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Kinetics and Mechanisms of Hydrolysis and Aminolysis of Thioxocephalosporins

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The effect of replacing the β-lactam carbonyl oxygen in cephalosporins by sulfur on their reactivity has been investigated. The second-order rate constant for alkaline hydrolysis of the sulfur analogue is 2-fold less than that for the natural cephalosporin. The thioxo derivative of cephalexin, with an amino group in the C7 side chain, undergoes β-lactam ring opening with intramolecular aminolysis by a reaction similar to that for cephalexin itself. However, the rate of intramolecular aminolysis for the S-analogue is 3 orders of magnitude greater than that for cephalexin. Furthermore, unlike cephalexin, intramolecular aminolysis in the S-analogue occurs up to pH 14 with no competitive hydrolysis. The rate of intermolecular aminolysis of natural cephalosporins is dominated by a second-order dependence on amine concentration, whereas that for thioxocephalosporins shows only a first-order term in amine. The Bronsted β_{nuc} for the aminolysis of thioxo-cephalosporin is +0.39, indicative of rate-limiting formation of the tetrahedral intermediate with an early transition state with relatively little C−N bond formation.

Introduction

Amide resonance is usually described in terms of charge transfer from N to O as shown in the traditional resonance formulation (Scheme 1). This, in turn, is then used to rationalize the large barrier to rotation in amides and their low chemical reactivity toward nucleophilic substitution at the acyl center. In thioamides it is expected that there would be greater π charge transfer from N to S due to the larger size of S and weaker π bond of C=S, despite the smaller electronegativity of S compared with O (Scheme 1). Hence, thioamides have a larger barrier to C−N bond rotation[1] and are more easily protonated on sulfur.[2] Nonetheless, the effect of substituting O for S on the chemical reactivity of amides is less clear. This is of particular interest in the reactivity of the cephalosporin (**1**) group of antibiotics and their thioxo analogues, the thioxocephalosporins (**2**), because of the alleged reduction of amide resonance in these bicyclic systems as a result of the pyramidalization of N.[3] However, the evidence for reduced amide resonance in penicillins and cephalosporins is minimal, and most experimental observations indicate that resonance stabilization is "normal" in these derivatives.[4,5] We were, therefore, interested in comparing the chemical reactivity of thioxo-β-lactams with their O-analogues.

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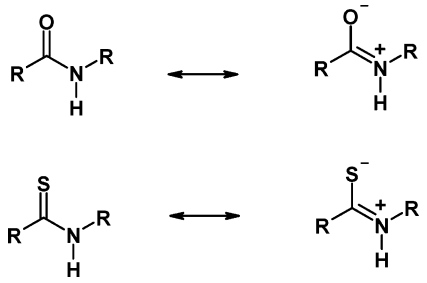

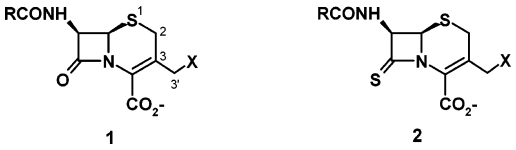

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Experimental Section

Kinetic Procedures. Standard UV spectroscopy was carried out on a Cary 1E UV−vis spectrophotometer (Varian, Australia) equipped with a 12-compartment cell block. The instrument was used in double beam mode, allowing six

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(1) Wiberg, K. B.; Rush, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 2038−2046.
(2) Min, B. K.; Lee, H.-J.; Choi, Y. S.; Park, J.; Yoon, C.-J.; Yu, J.-A. *J. Mol. Struct.* **1998**, *471*, 283−288.
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(4) Page, M. I. In *The Chemistry of β-Lactam Antibiotics*; Page, M. I., Ed.; Blackie: Glasgow, 1992; Chapter 2, pp 79−100.
(5) Page, M. I. *Adv. Phys. Org. Chem.* **1987**, *23*, 165.

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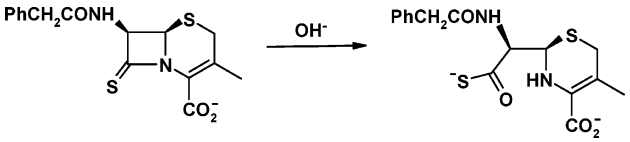
TABLE 1. Summary of Rate Constants for Thioxocephalosporins and Cephalosporins at 30 °C and Ionic Strength 1.0 M (KCl)

cephalosporin	pK_a[a]	k_{OH}[b] ($M^{-1}s^{-1}$)	k_o[c] (s^{-1})	k_{RNH_2}[d] (M^{-1} s^{-1})
thioxocephalexin (**7**)	6.86 ± 0.07	(1.29 ± 0.42) × 10^{-2}	(9.48 ± 0.78) × 10^{-3}	
cephalexin[e] (**5**)	7.02	5.67 × 10^{-2}	5.83 × 10^{-6}	
thioxocephalosporin (**3**)		(1.45 ± 0.05) × 10^{-2}		1.47 × 10^{-1}
cephalosporin (**4**)		2.90 × 10^{-2}		1.13 × 10^{-4}

[a] The acidity of the 7-side chain amino group. [b] The second-order rate constant for the hydroxide-ion catalyzed hydrolysis. [c] The first-order rate constant for uncatalyzed intramolecular aminolysis. [d] The second-order rate constant for uncatalyzed aminolysis with propylamine. [e] At 35 °C from ref 10.

SCHEME 2



reaction cells to be followed in a single run. The cell block was thermostated using a Peltier system.

pH measurements were made with a ϕ40 (Beckman, Fullerton, USA) pH meter using a semi-micro calomel electrode (Beckman). A calibration of the pH meter was carried out at 30 °C using pH 6.99 ±0.01, pH 4.01 ±0.02, or pH 9.95 ±0.02 calibration buffers.

AnalaR grade reagents and deionized water were used throughout. Organic solvents were glass distilled prior to use and stored under nitrogen. For solution pHs ≥3 and ≤11 the pH was controlled by the use of ≤0.2 M buffer solutions of formate (pK_a 3.75), ethanoate (pK_a 4.72), MES (pK_a 6.1), MOPS (pK_a 7.2), TAPS (pK_a 8.4), CAPSO (pK_a 9.6), and CAPS (pK_a 10.4). For general pH work, buffers were prepared by partial neutralization of solutions of their sodium salts to the required pH. In all experiments, temperatures were maintained at 30 °C and ionic strength at 1.0 M with AnalaR grade KCl unless otherwise stated. Reaction concentrations were generally within the range of 2 × 10^{-5}−2 × 10^{-4} M to ensure pseudo-first-order conditions.

Hydroxide ion concentrations were calculated using pK_w (H_2O) = 13.83 at 30 °C.

Reactions studied by UV spectrophotometry were commenced by injections of dioxan stock solutions of the substrate (5−50 μL) into the cells containing preincubated buffer (2.5 mL). Final reaction cells contained ≤5% dioxane v/v. The pH of the reaction cells was measured before and after each kinetic run at 30 °C; kinetic runs experiencing a change >0.05 units were rejected. Reactant disappearance or product appearance was followed at absorbance change maxima for individual compounds. The solubility of compounds was ensured by working within the linear range of absorbance in corresponding Beer−Lambert plots. Pseudo-first-order rate constants from exponential plots of absorbance against time or gradients of initial slopes were obtained using the CaryBio software (Varian). pH−rate profiles were modeled to theoretical equations using the Scientist program (V2.02, Micromath Software Ltd., USA).

Results and Discussion

1. Thioxocephalosporin Hydrolysis. The alkaline hydrolysis of the 3-methyl-7β-(phenylacetamido)thioxoceph-3-em-4-carboxylic acid (**3**) gives the ring-opened thio acid (Scheme 2), and the rates of hydrolysis were studied in water at 30 °C and an ionic strength of 1.0 M (KCl). The pH−rate profile is shown in Figure 1, which demonstrates that the pseudo first-order rate constant is linearly dependent on hydroxide-ion concentration. For comparison, the corresponding second-order rate constant

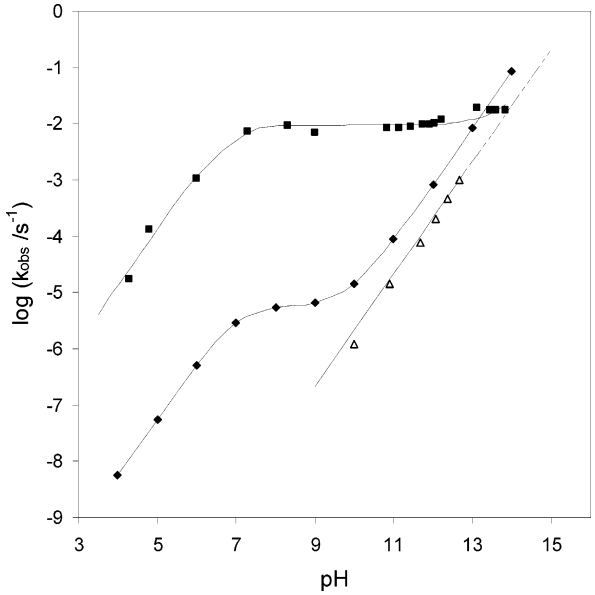
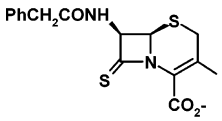


FIGURE 1. Dependence of the pseudo-first-order rate constant against pH for the degradation of thioxo- and oxocephalosporin derivatives in aqueous solution at 30 °C, I = 1.0 M (KCl): ■, thioxocephalexin (**7**); ◆, cephalexin (**5**); △, thioxocephalosporin (**3**).

for the alkaline hydrolysis of the O-analogue (**4**) is given in Table 1. The S-derivative (**3**) is just 2-fold less reactive than the O-cephalosporin (**4**), and at first glance, therefore, it appears that there is little difference in reactivity between the O- and S-analogues.



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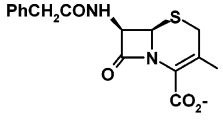

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Previous studies of the hydrolysis of thioamides are complicated by the slow reaction rates and S/O exchange.[6,7] Nonetheless, these earlier studies also appear to indicate that thioamides have a reactivity similar to that of the corresponding amide. If the rate-limiting step for alkaline hydrolysis is formation of the tetrahedral intermediate then any significant differences in resonance energies between amides and thioamides should be reflected in different activation energies. A more

(6) Peeters, O. M.; DeRanter, C. J. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1062−1065. Peeters, O. M.; DeRanter, C. J. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1832−1835. Rosenthal, D.; Taylor, T. I. *J. Am. Chem. Soc.* **1957**, *79*, 2684−2690.

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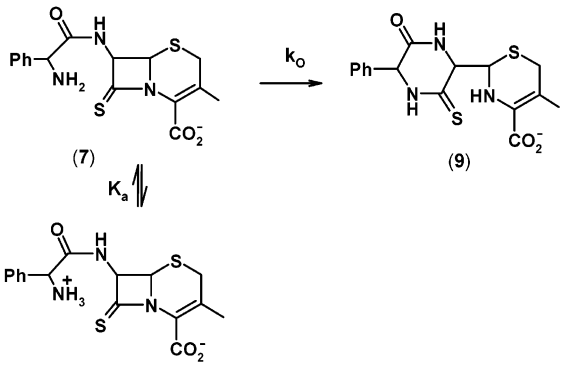
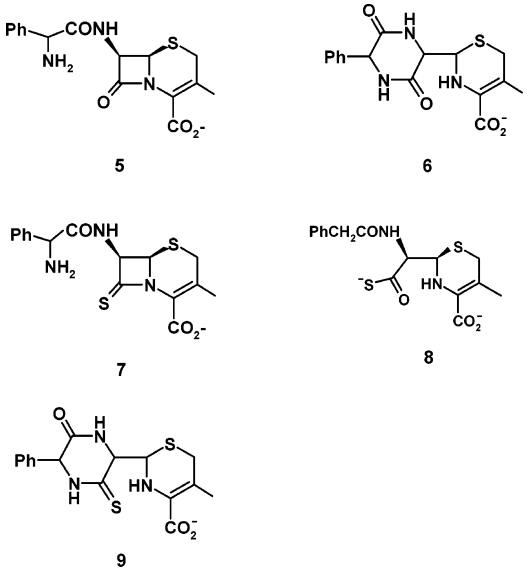
SCHEME 3



detailed discussion of the energetics of acyl transfer reactions of amides and thioamides is given later.

2. Intramolecular Aminolysis of Thioxocephalosporin. Many cephalosporins (**1**) possess a leaving group at C3′ which is generally expelled after β-lactam ring opening.[4,5,8,9] However, cephalexin (**5**) is a cephalosporin with a methyl group at C3 and with an amino group in the side-chain at C7. It is known that the degradation of cephalexin in water occurs with both hydrolysis and intramolecular aminolysis, the relative importance of which varies with pH.[10] Nucleophilic attack by the amino group in the C7 side chain on the β-lactam carbonyl carbon causes ring opening and formation of a piperazinedione derivative (**6**). The thioxo analogue of cephalexin, 3-methyl-7β-(2-aminophenylacetamido)-thioxoceph-3-em-4-carboxylic acid (**7**), also reacts in water with intramolecular aminolysis by the 7β-amino side chain to give (**9**) (Scheme 3). The rate of this reaction was studied in water at 30 °C and an ionic strength of 1.0 M (KCl), and the pH−rate profile is shown in Figure 1. The pseudo first-order rate constant for the degradation of (**7**) is linearly dependent on hydroxide-ion concentration below pH 7 and is independent of pH above pH 7. The break in the pH-rate profile indicates either a change in rate-limiting step or the ionization of a group in the substrate[11] with a pK_a of about 7. The latter seems more likely as this corresponds to the expected pK_a of the amino group in the C7 side chain (**7**).



The pseudo first-order rate constant for the reaction of (**7**) is satisfactorily described by eq 1 where k_{obs} is the observed first-order rate constant, K_a is the dissociation constant of the side chain amino group, k_o is the first-order rate constant for intramolecular aminolysis, and k_{OH} is the apparent second-order rate constant for hydroxide ion catalyzed hydrolysis or intramolecular aminolysis (Scheme 3). The latter is subject to significant error and possibly makes an only minor contribution to the observed rate of reaction.

$$k_{obs} = \frac{K_a}{K_a + [H^+]} \times k_o + k_{OH}[OH^-] \qquad (1)$$

The ratio $K_a/(K_a + [H^+])$ describes the fraction of the substrate present in the free base form, and the rate of intramolecular aminolysis is dependent on the concentration of the reactant with an unprotonated amino group. Curve-fitting by SCIENTIST gives $K_a = 1.38 \times 10^{-7}$ (i.e., p$K_a = 6.86$), $k_o = 9.48 \times 10^{-3}$ s^{-1} and $k_{OH} = 1.29 \times 10^{-2}$ M^{-1} s^{-1}. For comparison, the pH−rate profiles for the reaction of cephalexin (**5**) in water are also given in Figure 1. A similar sigmoidal dependence of the rate upon pH is seen between pH 4 and 9 for the oxygen derivative, but above pH 9 the rate increases with pH as the hydroxide-ion catalyzed hydrolysis and hydroxide-ion catalyzed intramolecular aminolysis become important. From the pH−rate profiles of the thioxo-β-lactam and its oxygen analogue, it is apparent that: (i) the rate of intramolecular aminolysis in the thioxo-β-lactam is about 10^3-fold faster than that in cephalexin; (ii) competitive hydroxide-ion catalyzed hydrolysis is observed with cephalexin at high pH[10] but with the thioxo-β-lactam intramolecular aminolysis occurs over the entire pH range studied (Figure 1). The rate constants for these reactions of thioxo-β-lactams and their oxygen analogues are compared in Table 1.

Extrapolation of the hydroxide-ion catalyzed hydrolysis of (**3**) indicates that a similar rate of hydrolysis for (**7**) would only be observed above pH 14 (Figure 1). This is consistent with the observation that no significant hydroxide-ion catalyzed hydrolysis was found for (**7**) in the pH range studied and that intramolecular aminolysis for the thioxo analogue of cephalexin (**7**) remains pH-independent even at high pH.

It is interesting to note that the thioxo-β-lactam and its oxygen analogue react at a similar rate toward hydroxide-ion catalyzed hydrolysis but the intramolecular aminolysis is 10^3-fold faster with thioxo-β-lactam than that of its oxygen analogue. This difference between O and N nucleophiles reacting with thioamides encouraged us to study the intermolecular aminolysis of thioxocephalosporins.

3. Intermolecular Aminolysis of Thioxocephalosporin. The rate of aminolysis of the thioxocephalosporins (**3**) was studied in water at 30 °C and ionic strength of 1.0 M (KCl) (Scheme 4), using the amine both as reactant and buffer. The dependence of the observed

(8) Page, M. I.; Proctor, P. *J. Am. Chem. Soc.* **1984**, *106*, 3820.
(9) Buckwell, S. C.; Page, M. I.; Longridge, J. L.; Waley, S. G. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1823.
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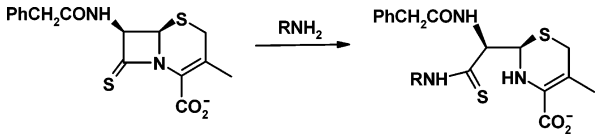
(11) Page, M. I.; Williams, A. *Organic and Bioorganic Mechanisms*; Longman: Essex, U.K., 1997; pp 30−36.

SCHEME 4



pseudo first-order rate constants for the reaction of (**3**) in aqueous solution buffered with 2-cyanoethylamine on total amine concentration is shown in Figure 2. The observed pseudo first-order rate constants are linearly dependent on the total concentration of amine. Unlike the aminolysis of natural cephalosporins[8] and penicillins,[12−14] there is no second-order dependence on amine concentration. The zero intercepts indicate the dominance of aminolysis at the expense of hydrolysis. The slopes of lines in Figure 2 are defined as k_{cat}, and increase with increasing pH. A plot of k_{cat} against the fraction of free base of 2-cyanoethylamine, α, in the solution gives a straight line (Figure 3). The linear dependence of k_{cat} on α indicates the insignificance of any hydroxide-ion catalyzed aminolysis. The left and the right intercepts give the catalytic constants for the acidic and the basic species of the amine. Since the left intercept is indistinguishable from zero, the deprotonated form of amine is the only species responsible for the catalysis.

The rate law that adequately describes the reaction of the thioxocephalosporin (**3**) in aqueous solutions of amine buffer is given by eqs 2−4

$$k_{obs} = k_{OH}[OH^-] + k_{cat}[RNH_2]_{tot} \quad (2)$$

$$k_{obs} = k_{OH}[OH^-] + k_{RNH_2}\alpha[RNH_2]_{tot} + k_{RNH_3^+}(1-\alpha)[RNH_2]_{tot} \quad (3)$$

$$k_{obs} = k_{OH}[OH^-] + k_{RNH_2}[RNH_2] \quad (4)$$

where k_{obs} is the observed pseudo first-order rate constant, k_{OH} is the second-order rate constant for hydroxide-ion catalyzed hydrolysis, $[RNH_2]_{tot}$ is the total concentration of amine, α is the fraction of free base, unprotonated amine, and k_{RNH_2} is the second-order rate constant for uncatalyzed aminolysis reaction. The aminolysis of the O-analogue of (**3**), the cephalosporin (**4**), has previously been studied, the rate law is dominated by general base- and hydroxide-ion catalyzed aminolysis,[8] and it is experimentally difficult to determine the rate constant for the uncatalyzed aminolysis reaction. However, a reasonable estimate of the second-order rate constant for uncatalyzed aminolysis of (**4**) with propylamine is given[8] in Table 1 and is about 10^3-fold less than that of (**3**). This is consistent with the observation that the rate of intramolecular aminolysis of the thioxo derivative (**7**) is about 10^3-fold greater than that in (**5**). It is interesting to note that the rate of aminolysis of the oxocephalosporin (**4**) is always slower than that of the thioxocephalosporin (**3**) in up to 2 M concentration of amine despite the former being second-order in amine because of general base catalysis.

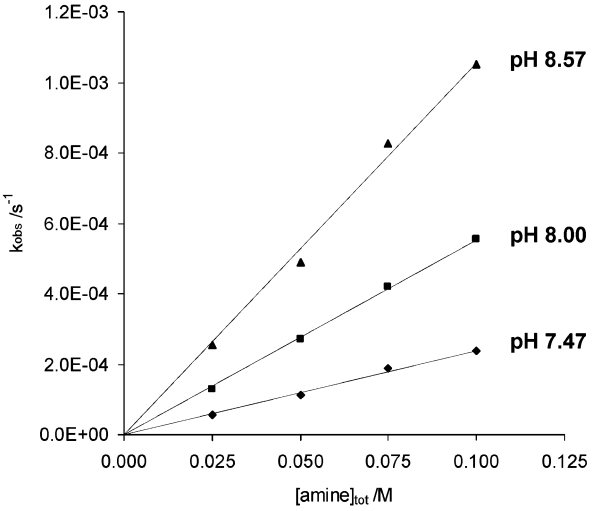


FIGURE 2. Dependence of observed pseudo-first-order rate constants for the reaction of 3-methyl-7β-(phenylacetamido)-thioxoceph-3-em-4-carboxylic acid (**3**) with 2-cyanoethylamine against total amine concentration at the pH indicated, 30 °C, I = 1.0 M (KCl).

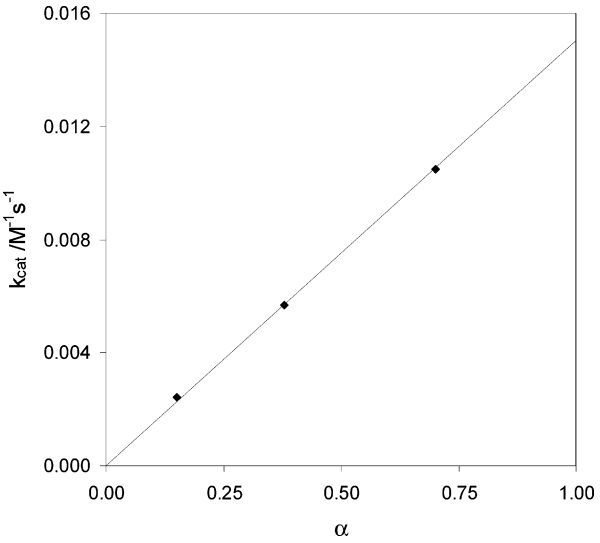


FIGURE 3. Dependence of the second-order rate constant, k_{cat}, on the fraction of free base, α, of amine for the aminolysis of 3-methyl-7β−(phenylacetamido)thioxoceph-3-em-4-carboxylic acid (**3**) with 2-cyanoethylamine in aqueous solution, 30 °C, I = 1.0 M (KCl).

The mechanism of the aminolysis of oxocephalosporins has been shown to involve the formation of a tetrahedral intermediate followed by diffusion of a base into the same solvent cage as the intermediate as shown in Scheme 5.[8] The generalized rate law for aminolysis is given by eq 5

$$k_{obs} = \frac{k_1 k_2 [RNH_2][base]}{k_{-1} + k_2[base]} \quad (5)$$

where k_1 and k_{-1} are the rate constants for formation of the tetrahedral intermediate and its reversal to reactants, respectively, and k_2 is the diffusion controlled rate

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(13) Morris, J. J.; Page, M. I. *J. Chem. Soc., Perkin Trans. 2* **1980**, 220.
(14) Gensmantel, N. P.; Page, M. I. *Chem. Commun.* **1978**, 374. Gensmantel, N. P.; Page, M. I. *J. Chem. Soc., Perkin Trans. 2* **1979**, 137.

SCHEME 5

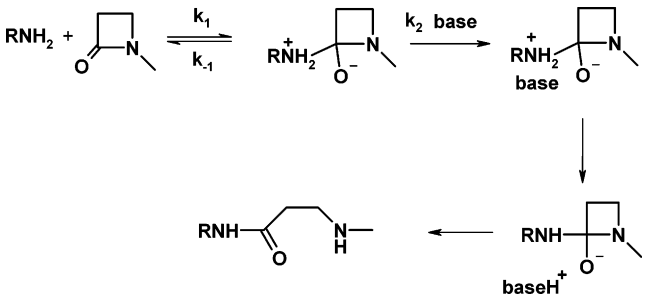


TABLE 2. Second-Order Rate Constants for the Uncatalyzed Aminolysis, k_{RNH_2}, of the Thioxocephalosporin (3) as a Function of the pK_a of the Conjugate Acid of the Amine at 30 °C and Ionic Strength 1.0 M (KCl)

amine	pK_a	k_{RNH_2}/M^{-1} s^{-1}
2-cyanoethylamine	8.21	$(1.50 \pm 0.02) \times 10^{-2}$
2-methoxyethylamine	9.66	$(5.93 \pm 0.31) \times 10^{-2}$
propylamine	10.79	$(1.47 \pm 0.06) \times 10^{-1}$

constant for the encounter of the intermediate with a base (Scheme 5). The rate-limiting step is determined by the relative rates of partitioning of the tetrahedral intermediate to reactants and products, k_2[base]/k_{-1}. For oxocephalosporins, the term in the rate law which is dependent on base concentration is dominant and the rate-limiting step is the encounter controlled step, k_2, because $k_{-1} \gg k_2$[base]. The observed pseudo first-order rate constant, k_{obs}, for the reaction which is base catalyzed is then given by eq 6. However, at high base concentration of hydroxide ion it is observed that the rate of aminolysis of oxo-cephalosporins becomes independent of base concentration because k_2[base]$\gg k_{-1}$, and k_1 becomes the rate-limiting step, eq 7.

$$k_{obs} = \frac{k_1 k_2}{k_{-1}}[RNH_2][base] \quad (6)$$

$$k_{obs} = k_1[RNH_2] \quad (7)$$

For the aminolysis of the thioxocephalosporin (**3**), however, no base catalysis is observed in the pH range studied. According to the mechanism for the aminolysis of cephalosporins described above, k_{-1} must then be smaller than k_2[base] and formation of the tetrahedral intermediate must be rate-limiting. In summary, the rate of aminolysis of cephalosporins is normally base catalyzed because the tetrahedral intermediate reverts to reactants faster than it reacts with base whereas for thioxocephalosporins the reverse is true.

To determine whether this was a general phenomenon and to elucidate the transition state structure, the aminolysis of (**3**) was also studied with a variety of amines of differing basicity. For all amines studied, there was no term in the rate law which showed a significant dependence on base concentration. Aminolysis of thioxocephalosporins (**3**) occurs with only a first-order dependence on amine concentration, and the overall second-order rate constants for several amines are given in Table 2, along with the pK_a of the conjugate acid of the amine. A Bronsted-type plot of the second-order rate constants,

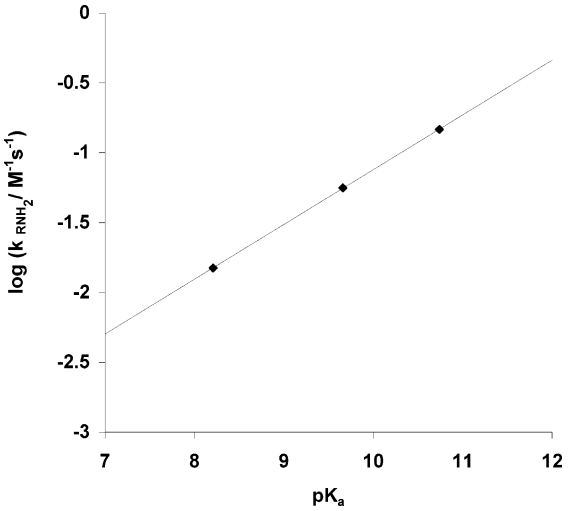
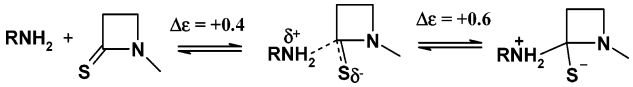


FIGURE 4. Bronsted plot for the second-order rate constants, k_{RNH_2}, for the aminolysis of the thioxocephalosporin (**3**) as a function of the pK_a of the attacking amine.

SCHEME 6



k_{RNH_2}, for the aminolysis of (**3**) against the pK_a of the conjugate acid of the amine is given in Figure 4, the slope of which gives a Bronsted β_{nuc} of +0.39. The β_{nuc} value for the formation of the tetrahedral intermediate is expected[8,12] to be about +1.0, so the observed value indicates a relatively early transition state with only a small amount of C−N bond formation (Scheme 6).

There are two observed rate constants which are first-order in amine concentration for the rate of aminolysis of cephalosporins.[8] Under most experimental conditions, the uncatalyzed aminolysis represents a very minor pathway and the observed rate constant corresponds to breakdown of the zwitterionic tetrahedral intermediate and shows a β_{nuc} of ca. 1.0 indicative of a unit positive charge on nitrogen in the transition state.[8,12] The major pathway for aminolysis is general base catalyzed, but in strongly basic conditions the rate of deprotonation of the tetrahedral intermediate by base becomes faster than that of the breakdown to reactants and so another term in the rate law becomes first-order in amine corresponding to rate-limiting formation of the tetrahedral intermediate. The β_{nuc} for this step is +0.3, suggesting a transition state with little charge development on the attacking amine and a small amount of C−N bond formation.[8,14] It thus appears that the transition state structures for nucleophilic attack of amines on cephalosporins and thioxocephalosporins are similar (Scheme 6).

The observed rate constant for the uncatalyzed aminolysis of the thioxocephalosporin (**3**) with 2-methoxyethylamine (5.93×10^{-2} dm^3 mol^{-1} s^{-1}) can be compared with that for the formation of tetrahedral intermediate in the aminolysis of the cephalosporin (**4**) with the same amine (1.76×10^{-1} dm^3 mol^{-1} s^{-1}). The thioxo-β-lactam is only 3-fold less reactive than the oxo-β-lactam. The second-order rate constants for the alkaline hydrolysis of (**3**) and (**4**) show a similar difference in reactivity.

Why does the rate of aminolysis of cephalosporins change from a dominant second-order term in amine to an exclusive first-order term as the β-lactam carbonyl oxygen is changed to sulfur? For natural cephalosporins, the rate-limiting step for aminolysis is breakdown of the tetrahedral intermediate, whereas for the thioxo derivative it is formation of the intermediate. If it is assumed, in the aminolysis of cephalosporin and analogous thioxo-β-lactam, that the acidity of the attacking amine in both tetrahedral intermediates are similar (Scheme 5) so that the k_2[base] term would not be significantly different, i.e., proton transfer to any catalyzing base is thermodynamically favorable and hence at the diffusion-controlled rate. The reason for different rate-limiting steps for the oxo and thioxo derivatives must then be due to different rates of reversion of the respective tetrahedral intermediates to reactants. The k_{-1} term must be smaller with thioxo-β-lactam. A smaller rate of C−N fission by expulsion of the attacking amine results from a greater activation energy which could indicate that the thioxo-β-lactam is less stable than β-lactam and/or the zwitterionic tetrahedral intermediate formed from the thioxo-β-lactam and amine is more stable than that formed with oxo-β-lactams. It is likely that a dominant feature controlling the relative stabilities of the zwitterionic tetrahedral intermediates is the more favorable sulfur anion compared with oxygen. A large contribution to the higher acidities of thiols compared with alcohols is the greater stability of sulfur anions compared with the heavily solvated alkoxide ions. In conclusion, thioxo-β-lactams and oxo-β-lactams show a similar reactivity toward nucleophiles, however for reactions of oxo-β-lactams which normally involve rate-limiting breakdown of the tetrahedral intermediate thioxo-β-lactams may have an earlier rate-limiting step because of the slower rate of reversion of the intermediate back to reactants and so occur at a faster overall rate.

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Supporting Information Available: Experimental details of synthesis and ^{1}H and ^{13}C NMR spectra for (**3**) and (**7**). This material is available free of charge via the Internet at http://pubs.acs.org.

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