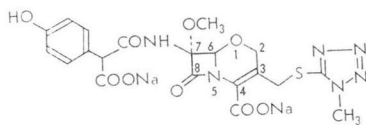


STRUCTURE-REACTIVITY
RELATIONSHIPS OF CEPHEM
ANALOGS STUDIED BY CARBON-13
NMR AND IR SPECTROSCOPIES.
REPLACEMENT EFFECTS OF SULFUR
WITH OXYGEN OR METHYLENE
AT THE 1-POSITION AND
INTRODUCTION EFFECTS OF
7 α -METHOXY GROUP

Sir:

In a series of ^{13}C NMR studies on structure-reactivity relationships of cephalosporin antibiotics,¹⁻³⁾ we have already reported the effects of the 3-methylene and 7-acylamino substituents on the ^{13}C NMR chemical shifts, $\delta(\text{C-3})$, $\delta(\text{C-4})$, $\delta(\text{CONH})$, and $\Delta\delta(4-3)[\delta(\text{C-4})-\delta(\text{C-3})]$ and also good correlations of the δ values with the reactivity. In connection with the high antibacterial activity exhibited by latamoxef disodium **1**,⁴⁻⁶⁾ we investigated the effects of its substituents on the reactivity of the β -lactam ring, which is known to be an important factor affecting the antibacterial activity. Here we wish to report the relationships between the structure and the reactivity, which is expressed by the pseudo-first-order rate constants (k_{obs}) of the β -lactam cleavage and interpreted in terms of the bond character around the β -lactam moiety estimated by using δ values as well as IR stretching frequencies of the β -lactam carbonyl (β -lactam $\nu_{\text{C=O}}$).



1 Latamoxef disodium

The δ and β -lactam $\nu_{\text{C=O}}$ values observed for cephem analogs **2a** ~ **12a** and the δ value for the corresponding benzhydryl esters **2b** ~ **4b**, **6b** ~ **11b** are compared in Table 1 with k_{obs} determined for **2a** ~ **12a** at pH 10.0 and 35.0°C. Before discussing the substituent effects upon δ and k_{obs} , alterations in molecular geometry should be taken into account. The X-ray data of **13**,⁷⁾ **14**,⁸⁾ **9b**,⁹⁾ and **11b**¹⁰⁾ (see Table 2) suggest that replacement of the sulfur atom with an oxygen atom increases the pyramidal structure of the lactam nitrogen atom (larger r) which results in diminishing the amide resonance¹¹⁾ described

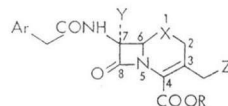
below. The replacement also seems to reduce the torsion angle ϕ between the carboxyl and C₃-



C₄ olefin groups. The X-ray data also suggest that introduction of the 7 α -methoxy group results in somewhat restoring a planar structure of the nitrogen atom. Although X-ray data of 1-carbacephem is not available yet, its geometry can be reasonably assumed to be similar to that of 1-oxacephem.

Since these geometrical alterations were anticipated to have a significant influence on the electron distribution, the cephem analogs were classified as A (**2a** ~ **5a**, **2b** ~ **4b**), B (**6ab**, **7ab**), C (**8ab**, **9ab**), D (**10ab**, **11ab**), and E (**12a**), according to X and Y. In fact, the $\delta(\text{C-8})$ values shown in Table 1 are characteristic to each of these classes. The negligible effect of Z upon $\delta(\text{C-8})$ of A (X=S, Y=H; 165.3 ppm) and the β -effect of the 7 α -methoxy group on that of B (X=S, Y=OCH₃; 161.1 ppm) have been already discussed by PASCHAL *et al.*¹²⁾ The $\delta(\text{C-8})$ of C (X=O, Y=H) is shifted lower contrary to the expectation from the γ -anti effect of an oxygen atom on the carbonyl carbon and has an intermediate value (169.0 ppm) between 174.9 ppm for penicillins and 165.1 ppm for cephalosporins,¹³⁾ which may be explained by the increase in the pyramidal structure of the lactam nitrogen atom. Also, upfield shifts in $\delta(\text{C-8})$ of B (X=S, Y=OCH₃; 161.1 ppm) and D (X=O, Y=OCH₃; 163.1 ppm) may have arisen from the flattening effect of the 7 α -methoxy group in addition to the β -effect described above.

The parallel arrows in Fig. 1 suggest that a good linear correlation of $\log k_{\text{obs}}$ with $\Delta\delta(4-3)$, similar to that for cepheids **2a** ~ **5a** with variation of Z, probably exists in every class of cephem analogs **6a** ~ **11a**. Analogous relationships also exist among the corresponding benzhydryl esters, though $\Delta\delta(4-3)$ take negative values. Although the trivial effect of the introduction of the remote 7 α -methoxy group upon $\Delta\delta(4-3)$ is reasonable, its insignificant effect upon k_{obs} is rather astonishing when the decrease in the r value for the 7 α -methoxy derivatives **14** and **11b** is taken into account. Some increment in k_{obs} ascribable to probable modification of the transition state in the alkaline hydrolysis¹⁴⁾ by the 7 α -methoxy group

Table I. ^{13}C NMR,^{a, b)} IR^{c)} and kinetic^{d)} parameters of β -cephem analogs.

Compound No.	Substituents					δ (ppm)				$\Delta\delta(4-3)$ (ppm)	β -Lactam $\nu_{\text{C=O}}$ (cm^{-1})	$k_{\text{obs}} \times 10^2$ (h^{-1})
	R	Ar	X	Y	Z	C-3	C-4	C-8	4-COOR			
2a	Na	Ph	S	H	H	123.1	127.4	165.1	170.7	4.3	1763.7	1.36
2b	CHPh ₂					133.6	121.6	164.8	161.0	-12.0		
3a	Na	Ph	S	H	TTZ ^{e)}	118.9	131.8	165.4	168.5	12.9	1772.7	9.21
3b	CHPh ₂					128.6	124.7	165.1	160.6	-3.9		
4a	Na	Th ^{f)}	S	H	OAc	117.3	132.4	165.5	169.0	15.1	1771.6	11.1
4b	CHPh ₂					126.3	124.9	164.9	160.5	-1.4		
5a	—	Th ^{f)}	S	H	C ₆ H ₅ N ⁺	113.0	136.1	165.2	167.7	23.1	1777.9	47.3
6a	Na	Ph	S	OCH ₃	H	124.0	127.6	161.0	170.3	3.6	1762.3	1.43
6b	CHPh ₂					137.6	121.7	160.6	160.8	-15.9		
7a	Na	Ph	S	OCH ₃	TTZ ^{e)}	119.7	132.0	161.2	168.1	12.3	1768.0	13.04
7b	CHPh ₂					131.5	124.7	160.7	160.1	-6.8		
8a	Na	Ph	O	H	H	128.7	125.0	169.0	169.9	-3.7	1769.1	3.16
8b	CHPh ₂					137.7	119.1	168.2	160.1	-18.6		
9a	Na	Ph	O	H	TTZ ^{e)}	124.9	129.2	169.0	167.6	4.3	1778.4	17.99
9b	CHPh ₂					134.5	122.0	168.5	159.8	-12.5		
10a	Na	Ph	O	OCH ₃	H	127.9	125.4	163.0	169.3	-2.5	1766.7	3.46
10b	CHPh ₂					137.7	119.3	162.5	159.8	-18.4		
11a	Na	Ph	O	OCH ₃	TTZ ^{e)}	124.4	129.6	163.1	167.1	5.2	1772.0	19.20
11b	CHPh ₂					134.1	122.3	162.5	159.3	-11.8		
12a	Na	Ph	CH ₂	H	TTZ ^{e)}	123.7	130.3	166.5	168.9	6.6	1756.0	26.54

a) ^{13}C NMR signals were assigned by various methods reported previously.¹⁾ Detailed spectral data with full signal assignments will be reported in our full paper.

b) ^{13}C NMR spectra for sodium salts **2a**~**12a** and esters **2b**~**4b**, **6b**~**11b** were recorded on a Varian XL-100-12A FT NMR spectrometer at 25.16 MHz in D₂O (internal dioxane reference, δ 67.4) and (CD₃)₂SO (internal TMS reference, δ 0.0), respectively, at ordinary probe temperature (30°C) using about 0.1 mmole/ml solutions in 5-mm spinning tubes. Typical FT NMR measurement parameters are: spectral width, 6016 Hz; pulse width, 7 μ s (flipping angle 17°); acquisition time, 0.8 s; number of data points, 9625.

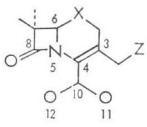
c) IR spectra were recorded using about 0.2 mmole/ml (CH₃)₂SO solutions and calibrated for the rotational bands of the vapor.

d) The pseudo-first-order rate constants of β -lactam hydrolysis at pH 10.0 and 35.0°C were determined by following the loss of the UV absorbance at ca. 260 nm using a Hitachi UV 320 automatic recording spectrometer.

e) TTZ: 1-methyl-1*H*-tetrazol-5-yl-thio.

f) Th: 2-thienyl.

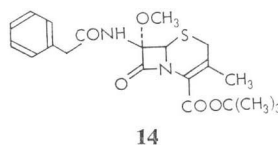
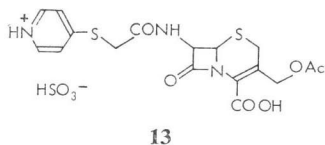
Table 2. Geometrical parameters of cephem analogs.

	Compound	13 ^{d)}	14 ^{b)}	9b ^{a)}	11b ¹⁰⁾
	$r^{a)}$ (Å)	0.22	0.15	0.30	0.22
	$\phi_1^{b)}$ (°)	-38.9	-46.7	5.8	7.6
	$\phi_2^{c)}$ (°)	-33.2	-37.2	4.4	1.9

^{a)} Distance of N(5) from C(4)-C(6)-C(8) plane.

^{b)} Torsion angle [C(3)-C(4)-C(10)-O(11)].

^{c)} Torsion angle [C(5)-C(4)-C(10)-O(12)].

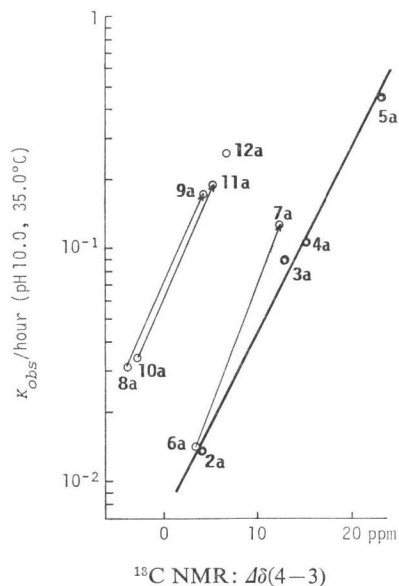


has been proposed.¹⁵⁾ It is interesting that although replacement of the sulfur atom with an oxygen atom augments k_{obs} , it reduces $\Delta\delta(4-3)$, contrary to the expectation from the effect of the substituent Z. This apparent discrepancy may be explained on the grounds that the k_{obs} value is mainly concerned with the pyramidal structure of the β -lactam nitrogen atom, whereas the $\Delta\delta(4-3)$ value is affected by the electronic effect* of the oxygen atom at the 1-position as well as a probable increase in the resonance between carboxyl and C₃-C₄ olefin groups in addition to the pyramidal structure of the nitrogen atom.

Interestingly, a good linear relationship between $\delta(\text{COO}^-)$ and $\log k_{obs}$ is observed (Fig. 2), whereas $\delta(\text{COOCHPh}_2)$ values remain without meaningful alteration.

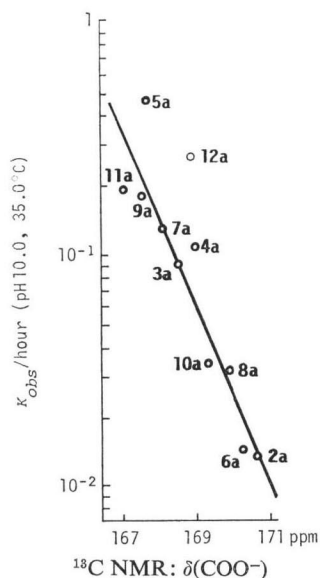
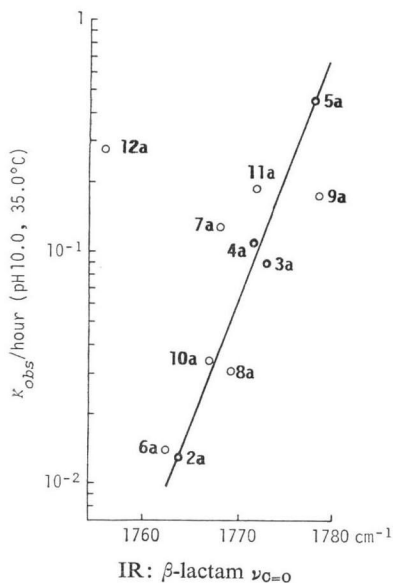
An excellent linear correlation of $\log k_{obs}$ with β -lactam $\nu_{\text{C}=\text{O}}$ is observed for cephems **2a**~**5a**, which vary in Z as shown in Fig. 3. For each class of cephem analogs, a similar correlation to that described above appears to exist. Higher and lower frequency shifts of β -lactam $\nu_{\text{C}=\text{O}}$ upon replacement of the sulfur atom with an oxygen and introduction of the 7 α -methoxy group, respectively, coincide with the results in other reports.^{15,17,18)} A good correlation of the β -lactam $\nu_{\text{C}=\text{O}}$ with the bending angle θ of the C₄-

* SENDA *et al.*¹⁰⁾ have reported that the β - and γ -effects of an oxygen atom on olefinic carbons in 5,6-dihydro-2H-pyran (-0.2 and -2.7 ppm, respectively) are different from those in 2-cyclohexenol (-3.6 and +3.3 ppm, respectively), probably because of configurational differences. This fact may clarify in part the unexpected effect of the replacement of the 1-position atom upon $\delta(4-3)$.

Fig. 1. $\log k_{obs}$ vs. $\Delta\delta(4-3)$ values in ¹³C NMR.

N₅ bond from the plane of C₆-N₅-C₈, is reported in the accompanying communication.¹⁵⁾ Although the lowest β -lactam $\nu_{\text{C}=\text{O}}$ was recorded for **12a**, it showed the highest k_{obs} , which suggests that the electronic effect of a hetero atom at the 1-position can not be negligible in determining the β -lactam $\nu_{\text{C}=\text{O}}$ and that k_{obs} may be mainly influenced by the pyramidal structure of the nitrogen atom.

We conclude that: 1) the pyramidal structure of the β -lactam nitrogen atom enforced by X primarily enhances the reactivity of the β -lactam ring, although the electronic effect of X is not negligible; 2) the 7 α -methoxy group has little

Fig. 2. Log k_{obs} vs. $\delta(\text{COO}^-)$ values in ^{13}C NMR.Fig. 3. Log k_{obs} vs. β -lactam $\nu_{\text{C=O}}$ values.

effect on the reactivity; 3) an electro-negative Z significantly increases the reactivity; 4) $\Delta\delta(4-3)$ is a good index for the reactivity of the β -lactam ring on Z variation after classification of cephem analogs according to X and Y, because it is affected not only by the inductive effect of Z but also by the size and the electronic properties of X; 5) β -lactam $\nu_{\text{C=O}}$ is a rough measure for changes in the reactivity on X and Z variations among 1-thia- and 1-oxacephems, because it

appears to reflect mainly the pyramidal structure of the β -lactam nitrogen atom and the inductive effect of Z.

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