The Indol-2-ylglyoxylamide Moiety: A New Building Block for the Design and Self-Assembly of Hydrogen Bond Networks

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We wish to report that the indol-2-ylglyoxylamide moiety, exemplified in **1a** and **1b**, is a previously unrecognized structural fragment for the self-assembly of hydrogen bond networks.[1] Amides have been used extensively in crystal engineering because of their propensity to form hydrogen bonds.[2−5] Acyclic secondary amides form chain motifs,[6] and primary amides generally form tape networks because of the additional hydrogen bond donor.[7]

The primary and secondary indol-2-ylglyoxylamides **1a** and **1b**, prepared by treating 3-(4′-chlorophenyl)-4,6-dimethoxyindole with oxalyl chloride followed by quenching with the appropriate amine, form new dimeric networks in the crystalline state. This is shown by X-ray crystallography which indicates a network of complementary intra- and intermolecular hydrogen bond motifs (Figure 1a,b). Glyoxylamides introduce a number of features for crystal engineering in addition to those provided by the simple amide functionality. Glyoxylamides offer a greater degree of versatility to the system by the presence of the additional hydrogen bond accepting keto group and the variable glyoxylamide torsional angle. The propensity of compounds **1a** and **1b** to form intramolecular hydrogen-bonded rings introduces rigidity into the system and eliminates the need to synthesize covalent rings. They adhere to the proposed criteria for the prediction of general hydrogen bond patterns.[8−13] Compounds **1a** and **1b** form two intramolecular hydrogen-bonded rings, a six-membered ring (S(6)), and a five-membered ring (S(5)).[1] These hydrogen bond networks effectively convert compounds **1a** and **1b** into 6,5,6,5 fused four-ring systems, which have a significant effect on the self-assembly of the molecules.

The S(6) system is formed by intramolecular hydrogen bonding from the indole NH to the amide carbonyl oxygen atom and is present in both molecules **1a** and **1b** (Figure 1a,b). This motif contains a strong hydrogen bond with ideal bond lengths and angles (Table 1). The S(6) system holds the glyoxylamide
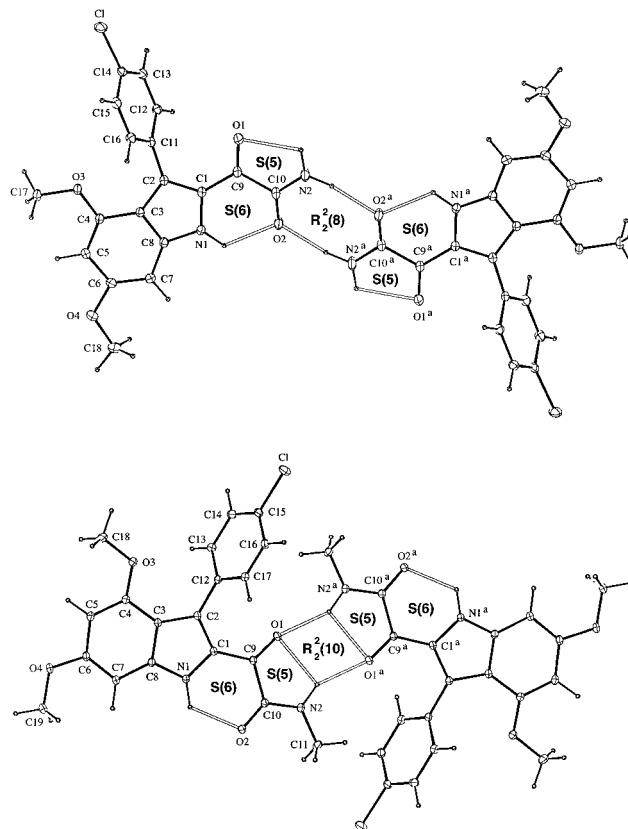

Figure 1. X-ray crystal structures and designated hydrogen bond motifs of primary glyoxylamide **1a** (top) and secondary glyoxylamide **1b** (bottom).

Table 1. Selected Structural Parameters for the Glyoxylamides **1a** and **1b**

structure	graph set	$r(\text{N}-\text{H}\cdots\text{O})$ (Å)	$r(\text{N}\cdots\text{O})$ (Å)	$\alpha(\text{N}-\text{H}\cdots\text{O})$ (deg)	torsional angle (deg)
1a	S(6)	2.051	2.703	120.8	165.2
	S(5)	2.248	2.637	101.6	
	$R_2^2(8)$	1.939	2.928	169.4	
1b	S(6)	2.004	2.664	121.3	178.8
	S(5)	2.224	2.646	103.7	
	$R_2^2(10)$	2.097	3.002	149.7	

moiety in the plane of the indole ring, and this maximizes steric interaction between approaching molecules.

A somewhat weaker—but also important—interaction is the intramolecular hydrogen-bonded five-membered ring from the amide NH to the keto group (S(5)) which is present in both structures. This hydrogen bond is longer and has smaller angles than the S(6) system but is still consistent with the hydrogen bond parameters found in a study of 1509 hydrogen bonds of the type C=O···H−N.[14] The S(5) N···O bond distnaces for compounds **1a** (2.637 Å) and **1b** (2.646 Å) are also significantly shorter than the sum of the van der Waals radii 3.20 Å (N = 1.70, O = 1.50)[15] or 3.24 Å (N = 1.60, O = 1.54)[16] depending on which reference is used. This interaction controls the glyoxyloyl torsional angle. The S(5) system holds the glyoxylamide in plane and results in a glyoxyloyl torsional angle which approximates 180°. The S(5) system gives rise to torsional angles of 165.2° for the primary glyoxylamide **1a** and 178.8° for the secondary glyoxylamide **1b**.

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Examination of the 11 previously existing X-ray crystal structures of molecules containing the glyoxylamide function ($RCOCONR_2$, where R = alkyl, aryl, or hydrogen)[17] obtained from the Cambridge Crystallographic Data File[18] show that primary and secondary glyoxylamides have torsional angles ranging from 162.4° to 179.4° while tertiary glyoxylamides, which lack the ability to form the S(5) system, have torsional angles ranging from 79.0° to 101.1°. Despite the small sample size, it is clear that the S(5) system has a dramatic effect on the torsional angle of the glyoxylamide. The S(6) and S(5) systems ensure that all hydrogen bond acceptors in molecules **1a** and **1b** participate in a hydrogen bond. Therefore the choice of which acceptor will be involved in intermolecular interactions will be based on acceptor strength.

The primary glyoxylamide **1a** preferentially dimerizes in the "down" direction (see structure **1**) as this involves the amide carbonyl oxygen, which is a stronger hydrogen bond acceptor than the keto carbonyl oxygen.[13] The resulting motif is an intermolecular eight-membered ring hydrogen bonded from the amide NH to the amide carbonyl oxygen ($R_2^2(8)$). The $R_2^2(8)$ system displays very strong hydrogen bonds (Table 1) and is almost completely coplanar with the indole ring. Unlike simple primary amides, the primary glyoxylamide **1a** does not form a tape motif, and this is most likely to be a consequence of steric hindrance because of the planarity of the dimer.

1
a; R=H
b; R=Me
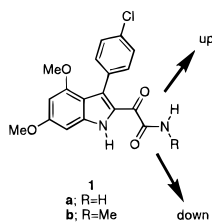
It is significant that the secondary glyoxylamide **1b** forms a dimer rather than the chain motif consistently favored by simple secondary amides. The dimer is in the "up" direction and involves the keto acceptor which is not available in simple secondary amides. The dimer is held together by an intermolecular 10-membered ring hydrogen bonded from the amide NH to the keto carbonyl oxygen ($R_2^2(10)$). As expected, the hydrogen bonds to the keto oxygen in compound **1b** are longer than those to the amide oxygen in compound **1a** (Table 1). Steric hindrance arising from the planarity of the system would necessarily exclude the translation chain motif[4] but would not necessarily exclude chain motifs related by a glide or 2_1 axis which could alleviate steric hindrance. However, the secondary glyoxylamide **1b** selectively forms a dimer in preference to a chain.

The primary glyoxylamide **1a** also dimerizes in solution. The amide NH involved in the intermolecular motif $R_2^2(8)$ shows a very large temperature dependence as observed by variable temperature ^1H NMR spectroscopy performed in $CDCl_3$ (-22.0 ppb/K at a concentration of 0.056 M), as well as shifting downfield with increased concentration. These data indicate an equilibrium between monomer and dimer.[19] The secondary glyoxylamide **1b**, however, does not associate in solution as indicated by the absence of any significant shift in the amide NH in the ^1H NMR spectrum on lowering temperature. The S(6) system is indicated in solution by the significant downfield shift of the indole NH resonance in the ^1H NMR spectra of both glyoxylamides **1a** and **1b**.

It is noteworthy that the indol-2-ylglyoxylamide **1a** in its dimer formation exhibits some structural similarities to the Watson−Crick base pairing of adenine with thymine[20] but is structurally different from the Hoogsteen pairing of the *N*-methyladenine dimer.[21]

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