Rates of Acid-Catalyzed NH Proton Exchange of Enaminones, an ^1H NMR Study

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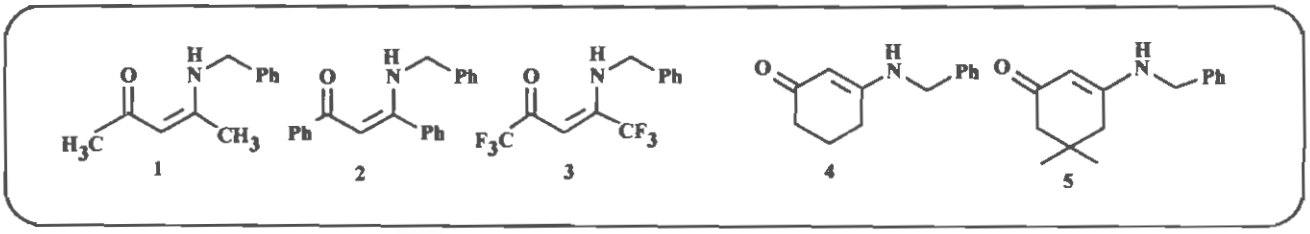
ABSTRACT: *^1H NMR spectra of a series of enaminones R-CO-CH=C(NHCH$_2$Ph)-R [1, R=CH3; 2, R=C$_6$H$_5$; 3, R=CF$_3$; 4, R=CH$_2$CH$_2$CH$_2$; 5, R=CH$_2$C(CH$_3$)$_2$CH$_2$], were obtained in the presence of trifluoroacetic acid in CDCl$_3$ or DMSO-d$_6$ at 28°C. Steric, solvent, electronic and hydrogen bonding effects on the rates of acid-catalyzed NH proton exchanges were investigated. Rate constants were calculated by the ^1H NMR line shape analysis.*

KEY WORDS: *Proton exchange reaction, Acid-catalyzed proton exchange, Dynamic NMR spectroscopy, Rate constants, Enaminones*

Proton exchanges catalyzed by acids and bases are one of the widely studied chemical reactions [1]. During the past three decades, by the development of relaxation spectroscopy [2] and dynamic NMR spectroscopy [3], it has been possible to study fast and "ultrafast" [4] proton exchange reactions, in particular those involving oxygen [5] and nitrogen [6,7] acids and bases.

In connection with our previous works [8], we report here the use of proton spin-spin spillitings in ^1H NMR spectroscopy to measure the rates of NH proton exchanges of five enaminones **1-5** in the presence of trifluoroacetic acid in $CDCl_3$ or DMSO-d_6 .

To the best of our knowledge, no investigation of proton exchange reactions of enaminones has been reported, despite their importance as versatile reagents in organic syntheses [9]. For suitably substi-



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tuted enaminones the NH proton exchange could be monitored by following the gradual collapse of the coupling constant of protons coupled to the exchanging protons. This technique has been successfully applied to substituted amides [10], hydrazines [11], ureas [12], thioureas [13], thioamides [13], thiolactams [13] and lactams [14].

The *N*-methylene proton signal of 3-benzylamino-cyclohex-2-ene-1-one **4** is a doublet with 5.3 Hz coupling constant under non-exchange condition. Fig. 1 shows the *N*-methylene proton signal of the experimentally observed spectra and their corresponding simulated spectra. As the $[H^+]$ is increased the valley-to-peak intensity ratio of *N*-methyl signal decreases significantly. By plotting the pseudo first-order rate constants k_{obs} estimated from lineshape analysis *vs.* $[H^+]$, the second-order rate constant ($k_H = 5.2\times10^3$ M^{-1} sec^{-1}) of acid catalyzed NH proton exchange is obtained. The same procedure was used for studying the rates of NH proton exchanges for other enaminones **2-5**. Table 1 lists the obtained second-order rate constants for enaminones **1-5** in $CDCl_3$ or DMSO-d_6.

EXPERIMENTAL

Chemical and sample preparation

Acetylacetone, trifluoroacetic acid, $CDCl_3$, DMSO-d_6 were obtained from Merck. Cyclohexane-1,3-dione, dimedon, and dibenzoylmethane were obtained from Fluka (Bachs, Switzerland). Hexafluoroacetylacetone was obtained from Sigma. These chemicals were used without further purification. Enaminones **1-5** were prepared from appropriate diketones and benzyl-

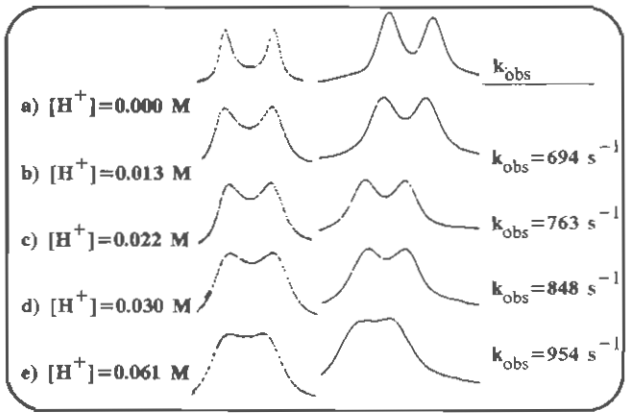

Fig. 1: Right: Expanded spectra of N-methylene regions of 4 in $CDCl_3$; Left: Simulated spectra

Table 1: Second-order rate constants for N-H proton exchange in enaminones 1-5 in $CDCl_3$ or DMSO-d_6 at 28°C

Entry	$k_H \times10^{-2}(M^{-1}sec^{-1})$	
	$CDCl_3$	DMSO-d_6
1	270	8
2	188	-
3	18	-
4	52	13
5	41	4

amine by using microwave irradiation [16].

Typical procedure of sample preparation is described for 4-benzylamino-pent-3-en-2-one (**1**).

To a 2 mL volumetric flask, containing 0.65 mmol (0.12 g) of **1** was added about 2 mL $CDCl_3$ or DMSO-d_6 to reach the mark. Each NMR tube was charged with only 300 μL of this solution and various amounts of trifluoroacetic acid was added.

Kinetics

The ^1H NMR spectra were recorded at 28°C on a JEOL-EX 90 FT NMR spectrometer, using deuterium signal of the solvent as the lock and TMS as internal standard. The most important measurement parameters were as follows: sweep with 800 Hz, pulse width 3 μs (ca. 40°flip angle), acquision time 4.550 s, number of scans 16 and computer memory of 16 K. Samples for kinetic measurement were allowed to equilibrate in the NMR probe for 5 min before taking the spectrum. NMR spectra of benzylic methylene protons were simulated using a computer program for an uncoupled two-site case, employing the Bloch equation modified for chemical exchange effects [17].

By varying the substituent from electron-donating (CH_3) to electron-withdrawing group (CF_3), the observed decrease in the second-order rate constants can be attributed to the increase in the strength of intramolecular hydrogen bonding. The lower exchange rate in compounds **4** and **5** may be due to the impossibility of the intramolecular hydrogen bonding or the steric inaccessibility of the NH proton.

According to Table 1 (entries 1, **4** and **5**), by changing the polar solvent ($CDCl_3$) to aprotic polar solvent, DMSO-d_6 , smaller second-order rate constants were observed. The smaller rate constant observed in

DMSO-d_6 could be rationalized on the basis of enhanced solvation of the NH proton in DMSO-d_6 solution [15].

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