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CIS-TRANS ISOMERISM IN FORMANILIDE

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Abstract—The proton resonance spectra of formanilide and formanilide-N^{15} show that two isomers exist in deuterochloroform solution. At 35° and for overall molar concentrations greater than 4% the predominant form has NH proton *cis* to the formyl proton. The NH resonances have large concentration dependencies due to hydrogen bonding, which have been used to confirm that the signs of the observed N^{15}—H coupling constants are the same. The relative thermodynamic stabilities of *cis*- and *trans*-formanilide are affected by hydrogen bonding. The shifts of the formyl protons are largely concentration independent. Shifts to lower field than in other formamides occur when a phenyl group is *cis* to the formyl proton.

INTRODUCTION

The presence of restricted rotation about the central C—N bond in amides has been extensively studied by NMR techniques.[2–5] In cases where the two substituents on the nitrogen atom are different, *cis-trans* isomerism is possible. The *cis-trans* ratios for N-monosubstituted amides[6] and for unsymmetrically N,N-disubstituted amides[7] have recently been determined for alkyl substituents.

We report two cases, *cis*- and *trans*-formanilide, where one of the nitrogen substituents is phenyl. The assignments are bases on a previous NMR double resonance study of N-methylformamides[8] which give all the proton proton couplings, and on infrared and Raman investigations[9–15] which give the configuration of the predominant species. These assignments are confirmed by measurements of J(N^{15}—H) coupling constants in both N-phenylformamide-N^{15} (formanilide-N^{15}) and N-methylformamide-N^{15}.[16]

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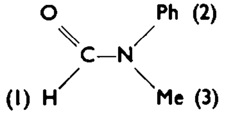
The positions in the amides are numbered as follows



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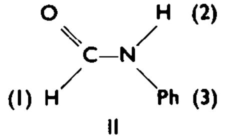

II

as before.[8] The notation for coupling constants is such that the coupling between the formyl proton and the methyl protons in the above configuration, I, of N-methylformanilide is denoted J_{13}(H—Me). All J_{13}'s are *cis* couplings and all J_{12}'s are *trans*.

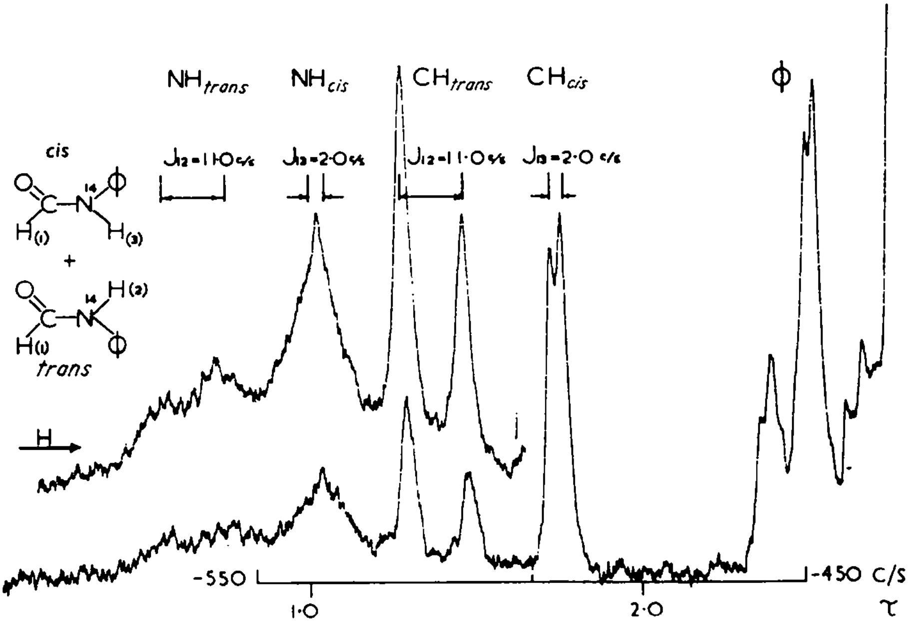

FIG. 1a. PMR spectrum of a 25% molar solution of formanilide in chloroform at 60 Mc/s and 35°.

In cases where one proton is bound directly to the nitrogen and the other directly to the carbonyl, the brackets are omitted, e.g., the *trans* coupling in (II) is denoted J_{12}. The above configuration, (II), for formanilide is referred to as *trans*. Other authors use a different convention.[6]

All molar concentrations refer to the total amount of amide.

RESULTS AND ASSIGNMENTS

The spectrum of a 25% molar solution of formanilide in chloroform is shown in Fig. 1a together with the assignment[17] in terms of *cis* and *trans* isomers. The band of resonances at high field is attributed to the phenyl group, and the remaining peaks to the CH and NH protons. The broader peaks at lowest field are assigned to the NH protons and the sharper peaks at slightly higher field to the CH protons,

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[17] J. D. Baldeschwieler, C. B. Krabek and E. W. Randall, unpublished results.

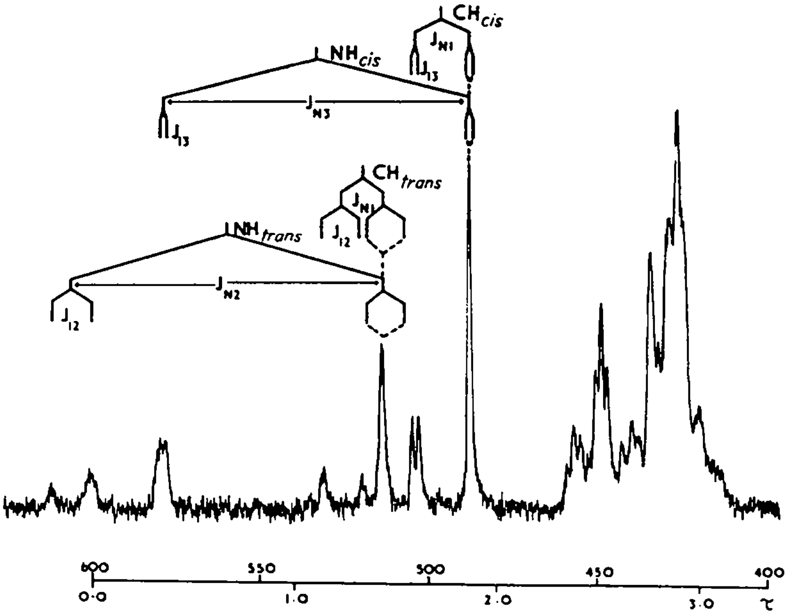

FIG. 1b. PMR spectrum of a 23·3% molar solution of formanilide-N^{15} in deuterochloroform at 60 Mc/s and 35°, with first order assignment.

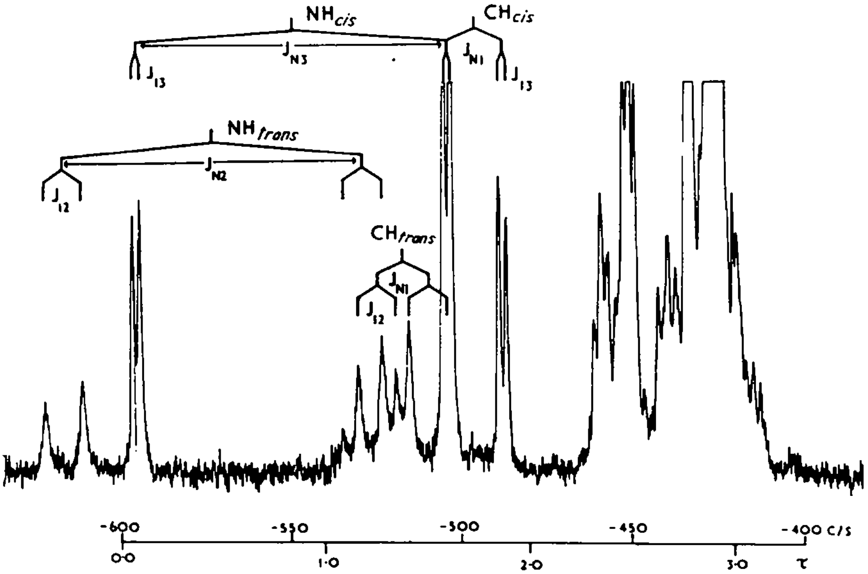

FIG. 1c. PMR spectrum of a 38·6% molar solution of formanilide-N^{15} in deuterochloroform at 60 Mc/s and 35°, with first order assignment.

since this was the line-width behaviour found in formamide[18] and in N-methylformamide.[8] The broadening is due to the electric quadruple effects of the N^{14} nucleus.

The presence of both *cis* and *trans* forms is indicated by the number of peaks in the spectrum. The method of differentiating between the peaks of the *cis* and *trans* forms depends upon the difference in the vicinal coupling constants J_{13} and J_{12}. The *trans* coupling, J_{12}, is larger[8] than the *cis*, J_{13}, and in formamide-N^{15} the values

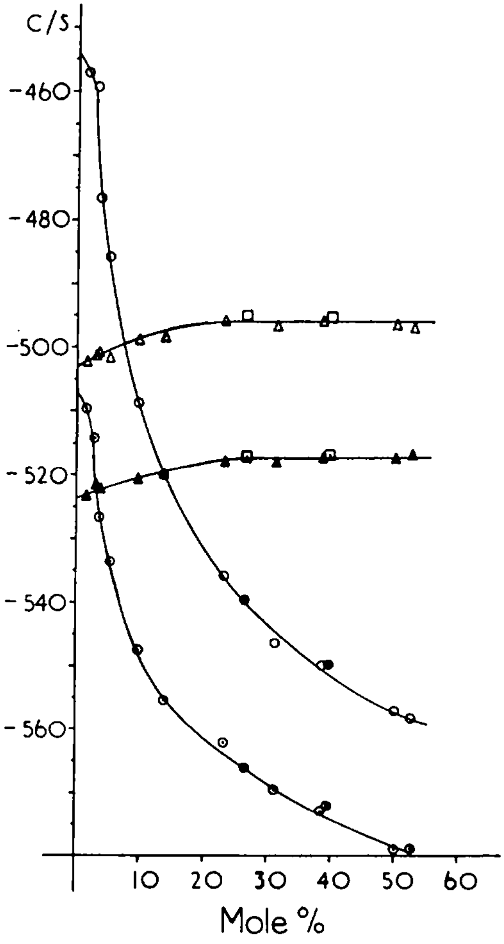

FIG. 2. Effect of concentration on the proton chemical shifts of formanilide in deuterochloroform (c/s at 60 Mc/s relative to tetramethylsilane).

Key: △ N^{15} molecule CH_{cis}
□ N^{14} molecule CH_{cis}
◬ N^{15} molecule CH_{trans}
⊡ N^{14} molecule CH_{trans}
○ N^{15} molecule NH_{cis}
⊖ N^{14} molecule NH_{cis}
○ N^{15} molecule NH_{trans}
⊗ N^{14} molecule NH_{trans}

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[18] L. H. Piette, J. D. Ray and R. A. Ogg, *J. Mol. Spectroscopy* **2**, 66 (1958).

are 12·9 c/s and 2·1 c/s respectively.[19,16] The corresponding couplings shown in Fig. 1a are 11·2 c/s and 2·1 c/s. In the *cis* form the coupling J_{13} on the NH proton is presumed to be unresolved. The NH and CH protons in the *trans* molecule form an AB set and thus the peak intensities are unequal.

The NH shifts are particularly concentration dependent in chloroform solution whereas the CH shifts are only slightly affected, Fig. 2. These changes are confirmed in the N^{15}-substituted molecules which are more suitable for detailed study because of their smaller line-widths.

TABLE 1. N^{15}—H COUPLING CONSTANTS (c/s)

	J_{N1}	J_{N2}	J_{N3}
cis N-Methylformamide-N^{15}	15·6^{a}	—	92·6^{a}
cis N-Phenylformamide-N^{15}	16.3^{b}	—	91·2^{b}
trans N-Phenylformamide-N^{15}	15·0^{b}	88·0^{b}	—
Formamide-N^{15}	19·0^{c}	88·0^{c}	92·0^{c}

^{a} pure liquid[16] ^{b} 38·6% molar in deuterochloroform
^{c} pure liquid[19]

Spectra obtained from N-phenylformamide-N^{15} in deuterochloroform solution are shown in Figs 1b and 1c. The chemical shift parameters and the proton-proton couplings are the same to within the experimental error for the N^{14} and N^{15} substituted molecules at the same concentrations. The $N^{15}H$ protons, however, give narrow lines since the electric quadrupole effect of the N^{14} nucleus are absent. In addition doublet splittings due to couplings JN^{15}—H are observed. These couplings, when compared with similar couplings in N-methylformamide-N^{15}[16] for which the configuration is known to be *cis* (in our convention), and in formamide-N^{15} [16,19], support the assignments made above. The comparisons are shown in Table 1. The couplings are slightly concentration dependent but the changes are too small to affect the conclusions made here.

TABLE 2. PERCENTAGE OF FORMANILIDE EXISTING AS *cis*-FORM *vs.* CONCENTRATION IN DEUTEROCHLOROFORM AT 35°

Mole % amide	1·5	2·9	3·6	5·1	9·7	23·3	31·3	38·6	50·0	52·5
% *cis*	45	48	49	50	58	62	64	66	70	73

The relative amounts of the *cis* and *trans* forms, as determined by integration of the downfield NH-features of each form, change with concentration as shown in Table 2. The error in the integration is ±3%. At 35° and for molar concentrations greater than 4%, the *cis*-form predominates. The ratio did not change with time after the initial spectrum was taken, i.e., approximately 5 minutes following dissolution of the amide in the solvent. Equilibrium was therefore established during this period.

The different solvent dependences of the NH and CH shifts have enabled us to determine the relative signs of J_{N1}, J_{N2}, and J_{N3}. When the overall amide concentration is 23·3% molar the up-field halves of the NH and CH multiplets overlap in

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[19] B. Sunners, L. H. Piette and W. G. Schneider, *Canad. J. Chem.* **38**, 681 (1960).

both the *cis* and *trans* forms and give single lines (2nd order spectrum), with the couplings J_{12} and J_{13} respectively not evident (Fig. 1b). Conversely, when the upfield half of the NH multiplet overlaps the downfield half of the CH multiplet, again fortuitously in *both cis* and *trans* cases at one concentration, such "decoupling" effects do not result, and the couplings J_{12} and J_{13} can still be discerned (Fig. 1c). Other spectra in which the peaks do not overlap so exactly confirm these contentions. These facts are compatible only with J_{N1} and J_{N2} having the same sign in the *trans* molecule, and J_{N1} and J_{N3} having the same sign in the *cis* molecule. We assume that the sign of J_{N1} does not change from *cis* to *trans* and consequently that J_{N1}, J_{N2}, and J_{N3} all have the same sign.

At other selected concentrations more complicated second-order spectra are produced. We have been fortunate in this investigation in being able to control the shifts because of their concentration dependence, and to pick out the simple second-order spectra shown in Figs 1b and 1c.

These experiments have certain superficial similarities with proton-proton decoupling experiments in which an audio-sideband of the NH signals is swept, using either "field-sweep" or "frequency-sweep", through the CH region to produce decoupling, the precise nature of which gives the relative signs of various coupling constants.[20] Our experiment might be termed, in the same vein, "dilution swept."

The spectrum of a 12·1% molar solution of N,N-diphenylformamide in chloroform contains, apart from the peaks due to the phenyl group, a peak due to the formyl proton at −516·6 c/s. This peak has a line-width of less than 1·5 c/s and shows no evidence of spin-spin splitting.

DISCUSSION

Coupling constants

We have presumed above that a given coupling constant does not vary markedly from one molecule to the next. This assumption has proved satisfactory, except apparently in the case of *trans* N-t-butylformamide for which the expected coupling J_{12} of approximately 12 c/s was not observed.[6]

The signs of the couplings J_{N1}, J_{N2} and J_{N3} are all the same, a result which supports proton-proton double resonance studies[16] on N-methylformamide-N^{15} and formamide-N^{15}. A detailed discussion of the signs and magnitudes of the couplings in all these amides will be given elsewhere.[16]

Chemical shifts

The shifts of the formyl-protons, δ_1, in both *cis* and *trans* formanilide are concentration independent in the range 25–50% molar (Fig. 2). The *trans* CH is to lower field than the *cis* due possibly to the closer proximity of the *trans* formyl proton to the phenyl ring, producing a larger ring-current shift to lower field than in the *cis* case.

This supposition is consistent with the observed formyl proton shift in N,N-diphenylformamide. In this molecule the formyl proton is expected to be shifted to low field by both phenyl groups. However, the contribution is expected to be low (~2 c/s) for the phenyl group *cis* to the carbonyl group. Hence the shift to

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[20] J. D. Baldeschwieler and E. W. Randall, *Chem. Rev.* **63**, 81 (1963).

low field should be near to that observed in *trans* formanilide. This is confirmed experimentally.

The above arguments are also consistent with the shifts reported in Table 3 for other N-monosubstituted formamides.

TABLE 3. SHIFTS (c/s) OF FORMYLPROTONS AT 60 Mc/s RELATIVE TO TETRAMETHYLSILANE IN N-MONOSUBSTITUTED FORMAMIDES

Substituent	H[16]	Me[6]	Et[6]	iso-Pr[6]	t-Bu[6]	Ph
cis	−490	−485	−482	−480	−489	−496
trans	−490	—	—	—	−475	−518

In the case of N,N-disubstituted formamides which have alkyl substituents, δ_1 is approximately −480 c/s.[7] Thus in the cases where the substituents on nitrogen are phenyl (*cis* to the carbonyl), *hydrogen* (*cis* or *trans*) or alkyl (*cis* or *trans*) δ_1 occurs in the range −480 c/s to −496 c/s. Lower shifts at -517 ± 1 c/s have been observed only in cases where a phenyl group is *trans* to the carbonyl, viz., *trans*-formanilide, and N,N-diphenylformamide. This may prove to be a convenient diagnostic test in the study of the configurations of N-alkylformanilides, e.g., N-methylformanilide. Work on these molecules using this and other approaches such as the use of dilution shifts in benzene[7] are in hand.

The pronounced solvent dependence of the NH shifts is compatible with solute-solute hydrogen bonding effects which are reduced on dilution for both the *cis* and *trans* forms.

Dilution breaks up the associated species and produces shifts to higher field. These dilution shifts are larger for the *cis* than for the *trans* molecules, hence dissociation of the former on dilution occurs to a greater extent than in the latter. The explanation may be the unique possibility of stable cyclic dismerization of the *trans*-molecule as in acetic acid.

Further studies on formanilide-N^{15} employing other solvents, and dilution studies on deuterochloroform solutions of formamide-N^{15} and N-methylformamide-N^{15} are being undertaken.

The NH resonances occur at lower field in formanilides relative to the CH than in N-methylformamide-N^{15} (pure)[16] and formamide-N^{15} (pure).[19] These differences could arise from different hydrogen bonding effects in these molecules, or from substituent effects, or both.

Rate of cis-trans *conversion*

The observation of separate spectra for the *cis* and *trans* forms enables a lower limit of about 10^{-2} sec to be placed on the lifetimes of these species, i.e., the rate of the *cis-trans* isomerization is too slow for averaging of the shifts to occur. However, it is fast enough to allow the attainment of a new equilibrium during the five minutes between dilution and measurement.

cis-trans *Ratio*

In the case of N,N- disubstituted formamides the effects of solute-solute hydrogen bonding upon the *cis-trans* ratio may presumably be neglected. Previous results (formamides have the bulkier group *trans* to carbonyl[7,21] whereas other amides have the bulkier group *cis* to carbonyl in the preferred orientation) have been examined on the basis of steric interaction between substituent groups.[7] La Planche and Rogers point out that if the order of size of groups is: higher alkyl $>$ CH_3 $>$ O $>$ H the results are easily understood on the above basis. This is true only if one makes some additional assumptions, e.g., that the only interaction which need be considered in any one molecule is between the two largest groups.

Additional factors must be introduced in the case of N-monosubstituted formamides[6] and hydrogen bonding effects, shown to be present in formanilides by the chemical shift data, may be considered. If such effects are important in determining the relative thermodynamic stabilities of the *cis* and *trans* forms, then, since the hydrogen bonding effects vary with dilution, the *cis-trans* ratio should also be concentration dependent. Experiment shows this to be so.

It is only at high dilutions that the *trans* form predominates. This may be explained in at least two ways: (i) the solvated *trans* form is thermodynamically more stable than the solvated *cis* form, or (ii) the *trans* form even at the high dilutions is stabilized by hydrogen bonding and exists as ring dimers whereas the *cis* form at the same concentration is hydrogen bonded to a lesser extent.

EXPERIMENTAL

All spectra were taken on a Varian A-60 Spectrometer (probe temp 35° ± 1°). Calibration was by the audio sidehand technique[22] using a Solartron audio-oscillator (type CO 546) and a Venner transistorized counter (type TSA 3336).

Chemical shifts are accurate to better than 0·5 c/s except for the shifts of broad resonances due to N^{14}-H protons where the precision is less. Shifts are in c/s downfield from tetramethylsilane as internal standard.

N-phenyl formamide-N^{15} was supplied by Mercke, Sharp and Dohme of Canada Ltd., with a percentage enrichment of 95%. N-phenyl formamide and N-phenyl formanilide were supplied by British Drug Houses Ltd.; each of these amides was used without further purification.

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[22] J. T. Arnold and M. E. Packard, *J. Chem. Phys.* **19**, 1608 (1951).