

# The Crystal and Molecular Structure of Bromhexine · HCl

Chung Hoe Koo, Yong Je Jung and Soon Won Lee

College of Natural Science, Seoul National University, Seoul 151, Korea

(Received 2 October 1984)

**Abstract** □ The crystals of bromhexine-HCl,  $C_{14}H_{21}N_2Br_2Cl$ , are orthorhombic, space group  $Pca2_1$  with  $a=14.598(2)\text{Å}$ ,  $b=12.461(3)\text{Å}$ ,  $c=9.186(1)\text{Å}$  and  $Z=4$ . Intensity data for 967 reflections ( $F_{obs}>6\sigma(F)$ ) were collected on a Rigaku-Denki automatic four-circle diffractometer. The structure was solved by the Patterson and Fourier methods. Refinements were carried out to the final R value of 0.082. The cyclohexane ring has a normal chair form and the benzene ring is planar. There are three independent hydrogen bonds in the structure. One is an intermolecular hydrogen bond ( $N-H\dots Cl^-$ ) and the others are intramolecular hydrogen bonds ( $N-H\dots Br$ ,  $N^+-H\dots Cl^-$ ). Apart from the hydrogen bonding system the molecules are held together in the crystal by van der Waals force.

**Keywords** □ Bromhexine-HCl, Patterson and Fourier methods, Four-circle diffractometer.

Bromhexine-HCl has a powerful expectorant activity. Structural information of the compound may be meaningful for the study of the activity. The structure determination of bromhexine·HCl has been completed using a single crystal X-ray diffraction method. The details of the crystal and molecular structure of this compound is presented.

The structure determination was undertaken in order to establish the conformation of a cyclohexane ring which was expected to be a chair form, and to examine the configuration around the nitrogen ion ( $N2^+$ ).

## EXPERIMENTAL METHODS

White, plate-like crystals were obtained by slow evaporation from an absolute ethanol solution. The orthorhombic symmetry and space group,  $Pca2_1$ , were determined by oscillation and Weissenberg photographs. The unit cell dimensions and their estimated standard deviation (Table I) were determined by the least-squares refinement of  $2\theta$  values of 25 reflections ( $20^\circ < 2\theta < 60^\circ$ ) measured on a Rigaku-Denki automatic four-circle diffractometer.

The density was measured by flotation method in a mixture of carbontetrachloride and methyl iodide.

The intensities of 1473 independent reflections with  $0^\circ < 2\theta < 120^\circ$  were recorded on a Rigaku-Denki automatic four-circle diffractometer with graphite-monochromatized  $CuK\alpha$  radiation in the  $\omega$ - $2\theta$  scanning mode, with a scan width of  $(1.2 + 0.5 \tan\theta)^\circ$  in  $\omega$ . At both ends of the scan range 10 seconds background counts were measured for each reflection. Three reference reflections were monitored after every 50 reflections and showed only small random deviations from their mean intensities. 967 reflections were considered to be observed ( $F_{obs}>6\sigma(F)$ ) and were included in the subsequent calculations. The intensity data were reduced to structure factors by the application of Lorentz and polarization factors, and no absorption corrections were applied.

**Table I: Crystal data for bromhexine·HCl.**

Molecular formular: C <sub>14</sub> H <sub>21</sub> N <sub>2</sub> Br <sub>2</sub> Cl	
Crystal system: orthorhombic	
Space group: Pca <sub>21</sub> from systematic absences	
a=14.598(2)Å	b=12.461(3)Å
c=9.186(1)Å	V=1670.9Å <sup>3</sup>
Z=4	F(000)=824.0
Dc=1.64gcm <sup>-3</sup>	Dm=1.62gcm <sup>-3</sup>
μ(CuKα)=71.3cm <sup>-1</sup> Crystal size;	
0.05×0.3×0.6mm <sup>3</sup>	

**Structure Determination and Refinement**

The structure was solved by Patterson and Fourier methods. After the structure factors (Fobs's) were converted into the normalized structure factors (E's), three dimensional sharpened E<sup>2</sup>-I Patterson synthesis was computed.

The positions of two bromine atoms (Br1, Br2) and one chlorine atom were deduced from the study of the Harker section (*U, V, 1/2*) and the Harker lines (*1/2, V, 0*), (*U, 0, 1/2*). Structure factor calculation on these 3 atoms gave R=0.29 and following three dimensional Fobs synthesis revealed all the remaining non-hydrogen atoms.

Positional and thermal parameters of the non-hydrogen atoms were refined by the block-diagonal least-squares method using the program written by Shiono<sup>1)</sup>. Five cycles of isotropic refinement decreased the *R* value to 0.166. Five cycles of anisotropic refinement resulted in the *R* value of 0.105. The subsequent refinements were carried out by the full matrix least-squares method using the *SHELX76*<sup>2)</sup> program system.

**Table II: The final fractional coordinates (×10<sup>4</sup>) and anisotropic thermal parameters (×10<sup>3</sup>) for the non-hydrogen atoms in bromhexine·HCl. The estimated standard deviations referred to the last figures are in parentheses. The Uij values were defined by the temperature factor; exp (-2π<sup>2</sup>(U<sub>11</sub>h<sup>2</sup>a\*<sup>2</sup>+U<sub>22</sub>k<sup>2</sup>b\*<sup>2</sup>+U<sub>33</sub>l<sup>2</sup>c\*<sup>2</sup>+U<sub>23</sub>klb\*c\*+U<sub>13</sub>hla\*c\*+U<sub>12</sub>hka\*b\*))**

ATOM	X	Y	Z	U11	U22	U33	U23	U13	U12
BR (1)	2,470 (4)	822 (3)	54 (0)	80 (3)	71 (2)	119 (4)	-41 (3)	33 (3)	-4 (3)
BR (2)	-785 (2)	1,074 (3)	3,226 (9)	52 (2)	57 (2)	112 (4)	14 (3)	28 (2)	-13 (2)
CL	-1,084 (3)	4,666 (4)	1,832(10)	9 (2)	23 (3)	19 (2)	4 (3)	-3 (3)	0 (2)
N (1)	2,737(14)	3,174(21)	1,145(32)	31(16)	54(15)	90(22)	-37(16)	20(15)	-3(11)
N (2)	1,003(13)	5,209(16)	2,191(24)	22(10)	32(11)	62(22)	-5(11)	9(11)	10 (9)
C (1)	1,342(16)	3,264(14)	2,553(33)	49(15)	29(13)	24(13)	9(14)	1(14)	2(12)
C (2)	1,956(18)	2,692(22)	1,647(30)	38(16)	52(17)	14(17)	-1(13)	-8(14)	16(12)
C (3)	1,708(20)	1,634(20)	1,270(34)	51(17)	15(15)	58(20)	7(14)	-7(15)	5(14)
C (4)	862(17)	1,162(20)	1,685(35)	42(13)	29(14)	37(15)	-1(15)	-3(13)	-1(12)
C (5)	297(18)	1,755(20)	2,507(37)	37(15)	29(14)	48(18)	14(16)	17(15)	-1(12)
C (6)	501(17)	2,761(16)	2,928(36)	40(15)	8(11)	66(25)	7(15)	22(16)	8 (9)
C (7)	1,474(15)	4,356(17)	3,024(29)	42(13)	26(12)	25(15)	9(12)	3(12)	7(10)
C (8)	1,300(19)	5,261(25)	560(38)	50(16)	59(19)	65(23)	13(17)	35(16)	8(14)
C (9)	955(14)	6,283(19)	2,949(36)	24(11)	32(15)	50(20)	11(15)	6(12)	9(10)
C (10)	1,851(16)	6,777(21)	3,273(45)	31(14)	35(14)	78(23)	-1(18)	8(19)	-2(11)
C (11)	1,697(21)	7,753(18)	4,308(44)	61(18)	5(13)	104(37)	-1(16)	-32(22)	-8(13)
C (12)	1,118(21)	8,553(22)	3,568(56)	81(20)	30(16)	134(38)	-11(24)	1(28)	-6(15)
C (13)	217(22)	8,078(19)	2,906(63)	63(22)	14(13)	247(50)	6(23)	-71(31)	0(14)
C (14)	368(18)	7,063(19)	2,090(33)	42(16)	23(13)	58(24)	-4(13)	-13(15)	1(12)

**Table III: Fractional atomic coordinates for the hydrogen atoms. The e.s.d.'s are given in parentheses. The isotropic thermal parameters  $U(\times 10^2)$  are all fixed.**

ATOM	X	Y	Z	U
H (1)	293	394	124	13
H (2)	305	260	72	13
H (3)	29	496	222	13
H (4)	70	34	139	13
H (5)	1	320	358	13
H (6)	133	442	417	13
H (7)	219	451	283	13
H (8)	91	588	1	13
H (9)	119	450	3	13
H(10)	202	546	52	13
H(11)	66	608	400	13
H(12)	231	622	381	13
H(13)	215	704	226	13
H(14)	235	811	460	13
H(15)	135	748	528	13
H(16)	93	917	434	13
H(17)	151	891	269	13
H(18)	-10	866	219	13
H(19)	-24	791	380	13
H(20)	-29	671	186	13
H(21)	71	724	108	13

All the coordinates of the hydrogen atoms were generated with C-H bond length constrained to 1.08Å. Finally, one cycle of full matrix least-squares refinement in which all the non-hydrogen atoms were refined anisotropically and the hydrogen atoms were fixed isotropically converged the *R* value to 0.082.

The final atomic coordinates and anisotropic thermal parameters of the non-hydrogen atoms are given in Table II. The coordinates of the hydrogen atoms are given in Table III. The bond distances and angles are given in Table IV.\*

#### *Description and Discussion of the Structure*

The molecular structure with atomic numbering scheme is shown in Fig. 1. The molecule is extended along the *b*-axis.

All the C-C bond lengths in the benzene ring vary from 1.342 to 1.441Å. The bond lengths of Br(1)-C(3) and Br (2)-C(5) are 1.873 and 1.910Å respectively, whereas a normal Br-C single bond length is 1.94Å. The N(1)-C(2) bond length of 1.369Å is slightly shorter than the one in *p*-Aminobenzoic acid.<sup>3)</sup> The C atoms of the six-membered benzene ring are coplanar within 0.02Å and the C(7) and Br(1) atoms lie

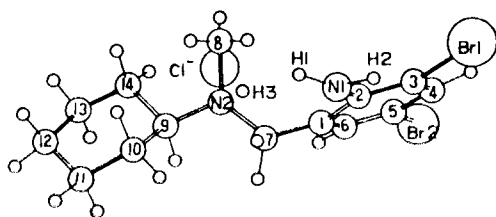
**Table IV: Bond distances (Å) and angles (°) in bromhexine·HCl. The e.d.s's are given in parentheses in units of the last decimal place.**

Bond length(Å)					
Br (1)-C (3)	1.873(29)	Br (2)-C (5)	1.910(29)	N (1)-C (2)	1.369(37)
N (2)-C (7)	1.479(31)	N (2)-C (8)	1.561(37)	N (2)-C (9)	1.510(33)
C (1)-C (2)	1.416(36)	C (1)-C (6)	1.421(36)	C (1)-C (7)	1.441(34)
C (2)-C (3)	1.410(39)	C (3)-C (4)	1.419(40)	C (4)-C (5)	1.342(39)
C (5)-C (6)	1.346(39)	C (9)-C (10)	1.476(41)	C (9)-C (14)	1.517(38)
C (10)-C (11)	1.560(45)	C (11)-C (12)	1.473(50)	C (12)-C (13)	1.566(56)
C (13)-C (14)	1.487(49)				

\* List of structure factors may be obtained from Prof. C.H. Koo, Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151, Korea.

## Bond angle(°)

BR (1)—C (3)—C (2)	119.9(21)	BR (1)—C (3)—C (4)	116.9(21)
BR (2)—C (5)—C (4)	117.3(21)	BR (2)—C (5)—C (6)	119.9(21)
N (1)—C (2)—C (1)	120.2(24)	N (1)—C (2)—C (3)	122.3(25)
N (2)—C (7)—C (1)	117.5(20)	N (2)—C (9)—C (10)	114.9(22)
N (2)—C (9)—C (14)	110.7(21)	C (1)—C (2)—C (3)	116.9(24)
C (1)—C (6)—C (5)	122.2(25)	C (2)—C (1)—C (6)	117.9(23)
C (2)—C (1)—C (7)	124.6(22)	C (2)—C (3)—C (4)	123.0(26)
C (3)—C (4)—C (5)	117.3(26)	C (4)—C (5)—C (6)	122.6(27)
C (6)—C (1)—C (7)	117.3(22)	C (7)—N (2)—C (3)	113.4(19)
C (7)—N (2)—C (9)	114.9(19)	C (8)—N (2)—C (9)	114.7(20)
C (9)—C (10)—C (11)	108.7(25)	C (9)—C (14)—C (13)	111.5(25)
C (10)—C (9)—C (14)	109.8(23)	C (10)—C (11)—C (12)	109.2(27)
C (11)—C (12)—C (13)	113.9(31)	C (12)—C (13)—C (14)	113.1(31)



○: C atoms, ○: H atoms

**Fig. 1:** The molecular structure with atomic numbering scheme.

approximately in the same plane within  $0.06\text{\AA}$ . But Br(2) and N(1) atoms are displaced significantly from this plane. The displacements are  $0.16$  and  $0.12\text{\AA}$  respectively. The equation of the least-squares plane of the benzene ring and that of cyclohexane ring are given in Table V.

The bond lengths of N(2)—C(7), N(2)—C(8) and N(2)—C(9) are  $1.479$ ,  $1.561$  and  $1.510\text{\AA}$  respectively, whereas a normal N—C single bond length is  $1.47\text{\AA}$ . The atoms around N(2) ion (C(7), C(8), C(9) and H(3)) are arranged in a slightly distorted tetrahedral configuration.

The cyclohexane ring maintains a chair conformation of the free cyclohexane ring.<sup>4)</sup>

A stereoscopic diagram illustrating the packing is given in Fig. 2. The molecules are linked by the hydrogen bonds whose description is given in Table VI. There are three hydrogen atoms in a molecule available for the hydrogen bond formation. All the hydrogen atoms take part in forming hydrogen bonds with a bromine atom and a chloride ion. There is an intramolecular hydrogen bond in which N(1) acts as a donor to Br(1). The N(1)⋯Br(1) distance of  $3.122\text{\AA}$  is significantly less than sum of the van der Waals radii. But this does not mean that a strong hydrogen bond exists. The N(1)—H(2)⋯Br(1) angle is  $128^\circ$  and thus the hydrogen bond is considerably weakened. In addition, N(1) forms an intermolecular hydrogen bond with Cl<sup>-</sup> ion of other molecule related to N(1) by a-glide plane perpendicular to the b-axis, with the distance of  $3.257\text{\AA}$ . There is another intramolecular hydrogen bond in which Cl<sup>-</sup> ion accepts H(3) from a quaternary nitrogen ion (N2<sup>+</sup>). The N(2)<sup>+</sup>—H(3)⋯Cl<sup>-</sup> distance is  $3.138\text{\AA}$ . This distance is shorter than the normal N—H⋯Cl hydrogen bond ( $3.21\text{\AA}$ ) indicating that N<sup>+</sup>—H⋯Cl<sup>-</sup> hydrogen bond is stronger than

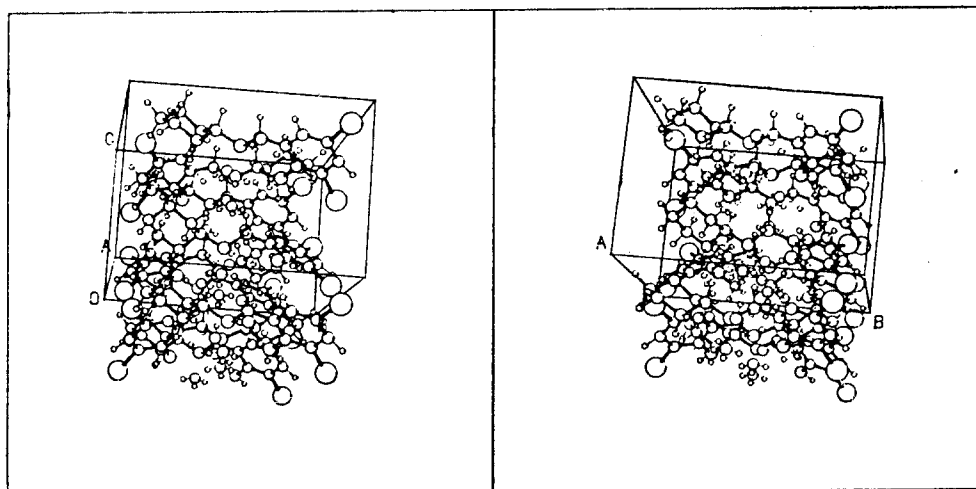


Fig. 2: Stereoscopic diagram showing the packing of the bromhexine·HCl molecules in the unit cell viewed along the a-axis.

Table V: Equations of two planes and deviations of atoms (Å) from the least-squares planes. (Atoms used in the calculation of the plane are indicated by an asterisk.)

Plane through the atoms of benzene ring			
$0.436X - 0.361Y + 0.825Z = 1.302$			
C(1)*	0.0186	Br(1)	-0.0595
C(2)*	-0.0208	Br(2)	0.1601
C(3)*	0.0118	N(1)	-0.1215
C(4)*	0.0005	C(7)	-0.0320
C(5)*	-0.0029		
C(6)*	-0.0071		
Plane through the atoms of cyclohexane ring			
$-0.501X - 0.286Y + 0.817Z = -0.101$			
C(9)*	0.2863	C(13)*	0.1551
C(10)*	-0.3008	C(14)*	-0.2060
C(11)*	0.2414	N(2)	0.0653
C(12)*	-0.1760		

\*\* A dihedral angle between two planes is 56.03°

Table VI: Hydrogen bonds in bromhexine·HCl.

Bond	Position of A	D—H	H···A	D···A	D—H···A
N(1)—H(2)···Br(1)	$x, y, z$	0.935	2.454	3.122	128°
N(2) <sup>+</sup> —H(3)···Cl <sup>-</sup>	$x, y, z$	1.080	2.076	3.138	167°
N(1)—H(1)···Cl <sup>-</sup>	$-1/2+x, 1-y, z$	1.000	2.320	3.257	156°

the one between neutral chlorine and nitrogen atom. Apart from the hydrogen bonding system the molecules are held together by van der Waals force.

#### ACKNOWLEDGEMENT

This research was supported by a grant of the Korea Science and Engineering Foundation

#### LITERATURE CITED

- Shiono, R.: *IBM 1130 Data Reduction and Least Squares Program, Technical Report*, Department of Crystallography, Pittsburgh (1968).
- Sheldrick, G.M.: *SHELX 76*, Program for X-ray structure determination, Univ. of Cambridge, England (1976).

- 3) Lai, T.F. and March, R.E.: The Crystal structure of *p*-Aminobenzoic acid. *Acta Cryst.* **22**, 885 (1967).
- 4) Davis, M. and Hassel, O.: Electron diffraction investigation of molecules containing a cyclohexane type six-membered ring. *Acta Chem. Scand.* **17**, 1181 (1963).
- 5) Savari, K., and Parkanyi, L.: Crystal and molecular structure of *p*-tercyclohexane-1 (isomeric form 1 of 1,4-dicyclohexylohexane), C<sub>18</sub>H<sub>32</sub>. *Acta Cryst.* **B32**, 1059 (1976).
- 6) Stergioudis, G.A., Christidis, P.C. and Rentzeperis, P.J.: The crystal structure of tetramethylammonium tris (O-cyclohexyl dithiocarbonato) nickelate (II) acetone solvate. *Acta Cryst.* **B35**, 612-620 (1970).
- 7) Huber, C.S.: The crystal structure of 1,5-endomethylenequinolizidinium *p*-toluenesulphonate. *Acta Cryst.* **B25**, 1140 (1969).
- 8) Pauling, L.: *The Nature of the Chemical Bond*, 3rd Ed., Cornell Univ. press, Ithaca, N.Y. (1960).