Further insight into three center hydrogen bonding. Participation in tautomeric equilibria of heterocyclic amides

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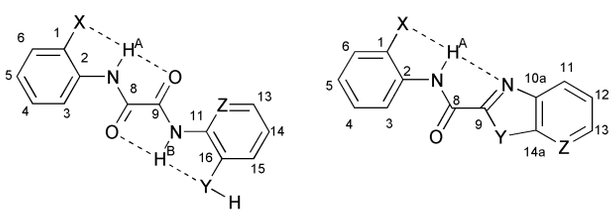
In this work the synthesis and characterization in solution and solid state of three heterocyclic oxamides and four amides capable of forming three center hydrogen bond (THB) interactions is described. The formation of THBs in solution was established and studied by multinuclear and VT ^{1}H magnetic resonance, by which the $\Delta\delta/\Delta T$ values could be directly related with proton mobility. The molecular structure of two oxamides in the solid state was determined by X-ray diffraction experiments. The results showed that amides with S(n)S(5)S(6) (n = 5, 6 for –OMe and –NO_2 respectively) motifs were less prone to establish tautomeric equilibria in solution than those with the simpler S(n)S(5) motif.

Introduction

Hydrogen bonds (HB) are of central importance for the maintenance of three-dimensional conformations of proteins and nucleic acids, and play key roles in the recognition of ligand molecules and in the modulation of enzymatic reactions.[1] Among the many forms of hydrogen bonding, the three center hydrogen bond (THB) has been a subject of increasing interest.[2] The THB can be described as that configuration where a H atom is surrounded by three electronegative atoms, lying in or close to the plane defined by them (the sum of the angles at H must be close to 360°). In this configuration the H atom is covalently bonded to one of them and hydrogen bonded to the other two[3] with interaction lengths shorter than the sum of their van der Waals radii. Currently, there is increasing interest in the design of synthetic building blocks for the study of the assembly of protein tertiary structures. In this sense, intramolecular three center hydrogen bonding makes an important contribution to backbone rigidification, and allows the formation of oligoamides with helical or curved conformations[4] and well defined cavities.[5] Recently, these uncommon and non-conventional HBs have been postulated to explain the transition state structure proposed for the oxygen transfer processes in MCPBA epoxidations.[6]

In a previous publication,[7] THB formation in a series of oxamides and its effect on their molecular conformation were demonstrated by multinuclear MR and VT experiments. Following on from this investigation, herein we present our results on a study of a series of heterocyclic oxamides **2**–**4**, amides **5**–**8**, and ethyl *N*-(2-nitrophenyl)oxalamate **9** in solution and in solid state in order to determine the role of tautomerism in intramolecular THB formation (Scheme 1). The link between the three centre hydrogen bonding properties of amides and their tautomerism is of primary importance since many amino acids are able to form tautomers, and hence the expected conformation of oligoamides could be modulated through these interactions. In addition the X-ray structures of **2** and **4** are discussed, comparing the results in the solid state with those obtained in solution.



1 X = OMe, Y = O, Z = CH
2 X = OMe, Y = O, Z = N
3 X = OMe, Y = NH, Z = N
4 X = NO_2, Y = O, Z = N

5 X = OMe, Y = O, Z = CH
6 X = OMe, Y = NH, Z = CH
7 X = OMe, Y = NH, Z = N
8 X = NO_2, Y = NH, Z = CH

Scheme 1

Results and discussion

Three centre hydrogen bonding in solution

The chemical shift of the amide proton NH^A of compounds **1**–**9** is strongly influenced by the nature of the group X (Table 1). The substituent change from OMe to NO_2 strongly deshields the NH^A resonance by more than 1.5 ppm, in agreement with the increased electronegativity of the nitro group. The signals of the OH and NH protons of **2** and **4** were observed at high frequencies as a set of one fine signal and two broad signals at room temperature. ^{15}N/^{1}H heteronuclear correlation experiments were carried out to confirm the assignments of these signals. In addition, NOE experiments were conducted to distinguish between NH^A and NH^B in compound **2**. Saturation of the NH fine signal at 9.83 ppm gave NOE effects of 2.5% and 1.2% on the characteristic signals of hydrogen 3-H and the OMe group, respectively. Therefore this signal was assigned to the NH^A and the signal at 10.47 to the NH^B hydrogen. The corresponding signals of the oxamide **3** were assigned for comparison.

An amide hydrogen already firmly involved in an intramolecular hydrogen bond can be only a poor hydrogen bond donor to a HBA (hydrogen bond acceptor) solvent. Equilibration between non-hydrogen bonded and hydrogen bonded forms is usually rapid on the NMR time scale for small

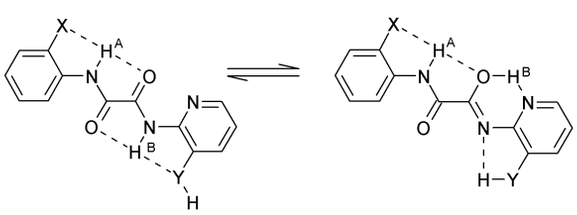
Table 1 ^{1}H NMR chemical shifts of 3-H, NH and OH (ppm) at 25 °C and $\Delta\delta/\Delta T$ (ppb K^{-1}) in [$^2H_6$]DMSO for compounds **1**–**9**

Compound	δ(3-H)	$-\Delta\delta(NH^A)/\Delta T$ [$\delta(NH^A)$]	$-\Delta\delta(NH^B)/\Delta T$ [$\delta(NH^B)$]	$-\Delta\delta(YH)/\Delta T$ [$\delta(YH)$][a]
1[b]	8.13	1.135 ± 0.01 [9.96]		
2	8.18	1.09 ± 0.01 [9.83]	4.53 ± 0.03 [10.47]	4.0 ± 0.1 [10.24]
3	8.25	0.91 ± 0.02 [9.79]	4.22 ± 0.01 [10.34]	3.8 ± 0.1 [5.88]
4	8.28	2.44 ± 0.01 [11.63]	4.31 ± 0.03 [10.51]	4.5 ± 0.1 [10.31]
5	8.20	1.17 ± 0.02 [9.89]		
6	8.36	0.50 ± 0.01 [9.91]		
7	8.33	1.10 ± 0.02 [9.94]		
8	8.42	2.44 ± 0.02 [11.80]		
9	8.10	3.19 ± 0.03 [11.38]		

[a] X = O, NH. [b] Data from ref. 7.

oligoamides, and therefore the observed amide chemical shifts [δ(NH)] values are only population weighted averages of the contributing forms. On the basis of these arguments, the chemical shift dependence on the temperature ($\Delta\delta/\Delta T$) in an HBA solvent such as [$^2H_6$]DMSO provides a very useful tool to establish THB formation. The NH^A of the heterocyclic oxamides **2**–**4** and the amide NH proton in **5**–**9** are involved in a strong THB interaction. This is shown by the low $\Delta\delta/\Delta T$ (Table 1) below 3.0 ppb K^{-1}, which is in close agreement with the values measured for the amide proton in model compound **1**.[8]

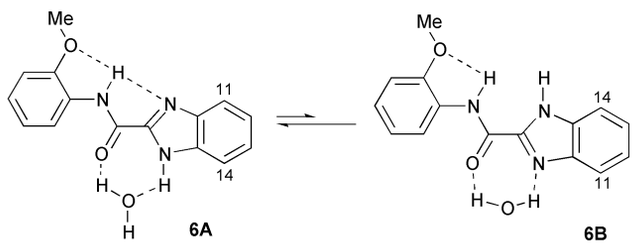
Although the chemical environment of the NH^B hydrogen in oxamides **2**–**4** is similar to the aforementioned NH^A group, it is not involved in THB interaction in solution ($\Delta\delta/\Delta T$ higher than 3.0 ppb K^{-1}). An explanation might be that in the heterocyclic oxamides **2**–**4** there exists an important contribution to the NH^B proton mobility due to its participation in tautomeric equilibria. It is well known that 3-hydroxypyridines are involved in a tautomeric equilibrium between the neutral and zwitterionic forms in highly polar solvents or in the presence of water.[9] The amide proton NH^B participates in this equilibrium (Scheme 2) as was observed in variable temperature experi-



Scheme 2

ments, which showed the coalescence of NH^B and OH signals at 100 °C for **2** and at 90 °C for **4**, respectively. In agreement, the $\Delta\delta$(YH)/ΔT values in **2**–**4** were lower than expected [$\Delta\delta$(OH)/ΔT = −6.5 ppb K^{-1}] in the analogous compound *N*,*N*′-bis-(2-hydroxyphenyl)oxamide[7] and very similar to the $\Delta\delta/\Delta T$ of the NH^B moiety (Table 1).

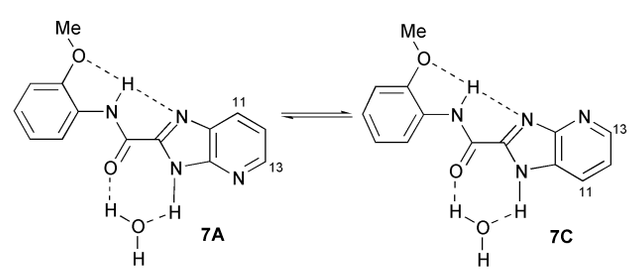
In contrast, for amides **5**–**8** the THB remains as strong as in those molecules that are not capable of tautomeric equilibrium (model compound **1**). In these amides the pyridine-like nitrogen N-10 is directly involved in the formation of a THB, nevertheless the tautomeric equilibrium is maintained as is shown by the broad signals in both ^{1}H and ^{13}C NMR spectra for the benzimidazole ring. In the presence of small quantities of water the tautomeric equilibrium is frozen and all the resonances for the benzimidazole ring can be observed and assigned. The pyrrole-like NH group realises a fast proton exchange with water while the pyridine-like nitrogen is strongly involved in the THB interaction. As shown in Scheme 3 for compound **6**, the water molecule can be intermolecularly hydrogen bonded to the C=O and NH groups. With increasing temperature the tautomeric equilibrium is restarted on the NMR time scale. At room



Scheme 3

temperature the 11-H and 14-H resonances of compound **6** (doped with eight water molecules), appeared at 7.84 and 7.59 ppm respectively. After heating, both signals became closer to each other, and at 150 °C the four benzimidazole ring hydrogens looked like an AA′BB′ spin system. For the nitro analogue **8** only one molecule of water was needed to freeze the equilibrium; at room temperature two independent signals for 11-H (7.85 ppm) and 14-H (7.60 ppm) could be observed, which coalesced over 120 °C.

In the case of the imidazo[4,5-*b*]pyridine derivative **7**, two signals of equal intensity could be observed for the pyrrole-like NH at 14.3 and 13.9 ppm. The signals for the pyridine hydrogens 11-H and 13-H appeared as broad singlets at 8.52 and 8.13 ppm, respectively, at room temperature. This means that the two isomers **A** and **C** (Scheme 4) are present in equal propor-



Scheme 4

tions.[10] With an increase in temperature, the equilibrium became faster, the pyrrole-like NH signals coalesced, and the broad 11-H and 13-H appeared as very well defined doublets of doublets with the same chemical shift. FT-IR studies in Ar matrices of hydrogen bonding between benzimidazole and water have indicated similar abundance of the NH···OH$_2$ and N···HOH tautomers.[11] In contrast to the above results it was inferred that the three hydrogen bonding interactions in **6**–**8**, in the presence of small quantities of water, are strong enough to shift the tautomeric equilibrium to the more bonded form **A** or **C** through the intermediate **B**.

Three centre hydrogen bonding in solid state

In the solid state, the oxamides **4** and **2** form the two expected THBs (Fig. 1 and 2, respectively). In both molecular structures the neighbouring amide moieties adopt an *anti* conformation relative to each other (O(7)C(7)C(8)O(9) = −179.0(2)°,

Table 2 Geometric features of some THB systems

Compound	Ring size	THB motif A···H···A	Interaction length/Å	A···H···A Angle/°	Σ∠(H)[h] /°
2	S(5)–S(5)	HO···H···O=C	2.316(2), 2.091(2)	144.4(2)	359.9(2)
	S(5)–S(5)	MeO···H···O=C	2.286(2), 2.317(2)	146.8(2)	348.4(2)
4	S(5)–S(5)	HO···H···O=C	2.115(2), 2.243(2)	174.2(2)	359.3(2)
	S(6)–S(5)	NO_2···H···O=C	1.780(2), 2.205(2)	121.0(2)	359.3(2)
From ref. 8[a]	S(5)–S(5)	HO···H···O=C	2.172(2), 2.138(2)	149.8(2)	360.3(2)
From ref. 8[b]	S(5)–S(5)	HO···H···O=C	2.15(3), 2.22(3)	135.3(3)	358.7(2)
From ref. 4b[c,g,i]	S(5)–S(6)	N(sp^2)···H···O=C	2.14, 2.08	111.8	354.8
	S(5)–S(6)	N(sp^2)···H···O=C	2.18, 1.90	107.5	358.3
From ref. 4b[d,g]	S(6)–S(6)	N(sp^2)O···H···O=C	1.83, 2.13	101.8	360.0
From ref. 5[e,g]	S(5)–S(6)	MeO···H···OMe	2.147, 1.926	108.0	359.9
From ref. 5[f,g]	S(5)–S(6)	MeO···H···OR	2.226, 2.021	115.0	359.3
	S(5)–S(6)	MeO···H···OMe	2.162, 1.960	111.9	358.3

[a] *N*,*N*′-Bis(2-hydroxyphenyl)oxamide. [b] Ethyl *N*-(2-methoxyphenyl)oxalamate. [c] Pyridinedicarboxamide. [d] *N*-Oxide of pyridinedicarboxamide. [e] 1-(2,4-Dimethoxy-4-nitrobenzoylamino)-2-methoxybenzene. [f] 1-{5-[2,4-Bis(octyloxy)-5-nitrobenzoylamino]-2,4-dimethoxybenzoylamino}-2-methoxybenzene. [g] Undefined mean deviations. [h] Sum of angles at H. [i] Mean value of two independent molecules in the asymmetric unit, taken directly from CCDC.

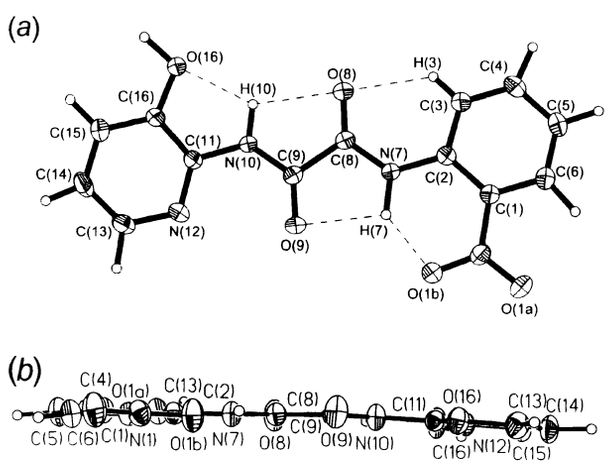


Fig. 1 Molecular structure of compound **4**, DMF molecule not shown. (a) Three center hydrogen bonding interactions (see text and Table 2); (b) lateral view, selected dihedral angles (°): O(9)C(9)C(82)-N(7) 178.3, N(10)C(11)C(16)O(16) 0.8, N(7)C(8)C(9)N(10) −177.4, C(9)C(8)N(7)C(2) 179.1, C(8)C(9)N(10)C(11) −176.8, N(7)C(2)C(1)-N(1) 2.27.

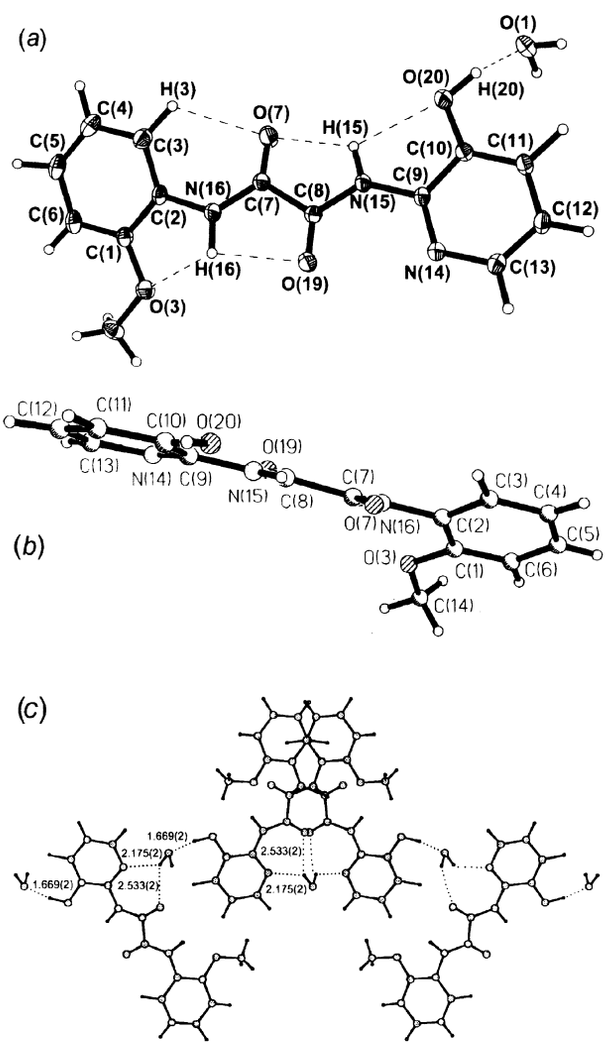


Fig. 2 Molecular structure of compound **2**. (a) Three center hydrogen bonding interactions (see text and Table 2); (b) lateral view, selected dihedral angles (°): O(3)C(1)C(2)N(16) 2.79, N(16)C(7)C(8)O(19) 1.19, N(16)C(7)C(8)N(15) −179.4, N(15)C(9)C(10)O(20)179.7, O(7)C(7)C(8)-O(19) −179.0; (c) crystal packing structure showing intermolecular HB interactions and the pair-wise arrangement of the methoxyphenyl rings which lead to non planar arrangement (view along *c* axis).

O(8)C(8)C(9)O(9) = 178.3(2)° for **2** and **4**, respectively). Both structures were almost planar forming four main rings due to the O···H···O hydrogen bonding interactions and at least one secondary ring due to the C–H···O close contacts. The shortest interaction corresponds to the six membered ring S(6)[12] in compound **4** with a N(7)H···ONO contact length of 1.780(2) Å. In the same compound, the five membered ring S(5) showed a larger N(7)H···OC contact length of 2.205(2) Å. The combined interactions define the first S(6)S(5) type THB with an O···H···O angle of 121.0(2)°. The three electronegative atoms lie almost in the same plane (Fig. 1a), since the sum of angles at H [Σ∠(H) = N–H···OC + N–H···O + O···H···O] is 359.3(2)°. The other THB is formed by two five-membered rings of the S(5)S(5) type, with contact lengths of HO···H(10) ···OC of 2.115(2) and 2.243(2) Å, respectively. The O···H···O angle of 174.2(2)° was linear and Σ∠H = 359.3(2)°. The planes of both THBs in **4** were parallel to each other [dihedral angle of 3.4(2)° between the nitrophenylamide plane and the hydroxypyridine-amide plane] resulting in a completely flat molecule (Fig. 1b).

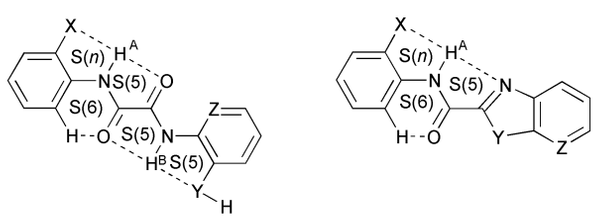
The molecular structure of compound **2** (Fig. 2a) showed the formation of two S(5)S(5) type THBs, with contact lengths of 2.286(2) and 2.317(2) Å for MeO···H(16)···OC moiety, an O···H···O angle of 146.8(2)° and Σ∠H = 348.4(2)° for the first THB system. The second THB system was consisted of HO···H(15)···OC interaction lengths of 2.316(2) and 2.091(2) Å, respectively, an O···H···O angle of 144.4(2)°, and Σ∠H = 359.9(2)°.

In contrast to the molecular structure of the nitro analogue **4**, the oxamide **2** is not as flat as expected since the dihedral

angle between the plane formed by the methoxyphenyl ring and the plane formed by the pyridine ring and the oxalyl moiety was of 29.5° (Fig. 2b). This important deviation from planarity was caused by intermolecular interactions with one molecule of water. This water molecule was bridging two molecules of compound **2** through the pyridine nitrogen atom and the hydroxy group with N···HOH and OH···OH_2 lengths of 2.175(2) and of 1.669(2) Å, respectively (Fig. 2c). These interactions imposed crystal packing constraints on the OMe group, bringing the methoxyphenyl ring out of plane. However, the dihedral angles next to the THB interaction were almost planar with values of 179.9(2)° for the O(20)C(10)C(9)N(15) and 0.44(2)° for the N(15)C(8)C(7)O(7) torsion angles.

THB geometry depends on the ring size and the type of acceptor: this conclusion can be drawn from A···H···A interaction lengths and angles obtained for **2** and **4** and from those values found in other systems.[4,5,8] A brief summary is shown in Table 2. As expected the A···H···A lengths are shorter in S(6) rings when compared to S(5) rings. The nature of the acceptor atom plays an important role in the interaction length, which becomes shorter when the acceptor atom bears a partial negative charge and remains almost constant with a neutral acceptor atom. The following series in decreasing order of A···H···A length can be established in both S(5) and S(6) rings: C=*O* ≈ N(sp^2) ≈ R*O* > N*O* > NO_2, considering only those systems in which the three acceptor and the hydrogen atom lie almost in the same plane.

The molecular structures of **2** and **4**, and the strong deshielding of the 3-H resonance (see Table 1) showed the formation of an additional intramolecular HB interaction between the aryl hydrogen C(3)–H and the carbonyl oxygen (O=C) of the amide group. The C–H···O lengths and bond angles [2.412(2) and 2.284(2) Å and 112.4(2) and 119.0(2)° for **2** and **4**, respectively] meet the geometry requirements to be considered as HB.[13] Recently estimated energies[13d] for this kind of interaction are in the range −3.0 ± 0.5 kcal mol^{-1}, suggesting its participation in the stabilization of the observed THB pattern. The role of secondary HB interactions in determining intermolecular HB networks have been widely studied,[14] and also as C=O lone pair intermolecular interactions with Cα–H and N–H protons have been observed in helical protein structures.[15] Therefore, the THB interactions described in this work, in solution and in the solid state, could be better depicted as a set of three hydrogen bonded rings forming a S(*n*)S(5)S(6) motifs (*n* = 5, 6 for OMe or NO_2, respectively) for the NH^A moiety in compounds **2**–**9** or as a simpler set of two rings forming a S(5)S(5) motif (Scheme 5)



X = -OMe (*n* = 5), -NO_2 (*n* = 6)

Scheme 5

for the NH^B moiety in compounds **2**–**4**. It is worthy of note that in solution this last hydrogen bond is disrupted due to the participation of the amide hydrogen NH^B in tautomeric equilibria in solution (*vide supra*).

Conclusions

The $\Delta\delta/\Delta T$ values have been shown to be a very useful tool to establish THB in solution. These values are directly associated with proton mobility, and allowed the establishment of amide NH participation in tautomeric equilibria. Two kinds of THB were described in this work, those composed of three rings S(*n*)S(5)S(6) (*n* = 5, 6), and those composed of two rings S(5)S(5), the former being less prone to participation in tautomeric equilibria. In the presence of small quantities of water, even in strong HA solvents such as DMSO, the THB interaction is strong enough to displace the tautomeric equilibria towards one preferred tautomer. The THB interaction is highly favoured as the principal interaction found in the solid state. In the solid state the geometry around a THB was dependent on the ring size and on the nature of the acceptor atoms. In contrast to the results obtained by *ab initio* calculations,[3] it was found that the distances and angles between the central amide NH group and the two neighbouring acceptor atoms (N(sp^2), –*O*R, *O*=C or –N*O*$_2$) are in agreement with the formation of a three center hydrogen bond. This was observed not only in those cases where six membered hydrogen bonded rings are formed but also for five membered rings. In those systems where the creation of a three center hydrogen bond has implied the formation of five membered rings, the distances between the central H atom and the acceptor atoms are longer than those expected for a six membered ring. Furthermore, the A···H···A angle in S(5)S(5) systems is almost linear whereas in S(6)S(5) systems it is between 110–120°, although the sum of angles at H (Σ∠H), in both systems, is close to 360°.

Experimental

Materials

1,2-Diaminobenzene, 2-aminophenol, 2,3-diaminopyridine, 2-amino-3-hydroxypyridine, 2-nitroaniline, ethyl chlorooxoacetate and toluene-*p*-sulfonic acid monohydrate were purchased from Aldrich and used as received. Ethyl *N*-(2-methoxyphenyl)oxalamate was synthesised as reported.[8] All new compounds were characterised by ^{1}H, ^{13}C and in the case of **4** additionally by ^{15}N NMR. The assignments were made on the basis of COSY and HETCOR experiments and compared to the reported values when possible.[16]

Methods

Melting points were measured on a Electrothermal IA 9100 apparatus, and are uncorrected. IR spectra were recorded on KBr discs using a Perkin-Elmer 16F PC IR spectrometer. Elemental analyses were performed in a Perkin-Elmer 2400 elemental analyser. Analytical data for compounds **2**–**4** and **6**–**9** are shown in Table 3. ^{1}H, ^{13}C and ^{15}N NMR spectra were recorded on a JEOL Eclipse 400 (^{1}H 399.78; ^{13}C 100.54 MHz) or Varian Mercury 300 (^{1}H, 300.08; ^{13}C 75.46 MHz) spectrometers in [$^2H_6$]DMSO solution, measured with $SiMe_4$ as internal reference following standard techniques.† Variable temperature experiments were performed on a JEOL Eclipse 400 spectrometer with a temperature controller to keep the temperature constant within 0.2 °C. The temperature was varied from 30–120 °C in 10° increments with a delay of 5 min for temperature stabilization. Each spectrum was obtained with 16 scans. ^{15}N NMR spectra were obtained as described[7] on a JEOL Eclipse 400 spectrometer at 40.53 MHz.

Preparation of oxamides and amides

Typical procedure. 0.50 g (2.24 mmol) of ethyl *N*-(2-methoxyphenyl)oxalamate or 0.50 g (2.1 mmol) of ethyl *N*-(2-nitrophenyl)oxalamate **9** and the equivalent amount of 1,2-diaminobenzene, 2-aminophenol, 2,3-diaminopyridine or 2-amino-3-hydroxypyridine and 10 mg of toluene-*p*-sulfonic acid as catalyst were suspended in 50 cm^3 of toluene. The

† The compound numbering used in the assignments in the NMR data does not correspond to systematic IUPAC numbering. The numbering system that has been used is given in Scheme 1.

Table 3 Analytical data for the oxamides **2**–**4**, amides **6**–**8** and oxalamate **9**

Compound (formula)	Yield (%)	Mp/°C (decomp.)	Found (%) (required)		
			C	H	N
2 ($C_{14}H_{13}N_3O_4$)	68	188 (decomp.)	58.2 (58.5)	4.6 (4.6)	14.6 (14.6)
3 ($C_{14}H_{14}N_4O_3$)	80	207	58.4 (58.7)	5.0 (4.9)	19.2 (19.6)
4 ($C_{13}H_{10}N_4O_5$)	60	211 (decomp.)	51.6 (51.7)	3.5 (3.3)	18.2 (18.5)
6 ($C_{15}H_{13}N_3O_2$)	63	274–275	67.3 (67.4)	5.0 (4.9)	15.1 (15.7)
7 ($C_{14}H_{12}N_4O_2$)	50	248–249	63.0 (62.7)	4.5 (4.5)	20.0 (20.9)
8 ($C_{14}H_{10}N_4O_3$)	62	314 (decomp.)	59.4 (59.6)	3.6 (3.6)	18.4 (19.8)
9 ($C_{10}H_{10}N_2O_5$)	90	105	50.2 (50.4)	4.1 (4.2)	11.5 (11.8)

resulting suspension was heated for 3 days under reflux with a Dean–Stark trap to eliminate water. The solution was cooled to room temperature and the resulting solid was filtered and crystallised from ethyl alcohol.

***N*-(3-Hydroxypyridine)-*N*′-(2-methoxyphenyl)oxamide 2.** Prepared from 0.50 g (2.24 mmol) of ethyl *N*-(2-methoxyphenyl)oxalamate, 0.25 g (2.24 mmol) of 2-amino-3-hydroxypyridine, and 0.010 g of the catalyst. After crystallisation, a slightly grey solid was obtained (0.44 g). ν_{max}(KBr)/cm^{-1} 3397 (NH), 1707 (CO); δ_H(399.78 MHz) 10.47 (1 H, s, NH^B), 10.26 (1 H, s, OH), 9.83 (1 H, s, NH^A), 8.18 (1 H, dd, *J* 8.3 and 1.2, 3-H), 7.93 (1 H, d, 13-H), 7.30 (1 H, dd, *J* 7.8 and 1.4, 15-H), 7.17 (3 H, m, 4-H, 5-H, 6-H), 7.03 (1 H, t, *J* 7.6, 14-H), 3.91 (3 H, s, OMe); δ_C(100.54 MHz) 158.4, 157.8 (C-8, C-9), 149.6 (C-1), 147.1 (C-16), 139.2 (C-11), 139.0 (C-13), 126.1 (C-4 and C-2), 124.0 (C-15), 123.6 (C-5), 121.2 (C-14), 120.3 (C-3), 118.8 (C-6), 56.6 (OMe).

***N*-(3-Aminopyridine)-*N*′-(2-methoxyphenyl)oxamide 3.** Prepared from 0.50 g (2.24 mmol) of ethyl *N*-(2-methoxyphenyl)-oxalamate, 0.24 g (2.24 mmol) of 2,3-diaminopyridine, and 0.010 g of the catalyst after reflux in 20 cm^3 of anhydrous ethyl alcohol for 24 h. After crystallisation, a slightly reddish solid was obtained (0.51 g). ν_{max}(KBr)/cm^{-1} 3370 (NH), 1679 (CO); δ_H(300.08 MHz) 10.34 (1 H, s, NH^B), 9.79 (1 H, s, NH^A), 8.25 (1 H, dd, *J* 8.1 and 1.8, 3-H), 7.88 (1 H, br d, *J* 1.8, 13-H), 7.46 (1 H, dd, *J* 7.7 and 1.7, 15-H), 7.15 (2 H, m, 4-H, 6-H), 7.03 (1 H, m, 5-H), 6.60 (1 H, dd, *J* 7.8 and 7.5, 14-H), 5.92 (2 H, s, NH$_2$), 3.91 (3 H, s, OMe); δ_C(75.5 MHz) 159.6, 157.8 (C-8, C-9), 155.3 (C-11), 149.4 (C-1), 146.6 (C-13), 134.5 (C-15), 126.5 (C-2), 125.9 (C-4), 121.3 (C-5), 119.9 (C-3), 117.4 (C-16), 111.9 (C-6), 112.7 (C-14), 50.8 (OMe).

***N*-(3-Hydroxypyridine)-*N*′-(2-nitrophenyl)oxamide 4.** From 0.50 g of **9** (2.10 mmol), 0.23 g (2.10 mmol) of 2-amino-3-hydroxypyridine and 0.010 g of the catalyst. After crystallisation, a yellowish solid was obtained (0.38 g). ν_{max}(KBr)/cm^{-1} 3290 (NH), 3096 (OH), 1702 (CO); δ_H(399.78 MHz) 11.63 (1 H, s, NH^A), 10.51 (1 H, s, NH^B), 10.30 (1 H, br s, OH), 8.28 (1 H, d, *J* 8.3, 3-H), 8.18 (1 H, d, *J* 8.3, 6-H), 7.94 (1 H, br d, 13-H), 7.85 (1 H, t, *J* 7.9, 4-H), 7.46 (1 H, t, *J* 7.8, 5-H), 7.31 (1 H, d, *J* 7.3, 15-H), 7.20 (1 H, dd, *J* 7.8 and 8.3, 4-H); δ_C(100.54 MHz) 158.1, 156.9 (C-8, C-9), 146.3 (C-16), 139.5 (C-11), 138.3 (C-1), 138.1 (C-13), 134.9 (C-4), 131.1 (C-2), 125.3 (C-5, C-6), 123.3 (C-3), 123.2 (C-15), 122.8 (C-14); $\delta_{^{15}N}$(40.52 MHz) −255.9 (N-7), −261.1 (N-10).

2-[*N*-(2-Methoxyphenyl)carbamoyl]benzoxazole 5. From 0.50 g (2.24 mmol) of ethyl *N*-(2-methoxyphenyl)oxalamate, 0.24 g (2.24 mmol) of 2-aminophenol and 0.010 g of the catalyst. After crystallisation a reddish solid was yielded (0.42 g, 70%), mp 237 °C (good elemental analysis from this sample could not be obtained). ν_{max}(KBr)/cm^{-1} 3368 (NH), 1670 (CO); δ_H(300.08 MHz) 9.90 (1 H, s, NH), 8.20 (1 H, d, *J* 7.9, 3-H), 8.15 (1 H, d, *J* 7.9, 11-H), 7.16 (2 H, m, 12-H, 14-H), 7.06 (1 H, t, *J* 7.6, 13-H), 7.05 (1 H, t, *J* 7.6, 4-H), 7.00 (1 H, d, *J* 7.6, 6-H), 6.89 (1 H, t, *J* 7.6, 5-H), 3.92 (3 H, s, OCH$_3$); δ_C(75.46 MHz) 157.2, 157.1, 156.9, 149.0, 147.2 (C-9, C-8, C-14a, C-10a, C-1), 125.6 (C-12), 125.3 (C-13), 120.6 (C-4), 119.9 (C-3), 119.8 (C-11), 119.3 (C-5), 115.0 (C-6), 111.2 (C-14), 56.0 (OCH$_3$).

2-[*N*-(2-Methoxyphenyl)carbamoyl]-1*H*-benzimidazole 6. Prepared from 0.50 g (2.24 mmol) of ethyl *N*-(2-methoxyphenyl)oxalamate, 0.24 g (2.24 mmol) of 1,2-diaminobenzene, 0.010 g of the catalyst and 20 cm^3 of nitrobenzene at reflux for 24 h. This solution was allowed to stand for 4 days. The resulting solid was filtered, washed with 20 cm^3 of acetone and crystallised from ethyl alcohol to yield a pale yellow solid (0.38 g). ν_{max}(KBr)/cm^{-1} 3237 (NH), 1668 (CO); δ_H(300.08 MHz) 13.63 (1 H, br s, NH), 9.91 (1 H, br s, OCNH), 8.36 (1 H, d, *J* 7.8, 3-H), 7.70 (2 H, br s, 11-H, 14-H), 7.35 (2 H, m, 12-H, 13-H), 7.16 (2 H, m, 4-H, 6-H), 7.03 (1 H, m, 5-H), 3.97 (3 H, s, OMe); δ_C(75.46 MHz) 157.1 (C-8), 149.4 (C-1), 146.1 (C-9), 127.3 (C-4), 125.6 (C-2), 124.7 (br, C-12, C-13), 121.5 (C-5), 112.0 (C-6), 56.9 (OMe) (C-10a, C-14a not observed). From a sample doped with water: δ_H(300.08 MHz) 7.84 (1 H, d, *J* 7.6, 11-H), 7.59 (1 H, d, *J* 7.6, 14-H), 3.39 (8 H, s, H$_2$O) the other signals were unchanged; δ_C(75.46 MHz) 143.0 (C-10a), 135.7 (C-14a), 125.3 (C-13), 123.7 (C-12), 120.8 (C-11), 113.4 (C14) the other signals remained unchanged.

2-[*N*-(2-Methoxyphenyl)carbamoyl]-3*H*-imidazo[4,5-*b*]-pyridine 7. Prepared From 0.50 g (2.24 mmol) of ethyl *N*-(2-methoxyphenyl)oxalamate, 0.24 g (2.24 mmol) of 2,3-diaminopyridine and 0.010 g of the catalyst using the same procedure as for the synthesis of **6**. Crystallisation from ethyl alcohol yielded a pale beige solid (0.30 g). ν_{max}(KBr)/cm^{-1} 3374 (NH), 1678 (CO); δ_H(300.08 MHz) 14.3 and 13.9 (1 H, br, NH), 9.94 (1 H, s, NH), 8.52 (1 H, br, 13-H), 8.33 (1 H, d, *J* 8.6, 3-H), 8.13 (1 H, br, 11-H), 7.38 (1 H, d, *J* 7.9, 12-H), 7.16 (1 H, m, 4-H), 7.15 (1 H, d, 6-H), 7.03 (1 H, m, 5-H), 3.96 (3 H, s, OMe); δ_C(75.46 MHz) 155.7 (C-8), 148.4 (C-1), 146.2 (C-9), 146.0 (C-13), 132.9 (br, C-10a, and or C-14a), 128 (br, C-11), 126.1 (C-2), 124.7 (C-4), 120.5 (C-5), 119.4 (C-3), 119.4 (br, C-12), 111.0 (C-6), 56.0 (OMe).

2-[*N*-(2-Nitrophenyl)carbamoyl]-1*H*-benzimidazole 8. Prepared from 0.50 g (2.10 mmol) of **9**, 0.23 g (2.10 mmol) of 1,2-diaminobenzene and 0.010 g of the catalyst using the same procedure as for the synthesis of **6**. Crystallisation from ethyl alcohol yielded a greenish yellow solid (0.37 g). ν_{max}(KBr)/cm^{-1} 3274 (NH), 1674 (CO); δ_H(399.78 MHz) 13.7 (1 H, s, NH), 11.8 (1 H, s, OCNH), 8.42 (1 H, dd, *J* 8.3 and 1.0, 3-H), 8.19 (1 H, dd, *J* 8.3 and 1.5, 6-H), 7.86 (1 H, dt, *J* 8.3 and 1.0, 4-H), 7.85 (1 H, d, *J* 7.8, 11-H), 7.60 (1 H, d, *J* 7.8, 14-H), 7.40 (2 H, m, 12-H, 13-H), 7.43 (1 H, dt, *J* 8.3 and 1.5, 5-H); δ_C(100.54 MHz) 157.9 (C-8), 145.2 (C-9), 142.9 (C-10a), 140.2 (C-1), 135.7 (C-4), 135.5 (C-2), 132.7 (C-14a), 126.2 (C-6), 125.5 (C-5, C-12 or C-13), 124.2 (C-3), 123.7 (C-13 or C-12), 120.9 (C-11), 113.4 (C-14).

Ethyl *N*-(2-nitrophenyl)oxalamate 9. Prepared from 4.0 cm^3 (36.2 mmol) of ethyl chlorooxoacetate and 5.0 g (36.2 mmol) of 2-nitroaniline using similar procedures as for the synthesis of ethyl *N*-(2-methoxyphenyl)oxalamate.[8] Crystallisation from hexane yielded a yellow solid (7.7 g). ν_{max}(KBr)/cm^{-1} 330.9 (NH), 1740 (CO); δ_H(300.08 MHz) 11.38 (1 H, s, NH), 8.10 (1 H, d, *J* 8.5, 3-H), 8.09 (1 H, d, *J* 8.5, 6-H), 7.78 (1 H, t, *J* 8.5, 4-H), 7.42 (1 H, t, *J* 8.5, 5-H), 4.32 (2 H, q, *J* 7.00, CH$_2$), 1.30

Table 4 Selected bond lengths (Å) and bond angles (°) for **2**

Atoms	Bond length/Å	Atoms	Bond length/Å
N(15)–C(8)	1.343(2)	N(15)–C(9)	1.403(2)
C(7)–C(8)	1.542(3)	N(16)–C(7)	1.332(2)
O(19)–C(8)	1.211(2)	O(7)–C(7)	1.215(2)
N(16)–C(2)	1.423(2)	O(1)–H(1B)	1.088(2)
O(1)–H(1A)	0.841(1)		
	Bond angle/°		Bond angle/°
C(8)–N(15)–C(9)	129.8(2)	C(7)–N(16)–C(2)	126.7(2)
H(1A)–O(1)–H(1B)	91.34(13)	O(7)–C(7)–N(16)	127.3(2)
O(7)–C(7)–C(8)	120.5(2)	N(16)–C(7)–C(8)	112.2(2)
O(19)–C(8)–N(15)	127.1(2)	O(19)–C(8)–C(7)	121.7(2)
N(15)–C(8)–C(7)	111.23(15)		

Table 5 Selected bond lengths (Å) and bond angles (°) for **4**

Atoms	Bond length/Å	Atoms	Bond length/Å
N(10)–C(9)	1.340(3)	N(1)–O(1B)	1.239(2)
N(10)–C(11)	1.407(3)	N(1)–O(1A)	1.226(2)
N(7)–C(8)	1.349(3)	O(9)–C(9)	1.220(3)
N(7)–C(2)	1.399(3)	O(8)–C(8)	1.217(3)
N(1)–C(1)	1.461(3)	C(8)–C(9)	1.527(3)
	Bond angle/°		Bond angle/°
C(9)–N(10)–C(11)	129.6(2)	C(8)–N(7)–C(2)	128.8(2)
O(8)–C(8)–N(7)	127.5(2)	O(8)–C(8)–C(9)	121.6(2)
N(7)–C(8)–C(9)	110.9(2)	O(9)–C(9)–N(10)	127.5(2)
O(9)–C(9)–C(8)	120.9(2)	N(10)–C(9)–C(8)	111.6(2)

(3 H, t, J 7.0, CH_3); δ_C(75.46 MHz) 160.4 (C-9), 155.7 (C-8), 141.2 (C-1), 135.7 (C-4), 131.6 (C-2), 126.6 (C-6), 126.2 (C-5), 123 (C-3), 63.7 (CH_2), 14.4 (CH_3).

X-Ray diffraction experiments. Single crystals of *N*-(3-hydroxypyridine)-*N′*-(2-methoxyphenyl)oxamide **2** monohydrate were recrystallised from ethyl alcohol after four weeks. For *N*-(3-hydroxypyridine)-*N′*-(2-nitrophenyl)oxamide **4**, suitable crystals were grown from a saturated solution of DMF by slow vapour diffusion of diethyl ether. Crystals of **4** grew with one molecule of DMF, however no intermolecular HB interactions were found. Selected bond and angles are shown in Tables 4 and 5, respectively. Direct methods (SHELXS-86) were used for structure solution, the SHELXL (Sheldrick)[17] software package was used for refinement and data output. All hydrogen atoms were determined by difference Fourier maps and refined in both structures. The analysis of short intermolecular and intramolecular contacts were carried out with PLATON[18] program.

Crystal data of compound 2‡. $C_{16}H_{17}N_5O_6$, $M = 375.35$, monoclinic, space group $P2_1/c$, $Z = 4$, $a = 7.2193(4)$, $b = 14.6988(7)$, $c = 16.6931(8)$ Å, $\alpha = 90$, $\beta = 91.3250(10)$, $\gamma = 90°$, $V = 1770.9(2)$ Å^3, $D_c = 1.408$ g cm^{-3}. Data were collected in the range $\theta = 1.85$–26.02 on a Bruker SMART 6000 CCD area detector diffractometer equipped with a graphite-monochromatised Mo-K_α tube. A total of 3467 independent reflections [$R_{int} = 0.0513$] were used in the refinement which converged with $R = 0.0490$ and $wR = 0.0922$ (GOF = 1.181).

Crystal data of compound 4‡. $C_{14}H_{15}N_3O_5$, $M = 305.29$, monoclinic, space group $P2_1/c$, $Z = 4$, $a = 12.825(3)$, $b = 15.110(3)$, $c = 7.3410(10)$ Å, $\alpha = 90$, $\beta = 101.02(3)$, $\gamma = 90$ °, $V = 1396.3(5)$ Å^3, $D_c = 1.408$ g cm^{-3}. Data were collected in the range $\theta = 2.70$–26.29 on an Enraf-Nonius CAD-4 diffractometer equipped with a graphite-monochromatised Mo-K_α tube. A total of 2825 independent reflections [$R_{int} = 0.071$] were used in the refinement which converged with $R = 0.0399$ and $wR = 0.1118$ (GOF = 1.014).

‡ CCDC reference numbers 161012 and 161013 for compounds **2** and **4**, respectively. See http://www.rsc.org/suppdata/p2/b1/b103063a/ for crystallographic data in .cif or other electronic format.

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