Tetrahedron Letters No. 9, pp 695 - 698, 1976. Pergamon Press. Printed in Great Britain.

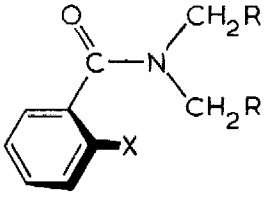
CONCERNING GEMINAL NONEQUIVALENCE IN BENZAMIDES AND THIOBENZAMIDES

W. Brian Jennings* and Malcolm S. Tolley

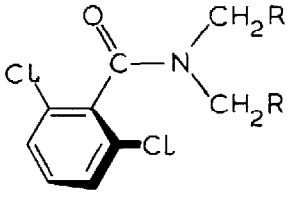
Department of Chemistry, University of Birmingham, P.O. Box 363, Birmingham, B15 2TT.

(Received in UK 19 November 1975; accepted for publication 23 January 1976)

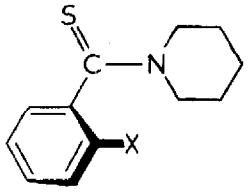
Differing views have been expressed in the literature regarding the cause of the geminal NCH_2 anisochronism observed in the ^1H NMR spectra of some N,N-dialkyl-benzamides (and thiobenzamides).[1,2,3] Opinion appears to vary as to the role of unsymmetrical substitution in the benzamide ring and restricted rotation around the aryl-carbonyl bond.



1



2



3

The criterion for the geminal methylene hydrogens to be diastereotopic is that the molecule must lack a molecular symmetry plane on the NMR time-scale containing the prochiral NCH_2 carbon atoms (assuming rapid rotation around the N-CH_2 bonds).[4] This criterion could be fulfilled in benzamides (1) with unsymmetrical ring substitution provided that the aryl ring is twisted out of the amide plane and rotates through that plane at a rate which is slow on the NMR time-scale. Thus several ortho-substituted benzamides (e.g. 1, X = F, Cl, NO_2, or CH_3; R = C_6H_5 or CH_3) show geminal anisochronism in either one or both NCH_2 groups below about 0°C (where rotation around the ring-carbonyl bond is presumably slow).[1,2,3,5]

According to the above analysis, symmetrically ortho-disubstituted benzamides (2) where R is achiral should not exhibit geminal anisochronism (in achiral media) since the prochiral methylene carbon atoms lie in a molecular symmetry plane even when the phenyl ring is orthogonal to the amide plane.[6] In principle geminal nonequivalence could be realized if the aryl ring

were twisted ca. 45° out of the amide plane and unable to rotate through both the orthogonal and planar conformations, or if the amide nitrogen atom were inverting slowly on the NMR time-scale. Neither of these conditions are likely to be fulfilled in practice.

Lewin et al[2] have indeed reported that symmetrically ring substituted benzamides do not show geminal nonequivalence. This conclusion has been challenged recently by Fulea et al[1] who cited an earlier report[3] of geminal anisochronism in 2,6-dichloro-N,N-diethylbenzamide (2, R = CH_3) to support their contention. It must be pointed out that the identity of the latter compound was later[7] established as 2,4-dichloro-N,N-diethylbenzamide which is unsymmetrically substituted. An authentic sample of the 2,6-dichloro compound has been prepared[8] in this laboratory. The PMR spectrum indeed shows normal quartets for both NCH_2 groups down to -65° in deuteriochloroform solution and to -90° in toluene-d_8 or acetone-d_6 (Fig. 1). Accordingly the original conclusions of Lewin et al[2] are clearly correct.

The role of the intrinsic term ($\Delta\delta_{id}$) has also been discussed.[1] This has been defined as the residual anisochronism when all three conformations are equally populated.[9,10] In the case of cyclic prochiral groups (as in 3), intrinsic diastereoisomerism cannot be realized in practice since at least one conformation cannot be attained due to the geometric restraints. In thioamides of type 3 there would still be a conformational imbalance around

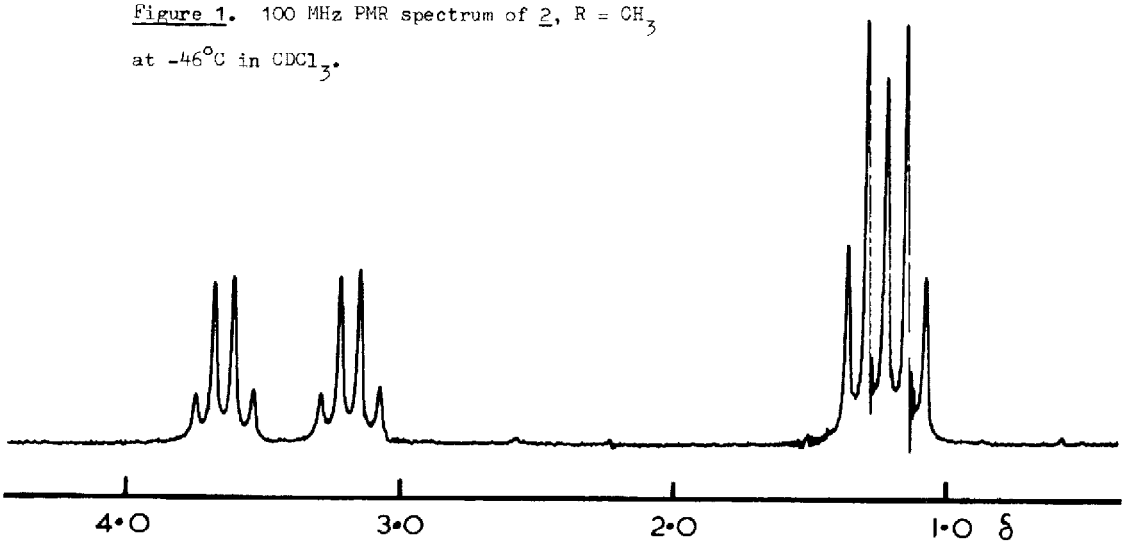
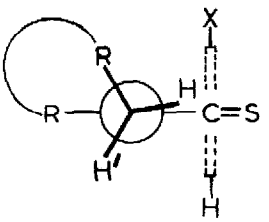
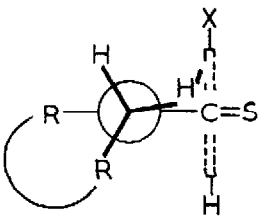


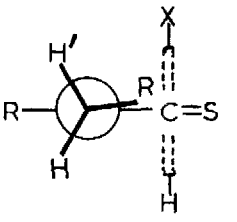
Figure 1. 100 MHz PMR spectrum of 2, R = CH_3 at -46°C in $CDCl_3$.



4a



4b



4c

the N-CH_2 bond even if the accessible conformers 4a and 4b were equally populated.[11] Accordingly, although studies of cyclic systems can provide useful information on geminal anisochronism, they do not establish that $\Delta\delta_{id} = 0$ for either NCH_2 group in 3.

Contrary to other suggestions,[1] the "origin" of the geminal nonequivalence in these compounds is clearly the molecular dissymmetry arising from slow rotation around the C-aryl bond. The results of Fulea et al[1] do suggest a considerable conformational contribution to the total anisochronism in 1 - 3, but the magnitude of the intrinsic term has not been assessed. We would emphasize that the conformational factor cannot cause non-equivalence in the absence of slow rotation involving an asymmetrically substituted aryl ring (assuming fast inversion of the amide nitrogen and of the piperidine ring in 3).

REFERENCES AND NOTES

1. A.O. Fulea and P.J. Krueger, Tetrahedron Letters, 3135 (1975).

2. A.H. Lewin and M. Frucht, Tetrahedron Letters, 1079 (1970); A.H. Lewin, M. Frucht, K.V.J. Chen, E. Benedetti and B. DiBlasio, Tetrahedron, 31, 207 (1975).

3. G.R. Bedford, D. Greatbanks, and D.B. Rogers, Chem. Commun., 330 (1966).

4. W.B. Jennings, Chem. Rev., 75, 307 (1975).

5. For a review see W.E. Stewart and T.H. Siddall, III, Chem. Rev., 70, 517 (1970).

6. Symmetrically ring substituted benzamides could however exhibit geminal anisochronism if the molecule contained a chiral substituent (this removes the σ'— plane). Thus the benzylic methylene protons are diastereotopic in 2,6-dimethoxy-N-methyl-N-(1-phenyl-2-propyl)benzamide [T.H. Siddall, III and R. Garner, Tetrahedron Letters, 3513 (1966)].

7. G.R. Bedford, D. Greatbanks, and D.B. Rogers, Chem. Commun., 144 (1967). We thank Dr. Bedford for drawing our attention to this corrigendum.

8. 2,6-Dichlorobenzoyl chloride reacted spontaneously with excess diethylamine in dichloromethane to afford the amide in 80% yield, m.p. 94 - 95° from hexane (Found: C, 53.55; H, 5.4; N, 5.6; Cl, 28.8. Calc. for $C_{11}H_{13}Cl_2NO$: C, 53.7; H, 5.3; N, 5.7; Cl, 28.8%). ^{13}C NMR signals (in $CDCl_3$ with TMS reference) at δ 12.4 (CH_3), 13.7 (CH_3), 38.9 (NCH_2), 42.7 (NCH_2), 128.1 (3,5-aryl), 130.1 (4-aryl), 131.8 (2,6-aryl), 135.8 (1-aryl), 164.5 (C=O). ^{13}C NMR spectra were recorded on a Jeol FX60 at 15 MHz and PMR spectra were obtained on a Varian XL-100 at 100 MHz.

9. H.S. Gutowsky, J. Chem. Phys., 37, 2196 (1962).

10. M. Raban, Tetrahedron Letters, 3105 (1966).

11. The previous authors have reported that derivatives of 3 with a "fixed" ring conformation (e.g. the 4-methylpiperidino analogue with X = OH) showed only one signal for the axial and one for the equatorial syn NCH_2 protons. This observation could indicate that only one diastereoisomer was present in significant abundance. However, even if the signals are superimposed for both diastereoisomers and if the perturbation of the methyl substituent can be neglected, these observations still do not establish that $\Delta\delta_{id} = 0$. Thus even if $\delta(H)$ in 4a were to equal $\delta(H')$ in 4b and $\delta(H')$ in 4a were equal to $\delta(H)$ in 4b, $\Delta\delta_{id}$ would not be zero unless $\delta(H) = \delta(H')$ in the inaccessible conformer 4c (see ref. 4). One might however argue intuitively that the chemical shift difference between H and H' in 4c should be fairly small for the syn NCH_2 group.