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ON THE ORIGIN OF THE MAGNETIC NON-EQUIVALENCE OF GEMINAL NCH_2 PROTONS IN THIOBENZAMIDES[1a,b]

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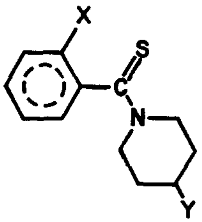
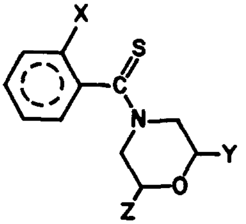
The problem of the magnetic non-equivalence of geminal groups was dealt with extensively in the last decade.[2a-g] However, unambiguous information about the exact contribution of the conformational and intrinsic asymmetry factors to $\Delta\nu_{AB}$ is virtually non-existent.[3]

Prompted by our previous studies on thioamides[4-6] and by some seemingly inconsistent conclusions by Lewin et al[7-10] we have investigated magnetically non-equivalent geminal protons which can take up only two defined positions in a known magnetic field, in an attempt to establish more precisely the relative importance of the above two factors. Due to the high anisotropy of the C=S bond, thiobenzamides are better model compounds than benzamides, but the conclusions concerning the relative importance of the intrinsic asymmetry will be equally applicable to benzamides. The following thiobenzoylpiperidines and thiobenzoylmorpholines were investigated by 100 MHz n.m.r. spectroscopy:



1a; X=OH, Y=H
1b; X=OH, Y=Me
1c; X=OMe, Y=H
1d; X=OMe, Y=Me



2a; X=OH, Y=Z=H
2b; X=OH, Y=Z=Me
2c; X=OMe, Y=Z=H

In both **1a** and **2a** the *syn* and *anti* NCH_2 protons are magnetically non-equivalent because of two unequally populated conformers.[4] This observation[11] must be contrasted with the assertion by Lewin et al[7,10] that in *o*-hydroxybenzamides this non-equivalence is prevented because the intramolecular hydrogen bond forms a six-membered ring which maintains the coplanarity of the aromatic ring and the amide group.[12]

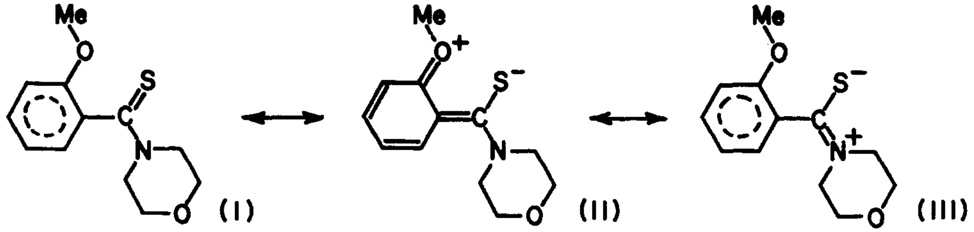
The center of the phenyl ring and the *syn* and *anti* C atoms adjacent to N are separated by about 5.2 and 3.5 A°, respectively, in both **1a** and **2a**. Thus the contribution of the phenyl ring to the magnetic anisochronism of the *syn* NCH_2 protons will be nearly zero.[13] Therefore the higher $\Delta\nu_{AB}$ value for the *syn* NCH_2 protons implies that the conformational factor and not the magnetic asymmetry is responsible for the magnetic non-equivalence. For the *anti* NCH_2 protons, considering that the equatorial positions will be almost identical in both conformers A and B as far as the phenyl ring is concerned, the maximum chemical shift difference between these protons should be ∿8 cps (100 MHz scale).

The magnetic anisotropy of the phenyl ring, determined according to Johnson and Bovey,[12] would be modified by the effect of the hydroxy and thioamide groups on the benzene π-electron density. However, the 100 MHz spectra of **1b** and **2b**, chosen because of simplification due to freezing of the hetero-ring inversion by the methyl substituent(s), in $CDCl_3$ at temperatures below 0°C where rotation around the CN bond is also frozen, give only one signal for the axial and one for the equatorial *syn* NCH_2 protons, independent of the conformation present. Slow rotation around the Ph-C(S) bond is thus not the cause of the magnetic non-equivalence. Therefore the Raban equation[14] relating $\Delta\nu_{AB}$ for both the *syn* and *anti* protons of **1a** and **2a** to the sum of "conformational population" and "intrinsic diastereoisomeric" terms simply becomes $\Delta\nu_{AB} = \Delta\nu_{cp}$, since $\Delta\nu_{id} = 0$, which is at variance with the conclusions of Lewin et al[7,10] but in agreement with those of Bedford et al.[15] For other benzamides and thiobenzamides where rotation about the Ph-C(S) bond is slow, the above equation may not be valid for the *anti* NCH_2 protons as opposed to the *syn* NCH_2 protons where it will always apply, i.e. the phenyl ring does not influence the chemical shift. As a corollary to this, it is only correct to apply Eliel's method[16] to *syn* protons.

In acetone-d_6 the intramolecular OH···S hydrogen bonds in **1a** and **2a** are broken and replaced by intermolecular OH···O bonds; here the *syn* NCH_2 protons are magnetically anisochronous in **1a** but isochronous in **2a**.[17] The intermolecularly hydrogen bonded OH signal is split into two peaks in 300 MHz n.m.r. spectra, corresponding to the conformers A and B in the ratios 40/60 and 50/50 in **1a** and **2a**, respectively.[17] When the intramolecular OH···S bond is broken the OH group can be considered as an ordinary *o*-substituent exerting no special effect driving the system toward coplanarity. However, magnetic anisochronism of the *syn* NCH_2 protons in **2a** in $CDCl_3$ can be attributed to the intramolecular OH···S bond, contrary to views that an *o*-OH group has an opposite effect.[7,10]

In pyridine-d_5 there is a competition between intramolecular OH···S and intermolecular OH···N hydrogen bonds. For **1a** this equilibrium is displaced in favour of the intramolecular bond at room temperature and lower. The *syn* NCH_2 protons of **1a** are magnetically non-equivalent at all temperatures investigated. In **2a** the intramolecular OH···S bond predominates at room temperature, but at -20°C or lower the intermolecular OH···N bond predominates,[18] and the *syn* NCH_2 protons are magnetically non-equivalent at room temperature but equivalent at -20°C and -30°C. In DMSO-d_6 solution, where a strong intermolecular OH···O bond replaces the intramolecular OH···S bond, the *syn* NCH_2 protons are magnetically non-equivalent in **1a** but isochronous in **2a** at room temperature.[19]

Furthermore, we have obtained 100 MHz n.m.r. spectra of **1c** and **2c** in a large number of solvents. The *syn* NCH_2 protons of **1c** are magnetically non-equivalent in all solvents investigated, but for **2c** they are equivalent in CCl_4 (ε=2.24)[20], C_6D_6 (2.28), CS_2 (2.64), $CDCl_3$ (4.81) Py-d_5 (12.3), CD_3COCD_3(20.7), but non-equivalent in benzonitrile (25.2), nitrobenzene-d_5 (34.8) and DMSO-d_6(46.7).[21,22] In both **1c** and **2c** the intrinsic magnetic asymmetry factor due to the slow rotation around the C(S)-Ph bond is identical, but this rotation is expected to be somewhat slower in **2c** than in **1c**, and thus the magnetic asymmetry due to the thiobenzoyl group will be greater in the morpholine compound. The conformational factor differs for **1c** and **2c** primarily due to the field effect of the oxygen on the nitrogen lone pair electrons in the morpholine ring of the latter, reducing the CN bond order and making it less rigid so that the steric interactions of the *anti* NCH_2 protons and the C-6' protons of the aromatic ring are more easily accommodated. Only as the solvent polarity increases does the contribution of the polar resonance forms (II) and (III) increase to the extent that magnetic non-equivalence sets in.



In pyridine-d_5 **1c** has a large $\Delta\nu_{AB}$ value, but the *syn* NCH_2 group of **1d** exhibits only single peaks for the equatorial and axial positions, respectively, in spite of the presence of two conformers. This is further evidence that magnetic asymmetry does not play a major role in inducing magnetic non-equivalence in the *syn* NCH_2 protons of **1c**.

The conclusions of Lewin et al that the intrinsic asymmetry factor determines the magnetic non-equivalence are inconsistent with earlier data[15], and also with their own data.[7] Thus the *syn* NCH_2 protons are magnetically non-equivalent in 2,6-dichloro-N,N-diethylbenzamide[15], contrary to the statement[7] that symmetrically 2,6-disubstituted benzamides do not exhibit geminal non-equivalence. In their own work Lewin et al[9,10] refer to the existence of "a preferred conformation in which the C-H bond is coplanar with and parallel to the C=O bond". The fact that $\Delta\nu_{AB} \neq 0$ for 2,6-dichloro-N,N-diethylbenzamide but $\Delta\nu_{AB} = 0$ for the corresponding N,N-dibenzyl compound also suggests that the conformational factor is responsible for magnetic non-equivalence.

With respect to the fact that $\Delta\nu_{AB}$ is generally larger for the *syn* NCH_2 protons than for the *anti* protons, it should be noted that at some temperatures this difference may be hidden by the partial or complete equalization of ν_A and ν_B due to higher amplitude torsional librations around the C-N bond, as found for **1a**.[6]

We conclude that in benzamides and thiobenzamides, at least for the *syn* NCH_2 protons, their magnetic non-equivalence is entirely due to the conformational factor, contrary to other reports.[7,23] Furthermore, in addition to the steric crowding arising from the N substituents, the C-N bond order and the locking of the phenyl ring with respect to the thioamide group play an important role in determining the effectiveness of this factor in **1a** and **2a**. These two structural features can accommodate the van der Waals interactions in these thioamides and will favour the conformer of lower energy. The difference between the piperidine and morpholine compounds studied here resides mainly in the reduced C-N bond order in the latter due to the field effect of the hetero-ring O atom.

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REFERENCES AND FOOTNOTES

1. (a) Supported by the National Research Council of Canada.
   (b) From the Ph.D. thesis of A. O. Fulea.
   (c) Izaak Walton Killam Scholar; on leave of absence from the University of Bucharest.

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11. While 220 MHz spectra of **1a** and **2a** have been reported in ref. 4, this magnetic non-equivalence can also be seen at 100 MHz. The coupling constants of the two NCH_2 protons with OCH_2 protons in a rapidly interconverting morpholine ring are given by J_{ae} and $pJ_{aa} + (1-p)J_{ee}$, and by $pJ_{ee} + (1-p)J_{aa}$ and J_{ae}, respectively; for $p = \frac{1}{2}$ the n.m.r. spectrum will be of the type AA'BB'. In the context of this note, magnetic equivalence of the *syn* NCH_2 protons refers only to their isochronous property, since only the chemical shift can be influenced by the intrinsic magnetic asymmetry of the benzene ring. For geminal protons $\Delta\nu_{AB}$ is a measure of magnetic non-equivalence.
12. Since the O···O distance in *o*-hydroxybenzamides is 2.6 A° whereas the sum of the van der Waals radii is 2.8 A°, complete coplanarity of the aromatic ring and the amide group may be precluded. In the corresponding thioamides the twist angle is greater. In **1a**-**1d** and **2a**-**2c** steric interference occurs mainly between the *trans* NCH_2 protons and the C-6' proton of the aromatic ring if the maximum conjugation in the thioamide group is retained.[5]
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18. This by itself is an unusual finding.
19. A comparison of **2a** with **2c** in $CDCl_3$ solution also confirms that the intramolecular hydrogen bond favours magnetic nonequivalence.
20. Dielectric constant values given in parentheses are for the normal solvents at 20 or 25°C (R. C. Weast, "Handbook of Chemistry and Physics", 54th ed., The Chemical Rubber Co., 1973).
21. The *anti* NCH_2 protons in **1c** are magnetically equivalent in all these solvents.
22. There is no correlation with the aromatic character of the solvent; the dielectric constant appears to play the major role.
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