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CORRELATION OF THE C-1' CHEMICAL SHIFTS WITH THE VICINAL SPIN—SPIN COUPLING CONSTANTS OF THE H-1' AND H-2' PROTONS IN NUCLEOSIDES.

II. 2'-, 3'-, AND 5'-O-SUBSTITUTED NUCLEOSIDES

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The existence of a correlation has been established for pyrimidine but not for purine, nucleosides. It is suggested that the change in the chemical shift of the anomeric carbon is a consequence of 1,2-eclipsing interaction between O-2' and N-1' in the S type of conformation of the ribose ring. Possible reason for the absence of a correlation in the case of purine nucleosides are discussed. It is shown that the chemical shift of the anomeric carbon can be used in the conformational analysis of the ribose rings of pyrimidine nucleosides.

Continuing a study of the correlation of the parameters of the NMR spectra for pyrimidine nucleosides that we established previously [1], we have investigated derivatives of pyrimidine nucleosides (I-IX) and of purine nucleosides (X-XVII). To study the correlation over a wider range and to exclude a possible influence of the considerable electronic effects on the (CSs) C-1' chemical shifts, we considered derivatives not containing substituents in the base part of the molecule. Because of substantial deviations for aqueous solutions [1], we used only aprotic solvents — dimethyl sulfoxide-d_6 (DMSO-d_6), pyridine-d_5, deuterochloroform ($CDCl_3$), and acetone-d_6.

A linear correlation is observed in the dependence obtained of the C-1' CSs for uridine derivatives (I-IX) on the vicinal spin—spin coupling constants (SSCCs) of the H-1' and H-2' protons (Fig. 1). The equation of the straight line was derived by the method of least squares and is described by the formula

$$\delta_{C\text{-}1'} = kJ_{1'-2'} + C. \quad (1)$$

where k = −1.07 ppm/Hz and C = 94.36 ppm (correlation coefficient, r = −0.987). It can be seen from Fig. 1 that no appreciable deviations from the correlation due to the influence of the solvent and of the electronic effects of the substituents are observed. The increase in the slope of the straight line in the case of 2',3',O-cyclic derivatives (k = −3.5 ppm/Hz and C = 100.9 ppm) is, as shown below, a consequence of the flattening of the ribose ring [2].

We initially suggested that the reason for the change in the C-1' CSs was formed by the dissimilar contributions of the α effect as a consequence of changes in the position of the conformational equilibrium of the ribose ring. However, it is known [3] that because of steric perturbations the α- and γ-carbon atoms usually give a resonance absorption line in a stronger field if the substituent is axial. In particular, this has been used previously

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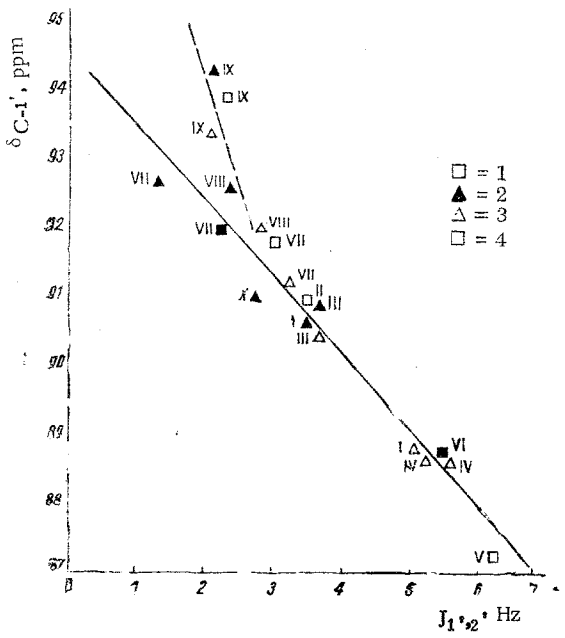


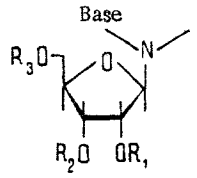
Fig. 1. Correlation of the C-1' CSs with the vicinal SSCCs of the H-1' and H-2' protons for uridine derivatives. 1) Acetone-d_6; 2) pyridine-d_5; 3) DMSO-d_6; 4) $CDCl_3$.

[4] for the conformational analysis of the pyranose ring of glycopyranosyl analogs of the nucleosides. Here an anomeric carbon atom with an axially oriented base appears in the stronger field. The results of our investigations, however indicate the existence of the opposite effect, i.e., when the base has the axial orientation in the N type of conformation of the ribose ring the signal of the anomeric carbon atom is shifted downfield as compared with the quasiequatorial position in the S type of conformation. From this it is possible to conclude that the chemical shifts of the anomeric carbon atoms in furanose and pyranose derivatives of nucleosides are determined by different factors.

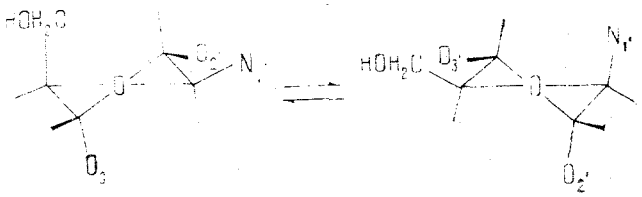
It is known [5] that 1,3-interactions are weakened in five-membered rings as compared with similar interactions in six-membered rings. Conversely, 1,2-interactions are intensified. This is shown, in particular, by the presence in furanoid systems of a 1,2-eclipsing effect — a high-field shift of the order of 5-6 ppm on passing from anomers with the trans-1,2 configuration to the cis anomers [6]. In addition to this, it can be seen from Fig. 2 that with the quasiequatorial orientation of the base in the S type of conformation of the ribose ring of a nucleoside, but not the N type, some eclipsing of O-2' and the nitrogen atom of the heterocyclic base takes place. All this, in combination with the results obtained permits the conclusion that the main cause of the upfield shift of the signal of the anomeric carbon in the S type of conformation is a 1,2-eclipsing interaction between O-2' and the nitrogen atom of the heterocyclic base.

In the case of the purine nucleosides (X-XVII), a substantial scatter of the points is observed (Fig. 3). In our view, this can be explained by the well-known influence of the position of the syn-anti equilibrium on the C-1' CS [7, 8]. To explain the upfield shift of the C-1' signal in the case of the S type of conformation, we assume that an increase in the screening of the anomeric carbon takes place because of a change in the polarization of the C—N bond on repulsion between the unshared electron pairs (UEPs) of O-2' and of the nitrogen atom of the base. Taking into account the fact that the electron density of the UEPs of O-2' is averaged in view of the free rotation around the C_2'—O_2' bond [10], the orientation of the UEP of the nitrogen atom acquires decisive importance. A comparison from this point of view of purine and pyrimidine nucleosides permits the assumption that the existence of a strict correlation in the case of compounds (I-IX) is due to the strictly determined orientation of the UEP of the nitrogen atom because of the narrow minimum of the conformational energy of rotation of the base around the glycosidic bond [9] and the substantial predomi-

TABLE 1



Compound	Nucleoside	R_1	R_2	R_3
I	Uridine	H	H	H
II		H	H	$C(C_6H_5)_3$
III		H	COC_6H_5	$C(C_6H_5)_3$
IV		COC_6H_5	H	$C(C_6H_5)_3$
V		COC_6H_5	COC_6H_5	H
VI		COC_6H_5	COC_6H_5	COC_6H_5
VII		CH_3	COC_6H_5	COC_6H_5
VIII			$C(CH_3)_2$	H
IX			$C(CH_3)_2$	$COCH_3$
X	Adenosine	H	H	H
XI		H	H	$C(C_6H_5)_3$
XII		H	H	$SO_2C_6H_4CH_3$
XIII		$COCH_3$	$COCH_3$	H
XIV	Inosine	H	H	H
XV		$COCH_3$	$COCH_3$	$COCH_3$
XVI		COC_6H_5	COC_6H_5	COC_6H_5
XVII	Guanosine	H	H	H



S type N type

Fig. 2. Types N and S conformations of the ribose rings of nucleosides.

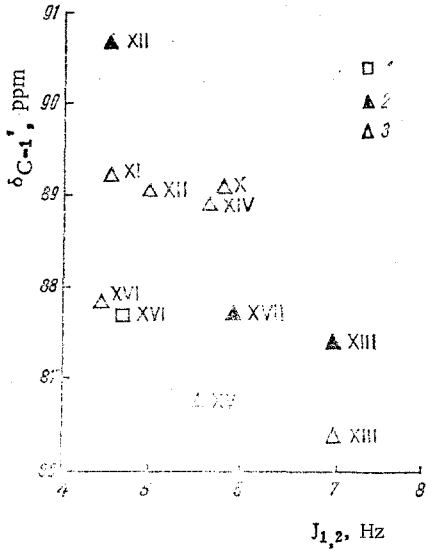


Fig. 3. Comparison of the C-1' CSs with the vicinal SSCCs with the H-1' and H-2' protons for purine nucleoside derivatives. Arbitrary symbols the same as in Fig. 1.

nance of the anti conformation in pyrimidine nucleosides [7]. In their turn, in the case of the purine nucleosides the broad and shallow minima of the conformational energy [9] indicate an indeterminacy of the orientation of the UEP of the nitrogen atom, which, in the final account, is shown in the scatter of the points in the dependence under study.

The existence of a clear correlation in the case of the pyrimidine nucleosides permits an estimate to be made of the position of the conformational equilibrium of the ribose ring by investigating the C-1' CS as the parameter Θ in the equation

$$\langle\Theta\rangle = \sum_j p_j\Theta_j = p_N\Theta_N + p_S\Theta_S, \quad (2)$$

where p_N and p_S are the molar fractions of conformers of types N and S. On substituting in Eq. (1) the values of the SSCCs for the N and S conformers (J_N = 0.4 Hz and J_S = 9.5 Hz [11]) we obtain the C-1' CSs of the individual conformers. For uridine, δ_N = 93.93 and δ_S = 84.20 ppm. From this it is possible to determine that the maximum contribution of the 1,2-eclipsing interaction in this case is −9.73 ppm (the negative sign shows an upfield shift).

Finally, let us consider the sense of the coefficients k and C in Eq. (1). It is possible to show that the constant C characterizes the influence of the electronic effects of the base on the C-1' CS when the eclipsing interaction is absent. The value of the coefficient k depends on the efficacy of the eclipsing interaction itself and of the range of changes of the SSCCs of the H-1' and H-2' protons and, consequently, depends on the amplitude of the wrinkling of the ribose ring τ_m. It can be seen from the example of 2',3'-O-cyclic uridine derivatives that with a flattening of the ribose ring the value of k increases.

In conclusion, it must be mentioned that the symbatic change in the C-2' CS relative to that of C-1' which we observed previously for uridine and cytidine [12] and the assignment according to Schweizer et al. [7] to the change in the syn-anti equilibrium must apparently be considered as a consequence of the corresponding change in the polarization of the C_2'—O_2' bond as the result of the 1,2-eclipsing interaction. In this work, the influence of electronic effects of substituents on the C-2' CSs makes it difficult to explain such changes.

Thus, the study of the correlation of the C-1' CSs with vicinal SSCCs of the H-1' and H-2' protons in 2'-, 3'-, and 5'-O-substituted nucleosides has permitted the possibility to be established of the use of C-1' CSs for the conformational analysis of the ribose rings of pyrimidine nucleosides and has revealed the causes of the absence of a correlation in the case of purine nucleosides.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were taken at 30°C on a WH-90 pulsed spectrometer at frequencies of 90 and 22.63 MHz, respectively. A deuterated solvent was used to stabilize the resonance conditions. The concentrations of the solutions did not exceed 0.2 M. To exclude a possible influence of the concentration on the correlation parameter, the ^1H and ^{13}C NMR spectra were taken directly on the same solutions. The deuterated solvents, acetone-d_6, DMSO-d_6, pyrimidine-d_5, and $CDCl_3$ were dried over 4 Å molecular sieves.

The ^{13}C NMR spectra were recorded under the conditions of complete suppresion of spin—spin coupling with protons. The numerical resolution of the spectrum at a width of 3000 Hz and with the collection of the data in 8K points of the computer amounted to 0.75 Hz per point, which corresponded to an accuracy of the measurement of the chemical shifts of 0.03 ppm. The measuring pulse for ^{13}C was 8 μsec (approximately 60°C). The chemical shifts were determined relative to an internal standard — cyclohexane — in the δ scale, with δ_{ch} = 27.42 ppm.

The numerical resolution of the ^1H NMR spectra at a width of 600 Hz and a sampling of the data in 8K points of the memory of the computer was 0.25 Hz per point, which corresponded to the accuracy of measurement of the spin—spin coupling constants.

SUMMARY

It has been shown that the chemical shifts of the anomeric carbon atoms of pyrimidine nucleosides can be used in the conformational analysis of the ribose rings. Possible reasons for the absence of a correlation for purine nucleosides has been considered.

It is suggested that the correlation of the C-1' chemical shifts with the vicinal spin-spin coupling constants of the H-1' and H-2' protons is a consequence of a 1,2-eclipsing interaction between O-2' and the nitrogen atom of the heterocyclic base with the ribose ring in the S type of conformation.

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CORRECTED STRUCTURE OF THE REACTION PRODUCT OF GIBBERELLIN A_3 WITH ACETIC ANHYDRIDE AND ZINC AND ITS CRYSTALLINE STRUCTURE. RARE CASE OF THE DIELS—ALDER REACTION

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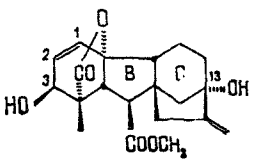
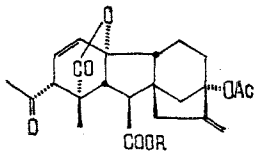
The correct structure has been established for the compound obtained on the treatment of the methyl ester of gibberellin A_3 with zinc in boiling acetic anhydride, to which the erroneous structure (II) was previously assigned. A mechanism of the formation of compound (II) is suggested which includes an intramolecular diene condensation between an acetate carbonyl group and the conjugated diene system in the intermediate mixed anhydride (V).

In the process of investigating derivatives of gibberellin A_3, we obtained a product of the interaction of the methyl ester of gibberellin A_3 (I) with zinc in boiling acetic anhydride which has been described by Jones, Growe, and MacMillan [1] and to which these authors ascribed structure (II). The corresponding acid (III) was obtained under the same conditions from gibberellin A_3 itself [1].



I



II. R = CH_3
III. R = H

Under the reaction conditions, the acetylation of the hydroxy groups first takes place [1] and the further transformation of the compound at ring A has a more complex nature, which Jones et al. [1] interpreted as a new reaction in which an acetoxy group was replaced

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