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KINETICALLY CONTROLLED PROTONATION AS AN AID TO CONFORMATIONAL ANALYSIS OF THE SYN-ANTI (NITROGEN INVERSION) EQUILIBRIUM IN 7-AZANORBORNENES AND 5-AZABICYCLO[2.2.2]OCTENES.

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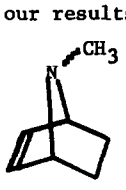
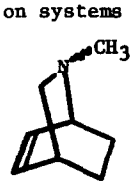
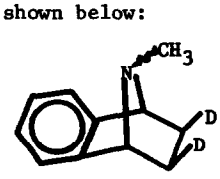
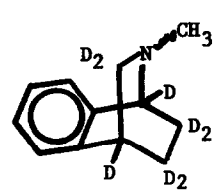
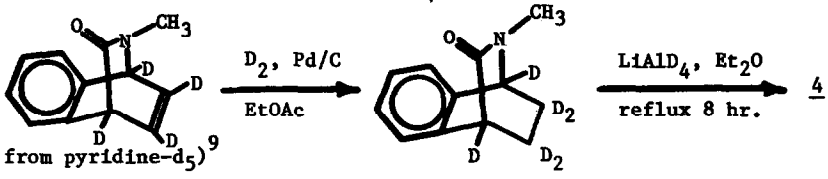
Recent interest in the use of kinetically controlled stereospecific protonation of nitrogen heterocycles as a method for studying nitrogen inversion equilibria in these systems[1-5] prompts us to report our results of studies on systems 1 - 4, shown below:

1a: N-CH_3 syn to C=C 2a: N-CH_3 syn to C=C 3a: N-CH_3 syn to 2,3-benzo 4a: N-CH_3 syn to 2,3-benzo
1b: N-CH_3 anti to C=C 2b: N-CH_3 anti to C=C 3b: N-CH_3 anti to 2,3-benzo 4b: N-CH_3 anti to 2,3-benzo

The syntheses of compounds 1,[6] 2,[7] and 3[8] have all been reported previously; compound 4 was synthesized by the following route:



5 (prepared from pyridine-d_5)[9]

Nitrogen inversion equilibria in systems 1 and 3 can be obtained conveniently via low temperature NMR experiments. Our attempts to study the corresponding conformational equilibria in 2 and 4 were frustrated by our inability to resolve the NMR signals corresponding to the diastereoisomeric nitrogen invertomers of these compounds at temperatures as low as 136°K. We therefore turned to kinetically controlled protonation of 2 and 4 as a means of studying their conformational equilibria. This method was also applied to the study of compound 3; the conformational equilibrium constant thus obtained could be directly compared with the corresponding value obtained via low temperature NMR experiments on 3. This comparison provides a needed[4,5] independent check on the applicability of the kinetically controlled protonation method[2] for studying nitrogen inversion equilibria.

The results of the temperature dependent NMR study on compounds 1 and 3 are shown in the Table. At the coalescence temperature (T_c), the major invertomer in 1 is present to the extent of 86% of the

TABLE: Spectral Parameters of 1 and 3 in $CDCl_3$ Solution at 100 MHz.

	1 (vinyl protons)	1 (bridgehead protons)	3 ($N-CH_3$)
Coalescence Temperature, T_c (°K)	295°	263°	233°
$\Delta\nu$(Hz)[a]	26	10	21
Rate Constant for N-Inversion, k_c (sec^{-1})[b]	58	22	47
$\Delta G^{\ddagger}$ for N-Inversion (kcal/mol)	14.9	13.7	13.0

[a]Chemical shift difference (in Hz) between the centers of the respective multiplets in both invertomers.

[b]Calculated using the Gutowsky-Holm equation; see H. S. Gutowsky and C. H. Holm, J. Chem. Phys., 25, 1228 (1956). See also reference 12 for a discussion of the approximations made in an application of the Gutowsky-Holm equation which is closely related to the present one.

equilibrium mixture; the observed value of K_{eq} for the nitrogen inversion equilibrium in 1 corresponds to a free energy difference ΔG° = ca. 1 kcal/mol between the respective invertomers at T_c. The predominant invertomer in 1 displays its vinyl proton resonance at higher field than does the corresponding minor invertomer (at or below T_c). We assign the syn configuration (1a) to the major invertomer in 1 on the basis of the anticipated antiaromatic electronic interaction between the nitrogen lone pair and the syn double bond in 1b[10] and by analogy to the results of similar low temperature NMR studies on other 7-azanorbornene and 7-azanorbornadiene derivatives.[11,12]

A similar study using 3 (see Table) indicated the major invertomer ($N-CH_3$ resonance upfield, corresponding to the syn isomer 3a[13]) to be present to the extent of 94% of the equilibrium mixture at coalescence (ΔG° = 1.3 kcal/mol). These results are in excellent agreement with published data for a similar study of the temperature dependent NMR spectrum of 3.[13]

Kinetically controlled protonation of 3 was effected by addition of 3 to excess 1:4 trifluoroacetic acid - chloroform solution at ambient temperature. Integration of the NMR spectrum of the mixture of protonated invertomers 3a and 3b indicated that the predominant diastereoisomer ($N-CH_3$ resonance upfield, corresponding to protonated 3a[13]) was again present to the extent of ca. 93% of the equilibrium mixture, a result virtually identical to that obtained for the free base at T_c via low temperature NMR studies. The value of the equilibrium constant obtained via protonation of 3 as described above did not change after two weeks at ambient temperature. We conclude that addition of 3 to 1:4 trifluoroacetic acid - chloroform solution as described above affords a mixture of ammonium salts which reflects the ratio of invertomers (free base) in solution at the time of quenching; (i.e., we conclude that protonation of 3 under these conditions is (i) irreversible, (ii) stereospecific, and (iii) kinetically controlled).[1] In contrast to this result, the hydrochloride

salt of 3 (prepared by bubbling hydrogen chloride gas through an ether solution of 3), when dissolved in water, afforded a mixture of 3a and 3b in the ratio (by NMR) of 12 : 1. This diastereoisomer ratio gradually decreased upon standing for several hours to 3a : 3b = 1.7 : 1. We consider this latter ratio to reflect the true equilibrium constant for protonated 3b⇌protonated 3a (rather than reflecting the equilibrium constant for the free base, 3b⇌3a).

Kinetically controlled protonations of 2 and of 4 were effected employing 1 : 4 trifluoroacetic acid - chloroform solution in the manner described above. In both cases, the predominant diastereoisomer was the one having the N-CH_3 resonance at higher field; this result corresponds with the syn isomer (2a and 4a, respectively) being the predominant isomer present in each case in the conformational equilibrium for 2 and for 4.[14-16] Our conclusion that 2a is the predominant invertomer in the 2b⇌2a equilibrium as determined by the foregoing kinetic protonation studies is in good agreement with conclusions reached by Morishima and Yoshikawa[14] from studies of the $Ni(acac)_2$-induced ^1H and ^{13}C NMR contact shifts on system 2.

We view the consistency of our conclusions for systems 2 and 3 with those published by Morishima and coworkers[13,14] to support the earlier contention[2] that kinetically controlled protonation of cyclic amines indeed offers a valid approach to measuring nitrogen inversion equilibria. Of particular interest in this connection is our independent confirmation of this conclusion through measurement of the nitrogen inversion equilibrium in 3 both by kinetic protonation studies and by an independent method (i.e., via temparature dependent NMR studies on 3). We are continuing to explore applications of kinetic protonation as a means of measuring nitrogen inversion equilibria in other rigid, nitrogen-containing bicyclic ring systems; we plan to report the results of these investigations shortly.

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15. E.g., taking as our model for 4 the carbocyclic molecule syn-5-anti-8-dimethyl-2,3-benzobicyclo[2.2.2]octene, δ(anti-8-CH_3) = 1.04 ppm, δ(syn-5-CH_3) = 0.47 ppm; see L. Billet and G. Descotes, Bull. Soc. Chim. France, 2617 (1971).

16. The chemical shift difference between syn- and anti-N-CH_3 resonances in kinetically protonated 4 was found to be 0.56 ppm. The 300 MHz proton NMR spectrum of kinetically protonated 4 was obtained for us by Professors M. Anteunis and J. Gelan, Rijksuniversiteit Gent, Belgium. We thank Professors Anteunis and Gelan for their kind assistance in this regard and for numerous helpful discussions.