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MAGNETIC NON-EQUIVALENCE IN N,N-DIETHYLBENZAMIDES AND -THIOBENZAMIDES
CONFORMATION OF THE N-ALKYL GROUPS

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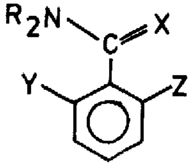
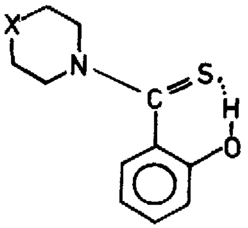
Two different rationalizations of magnetic non-equivalence of geminal methylene protons in *ortho* substituted N,N-diethylbenzamides and related compounds have been advanced. Bedford *et al.*[1] and more recently Fulea and Krueger[2] advocate a "conformational effect", whereas Siddall and Garner[3] and Lewin *et al.*[4,5] see hindered rotation of the aryl group as the reason for the non-equivalence. The controversy can be simplified as follows. According to Siddall *et al.*[3,6] and Lewin *et al.*[4,5] the aromatic ring and the (thio)amide group are more or less orthogonal. The process, which can average the methylene protons, is the rotation of these two parts *versus* one another, and its rate is determined by the size of the *ortho* substituent and of the (thio)-amide group. On slow rotation the molecule is chiral on the NMR timescale.

Bedford *et al.*[1] and Fulea and Krueger[2] on the other hand contend that the interaction between the E methylene group and the 6-hydrogen atom on the aromatic ring affects the populations of the different conformers of the N-alkyl groups. The conformations and thus the averaging process are not specified, but it is evident that fast rotation around the (thio)amide CN bond will average the geminal methylene protons.



Ia: X=O, Y=H, Z=Cl, R=Et
Ib: X=O, Y=Z=Cl, R=Et
Ic: X=S, Y=H, Z=Cl, R=Et
Id: X=S, Y=H, Z=OH, R=Et
Ie: X=S, Y=H, Z=OH, R=$PhCH_2$



IIa: X=CH_2
IIb: X=O

The main arguments advanced by Fulea and Krueger[2] are (1) that N,N-diethyl-2,6-dichlorobenzamide (Ib) according to Ref. 1 displays magnetic non-equivalence of the Z methylene protons below +24 °C in $CDCl_3$ solution, and (2) that 2-hydroxythiobenzpiperidide (IIa) and -morpholide (IIb) have non-equivalent protons in the methylene groups adjacent to the nitrogen atom. Both observations are explained by a similar conformational effect, which *per se* does not necessitate chirality of the Ar-C(X)N part of the molecule.

The first argument has been refuted in a recent communication by Jennings and Tolley.[7] Turning to the second argument, it appears well substantiated[8] that IIa and IIb exist as mixtures of two conformers, which differ in their interaction between the E NCH$_2$ group and the aromatic 6-hydrogen atom. The steric interaction is however strongly dependent on the hydrogen bond, which keeps the aromatic ring and the thioamide group in a fixed geometric relation. When the hydrogen bond is broken by basic solvents or when the 2-hydroxy group is replaced by other substituents, the aryl group has a much larger torsional freedom, and the reason for a strong (E CH$_2$)-6H interaction is no more at hand. Instead, the sizes of the ortho substituent and of the (thio)amide group become of prime importance. This is well illustrated by the free energy barriers to methylene averaging in N,N-diethyl-2-chlorobenzamide (Ia) and its thio analog (Ic) (Table). The difference is undoubtedly due to the difference in size between the oxygen and sulphur atoms.

TABLE

	Z-CH$_2$ [10]			E-CH$_2$ [10]			
Compound	$\Delta\nu_{AB}$(Hz)	J_{AB}(Hz)	T_cK	$\Delta\nu_{AB}$(Hz)	J_{AB}(Hz)	T_cK	$\Delta G^{\ddagger}_c$(kcal/mol)
Ia	32.1[a)]	13.5	303	-	-	-	14.9
Ic	68.5[b)]	13.1	>473	-	-	-	>23
Id	16.0[c)]	13.0	-	7.7	13.1	223	11.0
Ie	ca 60[d)]	14.3	266	ca 40[d)]	14.6	263	12.8

a) At 60 MHz in CDCl$_3$. b) At 100 MHz in o-dichlorobenzene. c) At 100 MHz in CHCl$_2$F.

d) Extrapolated.

We now wish to present evidence, which indicates that a conformational effect is of importance also in N,N-diethyl-2-hydroxybenzamide (Id). The PMR spectrum of this compound has been studied in CHCl$_2$F solution down to -100°, where crystallization occurs. The barriers to C-N rotation in 2-hydroxy-thiobenzamides are quite low,[9] but below -40° the ethyl groups display sharp triplets and quartets. On lowering the temperature the high-field (E)[10] methylene quartet broadens, and at -56 °C it displays a partly resolved AB part of an ABX$_3$ spectrum ($\Delta\nu_{AB}$=7.7Hz, J_{AB}=13.1Hz). At somewhat lower temperature the low-field quartet is split in a similar way, and on further cooling its A and B parts successively increase their separation due to a temperature-dependent downfield shift of the low-field resonance of the order of 0.5Hz/degree (Figure). An extrapolation to higher temperatures reveals that $\Delta\nu_{AB}$ goes to zero at about -55°. Thus it is only the high-field quartet, which is affected by the exchange process in the intermediate rate range, and the low-field quartet appears split only in the slow exchange limit and therefore gives no information about the rate of the process.

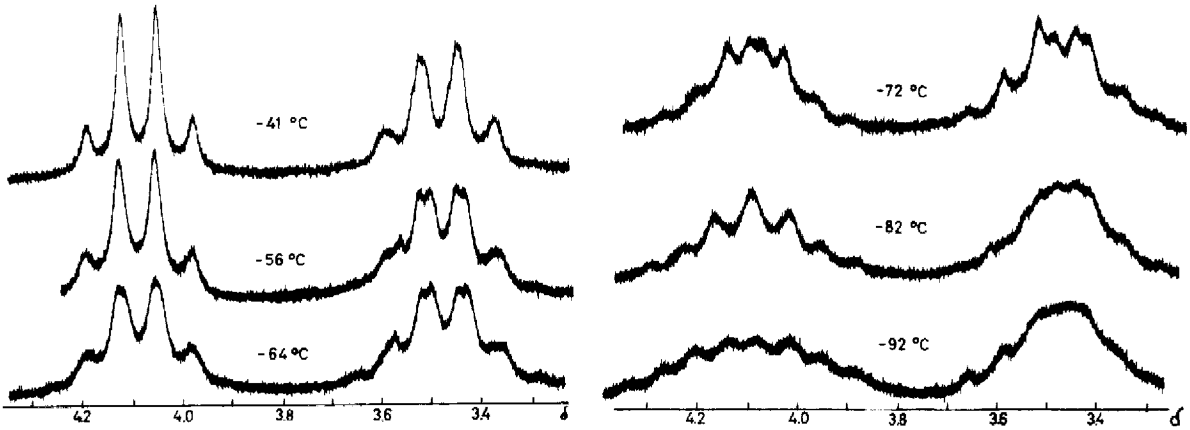
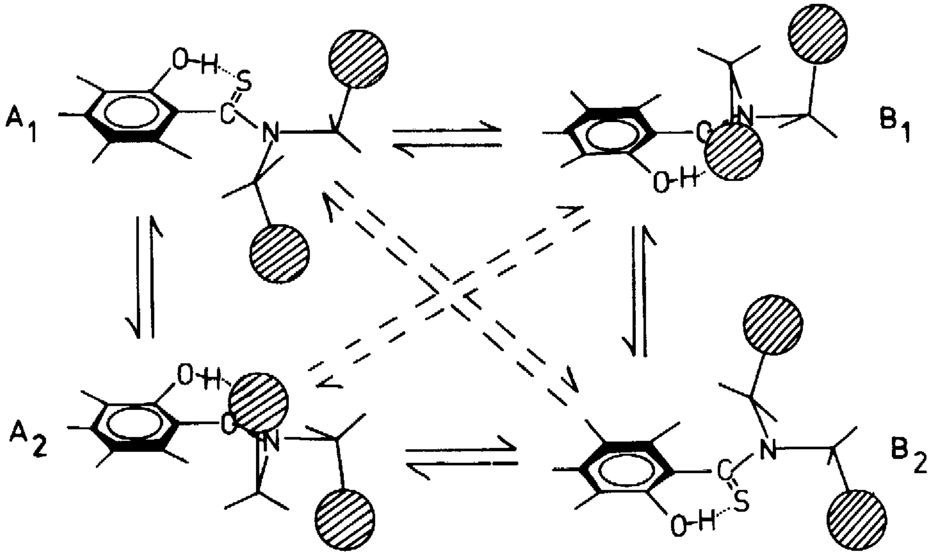


Figure. ^{1}H-NMR signals of methylene protons in Id ($CHCl_2F$).

Lewin and Frucht[4] proposed that a six-membered cyclic chelate prevents the occurence of a chiral center. Planarity, or near planarity, between the ring and the amide function desirable for effective intramolecular hydrogen bonding is, however, counteracted by steric interactions between the E substituent and the 6-hydrogen on the phenyl ring. As a consequence of these conflicting effects, the intramolecular hydrogen bond in thioamides is comparatively weak, the (thio)amide rotational barrier is low and the molecule is twisted around the pivot bond.[9]



SCHEME

To explain our observations on Id we propose the following tentative mechanism. We assume that the ethyl groups are nearly perpendicular to the thioamide plane[11] and antiparallel to each other. Each methylene proton takes part in a four-sites exchange process, where one exchange is effected by the simultaneous or stepwise rotation of the ethyl groups (e.g. $A_1 \rightleftarrows A_2$) and another by the inversion of the chelate ring (e.g. $A_1 \rightleftarrows B_1$, Scheme). Only one of the processes effects broadening but a temperature dependence of the equilibrium corresponding to the other process may explain the low-field shift of one of the Z methylene protons on cooling. The assumption that one of the processes is fast down to -90° is supported by the observation of only two sharp methyl triplets down to this temperature.

A similar investigation of N,N-dibenzyl-2-hydroxythiobenzamide (Ie) in $CHCl_2F$ shows AB spectra for both the E and Z methylene groups. Both $\Delta\upsilon_{AB}$ are strongly temperature dependent and even show sign reversal. Bandshape analysis of both quartets give a free energy barrier of 12.8 kcal/mol. Since exchange of methyl for phenyl should raise the barrier to the $A_1 \rightleftarrows A_2$ exchange but have a much smaller effect on the $A_1 \rightleftarrows B_1$ exchange, it seems probable that the first process is responsible for the band broadening and the second for the temperature dependence of the chemical shifts.

To conclude, the available data support the following picture. In hydrogen-bonded 2-hydroxythiobenzamides (and probably also in the corresponding benzamides, which should have stronger hydrogen bonds) the magnetic non-equivalence will be due to the "conformational effect", whereas for these compounds in basic solvents and for all other non-chelated *ortho* substituted (thio)benzamides the non-equivalence can be ascribed to non-coplanarity of the aromatic ring and the (thio)amide group, as proposed by Siddall *et al*. and by Lewin *et al*.

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