JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2000; **13:** 415–421

Optical enrichment in chiral crystal environment of [(*R*,*S*)-1-cyanoethyl][methyl (*S*)-alaninate]cobaloxime complex only by photoirradiation

Daisuke Hashizume[1] and Yuji Ohashi[2]*

[1]Department of Applied Physics and Chemistry, University of Electro-communications, Chofugaoka, Chofu, Tokyo 182-8585, Japan
[2]Department of Chemistry and Materials Science, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo 152-8551, Japan

Received 10 February 2000; revised 7 April 2000; accepted 10 April 2000

ABSTRACT: The diastereomeric pair of the [(*R*,*S*)-1-cyanoethyl][methyl (*S*)-alaninate]cobaloxime complex cannot be separated by the fractional crystallization method. Crystal structure analysis revealed that there are two crystallographically independent molecules which are diastereomers to each other in a unit cell. When the crystal was irradiated with a xenon lamp, the cell dimensions gradually changed. After about 70 h of exposure, the change became insignificantly small. Crystal structure analysis after irradiation indicated that only the (*R*)-1-cyanoethyl complex was epimerized and the (*S*)-1-cyanoethyl complex remained unaltered. This led to an increased amount of the (*S*)-1-cyanoethyl complex in the crystal. The optical enrichment occurred only by photoirradiation. The diastereomeric excess of the (*S*)-1-cyanoethyl complex became 32% in the final stage. The reason why only the (*R*)-1-cyanoethyl complex was epimerized was clearly explained by the size and shape of the reaction cavity for the 1-cyanoethyl group. Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: Cobaloxime complex crystal; optical enrichment; photoirradiation

INTRODUCTION

There are two approaches to obtaining chiral substances utilizing a chiral crystal environment. One is to produce the chiral compounds from prochiral compounds and the other is to obtain the chiral compounds from racemic compounds. The former method is well known as absolute asymmetric synthesis since the asymmetry is introduced from the physical conditions such as chiral crystal environment. Several examples have been reported.[1–8] On the other hand, there has been no report on the latter method until we found that racemic crystals of the (1-cyanoethyl)(piperidine)cobaloxime complex showed optical rotation on exposure to visible light.[9] Recently, racemic crystals of the (1-cyanoethyl) (pyrrolidine)cobaloxime complex were also found to show similar optical enrichment on exposure to visible light.[10] Such phenomena can be observed only in the solid state.

Fortunately, the above racemic-to-chiral transformation occurred with retention of the single crystal form. The crystal structures before and after the racemic-to-chiral transformation were analyzed using only one crystal. The racemic crystals of the piperidine and pyrrolidine complexes before irradiation have chiral space groups, $P2_12_12_1$ and $P1$, and have two and four crystallographically independent molecules in their asymmetric units, respectively. The ratio of *R*- and *S*-enantiomers is 1:1 in each crystal. This means that the crystal is racemic in spite of the chiral space group. Several examples of chiral crystals with racemic compositions have been reported.[11] There is no pseudo-symmetry between the two enantiomers in each crystal. If the *R*- and *S*-enantiomers, in general, crystallize together in a unit cell, they tend to make a pair and an inversion center will appear. This may be the reason why the racemic crystal has a center of symmetry in the process of crystallization.

Recently, a cobaloxime complex with a racemic 1-cyanoethyl group and methyl (*S*)-alaninate as axial ligands was prepared. In order to resolve the diastereomeric pair, fractional crystallization was performed several times. However, the optical rotation of the complex did not increase after numerous crystallizations. One of the crystals suitable for x-ray work was picked up and the structure was examined by x-ray analysis. To our surprise, there are two crystallographically independent molecules, which are a pair of diastereomers, in a chiral unit cell. This explains well why the fractional resolution of the diastereomeric pair was impossible in the usual way.

Moreover, the cell dimensions gradually changed

**Correspondence to:* Y. Ohashi, Department of Chemistry and Materials Science, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo 152-8551, Japan.
E-mail: yohashi@cms.titech.ac.jp
Contract/grant sponsor: JST.

when the crystal was exposed to a xenon lamp. The optical rotation of the chloroform solution in which the irradiated crystal was dissolved increased significantly. This indicates that optical enrichment was also observed.

This paper reports the crystal structures of the [(*R*,*S*)-1-cyanoethyl][methyl (*S*)-alaninate]cobaloxime complex before and after photoirradiation and discusses the optical enrichment process.

EXPERIMENTAL

Synthesis of [(R,S)-1-cyanoethyl][methyl (S)-alaninate]-cobaloxime. The complex was prepared as reported previously with some modifications.[12]

[(R,S)-1-Cyanoethyl](aniline)cobaloxime. Cobalt acetate tetrahydrate (12.45 g, 50 mmol) and dimethylglyoxime (11.61 g, 100 mmol) were added to aqueous methanol (150 cm^3) (methanol 140 cm^3 + water 10 cm^3) under a nitrogen atmosphere with stirring. After stirring for 10 min, acrylonitrile (5 cm^3, 76 mmol) and aniline (4.6 cm^3, 50 mmol) were added. The reaction vessel was then connected to a hydrogen-filed gas buret and purged with hydrogen. The reaction mixture was stirred under a hydrogen atmosphere. After the absorption of hydrogen was terminated, an aqueous solution of sodium hydroxide (200 cm^3) which contained 4.0 g (100 mmol) of sodium hydroxide was added. After 1 h, crude crystals were deposited and collected by filtration. The product was recrystallized from an aqueous methanol solution.

[(R,S)-1-Cyanoethyl][methyl (S)-alaninate]cobaloxime. (1-Cyanoethyl)(aniline)cobaloxime (4.36 g, 10 mmol) was dissolved in 150 cm^3 of 80% (v/v) a aqueous methanol and stirred overnight with 25 g of the cation-exchange resin Dowex 50W-X8. The resin was filtered and the filtrate was kept for use in the next manipulation.

Methyl (*S*)-alaninate hydrochloride (1.67 g, 12 mmol) was dissolved in a small portion of methanol and then triethylamine (1.66 cm^3, 12 mmol) was added. Immediately after the addition of triethylamine, a white precipitate of triethylammonium chloride was deposited. The precipitate was washed with 50 cm^3 of diethyl ether five times to extract liberated methyl (*S*)-alaninate. The ether solutions were concentrated *in vacuo*. Further experiments were carried out in the dark and using brownish flasks to avoid photoreaction of the cobaloxime complex.

To the concentrated ether solution was added the filtrate which was prepared by the manipulation described above. After stirring for 1 h, the reaction mixture was concentrated to give a crude product. The product was recrystallized from aqueous methanol solution.

Photochemical reaction. A single crystal was mounted on a four-circle diffractometer. The crystal was irradiated with an Xe lamp (San-ei Super Bright 150). The light was led from the lamp to a distance of 60 mm from the crystal by using a glass-fiber tube. The reaction was followed by the change of cell dimensions.

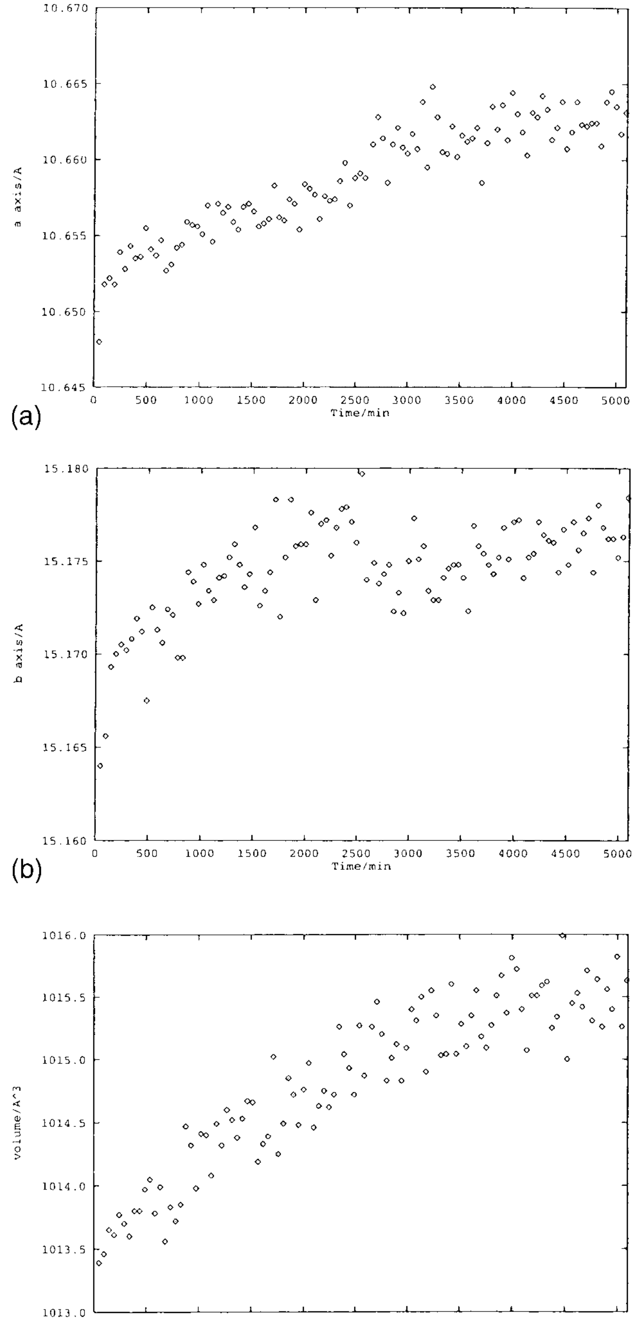

Figure 1. Changes of the cell dimensions; (a) a and (b) *b* axes and (c) unit-cell volume

The change of cell dimensions is plotted in Fig. 1. Significant changes were observed for the *a* and *b* axes. Although the change became insignificantly small after exposure for 4000 min, an additional 7000 min of photoirradiation was performed to ensure the change was complete.

Table 1. Crystal data and experimental details

	Before	After
Formula	$C_{15}H_{27}N_6O_6Co$	
Formula weight	446.36	
Crystal system	Triclinic	
Space group	$P1$	
a (Å)	10.6419(7)	10.662(2)
b (Å)	15.139(1)	15.169(3)
c (Å)	6.7554(7)	6.751(2)
α (°)	103.112(7)	103.20(2)
β (°)	107.068(8)	107.17(2)
γ (°)	84.315(6)	84.19(2)
V (Å^3)	1012.7(2)	1015.0(4)
Z	2	
D_X (mg m^{-3})	1.464	1.461
Radiation	MoKα	
λ (Å)	0.71069	0.71073
μ(mm^{-1})	0.891	0.889
T (K)	296	
Crystal description	Rectangular	
Crystal dimensions (mm)	0.20 × 0.25 × 0.45	
F(000)	468	
$2\theta_{max}$ (°)	55	
Index ranges	$-13 \leq h \leq 13$ $-19 \leq k \leq 19$ $-8 \leq l \leq 0$	
Measured reflections	4658	4665
Independent reflections	4658	4665
Parameters	522	525
Observed reflections ($I > 2\sigma(I)$)	3937	3805
R (F)	0.048	0.053
$wR(F^2)$	0.123	0.135
S	1.05	1.07
$(\Delta/\sigma)_{max}$	0.00	0.00
$\Delta\rho_{min}$, $\Delta\rho_{max}$ (e Å^{-3})	−0.43, 1.10	−0.70, 1.12

Crystal structure analysis. The crystal data and experimental details are summarized in Table 1. The Lorentz and polarization, absorption and decay corrections were applied. The structure before photoirradiation was solved by the direct method with the program SAPI 91.[13] The structure before photoirradiation was used as an initial model for that after photoirradiation. The structures before and after irradiation were refined by the full-matrix least-squares method with the program SHELXL-97.[14] The weighting schemes were $w = [\sigma\ (F_o{}^2)^2 + (0.0747P)^2 + 0.4818P]^{-1}$ and $[\sigma(F_o{}^2)^2 + (0.0786P)^2 + 0.6576P]^{-1}$, where $P = (F_o{}^2 + 2F_o{}^2)/3$, for the crystals before and after irradiation, respectively. The disordered 1-cyanoethyl groups after irradiation were refined as rigid bodies and the temperature factors of the atoms were constrained to have the same value as the corresponding atoms. Positions of several hydrogen atoms were located on the difference maps and others were calculated geometrically. The anisotropic temperature factors were used for non-hydrogen atoms in the final refinement. The coordinates of the hydrogen atoms were refined as riding models except those of the hydroxyl groups, which were fixed. The isotropic temperature factors of the hydrogen atoms were set to be 1.5 times greater than the equivalent isotropic temperature factors of the parent atoms. Atomic scattering factors were taken from the International Tables for Crystallography.[15] The absolute structures were determined as the configuration of the asymmetric carbon atom of the alaninate moiety to be *S*. This is in good agreement with the results from the Flack parameters,[16] which were −0.01(2) and 0.01(2) before and after irradiation, respectively.

All positional, geometric and thermal parameters and the observed and calculated structure factors have been deposited at the Cambridge Crystallographic Data Centre (CCDC Identity Number 141751–141752).

RESULTS AND DISCUSSION

Figure 2 shows the crystal structure before irradiation viewed along the *c* axis. There are two crystallographically independent molecules, A and B, which are diastereomers to each other, in a unit cell and there are no pseudo-symmetries between them. The molecules are arranged head-to-tail along the *a* axis. Layers of molecules A and B are stacked alternately along the *b* axis. The cyano group of the 1-cyanoethyl group of B is

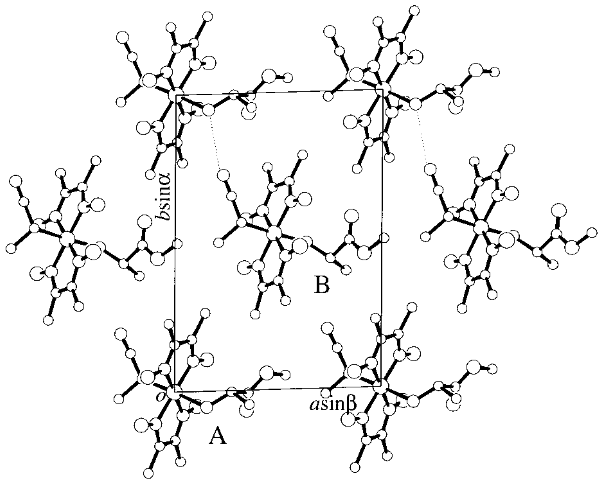

Figure 2. Crystal structure before irradiation viewed along the *c* axis. Broken lines indicate the hydrogen bonds

hydrogen bonded to the amino group of alaninate through N(5B)···H(2AN)—N(6A) and the hydrogen bond distances and angles are listed in Table 2.

On the other hand, the cyano group of the 1-cyanoethyl group of A has no hydrogen bond with the neighboring atoms. The methyne hydrogen atoms of A and B contact the oxygen atoms of dimethylglyoxime moieties. The corresponding distances of H(9A)···O(3A)^{i} and H(9B)···O(4B)^{ii} are 2.32 and 2.31 Å, respectively [symmetry codes: (i) *x*, *y*, *z*−1 and (ii) *x*, *y*, *z* + 1].

Figure 3(a) and (b) show the molecular structures of A and B, respectively, before irradiation. The configurations of the 1-cyanoethyl groups are *S* and *R* for A and B, respectively. The ester moieties of the two molecules are planar and take *syn* conformations. Selected bond distances and angles are listed in Table 2. These values are not significantly different from the corresponding ones in the related molecules.

The crystal structure after photoirradiation is shown in Fig. 4. Only the 1-cyanoethyl group of B was changed

Table 2. Selected bond distances (Å) and angles (°)

	Before irradiation		After irradiation	
Bond	A	B	A	B
Co—N(1)	1.893(5)	1.901(5)	1.879(6)	1.893(6)
Co—N(2)	1.886(5)	1.881(6)	1.898(6)	1.887(7)
Co—N(3)	1.888(5)	1.884(5)	1.890(6)	1.872(7)
Co—N(4)	1.879(5)	1.882(5)	1.872(6)	1.874(6)
Co—N(6)	2.090(5)	2.070(6)	2.085(6)	2.069(6)
Co—C(9)	2.059(6)	2.048(6)	2.052(8)	2.050(5)^{a} 2.050(5)^{b}
C(9)—C(10)	1.512(10)	1.518(10)	1.522(13)	1.53^{a} 1.53^{b}
C(9)—C(11)	1.460(11)	1.440(11)	1.457(13)	1.46^{a} 1.46^{b}
C(11)—N(5)	1.146(11)	1.142(11)	1.145(15)	1.15^{a} 1.15^{b}
C(14)—O(5)	1.182(9)	1.198(9)	1.186(10)	1.203(11)
C(14)—O(6)	1.331(9)	1.316(9)	1.332(10)	1.315(11)
Co—C(9)—C(10)	116.9(5)	116.4(5)	117.3(6)	119.6(9)^{a} 117(2)^{b}
Co—C(9)—C(11)	111.8(5)	112.7(5)	113.1(6)	112.2(5)^{a} 109.1(11)^{b}
Co—N(6)—C(12)	122.7(4)	123.2(4)	123.5(5)	123.1(5)
C(9)—Co—N(1)	93.9(3)	88.0(3)	93.9(3)	86.6(4)^{a} 89.8(10)^{b}
N(6)—Co—N(1)	84.6(2)	95.2(2)	84.4(3)	95.2(3)
C(9)—Co—N(6)	177.8(3)	176.4(3)	177.8(3)	177.2(3)^{a} 174.6(9)^{b}
C(10)—C(9)—C(11)	109.3(6)	111.6(7)	109.7(8)	109.5^{a} 109.5^{b}
C(9)—C(11)—N(5)	177.7(9)	179.4(9)	177.7(13)	180^{a} 180^{b}
N(6A)···N(5B)	3.350(11)	—		
N(6A)···N(5R)	—	3.373(12)		
N(5B)···H(2AN)	2.51	—		
N(5R)···H(2AN)	—	2.55		
N(5B)···H(2AN)—N(6A)	155	—		
N(5R)···H(2AN)—N(6A)	—	153		

[a,b] The disordered 1-cyanoethyl groups take *R* and *S* configurations, respectively.

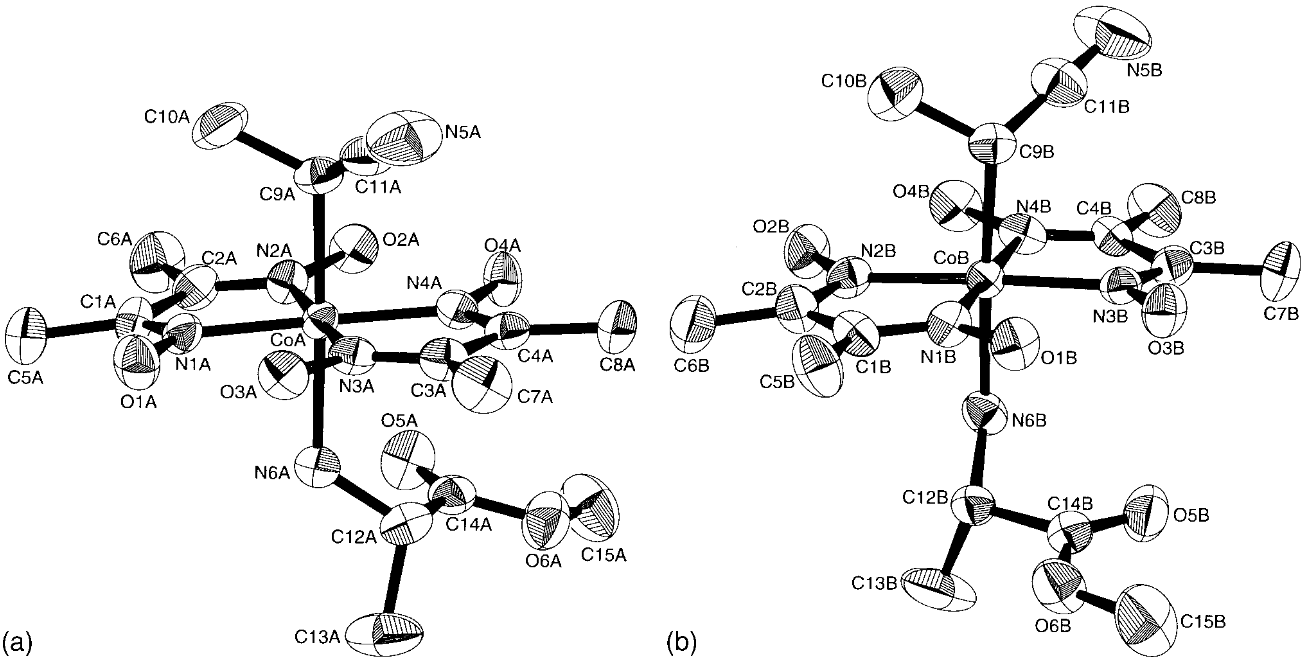

Figure 3. Molecular structures of (a) A and (b) B before irradiation

and the other moieties take nearly the same structures as before irradiation. It must be emphasized that the nitrogen of the inverted 1-cyanoethyl group of B, N(5*S*), has no hydrogen bond with the neighboring atoms, although the original N(5*R*) forms a hydrogen bond through N(5*R*)···H(2AN)—N(6A). This suggests that the entropy term is the driving force in this epimerization.[17]

The molecular structure of B in the crystal after photoirradiation is shown in Fig. 5. Only the 1-cyanoethyl group was changed after irradiation. The inverted 1-cyanoethyl group takes a different conformation from those observed in the related crystals; the cyano and methyl groups are replaced, whereas the methyl group and the hydrogen atom are replaced in the related crystals. Such an inversion has been found only in a crystal of (1-cyanoethyl)(3-hydroxypyridine)cobaloxime.[18] The occupancy factors for the disordered (*R*)- and (*S*)-1-cyanoethyl groups were 0.68(1) and 0.32(1), respectively. This means that the ratio of *R*- and *S*-enantiomers changed from 1:1 to 0.34 to 0.66 in a whole crystal. Thus the diastereomeric excess of the (*S*)-1-cyanoethyl complex became 32%.

In order to elucidate the reason why only B was epimerized, the cavities[19] around 1-cyanoethyl groups of

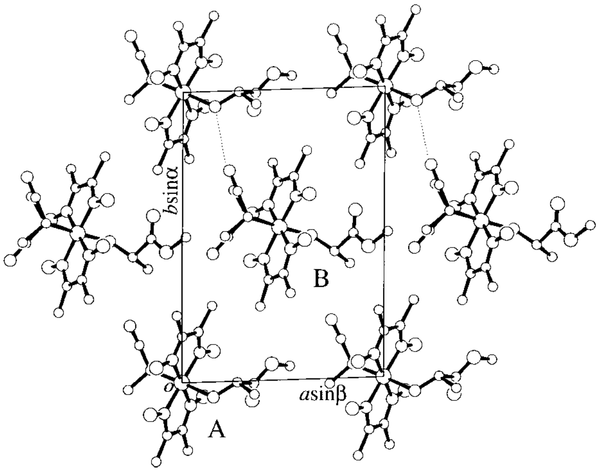

Figure 4. Crystal structure after irradiation viewed along the *c* axis. Broken lines indicate the hydrogen bonds

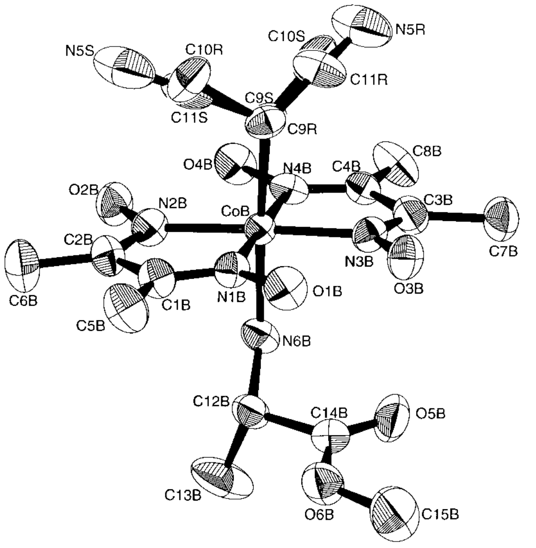

Figure 5. Molecular structure of B after irradiation

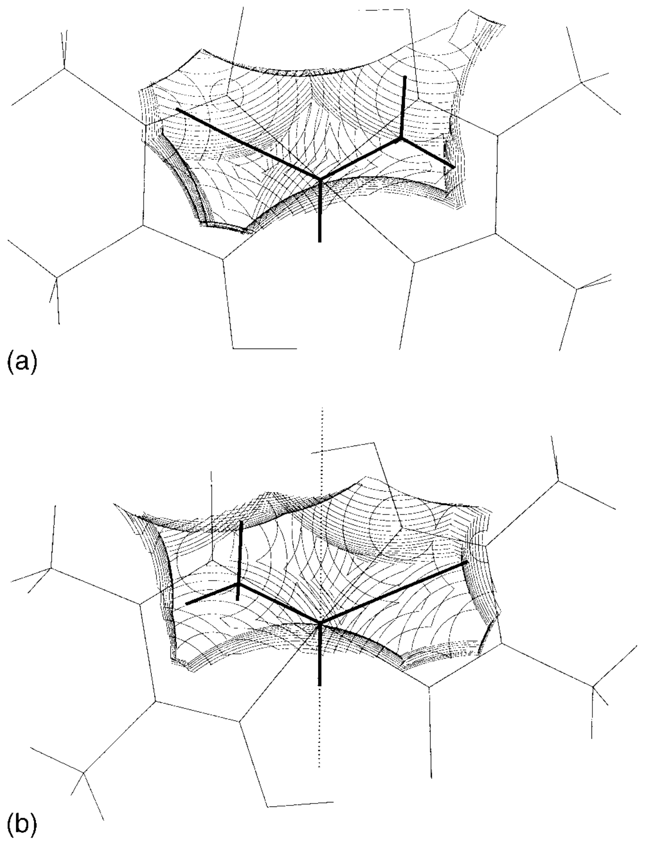

Figure 6. Cavities for the 1-cyanoethyl groups of (a) A and (b) B before irradiation. Broken line indicates the plane including the Co—C—H bond

A and B before irradiation were calculated and are shown in Fig. 6(a) and (b), respectively. The volumes of A and B are 11.5 and 13.1 Å^3, respectively. The volume of the A cavity is too small for the inversion of the 1-cyanoethyl group, while the B cavity is large enough for inversion.[20] The difference in cavity size explains well the different reactivities of the 1-cyanoethyl groups of A and B.

The B cavity has a void space along the C—C(methyl) bond, which can accommodate the inverted cyano group. On the other hand, there is no void space around the methyne hydrogen atom, H(9B). It seems impossible to accommodate the inverted methyl group in this area. Therefore, it is impossible to replace the methyl group and the hydrogen atom in the process of inversion. A similar cavity shape was observed in the crystal of (1-cyanoethyl)(3-hydroxypyridine)cobaloxime complex and the same conformation of the inverted group was observed.[18] Figure 7 indicates that the inverted 1-cyanoethyl group is well accommodated in the cavity.

After the prolonged irradiation for 7000 min, the ratio of (*R*)- and (*S*)-1-cyanoethyl groups of B became 68:32 instead of 50:50. To explain the reason, the B cavities before and after irradiation were divided into two parts by the plane composed of Co—C—H bonds and the volumes of two parts were calculated. The ratio of the two parts was 70:61 and 79:62 before and after irradiation, respectively. This indicates that the (*R*)-1-cyanoethyl group is favorable even after part of the *R*-isomer had been inverted to *S*, since the ratio of the *R*-part increased from 70 to 79. This is in contrast to the results for piperidine and pyrrolidine complex crystals,[3] in which the ratio became almost 1:1 after irradiation. Moreover, the inverted (*S*)-1-cyanoethyl group has no hydrogen bond with the neighboring amino group. This may suggest that the entropy term may compensate the increase in enthalpy. It remains uncertain why the final ratio became not 50:50 but 68:32. Further studies are in progress.

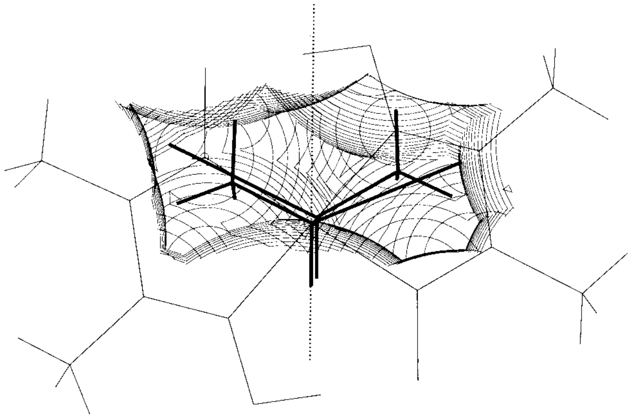

Figure 7. Cavity for the 1-cyanoethyl group of B after irradiation. Broken line indicates the plane including the Co—C—H bond

Acknowledgement

This work was supported by a CREST grant from JST.

REFERENCES

1. Addadi L, van Mil J, Lahav M. *J. Am. Chem. Soc.* 1982; **104**: 3422–3429.
2. Sekine A, Hori K, Ohashi Y, Yagi M, Toda F. *J. Am. Chem. Soc.* 1989; **111**: 697–699.
3. Suzuki T, Fukushima T, Yamashita Y, Miyashi T. *J. Am. Chem. Soc.* 1994; **116**: 2793–2803.
4. Saigo K, Sukegawa M, Maekawa Y, Hasegawa M. *Bull. Chem. Soc. Jpn.* 1995; **68**: 2355–2362.
5. Hashizume D, Kogo H, Sekine A, Ohashi Y, Miyamoto H, Toda F. *J. Chem. Soc., Perkin Trans. 2* 1996; 61–66.
6. Gamlin JN, Jones R, Leibovitch M, Patrick B, Scheffer JR, Trotter J. *Acc. Chem. Res.*, 1996; **29**: 203–209.
7. Sekine A, Tatsuki H, Ohashi Y. *J. Organomet. Chem.*, 1997; **536–537**: 389–398.
8. Sekine A, Yoshiike M, Ohashi Y, Ishida K, Arai Y, Ohgo Y. *Mol. Cryst. Liq. Cryst.* 1998; **313**: 321–326.
9. Osano YT, Uchida A, Ohashi Y. *Nature (London)* 1991; **352**: 510–512.
10. Nemoto T, Ohashi Y. *Bull. Chem. Soc. Jpn.* 1999; **72**: 1971–1983.
11. Brock C, Schweizer W, Dunitz J. *J. Am. Chem. Soc.* 1991; **113**: 9811–9820.

12. Ohgo Y, Takeuchi S, Natori Y, Yoshimura J, Ohashi Y, Sasada Y. *Bull. Chem. Soc. Jpn.* 1981; **54**: 3095–3099.
13. Fan H-F. SAPI 91, Structure Analysis Programs. Chinese Academy of Sciences: Beijing, 1991.
14. Sheldrick GM. *SHELXL-97. Program for the Refinement of Crystal Structures*. University of Göttingen, Göttingen, 1997.
15. *International Tables for Crystallography*, vol. C. Wilson AJC (ed). Kluwer: Dordrecht, 1992.
16. Flack HD. *Acta Crystallogr., Sect. A* 1983; **39**: 876–881.
17. Takenaka Y, Kojima Y, Ohashi Y. *Acta Crystallogr., Sect. B* 1993; **49**: 852–859.
18. Ohgo Y, Ohashi Y. *Bull. Chem. Soc. Jpn.* 1996; **69**: 2425–2433.
19. Ohashi Y, Yanagi K, Kurihara T, Sasada Y, Ohgo Y. *J. Am. Chem. Soc.* 1981; **103**: 5805–5812.
20. Takenaka Y, Ohashi Y, Tamura T, Uchida A, Sasada Y, Ohgo Y, Baba S. *Acta Crystallogr., Sect. B* 1993; **49**: 272–277.