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RESTRICTED ROTATION IN AMIDES III. RESONANCE ASSIGNMENTS IN TERTIARY AMIDES AND THIOAMIDES UTILIZING THE NUCLEAR OVERHAUSER EFFECT.[1]

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As part of our investigation of hindered rotation in amides[4,5] we have been interested in making NMR signal assignments for the N-substituents. Examination of the literature reveals some published conflicts[6] of chemical shift assignments in tertiary amides and several apparent conflicts.[5,7,8] Theoretical arguments for making resonances assignments in tertiary amides appear to be inconclusive[11] and most experimental methods appear not only limited but tenuous as well[4,5,12](vide infra). We have, therefore, utilized the Nuclear Overhauser Effect (NOE)[13] for making resonance assignments in a number of tertiary amides and thioamides. Our results, summarized in the Table, serve to clarify several contradictions and shed light on the validity of other experimental methods.

The upfield signals in diethylformamide, diethyl and di*iso*propyl acetamide among others were assigned to the group *cis* to the carbonyl oxygen by analogy with the assignments in dimethylformamide.[14,15] Our decoupling experiments on diethyl and di*iso*propylformamide in $CDCl_3$ show the upfield methyl to be associated with the downfield methylene and the downfield methine respectively and vice versa. In addition our NOE results on diethylformamide require the upfield methylene to be *cis* to the formyl proton (and *trans* to the carbonyl oxygen) in direct contradiction to previous assignments.[9] We conclude that *resonance assignments of tertiary amides based only on chemical shift*

Resonance Assignments in Tertiary Amides Based on the NOE.

Compound	Chemical Shift[a] of the N-substituent cis to the carbonyl oxygen in:					
	Non-Aromatic Solvent			Aromatic Solvent		
	$-CH_3$	$-CH_2$	-CH	$-CH_3$	$-CH_2$	-CH
Diisopropylformamide	+		-	-		-
Dimethylformamide	+			-		
Diethylformamide	+	-		-	-	
Benzylmethylformamide	+	-		-	-	
Dibenzylformamide		-			-	
Dimethylthioforamide	+			-		
Dibenzylthioformamide		-			-	
Dimethylacetamide[b]	+			-		
Diethylacetamide[b]	+	-		-	-	
Benzylmethylacetamide[b]	-	-		-	-	
Dibenzylacetamide[b]		-			-	
Dibenzylthioacetamide[b]		-			-	
2-Methyl-3,5-dinitro-N,N-dimethylbenzamide	-			-		
2-Methyl-3,5-dinitro-N,N-diethylbenzamide	-	-		-	-	
3,5-Dinitro-N,N-dibenzyl benzamide		-			-	

a) + stands for upfield; - stands for downfield.

b) The α position is dideuterated.

arguments are unreliable.[16]

It has been shown[18] that in unsymmetrically substituted acetamides the bulkier group preferentially occupies the position cis to the carbonyl oxygen; thus the configuration of the major amide isomer is known.[19] Bedford et.al.[21] used N-ethyl-N-methylbenzamide in order to assign the N-ethyl resonances in o-chloro-N,N-diethylbenzamide and concluded that the upfield methylene group was cis to the carbonyl oxygen. Our NOE results on 2-methyl-3,5-dinitro-N,N-diethylbenzamide,[22] however, show the upfield methylene group to be trans to the carbonyl oxygen, indicating that the assignment made by Bedford et.al.[21] is incorrect.[23] On the other hand, use of the same approach on o-fluoro-N-cyclohexyl-N-methylbenzamide as a model for o-fluoro-N,N-dimethylbenzamide[25] leads to results in agreement with those obtained from the NOE on 2-methyl-3,5-dinitro-N,N-dimethylbenzamide.[5] Resonance assignments based on steric arguments may lead to erroneous results.[26]

Configuration assignments based on coupling constants have been made for several formamides[6,14,17,27] based on the assumption that the *trans* "allylic" coupling constant is larger than the *cis* one. Resonance assignments in dimethylformamide made on this basis are in agreement with those obtained from contact shifts of Nickel II complexes[12] and from the NOE;[13] we have found, however, that this assumption does not appear to be general.[28] Results obtained from benzyl formamides and benzyl thioformamide show the upfield methylene resonances to be *trans* to the carbonyl oxygen. This signal, however, is definitely broader than the downfield one, indicating a larger coupling constant. *Resonances assignments based on the assumption that trans 1,3 coupling is larger than cis may be unreliable.*[16]

Since the mutual relaxation of geminal protons is efficient it is not likely that a NOE would be observed on methyl groups. Thus, no NOE would be expected for acetamides. To sidestep the problem we have synthesized α,α-dideuteroacetamides which yielded NOEs on the order of 10% signal enhancement. To our knowledge this is the first application of the technique.

In general, our results show that for tertiary amides in aromatic solvents the signals associated with the N-substituent *trans* to the carbonyl oxygen are upfield. No generalization can be made regarding the signal positions in non-aromatic solvents.[30]

References and Footnotes

1. Presented in part at METROCHEM 70, Hoboken, New Jersey, March 24-24, 1970.
2. Taken from the dissertation of M. Frucht to be submitted to the Faculty of the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry (1971).
3. This work was supported in part by PHS Research Grant No. GM16924-01 from the National Institute of General Medical Sciences.
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16. Rogers and Woodbrey[17] assigned resonances in N,N-dimethyl trifluoroacetamide based only on a chemical shift argument. The upfield methyl resonance was assigned as *cis* to the carbonyl oxygen requiring the *cis* coupling with the trifluoromethyl group to be larger than the *trans* coupling.

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19. The opposite assignment has been made.[20]

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21. G. R. Bedford, D. Greatbanks and D. B. Rogers, *ibid.*, 330 (1966).

22. This compound exhibits two sets of non-equivalent methylene hydrogens at low temperature (100 MHz) similarly to the situation reported for *o*-substituted N,N-dibenzylbenzamides.[4,5] The methylene group with the larger non-equivlance is once again located further from the asymmetric site.

23. The assignments for analogous *o*-substituted benzamides by Siddall[25] also appear to be incorrect.

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25. A. H. Lewin, *J. Amer. Chem. Soc.*, **86**, 2303 (1964).

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28. The relative magnitude of *cis* vs. *trans* allylic coupling has been shown to depend on geometry.[29]

29. R.R. Fraser and D.E. McGreer, *Can. J. Chem.*, **39**, 505 (1961); G.P. Newsoroff and S. Sternhell, *Tetrahedron Letters*, 6117, (1968).

30. There are indications that dilution shifts with aromatic solvents are unreliable where strong polar groups are present in the amide. This problem is currently being investigated.