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Non-equivalence of the Methylene Protons of I N-Benzyl, N-o-Chlorophenyl, 2-Chloroacetamide and II N-Nitroso, N-Benzyl, o-Chloroaniline

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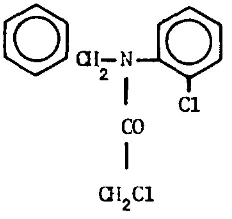
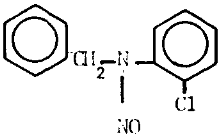
The non-equivalence of the N-methylene protons of amides R CO.N.CH_2R'.Ar (R' = CH_3,C_6H_5, Ar = C_6H_4X,X = ortho substituent) has been reported for a large number of compounds and attributed to (i) restricted rotation about the N-C_6H_4X bond and (ii) the unsymmetrical nature of the C_6H_4X group[1,2]. A further case is reported here of non-equivalence of methylene protons in such an amide (I) and also in a closely related N-nitroso compound (II). In direct relation to this general topic it has been reported that the line width of the ester methyl proton resonance of carbonates of the type Ar SO_2CH_2N RCO.OCH_3 (R = H,CH_3) is temperature dependent[3]. It was concluded that there is a barrier to internal rotation within the ester group itself which arises possibly as a result of a combination of electronic and steric effects and that the β-arylsulphonyl group (β to nitrogen) is an essential factor. A similar phenomenon has been observed in a study of the amide I which contains no β-arylsulphonyl group.



Amide, I.



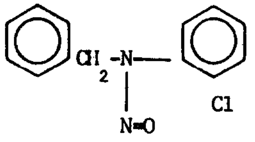
Nitrosamine, II.

Benzyl Methylene Protons of the Amide, I

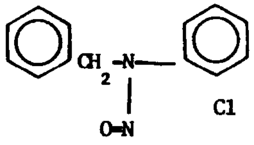
The non-equivalence of the benzyl methylene protons of I was observed in all solvents used, over a wide temperature range (up to the coalescence temperature), as expected[1]. This aspect will not be considered further since it reveals nothing new about the intramolecular dynamics of this type of amide.

Benzyl Methylene Protons of the Nitrosamine, II

The benzyl methylene resonance of the N-nitroso compound II however provides a hitherto unreported example of a very similar phenomenon enhanced by the observation of two structural isomers (IIA and IIB) with rather different properties.



IIA (cis)



IIB (trans)

The trans isomer is believed to be the predominant component in the mixture of the two isomers over a temperature range -60° to +40°C. The proton resonance spectrum of the neat liquid showed a sharp line at 5.17 ppm from TMS assigned to the trans isomer (63%). A much broader line (at 36°C) at 5.68 ppm from TMS has been assigned to the cis isomer. This broad resonance line first began to split at about 20°C and at lower temperatures (in acetone solution) a well resolved AB quartet ($|J| = 14.76$ cps) was observed while the trans isomer still gave the sharp single line. The temperature dependence of the AB chemical shift is given in table 1.

TABLE 1

AB Chemical Shift Temperature Dependence for the Cis Isomer, IIA

Temperature °C	30	20	10	0	-10	-20	-30	-40	-50	-60
Chemical Shift*	†	25.3	26.2	27.1	27.0	26.5	26.1	25.3	24.7	23.8

† Very broad lines. * $\nu_0\delta \pm 0.2$ cps.

A maximum was observed at about 0°. This behaviour is rather difficult to understand since at lower temperatures one would expect the time-averaged environments of the methylene protons to be most dissimilar. A possible explanation lies in solvent-solute association which fortuitously reduces the differences in the chemical environments. This association process may be related to the similar phenomenon discussed below.

The different behaviour of the cis and trans isomers is explicable in terms of steric effects which result in 'critical' restricted rotation about the N-O-chlorophenyl bond in the cis isomer but not in the trans isomer in the temperature range studied. There is evidence from molecular models that rotation about the relevant carbon-nitrogen bond is not completely free (disregarding mesomeric effects which appear not to be important) and that similar splitting might be observed for the trans isomer at even lower temperatures.

Chloroacetyl Methylene Protons of the Amide, I

The chloroacetyl methylene resonance of the amide, I has been observed to be solvent and temperature dependent. The proton resonance spectrum of the amide, I, in carbontetrachloride, chloroform and carbon bisulphide includes a very sharp line, attributable to the chloroacetyl methylene protons, which showed little or no temperature dependence. However in a number of other solvents the chloroacetyl methylene resonance was temperature dependent and a clear AB pattern of lines with varying $\nu_o\delta/J$ has been observed (for example see figure I). Table 2 includes the chemical shifts and coupling constants derived from the AB spectra for some solvents which induce the non-equivalence of the chloroacetyl methylene protons and others, which do not, are listed for comparison.

TABLE 2

Solvent Dependence of Chemical Shift and Coupling Constant for the Chloroacetyl Methylene AB of the Amide I, at 36°C

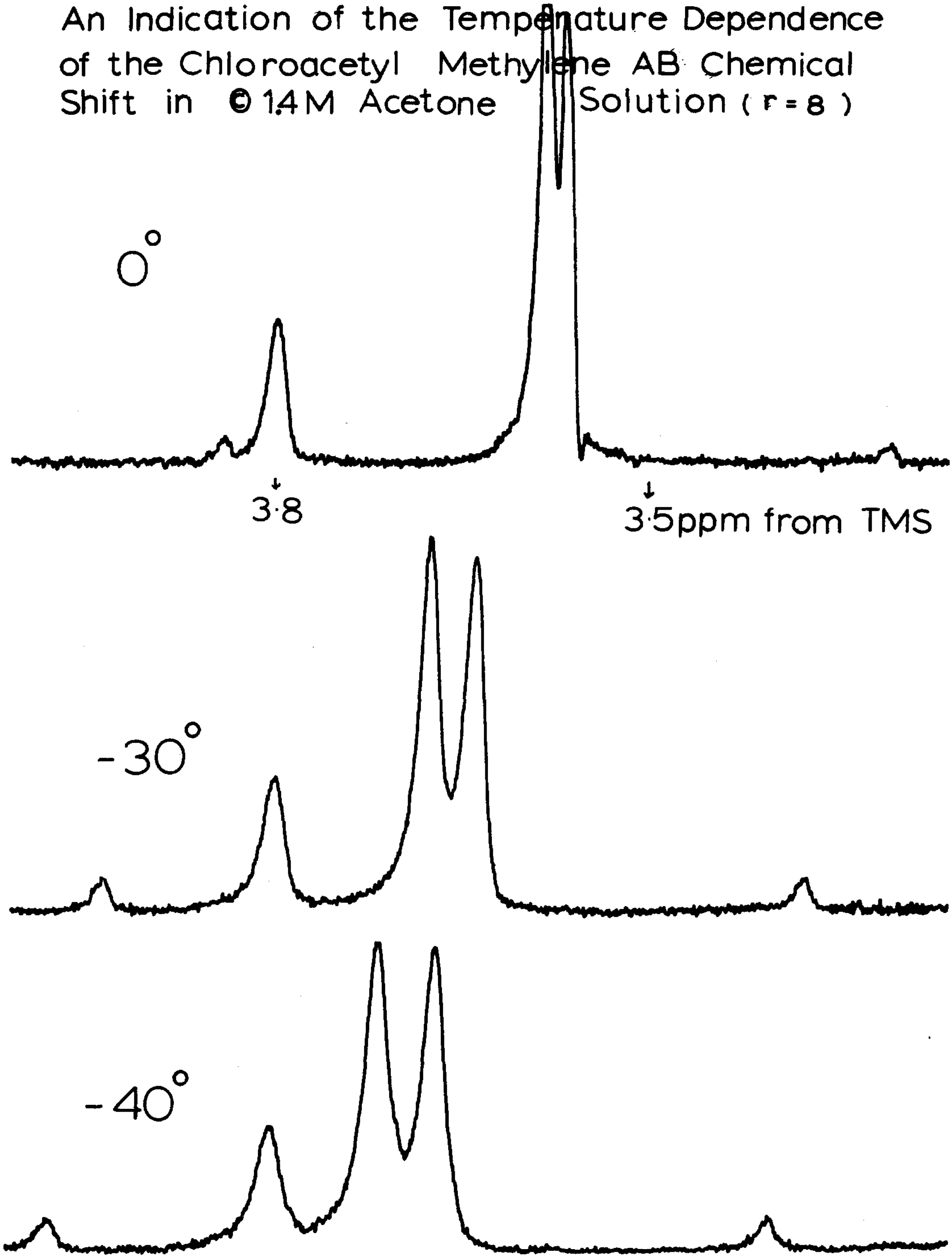
SOLVENT	CONCENTRATION†	$\nu_o\delta$*	J *
N,N, DIMETHYLFORMAMIDE	8.0	6.8	13.6
N,N, DIMETHYLACETAMIDE	6.0	8.4	13.7
METHYLACETATE	10	0	-
ACETONE	8.0	0	-
DIMETHYLSULPHOXIDE	8.0	8.9	13.5
SULPHALANE	6.0	0	-
BENZENE	6.7	4.4	13.2
TOLUENE	5.8	5.5	13.1
NITROBENZENE	5.0	0	-
m-NITROTOLUENE	4.6	0	-
PYRIDINE	6.7	0	-

† Concentration expressed as r = Mols. solvent/Mols. amide I.

* Units cps ± 0.2 (averaged over five spectra).

FIG 1

An Indication of the Temperature Dependence of the Chloroacetyl Methylene AB Chemical Shift in © 1.4M Acetone Solution (r = 8)



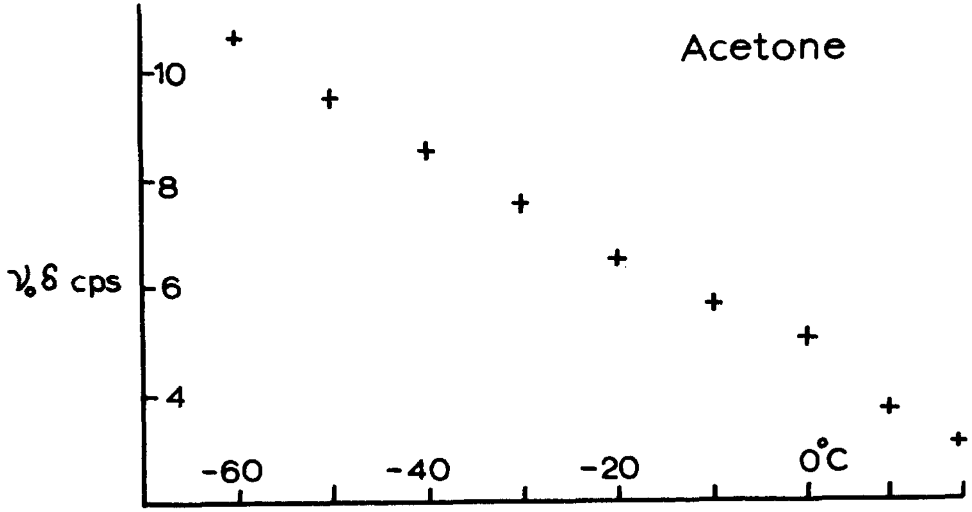


FIG 2

AB Chemical Shift/Temperature, r=8 for -CO-C$\underline{H_2}$Cl of the Amide, I

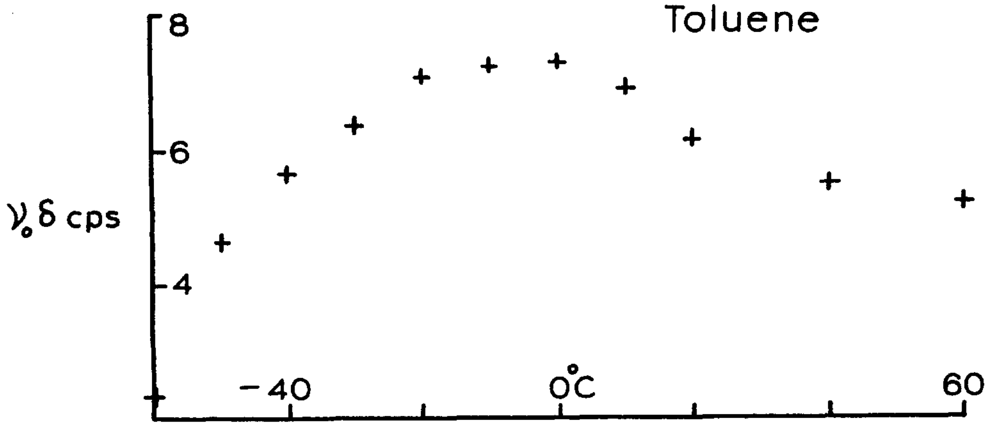


FIG 3

AB Chemical Shift/Temperature, r=5.8

Both the chemical shift $\nu_0\delta$ and the coupling constant J are solvent and temperature dependent. No clear correlation exists between the type of solvent or the dielectric of the solvent and the observed chemical shifts or coupling constants.

In acetone solution the coupling constant varied from 13.6 ± 0.2 cps at 10^o to 14.2 ± 0.2 cps at -60^oC, a small but significant change in magnitude. The chemical shift was more sensitive to temperature change in acetone solution and the results are illustrated in figure 2. Similar behaviour is expected of dimethyl sulphoxide but the temperature range is restricted to 5^o - 100^oC within which it is possible to observe collapse of the AB multiplet into a single line. The variation of the chemical shift with temperature in r = 5.8 toluene solution is shown in figure 3. It is interesting to note the maximum observed at about 0^o. Figure 4 summarises the concentration dependence of the AB chemical shift in toluene solution.

The physical constants of some of the solvents studied restricted the feasible temperature range so that even though no induced chemical shift was observed at the normal probe temperature it is conceivable that the effect responsible would be detected if low temperature studies were possible.

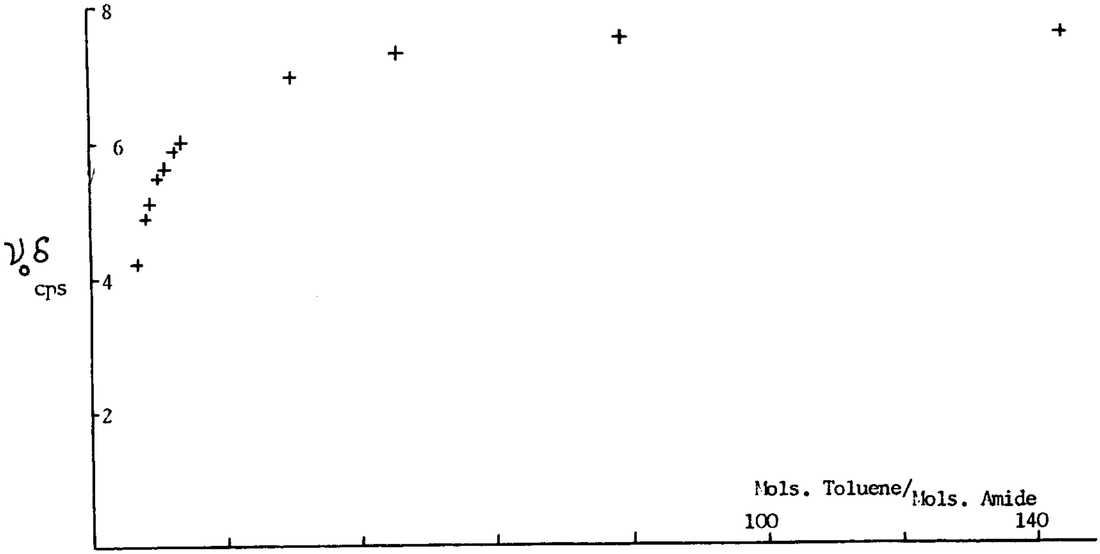


FIG 4 AB Chemical Shift/Concentration in Toluene 36^oC

The inference drawn from these results is that the non-equivalence of the chloroacetyl methylene protons is induced in specific cases by the association of solute and solvent molecules. The N.M.R. time-scale (relaxation times - 1 sec in mobile liquids) implies that such a molecular association can be thought of as a complex in which rotation about the amide I $CO-CH_2Cl$ bond is restricted. Cis-trans isomerism, theoretically possible in the amide I, was not observed in the temperature range studied and can play no part in producing the observed AB multiplets. A molecular model suggests that the isomer in which the benzyl group and the carbonyl oxygen are cis relative to the amide carbon-nitrogen bond is the more stable.

The results obtained for the aliphatic solvents, acetone in particular, are consistent with the formation of a complex involving solvation on one side of the planar amide group, within the temperature range studied. Such a complex would be more stable at lower temperatures and the time-averaged environments of the chloroacetyl methylene protons are then most dissimilar because one proton spends more time near to the associated solvent molecule. The data obtained for toluene however suggest a second step in the solvent-solute association process which occurs at low temperatures. The chemical shift in toluene solution reaches a maximum at about 0^o and falls off with both increasing and decreasing temperature (figure 3).

This is compatible with the association of a second toluene molecule on the side of the amide remote from the first solvent molecule, forming a "sandwich" complex. Therefore at the lower temperatures rotation about the $CO-CH_2Cl$ bond is restricted but the symmetrical environment of the methylene protons leads to a small, if observable, chemical shift. Raising the temperature results in dissociation of one toluene molecule preferentially leaving the relevant methylene protons in an unsymmetrical environment where the chemical shift is a maximum. In the higher temperature ranges complete dissociation occurs and the methylene proton environments are averaged by relatively free rotation about the $CO-CH_2Cl$ bond.

Preliminary studies of a second amide - N-benzyl, N-methyl, 2-chloroacetamide indicate that the chloroacetyl methylene protons are chemically equivalent in dimethyl sulphoxide, toluene and N,N-dimethylacetamide at 36^oC. The two possible isomers have been observed. These results infer that extended delocalisation involving the amide group and the N-phenyl group might be a significant factor facilitating complex formation.

All spectra were obtained using a Varian A60A instrument with a V6040 variable temperature accesory. The amide I (m.pt. 73^oC) was prepared by reacting chloroacetyl chloride with

N-benzyl, O-chloroaniline and was recovered unchanged from the solvents used. The nitrosamine, II, was prepared by the reaction of nitrous acid and the N-benzyl, O-chloroaniline.

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