Crystal Structure of an 8,5′-Iminocarbonyloxy-Bridged Guanine Nucleoside Methanol Solvate

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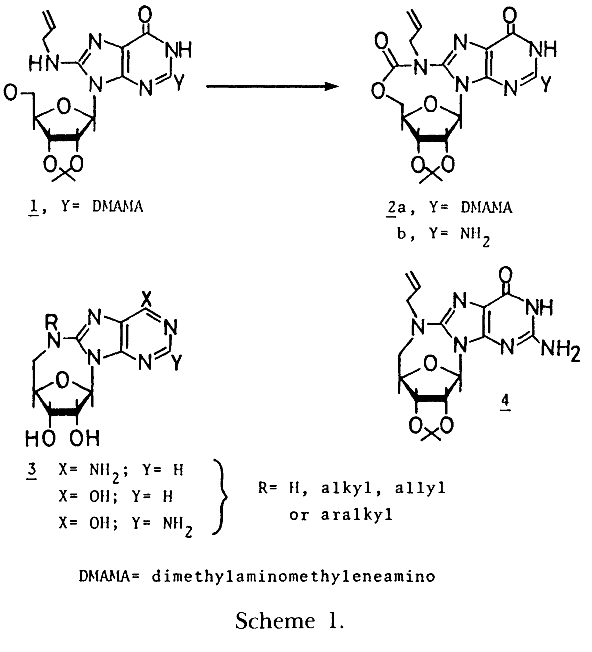
Synopsis. The crystal structure of 8,5′-[(allylimino)carbonyloxy]-2-*N*-dimethylaminomethylene-9-(2′,3′-*O*-isopropylidene-*β*-D-ribofuranosyl)guanine (**2a**) methanol solvate was determined by X-ray analysis. Its base-sugar torsion angle conforms to the CD spectral behavior of the partially deprotected compound **2b** in the sense of anti-conformation.

A recent report from this laboratory has described the direct cyclization of 8-allylamino-2-*N*-dimethylaminomethylene-2′,3′-*O*-isopropylideneguanosine (**1**) to 8,5′-[(allylimino)carbonyloxy]-2-*N*-dimethylaminomethylene-9-(2′,3′-*O*-isopropylidene-*β*-D-ribofuranosyl)guanine (**2a**) with the use of diphenyl carbonate or *N,N′*-carbonyldiimidazole (CDI) in an attempt to realize a general synthesis of purine 8,5′-imino- and substituted imino cyclonucleosides (**3**) (Scheme 1).[1] Compound **2a** was deblocked to 8,5′-[(allylimino)carbonyloxy]-9-(2′,3′-*O*-isopropylidene-*β*-D-ribofuranosyl)guanine (**2b**) (the allyl group was used as a *N*-protective group[2]). The facile formation of **2a** was interesting in view of our recent efforts to synthesize long-bridged cyclonucleosides for expanding the range of model base-sugar conformations[3] and hence we decided to determine the base-sugar torsion angle (Φ_{CN}) of the cyclized system **2** by X-ray analysis. Although the crystals of both **2a** and **2b** more or less had a propensity to effloresce in open atmosphere, the former proved to be more amenable to manipulation, and accordingly the results of its X-ray analysis are described herein.



Scheme 1.

Experimental

Compound **2a** (100 mg) was dissolved in methanol (1.5 ml) at 40 °C and left at room temperature. Small hexahedral crystals appeared after 24 h and were allowed to grow for 2 weeks. Since these crystals (mono-methanolate) proved to have a tendency to effloresce with releasing methanol of crystallization,[4] a crystal was quickly sealed inside a glass capillary containing a tiny volume of the saturated mother liquor at the tip. D_m was measured by flotation in a mixture of acetone and chloroform. All subsequent X-ray measurements were conducted using a Rigaku automated four-circles diffractometer, AFC-5, employing graphite monochromatized Cu$K\alpha$ radiation (λ=1.5418 Å). $C_{20}H_{25}N_7O_6 \cdot CH_3OH$, M_r=491.51, triclinic, $P1$, a=9.556 (1), b=11.171 (1), c=5.987(1) Å; α=106.28(1), β=83.70(1), γ=106.16(1)°; V=588.9(1) Å^3, D_x=1.386 g cm^{-3}, D_m=1.381 g cm^{-3}; Z=1; crystal size, 0.32×0.20×0.80 mm; 2156 measured reflections, $2\theta_{max}$=126.0°, $-11 \leqq h \leqq 10$, $-11 \leqq k \leqq 12$, $-4 \leqq l \leqq 0$, R_{int}=0.007. Three standard reflections after every 100 reflections (decay less than 18%). The structure was solved by the Monte-Carlo direct method[5] with the aid of MULTAN 78 program[6] using 1880 non-zero unique reflections, and refined by the full-matrix least-squaies procedure with the analytical absorption correction.[7] Non-H atoms assigned anisotropic temperature factors. All the H atoms (except for some H atoms of **2a**) could be located on a difference Fourier map and refined with the equivalent isotropic temperature factors to that for the bonded carbon or nitrogen atoms.

$$R=0.063,\ S=[\sum W(|F_o|^2-|F_c|^2)^2/(m-n)]^{1/2}=2.9,$$
$$W=1/\sigma^2(F^2),\ \Delta\rho_{max}=1.0\ \mathrm{e\,\AA^{-3}}.$$

Atomic scattering factors from International Tables for X-Ray Crystallography.[8] ORTEP employed for drawing the molecular structure. All the calculations were done on a FACOM M-382 computer at the Computation Center of Nagoya University.[9]

Discussion

Figures 1 and 2 show the selected bond lengths and bond angles of **2a**, respectively. When compared with the normal ribo-, deoxyribonucleosides or guanosine itself, it is seen from these figures that (a) the N9-C10-O18 (=N^9-$C_{1'}$-$O_{1'}$)[10] bond angle in **2a**, 113.9°, is significantly larger than 108—109° commonly shown by natural ribonucleosides[11] and the angle C13-C14-O15 ($C_{4'}$-$C_{5'}$-$O_{5'}$), 107.7°, is significantly smaller than normal 111—112°,[11] (b) the C13-C14 (=$C_{4'}$-$C_{5'}$) as well as C14-O15 (=$C_{5'}$-$O_{5'}$) bond length, 1.527 and 1.447 Å, respectively, is longer than corresponding values 1.507—1.514 and 1.42—1.43 Å for the normal nucleosides,[11] and (c) the N7-C8 (=N^7-C_8) bond length of the base, 1.298 Å, is shorter but the C8-N9 (=C_8-N^9) bond length, 1.414 Å, is significantly longer than the corresponding values, 1.306

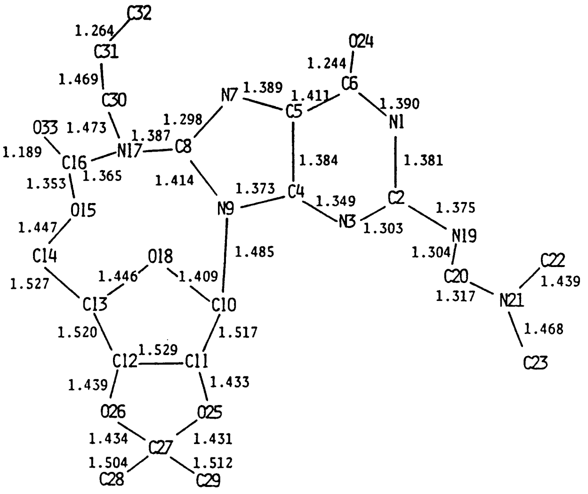


Fig. 1. Bond lengths of **2a** (l/Å).

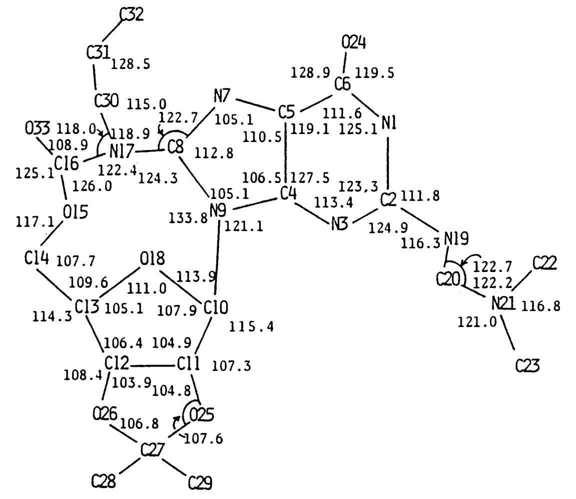


Fig. 2. Bond angles of **2a** (ϕ/°).

and 1.369 Å, shown by guanosine. These differences of the bond parameters seem to suggest the presence of some steric tension in the tricyclo[6.2.1] system including the bridge, which is probably reflected in our unsuccessful attempts to safely deisopropylidenate this type of compounds.

Figure 3 shows ORTEP drawing of the molecule as seen from over the base plane. It is recognized from this figure that the $O_{5'}$-CO-N^8(allyl)-bridge is located over the front side (2′,3′-side) of the nearly flat sugar ring. The base-sugar torsion angle (Φ_{CN}) defined as an angle from the $C_{1'}$-$O_{1'}$ bond was calculated as −90.20°, using the bond lengths and angles in Figs. 1 and 2. Here, the torsion angle was approximated by the dihedral angle between the plane C8-N9-C10 (=C_8-N^9-$C_{1'}$) and the plane O18-C10-N9 (=$O_{1'}$-$C_{1'}$-N^9). Similarly, the dihedral angle between the plane O18-C10-N9 (=$O_{1'}$-$C_{1'}$-N^9) and the plane C12-C10-N9 (=$C_{3'}$-$C_{1'}$-N^9) was calculated as −83.10° using appropriate bond parameters. Thus, the base-sugar torsion angle of **2a** has proved to reside between the two directions, $\overrightarrow{C_{1'}\text{-}C_{2'}}$ and $\overrightarrow{C_{1'}\text{-}C_{3'}}$, and quite near the $\overrightarrow{C_{1'}\text{-}C_{3'}}$ line.

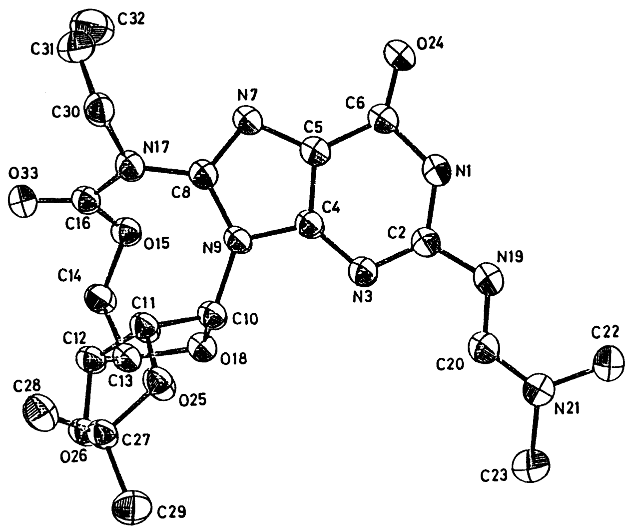


Fig. 3. An ORTEP drawing of **2a** as seen from the upside of the base plane. The H atoms and methanol of crystallization have been omitted for clarity (Thermal ellipsoids 30% probability level).

Table 1. UV and CD Spectra of **2b** and **4** in Methanol

Compd	UV[a)] λ_{max}/nm (ε)	CD λ_{max}/nm (θ)
2b	269 (25900)	259 (+66500) 222 (−20000)
4	263 (15600) 283 (7500)[b)]	259 (+28600) 223 (−4400)

a) Cited from Ref 1. b) Inflection.

CD spectra[13)] of **2b** and 8,5′-allylimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-*β*-D-ribofuranosyl)guanine (**4**)[1)] as an extreme anti conformer model are given in Table 1 together with their UV absorptions cited from Ref. 1. Although direct comparison between **2a** having an 8-iminocarbonyloxy group and **4** having an 8-amino group is rather inadequate, the strong positive Cotton effects of both compounds are in accord with the notion of the anti conformations of purine nucleosides.[14)] It is anticipated that this type of long-bridged purine nucleosides in completely deprotected form would afford a different torsion angle or/and a different stereochemistry of the sugar part with releasing steric strain and further studies along this line are under way.

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9) Listing of atomic parameters, thermal parameters and F_o-F_c table are deposited as Document No. 8854 at the Office of the Editor of Bull. Chem. Soc. Jpn.

10) The atom numberings in the parentheses are those commonly used to designate the atoms in the purine bases and furanoses.

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12) "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 2, ed by W. W. Zorbach and R. S. Tipson, Wiley-Interscience, New York, N. Y. (1973), p. 520.

13) The CD spectra were recorded on a JASCO J-500 Spectropolarimeter equipped with a JASCO DP-500 data processor for CD.

14) Ref. 10, p. 199.