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Hydrogen bonding in aromatic formamides

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The solid state structures of two *p*-substituted aromatic formamides have been determined. *p*-Nitro formamido benzene (**1**) crystallizes in the monoclinic space group C2/*c* with $a = 10.9859(7)$, $b = 10.0576(7)$, $c = 13.0331(9)$ Å, $\beta = 97.148(1)^\circ$ and $Z = 8$. *p*-formamido anisole (**2**) crystallizes in the orthorhombic space group $Pna2_1$ with $a = 10.5598(7)$, $b = 7.6553(5)$, $c = 9.2522(6)$ Å and $Z = 4$. Both compounds show hydrogen bonding in the solid state, forming infinite chains via N—H···O=C bridges. For the anisole formamide (**2**), the molecules exhibit in a zig-zag arrangement. The nitro compound (**1**) exhibits a spiral-like wavy line with a fourfold repeating unit, making it the first formamide having a chiral N—H···O bridged chain reminiscent of those found for α-helices in proteins. While the individual spirals of **1** are orientated either clockwise or counterclockwise, their orientation towards each other is random.

KEY WORDS: Formamides; hydrogen bonding; disorder; infinite chain; spiral; disorder.

Introduction

When polypeptides fold into proteins, dimers and chains of N—H···O amide hydrogen bonds are formed in various secondary structural motifs such as pleated β-sheets and α-helices.[1] In computational studies, these hydrogen bonds have usually been modeled by pair wise interactions between individual hydrogen bond donors and acceptors. Using these effective two-body interactions it was possible in some cases to simulate the actual many-body problem. However, it is becoming increasingly apparent that cooperative interactions involving many molecules have to be taken into account.[2,3]

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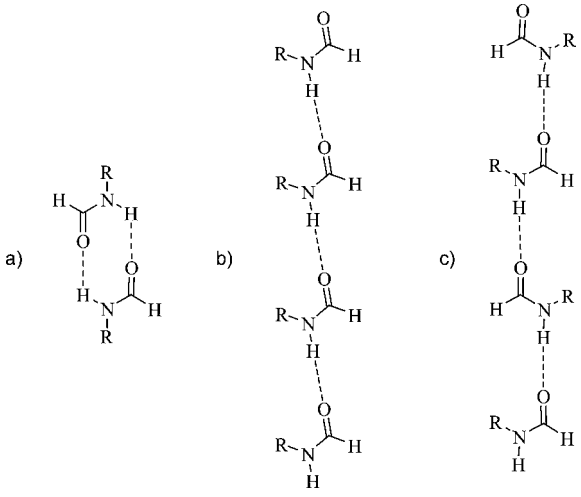
The need for a simplified model for biological macromolecules such as proteins is evident. This model has to contain both C=O and N—H units which are able to form N—H···O hydrogen bonds, and formamide, the smallest model to meet these requirements, becomes an obvious choice. In several computational-structural studies, monomeric and dimeric formamides were compared with one and two dimensional formamide chains as models for α-helices and β-pleated sheets in proteins.[4] One study on H-bonded formamide chains of various lengths revealed that the strength of internal hydrogen bonds in chains may be up to 2.5 times larger than that in an isolated dimer.[5] This emphasizes again the need for the incorporation of cooperative effects.

While formamide was successfully applied as a model compound in computational studies, it may not be the best choice as a real structural

model for proteins. In particular, formamide itself has an unsubstituted NH_2 group with two hydrogen atoms per amino group being available for hydrogen bonding. It therefore does not form chains in the solid state. Instead, its structure is composed of puckered layers and each layer can be described either as being built from alternating zig-zag chains or from cyclic dimers of the $HCONH_2$ unit.[6] The hydrogen bonds within the zig-zag chains seem to be stronger than those within the cyclic dimers, as is reflected by the N—H···O bond lengths of 2.88 and 2.93 Å, respectively. Proteins have only one amino hydrogen atom per formamide unit and the formation of multiple hydrogen bonds per amino group is therefore not possible. Thus, when looking for a structural model for the formation of hydrogen bonds in proteins N-substituted formamides may be a better choice.

To date three types of hydrogen bonding interactions have been found in N-substituted formamides: dimers and two types of chains with N—H···O bridges (Scheme 1). The chains are much more prevalent than dimers, and a search of the Cambridge Structural Database[7] revealed



Scheme 1. Hydrogen bond interactions found for N-substituted formamides in the solid state. (a) formamide dimers (b) chains with a repeating unit of one molecule (c) chains with a repeating unit of two (every second molecule is rotated with respect to the preceding one).

only 4 hydrogen bonded dimers, in contrast to 39 chain like hydrogen bonded networks (12 of type (b) and 27 of type (c)). The chain like structures (b) and (c) can serve as models for the hydrogen bonding networks found in pleated β-sheets, and form (c) resembles very closely the motif found in antiparallel β-pleated sheets. However, having repeating units of only one or two, neither motifs (b) nor (c) are good models for α-helices[8] since they lack the chiral characteristics of α-helices where each formamide unit is turned by 40° while the N—H···O chains spiral around the center of the α-helix.

In this context, we report two X-ray structures of aromatic formamides. By changing the substituent in their *para*-positions from a methoxy to a nitro group, a distinctive change of the hydrogen bonding arrangement is observed. In addition, *p*-nitro formamido benzene is the first structurally characterized formamide exhibiting a chiral spiral-like N—H···O chain similar to those found in an α-helices.

Experimental

The title compounds were synthesized from the amines by heating them at reflux in a solution of 80% formic acid for 1 hour. *p*-nitro formamido benzene was precipitated with water, filtered off, washed with water until neutral, dried in vacuo, and recrystallized from hot acetone to get a yellow microcrystalline powder. Single crystals were grown from acetone by cooling to 0 °C. *p*-Formamido anisole was extracted from the formic acid solution with ether. The ether extract was dried with $MgSO_4$ and the compound was crystallized from ether and recrystallized twice to get pale purple crystals.

Diffraction data of both compounds have been collected with a 'Bruker AXS SMART APEX CCD' diffractometer at 100 K using monochromated Mo Kα radiation with the omega scan technique. The unit cell was determined using SAINT+[9] and the structure was solved by direct methods and refined by full matrix least squares against F^2 with all reflections

using SHELXTL.[9] Refinement of an extinction coefficient was found to be insignificant. All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were taken from the difference Fourier map and were refined isotropically. Compound (**1**) exhibits a flipping disorder for the formamido substituent, and the N−H and C−H bond lengths in both disordered fragments have been restrained to be equal with an effective standard deviation of 0.02 using the SADI command. The occupancies were found to be 1:1. Crystal data and experimental details are listed in Table 1.

Results and discussion

Molecular representations of both molecules are shown in Figs. 1 and 2. Tables 2 and 3 summarize selected bond lengths and angles of the molecules. The nitro formamido benzene (**1**) shows a flip-flop disorder of the formamido group (Fig. 1), with the occupancies being each one half.

Neither molecule is perfectly planar and the functional groups are not totally in the planes of the benzene rings. For the nitro derivative (**1**), the deviation is less pronounced and the average torsion angle of the formamido group with the aromatic ring is 8.2(4)°. The torsion angle of the nitro group towards the aromatic ring is 16.0(2)°. For **1**, a substantial conjugation of both the nitro and the formamido group with the π-orbitals of the benzene ring can be assumed. For the anisole derivative (**2**), the torsion angle of the methoxy group is similar (11.7(1)°), but the average torsion angle of the formamido group

Table 1. Crystal Data and Structure Refinement of **1** and **2**

Empirical formula	$C_7H_6N_2O_3$	$C_8H_9NO_2$
Formula weight	166.14	151.16
Solvent	Acetone	Diethylether
Crystal habit	Yellow fragment	Pale purple fragment
Temperature (K)	100(2)	100(2)
Crystal system	Monoclinic	Orthorhombic
Space group	C2/*c*	$Pna2_1$
Unit cell dimensions		
a (Å)	10.9859(7)	10.5598(7)
b (Å)	10.0576(7)	7.6553(5)
c (Å)	13.0331(9)	9.2511(6)
β (°)	97.148(1)	
Volume (Å^3)	1428.86(17)	747.84(8)
Z	8	4
Density (calculated, g cm^{-3})	1.545	1.343
Absorption coefficient (mm^{-1})	0.124	0.097
F(0 0 0)	688	320
Crystal size (mm)	0.40 × 0.36 × 0.15	0.5 × 0.30 × 0.18
θ range for data collection (°)	2.76–28.31	3.29–28.30
Index ranges	$-14 \le h \le 14$, $-13 \le k \le 10$, $-17 \le l \le 17$	$-14 \le h \le 14$, $-10 \le k \le 10$, $-12 \le l \le 12$
Reflections collected	7118	7279
Independent reflections	1766 [$R_{int} = 0.0248$]	1855 [$R_{int} = 0.0267$]
Reflections with $I > 2\,\sigma(I)$	1722	1815
Absorption correction	Semiempirical from multi scans	Semiempirical from multi scans
Min./max. transmission	0.8367/0.9800	0.786/0.980
Data/restraints/parameters	1766/2/160	1855/1/136
Goodness-of-fit on F^2	1.170	1.075
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0431$, $wR_2 = 0.1154$	$R_1 = 0.0314$, $wR_2 = 0.0836$
R indices (all data)	$R_1 = 0.0436$, $wR_2 = 0.1158$	$R_1 = 0.0320$, $wR_2 = 0.0840$
Largest diff. peak and hole (eÅ^{-3})	0.383 and –0.424	0.263 and –0.171

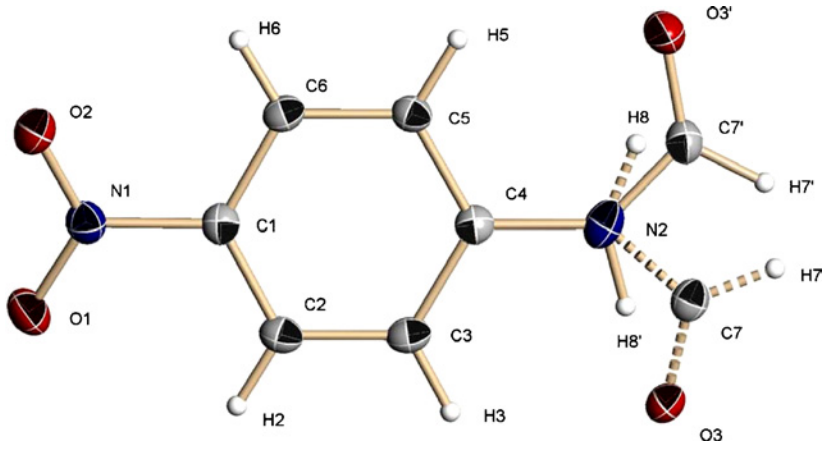


Fig. 1. ORTEP representation of **1**, ellipsoids at 50% probability. The occupancy ratio for the disordered fragments is 1:1.

with the benzene ring is 27.49(6)°, thus reducing the effective conjugation of the π-orbitals of formamido and aromatic moieties by about 50% compared to the coplanar case.

Both molecules form hydrogen bonded infinite chains in the solid state. For the anisole derivative (**2**), a zig-zag arrangement is found similar to those found for most other formamide derivatives (see Fig. 3). The N—H···O bonding distance is 2.830(2) Å which is in the usual range and is only slightly shorter than observed for the zig-zag chains of formamide itself.[6] The value for the H···O hydrogen bonding distance itself is 2.025(21) Å.

For the nitro formamido benzene (**1**), the hydrogen bonding situation is more complicated. The occupancies of the flip-flop disordered formamide groups is 1:1. In order to avoid overlap of the formamide groups of neighboring molecules, the orientation of the disordered formamide groups cannot be random, but every second molecule in the N—H···O chains has to be oriented in the opposite direction. This results in the formation of an infinite chain with a fourfold repeating unit (see Fig. 4). The N—H···O distances in (**1**) are 2.924(2) and 2.860(2) Å, respectively, and the corresponding H···O hydrogen bonding distances are 1.977(38) and 1.983(35) Å.

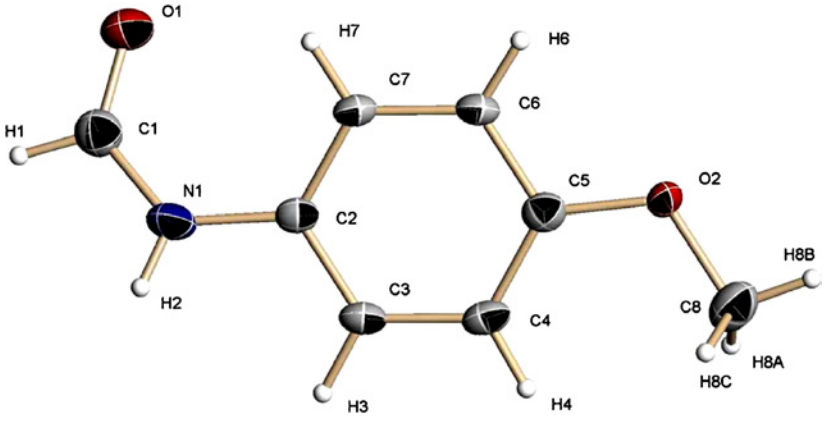


Fig. 2. ORTEP representation of **2**, ellipsoids at 50% probability.

Table 2. Selected Bond Lengths (Å) and Angles (°) for **1**.

Bond lengths (Å)	
N(2)–C(7′)	1.245(3)
N(2)–C(7)	1.308(3)
N(2)–H(8)	0.95(3)
N(2)–H(8′)	0.94(3)
C(7)–O(3)	1.222(3)
C(7′)–O(3′)	1.221(3)
C(7)–H(7)	0.98(2)
C(7′)–H(7′)	0.99(2)
N(2)–C(4)	1.4022(16)
C(2)–C(3)	1.3825(19)
C(2)–C(1)	1.3891(18)
C(4)–C(5)	1.4007(17)
C(4)–C(3)	1.4015(17)
C(1)–C(6)	1.3853(17)
C(6)–C(5)	1.3873(17)
N(1)–O(1)	1.2322(15)
N(1)–O(2)	1.2343(15)
N(1)–C(1)	1.4608(16)
Bond angles (°)	
C(7′)–N(2)–C(4)	134.27(18)
C(7)–N(2)–C(4)	136.73(17)
C(7)–N(2)–H(8)	112(3)
C(7′)–N(2)–H(8′)	120(3)
C(4)–N(2)–H(8′)	105(3)
C(4)–N(2)–H(8)	111(3)
O(1)–N(1)–O(2)	123.27(12)
O(1)–N(1)–C(1)	118.55(11)
O(2)–N(1)–C(1)	118.17(11)
C(3)–C(2)–C(1)	118.77(12)
C(5)–C(4)–C(3)	120.15(11)
C(5)–C(4)–N(2)	119.61(11)
C(3)–C(4)–N(2)	120.25(12)
C(6)–C(1)–C(2)	122.41(12)
C(6)–C(1)–N(1)	118.56(11)
C(2)–C(1)–N(1)	119.03(11)
C(1)–C(6)–C(5)	118.71(11)
C(6)–C(5)–C(4)	119.95(11)
C(2)–C(3)–C(4)	120.01(12)
O(3)–C(7)–N(2)	121.9(2)
O(3)–C(7)–H(7)	122(2)
N(2)–C(7)–H(7)	116(2)
O(3)–C(7)–H(7′)	158.8(10)
N(2)–C(7)–H(7′)	78.3(10)
H(7)–C(7)–H(7′)	38(2)
O(3)–C(7)–H(8′)	79(3)
N(2)–C(7)–H(8′)	44(3)
C(7)–O(3)–H(8′)	33(2)
O(3′)–C(7′)–N(2)	125.0(3)
O(3′)–C(7′)–H(7′)	128.0(19)
N(2)–C(7′)–H(7′)	106.9(19)

Table 3. Selected Bond Lengths [Å] and Angles [°] for **2**.

Bond lengths (Å)	
N(1)–C(1)	1.3377(16)
N(1)–C(2)	1.4203(15)
N(1)–H(2)	0.82(2)
O(2)–C(5)	1.3678(14)
O(2)–C(8)	1.4313(15)
C(2)–C(3)	1.3924(15)
C(2)–C(7)	1.3983(16)
C(5)–C(6)	1.3932(16)
C(5)–C(4)	1.3948(17)
C(7)–C(6)	1.3832(17)
C(4)–C(3)	1.3916(17)
O(1)–C(1)	1.2297(16)
C(1)–H(1)	0.936(18)
Bond angles (°)	
C(1)–N(1)–C(2)	126.53(11)
C(1)–N(1)–H(2)	116.1(14)
C(2)–N(1)–H(2)	117.1(13)
C(5)–O(2)–C(8)	116.83(10)
C(3)–C(2)–C(7)	119.45(10)
C(3)–C(2)–N(1)	118.44(10)
C(7)–C(2)–N(1)	122.08(10)
O(2)–C(5)–C(6)	115.53(10)
O(2)–C(5)–C(4)	124.69(10)
C(6)–C(5)–C(4)	119.78(11)
C(6)–C(7)–C(2)	119.71(10)
C(3)–C(4)–C(5)	119.34(11)
C(4)–C(3)–C(2)	120.88(10)
C(7)–C(6)–C(5)	120.80(11)
O(1)–C(1)–N(1)	126.30(12)
O(1)–C(1)–H(1)	119.3(12)
N(1)–C(1)–H(1)	114.4(12)

In contrast to the hydrogen bonded chains formed by α-helices in proteins, **1** does not form real spirals. Instead, all of the formamide units are located roughly in one plane (Fig. 5) and the hydrogen bonds exhibit a wavy line shape (Fig. 4). The aromatic substituents are sticking out above and below that plane (Fig. 5). This, combined with the polar directionality on the hydrogen bonded chain, makes each individual chain chiral and the wavy line has to be described as rotating either clockwise or counterclockwise. The space group of **1** is C2/*c*, which is not chiral, and the achirality of the crystal as a whole can thus only be explained by assuming that the orientation of each individual spiral like chain must be random, while that of the formamido

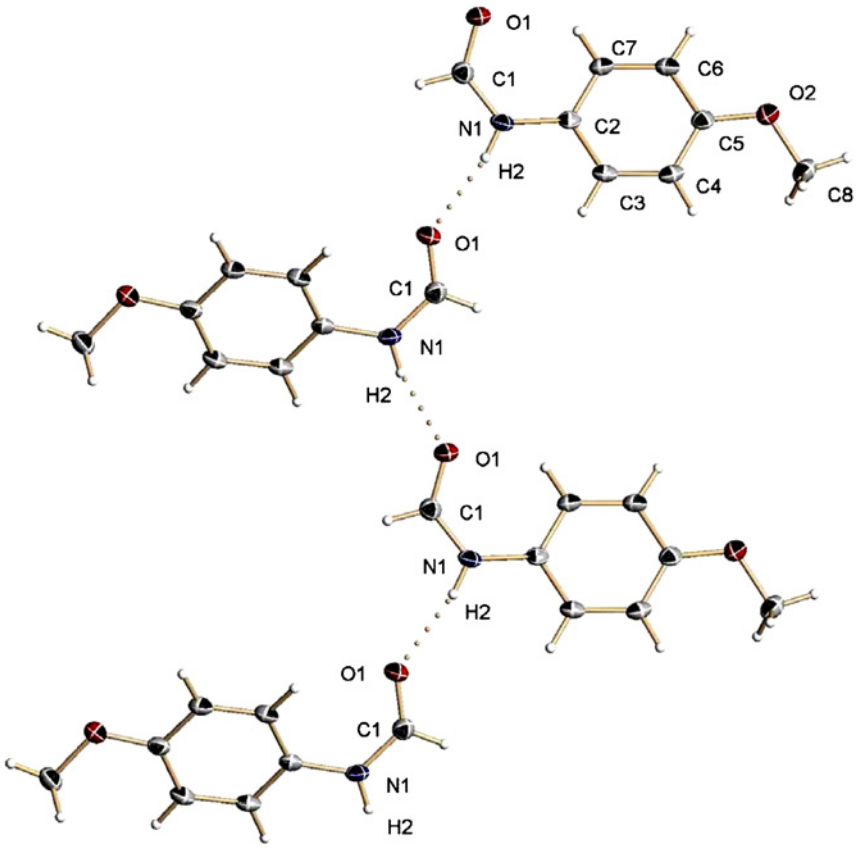


Fig. 3. Representation of the hydrogen binding in **2**. The hydrogen bond chain is aligned along the *c*-axis.

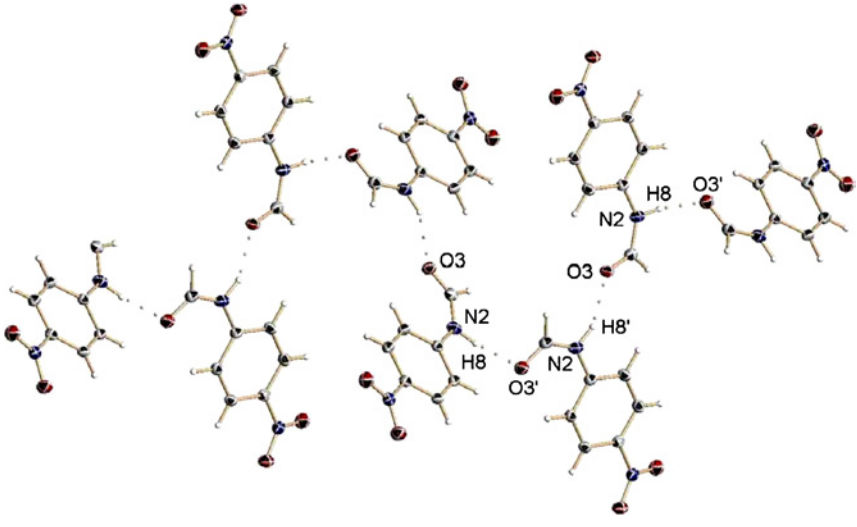


Fig. 4. Representation of the hydrogen binding in **1**. The hydrogen bond chain is aligned along the *c*-axis.

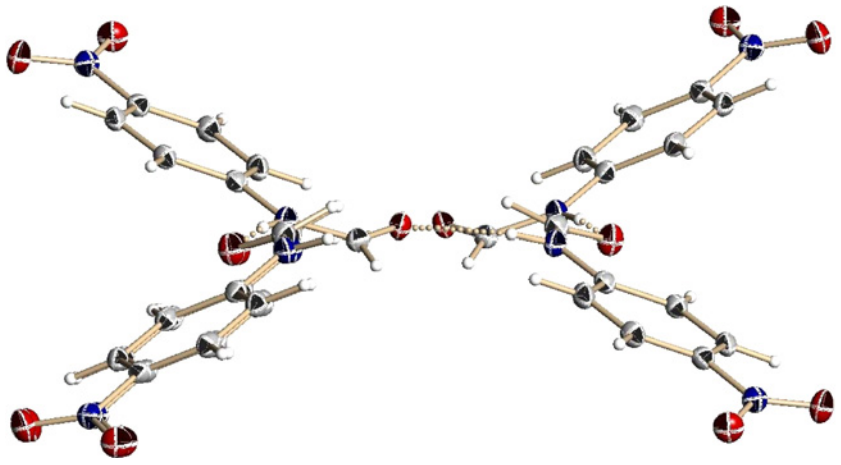


Fig. 5. Representation of the hydrogen binding in **1** showing the plane formed by the hydrogen bonded formamide units and the aromatic substituents pointing above and below the plane. View along the *c*-axis.

groups within each wavy chain is determined by the orientation of the neighboring molecules along the chain. This results in a random one to one occupation of the disordered formamido orientations with the individual spiral-like wavy chains being either clockwise or counterclockwise oriented.

Supplementary material CCDC-215451 and CCDC 215452 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033; email: deposit@ccdc.cam.ac.uk].

Acknowledgments

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