

Convergent-Beam Electron Diffraction Method for Chiral Identification of Enantiomorphic Crystals

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A new CBED method is proposed for chiral identification of enantiomorphic crystals, in which asymmetry in the intensity of reflections of Bijvoet pairs in an experimental symmetrical zone-axis CBED pattern is compared with that of an computer simulated CBED pattern. The intensity difference for reflections of these Bijvoet pairs results from multiple scattering (dynamical nature of electron diffraction) among relevant Bijvoet pairs of reflections, each pair of which have identical amplitude and different phase angles. With the present method, only a single CBED pattern is sufficient and chiral identification can be made for all possible enantiomorphic crystals that are allowed to exist in crystallography.

Key words: chirality, enantiomorphism, convergent-electron diffraction, transmission electron microscopy, handedness

1. INTRODUCTION

Enantiomorphism is usually referred to and used to describe objects that are lacking of improper rotation (rotoinversion and roto reflections). Because of the absence of a center of symmetry ($\bar{1}$), a mirror plane ($m=2$) and a 4 axis, such enantiomorphic (chiral) crystals or molecules can occur in two different forms that are related as a right hand and a left hand and these enantiomorphically-related crystals belong to either of the 11 crystal classes (point groups), as summarized in Table I [1,2]. In general, the right-handed crystal can be converted to the left-handed one by changing the coordinates of atom positions from (x,y,z) to $(-x,-y,-z)$. For the case of enantiomorphic crystals that are related to each other by a screw axis (they are called an enantiomorphic space group pair), the change in space group number is needed in addition to the atomic coordinate conversion [1]. These crystals are mirror related and are not superimposable with each other and one of the two enantiomorphic crystals exhibit optical bioactivities different from the other in most cases [3,4]. Therefore, distinction of chirality of enantiomorphic crystals is sometimes very important, as the well-known example of Thalidomide accident, which occurred as a tragedy due to the harmful side effect of one of the two members of the enantiomorphic crystals, has indicated. Distinction of chirality of enantiomorphic crystals is usually made by X-ray diffraction [5,6]. The Friedel's law states that members of a Friedel pair, which are Bragg reflections related to each other by inversion through the origin, have equal amplitude ($|F|$) and opposite phase (φ), as follows [7].

$$|F(hkl)| = |F(\bar{h}\bar{k}\bar{l})| \text{ and } \varphi(hkl) = -\varphi(\bar{h}\bar{k}\bar{l}), \quad (1)$$

Table I: Crystal system, crystal class (point group), equivalent indices of Bijvoet pairs of reflections in the asymmetric unit and appropriate zone-axis orientations for chiral identifications for crystals belonging to all possible enantiomorphic point groups. The nomenclature "ZOLZ" in the last column means that Bijvoet pairs of reflections that appear in ZOLZ as $\pm g$ are utilized for chiral identification. * The point group 32 in the rhombohedral coordinate system is divided into two space groups, 321 and 312 in the hexagonal coordinate system.

Crystal System	Point Group	Bijvoet Pairs		Appropriate Zone-Axis
		Equivalent indices	Equivalent indices	
Tric.	1	hkl	$\bar{h}\bar{k}\bar{l}$	ZOLZ
Monoc.	2	$hkl=\bar{h}\bar{k}\bar{l}$	$\bar{h}\bar{k}\bar{l}=hkl$	$\langle h0l \rangle$
Orth.	222	$hkl=\bar{h}\bar{k}\bar{l}=\bar{h}\bar{l}\bar{k}$	$\bar{h}\bar{k}\bar{l}=\bar{h}\bar{l}\bar{k}=hkl$	$\langle hk0 \rangle, \langle 0kl \rangle, \langle h0l \rangle$
Tet.	4	$hkl=\bar{k}\bar{h}\bar{l}=\bar{h}\bar{k}\bar{l}=\bar{h}\bar{l}\bar{k}$	$\bar{h}\bar{k}\bar{l}=\bar{k}\bar{h}\bar{l}=\bar{h}\bar{l}\bar{k}=hkl$	$\langle hk0 \rangle$
	422	$hkl=\bar{k}\bar{h}\bar{l}=\bar{h}\bar{k}\bar{l}=\bar{h}\bar{l}\bar{k}$ $=\bar{h}\bar{k}\bar{l}=\bar{k}\bar{h}\bar{l}=\bar{h}\bar{l}\bar{k}$	$\bar{h}\bar{k}\bar{l}=\bar{k}\bar{h}\bar{l}=\bar{h}\bar{l}\bar{k}=hkl$ $=\bar{h}\bar{k}\bar{l}=\bar{k}\bar{h}\bar{l}=\bar{h}\bar{l}\bar{k}$	$\langle hk0 \rangle, \langle h0l \rangle, \langle hhl \rangle$
Trig.	3	hkl	$\bar{h}\bar{k}\bar{l}$	ZOLZ
	32*	$hkl=\bar{h}\bar{k}\bar{l}$	$\bar{h}\bar{k}\bar{l}=\bar{h}\bar{l}\bar{k}$	$\langle h\bar{h}0l \rangle$
	312	$hkl=\bar{h}\bar{k}\bar{l}$	$\bar{h}\bar{k}\bar{l}=\bar{h}\bar{l}\bar{k}$	$\langle hh2hl \rangle$
hex.	6	$hkl=\bar{h}\bar{k}\bar{l}$	$\bar{h}\bar{k}\bar{l}=\bar{h}\bar{k}\bar{l}$	$\langle hki0 \rangle$
	622	$hkl=\bar{h}\bar{k}\bar{l}$ $=\bar{h}\bar{k}\bar{l}=\bar{h}\bar{l}\bar{k}$	$\bar{h}\bar{k}\bar{l}=\bar{h}\bar{k}\bar{l}$ $=\bar{h}\bar{k}\bar{l}=\bar{h}\bar{l}\bar{k}$	$\langle h\bar{h}0l \rangle, \langle hh2hl \rangle, \langle hki0 \rangle$
Cub.	23	$hkl=\bar{h}\bar{k}\bar{l}=\bar{h}\bar{l}\bar{k}$	$\bar{h}\bar{k}\bar{l}=\bar{h}\bar{k}\bar{l}=\bar{h}\bar{l}\bar{k}$	$\langle hk0 \rangle$
	432	$hkl=\bar{h}\bar{k}\bar{l}=\bar{h}\bar{l}\bar{k}$ $=\bar{h}\bar{l}\bar{k}=\bar{h}\bar{k}\bar{l}=\bar{h}\bar{l}\bar{k}$	$\bar{h}\bar{k}\bar{l}=\bar{h}\bar{k}\bar{l}=\bar{h}\bar{l}\bar{k}$ $=\bar{h}\bar{l}\bar{k}=\bar{h}\bar{k}\bar{l}=\bar{h}\bar{l}\bar{k}$	$\langle hk0 \rangle, \langle hhl \rangle$

where F and hkl stand for structure factor and index of reflection, respectively. In X-ray diffraction, the breakdown of the Friedel's law occurs through anomalous scattering, resulting in different intensity and phase angles for the Friedel pair of reflections [7]. Bijvoet pairs are Bragg reflections, which are space

group symmetry equivalents to the two members of a Friedel pair and they are usually utilized for identification of chirality of crystal instead of Friedel pairs through inspection of the intensity asymmetry between the pairs [8], as the Bijvoet relations states as follows.

$$F_R(hkl) = F_L(\bar{h}\bar{k}\bar{l}) \text{ and } F_R(\bar{h}\bar{k}\bar{l}) = F_L(hkl), \quad (2)$$

where the subscripts R and L stand for right- and left-handed crystals, respectively. However, distinction of chirality by X-ray diffraction usually needs a relatively large-sized single-crystal of high quality free from crystal lattice defects [9,10]. In addition, special techniques such as the multiple isomorphous replacement (MIR) method and sufficiently strong x-ray beam such as that from synchrotron radiation source are needed in many cases [9,10].

If the distinction can be made by electron diffraction in the transmission electron microscope (TEM), such difficulty is completely avoided because of the capability of the TEM obtaining a nano-meter-sized electron probe [11,12]. However, it is generally believed that electron diffraction is not a general method for chiral identification of enantiomorphic crystals since the intensity difference is not expected to occur for Bijvoet pairs of reflections through anomalous scattering, which does not occur in electron diffraction [13]. Thus, Bijvoet pairs of reflections have long been ignored by transmission electron microscopists. Here we show, however, that the intensity difference can be indeed observed for Bijvoet pairs even in electron diffraction through its dynamical nature (multiple scattering) once an appropriate zone-axis orientation is chosen so that Bijvoet pairs of reflections are arranged symmetrically in a zone-axis CBED pattern. Then, chiral identification is made by noting the intensity asymmetry between Bijvoet pairs of reflections. The proposed method can be easily extended to identify chirality of all crystallographically possible enantiomorphic crystals.

2. APPROPRIATE ZONE-AXIS ORIENTATIONS

One of the most important points of this new method is to choose an appropriate zone-axis orientation (incident beam direction) so that Bijvoet pairs of reflections appear symmetrically in a single CBED pattern. For this purpose, any reflections belonging to ZOLZ (zero-th order Laue zone) and FOLZ (first order Laue zone) can be used. Since which of hkl reflections correspond to Bijvoet pairs depend on point group (Table I), the appropriate symmetrical zone-axis orientations depend on point group of crystal. Appropriate zone-axis orientations can thus be found by plotting the distribution of Bijvoet pairs for a particular type of hkl reflections located in the standard triangles in the stereographic projection. The particular type of hkl reflections denotes, for example, twelve 1234-type reflections for a crystal with the hexagonal symmetry. Since Bijvoet pairs, for example, for crystals with the point group of 321 is

$$hkl = h\bar{k}l \text{ and } \bar{h}\bar{k}\bar{l} = \bar{h}\bar{i}\bar{k}l,$$

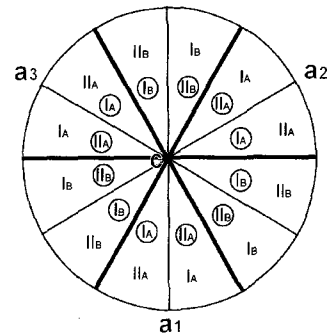


Fig. 1: Distribution of Bijvoet pairs of reflections located in the standard triangles for the point groups of 321. Bijvoet pairs of reflections are expressed as I_A - I_B and II_A - II_B and the symbols expressed with $\bigcirc$ indicate reflections that appear in the reverse side of the triangles.

Bijvoet pairs (expressed I_A and I_B) for a particular type of reflections distribute in the stereographic projection as shown in Fig. 1. Then, the appropriate zone-axis orientations at which Bijvoet pairs of reflection disks appear symmetrically in a single CBED pattern are readily known as those on $\langle 11\bar{2}0 \rangle$ zone-circles, as illustrated in Fig. 1. Therefore, the appropriate zone-axis orientations in this case are of the $\langle h\bar{h}0l \rangle$ -type. Similarly, the appropriate zone-axis orientations are determined in Table I (the fifth column) for all the point groups that have a pair of enantiomorphic crystals. As seen in Table I, nine of the eleven point groups that have enantiomorphic crystals have the appropriate zone-axis orientations in which Bijvoet pairs of reflections appear symmetrically in a single CBED pattern. The way of chiral identification for crystals belonging to these nine point groups will be described in the present paper. The other two point groups, 1 and 3, in which each of the two members of a Bijvoet pair of reflections do not have any equivalent reflections, do not have appropriate zone-axis orientations to observe Bijvoet pairs of reflections symmetrically. However, since Bijvoet pairs of reflections appear in ZOLZ as opposite reflections ($\pm \mathbf{g}$; $\mathbf{g}$ denotes a reflection vector) with respect to the transmitted (center) beam, chiral identification is possible even in these two cases by observing asymmetry of intensity for these ZOLZ reflections of opposite sign. The readers are referred to [14] for the details. The nomenclature "ZOLZ" in Table I for these two point groups therefore means that Bijvoet pairs of reflections that appear in ZOLZ as $\pm \mathbf{g}$ reflections are utilized for chiral identification without specifying zone-axis orientations.

3. INTENSITY ASYMMETRY OF BIJVOET PAIRS OF REFLECTIONS IN A SYMMETRICAL ZONE-AXIS CBED PATTERN

As described in the previous section, nine of the eleven point groups have appropriate zone-axis orientations in which Bijvoet pairs of reflections are observed symmetrically in terms of their positions, as

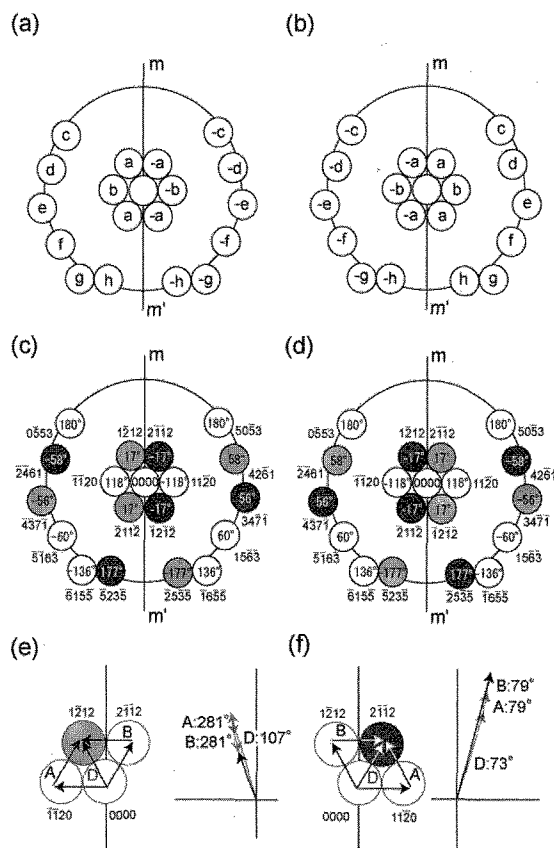


Fig. 2: Schematic illustration of appropriate zone-axis CBED patterns of (a) right-handed and (b) left-handed crystals, in which Bijvoet pairs of reflections are observed symmetrically with respect to the symmetry line $m-m'$. The nomenclatures a, b, c, ... indicated at reflection disk positions schematically depict phase angles of the corresponding reflection disks. The phase distribution for ZOLZ and FOLZ reflection disks that appear in a $[2203]$ CBED pattern of Te with the space groups of $P3_121$ and $P3_221$ is shown in (c) and (d), respectively. The amplitude-phase diagrams for $(1\ 2\ 12)$ and $(2\ 1\ 12)$ ZOLZ reflection disks in the $[2203]$ CBED pattern of Te with the space groups of $P3_121$ are shown in (e) and (f), respectively.

schematically illustrated in Figs. 2(a) and (b). Of HOLZ (higher-order Laue zone) reflection disks, only FOLZ disks are depicted in the figures for simplicity. The $m-m'$ line is the symmetry line in terms of their positions and corresponds to the trace of the zone-circle on which the appropriate zone-axis orientation is located. Many Bijvoet pairs are simultaneously observed in such a zone-axis CBED pattern, since reflections appeared symmetrically with respect to $m-m'$ are all Bijvoet pairs. In the kinematical approximation, structure factors for any hkl reflections are given as follows [11,12].

$$F(hkl) = \sum_i f_i(\theta) \exp \{-2\pi i (hx_i + ky_i + lz_i)\}$$

$$= |F| \exp(i\varphi), \quad (3)$$

where $f_i(\theta)$ is atomic scattering factor of i -th atom, θ is scattering angle and (x_i, y_i, z_i) are atomic coordinate of i -th atom. Since Bijvoet pairs are Bragg reflections which are space group symmetry equivalents to the two members of a Friedel pair $(hkl-hkl)$, the two members of a Bijvoet pair possess identical amplitude but opposite phase in principle, as is readily known from the following relationship.

$$\begin{aligned} F(hkl) &= |F(hkl)| \exp(i\varphi) \quad \text{and} \\ F(\overline{h}\overline{k}\overline{l}) &= |F(\overline{h}\overline{k}\overline{l})| \exp(-i\varphi). \end{aligned} \quad (4)$$

This occurs for any Bijvoet pairs of reflections that are arranged symmetrically with respect to the symmetry line $m-m'$ in a zone-axis CBED pattern. Then, although the arrangement of Bijvoet pairs of reflections in the CBED pattern is symmetrical with respect to $m-m'$, the phase distribution is asymmetrical with respect to $m-m'$ for each of the two members of enantiomorphic crystals, as schematically illustrated in Figs. 2(a) and (b). Since the right-handed crystal can be converted to the left-handed one by changing the coordinates of atom positions from (x, y, z) to $(-x, -y, -z)$, the following relationship analogous to the Bijvoet relations is obtained,

$$\begin{aligned} F_R(hkl) &= |F_R(hkl)| \exp(i\varphi), \\ F_R(\overline{h}\overline{k}\overline{l}) &= |F_R(\overline{h}\overline{k}\overline{l})| \exp(-i\varphi) \quad \text{and} \\ F_L(hkl) &= |F_L(hkl)| \exp(-i\varphi), \\ F_L(\overline{h}\overline{k}\overline{l}) &= |F_L(\overline{h}\overline{k}\overline{l})| \exp(i\varphi). \end{aligned} \quad (5)$$

This indicates that the asymmetrical phase distribution with respect to $m-m'$ in a zone-axis CBED pattern for each of the two members of enantiomorphic crystals is reversed with respect to $m-m'$ when the handedness is changed from one to the other. In other words, the phase distribution of these Bijvoet pairs of reflections for one of the two member of enantiomorphic crystals and that for the other are anti-symmetric with respect to $m-m'$ and are related with each other by a mirror reflection through the symmetry line $m-m'$. As is readily known from the fact that the right-handed crystal can be converted to the left-handed one by changing the coordinates of atom positions from (x, y, z) to $(-x, -y, -z)$, the symmetry line $m-m'$ in the CBED pattern, across which many Bijvoet pairs of reflections are arranged symmetrically, is mathematically a mirror for the phase distribution of these Bijvoet pairs of reflections for enantiomorphic crystals.

In the kinematical approximation, the intensity (amplitude) distribution in the CBED pattern is still considered to be symmetrical with respect to $m-m'$ for each of enantiomorphic crystals, since Bijvoet pairs, each of which have an identical amplitude, arrange symmetrically. However, it is well known that for noncentrosymmetric crystals, the breakdown of the

distribution in the zone-axis CBED pattern with respect to m - m' for each of the two members of enantiomorphic crystals. Of importance to note is that since the asymmetrical phase distribution of Bijvoet pairs of reflections in a zone-axis CBED pattern for a pair of enantiomorphic crystals is reversed with respect to m - m' when the handedness is changed from one to other, the asymmetric intensity distribution in the zone-axis CBED pattern is also reversed with respect to m - m' for the pair of enantiomorphic crystals. Then, the chiral identification can be made easily by inspecting the asymmetric (anti-symmetric) intensity distribution of Bijvoet pairs of reflections that are arranged symmetrically with respect to m - m' in a zone-axis CBED pattern for enantiomorphic crystals belonging to the nine point groups except for 1 and 3 in Table I.

4. EXPERIMENTAL CBED PATTERNS

We show some typical examples of chiral identification based on the above mentioned method. Tellurium is one of the very famous enantiomorphic crystals belonging to the space groups of $P3_121$ and $P3_221$, as quartz does [17]. The point group is 321 in the hexagonal coordinate system and thus the appropriate zone-axis orientations are of the $\langle h\ h\ 0 \rangle$ -type. Here we choose $[2203]$ as an appropriate zone-axis orientation to observe Bijvoet pairs of reflections symmetrically. The phase distribution of Bijvoet pairs of reflections that appear symmetrically in a $[2203]$ CBED pattern is shown in Figs. 2(c) and (d) for Te with the space groups of $P3_121$ or $P3_221$, respectively. The phase angles of Bijvoet pair reflections were calculated with the equation (3). As described in the previous section, the phase distribution of both ZOLZ and HOLZ reflections is asymmetric with respect to m - m' for each of the two patterns of Figs. 2(c) and (d) and is reversed with respect to m - m' when the space group is changed from one to the other. Amplitude-phase diagrams for $(1\ \bar{2}\ 12)$ and $(2\ \bar{1}\ \bar{1}\ 2)$ ZOLZ reflection disks in the $[2203]$ zone-axis CBED patterns of Te with the space groups of $P3_121$ are shown in Figs. 2(e) and (f), respectively. In addition to the direct scattering route (D), multiple scattering routes (A) and (B), which are the origin of the breakdown of the Friedel's law, are taken into account. Both multiple scattering routes include a partial route via either of two $(11\ 20)$ type ZOLZ reflections. The 90° phase difference of the diffracted beam with respect to the transmitted beam is taken into account in constructing these amplitude-phase diagrams [13]. For the phase of the $(2\ \bar{1}\ \bar{1}\ 2)$ ZOLZ reflection of the space group of $P3_121$, for example, the contribution from the direct route D is 73° ($=-17^\circ+90^\circ$) while that from the routes A and B are both 79° ($=(-118^\circ+90^\circ)+(17^\circ+90^\circ)$). When judged from the amplitude-phase diagrams, the intensity (amplitude) of the $(2\ \bar{1}\ \bar{1}\ 2)$ ZOLZ reflection is expected to be stronger than that of the $(1\ \bar{2}\ 12)$ ZOLZ reflection for the space group of $P3_121$. Amplitude-phase diagrams constructed for the space group of $P3_221$ indicates that the opposite is true. Of importance to note is that the intensities of the $(2\ \bar{1}\ \bar{1}\ 2)$ and $(1\ \bar{2}\ 12)$ ZOLZ reflections for the space group of $P3_121$ are expected to be identical with those of the

$(1\ \bar{2}\ 12)$ and $(2\ \bar{1}\ \bar{1}\ 2)$ ZOLZ reflections for the space group of $P3_221$, respectively. In other words, the intensity distribution of for these Bijvoet pairs is also anti-symmetric with respect to m - m' for the pair of enantiomorphic crystals. For other Bijvoet pairs of reflections, the intensity asymmetry with respect to m - m' is expected to occur, as the stronger and weaker reflections are indicated as darker and less darker disks, respectively, in Figs. 2(c) and (d). An experimental $[2203]$ zone-axis CBED pattern of Te is shown in Fig. 3(a). Two CBED patterns of Figs. 3(b) and (c) with the same incidence are those calculated based on the space groups of $P3_121$ and $P3_221$, respectively [18]. The asymmetric intensity distribution of Bijvoet pairs of reflections for these calculated patterns is consistent with the result of analysis of the amplitude-phase diagrams shown in Figs. 2(c) and (d) respectively for the space groups of $P3_121$ and $P3_221$. When the intensity for Bijvoet pairs of ZOLZ disks, $(1\ \bar{2}\ 12)$ - $(2\ \bar{1}\ \bar{1}\ 2)$ and $(2\ \bar{1}\ \bar{1}\ 2)$ - $(1\ \bar{2}\ 12)$ in the experimental pattern of Fig. 3(a) is compared with each other, the intensity of the latter disks is stronger than that of the former disks. This indicates that Te in this

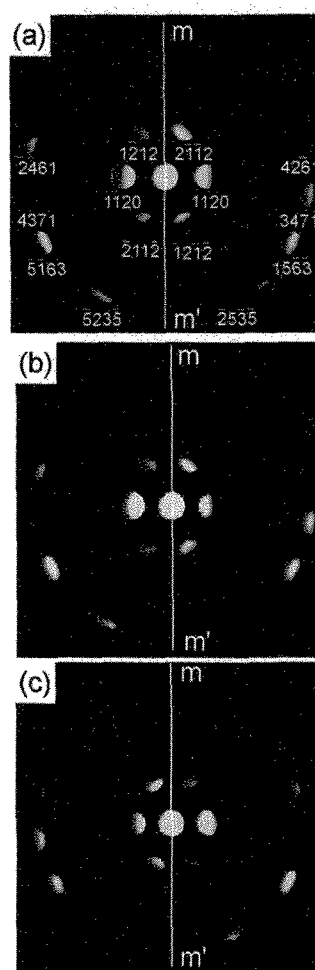


Fig. 3: Experimental (a) and calculated $[2203]$ zone-axis CBED patterns for Te with the space groups of (b) $P3_121$ and (c) $P3_221$.

case belongs to the space group of $P3_121$. There are six equivalent $\langle 2203 \rangle$ -type directions for crystals belonging to the point group of 321. All these six $\langle 2203 \rangle$ incidences produce the identical CBED patterns for each of the two space groups, indicating that only a single CBED pattern is sufficient to identify the chirality (either $P3_121$ or $P3_221$) of Te.

The last example for chiral identification is α glutamic acid, which is one of organic amino acid crystals. α Glutamic acid possesses an asymmetric (chiral) carbon atom and the glutamic acid molecules can be either left-handed or right-handed within the space group of $P2_12_12_1$, depending on how the surrounding substitutional groups attach to the carbon atom [19]. These crystals are called L- and D- α glutamic acid, respectively. Since the point group is 222, the appropriate zone-axis orientations are of the $\langle h k 0 \rangle$ -, $\langle 0 k l \rangle$ - and $\langle h 0 l \rangle$ -types (Table I). We choose $[012]$ as an appropriate zone-axis orientation. The phase distribution for Bijvoet pairs of ZOLZ reflections is illustrated in Figs. 4(a) and (b) for L- and D- α glutamic acid, respectively. Although the phase distribution for FOLZ reflections are not shown in the figures for simplicity, the phase distribution of both ZOLZ and HOLZ reflections is asymmetric with respect to m - m' for each of the two patterns of Figs. 4(a) and (b) and is reversed with respect to m - m' when the handedness is changed from one to the other. Because of the asymmetric phase distribution of Bijvoet pairs of ZOLZ and FOLZ reflections, their asymmetric intensity distribution with respect to m - m' is clearly observed in each of the corresponding calculated images in Figs. 4(c) and (d). The asymmetric intensity distribution is obviously reversed with respect to m - m' when the handedness is changed from one to the other. The chiral

identification can thus be easily made by noting the asymmetric intensity distribution of these Bijvoet pairs of reflections.

5. CONCLUSIONS

A new CBED method is proposed for chiral identification of enantiomorphic crystals, in which asymmetry in the intensity of reflections of Bijvoet pairs in an experimental symmetrical zone-axis CBED pattern is compared with that of an computer simulated CBED pattern. The intensity difference for reflections of these Bijvoet pairs results from multiple scattering (dynamical nature of electron diffraction) among relevant Bijvoet pairs of reflections, each pair of which have identical amplitude and different phase angles. Therefore, the crystal thickness where chiral identification is made with the present method is limited by the extinction distance of Bijvoet pairs of reflections relevant to multiple scattering to produce the intensity asymmetry, which is usually of the order of a few tens nm. With the present method, only a single CBED pattern is sufficient and chiral identification can be made for all possible enantiomorphic crystals that are allowed to exist in crystallography.

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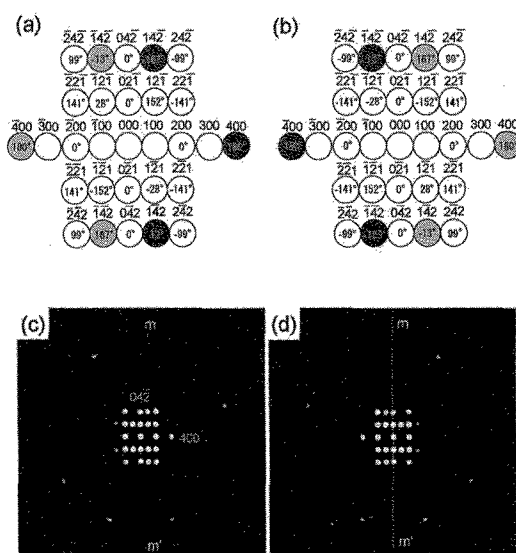


Fig. 4: Phase distribution for ZOLZ reflection disks that appear in a $[012]$ zone-axis CBED pattern of (a) L- and (b) D- α glutamic acid. The corresponding calculated CBED patterns are shown in (c) for L- and in (d) for D- α glutamic acid.

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