HYDROGEN BONDING OF SECONDARY AMIDES. THE CYCLIC DIMERIZATION OF *CIS* ISOMERS

By P. R. ANDREWS*
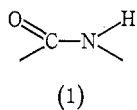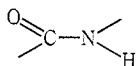
Since the coexistence of *cis* (1) and *trans* (2) isomers of secondary amides was demonstrated by Russell and Thompson[1] the conformational isomerism of the amide group has been the subject of many spectroscopic studies.[2] There has also been widespread interest in the self-association of *N*-methylacetamide, which is predominantly *trans*,[1] into linear hydrogen-bonded chains.[3] The self-association of *cis* amides has only motivated one study,[4] in which Bhaskar and Rao compared the hydrogen bonding properties of *N*-methylacetamide with those of *N*-phenylurethane, which was presumed to be 95% *cis*.[1] Their failure to observe any clear-cut difference between the hydrogen bonding behaviour of the two amides is readily explained by revised spectroscopic and theoretical data, which show that *N*-phenylurethane actually exists as the *trans* isomer.[5,6] Indeed, no noncyclic secondary amide is known to occur exclusively in the *cis* form, but there are several for which the *cis* and *trans* isomers coexist in significant proportions. The self-associations of two of these, formanilide and *o*-methylformanilide, have been investigated in CCl_4 using infrared spectroscopy.

The fundamental nonbonded ν_{NH} bands of secondary amides occur at 3400–3440 and 3430–3470 cm^{-1} for the *cis* and *trans* isomers respectively,[1] and bonded N–H stretching peaks are observed near 3080 and 3200 cm^{-1} (*cis*) and 3300 cm^{-1} (*trans*) in related compounds.[2] The infrared spectrum of *o*-methylformanilide, which has been interpreted by Siddall *et al.*,[7] has peaks in each of these regions, but as the concentration is lowered the bonded ν_{NH} peaks due to *cis* association persist after the corresponding *trans* peak vanishes.

* Department of Physical Biochemistry, John Curtin School of Medical Research, Australian National University, Canberra, A.C.T. 2600.

1 Russell, R. A., and Thompson, H. W., *Spectrochim. Acta*, 1956, **8**, 138.
2 Hallam, H. E., and Jones, C. M., *J. molec. Struct.*, 1970, **5**, 1, and references therein.
3 Graham, L. L., and Chang, C. Y., *J. phys. Chem.*, 1971, **75**, 776, and references therein.
4 Bhaskar, K. R., and Rao, C. N. R., *Biochim. biophys. Acta*, 1967, **136**, 561.
5 Andrews, P. R., *Biopolymers*, 1971, **10**, 2253.
6 Rao, C. N. R., Rao, K. G., Goel, A., and Balasubramanian, D., *J. chem. Soc. (A)*, 1971, 3077.
7 Siddall, T. H., Stewart, W. E., and Marston, A. L., *J. phys. Chem.*, 1968, **72**, 2135.

The *trans* population also remains effectively monomeric despite *cis* association in dilute solutions of formanilide, so that for both compounds it is possible to study the hydrogen bonding of *cis* isomers directly.

Furthermore, since *cis* association at these concentrations is presumably limited to the formation of cyclic dimers rather than trimers or linear chains, the total concentration of amide is given by

$$C = C_c + C_t + 2C_c{}^2 K_d \tag{1}$$

where C_c and C_t are the *cis* and *trans* monomer concentrations and K_d is the association constant for *cis* dimerization. The monomer concentrations are also related by an isomerism constant

$$K_i = C_c/C_t \tag{2}$$

If intrinsic intensity ϵ is assumed[1,2] to be the same for the nonbonded ν_{NH} peaks of both isomers, K_i may be determined directly from their measured absorbances A_t and A_c. Also, because both N–H groups are bound in the cyclic *cis* dimer

$$A_c = C_c l \epsilon \tag{3}$$

where l is the cell path length.

Substituting equations (2) and (3) into equation (1) then gives

$$C = aA_c{}^2 + bA_c \tag{4}$$

where

$$a = 2K_d/\epsilon^2 l^2 \tag{5}$$

$$b = (K_i + 1)/K_i \epsilon l \tag{6}$$

Curvilinear regression of total concentration of amide on A_c and $A_c{}^2$ provides values for the coefficients a and b, and thence for the association constant K_d and intrinsic intensity ϵ. It is noteworthy that the presence of significant proportions of open *cis* dimers or cyclic trimers would become apparent in the regression analysis, since the quadratic (4) would not account adequately for the observed data.

Experimental

Formanilide and *o*-methylformanilide were purchased from K&K Laboratories, Plainview, N.Y., and recrystallized from carbon tetrachloride, which was also chosen as solvent for the spectral studies. Spectroscopic quality carbon tetrachloride was purchased from Mallinckrodt Chemical Works, St. Louis, Mo. Spectra were recorded by slow scanning with a Perkin–Elmer 621 spectrophotometer using cells of 1 cm path length. The ambient temperature was $20 \pm 1°C$, and the cell compartment was flushed with 60 ft³ of dry air per hour. The temperature inside the cell at thermal equilibrium was not determined.

Results and Discussion

For both amides spectra were taken at 18 concentrations in the range 0·002–0·02M, with absorbance values between 0·15 and 0·8. The absorbance scale was verified by comparison of peak intensities in the ν_{CH} band with total amide concentration (standard deviation <2%). The measured absorbance of the *cis* ν_{NH} peak of *o*-methylformanilide is plotted against total amide concentration in Figure 1. Also

shown is the computed quadratic regression line (equation (4)), which gives an excellent account of the experimental data ($r = 0 \cdot 9999$, $P \ll 0 \cdot 001$). The resulting values of K_i, K_d, and ϵ are $1 \cdot 333$ ($1 \cdot 325$, $1 \cdot 341$), $148 \cdot 1$ l. mol^{-1} ($138 \cdot 3$, $158 \cdot 4$), and $132 \cdot 5$ l. mol^{-1} cm^{-1} ($129 \cdot 8$, $135 \cdot 3$). The numbers in parentheses are 99% confidence
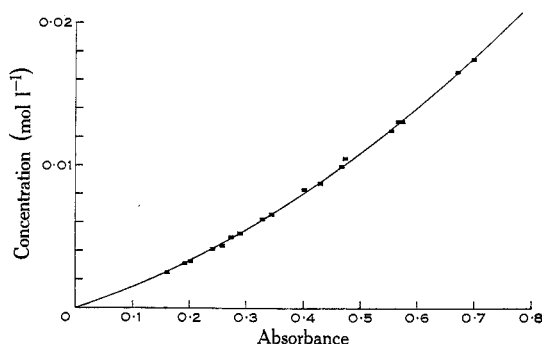

Fig. 1.—Plot of *o*-methylformanilide concentration against nonbonded *cis* ν_{NH} absorbance, and the quadratic regression line computed according to equation (4).

limits in the case of K_i, whilst for K_d and ϵ they are extreme values calculated directly from the 99% confidence limits of K_i, a, and b. The possibility of a systematic error due to overlap of nonbonded frequencies by hydrogen bonding bands at higher concentrations was tested by including six additional data points at concentrations between $0 \cdot 02$ and $0 \cdot 035$M. The correlation was again excellent ($r = 0 \cdot 9999$), and the scarcely altered values for K_d ($146 \cdot 6$ l. mol^{-1}) and ϵ ($132 \cdot 0$ l. mol^{-1} cm^{-1}) suggest that this source of error is insignificant over the concentration range used.

Similar results were obtained for formanilide, for which K_i, K_d, and ϵ were found to be $0 \cdot 615$ ($0 \cdot 605$, $0 \cdot 626$), $304 \cdot 8$ l. mol^{-1} ($275 \cdot 4$, $339 \cdot 5$), and $184 \cdot 5$ l. mol^{-1} cm^{-1} ($178 \cdot 3$, $191 \cdot 1$).

The K_d values for both amides are significantly greater than those for the initial dimerization of *trans*-N-methylacetamide, for which estimates range from 1 to 9 l. mol^{-1} at 20° in CCl$_4$.[3] In contrast to the conclusion of Bhaskar and Rao,[4] the association constant is thus seen to exhibit a clear-cut dependence on the configuration of the N–H bond. This reflects a decrease in free energy associated with the formation of an additional hydrogen bond in the *cis* dimer.

Infrared, n.m.r., and molecular weight measurements at higher concentrations are planned to provide information on *cis* trimerization and indefinite linear association of both *cis* and *trans* isomers.