

Calculated Reaction Paths for a Solid-State Reaction: Racemization of Chiral Crystalline Cobaloxime Complexes by Exposure to X-rays

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(Received 15 July 1989; accepted 13 September 1989)

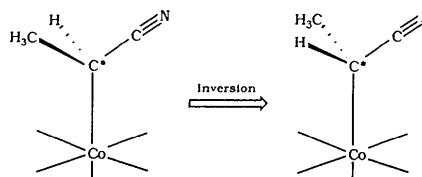
Abstract

We have used the *OPEC* (organic packing-energy calculations) set of programs [Gavezzotti (1983). *J. Am. Chem. Soc.* **105**, 5220–5225] to obtain reaction paths and differences in activation energies for the X-ray-induced, solid-state racemization of chiral cyanoethyl groups in crystalline cobaloxime complexes. Typical examples of three classes of such reactions have been studied, including the remarkable toposelective reactivity of [(*S*)-1-cyanoethyl]-bis(dimethylglyoximate)(pyridine)cobalt(III), where inversion of cyanoethyl group configuration occurs for only one of the two sets of independent molecules in the crystal. The results of the calculations are generally compatible with the experimental results and encourage the view that packing-energy calculations can illuminate the details of quite complex solid-state reactions.

Introduction

Organic solid-state chemistry deals, in the widest sense, with the packing of molecular solids and the chemical consequences thereof. For a good general coverage of this field see the recent collection of review articles in *Organic Solid State Chemistry* (Desiraju, 1987). One special feature of solid-state reactions is that the spatial arrangement of the atoms at the beginning and sometimes also at the end of the reaction can be mapped quite precisely. This distinguishes them from reactions in solution or in the gas phase and provides the possibility for new kinds of insight into the geometric aspects of chemical reactivity in general. The molecules in a given crystal occur in a single conformation (occasionally in more than one) and in well defined surroundings. Thus, differences in chemical behavior among crystals that differ mainly in the packing of otherwise similar molecules should be interpretable by studying the packing differences.

One of the most extensive and systematic experimental studies of a solid-state reaction up till now has been made by Ohashi, Sasada and their collaborators during the last 12 years or so. The reaction in question is the inversion of the sense of chirality of the 1-cyanoethyl group in several crystalline bis-(dimethylglyoximate)cobalt(III) (cobaloxime) complexes with various amine or phosphine ligands in the sixth coordination site (Ohashi, 1988). Parallel studies have also been made for analogous solid-state reactions involving inversion of the 1-methoxycarbonylethyl group in cobaloxime complexes with different ligands in the sixth coordination site (Kurihara, Ohashi, Sasada & Ohgo, 1983; Kurihara, Uchida, Ohashi, Sasada & Ohgo, 1984). The reaction occurs in solution on exposure to light and in the crystalline state on exposure to X-rays without appreciable loss of crystallinity. In both cases, the reaction is initiated by homolytic cleavage of the Co—C bond, as shown by ESR spectroscopy (Ohashi, Yanagi, Kurihara, Sasada & Ohgo, 1981). In the crystalline state the reaction can be followed by changes in the lattice parameters and often proceeds slowly enough to allow detailed crystal structure analyses to be made at the initial, final and sometimes even intermediate stages. The changes in lattice parameters against exposure time typically follow approximate first-order kinetics with rate constants of the order of 10^{-6} s^{-1} . In all cases the final crystal structure is very similar to the initial one, except that in the inverted cyanoethyl groups the positions of the methyl group and of the α -H atom are approximately interchanged.



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crystal structure (Fig. 1). In the first class, the initial chiral crystal structure contains one molecule per asymmetric unit and the final crystal structure is disordered, both configurations of the cyanoethyl group being present at a given lattice site (although not necessarily with equal occupancy). In this class, the volume of the unit cell increases slightly as the reaction proceeds. Examples of this type of reaction are provided by [(*R*)-1-cyanoethyl][(*S*)-1-methylbenzylamine]cobaloxime (Ohashi *et al.*, 1981) and [(*S*)-1-cyanoethyl][(*S*)-1-methylbenzylamine]cobaloxime (Ohashi, Sasada, Takeuchi & Ohgo, 1980).

In the second class, the initial chiral crystal contains two sets of independent molecules, say *R* and *R'*, related by a pseudo inversion center, *i.e.* the molecules take up an approximately centrosymmetric arrangement, except for the homochiral cyanoethyl groups (Fig. 1). In this class the final crystal structure is an ordered racemate, with a centrosymmetric space group, *i.e.* the pseudo inversion center is transformed into a crystallographic inversion center, a process that involves a reversal of the cyanoethyl configuration in one of the two initial sets of molecules, *R* or *R'*, but not in the other; the volume of the unit cell undergoes a slight contraction as the racemization reaction proceeds. The difference in reactivity between the two sets of molecules must depend on their environments. We can refer to a solid-state reaction that is specifically undergone by only one of several sets of otherwise identical molecules which differ in crystal environment as being toposelective [compare this definition with the introduction of the word topochemistry to cover chemical reactions that depend on crystal environment (Cohen & Schmidt, 1964)]. Examples are the [(*R*)-1-cyanoethyl]cobaloxime complexes with pyridine (Ohashi, Yanagi, Kurihara, Sasada & Ohgo, 1982), 4-cyanopyridine (Ohashi, Uchida, Sasada & Ohgo,

1983), or 4-methylpyridine (Uchida, Ohashi, Sasada, Ohgo & Baba, 1984).

In the third class, the asymmetric unit of the initial chiral structure again consists of two independent molecules related by a pseudo inversion center, but now both cyanoethyl groups can invert to yield a disordered racemate as the final structure (Fig. 1). An example is the complex with diphenylmethylphosphine (Tomotake, Uchida, Ohashi, Sasada, Ohgo & Baba, 1985).

Some crystals that have been studied do not fit very well into this classification scheme. For example, the complex with 3-methylpyridine appears to share properties of the second and third classes. Like them, the initial crystal structure contains two sets of independent molecules, again related by a pseudo inversion center. On irradiation, both sets of molecules racemize, but at different rates. As the reaction continues, the slower racemizing set of molecules appears to revert to its initial configuration while the faster set proceeds to complete inversion of configuration (Ohashi, Tomotake, Uchida & Sasada, 1986).

It seems clear that a change in the configuration of the cyanoethyl group in the crystal is possible only if sufficient space is available to allow the development of intermediate atomic arrangements without undue hindrance from atoms in neighboring molecules. This question has been discussed for most of the reactions mentioned in terms of a so-called reaction cavity (Ohashi *et al.*, 1983). For a given group in a given environment, this is defined as the concave space limited by the envelope surfaces of spheres placed at the positions of neighboring atoms, each sphere having a radius 1.2 Å greater than the corresponding van der Waals radius. Since the detailed crystal structures are known for both initial and final stages of most of these solid-state reactions, the appropriate reaction cavities have been derived and shown to correlate in a rough way with the solid-state reactivities, large cavities corresponding to fast observed rates, small cavities to slow ones. In particular, for reactions of the second class, where inversion of configuration is observed for only one of the two sets of independent molecules, the calculated reaction cavity is always larger for the reactive molecule than for the unreactive one, *e.g.*, 11.34 versus 8.89 Å³ for the two molecules in the pyridine complex (Ohashi *et al.*, 1982).

Nevertheless, there are some problems that cannot be ignored. Although observed reaction rates* tend to increase on warming the crystals and decrease on cooling them, as expected, the changes are much less

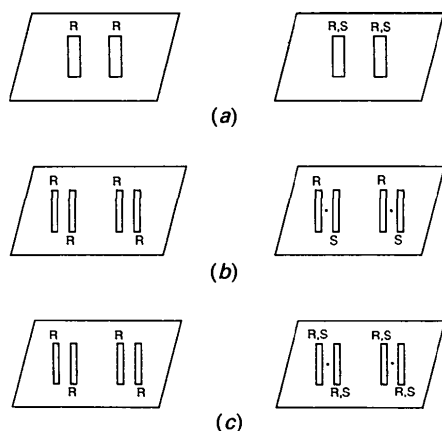


Fig. 1. Schematic drawings of the racemization process in the crystals of (a) the first class, (b) the second class, and (c) the third class.

* Reaction rates can be estimated from the changes in lattice parameters or from occupancy factors of appropriate atoms. In general, both kinds of estimate agree fairly well (Ohashi *et al.*, 1981).

than would be predicted by absolute reaction rate theory. One exception to this tendency is the 3-methylpyridine derivative (Ohashi *et al.*, 1986) with its complicated behavior. Moreover, as the cavity volume tends to increase on warming the crystals, one would surely expect this to be accompanied by a corresponding decrease in the activation energy. However, when activation energies E_a are estimated from the observed rate constants from the expression

$$k_r = (k_B T/h) \exp(-E_a/RT) \quad (1)$$

the estimated values often show the opposite behavior. For example, for the 1-methylbenzylamine complex (Ohashi *et al.*, 1981), estimated E_a values are 19.2 kcal mol⁻¹ at 223 K and 24.6 kcal mol⁻¹ at 293 K, whereas the cavity volume increases from 12.95 to 14.53 Å³ between 173 and 293 K (1 kcal mol⁻¹ = 4.1868 kJ mol⁻¹). Of course, for practical reasons, the observed rate constants cover only a rather limited range, from about 0.5–3 × 10⁻⁶ s⁻¹. An upper limit is imposed by the time to make the X-ray measurements required to define the progress of the reaction, a lower one by the need to complete the reaction within a reasonable period of time (1 month = 2.6 × 10⁶ s).

Although we cannot yet provide answers to these questions, we attempt in the present work to provide a little more insight into the details of the reaction mechanism than that given by mere inspection of the shape and volume of the reaction cavity. We attempt to follow the coupling among the various types of atomic motion that must take place during the course of the chemical reaction. These motions include at least: (a) translation of the cyanoethyl group away from the Co atom to produce the elongation of the Co-to-C interatomic distance (Δl) associated with initial homolytic rupture of the Co—C bond; (b) pyramidalicity of the resulting 1-cyanoethyl radical (P); (c) rotation of the radical about the C—Co vector (θ_1 , positive for clockwise rotation looking along this vector); (d) rotation of the radical about the C—CN vector (θ_2 , positive for clockwise rotation looking along this vector). The latter direction was chosen because it is quite close to the inertial axis of the group with the smallest moment of inertia. These motions are illustrated in Fig. 2.

The approach we have used involves the point-to-point calculation of the packing potential energy (PPE) with the help of the computer program *OPEC* (organic packing-energy calculations), as developed by Gavezzotti & Simonetta (Gavezzotti, 1983). For an account of the possibilities and limitations of this program see the recent review by Gavezzotti & Simonetta (1987). In these calculations we consider only the change in packing energy, that is, we ignore the energy changes associated with the purely 'chemical'

aspects of these reactions, the rupture of the Co—C bond and the inversion of the cyanoethyl group. We can afford to do so, because these contributions to the activation energies are the same for all the systems studied and we are interested only in relative energy differences, not in the absolute energy values. From a knowledge of the ground-state structures and some reasonable assumptions about pairwise interactions, we try to trace the reaction paths, follow the energy variation along them, and thus obtain estimates of differences in activation energies.

Procedure

The starting points for the calculations are the published descriptions (cell constants and atomic positions) of the crystal structures of [(*R*)-1-cyanoethyl]bis(dimethylglyoximate)((*S*)- α -methylbenzylamine)cobalt(III) (1) (Ohashi *et al.*, 1981), [(*S*)-1-cyanoethyl]bis(dimethylglyoximate)(pyridine)cobalt(III) (2) (Ohashi *et al.*, 1982), and [(*R*)-1-cyanoethyl]bis(dimethylglyoximate)(diphenylmethylphosphine)cobalt(III) (3) (Tomotake *et al.*, 1985). In the calculations the chirality sense of (2) was inverted in order to make the absolute configuration of the cyanoethyl group the same as those in the crystals (1) and (3).

Positions of all H atoms in the published structures were recalculated from stereochemical assumptions, as described in the *OPEC* input instructions (Gavezzotti, 1983). This was considered necessary as the intermolecular C...H and H...H interactions provide the dominant part of the packing energy and are sensitive to the H-atom positions. The published positions suffer from large systematic and random errors in the X-ray analyses (especially as heavy atoms are present), and the calculated positions are considered as being more accurate than the experimental ones. In the calculations, all C—H bond distances were set to 1.08 Å. Methine H atoms were

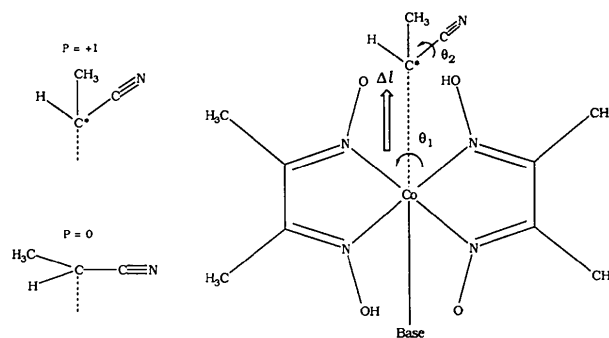


Fig. 2. Diagrammatic illustration of the atomic motions involved in these calculations. The rotations are counted as positive when they are clockwise, looking away from the α -C atom.

placed on bisector planes with approximately tetrahedral bond angles. Positions of methyl H atoms were calculated in two steps; first, one of the three H atoms was located so as to have the same dihedral angle as in the published structure, then the others were placed as if they belonged to a methylene group. The H atoms between oxime groups were placed at the midpoints of the O...O vectors. As the experimental coordinates of the methyl C atom of the cyanoethyl group are inaccurate owing to slight racemization during data collection, the position of this atom was also recalculated (in the same way as for methine H atoms).

The initial orientation of the pyramidal 1-cyanoethyl radical ($P = +1$, $\Delta l = \theta_1 = \theta_2 = 0$) was taken as in the observed crystal structures; for the initial orientation of the flattened radical ($P = 0$, $\Delta l = \theta_1 = \theta_2 = 0$) the methyl C atom, the H atom and the cyano group were moved into the plane perpendicular to the Co—C direction and passing through the α -C atom. Thus in our model the direction of the bonding (sp^3) orbital is preserved. In this coordinate system the reference molecule with inverted cyanoethyl group is described by $P = -1$, $\Delta l = \theta_1 = 0$, $\theta_2 = 180^\circ$.

The *OPEC* set of programs estimates the packing potential energy (PPE) as a sum of energy contributions:

$$\text{PPE} = \sum_i \sum_j A \exp(-BR_{ij}) - CR_{ij}^{-6} \quad (2)$$

for all intermolecular distances R_{ij} up to a variable cutoff distance (which we took as 7 Å). The index i runs over the atoms of the central molecule and the index j over those of surrounding molecules. The coefficients A , B and C vary for each type of contact between different atomic species; the values included in the program library (in kcal mol⁻¹) are taken from Mirsky (1978). No electrostatic contributions were included (the Co atom was regarded simply as a C atom as far as its nonbonded interactions with neighboring atoms are concerned). The PPE (divided by the Avogadro number!) is the negative of the energy involved in removing one molecule from the bulk of the crystal to infinity. The packing energy (PE), to be identified approximately with the sublimation energy, is the energy of bringing one mole of molecules from infinity to their equilibrium positions and orientations in the crystal; each molecule acquires an energy equal to PPE and thus:

$$\text{PE} = \text{PPE}/2 \quad (3)$$

where division by two is required to avoid counting each energy contribution twice (Gavezzotti & Simonetta, 1982).

The program allows the calculation of the PPE as a function of the motion (translation and rotation) of a central molecule or atomic grouping. The sur-

rounding molecules can be kept in their initial positions and orientations or allowed to relax; in the calculations described here, performed on a CYBER 180-855 computer at the Computing Center of the Swiss Federal Institute of Technology, Zurich, they were kept fixed in order to economize on computing time. Since our problem involves the more complex sequence of motions described above (Fig. 2), a sub-program was made to compute the positions of the atoms of the cyanoethyl group as a function of the three variables Δl , P ($= +1$ or 0), θ_1 , leaving θ_2 as the rotation to be handled by the program proper. Thus the PPE was calculated by *OPEC* as a function of θ_2 (rotation of the cyanoethyl group about the C—CN direction) for fixed values of the other three variables. Because of the structure of the program, our calculated energy includes contributions from interactions between the atoms of the cyanoethyl fragment and those of the remainder of the reference molecule.* On the other hand, as mentioned earlier, it does not include the energy change associated with rupture of the Co—C bond.

Results

[(*R*)-1-Cyanoethyl]bis(dimethylglyoximate)[(*S*)- α -methylbenzylamine]cobalt(III) (1)

This is an example of the first class of reactive crystals containing one molecule in the asymmetric unit, where the final crystal structure is disordered (Ohashi *et al.*, 1981) (Fig. 1).

For the initial crystal structure ($P = +1$, $\Delta l = \theta_1 = \theta_2 = 0$), the PPE was calculated to be -44 kcal mol⁻¹. If the configuration of the cyanoethyl group of the reference molecule is inverted by interchanging the directions of the C—H and C—CH₃ bonds the calculated PPE is -27 kcal mol⁻¹. This estimate would correspond to the PPE of a single inverted molecule in a crystal composed of non-inverted molecules, *i.e.*, to the PPE of the very first product molecule produced in the crystal in the orientation described. Rotation of this inverted molecule by about 120° round the Co—C bond interchanges the directions of the C—CH₃ and C—CN bonds with respect to the reference molecule and lowers the PPE to -45 kcal mol⁻¹, approximately the same as for the initial structure. Neither of these model structures corresponds to the inverted molecule that was derived from the X-ray analysis of the final product.

* Tables of packing potential energy (PPE) for crystals (1), (2) and (3) along the minimum energy paths at different values of Δl , θ_1 and θ_2 for pyramidal ($P = +1$) and planar ($P = 0$) cyanoethyl groups have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52281 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

One reason is that in our calculation the surrounding molecules have been kept in their initial positions and orientations, whereas in the product crystal the 'reference' molecule has the surroundings of a disordered crystal structure. Another possible reason is that in our calculation, the position of the α -C atom of the cyanoethyl group has been left unaltered in the initial and inverted molecules, whereas it seems to be perceptibly different in the actual crystal structures.

Starting at the initial structure, the PPE was calculated at intervals of 0.2 \AA in Δl , 10° in θ_1 , 20° in θ_2 , and contoured. For inversion of the cyanoethyl group, only the two structures corresponding to $P = +1$ and $P = 0$ were considered. In the calculations for the initial and inverted molecules, the interaction energy between the atoms of the cyanoethyl group and those of the rest of the molecule was ignored because the two fragments are part of the same molecule. In the other calculations with $\Delta l \neq 0$, this interaction energy is included and is obviously strongly repulsive, especially for small values of Δl . Indeed, as Δl increases from near zero to $0.6\text{--}0.8 \text{ \AA}$, the PPE decreases by more than 40 kcal mol^{-1} . From the contour map for $P = +1$ (Fig. 3a) a well defined energy valley can be discerned, starting at the minimum (PPE $\approx -44 \text{ kcal mol}^{-1}$) in the region around $\Delta l \approx 0.6\text{--}0.8 \text{ \AA}$, $\theta_1 \approx -30^\circ$, $\theta_2 \approx 0^\circ$, and

rising to a pass (PPE = $-27 \text{ kcal mol}^{-1}$) around $\Delta l \approx 2.0 \text{ \AA}$, $\theta_2 \approx -125^\circ$. The path then continues downhill to a structure with $\theta_1 \approx -50^\circ$, $\theta_2 \approx 180^\circ$ (not seen in the figure, PPE = $-33 \text{ kcal mol}^{-1}$). At this point the cyanoethyl group has been translated and rotated anticlockwise about both axes into an orientation close to its final one but it is still pyramidal with its initial configuration ($P = +1$). Fig. 4 shows how the position and orientation of the cyanoethyl group changes along the path just described.

A parallel set of calculations was made for the planar radical (Fig. 3b, $P = 0$). Here the energy minimum is found around $\theta_1 \approx 0^\circ$, $\theta_2 \approx 20^\circ$, corresponding to slight clockwise rotations of the cyanoethyl group about both axes, compared with $P = +1$. The energy valley leading out of this minimum is not too different from the one already described for $P = +1$, but the PPE is generally higher; at the pass ($\theta_1 \approx 20^\circ$, $\theta_2 \approx -80^\circ$) it is about 10 kcal mol^{-1} higher. The planarization of the cyanoethyl group leads to an increase in the nonbonded repulsions between the two molecular fragments. There is also an increase in the nonbonded repulsions between the cyanoethyl group and the surrounding molecules. The importance of such nonbonded repulsions is shown by the fact that the unit-cell volume of this crystal increases as the racemization reaction at the

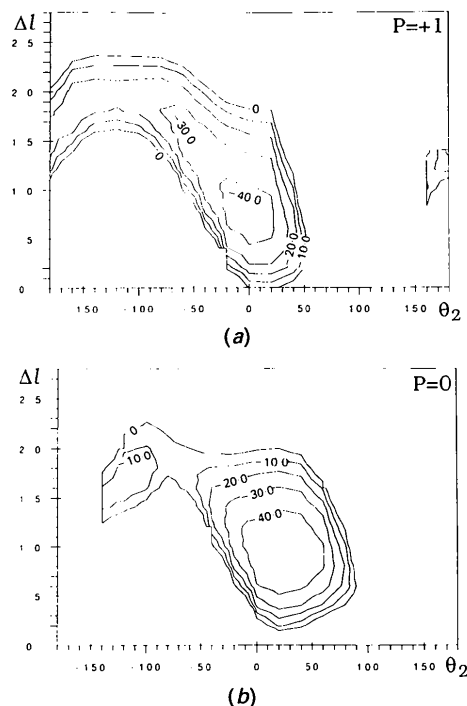


Fig. 3. Crystal (1) (293 K); contour maps of the Δl , θ_2 section of the packing potential energy (PPE) in units of kcal mol^{-1} for $\theta_1 = -30^\circ$, $P = +1$ (a) and $\theta_1 = 0^\circ$, $P = 0$ (b). In the empty parts of the map the PPE > 0 . $1 \text{ kcal mol}^{-1} = 4.1868 \text{ kJ mol}^{-1}$.

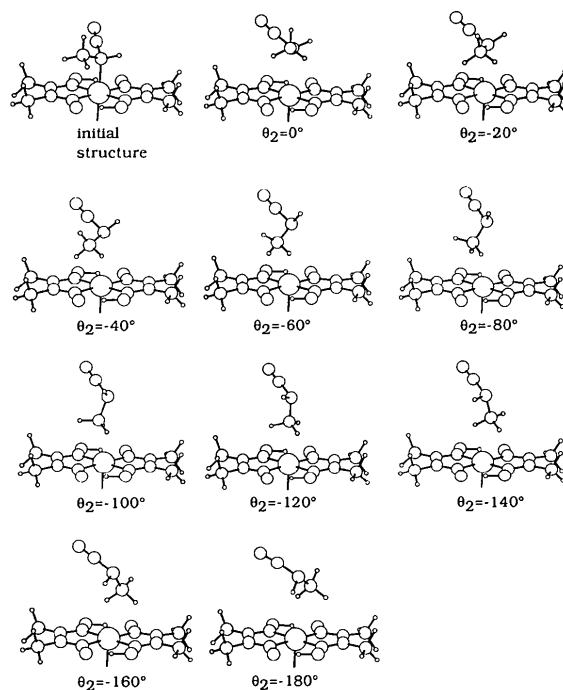


Fig. 4. Crystal (1) (293 K); sequence of structures along the path of minimum PPE with the cyanoethyl group held in its initial configuration ($P = +1$).

cianoethyl group proceeds (Ohashi *et al.*, 1981). The transition state is presumably fairly close to this point, and from here on, the Co—C bond can be reformed to produce the final structure with the inverted configuration of the cyanoethyl group.

Even if this description of the reaction path and the corresponding transition state is roughly correct, it must be stressed that the difference between the calculated PPE's for the initial structure ($-44 \text{ kcal mol}^{-1}$) and for the putative transition state ($-17 \text{ kcal mol}^{-1}$) cannot be identified with an activation energy. The interaction energy between the cyanoethyl group and the rest of the molecule is ignored in one calculation and included in the other. Besides, the reaction in the crystal is initiated photochemically, and, as mentioned earlier, the energies associated with the 'chemical' steps, the rupture of the Co—C bond and the inversion of the cyanoethyl radical, are ignored in the calculations.

When crystals of (1) are cooled to 173 K, the racemization reaction becomes so slow as to be unobservable. Since the crystal structure at this temperature has been determined (Ohashi *et al.*, 1981), PPE calculations were made along the same lines as for the room-temperature structure. The cell dimensions and atomic coordinates for this and for the other structures analyzed in this paper were retrieved

from the Cambridge Structural Database (Allen *et al.*, 1979). For the initial crystal structure ($P = +1$, $\Delta l = \theta_1 = \theta_2 = 0$) the PPE was $-45 \text{ kcal mol}^{-1}$, practically the same as for the room-temperature structure, but, as is evident from comparison of Figs. 3 and 5, the contour maps are noticeably different. The energy valley for the $P = +1$ section is wider and less steep for the 173 K structure. Indeed, the PPE for the 173 K crystal is lower up to about $\theta_2 \approx -120^\circ$, but further anticlockwise rotation of the radical makes the PPE higher than for the room-temperature structure. Moreover, the valley for the corresponding $P = 0$ section is steeper throughout, mainly because of more severe steric hindrance from atoms of neighboring molecules. At the transition state the PPE for the 173 K structure is higher by about 7 kcal mol^{-1} .

This may appear to be a satisfying result, but it should be noted that an increase in activation energy is not needed to explain the difference in rate between the two temperatures. From the observed rate constant of $3.3 \times 10^{-6} \text{ s}^{-1}$ at room temperature, expression (1) gives $F_a \approx 25 \text{ kcal mol}^{-1}$, corresponding to a rate constant at 173 K of 10^{-19} s^{-1} . Thus, the main factor hindering racemization at 173 K is not so much an increase in E_a but simply the decrease in kinetic energy of the cyanoethyl radical.

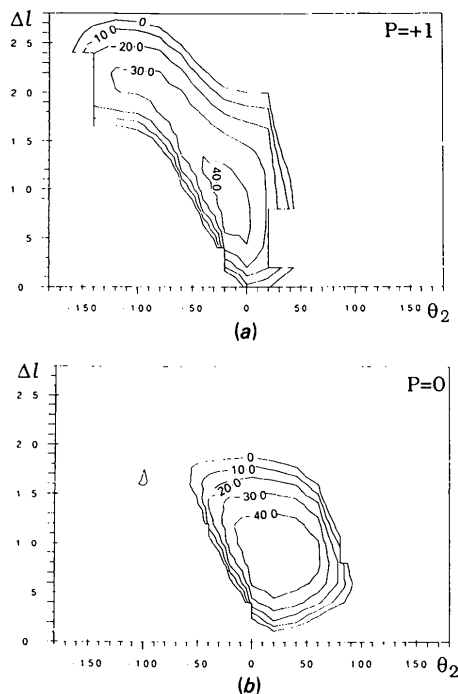


Fig. 5. Crystal (1) (low-temperature structure); contour maps of the Δl , θ_2 sections of the packing potential energy (PPE) in units of kcal mol^{-1} for $\theta_1 = -30^\circ$, $P = +1$ (a) and $\theta_1 = 0^\circ$, $P = 0$ (b). In the empty parts of the map the PPE > 0 .

[(S)-1-Cyanoethyl]bis(dimethylglyoximate)(pyridine)-cobalt(III) (2)

This is an example of the second class of reactions, where the initial chiral crystal structure contains two sets of independent molecules related by a pseudo inversion center and where the final structure is an ordered racemate (Fig. 1b). Thus, during the reaction, the configuration of the cyanoethyl group in only *one* of the two initial sets of molecules is inverted, an example of what we have called a topo-selective solid-state reaction. In the experimental study (Ohashi *et al.*, 1982) the two sets of molecules were designated *A* and *B*; only set *B* was found to be reactive.

The PPE for this crystal structure in its initial state ($P = +1$, $\Delta l = \theta_1 = \theta_2 = 0$) before rupture of the Co—C bond is $-83 \text{ kcal mol}^{-1}$. The same value is obtained when the cyanoethyl group of the reference molecule *B* is inverted by interchanging the directions of the C—CH₃ and C—H bonds. For the ordered, centrosymmetric racemate with inverted configuration of molecule *B* the PPE is slightly lower, $-90 \text{ kcal mol}^{-1}$, *i.e.*, the racemate is calculated to be thermodynamically more stable than the initial structure.

Separate calculations were made for the motion of the two symmetry-independent molecules in the initial structure. For the unreactive molecule *A* (Fig.

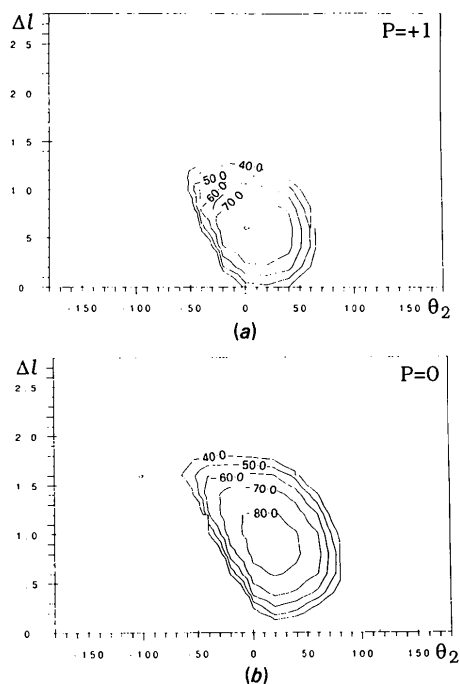


Fig. 6. Crystal (2) (molecule *A*); contour maps of the Δl , θ_2 sections of the packing potential energy (PPE) in units of kcal mol⁻¹ for $\theta_1 = 0^\circ$, $P = +1$ (a) and $\theta_1 = 0^\circ$, $P = 0$ (b). In the empty parts of the map the PPE > 40 kcal mol⁻¹.

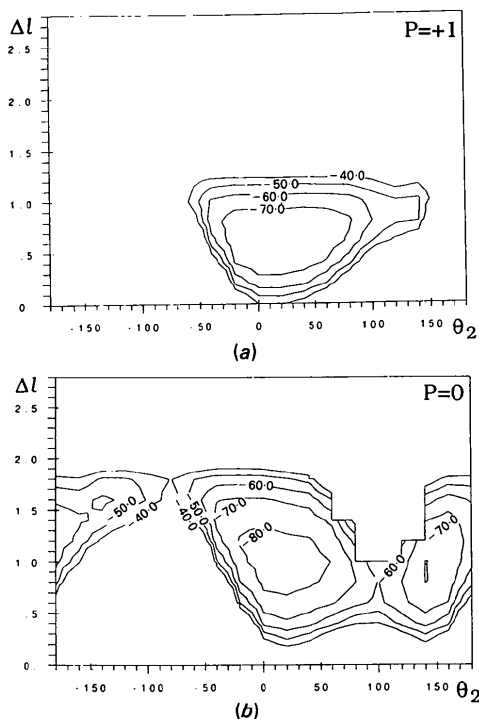


Fig. 7. Crystal (2) (molecule *B*); contour maps of the Δl , θ_2 sections of the packing potential energy (PPE) in units of kcal mol⁻¹ for $\theta_1 = 0^\circ$, $P = +1$ (a) and $\theta_1 = 0^\circ$, $P = 0$ (b). In the empty parts of the map the PPE > 40 kcal mol⁻¹.

6), the PPE contour maps show a deep energy minimum close to the initial orientation of the cyanoethyl group, with no obvious energy valley leading out of it. For the reactive molecule *B*, on the other hand, we find an energy valley corresponding to clockwise rotation of the cyanoethyl group round the C—N bond (Fig. 7, $P = 0$, $\theta_1 = 0$) with a pass (PPE ≈ -60 kcal mol⁻¹) leading to a second minimum with $\theta_2 \approx -160^\circ$. The sequence of structures along this path is shown in Fig. 8. Regardless of the sense of the θ_2 rotation and of the pyramidity of the radical, molecule *A* is calculated to have a much higher activation energy for inversion of configuration than molecule *B*.

When the central atomic grouping in *OPEC* consists of *two* independent molecules or fragments, interactions between them can be included in the contributions to the PPE. In the present case, we have three fragments, molecule *A* and the two parts of molecule *B*, and is not possible to include interactions among these fragments with our version of the program (Gavezzotti, 1983). For the initial structure, of course, there are only two fragments, and the interactions between them were estimated to contribute about -5 kcal mol⁻¹. Since these interactions remain relatively invariant with change in the position and orientation of the cyanoethyl groups, the PPE values in Figs. 6 and 7 should be corrected by about this amount.

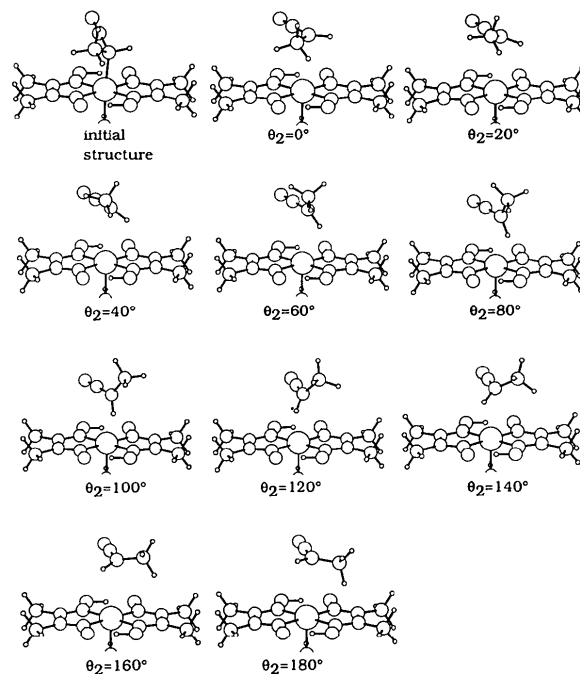


Fig. 8. Crystal (2) (molecule *B*); sequence of structures along the path of minimum PPE with the planar cyanoethyl group ($P = 0$).

[(*R*)-1-Cyanoethyl]bis(dimethylglyoximate)(diphenylmethylphosphine)cobalt(III) (3)

Our final example concerns the third class of reactions, where the initial chiral crystal structure contains two sets of independent molecules related by a pseudo inversion center and where the final crystal structure is a disordered racemate (Tomotake *et al.*, 1985).

The PPE for this crystal structure in its initial state ($P = +1$, $\Delta l = \theta_1 = \theta_2 = 0$) was calculated to be $-101 \text{ kcal mol}^{-1}$. PPE contour maps were calculated separately for the two independent molecules. The θ_1 sections (Figs. 9 and 10) look rather similar. For $P = +1$ there is a well defined energy trough and for $P = 0$ there are energy valleys corresponding to clockwise and anticlockwise rotation of the cyanoethyl group about the C—CN axis for both molecules. The anticlockwise rotation brings the methyl group into collision with the cobaloxime fragment. To reduce the concomitant repulsions, this motion is associated with elongation of the $\text{Co}\cdots\text{C}$ distance by approximately 2 \AA ; the clockwise rotation proceeds with much less elongation. For molecule *A*, Fig. 9 ($P = 0$ section) shows a pass (PPE $\approx -82 \text{ kcal mol}^{-1}$) at $\Delta l = 20 \text{ \AA}$, $\theta_2 = -80^\circ$, but there is a somewhat lower one (PPE $\approx -92 \text{ kcal mol}^{-1}$) at $P = 0$, $\Delta l = 0.8 \text{ \AA}$, $\theta_1 = 40^\circ$, $\theta_2 = 140^\circ$. For molecule *B* (Fig. 10, $P = 0$ section), the energy valley rises much more steep-

ly both for clockwise and anticlockwise rotations, reaching PPE values as high as $-40 \text{ kcal mol}^{-1}$. Thus, regardless of the sense of the θ_2 rotation and of the pyramidity of the radical, molecule *B* is calculated to have a much higher activation energy (*ca* 50 kcal mol^{-1}) than molecule *A*, which is clearly quite irreconcilable with the observed racemization of both molecules at comparable rates.

Fig. 11 shows stereoscopic drawings of cavities for the cyanoethyl groups of molecules *A* and *B*; the cyanoethyl groups are drawn with thicker lines, and the phosphine ligands are omitted for clarity. [The cavities were not drawn according to the *OPEC* procedure, but along the lines indicated in Ohashi *et al.* (1983)]. It is evident that for molecule *A* the positions of the methyl group and the α -H atom can be interchanged within the corresponding cavity, while for molecule *B* there is not enough room around the α -H atom (where the methyl group *would* be accommodated by rotation of the radical about either the C—CN or $\text{Co}\cdots\text{C}$ axes). This is the reason why molecule *B* has a much larger PPE as the cyanoethyl group is rotated from its equilibrium orientation.

In the search for a lower-energy path an additional motion of the cyanoethyl group was introduced into the calculations – translation (Δl) of the radical along the long axis of the cobaloxime fragment (Fig.

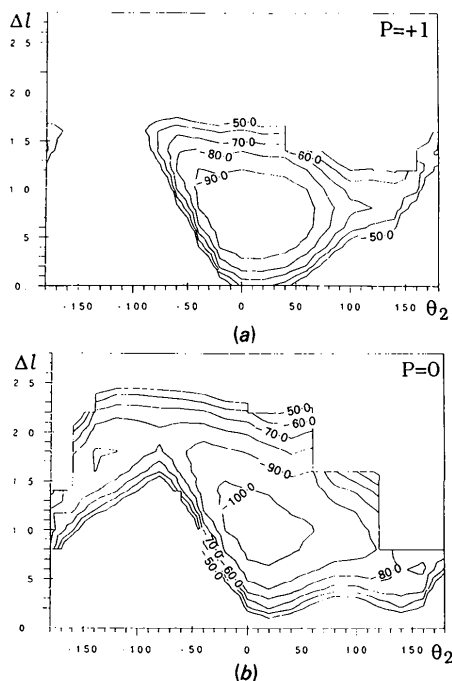


Fig. 9. Crystal (3) (molecule *A*); contour maps of the Δl , θ_2 sections of the packing potential energy (PPE) in units of kcal mol^{-1} for $\theta_1 = 0^\circ$, $P = +1$ (a) and $\theta_1 = 0^\circ$, $P = 0$ (b). In the empty parts of the map the PPE $> 50 \text{ kcal mol}^{-1}$.

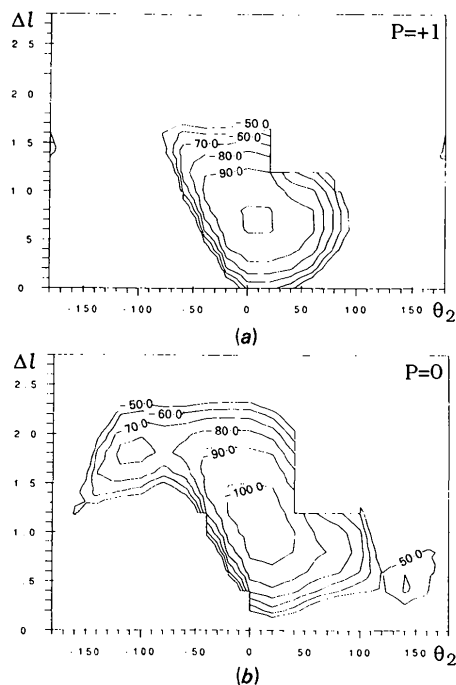


Fig. 10. Crystal (3) (molecule *B*); contour maps of the Δl , θ_2 sections of the packing potential energy (PPE) in units of kcal mol^{-1} for $\theta_1 = 0^\circ$, $P = +1$ (a) and $\theta_1 = 0^\circ$, $P = 0$ (b). In the empty parts of the map the PPE $> 50 \text{ kcal mol}^{-1}$.

11). Preliminary calculations for $P = 0$, $\Delta l = 1.0 \text{ \AA}$, $\theta_1 = 0$ indicated that the PPE for clockwise rotation (positive θ_2) could be considerably lowered with a translation of 0.5 \AA . This translation was then held constant and the PPE section for $P = 0$, $\theta_1 = 0$ was calculated (Fig. 12). It shows a pass (PPE = $-85 \text{ kcal mol}^{-1}$) for clockwise rotation in θ_2 and a somewhat higher one (PPE = $-75 \text{ kcal mol}^{-1}$) for

anticlockwise rotation. Although these values are still higher than for molecule *A* (PPE $\approx -92 \text{ kcal mol}^{-1}$), the result shows that by introducing the additional degree of freedom the cyanoethyl group in molecule *B* can indeed be inverted without running into an impossibly large activation energy.

Concluding remarks

The results of our calculations for the three examples chosen for detailed study are generally compatible with the experimental evidence: low barriers can be obtained for those rearrangements that have been observed to occur in the crystals. For the description of the motion of the cyanoethyl radical in the course of the rearrangements at least four (and in one case five) parameters were required. Even then, it is clear that our model is greatly oversimplified. It considers the movement of a central cyanoethyl group in a crystal environment of unreacted unrelaxed molecules and hence can apply at best only during the very earliest stage of the solid-state reaction. Relaxation of the positions, orientations and rigidity of the surrounding molecules could be included in a more elaborate model, but only at the cost of greatly increased computational time. In spite of these problems, we are encouraged to believe that the procedure of steering the molecular motions by way of packing-energy calculations can illuminate the structural course of quite complex solid-state reactions. Since the bond-breaking and -making steps are disregarded in this approach, it can most usefully be applied for comparing a series of related solid-state reactions that have these steps in common.

This work was carried out with the financial support of the Swiss National Science Foundation and Japan Society for the promotion of Science. We are grateful to Professor Angelo Gavezzotti for making his *OPEC* program available to us and for helpful discussions.

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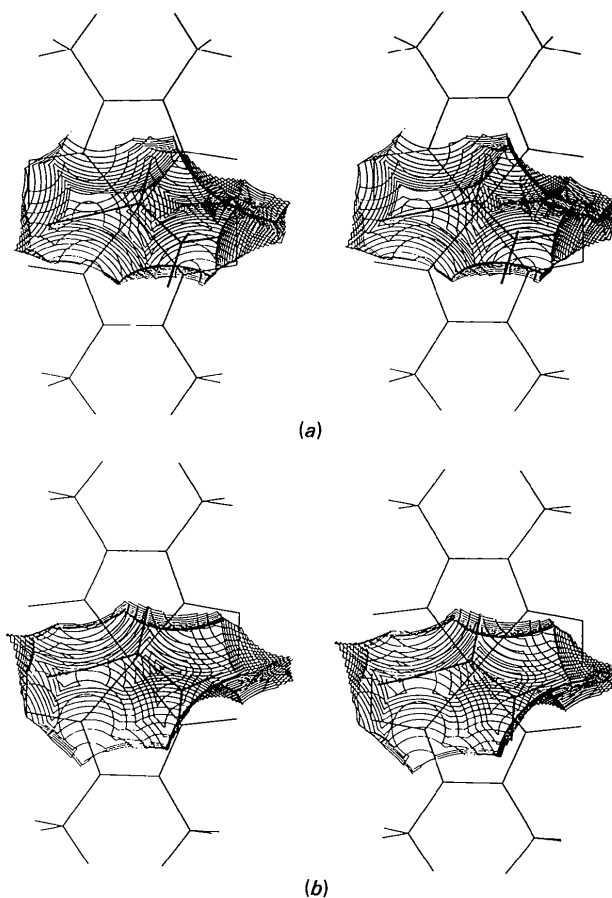


Fig. 11. Stereoscopic drawings of cavities for the cyanoethyl groups for (a) molecule *A* and (b) molecule *B* in crystal (3).

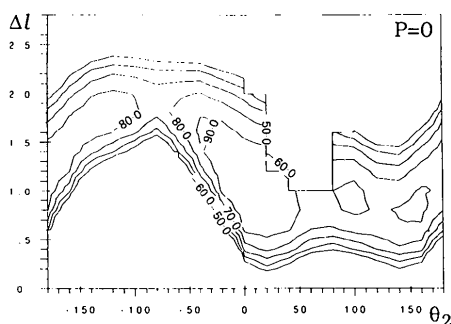


Fig. 12. Crystal (3) (molecule *B*); contour map of the Δl , θ_2 sections of the packing potential energy (PPE) in units of kcal mol^{-1} for $P = 0$, $\theta_1 = 0^\circ$ and $\Delta l = 0.5 \text{ \AA}$.

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Refinement of Triclinic Lysozyme: I. Fourier and Least-Squares Methods

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(Received 15 February 1989; accepted 7 August 1989)

Abstract

X-ray diffraction data to 1.5 Å resolution have been collected for triclinic crystals of hen egg white lysozyme. The triclinic model was derived from the tetragonal one by the rotation function and refined initially by $F_o - F_c$ and differential difference syntheses against 2 Å resolution data. Refinement was continued by differential difference cycles against the 1.5 Å data until R was reduced to 0.220. Although the initial refinement was rapid, it was subsequently a matter of attrition, leading to a complete recheck of the data and the discovery of systematic error which affected primarily the high-resolution data. Refinement was continued against the corrected 2 Å data by block-diagonal least squares. After five cycles the refinement was terminated at $R = 0.254$ because of the imminent availability of a preferred refinement program. Problems with the protein model, the solvent, and the interaction of the scale and thermal parameters are discussed. The experiences gained in this study are summarized.

Introduction

Lysozyme is an enzyme, widely distributed in biological systems, which catalyzes the hydrolysis of polysaccharides in the bacterial cell wall. The particular lysozyme found in the whites of hen eggs has a single polypeptide chain of 129 amino acids, cross-linked by four disulfide bridges. The molecule has

1001 nonhydrogen atoms and a mass of 14 300 daltons. Hen egg white (HEW) lysozyme crystallizes from aqueous solutions in at least four different crystal systems (Steinrauf, 1959), and the structure of the tetragonal form has been determined by the multiple-isomorphous-replacement method (Blake, Koenig, Mair, North, Phillips & Sarma, 1965).

Triclinic crystals of HEW lysozyme are unusual in that they have a relatively low solvent content, 26% by weight. They are also unusual in the sense that they diffract to high resolution, considerable intensity being observed for reflections to d spacings of at least 1.0 Å. It is clear, therefore, that sufficient data can be observed to yield a precise model of the molecule in this crystal form. Such a model will be useful in determining the extent of departure from ideal bond and torsion angles in proteins, in studying the solvent structure in protein crystals, in attempting to visualize the effects of radiation damage to triclinic lysozyme, in comparative studies of the effects of packing forces on the molecular structure of lysozyme in different crystal forms, and as the initial model for neutron diffraction studies of triclinic lysozyme. When this work was initiated (1971), it was not clear to what extent protein models could be refined nor the most effective way of doing so. One of our objectives, therefore, was to determine what was feasible in a favorable case and what could be learned about the methods of refinement and their limitations.

This paper provides an account of the initial efforts to derive an acceptable model for triclinic lysozyme.

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