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The Application of Intramolecular Saturation Transfer NMR Spectroscopy to Conformational Analysis. The Effect of Methyl Substituents on the Barrier Height and Conformational Isomer Population of the Tricyclo[9.3.1.$0^{3,8}$]pentadecane Ring System.

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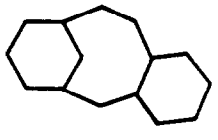
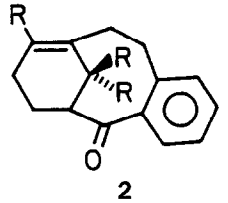
Summary: Intramolecular saturation transfer NMR spectroscopy has been used to establish the conformational equilibria of several tricyclo[9.3.1.$0^{3,8}$] pentadecanes.

The tricyclo[9.3.1.$0^{3,8}$]pentadecane ring system (1) contains a central fused-bridged cyclooctane ring that forms the basis of an important class of naturally occurring substances.[1] Our recent synthetic entry into representatives of this tricyclic ring system,[2] and our plan to utilize selected derivatives in the synthesis of taxane natural products, has prompted an investigation of the conformational behavior of several members of this interesting class of molecules.[3]



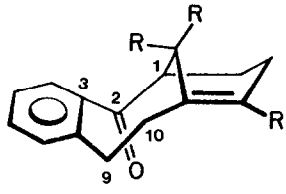
1



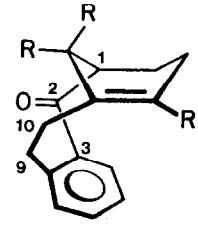
2 A; R = H
2 B; R = Me

2

Inspection of molecular models of 2 reveals two plausible low energy conformations, exo-2 and endo-2, shown in the figures below. At room temperature the ^{1}H-NMR spectrum of 2a reveals a single vinyl hydrogen at 5.60 ppm.



exo 2



endo 2

Upon cooling, the vinyl region broadens and at -50°C resolves into two broad peaks centered at 5.75 and 5.29 ppm. These absorptions are present in a ratio of 88:12 ($\Delta G^{\circ}_{-50^{\circ}C}$ = 0.88 ±

0.09 kcal/mol). The assignment of these signals to the exo-2a (5.75 ppm) and endo-2a (5.29 ppm) conformational isomers is based upon the anticipated shielding of the vinyl hydrogen by the aromatic ring in endo-2a.[4] The "coalescence temperature" is approximately 2°C from which a single point free energy barrier of $\Delta G^{\neq}$=13.2 ± 0.14 kcal/mol is obtained.[5]

An analysis of derivative 2b required unambiguous assignment of the methyl resonances. Efforts to establish their identity using chemical shift criteria or by difference NOE experiments were unsuccessful. The pertinent region of the ^{1}H NMR spectra (250 MHz, 35°C) is given in figure 1. Three prominent methyl absorptions at 1.33, 1.12, and 0.72 ppm are noted. Upon cooling no change in the spectra was observed. At elevated temperatures this region of the spectrum of 2b broadens, resulting in the disappearance of three minor absorptions at 1.68, 1.08, and 0.61 ppm (* figure 1). These three signals were tentatively assigned to the CH_3 resonances of the minor conformational isomer of 2b. Based upon the intensities of these signals the ratio of major to minor conformational isomer is 89:11 ($\Delta G^{\circ}_{25^{\circ}C}$ = 1.24 ± 0.15 kcal/mol).

The correspondence between methyl groups in the major and minor conformational isomers of 2b was established by "labelling" individual methyls using intramolecular saturation transfer NMR spectroscopy.[6] Thus, irradiation of the methyl resonance at 0.72 ppm with a second radio frequency of sufficient power to saturate the signal resulted in approximately 10% diminished intensity of the signal at 1.68 ppm. Similarly in separate experiments, irradiation at 1.33 and 1.12 ppm produced diminished intensities of the signals at 0.61 and 1.08 ppm respectively. The transfer of spin saturation between the three sets of resonances links these signals to groups that are exchanging environments and provides experimental proof of a dynamic conformational isomerization in 2b. The necessary conditions for saturation transfer $k_{exchange} \gtrsim T_1$ (spin lattice relaxation time) are satisfied over the temperature range studied (25-60°C).[7]

Having established the relationship between exchanging sites, assignment of the exo and endo conformational isomers follows from analysis of the chemical shifts of the methyl resonances. The environment of Me-17 (see figure for numbering) is not altered significantly in either conformation and can be assigned to the resonances at 1.12 and 1.08 ppm. The allylic Me-18 resonance in exo-2b is expected to be the most deshielded methyl signal in the molecule while the corresponding methyl in endo-2b will be strongly shielded due to its proximity to the aromatic ring. Me-16 in the endo conformation is expected to be the most shielded methyl due, in part, to its proximity to the aromatic ring, while in the exo conformation this resonance should appear at a "normal" frequency. On this basis the assignments can be made (see Figure 1).

The surprising result of this analysis is that methyl substitution (2a → 2b) results in a reversal of population of the exo and endo isomers; in 2b the endo isomer is favored by 1.2 kcal/mol.[8] Assignment of the exchanging sites also permits evaluation of the "coalesence temperatures" at Me-16 and Me-18 from which an average single point free energy barrier $\Delta G^{\neq}$ = 16.5 ± 0.1 kcal/mol is calculated.[5]

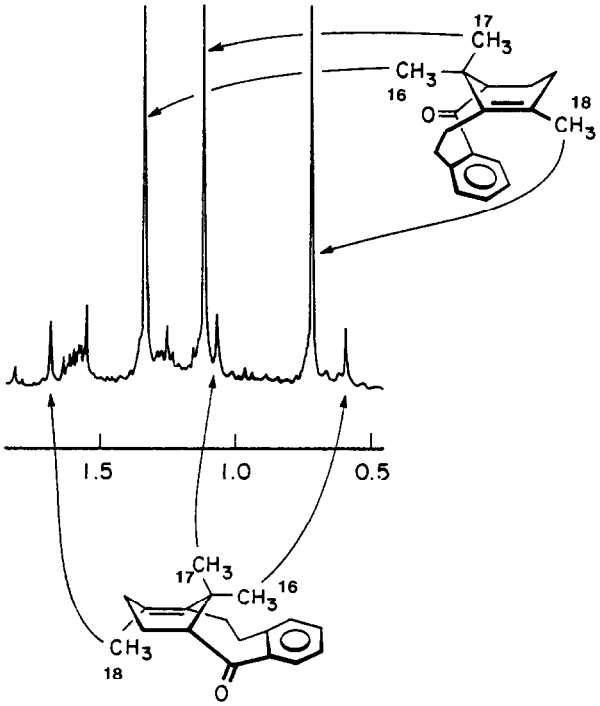


Figure 1. 250 MHz ^{1}H NMR spectra of 2b (29°C).

The origin of the reversal of conformational preference resulting from methyl substitution can be appreciated from inspection of molecular models. In exo-2b, Me-16 rests approximately 2Å above the carbon plane of the aromatic ring, well within the van der Walls radii of these two groups. The reversal of endo/exo preference amounts to a destabilization of exo-2b of ≃2 kcal/mol.

The origin of a heightened barrier ($\Delta\Delta G^{\neq} \simeq 3$ kcal/mol) separating exo and endo 2b compared with 2a is less clear. Interconverson of the two conformational isomers requires two torsional rotations about the $C_{1,2}$ or $C_{2,3}$ bond and the $C_{9,10}$ bond. Synchronous rotation about these bonds does not produce significant non-bonded interactions between the methyl groups (Me-16 and Me-18) and the remainder of the molecule. However, sequential rotation involving $C_{1,2}$ or $C_{2,3}$ bond rotation followed by $C_{9,10}$ rotation, produces significant non-bonded interactions between Me-16 and the C_9–C_{10} ethano bridge. This sequential motion may provide a plausible explanation for the increase in barrier height of 2b.

It should be pointed out that for any molecule undergoing conformational interconversion there will be a temperature at which $k_{exchange} \gtrsim T_1$, intramolecular saturation transfer NMR therefore is of general applicability in identifying groups undergoing exchange. The routine availability of difference NMR spectra greatly enhances the sensitivity of this technique and its potential utility.

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References and Footnotes

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2. K.J. Shea and P.D. Davis, Angew. Chem. Int. Ed. Eng., 1983, 22, 419.

3. For the conformational analysis of a related ring system see: W.T. Bell, C.M. Bowes, and F. Sondheimer, Tetrahedron Lett., 1980, 3299.

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5. Calculated from the chemical shift difference ($\Delta\nu$) extrapolated to T_c, using $k=\pi\Delta\nu/\sqrt{2}$. $\Delta G^{\ddagger}$ follows from transition state theory. Two factors contribute to the "less than ideal" conditions for the quantitative evaluation of two site exchange broadening; the presence of spin-spin coupling and the exchange between two sites of unequal populations. Since the magnitude of the spin-spin coupling is small and the population ratios are not significantly different from 1, the above relationship can still be used, albeit with less accuracy. See for example: Anet, F.A. and Basus, V.J., J. Mag. Resonance, 1978, 32, 339.

6. (a) Faller, J.W., in Determination of Organic Structures by Physical Methods, Nachod, F.C., and Zuckerman, J.T., Vol. 5, Academic Press, New York, 1973, 75; (b) Mann, B.F., Prog. Nuc. Mag. Res. Spectroscopy, 1977, 11, 95; (c) Anet, F.A.L., and Bourn, J. Am. Chem. Soc., 1967, 89, 760.

7. Spin saturation transfer data was obtained by use of an aquisition routine which first acquires the normal spectrum then the spin saturation spectrum. The difference between these spectra is then displayed.

8. The endo conformation is very similar to that found in the naturally occurring taxanes. See for example: reference 1 and Woods, M.C., Chiang, H.-C., Nadakaira, Y., Nakanishi, K., J. Am. Chem. Soc., 1968, 90, 522.

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