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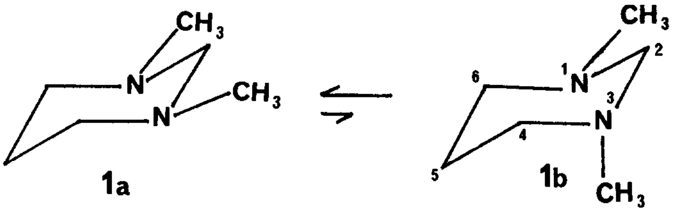
CONFORMATIONAL STUDY OF N,N-DIMETHYL-1,3-DIAZA-5,6-BENZOCYCLOHEPTENE

Robert St-Amour and Maurice St-Jacques*

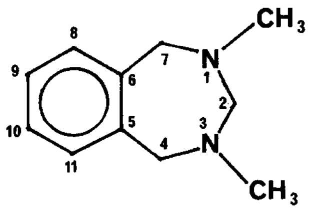
Département de Chimie, Université de Montréal, Montréal, Québec, H3C 3V1

Abstract: ^{1}H and ^{13}C variable temperature NMR results show that the seven-membered heterocycle 2 exists solely in the Cea form, a situation very different from the analogous six-membered 1 which exists predominantly in the Cee form.

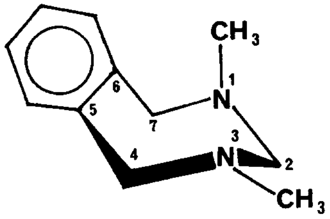
The heterocycle N,N-dimethyl-1,3-diazacyclohexane (1) exists as a mixture of two chair forms$^{1-5}$, Cee (1a) and Cea (1b), in rapid equilibrium. The detectable amount of the minor conformation Cea by NMR methods^{5} (10% at -150°C) is believed to result from a combination of reduced steric interaction for the axial methyl group together with some stabilization associated with the generalized anomeric effect. Because similar stereoelectronic effects have been found to preferentially stabilize the twist-boat (TB) form relative to the C form in seven-membered acetals such as 1,3-benzodioxepins^{6,7}, we wished to determine the conformational properties of N,N-dimethyl-1,3-diaza-5,6-benzocycloheptene (2). The results described herein show striking differences between 2 and 1 as well as between 2 and other analogous seven-membered heterocycles.



1a 1b



2



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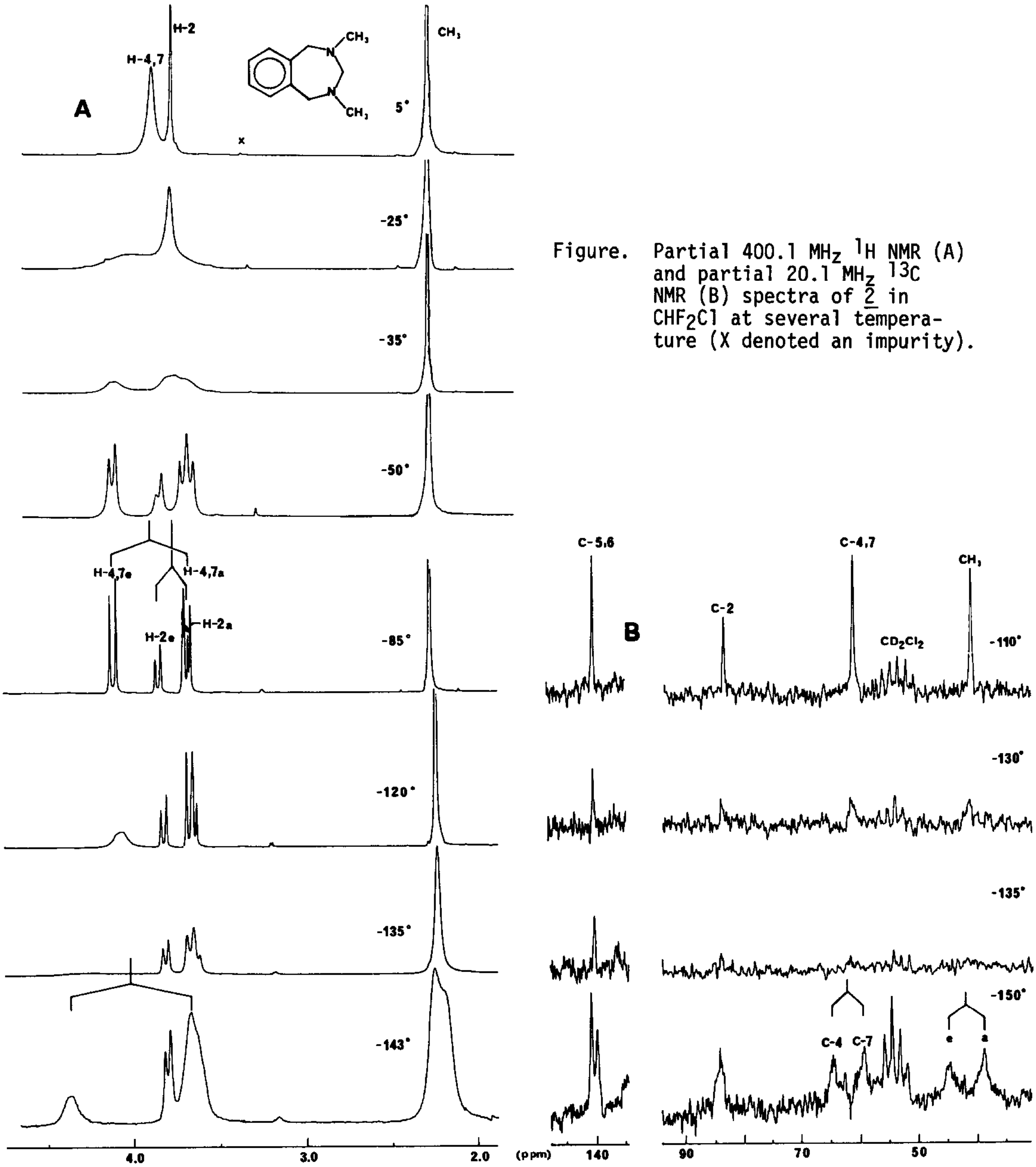

Figure. Partial 400.1 MH$_Z$ ^{1}H NMR (A) and partial 20.1 MH$_Z$ ^{13}C NMR (B) spectra of <u>2</u> in CHF$_2$Cl at several temperature (X denoted an impurity).

The Figure illustrates the variable temperature behavior of the 400.1 MHz ^{1}H NMR and 20.1 MHz ^{13}C NMR spectra of **2**. The left-hand side shows that the H-2 and H-4,7 signals broaden and then split into two overlapping AB patterns, well resolved at -85°, whose parameters are summarized in Table 1. A $\Delta G^{\neq}$ of 11.1 ± 0.3 kcal/mol at -35° is calculated from this spectral change using a transmission coefficient of one half[6]. At still lower temperature the ^{1}H spectrum undergoes another change whereby the doublet labeled H-4,7e broadens appreciably to split into two broad peaks at -143° as indicated by the splitting diagram. The other H-4,7a signal shows appreciable broadening but no clearly visible splitting whereas the H-2e doublet only broadens a little. The methyl signal, on the other hand, is not perturbed in the -25° to -100° range but splits into a poorly resolved doublet below -138°. A $\Delta G^{\neq}$ value of 6.2 ± 0.5 kcal/mol at -138° is estimated from the modification of the H-4,7e signal using a transmission coefficient of one half[6].

By comparison, the ^{13}C spectra show only one spectral change in the lower temperature range and the right hand side of the Figure reveals that the C-5,6, the C-4,7 and the CH_3 signals split into doublets with components of equal area (a line-fit was carried out for C-5,6) whereas C-2 does not split but only broadens at -150°. This spectral change is characterized by a $\Delta G^{\neq}$ value of 6.2 ± 0.3 kcal/mol at -138° using a transmission coefficient of one half[6].

The chemical shift assignments given in Tables 1 and 2 are based on comparison with data from refs. 3 and 5 and the spectral signals are labeled accordingly in the Figure.

TABLE 1. ^{1}H NMR chemical shifts[1] for **2**

Temp.	H-4,7	H-2	CH_3
+ 5° C	3.88	3.80	2.26
-85° C	4.08(e) 3.65(a) (J= -14.5 Hz)	3.82(e) 3.67(a) (J= -12.2 Hz)	2.25
-143° C	4.37 ~3.7 (2)	3.81(e) (J= -11.4 Hz) ~3.7 (2)	2.25 (3) ~2.20 (3)

(1) Obtained at 400 MHz.
(2) Group of overlapping signals further discussed in the text.
(3) These two signals were not assigned to axial or equatorial methyl groups.

TABLE 2. ^{13}C NMR chemical shifts[1] for **2**

Temp.	C-5,6	C-8,9,10,11	C-2	C-4	C-7	CH_3
+ 25° C	141.3	131.8, 130.5	84.7	62.7	62.7	42.0
-150° C	140.9 (2) 139.8 (2)	130.6, 128.4	84.2	64.7	59.4	45.8(e) 38.9(a)

(1) Obtained at 20 MHz.
(2) These two signals could not be assigned to C-5 and C-6 individually.

Both the ^{13}C and ^{1}H spectra recorded at the lowest temperatures point to only one conformation for **2** with two different methyl locations, two different benzylic carbon (C-4,7) environments but only one for C-2. The absence of symmetry thus indicated rules out the following symmetric forms: Cee, Caa, TBa'a' and TBe'e' (where the primes indicate that the axial and equatorial positions are not identical in the C and TB forms). Consequently only Cea and TBe'a' are possible conformations for 2.

Evidence in favor of the Cea form (3) as the most stable conformation is derived from $^2J_{HH}$ values and from the dynamic parameters $\Delta G^{\neq}$. First, the value of -11.4 Hz determined at -143° for the broadened H-2e doublet of 2 is quite similar to the -11.0 Hz value retained[2,3] for the Cea form of 1. Secondly, the two $\Delta G^{\neq}$ values of 11.1 and 6.2 kcal/mol determined for 2 are very similar to the values reported for the ring inversion[8] (11.3 kcal/mol at -29°) and the N-inversion[5] (7.0 kcal/mol at -120°) of the six-membered 1. Were TBe'a' the more stable conformation, then the two available dynamic processes would be TB-inversion and N-inversion. Although typical $\Delta G^{\neq}$ values for the TB-inversion in molecules such as 2 are not available, it is clear[6,7] that it ought to be considerably less than 10 kcal/mol. The TBe'a' form is therefore most unlikely.

The accrued stability of conformation 3 relative to 1b is believed to result in large part from differences in steric interaction of the axial N-methyl group which is less hindered in 3 because the syn-1,3 interaction between the methyl group and the axial H-5 proton of 1b is replaced by an interaction with the π-electrons of the aromatic ring in 3. The magnitude of this steric hindrance attenuation can be appreciated from a recent report that 4-methylbenzocycloheptene[9] exists as a mixture of Ce and Ca forms in the ratio 93:7 at -100°. Furthermore, stereoelectronic and dipolar effects also favor Cea. For example, the equatorial lone pair on N(1), being antiperiplanar[10] to the C(2)-N(3) bond, stabilizes the Cea form. No such favorable dispositions exist for the Cee form. The sum of these factors then account for the fact that the Cee form (the preferred one for 1) is not observed at all for 2.

Finally it is noteworthy to point out the absence of a detectable amount of a TB conformation for 2 even though there exist a TB geometry with an antiperiplanar disposition for one of the lone pairs and a C-N bond. This absence therefore suggests that stereoelectronic stabilization of the TB form is either less than or comparable to that existing in the Cea form and as such cannot overcome the other factors which favor the C form in the benzocycloheptene system[6,7].

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