The Crystal Structure of the Quasi-Racemate from (+)-*m*-Methoxyphenoxypropionic Acid and (−)-*m*-Bromophenoxypropionic Acid

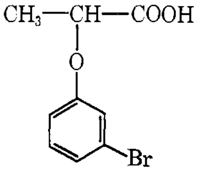
I. L. Karle and J. Karle

Contribution from the U. S. Naval Research Laboratory, Washington, D. C. 20390. *Received September 3, 1965*

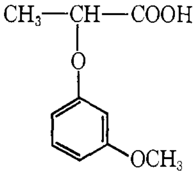
Abstract: A mixture of equal parts of (+)-*m*-methoxyphenoxypropionic acid and (−)-*m*-bromophenoxypropionic acid forms a quasi-racemic compound which crystallizes in the space group C2 with cell dimensions: $a = 33.48$, $b = 5.15$, $c = 11.43$ Å., and $\beta = 90.6°$. A three-dimensional least-squares refinement with isotropic temperature factors resulted in an R factor of 10% for 1170 X-ray intensities. The carboxyl groups of the two different molecules are held together by hydrogen bonds and form quasi-dimers. Except for the –Br and –OCH$_3$ groups, the molecules are related to each other by a pseudo-center of symmetry and are mirror images of each other.

The quasi-racemate method of establishing the configuration of optically active substances was suggested by the early observations of Centnerzwer[1] that (+)-chlorosuccinic acid and (−)-bromosuccinic acid form a molecular compound. The development of the method and its applications has been described by Fredga.[2] Briefly, if a mixture of two chemically similar, optically active materials A and B results in a mixture or solid solution, then both materials probably have the same stereoconfiguration, for example, (+)-A and (+)-B. On the other hand, if a new molecular compound is formed, then the two materials have opposite configurations, such as (+)-A and (−)-B. Compound formation can be established by several means. For example, melting point behavior, solid-state infrared spectra,[3,4] and X-ray powder patterns[5,6] have been used.

The purpose of this crystal structure analysis by X-ray diffraction is to establish the nature of the relationship between the chemically similar pair of optically active molecules, which form a quasi-racemate. In particular it is of interest to determine the spatial arrangement of these two components of the quasi-racemate. The crystals were kindly supplied by Professor Fredga of the University of Uppsala. A description of the compound formation and melting point behavior is contained in a paper by Fredga and Anderson.[7]


(−)

and


(+)

Experimental Section

The crystals were very thin, colorless, transparent laths with the long direction along the b axis. The lattice parameters as determined from precession photographs using Cu Kα radiation were: $a = 33.48 \pm 0.06$, $b = 5.15 \pm 0.01$, $c = 11.43 \pm 0.02$ Å., and $\beta = 90.6 \pm 0.25°$. The density measured by flotation in mixed solvents was 1.492 g. cm.$^{-3}$ while the value calculated from the cell parameters was 1.488 g. cm.$^{-3}$ for four pairs of molecules per unit cell. Systematic absences indicated the space group to be C2, Cm, or C2/m. Space groups Cm and C2/m both have equivalent positions at x, y, z and $x, \bar{y}, z$. Since the b axis is only ~5 Å. long, it seemed impossible to have two molecules stacked over each other in the y direction. Accordingly, space group C2 was chosen, which subsequently proved to be the correct choice.

X-Ray intensity data were collected by the multiple-film, equi-inclination Weissenberg techniques with the crystal mounted parallel to the b axis. The zero through the fourth layer were photographed, although the fourth layer was rather weak and was not used. Of the approximately 2500 independent reflections available in the copper sphere, 1170 were collected. The maximum sin θ value was 0.636 and the minimum $|F|$ observed was ~6.0. The intensities were estimated by visual comparison to a calibrated film strip. Corrections were made for spot size and Lorentz and polarization factors, but not for absorption. The data were placed on an absolute scale and corrected for thermal motion by means of a K curve.[8] Structure factor magnitudes $|F|$ and normalized structure factor magnitudes $|E|$ were computed where

$$E_{\vec{h}}^2 = F_{\vec{h}}^2/\epsilon \sum_{j=1}^{N} f_{j\vec{h}}^2 \qquad (1)$$

For space group C2, $\epsilon = 1$, N is the number of atoms in the unit cell, $f_{j\vec{h}}$ is the X-ray scattering factor for the jth atom, and the $F_{\vec{h}}$ values have been placed on an absolute scale and corrected for thermal motion.

Determination of the Crystal Structure

The structure was determined by two different procedures. Since a heavy atom was present, the classical heavy-atom procedure using the Patterson function could be applied quite readily. It was of interest to us, in addition, to apply the symbolic addition procedure[9,10] for obtaining phases directly from the structure factor magnitudes to a crystal with a heavy atom.

A three-dimensional Patterson function was computed using $(|E_{\vec{h}}|^2 - 1)$ values as coefficients. The *normalized* structure factors $|E_{\vec{h}}|$ describe the structure in terms of *point atoms*, hence the use of $(|E_{\vec{h}}|^2 - 1)$ as coefficients in the Patterson function yields a "sharpened" Patterson with the peak at the origin removed. The x and z coordinates of the Br atom were readily located. In space group C2, the position of the origin along the

---

(1) M. Centnerzwer, *Z. physik. Chem.*, **29**, 715 (1899).

(2) A. Fredga, *Tetrahedron*, **8**, 126 (1960).

(3) A. Rosenberg and L. Schotte, *Arkiv Kemi*, **8**, 143 (1955).

(4) S. Gronowitz, *ibid.*, **11**, 361 (1957).

(5) K. Pettersson, *ibid.*, **7**, 347 (1954).

(6) S. Gronowitz and S. Larsson, *ibid.*, **8**, 567 (1955).

(7) A. Fredga and M. Anderson, *ibid.*, **21**, 555 (1964).

(8) J. Karle and H. Hauptman, *Acta Cryst.*, **6**, 473 (1953).

(9) I. L. Karle and J. Karle, *ibid.*, **16**, 969 (1963); **17**, 1356 (1964); **18**, 345 (1965).

(10) I. L. Karle and J. Karle, *ibid.*, **17**, 835 (1964).

Table I. Set of Signs for Facilitating the Application of Σ_2 to the *h*0*l* Reflections

h k l	Sign	$\|E\|$
26 0 3	+	2.40
6 0 2	*a*	3.55
2 0 2	*b*	2.75
$\overline{12}$ 0 10	*c*	2.68
$\bar{4}$ 0 4	*d*	2.53

Table II. An Application of Σ_3. $sE_{2\vec{h}} \sim s\sum_{\vec{k}} E_{2\vec{k}}(E^2_{\vec{h}+\vec{k}} - 1)$

$2\vec{h}$	$\overline{28}$ 0 10 ($\|E\| = 3.06$)					
	$E_{2\vec{h}} = +2.34$		$E_{2k} = +2.23$		$E_{2\vec{k}} = +1.95$	
$2\vec{k}$	$\overline{20}$ 0 6	20 0 $\bar{6}$	$\overline{20}$ 0 4	20 0 $\bar{4}$	3 2 0 0	$\overline{32}$ 0 0
$\vec{h}+\vec{k}$	$\overline{24}$ 0 8	$\bar{4}$ 0 2	$\overline{24}$ 0 7	$\bar{4}$ 0 3	2 0 5	$\overline{30}$ 0 5
$E^2_{\vec{h}+\vec{k}} - 1$	−1.00	−0.94	−0.83	−0.93	−0.71	−1.00

$sE_{2\vec{h}} \sim +2.34(-1.00 - 0.94) + 2.23(-0.83 - 0.93) + 1.95(-0.71 - 1.00) + \ldots$

b axis is arbitrary and it is not possible to compute phases for general reflections from the position of one heavy atom. For convenience, the origin was so chosen that for the Br atom $y = 0$. From the position of the Br atom, it was possible to determine the phases of a sufficient number of *h*0*l* reflections to determine the structure in projection. Coordinates for the *y* direction were determined from several Br–O vectors recognized in the Patterson and from packing considerations.

In the symbolic addition procedure[9,10] for phase determination, it is generally not feasible to use only two-dimensional data since such a restricted set often leads to unreliable results. In this particular crystal, the presence of the Br atom made the use of two-dimensional data feasible. The phases of the *h*0*l* reflections, which are all real, were determined with the use of the Σ_2 relationship

$$sE_{\vec{h}} \sim s\sum_{\vec{k}} E_{\vec{k}}E_{\vec{h}-\vec{k}} \qquad (2)$$

where s means "sign of." In space group C2, only those reflections with $h + k = 2n$ occur; therefore, to specify the origin in the (010) projection, the sign of one g0u (where g ≡ even and u ≡ odd) reflection is assigned arbitrarily. Four other reflections, one at a time as needed, were assigned letter symbols for phases. From this starting set of five signs, listed in Table I, the signs of all other *h*0*l* reflections with $|E| > 1.4$ expressed as functions of *a*, *b*, *c*, and *d*, were obtained with the use of eq. 2.

In the course of application, many terms enter into the sum of eq. 2. For a particular $E_{\vec{h}}$, each term in the sum has a relatively high probability of indicating the correct phase if all the $|E|$ values are large. Since the individual terms are expressed in terms of different unknown symbols, *a*, *b*, *c*, or *d*, relationships can often be found among the unknowns. If the same relationships occur many times, then it is assumed that they are probably correct. In this investigation, it was found that $a = b$, but there were an insufficient number of relationships to determine or relate the unknowns *c* and *d*. Therefore the correct Fourier would be one among eight possibilities.

As an illustration of how auxiliary phase-determining formulas can facilitate the symbolic addition procedure, another phase-determining formula can be employed to obtain more information about the unknowns. The Σ_3 relationship[11] is

$$sE_{2\vec{h}} \sim s\sum_{\vec{k}} E_{2\vec{k}}(E^2_{\vec{h}+\vec{k}} - 1) \qquad (3)$$

Table III. Coordinates,[a] Standard Deviations, and Isotropic Temperature Factors

	x	10^4 $\sigma(x)$	*y*	10^4 $\sigma(y)$	*z*	10^4 $\sigma(z)$	*B*
Br	0.2205	0	1.1390	0	0.0711	12	3.9
C_1	0.0467	7	0.3797	83	0.1563	19	3.3
C_2	0.0795	7	0.2671	74	0.0826	19	3.7
C_3	0.0601	6	0.1471	132	−0.0280	18	4.1
C_4	0.1311	5	0.5988	93	0.1181	15	3.0
C_5	0.1558	6	0.7689	69	0.0666	17	2.9
C_6	0.1850	7	0.8888	81	0.1386	20	4.0
C_7	0.1848	7	0.8634	93	0.2624	21	3.4
C_8	0.1595	7	0.6812	139	0.3087	20	4.2
C_9	0.1292	6	0.5535	76	0.2392	18	3.7
O_1	0.0301	5	0.2212	52	0.2313	13	4.4
O_2	0.0324	5	0.6059	87	0.1430	14	4.8
O_3	0.1038	4	0.4789	47	0.0396	11	3.1
C_{11}	0.9557	6	0.6165	124	0.3398	17	3.0
C_{12}	0.9227	6	0.7344	70	0.4129	17	3.2
C_{13}	0.9423	6	0.8686	80	0.5227	18	3.5
C_{14}	0.8719	7	0.3866	79	0.3896	19	3.4
C_{15}	0.8493	6	0.2233	67	0.4428	16	2.8
C_{16}	0.8195	6	0.0893	93	0.3761	17	3.3
C_{17}	0.8180	6	0.1160	114	0.2555	18	4.0
C_{18}	0.8406	7	0.2935	82	0.2032	19	4.3
C_{19}	0.8712	7	0.4444	89	0.2633	21	4.3
C_{20}	0.7665	7	−0.2501	73	0.3756	19	4.1
O_{11}	0.9712	5	0.7827	54	0.2621	14	4.7
O_{12}	0.9705	5	0.4051	64	0.3512	16	5.3
O_{13}	0.9000	4	0.5269	43	0.4607	11	2.8
O_{14}	0.7981	4	−0.0907	50	0.4396	12	3.5

[a] These coordinates can be substituted directly into eq. 4–7 for the average planes.

In eq. 2, it was necessary to know the phases of both $E_{\vec{k}}$ and $E_{\vec{h}-\vec{k}}$, whereas in eq. 3, only the phase of $E_{2\vec{k}}$ must be known, since the term $E_{\vec{h}+\vec{k}}$ occurs as a square. The $(E^2 - 1)$ quantity ranges from −1.0 to about +10. An example of the application of eq. 3 is shown in Table II. The contributors shown in Table II plus many others indicated that the phase of the reflection $\overline{28}$ 0 10 was negative. Since this same phase was determined to be *cd* by eq. 2, the relationship that $c = -d$ was established. In a similar manner, it was shown that $c = +$ and $d = -$. Thus, from the application of eq. 2 and 3, it had now been

---

(11) H. Hauptman and J. Karle, "Solution of the Phase Problem. I. The Centrosymmetric Crystal," A.C.A. Monograph No. 3, Polycrystal Book Service, Brooklyn, N. Y., 1953.

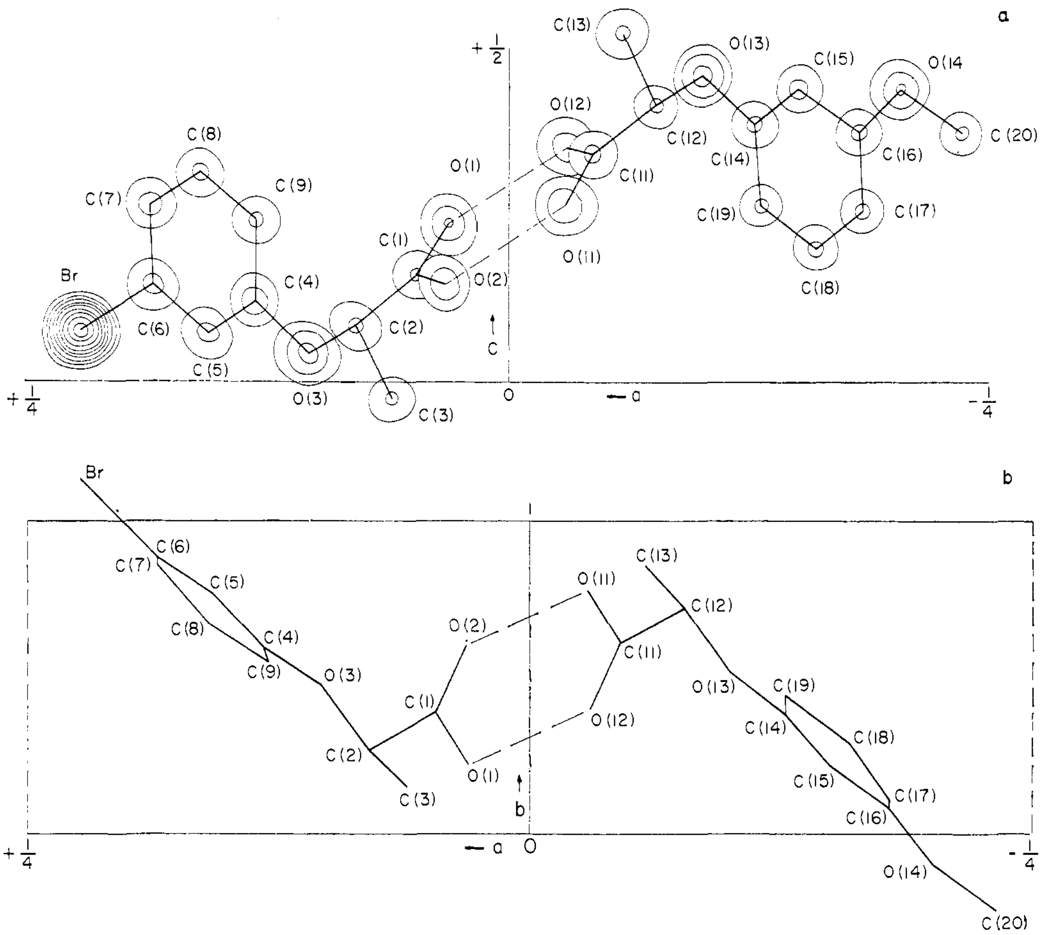


Figure 1. (a) Sections from a three-dimensional electron density map projected along the *b* axis. The contours are equally spaced at 2 electrons Å.$^{-3}$ beginning with the 2 electrons Å.$^{-3}$ contour. Every other contour is omitted for the Br atom. (b) An asymmetric unit viewed along the *c* axis.

established that $a = b$, $c = +$, $d = -$, and two possibilities existed, $a = -$ or $+$. Without further analysis, two Fourier maps were computed, one of which contained the correct structure. The correct sign for *a* was minus. The phases for the *h*0*l* reflections determined by the symbolic addition procedure were identical with those determined from the known position of the Br atom. The main advantage of the symbolic addition procedure is in applications to crystals in which there is no heavy atom or where there are many heavy atoms.

A least-squares refinement, using the program of Busing, Martin, and Levy,[12] was applied to the approximate structure. The function minimized was $\Sigma(F_0 - F_c)^2$ and individual scale factors were used for each layer. With isotropic temperature factors, the *R* factor was reduced to 10.0%.[13] Further refinement with anisotropic temperature factors was not attempted since the main purpose of this investigation was to establish the conformation of a quasi-racemate, and precise values for bond distances were of secondary importance.

The coordinates of the 27 atoms, expressed as fractional parts of a unit cell, and the isotropic temperature factors are listed in Table III. The contents of the asymmetric unit of the cell are illustrated in Figures 1a and 1b. Bond distances and angles are shown in Figure 2.

Discussion of the Structure

The most striking feature of the structure is that the pairs of molecules forming the quasi-racemate arrange themselves about a pseudo-center of symmetry with the (+) molecule being nearly a mirror image of the (−) molecule. Since these are carboxylic acid molecules they form quasi-dimers by hydrogen bonding across a pseudo-center of symmetry (0 0 $^1/_4$). The coordinates listed in Table III are so arranged that pairs of similar atoms in the two molecules, for example, C_I and C_{II}, are related very nearly by x, y, z and $\bar{x}, \bar{y}, {}^1/_2 - z$.

Even though the refinement was carried through to an $R = 10.0\%$, the Br atom scatters so strongly, that the coordinates of the lighter atoms were not obtained very precisely, as is indicated from the distortions in the phenyl rings (Figure 2). Nevertheless, the bond distances and angles are near expected values. Aside from the two hydrogen bonds at 2.60 and 2.62 Å. between the carboxyl groups, the nearest approaches between atoms of different molecules are all greater than 3.0 Å. Those intermolecular distances which are less than 3.5 Å. are listed in Table IV.

---

(12) W. R. Busing, K. O. Martin, and H. A. Levy, ORFLS, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1962.

(13) Observed and calculated structure factors have been deposited as Document No. 8580 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington, D. C. A copy may be secured by citing the document number and by remitting $2.50 for photoprints, or $2.00 for 35-mm. microfilm. Advance payment is required. Make checks or money orders payable to: Chief, Photoduplication Service, Library of Congress.

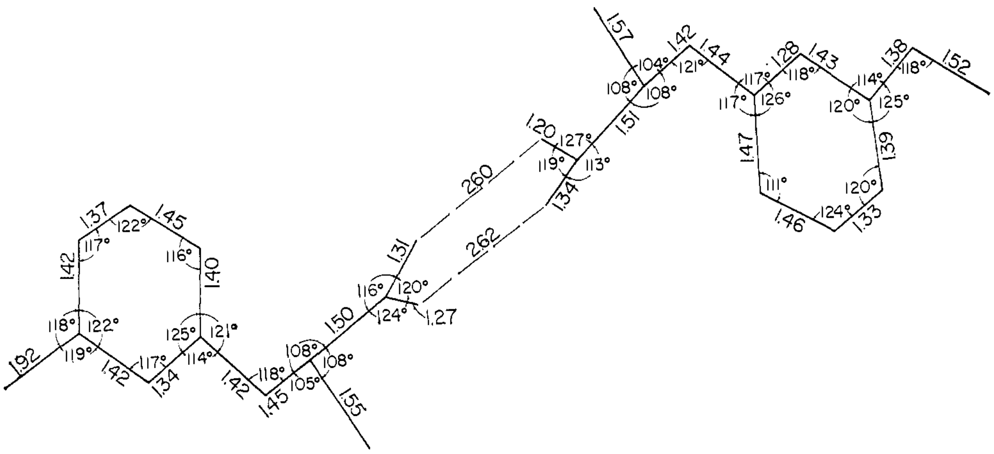


Figure 2. Bond distances and angles for the quasi-racemate. The standard deviations for the bond lengths are of the order of 0.02 Å. for C–Br, 0.05 Å. for C–C, and 0.04 Å. for C–O.

Table IV. Intermolecular Distances Less than 3.5 Å. [a]

$O_1'–O_{11}$	3.02 Å.	$x, y + 1, z$
$O_1'–O_2$	3.33	$x, y + 1, z$
$O_{11}–O_{12}'$	3.36	$x, y + 1, z$
$O_{14}–O_{20}'$	3.14	$^1/_2 - x, ^1/_2 + y, \bar{z}$
$C_8–O_{13}'$	3.40	$\bar{x}, y, \bar{z}$
$C_{18}'–O_3$	3.47	$\bar{x}, y, \bar{z}$
$O_1–C_{13}'$	3.47	$\bar{x}, y, \bar{z}$
$O_{11}'–C_3$	3.43	$\bar{x}, y, \bar{z}$

[a] The coordinates of the primed atom are obtained by the symmetry operation indicated in the third column.

The bromophenoxy group is nearly coplanar, as is the methoxyphenoxy group. The average planes through these two groups are nearly parallel. Their equations are, respectively

$$-0.65071ax + 0.74821by + 0.12939cz = -0.35698 \quad (4)$$

$$-0.67171ax + 0.72440by + 0.15511cz = -17.4689 \quad (5)$$

where a, b, and c are the cell lengths and the value on the right-hand side is the origin-to-plane distance in Å. The equations for the average planes through the carboxyl group plus the adjacent carbon atom for the bromo and methoxy molecules, respectively, are

$$0.63978ax + 0.31897by + 0.69919cz = 2.8400 \quad (6)$$

$$0.62284ax + 0.33509by + 0.70695cz = 23.7719 \quad (7)$$

Pairs of carboxyl groups bonded by the hydrogen atoms are essentially in the same plane. The dihedral angle formed by the planes of the phenoxy and carboxyl groups is ~85.5°.

Acknowledgment. We are indebted to Professor Arne Fredga of the University of Uppsala for supplying us with the crystals of the quasi-racemate and to Dr. Henry Fales of the National Institutes of Health for introducing us to the problem and for his helpful discussions. We wish to thank Mr. Stephen Brenner and Dr. Donald Mitchell of the Naval Research Laboratory for performing the computations.