# Correlation of Crystal and Solution Conformations of *N*-Acyl Prolines and Related Compounds using Nuclear Magnetic Resonance

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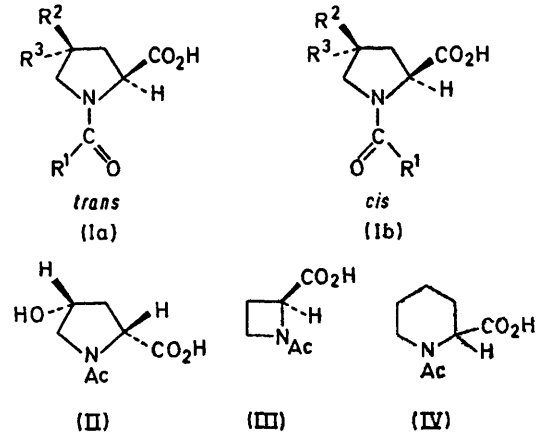
*Summary* A technique is described in which the solution conformation of acylimino-acids and small proline-containing peptides can be determined using high resolution n.m.r. spectroscopy and related to the corresponding conformation in the crystal.

RECENT interest in the *cis/trans* isomerism about amide bonds involving the nitrogen of proline,[1–4] prompted us to record our observations, which allow an unambiguous assignment of the crystal conformation about the peptide bond in a variety of *N*-acylated imino-acids.

Following dissolution of crystalline *N*-acetyl-L-proline (I; $R^1$ = Me, $R^2$ = $R^3$ = H) in $CD_3OD$ at −60°, the n.m.r. spectrum determined at this temperature showed the presence of only one form [$\tau$ 7·91 ($CH_3CO$)]. On warming the solution a new methyl singlet ($\tau$ 8·01) appeared in the spectrum. Equilibration about the amide bond was clearly occurring, the more stable form at equilibrium being that initially observed. The more stable form in solution is assigned as the *trans* form (Ia; $R^1$ = Me, $R^2$ = $R^3$ = H), by comparison with the Paulsen amide model, [5] and by use of benzene solvent shifts.[4] Similar experiments carried out



with the acetyl derivatives of 4-hydroxy-L-proline (I; $R^1$ = Me, $R^2$ = H, $R^3$ = OH), 4-*allo*-hydroxy-D-proline (II), and L-azetidine-2-carboxylic acid (III) showed that in all cases the *trans* orientation was the only form present in the crystal, which was also the more stable form in $CD_3OD$ and most other solvents, at equilibrium. However, a similar experiment with *N*-acetyl-DL-pipecolic acid (IV) established that the stable form found in the crystal by this low temperature n.m.r. technique was the *cis* form, which after equilibrium at room temperature was the less stable form in solution. It is interesting to compare these results with those obtained for the corresponding *N*-nitrosoimino-acids, in which the crystal conformation of the four-membered ring is the only anomaly with an *anti* nitroso-group.[6]

All compounds examined in this work are analytically pure. Details will be reported in the full paper. This technique, although used previously for determination of the crystal conformation of a variety of organic molecules[6,7] has not been tried with small peptides where there exists in the crystal or in solution the possibility of more than one conformation.

We thank Professor L. Fowden for a generous sample of L-azetidine-2-carboxylic acid, and the S.R.C. for a studentship (to M.K.W.).

(*Received, 8th May* 1972; *Com.* 789.)

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