A Kinetic Oxymoron: Concentration-Dependent First-Order Rate Constants for Hydrolysis of Ceftazidime

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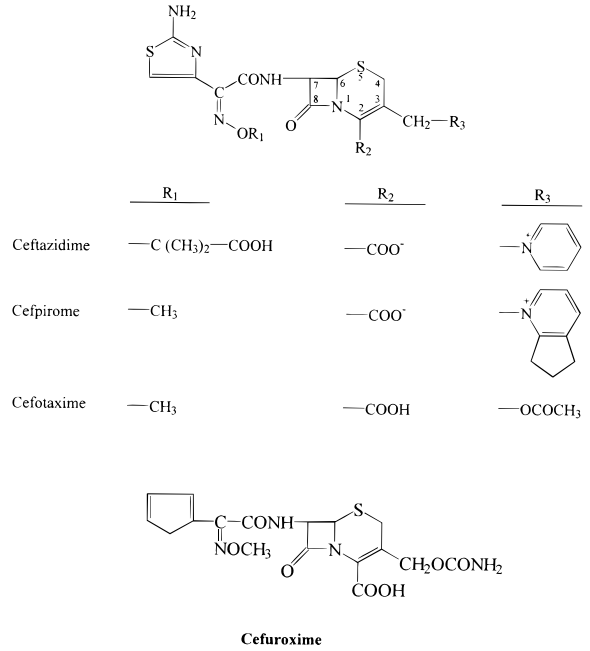
Abstract □ The influence of pH, temperature, and buffers on the hydrolysis of 10^{-4} M ceftazidime was previously reported. The pH–rate profiles showed that maximum stability occurred in the pH-independent region from 4.5 to 6.5. In the present study, hydrolysis rates of 0.031, 0.14, 0.25, and 0.35 M ceftazidime were measured at 30 and 65 °C, pH 5.5–6.2. The data were consistent with β-lactam hydrolysis and the rapid release of pyridine. The sum of the time-dependent concentrations of ceftazidime and pyridine provided mass balance. Simultaneous nonlinear regression for ceftazidime loss and pyridine formation provided similar rate constants (k) to those determined from first-order plots of ceftazidime loss. Although the loss of ceftazidime was first-order for each initial concentration, the k values increased as the initial concentrations increased. Plots of k versus initial concentration were linear with intercepts similar to the k values for 10^{-4} M solutions, thus implying that ceftazidime catalyzed its own degradation. At the pH of these studies ceftazidime exists as a base. The ceftazidime catalytic constant, calculated from the slope of the plot, was similar to that found for the general-base catalyst, HPO_4^{2-}. Therefore, it is feasible that ceftazidime also behaved as a intermolecular general-base catalyst. However, first-order plots exhibited excellent linearity even though the catalyst (ceftazidime) was consumed. This would require that the catalytic moieties on ceftazidime remained relatively constant throughout its hydrolysis. This hypothesis was shown to be consistent with literature reports which indicate that the general-base catalytic groups can remain relatively constant during cephalosporin hydrolysis.

The kinetics of dimerization of several aminopenicillins have been reported by Bundgaard.[1−3] Dimerization occurred via intermolecular nucleophilic attack by a side chain primary amine of one molecule on the β-lactam carbonyl carbon of a second. Storage of slightly alkaline, concentrated solutions of β-lactam antibiotics with side chain amines has resulted in further reaction to form polymers.[4−7] These polymers have been found to be antigenic and capable of inducing cellular immunity in animals.[5,6,8]

Ceftazidime is a semisynthetic, broad-spectrum cephalosporin with a primary amine on a thiazole ring (Scheme 1). While numerous dimerization and polymerization studies have been conducted with penicillins having primary amines, relatively few have been reported for aminocephalosporins. A dimer has been isolated from 50% w/v, pH 8.5, aqueous solutions of cefotaxime which has structural similarities to ceftazidime that include an aminothiazole (Scheme 1).[9]

Ceftazidime is clinically employed in aqueous solutions ranging from ∼10 to ∼280 mg/mL (∼0.02 M to ∼0.5 M) and pH values between ∼5 and ∼8.[10] Thus, clinical solutions of ceftazidime have all of the prerequisites for dimerization, i.e., high concentrations, alkaline pH, an amine, and a β-lactam. Although ceftazidime dimerization has not been reported, its potential for dimerization at clinically employed concentrations prompted the current investigation.



Scheme 1

Previous research in this laboratory has defined the influence of pH, temperature and buffers on the first-order hydrolysis of ceftazidime in dilute aqueous solutions.[11] Hydrolysis rate constants were pH-independent in the region 4.5−6.5. The goal of this research was to define the kinetics of ceftazidime degradation in the pH-independent region with concentrations within the clinically employed range.

Experimental Section

Materials—Ceftazidime pentahydrate was used as provided by SmithKline Beecham Pharmaceuticals (Philadelphia). All other chemicals were analytical or HPLC grade.

Ceftazidime HPLC Assays—The system consisted of a Waters M-510 solvent delivery module, a Waters M-481 variable wavelength detector, a Shimadzu C−R3A integrator, and a Rheodyne M-7125 manual injector. The injection volume was 20 μL. Chromatographic separations (Figure 1) were achieved on a

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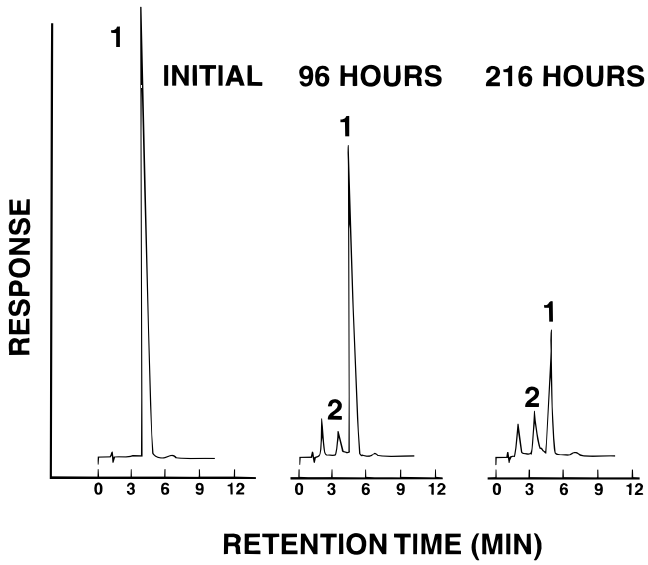


Figure 1—HPLC chromatograms as a function of time during hydrolysis of 0.35 M ceftazidime at 30 °C, pH 5.5–6.2. The retention time for ceftazidime is ~5.3 min (1) and that for pyridine is ~3.3 min (2). The other peaks were not identified.

Spherisorb C-6 column (5μm, 4.6-mm i.d. x 150 mm; Keystone Scientific Inc., State College, PA) at ambient temperature with a flow rate of 1.4 mL/min and UV detection at 258 nm. Mobile phases were filtered through a type HA, 0.45-μm membrane filter (Millipore Corporation) and deaerated under reduced pressure.

The quantitative separation of ceftazidime from its degradation products was achieved with a mobile phase consisting of aqueous 0.10 M acetic acid and 0.05 M sodium acetate with 6% (v/v) acetonitrile. The ceftazidime retention time was 5.3 min. Four linear calibration plots were constructed to accommodate the four initial concentrations. Reactions were diluted for analysis into the ranges (in M) 1.8×10^{-4} to 1.6×10^{-3}, 1.3×10^{-4} to 1.2×10^{-3}, 7.0×10^{-5} to 6.3×10^{-4}, and 1.5×10^{-5} to 1.4×10^{-4}. The coefficient of variation (CV) for ceftazidime analysis varied from 1.2 for the highest concentration range to 2 for the lowest concentration range. Recovery was 98 ± 3%.

Several methods were employed to ensure that assays were specific for ceftazidime in the presence of its degradation products. No residual peaks were found beneath the ceftazidime peak when reactions were allowed to proceed to completion. No deviations from linearity were observed in the first-order plots. Representative reactions were analyzed in duplicate with the mobile phase described above and a second mobile phase that provided a ceftazidime retention time of 7.2 min. This mobile phase consisted of aqueous 0.10 M acetic acid and 0.05 M sodium acetate with 4% (v/v) acetonitrile. The concentrations and first-order plots obtained for both methods were similar. Furthermore, as discussed in the Results, the first-order rate constants based on the formation of a degradation product (pyridine) agreed with those determined from ceftazidime loss.

Analysis of Pyridine in Reaction Solutions—The reaction solutions were found to acquire a characteristic pyridine odor as ceftazidime hydrolyzed. Pyridinium was found to be the best leaving group in a study which compared hydrolysis rates of 33 cephalosporins with various 3-methylene substituents.[12] Therefore, ceftazidime degradation was expected to release pyridine just as the hydrolysis of chemically similar cefpirome (Scheme 1) released 2,3-cylopentenopyridine.[13] Solutions were prepared to represent ceftazidime:pyridine ratios of 9:1, 5:5, and 2:8 and assayed by HPLC. The retention times for the ceftazidime and pyridine HPLC peaks in these mixtures agreed with those from the reactions (Figure 1). The molar absorptivity for ceftazidime at 258 nm is ~7 times greater than that for pyridine. Therefore, samples were more concentrated to assay pyridine relative to those for the ceftazidime assays. Reaction aliquots of 50 μL were added to 5 mL of water and assayed for pyridine. Linear calibration plots were constructed to assay these dilutions over the concentration range 0.43×10^{-3} to 4.72×10^{-3} M. The CV was 1.5 and recovery was 98 ± 1.5%.

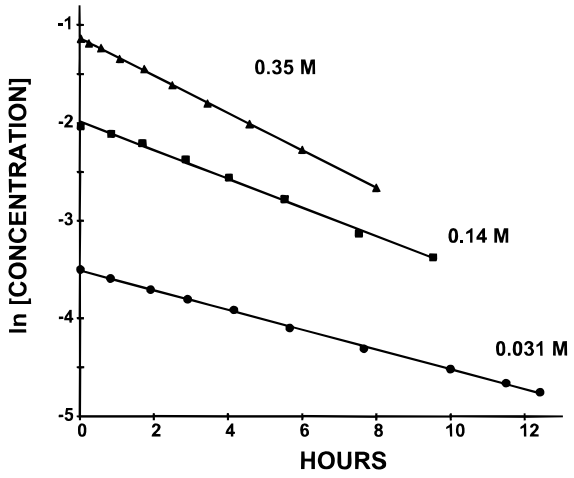


Figure 2—Typical first-order plots for loss of 0.35, 0.14, and 0.031 M ceftazidime in unbuffered aqueous solutions at 65 °C, pH 5.5–6.2.

In addition to the HPLC evidence, reactions in which 50 to 80% of the initial ceftazidime had degraded were freeze-dried. Part of the residue was dissolved in acetone and analyzed by GC/MS. The resulting mass spectrum matched that obtained with a pure sample of pyridine. The remaining residue was dissolved in D_2O, analyzed with proton nuclear magnetic resonance (NMR), and found to have peaks that were also obtained using pure pyridine.

Ceftazidime Hydrolysis Kinetics—The pH values for the reaction solutions were measured before and after each reaction at the experimental temperatures, 30 and 65 °C (stable to ±0.1 °C). The first-order hydrolysis rate constants of ceftazidime were previously shown to be pH-independent in the pH region of ~4.5 to ~6.5.[11] Aqueous solutions containing empirically determined concentrations of sodium hydroxide were prepared to facilitate dissolution and provide initial pH values of ~5.5 at the reaction temperatures for all initial ceftazidime concentrations. Following the reactions, the final pH values were determined to be 5.8−6.2.

Reactions were initiated by dissolving sufficient ceftazidime in 10 mL of the appropriate sodium hydroxide solution at 30 or 65 °C to provide initial concentrations of 0.031, 0.14, 0.25, or 0.35 M. A sample was removed as a function of time and cooled, and a 35 μL aliquot was diluted with 10 mL of water. Most dilutions were assayed within 12 h after sampling. No loss of ceftazidime was detected by HPLC when these dilutions were stored for 24 h in the refrigerator.

Buffers were not employed for three reasons. It was possible to maintain the pH within the pH-independent region without the addition of buffers. Previous studies have shown that ceftazidime hydrolysis is catalyzed by buffers.[11] The ceftazidime solutions were so concentrated that they would require high concentrations of buffers relative to the substrate concentrations to represent significant buffer capacity.

Results

Determination of the Kinetic Order for Ceftazidime Loss—For a given starting concentration at constant temperature and pH, ceftazidime loss was described by first-order kinetics. Pseudo-first-order rate constants (k) were calculated from first-order plots based on eq 1[14]

$$\ln [C] = \ln [C_0] - kt \qquad (1)$$

where the initial concentration of ceftazidime is $[C_0]$, the time-dependent concentration is $[C]$, and t is time. Each study was comprised of eight or more assays spaced to provide changes of ~0.1$[C_0]$ per sampling interval. Plots were linear over the decrease in concentration from $[C_0]$ to ~0.2$[C_0]$ (Figure 2). Rate constants were obtained by linear regression. For replicate studies the r^2 values exceeded 0.99, CV < 5%, and for duplicate studies the differences were <4% (Table 1).

Table 1—Experimental Conditions and Observed First-Order Rate Constants (10^2 k in h^{-1}) for Hydrolysis of Ceftazidime[a]

°C	concn (M)	10^2k (h^{-1})[b]	r^2	10^2k (h^{-1})[c]	r^2
65	0.35	20.0	0.999	—	—
		20.5	0.999	—	—
		19.3	0.999	—	—
		20.4	0.998	—	—
	mean (CV)	20.0(±2.7%)		—	—
				—	—
	0.25	18.5	0.999	—	—
		17.3	0.998	—	—
		17.1	0.998	—	—
	mean (CV)	17.6(±4.3%)		—	—
				—	—
	0.14	14.9	0.997	—	—
		14.2	0.997	—	—
		14.5	0.998	—	—
	mean (CV)	14.5(±2.4%)		—	—
				—	—
	0.031	10.3	0.999	—	—
		9.60	0.999	—	—
		9.48	0.998	—	—
	mean (CV)	9.79(±4.5%)		—	—
30	0.35	0.720	0.999	0.708	0.999
		0.720	0.999	0.720	0.999
		0.692	0.999	0.725	0.996
		0.701	0.999	0.722	0.997
	mean (CV)	0.708(±2.0%)		0.719(±1.0%)	
	0.25	0.612	0.999	0.618	0.999
		0.636	0.999	0.618	0.999
	mean (range)	0.624(±1.9%)		0.618(±0.0%)	
	0.14	0.528	0.999	0.516	0.999
		0.516	0.999	0.526	0.999
	mean (range)	0.522(±1.1%)		0.521(±1.1%)	
	0.031	0.378	0.998	—	—
		0.384	0.999	—	—
	mean (range)	0.381(±0.8%)		—	—

[a] Initial pH values were 5.5 and final pH values were between 5.8 and 6.2. Under these conditions hydrolysis rate constants were reported to be pH-independent.[11] [b] Determined from linear first-order plots for ceftazidime loss with eq 1. [c] Determined by simultaneous nonlinear regression of data for ceftazidime loss and pyridine formation with eqs 3 and 4.

Deviation from first-order rates is usually associated with higher order reactions such as the dimerization of amino β-lactam antibiotics.[1–3] Ceftazidime has an unprotonated amine at the pH values of this study. Therefore, additional measures were taken to ensure that the kinetics of ceftazidime loss did not indicate dimerization. Dimerization is represented by a second-order reaction, $C + C \rightarrow C_2$. Therefore, the data were also analyzed using the second-order eq 2[14]

$$1/[C] = 1/[C_0] + kt \quad (2)$$

Second-order behavior would be most evident in the most concentrated solutions. Figure 3 shows typical nonlinear second-order plots for 0.35 and 0.14 M ceftazidime. The inability of eq 2 to describe the data for any of the initial concentrations demonstrated that ceftazidime loss was not second-order. Furthermore, second-order data were synthesized to represent each of the sampling intervals and to provide 80% loss of ceftazidime over the experimental time. First-order plots for these data were not linear. However, no deviations from linearity were observed for the first-order plots of the experimentally measured ceftazidime loss.

Mass Balance and Kinetic Analyses of Ceftazidime Loss and Pyridine Formation—Pyridine was identified as a degradation product by HPLC, GC/MS, and NMR. The concentrations of ceftazidime and pyridine were simultaneously determined as a function of time. Figure 4 shows typical data for the time-dependent simultaneously measured concentrations of ceftazidime and pyridine. The sum of these concentrations as a function of time was consistent with the starting concentration of ceftazidime. Recovery was 98% (± 3%) as a function of time.

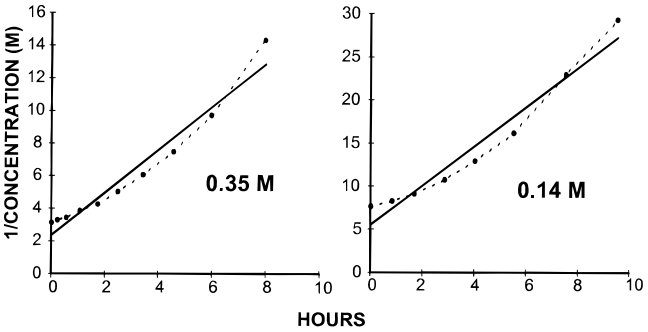


Figure 3—Typical second-order plots for loss of 0.35 and 0.14 M ceftazidime in unbuffered aqueous solutions at 65 °C, pH 5.5–6.2. The solid lines are based on eq 2 and the dashed lines connecting the data points show their deviation from linearity.

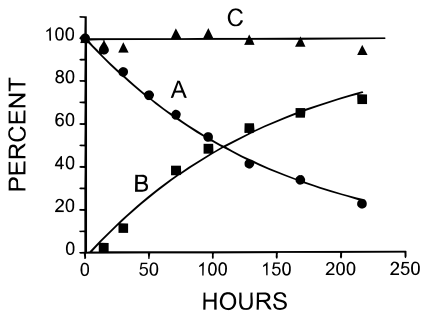


Figure 4—Mass balance data during the hydrolysis of 0.35 M ceftazidime at 30 °C, pH 5.5–6.2. Concentrations are expressed as percentage of the initial ceftazidime concentration: (A) ceftazidime (●); (B) pyridine (■); and (C) is the sum of ceftazidime and pyridine as a function of time (▲). The curves were obtained by simultaneous nonlinear regression with eqs 3 and 4 where [Cef] and [Pyr] were the percentage concentrations.

Thus, mass balance indicated that the loss of ceftazidime was accompanied by the formation of pyridine. These time-dependent data were analyzed by simultaneous nonlinear regression based on eqs 3 and 4

$$[Cef] = [Cef_o]e^{-kt} \quad (3)$$

$$[Pyr] = [Cef_o]\{1 - e^{-kt}\} \quad (4)$$

where [Cef] and [Pyr] are the concentrations of ceftazidime and pyridine as a function of time, t; $[Cef_o]$ is the initial ceftazidime concentration and k is the first-order rate constant for ceftazidime loss and pyridine formation. Simultaneous nonlinear regression for ceftazidime loss and pyridine formation provided first-order hydrolysis rate constant values that agreed with those determined from first-order plots of ceftazidime loss (Table 1).

Discussion

Evidence for First-Order Hydrolysis of Ceftazidime—The current studies were conducted at pH 5.5−6.2, which is the pH-independent region in ceftazidime hydrolysis pH−rate profiles.[11] Therefore, degradation would be primarily due to spontaneous (non-pH-catalyzed) water attack resulting in hydrolysis of the ceftazidime β-lactam.[15] All first-order plots for ceftazidime concentration as a function of time showed excellent linearity (Figure 2).

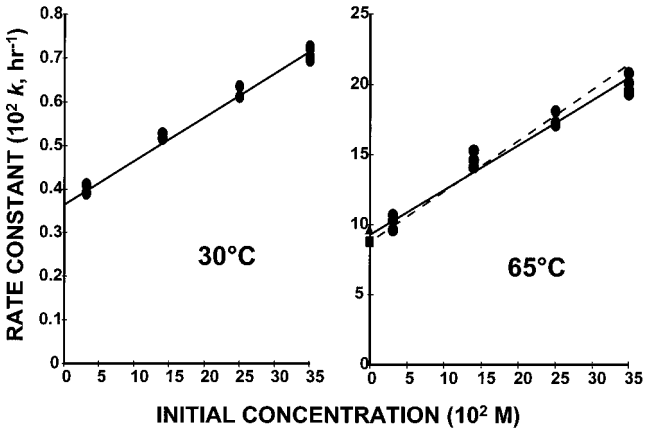


Figure 5—First-order hydrolysis rate constants (●) as a function of the initial ceftazidime concentrations for reactions initiated at pH 5.5 with final pH values ≤6.2. The data at the intercept represent the hydrolysis of 10^{-4} M ceftazidime at pH 5.5 (■) and 6.2 (▲) in the absence of buffer catalysis at 65 °C.[11] The dashed line, which shows the first-order rate constants as a function of HPO_4^{2-} concentration, was calculated with the HPO_4^{2-} catalytic constant of 0.349 M^{-1} h^{-1}.[11] The pH 5.5 value (■) is the reported intercept of *k* versus phosphate buffer concentration and the pH 6.2 value (▲) was calculated with the pH-rate expression.[11]

Furthermore, second-order plots that would accompany dimerization were not linear (Figure 3).

Additional evidence for first-order hydrolysis was obtained from the kinetic analysis of pyridine formation. Results of the simultaneous analysis of the concentration of ceftazidime and pyridine as a function of time, which include mass balance (Figure 4) and agreement of the hydrolysis rate constants (Table 1), were consistent with β-lactam hydrolysis followed by rapid release of pyridine. The significance of this agreement in rate constants can be realized by considering what is known about the hydrolysis of cephalosporins. It is well-established that hydrolysis of the β-lactam ring of cephalosporins, having a suitable leaving group at the 3-methylene position, results in rapid release of that group and formation of unstable exomethylene compounds.[12,13,16–18] Thus the data for the release of pyridine would be expected to mirror the data for hydrolysis of ceftazidime.

The Kinetic Oxymoron and Its Rationalization—A true first-order rate process is described by eq 5:

$$[C] = [C_o]e^{-kt} \tag{5}$$

Equation 5 can be rearranged and the logarithmic transformation provides eq 6:

$$\ln([C]/[C_o]) = \ln F = -k\,t \tag{6}$$

where $F = ([C]/[C_o])$ or the fraction remaining at time, t. Equation 6 may be written as eq 7

$$k = -\ln F/t \tag{7}$$

This clearly shows why a true first-order rate constant is independent of the starting concentration since only the fraction remaining appears in the equation.

In the current study, apparent first-order kinetics were observed for each initial ceftazidime concentration. However, contrary to eq 7, the observed first-order rate constant values increased as the initial concentrations increased (Figure 5). It was therefore necessary to rationalize the observation of concentration-dependent first-order rate constants for solutions that contained only ceftazidime and water.

As part of a previous study on the hydrolysis of cefuroxime (Scheme 1), a commercial product was reconstituted by dissolving 750 mg in 100 mL of water, in accordance with the prescribing information.[19] The hydrolysis rate constant for this ~0.02 M cefuroxime solution was adequately predicted from first-order hydrolysis constants and their energetics, which were determined from kinetic studies of 10^{-4} M solutions at elevated temperatures. However, cefuroxime hydrolysis was not catalyzed by formate, acetate, phosphate, or borate buffers. In contrast, previous research in this laboratory has demonstrated that every one of these buffers catalyzed the hydrolysis of ceftazidime.[11] Thus, ceftazidime hydrolysis, which is subject to buffer catalysis, elicits concentration-dependent first-order rate constants, whereas cefuroxime hydrolysis does not exhibit either of these traits. This suggests that ceftazidime is catalyzing its own hydrolysis.

The ceftazidime carboxylic acids and the protonated aminothiazolyl have pK_a values of 1.9, 2.7, and 4.1.[20] Therefore ceftazidime would be in the unprotonated form at the pH values of this study. These three basic groups should be capable of acting as intermolecular general-base catalysts on the basis of the previously observed catalysis by the basic components in formate, acetate, phosphate, and borate buffers.[11]

As the ceftazidime concentration was increased from 10^{-4} to 0.35 M, the hydrolysis rate constant at 65 °C increased from 0.09 to 0.20 h^{-1} (Figure 5). The value of the apparent catalytic constant, calculated from the slope of this line, is 0.314 M^{-1} h^{-1}. The feasibility of this value representing intermolecular general-base catalysis by ceftazidime can be assessed by comparing it to a known general-base catalyst.

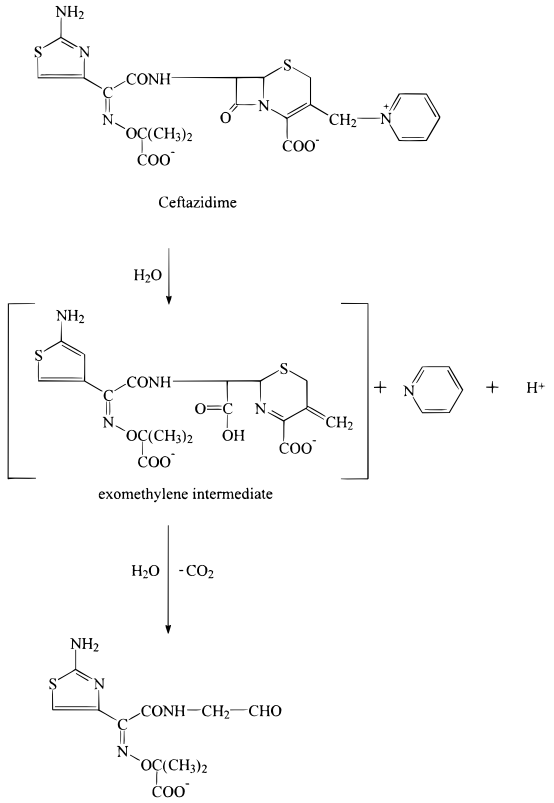
The pH region of the current study corresponds to the phosphate buffer region in our previous report.[11] The dashed line in Figure 5 illustrates the dependency of the first-order rate constants for ceftazidime hydrolysis on the concentration of HPO_4^{2-} at 65 °C according to eq 8:

$$k = k_{pH} + k_{HPO_4}[HPO_4^{2-}] \tag{8}$$

where $k_{pH} = 0.0875$ h^{-1} is the value in the absence of buffer catalysis and $k_{HPO_4} = 0.349$ M^{-1} h^{-1} is the catalytic constant for HPO_4^{2-} at 65 °C.[11] As shown in Figure 5, HPO_4^{2-} has the capacity to increase the hydrolysis constant from 0.0875 h^{-1} in the absence of HPO_4^{2-} to 0.210 h^{-1} in the presence of 0.35 M HPO_4^{2-}. The dashed line is similar to that of the ceftazidime line because the apparent catalytic constant for ceftazidime is comparable to the catalytic constant for HPO_4^{2-} . Although the quantitative similarity between catalytic constants is fortuitous, their agreement supports the hypothesis that it is feasible for ceftazidime to behave as a intermolecular general-base catalyst.

Therefore, the apparent catalytic constant suggests that ceftazidime loss was accelerated as its initial concentrations were increased because of intermolecular general-base catalysis by the aminothiazolyl and carboxylate groups. However, first-order plots exhibited excellent linearity even though the catalyst (ceftazidime) was consumed. This observation requires that the total catalytic activity must remain reasonably constant during the loss of ceftazidime. Such would be the case if the catalytic groups either remained intact throughout the reaction or were replaced by equivalent catalysts in reaction products.

Is This Rationalization in Accord with Known Cephalosporin Hydrolysis Products?—The proposed explanation for this unusual phenomenon is consistent with all known *kinetic* information. It must also be compatible with known cephalosporin hydrolysis *chemistry*. The data for ceftazidime loss and pyridine formation conform to a



Scheme 2—Expected products for ceftazidime degradation at pH 5.8 based on β-lactam hydrolysis pathways for cephalosporins with leaving groups at the 3-methylene position.[12,13,16−18]

widely recognized β-lactam hydrolysis pathway for cephalosporins with suitable leaving groups at the 3-methylene position.[12,13,16−18] For such cases, water cleaves the β-lactam ring[15] to form a cephalosporoate which spontaneously releases the leaving group. This results in the formation of an unstable exomethylene imine[16] which undergoes hydrolytic fission at the C_6-N_1 and C_6-S_5 bonds to form an intermediate aldehyde which decarboxylates.[13,17,18] This pathway has been reported for cepirome,[13] cefsulodin,[17] and many others.[18] For example, at 40 °C, pH 7, the primary degradation pathway for cefpirome, which is structurally similar to ceftazidime (Scheme 1), involved hydrolysis of the β-lactam followed by the loss of 2,3-cyclopentenopyridine and formation of an unstable exomethylene intermediate which rapidly formed an aldehyde as illustrated in Scheme 2 using ceftazidime in place of cefpirome.[13]

Cephalosporin β-lactam hydrolysis produces cephalosporoates which are generally too labile to isolate.[21] For example, the hydrolysis of cefixime, which has a vinyl group at C-3, formed an ethylidene cephalosporoate intermediate which was similar to the exomethylene in Scheme 2. The rate constant for conversion of that cephalosporoate to the aldehyde was 500 times faster than the rate constant for its formation.[22]

Thus, Scheme 2 represents the expected ceftazidime hydrolysis products under current conditions on the basis of the hydrolysis behavior for cephalosporins with suitable leaving groups at the 3-methylene position. The observed first-order behavior at each initial concentration required that the total catalytic concentration did not change to a kinetically distinguishable extent throughout the reaction.

Hydrolysis of the exomethylene intermediate gives rise to the open-chain counterpart of the dihydrothiazine moiety, which in turn degrades to products that have not been previously characterized. This degradation is likely to involve decarboxylation, thus resulting in the loss of the carboxylate originally located at the C-2 position. However, the loss of this catalyst would be offset by the formation of pyridine, which exists ~80% in the unprotonated form at pH ~5.8. Overall, the side chain carboxylate and aminothiazole groups would remain intact while loss of the C-2 carboxylate catalyst would be counterbalanced by pyridine formation. Consequently, although the relative contribution of each ceftazidime general-base catalytic group is not known, the total concentration of the potential general-base catalysts would remain practically constant in Scheme 2.

Significance—Substrate concentration-dependent first-order rate constants have been observed for electrode reactions involving complex ion radicals in nonaqeous solvents where diffusion-limited kinetics have rate law terms with substrate concentration in the denominator.[23] However, the current observation appears to be unprecedented for simple first-order hydrolysis in aqueous systems containing only substrate and water. A literature search did not disclose any previously reported substrate-concentration dependent first-order rate constants for such simple systems.

While ceftazidime hydrolysis in concentrated solutions appears to present a unique kinetic situation, the phenomenon may be of more widespread occurrence. Substrate-concentration accelerated first-order hydrolysis is feasible whenever hydrolysis is subject to general-acid and/or general-base catalysis, the substrate has one or more effective general-acid and/or general-base catalytic groups, the total concentration of the catalytic groups remains practically constant throughout the reaction, and the initial concentration is sufficiently large to elicit measurable intermolecular catalysis.

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