Carbon-13 Magnetic Resonance Spectroscopy of Drugs III: Penicillins

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Received April 3, 1978, from the *Department of Medicinal Chemistry and Pharmacognosy and the ‡Department of Industrial and Physical Pharmacy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN 47907. Accepted for publication June 14, 1978.

Abstract □ The natural abundance ^{13}C-NMR spectra of a series of penicillins (penicillin V methyl ester, penicillin V, penicillin G, methicillin, oxacillin, cloxacillin, and dicloxacillin) were studied. The chemical shifts were assigned using the pulse Fourier transform technique with the aid of long-range carbon-13 hydrogen coupling. The previous assignments of penicillin V methyl ester were revised.

Keyphrases □ Penicillins, various—^{13}C-NMR spectra, chemical shifts assigned □ ^{13}C-NMR spectroscopy—various penicillins, chemical shifts assigned □ Antibacterials—various penicillins, ^{13}C-NMR spectra, chemical shifts assigned

β-Lactam antibiotics are some of the most widely used drugs (1–3). Current research is focused in chemical manipulation (1–6) to produce antibiotics effective against resistant organisms. This advance depends heavily on the use of modern analytical techniques (1, 2, 7, 8).

Proton NMR spectroscopy (^{1}H-NMR) has been useful in determining configuration and conformation of β-lactam compounds (1–3, 8–14). Carbon-13 NMR (^{13}C-NMR) spectroscopy is becoming increasingly important in the study of drugs (15–20). The carbon-13 chemical shift analysis of simple compounds can be accomplished by the traditional approach based on the structural dissimilarity and the additivity principle of chemical shift (15–17, 21, 22). However, this approach often leaves some uncertainty in the assignments of all close signals because subtle steric and electronic effects cannot be precisely assessed. The differentiation of these carbon signals, however, is critical in biosynthetic studies and in elucidating the interactions of β-lactam drugs with biological molecules (23–27).

In this study, the nuclear spin–spin coupling patterns were applied to the ^{13}C-NMR analysis of penicillins.

EXPERIMENTAL

The NMR spectra[1] of about 1 *M* solutions in dimethyl sulfoxide-d_6 and 2 *M* in all other deuterated solvents were obtained in 10-mm (^{13}C-NMR) and 5-mm (^{1}H-NMR) spinning tubes. The carbon-13 resonances of the deuterated solvents and methanol (in deuterium oxide) served as the internal reference, and chemical shift values were converted to the tetramethylsilane (VIII) scale using the following equations:

$$\delta(\text{VIII}) = \delta(\text{dimethyl sulfoxide-}d_6) + 39.6 \text{ ppm} \quad \text{(Eq. 1)}$$

$$\delta(\text{VIII}) = \delta(\text{chloroform-}d_3) + 76.9 \text{ ppm} \quad \text{(Eq. 2)}$$

$$\delta(\text{VIII}) = \delta(\text{methanol-}d) + 49.0 \text{ ppm} \quad \text{(Eq. 3)}$$

$$\delta(\text{VIII}) = \delta(\text{methanol}) + 49.3 \text{ ppm} \quad \text{(Eq. 4)}$$

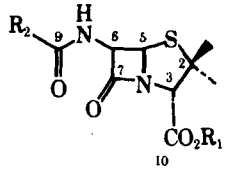
The carbon-13 spectra were recorded at ambient temperature and 50°. All proton lines were decoupled by a broad band (2.5 kHz) irradiation from an incoherent 99.99-MHz source. The chemical shifts were measured for a 5000-Hz sweepwidth. The carbon-13–hydrogen coupling constants or splittings were measured from proton-coupled spectra. The typical pulse width was 23.5 μsec, and the repetition time between pulses was 4 sec.

All penicillins were USP grade. Penicillin V methyl ester was prepared by treating penicillin V free acid with diazomethane in ether solution for 1 hr. Its ^{1}H- and ^{13}C-NMR and mass spectra confirm the structure. The partially deuterated methyl ether was made from the deuterated penicillin V, which was obtained by exchanging the labile protons with monodeuterated methanol. The mass spectrum of the product indicates that it contains monodeutero-, dideutero-, and trideuteromethyl groups.

RESULTS AND DISCUSSION

Single-frequency proton decoupling was used for the assignments of the methine carbon resonances of methyl and benzyl esters of penicillin derivatives (9, 28) and phenethicillin potassium (29). A complete interpretation of the ^{1}H-NMR spectrum is absolutely necessary for this approach. It is difficult to determine the methine proton resonances (H_5 and H_6) of penicillins, especially in solutions above the critical micelle concentration (30).

A more convenient method for distinguishing these peaks is the direct measurement of ^{13}C–^{1}H one-bond coupling constants ($^1J_{CH}$), as shown in the proton-coupled spectrum of penicillin V methyl ester (I) (Fig. 1). Based on the electronegativity of the adjacent groups (18, 21, 22, 31), it is reasonable to predict the relative coupling constant magnitude in the following order: $^1J(C_5\text{–}H_5) > {}^1J(C_6\text{–}H_6) > {}^1J(C_3\text{–}H_3)$. The values obtained for I confirm this prediction [$^1J(C_5\text{–}H_5)$ = 178.5, $^1J(C_6\text{–}H_6)$ = 153.2, and $^1J(C_3\text{–}H_3)$ = 145.3 Hz]. This method provides the unambiguous assignments of C_3, C_5, and C_6 resonances of all other penicillins in different solvents (Tables I and II).



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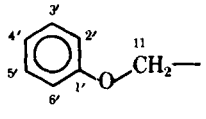
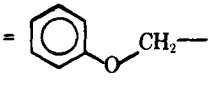
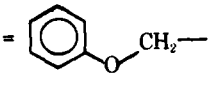
I: $R_1 = CH_3$, R_2 =



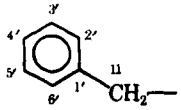
I-*d*: $R_1 = CH_2D + CHD_2 + CD_3$, R_2 =



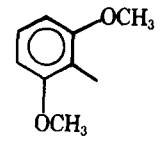
II: R_1 = K, R_2 =



III: R_1 = K, R_2 =



IV: R_1 = Na, R_2 =



[1] Jeol PFT-100 spectrometer, operating at 23.5 kg and interfaced with a Jeol EC-100 20K computer, and a Varian EM-360 60-MHz spectrometer.

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Table I—^{13}C-NMR Data of Penicillins in Deuterium Oxide Solution [a]

Carbon	I	II	III	IV	V	VI	VII
2	65.4 m[b]	64.8 m	64.6 m	64.8 m	64.9 m	64.9 m	65.1 m
3	71.7 dm 145.3 (H_3)	73.4 bd 147.1 (H_3)	73.5 bd 146.7 (H_3)	73.7 bd 145.2 (H_3)	73.5 bd 145.3 (H_3)	73.4 bd 143.4 (H_3)	73.5 bd 144.7 (H_3)
5	68.6 ddd 178.5 (H_5) 5.7 } H_3 4.1 } H_6	66.8 bd 180.0 (H_5)	66.9 bd 178.2 (H_5)	66.9 bd 180.1 (H_5)	66.4 bd 178.2 (H_5)	66.2 bd 177.6 (H_6)	66.3 bd 180.0 (H_6)
6	59.4 dd 153.2 (H_6) 2.5 (H_5)	57.5 bd 155.0 (H_6)	58.1 bd 153.8 (H_6)	57.9 bd 153.8 (H_6)	58.0 bd 154.4 (H_6)	57.7 bd 154.4 (H_6)	57.8 bd 155.0 (H_6)
7	173.5 ddd 10.8 } H_3 7.2 } H_5 3.7 } H_6	174.0 m	174.7 ddd 9.2 } H_3 7.0 } H_5 5.1 } H_6	175.0 dt 9.0 } H_3 4.9 } H_5 } H_6	174.9 m	174.7 m	174.5 dt 8.6 } H_3 4.6 } H_5 } H_6
9	169.8 td 4.5 (H_{11}) 2.6 (H_6)	169.6 bt 4.3 (H_{11})	173.1 bt 6.7 (H_{11})	167.1 bs	162.6 d 2.5 (H_6)	161.9 d 3.0 (H_6)	161.5 bs
10	169.1 qui 4.3 (H_3, OCH_3)	173.8 d 4.3 (H_3)	174.1 d 4.3 (H_3)	174.2 d 4.3 (H_3)	174.9 m	174.2 d 4.3 (H_3)	174.0 d 3.7 (H_3)
11	67.7 t 147.4 (H_{11})	66.8 t 148.3 (H_{11})	42.3 t 129.7 (H_{11})				
2α-CH_3	27.0 qm 128.2 (2α-CH_3)	26.8 qm 127.0 (2α-CH_3)	26.9 bq 127.8 (2α-CH_3)	27.0 bq 128.2 (2α-CH_3)	27.0 bq 129.4 (2α-CH_3)	27.0 bq 129.4 (2α-CH_3)	26.9 bq 125.7 (2α-CH_3)
2β-CH_3	32.2 qm 128.2 (2β-CH_3)	31.6 qm 127.0 (2β-CH_3)	31.1 bq 128.0 (2β-CH_3)	30.0 bq 128.8 (2β-CH_3)	31.0 bq 129.4 (2β-CH_3)	31.3 bq 129.4 (2β-CH_3)	31.8 bq 124.5 (2β-CH_3)
1′	158.3 bt 9.1 (H'_3, H'_5)	156.9 bt 9.5 (H'_3, H'_5)	134.7 bs 4.9 (H'_3, H'_5)	113.2 t 4.9 (H'_3, H'_5)	110.5 q 2.4 (2′-CH_3)	111.3 q 2.4 (2′-CH_3)	111.0 q 2.4 (2′-CH_3)
2′	115.6 ddd 159.5 (H'_2)	114.9 ddd 160.4 (H'_2)	129.5 bd 158.1 (H'_2)	157.5 m 6.7 (2′-CH_3)	174.3 q 6.7 (2′-CH_3)	174.7 q 6.7 (2′-CH_3)	175.8 q 6.9 (2′-CH_3)
3′	130.5 dd 160.8 (H'_3) 8.3 (H'_5)	130.1 dd 161.1 (H'_3) 8.5 (H'_5)	128.9 dd 160.2 (H'_3) 6.6 (H'_5)	104.7 dd 164.8 (H'_3) 6.7 (H'_5)			
4′	122.7 dt 162.1 (H'_4) 7.2 (H'_2, H'_6)	122.2 dt 161.8 (H'_4) 7.0 (H'_2, H'_6)	127.3 bd 161.1 (H'_4)	132.3 d 163.0 (H'_4)			
5′	130.5 dd 160.8 (H'_5) 8.3 (H'_3)	130.1 dd 161.1 (H'_3) 8.5 (H'_5)	128.9 dd 160.2 (H'_5) 6.6 (H'_3)	104.7 dd 164.8 (H'_5) 6.7 (H'_3)	160.7 bs	158.8 bs	156.5 s
6′	115.6 ddd 159.5 (H'_6) 7.8 (H'_4) 4.8 (H'_2)	114.9 ddd 160.4 (H'_6) 7.2 (H'_4) 4.4 (H'_2)	129.5 bs 158.1 (H'_6)	157.5 m	127.2 m	126.6 bt 4.9 (H'_8, H'_{10})	126.0 m
7′					128.8 bd 129.5 dd 163.0 (H'_8) 6.3 (H'_{10})	133.5 m 132.7[d] bd 165.4 (H'_8)	135.7 (135.5) m 129.4 (129.3) bd 170.6 (H'_8)
8′							
9′					131.0 bd 159.9 (H'_9)	131.9[b] bd 163.6 (H'_9)	133.4 bd 168.9 (H'_9)
10′					129.5 dd 163.0 (H_{10}) 6.3 (H'_8)	128.2 bd 164.8 (H'_{10})	129.3 (129.4) 170.6 (H'_{10})
11′					128.8 bd 162.4 (H'_{11})	130.9[b] bd 166.6 (H'_{11})	133.5 (133.7) m
2′-CH_3				56.2 q 145.9 (2′-OCH_3)	12.7 q 131.8 (2′-CH_3)	13.0 q 131.8 (2′-CH_3)	13.1 q (131.8) (2′-CH_3)

[a] The data of each carbon resonance are shown in the following order: chemical shift in deuterium oxide, multiplicity, and spin–spin splittings (coupled protons). All spectra were measured in deuterium oxide at about 25°, except the spectrum of I, which was measured in methanol-*d*, and the spectrum of VII, which was measured at 50°; b = broad, qui = quintet, and m = unresolved multiplet. [b] Signals in any vertical column may be reversed.

Table II—^{13}C-NMR Data of Penicillins in Dimethyl Sulfoxide-d_6 Solution [a]

Carbon	II	III	IV	V	VI	VII
2	64.9 m	64.4 m	64.5 m	64.8 m	64.7 m	64.8 m
3	74.0 dm 142.8 (H_3)	74.0 dm 140.4 (H_3)	74.3 dm 141.6 (H_3)	73.9 bd 141.6 (H_3)	73.9 dm 142.2 (H_3)	73.8 dm 144.0 (H_3)
5	67.1 ddd 176.1 (H_5) 5.2 H_3 3.1 H_6	66.9 dt 175.4 (H_5) 3.8 (H_3, H_6)	67.4 dt 173.3 (H_5) 3.6 (H_3, H_6)	67.2 dt 178.2 (H_5) 3.6 (H_3, H_6)	66.9 dt 178.2 (H_5) 4.2 (H_3, H_6)	67.1 ddd 180.7 5.4 H_3 3.7 H_6
6	57.5 dd 152.0 (H_6) 2.5 (H_5)	57.9 dd 151.0 (H_6) 1.5 (H_5)	58.0 bd 150.8 (H_6)	58.9 bd 152.6 (H_6)	58.3 bd 152.6 (H_6)	58.4 dd 153.2 (H_6) 2.7 (H_5)
7	172.6 ddd 8.6, 6.4, 4.3 (H_3, H_5, H_6)	172.7 ddd 9.8, 7.0, 4.9 (H_3, H_5, H_6)	174.3 dt 9.8, 5.1 (H_3, H_5, H_6)	172.5 ddd 9.8, 7.0, 4.9 (H_3, H_5, H_6)	173.1 m	172.8 m
9	167.9 q 4.9 (H_6, H_{11})	170.4 td 6.4 (H_{11})	165.1 d 3.4 (H_6)	161.7 bs	160.7 d 2.5 (H_6)	159.8 d 4.3 (H_6)
10	169.7 d 3.7 (H_3)	169.8 d 4.2 (H_3)	171.8 d 4.3 (H_3)	171.3 d 4.3 (H_3)	171.6 d 4.3 (H_3)	171.5 d 4.3 (H_3)
11	66.4 t 147.1 (H_{11})	41.6 bt 129.4 (H_{11})				
2α-CH_3	27.6 qm 127.6 (2α-CH_3)	27.5 qm 127.6 (2α-CH_3)	27.9 qm 127.6 (2α-CH_3)	27.6 qm 127.6 (2α-CH_3)	27.6 qm 125.9 (2α-CH_3)	27.5 qm 128.8 (2α-CH_3)
2β-CH_3	32.5 qm 127.6 (2β-CH_3)	31.8 qm 127.6 (2β-CH_3)	31.3 qm 127.6 (2β-CH_3)	32.1 bq 129.4 (2β-CH_3)	32.2 qm 128.1 (2β-CH_3)	32.5 qm 129.4 (2β-CH_3)
1′	157.7 m	135.8 m	115.8 t 5.8 (H'_3, H'_5)	112.0 q 2.4 (2′-CH_3)	112.8 q 2.4 (2′-CH_3)	112.3 d 3.0 (2′-CH_3)
2′	114.8 ddd 160.2 (H'_2) 7.9 (H'_4) 4.6 (H_6)	129.8 dm 157.3 (H'_2)	157.2 dq 10.7 (H'_4) 4.9 (OCH_3)	170.8 q 7.0 (2′-CH_3)	171.9 q 6.7 (2′-CH_3)	172.8 q 7.1 (2′-CH_3)
3′	129.8 dd 160.8 (H'_3) 8.1 (H'_5)	129.0 dd 159.9 (H'_3) 4.9 (H'_5)	104.6 dd 163.3 (H'_3) 7.7 (H'_5)			
4′	121.6 dt 162.3 (H'_4) 7.2 (H_2, H'_6)	126.4 dm 163.0 (H'_4)	130.9 d 160.5 (H'_4)			
5′	129.8 dd 160.8 (H'_3) 8.1 (H'_5)	129.0 dd 159.9 (H'_5) 4.9 (H'_3)	104.6 dd 163.3 (H'_5) 7.7 (H'_3)	160.3 t 3.7 (H'_7, H'_{11})	159.5 bs	157.4 s
6′	114.8 ddd 160.2 (H'_6) 7.9 (H'_4) 4.6 (H_2)	129.8 dm 157.3 (H'_6)	130.9 d 160.5 (H'_6)	128.3 t 6.7 (H'_6)	127.5 m	126.9 m
7′				128.1 dd 161.8 (H'_7) 6.1 (H_9, H'_{11})	133.0[b] m	135.1[b] m
8′				129.0 ddd 162.6 (H'_8) 5.7 (H'_{10}) 2.6 (H_7, or H'_9)	132.0[b] bm 165.4 (H'_8)	129.0 dm 169.7 (H'_8)
9′				130.3 dt 161.8 (H'_9) 7.2 (H'_7, H'_{11})	132.0[b] bm 165.4 (H'_9)	133.0 d 167.8 (H'_9)
10′				129.0 ddd 162.6 (H'_{10}) 5.7 (H'_8) 2.6 (H_9 or H'_{11})	127.8 dm 165.4 (H'_{10})	129.0 dm 169.7 (H'_{10})
11′				128.1 dt 161.8 (H'_{11}) 6.1 (H_9, H'_7)	130.2[b] dm 168.5 (H'_{11})	134.9[b] m

[a] The data of each carbon resonance are shown in the following order: chemical shift, multiplicity, and coupling constants (coupled protons). The chemical shift and multiplicity were measured at about 25 and 50°, respectively; b = broad, and m = unresolved multiplet. [b] Signals in any vertical column may be reversed.

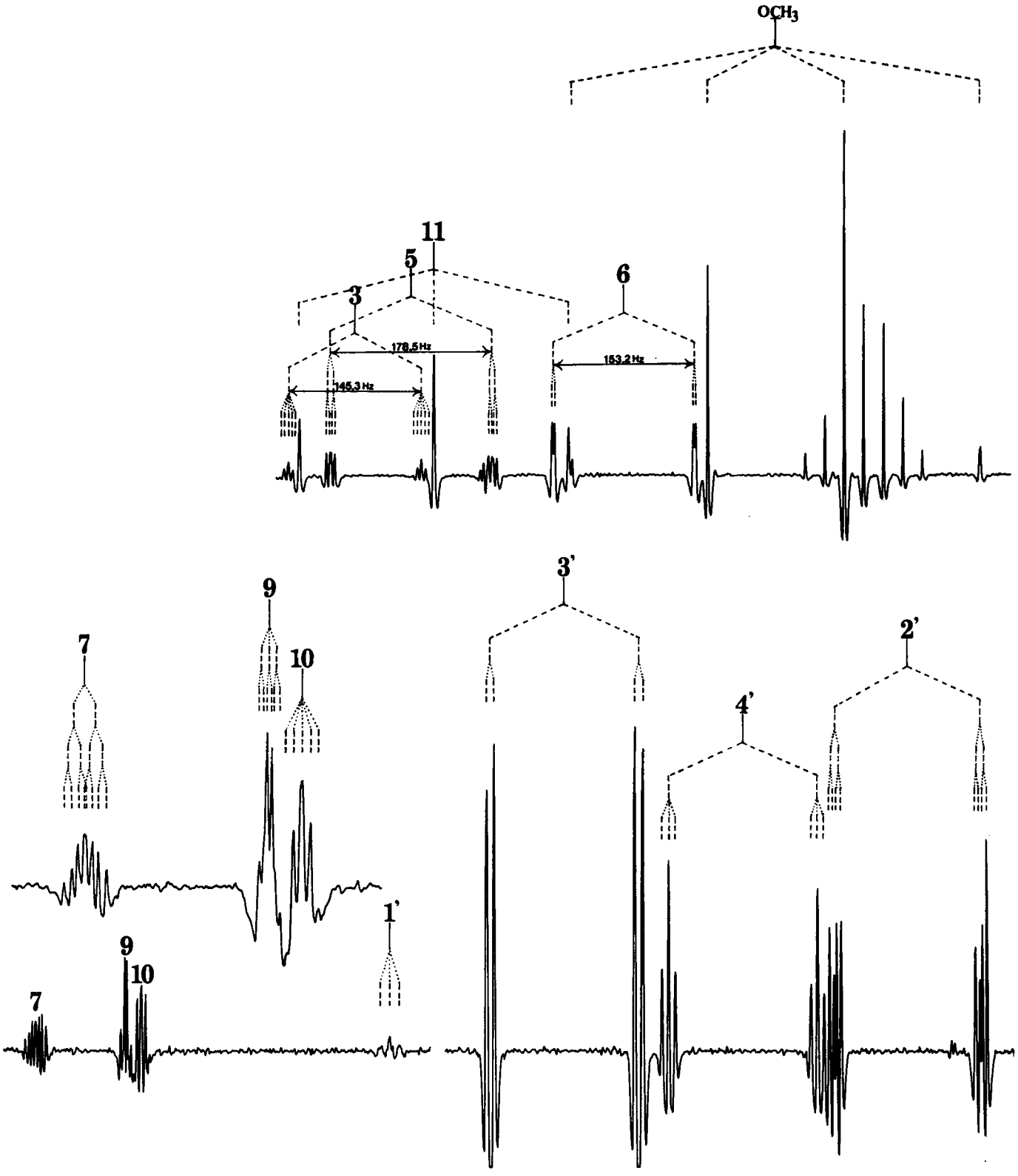


Figure 1—*High-resolution proton-coupled ^{13}C-NMR spectrum of penicillin V methyl ester (I) in methanol-d. A narrow (100–500 Hz) exponential (−3) window is used to measure small splittings.*

The application of ^{13}C–^{1}H one-bond coupling information in the ^{13}C-spectral analysis is limited to the protonated carbons. Coupling information also can be applied to the nonprotonated carbons (18, 19, 31–35). This application can be demonstrated fully in the chemical shift analysis of C_7, C_9, and C_{10} of penicillins.

In a previous report (28) on the ^{13}C-NMR assignments of I, the most downfield peak (172.6 ppm) was assigned to C_{10} and the 167.6-ppm peak was assigned to both C_7 and C_9. The proton-coupled spectrum of I was studied in methanol-*d*, chloroform-d_3, and dimethyl sulfoxide-d_6 solutions. The most downfield signal at about 173 ppm can be recognized as a doublet of double doublet (ddd) or a double quartet (dq) (Fig. 1). It thus can be designated to either C_7 (ddd) or C_{10} (dq).

To clarify this uncertainty, a deuteromethyl ester of penicillin V (I-*d*) was prepared. The proton-coupled spectrum of I-*d* shows that the most

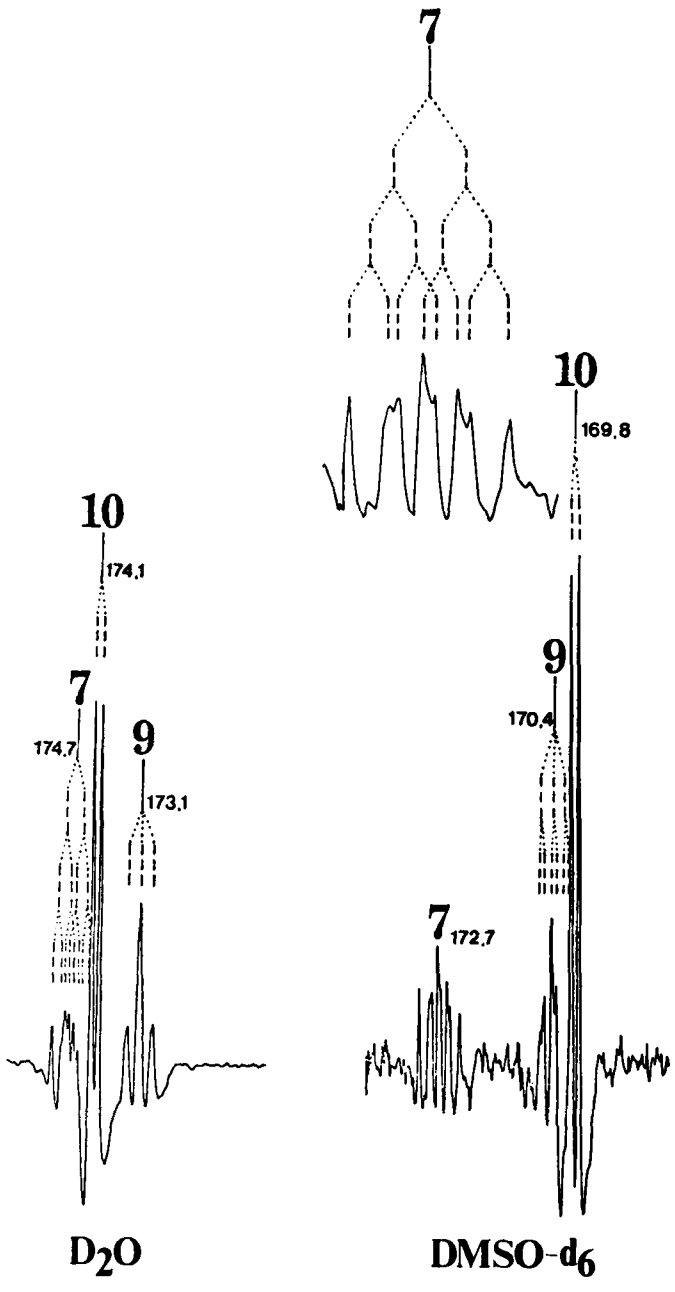
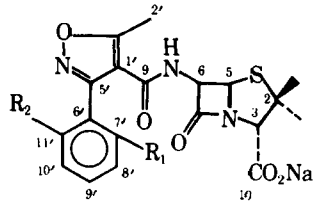


Figure 2—*High-resolution proton-coupled ^{13}C-NMR spectra of penicillin G potassium salt (III) in deuterium oxide and dimethyl sulfoxide-d_6 solutions. Only the carbonyl carbon signals are shown. A narrow (100–500 Hz) exponential (−3) window is used to measure small splittings.*



V: $R_1 = R_2 = H$
VI: $R_1 = Cl$, $R_2 = H$
VII: $R_1 = R_2 = Cl$

downfield peak at 173.5 ppm remains intact while the 169.1-ppm peak becomes an unresolved multiplet, arising from the ^{13}C–deuterium coupling. Therefore, the 169.1-ppm peak (quintet) must be assigned to C_{10} [$^2J(C_{10}\text{–}H_3) \approx {}^3J(C_{10}\text{–}CH_3) = 4.3$ Hz] in contradiction to the previous assignment (28). The C_9 signal appears as a triple doublet due to its coupling with H_{11} and H_6. This finding clearly demonstrates the invalidity of simple chemical shift theory or the additivity principle in the differentiation of the close resonance signals.

The ^{13}C–hydrogen coupling patterns of the phenoxy portion of I (Fig. 1 and Table I) can be analyzed by analogy to the coupling of phenols (33). The typical three-bond couplings of aromatic systems are seen. The magnitude of $^3J(C'_2\text{–}H'_6)$ is smaller than the usual three-bond coupling constants due to coupling through an oxygen-substituted carbon (32–34). Thus, C'_2 appears as a doublet of double doublet [$^1J(C'_2\text{–}H'_2 = 159.5$, $^3J(C'_2\text{–}H'_4) = 7.8$, and $^3J(C'_2\text{–}H'_6) = 4.8$ Hz]. Most aromatic carbon resonances of other penicillins can be determined similarly.

The proton-coupled spectra of penicillin in deuterium oxide solution display some useful features of ^{13}C–hydrogen long-range splitting patterns. The C_{10} signal always appears as a doublet because of the two-bond couplings with H_3. The C_7 resonance peak is shown as a doublet of double doublet or a double triplet due to the couplings with H_3, H_5, and H_6, revealing characteristics reminiscent of the spectrum of I.

The splitting patterns of C_9 vary according to the structure of the side chain (R_2). The broad linewidth often prohibits the measurement of the small coupling between C_9 and H_6. The coupling is apparent in the spectra of sodium salts of oxacillin (V) and cloxacillin (VI).

The chemical shift analysis of the isoxazole moiety is straightforward. The C'_1 resonance signal occurs at the highest field among all sp^2 carbon peaks and is the only carbon without a two- or three-bond proton in V and VI. The C'_2 signal can be differentiated from C_7 and C_{10} simply because of its unique two-bond coupling with C'_2–CH_3.

The C'_6, C'_7, and C'_{10} signals of VI can be determined from chemical shift calculations (15, 16, 21, 22). However, C'_8, C'_9, and C'_{10} cannot be firmly assigned since the calculated values are close and the rotation around the C'_5–C'_6 bond is probably partially restricted. This restricted rotation is indicated by the splitting of C'_7 (C'_{11}) and C'_8 (C'_{10}) of dicloxacillin (VII) into doublets in deuterium oxide.

Direct measurements from the proton-coupled spectra may sometimes provide line splittings instead of precise coupling constants due to the virtual couplings of the proton nuclei. However, the directly observed line splittings (coupling patterns) may be more useful.

Concentrated aqueous solutions of penicillins are too viscous to give fine spectra with good resolution, partially because of the formation of micellar solutions (30). The instability of penicillin in water prevents spectral determination at elevated temperatures. To confirm the coupling patterns, the ^{13}C-NMR spectra of penicillins were taken in dimethyl sulfoxide-d_6 at 50°. The linewidth was considerably reduced, allowing the measurement of the fine splittings of most carbon signals.

Comparative studies of the chemical shift in deuterium oxide and dimethyl sulfoxide-d_6 (Fig. 2) indicate that the solvent affects the relative chemical shift (Tables I and II) (15, 16, 21, 22). This effect prevents the use of simple chemical shift calculations to deduce the chemical shift directly from one solvent to the other solvent. However, the coupling patterns are not perturbed by the solvent effect (Fig. 2) unless a slowly exchangeable proton is involved.

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ACKNOWLEDGMENTS

The authors are grateful to Mrs. T.-L. Shieh for technical assistance.

First-Pass Effect after Rectal Administration of Thiazinamium Methylsulfate

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Abstract □ The absorption and metabolism of the quaternary ammonium compound thiazinamium methylsulfate were studied in humans using plasma concentration data and urinary excretion measurements. After giving a dose of 150 mg in suppositories, the relative bioavailability was 5.8 ± 3.2 (*SD*) % of the dose, comparable to the values obtained following oral administration. The degree of first-pass effect observed after rectal administration was comparable with that after oral administration.

Keyphrases □ Thiazinamium methylsulfate—rectal absorption and metabolism in humans □ Absorption, rectal—thiazinamium methylsulfate in humans □ Metabolism—thiazinamium methylsulfate in humans □ Phenothiazine derivatives—thiazinamium methylsulfate, rectal absorption and metabolism in humans □ Antihistaminics—thiazinamium methylsulfate, rectal absorption and metabolism in humans

It has been widely assumed that, after rectal administration, drugs mainly enter the general circulation without an initial passage through the liver, provided that the suppository does not reach the higher parts of the rectum (1, 2). The drug supposedly enters the inferior or middle rectal veins, which drain into the vena cava inferior. The blood in the superior rectal vein flows to the portal vein and subsequently enters the liver.

After oral administration, most drugs enter the portal vein, so a 100% passage through the liver is involved. Once a drug enters the general circulation, approximately 20% of the total blood flow passes through the liver during each circulation, whatever the route of administration. However, when drugs are administered parenterally, the total first passage through the liver does not occur. It has been assumed that the same condition would apply for the rectal route. For this reason, rectal administration has been recommended as a noninvasive alternative for drugs largely metabolized by the liver or excreted in the bile and for drugs subject to degradation in the GI tract.

Thiazinamium methylsulfate[1] (I) is a phenothiazine derivative with a quaternary ammonium group in the molecule. The drug is used for the treatment of some generalized obstructive lung diseases because it causes bronchodilatation (especially after intramuscular injection) as a result of substantial anticholinergic and antihistaminic properties (3–9).

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0022-3549/79/0100-0069$01.00/0