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Exo–Endo vs. Equatorial–Axial Equilibria. Assessment of Steric Crowding in the Endo Cavity

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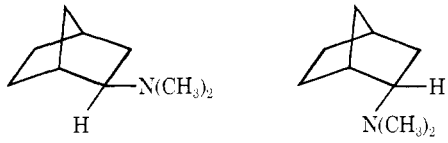
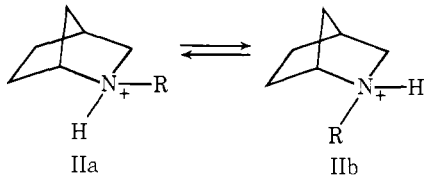
Abstract: ^{13}C NMR methods were used to determine the relative amounts of *exo*- and *endo*-*N*-alkyl-2-azanorbornane conjugate acid (where the alkyl group is methyl, ethyl, isopropyl, or *tert*-butyl). It is found that the N proton and the methyl, ethyl, and isopropyl groups all have similar ability to usurp the exo position. Steric effects in the endo cavity are too small to discriminate between moderately sized substituents and a solvated proton. This contrasts with an analogous study of *N*-alkyl-4-*tert*-butylpiperidinium ions in which the alkyl groups on the nitrogen reside in an equatorial configuration and the solvated N proton is relegated to the axial position.

The theme song of those who sing the praises of classical norbornyl cations is entitled "Crowding in the Endo". The lyrics create images of an endo 2-tosylate impaling itself on an endo 6 proton.[1] We recently set forth the proposition that if an endo leaving group is inhibited by special steric or solvation effects, then other functionalities within the endo cavity should display modified behavior as well.[2] Accordingly, we measured the pK_as and the rates of NH proton exchange, nitrogen inversion, and amine quaternization for *exo*- and *endo*-2-dimethylaminonorbornane (Ia and Ib). The two compounds

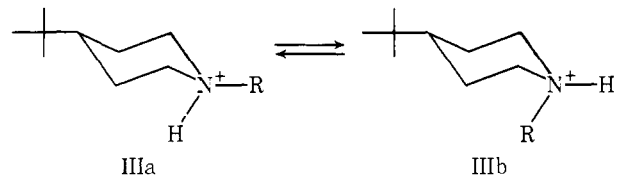


Ia Ib

differ only slightly as would be expected if the endo dimethylamino group were not subjected to unusual steric or solvation effects.[2] In the present communication we extend this line of reasoning by considering the configurational equilibria of *N*-alkyl-2-azanorbornanes (II where R = methyl, ethyl, isopropyl, and *tert*-butyl). "Crowding in the endo" should surely favor configuration IIa. For reference purposes we also evaluated analogous equilibria for *N*-alkyl-4-*tert*-butylpiperidines (III).



IIa IIb



IIIa IIIb

Experimental Section

Synthesis of *N*-Alkyl-2-azanorbornanes (II). The four *N*-alkyl derivatives of 2-azanorbornane were prepared by known methods:[3] cyclopentanecarboxylic acid to the acid chloride to *N*-alkylcyclopentanecarboxamide to *N*-alkylaminomethylcyclopentane to the *N*-chloro compound to *N*-alkyl-2-azabicyclo[2.2.1]heptane (II). The Hofmann–Löffler–Freytag reaction was carried out with a Rayonet reactor using 2735-Å light for 18 h at 35–40 °C. The only major departure from the literature procedure[3] consisted of using NaOCl for N-chlorination of the *tert*-butyl system (*N*-chlorosuccinimide did not give product). Yields were poor even with this modification, and the product required purification on a 6-ft SE-30 analytical GLC column. Suitable NMR, IR, and mass spectra as well as analytical data were obtained for many of the synthetic intermediates[4] and all four final products. Two of the four *N*-alkyl-2-azanorbornanes (the isopropyl and *tert*-butyl derivatives) are new compounds boiling at 150–155 °C (140 mm) and about 54 °C (6 mm), respectively.

Anal. Calcd for $C_9H_{17}N$: C, 77.63; H, 12.31; N, 10.06. Found: C, 77.44; H, 12.20; N, 10.31.

Anal. Calcd for $C_{10}H_{19}N$: C, 78.36; H, 12.50. Found: C, 78.11; H, 12.47.

Synthesis of *N*-Alkyl-4-*tert*-butylpiperidine (III). The parent amine, 4-*tert*-butylpiperidine, was prepared by hydrogenating the substituted pyridine with the aid of 5% Pd on carbon.[5] Compounds III (R =

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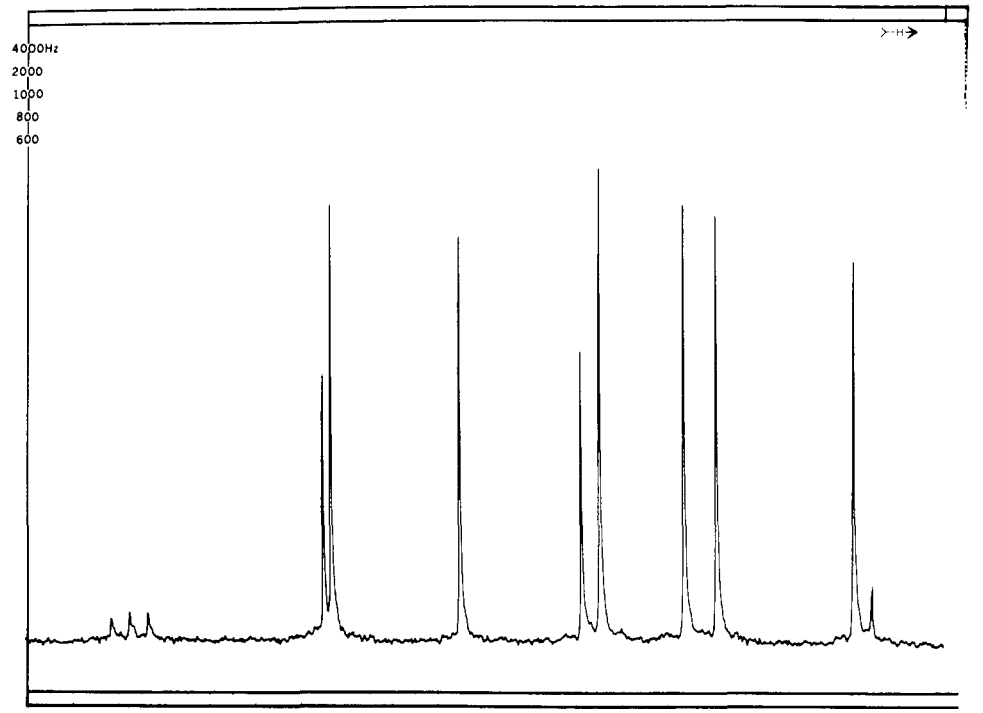

Figure 1. ^{13}C NMR spectrum of *N*-ethyl-2-azanorbornane in $CDCl_3$ (see footnote 7 for chemical shifts and peak assignments).

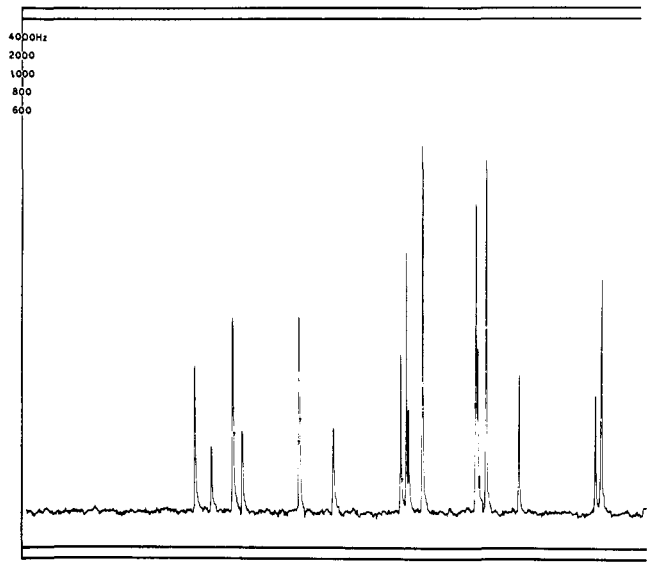

Figure 2. ^{13}C NMR spectrum of *N*-ethyl-2-azanorbornane in aqueous HCl.

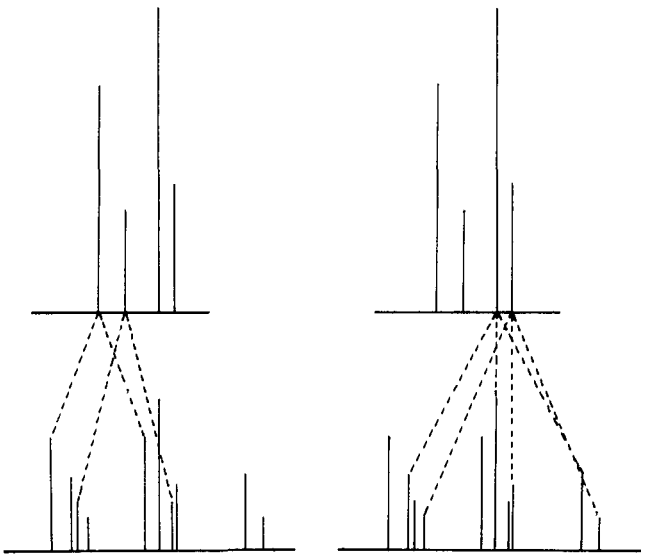

Figure 3. Decoupled and coupled ^{13}C NMR spectra of C-1 and C-3 of *N*-methyl-2-azanorbornane in aqueous HCl. Agreement between observed and theoretical spectra was secured using J_{CH} = 165 Hz for C-1 and 150 Hz for C-3. The first-order analysis is shown in two vertical sections for the sake of clarity.

methyl, ethyl, and isopropyl) were then secured by alkylating the piperidine with an alkyl iodide over Na_2CO_3.[6] Only the isopropyl derivative is a new compound, bp 120–121 °C (16 mm).

Anal. Calcd for $C_{12}H_{25}N$: C, 78.62; H, 13.74; N, 7.64. Found: C, 78.60; H, 13.78; N, 7.61.

Spectra. ^{13}C NMR spectra were recorded using a Varian CFT-20 spectrometer.

Results and Discussion

The four *N*-alkyl-2-azanorbornanes (II) give ^{13}C spectra in $CDCl_3$ having one peak per nonequivalent carbon (Figure 1).[7] Unprotonated amine inverts too rapidly to differentiate the exo and endo conformations.[8] In contrast, the amines in strongly acidic water (pH <2) generate two sets of peaks (Figure 2) owing to the presence of both IIa and IIb. Protonation freezes the positions of the alkyl groups.[9-11] We faced two problems interpreting the spectra of the salts: (1) selecting pairs of peaks that represent corresponding carbons in the exo and endo epimers and (2) assigning members of these pairs to exo and endo. Several peak pairs for the ethyl derivative (all with the same ratio) were identified in Figure 2 by inspection. Epimer ratios for the other amines were obtained with the aid of the four lowest field peaks (C_1 and C_3 of IIa and IIb). This series of peaks yielded a doublet-doublet-triplet-triplet in a gated decoupling experiment (Figure 3), so that the relevant pairs within the set of four were defined. Since unambiguous assignment of pair members to exo or endo proved unfeasible, percentages of exo-R (listed in Table I) were calculated assuming that (A) the upfield member of each peak pair arises from exo-R or (B) the exo/endo ratio exceeds unity in all cases. Table I shows that large percentages of exo-R and endo-R

Table I. Percentages of Exo Alkyl in the Conjugate Acids of *N*-Alkyl-2-azanorbornane[a,b]

Alkyl	A	B
CH_3-	28	72
CH_3CH_2-	31	69
$(CH_3)_2CH$-	55	55
$(CH_3)_3C$-	>95	>95

[a] See text for significance of assumptions A and B. [b] Error in values is estimated to be ±3.

coexist when R = methyl, ethyl, and isopropyl. This is true no matter how one assigns peaks. Clearly, *the three alkyl groups and the solvated N proton*[12] *are nearly equivalent in their ability to usurp the exo position.*[13,14]

In order to judge the import of the above conclusion, it was necessary to assess independently the sizes of the alkyl groups relative to the solvated N proton. For this reason we also studied the equilibria relating IIIa and IIIb by ^{13}C NMR. The *N*-methyl, *N*-ethyl, and *N*-isopropyl piperidinium salts were found to give only *one* set of peaks each (using 20% compound in aqueous HCl and 57 000 transients). Hence the axial-R configuration occurs in concentrations too small to detect (<5%).[15] Low-temperature NMR experiments (−50 °C) in acidic ethanol ruled out any possibility of rapid ring inversion destroying the axial–equatorial identity. Even a methyl group is considerably larger than a solvated N proton according to this classical test.

Given the results with the piperidine system, why should the 2-azanorbornyl compounds display negligible selectivity between the alkyl groups and the N proton (Table I)? Because unlike axial/equatorial, exo/endo are sterically too similar to discriminate between the substituents. As we demonstrated in previous work,[2] *moderately sized groups seem to experience no serious steric problems within the endo cavity.* Although we do not deny the presence of small steric factors in the endo cavity, they seem to be insufficient to explain, for example, the exo:endo solvolysis rate ratio of 1600.[16]

Our conclusion concerning the exo:endo rate ratio (like those of others) has its uncertainties which must be mentioned. Steric effects have been examined here using ground state molecules with substituents fixed to a tetrahedral nitrogen. In contrast, the solvolysis transition state (which undoubtedly bears responsibility for exo:endo ratios[17]) possesses a partially flattened C-2. Thus, our conclusions rest on the assumption that an isopropyl group has spatial requirements equivalent to or greater than a departing oxygen, hybridization differences at C-2 notwithstanding. If this assumption is valid, then steric effects in the norbornyl system cannot explain exo:endo rate ratios. Since the structure of the solvolysis transition state is unknown, we are unable to judge precisely the merits of the assumption. On the one hand, the bond between the 2 carbon and endo 2-tosylate elongates in the transition state, thereby projecting the departing oxygen outside the endo cavity (away from the endo C-6 proton). On the other hand, a hybridization change at C-2 "rotates" the oxygen atom into the cavity. Which predominates? How does solvation of the transition state affect matters? Such questions will probably remain unanswered. Ultimately the indeterminable[18] issue of the nonclassical norbornyl cation will be cast into the limbo of forgotten things.[19]

Acknowledgment. This work was supported by grants from the National Science Foundation and the National Institutes of Health. We thank Mr. Robert Bradshaw for his assistance with the synthetic work.

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