Crystal Structure of 5-Bromocytosine

Masuhiro KATO, Akio TAKENAKA,* and Yoshio SASADA*

Laboratory of Chemistry for Natural Products, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 227

(Received July 14, 1978)

The crystal structure of 5-bromocytosine has been determined by X-ray analysis to investigate the bromination effect on the cytosine moiety. The space group is $P2_1/a$, with dimensions $a=16.943(2)$, $b=9.155(1)$, $c=3.846(1)$ Å, $\beta=99.89(1)°$, and $Z=4$, The structure was solved by the heavy-atom method and refined by the full-matrix least-squares method. A comparison with the cytosine structure indicates some large deviations in bond lengths and angles, which are attributed to the steric and electronic effects caused by bromination. After the VSEPR theory, the slight increase of C(2)-N(3)-C(4) angle (0.8°) is interpreted as the decrease of the effective charge of the lone pair on N(3), and this is related to the difference of pK_a values between 5-bromocytosine and cytosine.

In the course of the studies on the elementary pattern of interactions between purine-pyrimidine base and amino acid, Ohki, Takenaka, Shimanouchi, and Sasada have found that the hydrogen bond scheme between 5-bromocytosine and *N*-acylglutamic acids is quite different from that found in the complexes between cytosine and some amino acids.[1-6] To explain this in terms of molecular structure, the crystal structure of 5-bromocytosine has been determined by X-ray diffraction method.

Experimental and Structure Determination

Colourless, needle-like crystals were obtained from an aqueous solution. The crystal density was measured by flotation in a mixture of bromoform and carbon tetrachloride. Weissenberg photopraphs showed systematic absences, $h0l$ $h=2n+1$ and $0k0$ $k=2n+1$, indicating the space group $P2_1/a$. Accurate unit cell dimensions and diffraction intensities were measured on a Rigaku four-circle automated diffractometer using graphite-monochromated Mo $K\alpha$ radiation ($\lambda=0.71069$ Å). Five reference reflexions monitored periodically showed no significant intensity fluctuations during the course of data collection. The intensities collected with an $\omega/2\theta$ scanning technique were corrected for Lorentz and polarization factors. Of the 1337 independent reflexions ($2\theta\leqq55°$), 1121 had intensities greater than $3\sigma(I)$. Crystallographic data are summarized in Table 1.

The structure was solved by the heavy-atom method and refined by the full-matrix least-squares method, the minimized function being $\sum w\{|F_o|-|F_c|\}^2$. All the hydrogen atoms, found on a difference map, were included in the subsequent refinement. In the refinement, the zero-reflexions for which $|F_c|$ values were smaller than $|F_o|_{lim}$ (3.748) were omitted

Table 1. Crystal data

5-Bromocytosine	
$C_4H_4N_3OBr$	
Crystal system: monoclinic	
Systematic absences: $h0l$ $h=2n+1$, $0k0$ $k=2n+1$	
Space group: $P2_1/a$	
$a=16.943(2)$ Å	$Z=4$
$b=9.155(1)$	$D_x=2.15$ g cm^{-3}
$c=3.846(1)$	$D_m=2.14$
$\beta=99.89(1)°$	
$U=587.7(1)$ Å^3	

Table 2. Final positional and thermal parameters

Standard deviations are given in parentheses. The anisotropic thermal factor has the form $\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+\beta_{12}hk+\beta_{13}hl+\beta_{23}kl)]$.

Atom	x*	y*	z**	β_{11}*	β_{22}*	β_{33}**	β_{12}*	β_{13}**	β_{23}**
N (1)	21717(40)	39815(74)	8023(21)	169(20)	406(64)	653(53)	−162(63)	−7(16)	2(29)
C (2)	25007(47)	26816(90)	9284(26)	159(22)	622(85)	674(67)	3(70)	17(19)	−60(35)
N (3)	21061(39)	14198(72)	8226(21)	183(19)	487(61)	665(52)	−85(61)	−4(16)	49(29)
C (4)	14089(41)	14615(71)	5989(21)	165(20)	375(64)	513(47)	56(63)	47(16)	−21(29)
C (5)	10693(48)	28424(76)	4690(23)	197(22)	508(76)	523(56)	112(67)	31(18)	66(30)
C (6)	14585(45)	40758(81)	5974(23)	177(21)	513(70)	556(52)	122(69)	30(17)	33(32)
O (2)	31553(44)	26479(67)	11364(26)	285(23)	391(57)	1136(79)	−127(59)	−59(22)	−7(32)
N (4)	10440(40)	1672(75)	5129(24)	167(20)	531(70)	781(60)	−72(62)	−40(18)	5(32)
Br	242(5)	28826(9)	2023(3)	227(4)	854(12)	565(8)	62(7)	−22(2)	42(3)

Atom	x**	y***	z***	B(Å^2)
H (1)	2381(69)	457(14)	843(28)	0.0(1.8)
H (41)	1295(57)	−94(11)	603(26)	0.0(1.6)
H (42)	583(60)	1(11)	355(28)	0.0(1.6)
H (6)	1205(93)	478(18)	496(41)	2.0(2.6)

* $\times10^5$, ** $\times10^4$, *** $\times10^3$.

in each cycle of refinement. The weight functions used were: $w=1/(\sigma_p^2+q|F_o|^2)$ for $|F_o|\geqq|F_o|_{lim}$, where σ_p is the standard deviations based on counting statistics; $w=w(|F_o|_{lim})$ for $|F_o|<|F_o|_{lim}$. The coefficient q was 0.883×10^{-3}, derived from the intensity variance of the monitored reflexions.[7] The refinement was terminated when the maximum shifts of positional and thermal parameters were less than 0.16σ and 0.22σ, respectively, for non-hydrogen atoms. The final value of R is 0.069 ($R=0.056$ for the non-zero reflexions). Atomic scattering factors used were taken from "International Tables for X-Ray Crystallography."[8] Atomic parameters are given in Table 2, and observed and calculated structure factors in Table 3.[9]

Results and Discussion

Bond lengths and angles are shown in Fig. 1, and a comparison with the cytosine values[10] is given in Fig. 2. Rather large deviations from cytosine bond lengths and angles may be attributed to the steric and electronic effects caused by bromination. The lengthening of C(4)–C(5) and C(5)–C(6) bonds accompanied by the decrease of C(5)–C(4)–N(3) and C(5)–C(6)–N(1) angles are due to repulsions from Br to C(4) and C(6) atoms. The marked deviation at C(5)–C(4)–N(4) angle is obviously ascribed to the repulsion between Br and N(4). After an interpretation for benzene ring deformation[11] on the basis of the valence shell electron pair repulsion theory, the bromination at C(5) makes the C(4)–C(5)–C(6) angle enlarge, but these repulsions cause the opposite effect, so that this angle is not so large. Such steric effect of bromination may spread to the C(2)–N(3)–C(4) and C(2)–N(1)–C(6) angles, and further the N(1)–C(2)–N(3) angle, so that they slightly expand. It is plausible that the shrinkage of lone-pair lobe on N(3), which is caused by electron-withdrawing property of bromine, facilitates the release of constrain by opening of the C(2)–N(3)–C(4) angle. Therefore, the slight increase of the angle (0.8°) supports the decrease of the effective charge of lone pair on N(3), and this is related to the difference of pK_a values between 5-bromocytosine and cytosine [4.58 and 3.04, respectively[12-13]].

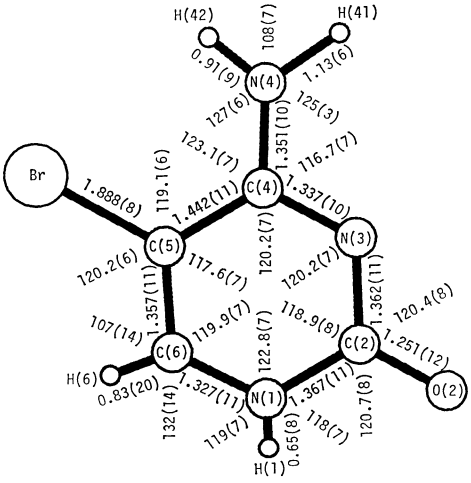

Fig. 1. Bond lengths (l/Å), angles (ϕ/°), and their standard deviations.

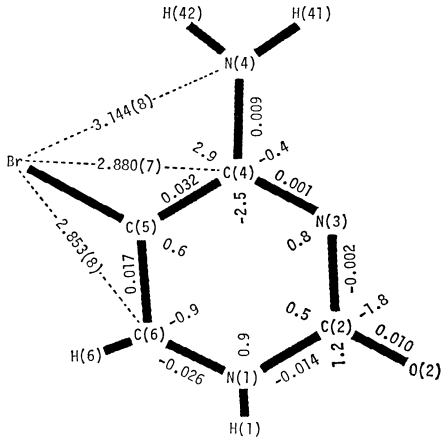

Fig. 2. Differences in bond lengths (l/Å) and angles (ϕ/°) between 5-bromocytosine and cytosine: (5-bromocytosine values) − (cytosine values).

On the other hand, the C(4)–N(4) length is considerably short, while the C(2)–O(2) length is rather long, as compared with the average distances.[14] Such a trend which is also found in cytosine[10] indicates the contribution from the canonical formulae 2, 3, and 4 in Fig. 3, in which the amino nitrogen and carbonyl oxygen carry positive and negative charges, respectively. The shortening of C(6)–N(1) bond is due to the electronic effect of bromine as described by canonical formulae 4 and 5 in Fig. 3. This suggests the ability of proton donation of N(1)–H to be rather strong.

The least-squares plane of 5-bromocytosine together with the deviations from the plane is listed in Table 4. Although the pyrimidine ring with carbonyl oxygen O(2) and amino nitrogen N(4) is planar within 0.04 Å, the bromine atom shifts by 0.18 Å from the mean plane to relieve its steric hindrance.

As shown in Fig. 4, two hydrogen bonds between molecules related by the 2_1 axis, N(4)–H···O(2) and N(1)–H···N(3), constitute a ribbon along [010] direction. Hydrogen bond distances and angles are

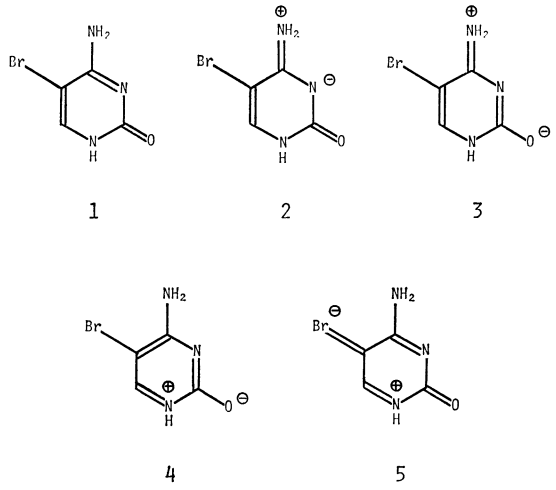

Fig. 3. Some possible canonical structures for 5-bromocytosine.

Table 4. Molecular plane

X, Y, and Z are in Å along the crystal axes, respectively
Asterisks denote atoms defining the plane.
Standard deviations are given in parentheses.

Equation to the pyrimidine ring
$-0.6242(27)X+0.0428(31)Y+0.8757(16)Z-0.587(15)=0$

Deviations (l/Å) of atoms from the plane

N(1)*	−0.025	O(2)	0.008
C(2)*	0.001	N(4)	0.043
N(3)*	0.012	Br	0.182
C(4)*	−0.002	H(1)	−0.08
C(5)*	−0.026	H(41)	0.04
C(6)*	0.043	H(42)	−0.01
		H(6)	0.00

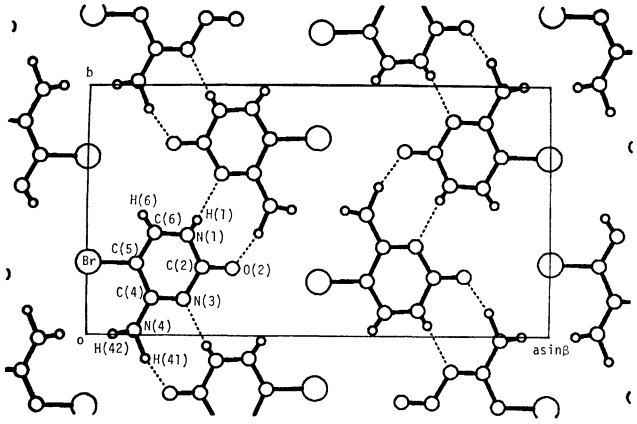

Fig. 4. The crystal structure viewed along the c axis.

Table 5. Hydrogen bond distances and angles
Standard deviations are given in parentheses.

Distance (l/Å)		Angle (ϕ/°)	
N(1)···N(3)[a]	2.820(10)	C(2)-N(1)···N(3)[a]	113.1(6)
H(1)···N(3)[a]	2.21(8)	C(6)-N(1)···N(3)[a]	121.6(6)
O(2)···N(4)[a]	2.890(11)	N(1)-H(1)···N(3)[a]	157(8)
O(2)···H(41)[b]	1.80(6)	C(2)-N(3)···N(1)[b]	111.8(6)
		C(2)-N(3)···H(1)[b]	111(2)
Symmetry codes		C(4)-N(3)···N(1)[b]	127.6(5)
(a) $\frac{1}{2}-x, \frac{1}{2}+y, 2-z$,		C(4)-N(3)···H(1)[b]	128(2)
		C(2)-O(2)···N(4)[a]	124.9(6)
(b) $\frac{1}{2}-x, \frac{1}{2}+y, 2-z$.		C(2)-O(2)···H(41)[a]	131(2)
		C(4)-N(4)···O(2)[b]	115.3(6)
		N(4)-H(41)···O(2)[b]	162(5)

listed in Table 5. The N···O and N···N distances are short as compared with the related compounds,[15] though the hydrogen bonds show poor linearity. Similar hydrogen bonding scheme is observed in the crystal structures of cytosine,[10] cytosine monohydrate,[10] and 5-bromocytosine: dioxan (2: 1) crystal.[16] Such a common feature can be interpreted by the preference of N–H···O hydrogen bond between positively charged amino group and negatively charged carbonyl group. The hydrogen donating property of the remaining N(4)–H becomes weak, so that N(1)–H is a hydrogen-donor to N(3).

The pyrimidine rings are stacked with the spacing of 3.368 Å along the c axis. There are no abnormal contacts between atoms.

Figures 1, 2, and 4 were drawn by TSD:XTAL which is a graphic display programme system for NOVA 3 mini-computer to produce crystal and molecular structures.[17] The present work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education.

References

1) M. Ohki, A. Takenaka, H. Shimanouchi, and Y. Sasada, *Bull. Chem. Soc. Jpn.*, **48**, 848 (1975).
2) M. Ohki, A. Takenaka, H. Shimanouchi, and Y. Sasada, *Bull. Chem. Soc. Jpn.*, **49**, 3493 (1976).
3) M. Ohki, A. Takenaka, H. Shimanouchi, and Y. Sasada, *Bull. Chem. Soc. Jpn.*, **50**, 90 (1977).
4) A. Takenaka, M. Ohki, and Y. Sasada, 36th National Meeting of the Chemical Society of Japan, Oasaka, April 1977, Abstr. I, 4M10.
5) C. Tamura, T. Hata, S. Sato, and N. Sakurai, *Bull. Chem. Soc. Jpn.*, **45**, 3254 (1972).
6) T. Hata, M. Yoshikawa, S. Sato, and C. Tamura, *Acta Crystallogr., Sect. B*, **31**, 312 (1975).
7) L. E. McCandlish and G. H. Stout, *Acta Crystallogr., Sect. A*, **31**, 245 (1975).
8) "International Tables for X-Ray Crystallography," Kynoch Press, Birmingham (1974), Vol. IV, p. 71.
9) Table 3 has been deposited as Document No. 7901, at the Office of the Bulletin of the Chemical Society of Japan.
10) R. J. McClure and B. M. Craven, *Acta Crystallogr., Sect. B*, **29**, 1234 (1973).
11) A. Domenicano, A. Vaciago, and C. A. Coulson, *Acta Crystallogr., Sect. B*, **31**, 1630 (1975).
12) A. Albert, in "Synthetic Procedures in Nucleic Acid Chemistry," ed by W. W. Zorbach and R. S. Tipson, John Wiley & Sons, Inc., New York (1973), p. 1.
13) I. Wempen and J. J. Fox, *J. Am. Chem. Soc.*, **86**, 2474 (1964).
14) "Tables of Interatomic Distances and Configuration in Molecules and Ions. Supplement 1956—1959," ed by L. E. Sutton, The Chemical Society, London (1965).
15) J. Donohue, in "Structural Chemistry and Molecular Biology", ed by A. Rich and N. Davidson, W. H. Freeman & Company, San Francisco (1968), p. 443.
16) M. Kato, A. Takenaka, and Y. Sasada, unpublished.
17) A. Takenaka and Y. Sasada, Annual Meeting of the Crystallographic Society of Japan, Hiroshima, November 1978, Abstr. p. 32.