STEREOCHEMICAL STUDIES OF 1-OXACEPHAMS BY MEANS OF NMR SPECTROSCOPY. A USEFUL SHIFT RULE FOR DETERMINATION OF THE 3-SUBSTITUENT CONFIGURATION

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Abstract — Conformation of 1-oxacephams with a carbon-substituent at C_3 was determined to be in a half chair by nmr spectroscopy. A useful shift rule for determination of the C_3 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-oxacepham derivatives, i.e. synthetic precursors of the antibiotics[1]. Conformation of the tetrahydroxazine ring in C_3-substituted cephams 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 C_3 stereochemistry in the 1-oxacepham benzhydryl esters and this finding led us to establish a useful shift rule for determination of configuration of the C_3 methyl or substituted methyl group. In this paper we describe the results of these studies.

Determination of the Tetrahydroxazine Ring Conformation and C_3 Configuration in C_3-Substituted 1-Oxacepham 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 C_3 epimeric pairs of 1-oxacepham benzhydryl esters **1a**-**8a** together with those for **9a** and **10a**[1]. In all compounds NOE enhancements (3-15%) were observed between

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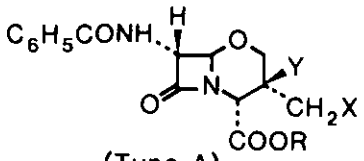
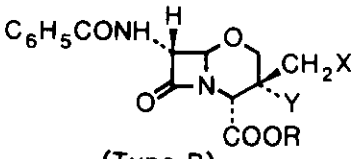


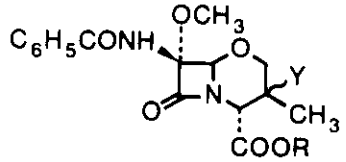
(Type A)

1a,b X=H , Y=OH
3a,b X=Cl , Y=OH
5a,b X=$OCOCH_3$, Y=OH
7a,b X=Cl , Y=Cl
9a X=OH , Y=Cl
10a X=Cl , Y=SCH_3
12a,b X=H , Y=$OCOCH_3$
13a,b X=$OCOCH_3$, Y=SCH_3
14a,b X=S·Tet , Y=SCH_3
15a,b X=Cl , Y=SC_6H_5

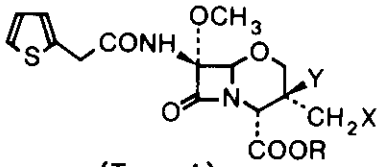


(Type B)

2a,b X=H , Y=OH
4a,b X=Cl , Y=OH
6a,b X=$OCOCH_3$, Y=OH
8a,b X=Cl , Y=Cl
11a,b X=H , Y=Cl

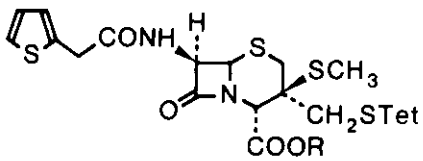


16a,b Y=α-OH (Type B)
17a,b Y=β-$OCOCH_3$ (Type A)



(Type A)

18a,b X=S·Tet , Y=SCH_3
19a,b X=$OCOCH_3$, Y=SCH_3
20a,b X=Cl , Y=SC_6H_5
21a,b X=OCH_3 Y=SCH_3



22a,b (Type A)

{ a : R=$CH(C_6H_5)_2$
b : R=CH_3

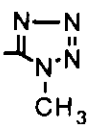
Tet = 

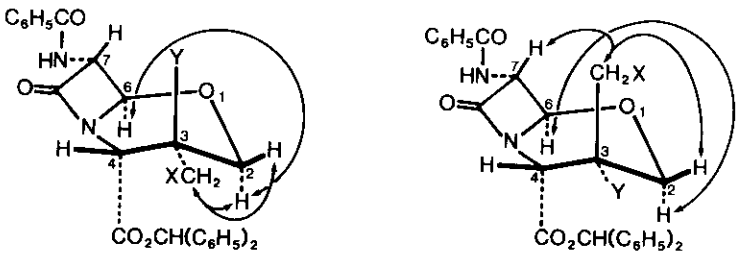
Fig. 1.

Table 1. ^{1}H 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-2β	3.57	3.76	3.76	3.87	3.84	3.88	3.54	3.82	3.77	4.01
H-2α	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-4β	4.57	4.76	4.73	4.96	4.90	4.56	4.57	4.90	4.79	5.03
H-6α	5.40	5.41	5.37	5.35	5.41	5.41	5.28	5.33	5.34	5.44
H-7β	5.09	5.06	5.13	4.99	5.02	5.01	4.95	4.93	4.93	4.96
$^4J_{H\text{-}2\beta,H\text{-}4}$	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-2α $\overset{1)}{\underset{2)}{\rightleftharpoons}}$ H-6α	1) 10 2) 10	10 5	10 10	15 5	5 5	10 10	3 5	15 5	10 10	5 10
H-2α $\overset{1)}{\underset{2)}{\rightleftharpoons}}$ 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' $\overset{1)}{\underset{2)}{\rightleftharpoons}}$ H-7β	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			

* $^4J_{H\text{-}2\alpha,H\text{-}3'\beta}$ values (in Hz) in parentheses. *2 NOE enhancement values (%) for H-i $\overset{1)}{\underset{2)}{\rightleftharpoons}}$ H-j: 1) H-i → H-j; NOE on the H-j signal when the H-i signal was saturated: 2) H-j → H-i; vice versa. *3 Unobservable owing to close signal positions. *4 Not observed. *5 NOE values of 5 and 3% for [O*H*-3β → H-7β] and [H-7β → O*H*-3β] were observed, respectively.

H-2α and H-6α, and also long range spin-spin couplings ($^4J_{H,H}$ = 0.2-1.0 Hz) were observed between H-2β and H-4β, providing strong evidence for a half-chair conformation of the tetrahydroxazine ring (Fig. 2)[3], while eliminating two possible boat conformations[4]. This half-chair conformation is in good accordance with that for the tetrahydrothiazine ring in the corresponding cepham (1-sulfur) nucleus[5].



Type A　　Type B

Fig. 2

The NOE enhancement was observed between H-3' and H-7β, but not between H-3' and H-2α, in compounds **2a**, **4a**, **6a**, and **8a**. In contrast, with no NOE enhancements being seen between H-3' and H-7β, NOE enhancement was observed between H-3' and H-2α in compounds **1a**, **3a**, **5a**, **7a**, **9a**, and **10a**. Clearly, the above NOE differences arise from the stereochemical difference in the C_3 substituents, indicating that β configuration can be assigned to the 3-substituent CH_2X 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 C_3 substituents in these 1-oxacepham derivatives was unequivocally determined.

In an attempt to correlate the ^{13}C chemical shifts with the C_3 configuration, the ^{13}C 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 C_3 configuration in the 1-oxacephams.

Table 2. ^{13}C Chemical shifts of 1-oxacephams (**1a**-**10a**) in DMSO-d_6[6]

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 *Cipso*	133.1	133.0	132.9	132.9	133.0	132.9	132.8	132.9	132.9	132.8
Ph_2CH *Cipso*	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 C_3 Stereochemistry in 1-Oxacepham Benzhydryl Esters

From the discussions made above it becomes clear that the C_3 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 C_3 stereochemistry. The idea has arisen from the observation that the nmr signals for the 3α methyl or substituted methyl protons ($\delta_{H\text{-}3'}$) 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 $C_{3'}$ 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 C_3 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 3α 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, $\Delta\delta_{(a\text{-}b)}$, 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 Δδ 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 C_3 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 established[8]. The data and the $\Delta\delta_{(a\text{-}b)}$ values are summarized also in Table 3. As expected, the $\Delta\delta_{(a\text{-}b)}$ values in the

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

** Similar difference in Δδ(a-b) can be observed between proton signals in α and β substituents at C_3, such as $OCOCH_3$, SCH_3, and tetrazolyl N-CH_3, 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	3.40	-0.31
					3.33	3.57	-0.24
	5	$OCOCH_3$	OH	H-3'	3.84	3.91	-0.07
					3.94	4.12	-0.18
				$OCOCH_3$	1.88	2.08	-0.20
	7	Cl	Cl	H-3'	3.40	3.68	-0.28
					3.58	3.85	-0.27
	12	H	$OCOCH_3$	H-3'	1.20	1.41	-0.21
				$OCOCH_3$	2.03	2.04	(-0.01)
	13	$OCOCH_3$	SCH_3	H-3'	3.83	3.98	-0.15
					4.12	4.30	-0.18
				$OCOCH_3$	1.76	2.05	-0.29
				SCH_3	2.10	2.13	(-0.03)
	14	STet	SCH_3	H-3'	3.36	3.61	-0.25
				N-CH_3	3.78	3.94	-0.16
				SCH_3	2.03	2.10	(-0.07)
	15	Cl	SPh	H-3'	3.04	3.38	-0.34
					3.24	3.55	-0.31
	17	H	$OCOCH_3$	H-3'	1.20	1.40	-0.20
				$OCOCH_3$	1.90	1.92	(-0.02)
	18	STet	SCH_3	H-3'	3.40	3.58	-0.18
				N-CH_3	3.80	3.92	-0.12
				SCH_3	1.97	2.01	(-0.04)
	19	$OCOCH_3$	SCH_3	H-3'	3.84	3.96	-0.12
					4.13	4.29	-0.16
				$OCOCH_3$	1.75	2.05	-0.30
				SCH_3	2.03	2.05	(-0.02)
	20	Cl	SPh	H-3'	2.97	3.27	-0.30
					3.20	3.50	-0.30
	21	OCH_3	SCH_3	H-3'	3.19	3.42	-0.23
					3.33	3.42	-0.09
				OCH_3	2.81	3.20	-0.39
				SCH_3	2.03	2.03	(0)
	22	STet (1-thia)	SCH_3	H-3'	3.53	3.69	-0.16
				N-CH_3	3.82	3.92	-0.10
				SCH_3	1.92	1.97	(-0.05)
Type B							
	2	H	OH	H-3'	1.43	1.45	(-0.02)
	4	Cl	OH	H-3'	3.73	3.74	(-0.01)
					3.83	3.86	(-0.03)
	6	$OCOCH_3$	OH	H-3'	4.25	4.25	(0)
					4.34	4.33	(+0.01)
				$OCOCH_3$	2.13	2.10	(+0.03)
	8	Cl	Cl	H-3'	3.90	3.90	(0)
					4.00	4.00	(0)
	11	H	Cl	H-3'	1.80	1.81	(-0.01)
	16	H	OH	H-3'	1.43	1.46	(-0.03)

* $\Delta\delta_{(a-b)} = \delta_{H(a)} - \delta_{H(b)}$; a plus sign represents downfield shift.
** $\Delta\delta_{(a-b)}$ value of the 3β-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 C_7. The consistency of this relationship between the shift values and the C_3 configuration is thus verified. This fact led us to establish a useful empirical rule that the configuraiton of the C_3 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. ^{1}H nmr spectra were recorded on a Varian XL-100-12A nmr spectrometer at 100.058 MHz using $CDCl_3$ 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 δ_H, $J_{H,H}$, and NOE values are ±0.01 ppm, ±0.1 Hz, and ±2%, respectively.
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6. ^{13}C nmr spectra were obtained with a Varian NV-14 FT nmr spectrometer at 15.087 MHz, using DMSO-d_6 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. ^{1}H nmr spectra were recorded on a Varian EM-360L nmr spectrometer at 60 MHz using $CDCl_3$ 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.
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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 = $CH_2C_6H_5$): 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 C_3 configuration in oxacephams, although we have not examined the relationship in derivatives other than **14**.

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