A CONFORMATIONAL REQUIREMENT FOR OBSERVABLE

MAGNETIC NON-EQUIVALENCE OF BENZYLIC METHYLENE PROTONS*

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The magnetic equivalence or non-equivalence of the methylene hydrogens of a benzyl group has proven to be an effective probe for chirality in a substrate.[1] An AB quartet for the nmr resonance signal of the aliphatic protons of a single benzyl substituent is positive evidence for chirality[¶] in the system but the absence of this feature is not conclusive for achirality. For the benzylic hydrogens to be diastereotopic[¶] is a necessary but not a sufficient requirement for observable non-equivalence in the nmr. For large chemical shift differences to be observed the rotamer distribution must differ in average population or the rotation of the bond connecting the benzyl group to the system must be slow, and the magnetic environment of the protons in these rotameric forms must differ sufficiently.[§] The structural features necessary to meet these conditions have not been elaborated, except for the spatial separation of the benzyl group from the chiral center.[2] The nmr spectral investigation of a number of N-benzyl derivatives of methyl piperazines suggested a conformational relationship which meets these requirements.[3]

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¶ For the benzylic hydrogens to be diastereotopic a chiral system is not required (See: W. F. Reynolds and T. Schaefer, *Can. J. Chem.*, 42, 2119 (1964) and M. Raban, et. al., *Tetrahedron Letters*, 5055 (1968)), but with a single benzyl substituent this restriction obtains.

§ Small chemical shift differences may be observed without either of the former requirements being met provided the magnetic environments of the diastereotopic protons differ. See: M. Raban, *Tetrahedron Letters*, 3105 (1968).

R"
R'—[structure]—R
CH₂Ph

[structure]—R
CH₂Ph

H
—CH₃
—CH₃
CH₂Ph

R
CH₃—[structure]—CH₃
CH₂Ph
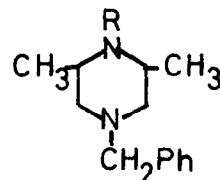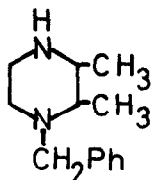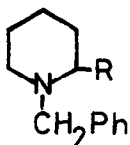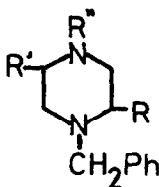
1. *trans* R=R'= CH₃; R"=H   5. R= CH₃
2. R= CH₃; R'= H; R"= PhCH₂   6. R= n-C₃H₇
3. *cis* R=R'= CH₃; R"=PhCH₂
4. *trans* R=R'= CH₃; R"= PhCH₂
8. R=R"= H; R'= CH₃

7. *cis*

9. R= H
10. R= PhCH₂
Methyls *cis*

The nmr spectra of **1-6** showed the protons of the benzyl group(s) vicinal to the substituent(s) as AB quartets while the nmr spectra of **7-10** had sharp singlets for the resonance signal of the benzylic protons. A comparison of the preferred conformation of the rings of these two groups of derivatives showed that with **1-6** the benzylic group on nitrogen was adjacent to an equatorial methyl group in the most stable conformer. The enantiotopic nature of the benzylic protons in **9** and **10** and the distance of the benzylic methylene from the chiral carbon in **8** explained the single resonance signal for the benzylic protons in the nmr spectra of these compounds. The rationale for the observed magnetic equivalence of the benzylic protons in **7** was not at first obvious. The *cis*-arrangement of the methyl substituents of **7** permits two conformations of comparable stability (**7a** and **7b**).* The *gauche* interaction of the benzyl group with the 2-methyl substituent should be relieved in **7b** by a bending of the benzyl-nitrogen bond in a direction away from the methyl. Such a mechanism of relief of strain is not available in **7a**. Thus **7b** should be the preferred ring conformation; however, a reliable estimate of the equilibrium composition cannot be made. This explanation is supported by the nmr spectrum of the phenylthiourea derivative of **7**. The unfavorable interaction of the anilino-

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*For these conformational comparisons it is assumed that the conformational equilibria contain more than 90% of the conformer with the ring in that chair conformation which places the maximum −C-CH₃ substituents in the equatorial arrangement and the N-benzyl substituent in an equatorial disposition by rapid inversion of nitrogen. These assumptions can be justified by approximations of free energy differences among the possible conformers.

carbonyl function with the adjacent equatorial methyl group in **7d** reverses the conformational bias to favor **7c**.[4] As expected, the resonance of the protons of the benzylic methylene now appears in the nmr as a pair of AB quartets. Thus all the N-benzyl groups which show magnetically equivalent methylene protons in chiral systems are vicinal to no methyl group or to one which is in the axial conformation.

7a R = H
7c R = PhNHC‖S

7b R = H
7d R = PhNHC‖S
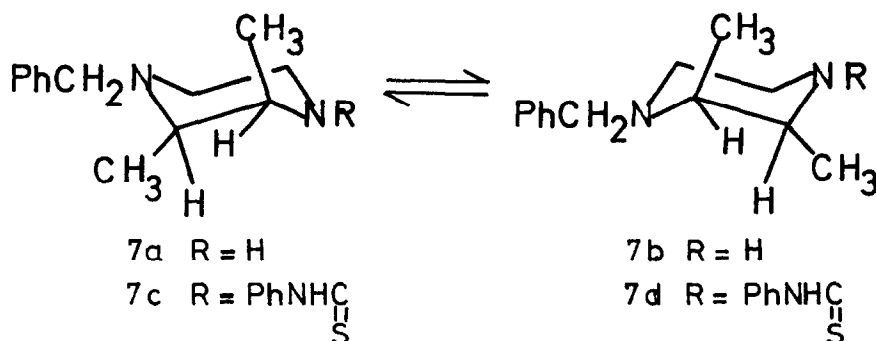
These correlations give a clear indication of the cause of the large difference in the chemical shifts of the methylene protons in **1-6** and the practical requirement for observable non-equivalence. The staggered rotational conformers of an N-benzyl group vicinal to an equatorial methyl are shown (**11a,b,c**). It is evident that rotamer **11b** has the lowest free energy of the three, for in **11c**

11a   11b   11c
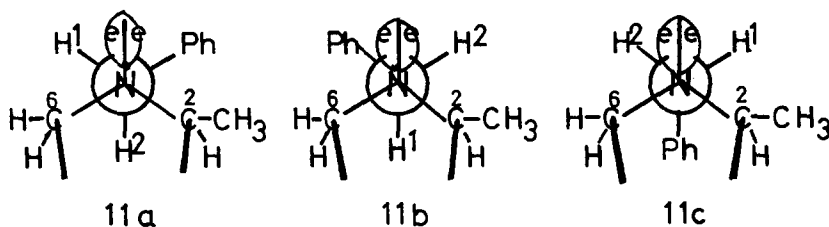
the phenyl is *gauche* to two substituents and in **11a** the phenyl is within a repulsive distance of the equatorial methyl. In rotamer **11b**, H^1 is *anti*-coplanar to the lone pair on nitrogen and is positioned relative to the nitrogen as an axial hydrogen. H^2 is comparable to an equatorial hydrogen. The difference in chemical shifts of these proton signals would be expected to be at

least 60 Hz.[5] The rotamers **12a,b,c** can be considered for those systems having an N-benzyl substituent vicinal to an axial methyl. The rotamer **12c** with the phenyl *gauche* to the two ring carbons would contribute little to the conformational equilibrium. The rotamers **12a** and **b** have the same interactions of the phenyl group with the piperazine ring. A conformational equilibrium of only **12a** and **b** in approximately equal amounts would be expected to have little or no difference in chemical shift between the methylene protons of the benzyl group as was observed for **7** and **8**.
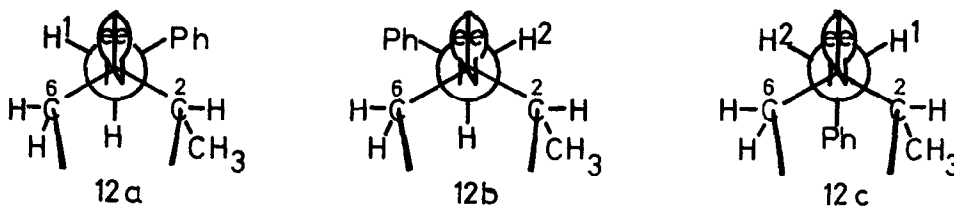
For N-benzyl groups in cyclic systems non-equivalence of the methylene protons will be observed if the conformer is chiral and the benzyl substituent is vicinal to a single equatorial alkyl substituent.

REFERENCES

1. This was suggested by a) R. K. Hill and T. H. Chan, *Tetrahedron,* **21,** 2015 (1965); b) D. R. Brown, *et al.*, *Chem. Commun.*, 719 (1966); c) R. W. Horobin, J. McKenna and J. M. McKenna, *Tetrahedron, Suppl.*, **7**, 35 (1966).

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