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Author(s)	Daly, Carla A.; Eccles, Kevin S.; Bateman, Lorraine M.; O'Boyle, Noel M.; Lawrence, Simon E.; Maguire, Anita R.
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ARTICLE TYPE

Investigating the influence of the sulfur oxidation state on solid state conformation

Carla A. Daly,[a] Kevin S. Eccles,[a] Lorraine M. Bateman,[a] Noel M. O' Boyle,[a] Simon E. Lawrence[a] and Anita R. Maguire[b]

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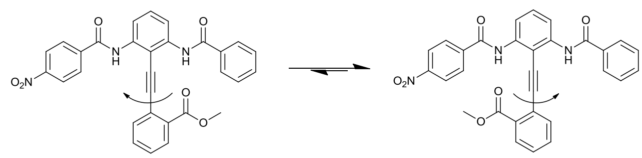
Design, synthesis and structural characterization of a series of diphenylacetylene derivatives bearing organosulfur, amide and amine moieties has been achieved in which the molecular conformation is controlled through variation of the hydrogen bond properties on alteration of the oxidation level of sulfur.

The ability to understand and rationally predict the conformation adopted by solid state structures has been actively pursued for many years.[1] Crystal engineering specifically focuses on intermolecular interactions with the aim to identify supramolecular synthons for the design of materials with specific properties e.g. optical, magnetic, electronic.[2,3] Control of the solid state physical properties of organic and inorganic materials e.g. solubility, bioavailability, dissolution rate, hygroscopicity also demands an understanding of the nature of the interactions in the solid state at a fundamental level.[4-6]

Previous research in our group focussed on organosulfur functional groups, specifically sulfides, sulfoxides and sulfones, with the aim to develop an understanding of how the molecular structure of the compounds impacts upon the solid state crystalline structure and, in particular, to probe the relative importance of different inter/intramolecular non-covalent interactions. In particular, our research highlighted the effective use of sulfoxides in supramolecular synthons, due to their nature as strong hydrogen bond acceptors,[7,8] including with amides as N-H donors.[9]

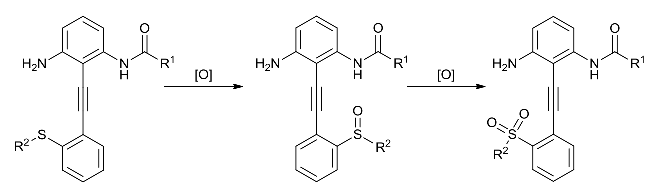
To further expand on this work we aimed to incorporate sulfur and amide functionalities within a single molecule and study the effects of varying the oxidation level of sulfur on the hydrogen bond interactions in the solid state. The diphenylacetylene unit involving ester and amide functionalities recently explored by Hamilton provided us with a suitable scaffold on which to construct this system (Scheme 1).[10,11] Their success in controlling the conformation of the molecule by varying the acidity of the amide encouraged us to expand this system by incorporating sulfur functionalities (Scheme 2).

The basic concept involves creating competition between hydrogen bond acceptors for the strongest hydrogen bond donor by altering the oxidation level of the sulfide and exploiting the difference in acidity between amides and amines.[12] At the sulfide level, interaction between the sulfur and amide or amine is not expected based on results from earlier fundamental studies[12] and the dominant solid state interaction predicted is the N-H···O=C



Scheme 1. Controlling the conformation of benzamidodiphenyl-acetylenes by changing the acidity of the hydrogen bond donors.[11]

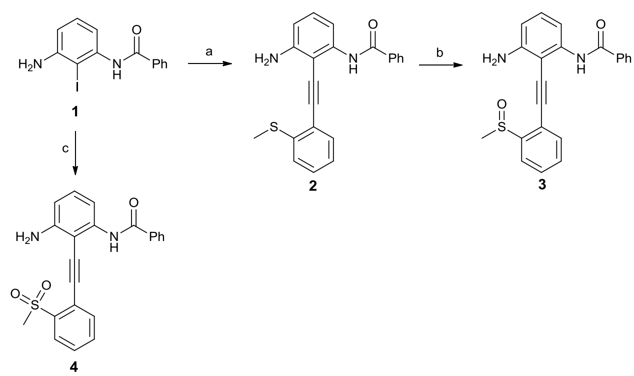
intermolecular interaction. As a result we would expect the sulfide to lie on the opposite side to the amide as illustrated (**A**), thereby enabling the intermolecular N-H···O=C interaction. On oxidation to the sulfoxide, the strong intramolecular N-H···O=S interaction should compete effectively with the intermolecular N-H···O=C interaction as sulfoxides are potent hydrogen bond acceptors[13] and amides are stronger hydrogen bond donors than amines.[12] In this case we expect the sulfoxide to lie on the same side as the amide (**B**), following Hamilton's model. On further oxidation to the sulfone, which is a weaker hydrogen bond acceptor than the sulfoxide, we anticipated at the outset that the strong N-H···O=C intermolecular interaction would once agan dominate, resulting in the sulfone lying on the opposite side to the amide (**C**).



A **B** **C**

Scheme 2. Predicting the conformation of **A**, **B** and **C** by applying the rationale of differential hydrogen bonding ability of sulfur functionalities.

To explore this concept, *N*-(2-iodo-3-aminophenyl)benzamide **1**, was synthesised following Hamilton's procedure.[10] Then the alkynes, bearing sulfide and sulfone functional groups, were attached via Sonogashira coupling to form **2** and **4** (Scheme 3). The sulfoxide, **3**, was readily obtained by oxidation of **2**. These systems with the substituents in the *ortho* position were designed to allow the exploration of intramolecular hydrogen bonding between the key functional groups. The successful Sonogashira coupling to provide the sulfide **2** is particularly interesting in the context of Larock's report involving a related system where the coupling product could not be obtained.[14]



Scheme 3. The synthesis of **2**, **3** and **4**. Reagents and conditions: a) 1-ethynyl-2-methylthiobenzene, $PdCl_2(PPh_3)_2$, CuI, DMF, NEt_3. b) $NaIO_4$, $MeOH/H_2O$**. c)** 2-methylsulfonylethynylbenzene, $PdCl_2(PPh_3)_2$, CuI, DMF, NEt_3.

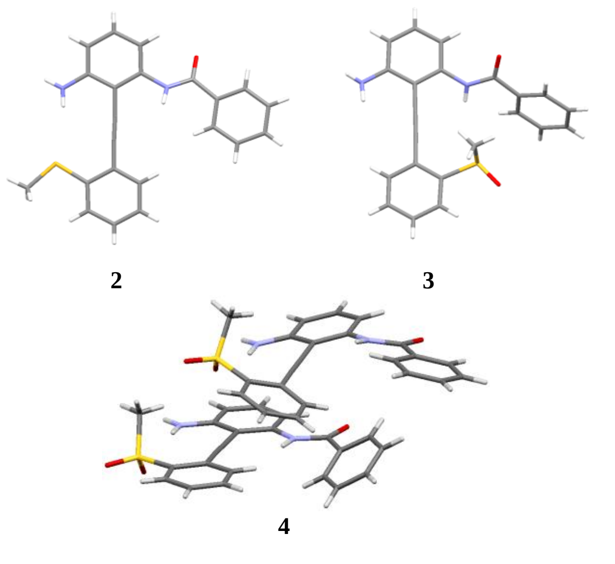


Fig. 1 Single crystal X-ray structures obtained for compounds **2**, **3** and **4**.

Single crystal X-ray diffraction of compounds **2**, **3** and **4**, each recrystallized from the same solvent, CH_2Cl_2, demonstrated the predicted conformational change as a result of altering the oxidation level of sulfur (Fig. 1). As expected the sulfide lies on the opposite side to the amide, then switches after oxidation to the sulfoxide and switches back again when the sulfone is formed. For compound **2**, the strong intermolecular N-H···O=C dominates the crystal packing, and the C=O of the amide is involved in bifurcated hydrogen bonding to both a neighbouring N-H of an amide and C-H of a methyl group (Fig. 2).

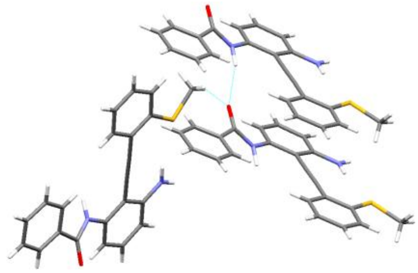


Fig. 2 Hydrogen bond interactions in compound **2**.

Interestingly, although the conformation switches in the sulfoxide, **3**, the key non-covalent interactions observed were not as anticipated (Fig. 3). Instead of an intramolecular N-H···O=S bond occurring between the amide and sulfoxide, an intermolecular N-H···O=S is formed between the sulfoxide and a neighbouring amine. The oxygen from the sulfoxide points away from the amide, with the result that intramolecular hydrogen bonding does not occur. The strong N-H···O=C interaction prevails in the crystal structure and oxidation to the sulfoxide has not disrupted this interaction. Comparison of the structural features of Hamilton's amide-ester system with our amide-sulfoxide system is very interesting. Although the sulfoxide is expected to be a stronger hydrogen bond acceptor than the ester, the planar intramolecular hydrogen bond which we anticipated to form did not occur in practice. Examination of the amide to sulfoxide N-H···O=S intramolecular distance available in **3** (~2.05 Å), together with analysis of the Cambridge Strucural Database[15] and comparison with the amide-ester N-H···O=C hydrogen bond distance (2.23 Å),[10] suggests that intramolecular hydrogen bonding, while not observed, is feasible in our system.

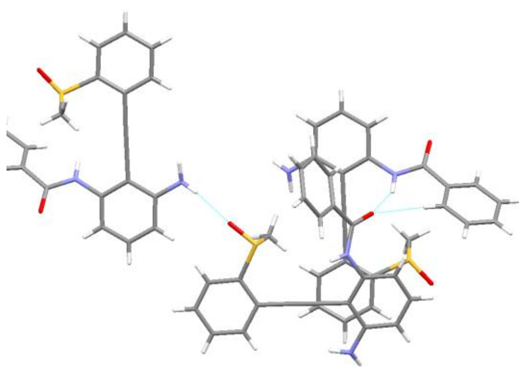


Fig. 3 Hydrogen bond interactions in compound **3**.

Overall the solid state structure of the sulfoxide adopts a conformation that enables two structure-defining intermolecular interactions: the amine N-H···O=S and the amide N-H···O=C. The key feature that arose was the unanticipated orientation of the sulfoxide out of the plane. While computational studies (see ESI) demonstrate that an intramolecular hydrogen bond is possible, it would require the axial phenyl rings to twist out of planarity, therefore leading to a decrease of extended conjugation and stabilisation. As a result, the observed conformation, which has the sulfoxide oxygen pointing away from the amide, is predicted to be slightly lower in energy.

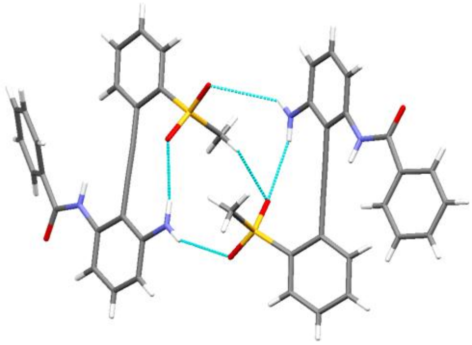


Fig. 4 Hydrogen bond interactions in compound **4**.

The sulfone, **4**, crystallises with *Z'*= 2, with both molecules adopting the same conformation as seen in the sulfide, *i.e*. the sulfone lies on the opposite side to the amide (Fig. 4). The key interactions involving the two crystallographically independent molecules are intra- and intermolecular N-H···O=S hydrogen-bonds. The combination gives rise to a visually appealing $R^{4}_{4}(12)$ motif at the binary level. Also present within this motif is a C-H···O=S intermolecular interaction between one of the sulfone oxygen atoms and a methyl group. Significantly, the strong intermolecular N-H···O=C between the amides, which was the key structure-defining feature in the sulfide and sulfoxide structures, was disrupted on oxidation to the sulfone, therefore altering very substantially the crystal packing of the molecule.

To investigate the solution properties of compounds **2** and **3** NMR studies were undertaken. Results from NOESY 2D NMR experiments did not result in any substantial correlation between spectroscopic features and the solid state interactions.

In conclusion, the predicted change in molecular conformation of the sulfide **2** to the sulfoxide **3** and sulfone **4** was observed as a direct result of altering the oxidation state of sulfur and therefore impacting on the key hydrogen bonding features in the solid state. This significant result, particularly the observed rotation of the diphenylacetylene unit after oxidation, may lead to future applications in a molecular switching mechanism.

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Notes and references

[a]*Department of Chemistry, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland.*

[b]*Department of Chemistry and School of Pharmacy, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland.*

† Electronic Supplementary Information (ESI) available: Synthetic procedures for **1**-**4**; computational studies on **3**.

‡Single crystal X-ray diffraction data were collected on either a Bruker SMART X2S diffractometer (**2**) or a Bruker APEX II DUO diffractometer (**3** and **4**). All calculations and refinement were made using the APEX software,[16,17] and diagrams prepared using Mercury.[18]

Crystal data for **2**: $C_{22}H_{18}N_2OS$, M = 358.44, a = 18.140(3) Å, b = 5.0400(9) Å, c = 19.369(3) Å, V = 1770.8(5) Å^3, T = 300.(2) K, orthorhombic, space group $Pna2_1$, Z = 4, 13743 reflections measured, 3012 independent reflections (R_{int} = 0.0631). The final R_1 value was 0.0548 [$I > 2\sigma(I)$] and the final $wR(F^2)$ value was 0.1638 (all data).

Crystal data for **3**: $C_{22}H_{18}N_2O_2S$, M = 374.44, a = 8.8488(15) Å, b = 21.149(4) Å, c = 10.0801(17) Å, β = 98.541(4)°, V = 1865.5(5) Å^3, T = 296.(2) K, monoclinic, space group $P2_1/c$, Z = 4, 19006 reflections measured, 3277 independent reflections (R_{int} = 0.0763). The final R_1 value was 0.057 [$I > 2\sigma(I)$] and the final $wR(F^2)$ value was 0.175 (all data).

Crystal data for **4**: $C_{22}H_{18}N_2O_3S$, M = 390.44, a = 10.511(2) Å, b = 34.171(8) Å, c = 11.778(3) Å, β = 113.517(5)°, V = 3879.0(15) Å^3, T = 296.(2) K, monoclinic, space group $P2_1/n$, Z = 8, 21664 reflections measured, 7387 independent reflections (R_{int} = 0.0505). The final R_1 value was 0.0504 [$I > 2\sigma(I)$] and the the final $wR(F^2)$ value was 0.1279 (all data).

The crystallographic data for **2**-**4** have been deposited with the Cambridge Crystallographic Data Centre, CCDC numbers 891708−891710. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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