The Barrier to Conformational Isomerism in an *N*-Acetylpyrrolidine by Total Nuclear Magnetic Resonance Line Shape Analysis and Direct Thermal Equilibration

C. Hackett Bushweller,*[1a] James W. O'Neil,[1a] Maurice H. Halford,[1b] and Frank H. Bissett[1b]

*Contribution from the Department of Chemistry,
Worcester Polytechnic Institute, Worcester, Massachusetts 01609, and
Pioneering Research Laboratory, U. S. Army Natick Laboratories,
Natick, Massachusetts 01760.* *Received August 20, 1970*

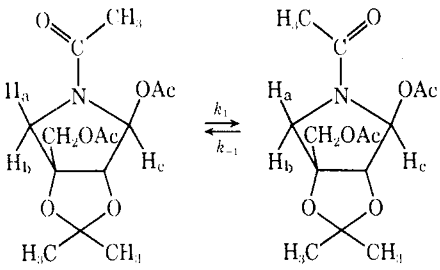
Abstract: A series of rate constants as a function of temperature for the equilibration I $\rightleftarrows$ II has been obtained from both a total nmr line shape analysis and thermal stereomutation of the conformationally pure rotamer I. Good agreement between both sets of data is observed. Activation parameters derived from a combination of both data sets have been obtained for the process I $\rightarrow$ II: $E_a = 18.9 \pm 0.3$ kcal/mol, $\Delta H^{\ddagger} = 18.2 \pm 0.3$ kcal/mol, $\Delta G^{\ddagger}_{72°} = 18.0 \pm 0.1$ kcal/mol, $\Delta S^{\ddagger} = 0.6 \pm 1.0$ eu, and, for the process II $\rightarrow$ I: $E_a = 18.7 \pm 0.3$ kcal/mol, $\Delta H^{\ddagger} = 18.0 \pm 0.3$ kcal/mol, $\Delta G^{\ddagger}_{72°} = 17.6 \pm 0.1$ kcal/mol, $\Delta S^{\ddagger} = 1.2 \pm 1.0$ eu.

Variable temperature nmr spectroscopy has proved to be a valuable technique for studying a variety of nondestructive rate processes[2] including barriers to rotation,[3] inversion processes,[4a] ring interconversions,[4b] and fluxional behavior.[5] Although there are no theoretical reasons to doubt the validity of the total nmr line shape technique, the wide divergence in activation parameters (especially $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) obtained for the same system using the nmr method[6] in different laboratories has caused the reliability of the technique to be questioned. The problems associated with obtaining kinetic parameters by total nmr line shape analysis have been discussed previously.[4b,7] In view of the wide use of nmr line shape analysis for obtaining kinetic parameters, there are relatively few reports concerning the use of a *combination* of both the line shape method and more direct techniques.[8]

This report concerns further evidence for the validity of total nmr line shape analysis for obtaining activation parameters by comparison of such data to that obtained from direct thermal stereomutation of the conformationally pure rotamer of an *N*-acetylpyrrolidine.

Results and Discussion

As part of an effort toward the synthesis of novel *N*-acetylpyrrolidines and their nucleosides, (2)-1-acetyl-*t*-3,*t*-4-isopropylidenedioxy-*c*-4-acetoxymethyl-2-acetoxypyrrolidine (NAP) was prepared.[9] In the course of elucidating the structure of this compound using nmr, we observed two conformational isomers in solution resulting from a not unexpected high barrier to rotation about the carbonyl carbon–nitrogen bond (eq 1).



I II (1)

Examination of the proton magnetic resonance spectrum of NAP in dimethylformamide-d_7 at 31° revealed two singlet resonances due to H_c in I and II at δ 6.51 and 6.32 with an intensity ratio of 0.58:1.00, respectively. The resonance due to H_a and H_b (eq 1) at 31° (Figure 1b) consisted of a singlet resonance (δ 3.88) superimposed on an AB pattern ($\Delta\nu_{AB} = 47.7$ Hz, $J_{AB} = 12.1$ Hz) with the respective intensity ratio of singlet to AB pattern being 0.6:1.0. The AB spectrum observed for H_a and H_b is assigned to conformer I based on the reasoning that the proximate carbonyl with a significant diamagnetic anisotropy will induce a significant chemical shift between H_a and H_b in I. The singlet resonance superimposed on the AB pattern (Figure 1b) is assigned to H_a and H_b in II with no appreciable diamagnetic anisotropic effect of the proximate methyl on H_a and H_b. Consistent with this reasoning, the two singlet resonances at δ 6.32 and 6.51 are assigned to H_c in I and H_c in II, respectively.

It has been shown in many instances that the crystalline form of a compound exists as a conformationally pure species,[8,10] and that dissolution of the crystalline material at temperatures where equilibration to other

---

[1] (a) Worcester Polytechnic Institute; (b) U. S. Army Natick Laboratories.

[2] J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, Pergamon Press, New York, N. Y., 1965, pp 481–588.

[3] (a) C. H. Bushweller, P. E. Stevenson, J. Golini, and J. W. O'Neil, *J. Phys. Chem.*, **74**, 1155 (1970), and references therein; (b) R. A. Newmark and C. H. Sederholm, *J. Chem. Phys.*, **43**, 602 (1965).

[4] (a) J. D. Andose, J. M. Lehn, K. Mislow, and J. Wagner, *J. Amer. Chem. Soc.*, **92**, 4050 (1970); C. H. Bushweller and J. W. O'Neil, *ibid.*, **92**, 2159 (1970); (b) D. A. Kleier, G. Binsch, A. Steigel, and J. Sauer, *ibid.*, **92**, 3787 (1970).

[5] F. A. Cotton, *Accounts Chem. Res.*, **1**, 257 (1968); H. Beall, C. H. Bushweller, W. J. Dewkett, and M. Grace, *J. Amer. Chem. Soc.*, **92**, 3484 (1970).

[6] For the case of cyclohexane, see compilation in F. A. L. Anet and A. J. R. Bourn, *ibid.*, **89**, 760 (1967).

[7] A. Allerhand, H. S. Gutowsky, J. Jonas, and R. A. Meinzer, *ibid.*, **88**, 3185 (1966); G. Binsch, *Top. Stereochem.*, **3**, 97 (1968).

[8] A. Jaeschke, H. Muensch, H. G. Schmid, H. Friebolin, and A. Mannschreck, *J. Mol. Spectrosc.*, **31**, 14 (1969); C. H. Bushweller, J. Golini, G. U. Rao, and J. W. O'Neil, *J. Amer. Chem. Soc.*, **92**, 3055 (1970); H. S. Gutowsky, J. Jonas, and T. H. Siddall, III, *ibid.*, **89**, 4300 (1967); M. Oki and H. Iwamura, *Tetahedron*, **24**, 2377 (1968).

[9] M. H. Halford, D. H. Ball, and L. Long, Jr., *Chem. Commun.*, 225 (1969).

[10] F. R. Jensen and C. H. Bushweller, *J. Amer. Chem. Soc.*, **91**, 3223 (1969).

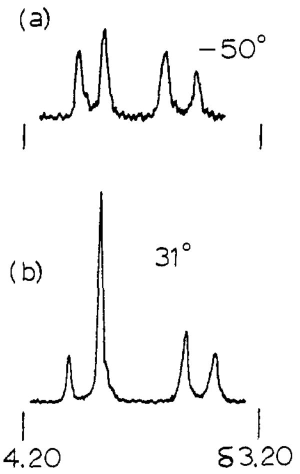


Figure 1. The pmr spectrum (100 MHz) of (a) H_a and H_b of the conformationally pure rotamer I and (b) H_a and H_b of the mixture of rotamers I and II.

conformers is very slow results in a solution of the pure conformer. Dissolution of NAP in dimethylformamide-d_7 at −50° and subsequent examination of the pmr spectrum showed a singlet resonance at δ 6.32 (H_c in I), no peak at 6.51 (H_c in II), only the AB pattern for H_a and H_b in I (Figure 1a), and no singlet at 3.88 (H_a and H_b in II), indicating a solution of conformationally pure I.[11] Upon warming the sample to higher temperatures, the singlets at δ 6.51 and 3.88 appeared and grew in intensity illustrating equilibration (I $\rightleftarrows$ II).

For the purpose of obtaining the activation parameters for C–N bond rotation (I $\rightleftarrows$ II), we studied the behavior of the singlet resonances at δ 6.32 (H_c in I) and 6.51 (H_c in II). Upon warming the sample above room temperature in dimethylformamide-d_7, these two resonances broadened and coalesced in a manner typical of an increasing rate of exchange on the pmr time scale. This spectral behavior was simulated using computer-calculated theoretical nmr spectra[12] taking into account the variation in certain critical parameters with temperature. The chemical shift difference between the two resonances as a function of temperature is substantial, *e.g.*, 16.8 Hz (0°) and 19.1 Hz (34°). Thus, the chemical shift difference in regions of peak collapse was obtained from an extrapolation of the behavior at lower temperatures. The small variation of relative populations with temperature was treated similarly. In addition, different widths at half-height ($W_{1/2}$) for the peak at δ 6.32 ($W_{1/2}$ = 1.8 Hz) and at 6.51 ($W_{1/2}$ = 1.4 Hz) were incorporated into the calculations. A series of rate constants (Table I) as a function of temperature were then obtained by normalization of the computed spectra and curve fitting by superposition of the calculated spectra on the experimental spectra.

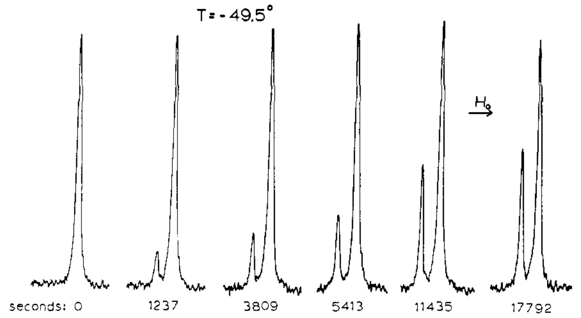


Figure 2. The pmr spectrum (60 MHz) of H_c in NAP at various times illustrating equilibration of the pure conformer I (0 sec) to conformer II.

Dissolution of crystalline NAP in dimethylformamide-d_7 at −50° gave a solution of conformationally pure I as described previously. Upon warming to slightly higher temperatures, the equilibration I $\rightleftarrows$ II occurred at a rate which can be determined by nmr peak area measurements as a function of time. Such measurements were easily performed by observing the resonances due to H_c in I and H_c in II (Figure 2).

Table I. Rate Constants as a Function of Temperature for the Equilibration I $\rightleftarrows$ II Obtained from Total Nmr Line Shape Analysis

Temp, °K	k_1,[a] sec^{-1}	k_{-1},[a] sec^{-1}
314.3	1.5	2.5
320.9	4.4	7.6
326.1	8.6	14.9
331.3	13.1	22.5
337.6	20.9	36.0
344.6	31.9	55.0
355.0	98.0	169
371.0	209	360

[a] According to eq 1.

The kinetic treatment of such an equilibration is summarized in eq 2–5 (I = concentration of I at time t; I_0 = concentration of I at t = 0; I_e = concentration of I at equilibrium)[13]

$$\frac{-\mathrm{d}I}{\mathrm{d}t} = k_1 I - k_{-1} II \tag{2}$$

If only I is present at the start

$$I_0 - I = II \tag{3}$$

$$\frac{-\mathrm{d}I}{\mathrm{d}t} = (k_1 + k_{-1})I - k_{-1}I_0 \tag{4}$$

Integration and introduction of I_e give

$$\ln \frac{I_0 - I_e}{I - I_e} = (k_1 + k_{-1})t \tag{5}$$

A representative plot of ln $(I_0 - I_e)/(I - I_e)$ *vs.* time for the run performed at −42° is illustrated in Figure 3. The convincing straight line (Figure 3) indicates strongly that the kinetic treatment of this stereomutation is correct. Using this direct equilibration method, pertinent rate constants (I $\rightleftarrows$ II) were obtained at three different temperatures (Table II).

An Arrhenius plot using *both* sets of data (Figure 4) illustrates good agreement between the slopes of the lines defined by points obtained from the two different techniques. A least-squares treatment of ln k_{-1} *vs.*

---

[11] Unequivocal assignment of the major isomer to Ia will result from an X-ray crystallographic study of I being conducted by Professor W. N. Lipscomb (Harvard University).

[12] The computer program was written by Professor M. Saunders (Yale University). For a desription of the background of the program, see M. Saunders in "Magnetic Resonance in Biological Systems," A. Ehrenberg, Ed., Pergamon Press, New York, N. Y., 1967.

[13] A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1965, p 186.

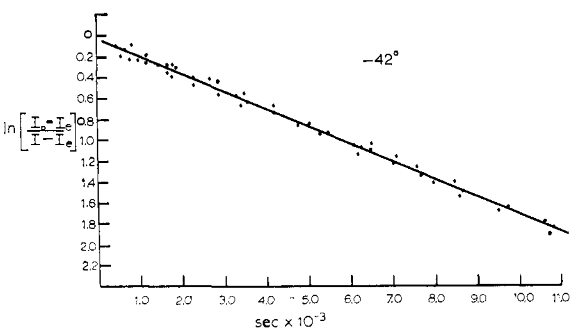


Figure 3. A plot of ln $(I_0 - I_e)/(I - I_0)$ *vs.* time (eq 5) using data from the direct thermal stereomutation of I at −42°.

$1/T$ (Figure 4) gave a correlation coefficient = 0.998. The pertinent activation parameters are compiled in Table III. An analogous plot of ln k_1/T *vs.* $1/T$ using the Eyring treatment gave $\Delta H^{\ddagger}$ = 18.2 ± 0.3 kcal/mol for the process I → II. The errors reported for E_a from the Arrhenius plot (Table III) and for $\Delta H^{\ddagger}$ from ln k_1/T *vs.* $1/T$ are maximum errors obtained by drawing straight lines through the respective plots giving fits which are reasonable though much poorer than that shown in Figure 4.

Table II. Rate Constants as a Function of Temperature for the Equilibrium I $\rightleftarrows$ II Obtained from the Direct Equilibration Method

Temp, °K	k_1,[a] sec^{-1}	k_{-1},[a] sec^{-1}
223.7	2.4×10^{-5}	4.1×10^{-5}
231.2	6.4×10^{-5}	1.1×10^{-4}
244.2	2.3×10^{-4}	4.0×10^{-4}

[a] According to eq 1.

Table III. Activation Parameters for the Process I $\rightleftarrows$ II Obtained from a Combination of Nmr Line Shape and Direct Equilibration Data

Process	E_a, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	$\Delta G^{\ddagger}$,[a] kcal/mol
I → II	18.9 ± 0.3	18.2 ± 0.3	0.6 ± 1.0	18.0 ± 0.1
II → I	18.7 ± 0.3	18.0 ± 0.3	1.2 ± 1.0	17.6 ± 0.1

[a] At 72° using the Eyring equation and assuming the transmission coefficient to be unity.

These data provide additional convincing evidence of the validity of total nmr line shape analysis for obtaining kinetic parameters. Providing the treatment used to generate the theoretical spectra is sound, the single most important source of error then becomes temperature measurement. Most commercially available variable temperature nmr probes exhibit serious temperature gradients in the sample region, especially at temperatures significantly different from ambient, rendering accurate measurement of the temperature at the sample site difficult.

A meaningful comparison can be made between the activation parameters for internal rotation of the *N*-acetyl group in NAP (Table III) and those for *N*-acetylpyrrole (E_a = 12.55 ± 0.09 kcal/mol; $\Delta H^{\ddagger}$ = 11.96 ± 0.09 kcal/mol; $\Delta G^{\ddagger}_{298°\mathrm{K}}$ = 12.14 ± 0.10 kcal/mol; $\Delta S^{\ddagger}$ = −0.6 ± 0.6 eu).[14] The significantly lower barrier ($\Delta H^{\ddagger}$) in *N*-acetylpyrrole as compared to NAP attests to effective delocalization of the nitrogen lone pair into the pyrrole ring with consequent lowering of π bonding across the carbonyl carbon–nitrogen bond as compared to NAP. This behavior is analogous to a host of other systems.[3a]

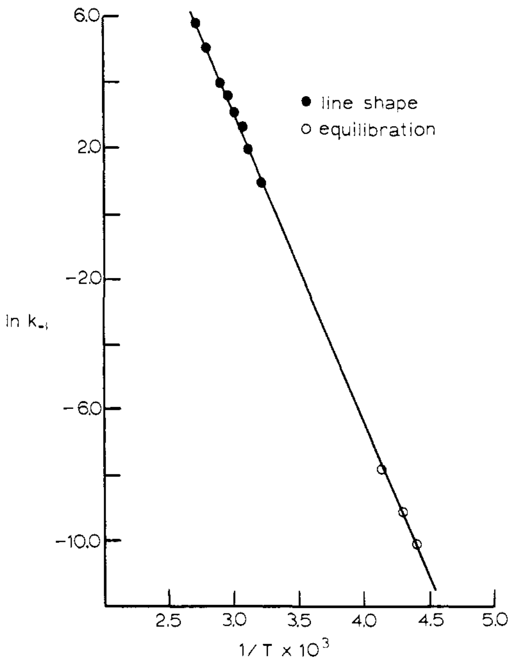


Figure 4. An Arrhenius plot for the process II → I illustrating good agreement between the line shape data and direct equilibration data.

Experimental Section

The direct equilibration data were obtained using a Varian HR-60A nmr spectrometer equipped with a custom-built variable-temperature probe. Temperature gradients within the sample region are 0.1°/5 in. rendering temperature measurements at the sample accurate to ±0.1° using a calibrated copper–constantan thermocouple. Peak area integrations were performed by cutting out the pertinent peaks and weighing on an analytical balance. The paper thickness was determined to be uniform within experimental error. The rate constants determined in this manner (Figure 3) exhibit a maximum error of ±5% determined by drawing a straight line through the plot of ln $(I_0 - I_e)/(I - I_e)$ *vs.* $1/T$ which gave a poorer though reasonable fit than the line used.

The spectra used in the total line shape analysis were obtained from a Varian HA-100 nmr spectrometer equipped with the Varian variable-temperature probe. The temperature was measured by inserting a copper–constantan thermocouple into the sample after each run. The temperature measurement can be considered to be accurate only to ±1.5° due mainly to temperature gradients in the probe. The theoretical spectra were generated using an available computer program[12] and were matched by comparison of widths at half-height, peak-to-valley ratios, and superposition of normalized theoretical spectra on experimental spectra. The error associated with the rate constants (±5%) is a maximum error established by obviously poor fits of theoretical spectra to experimental spectra at higher and lower values of the rate constant giving the best fit.

Acknowledgment. We are grateful to the National Science Foundation (GP-18197) for support of this work and to Professor M. Saunders (Yale University) for supplying the computer programs. We also thank the Worcester Area College Computation Center for donated computer time.

---

[14] K. Dahlqvist and S. Forsen, *J. Phys. Chem.*, 73, 4124 (1969).