NMR STUDIES OF PENICILLINS AND CEPHALOSPORINS. IV.[1] 7-ACYLAMINO SUBSTITUENT EFFECT ON STRUCTURE-REACTIVITY RELATIONSHIP OF CEPHALOSPORINS STUDIED BY CARBON-13 NMR SPECTROSCOPY

Sir:

In the preceding paper[1], we reported that the differences in ^{13}C NMR chemical shifts, δ, between C-4 and C-3, $\Delta\delta$(4–3), values of cephalosporins may be used as good reactivity indices for C-3 methylene substituent effects in both Na-salts and esters. It is well known that C-7 acylamino substituents have a great influence on antibacterial activities of cephalosporins[2]. They are considered to have some effects on the reactivities of the compounds also, although it has been suggested that C-7 acylamino substituents do not significantly affect the reactivity of the β-lactam ring[3,4]. As a result of an NMR study, PASCHAL *et al.*[5] described that the δ(C-8) and δ (N-5) values are essentially insensitive to the variations in the 7-acylamino moiety. By detailed examinations of 7-acylamino substituent effects on the ^{13}C NMR spectra of cephalosporins, we found that the δ(CONH) values correlate with the rate constants k_{OH} for the OH^--catalyzed degradations[4]. We report our results here.

The ^{13}C spectral parameters of sodium cephalosporanates (Y=$OCOCH_3$) and deacetoxycephalosporanates (Y=H) having a variety of 7β-acylamino substituents (XCONH) are listed in Table 1, which also includes data reported in the reference[5]. The ^{13}C signals were assigned according to the methods reported previously[5~9].

First, we plotted each δ(C-8) and $\Delta\delta$(4–3) against δ(CONH) observed for the deacetoxycephalosporanates (**1**~**9**) as shown in Fig. 1; similar plots for the cephalosporanates (**10**~**20**) are shown in Fig. 2. Although the $\Delta\delta$(4–3) and the δ(C-8) values changed only slightly with a change in the 7-acylamino substituents, each parameter exhibited a good linear relationship with the δ(CONH) value. In ^{13}C NMR spectra of *N*-methylamides, $RCONHCH_3$, a good linear relationship between the δ(CONH) values and the inductive σ_I constants of R has been found[10,11]. In the cephalosporins examined here, a similar correlation between the δ(CONH) values and the σ_I constants of X appears to exist at least partially (Fig. 3). This suggests that the δ(C-8) values should also be correlated with the σ_I values of X. Compounds having 7-acylamino groups other than RCH_2CONH, *e.g.*, HCONH, CH_3CONH, *p*-R-PhCONH, and Ft, appear not quite to fit into the correlations, which might be due to different molecular conformations including the 3-cephem-ring geometry.

The log k_{OH} values for the OH^--catalyzed degradation of cephalosporins reported by YAMANA and TSUJI[4] were found to correlate better with the δ(CONH) values of both cephalosporanate series

Fig. 1. δ(C-8) and $\Delta\delta$(4–3) *vs.* δ(CONH) for the deacetoxycephalosporanate series.

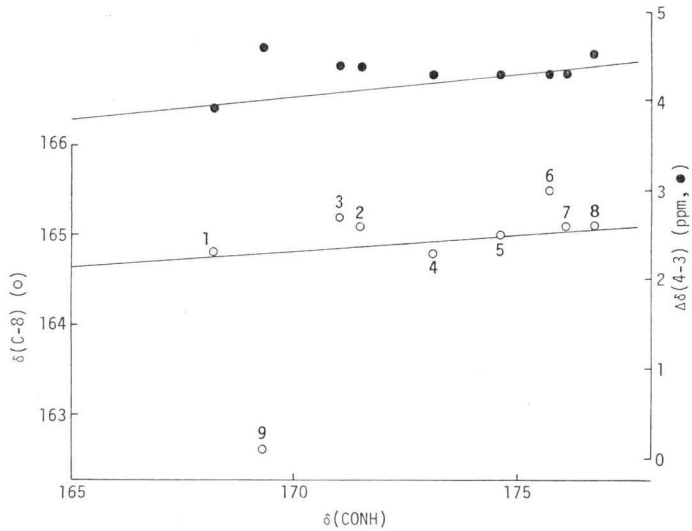
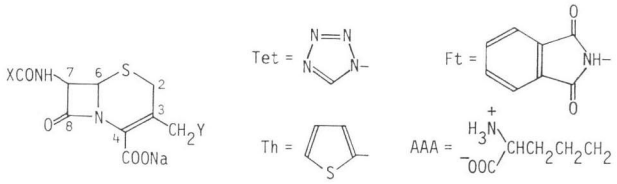


Table 1. Carbon-13 NMR spectral data on cephalosporins.[a,b]

Compound No.	Substituents		δ					δ(4–3) (ppm)	Reference
	X	Y	C-3	C-4	C-8	CONH	4-COO⁻		
1	$TetCH_2$	H	123.6	127.5	164.8	168.2	170.7	3.9	This work
2	Ph	H	123.2	127.6	165.1	171.5	170.7	4.4	This work
3	*p*-CH_3Ph	H	123.3	127.7	165.2	171.0	170.7	4.4	This work
4	$PhOCH_2$	H	123.1 123.4	127.4 127.6	164.8 164.7	173.1 172.3	170.8 170.4	4.3 4.2	This work 5)
5	$ThCH_2$	H	123.2	127.5	165.0	174.6	170.6	4.3	5)
6	CH_3	H	123.1	127.4	165.5	175.7	170.8	4.3	This work
7	$PhCH_2$	H	123.1	127.4	165.1	176.1	170.8	4.3	This work
8[c]	$PhCH(NH_2)$	H	123.2 122.7	127.7 127.4	165.1 164.8	176.7 176.9	170.4 170.6	4.5 4.7	This work 5)
9	Ft (XCONH)	H	127.0	131.6	162.6	169.3	170.5	4.6	This work
10	H	$OCOCH_3$	117.1	132.3	165.5[d]	165.4[d]	169.1	15.2	5)
11	$TetCH_2$	$OCOCH_3$	117.2	132.3	165.1	168.2	169.2	15.1	5)
12	Ph	$OCOCH_3$	116.8	132.5	165.5	172.0	169.3	15.7	This work
13	*p*-Cl-Ph	$OCOCH_3$	116.9	132.5	165.5	170.6	169.3	15.6	This work
14	$PhOCH_2$	$OCOCH_3$	117.0	132.3	165.1	172.7	169.1	15.3	5)
15	$ThCH_2$	$OCOCH_3$	116.9	132.3	165.4	174.8	169.1	15.4	5)
16	CH_3	$OCOCH_3$	116.9	132.3	165.9	175.5	169.2	15.4	5)
17	$PhCH_2$	$OCOCH_3$	116.9	132.3	165.5	176.0	169.2	15.4	5)
18	PhCH(OH)	$OCOCH_3$	116.8	132.3	165.2	176.2	169.0	15.5	5)
19	AAA	$OCOCH_3$	116.9	132.3	165.7	177.3	169.3	15.4	5)
20[c,e]	$PhCH(NH_2)$	$OCOCH_3$							This work



[a] Detailed spectral data with full signal assignments will be reported in our full paper.

[b] ^{13}C NMR spectra were recorded on a Varian NV-14 FT NMR spectrometer at 15.087 MHz in D_2O at ordinary probe temperature (30°C) using about 0.1 mmole/ml solutions containing internal dioxan reference (δ 67.4) in 8-mm spinning tubes. Typical FT NMR measurement conditions are: spectral width, 3923 Hz; pulse width, 13 μs (flipping angle, 19°); acquisition time, 0.6 s; number of data points, 4820.

[c] Measured at pD>10, since the spectra of these compounds were affected by the ionization of NH_2 in the substituent X at pD<10. The spectra of the other compounds were measured at pD 4~7; they were not changed at pD>4.

[d] Assignments may be reversed.

[e] Not observable because this compound was rapidly degraded at high pD. For the plot in Fig. 4, we therefore used the same δ(CONH) value as that for compound **8**, because the δ(CONH) values only changed within 0.5 ppm when Y changed from H to $OCOCH_3$.

than the δ(C-8) values, which change only slightly from compound to compound. Apparent linear relationships were found in the two cephalosporin series, as shown in Fig. 4. Therefore, the δ (CONH) value may be used as a good index for the 7-acylamino substituent effect on the reactivity of cephalosporins. A shift of the δ(CONH) value to a lower field parallels an increased reactivity.

We are now extending this work to examining the effects of the 7-acylamino substituent in both

Fig. 2. δ(C-8) and $\Delta\delta$(4–3) *vs.* δ(CONH) for the cephalosporanate series.

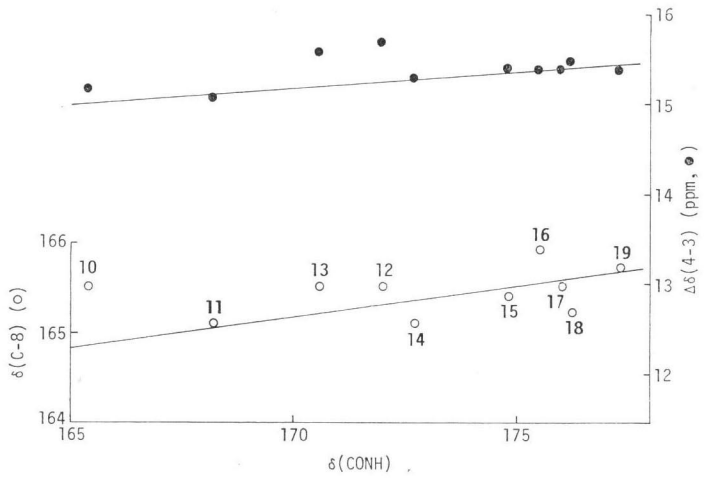


Fig. 3. δ(CONH) *vs.* σ_I[11].

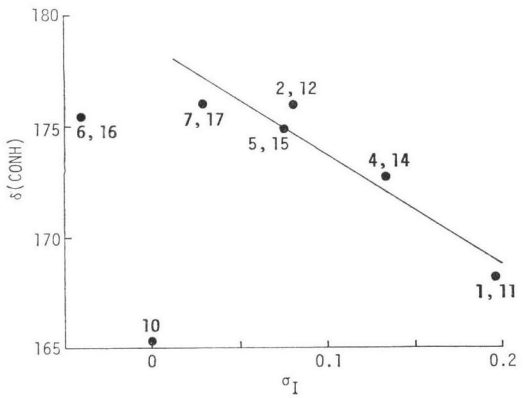
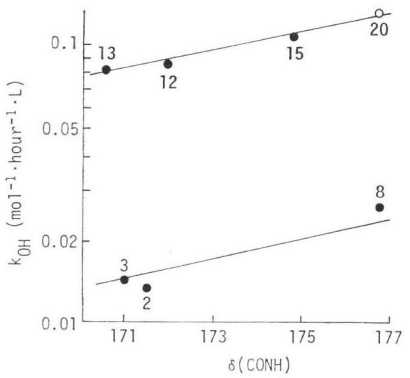


Fig. 4. Relationships between k_{OH} reported[4] and δ(CONH) (see footnote *e* in Table 1).



Na-salts and esters of penicillins and cephalosporins.

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References

1) NISHIKAWA, J. & K. TORI: NMR Studies of penicillins and cephalosporins. III. 3-Methylene substituent effect on structure-reactivity relationship of cephalosporins studied by carbon-13 NMR spectroscopy. J. Antibiotics 34: 1641～1644, 1981
2) FLYNN, E. H.: "Cephalosporins and Penicillins: Chemistry and Biology." Academic Press, New York, N. Y., 1972
3) INDELICATO, J. M.; T. T. NORVILAS, R. R. PFEIFFER, W. J. WHEELER & W. L. WILHAM: Substituent effects upon the base hydrolysis of penicillins and cephalosporins. Competitive intramolecular nucleophilic amino attack in cephalosporins. J. Med. Chem. 17: 523～527, 1974
4) YAMANA, T. & A. TSUJI: Comparative stability of cephalosporins in aqueous solution: kinetics and mechanisms of degradation. J. Pharm. Sci. 65: 1563～1574, 1976

5) PASCHAL, J.W.; D.E. DORMAN, P.R. SRINIVASAN & R. L. LICHTER: Nuclear magnetic resonance spectroscopy. Carbon-13 and nitrogen-15 spectra of the penicillins and cephalosporins. J. Org. Chem. 43: 2013~2016, 1978

6) MONDELLI, R. & P. VENTURA: ^{13}C Nuclear magnetic resonance of N-heterocycles. 3. ^{13}C Chemical shift assignments of the carbonyl groups in penicillins and cephalosporins. J. Chem. Soc., Perkin II 1977: 1749~1752, 1977

7) DEREPPE, J. M.; A. SCHANCK, B. COENE, C. MOREAU & M. VAN MEERSSCHE: Some features of the ^{13}C NMR of cephalosporins. Org. Magn. Resonance 11: 638~640, 1978

8) SCHANCK, A.; B. COENE, M. VAN MEERSSCHE & J. M. DEREPPE: Carbon-13 NMR of cephalosporins. Ibid. 12: 337~338, 1979

9) TORI, K.; J. NISHIKAWA & Y. TAKEUCHI: ^{13}C NMR spectra of cephalosporins. Signal assignments of free acids and esters. Tetrahedron Lett. 22: 2793~2796, 1981

10) DORIE, J.; J. P. GOUESNARD, B. MECHIN, N. NAULET & J. MARTIN: Applications of ^{15}N NMR spectroscopy to the study of unsymmetrically N-substituted amides and model peptide compounds. Org. Magn. Resonance 13: 126~131, 1980

11) EXNER, O.: A critical compilation of substituent constants. in "Correlation Analysis in Chemistry. Recent Advances." *Ed.* N. B. CHAPMAN & J. SHORTER, Chap. 10: 439~540, Plenum Press, New York, N.Y., 1978