PMR Study on the Absolute Structure of Kanamycins and Related Compounds†

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In this paper, we wish to report a simple empirical rule to determine linkage positions in the 2-deoxystreptamine component with sugars in amino sugar antibiotics such as kanamycins, neomycins and paromomycins.

The PMR spectra of N-acetyl derivatives of kanamycins and related compounds show a signal of anomeric proton of sugars at 4.62~4.72 τ (in D₂O) when sugars are linked in the α -form at C₄ position of N,N'-diacetyl-2-deoxystreptamine (DSTA), while at 4.86~4.95 τ (in D₂O) when linked at C₆ position (Table I. No. 1~12).

Comparing with the absolute configuration of kanamycin A which was determined by X-ray analysis,¹⁾ the pmr spectrum of tetra-N-acetylkanamycin A suggests that 1) the anomeric proton of 6-acetamido-6-deoxy-D-glucose moiety at the C₄ position is much closer to the plane

TABLE I. THE PMR DATA OF ANOMERIC PROTON SIGNALS OF α -GLYCOSIDES OF AMINOCYCLITOLS.

No.	Compound ^{a)}	Anomeric protons: τ (J =cps)	
1	6-AG(4)-DSTA	4.66(3.0)	
2	3-AG(4)-DSTA	4.70(3.0)	
3	2-AG(4)-DSTA	4.63(3.3)	
4	2, 6-AG(4)-DSTA	4.62(3.0)	
5	6-AG(6)-DSTA		4.93(3.5)
6	3-AG(6)-DSTA		4.90(3.5)
7	2-AG(6)-DSTA		4.87(3.0)
8	6-AG(4)-DSTA-3-AG(6)	4.65(3.0)	4.86(4.0)
9	2, 6-AG(4)-DSTA-3-AG(6)	4.62(3.5)	4.87(3.5)
10	2-AG(4)-DSTA-3-AG(6)	4.62(3.0)	4.87(3.5)
11	3-AG(4)-DSTA-6-AG(6)	4.70(3.0)	4.95(3.5)
12	3-AG(4)-DSTA-2-AG(6)	4.72(2.0)	4.88(1.5)
13	MN-DSTA	4.72(1.0)	4.89(1.0)
14	GL-DSTA	4.65(3.0)	4.90(3.0)
15	2-AG-DC	4.70(3.0)	4.88(3.5)
16	2-AG(4)-STA	4.62(3.0)	
17	2-AG(6)-STA		4.88(3.5)
18	2-AG-AC(+)	5.01(3.5)	
19	2-AG-AC(-)	4.99(3.0)	

^{a)} Abbreviations are as follows: 6-AG: 6-acetamido-6-deoxy- α -D-glucopyranosyl, 3-AG: 3-acetamido-3-deoxy- α -D-glucopyranosyl, 2,6-AG: 2,6-diacetamido-2, 6-dideoxy- α -D-glucopyranosyl, MN: α -D-mannopyranosyl, GL: α -D-glucopyranosyl, DSTA: N,N'-diacetyl-2-deoxystreptamine, STA: N,N'-diacetyl-2-deoxystreptamine, DC: N-acetyl-($\pm$)-dihydroconduramine F-4, AC: N-acetyl-(+)-[or (-)]-2-aminocyclohexanol. (These amino-cyclitols are shown in Fig. 1.) For example, 6-AG(4)-DSTA: N,N'-diacetyl-4-O-(6-acetamido-6-deoxy- α -D-glucopyranosyl)-2-deoxystreptamine. The number in parenthesis indicates the linkage position of sugar in DSTA or STA. The compounds (No. 13~15) are diastereomeric mixture.

† Synthetic Studies on Carbohydrate Antibiotics, Part XI. Part X, K. Kitahara, S. Takahashi, H. Shibata, N. Kurihara and M. Nakajima, *Agr. Biol. Chem.*, **33**, 748 (1969).

of N-acetyl carbonyl group of DSTA than that of 3-acetamido-3-deoxy-D-glucose moiety at the C₆ position, and 2) the free rotation of glycosidic linkage is more hindered at C₄ than at C₆ by non-bonded interactions between DSTA and sugar moiety.

Accordingly, the signal of anomeric proton of the sugar at C₁ shifts to a lower magnetic field by an anisotropy²¹ of the N-acetyl carbonyl group of DSTA, provided that the steric structures of the acetyl derivatives of kanamycin A and related compounds in D₂O are similar to that of kanamycin A determined by X-ray analysis.

In the case of α -glycosides having two sugar components at C₁ and C₆ of DSTA like kanamycins, the signals of anomeric protons appeared independently at the corresponding regions, and the same phenomena were also observed in the mixture of two diastereomers (No. 13~15). The same principle can be applied to the α -glycosides of N, N'-diacetyl-streptamine (No. 16, 17).

In N-acetyl-2-aminocyclohexanol, the difference in the chemical shift of anomeric protons of α -glycosides between (+)-(No. 18)

and (-)-isomer (No. 19) is very little since the free rotation of glycosidic linkage is not hindered.

This empirical rule can be applied to determine the absolute configuration of 2-deoxystreptamine derivatives and analogs together with conventionally used techniques such as Reeves' cuprammonium method.³¹

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REFERENCES

- 1) G. Koyama and Y. Iitaka, *Tetrahedron Letters*, **1968**, 1875.
- 2) L. M. Jackman, "Applications of NMR Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, pp. 122~124.
- 3) M. Hitchens and K. L. Rinehart, Jr., *J. Am. Chem. Soc.*, **85**, 1547 (1963); S. Umezawa, K. Tatsuta and T. Tsuchiya, *Bull. Chem. Soc. Japan*, **39**, 1244 (1966).