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^{15}N NUCLEAR MAGNETIC RESONANCE SPECTROSCOPIC INVESTIGATION OF DIFFERENTIAL RATES OF BASE-CATALYZED N-H PROTON-EXCHANGE REACTIONS OF 1-AZA-2-CYCLOHEPTANONE AND 1-AZA-2-CYCLOHEPTANETHIONE[1]

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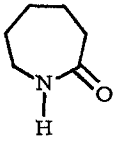
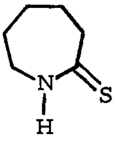
Summary: Natural-abundance proton-coupled ^{15}N NMR spectra of an equimolar solution of the title compounds in dimethyl sulfoxide, to which was added aqueous sodium hydroxide, show that N-H proton exchange of the thiolactam is about 1500 times faster than that of the lactam at 25°C. This rate difference is suggested to arise from a greater contribution of the polar resonance structure for the thiolactam.

Relaxation spectroscopy[2] and dynamic ^{1}H NMR spectroscopy[3] have been widely used to measure fast N-H proton-transfer reaction rates of amines, amides, and amino acids.[4] We herein describe the use of the ^{15}N-H splittings in ^{15}N NMR spectroscopy as an efficient tool for simultaneous study of the rates of base-catalyzed N-H proton exchange of 1-aza-2-cycloheptanone (I) and 1-aza-2-cycloheptanethione (II) in dimethyl sulfoxide solutions.


I


II

Nitrogen-15 NMR spectra of an equimolar solution of I and II in dimethyl sulfoxide at 25°C are shown in Figure 1 and the corresponding chemical shifts are given in Table 1. The ^{1}H noise-decoupled spectrum exhibits two sharp ($\omega_{1/2}$ = 3 Hz) resonances and these appear as two doublets in the gated ^{1}H noise-decoupled spectrum because of slow N-H proton exchange. Each component of the doublets has a line width about twice that of the proton-decoupled spectrum as the result of

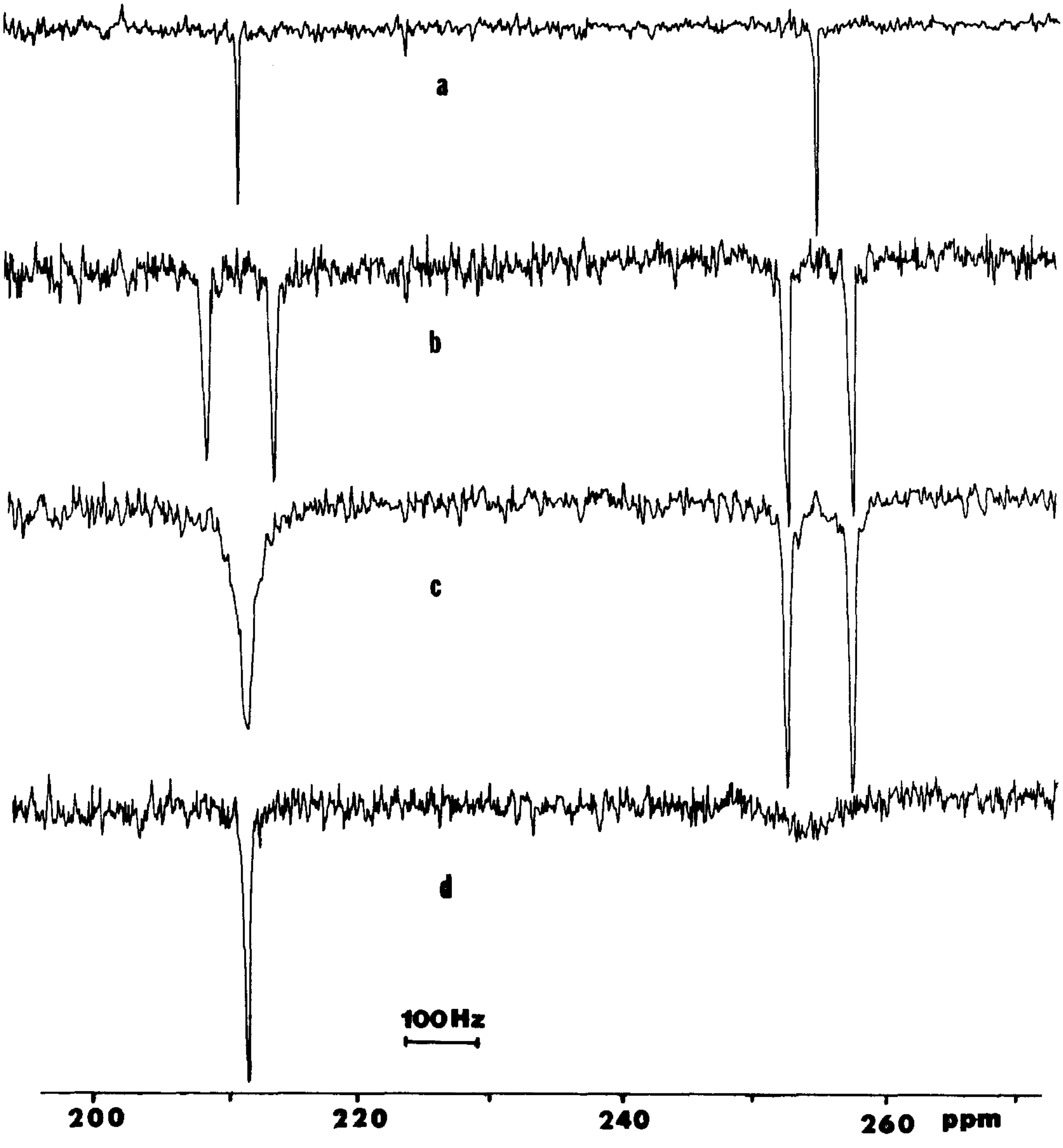


Figure 1. Natural-abundance 18.25-MHz ^{15}N NMR spectra of I and II in dimethyl sulfoxide (0.03 mole of each in 20 ml solvent) at 25° C: a, with ^{1}H noise decoupling, 60 transients; b, with gated ^{1}H noise decoupling, 720 transients; c, as b, but in the presence of 0.3 ml of 1 M aqueous sodium hydroxide, 2550 transients; d, as c, but in the presence of an additional 0.2 ml of the base, 560 transients. The ^{15}N NMR spectra are Fourier transforms of the sums of free-induction decays obtained with a 45° pulse angle, 4 K data points, 3000-Hz spectral width, and a pulse interval of 3 s.

unresolved long-range spin-spin coupling with the ring methylene protons. When about 0.3 ml of 1 M aqueous sodium hydroxide is added to the dimethyl sulfoxide solution of I and II, the doublet assigned to II in the proton-coupled ^{15}N spectrum collapses and appears as a single broad band while that of I is only slightly broadened. Further addition of about 0.2 ml of the base causes the doublet arising from I to become a broad singlet. Addition of 2 ml of the base results in two fairly sharp single resonances in the proton-coupled spectrum. Some conversion to the conjugate bases is apparent from the changes in ^{15}N chemical shifts of I and II as base is added. Thus, addition of sufficient NaOH to give a 1:0.05 mole ratio of amide to base causes a 2.4 ppm downfield shift of the nitrogen resonance of I and a 4.1 ppm downfield shift of II.

Table 1

Nitrogen-15 Resonance Positions[a] in I and II in Dimethyl Sulfoxide

1 M NaOH added, ml	I	II
None	256.2	212.5
0.5	254.8	211.6
2.5	253.8	208.4

[a] In parts per million upfield from external 1 M 98% ^{15}N-enriched nitric acid in D_2O.

Line shapes calculated for the proton-coupled ^{15}N NMR spectra obtained in the presence of aqueous sodium hydroxide, using an effective line width of 6 Hz and ^{15}N-^{1}H spin-spin coupling constants of 88 and 92 Hz for I and II, respectively, show that the rate of base-catalyzed N-H proton exchange of II is about 1500 ± 200 times faster than for I. Similar exchange-rate differences were obtained by addition of base to an equimolar solution of I and II in 70% aqueous dimethyl sulfoxide at 25 °C.

The free-energy barrier to internal rotation about the central N-C bond is 3-5 kcal/mol higher for thioamides than for the corresponding amides.[5] This difference can be attributed to higher double-bond character of the N-C bond in thioamides as a consequence of a greater contribution of the valence-bond structure $-H\overset{\oplus}{N}{=}C(\overset{\ominus}{S})-$ to the resonance hybrid.[5] While the barriers to internal rotation about the N-C_2 bonds in I and II are not known, the available data[5] on amides and thioamides suggest a higher value for the barrier in II. If so, then the N-H protons of II are expected to be more acidic than the corresponding protons in I, as appears to be the case. The present results suggest that there is no great effect on the N-H exchange rates because of differences in configuration of the amide groups. Thus, the rate ratio for I and II (1500) is similar to that (1000, in water) reported[6] for *N*-methylacetamide and *N*-methylthioacetamide where the *trans* configurations are dominant.

References and Notes

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