Dynamical Structure Analysis of Crystalline-State Racemization

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Since Cohen and Schmidt proposed the topochemical principle based on the solid-state photodimerization of cinnamic acid and its derivatives,[1] many solid-state reactions have been studied.[2] However, the detailed mechanism by which the reactions proceed within crystals is not completely understood. This is probably due to the fact that the initiation of the reaction often occurs at defect or surface sites in the crystal and that the crystal lattice is destroyed as the reaction proceeds. A single crystal-to-single crystal transformation in the solid state, on the other hand, is a very attractive system, since the reaction proceeds with retention of the single-crystal form and the movement of each atom can be presumed from the structures before and after the reaction. Noteworthy examples reported include the [2 + 2] photocycloaddition polymerization of 2,5-distyrylpyradine,[3] the photopolymerization of diacetylene derivatives,[4] the [2 + 2] photodimerization of 5-benzylidenecyclopentanone derivatives.[5] the photoaddition of p-fluoroacetophenone to deoxycholic acid,[6] and the thermal dimerization of (o-benzenedithiol)cobalt complex.[7] Although comparison of reactant and product structures in the single crystal-to-single crystal reaction is very informative in interpreting the reaction mechanism, the reaction does not always obey first-order kinetics. The structures at several intermediate stages are essential for elucidating the detailed reaction pathways. Moreover, a systematic analysis of related crystals is necessary to obtain a quantitative mechanism.

During several structure analyses of cobaloxime complexes aimed at interpreting their catalytic capability for asymmetric hydrogenation,[8] we have found that the chiral cyanoethyl (cn) group in a cobaloxime complex crystal is racemized by X-ray exposure without degradation of crystallinity (Figure 1).[9] The rate of racemization was so slow that several intermediate structures could be obtained by X-ray analyses. Moreover, we have observed various reaction pathways and obtained a quantitative relationship between the macroscopic reaction rate and the microscopic atomic arrangement in the crystal from intermediate structure analyses of a series of related crystals. Such a stepwise X-ray structure analysis is a very effective method in elucidating the reaction mechanism. We call the analysis "dynamical structure analysis", and the reaction that enables the dynamical structure analysis is termed the "crystalline-state reaction". In this Account the crystalline-state racemization of cobaloxime com-

plex crystals by the dynamical structure analysis method is discussed.[10]

Direct Observation of the Crystalline-State Racemization

The crystal with the structure shown in Figure 1 underwent a change in unit cell dimensions without degradation of crystallinity when it was exposed to X-rays. The space group, $P2_1$, remained unaltered.[11] If the irradiation was interrupted, the change in cell dimensions became undetectable. When irradiation was resumed, the change in cell dimensions continued as before. Figure 2 shows the changes in the cell dimensions, a, b, c, β, and V, with exposure time to the Mo $K\alpha$ radiation. The a and c values decrease slightly whereas b and β increase to a considerable extent. The unit cell volume, V, significantly increases. The variation curves are well represented by first-order kinetics. The rate constants for the variation of a, b, c, β, and V were obtained by least-squares fitting assuming first-order kinetics. The average value is 3.06×10^{-6} s^{-1}.

In order to follow the structural change, three-dimensional intensity data were collected at the A to G stages indicated in Figure 2. The structure analyses of

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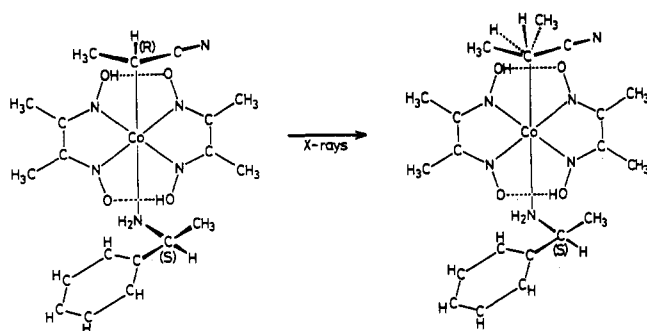(8) (a) Ohashi, Y.; Sasada, Y.; Tashiro, Y.; Takeuchi, S.; Ohgo, Y.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2589–2590. (b) Ohashi, Y.; Sasada, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1710–1715. (c) Ohashi, Y.; Sasada, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2863–2869. (d) Ohashi, Y.; Sasada, Y.; Takeuchi, S.; Ohgo, Y. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 627–634. (e) Ohashi, Y.; Sasada, Y.; Takeuchi, S.; Ohgo, Y. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1501–1509.
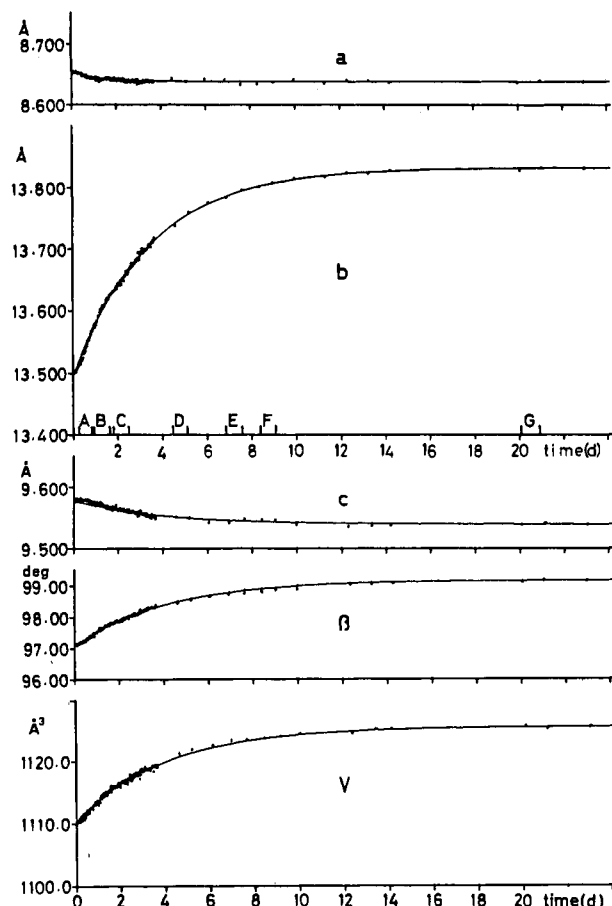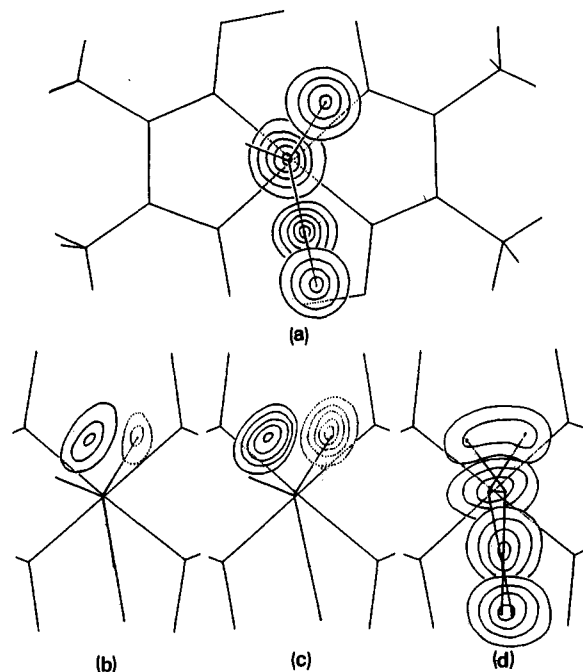(9) Ohashi, Y.; Sasada, Y. *Nature (London)* **1977**, *267*, 142–144.
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Figure 1. Racemization of the cn group in a crystal of [(R)-1-cyanoethyl][(S)-α-methylbenzylamine]bis(dimethylglyoximato)cobalt(III).

Figure 2. Change in the cell dimensions in the racemization. At early stages the dimensions were measured every 30 min. First-order kinetic curves were obtained by least-squares fitting.

Figure 3. (a) Composite electron density map of the cn group viewed along the normal to the cobaloxime plane at the initial A stage. The contour interval is 1.0 e Å^{-3}. (b,c) Composite difference electron density maps at the B and F stages, respectively. The solid and dotted curves indicate positive and negative densities, respectively. The contour interval is 0.2 e Å^{-3}. (d) Composite electron density map at the final stage G. the contour interval is the same as that of (a).

the seven stages revealed that significant changes were observed only in the vicinity of the cn group. Figure 3a shows the composite electron density map of the cn group viewed along the normal to the cobaloxime plane at stage A. The peaks of the cn substituents, especially the methyl group, were lowered and expanded at stage B. Figure 3b shows a composite difference electron density map at stage B. This figure corresponds to the difference between the two electron density maps at the A and B stages. A trough appears at the position of the methyl group and a peak appears in the neighborhood of the methyl group. Figure 3c is the corresponding composite difference electron density map at stage F. The new peak grows higher, and the trough becomes deeper. The composite electron density map at the final stage G is shown in Figure 3d. The height of the

new peak is the same as that of the original methyl carbon atom. The position of the new peak corresponds to that expected for a methyl substituent in a cn group of inverted configuration. We can see the racemization process as a gradual change of the electron density of the reactive group.

In this racemization, one or more of the four bonds around the chiral carbon atom, Co–C, NC–C, H$_3$C–C, and H–C, must be cleaved by X-rays in the transition state. ESR spectra obtained after the crystal was exposed to X-rays revealed that the Co–C bond was cleaved homolytically to produce the cn radical and the Co(II) complex.[12] The Co–C bond dissociation energy for these cobaloxime complexes has been determined to be 117–122 kJ mol^{-1}.[13] The racemization rate of the complex by X-rays is far lower than that by visible light not only in the solid state but also in an aqueous methanol solution.[21] These facts may indicate that the secondary radiation produced by the interaction with the Co atom may be responsible for the cleavage of the bond.

Reaction Cavity

In order to examine whether such crystalline-state racemization is also observed in other crystal environments, a series of cobaloxime complex crystals with different axial ligands were prepared (Figure 4). The structure analyses of these crystals revealed that crystals of 1–7 have only one molecule per asymmetric unit. The space groups of the crystals are $P2_1$ or $P2_12_12_1$. Each cn group in the crystals is mostly surrounded by

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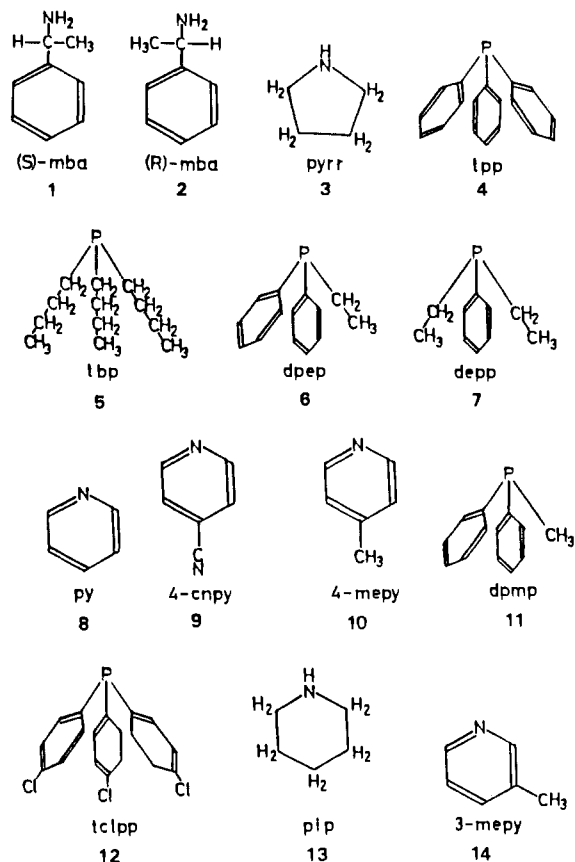(13) Ohgo, Y.; Orisaku, K.; Hasegawa, E.; Takeuchi, S. *Chem. Lett.* 1986, 27–30.

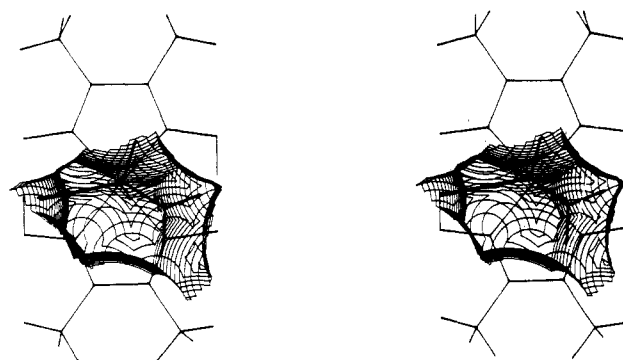Figure 4. Crystals 1–14 with various axial base ligands.

Figure 5. Stereoscopic drawing of the cavity for the cn group of crystal 1. The contours are drawn in sections separated by 0.1 Å.

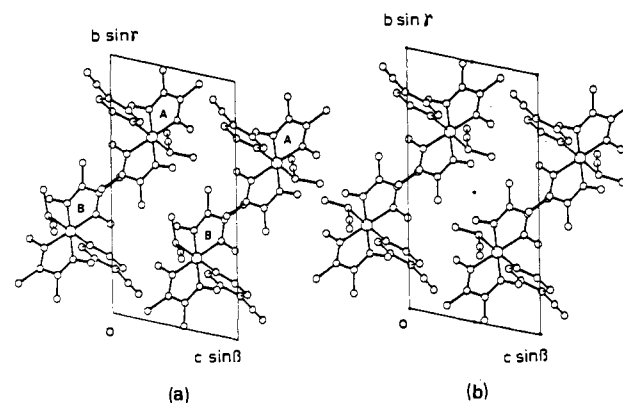Figure 6. Crystal structure of 9 viewed along the *a* axis at the initial stage (a) and the final stage (b).

Table I
Density, Rate Constant, and Cavity Volume of Crystals 1–7 at 293 K

crystal	density, g cm^{-3}	rate const, ×10^{-6} s^{-1}	cavity vol, Å^3
1	1.388	3.06	14.53
2	1.391	2.10	12.23
3	1.422	1.69	11.55
4	1.431		11.31
5	1.255		10.64
6	1.405		10.18
7	1.381		8.40

moieties other than the cn groups of neighboring molecules, and each is isolated from the other cn groups. Table I lists the reactivity of these crystals (mode I crystals). Crystalline-state racemization was observed for the crystals of 1, 2,[14] and 3,[15] although the reaction rates were different from each other. The other four, 4,[16] 5,[16] 6,[17] and 7,[17] were inactive at room temperature. Such differences in reactivity are likely to be due to differences in the packing of molecules in the crystals. However, there appears to be no correlation between the reactivity and the density of the crystal. In spite of having the lowest density, crystals of 5 were not racemized by X-rays at room temperature. These facts suggest that the packing around the reactive cn group, and not the packing of the whole molecule, plays an important role in determining the reactivity.

In order to represent the degree of packing around the reactive group, we have defined the reaction cavity

as the space limited by a concave surface of the spheres of the surrounding atoms around the reactive group in the crystal. The radius of each sphere is taken to be 1.2 Å greater than the van der Waals radius[18] of the corresponding atom. The value of 1.2 Å is taken from the van der Waals radius of the hydrogen atom, which often occupies the surface of the reactive group. Any point in the cavity is considered to be accessed by the centers of the atoms of the reactive group.[19] Figure 5 shows the reaction cavity for the cn group in 1. Similar cavities were obtained for the other crystals in Table I. The volume of each cavity was calculated and is given in the fourth column of Table I. The larger the volume, the greater is the reaction rate. The volume necessary for the racemization appears to be greater than 11.5 Å^3. These facts suggest that the cavity size for the reactive group should be a good criterion for this racemization.

Cooperative Racemization of Two Reactive Groups

Each of the cobaloxime complex crystals 8, 9, and 10 contains two molecules per asymmetric unit. Figure 6

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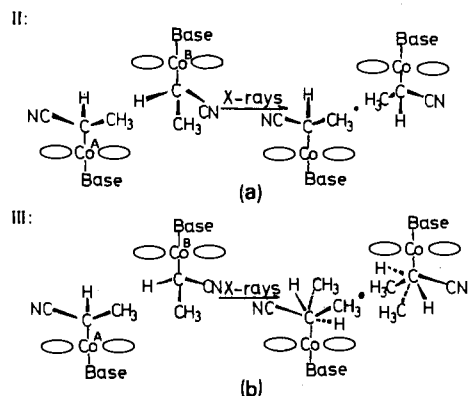
Figure 7. Schematic drawing of the racemization process in the crystals of **9** (a, mode II) and **11** (b, mode III).

Figure 8. Crystal structure of **13** viewed along the *a* axis at the initial stage.

shows the initial and final structures of **9**.[20] The two crystallographically independent molecules, A and B, in a noncentrosymmetric *P*1 cell of the initial structure approach inversion symmetry except for the chiral cn groups. When the crystal was exposed to X-rays for about 20 days, only the cn group of the B molecule, the B cn group, inverts to the opposite configuration, the A cn group being unaltered. The pseudo inversion center between the two molecules becomes a crystallographic one, and the space group changes to the centrosymmetric *P*1̄. This process is schematically drawn in Figure 7a. The volume of the unit cell decreased by 4 Å³ as the racemization proceeded. The same racemic crystal as that produced by X-ray irradiation was obtained from an aqueous methanol solution containing the racemic complex. Such a racemization, order-to-order racemization, was found for **8**[21] and **10**,[22] with the space groups changing from *P*2₁ to *P*2₁/*n* and from *P*2₁ to *P*2₁/*a*, respectively.

The crystal of **11** also underwent racemization.[23] At the initial stage two crystallographically independent molecules, A and B, are related by a pseudo inversion symmetry, which becomes a crystallographic one at the final stage. The space group changes from the noncentrosymmetric *A*2 to the centrosymmetric *A*2/*a*. Both the A and B cn groups are transformed to the disordered racemates in this racemization, which is schematically drawn in Figure 7b. Although it remains undetermined whether each cn group is *R* or *S*, the A and B cn groups around an inversion center would be expected to have opposite configurations to each other. Therefore, this mode of racemization is a combination of the order-to-disorder mode for one reactive group and the order-to-order one for two reactive groups.

Intermediate Mode of Racemization

Crystals of **12** also revealed crystalline-state racemization upon X-ray exposure, although the reaction rate was very low at room temperature.[24] The two crystallographically independent molecules, A and B,

are related by a pseudo glide symmetry. In order to increase the rate, the crystal was warmed to 343 K. The A and B molecules were gradually racemized involving disordered structures. However, the degree of the disorder was different between the A and B cn groups. After about 400 h of exposure, approximately 26% of the A cn groups were changed to the opposite configuration, whereas about 74% of the B cn groups were transformed to the opposite configuration, and the pseudo glide plane became a crystallographic one. The space group changed from *P*1 to *Cc*, the cell volume being doubled to obtain centering. Upon continued irradiation, further inversion was not observed, and the crystal decomposed when the temperature was raised above 343 K. Of course, the structure at the final stage is racemic since the A and B molecules are related by a glide symmetry, but it is different from the racemic structure of **9** or **11**.

Crystals of **13** also have two molecules, A and B, in the asymmetric unit of a *P*2₁2₁2₁ cell (Figure 8).[25] The racemization by X-rays was not observed at room temperature. When the crystal was warmed to 333 K, a part of the B cn group rotated around the Co–C bond, and then the B cn group gradually inverted to the opposite configuration. After about 400 h of exposure the change of the unit cell dimensions was no longer observed. The structure revealed that only 30% of the B cn group was inverted. Even when the temperature was raised to 348 K, further inversion was not found. Above 348 K the crystal decomposed. In all the processes, the A cn group remained unaltered. From a solution of racemic complex, racemic crystals were obtained. To our surprise, the space group was noncentrosymmetric *P*2₁2₁2₁, and the structure was isomorphous with that of **13** if the B cn group with *R* configuration is replaced by that of *S* configuration.[26]

The racemization process in the above crystals approximately follows first-order kinetics. Therefore, the process can be described by the initial and final structures and the reaction rate. However, the racemization of **14** did not obey first-order kinetics.[27] Figure 9 shows the variation of *a*, *b*, *c*, and *V* in the *P*2₁2₁2₁ cell with exposure time. The changes of *b* and *V* have maxima at the intermediate stage. Similar trends were also found at 343 K. The stepwise structure

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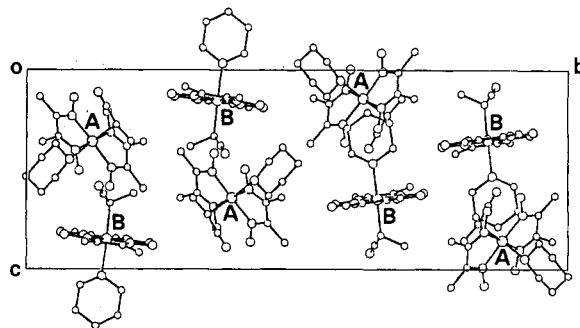(24) Danno, M.; Uchida, A.; Ohashi, Y.; Sasada, Y.; Ohgo, Y.; Baba, S. *Acta Crystallogr., Sect. B* **1987**, *B43*, 266–271.

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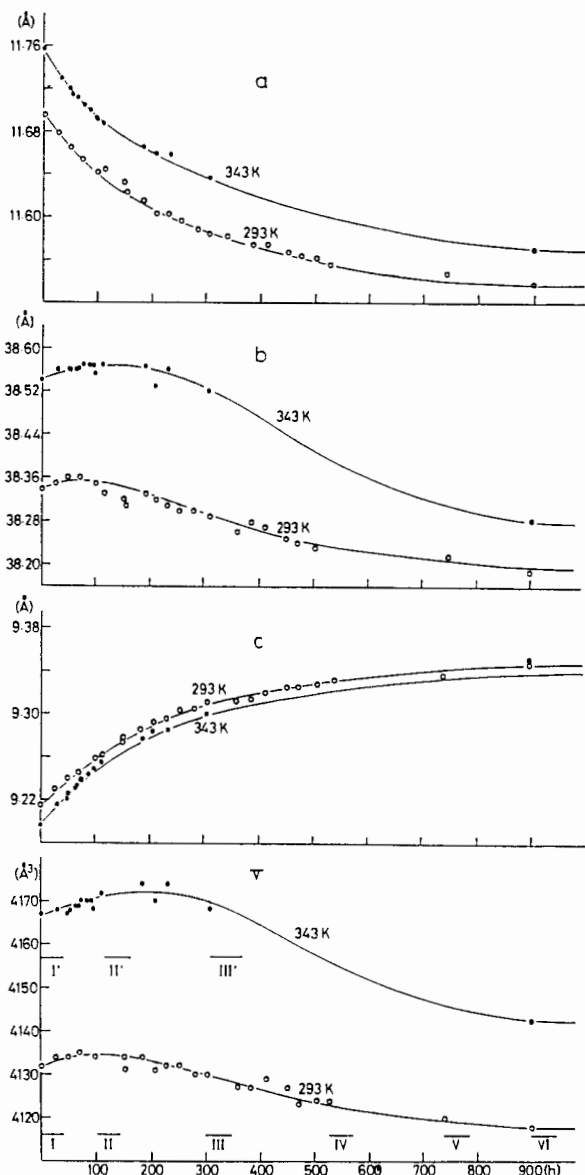
Figure 9. Change of the cell dimensions of **14** at 293 and 343 K. The structures were analyzed at the I to VI stages at 293 K and at the I' to III' stages at 343 K.
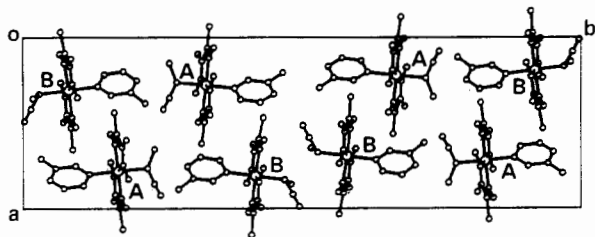

Figure 10. Crystal structure of **14** viewed along the *c* axis at the initial stage.

analyses were performed at six stages, I to VI, at 293 K and at three stages, I' to III', at 343 K. The crystal at the initial stage has two crystallographically independent molecules, A and B, as shown in Figure 10. On exposure to X-rays, both the A and B cn groups took the disordered structures. The inversion rates of the two cn groups were obtained from the structure analyses at the above six stages as well as three intermediate stages at 293 and 343 K, respectively. These are shown in Figure 11. The inversion of the B cn group follows first-order kinetics and reaches about 90% conversion.
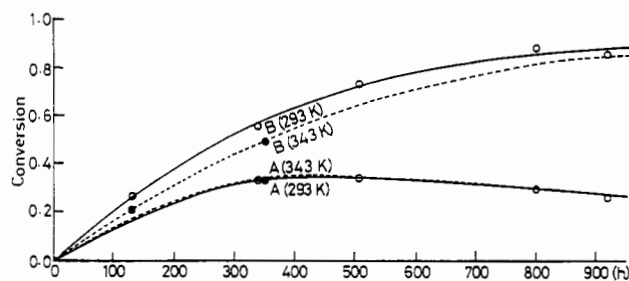
Figure 11. Inversion rates of the A and B cn groups of **14** at 293 and 343 K.
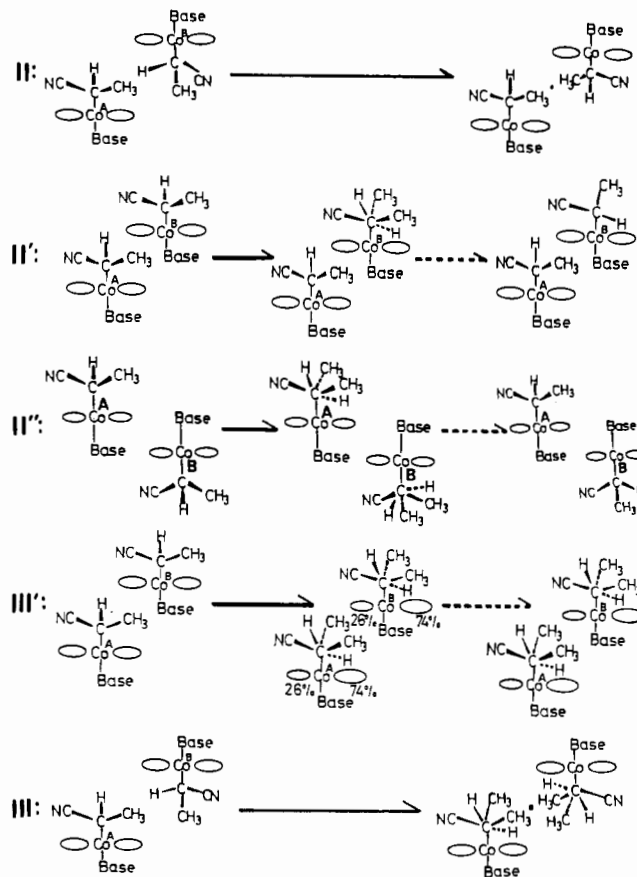
Figure 12. Schematic drawing of the racemization process for crystals 8–14, which have two molecules in the asymmetric unit.

The change of the A cn group, on the other hand, has a maximum of 0.35 at 400 h of exposure and becomes 0.25 at 900 h. It must be emphasized that the crystal is fully racemized at 400 h since 35% of A and 65% of B cn groups have opposite configuration.[28] However, the inversion of both groups still continued. After infinite exposure the B cn group will be completely inverted, and the A cn group will have the original configuration. Attempts to crystallize the racemic complex have so far been unsuccessful. However, the same racemic crystal as that produced by X-rays should be grown from a solution, since substantially the same racemic crystal has already been obtained for the complex of **13**. Another unusual fact is that the rate of inversion of the B cn group at 343 K is smaller than that

(28) The rate of inversion of the B cn group is greater than that of the reinversion of the A cn group. This indicates that the chirality of the molecules in a whole crystal becomes slightly opposite to their original chirality after 400 h. The change in the solid state does not appear to follow the ideal thermodynamic process as observed in solution.

Table II
Cavity Volume and Rate Constant of Crystals 8-14

crystal	mode	cavity vol, Å^3		rate const,[c] $\times10^{-6}$ s^{-1}		
		A	B	298 K	high	temp
8	II	8.89	11.34	2.86	50.6	(353 K)
9	II	7.97	10.37	1.56		
10	II	11.05	12.61	0.57		
11	III	17.08	18.01	4.81	5.07	(343 K)
12	III'	9.54	10.04			
		(11.50)	(12.00)[b]			
13	II'	7.49	11.57			
		(7.88)	(14.04)[a]			
14	II''	10.24	14.29			
		(10.84)	(12.79)[b]			

[a] Volume at 333 K. [b] Volume at 343 K. [c] Rate constants of 12-14 have not been obtained.

at 293 K, whereas the rates of the A cn groups at the two temperatures are approximately the same, although the volume of the unit cell significantly increased at 343 K.

Reaction Mechanism Based on the Cavity

Various racemization processes for the two reactive groups in the crystalline state are summarized in Figure 12. Table II gives the volume of the cavity for each cn group and the racemization rate. The second mode is observed in the crystals of **8**, **9**, and **10**, in which only the B cn group is fully inverted and a crystallographic inversion center appears between the two molecules. The cavity for the A cn group, the A cavity, is too small for the inversion of the cn group, whereas the B cavity is significantly larger than the A cavity. Only the B cn group, therefore, is inverted. Since the inversion causes closer packing of the molecules, the unit cell volume decreases. The driving force for this mode of racemization would be a decrease in enthalpy of the crystal. The rate of racemization seems to have a positive correlation with the volume of the B cn group.[29]

In the third mode (compound **11**), both the A and B cn groups change to disordered racemates, and a crystallographic inversion center emerges between the two molecules. Not only the B cavity but also the A cavity has enough size for the inversion of the cn group. The greatest rate of racemization corresponds to the largest cavities.

In the II' mode (compound **13**), only the B cn group is partly inverted at 333 K. Since the cavity wall is composed of nonreactive rigid groups, the volume of 14.0 Å may be insufficient for the inversion. However, the B cn group may be fully inverted after infinite exposure, and it would take the same structure as that of the racemic crystal grown from a solution.

The II'' mode, which is observed in **14**, is more interesting. Both the A and B cn groups are partly inverted, and at 293 K the rate of the inversion of the B cn group is twice that of the A cn group in the early stages. The B cavity has sufficient size to permit inversion. The volume of the A cavity is smaller than that of the B cavity but is comparable with that of the B cavity in **9**. Moreover, the pseudo inversion center

between the A and B cn groups can never be changed to a crystallographic one in the $P2_12_12_1$ cell. These facts are probably the reason why not only the B but also the A cn groups can be inverted at early stages. However, both the A and B cavities are too small to accommodate the disordered racemate, and the molecules are more closely packed when the two cn groups have opposite configurations. This causes the reinversion of the A cn group. Finally, all the B cn groups are converted to the opposite configuration, and all the A cn groups return to the original configuration. The B cavity at 343 K is smaller than at 293 K whereas the A cavity has nearly the same volume at the two temperatures. This is the reason why the inversion rate of the B cn group at 343 K is smaller than that at 293 K, whereas approximately the same rates at the two temperatures were observed for the A cn group.

Probably some portion of the A cn group in the II mode may be inverted at the intermediate stages. However, its reinversion would occur so fast, because of the small cavity and the developing crystallographic inversion symmetry, that the intermediate structure as observed in the II'' mode would be undetectable.

In the III' mode (compound **12**), uneven racemization of the A and B cn groups has been observed at 343 K. The A cavity is not too small for the inversion, but it is somewhat smaller than the B cavity at 343 K. Both the A and B cn groups, therefore, are partly inverted in the early stages, although the rates of inversion are different between the two groups. This situation is very similar to the process in mode II''. However, the unit cell volume does not decrease and the glide symmetry appears between the two groups when the inversion ratios reach 0.26 for A and 0.74 for B, resulting in complete racemization. The driving force for further structural change may be the entropy term, and both the A and B cn groups would take the 1:1 disordered structure after infinite exposure.

A variety of racemization modes and reaction rates have been successfully explained by the reaction cavity of the cn group. In order to study the crystalline-state racemization more comprehensively, the cyanoethyl group was replaced by the (methoxycarbonyl)ethyl (mce) group, $CH(CH_3)COOCH_3$. The mce group has a rotational freedom about the C–C bond. Several crystals with different axial base ligands were prepared.[30,31] The structure analyses at the intermediate stages revealed that the mce group underwent the conformational change before it was inverted by X-rays.[31]

Recently, complexes with the bis(methoxycarbonyl)ethyl group as reactive group, $CH(COOCH_3)CH_2COOCH_3$, were prepared. Racemization by X-ray exposure has not been observed at room temperature,[15] although the powdered sample was racemized by visible light.[32] Probably the reactive group is too large to be inverted with retention of the crystallinity.

(29) Although the volume of the B cavity of **10** is greater than those of **8** and **9**, the value of *k* is the smallest among the three. This is probably due to the fact that the B cn group in **8** and **9** contacts the A cn group around the pseudoinversion center and a part of the A cavity may be used in the inversion of the B cn group, whereas the B cn group in **10** lacks such a favorable condition.

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(32) Ohgo, Y., private communication.

Concluding Remarks

We can investigate the quantitative relationship between a reactive group and its environment by using the reaction cavity, that is, the free space given to the reactive group by the surrounding molecules in the crystal. The crystalline-state reaction is one of the best systems to obtain such quantitative relationships, since the intermediate structures can be examined. Crystalline-state reactions are, however, exceptional cases of solid-state reactions in general. It would be possible to obtain the intermediate structures for normal solid-state reactions if the time required for the three-dimensional data collection could be significantly shortened. Recently, synchrotron radiation has been used to collect millisecond X-ray diffraction data.[33] It can be anticipated that a wide variety of intermediate structures will be investigated, and the quantitative mechanisms will be proposed for solid-state reactions in the near future.

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