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A LINEAR RELATIONSHIP BETWEEN ELECTRONEGATIVITY OF 2'-SUBSTITUENTS AND CONFORMATION OF ADENINE NUCLEOSIDES

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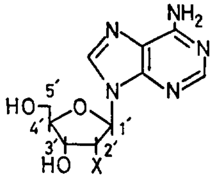
Summary

From the ^1H NMR studies of various 2'-substituted 2'-deoxyadenosines, a relationship between electronegativity of substituents and conformation of the sugar moiety was elucidated.

The difference on the structure of double-stranded DNA and RNA is believed to originate in the conformation of sugar moiety.[1] In fact the substitution of 2'-OH group of ribopolynucleotides by groups such as N_3, NH_2 and halogens affects the conformation and the thermal stability.[2] In this communication we wish to report results of ^1H NMR studies of 2'-substituted 2'-deoxyadenosine (1-9) and a linear relationship between electronegativity of substituents and conformation of the ribose moiety.

Nucleosides were synthesized as reported previously[3] and ^1H NMR spectra were measured at 100 MHz with a JEOL FX-100 pulse Fourier transform spectrometer locked on deuterium. Samples were dissolved in DMSO-d_6 and a drop of D_2O was added. The temperature of a probe was held at 25°. Chemical shifts were relative to internal TMS.

The proton chemical shifts of 2'-substituted 2'-deoxyadenosines are given in Table I.



1: X= H 4: X= OCH_3 7: X= Cl
2: X= OH 5: X= N_3 8: X= Br
3: X= NH_2 6: X= F 9: X = I

Table I ^{1}H Chemical shifts of 2'-substituted 2'-deoxyadenosines

Compound	8-H	2-H	NH_2	1'-H	3'-OH	5'-OH	2'-H	3'-H	4'-H	5'-H
1	8.33	8.14	7.29	6.35	5.29	5.22	2.25 2.74	4.41	3.89	3.57
2	8.34	8.14	7.32	5.88	5.16	5.40	4.61	4.16	3.99	3.57
3	8.31	8.14	7.33	5.68						
4	8.34	8.14	7.33	6.00	5.25	5.39	4.37		3.98	3.65
5	8.40	8.17	7.36	6.08	6.04	5.28	4.60			3.65
6	8.36	8.16	7.34	6.24	5.70	5.23	5.44	4.49	4.05	3.67
7	8.42	8.16	7.39	6.17	5.98	5.44	5.97	4.36	4.08	3.65
8	8.40	8.15	7.37	6.25	6.01	5.38	5.16	4.30	4.09	3.67
9	8.39	8.16	7.38	6.30	6.07	5.13	5.13	4.10		3.64

The resonance positions of the base protons are almost unaffected by substitution at the 2'-position. On the other hand there is a fairly large distribution in the chamical shifts of the sugar proton resonances. There seems to be a tendency following the order of the electronegativity of the substituents. When we plotted electronegativity parameter ι against chemical shifts of H-1', a linear relationship was observed, except for 2'-F and 2'-NH_2 compounds (Fig. 1a). F atom has extremely large negativity and the NH_2 group may be protonated in this condition.

In Table II proton spin-spin coupling constants are given together with % of N conformer calculated by method of Altona and Sundaralingam.[4] So far as to the halogen and azido derivatives, the population of the N conformaer decreases in the order of $F > N_3 > Cl > Br > I$. It corresponds to the electronegativity of these substituents and also to the atomic radii of these groups. It seems to be reasonable that the bulky groups are apt to come to the equatorial position of the sugar plane, which results in increase of the S conformer. However, the compounds substituted by OH, OMe, N_3 and NH_2, which are more bulkier than H, take more dominantly the N conformer than 2'-deoxyadenosine. Moreover, even F atom, which is only 0.15 A larger than H atom, has extremely large proportion of N conformer. Therefore, it is difficult to ascribe only the steric hindrance of the substituent groups to the origin of conformational change of the sugar moiety. When we plotted %N against l value (Fig. 1b), there is a relatively good correlation between % N and l value of F, N_3, Br, Cl and I substituted nucleosides. The OMe compound deviates slightly and OH(ribo) and NH_2 compounds deviate largely from the straight line. On the other hand H (deoxyribo) compound deviates largely to the opposite side of the line.

If we assume a polar effect of 2'-substituents due to C-X bond polarization, the magnitude of the effect might be in the order of electronegativity of the substituents. Therefore, the dipole moment of the sugar moiety should be subjected to change to adopt more energy-less form. This effect is noteworthy in the case of 2'-F compound. Presumably because of large electronegativity of the F atom, the conformation of this compound takes an extremely N-rich as high as 76 %. Groups such as N_3, Cl, Br and I make the conformations of 38-7 ,% of N conformers. The slight deviation of OMe compound may be due to its bulkiness. Deviations of NH_2 and OH compound might be ascribed to hydrogen-bonding with solvent molecules through their dissociable H atoms. 2'-H compound (deoxyribo) is rather exceptional, becuase $C^{2'}$-H bond polarization must be in an opposite direction as compared to other electronegative substituents.

Thus, we might be able to draw a conclusion that the conformation of the

Fig. 1

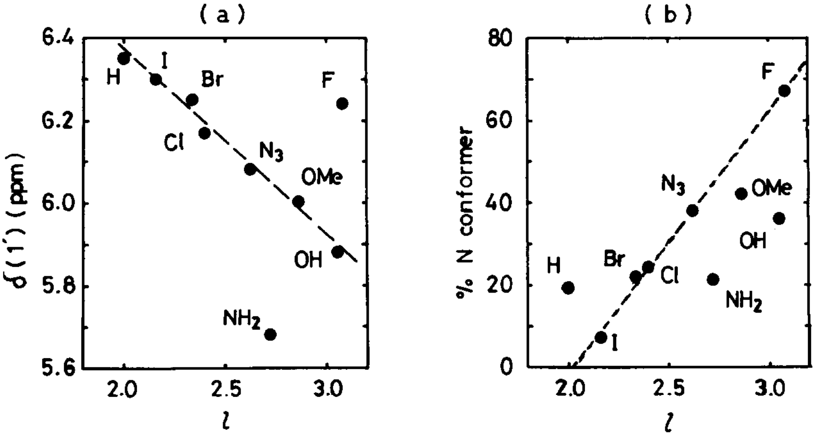


Table II Vicinal $^1H-^1H$ coupling constants (Hz) and conformation of the sugar moiety of 2'-substituted 2'-deoxyadenosines

Compound	$J_{1'2'}$	$J_{2'3'}$	$J_{3'4'}$	$J_{1'2'} + J_{3'4'}$	Population of N conformer (%)
1	6.2 7.7	3.0 5.6			19
2	6.1	5.1	3.1	9.2	36
3	7.5				21
4	5.5				42
5	5.9				38
6	3.1	4.3	6.0	9.1	67
7	7.2	4.8	2.7	9.9	24
8	7.4	4.7	2.4	9.8	22
9	8.8	4.5			7

sugar moiety in adenine nucleosides could be predicted nicely by electronegativity of the 2'-substituents. Furthermore this relationship must be applicable to other nucleosides having pentofuranose moieties. Studies along this line is in progress in our laboratory.

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