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RESTRICTED ROTATION IN AMIDES I. NON-EQUIVALENCE OF GEMINAL METHYLENE PROTONS DUE TO CHIRALITY.[1,2]

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In the course of our investigations of restricted rotation in amides we have examined the NMR spectra of a series of substituted N,N-dibenzylbenzamides and found the methylene proton region of the spectra to be dependent on temperature and upon both the nature and the symmetry of benzoyl substitution . Substituted N,N-dibenzylbenzamides (substituent = F, Cl, NO_2, Me) with no *ortho* substituents usually displayed a single methylene resonance at room temperature, which separated into two singlets at lower temperature consistent with the existence of a barrier to rotation around the carbonyl-nitrogen amide bond, commonly observed in amides.[3] Benzamides with a single *ortho* substituent (substituent = F, Cl, NO_2, Me, OMe) showed a methylene singlet at temperatures around 100°C and two methylene resonances at ambient temperature. *Both methylene signals appeared as AB quartets* at low temperatures (usually 0° and below). The chemical shift difference between the geminal protons of the downfield methylene group (τ=5.3ppm) was large ($\delta_{AB}\simeq$ 1ppm) while the upfield methylene (τ=5.8ppm) chemical shift difference was much smaller ($\delta_{AB}\simeq$0.15ppm).

Magnetic non-equivalence of the downfield geminal methylene hydrogens in o-substituted tertiary benzamides has been previously reported, and two different interpretations have been offered.[4,5] Thus, Bedford et al.[4] attributed the non-equivalence in o-chloro-N,N-diethylbenzamide to unequal populations of the three rotameric conformations of the methylene group, due to steric interference of the ethyl group with the ortho substituent. Siddall and Garner,[5] on the other hand, explained similar geminal non-equivalence by slow rotation around the phenyl-to-carbonyl bond. It has been pointed out that molecular asymmetry can convey geminal magnetic non-equivalence even when rotameric populations are equal;[6] however, the relative importance of rotameric population differences and intrinsic asymmetry is difficult to assess.[7] Although the observed geminal non-equivalence is temperature dependent and as such is consistent with the phenomenon of changing rotameric populations,[8] the following observations suggest an alternative explanation, preferred by us : (a) Examination of 3-dimensional Courtauld models indicates that it is sterically more favorable for the o-substituent to occupy the position next to the carbonyl oxygen than that next to the anti N-methylene group; (b) 2,6-Symmetrically disubstituted benzamides (e.g. 2,6-dichloro-N,N-dibenzylbenzamide) do not exhibit geminal non-equivalence although steric interference of the type proposed[4] should be at least as severe in these cases; (c) The NMR spectra of unsymmetrically ortho disubstituted N,N-dibenzylbenzamides (e.g., 2-chloro-6-nitro), by contrast, resemble those of benzamides with a single ortho substituent. These observations are consistent with slow rotation, on the NMR time scale, around the phenyl-to-carbonyl carbon-carbon bond, as proposed by Siddall and Garner;[5] however, lack of coplanarity between the benzoyl phenyl and the amide linkage is essential to cause geminal non-equivalence.[9,10]

Since these systems are cross-conjugated non-planarity will lead to decreased resonance interaction between the benzoyl phenyl and the carbonyl group, tending to enhance the double bond character of the amide linkage[4]. In agreement with this interpretation we have found that whereas m-nitro-N,N-dibenzylbenzamide exhibits two methylene singlets down to -80°C, 2,6-dichloro-3-nitro-N,N-dibenzylbenzamide displays an AB quartet for the downfield signal already at room temperature. Thus, a meta substituted benzoyl with no ortho groups can be planar, leading to a plane of symmetry and to a decreased barrier to rotation around the carbon-nitrogen amide bond. The presence of ortho substituents, however, forces the benzoyl phenyl out of the plane, increasing the amide rotational barrier as well as imparting asymmetry to the molecule.

The NMR spectra of o-hydroxy and o-amino N,N-dibenzylbenzamide provide additional support for our interpretation. In these amides the formation of a six-membered cyclic chelate, which includes the carbonyl oxygen and the hydrogen of the o-substituent,[11] might be expected to maintain the planarity of the benzoyl group, thus decreasing the barrier to rotation around the carbon-nitrogen amide bond and preventing the occurence of a chiral center. The NMR spectra of both o-amino and o-hydroxy-N,N-dibenzylbenzamide showed only a single methylene resonance down to -60°C; in the m and p analogues, by contrast, two methylene singlets appeared at 0°C, similar to other m and p substituted amides (vide supra). In solvent pyridine, at 0°C, the NMR spectra of the o-hydroxy and o-amino amides exhibit two methylene singlets, in agreement with disruption of the hydrogen bonding. Destruction of the chelate ring leads to a situation analogous to that of amides with non-hydrogen bonding substituents. Two methylene resonances are observed for acidic solutions of the o-amino derivative and for basic solutions of the o-hydroxy compound for similar reasons.

References and Footnotes

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