Communication to the editor

STRUCTURE OF K-41B, A NEW DIGLYCOSIDE POLYETHER ANTIBIOTIC

Sir:

Because of their coccidiostat effect in poultry and other biological activities of interest for agricultural use, new polyether antibiotics have appeared with increasing frequency in recent years. WESTLEY has suggested a classification into four groups by structure: monovalent polyether, monovalent monoglycoside polyether, divalent polyether and divalent pyrrole ether.[1] However, prior to a complete structure elucidation, a more detailed classification of a potentially novel antibiotic is desirable for comparative purposes with ionophores reported in the literature.

For this purpose, ^{13}C NMR spectroscopy is extremely useful because it provides unequivocal information about all the carbon atoms, especially ketal and acetal carbon atoms generally found in this family of antibiotics. Moreover, the ^{13}C signal assignments of known antibiotics, even if incomplete, can be used to assess the structure of a similar unknown polyether, and the results can be used for further assignments of uncertain ^{13}C signals. As an example, we report here that antibiotic K-41B (**1**) belongs to a new

Table 1. ^{13}C Chemical shifts of sodium salts of K-41B (**1**-Na) and K-41A (**2**-Na)[a]

Carbon type[b]	**1**-Na	**2**-Na	Carbon No.[c]	Carbon type[b]	**1**-Na	**2**-Na	Carbon No.[c]
C–Me (q)	10.91	10.97	6-Me[d]	O–CH< (d)	61.98	61.94	C-9
	11.13	11.71	14-Me		67.56	67.57	C-7
	12.50	12.51	4-Me[d]		72.45	72.50	C-2
	12.61	12.56	12-Me		74.57	74.61	C-25
	13.21	13.23	28-Me[e]		74.67	74.67	C-5′
	13.81	13.84	26-Me[e]		74.91*	—	C-5″
	18.47*	—	5″-Me		79.28	79.39	C-21[g]
	18.75	18.78	5′-Me		79.61	79.62	C-20[g]
	26.31**	28.71	16-Me		79.90	79.85	C-11[g]
	27.14	27.18	29-Me		80.23*	—	C-4″
					80.59	80.59	C-4′
C–CH_2– (t)	23.35	23.26	C-19[f]		81.08	81.12	C-24[g]
	24.27	24.25	C-23[f]		82.95	82.93	C-27
	25.75	25.91	C-18[f]		84.33	83.79	C-17
	27.14*	—	C-3″		86.89	86.90	C-5
	27.39	27.38	C-3′		93.25**	94.87	C-15
	29.19	29.24	C-22[f]				
	31.00	30.99	C-2′	O–C< (s)	78.79	78.77	C-6
	31.00*	—	C-2″		84.33**	83.69	C-16
	31.35	31.27	C-10[f]				
	33.29	33.30	C-8[f]				
				O>CH– (d)	102.96	102.99	C-1′
C–CH< (d)	37.22	37.04	C-12		103.76*	—	C-1″
	39.34	39.39	C-4				
	39.78	39.80	C-26				
	46.52	46.44	C-14	O>C< (s)	98.79	98.87	C-29
	48.22	48.24	C-28		99.72	99.76	C-3
					106.63**	107.16	C-13
O–Me (q)	50.90	50.92	6-OMe				
	56.22	56.20	4′-OMe				
	56.43*	—	4″-OMe	O=C< (s)	179.69	179.77	C-1
	59.45	59.40	11-OMe				
	60.77	60.77	5-OMe				
	—	59.86*	15-OMe				

a) ^{13}C NMR spectra were recorded on a Varian XL-100-12A spectrometer at 25.16 MHz in the FT mode using C_6D_6 solutions (*ca.* 0.25 mmol cm^{-3}) at 35°C; accuracies of values are ±0.05 ppm. Complete signal assignments of the other compounds examined here will be published elsewhere.

b) Signal multiplicities were obtained by ^1H single-frequency off-resonance decoupling spectra.

c) Primed and double primed numbers are carbons of O-Deo at C-27 and C-15, respectively.

d~g) Tentatively assigned and may be interchanged.

Fig. 1. IR spectrum of K-41B-Na in $CHCl_3$

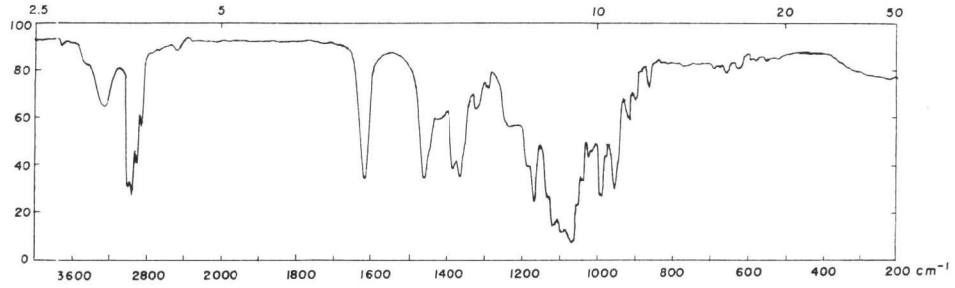
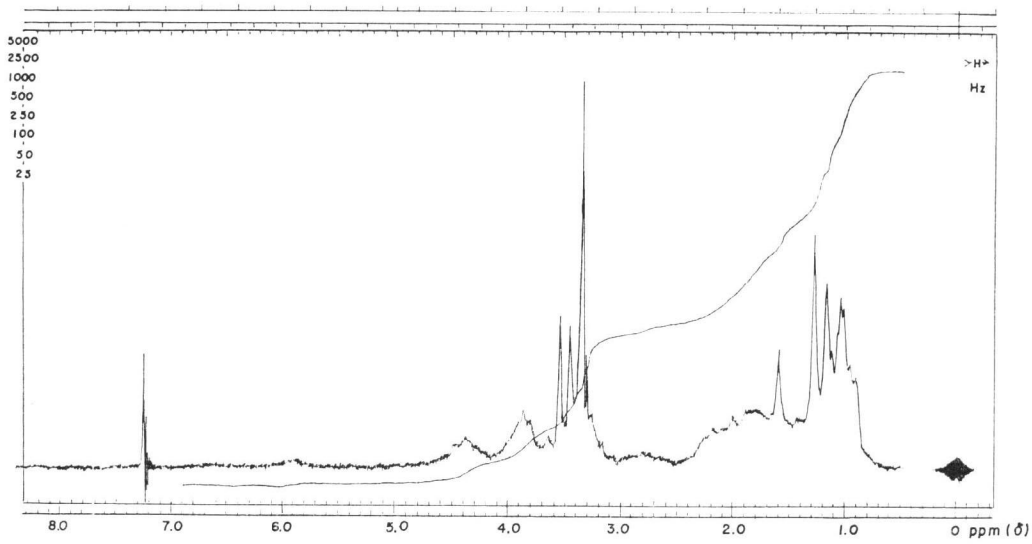


Fig. 2. ^1H NMR spectrum of K-41B-Na in $CDCl_3$ at 60 MHz



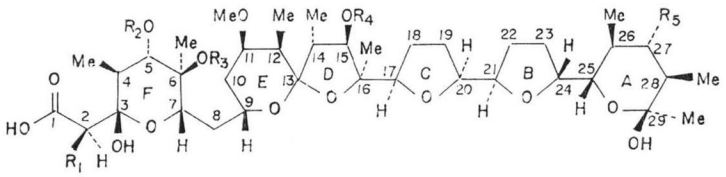
class of polyether type antibiotics which should be added to WESTLEY's classification.

Antibiotic K-41B was isolated as a minor component from the mother liquor of K-41A (formerly called K-41)[2] (**2**), which had been produced by a strain of *Streptomyces hygroscopicus*. The antibiotic was purified as a sodium salt (**1**-Na), m.p. 185~186°C (decomp.), $[\alpha]_D^{26}$ +4.3°C (MeOH). Like **2**, it is active against Gram-positive bacteria. The IR and ^1H NMR spectra of K41B-Na are shown in Figs. 1 and 2.

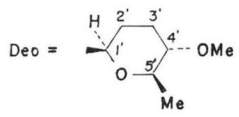
Table 1 shows all ^{13}C signals of **1**-Na and K-41A-Na (**2**-Na), whose structure has been established by an X-ray analysis.[3] The ^{13}C signals of **2**-Na were assigned by making reference to the ^{13}C spectra of A-28695-Na[4] (septamycin)[5] (**3**-Na), A-204A-Na[6] (**4**-Na), K-41A-K (**2**-K), and the following derivatives of **2**: a lactone (**5**) obtained by the $Pb(OAc)_4$ cleavage of **2**; an alcohol (**6**-Na) produced by acid fission of the deoxysugar (Deo) moiety; and a methyl ether (**7**-Na) prepared by methylation in an acidic methanol solution. Some signals of **3**-Na and **4**-Na were assigned by ^1H single-frequency selective decouplings because their ^1H signals had been analyzed previously by ANTEUNIS and his coworkers.[7]

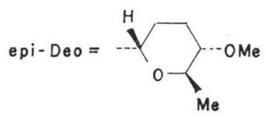
The spectrum of **5** confirmed the C-1~C-4, and C-7 signal assignments in **2**-Na, and the spectrum of **7**-Na verified the C-29 and 29-Me signal assignments. The signals due to Deo as well as C-25~C-28, and 26- and 28-Me in **2**-Na were easily assigned by comparison with those of **3**-Na and **6**-Na in which signals due to Deo disappear. The spectra of **3**-Na and **4**-Na differentiated the C-5 and C-6 signals. As a matter of course, two singlets at δ 107.16 and 83.69 were determined to be due to C-13 and C-16,

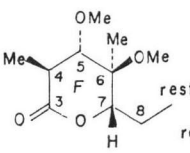
Table 2.



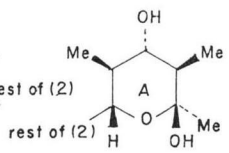
(1) R_1 = OH, R_2 = Me, R_3 = Me, R_4 = Deo, R_5 = O-Deo
(2) R_1 = OH, R_2 = Me, R_3 = Me, R_4 = Me, R_5 = O-Deo
(3) R_1 = Me, R_2 = Me, R_3 = Deo, R_4 = Me, R_5 = H
(4) R_1 = Me, R_2 = epi-Deo, R_3 = Me, R_4 = Me, R_5 = OMe



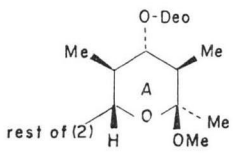




(5)



(6)



(7)

respectively. The doublet at δ 94.87 appears at an abnormally low field to assign to a carbon bearing one oxygen. However, it can be reasonably assigned to C-15 because this signal is also found in antibiotics such as **3**-Na, **4**-Na, and carriomycin,[8] which commonly have the same spiro-ring moiety as that of **2**-Na, but not in nigericin[9] which has no 15-OR.

The assignments of the five OMe signals were straightforward. Compounds **3**-Na, **4**-Na, and **6**-Na lack 6-, 5-, 4′-OMe, respectively. In the spectra of **2**-K, the OMe signal at δ 59.40 was shifted upfield to 57.58, whereas the other four remained unchanged. X-Ray analysis[8] showed that the 11-OMe group is arranged near the Na atom, and therefore the shifted signal should be assigned to 11-OMe. A similar shift was observed between the spectra of K and Na salts of nigericin, which also have an 11-OMe interacting with the metal. Thus, the remaining signal at δ 59.86, absent in the spectrum of **1**-Na must arise from 15-OMe.

As seen from Table 1, the ^{13}C signals of **1**-Na essentially correspond to those of **2**-Na, but **1**-Na has seven additional signals (* in Table 1) assignable to the second Deo moiety. Since **1**-Na lacks the 15-OMe signal, O-*Deo* is likely to be situated at C-15 instead of the O*Me* group. This is supported by the slightly shifted signals (** in Table 1) of C-13, C-16, 16-Me, and C-15. The other signals which shifted, δ 83.79→84.33 and 11.72→11.13, can be reasonably attributed to C-17 and 14-Me, respectively.

Thus, the structure of K-41B-Na was concluded to be **1**-Na, and its elemental analysis agreed well with $C_{54}H_{91}O_{20}Na$. K-41B is the first example of a monovalent diglycoside polyether and the first known polyether antibiotic having eight rings in a molecule. The molecular weight of K-41B (1061.28) is the largest of this family.

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