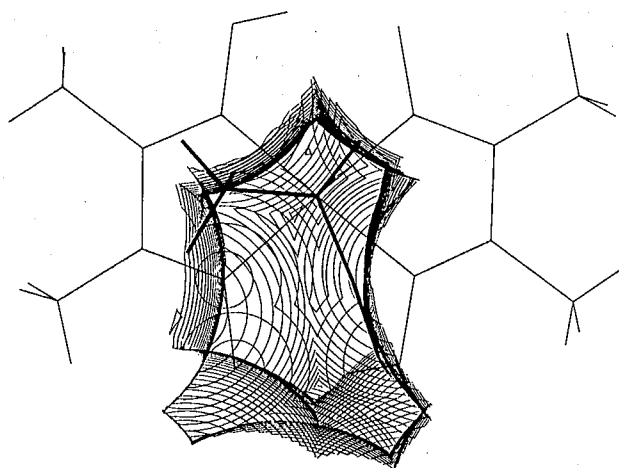
(a) **(S)**-1-cyanoethyl cobaloxime more stable



(b) **(R)**-1-cyanoethyl cobaloxime

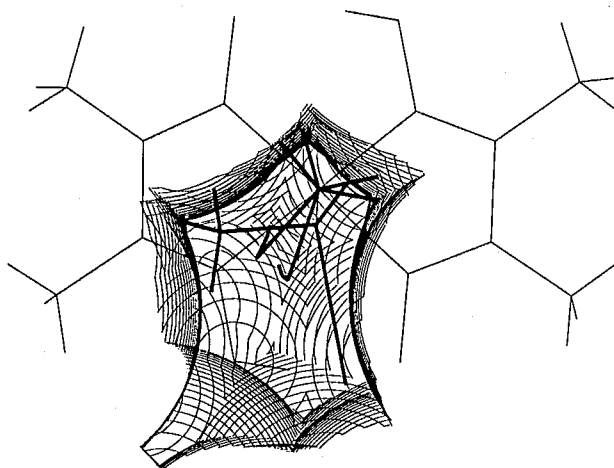
Figure 3-5 The calculated structure of **(S)**- and **(R)**-1-cyanoethyl group with lowest packing energy. The lowest energy of the **(R)**-1-cyanoethyl group was higher by 10.33 kJ mol⁻¹ than that for the **(S)**-1-cyanoethyl group.

(a)



calculated structure

(b)



X-ray structure

Figure 3-6 The comparison of the cavity shape between the (a) calculated and (b) the X-ray observed reaction cavity.

Reference

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- [6] Cerius² release 1.6, Molecular Simulation Inc.,Burlington, Massachusetts (1994).
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Chapter 4

Asymmetric Induction of Chiral Amine Derivatives

It has been found that the 2-cyanoethyl group in the cobaloxime complexes was isomerized to the 1-cyanoethyl group on exposure to visible light in the solid state [1]. This photoreaction proceeds only in the solid state, and the reverse reaction has not been observed. Notably the photoreaction accompanies the rearrangement of Co-C bond and the produced 1-cyanoethyl group has a chiral carbon atom bonded to the cobalt atom. This gave an idea that the asymmetric induction would be observed if the photoisomerization proceeded in the chiral crystal environment.

The extensive study of the solid-state photoisomerization in the cobaloxime complexes so far was carried out and it was mainly focused on the reaction rate in the optically inactive crystal [2][3][4][5], and three factors were found to effect the reaction rate [6]; (1) conformation of the reaction group, (2) hydrogen bond with the reaction group and (3) cavity volume around the reaction group, and but it is not the scope and purpose of the present study to examine this area.

It was described that the diastereocontrol was explained by the asymmetric cavity shape for the reactive group and the packing-energy difference in the chiral crystal environment. In order to examine the asymmetric induction in the solid state more precisely, the 2-cyanoethyl cobaloxime complexes coordinated by the amines as shown in Figure 1-5, 1,2-diaminopropane (**2**),

2-amino-1-propanol (**3**), 2-amino-1-butanol (**4**), 1-cyclohexylethylamine (**5**), *cis*-myrtanylamine (**6**) and pyrrolidine (**7**) were prepared. The process of the asymmetric induction obtained in these reactions will afford a good guide for the design of solid-state reactions.

4-1 1,2-diaminopropane

The chemical formula of 1,2-diaminopropane was given in Figure 1-5. The 1,2-diaminopropane $\text{CH}_3\text{CH}(\text{NH}_2)\text{CH}_2\text{NH}_2$ is a similar shape to *sec*-butylamine $\text{CH}_3\text{CH}(\text{NH}_2)\text{CH}_2\text{CH}_3$, so-called the isosteric pair of molecule. The 1,2-diaminopropane has two amino group ($-\text{NH}_2$) in a molecule, one is primary and the other is secondary amino group. Notice that the cobaloxime complex coordinated with the N atom in primary amino group is different in that in secondary amino group.

X-ray structure determination

The complex of (2-cyanoethyl)[(*R*)-1,2-diaminopropane]cobaloxime was prepared in a way similar to that reported previously [7]. The crystals were obtained from a dichloromethane-hexane mixed solution. The X-ray data were collected on a Rigaku AFC7R diffractometer. $\text{MoK}\alpha$ radiation monochromated with graphite was used. The structure was solved by the Patterson method with the program SAPI91 [8], and refined with the program SHELXL97 [9]. In the process of the refinement, the 2-cyanoethyl group was found to take a perpendicular conformation to the cobaloxime plane, and the cobalt atom is coordinated by the primary amino group but not the secondary amino group. All the hydrogen atoms were calculated geometrically and refined with a riding model. Non-hydrogen atoms were refined with the anisotropic temperature factors. The absolute configuration was determined to coincide with that of the (*R*)-1,2-diaminopropane, which was consistent with that obtained from the Flack χ parameter in the refinement. The atomic-scattering factors were taken from International Tables for Crystallography [10]. The crystal data and experimental details are given in Table 4-1. The final atomic coordinates with the equivalent isotropic temperature factors for non-hydrogen atoms are given in Table 4-2.

Photoisomerization and HPLC Analysis

The crystals scattered onto a Petri dish were irradiated with a xenon lamp for several hours at 300 K, in the same way as that for *sec*-butylamine. After photoirradiation, crystals were dealt with ion exchange resin, Dawex (100-200 mesh), for several hours in ethanol solution and then the complex was changed to *cis*-myrtanylamine derivatives in order to determine of the diastereomer excess using HPLC. The HPLC analysis of the sample was carried out using the chiral stationary phase. The HPLC system used was HITACHI L-7000 series system equipped with CHIRALPAK-AD column (Daisel Chem., Inc.) maintained at 300 K and with Model L-7420 UV-Vis absorbance detector monitored at 254 nm. The mobile phase consists of hexane with 10% v/v ethanol and its flow rate was 1.0 ml min⁻¹. Quantification was performed integrating the peak area. The chromatograms obtained indicates that the produced the 1-cyanoethyl group was not inverted to the opposite configuration when it migrated in the chiral stationary phase of HPLC.

Crystal and Molecular Structure

The X-ray crystal structure of (2-cyanoethyl)[(*R*)-1,2-diaminopropane]cobaloxime complex viewed along the *c*-axis and the ORTEP drawing [11] of the molecular structure with the numbering atoms was shown in Figure 4-1 and Figure 4-2, respectively. The 2-cyanoethyl group take a perpendicular conformation and it has no disordered structure. The 2-cyanoethyl group contact with each other. This brings about a fairly large cavity for the 2-cyanoethyl group. The 2-cyanoethyl group makes no hydrogen bond with the neighboring molecules. Contrary to the expectation, the cobalt atom is bonded to N6 atom in primary amino group but not N7 atom in secondary amino group. According to *ab initio* molecular orbital calculation, the negative charge densities on N6 atom in primary amino group are slightly localized than that on N7 atom in secondary amino group. Thus, it is considered that N6 atom in primary amino group was favorable to coordinate

to the cobalt atom than N7 atom in secondary amino group.

Diastereomer Excess

Table 4-3 shows the diastereomer excess and the reaction yield of the produced 1-cyanoethyl complex with the irradiation time. It was found that the (**S**)-1-cyanoethyl group was preferentially produced when the (**R**)-1,2-diaminopropane was used as an axial base ligand, and the diastereomer excess decreased as increasing the reaction yield or the irradiation time as shown in Figure 4-3. The reason why the diastereomer excess decreased as increasing the reaction yield may be attributed to the following factors; (1) the racemization of the produced 1-cyanoethyl group and (2) the change of the cavity shape for the 2-cyanoethyl group when the 1-cyanoethyl group is produced, and (3) the degradation of the crystallinity on exposure to visible light.

The conversion rate of the 2-cyanoethyl group to the (**R**)- and (**S**)-1-cyanoethyl group are shown in Figure 4-4. The conversion rate suggests that the epimerization for the produced complex does not occur during the process of the photoisomerization.

Cavity Shape of the 2-cyanoethyl group

In order to explain the reason why the (**S**)-isomer is produced when the (**R**)-1,2-diaminopropane is used as an axial base ligand, the reaction cavity for the 2-cyanoethyl group in the initial crystal structure was drawn, and its volume was calculated in the same way as previously reported [7]. Figure 4-5 shows the reaction cavity for the 2-cyanoethyl group. The volume of the reaction cavity for the 2-cyanoethyl group was 14 Å³. In order to examine the asymmetric shape, the cavity was divided into two parts by the average plane comprising the C-C-C-N atoms of the 2-cyanoethyl group, in the same way as that for *sec*-butylamine. The volumes of the two parts were also calculated, and are given in Figure 4-5, in which the C-C-N moiety of each conformer is drawn so as to occupy the same position to each other. The

right part of the cavity is significantly greater than the left part. Since the CN group has a greater volume than the CH₃ group, it is favorable that the CN and CH₃ groups occupy the greater and smaller parts of the reaction cavity, respectively, after conversion to the 1-cyanoethyl group. This explains the reason why the (**S**)-1-cyanoethyl group is preferentially produced from the (**R**)-1,2-diaminopropane complex after isomerization. Although the lower diastereomer excess was not explained since the conformation of the 2-cyanoethyl group has no disordered structure, like the 2-cyanoethyl sec-butylamine cobaloxime. Alternatively, the high diastereomer excess would be expected if the irradiation time is less than 30 min.

Table 4-1 Crystal Data and Experimental Details**Crystal data**

Chemical formula	[Co(C ₄ H ₇ N ₂ O ₂) ₂ (C ₃ H ₄ N)(C ₃ H ₁₀ N ₂)]
Formula weight	417.36
Cell system	Orthorhombic
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁
<i>a</i> /Å	11.079(2)
<i>b</i> /Å	18.833(2)
<i>c</i> /Å	9.456(2)
<i>V</i> /Å ³	1973.1(6)
<i>Z</i>	4
<i>D_x</i> /Mg m ⁻³	1.405
<i>F</i> (000)	880
Radiation type	Mo Kα
Wavelength/Å	0.71073
No. of reflections for cell parameters	25
θ range/°	12.5-15
μ /mm ⁻¹	0.903
Temperature/K	296
Crystal form	Prismatic
Crystal size/mm	0.4 x 0.3 x 0.05
Crystal color	Orange

Data collection

Diffractometer	AFC-7R
Data collection method	ω -2 θ
Scan rate/° min ⁻¹	16
Absorption correction	Ψ scan
No. of measured reflections	4057
No. of independent reflections	3756
No. of observed reflections	2588
Criterion for observed reflections	$I > 2 \sigma(I)$
$\theta_{\max}/^\circ$	27.50
Range of <i>h, k, l</i>	$0 \leq h \leq 14$ $0 \leq k \leq 24$ $-12 \leq l \leq 12$
No. of standard reflections	3
Frequency of standard reflections	Every 100 reflections
Intensity decay /%	1.7

Refinement

Refinement on	F^2
$R [I > 2\sigma(I)]$	0.0486
$wR(I)$	0.1253
<i>S</i>	1.010
No. of reflections used in refinement ($I > 0$)	3756
No. of parameters used	242
H-atom treatment	Calculated
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0885P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max}$	0.011
$\Delta\rho_{\max}/e\text{\AA}^{-3}$	1.064
$\Delta\rho_{\min}/e\text{\AA}^{-3}$	-0.515
Extinction correction	None
Flack χ parameter	-0.01(3)

Table 4-2 Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)

atom	x	y	z	U_{eq}^a
Co1	0.90951(5)	0.23168(3)	0.72249(6)	0.0316(2)
O1	0.7751(3)	0.2379(2)	0.4655(3)	0.0457(8)
O2	1.1007(4)	0.1378(2)	0.7945(4)	0.058(1)
O3	1.0440(3)	0.2262(2)	0.9783(4)	0.057(1)
O4	0.7120(3)	0.3210(2)	0.6557(4)	0.0480(9)
N1	0.8650(4)	0.2056(2)	0.5376(4)	0.0376(9)
N2	1.0221(4)	0.1591(2)	0.6931(5)	0.038(1)
N3	0.9538(4)	0.2576(2)	0.9076(4)	0.039(1)
N4	0.7938(3)	0.3020(2)	0.7531(4)	0.0339(9)
N5	0.6601(6)	0.0347(4)	1.0104(8)	0.101(2)
N6	1.0286(4)	0.3082(2)	0.6524(4)	0.037(1)
N7	1.030(1)	0.4594(3)	0.6561(7)	0.133(4)
C1	0.9278(5)	0.1560(3)	0.4775(5)	0.043(1)
C2	1.0199(5)	0.1273(3)	0.5716(6)	0.042(1)
C3	0.8945(5)	0.3095(3)	0.9654(5)	0.041(1)
C4	0.8005(5)	0.3375(3)	0.8712(5)	0.038(1)
C5	0.9056(7)	0.1306(3)	0.3317(6)	0.060(2)
C6	1.0978(6)	0.0649(3)	0.5385(7)	0.057(2)
C7	0.9156(7)	0.3366(4)	1.1120(6)	0.067(2)
C8	0.7219(6)	0.3998(3)	0.9026(6)	0.052(1)
C9	0.7913(5)	0.1590(3)	0.7914(6)	0.043(1)
C10	0.7847(7)	0.1464(3)	0.9469(6)	0.0600(2)
C11	0.7122(7)	0.0836(4)	0.9832(7)	0.066(2)
C12	1.0036(5)	0.3511(3)	0.5244(6)	0.042(1)
C13	1.0611(7)	0.4233(3)	0.5284(6)	0.056(2)
C14	1.0312(7)	0.4647(3)	0.3948(7)	0.067(2)

a) $U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$

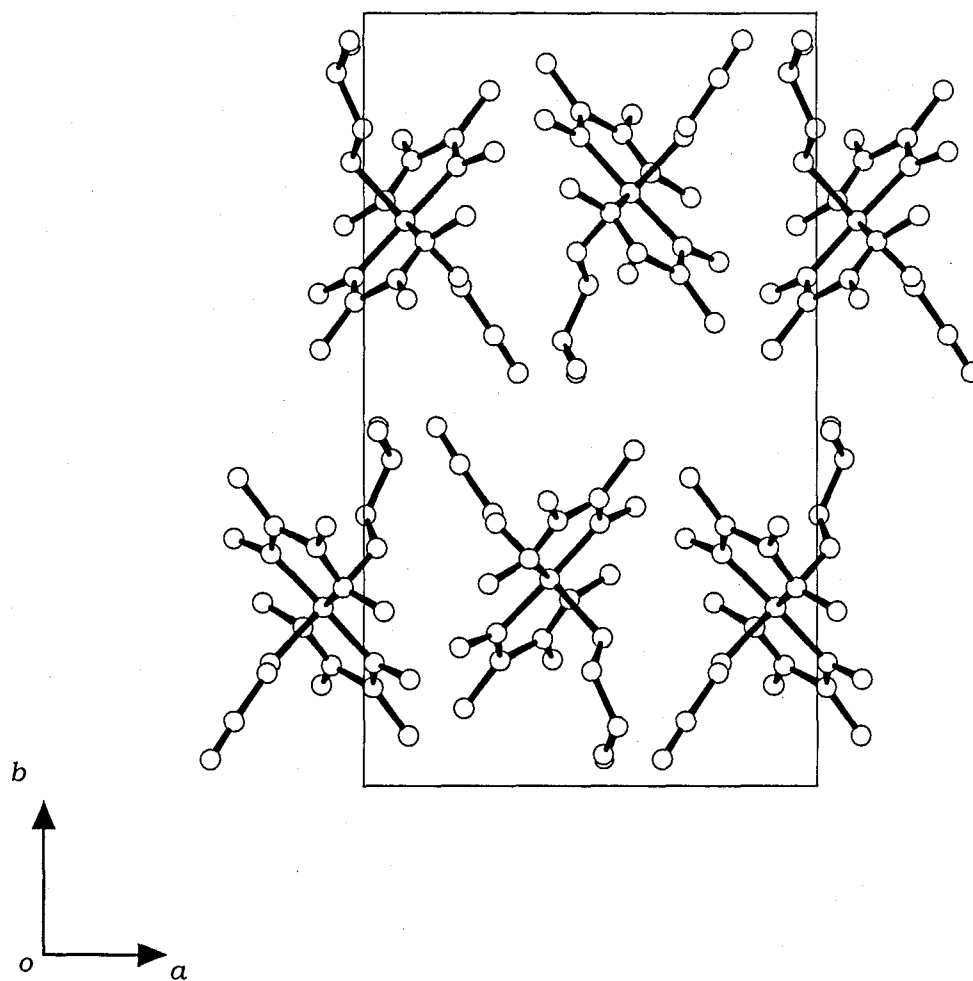


Figure 4-1 The crystal structure of (2-cyanoethyl)[(*R*)-1,2-diaminopropane]cobaloxime viewed along the *c*-axis.

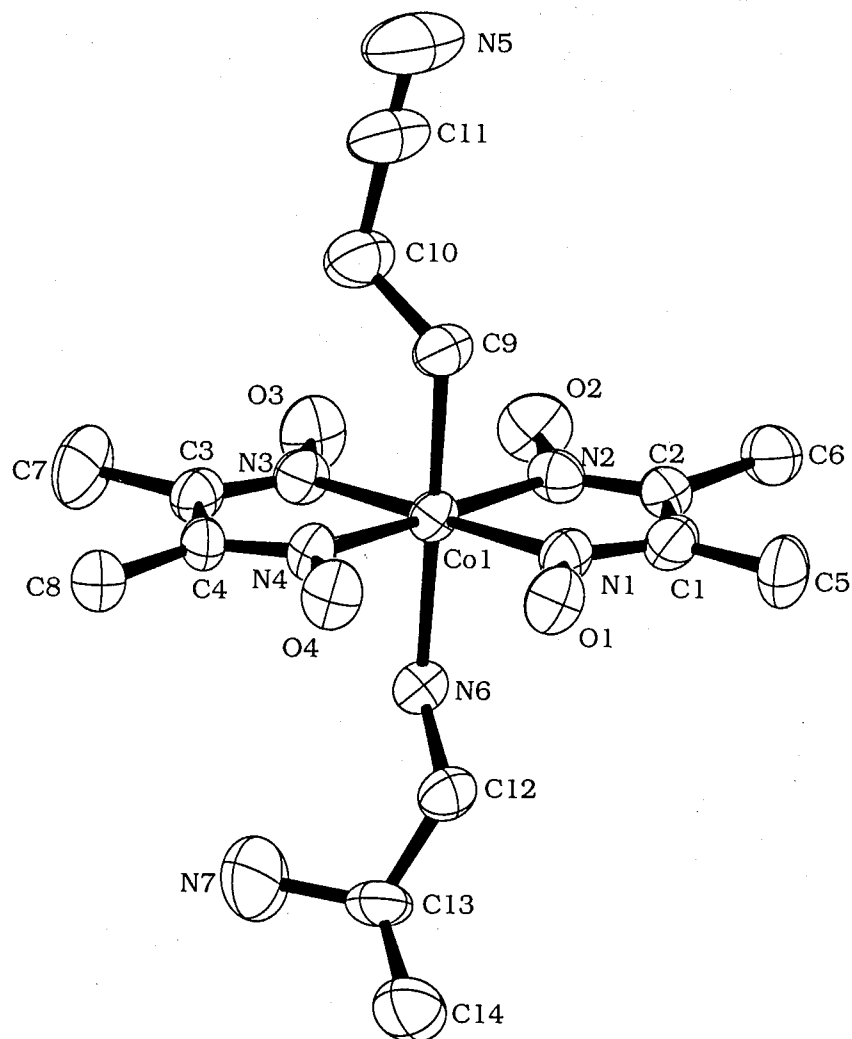


Figure 4-2 ORTEP drawing of the molecular structure of (2-cyanoethyl) [(*R*)-1,2-diaminopropane] cobaloxime with the numbering of the atoms. The thermal ellipsoids are 50% level. The cobalt atom bond to the N6 atom in primary amino group but not N7 atom in secondary amino group.

Table 4-3 The diastereomer excess of (2-cyanoethyl) [(**R**)-1,2-diaminopropane] cobaloxime

Irradiation time (min)	Diastereomer excess (%)	Major configuration	Reaction yield (%)
30	26	S	6
60	19	S	11
120	15	S	14

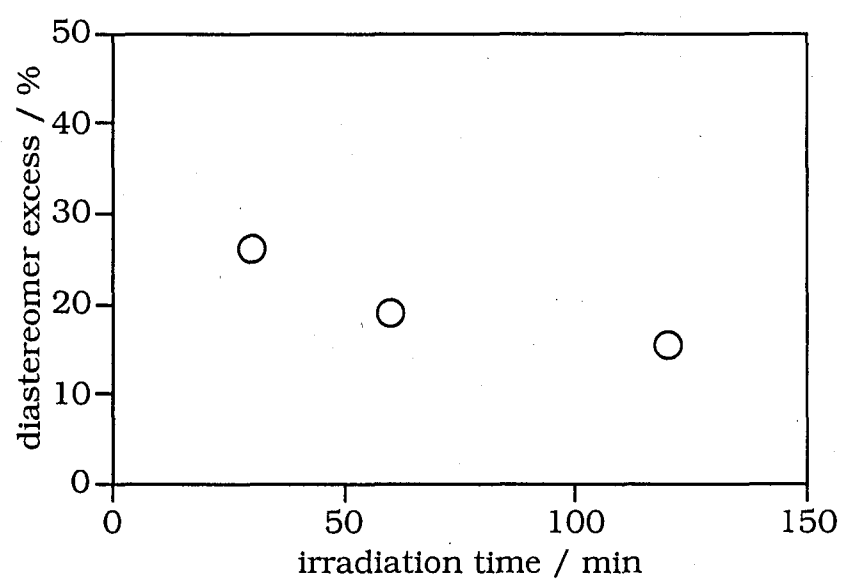


Figure 4-3 The diastereomer excess of (2-cyanoethyl) [(**R**)-1,2-diaminopropane] cobaloxime with the irradiation time.

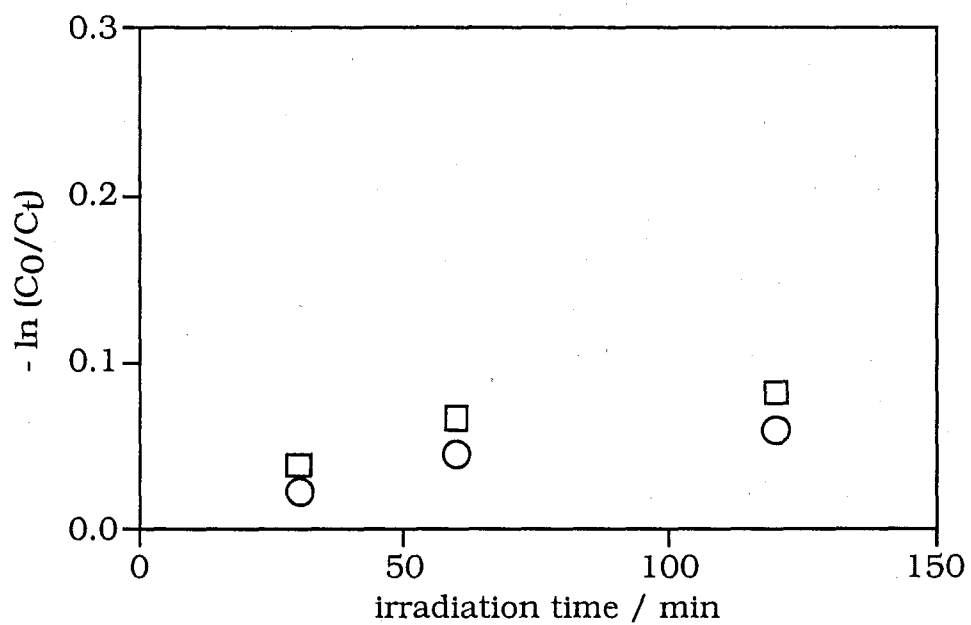


Figure 4-4 Conversion of the 2-cyanoethyl group to the (*R*)- and (*S*)-1-cyanoethyl groups in the (*R*)-1,2-diaminopropane complex with the irradiation time.

The values of C_0 and C_t denote the amounts of 1-cyanoethyl complex at the irradiation time , 0 and t , respectively.

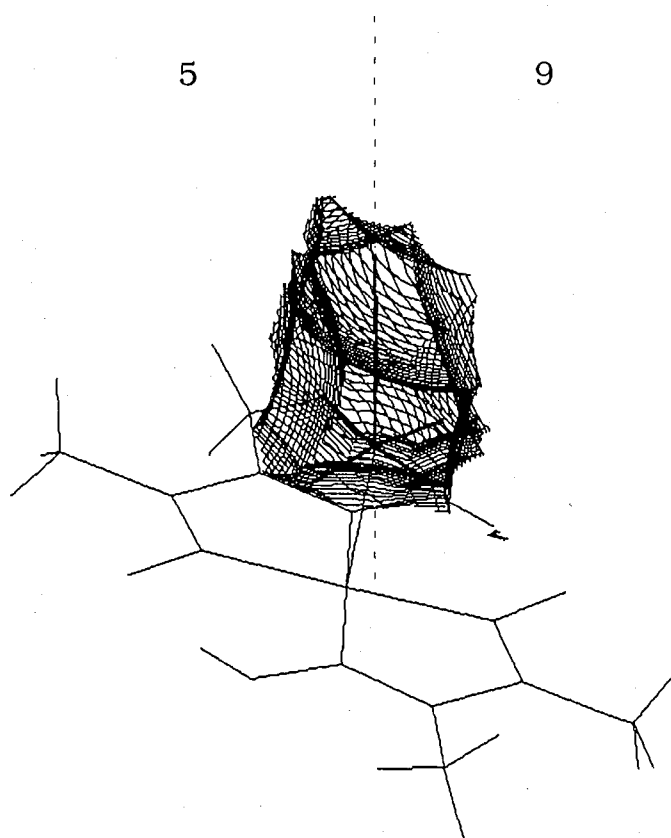


Figure 4-5 Reaction cavity for the 2-cyanoethyl group in (*R*)-1,2-diaminopropane cobaloxime complex, viewed along C10-C9 bond of the 2-cyanoethyl group. The contours are drawn at an interval of 0.1 Å. The cavity volumes (Å³) of left and right halves are also given

4-2 2-amino-1-propanol

The chemical formula of 2-amino-1-propanol was given in Figure 1-5. The 2-amino-1-propanol $\text{CH}_3\text{CH}(\text{NH}_2)\text{CH}_2\text{OH}$ is a similar shape to *sec*-butylamine $\text{CH}_3\text{CH}(\text{NH}_2)\text{CH}_2\text{CH}_3$, so-called the isosteric pair of molecule

X-ray structure determination

The complex of (2-cyanoethyl)[(*S*)-2-amino-1-propanol]cobaloxime was prepared in a way similar to that reported previously [7]. The crystals were obtained from an acetone-hexane mixed solution. The X-ray data were collected on a Rigaku AFC7R diffractometer. $\text{MoK}\alpha$ radiation monochromated with graphite was used. The structure was solved by the Patterson method with the program SAPI91 [8], and refined with the program SHELXL97 [9]. In the process of the refinement, the 2-cyanoethyl group was found to have three disordered conformations around the Co-C bond. The bond distances and the torsion angles around the C-C bond of the disordered 2-cyanoethyl groups were restrained to have fixed values in the further refinement cycles. All the hydrogen atoms were calculated geometrically and refined with a riding model. Non-hydrogen atoms were refined with the anisotropic temperature factors, except for the disordered atoms, which were refined isotropically. The absolute configuration was determined to coincide with that of the (*S*)-2-amino-1-propanol, which was consistent with that obtained from the Flack χ parameter in the refinement. The atomic-scattering factors were taken from International Tables for Crystallography [10]. The crystal data and experimental details are given in Table 4-4. The final atomic coordinates with the equivalent isotropic temperature factors for non-hydrogen atoms are given in Table 4-5.

Photoisomerization and HPLC Analysis

The crystals scattered onto a Petri dish were irradiated with a xenon lamp at

300 K, in the same way as that for *sec*-butylamine. After photoirradiation, crystals were dealt with ion exchange resin, Dawex (100-200 mesh), for several hours in ethanol solution and then the sample was changed to *cis*-myrtanylamine derivatives in order to determine the diastereomer excess using HPLC. The HPLC analysis of the crystals was carried out using the chiral stationary phase. The HPLC system used was HITACHI L-7000 series system equipped with CHIRALPAK-AD column (Daisel Chem., Inc.) maintained at 300 K and with Model L-7420 UV-Vis absorbance detector monitored at 254 nm. The mobile phase consists of hexane with 10% v/v ethanol and its flow rate was 1.0 ml min⁻¹. Quantification was performed integrating the peak area. The chromatogram obtained indicates that the produced 1-cyanoethyl group was not inverted to the opposite configuration when it migrated in the chiral stationary phase of HPLC.

Crystal and Molecular Structure

The X-ray crystal structure of (2-cyanoethyl)[(*S*)-2-amino-1-propanol]cobaloxime viewed along the c-axis and the ORTEP drawing [11] of the molecular structure with the numbering atoms was shown in Figure 4-6 and Figure 4-7, respectively. The crystal structure obtained by X-ray analysis was different from that of *sec*-butylamine complex, but the complex of (2-cyanoethyl)[2-amino-1-propanol]cobaloxime is a isosteric complex to the *sec*-butylamine complex. The 2-cyanoethyl group takes a perpendicular conformation to the cobaloxime plane, and has disordered conformations (A, B and C) around the Co-C bond. The occupancy factors of A, B and C are 0.42(2), 0.36(2) and 0.22(1), respectively. This ratio of the occupancy factor is roughly similar to that of *sec*-butylamine complex. because it may be considered that wide range of the bottom profile for the 2-cyanoethyl group caused the disordered conformers and their occupancy factors. The 2-cyanoethyl group makes no hydrogen bond with the neighboring molecules, in spite of the hydroxy group in the crystal structure. The hydroxy group does not orient to the 2-cyanoethyl group.

Diastereomer Excess

It was found that the (**R**)-1-cyanoethyl group was preferentially produced when the (**S**)-2-amino-1-propanol was used as an axial base ligand. The diastereomer excess indicated from 21% in 12% of the reaction yield.

Cavity Shape of the 2-cyanoethyl group

In order to explain the reason why the (**R**)-isomer is produced when the (**S**)-2-amino-1-propanol is used as an axial base ligand, the reaction cavity for the 2-cyanoethyl group in the initial crystal structure was drawn, and its volume was calculated in the same way as reported previously [7]. Figure 4-8 shows the reaction cavities for the 2-cyanoethyl group. In order to examine the asymmetric shape, the cavity was divided into two parts by the average plane comprising the C-C-C-N atoms of the 2-cyanoethyl group, in the same way as that of *sec*-butylamine. The volumes of the two parts were also calculated, and are given in Figure 4-8, in which the C-C-N moiety of each conformer is drawn so as to occupy the same position to each other. The right part of the cavity is significantly greater than the left part. Since the CN group has a greater volume than the CH₃ group, it is favorable that the CN and CH₃ groups occupy the greater and smaller parts of the reaction cavity, respectively, after conversion to the 1-cyanoethyl group. This explains the reason why the (**R**)-1-cyanoethyl group is preferentially produced from the (**S**)-2-amino-1-propanol complex after isomerization.

Table 4-4 Crystal Data and Experimental Details**Crystal data**

Chemical formula	[Co(C ₄ H ₇ N ₂ O ₂) ₂ (C ₃ H ₄ N)(C ₃ H ₉ NO)]
Formula weight	418.35
Cell system	Orthorhombic
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁
<i>a</i> /Å	13.248(3)
<i>b</i> /Å	16.175(3)
<i>c</i> /Å	9.305(3)
<i>V</i> /Å ³	1993.9(8)
<i>Z</i>	4
<i>D_x</i> /Mg m ⁻³	1.394
<i>F</i> (000)	880
Radiation type	Mo <i>K</i> α
Wavelength/Å	0.71073
No. of reflections for cell parameters	25
θ range/°	12.5-15
μ /mm ⁻¹	0.896
Temperature/K	296
Crystal form	Prismatic
Crystal size/mm	0.3 x 0.2 x 0.2
Crystal color	Orange

Data collection

Diffractometer	AFC-7R
Data collection method	ω -2 θ
Scan rate/° min ⁻¹	16
Absorption correction	Ψ scan
No. of measured reflections	2594
No. of independent reflections	2594
No. of observed reflections	1352
Criterion for observed reflections	$I > 2 \sigma(I)$
$\theta_{\max}$ /°	27.49
Range of <i>h, k, l</i>	$0 \leq h \leq 17$ $0 \leq k \leq 21$ $-12 \leq l \leq 12$
No. of standard reflections	3
Frequency of standard reflections	Every 100 reflections
Intensity decay /%	0.4

Refinement

Refinement on	<i>F</i> ²
$R [I > 2\sigma(I)]$	0.0598
$wR(I)$	0.1414
<i>S</i>	0.941
No. of reflections used in refinement ($I > 0$)	2594
No. of parameters used	246
H-atom treatment	Calculated
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0588P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max}$	0.045
$\Delta\rho_{\max}/e\text{\AA}^{-3}$	0.524
$\Delta\rho_{\min}/e\text{\AA}^{-3}$	-0.453
Extinction correction	None
Flack χ parameter	-0.04(6)

Table 4-5 Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)

atom	x	y	z	U_{eq}^a
Co1	0.60753(7)	0.74386(6)	0.7565(1)	0.0355(3)
O1	0.6748(4)	0.7329(4)	0.4672(5)	0.052(2)
O2	0.4618(5)	0.8512(4)	0.8758(6)	0.062(2)
O3	0.5392(5)	0.7526(4)	1.0460(5)	0.064(2)
O4	0.7570(5)	0.6358(4)	0.6405(6)	0.058(2)
O5	0.2790(5)	0.6662(5)	0.7281(9)	0.090(2)
N1	0.6119(5)	0.7722(4)	0.5611(6)	0.037(2)
N2	0.5107(5)	0.8286(4)	0.757(1)	0.039(2)
N3	0.6022(6)	0.7168(4)	0.9531(6)	0.050(2)
N4	0.7048(5)	0.6594(4)	0.759(1)	0.045(2)
N5A	0.914(2)	0.939(2)	0.953(3)	0.084(6)
N5B	0.881(2)	0.959(2)	0.980(3)	0.084(6)
N5C	0.916(3)	0.946(2)	0.886(5)	0.084(6)
N6	0.4899(5)	0.6601(4)	0.732(1)	0.050(2)
C1	0.5504(6)	0.8283(5)	0.5163(8)	0.041(2)
C2	0.4910(6)	0.8619(6)	0.633(1)	0.039(2)
C3	0.6609(6)	0.6569(5)	0.9972(9)	0.046(2)
C4	0.7245(7)	0.6248(5)	0.8818(9)	0.043(2)
C5	0.5372(6)	0.8506(6)	0.3614(8)	0.054(2)
C6	0.4145(7)	0.9289(5)	0.6157(9)	0.056(3)
C7	0.6661(8)	0.6274(6)	1.1486(8)	0.069(3)
C8	0.8034(6)	0.5604(5)	0.902(1)	0.053(2)
C9	0.7134(8)	0.8297(6)	0.785(1)	0.071(4)
C10A	0.770(2)	0.827(2)	0.927(2)	0.053(5)
C10B	0.721(2)	0.862(2)	0.940(2)	0.053(5)
C10C	0.816(2)	0.805(2)	0.847(4)	0.053(5)
C11A	0.848(2)	0.892(1)	0.932(3)	0.061(5)
C11B	0.810(2)	0.915(2)	0.966(3)	0.061(5)
C11C	0.873(3)	0.882(2)	0.872(4)	0.061(5)
C12	0.4340(7)	0.6403(6)	0.601(1)	0.054(3)
C13	0.4921(9)	0.5767(7)	0.510(1)	0.106(4)
C14	0.3307(7)	0.6105(7)	0.640(1)	0.080(4)

a) $U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$

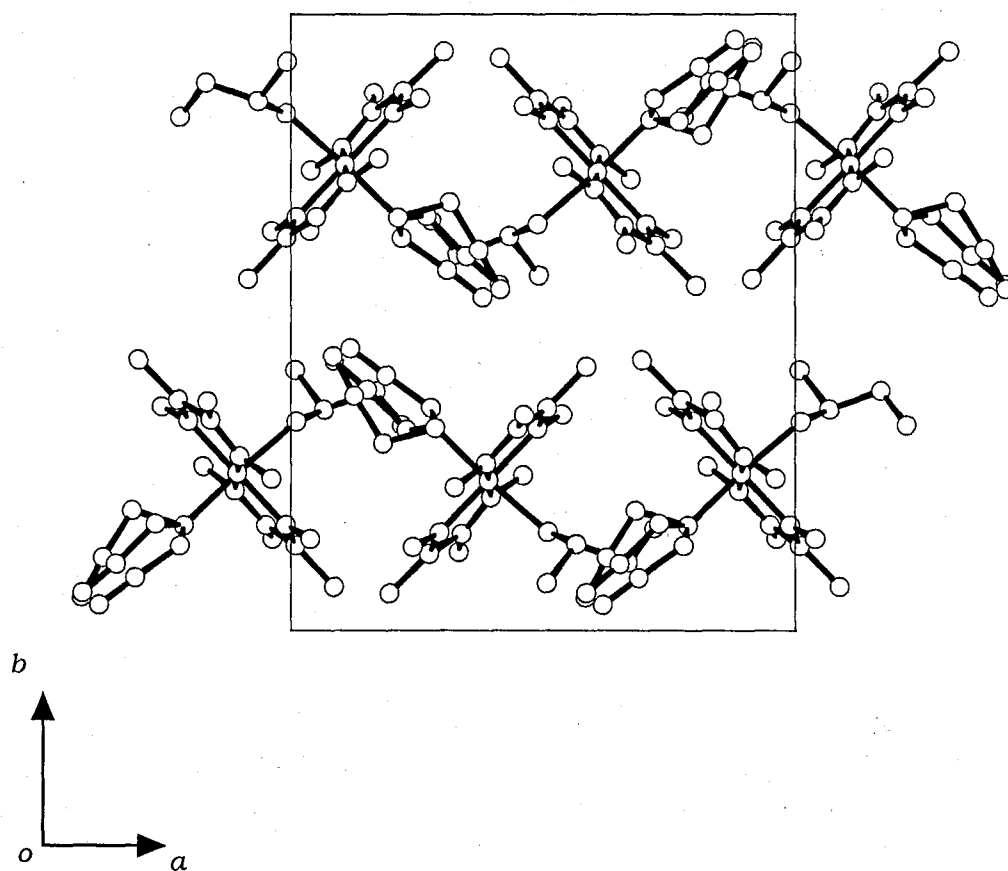


Figure 4-6 The crystal structure of (2-cyanoethyl)[(S)-2-amino-1-propanol] cobaloxime viewed along the *c*-axis.

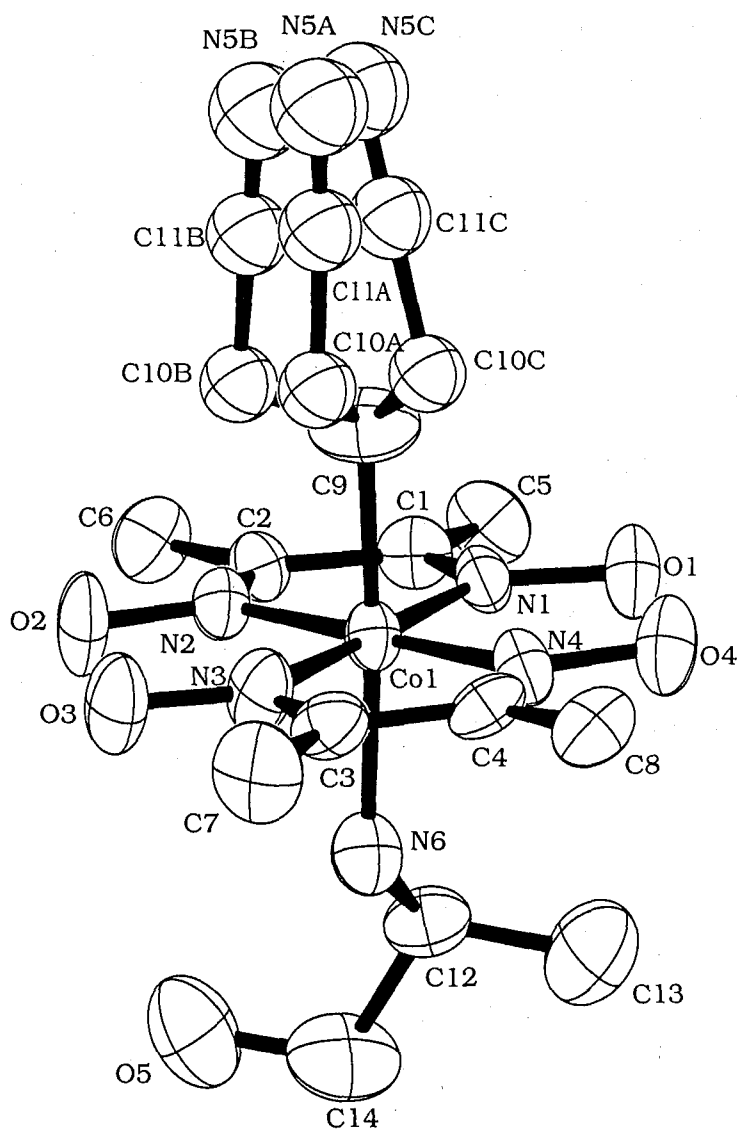


Figure 4-7 ORTEP drawing of the molecular structure of (2-cyanoethyl)[(S)-2-amino-1-propanol] cobaloxime with the numbering of the atoms. The thermal ellipsoids are 50 % level. The 2-cyanoethyl group has three disordered conformations.

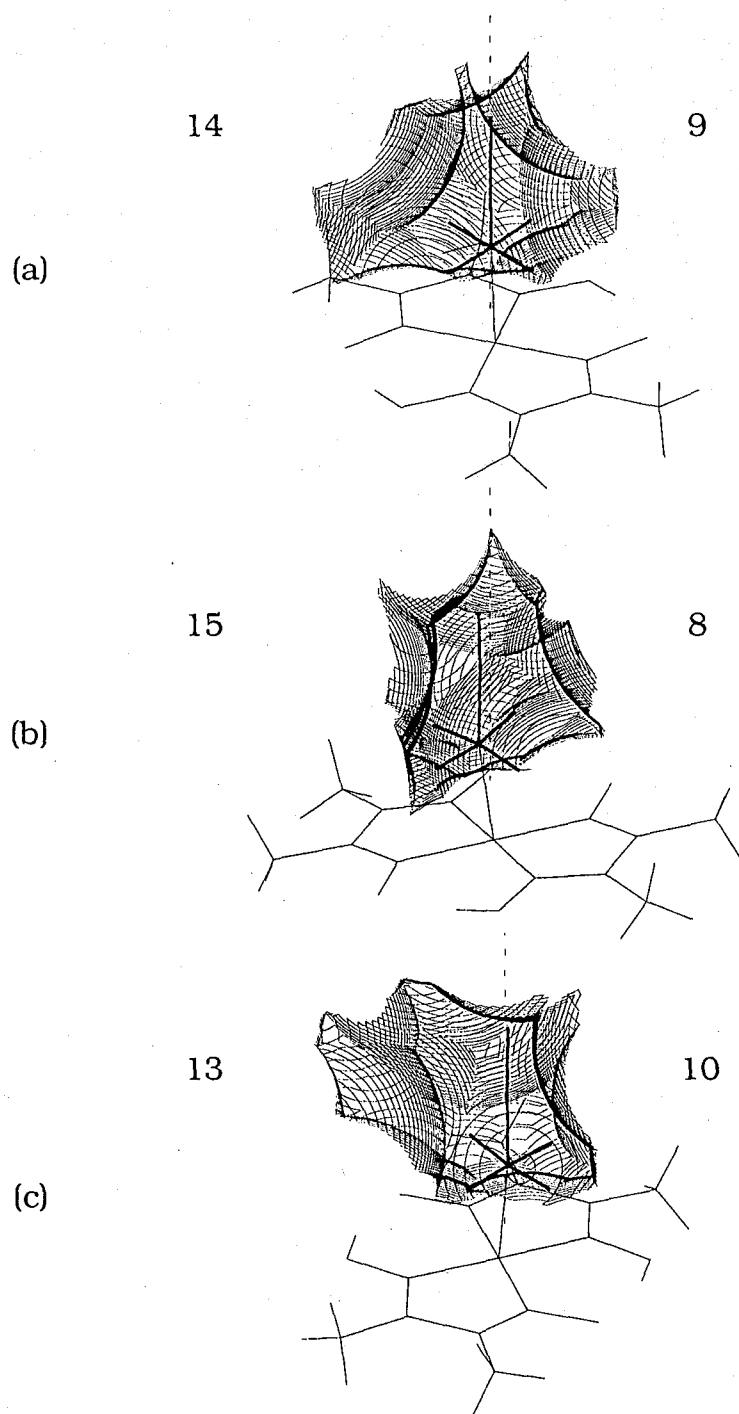


Figure 4-8 Reaction cavity for the 2-cyanoethyl group in (*S*)-2-amino-1-propanol complex, viewed along C10-C9 bond of the 2-cyanoethyl group. The contours are drawn at an interval of 0.1 Å. Each cavity is divided into two parts by the average plane composed on the C-C-C-N bond.

The cavity volumes (Å³) of left and right halves are also given.

4-3 2-amino-1-butanol

The chemical formula of 2-amino-1-butanol was given in Figure 1-5. The 2-amino-1-butanol $\text{CH}_3\text{CH}_2\text{CH}(\text{NH}_2)\text{CH}_2\text{OH}$ is a similar shape to 2-amino-1-propanol $\text{CH}_3\text{CH}(\text{NH}_2)\text{CH}_2\text{OH}$, but not the isosteric pair of molecule.

X-ray structure determination

The complex of the (2-cyanoethyl) [(**S**)-2-amino-1-butanol] cobaloxime was prepared in a way similar to that reported previously [7]. The crystals were obtained from an acetone-hexane mixed solution. The X-ray data were collected on a Rigaku AFC7R diffractometer. $\text{MoK}\alpha$ radiation monochromated with graphite was used. The structure was solved by the Patterson method with the program SAPI91 [8], and refined with the program SHELXL97 [9]. In the process of the refinement, the 2-cyanoethyl group was found to have two disordered conformations around the Co-C bond. The bond distances and the torsion angles around the C-C bond of the disordered 2-cyanoethyl groups were restrained to have fixed values in the further refinement cycles. All the hydrogen atoms were calculated geometrically and refined with a riding model. Non-hydrogen atoms were refined with the anisotropic temperature factors, except for the disordered atoms, which were refined isotropically. The absolute configuration was determined to coincide with that of the (**S**)-2-amino-1-butanol, which was consistent with that obtained from the Flack χ parameter in the refinement. The atomic-scattering factors were taken from International Tables for Crystallography [10]. The crystal data and experimental details are given in Table 4-6. The final atomic coordinates with the equivalent isotropic temperature factors for non-hydrogen atoms are given in Table 4-7.

Photoisomerization and HPLC Analysis

The crystals scattered onto a Petri dish were irradiated with a xenon lamp at

300 K, in the same way as that for *sec*-butylamine. After photoirradiation, crystals were dealt with ion exchange resin, Dawex (100-200 mesh), for several hours in ethanol solution and then the sample was changed to *cis*-myrtanylamine derivatives in order to determine the diastereomer excess using HPLC. The HPLC analysis of the sample was carried out using the chiral stationary phase. The HPLC system used was HITACHI L-7000 series system equipped with CHIRALPAK-AD column (Daisel Chem., Inc.) maintained at 300 K and with Model L-7420 UV-Vis absorbance detector monitored at 254 nm. The mobile phase consists of hexane with 10% v/v ethanol and its flow rate was 1.0 ml min⁻¹. Quantification was performed integrating the peak area. The chromatogram obtained indicates that the produced 1-cyanoethyl group was not inverted to the opposite configuration when it migrated in the chiral stationary phase of HPLC.

Crystal and Molecular Structure

The X-ray crystal structure of (2-cyanoethyl)[(*S*)-2-amino-1-butanol]cobaloxime viewed along the *c*-axis and the ORTEP drawing [11] of the molecular structure with the numbering atoms was shown in Figure 4-9 and Figure 4-10, respectively. The crystal structure obtained by X-ray analysis was almost the same to that of 2-amino-1-propanol complex. The 2-cyanoethyl group takes a perpendicular conformation to the cobaloxime plane, and has disordered conformations (A and B) around the Co-C bond. The occupancy factors of A and B are 0.84(1) and 0.16, respectively. The 2-cyanoethyl group makes no hydrogen bond with the neighboring molecules in spite of the hydroxy group in the crystal structure. The hydroxy group does not direct to the 2-cyanoethyl group.

Diastereomer Excess

It was found that the (*R*)-1-cyanoethyl group was preferentially produced when the (*S*)-2-amino-1-butanol was used as an axial base ligand. The diastereomer excess indicated from 32% in 9% of the reaction yield.

Cavity Shape of the 2-cyanoethyl group

In order to explain the reason why the (**R**)-isomer is produced when the (**S**)-2-amino-1-butanol is used as an axial base ligand, the reaction cavity for the 2-cyanoethyl group in the initial crystal structure was drawn, and its volume was calculated in the same way as reported previously [7]. Figure 4-11 shows the reaction cavities for the 2-cyanoethyl group. In order to examine the asymmetric shape, the cavity was divided into two parts by the average plane comprising the C-C-C-N atoms of the 2-cyanoethyl group, in the same way as that *sec*-butylamine. The volumes of the two parts were also calculated, and are given in Figure 4-11, in which the C-C-N moiety of each conformer is drawn so as to occupy the same position to each other.

The right part of the cavity is significantly greater than the left part. Since the CN group has a greater volume than the CH₃ group, it is favorable that the CN and CH₃ groups occupy the greater and smaller parts of the reaction cavity, respectively, after conversion to the 1-cyanoethyl group. This explains the reason why the (**R**)-1-cyanoethyl group is preferentially produced from the (**S**)-2-amino-1-butanol complex after isomerization.

Table 4-6 Crystal Data and Experimental Details

Crystal data	
Chemical formula	[Co(C ₄ H ₇ N ₂ O ₂) ₂ (C ₃ H ₄ N)(C ₄ H ₁₁ NO)]
Formula weight	432.37
Cell system	Orthorhombic
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁
<i>a</i> /Å	13.160(2)
<i>b</i> /Å	16.172(3)
<i>c</i> /Å	9.474(3)
<i>V</i> /Å ³	2016.3(7)
<i>Z</i>	4
<i>D_x</i> /Mg m ⁻³	1.424
<i>F</i> (000)	912
Radiation type	Mo <i>K</i> α
Wavelength/Å	0.71073
No. of reflections for cell parameters	25
θ range/°	12.5-15
μ /mm ⁻¹	0.889
Temperature/K	296
Crystal form	Prismatic
Crystal size/mm	0.4 x 0.3 x 0.05
Crystal color	Orange
Data collection	
Diffractometer	AFC-7R
Data collection method	ω -2 θ
Scan rate/° min ⁻¹	16
Absorption correction	Ψ scan
No. of measured reflections	2622
No. of independent reflections	2622
No. of observed reflections	1678
Criterion for observed reflections	<i>I</i> > 2 σ (<i>I</i>)
$\theta_{\max}$ /°	27.50
Range of <i>h, k, l</i>	0 ≤ <i>h</i> ≤ 17 0 ≤ <i>k</i> ≤ 21 0 ≤ <i>l</i> ≤ 12
No. of standard reflections	3
Frequency of standard reflections	Every 100 reflections
Intensity decay /%	0.1
Refinement	
Refinement on	<i>F</i> ²
<i>R</i> [<i>I</i> > 2 σ (<i>I</i>)]	0.0441
$\omega R(I)$	0.1251
<i>S</i>	0.986
No. of reflections used in refinement (<i>I</i> > 0)	2622
No. of parameters used	244
H-atom treatment	Calculated
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0613P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$
(Δ/σ) _{max}	0.005
$\Delta\rho_{\max}/e\text{\AA}^{-3}$	0.449
$\Delta\rho_{\min}/e\text{\AA}^{-3}$	-0.512
Extinction correction	None
Flack χ parameter	0.01(3)

Table 4-7 Fractional atomic coordinates and equivalent isotropic displacement parameters ($\text{\AA}^2$)

atom	x	y	z	U_{eq}^a
Co1	0.10227(5)	0.76010(4)	0.73716(7)	0.0301(2)
O1	0.0342(3)	0.7481(3)	0.4517(4)	0.053(1)
O2	0.2516(3)	0.8702(3)	0.8500(5)	0.051(1)
O3	0.1667(3)	0.7761(3)	1.0226(4)	0.048(1)
O4	-0.0414(4)	0.6490(3)	0.6222(5)	0.056(1)
O5	-0.2274(3)	0.8149(3)	0.7737(5)	0.070(2)
N1	0.0988(4)	0.7862(3)	0.5428(4)	0.037(1)
N2	0.1996(3)	0.8457(3)	0.7344(6)	0.037(1)
N3	0.1059(4)	0.7356(3)	0.9314(4)	0.0341(9)
N4	0.0072(4)	0.6735(3)	0.7390(6)	0.036(1)
N5A	0.3820(7)	0.5472(6)	0.529(1)	0.071(3)
N5B	0.411(4)	0.565(4)	0.547(6)	0.071(3)
N6	-0.0196(3)	0.8413(3)	0.7516(7)	0.039(1)
C1	0.1557(4)	0.8453(4)	0.4998(6)	0.039(2)
C2	0.2186(5)	0.8790(4)	0.6136(6)	0.040(2)
C3	0.0450(4)	0.6783(4)	0.9747(6)	0.036(1)
C4	-0.0142(4)	0.6423(4)	0.8602(6)	0.035(1)
C5	0.1592(6)	0.8746(5)	0.3512(7)	0.067(2)
C6	0.2998(5)	0.9416(4)	0.5889(8)	0.055(2)
C7	0.0298(5)	0.6554(5)	1.1271(6)	0.050(2)
C8	-0.0901(5)	0.5743(4)	0.8819(7)	0.053(2)
C9A	0.2128(5)	0.6774(5)	0.7096(7)	0.035(2)
C10A	0.2443(9)	0.6584(7)	0.567(2)	0.080(3)
C10B	0.294(5)	0.690(4)	0.630(6)	0.080(3)
C11A	0.3228(8)	0.5954(7)	0.550(1)	0.062(3)
C11B	0.358(4)	0.620(3)	0.574(6)	0.062(3)
C12	-0.0739(4)	0.8639(4)	0.8855(6)	0.042(2)
C13	-0.0224(6)	0.9377(5)	0.9527(9)	0.066(2)
C14	-0.1844(5)	0.8811(5)	0.8503(8)	0.058(2)
C15	-0.0644(7)	0.9587(6)	1.0994(9)	0.101(4)

a) $U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$

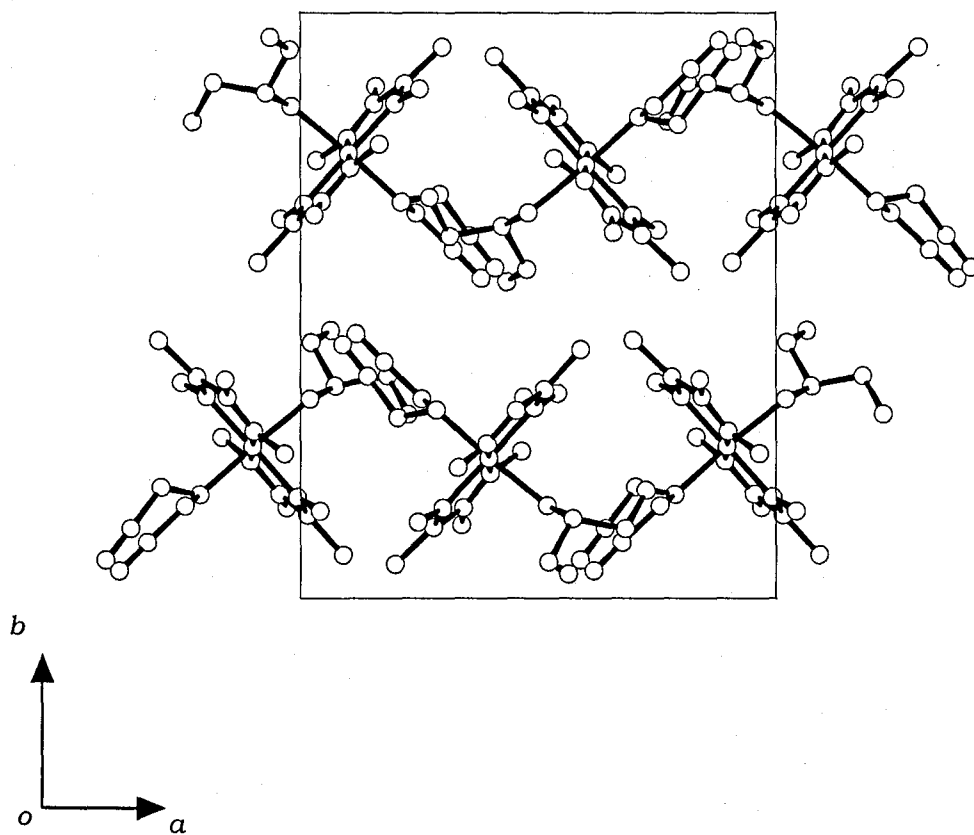


Figure 4-9 The crystal structure of (2-cyanoethyl)[(S)-2-amino-1-butanol] cobaloxime viewed along the c-axis.

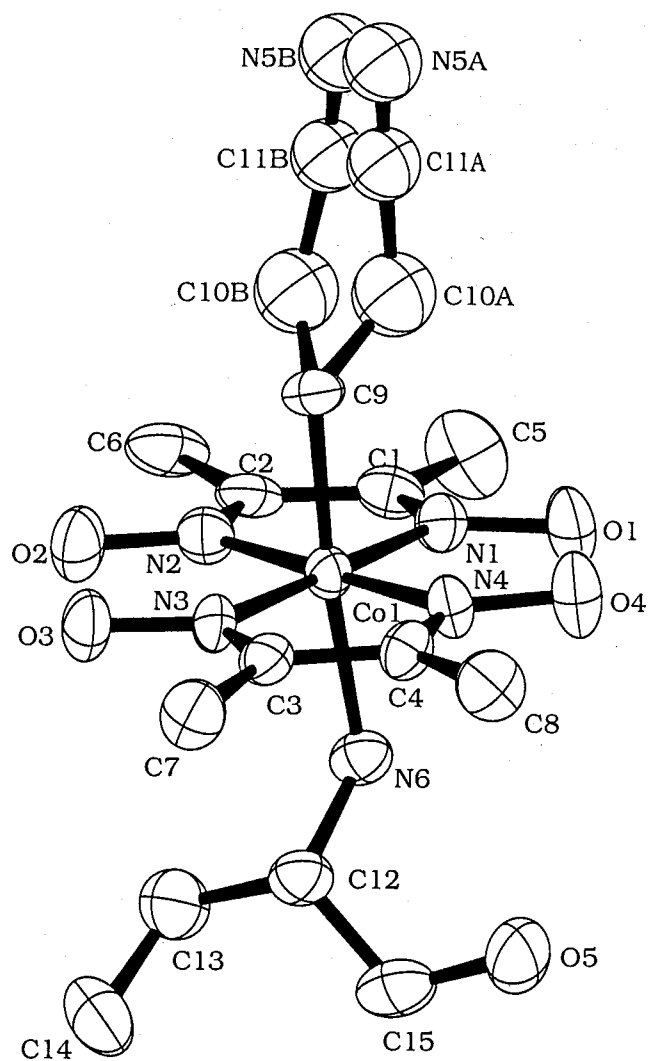


Figure 4-10 ORTEP drawing of the molecular structure of (2-cyanoethyl)[(S)-2-amino-1-butanol]cobaloxime with the numbering of the atoms. The thermal ellipsoids are 50 % level. The 2-cyanoethyl group has three disordered conformations. The occupancy factor of A and B are 0.84(1) and 0.16, respectively.

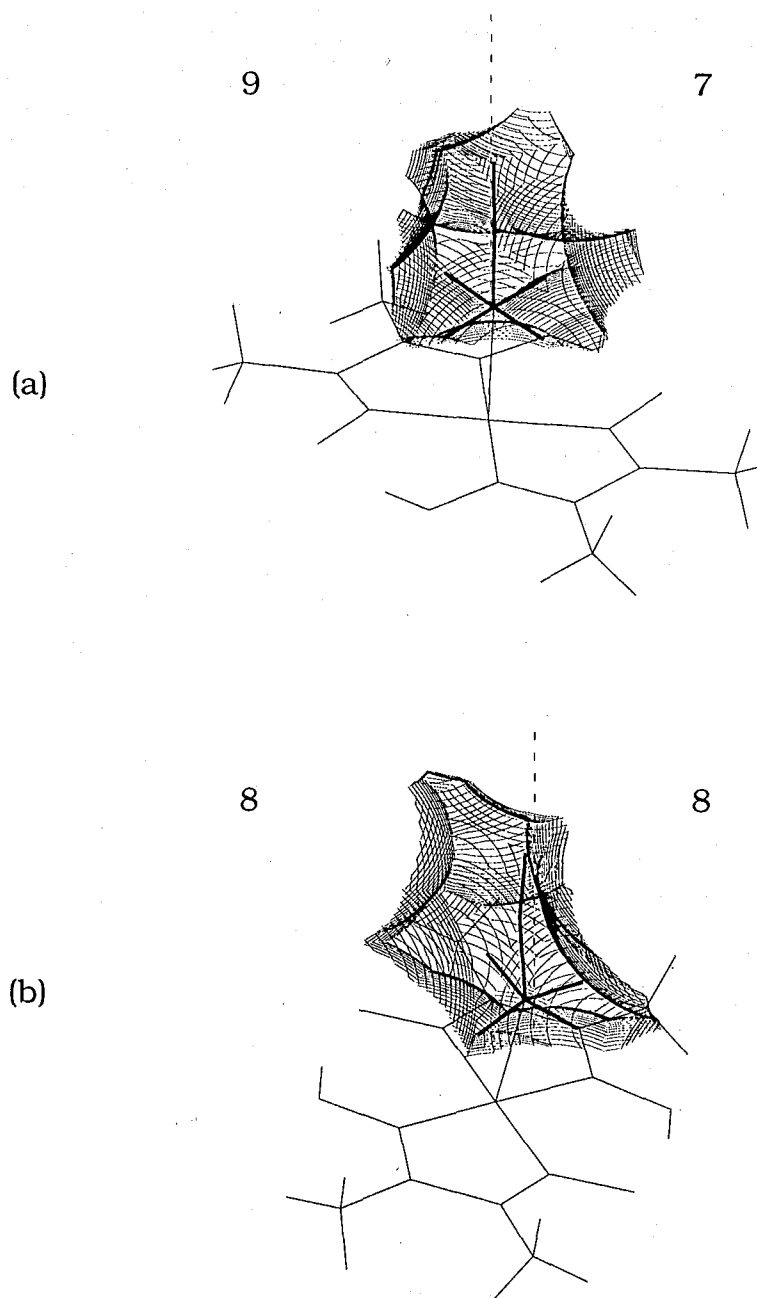


Figure 4-11 Reaction cavity for the 2-cyanoethyl group in (*S*)-2-amino-1-butanol complex, viewed along C10-C9 bond of the 2-cyanoethyl group. The contours are drawn at an interval of 0.1 Å. Each cavity is divided into two parts by the average plane composed on the C-C-C-N bond. The cavity volumes (Å³) of left and right halves are also given.

4-4 1-cyclohexylethylamine

The chemical formula of 1-cyclohexylethylamine was given in Figure 1-5. The 1-cyclohexylethylamine is the simplest chiral amine derivatives containing the non-aromatic six-membered ring.

X-ray structure determination

The complex of (2-cyanoethyl)[(**S**)-1-cyclohexylethylamine]cobaloxime was prepared in a way similar to that reported previously [7]. The crystals were obtained from an acetone-hexane solution. The X-ray data were collected on a smart CCD diffractometer. MoK α radiation monochromated with graphite was used. The structure was solved by the direct method with the program SIR92 [16], and refined with the program SHELXL97 [9]. In the process of the refinement, the 2-cyanoethyl group was found to have three disordered structure around the Co-C bond with a perpendicular conformation to the cobaloxime plane. The bond distances and the torsion angles around the C-C bond of the disordered 2-cyanoethyl groups were restrained to have fixed values in the further refinement cycles. All the hydrogen atoms were calculated geometrically and refined with a riding model. Non-hydrogen atoms were refined with the anisotropic temperature factors, except for the disordered atoms, which were refined isotropically. The absolute configuration was determined to coincide with that of the (**S**)-1-cyclohexylethylamine, which was consistent with that obtained from the Flack χ parameter in the refinement. The atomic-scattering factors were taken from International Tables for Crystallography [10]. The crystal data and experimental details are given in Table 4-8. The final atomic coordinates with the equivalent isotropic temperature factors for non-hydrogen atoms are given in Table 4-9.

Photoisomerization and HPLC Analysis

The crystals scattered onto a Petri dish were irradiated with a xenon lamp for several hours at 300 K, in the same way as that for *sec*-butylamine. After photoirradiation, the HPLC analysis of the crystals was carried out using the chiral stationary phase. The HPLC system used was HITACHI L-7000 series system equipped with CHIRALPAK-AD column (Daisel Chem., Inc.) maintained at 300 K and with Model L-7420 UV-Vis absorbance detector monitored at 254 nm. The mobile phase consists of hexane with 10% v/v ethanol and its flow rate was 1.0 ml min⁻¹. Quantification was performed integrating the peak area. The chromatograms obtained indicates that the produced 1-cyanoethyl group was not inverted to the opposite configuration when it migrated in the chiral stationary phase of HPLC.

Crystal and Molecular Structure

The X-ray crystal structure of (2-cyanoethyl)[(*S*)-1-cyclohexylethylamine] cobaloxime viewed along the c-axis and the ORTEP drawing [11] of the molecular structure with the numbering atoms was shown in Figure 4-12 and Figure 4-13, respectively. The 2-cyanoethyl group takes a perpendicular conformation to the cobaloxime plane, and has disordered conformations (A, B and C) around the Co-C bond. The occupancy factors of A, B and C are 0.40(1), 0.33(1) and 0.27(1), respectively. The 2-cyanoethyl group makes no hydrogen bond with the neighboring molecules.

Diastereomer Excess and Conversion Rate

Table 4-10 shows the diastereomer excess and the reaction yield of the produced 1-cyanoethyl complex with the irradiation time. It was found that the (*R*)-1-cyanoethyl group was preferentially produced when the (*S*)-1-cyclohexylethylamine was used as an axial base ligand, and the diastereomer excess decrease as increasing the reaction yield or the irradiation time as shown in Figure 4-14. The reason is probably due to the following facts; (1) the three disordered structure of the 2-cyanoethyl group and (2) the racemization of the produced 1-cyanoethyl group.

The conversion rates of the 2-cyanoethyl group to the (**R**)-1-cyanoethyl and (**S**)-1-cyanoethyl groups are shown in Figure 4-15. These results suggest that the epimerization of the complex does not occur during the of photoisomerization process.

Cavity Shape of the 2-cyanoethyl group

In order to explain the reason why the (**R**)-isomer is produced when the (**S**)-1-cyclohexylethylamine is used, the reaction cavity for the 2-cyanoethyl group in the initial crystal structure was drawn, and its volume was calculated in the same way as previously reported [7]. Figure 4-16 shows the reaction cavities for the three disordered conformers. In a calculation of the cavities, all of the conformations were included in the neighboring 2-cyanoethyl groups because a cavity with a similar shape and volume was obtained, even if any one of the three conformers was fixed to those of the neighboring 2-cyanoethyl groups. In order to examine the asymmetric shape, the cavity was divided into two parts by the average plane comprising the C-C-C-N atoms of the 2-cyanoethyl group. The volumes of the two parts were also calculated, and are given in Figure 4-16, in which the C-C-N moiety of each conformer is drawn so as to occupy the same position to each other.

For conformers A and C, the left part of the cavity is significantly greater than the right part. Since the CN group has a greater volume than the CH₃ group, it is favorable that the CN and CH₃ groups occupy the greater and smaller parts of the reaction cavity, respectively, after conversion to the 1-cyanoethyl group. This explains the reason why the (**R**)-1-cyanoethyl group is preferentially produced from the (**S**)-1-cyclohexylethylamine complex after isomerization.

For conformer B, on the other hand, the right part is slightly greater than the left part. From conformer B, a 1-cyanoethyl group with the opposite configuration would be produced. This may be a reason why this complex showed a low optical yield. This explains the reason why the (**R**)-1-cyanoethyl group is preferentially produced from the (**S**)-1-

cyclohexylethylamine complex after isomerization. Alternatively, the high diastereomer excess would be expected if the irradiation time is less than 60 min.

Table 4-8 Crystal Data and Experimental Details**Crystal data**

Chemical formula	[Co(C ₄ H ₇ N ₂ O ₂) ₂ (C ₃ H ₄ N)(C ₈ H ₁₇ N)]
Formula weight	470.46
Cell system	Orthorhombic
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁
<i>a</i> /Å	14.8117(1)
<i>b</i> /Å	18.1398(1)
<i>c</i> /Å	9.733
<i>V</i> /Å ³	2615.08(3)
<i>Z</i>	4
<i>D_x</i> /Mg m ⁻³	1.195
<i>F</i> (000)	1000
Radiation type	Mo Kα
Wavelength/Å	0.71073
No. of reflections for cell parameters	25
μ /mm ⁻¹	0.688
Temperature/K	296
Crystal form	Prismatic
Crystal size/mm	0.3 x 0.3 x 0.2
Crystal color	Orange

Data collection

Diffractionmeter	smart CCD
No. of measured reflections	18669
No. of independent reflections	6003
No. of observed reflections	4095
Criterion for observed reflections	$I > 2 \sigma(I)$
$\theta_{\max}/^\circ$	27.82
Range of <i>h, k, l</i>	$-19 \leq h \leq 17$ $-23 \leq k \leq 20$ $-11 \leq l \leq 12$
Intensity decay /%	0.12

Refinement

Refinement on	F^2
$R [I > 2\sigma(I)]$	0.0389
$wR(I)$	0.0742
<i>S</i>	0.762
No. of reflections used in refinement ($I > 0$)	4095
No. of parameters used	288
H-atom treatment	Calculated
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0000P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max}$	0.139
$\Delta\rho_{\max}/e\text{\AA}^{-3}$	0.310
$\Delta\rho_{\min}/e\text{\AA}^{-3}$	-0.501
Extinction correction	None
Flack χ parameter	-0.04(2)

Table 4-9 Fractional atomic coordinates and equivalent isotropic displacement parameters ($\text{\AA}^2$)

atom	x	y	z	U_{eq}^a
Co1	0.40264(2)	0.83911(2)	0.32172(3)	0.04106(9)
O1	0.5848(1)	0.8032(1)	0.4167(2)	0.0745(6)
O2	0.3314(1)	0.8315(1)	0.0434(2)	0.0813(6)
O3	0.2211(1)	0.8753(1)	0.2249(2)	0.0872(7)
O4	0.4730(1)	0.8466(1)	0.5987(2)	0.0682(5)
N1	0.5282(1)	0.8107(1)	0.3044(2)	0.0484(5)
N2	0.4066(2)	0.8217(1)	0.1275(2)	0.0516(5)
N3	0.2777(1)	0.8698(1)	0.3351(2)	0.0591(6)
N4	0.3986(2)	0.8570(1)	0.5159(2)	0.0516(5)
N5A	0.5554(9)	1.1159(4)	0.3775(9)	0.086(3)
N5B	0.520(1)	1.1246(4)	0.358(1)	0.052(3)
N5C	0.490(1)	1.1292(5)	0.323(1)	0.083(4)
N6	0.3804(1)	0.7265(1)	0.3659(2)	0.0468(5)
C1	0.5571(2)	0.7923(1)	0.1813(3)	0.0550(6)
C2	0.4841(2)	0.7995(2)	0.0739(2)	0.0561(7)
C3	0.2486(2)	0.8882(2)	0.4599(3)	0.0668(8)
C4	0.3209(2)	0.8819(2)	0.5665(3)	0.0597(8)
C5	0.6524(2)	0.7644(2)	0.1513(4)	0.103(1)
C6	0.4994(3)	0.7804(2)	-0.0758(3)	0.092(1)
C7	0.1508(2)	0.9130(2)	0.4868(4)	0.117(2)
C8	0.3091(3)	0.9040(2)	0.7162(3)	0.097(1)
C9	0.4377(2)	0.9471(2)	0.2888(3)	0.0653(8)
C10A	0.5264(6)	0.9736(4)	0.364(1)	0.066(3)
C10B	0.489(1)	0.9856(5)	0.408(1)	0.062(4)
C10C	0.437(1)	1.0000(5)	0.4107(8)	0.061(4)
C11A	0.5400(9)	1.0542(4)	0.3766(8)	0.067(3)
C11B	0.504(1)	1.0636(5)	0.3722(9)	0.045(3)
C11C	0.468(1)	1.0726(6)	0.363(1)	0.072(5)
C12	0.2911(2)	0.6945(2)	0.4193(3)	0.0533(6)
C13	0.2263(2)	0.6806(2)	0.2973(3)	0.0803(9)
C14	0.3051(2)	0.6261(2)	0.5157(3)	0.0615(8)
C15	0.3467(3)	0.5574(2)	0.4456(4)	0.084(1)
C16	0.3495(3)	0.4908(2)	0.5474(5)	0.115(2)
C17	0.4029(3)	0.5092(3)	0.6777(5)	0.131(2)
C18	0.3648(3)	0.5778(3)	0.7486(4)	0.134(2)
C19	0.3609(3)	0.6451(2)	0.6453(3)	0.087(1)

a) $U_{eq} = (1/3) \sum_i \sum_j U_{ij} D_i^* D_j^* D_i \cdot D_j$

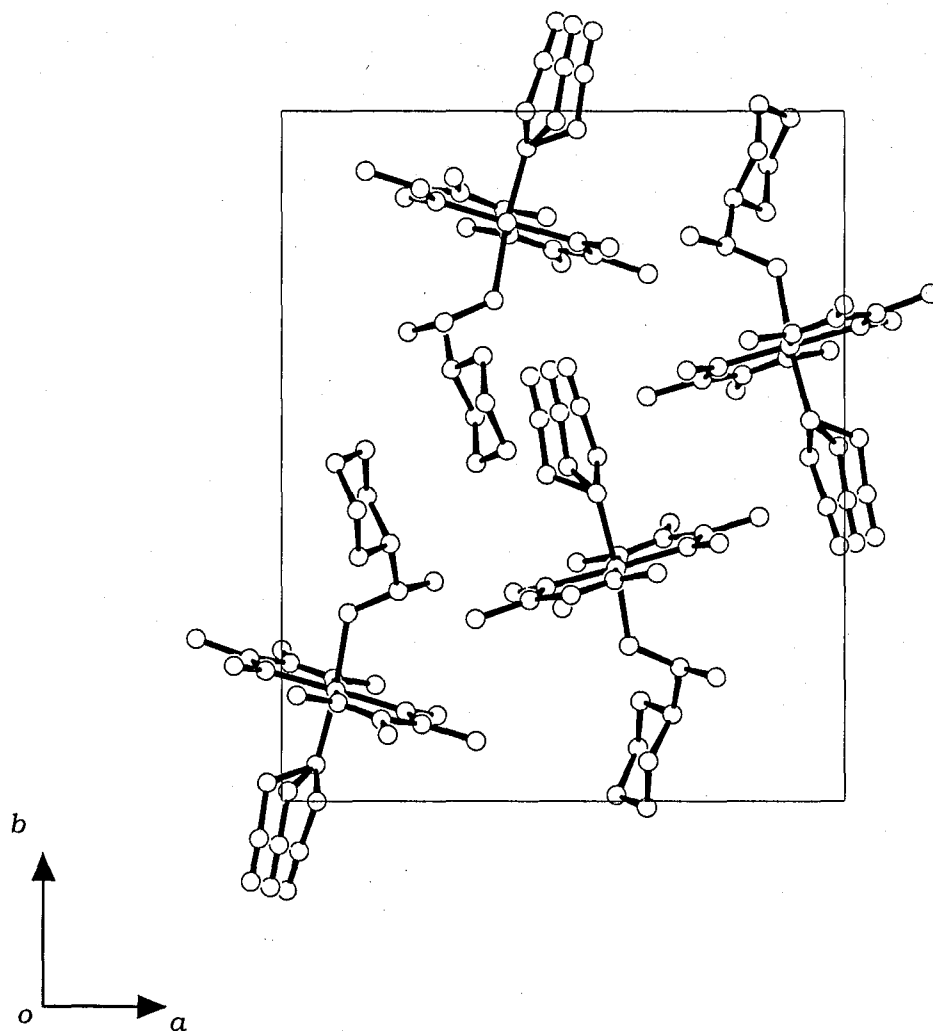


Figure 4-12 The crystal structure of (2-cyanoethyl)[(S)-1-cyclohexylethylamine] cobaloxime viewed along the c-axis.

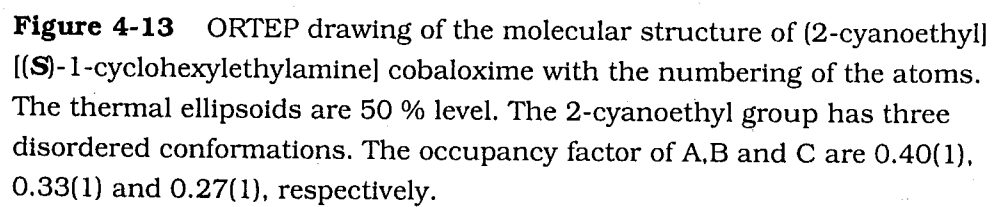


Table 4-10 The diastereomer excess of (2-cyanoethyl)[(S)-1-cyclohexylethylamine] cobaloxime

Irradiation time (min)	Diastereomer excess (%)	Major configuration	Reaction yield (%)
60	11	R	4
120	4	R	7
240	2	R	9

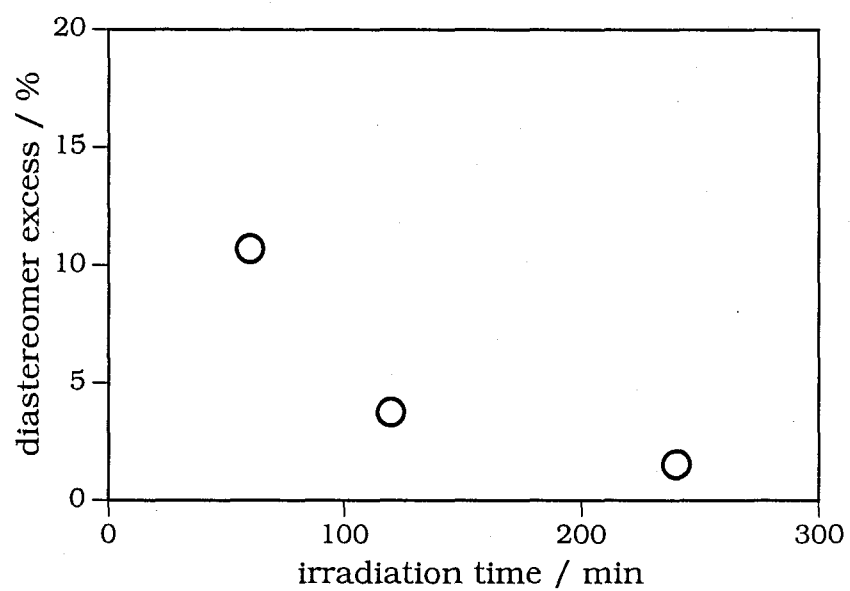


Figure 4-14 The diastereomer excess of (2-cyanoethyl) [(**S**)-1-cyclohexylethylamine] cobaloxime with the irradiation time.

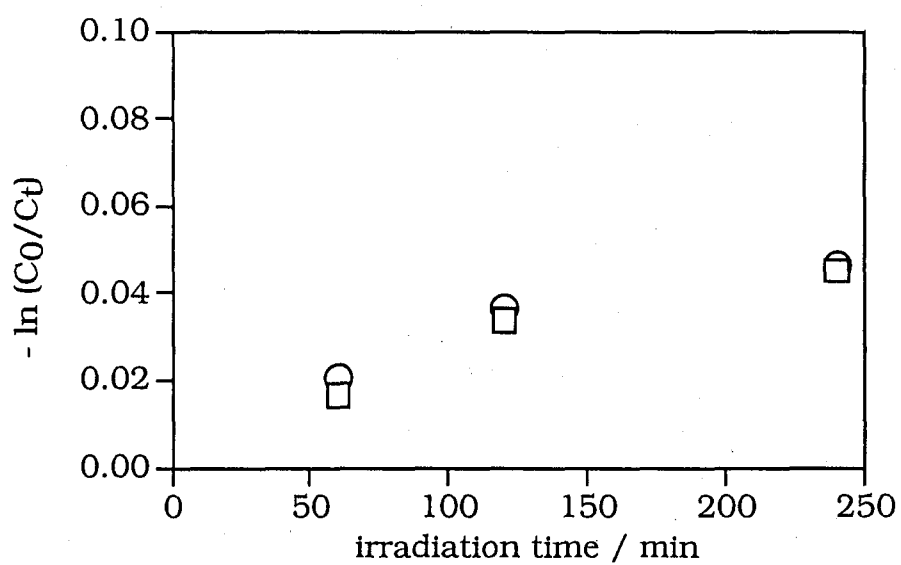


Figure 4-15 Conversion of the 2-cyanoethyl group to the (*R*)- and (*S*)-1-cyanoethyl groups in the (*S*)-1-cyclohexylethylamine complex with the irradiation time; (*R*)-isomer (circle) and (*S*)-isomer (square). The values of C_0 and C_t denote the amounts of 1-cyanoethyl complex at the irradiation time , 0 and t , respectively.

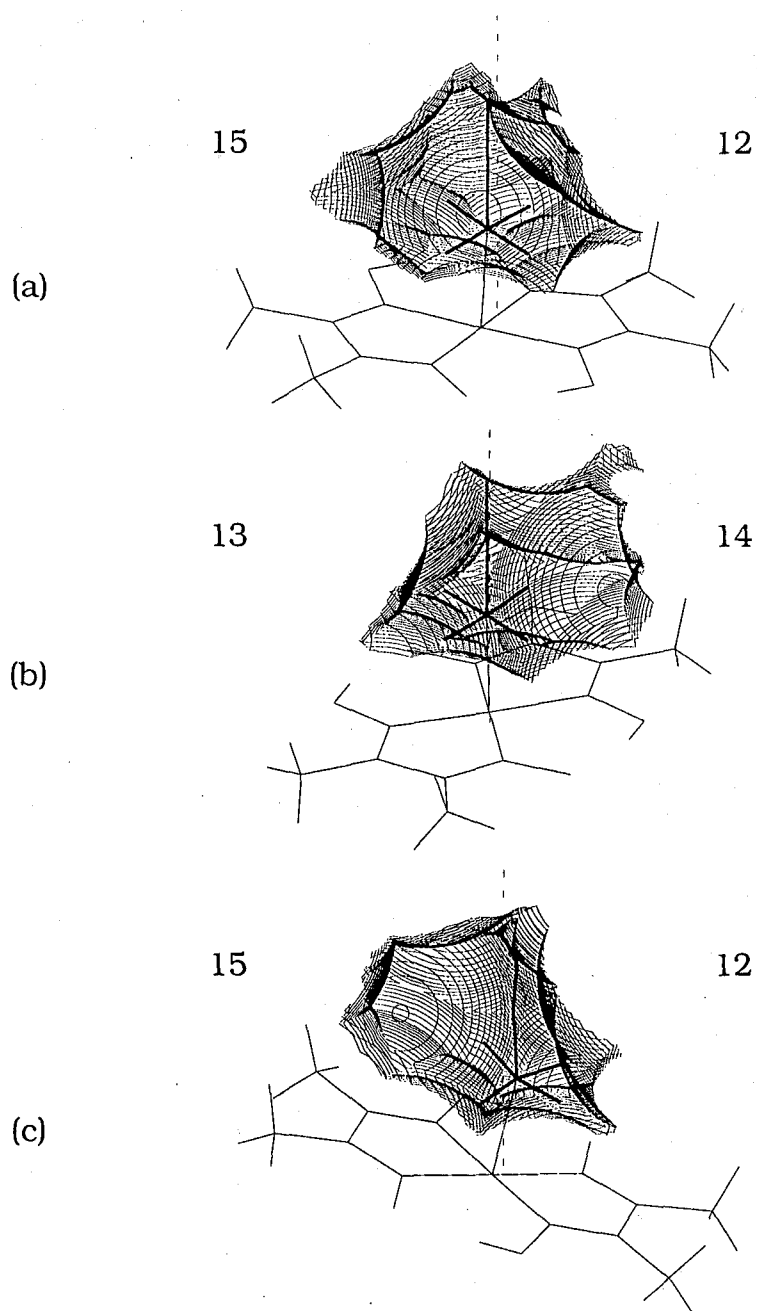


Figure 4-16 Reaction cavity for the 2-cyanoethyl group in (*S*)-1-cyclohexylethylamine cobaloxime complex, viewed along C10-C9 bond of the 2-cyanoethyl group. The contours are drawn at an interval of 0.1 Å³. Each cavity is divided into two parts by the average plane composed on the C-C-C-N bond. The cavity volumes (Å³) of left and right halves are also given.

4-5 *cis*-myrtanlyamine

The asymmetric induction of the 2-cyanoethyl cobaloxime with *cis*-myrtanlyamine was pointed out by Uchida [17].

X-ray structure determination

The complex of (2-cyanoethyl)[*cis*-myrtanlyamine]cobaloxime were prepared in a way similar to that reported previously [7]. The crystal were obtained from an acetone-hexane solution. The X-ray data were collected on a Rigaku IP-Weissenberg type diffractometer. MoK α radiation monochromated with graphite was used. The structure was solved by the Patterson method with the program SAPI91 [8], and refined with the program SHELXL97 [9]. In the process of the refinement, the 2-cyanoethyl group was found to take a perpendicular conformation to the cobaloxime plane, but it has no disordered structure. All the hydrogen atoms were calculated geometrically and refined with a riding model. Non-hydrogen atoms were refined with the anisotropic temperature factors. The absolute configuration was determined to coincide with that of the *cis*-myrtanlyamine, which was consistent with that obtained from the Flack χ parameter in the refinement. The atomic-scattering factors were taken from International Tables for Crystallography [10]. The crystal data and experimental details are given in Table 4-11. The final atomic coordinates with the equivalent isotropic temperature factors for non-hydrogen atoms are given in Table 4-12.

Photoisomerization and HPLC Analysis

The crystals scattered onto a Petri dish were irradiated with a xenon lamp for several hours at 300 K, in the same way as that for *sec*-butylamine. After photoirradiation, the HPLC analysis of the crystals was carried out using the chiral stationary phase. The HPLC system used was HITACHI L-7000 series system equipped with CHIRALPAK-AD column (Daisel Chem., Inc.)

maintained at 300 K and with Model L-7420 UV-Vis absorbance detector monitored at 254 nm. The mobile phase consists of hexane with 10% v/v ethanol and its flow rate was 1.0 ml min⁻¹. Quantification was performed integrating the peak area. The chromatogram obtained indicates that the produced 1-cyanoethyl group was not inverted to the opposite configuration when it migrated in the chiral stationary phase of HPLC.

Crystal and Molecular Structure

The X-ray crystal structure of (2-cyanoethyl)[*cis*-myrtaniline]cobaloxime viewed along the c-axis and the ORTEP drawing [11] of the molecular structure with the numbering atoms was shown in Figure 4-17 and Figure 4-18, respectively. The crystal structure is the same as the reported one [17]. The 2-cyanoethyl group has no disordered structure with a perpendicular conformation to the cobaloxime plane. The 2-cyanoethyl group makes no hydrogen bond with the neighboring molecules.

Diastereomer Excess and Conversion Rate

Table 4-13 shows the diastereomer excess and the reaction yield of the produced 1-cyanoethyl complex with the irradiation time. It was found that the (**S**)-1-cyanoethyl group was preferentially produced when the *cis*-myrtaniline was used as an axial base ligand, and the diastereomer excess was 9%. The value of the diastereomer excess is a constant with varying the reaction yield as shown in Figure 4-19.

The conversion rate of the 2-cyanoethyl group to the *cis*-myrtaniline and (**S**)-1-cyanoethyl groups are shown in Figure 4-20. These results strongly suggest that the epimerization of the complex does not occur during the photoisomerization process.

Cavity Shape of the 2-cyanoethyl group

In order to explain the reason why the (**S**)-isomer is produced when the *cis*-myrtaniline is used as an axial base ligand, the reaction cavity for the 2-

cyanoethyl group in the initial crystal structure was drawn, and its volume was calculated in the same way as reported previously [7]. Figure 4-21 shows the reaction cavities for the 2-cyanoethyl group. In order to examine the asymmetric shape, the cavity was divided into two parts by the average plane comprising the C-C-C-N atoms of the 2-cyanoethyl group. The volumes of the two parts were also calculated, and are given in Figure 4-21, in which the C-C-N moiety of each conformer is drawn so as to occupy the same position to each other. The right part of the cavity is significantly greater than the left part. Since the CN group has a greater volume than the CH₃ group, it is favorable that the CN and CH₃ groups occupy the greater and smaller parts of the reaction cavity, respectively, after conversion to the 1-cyanoethyl group. This explains the reason why the (**S**)-1-cyanoethyl group is preferentially produced from the *cis*-myrtanylamine complex after isomerization.

Table 4-11 Crystal Data and Experimental Details**Crystal data**

Chemical formula	[Co(C ₄ H ₇ N ₂ O ₂) ₂ (C ₃ H ₄ N)(C ₁₀ H ₁₉ N)]
Formula weight	496.50
Cell system	Orthorhombic
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁
<i>a</i> /Å	11.270(3)
<i>b</i> /Å	23.431(7)
<i>c</i> /Å	9.405(2)
<i>V</i> /Å ³	2484(1)
<i>Z</i>	4
<i>D_x</i> /Mg m ⁻³	1.328
<i>F</i> (000)	1056
Radiation type	Mo <i>K</i> α
Wavelength/Å	0.71073
<i>μ</i> /mm ⁻¹	0.728
Temperature/K	296
Crystal form	Prismatic
Crystal size/mm	0.3 x 0.3 x 0.1
Crystal color	Orange

Data collection

Diffractionmeter	Rigaku RAXIS-IICS diffractometer
Data collection method	Weissenberg Photograph scans
No. of measured reflections	9132
No. of independent reflections	5150
No. of observed reflections	2477
Criterion for observed reflections	<i>I</i> > 2 σ(<i>I</i>)
<i>θ</i> _{max} /°	27.65
Range of <i>h, k, l</i>	-14 ≤ <i>h</i> ≤ 12 -30 ≤ <i>k</i> ≤ 26 -10 ≤ <i>l</i> ≤ 10

Refinement

Refinement on	<i>F</i> ²
<i>R</i> [<i>I</i> > 2σ(<i>I</i>)]	0.0685
<i>wR</i> (<i>I</i>)	0.2026
<i>S</i>	0.950
No. of reflections used in refinement (<i>I</i> > 0)	5150
No. of parameters used	296
H-atom treatment	Calculated
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.1082P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$
(Δ/σ) _{max}	0.089
Δρ _{max} /eÅ ⁻³	0.468
Δρ _{min} /eÅ ⁻³	-0.523
Extinction correction	None
Flack <i>χ</i> parameter	0.01(4)

Table 4-12 Fractional atomic coordinates and equivalent isotropic displacement parameters ($\text{\AA}^2$)

atom	x	y	z	U_{eq}^a
Co1	0.89189(8)	0.24149(4)	0.2207(1)	0.0651(3)
O1	1.0202(5)	0.2307(3)	0.4776(6)	0.102(2)
O2	0.7073(4)	0.3199(2)	0.1538(6)	0.095(2)
O3	0.7627(4)	0.2524(2)	-0.0391(5)	0.080(1)
O4	1.0684(5)	0.1601(2)	0.2935(6)	0.097(2)
N1	0.9352(5)	0.2586(3)	0.4096(6)	0.069(2)
N2	0.7843(4)	0.3012(2)	0.2557(6)	0.064(1)
N3	0.8457(5)	0.2231(2)	0.0325(6)	0.066(2)
N4	0.9939(5)	0.1796(3)	0.1901(7)	0.0760(2)
N5	0.617(1)	0.0933(5)	0.5090(9)	0.160(4)
N7	1.0178(5)	0.2986(3)	0.1501(7)	0.091(2)
C1	0.8770(8)	0.3003(3)	0.4702(8)	0.078(2)
C2	0.7894(7)	0.3264(3)	0.3735(9)	0.076(2)
C3	0.9003(7)	0.1803(3)	-0.0231(7)	0.071(2)
C4	0.9863(7)	0.1529(3)	0.0715(9)	0.077(2)
C5	0.8941(9)	0.3169(4)	0.6246(8)	0.106(3)
C6	0.7149(8)	0.3768(4)	0.416(1)	0.103(3)
C7	0.8827(9)	0.1624(4)	-0.1776(8)	0.105(3)
C8	1.0518(8)	0.0996(4)	0.035(1)	0.109(3)
C9	0.7671(6)	0.1876(3)	0.2896(8)	0.075(2)
C10	0.774(1)	0.1668(6)	0.435(1)	0.164(6)
C11	0.683(1)	0.1244(5)	0.477(1)	0.121(4)
C12	0.9968(8)	0.3366(4)	0.0340(9)	0.109(3)
C14	1.0805(8)	0.3915(4)	0.0333(9)	0.092(2)
C15	1.0585(8)	0.4210(4)	-0.109(1)	0.098(3)
C16	1.149(1)	0.4701(5)	-0.114(1)	0.150(5)
C17	1.052(1)	0.5064(4)	-0.044(1)	0.132(4)
C18	1.066(2)	0.4966(5)	0.110(2)	0.22(1)
C19	1.071(2)	0.4339(6)	0.158(1)	0.220(9)
C20	0.961(1)	0.4675(4)	-0.112(1)	0.112(3)
C21	0.850(1)	0.4578(6)	-0.030(3)	0.29(1)
C22	0.936(2)	0.4887(5)	-0.259(2)	0.200(8)

a) $U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$

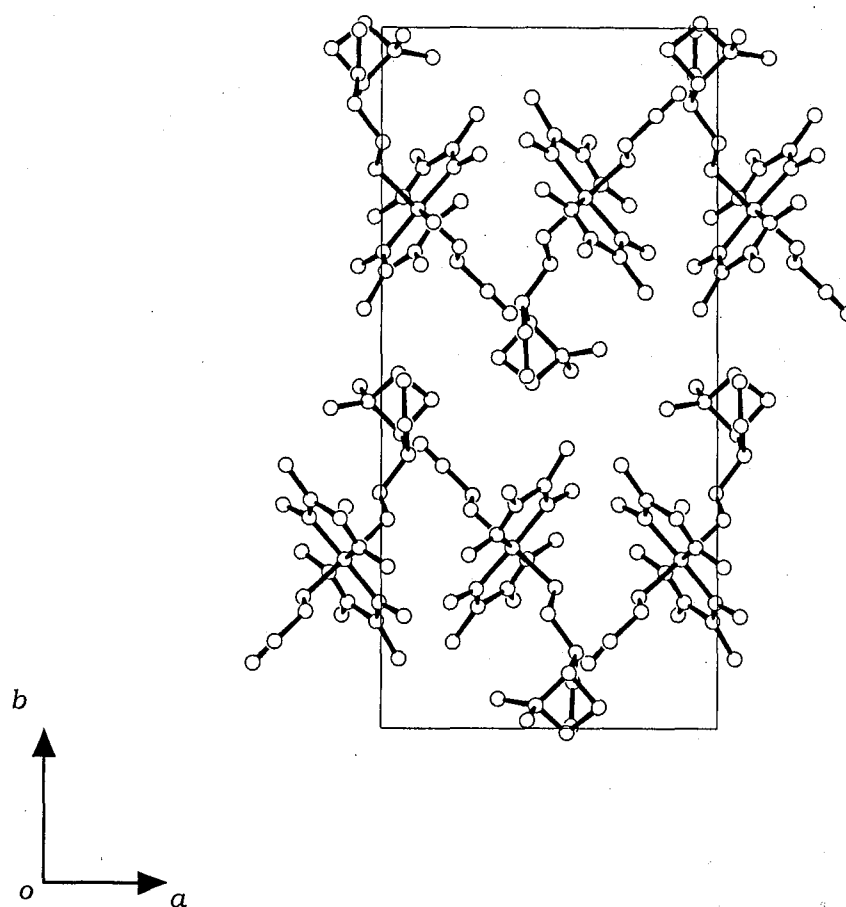


Figure 4-17 The crystal structure of (2-cyanoethyl)[*cis*-myrtanylamine]cobaloxime viewed along the c-axis.

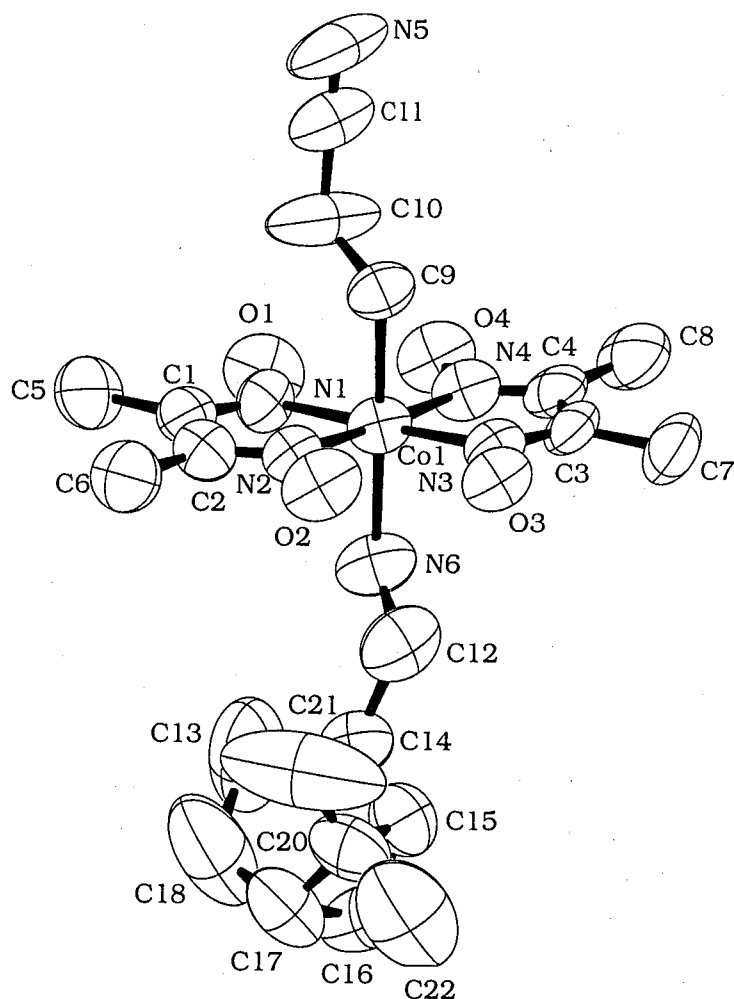


Figure 4-18 ORTEP drawing of the molecular structure of (2-cyanoethyl)[cis-myrtanylamine] cobaloxime with the numbering of the atoms. The thermal ellipsoids are 50 % level.

Table 4-13 The diastereomer excess of (2-cyanoethyl)[*cis*-myrtanylamine] cobaloxime

Irradiation time (min)	Diastereomer excess (%)	Major configuration	Reaction yield (%)
60	9	S	7
120	9	S	8
240	9	S	12

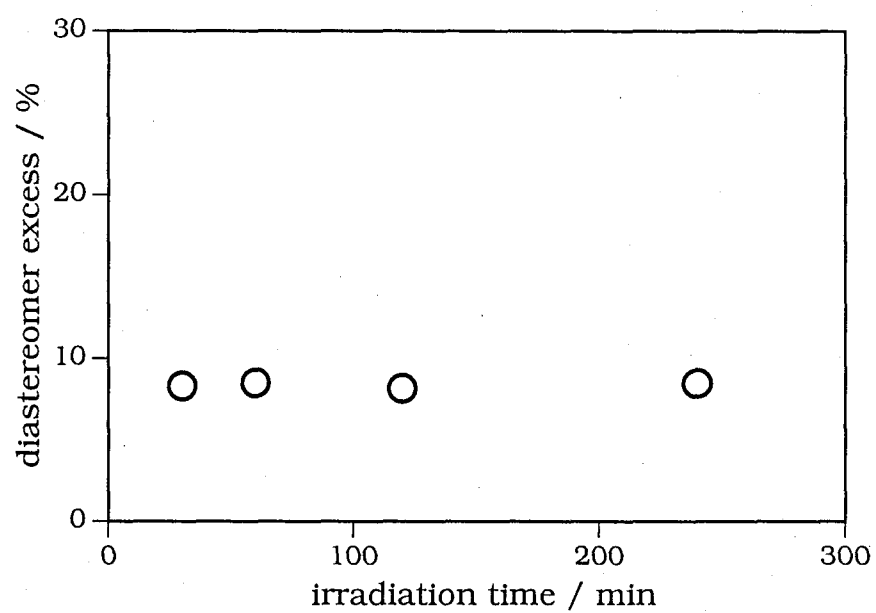


Figure 4-19 The diastereomer excess of (2-cyanoethyl) [*cis*-myrtaniline] cobaloxime with the irradiation time.

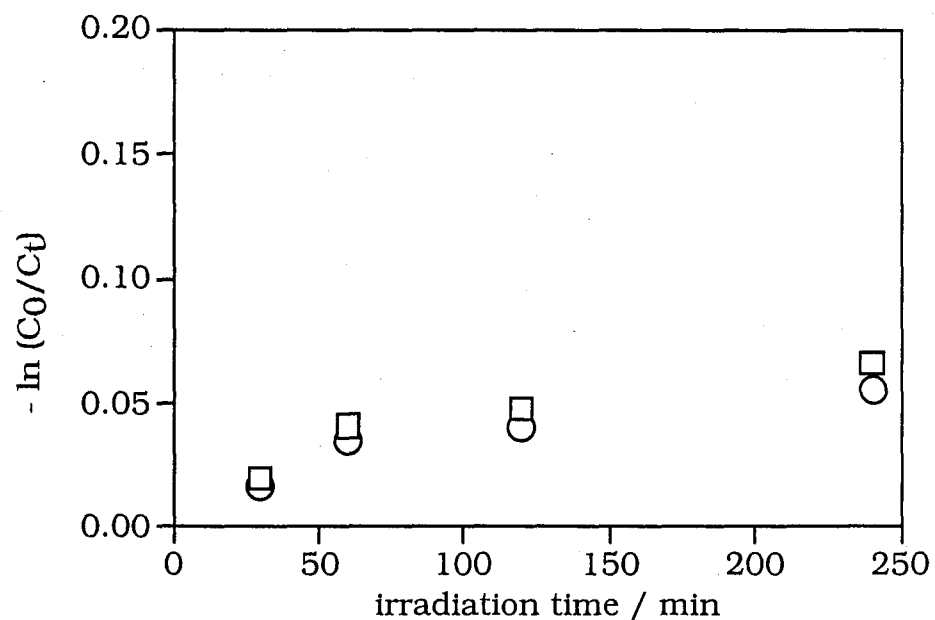


Figure 4-20 Conversion of the 2-cyanoethyl group to the (*R*)- and (*S*)-1-cyanoethyl groups in the *cis*-myrtamylamine complex with the irradiation time; (*R*)-isomer (circle) and (*S*)-isomer (square).

The values of C_0 and C_t denote the amounts of 1-cyanoethyl complex at the irradiation time , 0 and t , respectively.

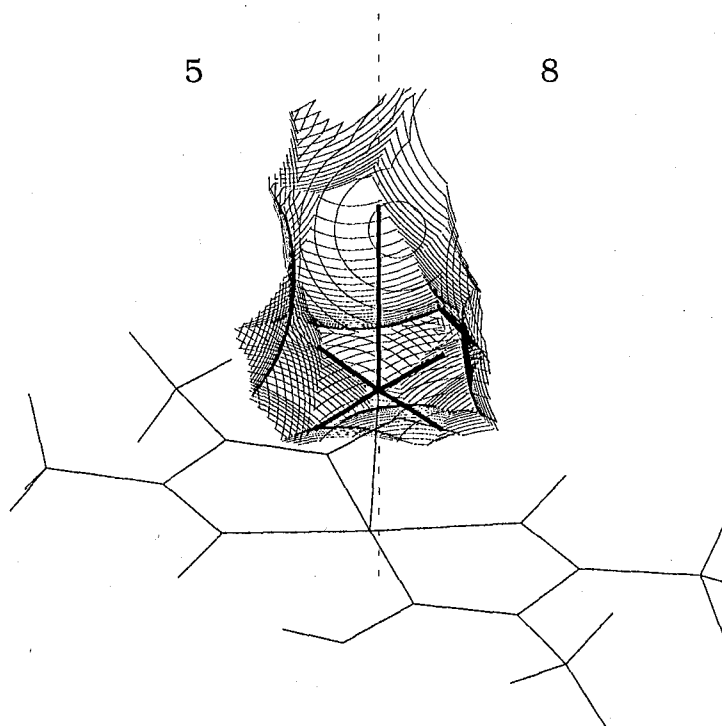


Figure 4-21 Reaction cavity for the 2-cyanoethyl group in *cis*-myrtanylamine cobaloxime complex, viewed along C10-C9 bond of the 2-cyanoethyl group. The contours are drawn at an interval of 0.1 Å. The cavity volumes (Å³) of left and right halves are also given

4-6 pyrrolidine

Although the pyrrolidine is an achiral molecule, it was found that a complex of the 2-cyanoethyl cobaloxime coordinated by pyrrolidine crystallized as an optically active crystal, which the space group is $P2_12_12_1$ [17], as well as the crystal of the 2-cyanoethyl piperidine cobaloxime, which the space group is $P2_12_12_1$ [18] and the 2-cyanoethyl triphenylphosphine cobaloxime, which the space group is $P2_12_12_1$ [19]. Thus, it was found that the absolute asymmetric induction if the crystal proceed the photoisomerization in the solid state.

X-ray structure determination

The complex of (2-cyanoethyl)(pyrrolidine)cobaloxime were prepared in a way similar to that reported previously [7]. The crystals were obtained from an acetone-hexane solution. The X-ray data were collected on a Rigaku AFC7S diffractometer. MoK α radiation monochromated with graphite was used. The structure was solved by the Patterson method with the program SAPI91 [8], and refined with the program SHELXL97 [9]. In the process of the refinement, the 2-cyanoethyl group was found to have two disordered structures of the 2-cyanoethyl group with a perpendicular conformation to the cobaloxime plane. All the hydrogen atoms were calculated geometrically and refined with a riding model. Non-hydrogen atoms were refined with the anisotropic temperature factors, except for the disordered atoms, which were refined isotropically. The absolute configuration was determined by the Flack χ parameter in the refinement. The atomic-scattering factors were taken from International Tables for Crystallography [10]. The crystal data and experimental details are given in Table 4-14. The final atomic coordinates with the equivalent isotropic temperature factors for non-hydrogen atoms are given in Table 4-15.

Photoisomerization and HPLC Analysis

The crystals scattered onto a Petri dish were irradiated with a xenon lamp for several hours at 300 K, in the same way as that for *sec*-butylamine. After photoirradiation, the HPLC analysis of the crystals was carried out using the chiral stationary phase. The HPLC system used was HITACHI L-7000 series system equipped with CHIRALPAK-AD column (Daisel Chem., Inc.) maintained at 300 K and with Model L-7420 UV-Vis absorbance detector monitored at 254 nm. The mobile phase consists of hexane with 10% v/v ethanol and its flow rate was 1.0 ml min⁻¹. Quantification was performed integrating the peak area. The chromatogram obtained indicates that the produced 1-cyanoethyl group was not inverted to the opposite configuration when it migrated in the chiral stationary phase of HPLC.

Crystal and Molecular Structure

The X-ray crystal structure of the (2-cyanoethyl)(pyrrolidine)cobaloxime viewed along the c-axis and the ORTEP drawing [11] of the molecular structure with the numbering atoms was shown in Figure 4-22 and Figure 4-23, respectively. The crystal belong to the orthorhombic system , and the space group is $P2_12_12_1$, $Z = 4$ with $a = 13.247(2)$, $b = 16.542(3)$, $c = 8.882(2)$ Å and $V = 1946.4(6)$ Å³. The obtained X-ray crystal structure is the polymorph to the reported structure [17], which the crystal belong to the orthorhombic system, and the space group is $P2_12_12_1$, $Z = 4$ with $a = 12.807(2)$, $b = 15.630(2)$, $c = 9.699(1)$ Å and $V = 1941.1(4)$ Å³. The 2-cyanoethyl group has two disordered structure around Co-C bond with a perpendicular conformation to the cobaloxime plane, but in the reported structure the 2-cyanoethyl group has no disordered structure with a perpendicular conformation to the cobaloxime plane [17]. The occupancy factors of A and B are 0.52(2) and 0.48, respectively. The 2-cyanoethyl group makes no hydrogen bond with the neighboring molecules. It was not found that the pyrrolidine ring of an axial base ligand has disordered structures.

Enantiomer Excess and Conversion Rate

Table 4-16 shows the enantiomer excess and the reaction yield of the produced 1-cyanoethyl complex with the irradiation time. It was found that the (**S**)-1-cyanoethyl group was preferentially produced when the crystal measured by X-ray analysis was irradiated by xenon lamp in the solid state. The enantiomer excess is slightly decreased as increasing the irradiation time. The enantiomer excess indicated 21%ee in 1.4% of the reaction rate.

The conversion rates of the (**R**)- and (**S**)-1-cyanoethyl groups are shown in Figure 4-25. These results strongly suggest that the racemization of the produced 1-cyanoethyl group does not occur during the photoisomerization process.

Cavity Shape of the 2-cyanoethyl group

In order to explain the reason why the (**R**)-isomer is produced when the pyrrolidine is used as an axial base ligand, the reaction cavity for the 2-cyanoethyl group in the initial crystal structure was drawn, and its volume was calculated in the same way as previously reported [7]. Figure 4-26 shows the reaction cavities for the 2-cyanoethyl group. In order to examine the asymmetric shape, the cavity was divided into two parts by the average plane comprising the C-C-C-N atoms of the 2-cyanoethyl group. The volumes of the two parts were also calculated, and are given in Figure 4-26, in which the C-C-N moiety of each conformer is drawn so as to occupy the same position to each other. The left part of the cavity is significantly greater than the right part. Since the CN group has a greater volume than the CH₃ group, it is favorable that the CN and CH₃ groups occupy the greater and smaller parts of the reaction cavity, respectively, after conversion to the 1-cyanoethyl group. This explains the reason why the (**R**)-1-cyanoethyl group is preferentially produced from this crystal after isomerization.

Table 4-14 Crystal Data and Experimental Details

Crystal data

Chemical formula	[Co(C ₄ H ₇ N ₂ O ₂) ₂ (C ₃ H ₄ N)(C ₄ H ₉ N)]
Formula weight	414.36
Cell system	Orthorhombic
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁
<i>a</i> /Å	13.247(2)
<i>b</i> /Å	16.542(3)
<i>c</i> /Å	8.882(2)
<i>V</i> /Å ³	1946.4(6)
<i>Z</i>	4
<i>D_x</i> /Mg m ⁻³	1.414
<i>F</i> (000)	872
Radiation type	Mo Kα
Wavelength/Å	0.71073
No. of reflections for cell parameters	25
θ range/°	12.5-15
μ /mm ⁻¹	0.914
Temperature/K	296
Crystal form	Prismatic
Crystal size/mm	0.3 x 0.2 x 0.2
Crystal color	Orange

Data collection

Diffractometer	AFC-7S
Data collection method	ω -2 θ
Scan rate/° min ⁻¹	8
Absorption correction	Ψ scan
No. of measured reflections	2546
No. of independent reflections	2546
No. of observed reflections	1471
Criterion for observed reflections	$I > 2 \sigma(I)$
$\theta_{\max}/^\circ$	27.50
Range of <i>h,k,l</i>	$0 \leq h \leq 17$ $0 \leq k \leq 21$ $0 \leq l \leq 11$
No. of standard reflections	3
Frequency of standard reflections	Every 100 reflections
Intensity decay /%	0.2

Refinement

Refinement on	<i>F</i> ²
$R [I > 2\sigma(I)]$	0.0577
$wR(I)$	0.1618
<i>S</i>	1.025
No. of reflections used in refinement ($I > 0$)	2546
No. of parameters used	237
H-atom treatment	Calculated
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0865P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max}$	0.011
$\Delta\rho_{\max}/e\text{\AA}^{-3}$	0.467
$\Delta\rho_{\min}/e\text{\AA}^{-3}$	-0.520
Extinction correction	None
Flack χ parameter	0.003(0.05)

Table 4-15 Fractional atomic coordinates and equivalent isotropic displacement parameters ($\text{\AA}^2$)

atom	x	y	z	U_{eq}^{a1}
Co1	0.10225(6)	0.76125(5)	0.2438(1)	0.0532(3)
O1	0.2015(4)	0.7626(4)	0.5260(6)	0.085(2)
O2	-0.0599(4)	0.6621(3)	0.1502(7)	0.083(2)
O3	0.0057(5)	0.7576(4)	-0.0409(6)	0.094(2)
O4	0.2699(4)	0.8561(3)	0.3341(7)	0.087(2)
N1	0.1277(5)	0.7285(4)	0.4416(7)	0.065(2)
N2	0.0033(4)	0.6811(3)	0.2632(8)	0.061(1)
N3	0.0770(5)	0.7920(4)	0.0439(7)	0.070(2)
N4	0.2053(5)	0.8383(3)	0.2229(8)	0.064(2)
N5A	0.380(2)	0.561(1)	0.015(2)	0.105(7)
N5B	0.362(1)	0.554(1)	-0.037(3)	0.102(7)
N6	0.0026(5)	0.8509(3)	0.3137(7)	0.061(2)
C1	0.0711(7)	0.6728(5)	0.4967(9)	0.070(2)
C2	-0.0016(7)	0.6441(4)	0.3879(9)	0.065(2)
C3	0.1361(8)	0.8492(5)	-0.0086(9)	0.081(3)
C4	0.2079(7)	0.8762(5)	0.096(1)	0.074(2)
C5	0.0798(9)	0.6410(6)	0.655(1)	0.108(4)
C6	-0.0752(7)	0.5773(5)	0.419(1)	0.093(3)
C7	0.124(1)	0.8795(6)	-0.170(1)	0.120(4)
C8	0.2870(7)	0.9390(5)	0.061(1)	0.100(3)
C9	0.1927(7)	0.6722(5)	0.179(1)	0.092(3)
C10A	0.292(1)	0.6926(9)	0.107(2)	0.090(7)
C10B	0.233(1)	0.665(1)	0.019(2)	0.083(7)
C11A	0.342(1)	0.618(1)	0.055(2)	0.093(6)
C11B	0.306(1)	0.6002(8)	-0.004(2)	0.076(6)
C12	-0.0957(6)	0.8328(5)	0.371(1)	0.098(3)
C13	-0.1379(8)	0.9132(6)	0.432(2)	0.112(4)
C14	-0.0501(7)	0.9621(6)	0.470(1)	0.102(3)
C15	0.0393(6)	0.9160(5)	0.413(1)	0.078(3)

a) $U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$
occupancy factors A:0.52(2) ; B:0.48

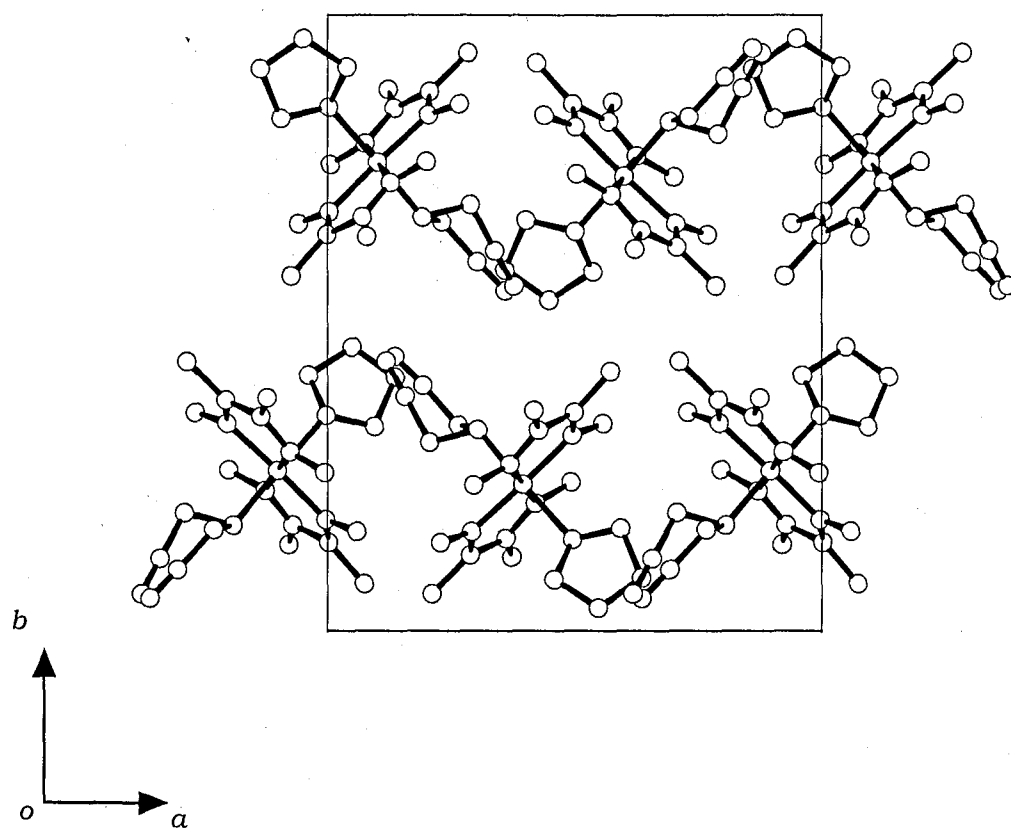


Figure 4-22 The crystal structure of (2-cyanoethyl)(pyrrolidine) cobaloxime viewed along c-axis.

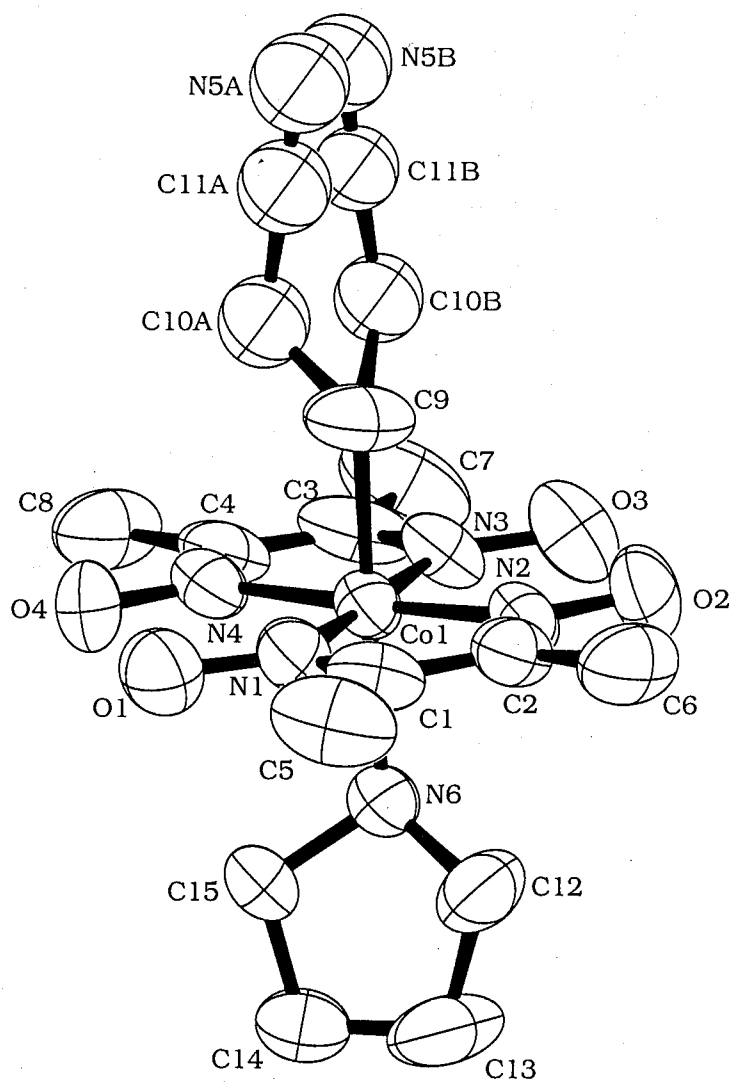


Figure 4-23 ORTEP drawing of the molecular structure of (2-cyanoethyl) (pyrrolidine) cobaloxime with the numbering of the atoms. The thermal ellipsoids are 50 % level. The 2-cyanoethyl group has three disordered conformations.

Table 4-16 The diastereomer excess of the 2-cyanoethyl pyrrolidine cobaloxime

Irradiation time (min)	Diastereomer excess (%)	Major configuration	Reaction yield (%)
120	21	R	1.4
240	19	R	2.9
480	20	R	6.7
960	20	R	6.0
1920	17	R	8.9

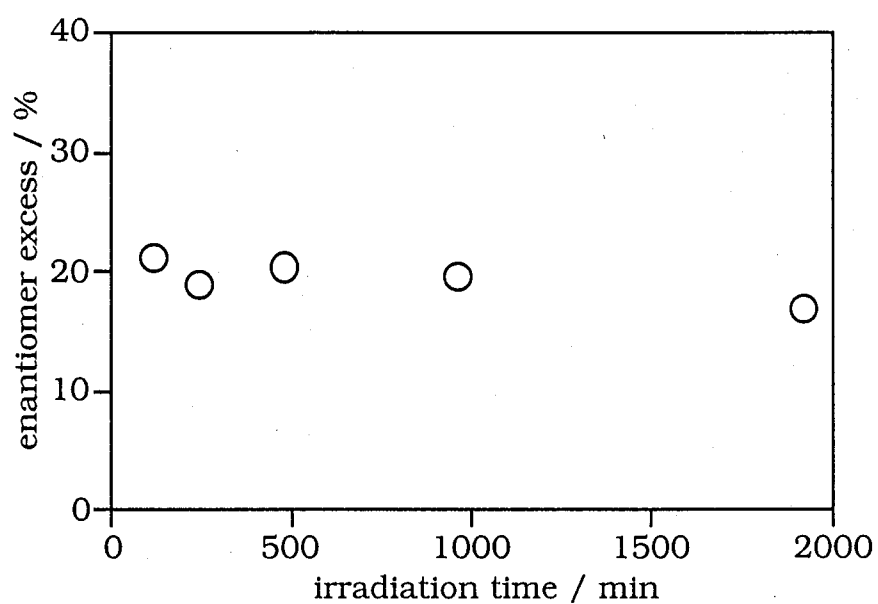


Figure 4-24 The enantiomer excess of (2-cyanoethyl)(pyrrolidine)cobaloxime with the irradiation time.

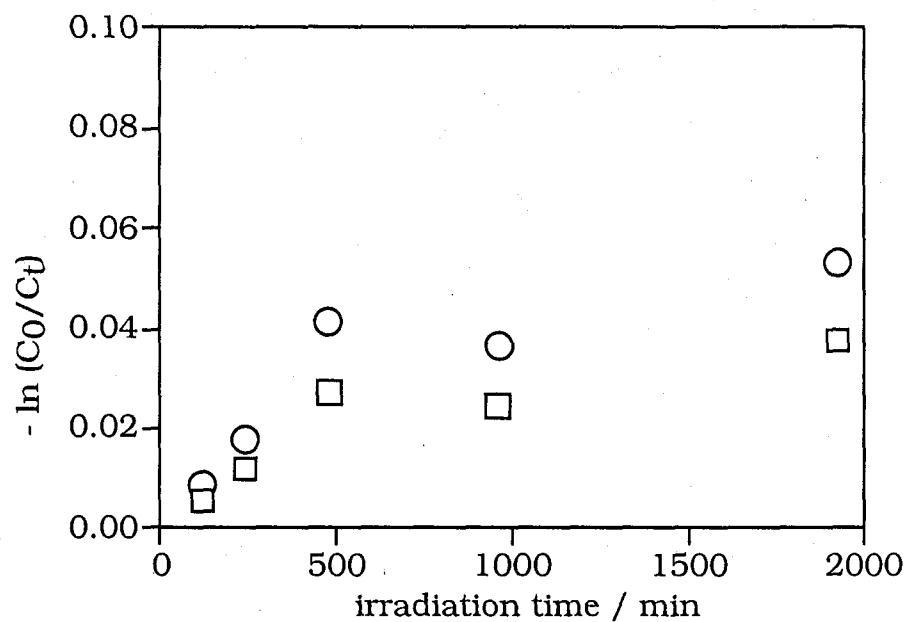


Figure 4-25 Conversion of the 2-cyanoethyl group to the (**R**)- and (**S**)-1-cyanoethyl groups in the pyrrolidine complex with the irradiation time; (**R**)-isomer (circle) and (**S**)-isomer (square).
The values of C_0 and C_t denote the amounts of 1-cyanoethyl complex at the irradiation time , 0 and t , respectively.

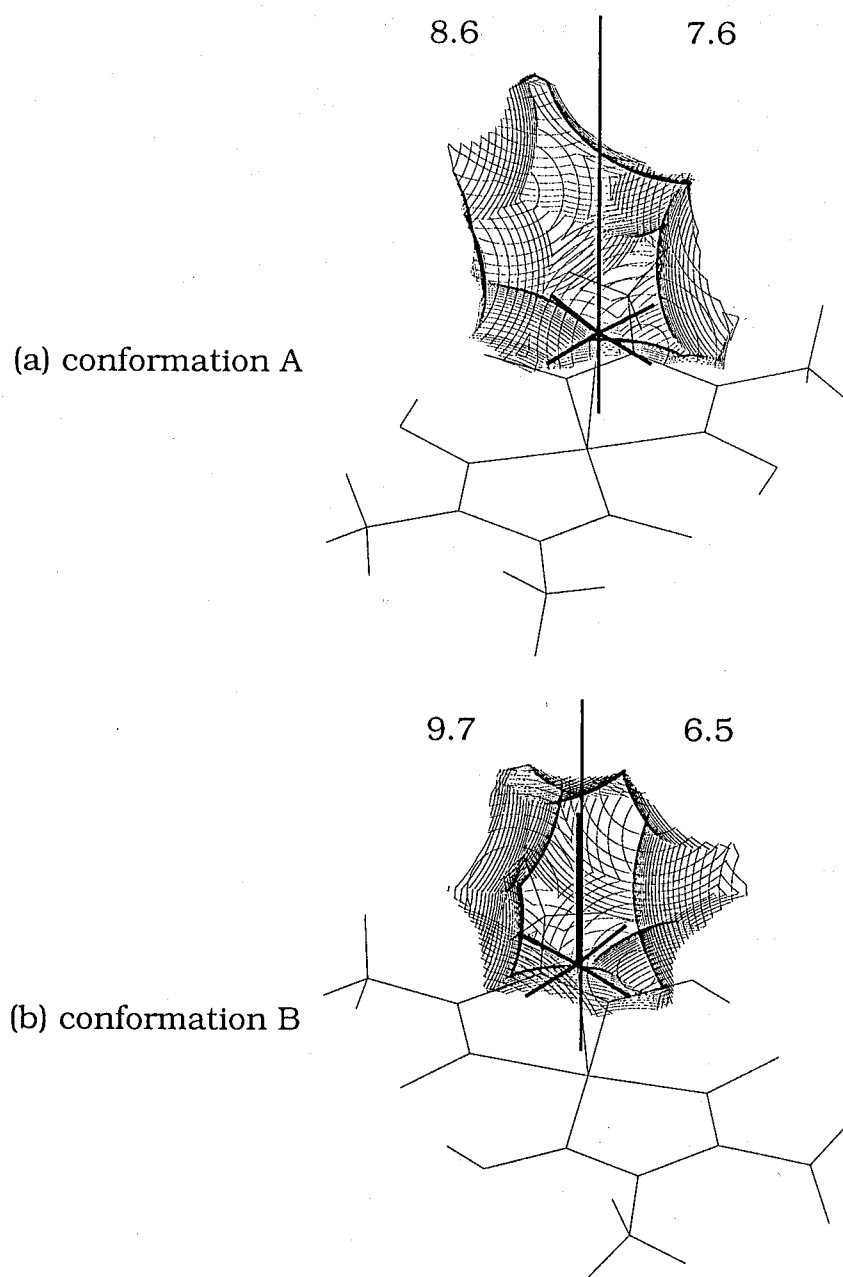


Figure 4-26 Reaction cavity for the 2-cyanoethyl group, viewed along C10-C9 bond of the 2-cyanoethyl group; (a) conformer A, (b) conformer B. The contours are drawn at an interval of 0.1 Å. Each cavity is divided into two parts by the average plane composed on the C-C-C-N bond. The cavity volumes (Å³) of left and right halves are also given.

4-7 Discussion

In a series of the 2-cyanoethylcobaloxime complexes examined, the result on the asymmetric induction is summarized in Table 4-17. It was found that the (**R**)-1-cyanoethyl group was preferentially produced in the solid state photoisomerization when the (**S**)-2-amino-1-propanol, (**S**)-2-amino-1-butanol, (**S**)-1-cyclohexylethylamine and pyrrolidine were used as axial base ligands and the (**S**)-1-cyanoethyl group was preferentially produced when the (**R**)-1,2-diaminopropane and *cis*-myrtanylamine were used as axial base ligands, although the reaction yield is small.

In chapter 2 and 3, the stereoselectivity in the solid state photoisomerization of the 2-cyanoethylcobaloxime complex was explained in terms of (1) the asymmetric cavity shape around the reactive group and (2) the lowest packing energy of the produced 1-cyanoethyl group into the reaction cavity for the 2-cyanoethyl group from the calculation by the molecular mechanics method. The reaction cavity was divided into two parts by the average plane comprising the C-C-C-N atoms of the 2-cyanoethyl group, in which the C-C-N moiety of each conformer is drawn so as to occupy the same position to each other, and then the volume of each part was calculated independently. When the left part of the cavity is significantly greater than the right part, (**R**)-1-cyanoethyl group was preferentially produced and vice versa. Since the CN group has a greater volume than the CH₃ group, it is favorable that the CN and CH₃ groups occupy the greater and smaller parts of the reaction cavity, respectively, after conversion to the 1-cyanoethyl group.

In order to explain the asymmetric cavity shape around the reactive group, the reaction cavity for the 2-cyanoethyl group in a series of 2-cyanoethylcobaloxime complexes examined was drawn in a way similar to that reported previously [7], and the volume of each part was calculated independently. This result explains that the stereoselectivity is controlled by the chiral crystal environment, and that the configuration of the produced 1-

cyanoethyl group reflects to steric hindrance between the greater CN group and neighboring molecule around the 2-cyanoethyl group.

In order to examine a value of the diastereomer excess, the diastereomer excess was plotted against to the difference (ΔV) between the larger and smaller volume or the absolute ratio (V_L/V_S) between the larger and smaller volume of the reaction cavity divided by average plane comprising the C-C-CN atoms of the 2-cyanoethyl group, as shown in Figure 4-28 and 4-29, respectively. Both ΔV and V_L/V_S give an expression to the asymmetric degree of the reaction cavity for the 2-cyanoethyl group. The value of the diastereomer excess is correlated with the asymmetry of the reaction cavity. This results indicate that the higher the asymmetry of the reaction cavity is, the greater the diastereomer excess is.

It was observed that the diastereomer or enantiomer excess decreased as increasing the reaction yield, when the 1,2-diaminopropane, 1-cyclohexylethylamine and pyrrolidine were used as axial base ligands. On the other hand, when the *sec*-butylamine, *cis*-myrtanylamine and 2-amino-2-phenylethanol were used as axial base ligands, the diastereomer or enantiomer excess does not depend on the reaction yield. This reason why the diastereomer or enantiomer excess decreased as increasing the reaction yield may be attributed to the following factors; (1) the racemization or epimerization of the produced 1-cyanoethyl group and (2) the change of the cavity shape for the 2-cyanoethyl group when the 1-cyanoethyl group is produced, and (3) the degradation of the crystallinity on exposure to visible light. Most of the chiral 1-cyanoethyl groups in some cobaloxime complexes with different base ligands are found to be racemized on exposure to visible light in the solid state. Since the diastereoselectivity of the produced 1-cyanoethyl group is governed by the asymmetric cavity shape around the 2-cyanoethyl group in the chiral crystal environment, the change of the cavity shape around the 2-cyanoethyl groups bring about a variation of the

stereoselective reaction, when both 2-cyanoethyl group significantly contact with each other such as 1,2-diaminopropane complex. As a result, it is considered that the diastereomer or enantiomer excess decrease with the reaction progress.

In order to examine the above discussion, the conformation and configuration of the produced 1-cyanoethyl group after irradiation were calculated by the molecular mechanics method using the program Cerius² [12] with the Universal Force Field (UFF) [13][14] parameter set. The UFF parameter set is applicable to organometallic compounds [13][14]. The initial model in molecular mechanics calculation was constructed on the basis of the observed X-ray crystal structure. At first, the initial model was calculated to assign to the point charge on the current atom using the charge equilibration method [15]. The energy of the analyzed crystal structure was minimized with the rigid-body model. Energy minimization was carried out by the conjugate-gradient method, at the end of which the value of the root-mean-square energy derivative of the atomic coordinates was less than 0.42 kJ mol⁻¹. The conformation of the (**S**)-1-cyanoethyl group was altered at a constant interval of 30° around the Co-C bond, and the model structure was minimized geometrically with the fixed unit-cell dimension. Figure 4-6 shows the structure of the (**S**)-1-cyanoethyl group with the lowest energy. The same calculation was performed for the (**R**)-1-cyanoethyl group. The lowest energy was higher by 12.9 kJ mol⁻¹ than that for the (**S**)-1-cyanoethyl group. This result is in good agreement with the observed configuration by X-ray analysis of the crystalline-state reaction. Although the (**R**)-1-cyanoethyl group was minimized to the structure with the lowest energy when the (**S**)-1-cyanoethyl group is the neighboring molecule. In this case, the lowest energy was lower by 12.7 kJ mol⁻¹ than that for the (**S**)-1-cyanoethyl group. The reason why low diastereomer excess and decreasing with the chemical yield were obtained is probably due to that

the photoisomerization proceeds followed by the change of the shape of the reaction cavity for the 2-cyanoethyl group of the neighboring molecule.

Table 4-17 List of the asymmetric induction in 2-cyanoethylcobaloxime complexes

Base ligand	Diastereomer excess (%)	Major configuration	Cavity volume ²⁾³⁾ (Å ³)				Reaction yield (%)
			Conformation	occ.	L	R	
(S)-sec-butylamine	28	R	A	0.48	20	7	36
			B	0.34	17	10	
			C	0.18	9	18	
(R)-1,2-diaminopropane	26	S	-	1.00	5	9	6
(S)-2-amino-1-propanol	21	R	A	0.42	14	9	12
			B	0.36	15	8	
			C	0.22	13	10	
(S)-2-amino-1-butanol	32	R	A	0.84	9	7	9
			B	0.16	8	8	
(S)-1-cyclohexylethylamine	11	R	A	0.40	15	12	4
			B	0.33	13	14	
			C	0.27	15	12	
cis-myrtanylamine	9	S	-	1.00	5	8	12
pyrrolidine	20 ¹⁾	R	A	0.52	9	8	6
			B	0.48	10	7	

1) Enantiomer excess.

2) The value of **L** and **R** in the cavity volume denote the volume of left and right part divided into two parts by the average plane comprising the C-C-C-N atoms of the 2-cyanoethyl group.

3) When the value of **L** in cavity volume is larger than that of **R**, (**R**)-1-cyanoethyl group will be produced preferentially by photoisomerization process.

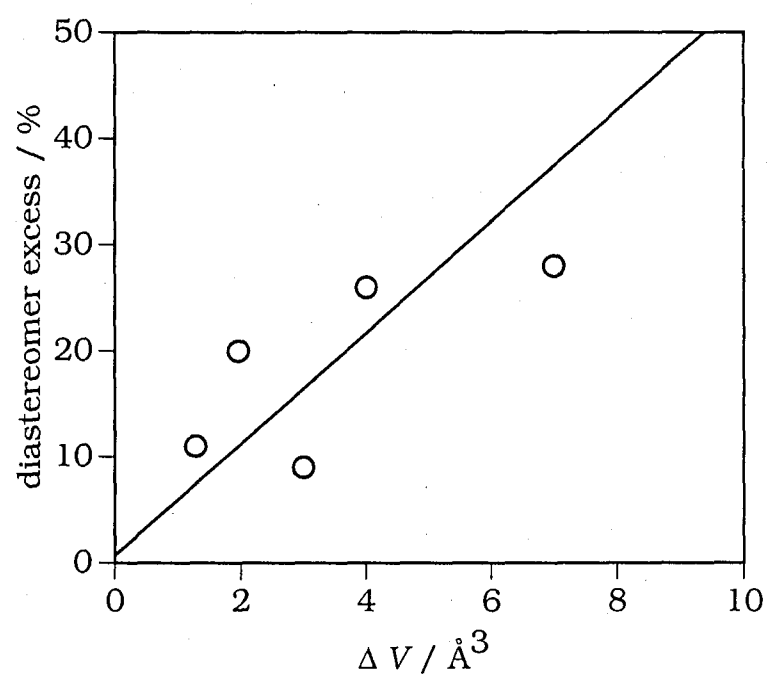


Figure 4-27 Relation between diastereomer excess and ΔV .

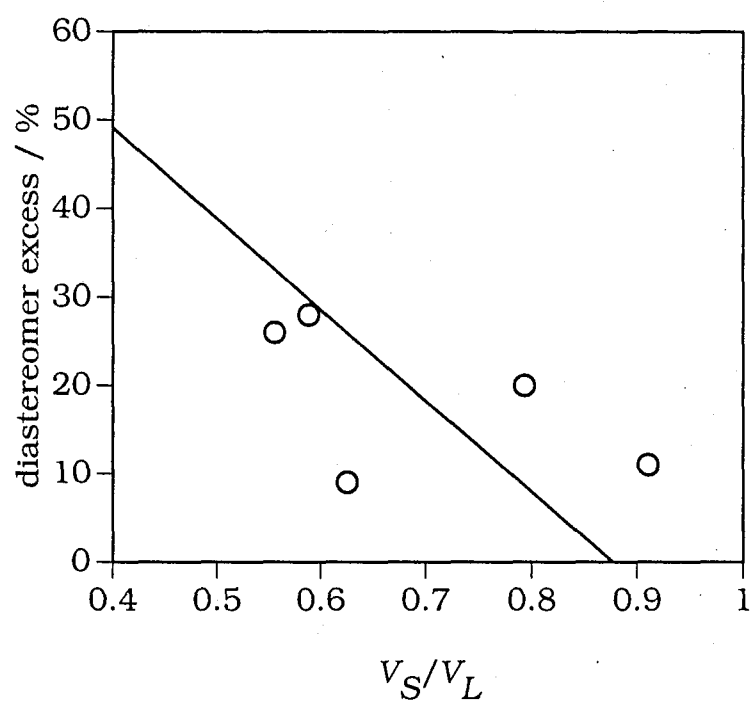


Figure 4-28 Relation between diastereomer excess and V_S/V_L .

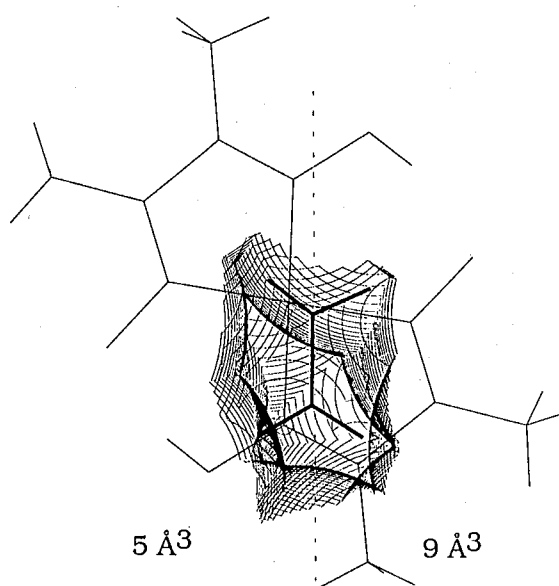
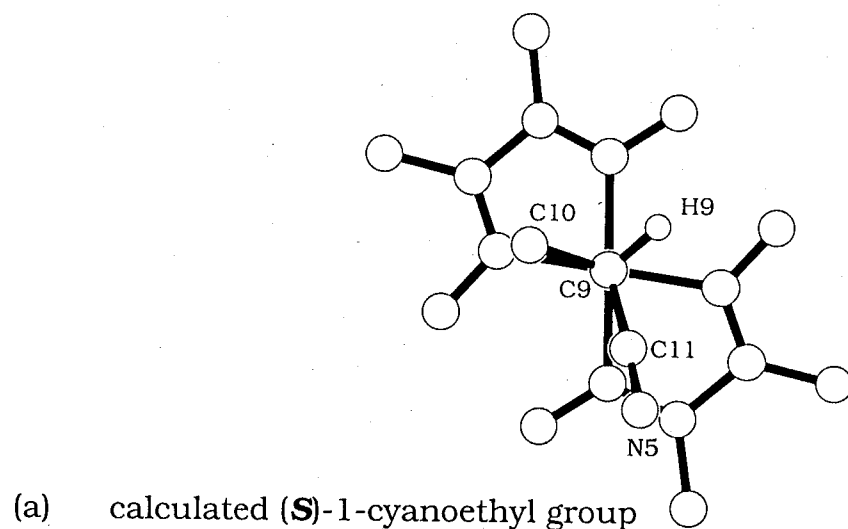


Figure 4-29 The calculated structure of (**S**)-1-cyanoethyl cobaloxime with the lowest energy (a) and the asymmetrical cavity shape for the 2-cyanoethyl group (b). It is found that the CN and CH₃ group occupy the greater and smaller parts of the reaction cavity.

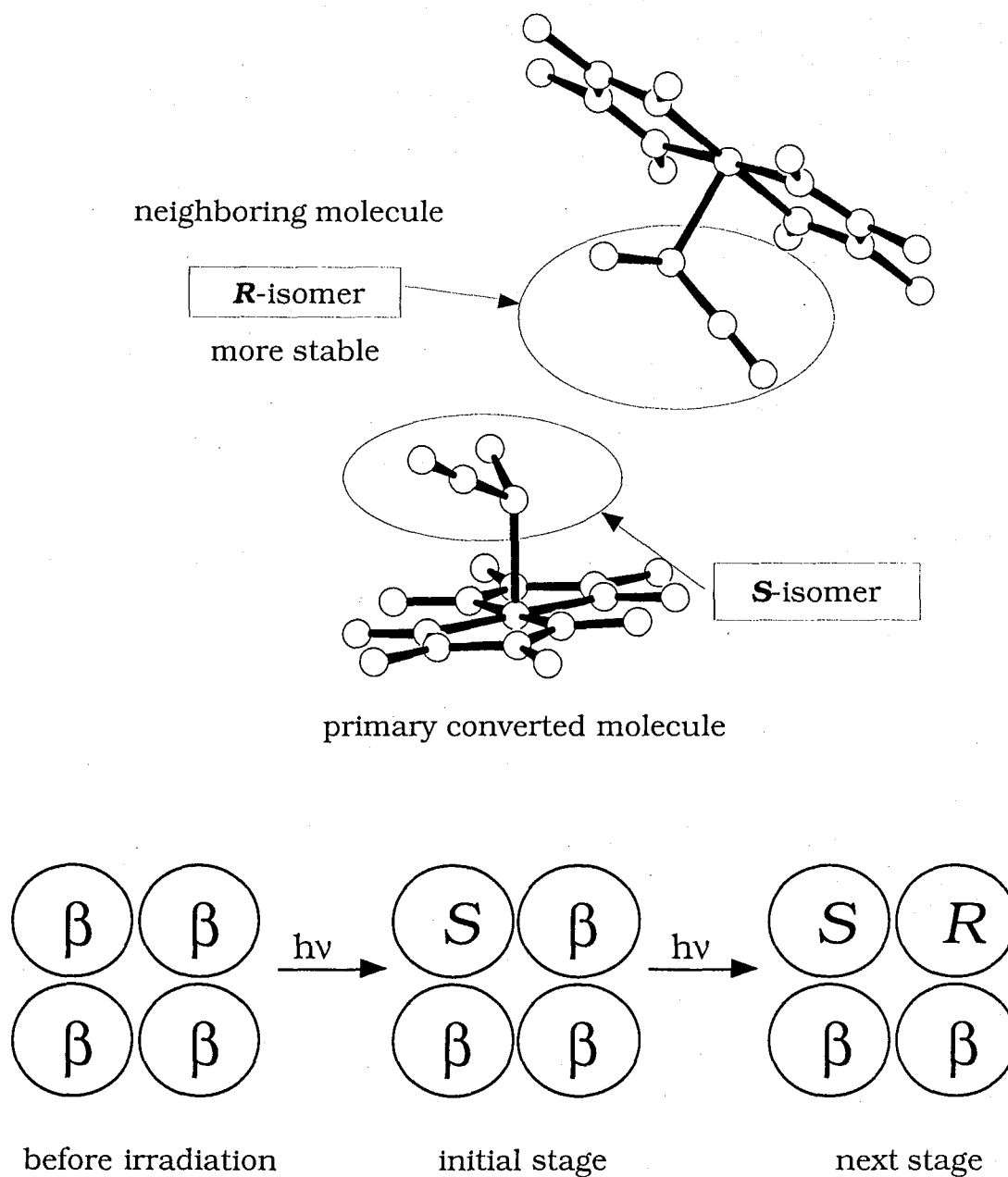


Figure 4-30 The lowest energy calculation of 1-cyanoethyl group when the (S)-1-cyanoethyl group is the neighboring molecule. In this case, the lowest energy of the (R)-1-cyanoethyl group was lower by 12.7 kJ mol⁻¹ than that for the (S)-1-cyanoethyl group.

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Chapter 5

Temperature Dependence of Asymmetric Induction

It is found that the rate of most chemical reactions increase as the temperature is raised, and that the asymmetric yield of most chemical reactions increase as the temperature is fallen. It is now generally accepted that the empirical observations were explained by the combination of the Arrhenius equation and the activation Gibbs energy, provided that the temperature range is not large.

The temperature dependence of the reaction rate of the racemization in cobaloxime complex was studied and it was explained that the cavity volume for the reaction group increases as the temperature increases, regardless the density of the crystal [1].

In order to examine the temperature dependence of the asymmetric induction in the solid state, several complex crystals of the 2-cyanoethyl cobaloxime coordinated with *sec*-butylamine, *cis*-myrtanylamine and 2-amino-2-phenylethanol as axial base ligands were prepared, since the complexes give the asymmetric yield independent of the reaction yield or the irradiation time. The 2-cyanoethyl group in cobaloxime complexes with *sec*-butylamine and *cis*-myrtanylamine take a perpendicular conformation but a parallel conformation with 2-amino-2-phenylethanol. It is known that the difference in the conformation of the reaction group gives rise to the influence for the reaction rate of the solid state photoisomerization.

5-1 Experimental

The crystals of (2-cyanoethyl)[(S)-sec-butylamine]cobaloxime complex was irradiated with a xenon lamp at the range of 270 to 330 K for several hours onto a Petri dish. The crystals was maintained at suitable temperature during photoirradiation. The temperature controller used was the Nissin Scientific Corporation Model NCP-2215. After Photoirradiation at suitable temperature, an HPLC analysis was carried out using the chiral stationary phase in order to determine the diastereoselectivity. The HPLC system used was a HITACHI L-7000 series system equipped with a CHIRALPAK-AD column (Φ 4.6 mm $\times$ 250 mm :10 mm, Daisel Chem., Inc.) maintained at 300 K and with a Model L-7420 UV-Vis absorbance detector monitored at 254 nm. The mobile phase consisted of hexane with 10% v/v ethanol , and its flow rate was 1.0 ml min⁻¹. Quantification was performed by integrating the peak area using an internal standard. No leading or tailing around the peaks corresponding to (R)- and (S)-1-cyanoethyl complexes was observed in the chromatogram. This indicates that the produced 1-cyanoethyl group was not inverted to the opposite configuration when it migrated in the chiral stationary phase of HPLC.

5-2 Result and Discussion

The temperature dependence of the diastereomer excess was given in Table 5-1, 5-2 and 5-3, respectively. The diastereoselectivity of the asymmetric photoisomerization in the 2-cyanoethyl cobaloximes is accounted for the influence of temperature, as well as the reaction rate of the crystalline-state racemization of the 1-cyanoethyl cobaloxime complexes [1]. The diastereomer excess significantly decreased as the temperature is raised. In particular, it was found that the larger the diastereomer excess is, the greater the temperature dependence is. Since the sample in this experiment was selected not to change the value of the diastereomer excess with the

photoirradiation time, the data on the diastereomer excess obtained does not depend on the reaction yield. Figure 5-1 shows the Arrhenius plots for these experiments. The reaction rate constant, K , was taken as the value that is greater than one, for convenient. The difference of activation enthalpy, $\Delta\Delta H^\ddagger$, was correlated by a single straight line in a Arrhenius plot with a gradient calculated by the least-square method. It is said that the value of $\Delta\Delta H^\ddagger$ is reasonable comparing it with the ordinary activation energy derived from the some experiment. The difference of activation entropy, $\Delta\Delta S^\ddagger$, was estimated by extrapolation to $T^{-1} = 0$, provided that the accuracy of $\Delta\Delta S^\ddagger$ normally less than that of the comparative methods. Therefore the influence of $\Delta\Delta S^\ddagger$ was not discussed here in detail. Table 5-4 lists the difference of activation enthalpy, $\Delta\Delta H^\ddagger$ and the difference of activation entropy, $\Delta\Delta S^\ddagger$, that was obtained from Figure 5-1. It was seemed that the degree of diastereomer excess in the asymmetric induction was governed mainly by $\Delta\Delta H^\ddagger$ than $\Delta\Delta S^\ddagger$. $\Delta\Delta H^\ddagger$ may come from the steric hindrance. The interpretation is consistent with the discussions derived from the reaction cavity for the reaction group in the crystal structure. It was found that the racemic crystal of the 2-cyanoethyl cobaloxime is more stable in enthalpy than chiral one and that the motive force for the racemization would be a decrease in enthalpy [2], which was calculated using the program OPEC in which packing potential energy was estimated as a sum of Buckingham type atom-atom potential energy [1]. It is noted that the diastereomer excess is governed by $\Delta\Delta H^\ddagger$ is similar to the topochemical principle.

Table 5-1 Temperature dependence of solid state asymmetric induction in 2-cyanoethyl (**S**)-*sec*-butylamine cobaloxime complex

Temperature (K)	Diastereomer excess (%)	ln K	Irradiation time (h)
270	37.1	0.778	16
285	32.7	0.679	
300	28.1	0.577	
315	23.6	0.482	
330	19.8	0.402	

Table 5-2 Temperature dependence of solid state asymmetric induction in 2-cyanoethyl *cis*-myrtanamine cobaloxime complex

Temperature (K)	Diastereomer excess (%)	ln <i>K</i>	Irradiation time (h)
270	7.0	0.140	4
285	9.0	0.180	
300	8.5	0.170	
315	7.3	0.146	
330	7.6	0.153	

Table 5-3 Temperature dependence of solid state asymmetric induction in (2-cyanoethyl)(2-amino-2-phenylethanol)cobaloxime complex

Temperature (K)	Diastereomer excess (%)	ln K	Irradiation time (h)
270	84.6	2.49	4
285	84.4	2.47	
300	73.8	1.89	
315	73.9	1.90	
330	-	-	

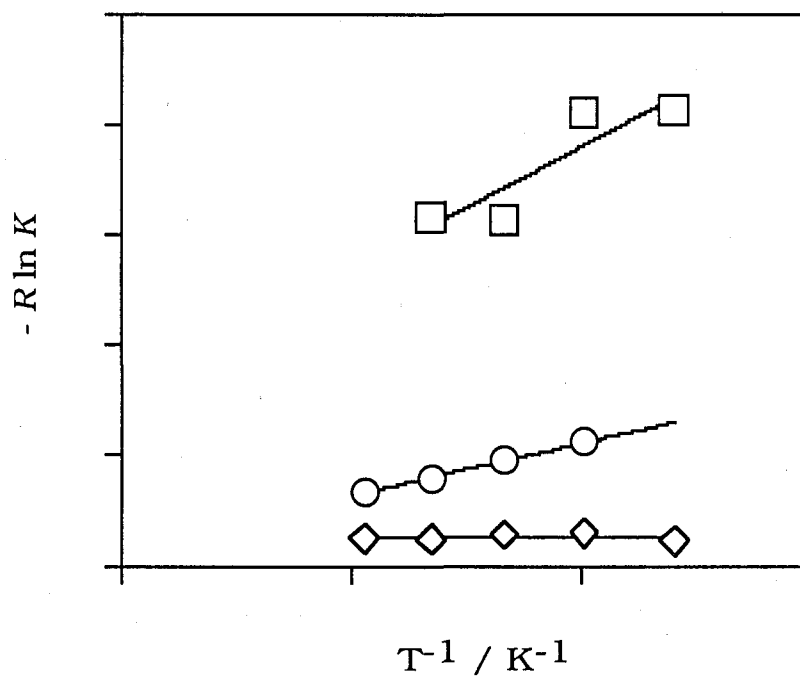


Figure 5-1 The Arrhenius plot for the 2-cyanoethyl cobaloxime complex in asymmetric inductions, where *sec*-butylamine (circle), *cis*-myrtaniline (diamond) and 2-amino-2-phenylethanol (square).

Table 5-4 The difference of activation enthalpy, $\Delta\Delta H^\ddagger$, and the difference of activation entropy, $\Delta\Delta S^\ddagger$, for temperature dependence in the 2-cyanoethyl cobaloxime

Base ligand	$\Delta\Delta H^\ddagger$ 1)	$\Delta\Delta S^\ddagger$ 2)
	(kJ mol ⁻¹)	(J K ⁻¹ mol ⁻¹)
sec-butylamine	-4.69	11
cis-myrtanylamine	-0.56	0.5
2-amino-2-phenylethanol	-11.0	19

1) The difference of activation enthalpy, $\Delta\Delta H^\ddagger$, was correlated by a single straight line in a Arrhenius plot with a gradient calculated by the least-square method.

2) The difference of activation entropy, $\Delta\Delta S^\ddagger$, was estimated by extrapolation to $T^{-1} = 0$.

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Chapter 6

Epimerization of *sec*-Butylamine Cobaloxime

The crystal structure determination before and after reaction is very powerful method for the study of the structure-reactivity correlation. Nowadays, most of 1-cyanoethyl cobaloxime complex was found to racemize with retention to the single crystal from and it was revealed the crystal structure in the initial and final stage. First observation of the crystalline-state racemization was reported by Ohashi et al. that [(*R*)-1-cyanoethyl] [(*S*)-phenylethylamine] cobaloxime gradually changed its unit cell dimensions by X-ray exposure without degradation of the crystallinity [1]. In order to examine why such a change was observed, the three-dimensional intensity data were collected at several stage. As a results, significant change in electron density was observed only in the vicinity of the cyanoethyl group. This is the first example of direct observation of a reaction process by X-ray diffraction technique [2][3][4]. A lot of examples of the crystalline-state racemization of 1-cyanoethyl cobaloxime coordinated with the different axial base ligand such as (*S*)-phenylethylamine [5], pyrrolidine [6], dimethylphosphine and triphenylphosphine complex were observed and it was found that the reaction rate of the racemization depend on the volume of the reaction cavity for the 1-cyanoethyl group, regardless the density of the crystal.

The combination of X-ray crystal structure determination and molecular

simulation gave useful information for the study of crystal structure-reactivity correlation. The motion of cyanoethyl radical in the crystal of [(**R**)-1-cyanoethyl] [(**S**)-phenylethylamine] cobaloxime was calculated using the program OPEC in which packing potential energy was estimated as a sum of Buckingham type atom-atom potential energy [7], but the cleavage and reformation of the Co-C bond were ignored in this calculation. As a results, a sequence of structures along the path of minimum packing potential energy for the cyanoethyl radical was obtained and the repulsive energy was estimated to about 60-70 kJ mol⁻¹ in rotational motion of cyanoethyl radical. A similar calculation was applied to pyridine complex and it was obtained that only the cyanoethyl group of the B molecule is completely inverted after racemization. The packing potential energy were calculated for the initial and final racemic crystals, which are -347 and -377 kJ mol⁻¹, respectively. This result suggested that the racemic crystal is more stable in enthalpy than chiral one and that the motive force for the racemization would be a decrease in enthalpy [8].

In order to examine the asymmetric reaction more precisely, chiral (**R**)-1-cyanoethyl cobaloxime complex coordinated with (**R**)-sec-butylamine was prepared, and it was investigated the crystal structure-stereoselectivity correlation by X-ray crystal structure determination, diastereoselectivity and packing energy calculation. This study reports the mechanism of the racemization process of produced 1-cyanoethyl group by photoisomerization.

6-1 Structure Determination

X-ray structure determination before photoirradiation

A complex of the [(**R**)-1-cyanoethyl] [(**R**)-sec-butylamine] cobaloxime was prepared in a way similar to that reported previously [9]. Orange crystals suitable for X-ray analysis were obtained from an acetone-hexane solution. Before photoirradiation, the X-ray data was collected on a Rigaku AFC7R

diffractometer. MoKa radiation monochromated with graphite was used. Crystal structures were solved by the Patterson method with the program SAPI91 [10] and refined by the full-matrix least-squares with the program SHELXE97 [11]. In the process of the refinement, only the (**R**)-1-cyanoethyl group was found before photoirradiation, the opposite configuration was not found. All the hydrogen atoms were calculated geometrically by a riding model. Non-hydrogen atoms were refined anisotropically. The absolute structure was determined to coincide with that of the 1-cyanoethyl group and *sec*-butylamine, which was consistent with that obtained from the Flack χ parameter in the refinement. The atomic scattering factors were taken from International Tables for Crystallography [12]. The crystal data and experimental details are given in Table 6-1. The final atomic coordinates and equivalent isotropic temperature factors for non-hydrogen atoms are given in Table 6-2.

X-ray structure determination after photoirradiation

The same crystal of the [(**R**)-1-cyanoethyl] [(**R**)-*sec*-butylamine] cobaloxime, which was measured by X-ray analysis, was irradiated with a xenon lamp for 4 hours at room temperature. After photoirradiation, the X-ray data was collected on a Rigaku AFC7R diffractometer. MoKa radiation monochromated with graphite was used. Crystal structures were solved by the Patterson method with the program SAPI91 [10] and refined by the full-matrix least-squares with the program SHELXL97 [11]. In the process of the refinement, (**R**)- and (**S**)-1-cyanoethyl group was found after photoirradiation. The torsion angle for 1-cyanoethyl group were restrained to have ideal values in the further refinement cycles. All the hydrogen atoms were calculated geometrically by a riding model. Non-hydrogen atoms were refined anisotropically, except for the disordered atom, which were refined isotropically. The absolute structure was determined to coincide with that of *sec*-butylamine, which was consistent with that obtained from the Flack χ

parameter in the refinement. The atomic scattering factors were taken from International Tables for Crystallography [13]. The crystal data and experimental details are given in Table 6-3. The final atomic coordinates and equivalent isotropic temperature factors for non-hydrogen atoms are given in Table 6-4.

Crystal and Molecular Structure before and after photoirradiation

The crystal structure before photoirradiation is shown in Figure 6-1. The crystal structures before photoirradiation belong to triclinic system and the space group is P1 and Z value is one. The ORTEP drawing [13] of the molecular structure with the numbering atoms before photoirradiation was shown in Figure 6-2. The 1-cyanoethyl group has only **R** configuration. This population of 1-cyanoethyl group agreement with the data on the diastereomer excess obtained from HPLC analysis, which was indicated to 97%d.e. as **R**-isomer excess. It is noted that the conformation of sec-butylamine as an axial base ligand is different in the direction of C15 atom from that of 2-cyanoethyl complex, as shown in Figure 2-2.

The crystal structure after photoirradiation is shown in Figure 6-3. The crystal structures after photoirradiation belong to triclinic system and the space group is P1 and Z value is one, similar to the crystal structure before photoirradiation. The crystal structure after photoirradiation was essentially the same as that before photoirradiation, except for the disordered structure of 1-cyanoethyl group. The unit cell dimension after photoirradiation significantly changed in contrast to that before photoirradiation and the unit-cell volume and the space group unchanged. The ORTEP drawing [13] of the molecular structure with the numbering atoms after photoirradiation was shown in Figure 6-4 and Figure 6-5. The 1-cyanoethyl group has the disordered structure of 1-cyanoethyl group. The occupancy factor of (**R**)- and (**S**)-1-cyanoethyl group are 0.39 and 0.61(1), respectively. This population of the 1-cyanoethyl group is in agreement with the data on the diastereomer excess obtained from HPLC analysis, which was indicated to 30%d.e. as **S**-

isomer excess. It is seemed that the disordered structure of (*R*)- and (*S*)-1-cyanoethyl group related to the real and its mirror image.

The reason why (*S*)-1-cyanoethyl group was alternated from initial (*R*)-1-cyanoethyl group as major configuration when crystals were irradiated with a xenon lamp in the crystalline state is probably due to the fact that the configuration and conformation would be preferred in the asymmetric crystal lattice, where the chiral-lattice control may influence to the determination of the configuration of main products.

6-2 Epimerization

Photoepimerization and HPLC Analysis

The crystals scattered in a Petri dish were irradiated with a xenon lamp for several hours at 300 K. After photoirradiation, the HPLC analysis of the crystals was carried out using the chiral stationary phase, in order to determine the diastereoselectivity. The HPLC system used was HITACHI L-7000 series system equipped with CHIRALPAK-AD column (Daisel Chem.) maintained at 300 K and with Model L-7420 UV-Vis absorbance detector monitored at 254 nm. The mobile phase consists of hexane with 10% v/v ethanol and its flow rate was 1.0 ml min⁻¹. Quantification was performed integrating the peak area. The chromatograms obtained indicates that the 1-cyanoethyl group was not inverted to the opposite configuration when it migrated in the chiral stationary phase of HPLC.

Epimerization

Change of molar fractions of (*R*)- and [(*S*)-1-cyanoethyl][(*R*)-sec-butylamine] cobaloxime is shown with the irradiation time in Figure 6-6. Before photoirradiation, the diastereomer excess indicated 97% as a (*R*)-isomer excess using by HPLC. The molar fraction or diastereomer excess changed dramatically increasing the irradiation time during the early stages (less than 60 min.), as shown in Figure 6-7, namely major configuration altered

from (**R**)-1-cyanoethyl group to (**S**)-1-cyanoethyl group. The molar fraction and diastereomer excess continued to change slightly after 60 minutes, and the diastereomer excess converged to about 30% as (**S**)-isomer excess at 480 min. The reason why the value of diastereomer excess dramatically changed to increase with the irradiation time is probably due to asymmetrical cavity around the reaction group, where the chiral lattice control may be governed by chiral *sec*-butylamine.

Cavity Shape of the 1-cyanoethyl group

In order to explain the reason why the (**R**)-isomer was inverted to (**S**)-isomer with the different population when the (**R**)-*sec*-butylamine is used, the reaction cavity for the (**R**)-1-cyanoethyl group in the initial and final crystal structure was drawn, and its volume was calculated in the same way as previously reported [9]. Figure 6-8 shows the reaction cavities before and after photoirradiation. The cavity volume for 1-cyanoethyl group in the initial crystal structure was calculated to 10.5 Å³. This cavity volume is relatively small considering from the criteria of the racemization in a crystal. It is seemed that the produced (**S**)-1-cyanoethyl group is better fitted to the asymmetric reaction cavity than (**R**)-1-cyanoethyl group. In many cases, only CH₃ group was displaced from initial site to inverted site in the opposite configuration, and the CN group remained closely at the position. This tendency was interpreted assuming that the smaller CH₃ group occupies the void space of the reaction cavity, but the larger CN group do not occupy the void space due to not enough space around 1-cyanoethyl group in the reaction cavity.

6-3 Packing Energy Calculation

In order to examine the above discussion more quantitatively, the conformation and configuration of the 1-cyanoethyl group were calculated by

the molecular-mechanics calculation using the program Cerius² [14] with the Universal Force Field [15] parameter set. The UFF parameter set is applicable to organometallic compounds [15][16]. The initial model in molecular mechanics calculation was constructed on the basis of the observed X-ray crystal structure. At first, the initial model was calculated to assign to the point charge on the current atom using the charge equilibration method [17]. The conformation of the (**S**)-1-cyanoethyl group in cobaloxime coordinated with (**R**)-*sec*-butylamine was altered at a constant interval of 30° around the Co-C bond, and the model structure was minimized geometrically with the fixed unit-cell dimension. Finally whole crystal structure was optimized. Energy minimization was carried out by the conjugate-gradient method, at the end of which the value of the root-mean-square energy derivative of the atomic coordinates was less than 0.42 kJ mol⁻¹. Figure 6-8 shows the structure of the (**S**)-1-cyanoethyl group with the lowest energy. The interest behavior was observed in this calculations. The conformation obtained from the optimization in the initial unit-cell dimension observed X-ray crystal structure determination was different from that in the final one, as shown in Figure 6-8. This is responsible to the slight difference in cavity shape. The same calculation was performed for the (**R**)-1-cyanoethyl group. The lowest energy was higher by 13.4 kJ mol⁻¹ than that for the (**S**)-1-cyanoethyl group. This result is in good agreement with the population obtained from X-ray crystal structure determination.

Table 6-1 Crystal Data and Experimental Details**Crystal data**

Chemical formula	[Co(C ₄ H ₇ N ₂ O ₂) ₂ (C ₃ H ₄ N)(C ₄ H ₁₁ N)]
Formula weight	416.37
Cell system	Triclinic
Space group	P1
<i>a</i> / Å	8.475(1)
<i>b</i> / Å	9.695(2)
<i>c</i> / Å	6.746(1)
α / °	108.45(2)
β / °	101.51(1)
γ / °	102.45(1)
<i>V</i> / Å ³	491.6(2)
<i>Z</i>	1
<i>D_x</i> / Mg m ⁻³	1.407
<i>F</i> (000)	220
Radiation type	Mo K α
Wavelength/Å	0.71073
No. of reflections for cell parameters	25
θ range/°	12.5-15
μ /mm ⁻¹	0.905
Temperature/K	296
Crystal form	Prismatic
Crystal size/mm	0.4 x 0.3 x 0.3
Crystal color	Orange

Data collection

Diffractionmeter	AFC-7R
Data collection method	ω -2 θ
Scan rate/° min ⁻¹	16
Absorption correction	Ψ scan
No. of measured reflections	2446
No. of independent reflections	2446
No. of observed reflections	2418
Criterion for observed reflections	$I > 2 \sigma(I)$
$\theta_{\max}$ / °	27.5
Range of <i>h, k, l</i>	-10 ≤ <i>h</i> ≤ 10 -11 ≤ <i>k</i> ≤ 12 - 8 ≤ <i>l</i> ≤ 0
No. of standard reflections	3
Frequency of standard reflections	Every 100 reflections
Intensity decay /%	0.7

Refinement

Refinement on	F^2
$R [I > 2\sigma(I)]$	0.027
$\omega R(I)$	0.074
<i>S</i>	1.079
No. of reflections used in refinement ($I > 0$)	2446
No. of parameters used	242
H-atom treatment	Calculated
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0600P)^2 + 0.02176P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max}$	0.098
$\Delta\rho_{\max}/\text{e}\text{\AA}^{-3}$	0.618
$\Delta\rho_{\min}/\text{e}\text{\AA}^{-3}$	-0.361
Extinction correction	None
Flack χ parameter	0.01(1)

Table 6-2 Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)

atom	x	y	z	U_{eq}^a
Co1	0.00184(2)	1.00135(2)	0.01139(2)	0.02529(9)
O1	0.0454(4)	1.2609(4)	0.3878(6)	0.0446(7)
O2	-0.1880(4)	0.9271(5)	-0.4252(5)	0.0474(8)
O3	-0.0404(5)	0.7427(4)	-0.3687(7)	0.0515(9)
O4	0.1755(4)	1.0650(4)	0.4517(6)	0.0456(8)
N1	-0.0211(4)	1.1894(4)	0.1690(6)	0.0315(7)
N2	-0.1328(4)	1.0305(4)	-0.2206(7)	0.0353(8)
N3	0.0308(4)	0.8147(4)	-0.1519(6)	0.0349(8)
N4	0.1362(4)	0.9706(4)	0.2424(7)	0.0314(7)
N5	-0.4735(4)	0.9658(5)	-0.0512(7)	0.0678(9)
N6	0.2139(3)	1.1047(3)	-0.0590(5)	0.0297(6)
C1	-0.0993(5)	1.2551(5)	0.0610(9)	0.0367(9)
C2	-0.1645(5)	1.1617(5)	-0.1746(9)	0.0372(9)
C3	0.1312(5)	0.7621(5)	-0.043(1)	0.042(1)
C4	0.1935(5)	0.8539(5)	0.1902(9)	0.040(1)
C5	-0.1152(5)	1.4113(5)	0.167(1)	0.058(1)
C6	-0.2573(6)	1.2039(6)	-0.342(1)	0.058(1)
C7	0.1789(7)	0.6237(5)	-0.150(1)	0.066(1)
C8	0.3056(6)	0.8161(6)	0.358(1)	0.063(1)
C9	-0.2020(4)	0.9031(4)	0.0924(6)	0.0327(7)
C10	-0.3532(3)	0.9388(3)	0.0088(5)	0.0407(6)
C11	-0.2431(5)	0.7319(4)	0.0409(8)	0.0547(9)
C12	0.3078(3)	1.2712(3)	0.0541(5)	0.0337(5)
C13	0.3970(4)	1.3284(4)	-0.0912(6)	0.0517(7)
C14	0.4291(4)	1.2992(4)	0.2705(5)	0.0508(7)
C15	0.4964(7)	1.4657(5)	0.4238(8)	0.080(1)

a) $U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$

Table 6-3 Crystal Data and Experimental Details**Crystal data**

Chemical formula	[Co(C ₄ H ₇ N ₂ O ₂) ₂ (C ₃ H ₄ N)(C ₄ H ₁₁ N)]
Formula weight	416.37
Cell system	Triclinic
Space group	P1
<i>a</i> / Å	8.437(1)
<i>b</i> / Å	9.754(1)
<i>c</i> / Å	6.891(1)
α / °	108.74(1)
β / °	104.62(1)
γ / °	102.35(1)
<i>V</i> / Å ³	492.0(1)
<i>Z</i>	1
<i>D_x</i> / Mg m ⁻³	1.405
<i>F</i> (000)	220
Radiation type	Mo K α
Wavelength/Å	0.71073
No. of reflections for cell parameters	25
θ range/°	12.5-15
μ /mm ⁻¹	0.904
Temperature/K	296
Crystal form	Prismatic
Crystal size/mm	0.4 x 0.3 x 0.3
Crystal color	Orange

Data collection

Diffractometer	AFC-7R
Data collection method	ω -2 θ
Scan rate/° min ⁻¹	16
Absorption correction	ψ scan
No. of measured reflections	2440
No. of independent reflections	2440
No. of observed reflections	2308
Criterion for observed reflections	$I > 2 \sigma(I)$
$\theta_{\max}$ / °	27.49
Range of <i>h, k, l</i>	-10 ≤ <i>h</i> ≤ 10 -11 ≤ <i>k</i> ≤ 12 - 8 ≤ <i>l</i> ≤ 0
No. of standard reflections	3
Frequency of standard reflections	Every 100 reflections
Intensity decay /%	0.7

Refinement

Refinement on	<i>F</i> ²
<i>R</i> [$I > 2\sigma(I)$]	0.0264
$wR(I)$	0.0690
<i>S</i>	1.057
No. of reflections used in refinement ($I > 0$)	2446
No. of parameters used	242
H-atom treatment	Calculated
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0397P)^2 + 0.1245P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max}$	0.050
$\Delta\rho_{\max}/e\text{\AA}^{-3}$	0.249
$\Delta\rho_{\min}/e\text{\AA}^{-3}$	-0.284
Extinction correction	None
Flack χ parameter	0.0(0916)

Table 6-4 Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)

atom	x	y	z	U_{eq}^a
Co1	0.00147(6)	1.00038(6)	0.00880(7)	0.0349(1)
O1	0.0433(5)	1.2505(4)	0.3959(6)	0.057(1)
O2	-0.1876(5)	0.9366(5)	-0.4291(6)	0.060(1)
O3	-0.0340(5)	0.7525(4)	-0.3723(8)	0.069(1)
O4	0.1747(6)	1.0559(5)	0.4518(7)	0.062(1)
N1	-0.0238(5)	1.1829(5)	0.1751(6)	0.0377(9)
N2	-0.1324(5)	1.0366(4)	-0.2216(7)	0.041(1)
N3	0.0336(6)	0.8182(5)	-0.1551(8)	0.049(1)
N4	0.1365(5)	0.9675(5)	0.2403(8)	0.046(1)
N5A	-0.449(1)	0.9981(8)	0.0514(1)	0.064(2)
N5B	-0.472(2)	0.972(1)	-0.039(2)	0.061(3)
N6	0.2195(4)	1.1114(4)	-0.0361(6)	0.0369(7)
C1	-0.1003(6)	1.2540(6)	0.0670(1)	0.044(1)
C2	-0.1656(6)	1.1646(6)	-0.1685(9)	0.041(1)
C3	0.1330(7)	0.7659(6)	-0.046(1)	0.051(1)
C4	0.1960(7)	0.8525(7)	0.191(1)	0.055(2)
C5	-0.1124(6)	1.4067(5)	0.179(1)	0.062(1)
C6	-0.2596(7)	1.2124(6)	-0.335(1)	0.062(1)
C7	0.1828(8)	0.6298(6)	-0.152(1)	0.090(2)
C8	0.3099(8)	0.8137(8)	0.353(1)	0.080(2)
C9A	-0.2339(7)	0.8542(6)	-0.038(1)	0.035(1)
C10A	-0.353(2)	0.937(2)	0.006(2)	0.060(5)
C11A	-0.225(1)	0.7480(9)	0.088(2)	0.042(2)
C9B	-0.193(2)	0.912(1)	0.107(2)	0.044(3)
C10B	-0.351(2)	0.942(2)	0.023(1)	0.031(5)
C11B	-0.243(2)	0.735(2)	0.033(3)	0.056(4)
C12	0.3100(4)	1.2791(4)	0.0748(6)	0.0413(7)
C13	0.4013(6)	1.3344(5)	-0.0625(8)	0.064(1)
C14	0.4313(5)	1.3154(4)	0.3007(6)	0.0545(9)
C15	0.5012(9)	1.4848(6)	0.4475(9)	0.091(2)

a) $U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$

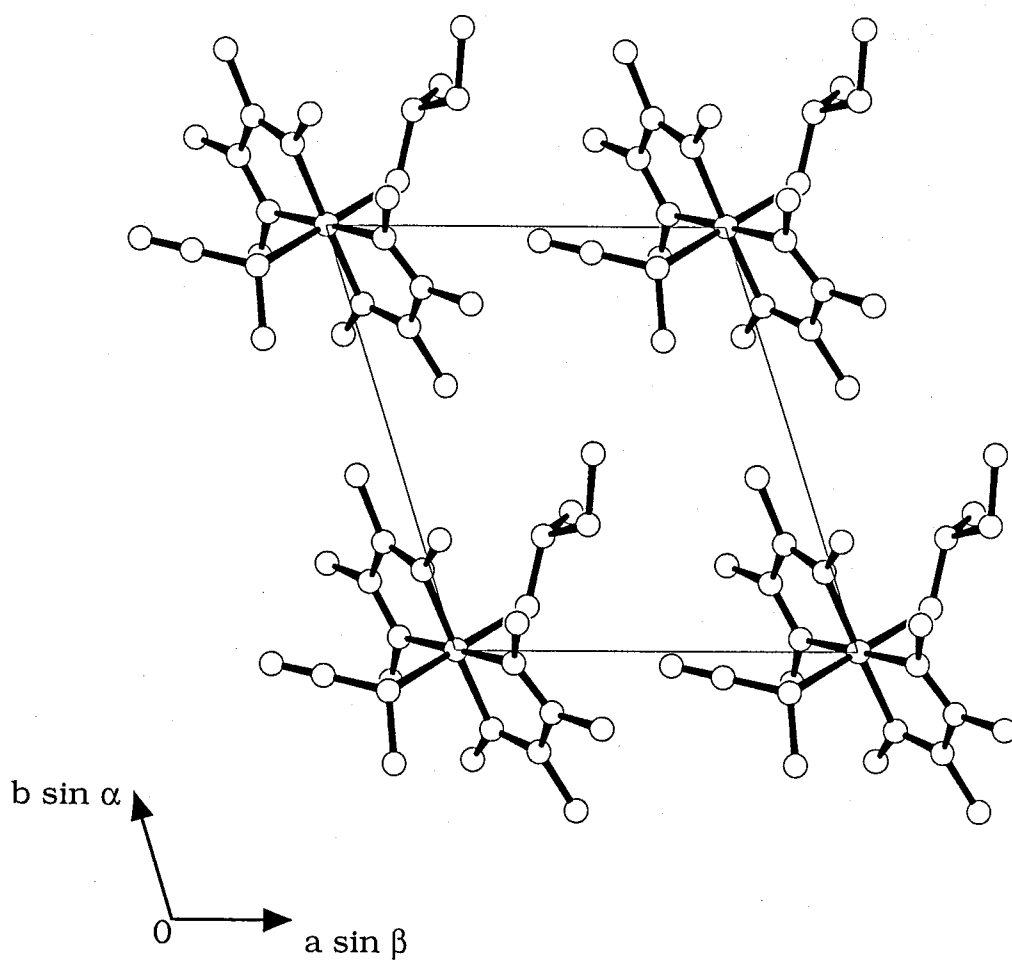


Figure 6-1 The crystal structure of [(*R*)-1-cyanoethyl][(*R*)-*sec*-butylamine] cobaloxime

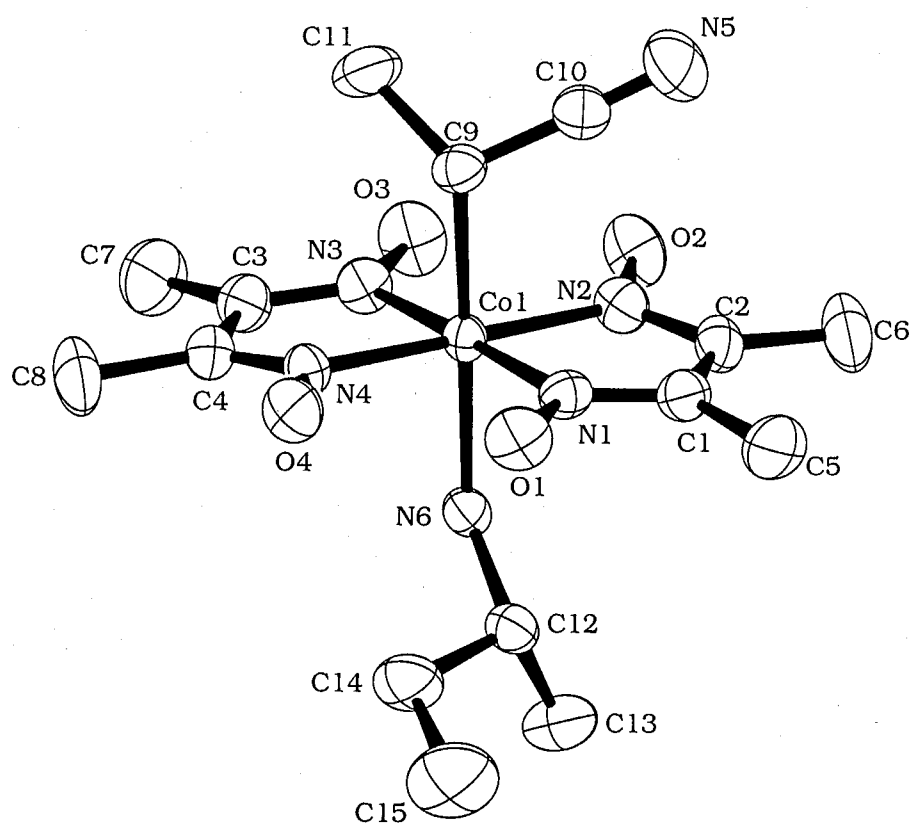


Figure 6-2 The molecular structure of [(*R*)-1-cyanoethyl] [(*R*)-sec-butylamine] cobaloxime

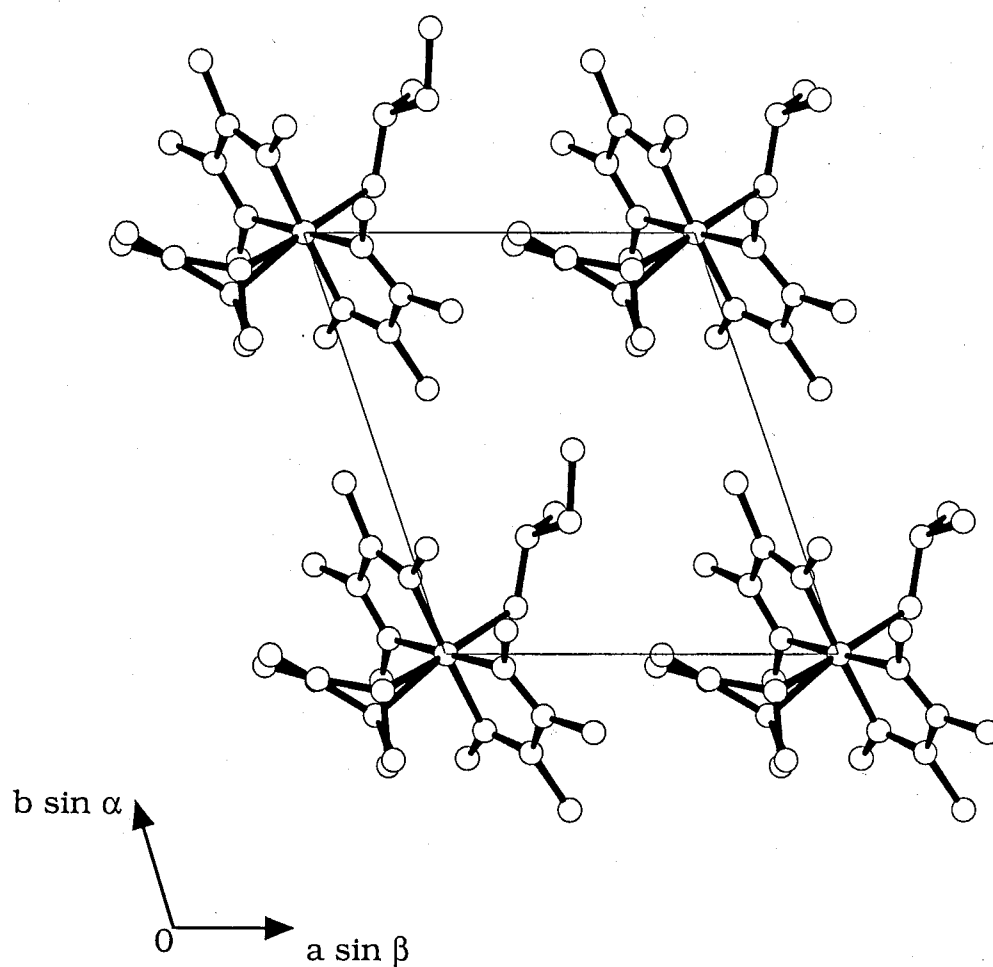


Figure 6-3 The crystal structure of $[(R)\text{-1-cyanoethyl}][(R)\text{-sec-butylamine}]$ cobaloxime after photoirradiation

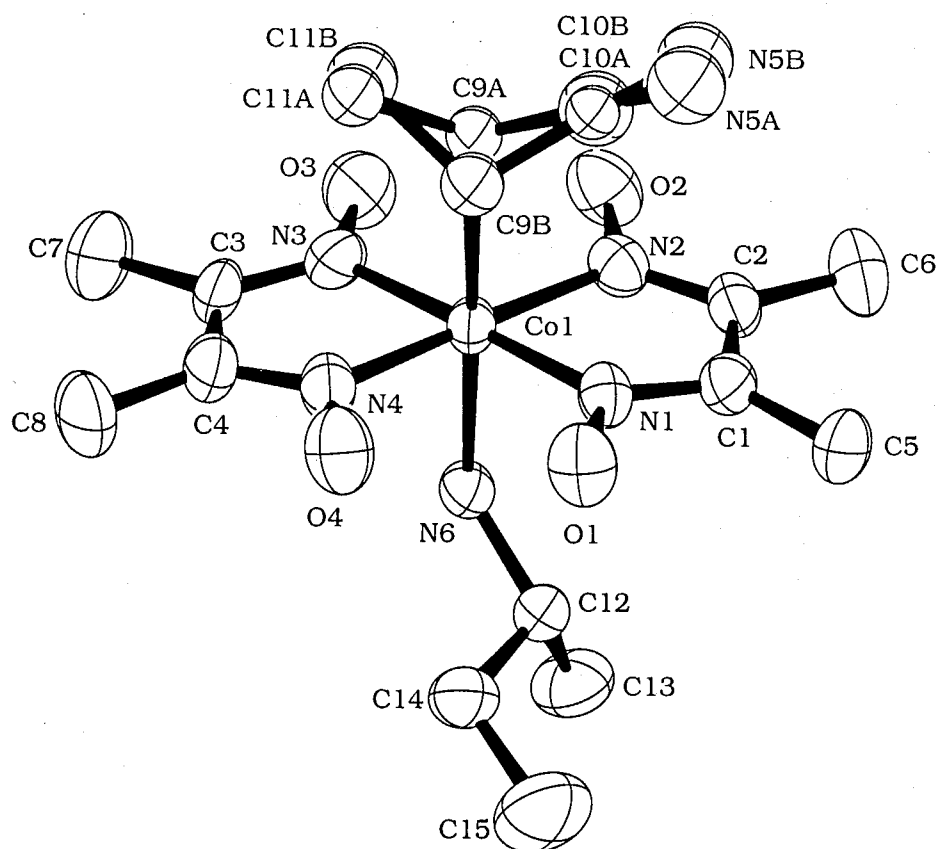


Figure 6-4 The molecular structure of [(*R*)-1-cyanoethyl] [(*R*)-*sec*-butylamine] cobaloxime after photoirradiation. The occupancy factor of (*R*)- and (*S*)-1-cyanoethyl group are 0.39 and 0.61(1), respectively.

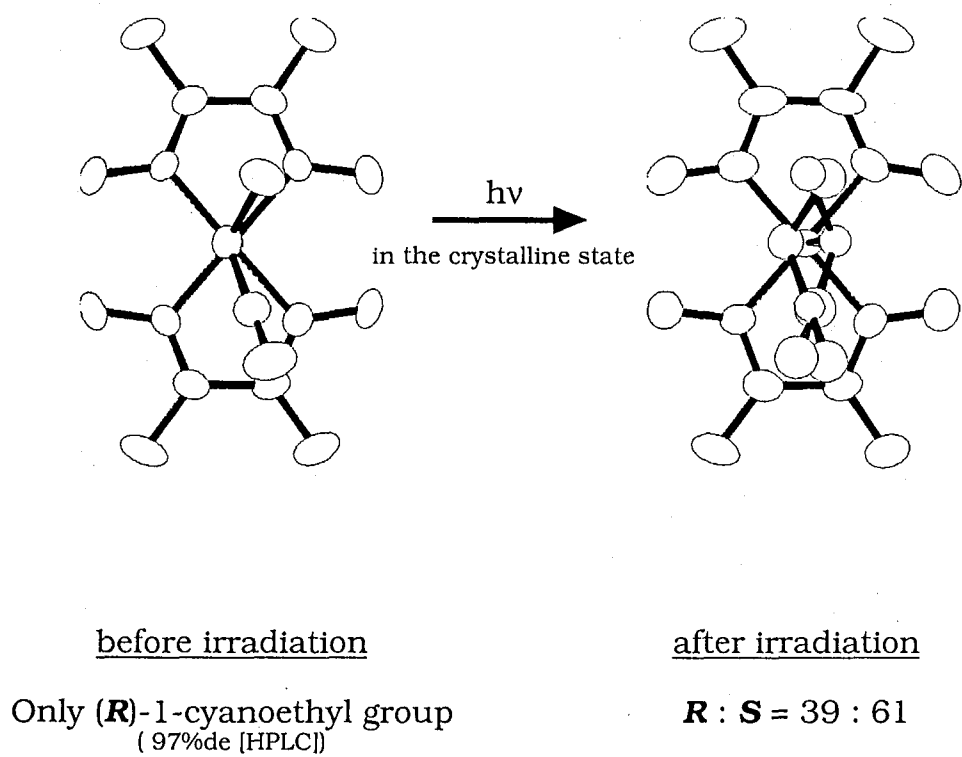


Figure 6-5 ORTEP drawing of the structure of 1-cyanoethyl group before (left) and after photoirradiation (right) in the crystalline state. The thermal ellipsoids are 50 % level.

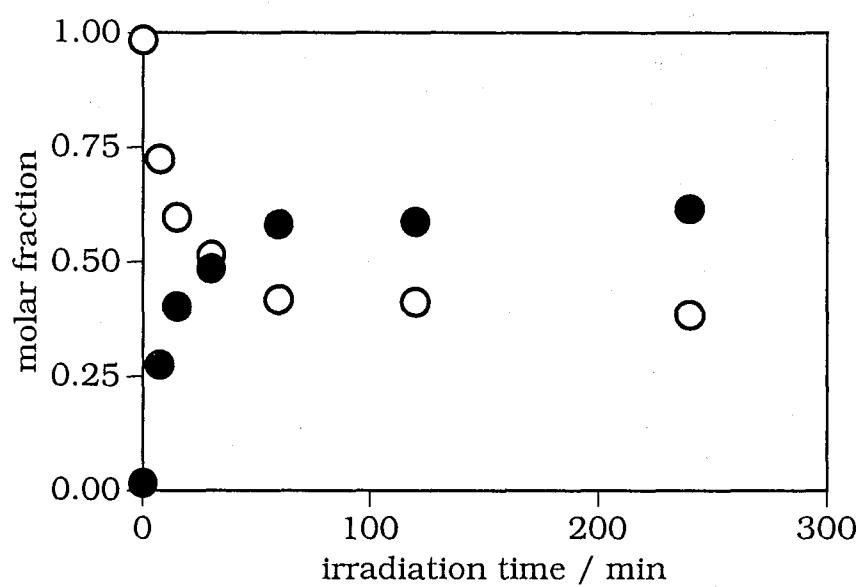


Figure 6-6 The change of the molar fraction of (*R*)- and (*S*)-1-cyanoethyl group in the (*R*)-*sec*-butylamine complexes in the solid-state epimerization.

open circle : (*R*)-1-cyanoethyl cobaloxime
 filled circle : (*S*)-1-cyanoethyl cobaloxime

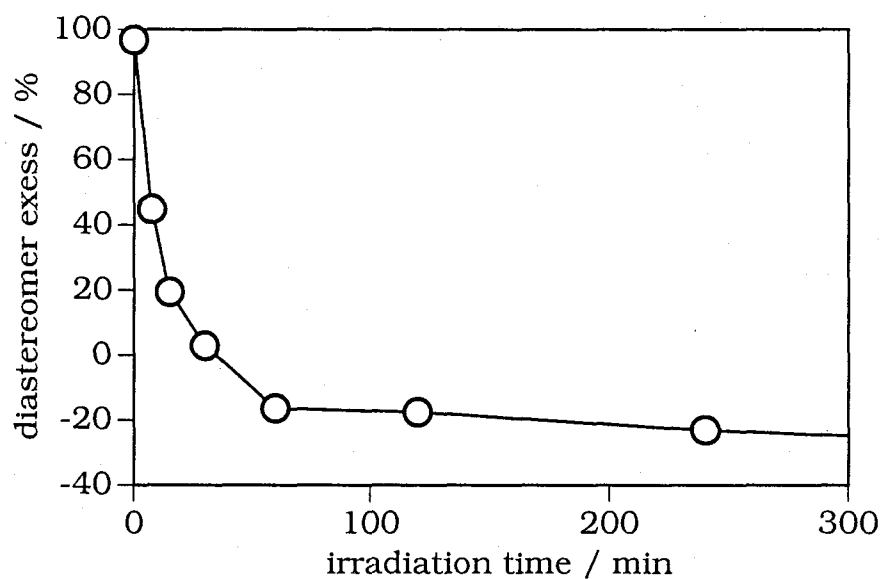


Figure 6-7 Diastereomer excess of [(*R*)-1-cyanoethyl][(*R*)-*sec*-butylamine] cobaloxime in the solid state epimerization. Diastereomer excess is defined as $(RR-SR)/(RR+SR)$, for convenience. Thus, positive and negative values of the diastereomer excess means *R*-isomer excess and *S*-isomer excess, respectively.

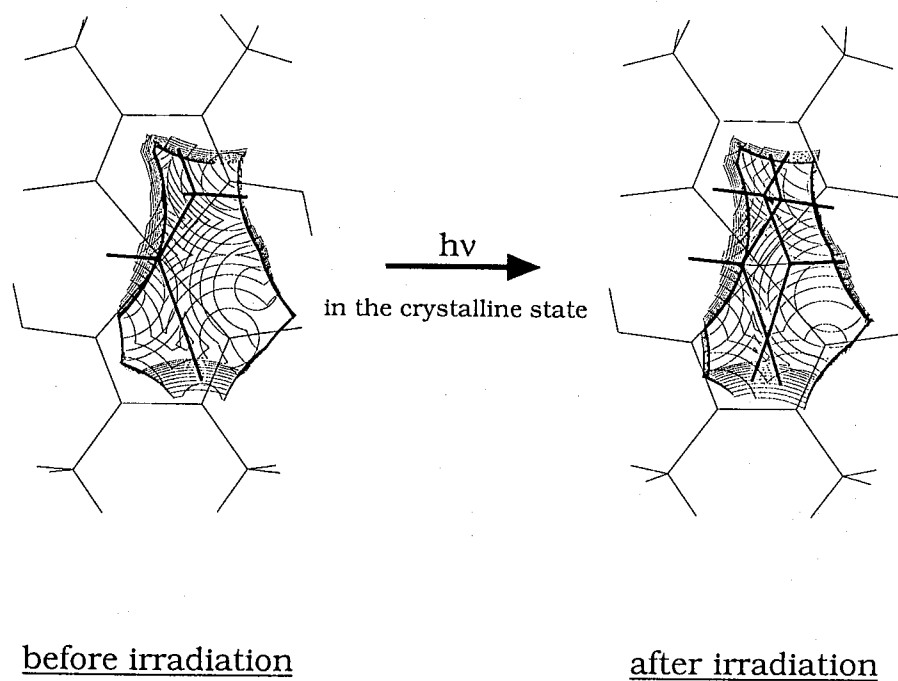


Figure 6-8 The cavity shape before and after photoirradiation

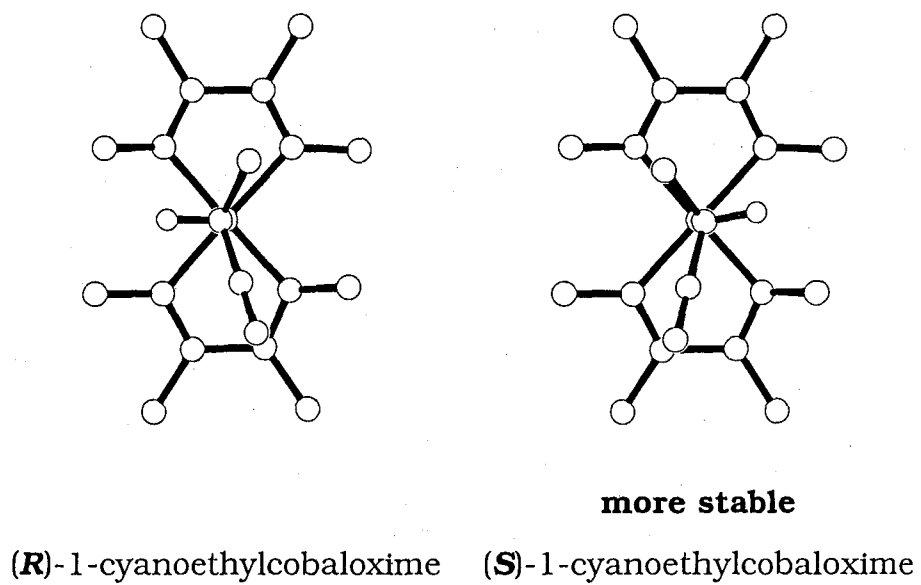
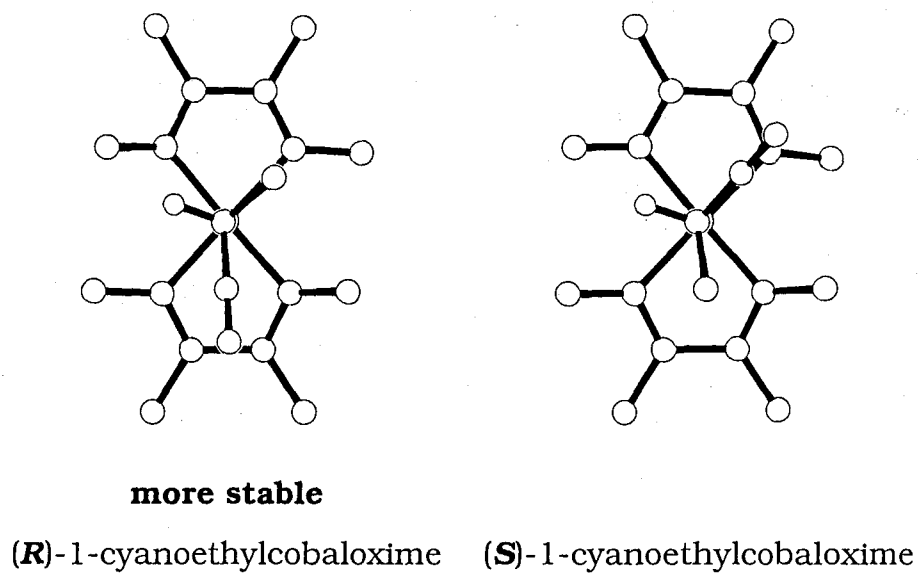


Figure 6-9 The calculated structure of 1-cyanoethyl group with lowest energy by packing energy calculation with fixed unit-cell dimension before (top) after irradiation (bottom).

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Chapter 7

Conclusion

The important role of the chiral crystal environment in controlling asymmetric reaction of cobaloxime complexes was investigated on the basis of the structures obtained by X-rays, the synthetic data on diastereomer excess and the calculations of packing energy.

Asymmetric Cavity Shape

The 2-cyanoethyl group bonded to the cobalt atom was isomerized to the 1-cyanoethyl group. The chirality of the produced 1-cyanoethyl group should depend on the chiral environment of the crystal structure. The reaction cavity for the 2-cyanoethyl group was divided into two parts by the average plane comprising the C-C-C-N atoms of the 2-cyanoethyl group and the volumes of the two parts were calculated. Since the CN group has a greater volume than the CH₃ group, it is favorable that the CN and CH₃ groups occupy the greater and smaller parts of the reaction cavity, respectively, after the conversion to the 1-cyanoethyl group. The reason why the (*R*)- or (*S*)-1-cyanoethyl group was produced in the different population is explained in terms of the asymmetric shape of the reaction cavity for the reactive group. This is clearly confirmed by the crystal structure after photoirradiation of (2-cyanoethyl)[(*R*)-*sec*-butylamine]cobaloxime.

Structure with the lowest packing energy

The packing energy calculation of (2-cyanoethyl)[(*R*)-*sec*-butylamine]cobaloxime complex crystal has been carried out by the molecular mechanics method. The lowest energy of the (*R*)-1-cyanoethyl group was higher than that of the (*S*)-1-cyanoethyl group, and that the conformation of the (*S*)-1-cyanoethyl group with the lowest energy was in good agreement with that of the observed structure of the (*S*)-1-cyanoethyl group after photoirradiation. This results strongly suggest that the asymmetric photoisomerization is caused by the chiral crystal environment.

The difference of the activation enthalpy

The temperature dependence of the asymmetric induction was examined in three different 2-cyanoethyl cobaloxime complexes. All the data on the diastereomer excess increased as the temperature decreased, although the degrees of the decrease were different. The difference of activation enthalpy was explained by a straight line in an Arrhenius plot, the gradient of which was calculated by the least-square method. The difference of the activation enthalpy represented the different degree of the diastereomer excess in the asymmetric induction of the 2-cyanoethyl cobaloxime complexes.

Control in the shape of the reaction cavity

Crystalline-state photoirradiation of the crystal of (*R*)-1-cyanoethyl cobaloxime coordinated with (*R*)-*sec*-butylamine as an axial base ligand revealed that most of the chiral 1-cyanoethyl group was inverted to the opposite configuration. This result is in good agreement with the diastereomer excess measured by HPLC analysis. This indicates that the produced (*S*)-1-cyanoethyl group is better fitted to the reaction cavity than the *R* group and the packing energy calculation suggests that the produced (*S*)-1-cyanoethyl group was more stable than the (*R*)-1-cyanoethyl group in the final crystal structure. The configuration of the product in the

stereoselective reaction was controlled by the shape of the reaction cavity.

In this thesis the author proposed an important role of the shape of the reaction cavity. This method will bring about the breakthrough not only in analysis of the mechanism in the asymmetric induction but also the catalytic reaction and the enzymatic reaction.