Synthesis and Dynamic NMR Studies of the 3,7-Diazabicyclo[4.1.0]heptane System

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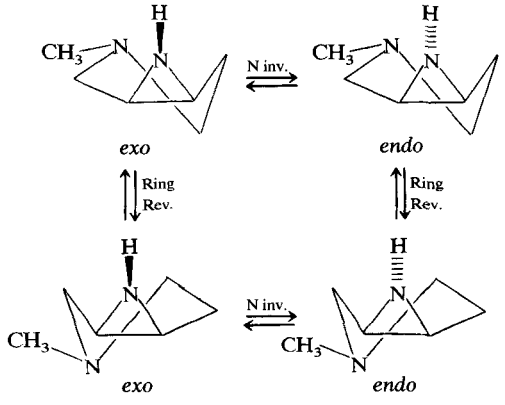
A new bicyclic system, 3,7-diazabicyclo[4.1.0]heptane, has been prepared from 3-(ethoxycarbonyl)-7,3-oxazabicyclo[4.1.0]heptane by reaction with sodium azide and reduction of the resulting tosyloxy azide with lithium aluminum hydride. The molecule can exist in four stereoisomeric half-chairs, depending on the configuration of the two nitrogen atoms. Half-chair ring reversal and piperidine nitrogen inversion are fast on the NMR time scale at all observed temperatures. Inversion of the secondary aziridine nitrogen becomes slow as the temperature is lowered ($T_c = -10$ °C). Complete analysis of the ^{1}H spectrum was possible with the 1,5,5-trideuteriated analog. At slow exchange, two aziridine invertomers are present with an *exo*/*endo* ratio of approximately 0.7 in toluene-d_8, 0.7 in CH_2Cl_2 and 1.7 in $CHCl_3/CH_2Cl_2$. The free energy of activation for nitrogen inversion is 13.2 kcal mol^{-1} at −10 °C in $CHCl_3/CH_2Cl_2$.

INTRODUCTION

Conformational analysis of bicyclo[4.1.0]heptane systems show that they resemble that of cyclohexenes, in that the predominant conformation is the half-chair, which can undergo a rapid ring reversal.[1] The three-membered ring fulfills the same conformational function as the double bond in the monocyclic system. The presence of nitrogen atoms in the ring suggests that several rapidly interconverting inversional isomers may exist.

We have prepared the first example of the 3,7-diazabicyclo[4.1.0]heptane system in order to examine its biological and conformational properties. The operation of half-chair ring reversal and of aziridine nitrogen inversion is illustrated in Scheme 1.

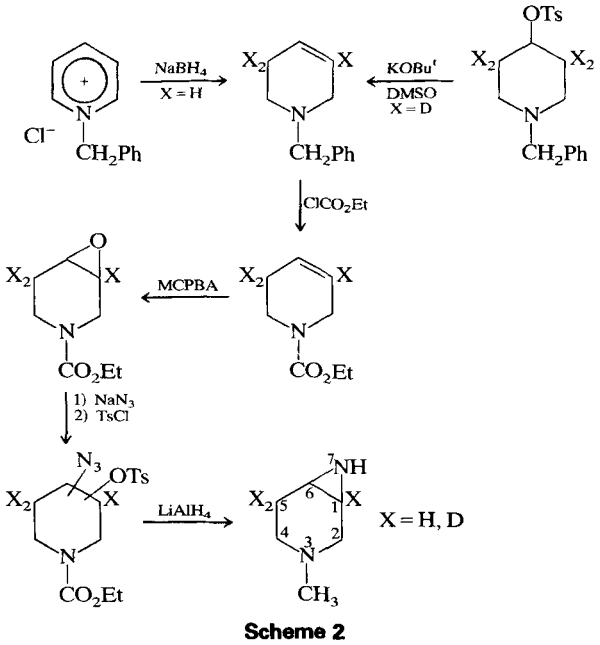


Scheme 1

We ignore the effects of piperidine nitrogen inversion, since the process should be fast on the NMR time scale at the temperatures observed. The barrier to inversion of nitrogen in *N*-methylpiperidine can be estimated to be 7.5–8.0 kcal mol^{-1}, with a T_c of approximately −110 °C.[2,3] Consequently, in Scheme 1 we represent the piperidine nitrogen in its more stable, pseudoequatorial arrangement.

RESULTS

The successful synthesis of 3-methyl-3,7-diazabicyclo[4.1.0]heptane is shown in Scheme 2. The un-



Scheme 2

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deuteriated material was prepared in five steps from 1-benzylpyridinium chloride.[4] Reduction of the pyridinium salt with sodium borohydride, reaction with ethyl chloroformate and epoxidation produced 3-(ethoxycarbonyl)-7,3-oxazabicyclo[4.1.0]heptane.[5]

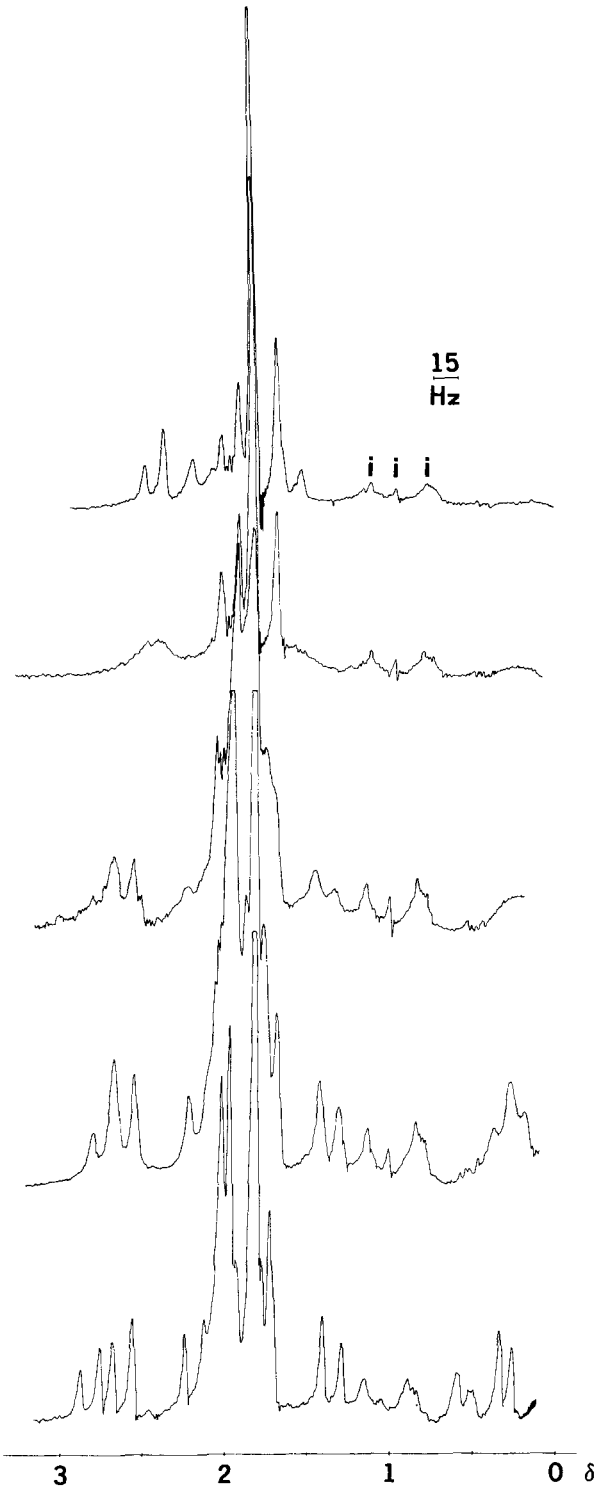

Figure 1. ^{1}H NMR spectrum of 3-methyl-3,7-diazabicyclo-[4.1.0]heptane-1,5,5-d_3 as a function of temperature in toluene-d_8: (top to bottom) room temperature, −1, −20, −35 and −60 °C. Impurities from incomplete deuteriation of substrate and solvent are signified by the letter i at the top and are present at all temperatures. This highest temperature has not quite reached fast exchange.

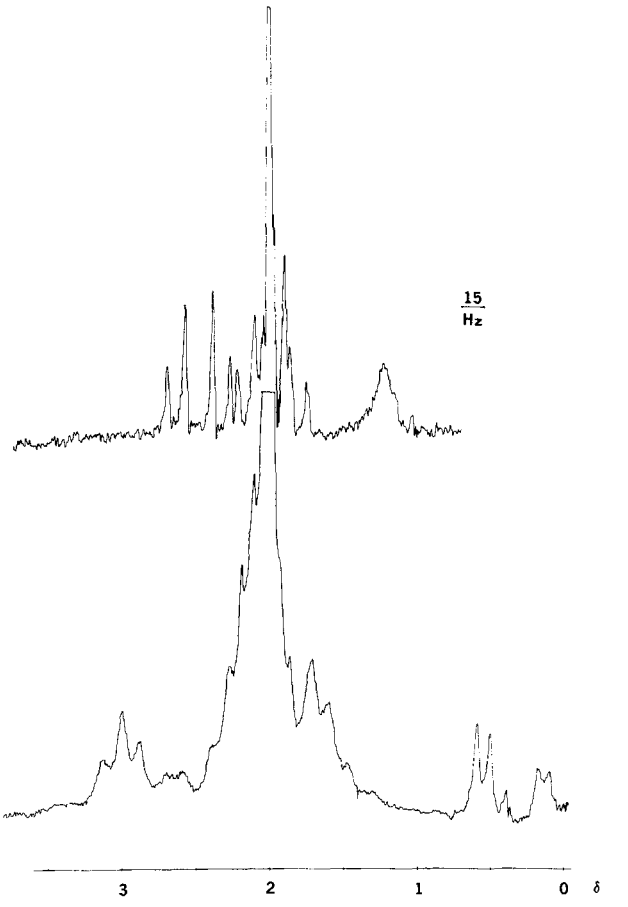

Figure 2. ^{1}H NMR spectrum of 3-methyl-3,7-diazabicyclo[4.1.0]heptane-1,5,5-d_3 in $CH_2Cl_2/CHCl_3$ at room temperature (top) and −95 °C (bottom).

Opening of the epoxide ring with sodium azide and treatment with tosyl chloride gave the tosyloxy azide, which was ring-closed with lithium aluminium hydride to the desired product.

Deuteriation at the 1,5,5-positions was effected through the same sequence, with deuterium introduced by base-catalyzed exchange of 1-benzyl-4-piperidone, which was reduced and tosylated to give the piperidine tosylate shown in Scheme 2 (X = D). The ^{1}H spectra of the deuteriated modification were recorded as a function of temperature in toluene-d_8 (Fig. 1), methylene chloride and a mixture of chloroform and methylene chloride (Fig. 2).

DISCUSSION

The remaining protons in the deuteriated sample consisted of those at the 2-, 4-, 6-, 7-(NH) and methyl positions. The methyl resonance is a singlet at approximately δ1.9 for all temperatures. At room temperature in toluene-d_8 (Fig. 1), the 6-proton resonance is a singlet at δ1.75 and the 2- and 4-proton resonances each consist of an AB quartet, at δ2.40 ($\Delta\nu = 29$ Hz, $J = 11.2$ Hz) and δ1.90 ($\Delta\nu = 37$ Hz, $J = 10.6$ Hz), respectively. One member of the H-4 quartet coincides with the H-6 singlet. The non-equivalence of the

members of each geminal pair results from the geometry of the bicyclic system. The aziridine ring remains on the same side of the six-membered ring, even when all rate processes are fast. The presence at room temperatue of only one AB quartet for each of the geminal pairs, however, indicates that nitrogen inversion at both centers and ring reversal are rapid on the NMR time scale or, less likely, that all processes are severely biased in favor of a single conformation. The resonances for the 2- and 4-protons have the same pattern in $CHCl_3/CH_2Cl_2$ (Fig. 2). The NH resonances in toluene-d_8 are broad and partially obscured by residual nondeuteriated solvent. In $CHCl_3/CH_2Cl_2$, however, the NH resonance is clearly visible as a broad peak around δ1.2, which shifts upfield as the temperature is lowered. The results in pure CH_2Cl_2 are very similar to those in toluene and will not be discussed further.

As the temperature is lowered, in toluene-d_8 the AB quartets for the 2- and 4-protons undergo decoalescence with a coalescence temperature of about -10 °C, each into a pair of AB quartets of unequal intensity. For the 2-protons, the quartets are at δ2.55 ($\Delta\nu = 62$ Hz and $J = 11.2$ Hz) and δ2.30 ($\Delta\nu = 62$ Hz, $J = 11.2$ Hz). Since piperidine nitrogen inversion and half-chair ring reversal should still be rapid in this temperature range, the rate process must be associated with the aziridine nitrogen, either atomic inversion or intermolecular exchange. The averaging process for the 2-protons appears to be cross-over exchange,[6] whereby the low-field resonance of one AB quartet exchanges with the high-field resonance of the other AB quartet. The peak positions observed at slow exchange (-60 °C) do not precisely average to the positions at room temperature, including proper weighting factors. The disagreement, however, is not large (*ca* 0.1 ppm) and probably results from the inherent temperature dependence of resonance positions. For the 4-protons, the pair of AB quartets are at δ1.60 ($\Delta\nu = 41$ Hz, $J = 11.2$ Hz) and δ2.00 ($\Delta\nu = 19$ Hz, $J = 11.2$ Hz). Because of the small chemical shift difference for the lower field AB quartet, the averaging process is less clear but appears to be direct rather than cross-over (low-field components exchange with low-field components). The slow exchange spectrum in $CHCl_3/CH_2Cl_2$ for these protons is analogous.

The aziridine resonances are best seen in the $CHCl_3/CH_2Cl_2$ spectra. The broad resonance at room temperature decoalesces into a pair of doublets, due to coupling to the 6-proton, δ0.55 ($J = 8.7$ Hz) and 0.28 ($J = 7.5$ Hz), relative ratio approximately 10:7. At low temperatures, the same pair of doublets is clearly visible in the toluene-d_8 spectra (ratio 7:10). From the coalescence of these peaks in $CHCl_3/CH_2Cl_2$, the free energy of activation at coalescence ($T_c = -10$ °C) was calculated to be $\Delta G^{\ddagger} = 13.2$ kcal mol^{-1}. Although this value is close to the inversion barrier for other secondary aziridines,[7] the loss of configuration at the aziridine nitrogen can also be explained by rapid intermolecular exchange of the NH proton. The fact that fast exchange of the AB quartets for the 2- and 4-protons is accompanied by loss of the coupling constant between the 6-(CH) and 7-(NH) protons suggests that the rate process is intermolecular. Further, as the substrate concentration increases, T_c decreases. The exchange rate is expected to increase in this fashion for a second-order process. Thus the barrier to aziridine nitrogen inversion is >13.2 kcal mol^{-1}. In aziridine itself, NH inversion has a $\Delta G^{\ddagger}$ of 17.3 kcal mol^{-1} ($T_c = 68$ °C),[8] so that the value in the present system does seem low and is best interpreted by the intermolecular mechanism.

The vicinal coupling constants between the 6- and 7-protons can be used to identify the *endo* (NH over the six-membered ring) or *exo* (NH extended away from the larger ring) nature of the two conformers (Scheme 1). The more intense doublet at -60 °C in toluene-d_8 is located at δ0.28 and exhibits a $^3J(67)$ of 7.5 Hz. The less intense doublet is located at δ0.55 and exhibits a $^3J(67)$ of 8.75 Hz. The relative intensities are approximately 7:10. The larger vicinal coupling constant in three-membered rings is associated with the *cis* HCNH geometry, so that the less populated conformer with the larger coupling constant has the *exo* geometry. The values in aziridine itself are $J(cis) = 9.6$ Hz and $J(trans) = 7.6$ Hz.[8]

Thus the favored conformer has the NH proton extended over the molecule (*endo*), in a presumably more sterically hindered position. One possible explanation for this result is that the NH proton is partially hydrogen bonded to the piperidine nitrogen. As can be seen most readily in the upper right structure in Scheme 1, an *endo* arrangement for the aziridine proton and a pseudoequatorial arrangement for the piperidine methyl group can permit hydrogen bonding. The more polar, better hydrogen-bonding solvent $CHCl_3/CH_2Cl_2$ reverses the *exo*/*endo* ratio (compare Figs 1 and 2). Chloroform should be able to hydrogen bond to the piperidine nitrogen, disrupting in part the intramolecular hydrogen bond of the *endo* form and increasing the proportion of the sterically less hindered *exo* form. Alternatively, the *endo* form may be favored by intramolecular dipole-dipole interactions, and a more polar *exo* form by solvent interactions in chloroform. Dipolar differences, however, are difficult to assess in secondary amines, so we cannot test this interpretation.

CONCLUSIONS

At -60 °C, 3-methyl-3,7-diazabicyclo[4.1.0]heptane exhibits fast half-chair ring reversal, fast piperidine nitrogen inversion but slow aziridine nitrogen inversion in toluene-d_8, CH_2Cl_2 and $CHCl_3/CH_2Cl_2$. As the temperature is raised, aziridine nitrogen inversion becomes fast on the NMR time scale through an intermolecular process, with $T_c = -10$ °C and $\Delta G^{\ddagger} = 13.2$ kcal mol^{-1} in $CHCl_3/CH_2Cl_2$. Analysis of the ^{1}H spectra of the 1,5,5-trideuteriated modification showed that there are two conformations present at low temperatures, corresponding to *endo* and *exo* geometries of the aziridine NH proton. The 2- and 4-protons each give rise to an unequal pair of AB quartets at low temperatures, and the 7-(NH) proton gives rise to an unequal pair of doublets. The vicinal couplings (HNCH) in the aziridine ring show that the

major conformer (about 60%) in toluene-d_8 has the NH proton extended over the six-membered ring, i.e. in the more crowded *endo* geometry, possibly because of intramolecular hydrogen bonding with the piperidine lone pair or intramolecular dipolar interactions. In $CHCl_3/CH_2Cl_2$ the isomer ratio is reversed, with the *exo* form favored (about 60%).

EXPERIMENTAL

Room-temperature ^1H spectra were recorded on a Varian EM-360 spectrometer operating at 60 MHz. Variable-temperature spectra were recorded on a JEOL JNM-100 spectrometer, operating at 100 MHz. The probe temperature was calibrated with methanol. Preparative gas chromatography was carried out on a Varian Aerograph Model 710 instrument, with a silicone oil OV-15 column.

1-Benzyl-4-piperidone-3,3,5,5-d_4

Deuteriation of 1-benzyl-4-piperidone (50 g, 0.26 mol) was effected with D_2O (50 g, 2.5 mol) containing NaCl (5.8 g, 0.1 mol) and Na_2CO_3 (10.6 g, 0.1 mol). The mixture was stirred and heated at 100 °C for 5 h. The layers were cooled and separated, and the organic phase was treated again with the above set of reagents. After a total of five treatments, the organic layer was dissolved in dry diethyl ether, dried over $MgSO_4$, concentrated and distilled: 42.5 g (94%), b.p. 130 °C (20 mmHg); ^1H NMR δ2.70 (4, s, CH_2), 3.50 (2, s, CH_2Ph), 7.30 (5, s, arom).

1-Benzyl-4-*p*-toluenesulfonyloxypiperidine-3,3,5,5-d_4

Reduction of the ketone with $LiAlH_4$ by standard procedures gave a 93% yield of the alcohol (Scheme 2). Tosylation by standard procedures gave a 46% yield of the tosylate. Calculated for $C_{19}H_{19}D_4NO_3S$: C, 65.31; H, 7.77; N, 4.01%. Found: C, 65.01; H, 7.28; N, 4.10%.

1-Benzyl-1,2,5,6-tetrahydropyridine-3,5,5-d_3

The tosylate (5.2 g, 0.015 mol) and potassium *tert*-butoxide (3.3 g, 0.029 mol) were stirred in dimethyl sulfoxide (70 ml) at room temperature for 7 h. The mixture was poured into 400 ml of water and extracted with 4 × 50 ml of diethyl ether. The layers were separated and the organics were washed with water (2 × 20 ml), dried over $MgSO_4$, concentrated and distilled to give 2.5 g (95%), b.p. 126–128 °C (15 mmHg); ^1H NMR δ2.45 (2, s, CH_2), 2.95 [2, d(J = 2 Hz), CH_2CD], 3.45 (2, s, CH_2Ph), 5.66 (1, s, CH), 7.30 (5, s, arom).

1-(Ethoxycarbonyl)-1,2,5,6-tetrahydropyridine-3,5,5-d_3[5]

1-Benzyl-1,2,5,6-tetrahydropyridine-3,5,5-d_3 (16 g, 0.09 mol) was heated with 10.8 g (0.1 mol) of ethyl chloroformate in toluene at reflux for 18 h, concentrated and distilled to give the desired product: 12 g (84%), b.p. 130–135 °C (15 mmHg) [lit.[5] (undeuteriated) 120–125 °C (25 mmHg)].

3-(Ethoxycarbonyl)-7,3-oxazabicyclo[4.1.0]heptane-1,5,5-d_3[5]

To 6.5 g (0.04 mol) of the ethoxycarbonyltetrahydropyridine in 120 ml of CH_2Cl_2 were added 10.2 g (0.049 mol) of 80% *m*-chloroperoxybenzoic acid in portions below 0 °C with vigorous stirring. Stirring and cooling were continued for 10 h; stirring was continued at room temperature for another 5 h. The white precipitate was filtered off and the filtrate was washed with 20% aqueous NaOH to pH 9 and then with water to pH 7. The solution was dried ($MgSO_4$), concentrated and distilled to give 4.8 g (69%) of the product: b.p. 136–138 °C (13 mmHg) [lit.[5] (undeuteriated) 120–123 °C (7 mmHg)].

3-Methyl-3,7-diazabicyclo[4.1.0]heptane-1,5,5-d_3

The epoxide (11 g, 0.063 mol) was stirred and heated to reflux for 15 h with 20.4g (0.315 mol) of sodium azide and 15 g (0.285 mol) of ammonium chloride in aqueous ethanol (150 ml). The inorganic salts were filtered off and the filtrate was concentrated. The residue and the filter cake were dissolved in water and extracted with 4 × 70 ml of diethyl ether and 3 × 50 ml of $CHCl_3$. The extracts were dried over $MgSO_4$ and concentrated. The oily residue of crude azido alcohol (12.5 g, 92%) was dissolved in 70 ml of pyridine. Tosyl chloride (10 g, 0.052 mol) was added at 0 °C and the mixture was allowed to stand in a refrigerator for 48 h. The solution was poured on to ice–water (1000 ml), extracted with 5 × 100 ml of $CHCl_3$, dried ($MgSO_4$) and concentrated. The residue (13 g, 0.035 mol) of crude tosyloxy azide was dissolved in 80 ml of tetrahydrofuran (THF) and added below 10 °C to 2.67 g (0.07 mol) of $LiAlH_4$ suspended in 50 ml of diethyl ether. Stirring was continued at 10 °C for 3 h and at reflux for 4 h. The complex was decomposed with 10% aqueous NaOH. The precipitate was filtered off, washed with diethyl ether and THF, dried (KOH), concentrated and distilled to give 2.6 g (65%) of the desired product: b.p. 62–65 °C (13 mmHg), n_D^{20} 1.4820. An analytical sample was purified by preparative GLC: n_D^{20} 1.4870; ^1H NMR ($CDCl_3$) δ0.90 (1, br s, NH), 2.05 (1, s, CH), 2.10 (3, s, CH_3), 2.10 [2, ABq(J = 12 Hz), CH_2], 2.60 [2, ABq(J = 12 Hz), CH_2CD]; IR (film) 3150 (NH) cm^{-1}. Calculated for $C_6H_9D_3N_2$: C, 62.57; H, 13.08; N, 24.33%. Found: C, 62.31; H, 13.09; N, 24.02%.

Acknowledgments

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