

## An Essentially Planar Conformation Determined for an Arylsulphonylurea by Low-temperature Nuclear Overhauser Effect Spectroscopy

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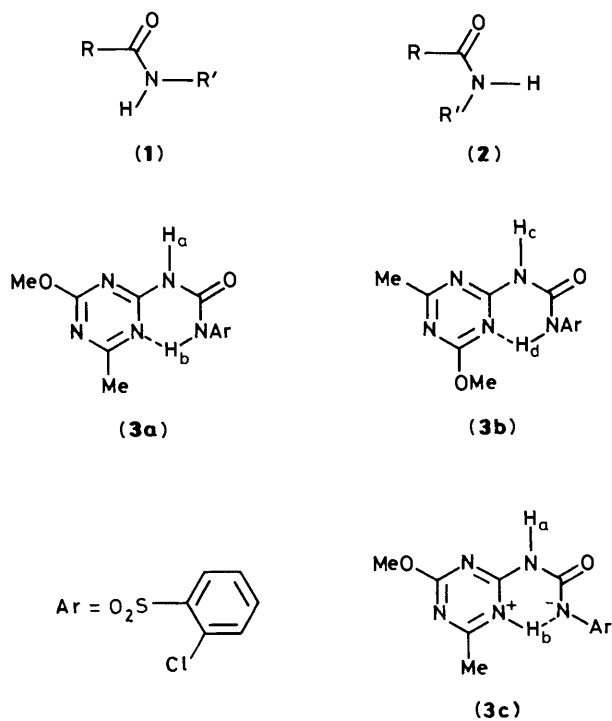
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2-[3-(*o*-Chlorophenylsulphonylureido)-4-methoxy-6-methyl-1,3,5-triazine (**3**) adopts a coplanar *cis*-amide conformation in non-aqueous solvents, in contrast to the *trans*-conformation normally preferred by simple arylamides; the planar conformation in (**3**) arises as a result of intramolecular NH --- N hydrogen bonding.

As the amide group is a fundamental unit in polypeptides, much interest exists in the conformation it adopts under a variety of conditions. The *trans*-isomer (**1**) is the normally the more stable, although bulky substituents<sup>1-3</sup> are known to promote the *cis*-isomer (**2**) and also to increase  $\Delta G^\ddagger$  for rotation about the C-N bond.<sup>2</sup>

In arylureas (**1**; R' = aryl, R = NHR'') R' is normally twisted with respect to the N-C=O plane, and in tertiary arylureas in particular the barrier to rotation about this nitrogen-aryl bond *via* a planar transition state can be quite significant if R' bears *ortho*-substituents.<sup>4</sup> We report here <sup>1</sup>H n.m.r. results in non-aqueous solvents which show that if the *ortho*-carbon atoms in R' are replaced by nitrogen, as in the triazine (**3**), the equilibrium geometry corresponds to a coplanar *cis*-amide conformation as in (**3a**) and (**3b**), and a significant barrier to twisting is induced as a result of intramolecular NH --- N hydrogen bonding.

Solutions of (**3**) in acid-free CDCl<sub>3</sub> or CD<sub>2</sub>Cl<sub>2</sub> display noticeable <sup>1</sup>H n.m.r. exchange broadening slightly below room temperature. At temperatures below about 258 K, pairs of signals of unequal intensity are seen for the methyl and methoxy resonances, together with two pairs of broad NH peaks. Of these, only the downfield NH pair exhibit the small solvent and temperature dependence typical of intramolecular hydrogen bonds,<sup>5</sup> which suggests an equilibrium between the two isomers (**3a**) and (**3b**).



More conclusive evidence for these structures was obtained using <sup>1</sup>H nuclear Overhauser effect (n.O.e.) difference spectroscopy.<sup>6,7</sup> For an n.O.e. to be sufficiently selective to distinguish between several conformers, it is essential that their mutual exchange is slow on the n.O.e. timescale (*ca.* 3 s). Saturation transfer experiments on the NH resonances revealed that intermolecular proton exchange on such a timescale (catalysed by traces of acid present) was only suppressed below 225 K, and that intramolecular exchange was predominantly suppressed at 210 K. At this temperature (Figure 1), the low-field resonance at  $\delta$  13.3 shows a selective n.O.e. only on the corresponding methyl peak and is assigned on this basis to NH<sub>b</sub> in the minor isomer (in CD<sub>2</sub>Cl<sub>2</sub>) (**3a**); the

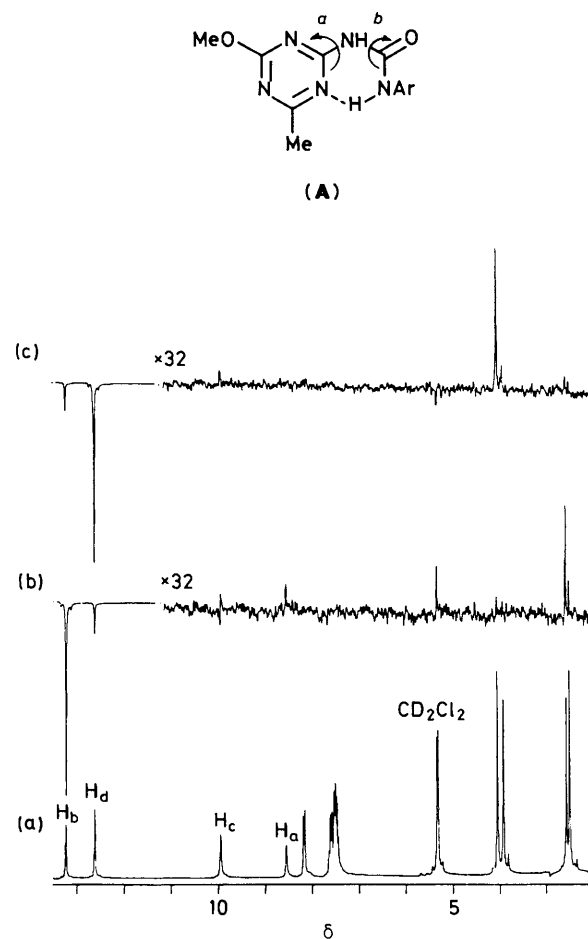


Figure 1. (a) <sup>1</sup>H N.m.r. spectrum of (**3**) in CD<sub>2</sub>Cl<sub>2</sub> at 210 K; (b) n.O.e. difference spectrum obtained by pre-irradiation at  $\delta$  13.3, showing enhancement of the methyl but not the methoxy resonance; (c) n.O.e. difference spectrum obtained by pre-irradiation at  $\delta$  12.7, showing enhancement of the methoxy but not the methyl resonance.

other NH resonance at  $\delta$  12.7 displays a selective n.O.e. only on the methoxy peak and is hence assigned to  $H_d$  in (3b). These results do not rule out the possibility of zwitterionic tautomers such as (3c), although the low temperature and solvent dependence of  $\delta$  ( $H_b$ ) or  $\delta$  ( $H_d$ ) argues against a major contribution from such forms.

The interconversion of (3a) and (3b) can in principle proceed either directly by rotation about the aryl-N bond *a* via an orthogonal transition state, or indirectly by initial rotation about the amide bond *b* to give a linear all *trans*-amide conformation, followed by rotation about bond *a* and reformation of the hydrogen bond.

Variable temperature lineshape analysis (in  $CDCl_3$ ) of the pairs of methyl and methoxy peaks gave values for  $\Delta G^\ddagger$  and  $\Delta H^\ddagger$  of approximately 55 and 44  $\text{kJ mol}^{-1}$ , respectively, for the dynamic process. If an NH---N hydrogen bond enthalpy of 15–20  $\text{kJ mol}^{-1}$  is subtracted,<sup>†</sup> the resultant barrier of approximately 24–30  $\text{kJ mol}^{-1}$  is more in accord with rotation about bond *a* than bond *b*, the latter being an amide-type bond

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<sup>†</sup> AMI calculations on the model compound (3; Ar = CN), employing a modified core repulsion function for nitrogen as suggested by one of us,<sup>8</sup> support the view that the planar configurations (3a) and (3b) are *ca.* 18  $\text{kJ mol}^{-1}$  lower in energy than the linear conformation not containing a hydrogen bond.

with a much higher expected barrier. These results contrast with those for *ortho*-substituted phenylureas,<sup>4</sup> which adopt an orthogonal equilibrium conformation to avoid overcrowding, and in which rotation proceeds *via* a planar transition state for which  $\Delta G^\ddagger$  is significantly higher than 55  $\text{kJ mol}^{-1}$ .

We are currently studying how the unusual conformations adopted by (3a) and (3b) influence their binding with organic acids, in the light of the structural similarity of these compounds to *e.g.* the nucleic acid bases.

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