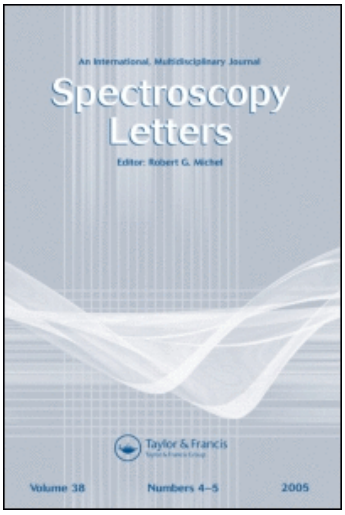

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Conformational Studies of 1-(2'-Hydroxythiobenzoyl)piperidine and 4-(2'-Hydroxythiobenzoyl)morpholine by High Resolution N.M.R. Spectroscopy

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CONFORMATIONAL STUDIES OF 1-(2'-HYDROXYTHIOBENZOYL)PIPERIDINE AND 4-(2'-HYDROXYTHIOBENZOYL)MORPHOLINE BY HIGH RESOLUTION N.M.R. SPECTROSCOPY[1]

Keywords: Distorted interconverting chair forms, intramolecular OH···S hydrogen bond.

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ABSTRACT

The 220 MHz ^1H nmr spectra of the title compounds (1a) and (2a), respectively, at low temperature in $CDCl_3$ solution are interpreted in terms of two interconverting chair forms with unequal populations (K_e = 1.17, $\Delta G°$ ~70 cals/mole for 1a and K_e = 1.8, $\Delta G°$ ~0.2 kcal/mole for 2a at -30°C). A strong intramolecular OH···S hydrogen bond in both compounds reduces the number of degrees of freedom of the bulky N-thiobenzoyl substituent, which nearly eclipses the equatorial α-CH_2 hydrogen atoms in both comformations. Steric interactions between the 6' phenyl proton and the hetero-ring α-CH_2 protons *trans* to the thiocarbonyl group are different in the two conformations of 1a and 2a.

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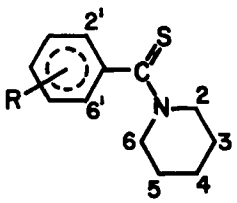
INTRODUCTION

N.m.r. studies of the following compounds in $CDCl_3$ solution at temperatures below that where rotation about the C-N bond is frozen out indicate that 1a and 2a have unique conformational properties:



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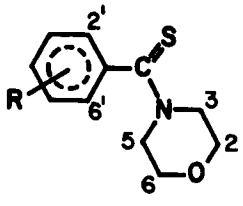

2

1a,2a,R = o-OH	1d,2d,R = H	1g,2g,R = m-NO_2
1b,2b,R = p-NMe_2	1e,R = p-Cl	1h,2h,R = p-NO_2
1c,2c,R = p-OMe	1f,R = o-Cl	2i,R = p-NHCOMe

From i.r. and u.v. data it can be inferred that the intramolecular OH···S hydrogen bond in 1a is a little stronger than in 2a[2,3]. The N lone pair electrons remain in cross-conjugation with the π-electrons of the thiocarbonyl group, since the coalescence temperature for rotation around the C-N bond on the 220 MHz nmr scale is near 18°C for 1a and somewhat lower for 2a.

RESULTS AND DISCUSSION

In 1a the C_2 and C_6 proton signals are split in the 220 MHz nmr spectra at -40° and -50°C (Fig. 1). Under the same conditions compounds 1b-1h have a broad triplet at τ ∿5.7 ppm (C_2 protons), the broadening being due to virtual coupling with the C_4 protons, and a sharp triplet at τ ∿6.5 ppm (C_6 protons) in $CDCl_3$ solution.[4] In 2a the C_3 proton signals are split at -20°C or lower (Fig. 2). At 18°C rotation around the C-N

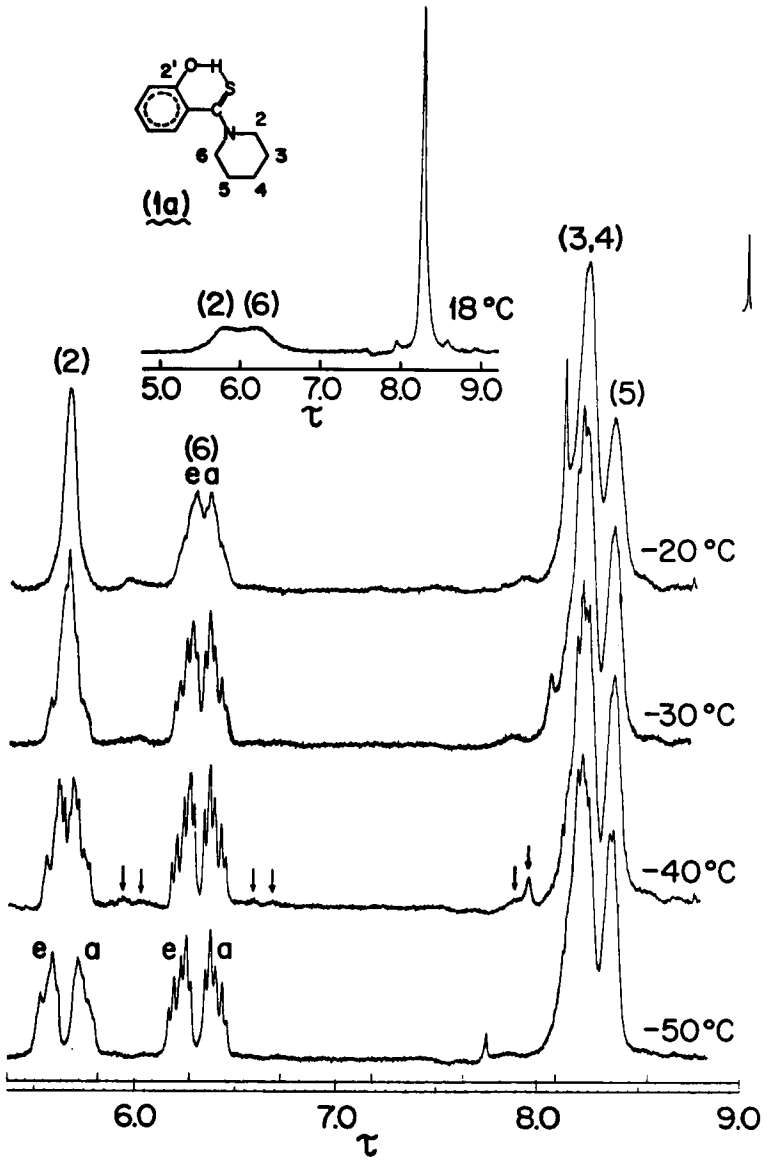

FIG. 1

^{1}H 220 MHz n.m.r. spectra of piperidine protons of 1a in $CDCl_3$ solution. Internal TMS reference. The notation "equatorial" refers to the proton which statistically spends more time in the equatorial position than in the axial position; similarly for the "axial" assignment.

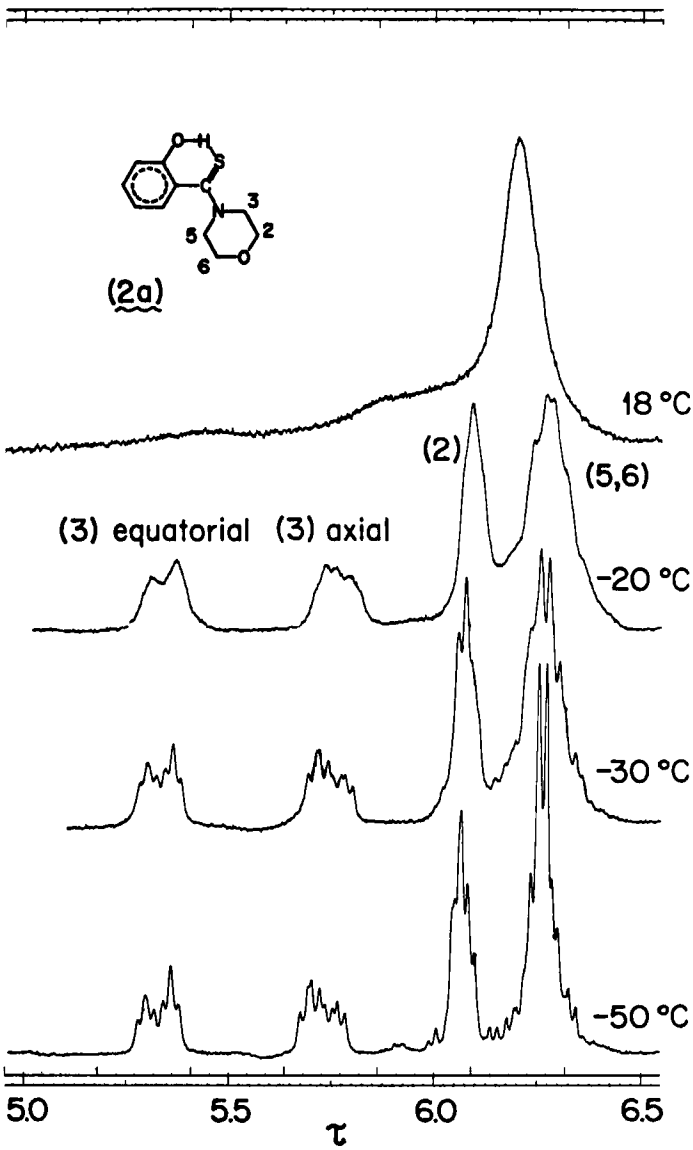

FIG. 2
^{1}H 220 MHz n.m.r. spectra of morpholine protons of 2a in $CDCl_3$ solution. For other details see caption to Fig. 1.

bond is observed and this kinetic phenomenon also produces the broadening observed at -20°C. Compounds 2b-2j exhibit a triplet for the C_3 protons (τ = 5.5-5.6 ppm) and for the C_2 protons, ($\tau \approx$ 6.1 ppm), plus a singlet or doublet for the C_5 and C_6 protons ($\tau \approx$ 6.4 ppm) at temperatures down to -60°C. The spectra of 1b-1h and 2b-2j show that the hetero-rings engage in rapid chair-chair interconversion between two equally populated conformers down to -60°C, on the 100 MHz time scale.

The low temperature features for 1a and 2a in Figs. 1 and 2 can be assigned to two interconverting chairs with *unequal* populations. The bulky N-thiobenzoyl substituent nearly eclipses the equatorial α-CH_2 protons and the phenyl ring is twisted out of the plane of the thioamide group in both conformations[5], as shown in Fig. 3. The principal difference between the two conformations is the interaction between the 6' proton on the aromatic ring and the C_6 proton(s) or the C_5 proton(s) of the hetero-ring in 1a and 2a, respectively -- in conformation (A) only the equatorial C_6 proton in 1a (or the C_5 proton in 2a) interacts with the phenyl 6' proton, while in the other conformation (B) both C_6 protons in 1a (or both C_5 protons in 2a) interact with the 6' proton. While rotation about

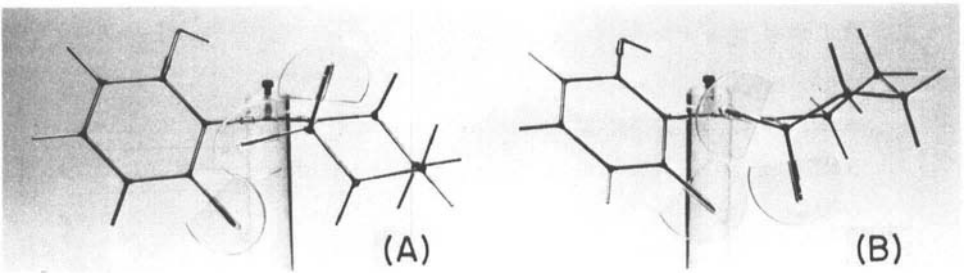

FIG. 3

Dreiding models of the two conformations of 1a. The camera is in the plane of the thioamide group and the thiocarbonyl S atom is not visible since it is directed away from the observer, with the C=S bond held by the screw in the top of the support rod. A and B are related by ring inversion.

the C-N bond is equivalent to chair-chair interconversion, the former requires breaking of the OH···S hydrogen bond, which is slow on the nmr time scale.

The pattern of the C_2 proton signals in 1a are complicated by virtual coupling with the C_4 protons. The C_6 protons each give rise to a quintet due to the overlapping of the X parts of two deceptively simple ABX spectra[6] for which $\delta_{AB} = 0$ and $(L/J_{AB}) \rightarrow 0$.

Using Eliel's method[7], the chemical shifts of the C_2 protons give the relative populations of the two chair conformations of the piperidine ring in 1a as approximately 0.54 and 0.46, respectively, at -30°C. Decoupling at -50°C gives $J_{gem} = 13$ cps for both the C_2 and C_6 protons, in agreement with the known geminal coupling constant in piperidine[8], thus indicating that the HCH angles at these two carbon atoms are not distorted. The sum of the coupling constants $(J_{AX} + J_{BX})$ is 10.6 and 11.4 cps for the "equatorial" and "axial" protons, respectively, at C_6[9]. These sums lead to two *different* values of 0.7 and 0.4 for p, the fractional population of that conformer, if coupling constants for an undistorted chair are used in both conformations. This indicates that at least one of the conformers is a distorted chair. If it is assumed that only one conformer of 1a is distorted then a large distortion must be present; using the Karplus equations[10], Lambert's R value[11] for the *trans* NCH_2CH_2 group is approximately unity, which appears to be contrary to the very small $\Delta G°$ of ∿70 cals/mole between the two conformations obtained from $K_e = (0.54/0.46) = 1.17$ at -30°C.[12] Distortion at C_6 in *both* conformations is likely due to steric interference from the phenyl 6' proton. Distortion of the chair conformations is further supported by the fact that both sums of the coupling constants at C_6 referred to above have higher values than the corresponding sum for the "axial" *cis* NCH_2 protons in 2a. The fact that

the average of the chemical shift for the C_6 protons in 1a differs from corresponding values in other N-thiobenzoylpiperidines[13], whereas the C_2 protons in 1a have the same average shift as those in other N-thiobenzoylpiperidines, may also indicate distortion at C_6.[14]

In Fig. 2 the "equatorial" *cis* $NCH_2(C_3)$ proton signal (X) for 2a gives $J_{AX} + J_{BX} = 8.2$ cps, from which p = 0.64 (the fractional population of the most populated conformation) around 243K, with $K^{243}_{equil} \approx 1.8$ and $\Delta G_o \approx 0.2$ kcal/mole. From the value of p and the observed C_3 τ values (5.70 and 5.32 ppm), τ_a^{cis} and τ_e^{cis} are determined to be 6.2 and 4.8 ppm. respectively, in the deshielding cone of sulfur. These values are in good argeement with corresponding N-thiobenzoylpiperidine values.[4] No evidence for distortion of chair conformations could be seen in the nmr spectra of 2a because the C_5 and C_6 proton signals overlap.

Conformational A values have so far been associated with the axial-equatorial preference of ring substituents[15]; here we demonstrate a free energy difference between two chair conformations which arises indirectly due to the substituent, but where the substituent remains in the same position, i.e. eclipses the equatorial protons in both conformations.

Finally, several temperature dependent weaker spectral features should be noted, e.g. those marked with arrows in the -40°C spectrum in Fig. 1. These also appear in low temperature 300 MHz spectra, and may be due to a low concentration of another higher energy conformation.

The collapse of the C_2 proton signals in 1a before those of the C_6 proton signals as the temperature is raised is another interesting feature which will be discussed elsewhere.

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1. This work was supported by the National Research Council of Canada. High resolution n.m.r. spectra were obtained at the Canadian 220 MHz N.M.R. Centre, Sheridan Park, Ontario. We are indebted to Prof. M. Anteunis, State University of Gent, Belgium, for some 300 MHz spectra. This work is part of the Ph.D. thesis of A. O. Fulea.

2. I.r. spectra of dilute ($c < 0.003$ M) solutions in CCl_4 exhibit the following normal "free" ν_{OH} (trace only), $\nu_{OH\cdots S}$ intramol. (broad and intense), and $\Delta\nu_{OH}$ values: (1a) 3605, 3255, 350; (2a) 3607, 3266, 341 cm^{-1}. At this low concentration intermolecular association can be excluded. In the u.v. the $n \rightarrow \pi^*$ transition in n-hexane solution shifts from 389 nm in 1a to 401 nm in 1c, and from 389 nm 2a to 403 nm in 2c.

3. Since intermolecular OH···S hydrogen bonds between phenol and N,N-dimethylthioacetamide and N,N,N',N'-tetramethylthiourea in CCl_4 lead to OH frequency shifts of 301 and 317 cm^{-1} respectively, corresponding to ΔH values of -5.5 and -5.7 kcal/mole (R. J. Niedzielski, R. S. Drago and R. L. Middaugh, J. Amer. Chem. Soc., 86, 1694 (1964)), a very strong hydrogen bond is also expected in 1a and 2a as the underlying cause for the conformational effects reported here.

4. Both of these τ values are in good agreement with averages of τ_a and τ_e found by Walter and co-workers for thiobenzoylpiperidines substituted at C_4 (W. Walter, E. Schaumann and H. Paulsen, Justus Liebigs Ann. Chem., 727, 61 (1969)).

5. Space filling models show that all the compounds referred to are sterically crowded, the main van der Waals interactions of the α-CH_2 groups of the piperidine ring being with the S atom and the 6'-hydrogen atom of the phenyl ring. A somewhat similar N-substituent in a piperidine ring is described by T. P. Forrest and S. Ray, Chem. Commun., 1537 (1970). An out-of-plane twist angle of 50-60° is estimated for both 1a and 2a from models, with an OH···S distance of 3.00-3.05 A°, slightly less than the sum of van der Waals radii for O and S atoms. Twisting in benzamides and thiobenzamides has recently been discussed by G. A. Baramki, G. Derdall and J. T. Edward, Can. J. Spec., 18, 160 (1973).

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9. See caption of Fig. 1 for definition of "equatorial" and "axial" notation.

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12. Alternatively, a low value of R is also consistent with a single frozen highly distorted piperdine ring in which the C_2 protons are pseudoaxial and pseudoequatorial and are subject to near identical deshielding from the C=S bond. Such a flat ring form is deemed to have too high an energy, and is also inconsistent with the observation that the average C_2 chemical shift in 1a and the average C_3 chemical shift in 2a are the same as those observed in 1b-1h and 2b-2i, respectively. Other possible explanations considered are an interconversion between two skew conformers, or the diastereotopic nature of the NCH_2 protons due to the asymmetry of the 2'-hydroxythiobenzoyl portion of the molecule, together with slow rotation around the C-phenyl bond on the n.m.r. time scale, but neither accomodate all the experimental data. A more complete discussion of all the possibilities will be presented elsewhere.

13. Alternatively, or in addition, the C_6 protons in conformation B of 1a may experience different shielding from the phenyl ring, relative to that in other N-thiobenzoylpiperidines.

14. The observation of higher piperidine CH stretching frequencies in 1a (Raman, solid: 2951, 2928, 2900, 2865, 2858 cm^{-1}; ir, CCl_4 solution: 2944, 2926, 2858 cm^{-1}) relative to those found in all other related thioamides studied (e.g. in N-benzoylpiperidine, Raman, solid: 2943, 2901, 2865 cm^{-1}) provides further evidence for the steric hindrance of NCH_2 groups (L. S. Bartell, J. Amer. Chem. Soc., 81, 3497 (1959); D. Kivelson, S. Winstein, P. Euck and R. L. Hansen, ibid, 83, 2938 (1961)). Destruction of the local symmetry of the piperidine ring due to distortion may also be reflected in the increase in the number of bands observed in the CH stretching region of 1a.

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