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Pyrolysis of Azetidinones. Part 2. Kinetics and Mechanism of Thermolysis of β -Lactams and β -Thiolactams

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Draft

Abstract: The kinetics of the gas-phase thermolysis reaction of seven β -lactams and their thione analogues were investigated over the temperature range 533-603 K for the β -lactams, and 463-542 K for the β -thiolactams. The average values of the energy of activation ($E_a/\text{kJ mol}^{-1}$) and Arrhenius log A/s^{-1} were respectively, 170.8 ± 18.6 and 12.4 ± 1.6 for the lactams, and 131.7 ± 18.2 and 11.0 ± 2.0 for the thione analogues. The entropy of activation ($\Delta S^\ddagger$), was negative for eleven of the substrates, and slightly positive for three. The rate constants (k/s^{-1}) were calculated for 510 K, and compared for the two series of azetidinones. The effects of substituents on rates, and the novel role played by the (C=O) and (C=S) moieties on the relative reactivities of the cyclic amides are rationalized on the basis of a formal *retro*[2+2]cycloaddition mechanism used earlier to explain the products of the gas-phase thermolysis reaction of the present azetidinones.

Key words: β -Lactams, gas-phase, thermolysis, kinetics, mechanism

Introduction

The synthesis and characterization of the fourteen azetidinones under study are described in Part 1.¹ Nine of these compounds were novel: two of the β -lactams and all seven β -thiolactams. The earlier communication also described the gas-phase thermolysis of these compounds in which both static (sealed-tube) pyrolysis (STP), and flash vacuum pyrolysis (FVP) techniques were employed. The mechanism used to explain reaction products involves two routes of formal *retro*[2+2]cycloaddition process: pathways (A) and (B) in (Fig. 1).¹

Fig.1. Routes (A) and (B) of *retro* [2+2]cycloaddition mechanism.

The aryl groups (Ar, Ar') had the following substituents (Y, Z) all at the *para* position of a benzene ring: CH₃;CH₃O; Cl: a total of seven compounds in which X = O, and seven where X = S. The complete

list of the fourteen substrates under study **1a-g**; **2a-g** is given in (Fig. 2). The kinetic results reported here are for the individual compounds in *cis*-configuration and racemic form.

	<u>X=O</u>			<u>X=S</u>	
	<u>Y</u>	<u>Z</u>		<u>Y</u>	<u>Z</u>
1a	H	H	2a	H	H
1b	CH ₃	H	2b	CH ₃	H
1c	CH ₃ O	H	2c	OCH ₃	H
1d	Cl	H	2d	Cl	H
1e	H	CH ₃	2e	H	CH ₃
1f	H	CH ₃ O	2f	H	OCH ₃
1g	H	Cl	2g	H	Cl

Fig.2. Substituents and functionalities of β -lactams and β -thiolactams.

Three aspects of the present kinetic study are worthy of note: (a) The work represents the first investigation on structure/reactivity correlation for gas-phase pyrolysis reactions of these biologically important groups of compounds; (b) Thermal gas-phase reactions, under the conditions described here, provide an ideal model for comparative computational calculations of molecular parameters of biologically active systems; (c) The β -lactam ring represents the core of numerous anti-bacterial and anti-fungal agents, including penicillins and cephalosporins.²

Two investigations of relevance to the present study merit citation: (a) thermal and photolytic fragmentation of β -lactams to give alkenes and imines;³ (b) a more recent study on the cleavage of a β -lactam through mechanical activation using ultrasound.⁴

Results and Discussion

Kinetic Data Analysis

The first-order rate coefficients (k/s^{-1}) of the seven β -lactams are recorded in (Table 1), and the rates of the seven β -thiolactams are in (Table 2). Besides, the two tables include the values of the Arrhenius ($\log A/s^{-1}$) and energy of activation ($E_a/kJ\ mol^{-1}$) of the lactams. Each rate coefficient at any given reaction temperature represents an average from at least three measurements in agreement to within $\pm 2\%$. To obtain reliable kinetic data, the rates were calculated over a temperature range of $50 \pm 10\ K$ between 533 - 603 K for the β -lactams, and $50 \pm 10\ K$ between 463-542 K for the β -thiolactams.⁵⁻
⁸Kinetic runs were analyzed by monitoring the disappearance of substrates during the reactions, which were allowed to proceed for 92-98% pyrolysis (**series 1**) and 75-99% pyrolysis (**series 2**).

Table 1. Rate coefficient (k/s^{-1}), Arrhenius parameters, and $\Delta S^\ddagger$ of **1a-g**.

Cpd	Y	Z	T/K	$10^4\ k/s^{-1}$	$\log A/s^{-1}$	$E_a/kJ\ mol^{-1}$	$k_{510\ K}/s^{-1}$	$\Delta S^\ddagger_{510\ K}\ J\ K\ mol^{-1}$
1a	H	H	557.75	2.498	11.75 ± 0.87	164.36 ± 2.30	8.36×10^{-6}	-24.3
			568.05	4.335				
			577.75	6.951				
			587.65	13.27				
			597.65	27.33				
1b	CH ₃	H	552.85	2.416	11.94 ± 0.58	164.50 ± 1.50	1.24×10^{-5}	-20.7
			562.65	5.113				

			572.55	8.019				
			582.65	16.37				
			592.95	27.74				
1c	OCH ₃	H	542.85	2.210	13.71 ± 0.76	180.65 ± 1.97	1.63x10 ⁻⁵	13.2
			552.85	3.958				
			562.55	9.804				
			572.65	16.59				
			582.85	33.22				
1d	Cl	H	563.05	3.020	14.03 ± 0.15	189.32 ± 0.41	4.44x10 ⁻⁶	19.4
			572.95	5.835				
			582.45	11.62				
			593.15	23.23				
			602.95	43.26				
1e	H	CH ₃	532.75	1.639	10.99 ± 0.55	153.71 ± 1.46	1.76x10 ⁻⁵	-39.2
			562.45	5.009				
			572.55	8.524				
			582.95	15.65				
			592.45	30.22				
1f	H	OCH ₃	552.55	2.273	12.82 ± 0.50	174.22 ± 1.33	9.56x10 ⁻⁶	-3.81
			562.95	4.366				
			572.55	9.223				
			582.65	15.11				
			592.95	30.37				
1g	H	Cl	563.55	5.241	10.75 ± 1.77	152.27 ± 4.07	1.43x10 ⁻⁵	-43.5
			573.45	6.774				
			583.25	10.86				
			593.55	21.42				
			603.45	43.73				

Table 2. Rate coefficient (k/s^{-1}), Arrhenius parameters, and $\Delta S^\ddagger$ of **2a-g**.

Cpd	Y	Z	T/K	$10^4 k/s^{-1}$	$\text{Log } A/s^{-1}$	$E_a/kJmol^{-1}$	$k_{510\text{ K}}/s^{-1}$	$\Delta S^\ddagger_{510\text{ K}}/J\text{ K mol}^{-1}$
2a	H	H	492.35	2.780	9.91 ± 0.66	127.38 ± 1.56	7.40×10^{-4}	-59.5
			502.35	4.146				
			512.45	8.401				
			522.35	14.97				
			532.45	27.42				
2b	CH ₃	H	473.05	1.792	10.36 ± 0.90	128.00 ± 2.0	1.80×10^{-3}	-51.7
			483.25	2.896				
			493.15	6.851				
			502.65	12.98				
			512.85	19.58				
2c	OCH ₃	H	463.75	1.515	13.10 ± 0.21	149.85 ± 2.0	5.48×10^{-3}	1.21
			473.75	3.958				
			483.85	8.155				
			493.75	17.49				
			503.75	33.94				
2d	Cl	H	492.75	1.589	11.43 ± 1.38	142.65 ± 3.25	6.79×10^{-4}	-23.0
			502.25	5.236				
			512.25	8.704				
			522.35	14.24				
			542.35	46.27				
2e	H	CH ₃	463.05	1.400	8.94 ± 0.74	113.51 ± 1.60	2.05×10^{-3}	-78.2
			473.15	2.622				
			482.65	4.327				
			492.35	6.846				
			502.25	15.23				

2f	H	OCH ₃	473.15	0.840	7.42 ± 1.19	103.22 ± 5.45	7.08×10^{-4}	-107
			483.65	2.113				
			503.65	7.471				
			523.75	11.24				
			533.65	19.51				
2g	H	Cl	482.75	2.098	10.41 ± 1.55	130.35 ± 3.57	1.16×10^{-3}	-49.9
			492.85	3.512				
			502.75	9.755				
			512.75	10.80				
			522.85	26.76				

The Arrhenius plots from which $\log A/s^{-1}$ and $E_a/kJ\ mol^{-1}$ data were calculated, were strictly linear with correlation coefficients in the order of 0.997 ± 0.002 . Typical plots for β -lactam **1a** and its analogue β -thiolactam **2a** are shown in (Fig. 3a and Fig. 3b), respectively. The correlation coefficients of the two plots were 0.995 and 0.996, for 92% pyrolysis in each case. Tables (1) and (2) also include entropies of activation as well as rate constants at 510 K for the substrates under study; rates at ($T = 510\ K$) being obtained using the kinetic relation: $\log k = \log A - E_a/4.575T$.⁸⁻¹⁰ The rates at $T = 510\ K$ are used and reported for two practical reasons: (i) This temperature lies within the range over which kinetic measurements were conducted; (ii) Rate constants at this temperature allow comparisons of molecular reactivity to be made between the azetidinone compounds in the two series.⁵

Fig. 3(a) Log k vs $1000/T$ for pyrolysis of azetidinone **1a**.

Fig. 3(b) Log k vs 1000/T for pyrolysis of azetidinethione **2a**.

Pyrolysis Reaction Mechanism

The kinetic results of the pyrolysis of the azetidinones under study are rationalized on the basis of the same mechanism that was used earlier to explain reaction products. This mechanism consists of two steps (A,B), and has been described as a *retro*[2 + 2]cycloaddition-type fragmentation of the β -lactam ring (Figure 1).¹ It is instructive to note that the mechanism offered to explain the synthetic route to the β -lactams was formulated as initial formation of zwitterionic adduct which then undergoes a conrotatory ring closure to form the β -lactam. This conclusion was largely based on a kinetic analysis of substituent effects, and an application of Hammett linear free energy relationship (LFER) correlation.¹¹

The major contribution to the molecular reactivity of the azetidinone compounds comes from the (C-N) bond (i) of route (A), and the (C-NX) bond (ii) of route (B), as shown in Figure(4).

The (C-N) bond (i), having the lower enthalpy, is polarized, with partial negative charge accruing on the more electronegative (N) atom, and concomitant and commensurate positive charge on (C). The ease of (C-N) bond cleavage in four-membered azetidinone rings has been reported, albeit for enzymatic solution reactions.¹²

The (N-CX) bond (ii) forms part of a cyclic four-membered amide ring. This cyclic structure is under ring strain, which is further augmented by deviation from an expected trigonal planar angle of 120° at the (CX) carbon for an acyclic amide.¹³ The (N-CX) bond (ii) is also influenced by the lone pair of electrons on the (N) atom, that is subject to resonance delocalization incorporating the substituents on the aryl (Ar') group, and extending it to the amide (C=X) moiety. Besides, the difference in electronegativity between (O) and (S) is also known to influence the comparative behaviour of the amide/thioamide bond.^{13,14}

Relative Rates and Substituent Effects

The rates at 510 K (k/s^{-1}), and the relative rates (k_{rel}) of the seven β -lactams (X=O) and seven β -thiolactams (X=S) are together given in (Table 3).

Table 3. Rates at 510 K, and relative rates (k_{rel}) of β -lactams **1a-g**, and β -thiolactams **2a-g**.

(i)

Substrate (X=O)					Substrate (X=S)				
	<u>Y</u>	<u>Z</u>	<u>$10^6 k/s^{-1}$</u>	<u>k_{rel}</u>		<u>Y</u>	<u>Z</u>	<u>$10^4 k/s^{-1}$</u>	<u>k_{rel}</u>
1a	H	H	8.36	1	2a	H	H	7.40	1
1b	CH ₃	H	12.4	1.5	2b	CH ₃	H	18.0	2.4
1c	CH ₃ O	H	16.4	2.0	2c	CH ₃ O	H	54.8	7.4
1d	Cl	H	4.44	0.53	2d	Cl	H	6.71	0.91
1e	H	CH ₃	17.6	2.1	2e	H	CH ₃	20.5	2.8
1f	H	CH ₃ O	9.56	1.1	2f	H	CH ₃ O	7.08	0.96
1g	H	Cl	14.3	1.7	2g	H	Cl	11.6	1.6

Electron-donating groups (EDG) substituted at the (C) atom of the (C-N) bond enhance reactivity by stabilizing the positive charge being developed at the carbon centre; bond (i) pathway (A). An electron-withdrawing group (EWG) would be expected to have a stabilizing effect on the negative charge being developed at (N). The relative rates (Table. 3) support this analysis. The highest relative rates (2.0;7.4) are obtained in the β -lactam and β -thiolactam series, for (ρ -CH₃O) in **1c, 2c**, and the lowest (0.53;0.91) for (ρ -Cl) in **1d, 2d**. These substituents display mesomeric (resonance) effects, with Hammett substituent constants: $\sigma_p = -0.29$ and 0.22 , respectively.¹⁵ The methyl substituent has an inductive/hyperconjugative effect ($\sigma_p = -0.16$) and leads to a relative rate of intermediate magnitude. The three substituents (CH₃, CH₃O, Cl) produce the expected reverse effect on reactivity, when forming part of the aryl group (Ar') at the (N) end of the (C-N) bond (i). The relative rates for (ρ -Cl) are 1.7 and 1.6 (**1g, 2g**), compared with 1.1 and 0.96 for the (ρ -CH₃O) substituent.

Structure - Reactivity Correlation for β -Lactams/ β -Thiolactams

The comparative reactivities of the seven pairs of β -thiolactams/ β -lactams (C=S/C=O) are given in Table (4). These values are based on the rate constants (k/s^{-1}) at 510 K of Tables (1) and (2). Apart from the ketone/thione moieties, the substrates in each pair have the same structure. The difference in molecular reactivity observed for all seven pairs of compounds is, however, striking.

Table 4. Comparative reactivities ($k_{C=S}/k_{C=O}$) of the substrate pairs (**2a-g/1a-g**)

Lactam Pair:	2a/1a	2b/1b	2c/1c	2d/1d	2e/1e	2f/1f	2g/1g
$k_{C=S}/k_{C=O}$:	88.5	145	334	151	116	74.1	81.1

The β -thiolactams are significantly more reactive than their β -lactam counterparts by rate factors that are ca 74-334 times higher for X=S (Table 4). The relative rate factors ($C=S/C=O$) appear to be also influenced by substituents, the factors being of lower magnitude for compounds with substituents in the aryl (Ar') group.

The β -lactam core is a cyclic four-membered amide ring, that is kinetically reactive. This property has been utilized in the development of the "synthon method", by which β -lactams are prepared and then further used as precursors to novel organic compounds.^{11,16,17} However, as an amide, the (N-CX) bond has partial double bond character (bond order between double and single) due to resonance and delocalization of the lone pair of electrons of the (N) centre to the ($C=X$) moiety with which it is conjugated. Stronger resonance interaction produces a stronger (N-CX) bond (ii), and consequently a substrate of lower reactivity. Oxygen (O) exhibits stronger resonance interaction because of two main reasons: (1) Oxygen (O) has a much higher electronegativity compared with (S), and, therefore, promotes more effective electron delocalization; (2) Oxygen (O) uses (2p) orbital for overlap and bond formation, which is compatible with the (2p) orbital of the (C) atom to which it is bonded. Sulfur (S), on the other hand, uses a less compatible (3p) orbital for bond formation. It is perhaps informative to note that the (N) atom also uses (2p) orbital in the extended orbital overlap.

Conclusion

This kinetic investigation complements the earlier work on synthesis, and analysis of the products of STP and FVP reactions of the present substrates. The study represents the first kinetic analysis of the gas-phase thermolysis of azetidinones and their thione analogues. It is of interest to note that the four-membered ring of these compounds represents the core of a large number of important anti-bacterial and anti-fungal agents, including the penicillin and cephalosporin families. Further, the study presents kinetic evidence in support of the mechanism offered earlier to explain reaction products: namely, a formal [2 + 2] cycloreversion pathway. The investigation also provided data on a noteworthy effect of the ($C=O$) and ($C=S$) moieties of the azetidinones under study. Besides, the gas-phase thermolysis reactions are conducted in absence of reagents, solvents and catalysts, and hence structural effects and

reactivity correlations could be deemed intrinsic, which could be also of interest in comparative theoretical studies.

Experimental

Substrates and Pyrolysis

The details of the synthesis of the seven β -lactam compounds, and their seven β -thiolactam analogues were described in Part 1 of the present study.¹ The fourteen substrates are all 1,4-diarylderivatives of ($\pm$)-*cis*-3-phenoxyazetidin-2-one (β -lactams), and ($\pm$)-*cis*-3-phenoxyazetidine-2-thione (β -thiolactams). The mechanism of the synthetic reactions is explained in the earlier communication. The fourteen compounds were analyzed and fully characterised. Part 1 of the study also describes the techniques used for the pyrolysis of the β -lactams and β -thiolactams, and the analysis of the products of pyrolysis and the mechanism of the pyrolytic reactions.

Kinetic Measurements and Data Analysis

The quantitative measurements in the kinetic runs were made using (a) Waters HPLC, which consists of Waters HPLC pump model 515 and Waters UV detector model 2487; (b) Metrohm 709 IC Model, HPLC pump, and SPD 10 AV Shimadzu UV detector. The HPLC columns used in the analyses are Supelco ABZ⁺ 59197; (c) Chemical Data System (CDS) custom-made reactor and accessories.⁹

The required substrate (6-10 mg) was dissolved in acetonitrile (7 mL) as solvent to give a concentration of ca 1000-2000 ppm. An internal standard was then added to the solution and its amount was adjusted so as to give the desired peak area ratio of substrate to standard (2.5:1). Further, the solvent is chosen so as to dissolve the substrate completely at room temperature. Both the solvent and the internal standard are required to be stable under the pyrolysis conditions, and not to react with either substrate or products. Each mixture is then filtered to ensure that a homogeneous solution is obtained. The internal standards and the conditions for the kinetic investigation are given in (Table 5).

Table 5. Conditions for kinetics and HPLC analysis of substrate (**1a-g;2a-g**)

Substrate	Internal Standard	HPLC Column	λ/nm	Range (T/K)	Eluent (%) i : ii
1a	Chlorobenzene	ABZ ⁺	256	558-598	58:42
1b	1,3- Dichlorobenzene	ABZ ⁺	256	553-593	56:44
1c	1,3- Dichlorobenzene	ABZ ⁺	256	543-583	56:44
1d	1,3- Dichlorobenzene	ABZ ⁺	256	563-603	56:44
1e	1,3- Dichlorobenzene	ABZ ⁺	256	533-592	56:44
1f	Chlorobenzene	ABZ ⁺	256	553-593	56:44
1g	1,3- Dichlorobenzene	ABZ ⁺	256	564-603	52:48
2a	Chlorobenzene	ABZ ⁺	256	492-532	58:42
2b	1,2,4-Trichlorobenzene	ABZ ⁺	256	473-513	50:50
2c	1,2,4-Trichlorobenzene	ABZ ⁺	256	463-504	48:52
2d	Chlorobenzene	ABZ ⁺	256	493-542	55:45
2e	1,2,4-Trichlorobenzene	ABZ ⁺	256	463-502	49:51
2f	Chlorobenzene	ABZ ⁺	256	473-533	56:44
2g	1,3-Dichlorobenzene	ABZ ⁺	256	483-523	55:45

(i) CH_3CN (ii) H_2O

The weight ratio of the substrate with respect to the internal standard was calculated from the ratio of the substrate peak area to the peak area of the internal standard. The kinetic rate was obtained by tracing the rate of disappearance of the substrate with respect to the internal standard as follows:

Aliquot part (0.2mL) of each solution containing the substrate and the internal standard was pipetted into the reaction tube which was then sealed under vacuum, and placed in the pyrolyzer for six minutes under non-thermal conditions (ambient temperature). A sample was then analyzed using the HPLC probe, and the standardization value (A_0) was then calculated. Several HPLC measurements

were obtained with a consistency of ratio of $\pm 2\%$. The temperature of the pyrolysis block was then raised until approximately 10% pyrolysis was deemed to occur over a given period of residence time. This process was repeated after each 10-15°C rise in the temperature of the pyrolyzer until an average ca 90% pyrolysis was achieved. The relative ratios of the integration values of the sample and the internal standard (*A*) at the pyrolysis temperature were then calculated. A minimum of at least three reproducible kinetic runs were carried out at each 10-15°C rise in the temperature of the pyrolyzer to ensure acceptable values of (*A*).

Treatment of the kinetic data, and calculation of Arrhenius parameters and reaction rate constants have been detailed elsewhere.^{6,9,18}

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Graphical Abstract

Contribution to the molecular reactivity of β -lactam and β -thiolactam compounds is assessed from kinetic analysis of substituent and structural effects influencing bonds (i) and (ii).

Draft