THE INFLUENCE OF THE MEDIUM UPON THE *cis-trans* EQUILIBRIUM IN N-METHYLFORMAMIDE*

F.ALLMER, J.KŘÍŽ and D.DOSKOČILOVÁ

Institute of Macromolecular Chemistry,
Czechoslovak Academy of Sciences, 162 06 Prague 6

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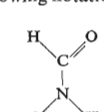
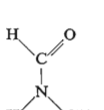
The *cis–trans* equilibrium in N-methylformamide is found to be influenced chiefly by the H-bond and π-overlap interactions with the solvent.

The *cis–trans* isomeric equilibrium of amide and peptide groups has been studied by various spectroscopic techniques in a number of substances[1,2]. The equilibrium was found to be most strongly affected by various substituents through their steric effects, but more subtle interactions, *e.g.* the effects of the surrounding medium, have not been systematically studied so far. We have attempted to obtain quantitative data on the medium effects upon the *cis–trans* isomeric equilibrium of N-methylformamide. This molecule is not a very good model of a polypeptide unit, but it has the advantage that the behaviour of the amide bond is not complicated by steric effects of substituents.

In accord with the convention currently applied for more highly substituted amides and peptides, the following notation will be used:



cis



trans

even though it is not quite logical for N-methylformamide.

EXPERIMENTAL

N-Methylformamide and the solvents, all of them of commercial origin, were purified by double rectification on a column with 30 e.p. and dried on a molecular sieve. Their purity was controlled by gas chromatography and infrared spectra, and was better than 99·9%.

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NMR spectra of solutions of N-methylformamide were recorded on the 100 MHz PS-100 (JEOL) spectrometer. The relative amounts of both forms were determined by planimeter evaluation of the areas of the corresponding methyl group signals. Experimental conditions were selected so as to exclude saturation or other relaxation phenomena, and this was also verified by computation.

RESULTS AND DISCUSSION

The isomeric equilibrium was followed: (*a*) in media exerting only dipolar and non-specific Van der Waals interactions, like CH_2Cl_2, $CDCl_3$, CCl_4; (*b*) in media exerting also specific π-interactions, like benzene, chlorobenzene and bromobenzene; (*c*) in media which are active acceptors of hydrogen bonds and thus able to disrupt hydrogen bonds between N-methylformamide (*I*) molecules, like pyridine, dimethyl sulphoxide, benzaldehyde, nitrobenzene and nitromethane. Of the last group, only in the case of pyridine the chemical shift between the signals of the *cis*- and *trans*-forms was sufficient for a quantitative study of the equilibrium; of group (*a*), the experimentally accessible temperature and concentration range of CCl_4 was too small for quantitative evaluation.

The dependence of the relative amounts of the *cis* and *trans* forms on the concentration of *I* at different temperatures is shown in Figs 1–6. The measured temperature interval was limited from above by the coalescence of signals in consequence of rapid conformer transitions, from below by the limited solubility of *I* or by the melting point of the solvent.

From Figs 1–6 it can be seen that the contents of the *cis* form decreases with increasing concentration of *I* in all cases, with the exception of the solution in pyridine at very low temperatures. This trend is evident already at relatively low concentrations where the dissolved *I* does not appreciably affect the polarity of the medium. In analogy to Mizushima's conclusions drawn from the study of the concentration dependence of N-methylacetamide[3], and with respect to the results of Lumley–Jones' infrared studies of dilute solutions of N-methylformamide[4], the observed trend seems to indicate that at higher concentrations the *trans* form is favoured by the formation of H-bonded multimers, whereas at low concentrations the *cis* form is favoured by the formation of cyclic dimers. In the case of the pyridine solution, especially at low temperatures, H-bonding of *I* to the solvent has to be considered as an additional mechanism determining the shape of the concentration dependence.

For the evaluation of the medium effects upon the *cis–trans* equilibrium it is useful to exclude the effects of autoassociation of N-methylformamide molecules, taking place at higher concentrations. Formally this can be achieved by extrapolation of our concentration dependence to a zero concentration of *I*. The temperature dependence of these extrapolated values for various media is summarized in Fig. 7. At higher temperatures, the plot of log *K* against T^{-1} is in all cases linear, but at temperatures below 10°C, it exhibits an anomalous shape.

The limiting values in Fig. 7 were obtained by extrapolation from experimental points lying in the range 0·15–3·0 mol/l. From infrared evidence[4], in tetrachloromethane a large portion of the molecules is bound in H-bonded associates even at a concentration of 0·05 mol/l. The influence of cyclic dimers becomes important at further dilution, when the amounts of *cis* and *trans* forms in hydrogen bonded molecules get comparable; at still lower concentrations free, non-bonded molecules become important.

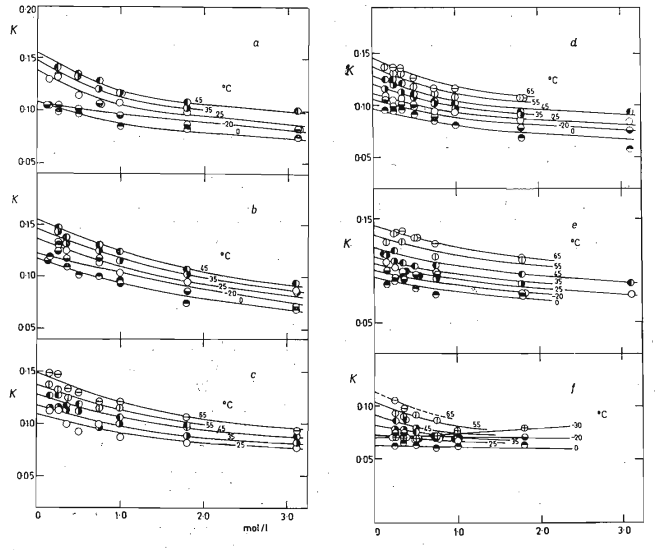


FIG. 1

Concentration Dependence of the Relative Amounts of *cis*- and *trans*-N-Methylformamide in Various Media

Medium: *a*) methylene chloride, *b*) deuteriochloroform, *c*) benzene, *d*) chlorobenzene, *e*) bromobenzene, *f*) pyridine.

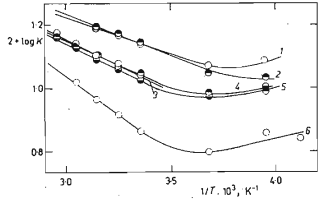


FIG. 2

Temperature Dependence of the Logarithm of the Relative Amounts of *cis*, and *trans*-N-Methylformamide

Medium: *1* $CDCl_3$, *2* CH_2Cl_2 *3* C_6H_6, *4* C_6H_5Cl, *5* C_6H_5Br, *6* C_5H_5N.

$$P_{nco} \overset{K_{2co}^{(n-1)}}{\rightleftharpoons} D_{co} \overset{K_{2co}}{\underset{K_{2cc}}{\rightleftharpoons}} M_c \overset{K_1}{\rightleftharpoons} M_t \overset{K_{2to}}{\rightleftharpoons} D_{to} \overset{K_{2to}^{(n-1)}}{\rightleftharpoons} P_{nto} \qquad (A)$$

$$D_{cc}$$

For a quantitative discussion of the studied systems, let us consider the simplified equilibrium (*A*) for which the apparent equilibrium constant from NMR spectra has the value

$$K_{app} = \frac{cis}{trans} = \frac{[M_c] + 2[D_{co}] + 2[D_{cc}] + n[P_{nco}]}{[M_t] + 2[D_{to}] + n[P_{nto}]} =$$

$$= \frac{K_1[1 + 2(K_{2co} + K_{2cc})[M_c] + nK_{2co}^{(n-1)}[M_c]^{(n-1)}]}{1 + 2K_{2to}[M_t] + nK_{2to}^{(n-1)}[M_t]^{(n-1)}}, \qquad (1)$$

with a zero-concentration limit

$$\lim K_{app} = K_1 . \qquad (2)$$

The symbols M, D and P designate the monomer, dimer and polymer, the subscripts c, t designate *cis* and *trans*, and the subscripts o, r in dimers and multimers designate the open and ring forms.

If the relative amount of monomeric molecules can be neglected in the measured concentration range, the functional shape of K_{app} cannot be differentiated from K'_{app} given by the expression

$$K'_{app} = \frac{K_1^2[2(K_{2co} + K_{2cc}) + nK_{2co}^{(n-1)}[M_c]^{(n-2)}]}{2K_{2to} + nK_{2to}^{(n-1)}[M_t]^{(n-2)}} . \qquad (3)$$

Extrapolation of K'_{app} to zero concentration then gives

$$\lim K'_{app} = K_1^2(K_{2co} + K_{2cc})/K_{2to} . \qquad (4)$$

For $K_{2cc} \gg K_{2co}$, $\ln K'_{app}$ (contrary to $\ln K_{app}$) will increase with increasing $1/T$, if

$$2\,\Delta H_1 + \Delta H_{2cc} - \Delta H_{2to} < 0 . \qquad (5)$$

The indexes of various enthalpy symbols are the same as for the corresponding equilibrium constants in equilibrium (*A*). If we assume that the difference of the two

last members in Eq. (5) is approximately equal to the energy of one hydrogen bond (about 5 kcal/mol) and that ΔH_1 probably is not higher than 2 kcal/mol, then condition (5) can be fulfilled. The nonlinear part of the plot in Fig. 7 can therefore be interpreted so that at low temperatures, the influence of the energetically more favoured cyclic dimers dominates over the effect of monomers upon the apparent equilibrium, so that the extrapolated values behave as K'_{app}, whereas at temperatures above 10°C they behave as K_{app}. The general character of the $\ln K_{exp}$ *vs* T^{-1} plots remains very similar even at higher concentrations, indicating that the cyclic dimers are favoured even with respect to linear multimers.

The linear parts of the temperature dependences of K_{exp} for various media form three distinct groups. From the formal values of ΔH and ΔS obtained from the linear parts of the plots and summarized in Table I it can be seen that the influence of isotropic, especially dipolar interactions upon the equilibrium is very small. The difference between the halogenated solvents and the aromatics indicates that specific π-interactions are more important; this is also evident from the different shielding of the *cis*- and *trans*-methyl protons in these solvents[6]. The total free energy (and also free enthalpy) change can be expressed as a linear sum of the increments of various types of interactions,

$$\Delta F_1 = \Delta F_0 + \Delta F_{dip.} + \Delta F_{disp.} + \Delta F_{sp.} + \Delta F_H , \qquad (6)$$

with the individual members corresponding to the isolated molecule, dipolar interation, non-specific isotropic dispersion interaction, anisotropic specific π-interaction and the hydrogen bond, respectively (cavitation energy probably can be neglected).

TABLE I

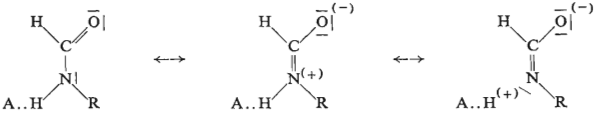
Formal Values of Enthalpy and Entropy Differences between the *trans* and *cis* Isomers of N-Methylformamide in Various Media[a]

Medium	Dipole moment[b]	ΔH kcal/mol	ΔS cal/mol grad
CH_2Cl_2	1·85	1·2	0·2
$CDCl_3$	1·15	1·1	−0·4
C_6H_6	0	1·5	0·5
C_6H_5Cl	1·50	1·4	0·2
C_6H_5Br	1·50	1·5	0·6
C_5H_5N	2·36	2·3	2·5?

[a] Values obtained from the linear portion of the plot in Fig. 2. [b] Values of McClellan[5].

From Table I, the formal average value ΔH_{sp} can be obtained, amounting to 0·3 kcal/mol. In the case of pyridine, the influence of the hydrogen bond, preferring the *trans* form, is also manifested, in addition to the π-interactions. If the H-bond is considered responsible for the whole difference between the behaviour of pyridine and the rest of the aromatics, we obtain an indicative value ΔH_H of roughly 0·8 kcal/mol.

In oligomers of N-methylformamide itself, the hydrogen bond has a similar effect as in pyridine, as seen from the concentration dependences in the "normal" temperature range. It may be speculated that the hydrogen bond favours the dipolar resonance form, to which the amides have a natural tendency[1,2].



The resulting space separation of charge is larger in the *trans* than in the *cis*-form. The larger distance from the negatively charged carbonyl oxygen is probably also more favourable for the acceptor base (see ref.[6]).

As a result of this study it may be stated that the isomeric equilibrium is relatively little affected by medium, even including the effects of hydrogen bonding. This conclusion may be considered to support the previously presented hypothesis[1,2,4] that in more highly substituted amides and peptides, the isomeric ratio is predominantly determined by mutual steric interactions of the substituents.

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