Lanthanide-induced Shifts in ^{1}H Nuclear Magnetic Resonance Spectroscopy: Resonance Assignments in Tertiary Amides

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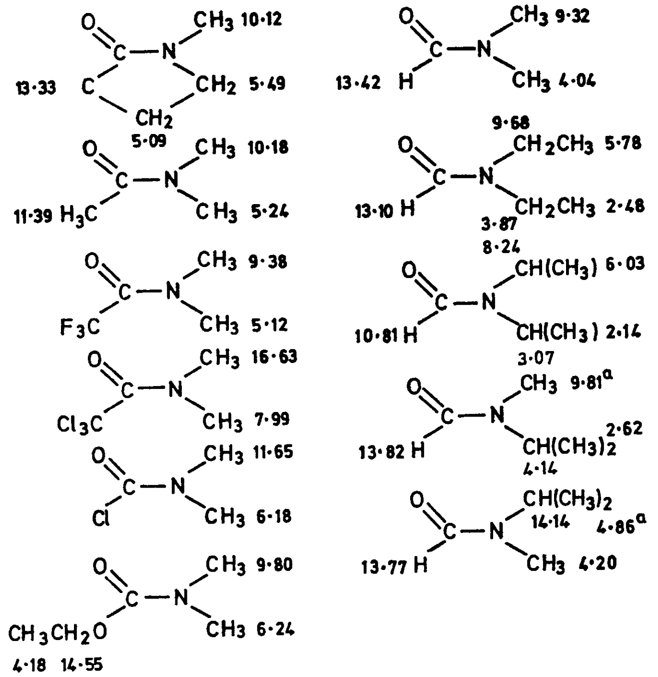
Summary The utility of the chemical shift reagent tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato)europium(III) in assigning resonances for protons of n-alkyl groups in amides has been established.

THE anisotropy of the magnetic susceptibility of the amide group in tertiary amides, RCONR′R″, leads to a chemical shift between the *cis* (to carbonyl oxygen) and *trans* substituents on nitrogen and this shift is normally observable when rotation about the central C–N bond is slow on the n.m.r. time scale. Several criteria have been used to identify the proton resonances for R′ and R″ as *cis* or *trans*. These include (1) inequality of the *cis* and *trans* spin–spin coupling constants[1] with the protons of R, (2) differential solvent shifts in an aromatic solvent,[2,3] (3) the nuclear Overhauser effect,[4,5] and (4) contact shifts induced by complex formation with paramagnetic metal ions.[6] Most of these methods are quite limited in scope of application and the assignments may not be unequivocal,[5] particularly when R, R′ are larger groups. We report here the use of Eu(fod)$_3$, tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato)europium(III), a paramagnetic shift reagent,[7] in assigning the proton resonances in substituted amides.

The use of lanthanide complexes as reagents to induce paramagnetic shifts in the nuclear magnetic resonance spectra of polar organic molecules is now well established.[8] The paramagnetic shift arises from the association of the lanthanide complex with the polar organic substrate and is dominated by dipolar (pseudo-contact) interactions.[8] The magnitude of the paramagnetic shift is largely determined by the distance of the given protons from the lanthanide ion. Amides are known to protonate preferentially on the carbonyl oxygen,[9] since the nitrogen lone pair is extensively delocalized; one would, therefore, expect that the chemical shift reagent would be complexed through the lone pairs of electrons on oxygen and that the induced shifts in *cis* and *trans* *N*-alkyl substituents would differ.

TABLE 1

Shifts, ΔEu, *induced by* Eu(fod)$_3$ *in p.p.m.*



[a] Both isomers of CHON(CH$_3$) (iso-C$_3$H$_7$) are present in the same solution.

Spectra were obtained at 100 MHz using a Varian HA-100 n.m.r. spectrometer with V-4330 variable temperature accessory. Samples were 0·2M-amide in CCl$_4$ with increasing amounts of Eu(fod)$_3$ (Norell Chemical Co., Landing, N.J.), up to a 0·4 mol ratio of shift reagent to amide. The chemical shifts relative to Me$_4$Si were plotted *versus* the mol ratio and a linear correlation found for each group of protons. Extrapolation of these lines to an equimolar ratio of Eu(fod)$_3$ to amide gave values of Δ_{Eu} [$=\delta^{n=1}(\mathrm{CCl_4}) - \delta n^{n=0}(\mathrm{CCl_4})$] for each group of protons (Table 1). Extrapolation of the lines to a mol ratio of zero allows assignments to be made for the resonances in the uncomplexed amide (Table 2).†

To establish the validity of the method, 1-methylpyrrolidin-2-one was chosen as a model system since the *N*-methyl group is fixed in the *cis* position. As expected, the *cis*-methyl protons were shifted to a greater extent than the *trans*-methylene protons in the solutions containing the complexed amide. For the remaining amides the resonances of the *cis–trans* pair shifted the greater amount are assigned to the *cis* group (Tables 1 and 2).

The assignments of Table 2 for the uncomplexed amides confirm those previously made by other methods for *NN*-dimethylformamide,[1,2,4–6] *NN*-dimethylacetamide,[1,2,4–6] *NN*-dimethyltrifluoroacetamide,[10] *NN*-diethylformamide,[6,11] *NN*-di-isopropylformamide,[6] and *N*-methyl-*N*-isopropylformamide.[3] The method is rapid, readily applicable to a wide variety of amides and, to the extent of this investigation, appears to be generally valid. Where a single resonance is observed for the *cis* and *trans* protons this method can be used to determine whether the chemical shifts are accidentally equal or whether the amide is above the coalescence temperature.

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TABLE 2

Proton resonance assignments in some (uncomplexed) tertiary amides in CCl$_4$ *solution.*

Compound	Assignment of upfield resonance of *cis–trans* pair[a]			
	-C*H*$_3$	-C*H*$_2$	-C*H*	*T* °C[b]
NN-Dimethylformamide	*cis*			32
NN-Dimethylacetamide[c]	*cis*			32
NN-Dimethyltrifluoroacetamide[d]	*cis*			32
NN-Dimethyltrichloroacetamide	*cis*			−22
NN-Dimethylcarbamylchloride	*cis*			−22
NN-Diethylformamide	*cis*	*trans*		32
NN-Di-isopropylformamide[e]	*cis*		*trans*	32
	-C*H*$_3$	-C*H*	-CH(C*H*$_3$)$_2$	
N-Methyl-*N*-isopropylformamide[f]	*cis*	*trans*	*cis*	32

[a] The designation *cis* in this table indicates that the upfield resonance of the *cis–trans* pair for the indicated group is *cis* to oxygen in the CCl$_4$ solution containing no shift reagent. [b] The temperature was chosen, in each case, to be well below the coalescence temperature so that the isomers are distinguishable by n.m.r. [c] Use of Pr(fod)$_3$ gave upfield induced shifts but the assignment of the proton resonances was the same. *d* In this amide the spin–spin couplings $J_{\mathrm{H-F}}$ are anomalous in that $J_{\mathrm{H-F}}(cis) > J_{\mathrm{H-F}}(trans)$.[11] *e* This result is less certain than the others since the chemical shift between the methyl protons in the uncomplexed amide (*ca.* (1 Hz) is the same order of magnitude as the error in carrying out the extrapolation. f The major isomer (67%) has the *N*-methyl substituent *cis* to oxygen.[3]

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† The differences between δ (observed) and δ (extrapolated) were never greater than 2%. The assignment of resonances in uncomplexed ethyl-*N*,*N*-dimethylcarbamate could not be made because the small chemical shift (2·0 Hz) between the *cis* and *trans* resonances.

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