Tetrahedron Letters No. 46, pp 4063 - 4066, 1974. Pergamon Press. Printed in Great Britain.

BARRIERS TO INTERNAL ROTATION AROUND THE GLYCOSIDIC BOND OF NUCLEOSIDES WITH SYMMETRIC AGLYCONES

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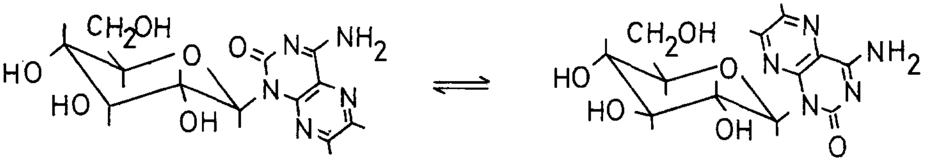
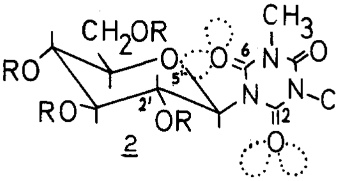
(Received in UK 30 September 1974; accepted for publication 10 October 1974)

A full understanding of the stereochemistry of nucleic acids implies knowledge of the preferred orientation of the aglycone bases relative to the sugar moieties. Although the existence of two preferred rotamers (syn-anti-isomerism) was postulated 14 years ago [1)] and many theoretical and experimental investigations supported this idea, the first measurements of heights of these barriers to internal rotation around the glycosidic bond of N-glycosides have been reported only recently [2-5)]. At low temperature the NMR signals of the sugar protons, especially of the anomeric protons of pteridine nucleosides e.g. 1 appear doubled, collapsing at a coalescence temperature. The calculations of the free energies of activation, $\Delta G^{\ddagger}$, were rendered difficult owing to (1) insufficient solubility of the nucleosides at low temperature, (2) complicated splitting of the proton resonances by coupling to other protons, and (3) marked differences in the populations of the two rotamers in some cases. All these problems are overcome in nucleosides of the kind 2 - 4, the aglycones of which have C_{2v} symmetry along the glycosidic bond. Consequently, the two energetically preferred rotamers are identical and the difficulty of syn-anti-assignment is separated from the problem of determining the activation



1 syn $\Delta G^{\ddagger} = 75\ \text{kJ}\cdot\text{mole}^{-1}$ anti

parameters for the hindered rotation around the N-glycosidic bond. A kinetic process due to this rotation should only change the NMR line shapes of the aglycone with variable temperature. For instance the methyl protons and the ^{13}C signals of the carbon atoms 2 and 5, the methyl carbons and the olefinic C-3 and -4 in compound 3 should be affected, while the resonances of the sugar moiety should not change. This is actually observed as shown in the Figure.



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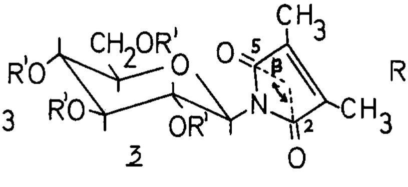
R = COCH$_3$



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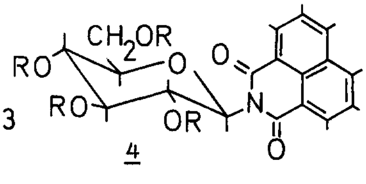
R' = COC$_6$H$_5$



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Since the signals of each pair of diastereotopic nuclei are of equal intensity, not being complicated by any coupling, the signal to noise ratios, especially of the proton resonances, are good enough to permit calculation of accurate values for the free energies of activation, $\Delta G^{\ddagger}$, by computer simulation 6) of the spectra around the coalescence temperatures. The results are given in the Table. For compound 2 in pyridine one finds the activation parameters $\Delta H^{\ddagger}$ = (64,0 ± 4) kJ·mole^{-1} and $\Delta S^{\ddagger}$ = (-21 ± 13) J·mole^{-1}K^{-1} 12). The influence of

Table

Compound 7)	Solvent	Nuclei	T_c (K) 8)	$\Delta\nu$ (Hz) 9)	$\Delta G^{\ddagger}_{T_c}$: kJ·mole^{-1}	kcal/mole
2	pyridine-d_6	$N\text{-}C\underline{H}_3$	307,5	3,9	70,42 ± 0,3	16,83
"	"	$N\text{-}^{13}\underline{C}H_3$	327	15,9	70,79 ± 0,5	16,92
"	acetone-d_6	$N\text{-}C\underline{H}_3$	300	3,2	69,12 ± 0,3	16,52
"	CD_3NO_2	$N\text{-}C\underline{H}_3$	278	0,7	69,37 ± 1,7	16,58
"	$CDCl_3$	$N\text{-}^{13}\underline{C}H_3$	321	13,7	69,91 ± 0,8	16,71
"	"	$N\text{-}^{13}C{=}O$	331,5	48,0	68,78 ± 0,8	16,44
3 10)	acetone-d_6	$N\text{-}^{13}\underline{C}{=}O$	250	8,8	55,02 ± 0,8	13,15
"	"	$^{13}\underline{C}{=}C$	254,5	28,6	53,35 ± 0,4	12,75
4 11)	$CDCl_3$	$N\text{-}^{13}\underline{C}{=}O$	327,5	28	69,37 ± 0,8	16,58
"	"	$^{13}\underline{C}\text{-}\underset{N}{C}{=}O$	328	25	69,66 ± 0,8	16,65

the solvent on the barrier is small. Going from a six membered (e.g.2) to a five membered cyclic aglycone (e.g.3) the barrier to hindered rotation is lowered by about 16 kJ·mole^{-1}, while different six membered aglycones (e.g.2 and 4) show very similar barriers. Apparently the height of the barrier is a function of the angle ß between the two C=O bonds of the aglycon which, according to X-ray data, should be about 139^{o} in maleic imides like 3 13) and 129^{o} in isocyanuric acid derivatives like 2 14). We assume that the barrier height is mainly determined by two interactions: interference of (1) the axial pair of free electrons of the (assumed) sp^3 hybridised ring oxygen O-5' and (2) the electron lone pairs at O-2', with the pairs of free electrons cis to the glycosidic bond, for instance of the carbonyl oxygens 2 and 6 in 2.

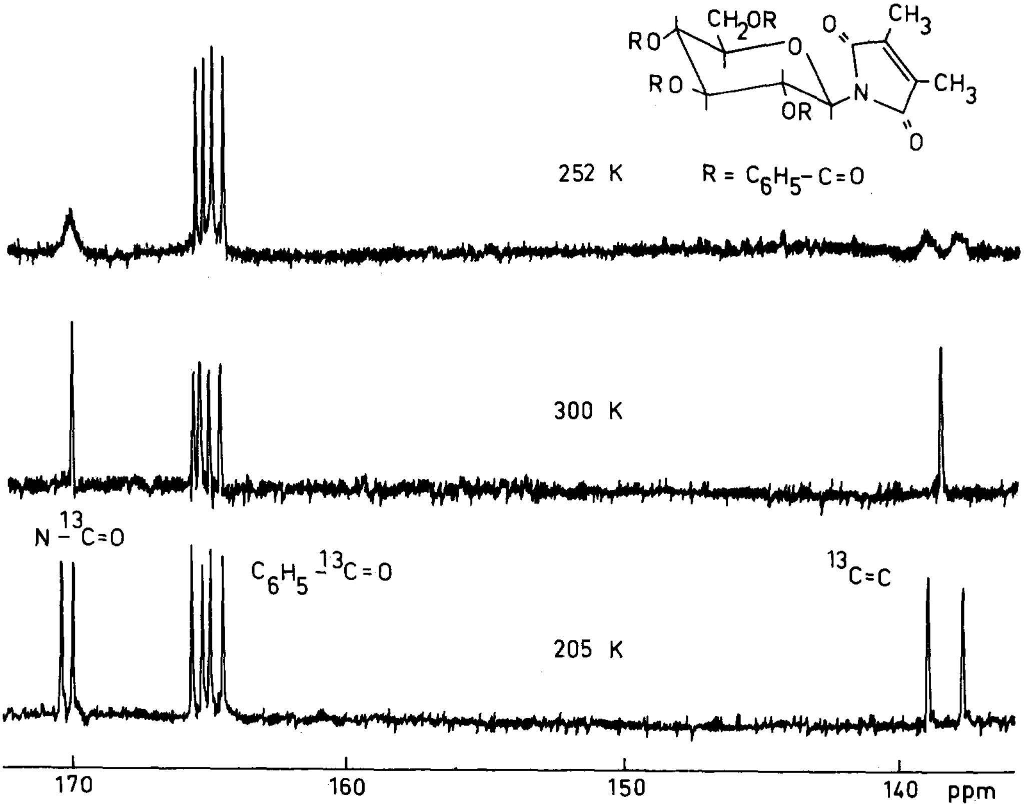

Figure. Part of the ^{13}C NMR spectrum of compound 3 in acetone-d_6 at 20,63 MHz.

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6) A computer program using the modified Bloch equations has been written for the Nicolet computer connected to our WHX 90 Bruker NMR spectrometer.

7) All samples were degassed by five freeze thaw cycles in vacuum. TMS was used as internal reference. The proton resonance spectra were recorded at 90 MHz, the ^{13}C spectra at 22,63 MHz. Temperatures were measured with a calibrated thermocouple and are assumed to be accurate to ± 1 K.

8) Coalescence temperature.

9) The shift differences of diastereotopic nuclei were plotted as a function of temperature starting 50 K below coalescence. Extrapolation gave the shift difference at T_c.

10) Homoallylic coupling of the methyl protons together with only 3 Hz shift differences prevent simple evaluation of the activation parameters. Therefore only the ^{13}C data were used.

11) All five pairs of diastereotopic nuclei of the naphthalimide appear as doublets at low temperature while none of the diastereotopic protons show a resolvable shift difference at 90 MHz.

12) These values were calculated from the two different coalescence temperatures given in the Table, and are in good agreement with data obtained from a complete line shape analysis of the $N-CH_3$ proton resonance alone ($\Delta H^{\ddagger} = 64,2\ kJ \cdot mole^{-1}$).

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Acknowledgement: This work was supported by the Deutsche Forschungsgemeinschaft and Stiftung Volkswagenwerk.