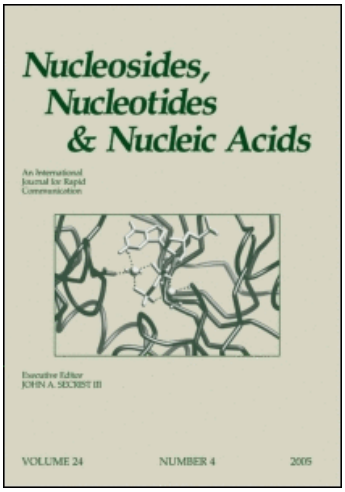

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Influence of Acetyl and Bromine Substitutions on Stacking. Crystal and Molecular Structures of 8-Bromo 2',3',5'-Triacetyl Adenosine and 8-Bromo 2',3',5'-Triacetyl Guanosine

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INFLUENCE OF ACETYL AND BROMINE SUBSTITUTIONS ON STACKING. CRYSTAL AND MOLECULAR STRUCTURES OF 8-BROMO 2',3',5'-TRIACETYL ADENOSINE AND 8-BROMO 2',3',5'-TRIACETYL GUANOSINE

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ABSTRACT: The three dimensional structures of 8-bromo 2',3',5'-triacetyl adenosine (8-Br Tri A) and 8-bromo 2',3',5'-triacetyl guanosine (8-Br Tri G) have been determined by single crystal X-ray diffraction methods to study the combined effect of bromine and acetyl substitutions on molecular conformation and interactions. The ribose puckers differ from those found in unbrominated Tri A and Tri G and unacetylated 8-Br A and 8-Br G analogues. The adenine bases in 8-Br Tri A form A.A.A base triplets using both Watson-Crick and Hoogsteen sites. Br atoms are not involved in stacking unlike most halogenated structures. The 'scorpion tail' positioning of acetyl over base in 8-Br Tri G is different from Tri G and is an interesting consequence of bromine substitution.

INTRODUCTION

Recent investigations on ribose acetylated nucleosides demonstrate that the acetyl group significantly influences base stacking[1-7]. Halogenated bases are also known to affect the stacking patterns[8-10]. The 8-bromo substitution in purines also restricts the nucleoside conformation to the **syn** region[11-16]. Crystal structure studies on 2',3',5'-triacetyl adenosine and 2',3',5'-triacetyl guanosine (abbreviated Tri A and Tri G) and 8-bromo adenosine and 8-bromo guanosine (8-Br A and 8-Br G) have recently brought to light the individual influence of acetyl groups and bromine atoms on molecular conformation and

TABLE 1

Crystal Data

	8-Br Tri A	8-Br Tri G
Formula	$C_{16}H_{18}N_5O_7Br$	$C_{16}H_{18}N_5O_8Br$
Molecular weight	472.25	488.25
Space group	$P2_12_12_1$	P1
a	7.885(1) Å	8.201(1) Å
b	15.047(2) Å	8.753(1) Å
c	16.970(1) Å	15.700(2) Å
α	90.0°	74.20(1)°
β	90.0°	72.54(1)°
γ	90.0°	69.76(1)°
Volume	2013.42 $Å^3$	990.66 $Å^3$
Z	4	2
$D_{calculated}$	1.56 Mg/m^3	1.64 Mg/m^3
$D_{measured}$	1.56 Mg/m^3	1.63 Mg/m^3
λ(CuKα)	3.51 mm^{-1}	3.63 mm^{-1}
Crystal size	0.25X0.30X0.55 mm	0.30X0.35X0.45 mm
$\sin\theta_{max}/\lambda$	0.617 $Å^{-1}$	0.617 $Å^{-1}$

interactions[4,6,7,17]. The X-ray studies on the title compounds (8-Br Tri A and 8-Br Tri G) were taken up to investigate the effect of these groups when they are present together within the same molecule.

EXPERIMENTAL

Cuboidal crystals of both the samples (SIGMA Chemicals Co.) were obtained by slow evaporation of ethanol-water mixtures heated to 35°C, as the solubility of the samples at room temperature was poor. The crystal data are given in Table 1.

Three dimensional CuKα intensity data for the two crystals were collected on a CAD-4 diffractometer up to $\theta = 75°$ using $\omega - 2\theta$ scan. The data were corrected for Lorentz, polarization, absorption and anomalous dispersion effects. The structure of 8-Br Tri A was solved using Patterson and difference Fourier

syntheses. It was refined by full matrix least squares methods (enhanced version of SHELX76[18]), anisotropically for non-hydrogens and isotropically for hydrogen atoms. The final R=0.062 (R_w=0.060). All the hydrogens were located from difference Fourier maps. The function minimized during refinement was $\Sigma w(|Fo|-|Fc|)^2$, where $w=1/\sigma^2(F)$. The structure of 8-Br Tri G was solved by the interpretation of Patterson and weighted Fourier maps. Full matrix least squares refinement (SHELX400[18]) with anisotropic temperature factors for non-hydrogens and isotropic for hydrogens converged at 0.070 (R_w=0.065). Hydrogen atoms not located from difference Fourier maps were fixed from geometric considerations. The function minimized during refinement was $\Sigma w(|Fo|-|Fc|)^2$ where $w=1/(\sigma^2(F)+0.018789|F|^2)$.

RESULTS AND DISCUSSION

Figure 1 shows the nucleoside molecules schematically with atomic labelling. Tables 2 and 3 list atomic coordinates and selected torsion angles respectively. The C=O bond in the acetyl groups varies from 1.15(1) to 1.22(1) Å, a range found in many related structures. The acetyl oxygens O(22'), O(23') and O(25') are **cis** to C(2'), C(3') and C(5') atoms respectively. The molecular conformations are shown in Fig. 2 and compared with unbrominated and unacetylated analogues in table 4. The conformation about the glycosyl bond in both the structures is **syn** except for molecule B in 8-Br Tri G. The **high syn** conformation, as observed in this molecule can be considered as part of **anti** region[19]. Bulky substitutions at 8-position are known to restrict nucleoside conformations essentially to **syn**[11,17,20,21] . There are however suggestions from NMR studies that neither Br nor CH_3 is sufficiently bulky to exclude the **anti** conformation[22]. An **anti** conformation has in fact been seen in crystals of dehydrogenase enzyme complexed with 8-substituted purine nucleotides[23-25].

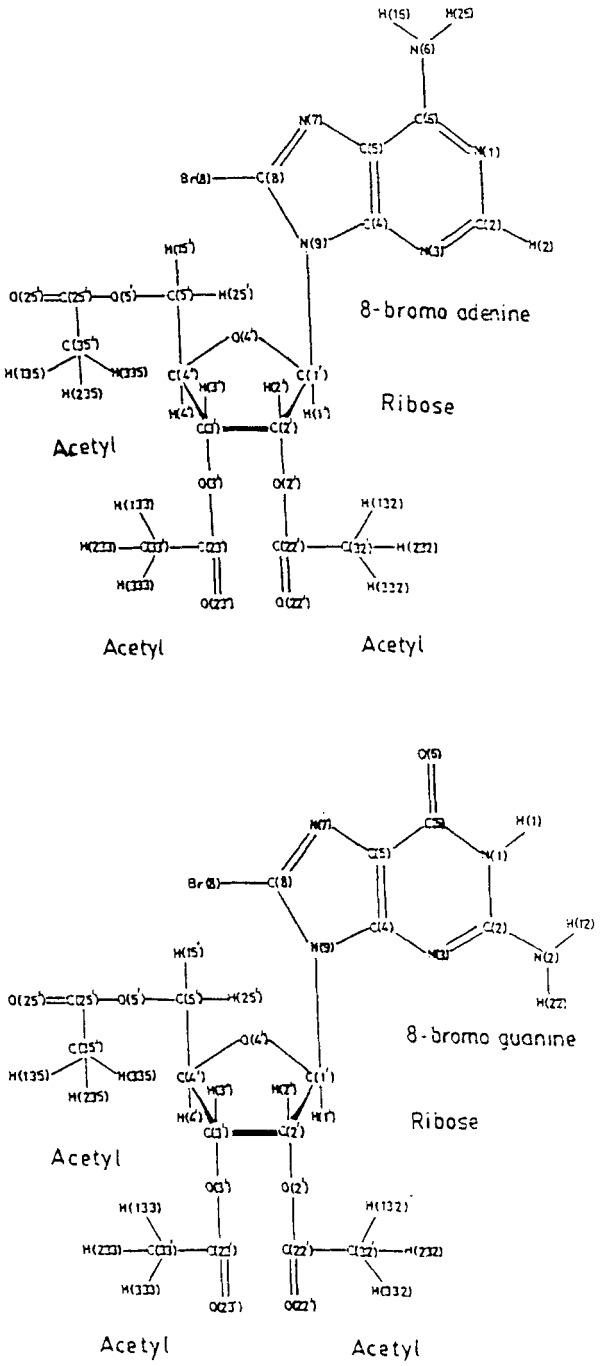

FIG. 1. Chemical structure and numbering scheme for 8-Br Tri A (top) and 8-Br Tri G (Bottom).

TABLE 2.

Final positional parameters of non hydrogen atoms ($X10^4$) and equivalent temperature factors with e.s.d s in parentheses.

$$Beq = (4/3)\Sigma\Sigma Bij\ a_i.a_j$$
$$ij$$

ATOM	X	Y	Z	EQUIVALENT B ($Å^2$)	ATOM	X	Y	Z	EQUIVALENT B ($Å^2$)
8-Br-Tri A									
N(1)	1035(1)	6528(4)	4448(4)	3.4(2)	O(22')	1110(1)	7190(5)	800(5)	7.4(3)
C(2)	1075(1)	6032(6)	3817(6)	3.8(2)	C(32')	919(2)	8340(8)	363(9)	7.2(4)
N(3)	988(1)	5870(5)	3166(4)	3.7(2)	C(3')	898(1)	5443(6)	785(4)	3.5(2)
C(4)	837(1)	6278(5)	3200(4)	3.1(2)	O(3')	826(1)	5704(4)	45(3)	4.6(2)
C(5)	773(1)	6794(5)	3816(4)	3.1(2)	C(23')	903(2)	5451(6)	-602(5)	4.4(3)
C(6)	882(1)	6930(5)	4456(4)	3.1(2)	O(23')	1021(1)	4953(6)	-593(5)	8.3(3)
N(6)	843(1)	7449(5)	5071(4)	3.7(2)	C(33')	824(2)	5841(9)	-1317(6)	5.5(4)
N(7)	611(1)	7100(4)	3644(3)	3.2(1)	C(4')	797(1)	4668(6)	1146(5)	3.6(2)
C(8)	582(1)	6777(5)	2955(4)	3.1(2)	O(4')	903(2)	3845(7)	1280(7)	4.9(3)
BR(8)	3770(1)	6964(1)	2419(1)	4.4(2)	C(5')	1059(1)	4092(5)	1626(4)	5.4(2)
N(9)	710(1)	6277(4)	2635(4)	2.8(1)	O(5')	1106(2)	3706(7)	2258(6)	5.8(3)
C(1')	718(1)	5910(6)	1841(5)	3.2(2)	C(25')	1022(1)	3144(6)	2600(5)	8.9(3)
C(2')	870(1)	6204(6)	1381(4)	3.5(2)	O(25')	1271(2)	4060(10)	2556(8)	7.1(4)
O(2')	834(1)	7042(4)	1020(3)	3.9(2)	C(35')	734(1)	4975(4)	1895(3)	4.2(2)
C(22')	973(2)	7479(7)	744(6)	5.2(3)					
8-Br-Tri G									
MOLECULE A					**MOLECULE B**				
N(1)	1666(1)	-5010(7)	11280(4)	3.2(2)	N(1)	2257(1)	-8637(7)	11955(4)	3.4(2)
C(2)	1746(1)	-3773(8)	10792(4)	3.2(2)	C(2)	2388(1)	-9941(9)	12302(5)	3.4(2)
N(2)	1918(1)	-4131(9)	10748(5)	4.4(2)	N(2)	2541(1)	-9624(9)	12223(7)	5.2(3)
N(3)	1659(1)	-2347(7)	10360(4)	3.3(1)	N(3)	2366(1)	-11423(7)	12701(4)	3.3(2)
C(4)	1486(1)	-2249(7)	10443(4)	3.0(2)	C(4)	2206(1)	-11515(7)	12706(4)	3.1(2)
C(5)	1395(1)	-3396(8)	10901(4)	3.1(2)	C(5)	2070(1)	-10333(9)	12345(4)	3.2(2)
C(6)	1489(1)	-4926(7)	11387(4)	3.0(2)	C(6)	2094(1)	-8712(9)	11925(5)	3.4(2)
O(6)	1431(1)	-6086(7)	11859(4)	3.9(2)	O(6)	1989(1)	-7498(7)	11563(5)	4.7(2)
N(7)	1219(1)	-2838(8)	10843(4)	3.6(2)	N(7)	1926(1)	-10901(8)	12455(4)	3.6(2)
C(8)	1209(1)	-1408(8)	10332(4)	3.3(2)	C(8)	1979(1)	-12422(9)	12866(5)	3.6(2)
BR(8)	996	-3	9989	4.54(2)	BR(8)	18428(1)	-13912(1)	13147(1)	4.70(3)
N(9)	1366(1)	-928(7)	10055(4)	3.2(2)	N(9)	2145(1)	-12909(7)	13048(4)	3.3(1)
C(1')	1392(1)	426(8)	9284(4)	3.3(2)	C(1')	2204(1)	-14454(8)	13693(5)	3.2(2)
C(2')	1547(1)	1070(8)	9178(4)	3.2(2)	C(2')	2393(1)	-14911(7)	13797(4)	3.1(2)
O(2')	1500(1)	2781(6)	8719(3)	3.9(1)	O(2')	2431(1)	-16690(6)	14137(3)	3.5(1)
C(22')	1393(1)	3894(10)	9264(6)	4.4(2)	C(22')	2605(1)	-17600(9)	13923(6)	4.1(2)
C(32')	1337(2)	5601(11)	8725(8)	6.0(3)	C(32')	2623(2)	-19370(11)	14389(9)	5.5(3)
O(22')	1347(2)	3521(10)	10040(5)	7.1(3)	O(22')	2720(1)	-17057(9)	13445(6)	5.6(2)
C(3')	1696(1)	116(8)	8492(5)	3.5(2)	C(3')	2373(1)	-14102(7)	14567(5)	3.4(2)
O(3')	1821(1)	1012(6)	7986(3)	3.8(1)	O(3')	2506(1)	-15046(7)	15077(4)	3.9(2)
C(23')	1987(1)	83(11)	7676(5)	4.1(2)	C(23')	2547(1)	-14233(12)	15576(7)	4.9(3)
C(33')	2109(1)	1142(17)	7162(7)	5.6(4)	C(33')	2689(2)	-15344(18)	16045(9)	6.3(5)
O(23')	2031(1)	-1422(10)	7501(6)	6.1(2)	O(23')	2474(2)	-12806(11)	15621(7)	7.6(4)
C(4')	1591(1)	-109(9)	7897(4)	3.6(2)	C(4')	2182(1)	-14069(8)	15139(5)	3.8(2)
C(5')	1673(2)	-1656(10)	7500(6)	4.4(3)	C(5')	2076(2)	-12557(10)	15532(5)	4.7(2)
O(5')	1704(1)	-3037(7)	8232(4)	5.1(2)	O(5')	2100(1)	-11128(7)	14817(4)	5.1(2)
C(25')	1637(2)	-4389(10)	8053(6)	4.9(3)	C(25')	2019(1)	-9670(9)	15077(6)	4.1(2)
C(25')	1860(3)	-5660(14)	8909(7)	7.2(6)	C(25')	2070(2)	-8268(12)	14364(9)	5.6(3)
O(25')	1921(2)	-4531(10)	7302(5)	6.9(3)	O(25')	1914(1)	-9489(8)	15786(5)	5.7(2)
O(4')	1420(1)	-134(9)	8474(4)	4.6(2)	O(4')	2092(1)	-14324(7)	14552(4)	4.1(1)

TABLE 3

Major torsion angles (°) with e.s.ds in parentheses.

		8-Br Tri A	8-Br Tri G Mol. A	8-Br Tri G Mol. B
χ_{CN}	C(4) -N(9) -C(1')-O(4')	66.4(10)	83.8(9)	98.5(9)
ϕ_{OC}	C(3')-C(4')-C(5')-O(5')	44.9(11)	53.5(10)	-65.1(9)
ϕ_{OO}	O(4')-C(4')-C(5')-O(5')	-73.3(10)	44.5(10)	-76.7(8)
	Ribose			
θ1	C(1')-C(2')-C(3')-C(4')	-17.8(9)	32.1(7)	28.5(7)
θ2	C(2')-C(3')-C(4')-O(4')	-4.6(9)	-28.5(7)	-17.4(7)
θ3	C(3')-C(4')-O(4')-C(1')	27.1(9)	13.6(8)	-1.8(8)
θ4	C(2')-C(1')-O(4')-C(4')	-39.2(9)	7.4(8)	20.6(8)
θ5	O(4')-C(1')-C(2')-C(3')	34.9(9)	-25.2(7)	-31.0(7)

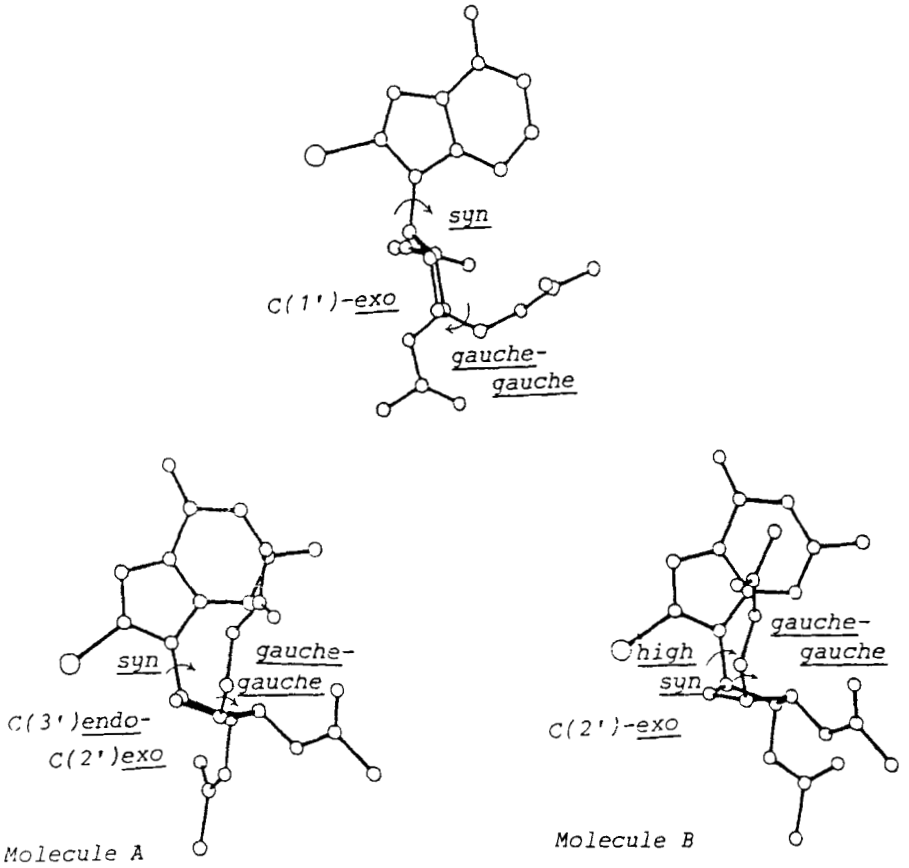

FIG. 2. Conformations of 8-Br Tri A (top) and the two molecules of 8-Br Tri G (bottom).

TABLE 4

Conformations of 8-Br Tri A and 8-Br Tri G compared with unbrominated and unacetylated analogues.

Compound		syn/anti	Sugar pucker	about C(4')-C(5') bond
8-Br Tri A		syn	C(1')-exo	gauche–gauche
Tri A		syn	C(2')endo-C(3')exo	gauche–trans
8-Br A		syn	C(2')-endo	gauche–gauche
8-Br Tri G	A:	syn	C(3')endo-C(2')exo	gauche–gauche
	B:	high syn	C(2')-exo	gauche–gauche
Tri G orthorhombic	A:	anti	C(2')endo-C(1')exo	gauche–gauche
	B:	anti	C(3')exo-C(4')endo	gauche–gauche
Tri G monoclinic		anti	C(2')-endo	gauche–gauche
8-Br G		syn	C(2')-endo	gauche–gauche

The ribose puckers differ in the two structures as well as from those in Tri A, Tri G, 8-Br A and 8-Br G (Table 4). 8-substituted purine nucleosides generally show C(2')-**endo**, a pucker commonly found in unmodified nucleosides/nucleotides. In contrast, ribose acetylation seems to bring about a wide range of sugar conformations. The conformation about the C(4')-C(5') bond is **gauche–gauche** (g^+).

Intermolecular interactions:

With the ribose hydroxyls blocked, the only hydrogen bond donors are N(6) in the adenosine and N(1) and N(2) in the guanosine derivative (Table 5). 8-substituted nucleosides often show intramolecular O(5')-H...N(3) hydrogen bonds. The acetyl group at O(5') in the present structures excludes this possibility. Several close van der Waals contacts involving methyl carbons stabilize the structure (Table 6).

TABLE 5

Hydrogen bond distances (Å) and angles (°)

Donor (A)	Acceptor (B)	A...B (Å)	H...B (Å)	A-H...B (°)	Symmetry of B*	Translation of B
8-Br Tri A						
N(6)	N(1)	2.991(10)	2.39(9)	158(6)	1	-1 1 1
N(6)	N(7)	3.108(10)	2.11(7)	176(9)	1	0 1 1
8-Br Tri G#						
N(1)A	O(6)B	2.855(8)			1	0 0 0
N(2)A	O(6)B	2.805(9)			1	0 0 0
N(2)A	N(7)A	3.104(12)			1	1 0 0
N(1)B	O(6)A	2.984(11)			1	1 0 0
N(2)B	O(6)A	2.854(9)			1	1 0 0
N(2)B	N(7)B	3.062(11)			1	1 0 0
N(1)B	O(22')B	3.112(9)			1	1 -1 0

* Symmetry codes:

for 8-Br Tri A: 1. x+1/2 , -y+1/2 , -z

for 8-Br Tri G: 1. x, y, z

\# Possible hydrogen bonds. Bond parameters involving H atoms are not given as the hydrogen positions were fixed from geometrical considerations.

TABLE 6

Short contacts involving methyl groups

Atom A	Atom B	Dist. (Å)	Symmetry of B*	Translation of B
8-Br Tri A				
C(32')	O(22')	3.23(2)	2	-1 1 0
C(33')	O(4')	3.30(1)	1	1 1 -1
8-Br Tri G				
C(32')A	O(23')A	3.28(1)	1	-1 1 0
C(32')A	O(5')A	3.41(2)	1	0 1 0
C(33')A	O(25')B	3.29(2)	1	0 1 -1
C(33')A	O(4')A	3.45(1)	1	1 0 0
C(32')B	O(23')B	3.50(1)	1	0 -1 0
C(33')B	O(25')A	3.46(2)	1	1 -1 1
C(35')B	O(22')B	3.32(2)	1	-1 1 0

* Symmetry codes

1. x, y, z

2. x+1/2, -y+1/2, -z

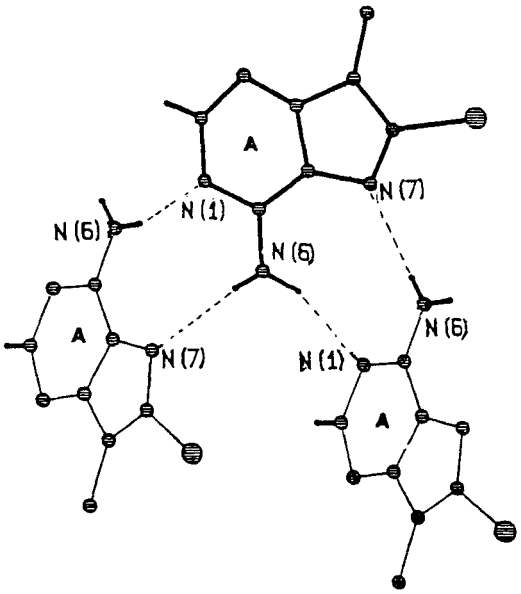

FIG. 3. A.A.A base triplet observed in 8-Br Tri A

A.A.A base triplet:

The N(6) atom in 8-Br Tri A is hydrogen bonded to the N(1) and N(7) atoms of symmetry related molecules. Thus both Watson-Crick and Hoogsteen sites of adenine are used, giving rise to A.A.A base triplets (Fig. 3) similar to those found in Tri A, 8-bromo 2',3'-O-isopropylidene adenosine[26] and 2'-deoxyadenosine[27]. Recent years have seen considerable interest in nucleic acid structures containing triple helices[28-30]. The pairing of adenine in the A.A.A triplet found in the crystals is analogous to U.AU/ T.AT/ A.AT H-bonding schemes proposed for the triple helices[29, 31-33].

The dihedral angle between the paired bases is 46.7° in 8-Br Tri A and 21.3° in Tri A indicating a significantly higher propeller like twist in 8-Br Tri A. The observed propeller twists in various nucleoside/nucleotide structures have recently been well documented by Wilson[34, 35].

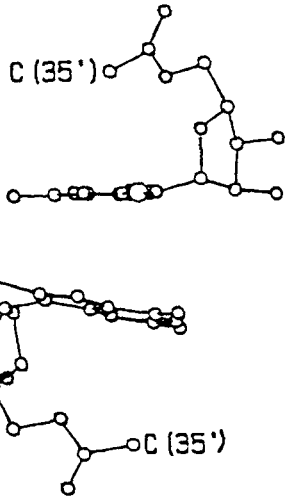

FIG. 4 'Scorpion tail' stacking of acetyl group on base in 8-Br Tri G. Only the 5' acetyl group is shown for the sake of clarity

Stacking:

8-Br Tri A does not show any base-base stacking. The carbonyl oxygens O(23') and O(25') of the acetyl groups stack on symmetry related bases (3.5 and 3.3 Å) as in Tri A. In 8-Br Tri G, the acetyl group at C(5') end folds back so that C(35') methyl sits over the parent base in a 'scorpion tail' fashion (Fig. 4). This is unlike Tri G where the 2' instead of the 5' acetyl group bends back bringing the O(22') atom over the base. The differences observed in the nature of acetyl-base stacking in the two structures is an interesting consequence of bromine substitution. The **syn** conformation in 8-Br Tri G brings the base close to the 5' instead of the 2' acetyl group. In Tri G where the conformation is **anti**, 5' acetyl is too far removed from the base to allow any stacking.

The bases of independent molecules in 8-Br Tri G are 3.4 Å apart. There is however no overlap of Br over base, as observed

in 8-Br G and most other halogenated crystals. The acetyl-base-base-acetyl stacking interaction seen in 8-Br Tri G (Fig. 3) is also different from Tri G. While monoclinic Tri G shows a base-acetyl-base-acetyl stacking with acetyl O(22') between the bases, the orthorhombic form shows ribose O(4') and acetyl O(25') atoms placed over the base.

Earlier structural studies of ribose acetylated nucleosides have demonstrated that stacking of acetyl oxygens on base plays an important role in crystal packing[1-7]. The present structure, with methyl groups in intimate contact with the base instead of the polar oxygens, suggests that acetyl-methyl stacking on base may also play a significant role.

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