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A novel guanine-guanine base pairing: crystal structure of a complex between 7-methylguanosine and its iodide

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ABSTRACT

7-Methylguanosine, one of the biologically important minor nucleosides, could be crystallized as a complex of its zwitterionic form and its iodide, and the crystal structure was determined by the X-ray diffraction method. The crystals belong to the triclinic space group P1 with the unit cell dimensions: a=7.678(1), b=18.094(3), and c=5.711(1) Å, α=79.32(1), β=80.14(1) and γ=76.90(1)°. The structure was solved by the heavy atom method and refined by the least-squares method to give a final R index of 0.075. The novel reverse Watson-Crick type base pairing observed between a positively charged molecule and a deprotonated one indicates that the deprotonation at the N(1) position promoted by the alkylation at the N(7) position may interrupt the formation of the normal Watson-Crick type GC base pair. The conformations about the glycosidic bond and the sugar puckering are quite different between the two molecules: the former has anti and C(4')-exo,C(3')-endo and the latter syn and C(1')-exo-C(2')-endo.

INTRODUCTION

7-Methylguanosine is a biologically important minor nucleoside isolated from a variety of RNAs. In addition to its finding at 5'-terminal "cap" structure of eukaryotic mRNAs (1), 7-methylguanine base is of great interest because it is a main reaction product if nucleic acids are treated with alkylating agents which are usual mutagens (2). Therefore, we carried out an X-ray crystallographic study of a complex between 7-methylguanosine and its iodide. The analysis revealed a novel reverse-Watson-Crick type base pairing between a positively charged base and one deprotonated at the N(1) position. On this basis, we discuss the effects of the alkylation of the N(7) position of guanine by alkylating agents on the secondary or tertiary polynucleotide structures and also the inductive effects of 7-methylguanine in mutations.

EXPERIMENTAL PROCEDURES

7-Methylguanosine was synthesized as its iodide by the methylation of guanosine with methyl iodide (3). The oily product was left in acetone for

Table 1. The final positional and thermal parameters for the nonhydrogen atoms with their estimated standard deviations[a].

Atom	x	y	z	B_{11}[b]	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
I	0(3)	0(1)	0(4)	149(2)	10(0)	400(5)	26(1)	-121(5)	-63(2)

Atom	x	y	z	B(Å^2)	x	y	z	B(Å^2)
	molecule(a)				molecule(b)			
N(1)	3321(16)	2148(8)	9276(25)	2.4(3)	2796(16)	3296(8)	2404(25)	2.5(3)
C(2)	4911(21)	1594(10)	9193(33)	3.0(4)	1357(22)	3886(10)	2534(34)	3.3(4)
N(3)	5237(16)	1059(8)	7771(26)	2.7(3)	1046(16)	4463(7)	3884(24)	2.4(3)
C(4)	3882(19)	1083(9)	6598(30)	2.4(3)	2377(21)	4393(10)	5180(32)	2.8(3)
C(5)	2317(20)	1612(10)	6471(30)	2.4(3)	3896(19)	3823(9)	5227(31)	2.4(3)
C(6)	1926(20)	2203(10)	7952(31)	2.6(3)	4186(22)	3250(10)	3675(33)	2.9(4)
N(7)	1323(16)	1425(8)	4935(25)	2.6(3)	4939(16)	3973(7)	6811(24)	2.3(3)
C(8)	2221(23)	759(11)	4236(36)	3.7(4)	4056(20)	4609(10)	7709(30)	2.6(3)
N(9)	3867(16)	566(8)	5058(25)	2.6(3)	2508(16)	4862(8)	6756(25)	2.3(3)
N(2)	6136(17)	1640(8)	10524(26)	3.2(3)	28(17)	3887(8)	1184(26)	3.0(3)
O(6)	557(14)	2732(7)	8106(21)	3.2(2)	5553(14)	2719(7)	3608(22)	3.4(2)
C(7)	-500(22)	1780(11)	4439(34)	3.5(2)	6767(21)	3533(10)	7306(26)	2.8(3)
C(1')	5363(22)	-101(11)	4612(34)	3.0(4)	1303(20)	5615(10)	7209(31)	2.7(3)
C(2')	5741(22)	-663(10)	6921(33)	3.0(4)	1344(20)	6214(9)	4987(30)	2.4(3)
C(3')	4936(20)	-1335(9)	6694(30)	2.4(3)	-541(21)	6724(10)	5294(33)	3.1(4)
C(4')	4990(20)	-1313(10)	4042(30)	2.4(3)	-1651(20)	6200(10)	6896(31)	2.6(3)
C(5')	3566(21)	-1641(10)	3291(32)	2.8(3)	-2940(25)	5911(12)	5528(38)	4.6(5)
O(1')	4659(13)	-475(6)	3081(20)	2.9(2)	-478(13)	5493(6)	7737(20)	2.7(2)
O(2')	7645(13)	-917(6)	6741(21)	2.9(2)	2807(15)	6584(7)	4765(24)	4.4(3)
O(3')	5773(14)	-2042(6)	7846(21)	2.9(2)	-516(15)	7336(7)	6598(23)	4.2(3)
O(5')	1833(15)	-1472(7)	4600(23)	3.8(3)	-1967(16)	5645(8)	3380(25)	4.8(3)
	water							
O(W1)	5113(16)	5392(7)	1381(24)	4.6(3)				
O(W2)	3323(18)	6962(9)	9194(28)	6.0(4)				
O(W3)	3(19)	7979(9)	794(30)	6.8(4)				

a) All values are multiplied by 10^4. b) The form of the anisotropic thermal ellipsoid is : $\exp[-(B_{11}h^2+B_{22}k^2+B_{33}l^2+B_{12}hk+B_{13}hl+B_{23}kl)]$.

several days and the small crystals obtained as precipitate were dissolved in small amounts of water. After one week, plate-like crystals were obtained consisting of a complex of 7-methylguanosine iodide and 7-methylguanosine trihydrate, chemical formula $C_{11}H_{16}N_5O_5I \cdot C_{11}H_{15}N_5O_5 \cdot 3H_2O$. The crystal data are : space group P1, a=7.678(1), b=18.094(3), and c=5.711(1) Å, α=79.32(1), β=80.14(1), and γ=76.90(1)°, V=752.4(2) Å^3, Z=1, Dx=1.741 Mgm^{-3}.

Intensities of 2388 independent reflexions ($0<2\theta<125°$) were measured on a Rigaku automatic four-circle diffractometer with Cu Kα radiation using the

Table 2. The final positional for the hydrogen atoms with their estimated standard deviations.[a)]

Atom	x	y	z	x	y	z
	molecule(a)			molecule(b)		
H(N1)[b)]	309(22)	257(10)	1048(34)			
H(N2a)	590(21)	206(10)	1166(34)	18(21)	348(10)	10(34)
H(N2b)	744(21)	120(10)	1036(35)	-119(21)	433(10)	121(33)
H(7a)	-141(21)	153(10)	566(34)	664(22)	295(10)	806(34)
H(7b)	-68(22)	177(10)	255(34)	770(21)	354(10)	575(34)
H(7c)	-79(22)	240(10)	457(34)	725(22)	376(10)	857(34)
H(8)	174(22)	41(10)	306(34)	440(21)	485(10)	907(34)
H(1')	664(22)	5(10)	389(34)	175(22)	581(10)	864(34)
H(2')	518(21)	-42(10)	860(32)	157(23)	600(10)	325(33)
H(3')	360(21)	-127(10)	756(34)	-99(21)	698(10)	354(32)
H(4')	627(22)	-163(10)	340(33)	-250(22)	654(10)	839(34)
H(5'a)	343(22)	-146(10)	144(34)	-342(22)	542(10)	674(33)
H(5'b)	401(22)	-225(10)	347(33)	-407(21)	636(10)	504(34)
H(02')	823(21)	-74(10)	760(34)	293(21)	656(10)	603(32)
H(03')	700(21)	-215(10)	755(34)	61(22)	764(10)	552(33)
H(05')	133(22)	-88(10)	325(34)			
	water					
H(W1a)	611(21)	547(10)	211(33)			
H(W1b)	454(21)	584(10)	30(34)			
H(W2a)	244(22)	712(10)	1022(33)			
H(W2b)	453(21)	717(10)	911(33)			
H(W3a)	7(21)	864(10)	37(33)			

a) All values are multiplied by 10^3. b) The overall isotropic temperature factors are 3.5 $Å^2$.

ω-2θ scan technique. Because of the large linear absorption coefficient (μ=9.27 mm^{-1}) and the use of a glass capillary, an absorption correction by the Furnas method (4) was applied.

The structure was solved by the heavy atom method and refined by full-matrix least-squares techniques with anisotropic temperature factor for iodine atom and isotropic temperature factors for all the other nonhydrogen atoms. The positions of all the hydrogen atoms except those of the O(5') atom of molecule(b) and of water molecule (W3) were determined from a difference Fourier map. The final refinement including the hydrogen atoms with isotropic temperature factors reduced the R value to 0.075 (Rw=0.071). The quantity minimized was $\sum w(|Fo|-k|Fc|)^2$ where weight $w=1/\sigma^2(Fo)$ and k is the scale factor. All numerical calculations were carried out on an ACOS Series 77 NEAC ACOS 700 at the Crystallographic Research Center, Institute for Protein Research, Osaka University, with the programs of The Universal Crystallographic Computing System-Osaka (1979) (5). The atomic and anomalous

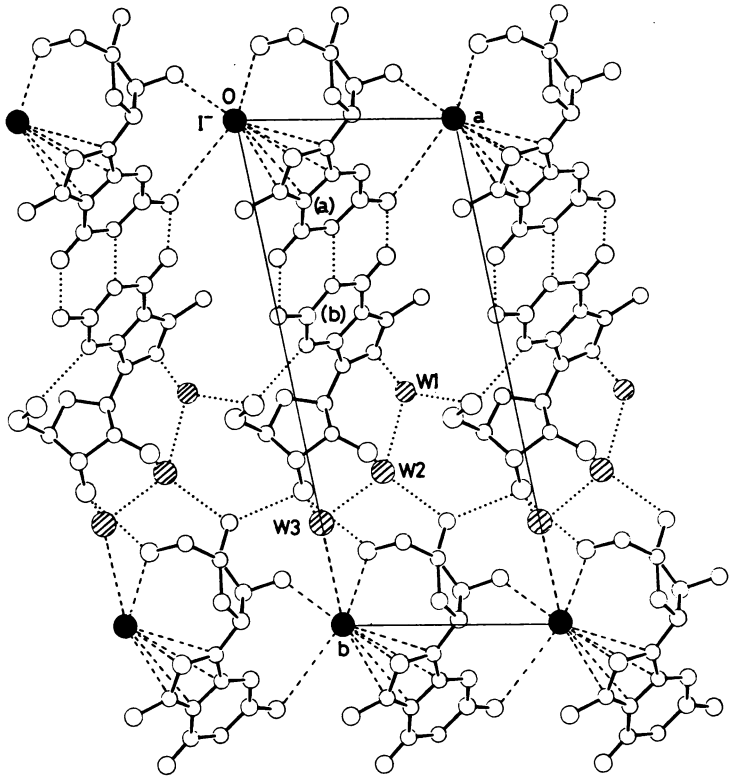


Fig. 1. A projection of the structure viewed along the c axis. Hydrogen bonds are indicated by the dotted lines and atomic distances shorter than normal van der Waals contacts by the broken lines. W1, W2 and W3 indicate three water molecules.

scattering factors used were those cited in International Tables for X-ray Crystallography (1974) (6).

RESULTS

The final atomic parameters are listed in Tables 1 and 2.

A hydrogen peak at the N(1) position of molecule(a) was easily found on a difference Fourier map but that of molecule(b) was not. These facts indicate that the molecule(a) with the positively charged N(7) atom might be neutralized by the iodide anion but the molecule(b) takes a zwitterionic form with deprotonation of the N(1) atom.

(a) Base pairing and crystal packing

Fig. 1 shows the crystal structure projected down to the c axis. The

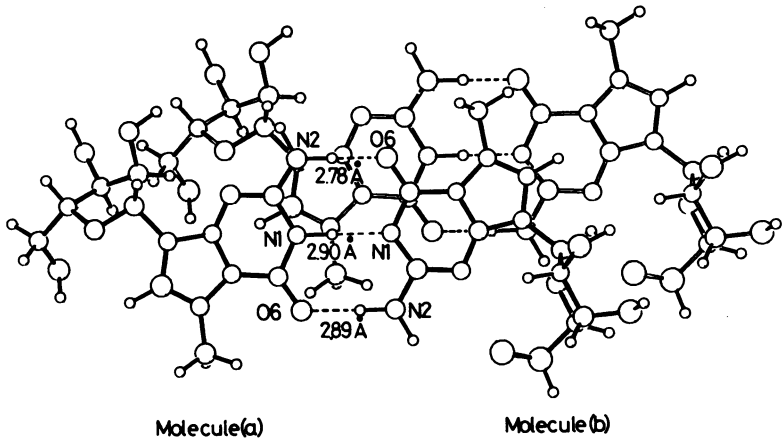


Fig. 2. The hydrogen bond paired molecules viewed perpendicular to the base-pair plane of the upper molecules drawn in heavy lines.

most pronounced structural feature is a novel reverse-Watson-Crick type base pairing with three hydrogen bonds between positively charged (a) and zwitterionic (b) molecules [N(2)-H---O(6) (2.78(2) Å), N(1)-H---N(1) (2.90(2) Å) and O(6)---H-N(2) (2.89(2) Å)] as shown in Fig. 2. The paired bases between molecules (a) and (b) are approximately coplanar with a dihedral angle of 1.8°. Furthermore, as shown in Fig. 2, stacking interactions occur between bases related by one unit translation along the c axis. The major overlapping is between the carbonyl C(6)-O(6) group and the pyrimidine moiety, and the separation is about 3.3 Å.

An iodine atom lies over the positively charged imidazole ring portion of molecule(a) with several close contacts as shown in Fig. 1 and Table 3. The perpendicular distance to iodide ion from the imidazole ring plane in molecule(a), 3.59 Å, is significantly shorter than the sum of the van der Waals radii, 3.9 Å, and indicates the formation of a charge-transfer interaction between the occupied π orbitals of the heterocycle and the vacant 5d orbital of the iodide ion. Similar base-iodide interactions were observed in the crystal structures of 1,7-dimethylguanosine iodide (7) and 5'-methylammonium-5'-deoxyadenosine iodide monohydrate (8). Three water molecules interact mainly with the ribose moieties of both molecules (a) and (b) by hydrogen bonds as summarized in Table 3.

(b) Molecular conformation

The conformations of the two independent molecules(a) and (b) are shown by a stereographic representation(9) in Fig. 3. The relevant torsion angles

Table 3. The distances of hydrogen bonds and short contacts.

(A)Hydrogen bonds

bond A-H·····B			Distances(Å) A·····B	H····B
N(1)a-H	N(1)b	(x,y,z+1)	2.90(2)	1.8(2)
N(2)a-H	O(6)b	(x,y,z+1)	2.78(2)	1.7(2)
N(2)b-H	O(6)a	(x,y,z-1)	2.89(2)	1.7(2)
C(8)b-H	O(W1)	(x,y,z+1)	3.05(2)	2.0(2)
O(5')b	N(3)b	(x,y,z)	2.79(2)	-
O(3')b-H	O(5')a	(x,y+1,z)	3.06(2)	2.0(2)
O(3')a-H	O(3')b	(x+1,y-1,z)	2.84(2)	2.0(2)
O(2')b-H	O(W2)	(x,y,z)	2.85(2)	2.1(2)
O(W1)-H	O(5')b	(x+1,y,z)	2.84(2)	1.9(2)
O(W2)-H	O(3')a	(x,y+1,z)	2.81(2)	1.9(2)
O(W3)	O(3')b	(x,y,z-1)	2.97(2)	-
O(W1)-H	O(W2)	(x,y,z-1)	3.00(2)	2.1(2)
O(W2)-H	O(W3)	(x,y,z+1)	2.90(2)	2.2(2)

(B)Iodide anion-hydrogen interactions

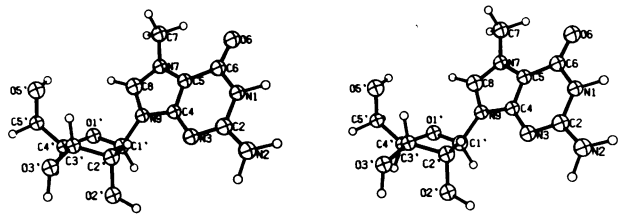
bond A-H·····B			Distances(Å) A·····B	H·····B
C(8)a-H	I^-	(x,y,z)	3.79(2)	2.7(2)
O(5')a-H	I^-	(x,y,z)	3.60(1)	2.4(2)
O(2')a-H	I^-	(x+1,y,z+1)	3.63(1)	2.8(2)
N(2)a-H	I^-	(x+1,y,z+1)	3.71(1)	2.6(2)
O(W3)-H	I^-	(x,y+1,z)	3.60(2)	2.4(2)

(C) Iodide anion-imidazol ring interactions

A·····B			Distances(Å)
I^-	N(7)a	(x,y,z-1)	3.67(1)
I^-	C(8)a	(x,y,z-1)	3.62(2)
I^-	N(9)a	(x,y,z-1)	3.91(2)
I^-	C(4)a	(x,y,z-1)	3.97(2)
I^-	C(5)a	(x,y,z-1)	3.83(2)

and pseudorotation parameters are given in Table 4.

Large structural differences are found between the positively charged molecule (a) and the one deprotonated at the N(1) position (b) as suggested by conformations about glycosidic bonds and sugar rings. The molecule (a) is in the anti conformation (χ_{CN}=1(2)) and the other one (b) in the syn conformation (χ_{CN}=224(2)) (Table 4). Other examples where two or more independent nucleoside or nucleotide molecules in an asymmetric unit exhibit different conformations about the glycosidic bond are found in 3',5'-cyclic adenosine monophosphate (10), 2'-deoxy-2'-fluoroinosine (11),



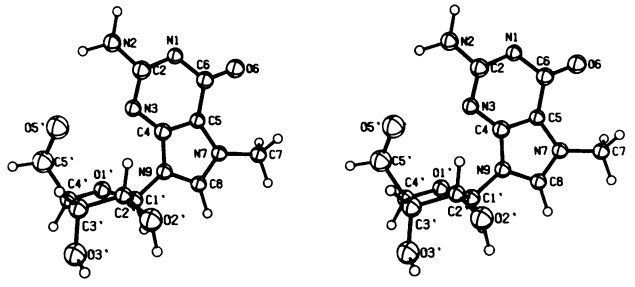


Fig. 3 Stereoview of the independent molecules(a) and (b) with atomic numberings.

2'-deoxy-2'-chloroadenosine (unpublished data) and 2'-deoxy-2'-fluoroguanosine (unpublished data). The fact that the anti and syn conformations can coexist in a crystal suggests that the rotational barrier about the glycosidic bond is relatively small and the energy needed for the conformational change in the β-purine nucleoside is especially low (12,13).

Table 4. Conformational parameters (°)

		molecule(a)	molecule(b)
χ	O(1')-C(1')-N(9)-C(8)	1(2)	224(2)
τ_0	C(4')-O(1')-C(1')-C(2')	-14(2)	-30(2)
τ_1	O(1')-C(1')-C(2')-C(3')	-8(2)	34(2)
τ_2	C(1')-C(2')-C(3')-C(4')	26(2)	-25(2)
τ_3	C(2')-C(3')-C(4')-O(1')	-35(2)	8(2)
τ_4	C(3')-C(4')-O(1')-C(1')	30(2)	13(2)
P	phase angle of pseudorotation	40	137
τ_m	max amplitude of pseudorotation	33	33
ψ	C(3')-C(4')-C(5')-O(5')	40(2)	48(2)

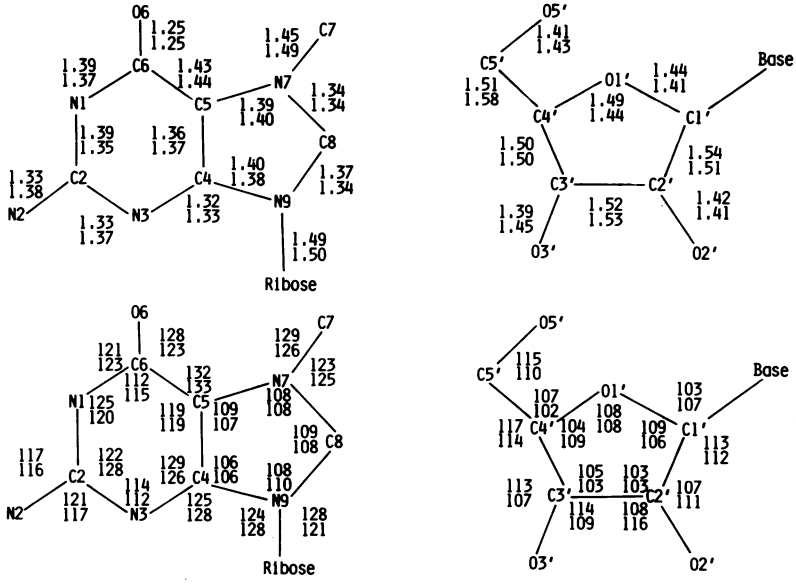


Fig. 4. Bond distances (Å) and angles(°). The upper numbers are for molecule(a) and the lower ones for molecule(b). The averaged estimated standard deviations in the bond distances and angles are 0.024 Å and 1.5°, respectively.

Therefore, in the case of 7-methylguanosine, the observed anti and syn conformations may be due to rotational freedom rather than to the positive charge localized in the base. Indeed, the glycosidic conformation of guanosine (14) or adenosine (15) is similar to that of guanosine hydrobromide (16) with protonated N(7) or of adenosine hydrochloride (17) with protonated N(1).

The sugar conformation of molecule(a) is C(4')-exo,C(3')-endo (P=40°, τ_m=33°), whereas molecule (b) has C(1')-exo,C(2')-endo (P=137°, τ_m=33°). Although the former belongs to the N-type (C(3')-endo type) conformer and the latter to the S-type (C(2')-endo type), both conformations deviate somewhat from the usual pseudorotation range for the N-type (P=0-36°) or S-type (P=144-180°) (18). As pointed out theoretically, the energy barrier between S-type and N-type conformers is relatively small so that the ribose ring is rather flexible (19).

7-Methylguanosine is the first example of a β-purine nucleoside having both the anti conformer with the N-type sugar puckering and the syn conformer with the S-type sugar puckering in one crystal structure.

The orientation of the C(5')-O(5') bond is gauche-gauche for both

Table 5. Comparison of bond angles(°) in molecules(a),(b) and related nucleosides

	molecule(a)	molecule(b)	guanosine[a]	guanosine·HBr[b]
pyrimidine moiety				
C(6)-N(1)-C(2)	125	120	125	125
N(1)-C(2)-N(3)	122	128	124	124
N(3)-C(2)-N(2)	121	117	120	121
N(1)-C(6)-O(6)	121	123	121	119
N(1)-C(6)-C(5)	112	115	111	111
C(5)-C(6)-O(6)	128	123	128	130
imidazole moiety				
C(5)-N(7)-C(8)	108	108	104	108
N(7)-C(8)-N(9)	109	108	113	109
	molecule(a) anti	molecule(b) syn	anti[c]	syn[c]
glycosidic bond				
C(4)-N(9)-C(1')	124	128	125	129
C(8)-N(9)-C(1')	128	121	129	124
	$_4T^3$	$_1T^2$	N-type	S-type[d]
sugar ring				
C(1')-C(2')-O(2')	107	111	107	113
C(3')-C(2')-O(2')	108	116	111	114
C(2')-C(3')-O(3')	114	109	114	110
C(4')-C(3')-O(3')	113	107	113	109

a) ref. 14. b) ref. 16. c) ref. 27. d) ref. 18.

molecules. Molecule(b) is capable of forming an intramolecular hydrogen bonding between N(3) of the base and O(5') of the sugar moiety with a distance of 2.79(2) Å.

(c) Bond distances and angles

The bond distances and angles are shown in Fig. 4. There are some interesting features in the bond angles (Table 5), although the standard deviations are somewhat larger than those of the other related nucleosides, probably owing the large absorption of the iodine atom; the bond angles in the imidazole moiety are in good agreement with those found in N(7) protonated guanosine hydrobromide rather than those in guanosine; on the other hand, in the pyrimidine moieties, the bond angles of molecule(a) are significantly different from those of the N(1) deprotonated molecule (b) but very similar to those in guanosine; the defferences in bond angles around N(9), C(2') and C(3') atoms between the two molecules (a) and (b) are

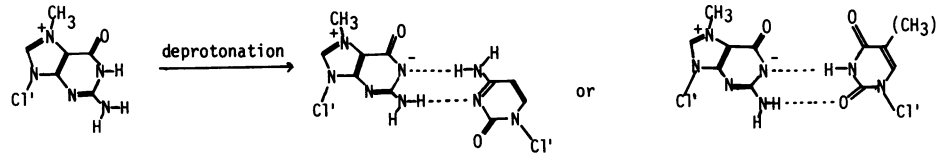


Fig. 5. The proposed base pairing between N(1) deprotonated 7-methylguanine base and other bases.

probably due to the differences in the glycosidic torsion angle and in the sugar ring puckering.

DISCUSSION

7-Methylguanosine has been isolated from a variety of RNAs, for example it was found in the 5'-terminal "cap" structure of most eukaryotic mRNAs and viral mRNAs, and in many tRNAs.

The alkylation at the N(7) position of the guanine residue increases the acidity of the N(1) atom, and decreases the pKa value from 9.2 (20) to 7.1 (21). Therefore, the ratio of the deprotonated form such as molecule (b) at neutral pH will much more increase in comparison with the normal guanine base. In our case, at first the reaction of guanosine with CH_3I was expected to completely produce 7-methylguanosine iodide (3). However, during the process of purification or crystallization, some iodide ions were liberated and the crystals contained the complex of 7-methylguanosine and its iodide. These findings suggest that such N(1) deprotonated 7-methylguanine residues

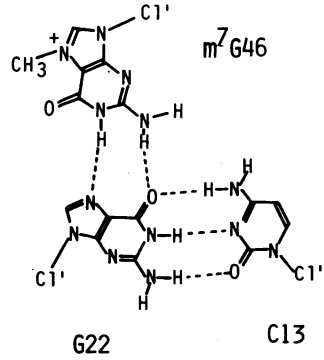


Fig. 6. A tertiary structure hydrogen bond interaction found in $tRNA^{Phe}$.

may be present in RNAs under physiological conditions. If that is the case, then the deprotonated 7-methylguanine base may form a wobble base-pair with cytosine or a false base-pair with uracil or thymine residues as shown in Fig. 5. Such unusual base-pairing may cause significant changes in the secondary structures of nucleic acids, and furthermore the N(1) deprotonation of 7-methyguanosine may destabilize the tertiary hydrogen bonding structure found in yeast $tRNA^{Phe}$ as shown in Fig. 6 (22-25).

7-Methylguanine is a major reaction product of nucleic acids with alkylating agents which are mostly mutagens and carcinogens. However, up to date, experimental evidences supporting participation of 7-methylguanine residue in the mutagenesis have not been reported. It was shown that O^6-alkylguanine is one of the most plausible candidates of directly induced mutagenesis by alkylations, its mutational mechanism being due to the formation of anomalous base pairings(26). When 7-methylguanine base would be converted to the N(1) deprotonated form, the formation of the unusual base pairing as shown in Fig. 5 would be possible similar as in the case of O^6-alkylguanine base. Therefore, 7-methylguanine base seems to be one of the methylated bases which are capable of inducing mutagenesis.

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