

Intramolecular base-backbone association in 8-bromo-2',3'-O-isopropylidene-adenosine : detection of an O(5')-H...N(3) hydrogen bond via a long range H(5'')-N(3) spin-spin coupling

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Intramolecular Base-Backbone Association in 8-Bromo-2',3'-O-isopropylidene-adenosine. Detection of an O(5')-H ··· N(3) Hydrogen Bond *via* a Long Range H(5'')-N(3) Spin-Spin Coupling

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A completely rigid conformation is found for the *syn*-nucleoside 8-bromo-2',3'-O-isopropylidene-adenosine in apolar solvents, which is due to an effective O(5')-H ··· N(3) hydrogen bond, as is demonstrated by a substantial N(3) quadrupolar broadening of the H(5'') resonances in the ¹H n.m.r. spectra.

In this communication we report the results of a 200 and 300 MHz ¹H n.m.r.† conformational study on the modified *syn*-nucleoside 8-bromo-2',3'-O-isopropylidene-adenosine¹

† ¹H N.m.r. spectra were run at 200 MHz on a Bruker WM-200 spectrometer (SON high-field n.m.r. facility, Nijmegen), or at 300 MHz on a Bruker CXP-300 spectrometer (n.m.r. facility, Eindhoven University of Technology). ¹⁴N Decoupled spectra were run at 200 MHz.

(1) in various solvents. It is found that (1) displays a conformational rigidity in apolar solvents such as CDCl₃ and C₆D₆, owing to an effective hydrogen bond between O(5') and N(3). Uniquely, this hydrogen bond could be clearly established by a substantial broadening of the H(5'') resonances which is absent in the ¹⁴N decoupled spectrum (Figure 1). Apparently, in apolar media the O(5')-H ··· N(3) hydrogen bond accommodates a planar arrangement of H(5'')-C(5')-O(5')-H ··· N(3) which is a prerequisite for the long-range

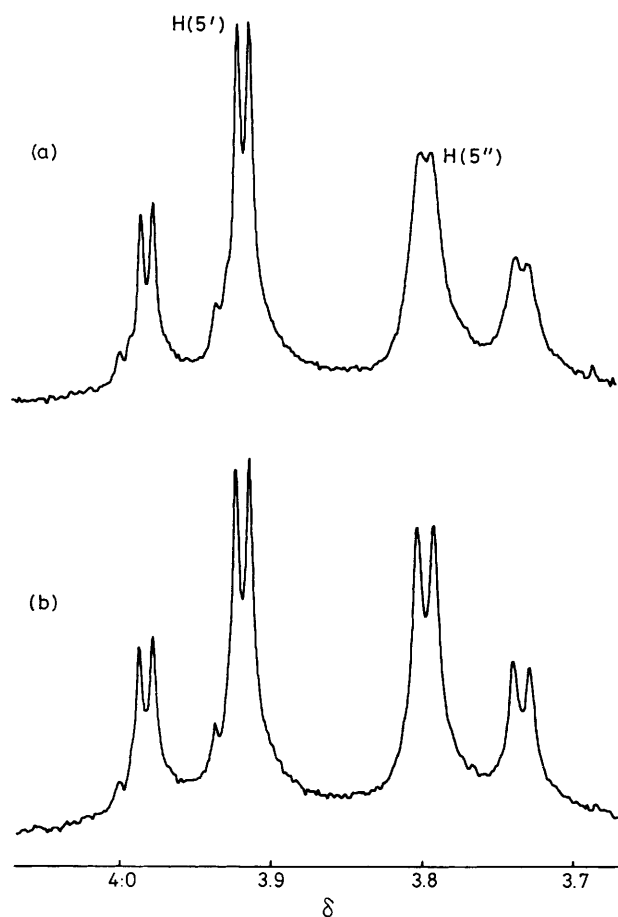
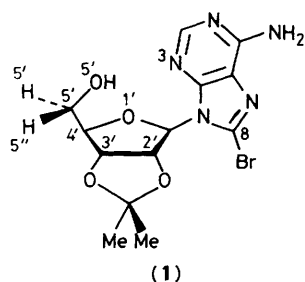


Figure 1. (a) Expansion of the H(5'), H(5'') region of the 200 MHz ^1H n.m.r. spectrum of (1) in CDCl_3 . The broadening of the H(5') resonances is clearly visible. (b) Corresponding ^{14}N decoupled spectrum.

H(5'')–N(3) spin–spin coupling.‡ This geometrical situation is also present in the crystalline state, as could be deduced from the published crystallographic data (Figure 2).² Correspondingly, the ^1H n.m.r. spectra in CDCl_3 and C_6D_6 show that the C(4')–C(5') conformation is 100% *gauche* (+) (g^+) (Table 1).§ The complete conformational rigidity is also reflected in

‡ Variable temperature ^1H n.m.r. measurements have shown that the observed H(5'') broadening is not due to coupling with the OH proton, since no sharpening is observed upon increasing the temperature of the CDCl_3 sample to ca. 50 °C.

§ In the g^+ rotamer, O(5') is in a *gauche* orientation with respect to O(1') and C(3'). The g^+ populations were calculated from $J_{4',5'}$ and $J_{4',5''}$ using the generalised Karplus relation developed by Altona *et al.* See ref. 3.

Table 1. Spectral data and the populations of the g^+ rotamer around C(4')–C(5') in various solvents.

Solvent	$J_{4',5'}/\text{Hz}$	$J_{4',5''}/\text{Hz}$	$x(g^+)^a$
CDCl_3	1.5	1.8	1.00
C_6D_6	1.6	1.9	1.00
CD_3CN	2.7	2.8	0.82
$(\text{CD}_3)_2\text{CO}$	3.5	3.5	0.68
CD_3OD	4.1	4.7	0.48
$(\text{CD}_3)_2\text{SO}$	5.8	5.8	0.22
$(\text{Me}_2\text{N})_3\text{PO}$	5.3	7.5	0.08

^a Fraction of the g^+ rotamer around C(4')–C(5').

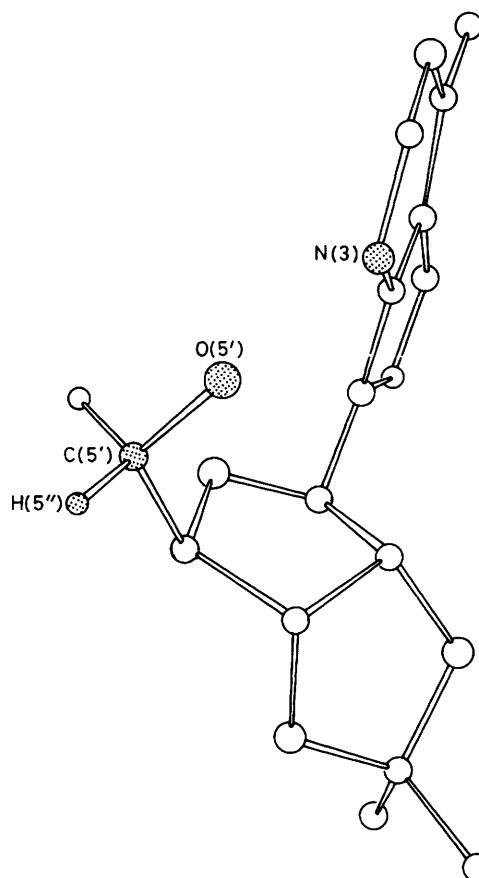


Figure 2. Crystal structure of (1), published in ref. 2, viewed along the plane through H(5''), C(5'), O(5'), and N(3).

the conformation of the ribose ring which is fully locked in a pucker form I (Figure 3) with $P_{\text{I}} = 200^\circ$ and $\nu_{\text{max, I}} = 26^\circ$,[¶] differing only slightly from the ring pucker in the crystal structure ($P = 160^\circ$, $\nu_{\text{max}} = 26^\circ$).² Increasing the medium polarity by using the solvents CD_3CN , $(\text{CD}_3)_2\text{CO}$, and CD_3OD leads to a sharpening of the H(5'') resonances, indicating that the O(5')–H...N(3) bond is weakened, which results in an overall increased conformational flexibility. This is consistent with the observations that (i) the ribose ring is involved in a two-state conformational equilibrium between the pucker forms I and II ($P_{\text{II}} = 300^\circ$, $\nu_{\text{max, II}} = 26^\circ$;

¶ The conformation of the ribose ring was analysed according to Olson and Sussman (see ref. 5), using Figure 3, which was calculated for $\nu_{\text{max}} = 26^\circ$.

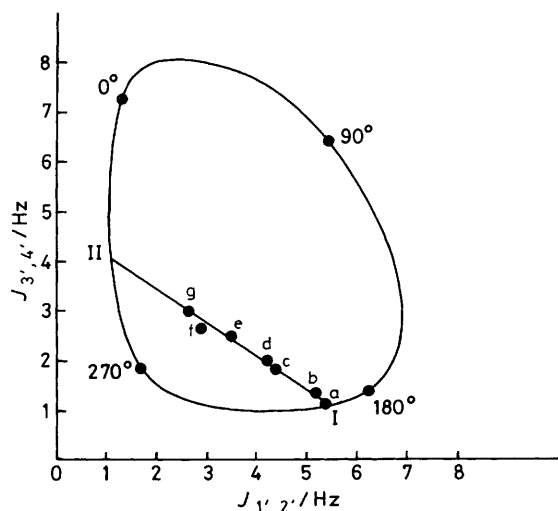


Figure 3. Dependence of the transoidal proton-proton coupling constants $J_{1',2'}$ and $J_{3',4'}$ upon P in ribose systems.⁵ The experimental data refer to CDCl_3 (a), C_6D_6 (b), CD_3CN (c), $(\text{CD}_3)_2\text{CO}$ (d), CD_3OD (e), $(\text{Me}_2\text{N})_3\text{PO}$ (f), and $(\text{CD}_3)_2\text{SO}$ (g).

see Figure 3), and (ii) the fraction of the g^+ conformation around $\text{C}(4')\text{--}\text{C}(5')$, decreases markedly from 1.00 for CDCl_3 and C_6D_6 to 0.48 for CD_3OD (Table 1). Very small g^+ populations are found for the hydrogen-bond disrupting solvents $(\text{CD}_3)_2\text{SO}$ and $(\text{Me}_2\text{N})_3\text{PO}$ ⁶ (respectively 0.22 and

0.08; see Table 1). Consequently, the broadening of the $\text{H}(5'')$ resonances in these media is completely absent.

The present results reveal that the $\text{O}(5')\text{--}\text{H} \cdots \text{N}(3)$ hydrogen bond favours the g^+ conformation around the $\text{C}(4')\text{--}\text{C}(5')$ linkage and *syn* base-conformation in apolar solvents. Obviously, this hydrogen bond is so tuned that $\text{H}(5'')$ – $\text{N}(3)$ spin–spin coupling is observable on account of the unique planar arrangement $\text{H}(5'')\text{--}\text{C}(5')\text{--}\text{O}(5')\text{--}\text{H} \cdots \text{N}(3)$. To the best of our knowledge this is the first experiment which provides information about an intramolecular long range spin–spin coupling *via* a distinct hydrogen bridge.

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