Conformational Properties of Azacyclooctanes

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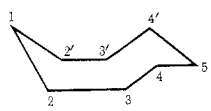
The 270-MHz ^1H spectra and the 22.6-MHz ^{13}C spectra have been obtained for azacyclooctane (azocane) and its *N*-methyl and *N*-chloro derivatives between room temperature and −120°. A coalescence is observed in each case at about −95° in the ^1H spectra. The ^{13}C spectra remain unchanged throughout the temperature range. The results are consistent with a boat–chair conformation in which the nitrogen resides at the BC(1) position on the molecular plane of symmetry. Pseudorotation is ruled out as the process responsible for the changes in the ^1H spectra because of the temperature invariance of the ^{13}C spectra. The spectral changes are therefore attributed to the slowing of boat–chair/boat–chair ring reversal. For the N–H and N–CH_3 systems, nitrogen inversion is fast at these temperatures, but for N–Cl the process should be slow on the nmr time scale.

Theory and experiment alike have gravitated to the boat–chair (1) as the favored conformation for cyclooctane



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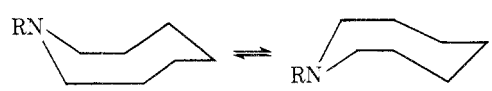
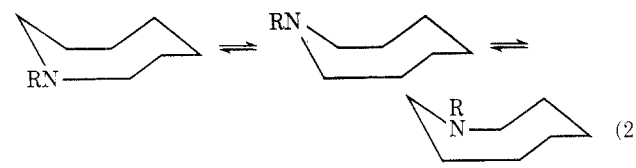
and many of its derivatives.[2,3] When one or more methylene groups in cyclooctane are replaced with a heteroatom, nonbonded and eclipsing interactions are changed considerably, so that conformational minima may differ. Nmr studies of oxygen derivatives[4] have indicated that oxocane (one oxygen) exists as a boat–chair with the oxygen in the BC(1) position, 1,3-dioxocane exists as a boat–chair with the oxygens in the BC(1) and BC(3) positions, 1,3,6-trioxocane exists as a mixture of twist–boat–chair and twist–chair–chair conformations, and 1,3,5,7-tetraoxocane exists as a mixture of twist–boat–chair and symmetrical crown conformations.

The present study was initiated to examine the conformational properties in solution of azacyclooctanes, in which one methylene group of cyclooctane has been replaced with NR. Such a change in the molecular structure raises a number of questions. (1) What conformation do azacyclooctanes assume? (2) At what position does the nitrogen atom reside? In conformations other than the symmetrical crown, there are several distinct positions, in contrast to cyclohexane. In the boat–chair (1), for example, the nitrogen has the choice of five positions. (3) Does the substituent on nitrogen assume an axial-like or an equatorial-like position? (4) What dynamic processes operate in the molecule? If there is a preference for the boat–chair, which possesses a plane of symmetry, the molecule may undergo a ring reversal process (eq 1) very similar to that of cyclohexane. By this process, an axial group is interchanged with its geminal equatorial counterpart. If the time scale of the nmr experiment is responsive to this process, then the protons in a given CH_2 group (disregarding for the time being effects of substituents on nitrogen) will change from enantiotopic to diastereotopic, as the temperature is lowered. This process does not affect the positional identity of the various atoms, as numbered in **1**. Pseudorotation, on the other hand, averages ring positions as well as substituent identities. A boat–chair can be transformed into another boat–chair, probably through a twist–boat–chair intermediate, with alteration of positional identity, as in eq 2. In this manner the nitrogen atom can be moved around the ring in an orderly fashion. The substituents are averaged to two noninterconverting sets: 1e, 2e, 3a, 4a, 5a, 4′a, 3′a, 2′e; and 1a, 2a, 3e, 4e, 5e, 4′e, 3′e, 2′a. Thus, geminal groups are not interchanged by pseudorotation. In cyclooctane, only when all positions are averaged by pseudorotation and when geminal groups are interchanged by ring reversal do all protons become equivalent. In azacyclooctanes, the ^{13}C spectrum can thus be of use to determine the location of the nitrogen. If it is located on the boat–chair plane of symmetry (positions 1 or 5), the ^{13}C spectrum will not change with temperature. If it is located off the plane of symmetry (positions 2, 3, or 4), changes will be observed as pseudorotation is frozen out. For example, if azacyclooctane should exist as the BC(2) form, a dynamic process would be observed (see eq 2), and at the slow-exchange limit carbons 3,3′ and 4,4′ (respectively) would become nonequivalent. The ^{13}C spectrum is not sensitive to the process of ring reversal, so that spectral changes can only derive from hindered pseudorotation. A third dynamic process, inversion about nitrogen, is also possible in azacyclooctanes. This process interconverts the axial and equatorial positions on nitrogen without involving the remainder of the ring. Only if nitrogen inversion is frozen out can the conformational preference of the substituent on nitrogen be determined. If the molecule is biased entirely toward one substituent position, then the spectrum will not be altered as nitrogen inversion is slowed.



(1)

2H, R = H
2M, R = CH_3
2C, R = Cl



(2)

In order to answer these questions, we have examined the ^1H spectra at 270 MHz and the ^{13}C spectra at 22.6 MHz of azacyclooctane (**2H**) and its *N*-methyl (**2M**) and *N*-chloro (**2C**) derivatives. A high-field, superconducting magnet system was necessary to differentiate proton resonances. From the temperature dependence of the ^1H spectra and the temperature independence of the ^{13}C spectra, we conclude that all these azacyclooctanes exist in the boat–chair conformation with the nitrogen at the BC(1) position. Tentative conclusions about the location of the substituents on nitrogen are reached.

Results

The 270-MHz ^1H spectrum of azocane (heptamethylenimine or azacyclooctane, **2H**) at room temperature (Figure

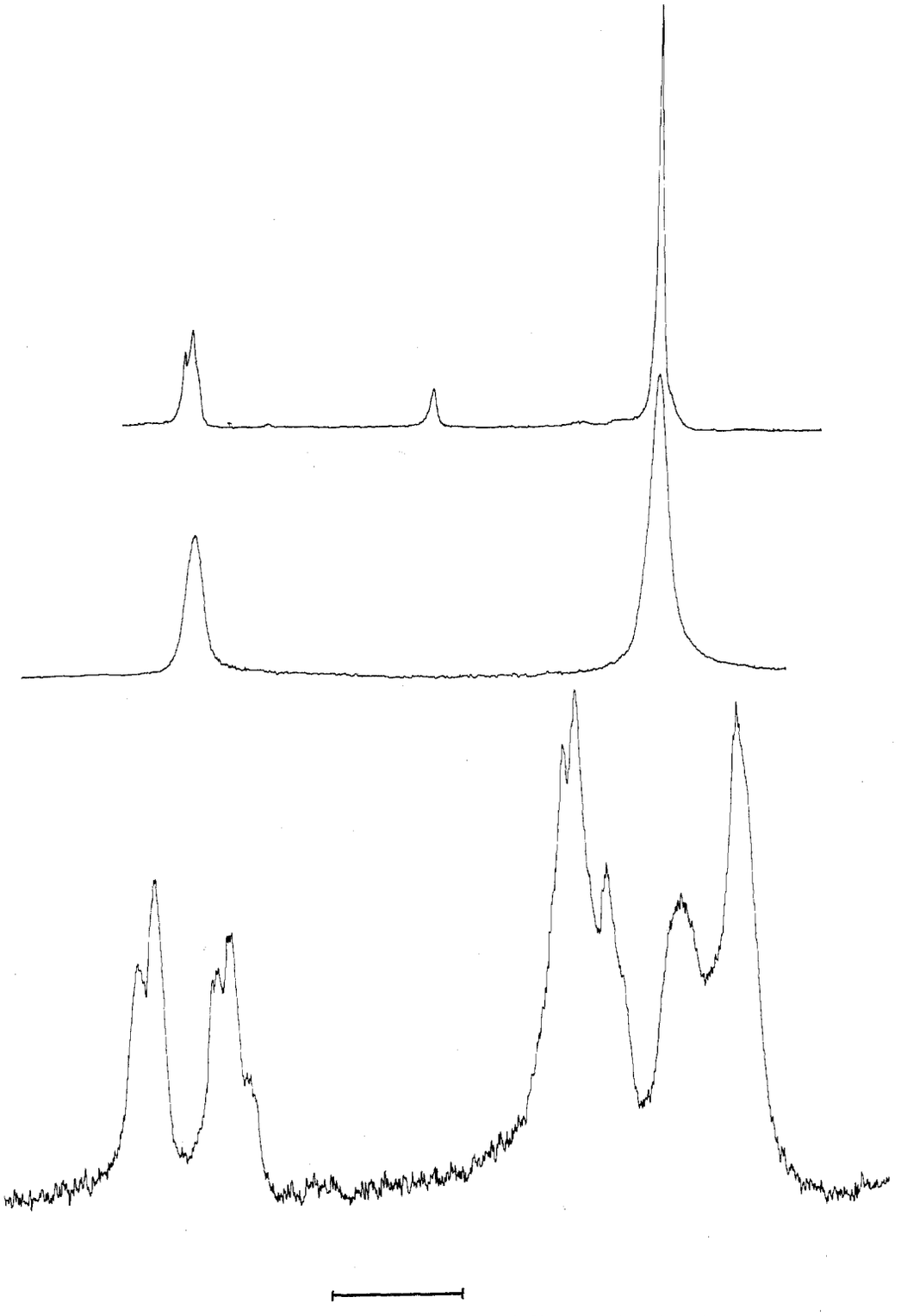


Figure 1. The 270-MHz ^1H spectrum of azocane (**2H,** heptamethylenimine) in $CHClF_2$ as a function of temperature (top to bottom, +19, −80, −107.5°). The room-temperature peaks occur approximately at δ 2.2, 2.8, and 3.4. The calibration bar represents 90 Hz.

1) contains a broad singlet at δ 2.2 for the ten β, γ, and δ protons. The NH proton falls at 2.8, and the α-methylene protons give a second-order triplet at 3.4. As the temperature is lowered, the resonances from the protons on carbon broaden. The resonance from the proton on nitrogen broadens, moves downfield, and ultimately disappears because of quadrupolar relaxation and a lower rate of proton exchange. At −107.5°, the α-methylene resonance has reached the slow-exchange limit as a pair of 1:1 multiplets, which form essentially an AB quartet ($\Delta\nu$ = 0.22 ppm) with additional vicinal splitting. The remaining methylene protons produce a multiplet at higher field, with at least five overlapping components, which arise from chemical-shift differences of three distinct sets of diastereotopic geminal protons (β, γ, and δ).

The room-temperature 270-MHz ^1H spectrum of *N*-methylheptamethylenimine (**2M**) is given in Figure 2. The methyl singlet occurs at δ 2.3, the α-methylene resonance at 2.5, and the resonances of the remaining protons at 1.6. As the temperature is lowered to −109°, the methyl and α-methylene resonances undergo only slight broadening. The resonance of the remaining methylene groups, however,

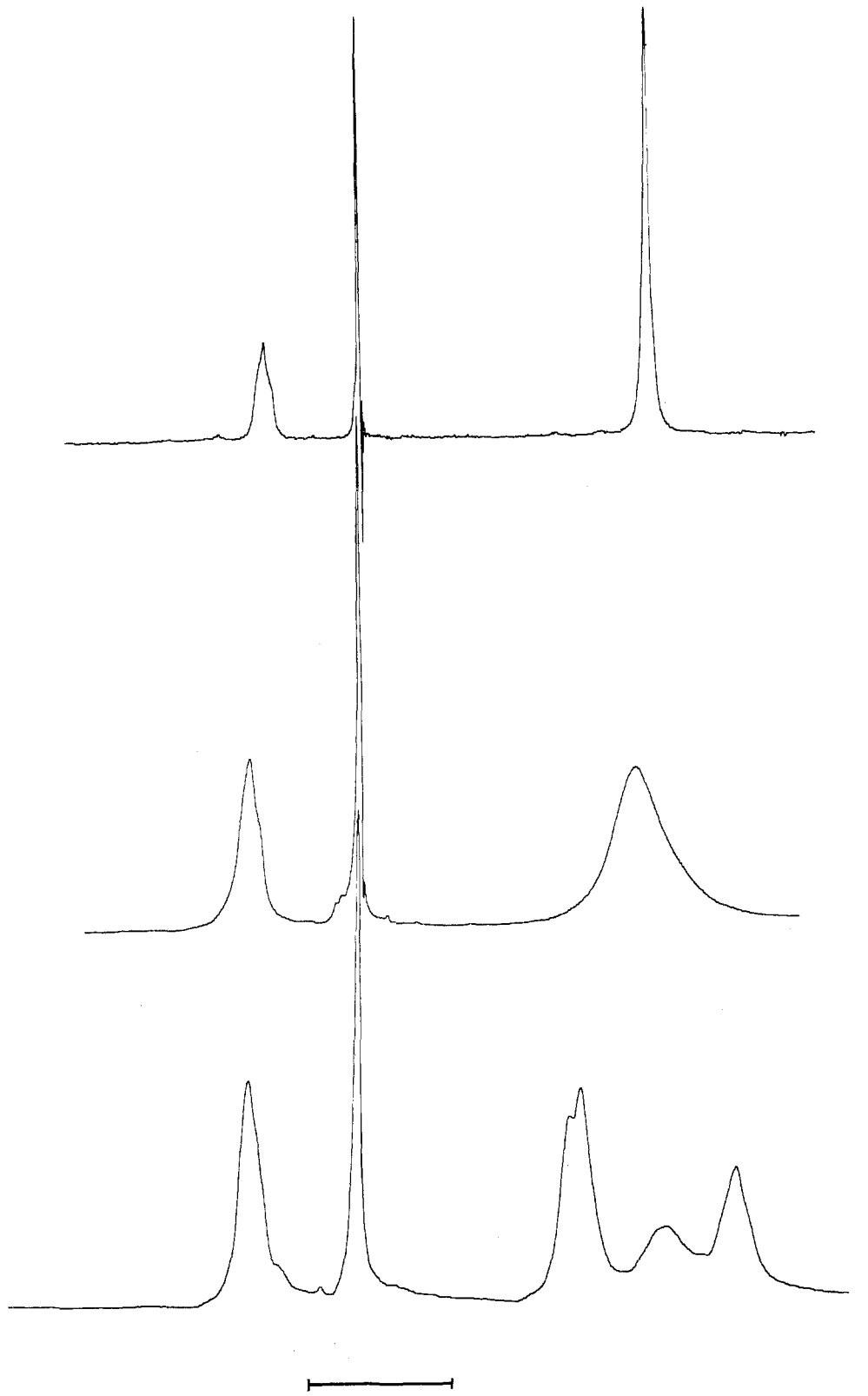


Figure 2. The 270-MHz ^1H spectrum of *N*-methylheptamethylenimine (**2M**) in $CHClF_2$ as a function of temperature (top to bottom, +19, −80, −109°). The room-temperature peaks occur approximately at δ 1.6, 2.3, and 2.5. The calibration bar represents 90 Hz.

broadens considerably at −80° and becomes a multiplet containing at least four components at the slow-exchange limit.

At room temperature, the α-methylene protons of *N*-chloroheptamethylenimine (**2C**) produce a sharp, well-resolved triplet at δ 3.2 (Figure 3). The two-peak resonance from the remaining methylene groups contrasts with the analogous singlet resonances of the NCH_3 and NH compounds. Most likely, the electron-withdrawing nature of the *N*-chloro group has pulled the resonance of the β protons to a lower field (1.9) than that of the γ and δ protons (1.6). As the temperature is decreased, all resonances broaden. The α-methylene triplet loses its fine structure at −80°, and finally becomes a doublet of unequal intensities (about 1:3) at −109°. This result contrasts with the 1:1 doublet for the NH compound and the singlet for the NCH_3 compound. The high-field peaks broaden, merge, and resolve into at least two very broad multiplets. There is

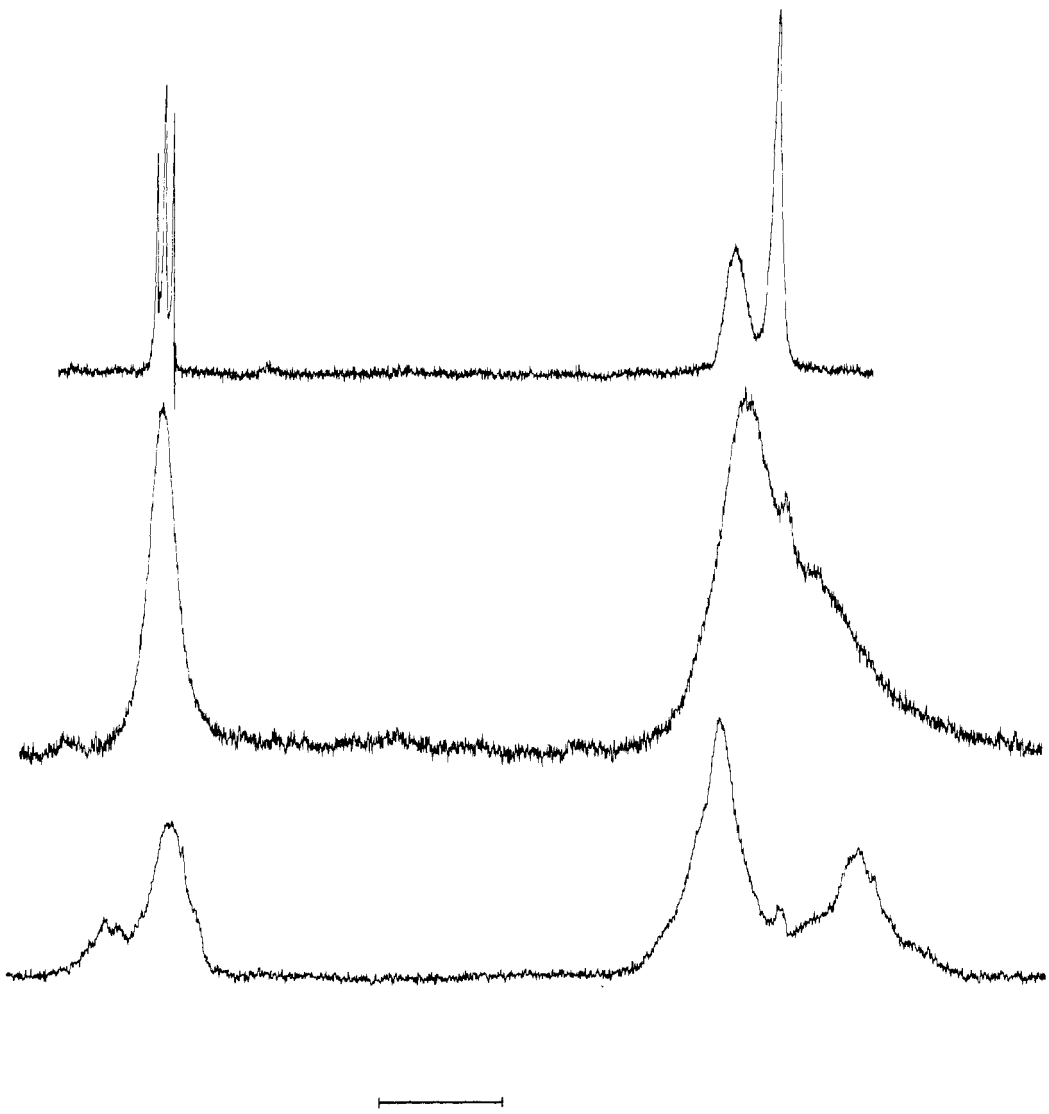


Figure 3. The 270-MHz ^1H spectrum of *N*-chloroheptamethylenimine (**2C**) in $CHClF_2$ as a function of temperature (top to bottom, +19, −80, −109°). The room-temperature peaks occur approximately at δ 1.6, 1.9, and 3.2. The calibration bar represents 90 Hz.

a strong similarity among the β, γ, and δ resonances for all three systems at −109°.

The ^{13}C spectra of **2H, 2M,** and **2C** were examined at 22.6 MHz between room temperature and −120° (Figure 4). The α-carbon resonances fall at lowest field. The β, γ, and δ carbons each give distinct resonances at higher field, with the δ-carbon peak recognized by its lower intensity. There was essentially no change with temperature over this 150° range in any of the spectra.

Discussion

The ^{13}C spectra of all three systems under study (**2H, 2M, 2C**) contain four resonances (ignoring the methyl peak) in the approximate ratio 2:2:2:1, and do not exhibit changes as the temperature is lowered to −120°. The ^1H spectra of the three compounds, on the other hand, pass through an exchange process over this same temperature range. Because a slowing of pseudorotation should have been evident in the ^{13}C spectrum, we can conclude without equivocation that the observed changes in the ^1H spectra are due to a slowing of ring reversal. Because only four peaks are observed in the ^{13}C spectra, the preferred conformation, assuming a boat–chair, must either possess a plane of symmetry [BC(1) or BC(5)] or undergo rapid pseudorotation to produce a plane of symmetry on the average [BC(2) ⇌ BC(2′), etc.]. The present data do not differentiate between these two possibilities. A similar quandary was reached in the oxocane study,[4] but the authors favored the BC(1) form with a static plane of symmetry. The azocane and oxocane data are essentially identical. We likewise favor the BC(1) conformation because it permits the largest amount of relief from nonbonded interactions. The remarkable similarity between the high-field multiplets in the ^1H slow-exchange spectra of **2H, 2M,** and **2C** points toward a common conformation. Although no attempt was made to measure accurate barriers from the changes in the ^1H spectra, the approximate coalescence temperatures (∼−95°) and chemical-shift differences (0.22 ppm for the α protons of **2H**) lead to barriers for boat–chair/boat–chair ring reversal of about 8–9 kcal/mol.

We do not believe that the spectral changes in any of the systems are due to nitrogen inversion. We have previously studied this process in the *N*-methyl and *N*-chloro cyclic imines of ring size four through seven.[5] It is clear from our earlier investigations that nitrogen inversion or proton exchange is very rapid in secondary imines such as **2H,** so that no spectral changes are expected in the temperature range examined in the present study. One can estimate a barrier to nitrogen inversion for the *N*-methyl system from data in other ring systems.[5] The expected result (∼6.5 kcal/mol) does not correspond to the present observations (8–9 kcal/mol). Furthermore, the *N*-methyl compound is ex-

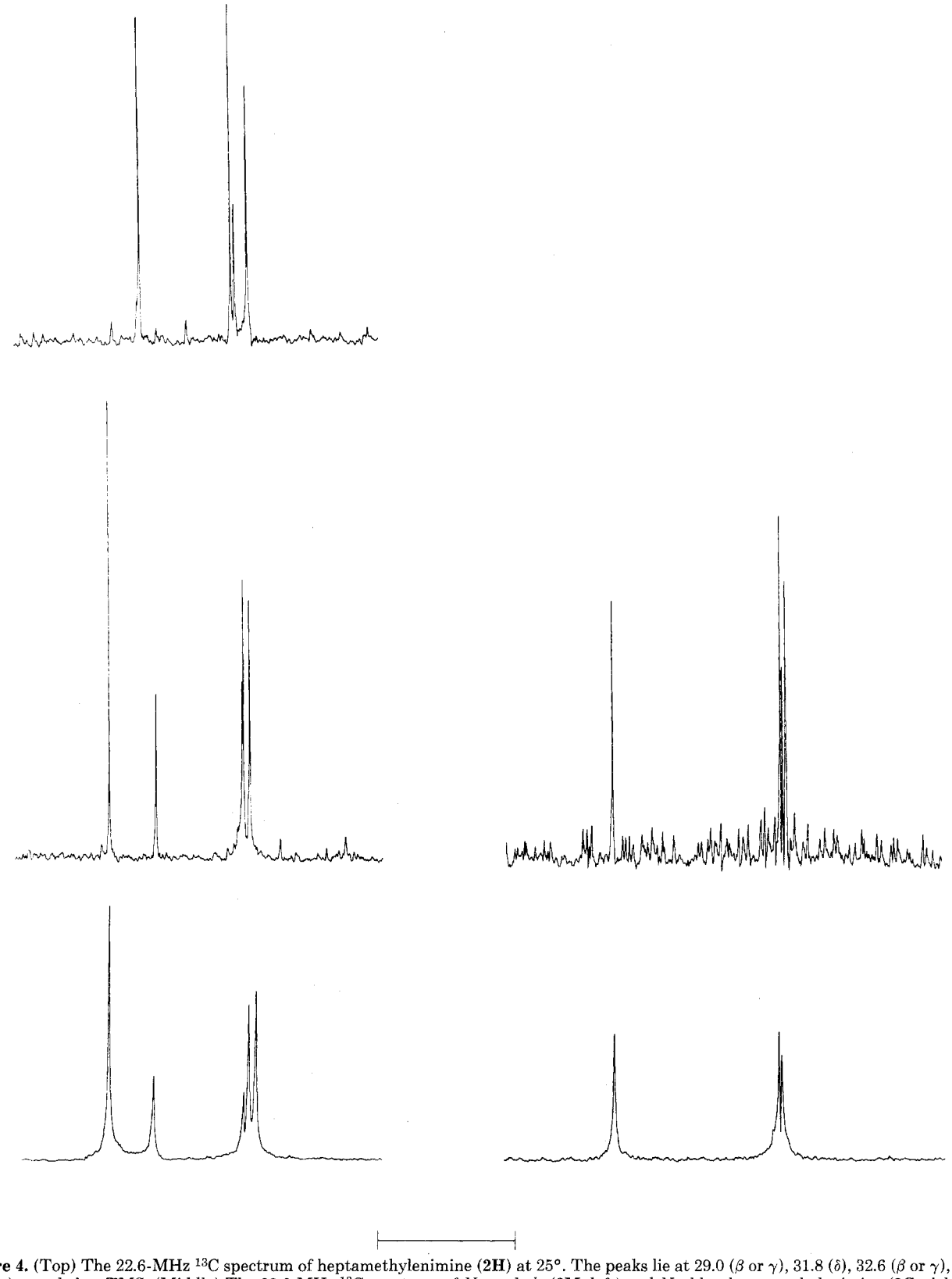


Figure 4. (Top) The 22.6-MHz ^{13}C spectrum of heptamethylenimine (**2H**) at 25°. The peaks lie at 29.0 (β or γ), 31.8 (δ), 32.6 (β or γ), and 52.0 (α) ppm below TMS. (Middle) The 22.6-MHz ^{13}C spectrum of *N*-methyl- (**2M**, left) and *N*-chloroheptamethylenimine (**2C**, right) at 25°. The peaks for **2M** lie at 30.0 (β or γ), 31.2 (β or γ), 31.5 (δ), 49.8 (CH_3), and 59.8 (α) ppm below TMS. The peaks for **2C** lie at 29.5 (β or γ), 30.3 (δ), 30.7 (β or γ), and 66.5 (α) ppm below TMS. (Bottom) The ^{13}C spectra of **2M** (left) and **2C** (right) at −120°. The calibration bar represents 30 ppm. In collection of the data, a pulse width of 80–100 μsec, a dwell time of 100 μsec, a delay time of $\frac{1}{16}$ μsec, and a total sweep width of 5000 Hz were used. Each spectrum is the average of 512 transients.

pected to exist as a biased equilibrium. The axial BC(1) form should be much less favored than the equatorial form, since the 1–3 interactions are even greater than in cyclohexane.[6] Thus, even if nitrogen inversion becomes slow on the nmr time scale, the spectrum of **2M** will not be altered. The situation is much the same as that in *N*-methylpiperidine, which exhibits hindered ring reversal[7] but gives no evidence for hindered nitrogen inversion even though the barrier is not excessively low, since the equilibrium lies well on the side of the equatorial form.[8]

The α-proton resonance of **2H** is a well-spaced AB quartet (Figure 1). The axial proton at the 2 position of a boat–chair is shielded to a greater extent by the 1–2′ and 3–4 bonds than is the 2-equatorial proton, just as in cyclohexane. The 1-equatorial position in the boat–chair is nearly eclipsed with the 2-equatorial position, so that introduction of a 1-methyl group will strongly shield the 2-equatorial proton but have little effect on the 2-axial proton. As can be seen from Figure 2, the α-equatorial proton resonance of **2M** has indeed moved upfield to a point of superposition with the axial proton resonance. This frequency lies very close to that of the high-field (2-axial) resonance in **2H.**

The asymmetry of the α-proton resonance of the *N*-chloro derivative **2C** is puzzling. Below −100°, inversion about nitrogen bearing a chlorine substituent should be slow.[5] Therefore, if both the axial and equatorial chlorine conformations are populated, separate ^1H and ^{13}C resonances should be observable. One possible explanation of the spectral asymmetry of the α-proton resonance thus is the presence of two conformers. This explanation is unlikely, however, because of the insensitivity to temperature of the ^{13}C spectrum over a range that should have revealed multiple conformations, if present. We are not able to provide an explanation for the asymmetry of the α-proton resonance in the spectrum of the *N*-chloro compound without invoking a second conformation that for some reason is not manifested in the ^{13}C spectrum.

To summarize these studies, we have found that the ^1H and ^{13}C spectra of azocane (azacyclooctane, heptamethylenimine) and of its *N*-methyl and *N*-chloro derivatives are consistent with the boat–chair conformation, in which the nitrogen atom is at the BC(1) position on the plane of symmetry. As in the case of oxocane,[4] other explanations are not excluded. Changes in the ^1H nmr spectrum below −80° and the lack thereof in the ^{13}C spectrum indicate that the process of boat–chair/boat–chair ring reversal becomes slow on the nmr time scale, and possesses a barrier of about 8–9 kcal/mol. There is no evidence for a slowing of pseudorotation over this temperature range. Inversion about nitrogen in the NH and NCH_3 molecules appears to be nmr fast, although in the latter case the point is moot because a biased equilibrium prevails, with the methyl group entirely equatorial. The configuration of chlorine is not determined with certainty.

Experimental Section

Infrared spectra were measured on a Beckman IR-5 spectrophotometer. Preliminary and routine nmr spectra were recorded on Varian Associates T-60 or Hitachi Perkin-Elmer R20B spectrometers operating at 60 MHz. All ^1H spectra reported in this paper were obtained at 270 MHz on the Bruker HX-270 equipped with a variable temperature probe.[9] The ^{13}C spectra were obtained on a Bruker HFX-10 spectrometer operating at 22.6 MHz and equipped with a variable-temperature probe, broad-band decoupler, Nicolet Model 1074 computer for data acquisition, and Digital Corp. Model PDP8/L computer with Teletype I/O for Fourier transformation. The ^{13}C spectra were obtained as the free induction decay with broad-band ^1H decoupling and converted to the frequency domain by Fourier transformation. Further details are given in the caption of Figure 4. Elemental analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. 60076.

Heptamethylenimine (2H, azocane, azacyclooctane) was obtained from Aldrich Chemical Co. and used without further purification. *Anal.* Calcd for $C_7H_{15}N$: C, 74.27; H, 13.36; N, 12.37. Found: C, 74.52; H, 13.43; N, 12.32.

***N*-Methylheptamethylenimine (2M).** A solution of formic acid (2.12 ml, 56 mmol, Allied Chemical Co.) and heptamethylenimine (2 g, 18 mmol) was cooled in running tap water. This mixture was added to a 36% formaldehyde solution (1.92 g, 23 mmol, J. T. Baker) and heated to 95–100°. When CO_2 began to evolve, the flask was removed from the heating bath. After the evolution of CO_2 had ceased, the mixture was heated again for 7 hr at 95–100°. To the cooled mixture was added 8 ml of 2 *N* HCl, and the water was removed by distillation *in vacuo*. The syrupy yellow residue was dissolved in 8 ml of distilled water. To this solution, 8 ml of saturated aqueous KOH was added to effect separation of the imine. The product was extracted with ether (3 × 20 ml), and the ether solution was filtered, washed with brine, dried ($MgSO_4$), and filtered, and the ether evaporated. The colorless product was purified by distillation: bp 144–146° (760 mm); yield 45%,[10] *Anal.* Calcd for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.00. Found: C, 75.70; H, 13.55; N, 10.98.

***N*-Chloroheptamethylenimine (2C).** Heptamethylenimine (2 g, 18 mmol) in 50 ml of dry ether was carefully added to *N*-chlorosuccinimide (3.85 g, 29 mmol, Aldrich Chemical Co.) in 40 ml of dry ether. The mixture was stirred for 1.5 hr and then washed with distilled water and 5 *N* HCl. The ether layer was filtered, washed with brine, dried ($MgSO_4$), and filtered, and the ether evaporated. The colorless product was purified by bulb-to-bulb distillation: yield 58%.[10] *Anal.* Calcd for $C_7H_{14}NCl$: C, 56.94; H, 9.55; N, 9.48. Found: C, 56.70; H, 9.50; N, 9.40.

Registry No. —**2H,** 1121-92-2; **2M,** 19719-81-4; **2C,** 37546-26-2.

References and Notes

(1) (a) This work was supported by the National Science Foundation (Grants GP-34259X and GP-35868X) and by the donors of the Petroleum Research Fund, administered by the American Chemical Society; (b) UNESCO Fellow, 1970–1974.

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(9) We wish to thank the staff of the Department of Chemistry, University of Chicago, for the opportunity to utilize their HX-270, which was purchased in part with funds from the National Science Foundation (Grant GP-33116).

(10) The infrared spectrum may be found in S. A. Khan, Ph.D. Dissertation, Northwestern University, 1974.