X-Ray Crystallographic and NMR Evidence for a Uniquely Strong OH · · · N Hydrogen Bond in the Solid State and Solution

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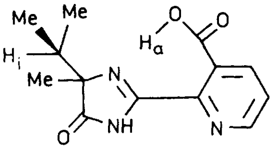
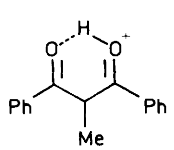
Crystallographic and NMR evidence indicates that the neutral compound (1) has a strong and essentially linear [170(1)°] O–H · · · N intramolecular hydrogen bond as part of a seven membered ring, with uniquely short O · · · N and H · · · N distances of 2.465(5) and 1.32(2) Å and an O–H distance of 1.16(2) Å respectively.

Strong hydrogen bonds are frequently associated with the homonuclear nature of the two non-hydrogen atoms, their co-linearity with and symmetry about the central hydrogen atom, and an overall positive or negative charge.[1] In contrast, hydrogen bonds involving hetero-nuclear pairs such as nitrogen and oxygen tend to be asymmetric, the great majority involving NH · · · O interactions as in *e.g.* peptides.[2] Fewer examples of OH · · · N bonding are known[3] and these are also all asymmetric with H · · · N distances greater than 1.7 Å. We report here the crystal structure† and ^{1}H NMR properties of the neutral molecule (**1**) which is shown to contain an essentially linear and uniquely short intramolecular OH · · · N hydrogen bond forming a seven membered ring.



(**1**)



(**2**)

Compound (**1**) crystallises readily from non-polar solvents such as dichloromethane, and the room temperature *X*-ray structure analysis revealed several unusual features. The five membered ring (Figure 1) is clearly revealed as the amide tautomer[4] and lies almost co-planar with the pyridine ring (dihedral angle 4.5°). This planarity is achieved at the expense of an unusually large (130.0°) bond angle between the carbon of the carboxyl group and the pyridine ring, and must represent a measure of the strength of the OH · · · N hydrogen bond. The heteroatom separation of 2.47 Å is uniquely short[3] for a hydrogen bond of this type, and the non-bonding N–H distance of only 1.3 Å compares with values in the range 1.7—2.2 Å for other OH · · · N hydrogen bonds.[3] The short O · · · N interaction in (**1**) is associated with an essentially linear OHN bond angle (170°), a result which supports the assertion by Houk[5] that seven membered ring transition states are particularly favoured for linear hydrogen transfers.

In view of the exceptional nature of the distances observed and the slightly large anisotropic thermal parameters for the donor oxygen O(13), the structural data were recollected at liquid nitrogen temperature. This refinement of the low temperature data resulted in a uniform reduction of the thermal motion of all the atoms in the structure, thus eliminating the possibility of the short N(4)–O(13) distance representing the average of two non-planar conformations of the acid group. The overall molecular geometry at low temperature is unchanged within statistical significance.

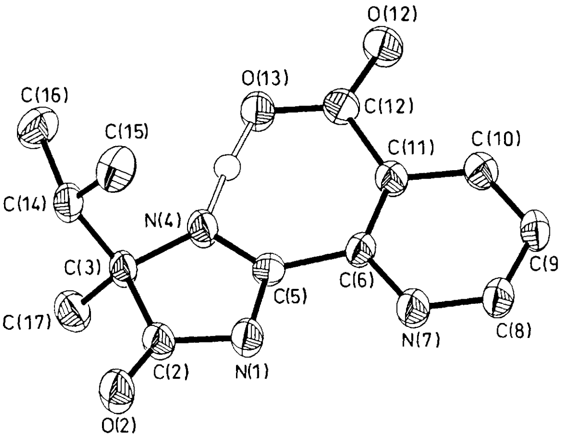


Figure 1. The low temperature molecular structure of (1), showing crystallographic numbering. Thermal ellipsoids correspond to 60% probability. The C(6)–C(11)–C(12)–O(13) torsion angle is −10.1(4)°. There is an intermolecular hydrogen bond (2.85 Å) between the amide nitrogen N(1) and the carbonyl oxygen O(12).

The two acidic protons in (**1**) have ^{1}H chemical shifts of δ 19 ± 0.5 and 10 ± 1, which were found to be relatively insensitive to concentration, solvent, or temperature. This unusually high chemical shift is similar to that recently reported for the charged homonuclear system 2 (δ 20.4),[6] which was interpreted in terms of a symmetrical and strong O · · H · · O hydrogen bond. Our observation of a similar chemical shift value for a neutral system suggests that the hydrogen bonding interaction in (**1**) is also unusually strong, probably as a consequence of the favourable geometry of the seven membered ring and an accidental coincidence of the pK_a values for the O and N basic sites. It is interesting to speculate whether these characteristics could be 'fine tuned' by modification of the pK_a values with suitable ring substituents.

Unambiguous evidence for the specific tautomer and conformation of (**1**) in solution was difficult to obtain for

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† *Crystal data* for (1) (room temperature): $C_{13}H_{15}N_3O_3$, $M = 261.3$, monoclinic, $a = 7.268(2)$, $b = 16.317(4)$, $c = 10.863(3)$ Å, $\beta = 94.96(2)°$, $U = 1283$ Å^3, space group $P2_1/a$, $Z = 4$, $D_c = 1.35$ g cm^{-3}, $\mu = 8$ cm^{-1}. Data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. The structure was solved by direct methods and refined anisotropically to give $R = 0.043$, $R_w = 0.050$ for 1985 independent observed reflections [$|F_o| > 3\sigma(|F_o|)$, $2\theta \leq 150°$]. *Crystal data* for (1) (liquid nitrogen temperature): monoclinic, $a = 7.168(3)$, $b = 16.306(6)$, $c = 10.776(5)$ Å, $\beta = 94.40(4)°$, $U = 1256$ Å^3, space group $P2_1/a$, $Z = 4$, $D_c = 1.38$ g cm^{-3}, $\mu = 8$ cm^{-1}. The structure was refined anisotropically to give $R = 0.051$, $R_w = 0.055$ for 1482 independent observed reflections [$|F_o| > 3\sigma(|F_o|)$, $2\theta \leq 116°$]. Atomic co-ordinates, bond lengths and angles, and thermal parameters for both determinations have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

several reasons. Unlike the chemical shifts, both $^1H\{^1H\}$ and $^{13}C\{^1H\}$ nuclear Overhauser effects (NOEs) proved to be highly solvent, concentration, and temperature dependent. In $CDCl_3$ at 240 K, saturation transfer showed that chemical exchange between the two acidic protons remained fast on the NOE time scale. At this temperature, a positive NOE was observed from these protons (irradiation at δ 19.4) to the two diastereotopic methyl doublets and the methyl singlet of the isopropyl group, supporting structure (**1**), but not excluding other conformations. Cooling to 170 K[6] in CBr_2F_2/CD_2Cl_2 suppressed the chemical exchange and enabled more selective irradiation of the acidic protons,[7] but the longer correlation times eliminated the positive NOE effects, and only negative NOEs to the three aromatic protons were observed.[8] Such NOEs were also observed at 240 K in $CDCl_3$, but their sign proved very sensitive to the concentration of (**1**). A $^{13}C\{^1H\}$ NOE experiment in saturated CD_2Cl_2 at room temperature involving irradiation at δ 19 gave a large positive NOE only to C(8), C(9), and C(10), with the expected positive NOEs to the carboxyl and adjacent carbon being much smaller. These results indicate an unusual degree of aggregation in relatively non-polar solutions, and the absence of any relevant short intermolecular contacts between these atoms in the crystal lattice suggests intermolecular contacts in solution which are quite different to that found in the crystal structure.

Compound (**1**) represents a challenging case for molecular modelling. The unusual functionality and structure means that reliable molecular mechanics parameters are not available and the size precludes an *ab initio* treatment at an adequate basis set level. Of the semi-empirical SCF-MO methods, only AM1 reproduces hydrogen bond energies correctly, but fails qualitatively to reproduce the geometries.[9] The recently reported PM3 procedure represents a marked improvement over AM1 in correctly reproducing the observed OH · · · N hydrogen bonding structure of salicaldoxime[10] and the structure and vibrational frequencies of water dimer and trimer.[11] For (**1**), PM3 predicts a significant relative rotation of the two rings (38.6°), an OHN angle of 150.2° and H · · · N and O · · · N distances of 1.798 and 2.681 Å respectively. However, constraining the PM3 geometry to be planar raises the calculated energy by only 2.5 kcal mol^{-1} (1 kcal = 4.184 kJ) (O · · · N 2.661 Å and H · · · N 1.730 Å), an effect that could be readily accommodated by crystal packing forces.

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