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Carbon-13 Magnetic Resonance Spectra of 8-Substituted Purine Nucleosides. Characteristic Shifts for the Syn Conformation

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Abstract: Carbon-13 magnetic resonance spectra of 8-substituted purine nucleosides were measured. Substitution of the 8-position of adenosine with various substituents (-Br, -Cl, $-SCH_3$, $-SCH_2CH_3$, -SH, $-OCH_3$, -OH, and $-CH_3$) caused characteristic upfield shifts (−2 to −3 ppm) of the 2′-carbon signal. The same phenomena was also observed in the case of 8-substituted guanosines (-Br, $-SCH_3$, -OH, and $-CH_3$), 8-substituted inosines (-Br, -OH, and $-CH_3$), and 2-ethylthio-8-methylinosine. This upfield shift of the 2′-carbon signal for these nucleosides was assumed to be due to their syn conformation placing the lone pair of electrons of base N(3) close to the sugar C(2′)-H(2′) bond. The effects of 8-substituents on the chemical shifts of base carbons are also discussed.

The direction of the base plane relative to the sugar moiety, the glycosidic torsion angle, in a nucleoside is one of the most important parameters determining its conformational properties. It is well known that most of the natural nucleosides take an anti[1] conformation in crystals[2] and in solution.[3] A syn[1] conformation, in which the base direction is reversed with re-

Table I. Carbon-13 Chemical Shifts[a] (ppm) for Various Purine Nucleosides

Nucleoside[b]	C(2)	C(4)	C(5)	C(6)	C(8)	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)
A(I)	112.73	109.49	79.75	116.51	100.32	48.39	33.88	31.06	46.29	22.13
8-BrA (II)[c]	112.78	110.32	80.04	115.54	87.54	50.84	31.54	31.30	47.12	22.54
8-ClA (III)[d]	113.03	110.08	78.37	115.61	97.28	49.77	31.66	31.24	47.13	22.49
8-SCH_3A (IV)[e]	111.55	111.13	79.96	114.79	110.11	49.33	31.71	31.35	46.99	22.60
8-SCH_2CH_3A (V)[f]	111.67	110.83	80.08	114.97	108.97	49.33	31.77	31.41	46.99	22.66
8-SHA (VI)[g]	112.34	108.62	67.50	108.32	128.40	49.22	31.17	31.17	46.10	22.66
8-OCH_3A (VII)[h]	110.90	109.16	75.35	114.44	114.80	47.18	31.53	31.29	46.40	22.66
8-OHA (VIII)[i]	110.96	106.95	63.96	107.55	111.92	46.16	31.35	30.75	45.86	22.78
8-CH_3A (IX)[j]	111.66	110.04	78.51	115.79	109.38	49.02	32.48	31.40	47.05	22.59
G (X)	114.11	111.77	77.18	117.23	96.06	46.95	34.18	30.88	45.69	21.95
8-BrG (XI)[k]	113.81	112.43	77.97	115.79	81.45	50.16	30.86	30.86	46.32	22.47
8-SCH_3G (XIII)[e]	113.43	113.19	77.58	116.07	104.56	48.68	31.05	31.05	46.16	22.60
8-OHG (XIII)[l]	113.03	107.88	59.09	114.53	112.25	46.09	31.34	30.44	45.49	22.83
8-CH_3G (XIV)[m]	113.30	112.16	75.74	116.60	105.26	48.13	31.71	30.75	45.92	22.30
I (XV)	106.26	108.65	84.91	116.99	99.12	47.97	34.60	30.76	46.05	21.77
8-BrI (XVI)[e]	106.63	109.57	85.80	115.63	86.36	50.92	31.61	30.89	46.66	22.25
8-OHI (XVII)[n]	105.30	104.76	69.02	112.25	111.35	46.41	31.18	31.00	45.63	22.73
8-CH_3I (XVIII)[o]	105.25	109.21	83.82	116.46	108.73	48.79	32.43	30.87	46.45	22.24
2-SCH_3I (XIX)[p]	117.23	108.95	81.61	118.13	98.52	47.85	34.36	30.76	45.93	21.83
2-SCH_2CH_3-8-CH_3I (XX)[q]	116.19	109.59	80.52	116.97	107.97	48.11	31.54	30.28	45.38	22.12

[a] Measured from the highest peak of Me_2SO-d_6 signals. The chemical shift of internal dioxane (0.5%, v/v) is 26.80 ± 0.05 ppm. [b] 0.2 M solution in Me_2SO-d_6 except for 8-SCH_3A (0.1 M) and 2-SCH_2CH_3-8-CH_3I (0.12 M). [c] M. Ikehara and M. Keneko, *Tetrahedron*, **26**, 4251 (1970). [d] H. J. Brentnall and D. W. Hutchinson, *Tetrahedron Lett.*, 2595 (1972). [e] R. E. Holmes and R. K. Robins, *J. Am. Chem. Soc.*, **86**, 1242 (1964). Methylthio group at −24.93 ppm. [f] Synthesized by an analogous procedure to that for 8-SCH_3A. Ethylthio group at −12.77 and −24.75 ppm. [g] M. Ikehara and S. Yamada, *Chem. Pharm. Bull.*, **19**, 104 (1971). [h] R. E. Holmes and R. K. Robins, *J. Am. Chem. Soc.*, **87**, 1772 (1965). Methoxy group at 17.63 ppm. [i] M. Ikehara, H. Tada, and M. Kaneko, *Tetrahedron*, **24**, 3489 (1968). [j] W. Limn, unpublished work. Methyl group at −25.23 ppm. [k] R. Shapiro and S. C. Agarwal, *Biochem. Biophys. Res. Commun.*, **24**, 401 (1966). [l] M. Ikehara, H. Tada, and K. Muneyama, *Chem. Pharm. Bull.*, **13**, 1140 (1965). [m] M. Maeda, K. Nushi, and Y. Kawazoe, *Tetrahedron*, **30**, 2677 (1974). Methyl group at −25.00 ppm. [n] Prepared from 2′,3′,5′-*O*-triacetyl-8-oxyinosine; M. Ikehara and T. Maruyama, *Chem. Pharm. Bull.*, **24**, 565 (1976). [o] W. Limn, unpublished work. Methyl group at −24.99 ppm. [p] A. Yamazaki, I. Kumashiro, and T. Takenishi, *J. Org. Chem.*, **32**, 3032 (1967). Methylthio group at −26.32 ppm. [q] We thank Dr Yamazaki, Ajinomoto Co. Inc., for his gift of this compound. Methyl group at −25.18 ppm and ethylthio group at −14.93 and −25.18 ppm.

spect to the sugar moiety, was found in crystals of 8-bromo derivatives of adenosin and guanosine by x-ray analysis.[4] By CD and ^{1}H NMR studies we have shown that purine nucleosides and nucleotides with a bulky substituent at the 8-position are in a syn conformation in aqueous solution.[5] In the ^{1}H NMR study a characteristic downfield shift of the H(2′) signal was noted in 8-substituted purine nucleotides.[5,6] This shift was assumed to be associated with the syn conformation of purine nucleosides, where the lone pair of electrons on N(3) come close to the C(2′)–H(2′) bond of the C(2′)-endo sugar moiety.[4] We wish to report here on the carbon-13 NMR properties of 8-substituted purine nucleoside derivatives.

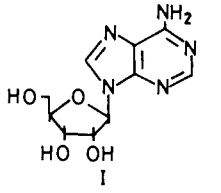
Experimental Section

The sources of nucleosides are listed in the legend to Table I. Deuterated solvent Me_2SO-d_6 (99.8% ^{2}H) was from CEA, France.

The natural-abundance ^{13}C spectra were taken on a Hitachi R-22 (22.63 MHz, ambient probe temperature 32 °C) spectrometer operating in the Fourier transform mode in connection with a Hitachi HITAC-10II computer package with 8K memory. ^{13}C chemical shifts were obtained from noise-decoupled spectra using Me_2SO-d_6 as internal reference. The chemical shift of internal dioxane (0.5%, v/v) is 26.80 ± 0.05 ppm. A chemical shift change in the downfield direction is expressed as a positive value and an opposite change is expressed as a negative value.

Results and Discussion

The chemical shifts for various 8-substituted purine nucleosides are presented in Table I. The chemical shifts for the parent compounds are also given for comparison. Assignments of ^{13}C signals were made mainly according to the work of Jones et al.[7] except for a reversal of C(2′) and C(3′) as indicated by Mantsch et al.[8] and a reversal of C(4) and C(2) for inosine derivatives.[9] The relative peak heights of signals and the results of off-resonance studies were also taken into consideration for assignments. For example, in the case of 8-substituted aden-



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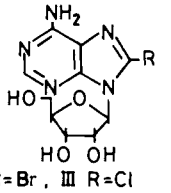
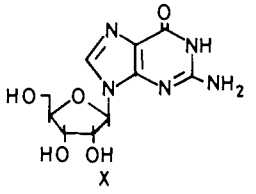
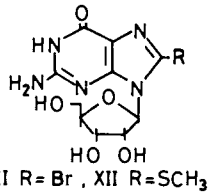


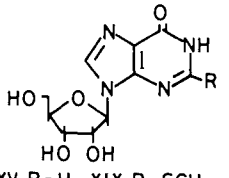
II R=Br, III R=Cl
IV R=SCH_3, V R=SCH_2CH_3
VI R=SH, VII R=OCH_3
VIII R=OH, IX R=CH_3



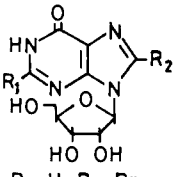
X



XI R=Br, XII R=SCH_3
XIII R=OH, XIV R=CH_3



XV R=H, XIX R=SCH_3



XVI R_1=H, R_2=Br
XVII R_1=H, R_2=OH
XVIII R_1=H, R_2=CH_3
XX R_1=SCH_2CH_3, R_2=CH_3

Table II. Chemical Shift Changes ($\Delta\delta$) Relative to the Parent Compound[a]

Nucleoside	C(8)	C(5)	C(4)	C(2)	C(6)	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)
A(I)	0	0	0	0	0	0	0	0	0	0
8-BrA (II)	−12.78	0.29	0.83	0.05	−0.97	2.45	2.34	0.24	0.83	0.41
8-ClA (III)	−3.04	−1.38	0.59	0.30	−0.90	1.38	−2.22	0.18	0.84	0.36
8-SCH_3A (IV)	9.79	0.21	1.64	−1.18	−1.72	0.94	−2.17	0.29	0.70	0.47
8-SCH_2CH_3A (V)	8.64	0.32	1.32	−1.08	−1.56	0.93	−2.12	0.34	0.69	0.52
8-SHA (VI)	28.08	−12.25	−0.87	−0.39	−8.19	0.83	−2.71	0.11	−0.19	0.53
8-OCH_3A (VII)	14.48	−4.40	−0.33	−1.83	−2.07	−1.21	−2.35	0.23	0.11	0.53
8-OHA (VIII)	11.60	−15.79	−2.54	−1.77	−8.96	−2.23	−2.53	−0.31	−0.43	0.65
8-CH_3A (IX)	9.06	−1.24	0.55	−1.07	−0.72	0.63	−1.40	0.34	0.76	0.46
G (X)	0	0	0	0	0	0	0	0	0	0
8-BrG (XI)	−14.61	0.79	0.66	−0.30	−1.44	3.21	−3.32	−0.02	0.63	0.52
8-SCH_3G (XII)	8.50	0.40	0.42	−0.68	−1.16	1.73	−3.13	0.17	0.47	0.65
8-OHG (XIII)	16.19	−18.09	−3.89	−1.08	−2.70	−0.86	−2.84	−0.44	−0.20	0.88
8-CH_3G (XIV)	9.20	−1.44	0.39	−0.81	−0.63	1.18	−2.47	−0.13	0.23	0.35
I (XV)	0	0	0	0	0	0	0	0	0	0
8-BrI (XVI)	−12.76	0.89	0.92	0.37	−1.36	2.95	−2.99	0.13	0.61	0.48
8-OHI (XVII)	12.23	−15.89	−3.89	−0.96	−4.74	−1.56	−3.42	0.24	−0.42	0.96
8-CH_3I (XVIII)	9.61	−1.09	0.56	−1.01	−0.53	0.82	−2.17	0.11	0.40	0.47
2-SCH_3I (XIX)	0	0	0	0	0	0	0	0	0	0
2-SCH_2CH_3-8-CH_3-I (XX)	9.45	−1.09	0.64	−1.04	−1.16	0.26	−2.82	−0.48	−0.55	0.29

[a] $\Delta\delta = \delta$ (nucleoside) − δ (parent compound). Positive value represents a downfield shift.

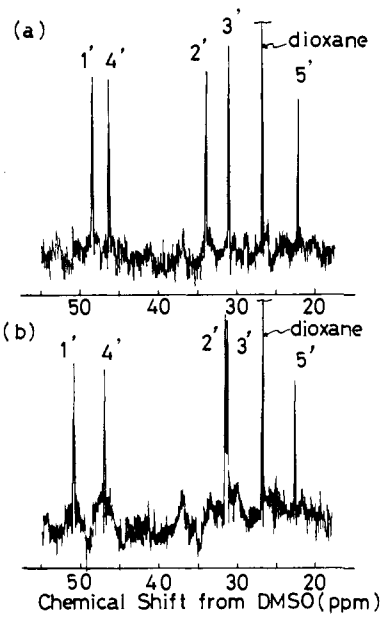


Figure 1. ^{13}C NMR spectra of adenosine (a) and 8-bromoadenosine (b) in the sugar carbon region, 0.2 M in Me_2SO-d_6, 32 °C.

osine nucleosides, the signal intensities of C(4), C(5), and C(8) are generally smaller than those of C(2) and C(6). Though C(6) has no directly attached hydrogen, it has been observed that the T_1 value of C(6) of the adenine residue in 5′-AMP[10] and NAD[10b] is much smaller than those of C(4) and C(5). Moreover, the C(2) signal of the base moiety and the C(5′) signal of the sugar moiety can be distinguished from the other base or sugar signals respectively, by off-resonance studies. Any assignment on a set of signals having very close chemical shifts could be reversed if no discrimination is possible. For adenosine derivatives, ambiguity remains in the assignment of the close C(4) and C(8) signals as in the case of 8-methylthioadenosine (IV) and 8-methyladenosine (IX). For inosine derivatives, ambiguity remains in the assignment of the close C(6) and C(8) or C(4) and C(8) signals as in the case of 8-oxyinosine (XVII) and 8-methylinosine (XVIII). Similarly, assignments of C(2), C(6), and C(8) signals in 8-oxyguanosine (XIII) as well as C(2) and C(6) signals in 2-ethylthio-8-methylinosine (XX) are not definitive. As to the sugar carbon assignments of the close C(1′) and C(4′) or C(2′) and C(3′) signals present the same problem. In all these cases, assignments were made assuming that the order of signal appearance in the parent compound was maintained in its derivative. However, these possible but minor changes in assignment do not affect our main conclusions.

Chemical Shift Changes in Sugar Resonances. The ^{13}C spectra of adenosine (I) and 8-bromoadenosine (II) are shown in Figure 1 and the chemical shift changes of sugar carbons upon substitution at the 8-position are presented in Table II. As can be readily seen from Figure 1, the 2′-carbon signal shifts upfield by −2.3 ppm and comes close to the 3′-carbon signal upon substitution with bromine at the 8-position of adenosine. The chemical shifts of C(3′) and C(5′) show only a slight change, but a significant downfield shift of the C(1′) signal is observed. All other 8-substituted adenosines studied (III–IX) show similar upfield shifts (−1.4 to −2.7 ppm) of the C(2′), signal and in the case of 8-mercaptoadenosine (VI), the 2′- and 3′-carbon appear at the same position. The chemical shift change of the C(1′) signal seems dependent on the nature of the substituent because degree and direction of the chemical shift vary with the substituents. Another common feature among 8-substituted adenine nucleosides is a small downfield shift of the C(5′) signals (0.3–0.6 ppm). The chemical shifts of C(3′) and C(4′) also seem to be affected by 8-substituents. The carbonyl or thiocarbonyl group at C(8) in VIII or VI have some effect on these sugar carbons. In the case of 8-substituted guanosines (XI–XIV), upfield shifts of the C(2′) (−2.5 to −3.3 ppm) and small downfield shifts of the C(5′) signals (0.4–0.9 ppm) are again observed. In the case of 8-substituted inosines (XVI–XVIII) upfield shifts of the C(2′) (−2.2 to −3.4 ppm) and small downfield shifts of the C(5′) signals (0.5–1.0 ppm) are also observed. In the case of the 8-methyl derivative of 2-ethylthioinosine (XX), an upfield shift (−2.82 ppm) of the C(2′) signal and a small downfield shift (0.29 ppm) of the C(5′) signal are also noted when compared with those of 2-methylthioiosine (XIX), which gives almost the same ^{13}C spectrum in the sugar carbon region as that of inosine (XV). From x-ray crystallography, a syn conformation similar to that of 8-bromoadenosine is found in a crystal of 2-ethylthio-8-methylinosine (XIX).[11]

As described above, all 8-substituted purine nucleosides measured exhibit a significant upfield shift of their 2′-carbon signal and a small downfield shift of the 5′-carbon signal with respect to those of the corresponding unsubstituted nucleosides. These changes seem independent of the nature of the various substituents and are thought to occur as a consequence of a conformational change from *anti* to *syn*. An electric field effect of the lone pair of electrons on the N(3) atom may polarize the C(2′)-H(2′) bond of a C(2′)-endo sugar moiety and cause an upfield shift of the 2′-carbon signal in ^{13}C NMR and a downfield shift of the 2′-hydrogen signal in ^{1}H NMR. Batchelor et al.[12] have reported that an electric field effect of a terminal carbonyl group polarizes a carbon-carbon double bond within a fatty acid chain and causes an upfield shift of the unsaturated carbon closer to the carbonyl group. Similar phenomena to our results are also observed in pyrimidine nucleosides having a syn conformation[13] and in β-cyanuric acid riboside.[14] In those cases the carbonyl group at C(2) is assumed to cause an upfield shift of the 2′-carbon signal. As to the downfield shift of the C(5′) signal in 8-substituted purine nucleosides the cause is not clear. In conclusion, this upfield shift of the 2′-carbon signal, or decrease in chemical shift difference between the C(2′) and C(3′) signals, would seem to provide a useful diagnostic criterion for the presence of a *syn* conformation in purine nucleosides.

Effect of 8-Substitution on Base Carbon Resonances. The chemical shift changes ($\Delta\delta$) of base carbon signals upon substitution at the 8-position are also included in Table II. The largest change occurs at C(8) except for 8-oxy derivatives (VIII, XIII, and XVII). The halogen groups cause an upfield shift of the C(8) signal and the other substituents cause a downfield shift. An unusualy large upfield shift (−12 to −18 ppm) of the C(5) signal is observed in the case of 8-oxy derivatives (VIII, XIII, and XVII) and 8-mercaptoadenosine (VI). Because this unusual shift is not observed in the closely related derivatives, 8-methoxyadenosine (VII), 8-methylthioadenosine (IV), and 8-methylthioguanosine (XII), it must reflect a difference in their tautomeric forms. They may adopt mainly the carbonyl or thiocarbonyl form at C(8) under the present conditions.

As to the general pattern of chemical shift changes, three types of sequential change from C(8) to C(6) (in the order presented in Table II) are observed. The first type is for halogen substituents. 8-Bromoadenosine (II), 8-bromoguanosine (XI), and 8-bromoinosine (XVI) show very similar sequential changes through C(8) to C(2). 8-Chloroadenosine (III) and 8-bromoadenosine (II) show nearly identical shifts of C(4), C(2), and C(6). The second type is for alkylthio, methoxy, and methyl substituents. In this type, the relative direction of chemical shift change varies from an upfield change to a downfield change at alternate carbons in going from C(8) to C(2) in the order shown in Table II. In the case of 8-methylthioadenosine (IV), for example, $\Delta\delta$ value changes from 9.79 on C(8) to 0.21 on C(5) in a negative direction, from 0.21 on C(5) to 1.64 on C(4) in a positive direction and from 1.64 on C(4) to −1.18 on C(2) again in a negative direction. The shift of C(2) is almost identical with that of C(6). Methyl substitution on adenosine, guanosine, inosine, and 2-ethylthioinosine produces almost identical shifts of each base carbon. Methylthio substitution on adenosine and guanosine also produces almost identical shifts. The third type is for mercapto and oxy substituents. In this type, an alternate change of $\Delta\delta$ through C(8) to C(4) is also observed, but not on C(2). In the case of adenosine derivatives, an unusually large shift of the C(6) signal is noted. 8-Mercaptoadenosine (VI) and 8-oxyadenosine (VIII) give different $\Delta\delta$ values in magnitude, but almost identical patterns of $\Delta\delta$ change. Oxy substitution on adenosine, guanosine, and inosine also produces very similar shifts of each carbon. Consideration of these characteristic patterns of effects of 8-substituents may be helpful for assignment of the base carbon signals of other 8-substituted purine nucleoside derivatives.

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