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Self-assembly of an Indolyl-glyoxylamide by Unusual Hydrogen Bonding

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Abstract: The tertiary indol-7-ylglyoxylamide, 2-(3'-(4"-chlorophenyl)-4',6'-dimethoxyindol-7'-yl)glyoxyl-1-pyrrolidide self-assembles into a "step" shaped hydrogen bonded dimer in the crystalline state *via* the preferential use of π-hydrogen bonding from an indole NH to a carbonyl acceptor.
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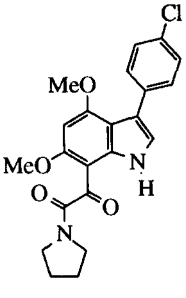
We wish to report that the indol-7-ylglyoxylamide **1** [1] self-assembles into a dimeric structure in the crystalline state *via* NH...O=C hydrogen bonds directed towards the π-orbital of the carbonyl group. X-ray crystallography indicates that a π-hydrogen bond is formed between the indole NH and the amide carbonyl oxygen atom, giving rise to a 14-membered intermolecular hydrogen bonded ring ($R_2^2(14)$) [2] (Figure 1). Significantly, this hydrogen bond is the only one formed to the amide carbonyl group and is the result of a combination of intramolecular hydrogen bonded ring formation, the ~90° glyoxyloyl torsional angle and the preference for dimer formation over chain formation.



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Hydrogen bonds to the π-system of aromatic rings, alkynes and alkenes have been reported.[3] Hydrogen bonds of the type X-H...O=C (X=N or O) [4,5] and C-H...O=C[6] are generally formed in the plane of the carbonyl moiety and are directed at the conventionally viewed lone pairs of electrons: hydrogen bonds to the π-orbital of a carbonyl group are very rare.[4-6] An idealised conventional hydrogen bond would have the parameters of $\theta_H = 90°$ and $\phi_H = 30°$ (θ_H being the angle between the z axis and O...H vector and ϕ_H being the angle between the x axis and the projection of the O...H vector on to the xy plane (Figure 2)). In a study of 1357 cases of intermolecular hydrogen bonds with a value of ($0° < \theta_H < 27.27°$), only one contains a carbonyl group with no other hydrogen bond contacts.[4] Clearly, hydrogen bonding orthogonal to the plane of the carbonyl group is extremely rare in the absence of other hydrogen bonds to the carbonyl group.

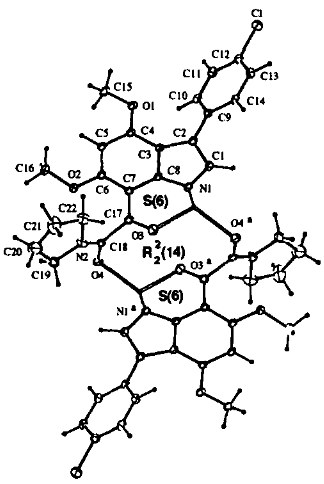

Figure 1. X-ray crystallographic structure and designated hydrogen bond motifs of glyoxylamide **1**.

The π-hydrogen bond of the glyoxylamide dimer (Figure 1) has a θ_H angle of 25.9° indicating that the hydrogen bond is formed from above the plane of the carbonyl group (Figure 3a). The angle $\phi_H = 24.0°$ suggests that although the hydrogen bond is directed toward the π-orbital of the carbonyl group it is also directed at the lone pair of electrons (Figure 3b). This indicates that the hydrogen bond is best explained as a hybrid between the two extreme situations ($\theta_H = 90°$ and $\phi_H = 30°$ - hydrogen bonding to the lone pairs of electrons, $\theta_H = 0°$ and $\phi_H = 0°$ - hydrogen bonding from directly above the oxygen atom). The hydrogen bond lengths are 2.24 Å (NH...O) and 3.02 Å (N...O), which are consistent with moderately strong hydrogen bonds, being well within the sum of the van der Waals radii 3.20 Å (N=1.70, O=1.50)[7] or 3.24 Å (N=1.60, O=1.54)[8] depending on which reference is used.

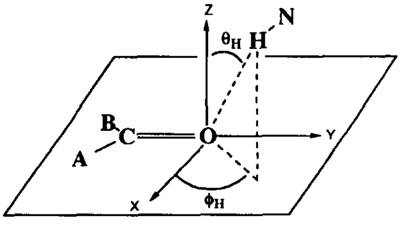

Figure 2. Directionality of hydrogen bonding showing spherical polar coordinates.

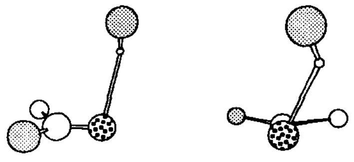

Figure 3. Hydrogen bonding viewed along (**a**) the x axis and (**b**) the y axis.

The keto oxygen atom of the tertiary glyoxylamide **1** forms a six-membered intramolecular hydrogen bonded ring to the indole NH (S(6)) (Figure 1). The S(6) system is a strong intramolecular hydrogen bond which is also present in solution. The S(6) system is observed for a number of other 7-substituted indole analogues with various keto acceptors.[9] The six-membered intramolecular hydrogen bonded ring deviates only slightly from the plane of the indole ring and effectively makes a flat 6,6,5 fused ring system. Primary and secondary glyoxylamides usually form glyoxyloyl torsional angles (O=C-C=O) which approximate 180° because of the S(5) hydrogen bond system, while tertiary glyoxylamides which lack an amide NH adopt a glyoxyloyl torsional angle which approximates 90°.[10] The tertiary glyoxylamide **1** adopts a torsional angle of 93.4°. The S(6) system and the 90° degree glyoxyloyl torsional angle combine to form a structure which is held rigid and has an amide carbonyl group oriented at ~90° to the plane of the indole ring. This provides the optimum geometry for π-hydrogen bond formation and dimerisation. The result is a three-centre hydrogen bond leading to a dimeric structure which adopts a "step" shape (Figure 4).

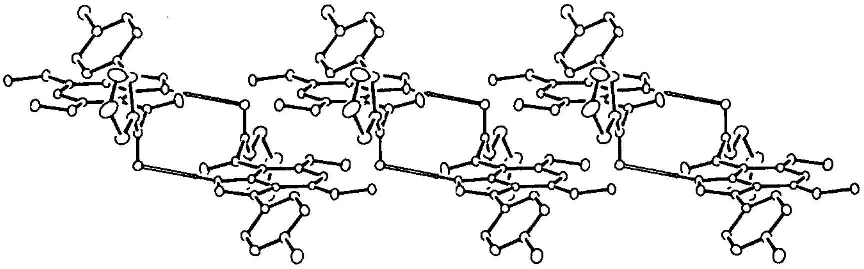

Figure 4. X-ray crystallographic packing diagram for glyoxylamide **1**.

The statistical study of Taylor *et al.*[4] suggests that the carbonyl oxygen atom preferentially accepts two hydrogen bonds directed at the lone pairs of electrons and if another hydrogen bond is formed it will do so orthogonal to the plane of the carbonyl group. The intermolecular hydrogen bond formed by the tertiary glyoxylamide **1** at right angles to the plane of the carbonyl group is the only hydrogen bond observed for this group and is not forced on the molecule by any steric hindrance. It would be possible for compound **1** to form hydrogen bonds in the plane of the carbonyl group and give rise to a chain structure, but a preference for dimerisation is observed.

The tertiary glyoxylamide **1** contains two hydrogen bond acceptors and only one hydrogen bond donor, so the combination of intramolecular hydrogen bonded ring formation and dimerisation ensures that all proton donors and acceptors are used in hydrogen bonding.[11] We have previously shown that the primary and secondary indol-2-ylglyoxylamide moieties can act as building blocks for the self-assembly of hydrogen bonded dimers.[5] The formation of "step" dimers of the glyoxylamide **1** could also provide a useful design feature in the construction of precisely engineered structures for molecular recognition.

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Supporting Information Available: Details of the X-ray structure determination, atomic parameters and standard deviations, interatomic distances, interatomic angles, and torsional angles for compound **1** (these data have been deposited with the Cambridge Crystallographic Data File, 12 Union Road, Cambridge, CB2 1EZ, U.K.).

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