Variation of ^1J(C1′, H1′) with Glycosidic Bond Conformation of Pyrimidine Nucleosides

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^1J(C1′, H1′) magnitudes of a series of pyrimidine cyclonucleosides are found to vary quantitatively with glycosidic bond conformation. Measurements of ^1J(C1′, H1′) in pyrimidine nucleosides and nucleotides can be used to determine the range of allowed *syn* and *anti* conformations.

The glycosidic bond *syn* ⇌ *anti* conformer equilibrium of base with respect to sugar ring is of fundamental importance in determining the conformations of nucleic acids in solution. The majority of *X*-ray structure determinations of nucleosides, nucleotides, and oligo- and poly-nucleotides in the solid state show that the purine or pyrimidine ring exists in the *anti* conformation and that the *syn* conformation is promoted when the base ring contains a bulky substituent (at C8 for purine and C6 for pyrimidine).[1,2] Many n.m.r. methods (chemical shift changes, lanthanide ion probe techniques, vicinal carbon–proton coupling constants, nuclear Overhauser enhancements, and proton spin–lattice relaxation times)[3] have been used to investigate the glycosidic bond conformations in a qualitative manner. Although attempts have been made, especially with purine derivatives, to provide a quantitative assessment of the *syn* ⇌ *anti* equilibrium there are large discrepancies between results determined by different methods.[4] A major limitation for comparison of such results is an independent assessment of the *syn* and *anti* conformations for molecules in solution. In this work the variation in ^1J(C1′, H1′) magnitudes of pyrimidine nucleosides is investigated and interpreted in terms of the allowed glycosidic bond conformations in equilibrium.

A number of cyclonucleosides (Figure 1) have been synthesised as model compounds in which the base ring exhibits different glycosidic bond conformations, charac-

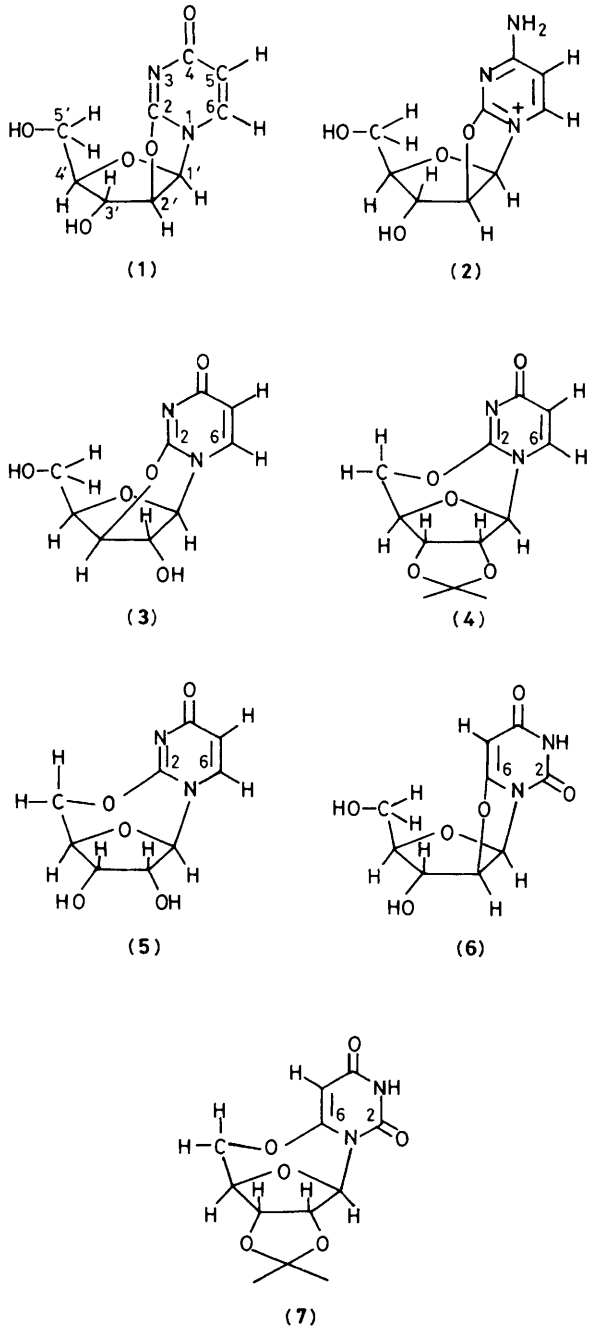

Figure 1. Structures of cyclonucleosides.

	χ/°	^1J(C1′, H1′) /Hz
(**1**) 2,2′-Anhydro-1-(β-D-arabinofuranosyl)-uracil	115	184.7
(**2**) 2,2′-Anhydro-1-(β-D-arabinofuranosyl)-cytosine	115	186.6
(**3**) 2,3′-Anhydro-1-(β-D-xylofuranosyl)-uracil	85	180.5
(**4**) 2,5′-Anhydro-2′,3′-*O*-isopropylidene-uridine	65	174.2
(**5**) 2,5′-Anhydro-1-(β-D-ribofuranosyl)-uracil	65	172.0
(**6**) 2′,6-Anhydro-1-(β-D-arabinofuranosyl)-6-hydroxyuracil	290	184.3
(**7**) 5′,6-Anhydro-2′,3′-*O*-isopropylidene-uridine	245	168.5

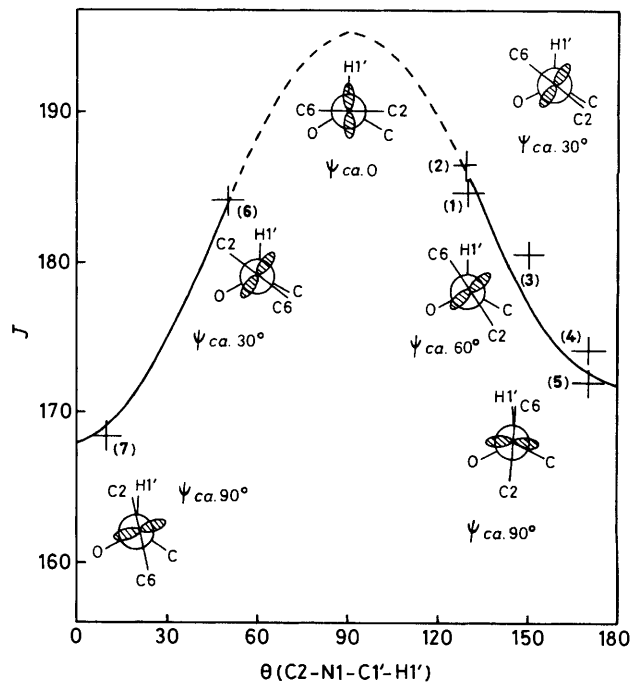

Figure 2. Variation of ^1J(C1′, H1′) of compounds (**1**)—(**7**) with dihedral angle θ (C2–N1–C1′–H1′). Inset structures show the approximate relation of the C1′–H1′ bond to the nitrogen atom p orbital (denoted by angle Ψ).

terised by angle χ.[5] Two conformational regions are denoted as *syn* (χ, 0 ± 90°) and *anti* (χ, 180 ± 90°) conformations. Cyclisation from base to sugar ring produces relatively rigid molecules in which χ can be taken from crystal structures when available [(**1**) χ 114.5,[6,7] (**4**) χ 66.4,[6] 71.2°[8]] or estimated from molecular models [(**2**) χ *ca.* 115, (**3**) χ *ca.* 85, (**5**) χ *ca.* 65, (**6**) χ *ca.* 290, (**7**) χ *ca.* 245°]. ^1J(C1′, H1′) magnitudes were determined for compounds (**1**)—(**7**) from proton-coupled ^{13}C n.m.r. spectra (observed under gated decoupling conditions to a data resolution of 0.3 Hz per point) and a variation from 168.5 Hz (**7**) to 184.7 Hz (**1**) is observed. It is known that magnitudes of ^1J(C,H) vary markedly with s character of the carbon atom to give typical values for sp^3, sp^2, and sp carbon atoms which are modified by variations in substituent electronegativity, bond angle effects, *etc.*[9] Also lone pair effects have been used to explain differences in the ^1J(C, H) magnitudes of axial and equatorial C–H in carbohydrates,[10] variations in ^1J(αC,H) of linear and cyclic peptides,[11] and the fact that the larger coupling constant occurs for a C–H *cis* to the nitrogen lone pair rather than *trans*.[12] Hence we might expect ^1J(C1′, H1′) to depend on both the glycosidic bond (N–C1′) and sugar ring (O4′–C1′) conformations.

For the cyclonucleosides studied here, only small variations in sugar ring conformations [*viz.* C4′–O4′–C1′–H1′ has magnitudes *ca.* 130 (**1**), (**2**), (**6**), *ca.* 150 (**4**), (**5**), (**7**), and *ca.* 160° (**3**)] are estimated in comparison to the glycosidic bond conformation [*viz.* C2–N1–C1′–H1′ has magnitudes *ca.* 10 (**7**), *ca.* 50 (**6**), *ca.* 130 (**1**), (**2**), *ca.* 150 (**3**), and *ca.* 170° (**4**), (**5**)] and so, to a first approximation, the variation in ^1J(C1′, H1′) magnitudes with conformation has been fitted to torsion angle θ (C2—H1′) in a generalised equation of the form of equation (1) with the magnitudes of the constants being $A = -26$, $B = -2$, and $C = 196$ Hz.

$$^1J(\text{C1′, H1′}) = A\cos^2\theta + B\cos\theta + C \qquad (1)$$

As shown in Figure 2, the calculated curve fits the observed ^1J magnitudes and predicts a minimum in ^1J(C1′, H1′) for conformations corresponding to $\theta = 0°$ (^1J *ca.* 168 Hz, C2–N1 eclipsed with C1′–H1′) and $\theta = 180°$, (^1J *ca.* 172 Hz, C6–N1 eclipsed with C1′–H1′) which is verified by compounds (**4**), (**5**), and (**7**). The curve also predicts a maximum of ^1J(C1′, H1′) of *ca.* 196 Hz for $\theta = 90°$ where both C2–N1 and C6–N1 are perpendicular to C1′–H1′; in this conformation the p orbital of the trigonal nitrogen atom (involved in weak π bonding with adjacent C2 and C6) is coplanar with the C1′–H1′ bond and may be responsible for the increase in ^1J(C1′, H1′).

In principle the variation in ^1J(C1′, H1′) with θ may be used to determine the glycosidic bond conformational angle χ, though in practice observation of one coupling constant gives rise to four possible χ values (two *syn* and two *anti*). Magnitudes of ^1J(C1′, H1′) of a number of pyrimidine nucleosides and nucleotides in solution[13] are found to vary between 168 and 172 Hz which limits the glycosidic bond to a narrow range of *syn* (χ 60 ± 10° corresponding to θ 180 ± 10°) and *anti* (χ 240 ± 20° corresponding to θ 0 ± 20°) conformational regions, assuming that variations in sugar ring conformation have only minor effects on ^1J(C1′, H1′) magnitudes.† Although the *syn* and *anti* conformations determined from ^1J(C1′, H1′) magnitudes are consistent with those observed in the solid state by *X*-ray crystallography,[1,2] determination of the position of the *syn* ⇌ *anti* equilibrium requires additional information such as vicinal proton–carbon coupling constants.[13,14] It is also expected that ^1J(C1′, H1′) magnitudes of purine nucleosides will vary with conformation in a manner analogous to that found for pyrimidine nucleosides, providing a new and general method for determination of glycosidic bond conformations of nucleosides and nucleotides in solution.

Received, 22nd December 1983; Com. 1648

† We are grateful to a referee for pointing out that ^1J(C1′, H1′) magnitudes should depend on sugar ring conformation (ν_0, O4′–C1′) as well as glycoside bond conformation (χ, N1–C1′).

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