Hindered Internal Rotation Around the C-N Bond in 1*H*-Azepine Derivatives as Studied by the NMR Techniques

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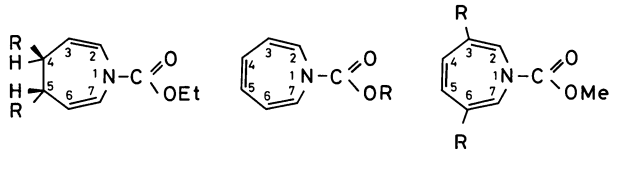
Thermodynamical parameters for the restricted rotation of seven title derivatives have been obtained by means of DNMR techniques. The results were explained in terms of a conjugation of the nitrogen atom in the seven-membered ring with the adjacent carbonyl carbon.

The internal rotations around the carbonyl carbon to the nitrogen bond (referred to as the amide bond) in many amides were extensively studied by the NMR techniques.[1]

In our previous papers we reported that the reactions of 1-ethoxycarbonyl-1*H*-azepine and chlorosilanes in HMPA in the presence of magenesium afforded 4,5-dihydro-1*H*-azepine derivatives, the NMR spectra of which were influenced by the temperature.[2] In order to investigate the effect of the ring size and the conjugation on the rotation around the amide bond, we intended to obtain thermodynamical parameters of the internal rotations around the amide bonds of several 1-alkoxycarbonyl-1*H*-azepine derivatives. Here, we wish to discuss these results circumstantially, although preliminary results have already been reported in brief.[3]

Experimental

The samples studied(Scheme 1) were prepared by methods previously reported.[2,4-7] The samples were dissolved in acetone-d_6, $CDCl_3$, or CH_3OH, ranging in concentration from about 0.02 to 0.25 g ml^{-1}. The solvent or tetramethylsilane peak was used as a reference signal of the chemical shifts and was used for calibrating the natural line width and adjusting the field-homogeneity. ^1H NMR spectra of **1** were measured with a Hitachi R-20B spectrometer at 60 MHz equipped with a R-202VTC variable temperature controller. Those of **3** were measured with a Varian VXR-500 spectrometer. Sample temperatures of **1** and **3** were calibrated by a copper–constantan thermocouple with an accuracy of ±0.6 °C. The ^{13}C NMR spectra were measured with a Varian XL-200 spectrometer at 50.3 MHz, in which the sample temperatures were calibrated with temperature-dependent chemical shifts of methanol (low-temperature range) or ethylene glycol (high-temperature range) using the standard equation with an accuracy of ±0.2 °C. Theoretical DNMR spectra were calculated with HITAC-8450, M160-II, or ACOS 2010 computer using a modified QCPE program.[8]



1. R = Si(Me)$_3$

2. a: R = Me
   b: R = Et

3. a: R = Me
   b: R = i-Pr
   c: R = t-Bu
   d: R = -(CH$_2$)$_8$-

Scheme 1.

Results and Discussion

NMR Spectra. An entire typical ^1H NMR spectrum of **1** is shown in Fig. 1, where the H_4 and H_5 signals overlap with solvent peaks. Because ethyl protons are isolated from other ones in the molecule, the ring proton spectra of **1** were analyzed as a four-spin system when the H_4 and H_5 signals were irradiated. The H_2 and H_7 signals are split into two quartets at −56 °C. The ^1H NMR spectra at −56 °C

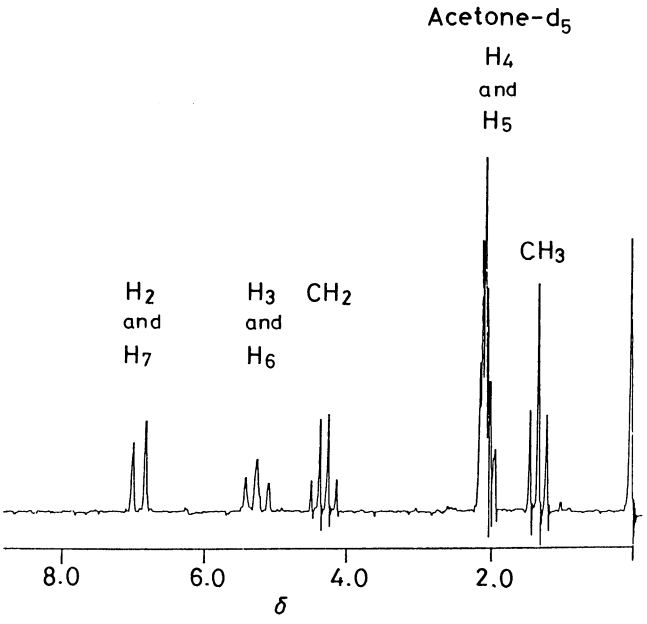


Fig. 1. ^1H NMR spectrum of **1** dissolved in acetone-d_6 at 60 MHz and 31.5 °C.

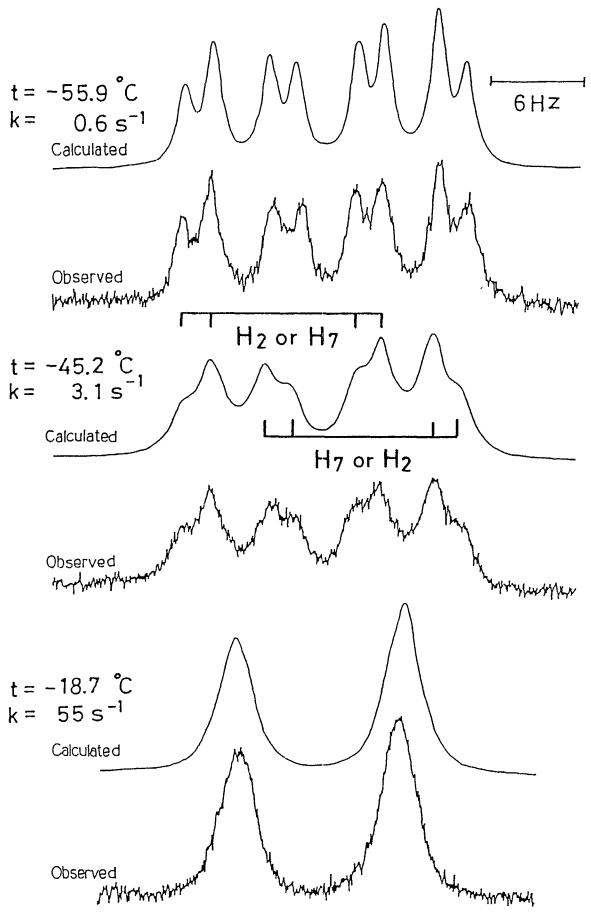


Fig. 2. Examples of observed (lower) and calculated (upper) spectra of H_2 and H_7 of **1** measured at −18.7, −45.2, and −55.9 °C respectively.

were analyzed by the LAOCN3 program.[9] The differences in the chemical shifts of H_2 and H_7, as well as H_3 and H_6 of **1** are 5.2 and 1.9 Hz, respectively. The temperature-dependent expanded spectra of H_2 and H_7 of **1** are given in Fig. 2. The signals of the ethyl group of **1** appeared at δ=1.30 and 4.25 and those of the trimethylsilyl groups were at δ=0.00. The ring-proton spectra of **2a** and **2b** at room temperature are shown in Fig. 3. The spectral patterns are similar to those given by Paquette et al.[4] They stated that the assignment of their spectra was based on Schmid's molecular orbital calculations.[10] As shown in Fig. 3, the spectral pattern of **2a** is quite similar to that of **2b**. Their signals can be assigned to those coming from the H_3, H_2, and H_4 from higher to lower field. Their pattern shows a quite characteristic feature; the line widths of the H_2 and H_3 signals are broad and that of the H_4 is narrow. The temperature-dependent spectral changes of **2a** or **2b** are rather difficult to observe in their ^{1}H NMR spectra. Paquette et al. also stated that all of the ^{1}H NMR spectra of the 1*H*-azepines proved to be invariant over a substantial temperature range from −90 to 130 °C.[4] However, we noticed that ^{13}C spectral patterns are

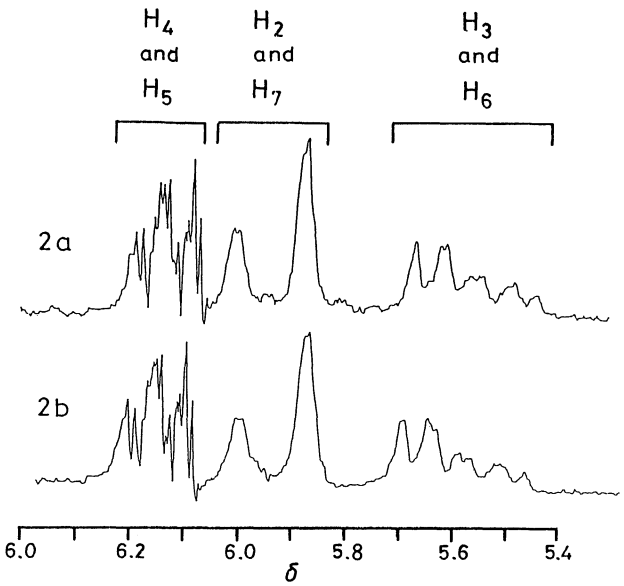


Fig. 3. Expanded ^{1}H NMR spectra of the ring protons of **2a** (upper) and **2b** (lower) at 60 MHz and 31.5 °C.

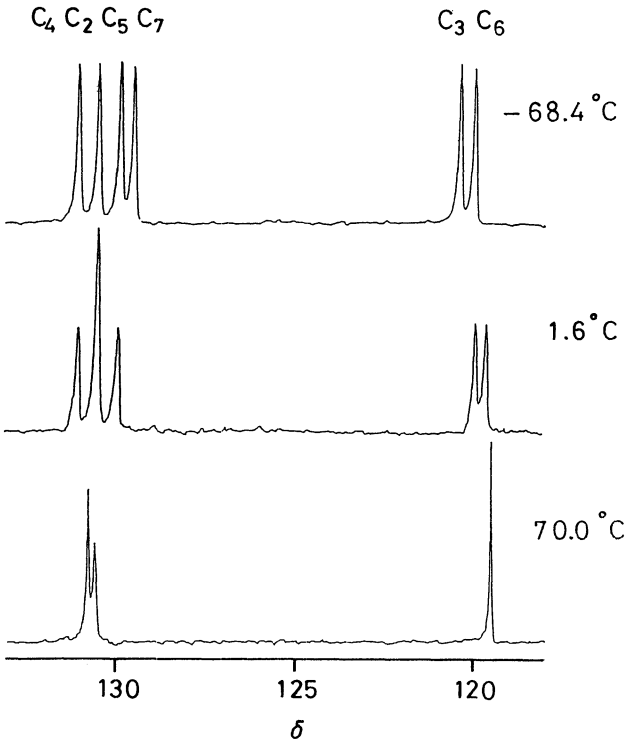


Fig. 4. Temperature-dependent ^{13}C NMR spectra of the ring carbons of **2a** at 50.3 MHz in $CDCl_3$ and at (a) 70.0, (b) 1.6, (c) −68.4 °C. The assignment of the C_2, C_3, or C_4 signal can be exchanged with that of the C_7, C_6, or C_5 one respectively.

convenient to observe their temperature dependencies, examples of which are shown in Fig. 4. The spectral patterns of the ring carbons of **2a** and **2b** are temperature-dependent. As can be seen in Fig. 4, there

are six signals of the ring carbons of **2a** at lower temperature, but they become three coalesced signals at higher temperature although their line widths seem to be different even at 70 °C, as expected from their different signal heights. On the other hand, the spectra of the ring-protons of **3** showed a very simple pattern because of introducing alkyl substituents at the 3,6-positions on the ring. The temperature-dependencies of the spectal lines of H_2 and H_7 were observed from room temperature to 60 °C using a 500-MHz spectrometer.

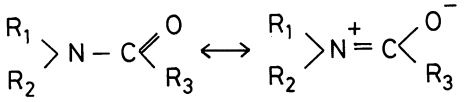
Temperature-dependent NMR spectra of nitrogen-containing compounds are one of the controversial subjects concerning their explanation whether they should be ascribed to an inversion of the nitrogen atom or a rotation around the amide bond. In the present case, however, the situation is explained by considering the temperature-dependent ^{13}C NMR spectra. As stated before, the six signals of the ring carbons of **2a** were observed at lower temperature. They coalesced to three signals at higher temperature (Fig. 4). This result was only explained to be caused by hindered internal rotation around the amide bond, but not by nitrogen inversion. Then, the characteristic features of the spectral patterns of $H_2(H_7)$ and $H_3(H_6)$ in **2a** and **2b** (Fig. 3) can be attributed to the partly coalesced spectra of H_2 and H_7, and H_3 and H_6.

Table 1. Rate Constants of the Hindered Rotations around the C–N Bond of **1**, **2a**, and **3a**

1	**2a**	**3a**
Temp(K)/k(s^{-1})	Temp(K)/k(s^{-1})	Temp(K)/k(s^{-1})
269.5/290	343.2/1700	337.9/168
265.1/170	323.1/ 380	330.0/124
259.4/ 90	313.2/ 160	328.2/ 92
254.5/ 55	308.2/ 110	326.2/ 82
249.0/ 32	303.2/ 65	323.0/ 67
243.9/ 16	300.1/ 48	317.8/ 46
238.5/ 9.5	295.0/ 34	312.7/ 34
233.4/ 5.8	290.0/ 21	307.5/ 22
228.0/ 3.1	284.8/ 16	300.1/ 12
223.0/ 1.5		295.7/ 9.0
217.3/ 0.6		

DNMR Analyses. Examples of the calcualted and experimental ^1H DNMR spectra of **1** are shown in Fig. 2. The kinetic parameters have been determined by visual fittings of the calculated line-shapes with the experimental ones. DNMR analyses for C_3 and C_6 of **2a** and **2b** were carried out as an AX spin system without any coupling. Several examples of the rate constants, thus determind, are given in Table 1. Thermodynamical parameters were obtained by the Eyring and Arrhenius plottings of the rate constants with the inverse temperatures, one example of which is shown in Fig. 5. The thermodynamical parameters, thus obtained, are given in Table 2.

The internal rotations around the C–N bond in amides were given much attention by chemists, since they were earlier studied by Gutowsky and Holmes.[11] It is considered that the hindered rotations is related to a conjugation between the nitrogen atom and the carbonyl group, as shown in Scheme 2. Therefore, the



Scheme 2.

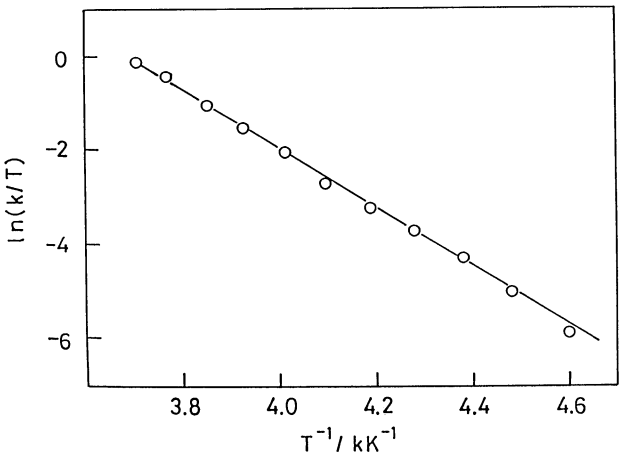


Fig. 5. An Eyring plot for the rotation of the amide bond of **1** in acetone-d_6.

Table 2. Thermodynamic Parameters for the Hindered Rotation Around the Amide Bond of 1*H*-Azepine Derivatives Obtained from DNMR Analyses

No./Solvent	E_a / kJ mol^{-1}	log A	$\Delta H^{\ddagger}$ / kJ mol^{-1}	$\Delta S^{\ddagger}$ / J K^{-1} mol^{-1}
1/$(CD_3)_2CO$	55.7±2.1	13.2±0.5	53.7±2.1	1.2±3.5
2a/$CDCl_3$	66.6±1.7	13.3±0.3	64.0±1.7	1.7±5.5
2b/$CDCl_3$	61.3±1.2	12.4±0.2	58.8±1.2	−15.8±3.9
2b/CH_3OH	59.8±2.7	12.1±0.5	57.3±2.7	−21.3±9.1
3a/$CDCl_3$	59.3±1.2	11.4±0.2	56.7±1.2	−35.2±3.9
3b/$CDCl_3$	51.1±1.3	10.4±0.2	48.6±1.3	−55.4±4.2
3c/$CDCl_3$	53.6±0.8	11.0±0.1	51.0±0.8	−43.4±2.5
3d/$CDCl_3$	53.5±0.6	10.7±0.6	50.9±0.6	−48.0±1.8

Table 3. Free Energies of Activation of Hindered Rotation around the Amide Bond in 1*H*-Azepine Derivatives (**1**—**3**) Calculated from their ^1H and ^{13}C NMR Spectra

Compounds	Solvent	T_c	$\Delta\nu$	$\Delta G_c^{\neq}$ [a]
		K	Hz	kJ mol^{-1}
1	$(CD_3)_2CO$	242 (C_2, C_7)	8.0[b]	53.0
		237 (C_3, C_6)	4.5[b]	53.0
2a	$CDCl_3$	293 (C_3, C_6)	21.2[b]	62.3
2b	$CDCl_3$	300 (C_3, C_6)	27.5[b]	63.2
	CH_3OH	295 (C_3, C_6)	20.6[b]	62.8
3a	$CDCl_3$	326 (H_2, H_7)	37.0[c]	68.1
3b	$CDCl_3$	320 (H_2, H_7)	40.4[c]	66.6
3c	$CDCl_3$	313 (H_2, H_7)	49.5[c]	64.5
3d	$CDCl_3$	315 (H_2, H_7)	27.8[c]	66.5

a) $\Delta G_c^{\neq}$ are calculated with an equation ($\Delta G_c^{\neq}=19.14\times T_c\,(9.972+\log(T_c/\Delta\nu))$ in Ref. 20), using $\Delta\nu$ and T_c. b) At 50.3 MHz. c) At 500 MHz.

barriers of the rotations around the amide bond would be related to the electronic properties of the R_1, R_2, and R_3 groups. If R_3 is an electron-attracting group, the barrier increases. If R_3 is an electron-donating group, the barrier decreases.[12]

The values of **1**, **2**, and **3** found in this study are appreciably lower than those of the acid amides observed earlier.[1,13] The free energies of activation of **1**, **2**, and **3** for their rotations can be calculated in another way from their coalescence temperatures and chemical-shift differences of ^1H and ^{13}C NMR spectra, as given in Table 3. The values are consistent with those calculated from the parameters given in Table 2. As can be seen in Table 3, the coalescence temperatures of **2** and **3** are higher than that of **1**. Further, the values of $\Delta\nu$ for **2** and **3** are also larger than that of **1**. The difference of the corresponding values between **1** and **2** or **1** and **3** can be ascribed to the difference of their frameworks of the seven-membered ring. Six-ring carbons of **2** and **3** construct a conjugate system. Those of **1**, however, are separated into two parts because of the absence of a double bond between C_4 and C_5. This situation affects the whole conjugation system, including the nitrogen atom. In other words, the bond order of C_2 (or C_7) and N becomes larger in **1** than that in **2** or **3**. This affects the bond order of the amide bond in question. That is to say, the amide bond of **1** is weaker than that of **2** or **3**. The data in Table 2 support this explanation. This means that in Scheme 2 the conjugation power of R_1 or R_2 to nitrogen is important for the restricted rotation around the amide bond.

Another point of interest is that sterically large substituents seem to be effective to the E_a values. The value of **3a** is larger than those of **3b**, **3c**, and **3d**, but it is smaller than that of **2a**. Further, it is not curious that **2b** gave similar thermodynamical data in two different solvents. Such data for *N*,*N*-dimethylformamide were compared in a number of solvents.[1]

The compounds studied here are considered to be kinds of carbamates. Recently, Julia et al. reported kinetic data concerning restricted rotations of the amide bonds of some carbamates.[14] The $\Delta G_c^{\neq}$ values of **2** and **3** are similar to those of Julia et al., but that of **1** is lower than theirs. Further, our present values of **2** and **3** are similar to those in several simple dimethylcarbamates, which are estimated to be 62—70 kJ mol^{-1} from Table 1 of Ref. 15. Other examples were reported by Sato et al., in which sterically limited situations were considered around the nitrogen atom and extremely large barriers were measured.[16] Further, the $\Delta G_c^{\neq}$ of **2b** is higher than that previously reported by Günther and Wenzl for the tricarbonyliron complex of **2b**.[17] This fact seems to suggest that the complexation weakens the ability of the conjugation of the nitrogen atom with the carbonyl carbon in the amide bond. Further, two nitrogen-containing heterocycles, 1-acetylaziridine (**4**) and 1-acetylpyrrole (**5**), are considered to be compared with interest concerning their ring sizes and strains. The barrier of **4** could not be measured, even at appreciably lower temperature.[18] The barrier of **5**, however, was reported to be 52.51 or 52.7 kJ mol^{-1},[19] which is similar to that of **1**.

As a conclusion, for the nitrogen-containing ring compounds, the barriers seem to increase with their ring sizes. That is to say, the barriers are **4**<**5**≈**1**<**2** (or **3**). However, as stated before in comparison with **1** and **2** (or **3**), the conjugation ability of the adjacent carbon with nitrogen is also important.

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