Chemistry of Thienopyridines. XL. Reactions of 7-Acetyl-4-(1-carboethoxy-1-cyano)methylene-4,7-dihydrothieno-[2,3-b]pyridine. Part 3: Kinetics of Hydrolysis [1-3]

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The kinetics of hydrolysis of 7-acetyl-4-(1-carboethoxy-1-cyano)methylene-4,7-dihydrothieno[2,3-b]pyridine (1) in undried DMSO-d_6 to give ethyl 2-(4-thieno[2,3-b]pyridyl)cyanoacetate and acetic acid at ambient temperature was investigated by ^{1}H nmr spectrometry. The reaction is pseudo first order in the concentration of 1 with a rate constant of 9 x 10^{-4} per minute, not noticeably altered by the addition of deuteriotrifluoroacetic acid. The hydrolysis is, however, catalyzed by means of added pyridine-d_5 ($k = 37$ x 10^{-4} per minute). The pyridine is presumed to serve as a transfer agent for the acetylium ion as in acetylations with acetyl chloride and acetic anhydride.

In a previous publication we described the synthesis of 7-acetyl-4-(1-carboethoxy-1-cyano)methylene-4,7-dihydro-thieno[2,3-b]pyridine (1) and its solvolysis to ethyl 2-(4-thieno[2,3-b]pyridyl)cyanoacetate (2) by means of aqueous ethanol, anhydrous hydrogen chloride, and undried dimethyl sulfoxide [1]. In a preliminary, crude rate study it was ascertained that a sample of 1 in undried hexadeuteriodimethyl sulfoxide (DMSO-d_6) undergoes hydrolysis at room temperature over a period of 45 hours as per the equation 1 + H_2O → 2 + HOAc, where 2 was determined by isolation and acetic acid was determined by change in acidity of the solution plus ^{1}H nmr measurement for the methyl group present [1]. We now report a quantitative study of the kinetics of this reaction in (a) undried DMSO-d_6 alone, (b) solvent (a) plus added pyridine-d_5, and (c) solvent (a) plus added trifluoroacetic acid-d_1, all at ambient temperature.

The relative concentrations of 1 and acetic acid were determined as functions of time by comparison of the integration of the ^{1}H nmr singlet at δ 2.78 for the acetyl protons in 1 (designated $I_{2.78}$) with the integration of the singlet at δ 1.91 for the methyl protons of acetic acid formed (designated $I_{1.91}$). The extent of reaction, R_{TP},

$$R_{TP} = \frac{I_{1.91}}{I_{2.78} + I_{1.91}} \ ,$$

expressed by the relationship was then calculated as a function of time. The initial molar ratio of adventitious water to 1, W_O, at time $t = 0$ was also calculated from the

$$W_0 = \frac{I_{3.32}/2 + I_{1.91}/3}{I_{2.78}/3 + I_{1.91}/3}$$

relationship for the first ^{1}H nmr spectrum taken in the experiment, where $I_{3.32}$ refers to the integration of the singlet for water at δ 3.32. Typical data (for experiment 1, in

DMSO-d_6 alone) are shown in Table II in the Experimental. Four experiments were conducted, as indicated in Table I. All give linear plots of $\ln[1/(1-R_{TP})]$ versus time (t), consistent with kinetics which are pseudo first order in the concentration of 1. Two of these plots, for experiments 1 and 3 (the latter with added pyridine-d_5) are presented in Figure 1.

As noted in Table I two different nmr instruments were used in this study. The QE-300 instrument was less cumbersome to use than the XL-100A instrument and gave less scatter in experimental points. However, experiments 1 and 2, designed to be identical, gave the same first-order rate constants k within experimental error. While initial concentration of 1 was approximately 0.4-0.5 M in all four experiments the initial concentration of water varied more widely, from *ca.* 1.5-5 M. Ostensibly the concentration of water was always sufficiently large that it did not affect the
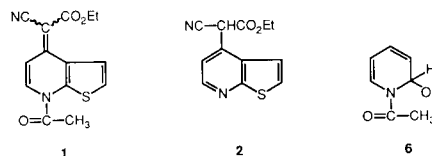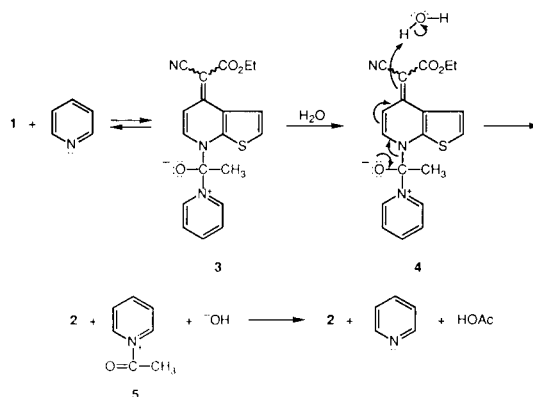

Scheme 1

Table I

Experimental Data for Kinetics of Hydrolysis of Compound 1 in Undried DMSO-d_6 at Ambient Temperature

Experiment No.	Instrument used	Inital reaction conditions			First-order rate constant $10^4 \times k$ (min^{-1}) [b]	Intercept on ordinate axis, [b]	Half life $t_{1/2}$ (min) [c]
		Molarity of 1	W_0 [a]	Additive			
1	QE-300	0.40	3.75	none	9.6 ±0.3	0.047 ±0.007	722
2	XL-100A	saturated [d]	12.70	none	9.0 ±0.5	0.143 ±0.025	770
3	QE-300	0.45	11.64	pyridine-d_5 0.45 M	37.0 ±0.2	0.069 ±0.007	187
4	XL-100A	0.52	8.70	CF$_3$CO$_2$D 0.24 M	9.3 ±1.3	0.248 ±0.150	745

[a] W_0 is the molar ratio of water to 1 at $t = 0$. [b] The variation shown in these values corresponds to one standard deviation, σ. [c] Calculated from $t_{1/2} = 0.693/k$, without consideration of σ. [d] Concentration is approximately 0.4 M.
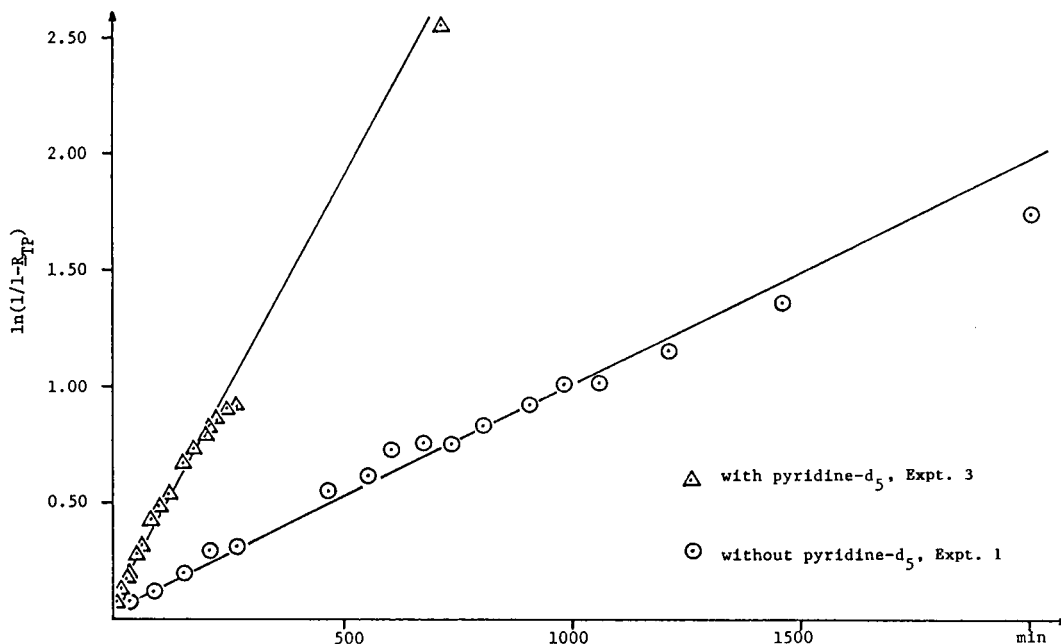

Figure 1. First order plots for kinetics of hydrolysis of compound 1 in undried DMSO-d_6.

observed first-order kinetics which persisted for approximately three half-lives. Nonetheless, the solubility of 1 in the DMSO-d_6 solvent clearly decreased with increasing concentration of water (compare Experiments 1 and 2) and increasing concentration of water may serve to slow the rate of hydrolysis due to alteration of solvent effects (compare $t_{1/2}$ in Experiments 1,2, and 4). Addition of the strong acid deuteriotrifluoroacetic acid to the reaction mixture (Experiment 4) showed little, if any, change in the rate of reaction. Thus, it appears that the hydrolysis is not catalyzed by deuterons (or protons). Contrariwise, addition of a molar quantity of pentadeuteriopyridine (Experiment 3) caused a marked increase (by a factor of *ca.* 4) in the rate of reaction, a phenomenon attributed to base catalysis. It

is well known that pyridine catalyzes the acylation of alcohols by acetic anhydride or acyl halides [5,6]. The hydrolysis of 1 is, of course, an acetylation of water. While we have not determined the order of reaction in either pyridine or water we are attracted to Scheme 1 as a mechanistic rationale for the catalysis of hydrolysis by pyridine [7]. In Scheme 1 compound 1 undergoes nucleophilic attack by pyridine onto the N-carbonyl carbon to produce complex 3. This activates the molecule to attack by water, which may occur as illustrated in structure 4. In the overall process pyridine serves as a transfer agent for the acetylium ion. In fact, cation 5 has been assumed to form when acetyl chloride or acetic anhydride interacts with pyridine [8,9]. This cation then reacts with anions (hydrox-
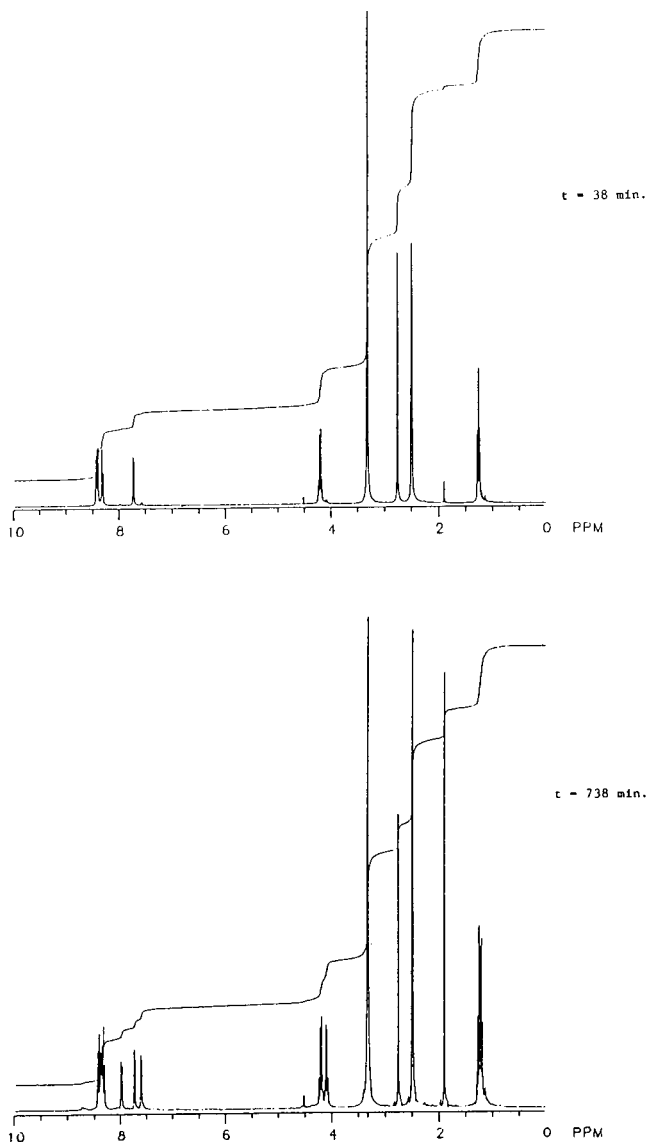
Figure 2. Comparison of ^{1}H nmr spectra for Experiment 1 at two different reaction times.

Table II

Measured and Calculated Data for Kinetic Experiment Number 1: Initial concentration of 1, $0.4\,M$, $W_0 = 3.75$, solvent: undried DMSO-d$_6$ [a]

Time t (minutes)	$I_{2.78}$ measured	$I_{1.91}$ measured	Extent of reaction, R_{TP}	$\ln\left(\dfrac{1}{1-R_{TP}}\right)$
0 [b]	(——)	(0.00)	(0.000)	(0.000)
38	1.80	0.15	0.077	0.080
91	1.60	0.20	0.111	0.118
152	1.60	0.35	0.179	0.197
213	1.50	0.50	0.250	0.288
265	0.80	0.30	0.273	0.319
467	0.82	0.60	0.423	0.550
550	0.90	0.75	0.455	0.607
610	0.80	0.85	0.515	0.724
678	0.89	1.00	0.529	0.753
738	1.00	1.11	0.526	0.747
811	1.00	1.30	0.565	0.832
907	0.72	1.10	0.604	0.926
985	0.80	1.38	0.633	1.002
1056	0.70	1.22	0.635	1.008
1210	0.58	1.27	0.686	1.158
1456	0.36	1.05	0.745	1.366
2000	0.45	2.16	0.828	1.760

[a] See text for meaning of various symbols. [b] Data for $t = 0$ are not measured directly.

means of a General Electric QE-300 nmr instrument with the internal clock used for timing and with automatic computer integration for each signal over the interval 0-10 ppm. About 100 mg of 1 (mp 216-218° [1]) was placed in an nmr tube (Wilmad Glass Co., 512-RP), followed by the addition of about 1 ml (measured) of hexadeuteriodimethyl sulfoxide (Mallinckrodt, 99.5% minimum isotopic purity), either alone (Experiments 1 and 2) or plus a measured quantity of pentadeuteriopyridine (Diaprep, Inc., 99 atom % D, Experiment 3) or of deuteriotrifluoroacetic acid (Aldrich, 99 atom % D, Experiment 4). The nmr tube was capped immediately and shaken vigorously for a few seconds. Timing was started and the ^{1}H nmr spectrum was measured at selected reaction times, t (minutes). Two typical measured nmr spectra from Experiment 1 are shown in Figure 2. The chemical identification of the signal at δ 3.32 as derived from water was checked on the DMSO-d$_6$ solvent by itself, while that of the signal at δ 1.91 as derived from acetic acid was checked by noting signal enhancement of this singlet when *bona fide* acetic acid was added to the reaction mixture. No effort was made to control the concentration of water in the starting solution. Values for the extent of reaction, R_{TP}, and $\ln[1/(1-R_{TP})]$ were calculated for each measurement as indicated in the discussion. Plots of the latter function versus time (t) in minutes were fit with the best straight lines by means of a least squares computer program. The slope, vertical intercept, and corresponding standard deviations (σ) were determined from these plots and are the bases of the data on the rate constants and intercepts given in Table I.

Acknowledgment.

ide in this case), perhaps *via* intermediate **6** to yield acetic acid [7,9]. Several less elegant mechanisms seem possible for the direct hydrolysis of **1**.

EXPERIMENTAL

Initial kinetic studies (Experiments 2 and 4) were conducted by means of a Varian XL-100A nmr instrument using a stopwatch for timing and 2-6 integrations of the proton signals over an interval of 1-4 ppm at each reaction time. For each set of integrations a Q-test was used to reject data which were out of range [10]. Then the average of the remaining data was taken as the measured integration, I. Experiments 1 and 3 were conducted much more conveniently and with considerably less scatter of points by

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[6] Pyridine was also used to catalyze the acetylation of cholesterol by **1** [2].

[7] An extension of this Scheme to include acetylation of both water and acetic acid may be invoked to rationalize the reaction of the quinoline analog of **1** with undried DMSO-d_6 [unpublished results from this laboratory].

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