Activation Parameters for Conformational Isomerism in an *N*-Acetylpyrrolidine by Total Nuclear Magnetic Resonance Line Shape Analysis and Direct Thermal Stereomutation

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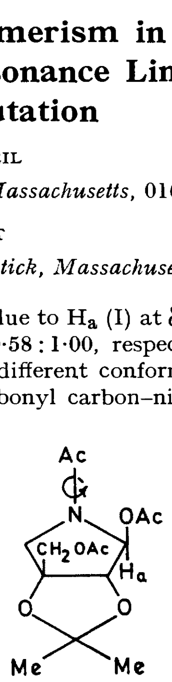
Summary Additional experimental evidence supporting total n.m.r. line shape analysis for obtaining activation parameters results from a comparison of rate data derived from the direct equilibration at low temperatures of a conformationally pure rotamer of (I) and rate data from a total n.m.r. line shape analysis at higher temperatures.

VARIABLE-TEMPERATURE n.m.r. spectroscopy is a widely applied technique for obtaining kinetic parameters for a variety of non-destructive rate processes, *e.g.*, rotational barriers and ring interconversions. However, by comparison with the number of applications of dynamic n.m.r. spectroscopy, there exists relatively little experimental evidence substantiating the technique by comparison with rate data obtained by more direct methods.[1] Although there are no theoretical reasons for doubting the n.m.r. method, widely divergent activation parameters particularly $\Delta S^{\ddagger}$ have been obtained for the same compound in different laboratories, causing the technique to be subject to question.

In the course of elucidating the structure of novel *N*-acetylpyrrolidines,[2] we observed two conformational isomers for (I) in solution resulting from a not unexpected high barrier to rotation about the carbonyl carbon–nitrogen bond. In addition, (I) is observed to be conformationally homogeneous in the crystalline state.[†]

We report the measurement of activation parameters for C–N bond rotation in (I) using both a total n.m.r. line shape analysis and direct thermal stereomutation of one pure rotamer.

The ^1H n.m.r. spectrum of (I) in $DCON(CD_3)_2$ at 31° gave two singlet resonances due to H_a (I) at δ 6·51 and 6·32 with an intensity ratio of 0·58 : 1·00, respectively. These two peaks are due to two different conformers resulting from rotation about the carbonyl carbon–nitrogen bond in (I).



(I)

At higher temperatures, the two lines broadened and coalesced in a manner typical of an increasing rate of exchange on the n.m.r. time scale. This spectral behaviour was simulated using computer-generated theoretical spectra[3] taking into account the temperature dependence of the chemical shifts of the two resonances, the variation of relative populations with temperature, and different widths at half-height. In addition, dissolution of crystalline (I) in $DCON(CD_3)_2$ at $-50°$ revealed only one resonance due to H_a at δ 6·38 indicating 100% conformational purity for crystalline (I) and slow C–N bond rotation at $-50°$. Upon warming the sample to slightly higher temperatures, equilibration of the pure conformer occurred at a rate which could be determined by n.m.r. peak area measurements as a function of time. Thus, two series of rate constants as a function of temperature from fundamentally

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[†] The crystal and molecular structure of (I) is being determined by Professor W. N. Lipscomb's group at Harvard University.

different methods were obtained. A least-squares treatment of ln *k versus* $1/T$ (Figure, correlation coefficient = 0·998) for the rate of isomer (B) (δ 6·51) going to isomer (A) (δ 6·38) using both sets of data indicates good agreement. Activation parameters are compiled in the Table.

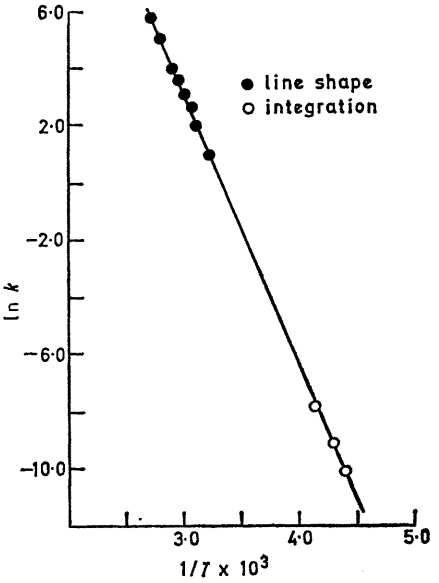

FIGURE. *Arrhenius plot for the isomer* (B) (δ6·51) *to isomer* (A) (δ6·38) *process.*

Activation parameters for C–N *bond rotation in* (I)

	(A)[a] → (B)[b]	(B) → (A)
E_a (kcal mol^{-1})	18·9 ± 0·3	18·7 ± 0·3
$\Delta H^\ddagger$ (kcal mol^{-1})	18·2 ± 0·3	18·0 ± 0·3
$\Delta G^\ddagger$ (72°) (kcal mol^{-1}) ..	18·0 ± 0·1	17·6 ± 0·1
$\Delta S^\ddagger$ (e.u.)	0·6 ± 1·0	1·2 ± 1·0

[a] Isomer giving resonance at δ6·38.
[b] Isomer giving resonance at δ6·51.

Although the difference in temperatures used in the above techniques are so large as to exclude a totally rigorous test of each method, the agreement between the line shape and equilibration rate data provides evidence that n.m.r. line shape analysis is fundamentally sound. In our opinion, the single most important source of error in such studies is the determination of temperature at the sample site.

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