STEREOCHEMISTRY OF THE ANTIBIOTIC CARMINOMYCIN

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The properties and the structure of a new anthracycline antibiotic carminomycin, were described recently.[1] In this paper we wish to discuss the stereochemistry of carminomycin.

We have studied the NMR and CD spectra of carminomycin, its aglycone (carminomycinone) and 7-deoxycarminomycinone. For comparative purposes the corresponding derivatives of daunomycin (rubomycin) were prepared and investigated.

It has been shown[2] that the differences between the structures of carminomycin and daunomycin lie in the aglycones of these compounds. In contrast to daunomycinone, C-4 of carminomycinone is substituted with a hydroxyl instead of methoxyl.

The NMR spectra of both aglycones are very similar to each other (Table 1). There are, however, differences in the chemical shifts of the aromatic protons (not listed in the table). A pseudoequatorial orientation of the C-7 proton is apparent for both of these compounds. The coupling constants (J_{AX}=4.7 Hz; J_{BX}=1.3 Hz) are too small for axial-axial coupling. The chemical shifts and coupling constants of the protons at C-10 and C-8 are essentially the same for both compounds.

As shown in Fig. 1, the CD curves of the two aglycones are very similar in the region of 280~380 nm demonstrating the same configuration at the chiral centers C-7 and C-9.[3]

These results have been further substantiated through comparison of the 7-deoxycompounds. The CD curve of 7-deoxycarminomycinone is essentially identical to that of 7-deoxydaunomycinone. The close correspondence of the two curves indicates the same configuration of the only chiral center, C-9 of both compounds. One can conclude from these results that carminomycinone has the configuration, *i.e*, 7S, 9S and conformation as daunomycinone.

The physico-chemical data for the newly prepared tetramethyl ethers of carminomycinone and daunomycinone show no significant differences ($[\alpha]_D$+189° and +186° correspondingly).

We have also obtained the monomethyl ether of 7-deoxycarminomycinone, which possesses the same physico-chemical properties as 7-deoxydaunomycinone (tlc, optical rotation).

The NMR spectrum of the antibiotic carminomycin is shown in Fig. 2. The 4 Hz coupling constants of the H-1′ proton (δ= 5.64 ppm) correlates with that expected for an

Table 1. NMR spectral data (80 MHz in pyridine-d_5)
Chemical shifts and coupling constants for daunomycinone and carminomycinone.

	Daunomycinone (ppm)	Carminomycinone (ppm)
-O-CH_3	3.88 singlet	—
-C-CH_3	2.44 singlet	2.45 singlet
H-10	3.18 (A) AB system	3.22 (A) AB system
	3.41 (B)	3.44 (B)
	J_{AB}=19 Hz	J_{AB}=19 Hz
H-8	2.18 (A) AB part of an ABX system	2.19 (A) AB part of an ABX system
	2.54 (B)	2.55 (B)
	J_{AB}=14 Hz	J_{AB}=14 Hz
	J_{AX}=4.7 Hz	J_{AX}=4.7 Hz
	J_{BX}=1.3 Hz	J_{BX}=1.3 Hz
H-7	5.49 (X) X part of an ABX system	5.47 (X) X part of an ABX system
	$J_{AX}+J_{BX}$=6 Hz	$J_{AX}+J_{BX}$=6 Hz

Fig. 1. CD spectra of daunomycin (**1**), carminomycin (**2**) in methanol and daunomycinone (**3**), carminomycinone (**4**), 7-deoxydaunomycinone (**5**), 7-deoxycarminomycinone (**6**), in dioxane.

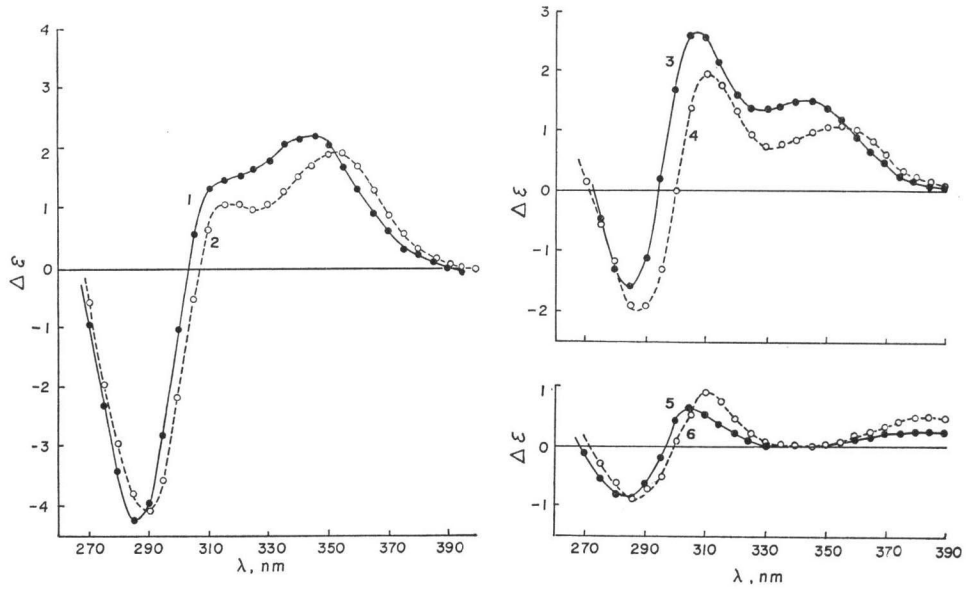


Fig. 2. NMR spectrum of carminomycin (100 MHz in pyridine-d_5)

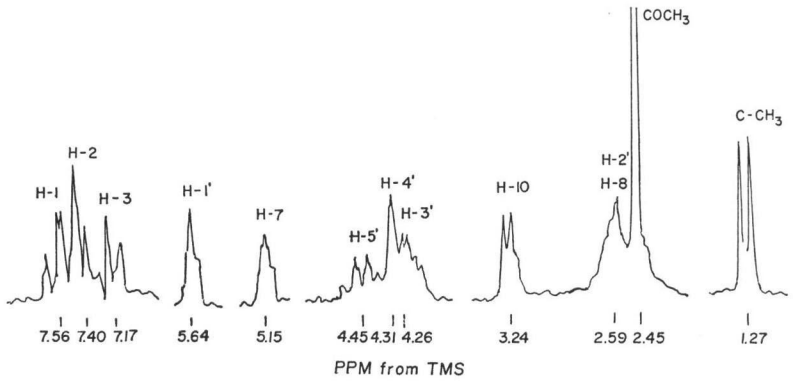
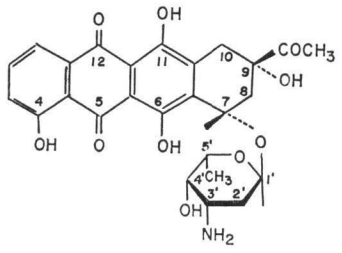


Fig. 3. Structure of carminomycin.



equatorial orientation of the anomeric proton.

An equatorial orientation is also evident for the proton H-4′, while the orientation of H-3′ was found to be axial. These data indicate a 1C-conformation for the aminosugar and an α-glycosidic linkage in carminomycin. It follows therefore, that the configuration at C-1′ is R.

That there is no change in stereochemistry at C-7 of carminomycin during hydrolysis follows from a comparison of the CD spectra and of these NMR spectra (Table 1 and Fig. 2; H-7; δ 5.15 ppm, $J_{AX}+J_{BX}\sim 5$ Hz) of carminomycin and carminomycinone.

Carminomycin and daunomycin were used as crystalline hydrochloric salts. Carminomycinone and daunomycinone have been prepared by acidic hydrolysis with subsequent crystallization. The 7-deoxycompounds of both

aglycones were obtained by catalytic hydrogenolysis.

The monoethyl ether of 7-deoxycarminomycinone and the tetramethyl ethers of both aglycones were obtained by methylation with dimethyl sulfate.

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