Inversion and Tunneling in Aziridine and Aziridine-*N-d*. Gas-Phase Nuclear Magnetic Resonance Band Shape Analysis and Model Calculations of the Isotope Effect

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Abstract: The inversion barriers in aziridine and aziridine-*N-d* have been measured in the gas phase by NMR total band shape analysis. The isotope effect on the inversion barrier may be described by the following parameters (at 65°C): $\Delta\Delta G^{\ddagger}(= \Delta G^{\ddagger}_{D} - \Delta G^{\ddagger}_{H}) = 0.57 \pm 0.07$ kcal/mol, $\Delta\Delta H^{\ddagger} = 2.1 \pm 1.2$ kcal/mol, $\Delta\Delta S^{\ddagger} = 4.8 \pm 3.6$ cal/(mol K), and $k_H/k_D = 2.34$. Model calculations of the isotope effect, including complete vibrational analyses of the two isotopic species, are able to reproduce the experimental data only if tunneling is taken into account. Reaction coordinate frequencies of $|\nu^{\ddagger}_{H}| = 1050 \pm 50$ cm^{-1} and $|\nu^{\ddagger}_{D}| = 800 \pm 40$ cm^{-1} for the protium and deuterium compounds, respectively, have been estimated, and the barrier height, corrected for zero-point energy differences between initial and transition states (and thus comparable with theoretical inversion barriers obtained by molecular orbital methods), is found to be 19.1 kcal/mol.

The barrier to nitrogen inversion in aziridines has received a great deal of attention from both experimental[3,4] and theoretical[4,5] points of view during the past 20 years. The inversion barrier in aziridine (ethylenimine) itself, the "mother" compound, had until recently[6-8] eluded experimental efforts at its determination, except for two "lower-limit" microwave estimations.[9,10] On the other hand, theoretical calculations of this barrier,[5] ranging in sophistication and complexity from extended Hückel[5e] and valence force field[5a] to ab initio,[5b-d,7] have not been lacking. Our own interest in this molecule arises from two equally intriguing sources: first, we wished to establish a reliable *gas-phase* value for the inversion barrier from complete band shape analysis of Fourier transform (FT) NMR spectra, for comparison with the theoretical data; and second, we wished to determine the kinetic deuterium isotope effect on the barrier in the gas phase, and to carry out a detailed theoretical calculation of the isotope effect using the method of Wolfsberg and Stern,[11] and including consideration of tunneling. In the present paper we report the results of our efforts along these two lines of investigation, and we make an attempt to use the results to aid in the elucidation of the details of the inversion process, in particular the shape and dimensions of the potential barrier, and the structure of the transition state.

Experimental Section

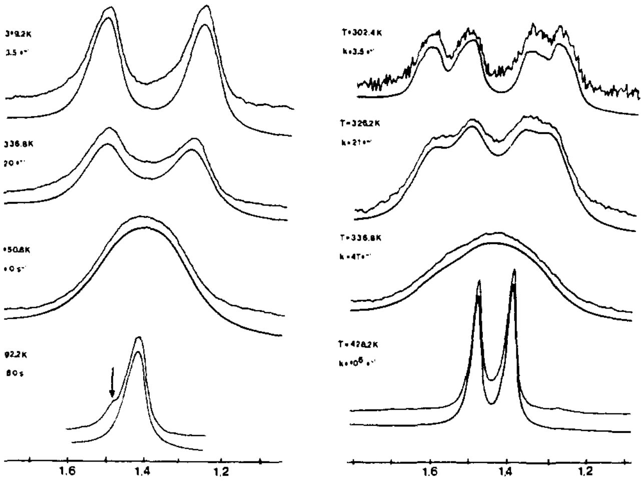
Materials. The aziridine used in this work was a commercial product, which was stored over KOH in a refrigerator. Aziridine-*N-d* was prepared by exchange with D_2O, after which the resulting solution was made basic with KOD (from repeated exchange of KOH with D_2O), and the aziridine-*N-d* was distilled off into a receiver containing KOD. The product was redistilled in vacuo onto fresh KOD and stored under vacuum in a refrigerator. The degree of deuteration was roughly estimated[12] to be about 86% by means of an NMR spectrum recorded at +150°C, at which temperature part of the signal due to the protium compound appeared at the base of the singlet from aziridine-*N-d*. The presence of the protium compound did not unduly affect the estimation of the rate constants for the deuterium compound, except for those at the highest temperatures. The effect of the protium compound could be estimated by superposition of Lorentzian lines corresponding to the deuterium and protium band shapes. The inclusion of the protium lines increased the apparent rate constant by about 10% at 106 and 119°C. The spectrum at the latter temperature was omitted from the calculation of the activation parameters.

Sample Preparation. Gas-phase samples were prepared on a vacuum line (10^{-2} mm) by distillation of a small amount of the aziridine (containing TMS) from KOH or KOD into the bulb of a 2.5-cm long ampoule with o.d. 8.9 mm. The ampoules were sealed off and transferred to standard 10 mm o.d. NMR sample tubes. At room temperature, a small amount of condensed phase remained at the bottom of the ampoule. The samples were completely gas phase at temperatures ≥50°C. This ampoule technique was employed to minimize temperature gradients in the samples.

Apparatus and Measurements. The FT ^{1}H NMR spectra were obtained on a Varian VFT-XL-100-15 spectrometer, equipped with external lock and variable temperature accessory, and using a pulse width of 60 μsec, an acquisition time of 4 sec, and a spectral width of 1000 Hz. The spectral plots were 100 Hz expansions, and in all cases both the aziridine methylene proton signal(s) and the TMS peak (used as shift and resolution standard) were recorded. Spinning of the samples at rates of the order of 20 rps improved the resolution, and did not, in contrast to the preliminary work,[6] give rise to interfering side bands. The spectra were also stored on magnetic tape (cassette); this was found to be extremely convenient during the band shape analyses, as a given spectrum could be recalled, e.g., for phase adjustment, when this was found necessary.

The temperature was measured by means of the replacement technique, using a copper–constantan thermocouple inserted into a spinning, empty, open-ended, long-necked ampoule of the same type as those used for the aziridine samples. The sensing point of the thermocouple was adjusted to reach the level of the receiver coil, and voltage readings were made with a digital voltmeter (Hewlett Packard Model 3450A). The temperature was measured before and after each FT accumulation, and the difference between these two measurements never exceeded 0.5°. The replacement technique was used in these runs instead of direct temperature measurement by means of a thermocouple fixed inside a normal 12 mm insert, since it was observed that in the FT mode a broad background signal was obtained from the probe (in the absence of sample), apparently due to the glue used to fix the thermocouple to the wall of the insert.

NMR Calculations. The band shape calculations were carried out with the DNMR3 computer program developed by Kleier and Binsch.[13] The spin system in aziridine itself was treated as an AA′BB′C system, while that in aziridine-*N-d* was treated as three overlapping AA′BB′ spin systems, with separations corresponding to the mean of the two H–C–N–D coupling constants. One DNMR3 calculation of the AA′BB′ system was performed for each value of the rate constant, and the resulting shape and spectral vectors were used in conjunction with a slightly modified DNMR3 plot



igure 1. Experimental and theoretical band shapes for aziridine ight) and aziridine-*N-d* (left). The arrow denotes the shoulder due to e presence of protium compound in the sample of aziridine-*N-d*. The ale is in ppm downfield from TMS.

outine to "synthesize" a theoretical spectrum. The absence of fine tructure in our spectra (except for that due to the H-N-C-H coulings in aziridine; see Figure 1) precluded their use to obtain the A'BB' coupling constants required as input data for DNMR3. Intead, we used the values recently reported by Nakanishi and amamoto[8] in connection with their density matrix complete band hape analysis of the temperature-dependent NMR spectrum of ziridine in decalin-d_{18} solution. Values of the line width parameer, T_2, could be obtained at both the high- and low-temperature mits of the exchange process by visual fitting of theoretical to experimental spectra. Comparison was made with the line width of e TMS reference signal, and values of T_2 at intermediate temeratures were calculated from the equation

$$1/T_2 = 1/T_2^{\mathrm{TMS}} + \pi\Delta\nu^{\mathrm{corr}} \qquad (1)$$

here $\Delta\nu^{\mathrm{corr}}$ is a line width correction measured at the high- and w-temperature limits, and obtained at intermediate temperatures y (linear) interpolation.

An estimated temperature dependence of the N-H resonance as taken into account in the band shape calculations, based on bservations of the temperature dependence of the N-H signal of ziridine in dry carbon tetrachloride solution. This was more conenient (and perhaps even more accurate) than attempting to folw the shift of the broad, featureless N-H band in the gas phase.

All band shape calculations were performed on a Univac 1108 omputer at the University of Lund.

Isotope Effect Calculations. The model calculations of the isoope effect were made with a program developed by Wolfsberg and tern[11] from a program by Schachtschneider and Snyder[14] for calulating normal molecular vibrational frequencies using the **FG** atrix method of Wilson, Decius, and Cross.[15] The rather limited umber of atoms in aziridine made it possible to perform the calulations on the complete molecule, thus obviating the necessity to se the cut-off procedure[11,16] employed with larger molecules.

The molecular geometry of aziridine used in the calculations as that employed by Lehn et al.,[5b] determined by microwave pectroscopy.[17] (See Table I and Figure 2.) The geometry assumed r the transition state was the same as that of the initial state, exept that the angle between the ring plane and the N-H bond, ϕ, as set equal to 0°. The choice of internal coordinates (necessary calculate the **G** matrix[15]) was made as described by Decius,[18] hich in the present case leads to six redundant coordinates. However, these coordinates are removed in a proper manner in the calulations, and thus cause no difficulties.

The values of the force constants (see Table II) were estimated n the basis of literature values for similar bonds in other moleules, and were adjusted to give the best agreement between oberved and calculated frequencies (see below). An imaginary reacon-coordinate frequency was obtained in a somewhat different ay than in the previous calculations.[19] Instead of using off-diagonal elements of the **F** matrix for this particular purpose, the force constant for the N-H out-of-plane vibration was assigned a negative value, estimated in the following way from the ab initio calculation by Lehn et al.[5b] of the inversion barrier in aziridine: the curvature of the energy surface in the vicinity of $\phi = 0$ can be approximated as the force constant for the vibration along the reaction coordinate, and is easily obtained from the polynomial relation between E and ϕ given by Lehn et al.[5b] as the second derivative $(d^2E/d\phi^2)_{\phi=0}$. Expressed in the usual units, this magnitude equals -0.41 (mdyn Å)/rad^2, which is the value assumed for the force constant ($F^\ddagger$) of the out-of-plane vibration in the transition state in the computations summarized in Table V. This force constant has also been varied (see Table VII).

The isotope-effect calculations were carried out on an IBM 360/65 computer at Göteborgs Datacentral.

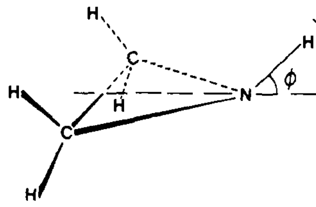


Figure 2. The aziridine molecule. The plane of the paper is thought to bisect the CNC angle. The arrow indicates approximately the normal mode which corresponds to the motion along the reaction coordinate in the transition state.

Table I. Structural Parameters for Aziridine[17] (cf. Figure 2)

Distances	Å	Angles	Deg
N-H	1.000	HCH	117
C-C	1.480	HCH, CC	159
C-N	1.488	CNC, NH (ϕ)	68
C-H	1.083		

Table II. Force Constants Used in the Isotope-Effect Calculations on the Inversion of Aziridine

Type of force constant[a]	Value[b]	Type of force constant[a]	Value[b]
C-H, s	4.9	HCN, b	0.7
N-H, s	*6.15*[c]	CNH, b	*0.5*[c]
		CNC, b	1.1
C-N, s	5.0	HC-NH, t	*0.03*[c]
C-C, s	4.0	HC-CH, t	0.03
HCH, b	0.3	$F^\ddagger$, b	*−0.41*[c, d]
HCC, b	0.6		

[a] s = stretching force constant, b = bending force constant, t = torsional force constant. [b] Stretching force constants are in mdyn/Å; bending and torsional force constants are in (mdyn Å)/rad^2. [c] Force constants in italics were varied in the transition-state calculations, and (except for $F^\ddagger$) are initial-state values. [d] $F^\ddagger$ is the force constant for the out-of-plane vibration in the transition state. The value given here was obtained from ref 5b.

Results

NMR Band Shape. The gas-phase FT spectrum of aziridine at 29°C (see Figure 1) consisted of a broad (ca. 41 Hz), slightly unsymmetrical band centered at δ 1.44, the downfield half of which was split by a 9.8 Hz coupling to the N-H proton, while the corresponding splitting in the upfield half was 7.8 Hz. These couplings were obtained from the band shape analysis of a spectrum at 10.4°C, where broadening due to the exchange process does not measurably affect the band shape.

The tentative assignment of the low-field resonance to the C-H protons anti to the N-H proton, suggested in the preliminary communication[6] on the basis of analogy with

Table III. Thermodynamic Activation Parameters for the Inversion Process in Aziridine and Aziridine-*N-d*

Compd (conditions)	$\Delta G^{\ddagger}$, kcal/mol (T, K)	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, cal/(mol K)	r[a]
Aziridine[b] (gas phase)	17.23 ± 0.05[c] (338)	15.2 ± 0.4	−6.2 ± 1.4	0.999
Aziridine-*N-d*[b] (gas phase)	17.80 ± 0.05[c] (338)	17.3 ± 0.6[d]	−1.4 ± 2.0[d]	0.998
Aziridine[7] (CCl_4 solution)	17.4[e] (298)	18.2 ± 0.5[e] (298)	+2.7[e] (298)	
Aziridine[8] (Decalin-d_{18} solution)	17.1 ± 0.8[f] (298)	15.3 ± 0.4[f] (298)	−6.2 ± 1.2[f] (298)	

[a] Regression coefficient from least-squares treatment of Eyring plot. [b] Present work; the error limits are random errors (95% confidence). [c] Error limits estimated from a plot of $\Delta G^{\ddagger}$ vs. T; the value of $\Delta G^{\ddagger}_{298\text{K}}$ is 16.99 ± 0.05 kcal/mol for the protium compound. [d] The $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ parameters for the deuterium compound are those obtained after taking into account the effect of the presence of the protium compound on the band shape (see text); without this correction, the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values were 17.0 kcal/mol and −2.4 cal/(mol K), respectively. [e] Estimated from the data given in ref 7. Skaarup[7] gives a value of 18.8 ± 0.5 kcal/mol for E_a. $\Delta H^{\ddagger}$ is treated as temperature dependent, and $\Delta S^{\ddagger}$ is calculated from $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$. [f] These values were calculated by Nakanishi and Yamamoto[8] on the basis of an Arrhenius plot. Consequently, the error in $\Delta G^{\ddagger}$ is unreasonably large, and $\Delta H^{\ddagger}$ is treated as temperature dependent.

the work of Saitô et al.,[20] has been reversed in the present work in the light of the recent discussion by Nakanishi and Yamamoto[8] on this point. These authors point out, for example, that the syn H-C-N-H coupling is expected to be larger than the corresponding anti coupling, in view of the difference in dihedral angle.

The "coalescence temperature" for this spectrum was ca. 63°C[21] (cf. Figure 1); above coalescence a well-resolved doublet ($\Delta\nu_{1/2}$ = 2.98 Hz at +155°C) developed, with a separation of 8.9 Hz, demonstrating the absence of N-H proton exchange, even at +155°C.

The spectrum of aziridine-*N-d* at 46°C consisted of two broad bands centered at δ 1.42 and separated by 25.5 Hz. The half-width of the low-field band was 9.8 Hz, while that of the high-field band was 9.2 Hz. This difference in width is of the order of magnitude expected on the basis of the different proton-deuterium couplings in the molecule, as deduced from the H-N-C-H couplings in aziridine itself. This spectrum coalesced at ca. 73°C,[21] after which the bandwidth decreased to a value of 4.5 Hz at +155°C, taken to be the high-temperature limit of the exchange process. A deuterium decoupling experiment at ca. +150°C decreased the bandwidth by about 2.5 Hz, showing that exchange of deuterium must be slow on the NMR time scale at this temperature.

Within the experimetal error limits for shift measurements on broad bands such as those observed in this work (~±0.5 Hz),[22] the chemical shift between the TMS signal and the center of the methylene proton band did not change appreciably over the temperature interval 20-100°C. The shift between the methylene protons was found to be temperature independent, and a value of 25.5 Hz was used in all band shape calculations for both the protium and deuterium compounds. As noted in the preliminary communication,[6] shift effects due to pressure changes are not expected to be of any significance over the temperature range of our experiments.

The rate constants (k) obtained from the band shape analyses at temperatures between 37 and 85°C for aziridine and between 53 and 106°C for aziridine-*N-d* were used to derive the thermodynamic activation parameters via the Eyring equation.[23] These parameters, along with their statistical errors (95% confidence limits), are listed in Table III, and the results are presented graphically in the form of plots of $-\ln(k/T)$ vs. $1/T$ in Figure 3. The errors in the $\Delta G^{\ddagger}$ values were estimated from plots of $\Delta G^{\ddagger}$ vs. T. The isotope effect on the inversion barrier (at 65°C) may then be described by the following parameters: $\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}_{D} - \Delta G^{\ddagger}_{H} = 0.57 \pm 0.07$ kcal/mol, $\Delta\Delta H^{\ddagger} = 2.1 \pm 0.7$ kcal/mol, $\Delta\Delta S^{\ddagger} = 4.8 \pm 2.4$ cal/(mol K), and $k_H/k_D = 2.34$. The error limits were obtained by statistical combination of the appropriate data in Table III. More realistic error limits, taking into consideration an estimated maximum possible error of ±5% in the rate constant at the highest temperatures used in the band shape analysis of aziridine-*N-d*, due to the presence of the protium compound, are ±1.2 kcal/mol in $\Delta\Delta H^{\ddagger}$ and ±3.6 cal/(mol K) in $\Delta\Delta S^{\ddagger}$.

Data from the work of Skaarup[7] and that of Nakanishi and Yamamoto[8] on the inversion of aziridine in carbon tetrachloride and decalin-d_{18} solutions, respectively, are also included in Table III, for the sake of comparison (see Discussion).

Model Calculations of the Isotope Effect. The fundamental frequencies necessary for the isotope effect calculations have been determined for both aziridine and aziridine-*N-d* in the gas phase by Mitchell et al.[24] This is a very favorable situation, since the main problem in calculations of this type is the choice of a force field for the initial-state molecule and for the transition state, in order to obtain the appropriate fundamental frequencies. In the present case, the experimentally observed frequencies can be used to establish a force field for the initial state, which can also be applied to the transition state. As we have used only diagonal force constants in setting up the force field, we are of course unable to reproduce each individual frequency, but the isotopic dependence should be the same for both the observed and calculated sets of frequencies. Thus, the initial-state factors determining the isotope effect[11] were calculated, starting both from the experimentally determined frequencies and from assumed force constant data (see Table IV). The agreement is rather encouraging, and consequently we feel that this simple force field may be applied with some confidence to the transition state, with a few necessary minor modifications. Due to the uncertainties surrounding the values of the force constants in the transition state, we have investigated the influence of changes in four parameters on the isotope effect: (i) the N-H stretching force constant, $F^{\ddagger}_{NH}$; (ii) the C-N-H in-plane blending force constant, $F^{\ddagger}_{CNH}$; (iii) the force constant for the H-C-N-H torsional mode, $F^{\ddagger}_{HCNH}$; and (iv) the negative force constant, $F^{\ddagger}$, associated with the imaginary reaction-coordinate frequency. All other force constants have been assigned the same values as in the initial state. The parameters for the initial state were not varied, in view of the close agreement between the two sets of data in Table IV.

The effect of an increase in the N-H stretching force constant in the transition state, reflecting a somewhat higher N-H stretching frequency, is shown in Table V, along

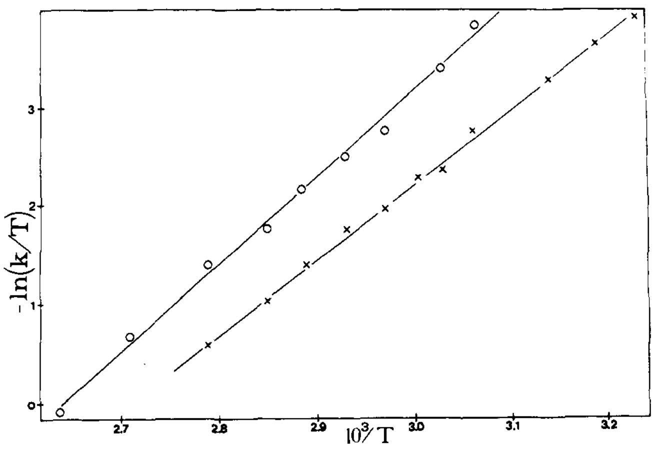


Figure 3. Plots of $-\ln(k/T)$ vs. $1/T$ for aziridine (+) and aziridine-*N-d* (O).

Table IV. Sum of Isotopic Frequency Differences and Partition Function Factors (at 298.16 K) for the Initial State, Calculated from Observed Frequencies,[24] and Calculated Starting with Force-Constant Data

Term	From obsd frequencies	From force-constant data
$\frac{1}{2}\sum_{i=1}^{18}(\nu_{D_i} - \nu_{H_i})$	-705.5 cm^{-1}	-706.3 cm^{-1}
$\text{ZPEF} = \exp\left[\sum_{i=1}^{18}(u_{H_i} - u_{D_i})/2\right]^a$	30.084	30.199
$\text{EXCF}^a = \prod_{i=1}^{18}\frac{1 - e^{-u_{H_i}}}{1 - e^{-u_{D_i}}}{}^a$	1.037	1.057
$\text{MMIF}^b = \frac{[I_{AD}I_{BD}I_{CD}]^{1/2}}{[I_{AH}I_{BH}I_{CH}]^{1/2}}\frac{[M_D]^{3/2}}{[M_H]^{3/2}}{}^b$	1.124	1.124
$\text{QRAT} = \text{MMIF} \times \text{EXCF} \times \text{ZPEF}^c$	35.066	35.878

[a] ZPEF is the zero-point energy factor for the initial state; EXCF is the excitation factor for the initial state; $u = h\nu/kT$. [b] MMIF is the mass and moment of inertia factor for the initial state, and is calculated solely from the geometry of the molecule. [c] QRAT is the partition function ratio, and is directly involved in the expression for the isotope effect: k_H/k_D = QRAT (initial state)/QRAT (transition state).

Table V. Calculated Isotope Effects (at 298.16 K) in the Inversion of Aziridine. ($F^\ddagger = -0.41$ (mdyn Å)/rad^2; $F_{HCNH}{}^\ddagger$ – 0.03 (mdyn Å)/rad^2)[a]

$F_{CNH}{}^\ddagger$, (mdyn Å)/rad^2	k_H/k_D	
	$F_{NH}{}^\ddagger = 6.15$ mdyn/Å	$F_{NH}{}^\ddagger = 6.46$ mdyn/Å
0.65	1.489	1.411
0.5	1.589	1.505
0.35	1.704	1.615
0.2	1.841	1.744

[a] Force constant values refer only to the transition state.

Table VI. Variation of the Torsional Force Constant ($F_{HCNH}{}^\ddagger$) in the Transition State (298.16 K). ($F^\ddagger = -0.41$ (mdyn Å)/rad^2: $F_{CNH}{}^\ddagger = 0.5$ (mdyn Å)/rad^2; $F_{NH}{}^\ddagger = 6.46$ mdyn/Å)

$F_{HCNH}{}^\ddagger$, (mdyn Å)/rad^2	k_H/k_D	$\lvert\nu_H{}^\ddagger\rvert$, cm^{-1}	$\lvert\nu_D{}^\ddagger\rvert$, cm^{-1}
0.04	1.489	478.0	369.7
0.03	1.505	611.6	470.7
0.02	1.515	726.2	557.3
0.01	1.519	828.7	635.0
0.00	1.521	922.3	706.3
−0.01	1.521	1009.0	772.6
−0.02	1.519	1090.2	835.0

Table VII. Variation of the Force Constant, $F^\ddagger$, for the Out-of-Plane Bending Mode in the Transition State (298.16 K) ($F_{NH}{}^\ddagger$ = 6.46 mdyn/Å; $F_{CNH}{}^\ddagger = 0.5$ (mdyn Å)/rad^2; $F_{HCNH}{}^\ddagger = 0.03$ (mdyn Å)/rad^2)

$F^\ddagger$, (mdyn Å)/rad^2	k_H/k_D	$\lvert\nu_H{}^\ddagger\rvert$, cm^{-1}	$\lvert\nu_D{}^\ddagger\rvert$, cm^{-1}
−0.410	1.505	611.6	470.7
−0.533	1.507	792.6	609.7
−0.656	1.507	940.1	723.1
−0.779	1.507	1067.9	821.5
−0.902	1.506	1182.3	909.5

with the effect of a variation of the C–N–H in-plane bending force constant. An increase in the N–H stretching force constant is to be expected, since the relative s character of the nitrogen bonding orbitals increases on going to the transition state. This increase in the N–H bond strength is also reflected by an 8% increase in the overlap population for the N–H bond, as derived from the ab initio calculation of Lehn et al.[5b] An increase in $F^\ddagger{}_{NH}$ (by 5%) results in a decrease in the isotopic rate ratio for a given constant value of $F^\ddagger{}_{CNH}$ (with $F^\ddagger = -0.41$ (mdyn Å)/rad^2 and $F^\ddagger{}_{HCNH}$ = 0.03 (mdyn Å)/rad^2), as would be anticipated. An increase in $F^\ddagger{}_{CNH}$ also weakens the isotope effect, but the magnitude of this increase is rather difficult to predict, and in the remaining calculations, $F^\ddagger{}_{CNH}$ was given the same value as in the initial state (0.5 (mdyn Å)/rad^2). As shown in Table V, a 30% increase in $F^\ddagger{}_{CNH}$, which intuitively seems rather excessive, leads to only a ca. 7% decrease in k_H/k_D.

A change in the force constant, $F^\ddagger{}_{HCNH}$, for the HCNH torsional frequency was found to have an essentially negligible effect on k_H/k_D. (See Table VI.) A decrease by a factor of 3 from the initial state value led to only a 1% increase in k_H/k_D. However, the imaginary reaction-coordinate frequency ($\nu^\ddagger{}_L$) is very sensitive to the magnitude of the torsional force constant ($F^\ddagger{}_{HCNH}$). For example, a decrease in this force constant from the initial-state value (0.03 (mdyn Å)/rad^2) to 0.0 increases the absolute value of the imaginary frequency by more than 300 cm^{-1}. Although this change in the imaginary frequency has very little influence on the "classical" isotope effect, it is quite significant from the point of view of tunneling, as will be shown below. It was also demonstrated in previous work[19] that reasonable variations in the reaction coordinate frequency have rather little influence on the "classical" isotope effect. The force constant which primarily determines the reaction-coordinate frequency in the present case is $F^\ddagger$, the force constant for the out-of-plane bending mode. As shown in Table VII, an increase by a factor of 2 in this force constant has a negligible influence on the "classical" isotope effect, while leading to a nearly twofold increase in the reaction-coordinate frequency.

A much simplified estimation of the isotope effect may be carried out by assuming that the only change that occurs on passing into the transition state is the loss of the normal vibration approximately representing the N–H bending mode indicated by an arrow in Figure 2. This vibration, which belongs to the A′ species, has a frequency of 1096 cm^{-1} in aziridine itself.[24] The corresponding value[24] for aziridine-*N-d* is 864 cm^{-1}. This treatment only takes into account the contribution to the isotope effect from the zero-point energy difference for this particular vibration, and leads to a k_H/k_D value of 1.751 at 298 K.

Table VIII. "Classical" Isotopic Rate Ratios and Tunnel Corrections According to Bell's Equation[25a] at Temperatures between 308.16 and 373.16 K. ($F_{NH}^{\ddagger}$ = 6.46 mdyn/Å; $F_{CNH}^{\ddagger}$ = 0.5 (mdyn Å)/rad²; $F^{\ddagger}$ = −0.41 (mdyn Å)/rad²)

	$F_{HCNH}^{\ddagger}$ = 0.03 (mdyn Å)/rad² $\lvert\nu_H^{\ddagger}\rvert$ = 611.6 cm⁻¹ $\lvert\nu_D^{\ddagger}\rvert$ = 470.7 cm⁻¹			$F_{HCNH}^{\ddagger}$ = −0.01 (mdyn Å)/rad² $\lvert\nu_H^{\ddagger}\rvert$ = 1009.0 cm⁻¹ $\lvert\nu_D^{\ddagger}\rvert$ = 772.6 cm⁻¹			$F_{HCNH}^{\ddagger}$ = −0.02 (mdyn Å)/rad² $\lvert\nu_H^{\ddagger}\rvert$ = 1090.2 cm⁻¹ $\lvert\nu_D^{\ddagger}\rvert$ = 835.0 cm⁻¹		
T, K	k_H/k_D	Q_H/Q_D	$(k_H/k_D)(Q_H/Q_D)$	k_H/k_D	Q_H/Q_D	$(k_H/k_D)(Q_H/Q_D)$	k_H/k_D	Q_H/Q_D	$(k_H/k_D)(Q_H/Q_D)$
308.16	1.491	1.169	1.743	1.506	1.797	2.706	1.504	2.161	3.251
318.16	1.478	1.157	1.710	1.492	1.697	2.532	1.490	1.983	2.954
328.16	1.466	1.145	1.679	1.479	1.618	2.393	1.478	1.849	2.733
338.16	1.455	1.135	1.651	1.468	1.553	2.280	1.467	1.745	2.560
348.16	1.445	1.126	1.627	1.458	1.500	2.187	1.456	1.662	2.420
358.16	1.436	1.118	1.605	1.448	1.455	2.107	1.447	1.595	2.307
368.16	1.427	1.111	1.585	1.439	1.416	2.038	1.438	1.538	2.212
373.16	1.423	1.108	1.577	1.435	1.399	2.008	1.434	1.513	2.170

Table IX. Isotopic Differences in Free Energy, Enthalpy, and Entropy of Activation[d]

$F_{HCNH}^{\ddagger}$,[a] (mdyn Å)/rad²	$\Delta\Delta G_{338K}^{\ddagger}$, kcal/mol	$\Delta\Delta H^{\ddagger}$,[b] kcal/mol	$\Delta\Delta S^{\ddagger}$,[b] cal/(mol K)
		"Classical"	
0.03	0.252	0.164 ± 0.001	−0.262 ± 0.003
−0.01	0.258	0.169 ± 0.002	−0.264 ± 0.005
−0.02	0.257	0.167 ± 0.001	−0.268 ± 0.004
		With Tunnel Correction	
0.03	0.337	0.350 ± 0.005	0.05 ± 0.01
−0.01	0.554	1.04 ± 0.03	1.41 ± 0.09
−0.02	0.631	1.40 ± 0.05	2.23 ± 0.16
		Experimental	
	0.57 ± 0.07	2.1 ± 1.2[c]	4.8 ± 3.6[c]

[a] The reaction-coordinate frequencies associated with these $F_{HCNH}^{\ddagger}$ values are listed in Table VI. [b] The error limits for the theoretical values are random errors from least-squares treatments of the data in Table VIII, assuming a linear relationship between the logarithm of the isotopic rate ratio and $1/T$. [c] Error limits estimated to include presence of protium compound in sample of aziridine-*N-d* (see text). [d] The theoretical data are based on the k_H/k_D and $(k_H/k_D)(Q_H/Q_D)$ values given in Table VIII.

Tunnel Effect Calculations. The contribution of tunneling (Q_H/Q_D) to the isotopic rate ratio was estimated by the use of Bell's[25a] approximate equation for tunneling through a parabolic barrier (eq. 2), in conjunction with the reaction-

$$Q_H/Q_D = (u^{\ddagger}_H/u^{\ddagger}_D)\sin(u^{\ddagger}_D/2)/\sin(u^{\ddagger}_H/2) \qquad (2)$$

$$u^{\ddagger} = h|\nu^{\ddagger}_L|/kT$$

coordinate frequencies ($\nu^{\ddagger}_L$) from the various "classical" isotope effect calculations. The Q_H/Q_D ratios at temperatures from 308.16 to 373.16 K (more or less the experimental range) for three cases with different reaction-coordinate frequencies are collected in Table VIII. The three cases correspond to three values of the torsional force constant, $F^{\ddagger}_{HCNH}$, differing in magnitude and sign. The first case corresponds to $F^{\ddagger}_{HCNH}$ = 0.03 (mdyn Å)/rad² (the initial-state value), while in the second and third, $F^{\ddagger}_{HCNH}$ = −0.01 and −0.02 (mdyn Å)/rad², respectively. All three sets include a stretching force constant, $F^{\ddagger}_{NH}$, equal to 6.46 mdyn/Å, $F^{\ddagger}_{CNH}$ = 0.5 (mdyn Å)/rad², and $F^{\ddagger}$ = −0.41 (mdyn Å)/rad². In the first case, the torsional force constant has the same value as in the initial state, while in the other cases, this force constant is given values which, together with $F^{\ddagger}$ = −0.41 (mdyn Å)/rad², satisfactorily reproduce the experimental results.

The total isotopic rate ratios are calculated as products of Q_H/Q_D and the "classically" obtained k_H/k_D ratios, and the resulting values at temperatures between 308.16 and 373.16 K are also presented in Table VIII. The data in this table were used to find $\Delta\Delta H^{\ddagger} = \Delta H^{\ddagger}_D - \Delta H^{\ddagger}_H$ and $\Delta\Delta S^{\ddagger}$ values from the slopes and intercepts of plots of ln (k_H/k_D) or ln [$(Q_H/Q_D)(k_H/k_D)$] vs. $1/T$. In each case, $\Delta\Delta G^{\ddagger}$ was calculated at 338.16 K. The results are summarized in Table IX, along with the experimental data.

Discussion

A comparison of our gas-phase results on aziridine with those of Nakanishi and Yamamoto,[8] obtained in decalin-d_{18} solution, and those of Skaarup,[7] in carbon tetrachloride solution (see Table III), shows excellent agreement in the first case, but less satisfactory agreement in the second. This discrepancy is not likely to be due to solvent effects on going between decalin-d_{18} and carbon tetrachloride solution, or between the latter and the gas phase.[26] Since the Japanese workers[8] used a program which allowed them to take into account the different line widths in the high- and low-field halves of the methylene proton spectrum (due to stereospecific ^{14}N-^{1}H coupling), whereas Skaarup,[7] using DNMR3,[13] was presumably unable to do this, we suggest an explanation at least partly in terms of incorrect T_2 values used by Skaarup[7] at the lower end of the temperature range. In our gas-phase spectra, this differential broadening effect was undetectable, due to the predominance of broadening ascribable to short relaxation times.[30]

The type of isotope effect observed in this work may be categorized as a special case of a primary isotope effect. Ordinarily, primary isotope effects are characterized by bond breaking or bond formation involving the isotopic atom along the reaction coordinate, and by magnitudes of the order of 10 (for the isotopic rate ratio) in the absence of tunneling. Isotopic rate ratios (k_H/k_D) as large as 45 at 25°C, due to the incursion of the tunnel effect, have been reported.[31,32] In the present case, the isotope effect involves bond *bending* along the reaction coordinate, and is consequently expected to be relatively weak. This expectation is borne out by the experimental results (e.g., k_H/k_D = 2.34 at 338 K), which apparently even include a tunnel effect (see below). The "classically" calculated isotopic rate ratios in Table V only range from 1.411 to 1.841 (at 298.16 K), and as described in the Results section, variation of the relevant transition-state force constants within reasonable limits cannot reproduce the experimental values. The inclusion of a contribution from tunneling brings us much closer to the observed isotope effect (see Tables VIII and IX). Furthermore, since the reaction-coordinate mode mainly involves the motion of a hydrogen atom, the reduced mass along this coordinate is small, and thus the inclusion of tunneling may be required a priori.

Previous work by Bardos et al.[33] on 2,2,3,3-tetramethylaziridine and its N-deuterio analog (in carbon tetrachloride solution) led to collapse temperatures of 52 and 68°C, respectively, from which a $\Delta\Delta G^\ddagger$ value of 0.9 kcal/mol may be estimated. Although this value appears to be somewhat too large in the light of our own results, the operation of the tunnel effect is certainly indicated in this case as well.

For an accurate calculation of the contribution of tunneling, knowledge of the vibrational energy levels is necessary, as well as their splitting for the mode leading to inversion. An analytical expression describing the shape of the potential-energy curve is also required. The splitting of the vibrational energy levels can in principle be determined by microwave spectroscopy, if the barrier height is not greater than ca. 10 kcal/mol. Our experimental results indicate that the barrier in aziridine is of the order of 18 kcal/mol (see below), and thus far outside of the range accessible to the microwave technique. The "lower-limit" microwave estimations of the barrier height (11.6[10] and 12[9] kcal/mol) are seen to be too low by at least 5-6 kcal/mol, and since the inversion splitting varies inversely as the barrier height, the actual splitting in the vibrational ground state is almost certainly undetectable by present microwave techniques.

The tunnel effect ratios ($Q_{\mathrm{H}}/Q_{\mathrm{D}}$) calculated by means of the approximate eq 2 (Table VIII) are indeed relatively small at temperatures above room temperature, but are definitely nonnegligible, and assuming quite reasonable values for the transition-state force constants, reproduce the experimental data quite satisfactorily (see Table IX and discussion below).

One of the experimental manifestations of the tunnel effect, as discussed by Bell[25b] and by Caldin,[32a] is a significant difference in the activation entropies for the two isotopic compounds. It is well known, however, that the activation parameter most difficult to derive accurately from NMR band shape analysis is $\Delta S^\ddagger$, whereas the corresponding value of $\Delta G^\ddagger$ is in general quite reliable. A determination of the *true magnitude* of $\Delta\Delta S^\ddagger$ is thus fraught with uncertainty, but we can at least definitely establish its *sign* to be positive (see Table IX). $\Delta\Delta G^\ddagger$ is very well determined, and is too large (by a factor of the order of 2) to be accounted for solely on the basis of "classical" isotope effect calculations. Thus, it is quite clear that we have observed a significant tunnel effect on the inversion barrier. Consideration of the values of $\Delta\Delta H^\ddagger$ and $\Delta\Delta S^\ddagger$ obtained theoretically (Table IX) shows that only reaction-coordinate frequencies in the ranges $|\nu^\ddagger_{\mathrm{H}}| = 1050 \pm 50$ cm^{-1} and $|\nu^\ddagger_{\mathrm{D}}| = 800 \pm 40$ cm^{-1} are compatible with the experimental data, if the error limits given for the experimental $\Delta\Delta H^\ddagger$ and $\Delta\Delta S^\ddagger$ values are taken into account. This result is a significant piece of otherwise unattainable information about the structure of the transition state.

The thermodynamic activation parameter of greatest relevance for the height of the barrier is the enthalpy of activation, as discussed by Lehn in his review.[4a] The *experimental* $\Delta H^\ddagger$ is, however, only a lower limit of the true barrier height in aziridine, since it is in effect lowered by tunneling. The $\Delta H^\ddagger$ of 17.3 kcal/mol obtained for the deuterium compound should nonetheless be a rather adequate starting point from which to make a reasonable estimate, in view of the smaller tunnel effect involved. A simple calculation using eq 3, with $|\nu^\ddagger_{\mathrm{D}}| = 800 \pm 40$ cm,$^{-1}$ provides values of 1.77 ± 0.06 and 1.58 ± 0.04 for the tunnel correction,

$$Q_{\mathrm{D}} = (u^\ddagger_{\mathrm{D}}/2)/\sin(u^\ddagger_{\mathrm{D}}/2) \qquad (3)$$

$$u^\ddagger_{\mathrm{D}} = h|\nu^\ddagger_{\mathrm{D}}|/kT$$

Q_{D}, at 338 and 373 K, respectively. The corresponding rate constants, calculated from the regression equation for the Eyring plot, can then be corrected to obtain rate constants in the absence of tunneling, which in turn may be used to calculate values for $\Delta G^\ddagger$ at 338 and 373 K. At both temperatures, $\Delta G^\ddagger = 18.1_6$ kcal/mol, and thus these data imply a $\Delta H^\ddagger$ of 18.2 kcal/mol. Correction of this value for the total difference in zero-point energy between initial and transition states (obtained from the model calculations of the isotope effect) leads to a value of 19.1 kcal/mol, which may be compared with the ab initio theoretical values of 18.3[5b] and 18.0[5c] kcal/mol, calculated by Lehn and his coworkers. Other theoretical barrier heights calculated by ab initio type methods, but with somewhat different basis sets, are 15.5 and 16.6 kcal/mol, reported by Clark[5d] and Skaarup,[7] respectively. More approximate molecular orbital calculations have provided barrier heights (in kcal/mol) of 13.8[5f] (MINDO), 20.9[5e] (Extended Hückel), 21.4[5g] (CNDO/2), and 34[5a] (Valence Force Field).

The curvature at the top of the barrier, in the transition state, as indicated implicitly by the agreement between theoretical and experimental $\Delta\Delta G^\ddagger$, $\Delta\Delta H^\ddagger$, and $\Delta\Delta S^\ddagger$ values discussed above, is similar to that governing the corresponding mode in the initial state (but with opposite sign). The frequency of the N-H bending mode is 1096 cm^{-1} in the initial state[24] ($F_{\mathrm{CNH}} = 0.5$ (mdyn Å)/rad^2) and, as pointed out above, our experimental data are quite well reproduced by a transition state reaction-coordinate frequency of $|\nu^\ddagger_{\mathrm{H}}| = 1050 \pm 50$ cm^{-1}.

Acknowledgment. We are most grateful to Professor Lars Melander, University of Göteborg, for his active interest, and for many stimulating and illuminating comments on the manuscript. The cost of the XL-100-15 spectrometer used in this work was defrayed by a grant from the Knut and Alice Wallenberg Foundation. Support by the Swedish Natural Science Research Council is gratefully acknowledged.

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Role of Structural Flexibility in Conformational Calculations. Application to Acetylcholine and β-Methylacetylcholine[1]

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Received March 7, 1975

Abstract: The conformational properties of acetylcholine and β-methylacetylcholine are examined using an empirical energy function technique which permits energy minimization in the full conformational space of the molecule. Energy surfaces corresponding to rigid rotations about bonds are compared with those obtained by a complete energy minimization at each point. For the relatively uncrowded acetylcholine molecule, the differences between the two sets of calculations are minor. However, for β-methylacetylcholine, there is a significant reduction in the barrier heights and a large increase in the accessible conformational space. The geometric changes that relieve the large nonbonded repulsive contacts are analyzed and the results are compared with a series of INDO calculations based on the energy-minimized geometries. The sensitivity of conformational maps to the choice of starting geometry is also examined and an evaluation is given of the X-ray data used in previous conformational calculations.

I. Introduction

There have been many recent attempts to calculate conformational properties of pharmacologically interesting molecules.[3] Particular attention has focused on acetylcholine and related compounds which have served as the testing ground for a variety of theoretical methods.[4-12] Most of the conformational calculations have been carried out by selecting a geometry with fixed bond lengths and bond angles and systematically varying one or more dihedral angles of interest to produce an energy curve or surface. The methods used to obtain the conformational energy of the molecule as a function of the conformational parameters include empirical energy functions,[4b,5,6] Extended Hückel Theory (EHT),[4a,10] Intermediate Neglect of Differential Overlap (INDO),[8,9] Perturbative Configuration Interaction of Localized Orbitals (PCILO),[4c,11,12] and ab initio formulations of the STO-3G[13] and molecular fragment[7] types.

Typically the resulting energy surfaces show several low-energy valleys separated by barriers of various heights and surrounded by regions of such high energy as to preclude the molecule's existence in those areas. It has been assumed as a consequence that properties of the molecule, either in solution or when bound to a receptor site, may be understood by considering the low-energy regions. For a molecule like acetylcholine, where the maps found by most workers are rather nonrestrictive, such an assumption is possibly a reasonable one. However, for systems with a highly restrictive map, such as β-methylacetylcholine, a question must be raised concerning the possibility that "forbidden" regions might be made more accessible by relaxing some of the molecular constraints implicit in the calculations; that is, some of the strong steric repulsions that are involved in producing the high-energy regions may well be significantly reduced by including bond length and bond angle adjustment in the calculation. Production of a torsional angle conformational map with such "adiabatic" minimization of energy along all degrees of freedom is clearly a much larger task than that involved in the usual fixed-geometry maps. To investigate the importance of such effects without using excessive computer time, we have chosen an empirical energy-function