Purines. XXXI.[1] An X-Ray Crystallographic Structure Analysis of 3-Methyladenosine *p*-Toluenesulfonate

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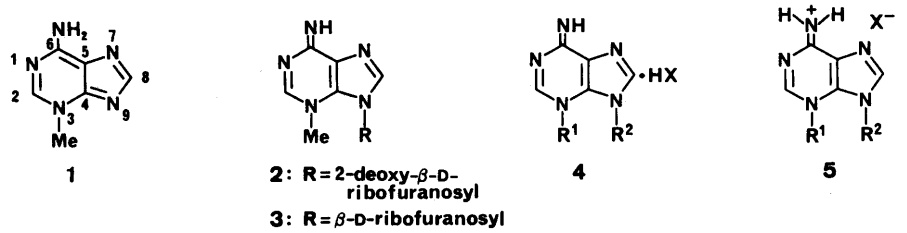
The X-ray crystal structure of the title compound (3·TsOH) has been determined. In the crystal, this salt has the exocyclic iminium structure (type 5). The adenine moiety is almost planar, and the N(9)–C(1′) bond is almost coplanar with the adenine ring. However, the N(3)-methyl group is displaced rather significantly from planarity, and the endocyclic and exocyclic angles at N(3), C(4), and N(9) notably depart from those of the usual adenosine systems. The ribose moiety is in the C(2′)-*endo* puckering conformation and in the *high-anti* conformation [with the torsion angle O(1′)–C(1′)–N(9)–C(4), $\chi = -72.3°$] with respect to the adenine moiety.

Keywords 3-methyladenosine *p*-toluenesulfonate; X-ray crystal structure; exocyclic iminium structure; *high-anti* conformation; hydrogen bonding; 3,9-dimethyladenine; molecular orbital calculation; protonation site

Since methylation of deoxyribonucleic acid (DNA) causes release of 3-methyladenine (**1**), 3-methyl-2′-deoxyadenosine (**2**) has been assumed to occur in methylated DNA molecules as a part structure.[2] Because of the extraordinary instability of its glycosidic bond to hydrolysis at the polynucleotide level,[2b,c,j] it is of prime importance to learn the nature of this part structure at the nucleoside level. We have synthesized 3-methyladenosine (**3**)[3] and 3-methyl-2′-deoxyadenosine (**2**),[4] both in the form of the *p*-toluenesulfonate salt, and found that they are readily susceptible to hydrolysis leading to 3-methyladenine (**1**) in aqueous acidic solution and to ring opening of the adenine moiety at the 2-position under basic conditions.[3,4] We have also synthesized a series of 3,9-dialkyladeninium salts (**4**)[5] and observed their easy ring opening[1] at the 2-position under basic conditions.[5b,c] For a better understanding of such instability, it is essential to know the exact molecular structures of these 3,9-disubstituted adenine salts. This paper reports the crystal structure of 3-methyladenosine *p*-toluenesulfonate (**3**·TsOH), which was the only one that yielded an adequate single crystal for X-ray diffraction among the 3,9-disubstituted adenine salts (type **4**) in hand.



Experimental

X-Ray Analysis 3-Methyladenosine *p*-toluenesulfonate (**3**·TsOH) was prepared as described previously,[3] and colorless transparent plates [mp *ca.* 150 °C (dec.)] of **3**·TsOH were grown from MeOH. A crystal measuring 0.5 × 0.3 × 0.4 mm was selected and used for all data collection. Unit cell constants and intensity data were obtained with a Rigaku AFC/2 automatic diffractometer using graphite-monochromated Cu$K\alpha$ radiation (λ = 1.5418 Å). The unit cell dimensions were determined from angular settings of 20 2θ-values in the range of 40—60 °, giving the following crystal data: a = 16.604(1) Å; b = 8.541(1) Å; c = 6.791(1) Å; β = 96.22(1) °; U = 957.3 Å^3; space group $P2_1$; Z = 2; D_x = 1.576 g/cm^3; $F(000)$ = 478; μ(Cu $K\alpha$) = 19.691 cm^{-1}. Out of 1964 unique reflections ($2\theta \leqq 130$ °) measured by using the $\omega/2\theta$ scan technique, 1724 with $|F_{obs}| \geqq 3\sigma(F)$ were considered reliable. No absorption corrections were applied.

Structure Determination and Refinement The structure was solved by direct methods using the program MULTAN[6] and the difference Fourier method. Refinement of atomic parameters was carried out using the block-diagonal least-squares method with anisotropic temperature factors. The hydrogen atoms were located on a difference Fourier map and refined with isotropic temperature factors. Throughout the refinement, the function $\sum w(|F_o| - |F_c|)^2$ was minimized. The weight $1/\sigma^2(F)$ was used during the final refinement stage and 7 reflections were deleted; the final R value was 0.048 (R_w = 0.051). The atomic scattering factors were taken from the literature.[7]

Results

For convenience of designating the non-hydrogen atoms in the nucleoside salt **3**·TsOH, they are numbered as shown in Fig. 1. The final atomic positions and equivalent isotropic thermal parameters of the non-hydrogen atoms are listed in Table I. The bond lengths and angles are given in Tables II and III, respectively, and a stereoscopic view of the structure and conformation of the protonated nucleoside residue is presented in Fig. 2.

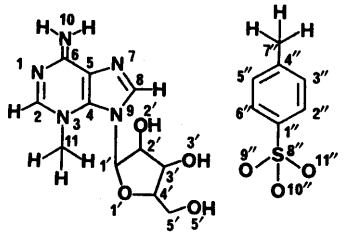


Fig. 1. Schematic Drawing of **3**·TsOH Showing the Numbering of Non-hydrogen Atoms

Discussion

Geometry of the Adenine Moiety It may be seen from

TABLE I. Positional Parameters ($\times 10^4$)[a] and Equivalent Isotropic Temperature Factors for Non-hydrogen Atoms of 3·TsOH

Atom	x	y	z	B_{eq} (Å^2)	Atom	x	y	z	B_{eq} (Å^2)
N(1)	898 (2)	6076 (5)	9462 (6)	1.97	O(2′)	3731 (3)	11943 (5)	7892 (5)	3.30
C(2)	1650 (3)	5732 (6)	9403 (7)	1.98	O(3′)	5105 (3)	10454 (5)	9260 (5)	3.30
N(3)	2291 (2)	6706 (5)	9564 (5)	1.72	C(5′)	4484 (4)	10693 (7)	14279 (7)	3.08
C(4)	2098 (3)	8259 (6)	9773 (6)	1.69	O(5′)	5227 (3)	11379 (5)	15110 (6)	4.04
C(5)	1321 (3)	8725 (6)	9840 (6)	1.77	C(1″)	7882 (3)	1215 (6)	5437 (7)	2.20
C(6)	687 (3)	7619 (5)	9706 (7)	1.87	C(2″)	7411 (3)	2573 (7)	5309 (7)	2.53
N(7)	1285 (2)	10338 (6)	10078 (7)	2.10	C(3″)	7789 (3)	4020 (6)	5181 (7)	2.40
C(8)	2039 (3)	10773 (5)	10157 (7)	2.20	C(4″)	8607 (3)	4132 (6)	5175 (7)	2.40
N(9)	2579 (2)	9557 (5)	9962 (5)	1.75	C(5″)	9065 (4)	2769 (7)	5191 (8)	2.86
N(10)	−77 (3)	7951 (5)	9765 (7)	2.67	C(6″)	8705 (3)	1318 (6)	5428 (7)	2.55
C(11)	3128 (3)	6107 (7)	9608 (7)	2.43	C(7″)	9032 (4)	5732 (7)	5064 (9)	3.78
C(1′)	3457 (3)	9708 (6)	9960 (7)	1.84	S(8″)	7431 (1)	−661 (2)	5548 (2)	2.78
C(2′)	3768 (3)	11376 (6)	9825 (7)	2.02	O(9″)	6592 (3)	−460 (6)	5696 (7)	4.96
C(3′)	4647 (3)	11159 (6)	10677 (7)	2.17	O(10″)	7598 (3)	−1456 (5)	3741 (5)	3.12
C(4′)	4583 (3)	9967 (6)	12279 (7)	2.09	O(11″)	7855 (4)	−1418 (5)	7253 (5)	5.02
O(1′)	3834 (2)	9110 (4)	11732 (5)	2.50					

a) Estimated standard deviations are given in parentheses and denote the least significant digits.

TABLE II. Bond Lengths in 3·TsOH

Bond	Length[a] (Å)	Bond	Length[a] (Å)	Bond	Length[a] (Å)
N(1)–C(2)	1.287 (6)	C(8)–N(9)	1.388 (6)	C(1″)–C(2″)	1.397 (7)
N(1)–C(6)	1.378 (7)	N(9)–C(1′)	1.463 (5)	C(1″)–C(6″)	1.370 (7)
C(2)–N(3)	1.346 (6)	C(1′)–C(2′)	1.521 (7)	C(1″)–S(8″)	1.774 (5)
N(3)–C(4)	1.376 (6)	C(1′)–O(1′)	1.392 (5)	C(2″)–C(3″)	1.392 (7)
N(3)–C(11)	1.479 (6)	C(2′)–C(3′)	1.522 (6)	C(3″)–C(4″)	1.363 (7)
C(4)–C(5)	1.356 (6)	C(2′)–O(2′)	1.395 (6)	C(4″)–C(5″)	1.388 (8)
C(4)–N(9)	1.364 (6)	C(3′)–C(4′)	1.502 (7)	C(4″)–C(7″)	1.503 (8)
C(5)–C(6)	1.410 (6)	C(3′)–O(3′)	1.423 (6)	C(5″)–C(6″)	1.383 (8)
C(5)–N(7)	1.388 (6)	C(4′)–O(1′)	1.456 (5)	S(8″)–O(9″)	1.419 (4)
C(6)–N(10)	1.305 (6)	C(4′)–C(5′)	1.518 (7)	S(8″)–O(10″)	1.455 (4)
N(7)–C(8)	1.302 (6)	C(5′)–O(5′)	1.426 (6)	S(8″)–O(11″)	1.441 (4)

a) Estimated standard deviations are given in parentheses for the last digits.

TABLE III. Bond Angles in 3·TsOH

Bond	Angle[a] (°)	Bond	Angle[a] (°)
C(2)–N(1)–C(6)	118.8 (4)	C(2′)–C(3′)–C(4′)	102.6 (4)
N(1)–C(2)–N(3)	128.1 (5)	C(2′)–C(3′)–O(3′)	110.8 (4)
C(2)–N(3)–C(4)	114.4 (4)	C(4′)–C(3′)–O(3′)	106.7 (4)
C(2)–N(3)–C(11)	121.4 (4)	C(3′)–C(4′)–O(1′)	106.4 (3)
C(4)–N(3)–C(11)	124.1 (4)	C(3′)–C(4′)–C(5′)	113.2 (4)
N(3)–C(4)–C(5)	121.3 (4)	O(1′)–C(4′)–C(5′)	105.2 (4)
N(3)–C(4)–N(9)	130.7 (4)	C(1′)–O(1′)–C(4′)	109.1 (4)
C(5)–C(4)–N(9)	108.0 (4)	C(4′)–C(5′)–O(5′)	110.5 (4)
C(4)–C(5)–C(6)	120.5 (4)	C(2″)–C(1″)–C(6″)	119.9 (5)
C(4)–C(5)–N(7)	110.4 (4)	C(2″)–C(1″)–S(8″)	121.1 (4)
C(6)–C(5)–N(7)	129.2 (4)	C(6″)–C(1″)–S(8″)	119.0 (4)
N(1)–C(6)–C(5)	116.8 (4)	C(1″)–C(2″)–C(3″)	119.1 (4)
N(1)–C(6)–N(10)	118.2 (4)	C(2″)–C(3″)–C(4″)	121.3 (4)
C(5)–C(6)–N(10)	125.0 (5)	C(3″)–C(4″)–C(5″)	118.7 (5)
C(5)–N(7)–C(8)	103.6 (4)	C(3″)–C(4″)–C(7″)	121.9 (5)
N(7)–C(8)–N(9)	114.2 (4)	C(5″)–C(4″)–C(7″)	119.4 (4)
C(4)–N(9)–C(8)	103.8 (3)	C(4″)–C(5″)–C(6″)	121.1 (5)
C(4)–N(9)–C(1′)	130.2 (4)	C(1″)–C(6″)–C(5″)	119.8 (5)
C(8)–N(9)–C(1′)	126.0 (4)	C(1″)–S(8″)–O(9″)	108.4 (3)
N(9)–C(1′)–C(2′)	115.3 (4)	C(1″)–S(8″)–O(10″)	105.4 (2)
N(9)–C(1′)–O(1′)	108.8 (3)	C(1″)–S(8″)–O(11″)	105.5 (2)
C(2′)–C(1′)–O(1′)	105.8 (3)	O(9″)–S(8″)–O(10″)	113.2 (2)
C(1′)–C(2′)–C(3′)	100.4 (4)	O(9″)–S(8″)–O(11″)	113.3 (3)
C(1′)–C(2′)–O(2′)	113.7 (4)	O(10″)–S(8″)–O(11″)	110.3 (2)
C(3′)–C(2′)–O(2′)	110.0 (4)		

a) Estimated standard deviations are given in parentheses for the last digits.

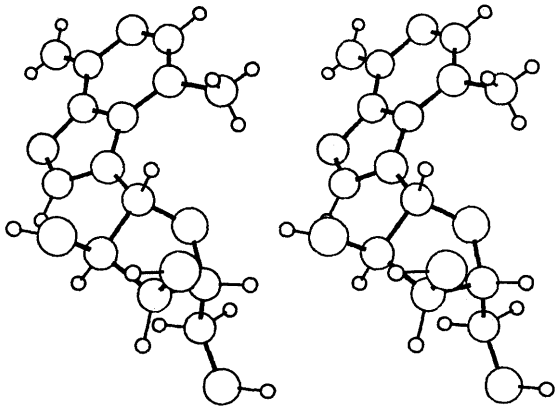
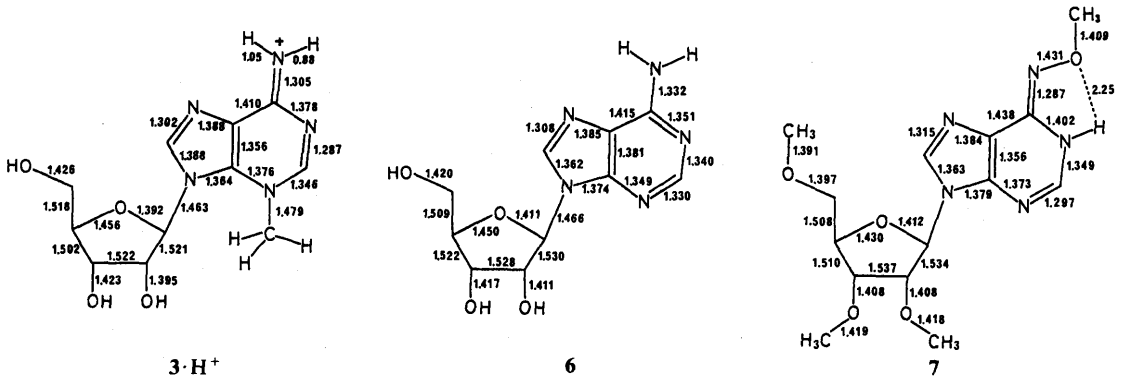


Fig. 2. Stereoview of the Structure of the Nucleoside Cation Moiety in 3·TsOH

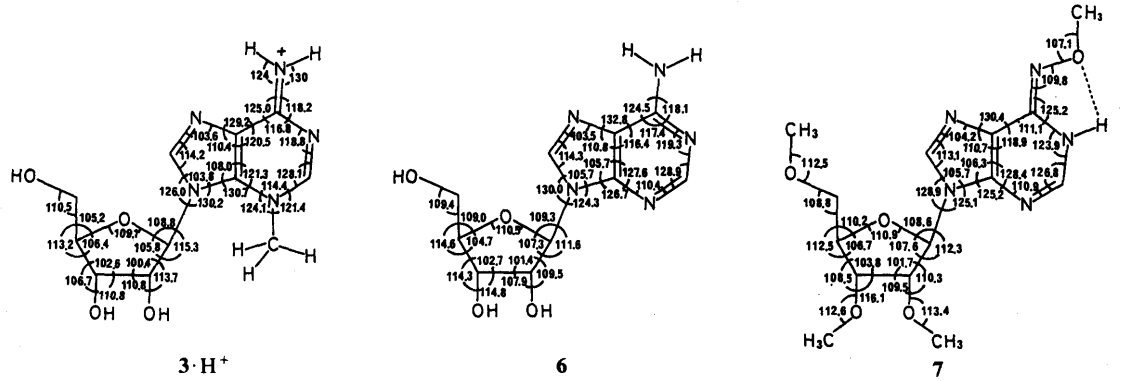
Tables II and III that the bond lengths and angles are not always in agreement with the average values found for the natural purine bases.[8] One of the most notable departures from the dimensions of the usual adenine systems, mainly occurring in the pyrimidine part, indicates the localization of double bonds at N(1)=C(2), C(4)=C(5), and C(6)=N(10). The C(6)=N(10) bond length of 1.305 Å is shorter than the corresponding bond length (1.332 Å)[9] in adenosine (**6**), but longer than that (1.287 Å)[10] in N^6-methoxy-2′,3′,5′-tri-*O*-methyladenosine (**7**) (Fig. 3). The angles of C(2)–N(1)–C(6) (118.8°) and N(1)–C(6)–C(5) (116.8°) are not similar to those (123.9° and 111.1°, respectively)[10] in **7**, but are rather similar to those (119.3° and 117.4°, respectively)[9] in **6** (Fig. 4). These results suggest protonation at the exocyclic imino nitrogen [N(10)] in 3·TsOH, and this was clearly recognized in the difference electron density maps. The positional parameters ($\times 10^3$, with estimated standard deviations in parentheses) and isotropic temperature factor for N(10)–H [*syn* with respect to N(1)] are $x=-31(4)$, $y=883(9)$, $z=1008(10)$, and $B_{iso}=0.4$; those for N(10)–H (*anti*) are $x=-54(4)$, $y=710(10)$, $z=1029(11)$, and $B_{iso}=0.2$.

Interestingly, the adenine moiety in 3·TsOH is almost planar, with the largest deviation (−0.015 Å) from the least-squares plane being that of the N(10) atom. The



3·H⁺ 6 (taken from ref. 9) 7 (taken from ref. 10)

Fig. 3. Bond Distances in Adenosine and Its Derivatives



3·H⁺ 6 (taken from ref. 9) 7 (taken from ref. 10)

Fig. 4. Bond Angles in Adenosine and Its Derivatives

TABLE IV. Deviations (in Å) of the Atoms in 3·TsOH from the Least-Squares Planes[a)]

Base	$(0.00161X-0.11458Y+0.99341Z-0.00100=0)$				
N(1)	0.002	C(5)	0.006	N(9)	0.003
C(2)	0.006	C(6)	−0.010	N(10)	−0.015
N(3)	−0.009	N(7)	−0.005	C(11)	−0.099
C(4)	0.004	C(8)	−0.007	C(1′)	0.017
Sugar	$(0.55575X-0.65619Y-0.51044Z+5.85860=0)$				
O(1′)	0.000	C(3′)	0.009	N(9)	−0.726
C(1′)	0.000	C(4′)	0.000		
C(2′)	−0.596	C(5′)	−1.217		
Tosylate	$(0.00109X+0.06930Y+0.99760Z+3.59897=0)$				
C(1″)	−0.002	C(4″)	0.000	C(7″)	−0.020
C(2″)	0.004	C(5″)	0.002	S(8″)	0.035
C(3″)	−0.002	C(6″)	0.000		

a) Estimated standard deviations are *ca.* 0.005 Å. *X*, *Y*, and *Z* directions correspond to the *a*, *b*, *c* crystallographic directions.

TABLE V. Conformational Parameters[11)] in the Sugar Moiety of 3·TsOH

Glycosyl angle (°)		Sugar torsion angles (°)	
χ	−72.3	τ_0	−24.0
Backbone torsion angles (°)		τ_1	38.0
ψ'	152.6	τ_2	−36.8
ψ_{oc}	−72.7	τ_3	24.2
ψ_{oo}	171.6	τ_4	−0.3
		P	161.6

TABLE VI. Hydrogen-Bond Distances (in Å)

Donor	Acceptor	Distance	Symmetry on acceptor
N(10)	N(1)	3.07	$2-x, 1-y, -z$
N(10)	N(7)	3.01	$2-x, -y, -z$
O(2′)	O(10″)	2.73	$1-x, 3/2+y, 1-z$
O(3′)	O(5′)	2.96	$x, y, 1-z$
O(5′)	O(9″)	2.75	$x, 1-y, 1-z$

substituents C(1′) (ribosyl group) and C(11) [N(3)-methyl group] are displaced on opposite sides of the plane by 0.017 and −0.099 Å, respectively (Table IV). The deviation of the latter from planarity is rather significant. Moreover, it may be seen from Fig. 4 that the endocyclic and exocyclic angles at N(3), C(4), and N(9) are also in favor of keeping both substituents away from each other, representing another notable departure from the dimensions of **6**[9)] and **7**.[10)]

Glycosidic and Sugar Conformation The torsion angles of the ribose ring listed in Table V indicate that the ring is in the C(2′)-*endo* (^{2}E) puckering conformation.[11)] This may also be seen from Table IV. The glycosidic torsion angle χ [O(1′)–C(1′)–N(9)–C(4)] is −72.3°, revealing that the sugar moiety is in the *high-anti* conformation with respect to the adenine moiety. Although the *syn* conformation is usually preferred for ^{2}E purine ribonucleosides substituted or unsubstituted at the 8-position, the value −72.3° belongs to the so-called *high-anti* range (part of *syn*).[11b)] This is probably due to steric repulsion operating between the C(2′)–OH group and N(3)-methyl group.

The conformation about the exocyclic C(4′)–C(5′) bond

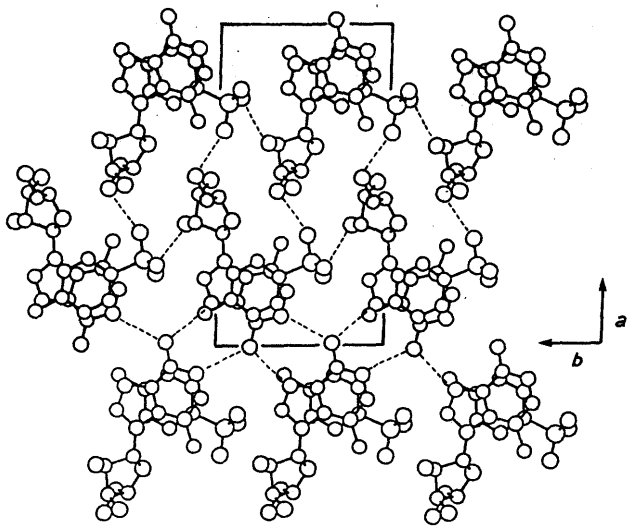
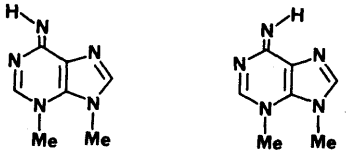


Fig. 5. A Perspective View of **3**·TsOH along the *c* Axis[12]

is usual *trans-gauche* (ψ_{OO} = 171.6°, ψ_{OC} = −72.7°), and the 5′-hydroxy group O(5′)–H forms an intermolecular hydrogen bond with the O(9″) atom of tosylate ion, as shown in Table VI and Fig. 5.

Hydrogen Bonding and Packing of the Molecules All protons attached to the O and N atoms are involved in hydrogen bonds (Table VI), forming an extensive intermolecular network (Fig. 5).[12] The adenine moiety lies nearly parallel to the *ab* plane, as shown in Fig. 5, to form a stacked column with the tosylate molecule. The interplanar separation is 3.6 Å, and the dihedral angle is 10.6°.

An Approach through Molecular Orbital (MO) Calculation In order to predict the site of protonation in the adenine moiety of 3-methyladenosine *p*-toluenesulfonate (**3**·TsOH), the semiempirical MO calculation method MNDO (modified neglect of diatomic overlap)[13,14] was applied to 6-imino-3,9-dimethylpurine, which is structurally analogous to **3** and the simplest in the 3,9-disubstituted adenine series. For this base, the N^6-H *syn* (**8**) and *anti* (**9**) configurations are possible with respect to N(1). The geometries were optimized by the DFP (Davidon–Fletcher–Powell) optimization procedure[15] using the results of the present X-ray analysis as initial geometry, and assuming C_s symmetry. The heats of formation thus estimated for **8** and **9** were 82.970 and 84.238 kcal/mol, respectively. It may be seen from Table VII that the HOMO density at N^6 [N(10)] is greater than that at N(1) in both configurations. This supports preferential protonation of **3** at N(10) in the salt form (**3**·TsOH), as evidenced by the above X-ray crystallographic results.



8 (*syn*) **9** (*anti*)

TABLE VII. Atomic Orbital Coefficients for the HOMO of the *Syn* (**8**) and *Anti* (**9**) Forms of 6-Imino-3,9-dimethylpurine

Syn form (**8**)[a]				*Anti* form (**9**)[a]			
ε = −8.47464 kcal/mol				ε = −8.54276 kcal/mol			
N(1) (p_z)	0.2336	C(6) (p_z)	−0.1251	N(1) (p_z)	0.2452	C(6) (p_z)	−0.1361
C(2) (p_z)	0.0331	N(7) (p_z)	−0.1166	C(2) (p_z)	0.0598	N(7) (p_z)	−0.1152
N(3) (p_z)	−0.3964	C(8) (p_z)	−0.4081	N(3) (p_z)	−0.4099	C(8) (p_z)	−0.3961
C(4) (p_z)	0.4134	N(9) (p_z)	−0.0467	C(4) (p_z)	0.3852	N(9) (p_z)	−0.0314
C(5) (p_z)	0.4933	N^6 (p_z)	−0.4025	C(5) (p_z)	0.4937	N^6 (p_z)	−0.4154

a) The *z* axis was taken in the direction of the molecular plane. Coefficients for the *s*, p_x, and p_y orbitals are substantially 0.

Conclusion

In the crystal, the *p*-toluenesulfonate salt of 3-methyladenosine (**3**) has the oxocyclic iminium structure (type **5**). The adenine moiety is almost planar, and the N(9)–C(1′) bond is almost coplanar with the adenine ring. However, the displacement of the N(3)-methyl group from planarity and the endocyclic and exocyclic angles at N(3), C(4), and N(9) are in favor of keeping the N(3)-methyl and N(9)-ribosyl groups away from each other, representing a notable departure from those of the usual adenosine systems. The ribose moiety is in the C(2′)-*endo* (^{2}E) puckering conformation and in the *high-anti* (part of *syn*) conformation with respect to the adenine moiety. By analogy with this as well as from the results of the semiempirical calculation of the atomic orbital coefficients for the HOMO of 6-imino-3,9-dimethylpurine (**8** or **9**), similar exocyclic iminium structures (type **5**) are inferred for the previously synthesized salts of 3-methyl-2′-deoxyadenosine (**2**)[4] and 3,9-dialkyladenines.[5] Thus, the present findings may shed light on factors responsible for the previously described, extraordinary instability[3,4,5b,c] of 3,9-disubstituted adenines at both the base and the nucleoside levels.

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References and Notes

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