

KINETIC COMPARISON OF ACID-CATALYZED INTRAMOLECULAR
REACTION BETWEEN
PENICILLIN AND CEPHALOSPORIN

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The rates of acid-catalyzed intramolecular degradation of ampicillin (1) and cephalexin (3) were assessed by specified kinetic treatment.

The susceptibility of penicillins to acid-catalyzed degradation is attributed not only to its structural instability due to the strained ring,¹ but also to the intramolecular attack of the side-chain amide on the β -lactam moiety.² The rate of cleavage of the β -lactam largely depends on the polar nature of the side chain.^{3,4} In spite of the structural similarity, cephalosporins are surprisingly stable to acid.⁵ The question now arises whether the stability of the β -lactam of cephalosporin molecules is due partially to the lack of neighboring group participation. In addition, a mechanism of the acid degradation of β -lactam antibiotics has not completely been understood as yet.

The present investigation was undertaken to evaluate kinetically the relative rates between intramolecularly and intermolecularly catalyzed degra-

dations, of both penicillins and cephalosporins. Degradations of a pair of ampicillin (1) and 6-aminopenicillanic acid (2) for penicillins and a pair of cephalexin (3) and 7-aminodeacetoxycephalosporanic acid (4) for cephalosporins were carried out for the present purpose. 1 is known to be one of acid-stable penicillins.^{3,6} Neighboring group participation in 2 and 4 is structurally impossible.

The rates of degradation of each β -lactam compound in solutions of 5×10^{-3} M were measured at 35° in 2 N, 4 N, 6 N, and 8 N perchloric acid solutions. The aliquots of samples at suitable time intervals were neutralized with an alkali and analyzed by iodometric titration⁷ for 1 and 2 and by hydroxamic acid assay⁵ for 3 and 4. The pseudo-first-order rate constants are listed in Table 1. In all cases, increased acidity of the solution is reflected in the increase of the apparent rate constants, suggesting that protonation of β -lactam is apparently responsible for the degradation rate.

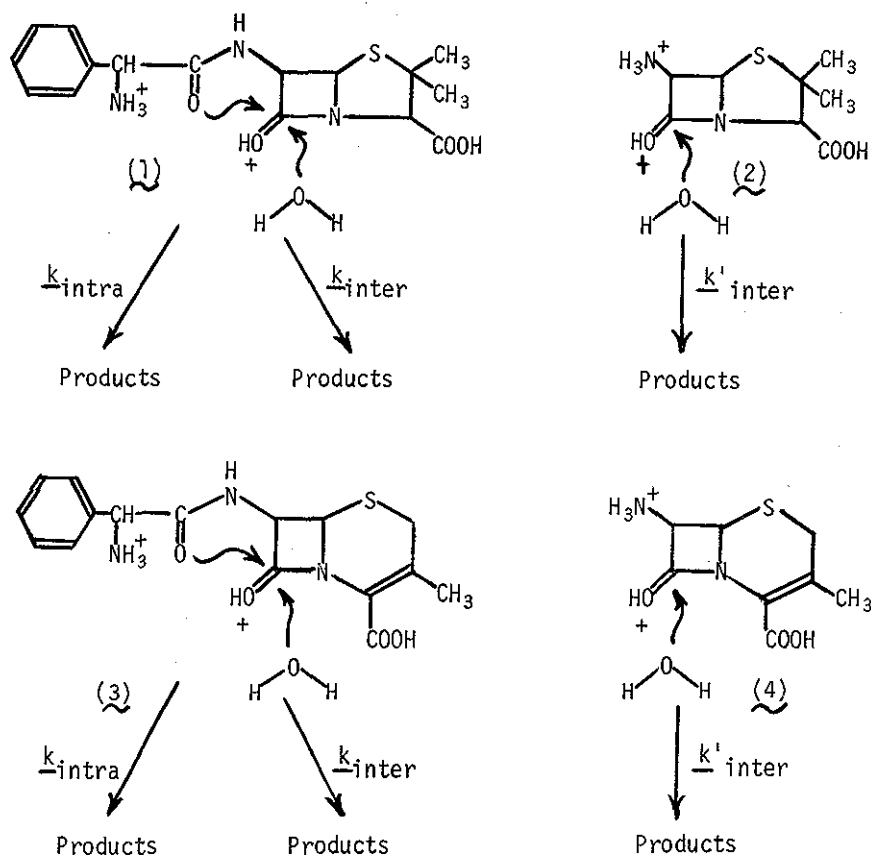
On this basis, together with our previous observations^{4,5} including neighboring amide group participation in acid hydrolysis of diamide derivatives,⁸

Table 1 Pseudo-first-order Rate Constants for the Degradation of β -Lactam Antibiotics in Perchloric Acid Solution at 35°

<u>HClO₄</u> <u>N</u>	<u>a</u> H ₂ O*	Pseudo-first-order rate constant, <u>k_{app}</u> , hr ⁻¹			
		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>
2	0.906	2.54	0.654	0.280×10^{-2}	0.240×10^{-2}
4	0.733	10.6	1.70	0.750×10^{-2}	0.410×10^{-2}
6	0.468	93.2	4.03	2.25×10^{-2}	0.720×10^{-2}
8	0.193	—	13.8	24.0×10^{-2}	1.35×10^{-2}

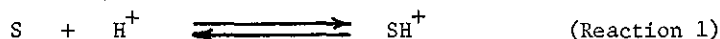
* Reference 10

it is proposed that the degradation of β -lactam antibiotics in acidic solution is characterized by two parallel reactions, one obeying the A2 mechanism and the other being the rate-determining intramolecularly catalyzed degradation of the protonated species. These processes can be illustrated as shown in Scheme I. These consist essentially of three reactions similar to those for ordinary

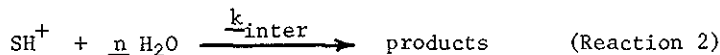


Scheme I Possible Pathways for the Acid Degradation of β -Lactam Antibiotics

amides.⁹ An equilibrium (Reaction 1) is set up rapidly:



followed by parallel slow reactions (Reaction 2 and Reaction 3):



where S and SH^+ are the starting and protonated β -lactam compounds, and k_{inter} and k_{intra} represent the rate constants of A2 and intramolecular reactions, respectively.

If it can be assumed that an acid-catalyzed intramolecular mechanism (Reaction 3) contains no water molecules covalently bonded in the transition state,⁸ the apparent first-order rate constant, k_{app} , of the β -lactam cleavage of 1 and 3 can be expressed as:

$$k_{\text{app}} = (k_{\text{inter}} a_{H_2O}^n + k_{\text{intra}}) f_{SH^+} \quad (\text{Eq. 1})$$

where a_{H_2O} represents water activity and f_{SH^+} is the protonization ratio.

For the degradation from which Reaction 3 can be excluded as expected for 2 and 4, the apparent first-order rate constant, k'_{app} , can be expressed as:

$$k'_{\text{app}} = k'_{\text{inter}} a_{H_2O}^n f'_{SH^+} \quad (\text{Eq. 2})$$

If a number of water molecules participating in the transition state of Reaction 2 and the ratio of protonation in the β -lactam moiety is assumed to be almost the same within a homologous series of β -lactam antibiotics, Eq. 3 can easily be derived from Eqs. 1 and 2 as:

$$\frac{k_{\text{app}}}{k'_{\text{app}}} = \frac{k_{\text{inter}}}{k'_{\text{inter}}} + \frac{k_{\text{intra}}}{k'_{\text{inter}}} \cdot \frac{1}{a_{H_2O}^n} \quad (\text{Eq. 3})$$

Thus, a plot of $k_{\text{app}}/k'_{\text{app}}$ vs. $1/a_{H_2O}^n$ should give a straight line with a slope of $k_{\text{inter}}/k'_{\text{inter}}$ and an intercept of $k_{\text{intra}}/k'_{\text{inter}}$. Figure 1 shows

such a plot for 1 vs. 2 and 3 vs. 4 by employing the average value of $\bar{n} = 3$ determined for acid hydrolysis of wide variety of amides.⁹ The respective plots show good linear relationship with slopes of 2.2 from a couple of 1 and 2 and 0.13 from 3 and 4, both intercepts exhibiting almost unity.

Although the present ideas on the kinetic assessment of relative rate of inter- and intra-molecular reactions were made under some simplified assumptions but widely accepted for the acid hydrolysis of amides,⁹ the results thus obtained are fairly consistent with the previous findings and discussions^{4,5,8} from our laboratory. One of these results⁴ gave the ratio of the

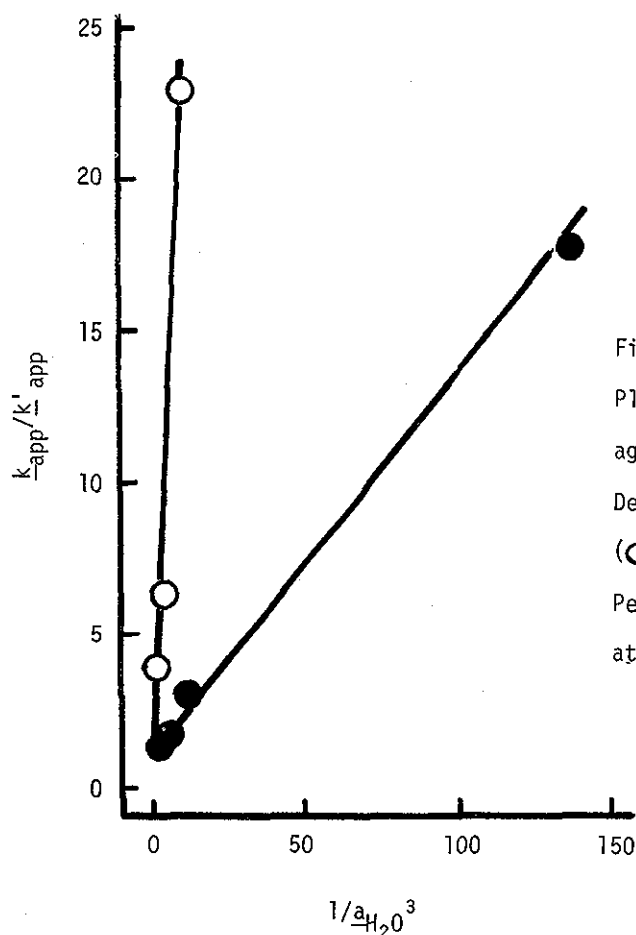


Figure 1
Plots of k_{app}/k'_{app}
against $1/a_{H_2O}^3$ for the
Degradation of 1 and 2
($\circ$) and 3 and 4 ($\bullet$) in
Perchloric Acid Solution
at 35°

rate of A2 reactions between penicillins and 2 to be 1.2, being in good agreement with the intercept of approximately unit in Fig. 1.

In conclusion, the magnitude of the slope of Fig. 1 suggests that 1 proceeds two times faster in intramolecular reaction than in A2 reaction, whereas 3 exclusively proceeds by A2 reaction, the intramolecular reaction being ten times slower.

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