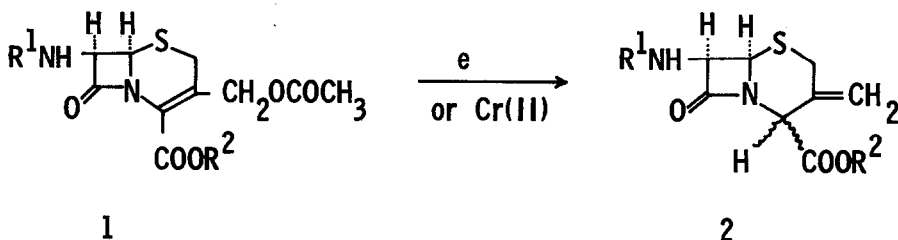


THE DETERMINATION OF STEREOCHEMISTRY OF 3-METHYLENECEPHAM DERIVATIVES
BY MEANS OF LANTHANIDE-INDUCED SHIFTS

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(Received in Japan 23 June 1972; received in UK for publication 26 June 1972)

We have recently reported facile syntheses of 3-methylenecepham derivatives (2) by an electrochemical reduction¹⁾ and by chromium(II) salts reduction²⁾ of the corresponding cephalosporanic acids (1). We now wish to



report the determination of stereochemistry of 2 by means of lanthanide-induced NMR shifts combined with computer calculation.

Among a number of stereochemical studies³⁾ using lanthanide shift reagents, several efforts^{4,5)} have been made to demonstrate the significance of the angle term in the McConnell-Robertson equation:⁶⁾

$$\Delta H_i = k(3\cos^2\theta_i - 1)/R_i^3 \quad (1)$$

where ΔH_i is the induced shift of the i th proton, R_i the distance between the metal and the i th proton, and θ_i the angle between this vector and the principal molecular axis.

A program has been written for a Model JEC-6 (JEOL) computer essentially based on the method of Farid *et al.*⁴⁾ The program was used to determine the three-dimensional position of europium metal which maximizes the correlation between the induced shifts and the pseudo-contact equation (1). The input to the program is the position of the heteroatom and protons as well as the corresponding shifts. The positions of protons and the heteroatom are represented by the cartesian co-ordinates with reference to an arbitrary origin. The co-ordinates of the heteroatom and protons were determined by

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- 9) An additional calculation was done on an assumed α -orientation, which gave a poorer correlation.
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Table. Observed and calculated $\text{Eu}(\text{fod})_3$ -induced shifts in 2a (ppm).

Position of proton	Observed shift ^a	Conformation A		Conformation B	
		Calc. shift	Calc. shift ^b	Calc. shift	Calc. shift ^b
7	10.35	10.34	10.34	10.35	10.31
6	2.39	2.45	2.46	2.41	2.60
2- α^c	1.07	1.19	1.17	1.00	1.10
2- β^c	1.48	1.50	1.44	1.52	1.68
3-exo- a^d	0.91	0.74	0.73	0.95	1.08
3-exo- b^d	0.93	0.75	0.74	0.87	0.99
4- α	} 1.81	1.25	1.23	0.96	1.10
4- β		1.96	1.88	0.99	1.15
ϵ^e		0.040	0.041	0.016	0.103
Eu-N distance (Å)		4.3	4.6	6.2	6.3
\angle Eu-N-C(7) (°)		93	90	52	54

^a Shifts are normalized to a 1:1 molar ratio of $\text{Eu}(\text{fod})_3$ to 2a from the slopes of shifts against molar ratio of $\text{Eu}(\text{fod})_3$; concentration of 2a, 0.2 molar in CDCl_3 .

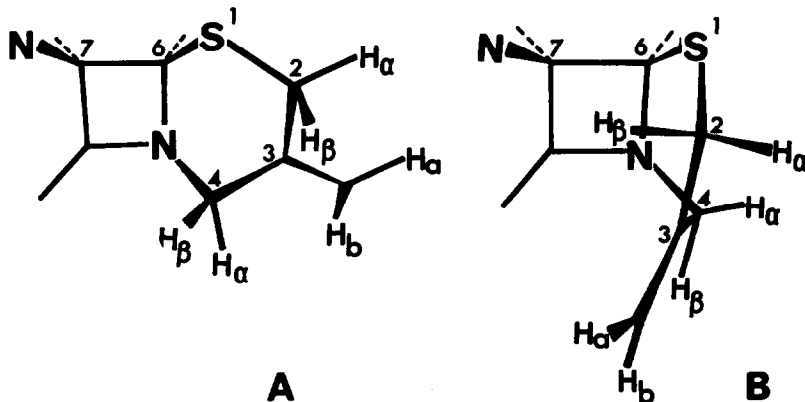
^b The calculation was done by adding the observed shift at position 4 to the original input.

^c When the observed shifts at position 2 assigned reversely, less satisfactory correlations were obtained.

^d The symbols a and b correspond to the ones depicted in the figure.

^e Dimensionless error (ϵ):

$$\epsilon = \frac{\sqrt{\text{sum of the square errors}}}{\text{number of the points}} \bigg/ \text{average shift}$$



an iterative calculation in which the calculated distances between each atom were brought as close as possible by the least squares method to the atomic distances measured from a Dreiding stereomodel.

Methyl 7-(2-thienylacetamido)-3-methylenecepham-4-carboxylate (2a: R¹=2-thienylacetyl, R²=CH₃) was chosen as a model. The induced shifts of each proton in 2a were determined in CDCl₃ in the presence of Eu(fod)₃⁷⁾ at 100 MHz, which are summarized in the Table.⁸⁾ The proton at position 7 showed the largest shift, which indicated that the europium complex co-ordinates almost exclusively with the nitrogen at position 7.

The stereomodel showed that two conformations A and B are possible in 2a. The positions of protons and the observed shift data except that of the proton at position 4 were put in to the computer and the position of europium metal was calculated in both conformations A and B, respectively.

The calculated shifts of each proton in the conformation A were then obtained on the basis of the position of europium metal which was determined as above. After confirming the good correlation between the calculated and the observed shifts, two possible shifts of the proton at position 4 in α - and β -orientations were calculated. The observed shift of proton at position 4 (1.81) is in good agreement with the calculated shift in β -orientation (1.96). In order to verify these results, an additional calculation was carried out in which the observed shift of proton at position 4 was added to the original input on an assumption that the proton is in β -orientation.⁹⁾ An excellent agreement was attained between the observed and the calculated shift (1.88). The same treatments were done on the conformation B with less satisfactory results.

These results led us to a conclusion that the proton at position 4 is in β -orientation and 2 exists mainly in the conformation A in solution phase in the presence of Eu(fod)₃.

Our attempt to determine the stereochemistry of 2 by means of NOE was not successful, however, a detailed study of NMR with the corresponding sulfoxides¹⁰⁾ reached the same conclusion, which will be reported elsewhere.

The method described here will find wide application to the determination of the stereochemistry of other complex molecules.

Acknowledgements The authors are grateful to Dr. K. Morita for his encouragement throughout this work. They are also indebted to Miss F. Kasahara for NMR measurements and to Mr. Y. Miyake for computational assistance.