

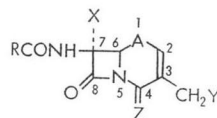
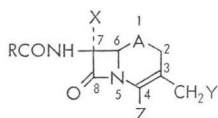
RELATIONSHIPS BETWEEN
STRUCTURE AND CARBONYL
STRETCHING FREQUENCIES OF THE
 β -LACTAM RING AND THE
7-ACYLAMINO GROUP IN 1-THIA-
AND 1-OXA-CEPHEM ANTIBIOTICS.
IMPORTANCE OF THE BENDING
ANGLE OF THE C(4)-N(5)-C(8)
FROM PLANE C(6)-N(5)-C(8)
IN THE β -LACTAM RING

Sir:

The useful antibacterial activity arising from the β -lactam ring in β -lactam antibiotics has attracted much attention¹⁾. The β -lactam IR stretching frequency (β -lactam $\nu_{C=O}$) has been regarded as an important index for investigating the structure-activity relationship of the β -lactam antibiotics²⁻⁵⁾. However, only a few studies have focused attention on the change in the β -lactam $\nu_{C=O}$ in the cases of replacement of the 7 α -hydrogen atom by a methoxy group and that of the sulfur by an oxygen atom at the 1-position of cephalo-

sporin antibiotics⁵⁾. In the preceding paper⁶⁾, we presented some β -lactam $\nu_{C=O}$ data related to these points, comparing them with ¹³C NMR and the pseudo-first-order rates of the 3-cephem β -lactam ring opening at pH 10 and 35°C, k_{obs} . Further detailed examinations of the β -lactam $\nu_{C=O}$ of several cephalosporin derivatives have revealed that the $\nu_{C=O}$ values can be correlated with the geometrical structure parameters obtained from X-ray analyses^{3,7-11)}. In order to explain these results theoretically, we also carried out CNDO/2 calculations for simple model compounds.

Table 1 lists the IR and NMR spectral data of the cephalosporin derivatives together with the available structural parameters^{3,7-11)}. The β -lactam $\nu_{C=O}$ shifts to a higher wavenumber with an increase in bending angle θ when the 1-sulfur atom is replaced by an oxygen atom, but to a lower wavenumber with a decrease in θ when the 7 α -hydrogen atom is substituted by a methoxy group. An important factor for these shifts is considered to be a resonance change such as



	A	X	Y	Z	R
1	O	H	Tet	COOCHPh ₂	Ph
2	S	H	Tet	COOCHPh ₂	Ph
3	O	OMe	Tet	COOCHPh ₂	Ph
4	S	OMe	Tet	COOCHPh ₂	Ph
9	O	H	Tet	COONa	CH ₂ Ph
10	S	H	Tet	COONa	CH ₂ Ph
11	O	OMe	Tet	COONa	CH ₂ Ph
12	S	OMe	Tet	COONa	CH ₂ Ph
13	O	H	H	COONa	CH ₂ Ph
14	S	H	H	COONa	CH ₂ Ph
15	O	OMe	H	COONa	CH ₂ Ph
16	S	OMe	H	COONa	CH ₂ Ph
17	O	H	Tet	COOCHPh ₂	CH ₂ Ph
18	S	H	Tet	COOCHPh ₂	CH ₂ Ph
19	O	OMe	Tet	COOCHPh ₂	CH ₂ Ph
20	S	OMe	Tet	COOCHPh ₂	CH ₂ Ph
25	S	H	H	COMe	CH ₂ OPh
26	S	OMe	H	COOMe ₃	CH ₂ Ph

	A	X	Y	Z	R
5	O	H	Tet		Ph
6	S	H	Tet		Ph
7	O	OMe	Tet		Ph
8	S	OMe	Tet		Ph
21	O	H	Tet		CH ₂ Ph
22	S	H	Tet		CH ₂ Ph
23	O	OMe	Tet		CH ₂ Ph
24	S	OMe	Tet		CH ₂ Ph
27	S	H	H		CH ₂ OPh
28	S	COOMe	H		CH ₂ OPh

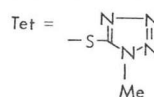


Table 1. IR and ^{13}C NMR spectral data and structural parameters of cephalosporin derivatives.^a

Compound No.	IR stretching frequency, $\nu_{\text{C=O}}$ (cm^{-1}) ^c						^{13}C NMR ^d		Structural parameters ^b				
	β -Lactam	7-Amide	Compound No.	β -Lactam	Compound No.	β -Lactam	Compound No.	$\delta_{\text{C}(8)}$	Compound No.	$\theta(^{\circ})$ ^e	$\phi_1(^{\circ})$ ^f	$\phi_2(^{\circ})$ ^g	Reference
1	1797.1	1676.0	9	1778.4	13	1769.1	17	168.5	17	29.6	138.7	-1.8	11)
2	1791.0	1678.0	10	1772.7	14	1763.7	18	165.1	25	20.5	118.9	2.8	7)
3	1787.1	1688.5	11	1772.0	15	1766.7	19	162.5	19	21.9	74.8	-12.2	8)
4	1781.5	1684.5	12	1768.0	16	1762.3	20	160.7	26	14.5	69.7	-7.6	9)
5	1793.5	1676.2					21	167.1					
6	1781.2	1675.6					22	163.9	27	6.7	98.4	-1.6	3)
7	1789.1	1685.6					23	162.1					
8	1778.0	1681.6					24	160.3	28^h	-3.0	71.8	-6.9	10)

^a Compounds **1~8** were kindly supplied by SENDO *et al.*¹⁷⁾

^b Data on salts are excluded from this list because strong interaction may exist in crystals.

^c IR spectra were recorded on a JASCO DS-403G grating spectrometer calibrated in a usual manner. Compounds **1~8** were dissolved in CHCl_3 at *ca.* 0.002 M (cell length 0.5 cm). Accuracies of $\nu_{\text{C=O}}$ are within $\pm 1.0 \text{ cm}^{-1}$. Data on compounds **9~16** are taken from reference 6.

^d ^{13}C NMR spectra were recorded and assigned as reported previously⁹⁾.

^e Bending angle of C(4) from plane C(6)N(5)C(8).

^f Torsion angle C(6)C(7)N(10)C(11).

^g Torsion angle C(7)N(10)C(11)O(12).

^h Data for this molecule were used because of the lack of X-ray crystallographic data on appropriate analogous compounds.

Table 2. Bond lengths (Å), bond angles ($^{\circ}$)^{8,7-11,13-15} and model molecules used in CNDO/2 calculations.

Geometry ^a		Y, X, B	Geometry
	$R_{N(1)-C(2)}$ 1.48	H	R_{C-H} 1.0
	$R_{N(1)-C(4)}$ 1.38	Me	R_{N-C} 1.45
	$R_{C(2)-O(3)}$ 1.538		R_{C-H} 1.0
	$R_{C(3)-O(4)}$ 1.55	CH=CH ₂	R_{N-C} 1.42
	$R_{C(4)=O}$ 1.21		$R_{C=C}$ 1.38
			R_{C-H} 1.1
		OMe	R_{C-O} 1.43
		SMe	R_{C-S} 1.82
		SCH=CH ₂	R_{C-S} 1.82
			R_{C-S} 1.80

Geometry ^a	Bond Length (Å)	Bond Angle ($^{\circ}$)
	$R_{C(2)-C(4)}$ 1.538	$\angle C(2)N(1)C(4)$ 95.0
	$R_{C(2)-C(4)}$ 1.38	$\angle C(2)C(3)C(4)$ 86.1
	$R_{C(2)-O(3)}$ 1.538	$\angle C(3)C(4)N(1)$ 91.1
	$R_{C(3)-O(4)}$ 1.55	$\angle N(1)C(2)C(3)$ 87.7

Y:^b Me, CH=CH₂ R_{C(4)=O} 1.21

X:^c H, OMe

B:^d H, OMe, SMe, SCH=CH₂

Model molecules:

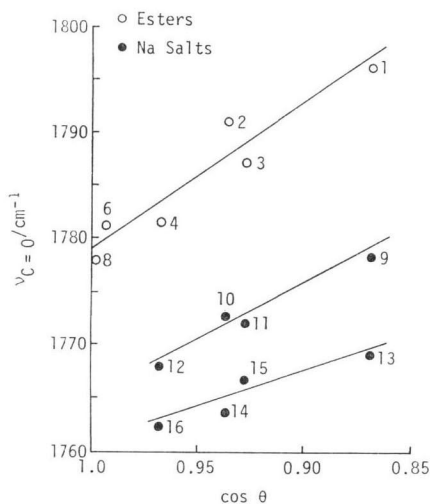
(I)

(II)

(III)

(IV)

- ^a The assumptions were made that all atoms of the β -lactam ring lie on the same plane and that the atoms connected to the β -lactam ring are located in the bisecting plane of the respective endocyclic bond angle.
- ^b The H_a atom of the Me group is placed in the bisecting plane of angle C(2)N(1)C(4), and the plane of the CH=CH₂ group is perpendicular to the bisecting plane.
- ^c Torsion angle C(4)C(3)CO was adopted as the one-half value of the dihedral angle between C(4)C(3)O and HC(3)O, and the geometry of the methyl moiety was assumed to be of the exact staggered form.
- ^d Torsion angles N(1)C(2)OC and N(1)C(2)SC were adopted as the one-half value of the dihedral angle between N(1)C(2)B and HC(2)B, the geometries of Me moieties of the OMe and SMe groups were assumed to be the exact staggered forms, and the torsion angle C(2)SCC of the SCH=CH₂ group was assumed to be equal to 0 $^{\circ}$.

Fig. 1. Relationships between β -lactam $\nu_{C=O}$ and $\cos \theta$.

$\text{O}=\text{N} \leftrightarrow \text{O}^-\text{N}^+$; the polar structure may be suppressed if θ increases. The increase in θ strengthens the double-bond character of the β -lactam

carbonyl group, causing a shift to a higher wavenumber of $\nu_{C=O}$. Since an excellent linear relationship (correlation coefficient, $r=1.00$) was found between $\cos \theta$ and the π -bond order of the β -lactam C=O bond obtained by the CNDO/2 calculation in the model molecule (I) shown in Table 2, the experimental $\nu_{C=O}$ values were plotted against $\cos \theta$. As shown in Fig. 1, the plots give good linear relationships. This suggests that the effect of the change in θ is more important than any other electronic effect due to an atom at the 1-position, a 7 α -methoxy group, and a Δ^8 double bond.

We found that the substitution of the 7 α -hydrogen atom by a methoxy group is attended by a decrease in torsion angle ϕ_1 . This may be ascribed to a decrease in θ in the 7 α -methoxy-substituted compounds, because the repulsion increases between a 7 β -amide group and an atom at the 1-position, causing transformation of the six-membered ring. This repulsion influences the geometry of the 7 β -amide group. As expected, the amide $\nu_{C=O}$ shifts to a higher wavenumber with

Table 3. Bond energies of C=O bond ($E_{C=O}$) and π -electron densities on the carbon atom of C=O bond (D_π) by CNDO/2 calculations in model molecules (I)~(IV).

Compound	$E_{C=O}$ (I) a.v.	$E_{C=O}$ (II) a.v.	$E_{C=O}$ (III) a.v.	$E_{C=O}$ (IV) a.v.	Compound	D_π (I)	D_π (II)	D_π (III)	D_π (IV)
1	1.60631	1.60805	1.60805	1.60568	17	0.79532	0.79802	0.79802	0.79933
2	1.60438	1.60643	1.60643	1.60414	18	0.79661	0.79988	0.79988	0.80185
3	1.60456	1.60667	1.60249	1.60089	19	0.79618	0.79970	0.80767	0.80780
4	1.60335	1.60535	1.60128	1.59947	20	0.79688	0.79993	0.80810	0.80948
6	1.60249	1.60249	1.60249	1.60285	22	0.79699	0.79699	0.79699	0.79969
8	1.60213	1.60213	1.59829	1.59858	24	0.79657	0.79657	0.80459	0.80658
r^a	0.96	0.89	0.95	0.86		0.70	0.01	0.75	0.83

^a Correlation coefficient of relationships between $E_{C=O}^{1/2}$ and β -lactam $\nu_{C=O}$ and D_π and δ_C of the corresponding compounds shown in Table 1.

increasing torsion angle $|\phi_2|$, when the 7α -hydrogen atom is substituted by a methoxy group. The increase in $|\phi_2|$ suppresses the resonance in the amide moiety, and therefore strengthens the double-bond character of the amide C=O.

The CNDO/2 calculations were carried out using the program of POPLE and BEVERIDGE¹²⁾. On the basis of the available electron-diffraction and X-ray analysis data on analogous compounds^{8,7~11,13~15)}, we adopted the geometries of model molecules (I)~(IV) shown in Table 2. For the calculations for molecules (I)~(IV), the θ , the θ and Y, the θ , Y, and X, and the θ , Y, X, and B listed in Table 1 were taken into account, respectively; here, Y is CH=CH₂ for **1**~**4** and CH₃ for **6** and **8**; X is H for **1**, **2**, and **6** and OCH₃ for **3**, **4** and **8**; and B is OCH₃ for **1** and **3**, SCH₃ for **2** and **4**, and SCH=CH₂ for **6** and **8**. The $E_{C=O}$ and D_π values obtained from the CNDO/2 calculations are given in Table 3, where $E_{C=O}$ is the bond energy of the C=O bond and D_π is the π -electron density on the carbon atom of the C=O bond. When the potential energy is represented by the Morse function, the force constant is proportional to the dissociation energy. Because the dissociation energy of the C=O bond is primarily proportional to the $E_{C=O}$, the $E_{C=O}^{1/2}$ is proportional to the $\nu_{C=O}$. According to POPLE's theory¹⁶⁾, the ¹³C chemical shift, δ_C , is primarily proportional to the π -electron density. Thus, regression analysis was carried out between the β -lactam $\nu_{C=O}$ and $E_{C=O}^{1/2}$ values and between the δ_C of C(8) and D_π values. The correlation coefficients, r , obtained are given in Table 3. The r values of the β -lactam $\nu_{C=O}$ vs. $E_{C=O}^{1/2}$ correlations are more than 0.86 for all model molecules (I)~(IV). This suggests theoretically that the change

in β -lactam $\nu_{C=O}$ is primarily governed by θ , as pointed out experimentally above. However, the r values of the δ_C vs. D_π correlations are respectively 0.70, 0.01, 0.75 and 0.83 for model molecules (I)~(IV). This suggests that the electronic effects due to the X and B moieties are of importance in this case. These results should be useful when considering the antibacterial reactivity of β -lactam ring in cephem derivatives⁹⁾.

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