

STEREOCHEMICAL STUDIES OF 1-OXACEPHAMS BY MEANS OF NMR
SPECTROSCOPY. A USEFUL SHIFT RULE FOR DETERMINATION
OF THE C₃-SUBSTITUENT CONFIGURATION

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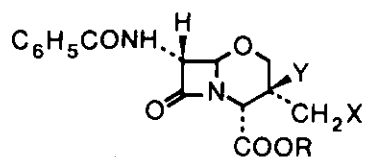
Abstract — Conformation of 1-oxacephams with a carbon-substituent at C₃ was determined to be in a half chair by nmr spectroscopy. A useful shift rule for determination of the C₃ configuration in both 1-oxacepham and cepham derivatives has been established on the basis of difference in H-3' chemical shifts between the methyl and benzhydryl esters. This rule, proposedly called "the benzhydryl shift rule," has been proved to be generally applicable.

For sophisticated syntheses in the field of oxacephem antibiotics we needed to elucidate the stereochemistry of 1-oxacephem derivatives, i.e. synthetic precursors of the antibiotics¹. Conformation of the tetrahydroxazine ring in C₃-substituted cepham was first determined by application of the nuclear Overhauser effects (NOE) in ¹H nmr spectroscopy and a long range spin-spin coupling. Secondly we found a close relationship between the H-3' chemical shifts and the C₃ stereochemistry in the 1-oxacephem benzhydryl esters and this finding led us to establish a useful shift rule for determination of configuration of the C₃ methyl or substituted methyl group. In this paper we describe the results of these studies.

Determination of the Tetrahydroxazine Ring Conformation and C₃ Configuration in C₃-Substituted 1-Oxacephem Derivatives by Application of the ¹H Nuclear Overhauser Effect

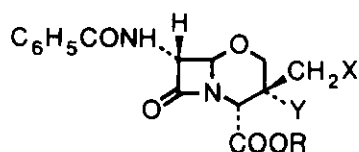
Table 1 lists ¹H nmr spectroscopic data (chemical shifts, δ , long-range spin-spin coupling constants, J, and values of ¹H NOE) obtained for a number of the C₃ epimeric pairs of 1-oxacephem benzhydryl esters 1a-8a together with those for 9a and 10a¹. In all compounds NOE enhancements (3-15%) were observed between

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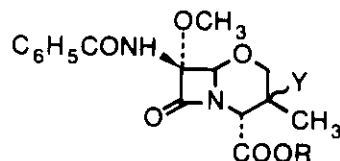
(Type A)

- 1a,b X=H, Y=OH
 3a,b X=Cl, Y=OH
 5a,b X=OCOCH₃, Y=OH
 7a,b X=Cl, Y=Cl
 9a X=OH, Y=Cl
 10a X=Cl, Y=SCH₃
 12a,b X=H, Y=OCOCH₃
 13a,b X=OCOCH₃, Y=SCH₃
 14a,b X=S-Tet, Y=SCH₃
 15a,b X=Cl, Y=SC₆H₅

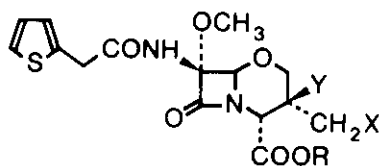


(Type B)

- 2a,b X=H, Y=OH
 4a,b X=Cl, Y=OH
 6a,b X=OCOCH₃, Y=OH
 8a,b X=Cl, Y=Cl
 11a,b X=H, Y=Cl

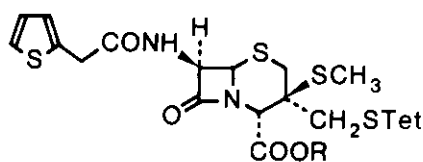


- 16a,b Y=α-OH (Type B)
 17a,b Y=β-OCOCH₃ (Type A)



(Type A)

- 18a,b X=S-Tet, Y=SCH₃
 19a,b X=OCOCH₃, Y=SCH₃
 20a,b X=Cl, Y=SC₆H₅
 21a,b X=OCH₃, Y=SCH₃



22a,b (Type A)

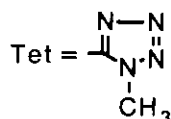
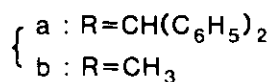


Fig. 1.

Table 1. ^1H nmr data on 1-oxacephams (1a-10a) in CDCl_3

Compound	1a	3a	5a	7a	9a	10a	2a	4a	6a	8a
Chemical shift, δ_{H}										
H-2 β	3.57	3.76	3.76	3.87	3.84	3.88	3.54	3.82	3.77	4.01
H-2 α	3.89	3.88	4.03	4.16	4.09	4.14	3.80	3.89	3.88	4.30
H-3'	0.92	3.09 3.33	3.84 3.94	3.40 3.59	3.50 3.57	3.21 3.51	1.45	3.73 3.83	4.25 4.34	3.90 4.00
H-4 β	4.57	4.76	4.73	4.96	4.90	4.56	4.57	4.90	4.79	5.03
H-6 α	5.40	5.41	5.37	5.35	5.41	5.41	5.28	5.33	5.34	5.44
H-7 β	5.09	5.06	5.13	4.99	5.02	5.01	4.95	4.93	4.93	4.96
$^4J_{\text{H-2}\beta, \text{H-4}}$	1.0	1.0	1.0	1.2	1.0	1.0	0.2(0.2)*	0.2	0.3(0.2)*	0.5
NOE (%) ^{*2}										
H-2 α $\xrightleftharpoons[2)]{1)}$ H-6 α	1) 10 2) 10	10 5	10 10	15 5	5 5	10 10	3 5	15 5	10 10	5 10
H-2 α $\xrightleftharpoons[2)]{1)}$ H-3'	1) 3 2) 5	10 0	-*3 -*3	10 -*4	0 10	5 5	0 0	-*3 -*3	-*3 0	-*3 -*3
H-3' $\xrightleftharpoons[2)]{1)}$ H-7 β	1) 0 2) 0	0 0	0*5 0	0 0	0 0	0 0	5 3	5 5	3 10	15 -*3
Type	A						B			

* $^4J_{\text{H-2}\alpha, \text{H-3}\beta}$ values (in Hz) in parentheses. *2 NOE enhancement values (%) for H-i $\xrightleftharpoons[2)]{1)}$ H-j:

1) H-i $\rightarrow$ H-j; NOE on the H-j signal when the H-i signal was saturated: 2) H-j $\rightarrow$ H-i;

vice versa. *3 Unobservable owing to close signal positions. *4 Not observed. *5 NOE values of 5 and 3% for [OH-3 β $\rightarrow$ H-7 β] and [H-7 β $\rightarrow$ OH-3 β] were observed, respectively.

H-2 α and H-6 α , and also long range spin-spin couplings ($^4J_{\text{H,H}} = 0.2\text{-}1.0$ Hz) were observed between H-2 β and H-4 β , providing strong evidence for a half-chair conformation of the tetrahydroxazine ring (Fig. 2)³, while eliminating two possible boat conformations⁴. This half-chair conformation is in good accordance with that for the tetrahydrothiazine ring in the corresponding cepham (1-sulfur) nucleus⁵.

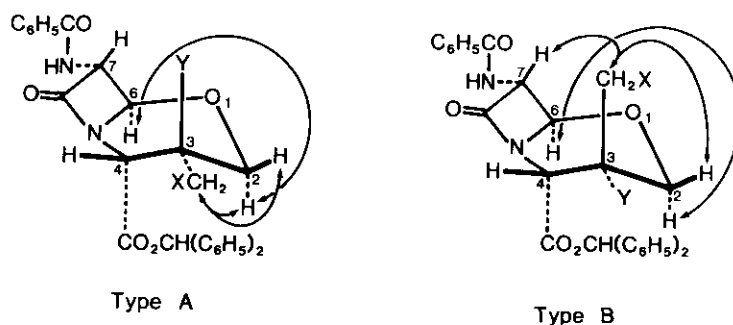


Fig. 2

The NOE enhancement was observed between H-3' and H-7 β , but not between H-3' and H-2 α , in compounds 2a, 4a, 6a, and 8a. In contrast, with no NOE enhancements being seen between H-3' and H-7 β , NOE enhancement was observed between H-3' and H-2 α in compounds 1a, 3a, 5a, 7a, 9a, and 10a. Clearly, the above NOE differences arise from the stereochemical difference in the C₃ substituents, indicating that β configuration can be assigned to the 3-substituent CH₂X in compounds of the former type, classified as Type B, and α configuration to compounds of the latter type, classified as Type A. In this way, stereochemistry of the C₃ substituents in these 1-oxacepham derivatives was unequivocally determined.

In an attempt to correlate the ¹³C chemical shifts with the C₃ configuration, the ¹³C nmr data are compared in compounds 1a-10a (Table 2). Although C-7, C-4 and C-2 signals appear in the lower field and the C-3' and C-6 signals in the higher field in compounds 1a, 3a, 5a and 7a than those in 2a, 4a, 6a and 8a, the chemical shift differences (0.2 to 4.1 ppm) may not be consistently large enough to determine the C₃ configuration in the 1-oxacephams.

Table 2. ¹³C Chemical shifts of 1-oxacephams (1a-10a) in DMSO-d₆

Compound	1a	2a	3a	4a	5a	6a	7a	8a	9a	10a
C-2	70.3	70.1	67.7	66.5	67.1	65.7	65.7	68.2	66.8	65.6
C-3	65.1	65.4	67.2	66.9	66.6	66.1	67.9	62.9	69.4	49.8
C-3'	21.5	25.6	47.3	49.3	65.1	65.7	47.3	48.8	63.8	45.3
C-4	60.6	60.4	58.3	56.3	58.1	55.8	58.7	56.2	58.7	55.4
C-6	82.5	83.2	82.7	83.4	82.7	83.2	82.8	83.2	82.9	83.1
C-7	63.7	63.3	63.7	63.1	63.8	63.2	64.4	63.8	64.3	64.1
C-8	167.3	167.3	166.4	166.6*	166.6	166.8	164.8*	165.6	165.4	166.0
COOBH	164.9	164.3	164.7	164.1	164.9	164.2	164.5*	164.1	164.6	164.9
CONH	166.4	166.4	166.4	166.4*	166.4	166.4	166.5	166.6	166.5	166.5
CHPh ₂	77.9	77.6	78.3	77.8	77.9	77.8	79.1	78.6	78.7	78.7
PhCO C _{ipso}	133.1	133.0	132.9	132.9	133.0	132.9	132.8	132.9	132.9	132.8
Ph ₂ CH C _{ipso}	139.6 139.5	140.0	139.6 139.4	139.9	139.8 139.6	139.9	139.2	139.3	139.7 139.6	139.7 139.5
Type	A	B	A	B	A	B	A	B	A	A

* Assignments may be interchanged.

The "Benzhydryl Shift Rule" for Determination of the C₃ Stereochemistry in 1-Oxacepham Benzhydryl Esters

From the discussions made above it becomes clear that the C₃ stereochemistry of 1-oxacepham derivatives can be determined by application of NOE and a long range spin-spin coupling in ¹H nmr spectroscopy.

However, such a measurement is not always simple for most synthetic organic chemists who usually operate compact nmr spectrometers only. Fortunately we were able to find a more practical and useful method for determination of the C₃ stereochemistry. The idea has arisen from the observation that the nmr signals for the 3a methyl or substituted methyl protons ($\delta_{H-3'}$) in Type-A 1-oxacepham benzhydryl esters appear in an unusually higher field while no such irregularity is seen in Type-B 1-oxacepham esters. This high field shifts seem to be characteristic of the Type-A 1-oxacepham benzhydryl esters, since the signals for the C₃ protons in compounds of this type were shifted without exceptions to the higher field by 0.40-0.64 ppm relative to those in Type-B compounds. The shift values are significantly large and provide a convenient diagnosis for differentiating Type-A 1-oxacephams from Type-B compounds. However, this diagnosis can be applied only when both epimers are available. We thus searched for a more useful and general method for determination of the C₃ configuration. It was assumed that a magnetic anisotropic effect due to the two phenyl groups in the benzhydryl ester might be responsible for this marked shift, since only the 3a methyl or substituted methyl in Type-A compounds is in proximity with the α -oriented benzhydryl ester group, as can be visualized by the two steric diagrams of oxacephams of the two types (Fig. 2). In order to confirm this view we prepared the corresponding methyl esters **1b-8b**, in which the anisotropic effects due to the two phenyl groups should be eliminated. The methyl esters **1b-8b** were readily prepared from the corresponding benzhydryl esters, **1a-8a**, by deprotection followed by methylation with diazomethane. Table 3 lists ¹H chemical shifts of the methyl esters as compared with those of benzhydryl esters together with chemical shifts differences, $\Delta\delta_{(a-b)}$, between the 3' proton in a benzhydryl ester (series a) and that in the corresponding methyl ester (series b) in Type-A and -B oxacephams. This $\Delta\delta$ value indicates a net shift of a 3' proton signal caused by substitution of methyl group for benzhydryl group. We have found that this shift value is considerably large, ranging from -0.18 to -0.31 ppm,* in the Type-A oxacephams **1**, **3**, **5**, and **7** and negligibly small (0 to -0.03 ppm) in the Type-B oxacephams **2**, **4**, **6**, and **8**. This remarkable difference in the shift values might provide an excellent diagnosis for differentiation of Type-A from Type-B oxacephams, namely, for determination of the C₃ configuration in an oxacepham derivative.**

In order to confirm validity of this diagnosis we measured ¹H nmr spectra of other benzhydryl and methyl esters of oxacepham or cepham derivatives **11-22**, the stereochemistry of which had been well established⁸. The data and the $\Delta\delta_{(a-b)}$ values are summarized also in Table 3. As expected, the $\Delta\delta_{(a-b)}$ values in the

* This range is valid when a larger $\Delta\delta_{(a-b)}$ value in two AB type signals was adopted.

** Similar difference in $\Delta\delta_{(a-b)}$ can be observed between proton signals in α and β substituents at C₃, such as OCOCH₃, SCH₃, and tetrazolyl N-CH₃, as can be seen from Table 3. This difference has not been discussed in the text, since these protons are not common in all compounds.

Table 3 ^1H Chemical shifts (δ) and Benzhydryl shifts $\Delta\delta_{(a-b)}$ * of 1-oxacephams and cepham in CDCl_3 ⁷

	X	Y	Proton	δ a (R=BH)	δ b (R=CH ₃)	$\Delta\delta_{(a-b)}$ **
Type A						
1	H	OH	H-3'	0.92	1.13	-0.22
3	Cl	OH	H-3'	3.09 3.33	3.40 3.57	-0.31 -0.24
5	OCOCH ₃	OH	H-3'	3.84 3.94	3.91 4.12	-0.07 -0.18
			OCOCH ₃	1.88	2.08	-0.20
7	Cl	Cl	H-3'	3.40 3.58	3.68 3.85	-0.28 -0.27
12	H	OCOCH ₃	H-3' OCOCH ₃	1.20 2.03	1.41 2.04	-0.21 (-0.01)
13	OCOCH ₃	SCH ₃	H-3'	3.83 4.12	3.98 4.30	-0.15 -0.18
			OCOCH ₃ SCH ₃	1.76 2.10	2.05 2.13	-0.29 (-0.03)
14	STet	SCH ₃	H-3' N-CH ₃ SCH ₃	3.36 3.78 2.03	3.61 3.94 2.10	-0.25 -0.16 (-0.07)
15	Cl	SPh	H-3'	3.04 3.24	3.38 3.55	-0.34 -0.31
17	H	OCOCH ₃	H-3' OCOCH ₃	1.20 1.90	1.40 1.92	-0.20 (-0.02)
18	STet	SCH ₃	H-3' N-CH ₃ SCH ₃	3.40 3.80 1.97	3.58 3.92 2.01	-0.18 -0.12 (-0.04)
19	OCOCH ₃	SCH ₃	H-3'	3.84 4.13	3.96 4.29	-0.12 -0.16
			OCOCH ₃ SCH ₃	1.75 2.03	2.05 2.05	-0.30 (-0.02)
20	Cl	SPh	H-3'	2.97 3.20	3.27 3.50	-0.30 -0.30
21	OCH ₃	SCH ₃	H-3'	3.19 3.33	3.42 3.42	-0.23 -0.09
			OCH ₃ SCH ₃	2.81 2.03	3.20 2.03	-0.39 (0)
22	STet (1-thia)	SCH ₃	H-3' N-CH ₃ SCH ₃	3.53 3.82 1.92	3.69 3.92 1.97	-0.16 -0.10 (-0.05)
Type B						
2	H	OH	H-3'	1.43	1.45	(-0.02)
4	Cl	OH	H-3'	3.73 3.83	3.74 3.86	(-0.01) (-0.03)
6	OCOCH ₃	OH	H-3'	4.25 4.34	4.25 4.33	(0) (+0.01)
			OCOCH ₃	2.13	2.10	(+0.03)
8	Cl	Cl	H-3'	3.90 4.00	3.90 4.00	(0) (0)
11	H	Cl	H-3'	1.80	1.81	(-0.01)
16	H	OH	H-3'	1.43	1.46	(-0.03)

* $\Delta\delta_{(a-b)} = \delta_{\text{H(a)}} - \delta_{\text{H(b)}}$; a plus sign represents downfield shift.

** $\Delta\delta_{(a-b)}$ value of the β -substituent is shown in parentheses.

compounds of type A range from -0.16 to -0.34 ppm and those in the compounds of type B were negligibly small (-0.03 to +0.03 ppm), irrespective of the configuration or structure of the side chain at C₇. The consistency of this relationship between the shift values and the C₃ configuration is thus verified. This fact led us to establish a useful empirical rule that the configuration of the C₃ methyl or substituted methyl group in an oxacepham or cepham derivative can be assigned α or β from a large (-0.16 to -0.34) or small (± 0.03 ppm) $\Delta\delta_{(a-b)}$ value observed. We propose to call this empirical rule "the benzhydryl shift rule"⁹ and believe that this rule is convenient and useful for stereochemical studies of oxacepham or cepham derivatives.

REFERENCES AND NOTES

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2. ¹H nmr spectra were recorded on a Varian XL-100-12A nmr spectrometer at 100.058 MHz using CDCl₃ in 5-mm spinning tubes at normal probe temperature (28°C) containing tetramethylsilane (TMS) as internal reference in the frequency-swept mode. NOE experiments were carried out by measuring the integrated intensities of a signal with and without irradiation at the resonance frequency of another signal. Accuracies of $\delta_{H,I}$, $J_{H,I}$, and NOE values are ± 0.01 ppm, ± 0.1 Hz, and $\pm 2\%$, respectively.
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6. ¹³C nmr spectra were obtained with a Varian NV-14 FT nmr spectrometer at 15.087 MHz, using DMSO-d₆ in 8-mm spinning tubes at normal probe temperature containing TMS as internal reference. Typical FT measurement conditions were as follows: SW, 3923 Hz; AT, 0.6 s; pulse flipping angle, 25°. Accuracies of δ_C are ± 0.1 ppm.
7. ¹H nmr spectra were recorded on a Varian EM-360L nmr spectrometer at 60 MHz using CDCl₃ in 5-mm spinning tubes at normal probe temperature in the frequency-swept and internal-TMS-locked mode. Accuracies of δ_H are ± 0.01 ppm.
8. T. Aoki, T. Konoike, H. Itani, T. Tsuji, M. Yoshioka, and W. Nagata, *Tetrahedron*, 1983, 39, 2515.
9. A similar but smaller shift difference was observed between a methyl ester 14b and the corresponding benzyl ester 14c (14 in Fig. 1, R = CH₂C₆H₅): the $\Delta\delta_{(c-b)}$ for H-3' was -0.09 ($\Delta\delta_{(a-b)}$ for H-3' was -0.25). Thus, the benzyl shift values, $\Delta\delta_{(c-b)}$, will not be large enough to determine the C₃ configuration in oxacephams, although we have not examined the relationship in derivatives other than 14.

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