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 x 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 titration[7] for 1 and 2 and by hydroxamic acid assay[5] 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.

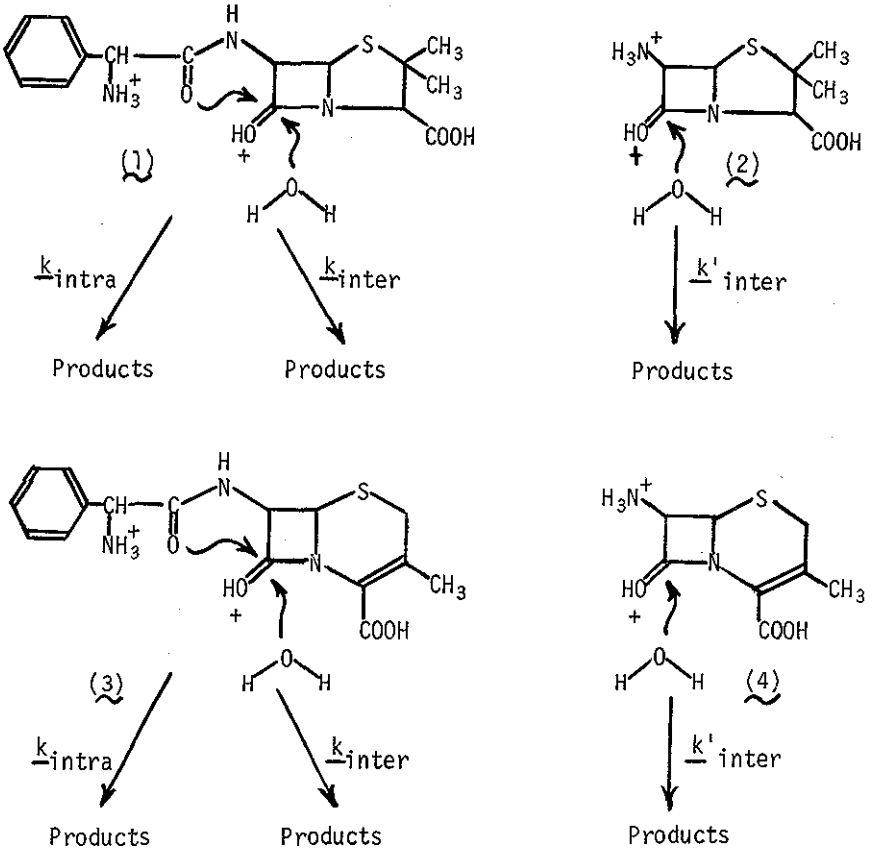
On this basis, together with our previous observations[4,5] including neighboring amide group participation in acid hydrolysis of diamide derivatives,[8]

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

$HClO_4$ N	$-a_{H_2O}$*	Pseudo-first-order rate constant, k_{app}, hr^{-1}			
		1	2	3	4
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 1 Possible Pathways for the Acid Degradation of β-Lactam Antibiotics

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

$$S + H^+ \rightleftharpoons SH^+ \qquad \text{(Reaction 1)}$$

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

$$SH^+ + \underline{n}\ H_2O \xrightarrow{\underline{k}_{inter}} \text{products} \qquad \text{(Reaction 2)}$$

$$SH^+ \xrightarrow{\underline{k}_{intra}} \text{products} \qquad \text{(Reaction 3)}$$

where S and SH^+ are the starting and protonated β-lactam compounds, and $\underline{k}_{inter}$ and $\underline{k}_{intra}$ 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 covelently bonded in the transition state[8], the apparent first-order rate constant, $\underline{k}_{app}$, of the β-lactam cleavage of 1 and 3 can be expressed as:

$$\underline{k}_{app} = (\underline{k}_{inter}\,\underline{a}_{H_2O}^{\underline{n}} + \underline{k}_{intra})\,\underline{f}_{SH^+} \qquad \text{(Eq. 1)}$$

where $\underline{a}_{H_2O}$ represents water activity and $\underline{f}_{SH^+}$ 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, $\underline{k'}_{app}$, can be expressed as:

$$\underline{k'}_{app} = \underline{k'}_{inter}\,\underline{a}_{H_2O}^{\underline{n}}\,\underline{f'}_{SH^+} \qquad \text{(Eq. 2)}$$

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:

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

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

such a plot for 1 vs. 2 and 3 vs. 4 by employing the average value of 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 results[4] gave the ratio of the

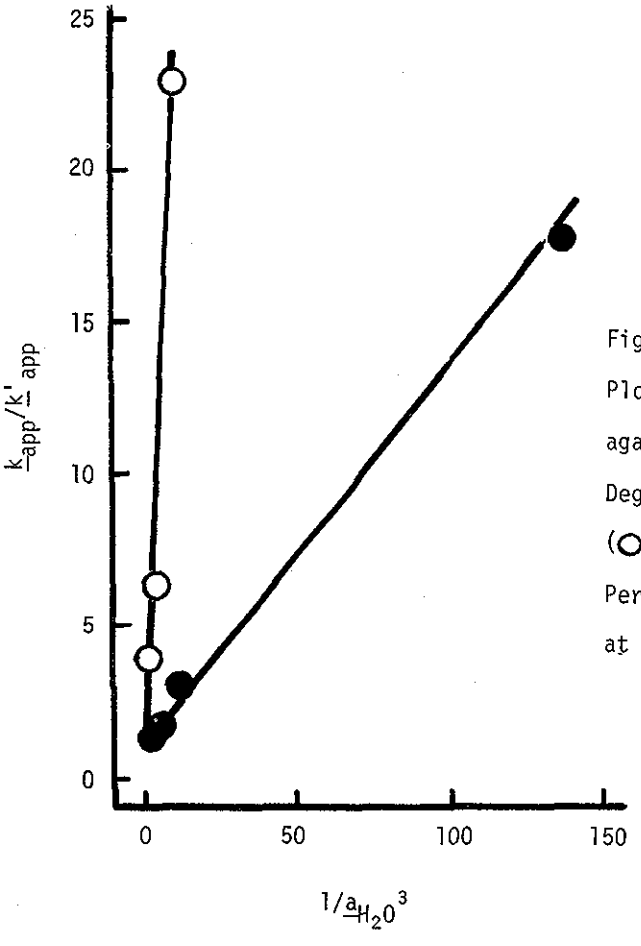


Figure 1
Plots of k_{app}/k'_{app} against $1/a_{H_2O}^3$ for the Degradation of 1 and 2 (○) and 3 and 4 (●) in Perchloric Acid Solution at 35°

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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