Three-center intramolecular hydrogen bonding in oxamide derivatives. NMR and X-ray diffraction study

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This contribution describes the synthesis and structural investigation of the symmetric and non-symmetric oxamides *N*,*N*′-bis(2-hydroxyphenyl)oxamide 1, *N*,*N*′-bis(5-*tert*-butyl-2-hydroxyphenyl)-oxamide 2, *N*,*N*′-bis(3,5-dimethyl-2-hydroxyphenyl)oxamide 3, *N*,*N*′-bis(2-hydroxybenzyl)oxamide 4, *N*,*N*′-diphenethyloxamide 5, *N*-(2-hydroxyphenyl)-*N*′-(2-methoxyphenyl)oxamide 6, *N*-(2-hydroxyphenyl)-*N*′-phenethyloxamide 7, (1*S*,2*R*)-(−)-*N*-(2-hydroxyphenylcarbamoylcarbonyl)norephedrine 8, (1*R*,2*S*)-(−)-*N*-(2-hydroxyphenylcarbamoylcarbonyl) 9, ethyl *N*-(2-hydroxyphenyl)oxalamate 10 and ethyl *N*-(2-methoxyphenyl)oxalamate 11. The structures were established by ^{1}H, ^{13}C, ^{15}N and variable temperature NMR spectroscopy. Compounds 1–4 and 6–11 are stabilized by intramolecular three-center hydrogen bonding between the amide proton and two oxygen atoms. The ^{1}H NMR $\Delta\delta/\Delta T$ value of the amide proton correlates with the ^{15}N NMR chemical shift. The X-ray diffraction molecular structures of 1 and 11 showed a planar conformation with *trans* configuration in the solid state, corresponding to the preferred conformation found in solution.

Introduction

The concept of intermolecular and intramolecular hydrogen bonding was originally used to explain physical properties of organic compounds and the formation of molecular aggregates.[1,2] Hydrogen bonding is relevant in the conformation of proteins and biochemical systems.[3–5]

Several methods have been developed to study the conformation and hydrogen bonding of peptides and proteins.[6] One of the most used is the study of N–H by NMR spectroscopy. Small molecules have been extensively used to model the specific hydrogen bonding interactions found in bigger biochemical systems.[7] Oxamides provide a simple model to study peptide bonds, particularly the hydrogen bonding interactions that give rise to molecular recognition processes such host–guest interactions. Amide groups generally adopt a *trans* configuration which facilitates linear chain networks suitable to form important supramolecular structures.[8,9]

We have previously found by solution NMR that the preferred conformation of compound **1** is planar, involving three-center-hydrogen bonding (bifurcated).[10] Therefore, we were interested in finding other examples of this conformation by varying the ring substituents (**2**, **3**), the effect of five- or six-membered ring formation (**4**), or aromatic *versus* aliphatic groups in symmetric (**5**) and non-symmetric oxamides (**6**–**11**). In this work a method based on the temperature dependence of amide NH hydrogen chemical shift[11,12] has been used to study the intramolecular hydrogen bonding interactions in eleven oxamide derivatives, as model compounds. Thus compounds **1**–**11** were prepared and hydrogen bonding interactions analyzed by ^{1}H, ^{13}C and ^{15}N variable temperature NMR in solution. It is shown that a three-center intramolecular hydrogen bonding interaction is the common pattern of all oxamides **1**–**11**. The molecular structure of **1** and **11** confirmed the same conformational preference in the solid state and in solution.

Results and discussion

NMR Spectroscopy

The conformational study in solution of the oxamides **1**–**11** was carried out using ^{1}H, ^{13}C and ^{15}N NMR spectroscopy. The ^{13}C NMR spectra of compounds **1**–**5** showed one half of the total carbon atoms because of the symmetry plane (Table 1). The oxamide carbon chemical shifts of **1**–**11** were in the characteristic range of this group (154.3–159.7 ppm)[13] disregarding some π conjugation through the OC–CO bond.

The ^{1}H NMR chemical shifts of compounds **1**–**11** in [^{2}H$_6$]DMSO (DMSO = dimethyl sulfoxide) are shown in Table 2. The chemical shift of the N–H hydrogen lies between 8.4 and 11.0 ppm for **1**–**3** and **5**–**11**. The signals of the aryl hydrogens appeared in two regions, the H4–H6 hydrogens were found between 6.83–7.70 ppm and the signals at high frequencies (7.73–8.17 ppm) were assigned to H3 hydrogens which are deshielded by the carbonyl group[10] (*vide infra*).

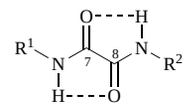
The ^{1}H NMR chemical shift dependence on the temperature gave support to the role of intramolecular three-center hydrogen bonding in stabilizing the planar conformation. Due to intramolecular hydrogen bonding formation in oxamides **1**–**11**, a small value of $\Delta\delta/\delta T$ for the NH hydrogen is expected in a polar solvent.[11] The ^{1}H NMR $\Delta\delta/\delta T$ experiments were done in [^{2}H$_6$]DMSO at 30–150 °C with increments of 10 °C. The $\Delta\delta/\delta T$ values are shown in Table 3.

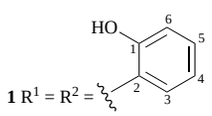
The chemical shifts of NH$_A$ signals in compounds **1**–**3** and **6**–**11** showed a small variation with the temperature ($\Delta\delta/\delta T$ from −0.5 to −2.2 ppb K^{-1}). It is known that the $\Delta\delta/\delta T$ values of the NH hydrogen are directly related to the proton mobility.[14] Thus, these small $\Delta\delta/\delta T$ values can be explained by the formation of a three-center hydrogen bond shown schematically for compounds **1**, **4** and **8**. The bonding interaction of the NH$_A$ moiety is stabilized by two five-membered chelate rings and favors a planar conformation and *trans* configuration of

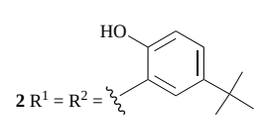
Table 1 ^{13}C NMR chemical shifts of compounds **1**–**11** in ppm (in [$^2H_6$]DMSO)

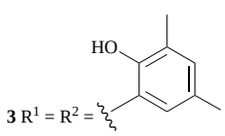
Comp.	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8
1[a]	147.2	124.5	119.8	119.3	125.4	115.1	156.9	
2[b]	144.7	124.1	116.6	144.5	121.9	114.4	156.9	
3[c]	142.9	125.2	118.5	128.3	122.5	125.5	157.3	
4[d]	132.0	135.7	121.4	128.1	124.7	127.7	157.8	
5[e]	137.4	128.4	128.4	126.5	128.4	128.4	159.7	
6[f]	149.0	125.6	119.7	119.2	125.8	115.1	156.8	157.1
7[g]	146.8	124.8	119.2	119.1	126.1	114.8	156.9	159.5
8[h]	146.8	124.8	119.2	119.1	124.9	114.8	156.9	158.6
9[i]	146.8	124.8	119.3	119.2	125.0	114.9	157.0	158.9
10[j]	147.5	124.7	120.8	119.1	125.5	115.1	154.3	160.5
11[k]	149.3	125.5	120.6	120.5	125.6	111.2	154.7	160.5

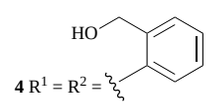
[a] Data taken from ref. 8. [b] Ar–C 31.2, Ar–C–CH_3 33.8 ppm. [c] C4-CH_3 20.4, C6–CH_3 16.3 ppm. [d] Ar–CH_2–O 62.6 ppm. [e] N–CH_2 39.8, Ar–CH_2 32.7 ppm. [f] Cl′ 149.0, C2′ 125.4, C3′ 119.8, C4′ 120.5, C5′ 125.5, C6′ 111.2, OMe 55.9 ppm. [g] N–CH_2 40.6, Ar–CH_2 34.3, phenyl: *ipso* 138.9, *ortho* 128.5, *meta* 128.2, *para* 124.9 ppm. [h] N–CH 51.3, HO–CH 73.7, C–CH_3 14.6, phenyl: *ipso* 142.8, *ortho* 126.1, *meta* 127.7, *para* 126.8 ppm. [i] N–CH 51.4, HOCH 74.1, C–CH_3 17.2, phenyl: *ipso* 142.9, *ortho* 126.3, *meta* 127.9, *para* 127.0 ppm. [j] O–CH_2 62.6, C–CH_3 13.7 ppm. [k] O–CH_2 62.6, C–CH_3 13.7, OCH_3 55.8 ppm.

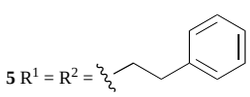


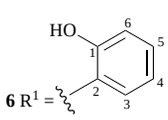


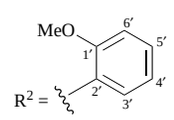


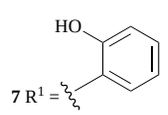


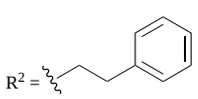


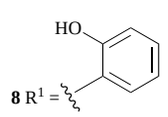


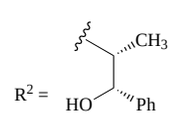


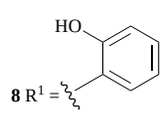


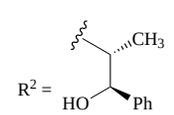


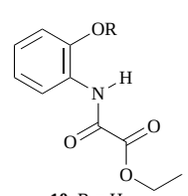






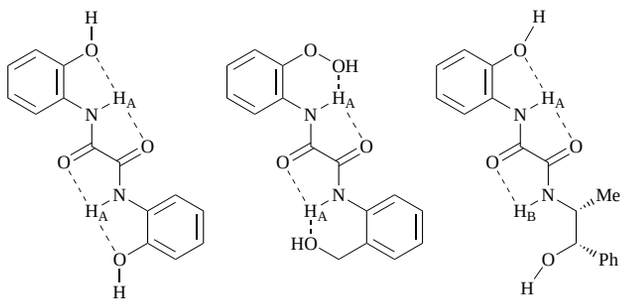






10 R = H
11 R = Me

the oxamides **1**–**3** and **6**–**11**. Compound **4** showed a slight increase in the $\Delta\delta/\Delta T$ absolute value (-3.4 ppb K^{-1}) probably due to the weaker interaction of the N–H hydrogen with the



1 **4** **8**

two nearer oxygen atoms, because of the presence of six-membered rings formed by intramolecular hydrogen bonding. The signals for NH_A in **5** and NH_B in **7**–**9** showed a large low-frequency shift with increasing temperature ($\Delta\delta/\delta T > -4.1$ ppb K^{-1}). These NH protons form only a simple intramolecular hydrogen bond.

The ^{15}N NMR spectra showed typical values for an oxamide group (Table 3).[15] In the NH_A or NH_B groups which showed intramolecular three-center hydrogen bonding by ^1H NMR, the ^{15}N chemical shift appeared at low frequencies (*ca.* -263 to -266 ppm) and those with more mobility were observed at high frequencies (*ca.* -258 to -260 ppm). The ^{15}N chemical shift of the phenolic oxamides **1**–**3** and **6**–**11** depends on the N–H mobility as is shown by the linear correlation found between the $\Delta\delta/\Delta T$ (^1H) and the $\delta(^{15}N)$ of the oxamide nitrogen (Fig. 1) described by eqn. (1).

$$\Delta\delta/\Delta T(^1H) = 106.9\ (\pm 9.5) + 0.40\ (\pm 0.04)\delta(^{15}N);\quad n = 11,\ r = 0.97 \quad (1)$$

X-Ray diffraction analysis

The oxamide **1** and the oxalyl **11** compounds may exist in two conformations, *cis* and *trans*,[10] differentiated by the relative positions of the carbonyl group. The X-ray molecular structure of **1** and **11** was determined in order to provide an insight into the role that hydrogen bonding plays in the molecular conformation of the aromatic oxamides in the solid state. The X-ray molecular structure of **1** and **11** showed the same conformation found in solution by NMR spectroscopy.

The selected bond lengths and bond angles are shown in Tables 4 and 5 and the molecular structure in Figs. 2 and 3 for compounds **1** and **11**, respectively. The oxamide group in compound **1** has the structure of two independently amides disregarding a π conjugation across the central C–C bond as is shown by the oxalyl OC–CO average bond length value of 1.541(5) Å (1.53 Å in other examples).[16] The structures showed

Table 2 ^{1}H NMR chemical shifts of compounds **1**–**11** in ppm (in [$^2H_6$]DMSO)

Comp.	H-3	H-4	H-5	H-6	NH_A	NH_B	OH
1[a]	8.13	6.89	7.06	7.00	9.82		10.43
2[b]	8.24		7.05	6.88	9.86		10.19
3[c]	7.73		6.76		10.05		8.97
4[d]	8.07	7.17	7.36	7.34	11.01		5.83
5[e]		7.17–7.35			8.69		
6[f]	8.17	7.02	7.20	7.15	9.90	9.88	10.42
7[g]	8.12	6.83	6.99	6.92	9.73	9.16	10.37
8[h]	8.09	6.83	6.99	6.92	9.69	8.71	10.24
9[i]	8.12	6.85	6.99	6.95	9.73	8.46	10.36
10[j]	7.98	6.84	7.02	6.94	9.63		10.26
11[k]	8.08	7.02	7.20	7.13	9.70		

[a] Data taken from ref. 8. [b] Bu^t 1.26 ppm. [c] C4-Me 2.15, C6-Me 2.21 ppm. [d] $-CH_2-$ 4.64 ppm. [e] Ar–CH_2- 2.79, $-CH_2-$N 3.38 ppm. [f] Second ring H3′ 8.12, H4′ 6.89, H5′ 7.05, H6′ 6.97, OMe 3.92 ppm. [g] N–CH_2- 3.43, Ar–CH_2- 2.83, ArH 7.17–7.33 ppm. [h] N–CH 4.02, N–C–CH_3 1.09, Ar–CH 4.70, C–OH, 5.6 ArH 7.18–7.37 ppm. [i] N–CH 4.04, N–C–CH_3 1.09, Ar–CH 4.66, C–OH 5.6 ArH 7.15–7.35 ppm. [j] O–CH_2 4.31, C–CH_3, 1.32 ppm. [k] O–CH_2 4.34, C–CH_3, 1.35 ppm.

Table 3 Temperature dependence ($\Delta\delta/\Delta T$ in ppb K^{-1}) and ^{15}N chemical shifts (ppm) of compounds **1**–**11**

Comp.	$-\Delta\delta/\Delta T$ NH_A	$-\Delta\delta/\Delta t$ NH_B	δ ^{15}N NH_A	δ ^{15}N NH_B
1	0.5		−266.0	
2	1.2		−263.9	
3	1.5		−263.8	
4	3.4		−258.9	
5	5.2		−264.6	
6	1.1	1.1	−264.0	−265.0
7	1.1	5.8		
8	1.1	4.6	−265.1	−256.9
9	1.2	4.1	−265.2	−260.6
10	2.0		−260.7	
11	2.2		−262.5	

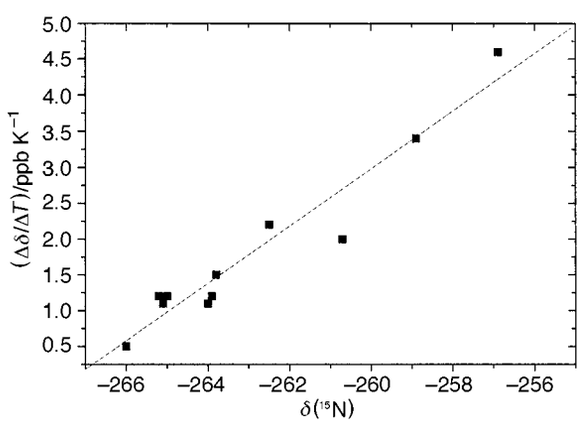


Fig. 1 $\Delta\delta/\Delta T$ ^{1}H NMR *vs.* δ(^{15}N) NMR plot for **1**–**11** compounds [eqn. (1)]. NH_B of oxamide **9** is out of correlation probably due to steric effects.

a OC–CO torsion angle value of 180.0(2)° for a *trans* conformation in contrast with other oxamides which show a torsional angle between 90° and 115°.[16] The oxalyl **11** presents the same characteristic values, 1.541(4) Å for the C–C bond and −170.0(2)° for the OC–CO torsion angle.

The planar conformation of **1** and **11** is stabilized by a three-center (bifurcated) intramolecular hydrogen interaction between the N–H amide hydrogen with two oxygen atoms. Both hydrogen bond lengths with values of [N(9)–H(91)···O(10)–H = 2.172(2) Å] and [N(9)–H(91)···O(8a) = 2.138(2) Å] for oxamide **1** (Fig. 2) and [N(12)–H(121)···O(15)–Me = 2.15(3) Å] and [N(12)–H(121)···O(14) = 2.22(3) Å] for **11** (Fig. 3) are below the sum of the van der Waals radii of hydrogen (r_{VDW} = 1.20 Å) and oxygen (r_{VDW} = 1.50 Å)[17] in both compounds. The arrangement of the three atoms involved in the intramolecular interaction O···*H*···O is almost colinear

Table 4 Selected bond lengths (Å), bond angles (°) and torsion angles (°) of **1**

Interatomic bond lengths/Å			
O(10)–C(1)	1.357(3)	C(1)–C(6)	1.376(3)
O(9)–C(7)	1.219(3)	C(3)–C(4)	1.384(4)
C(1)–C(2)	1.395(3)	C(4)–C(5)	1.379(3)
C(2)–C(3)	1.382(3)	C(6)–C(5)	1.377(3)
C(2)–N(9)	1.415(3)	C(7)–C(7A)	1.541(5)
C(7)–N(9)	1.336(3)		
Bond angles (°)			
C(1)–C(2)–O(10)	115.6(2)	O(10)–C(1)–C(6)	124.1(2)
C(2)–C(3)–C(4)	119.4(2)	C(6)–C(1)–C(2)	120.3(2)
C(3)–C(2)–N(9)	125.3(2)	C(3)–C(2)–C(1)	119.7(2)
C(3)–C(4)–C(5)	120.6(2)	C(1)–C(2)–N(9)	115.1(2)
C(6)–C(5)–C(4)	120.1(2)	C(1)–C(6)–C(5)	119.9(2)
O(7)–C(7)–C(7A)	121.7(2)	O(8)–C(7)–N(9)	126.3(2)
C(7)–N(9)–C(2)	128.5(2)	N(12)–C(7)–O(13)	127.2(3)
N(9)–C(7)–C(7A)	112.0(2)		
Torsion angles (°)			
O(10)–C(1)–C(2)–N(9)	1.9	C(3)–C(2)–N(9)–C(7)	5.1
C(1)–C(2)–N(9)–C(7)	−174.7	O(8)–C(7)–N(9)–C(2)	−0.31
C(7A)–C(7)–N(9)–C(2)	179.8		

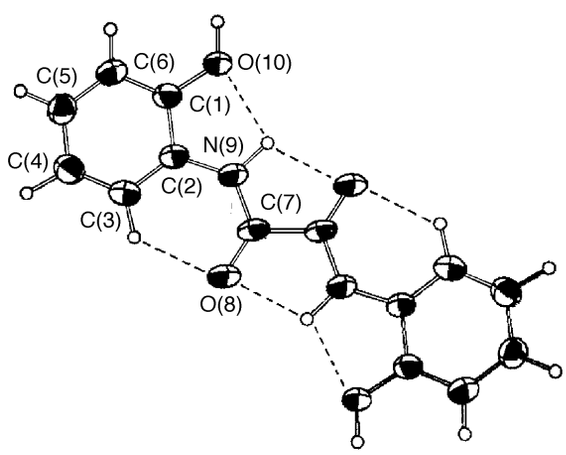


Fig. 2 The molecular structure of **1** showing the three-center hydrogen bonding interaction [N(9)–H(91)···O(10)–H = 2.172(2) Å] and [N(9)–H(91)···O(8a) = 2.138(2) Å]

with the angle O(10)···H(91)···O(8a) being 149.8(2)° in oxamide **1**. This intramolecular hydrogen bond in both compounds forms an arrangement of two five-membered chelate rings in agreement with Hamilton *et al.* who reported similar structures stabilized by intramolecular three-center hydrogen

Table 5 Selected bond lengths (Å), bond angles (°) and torsion angles (°) of **11**

Interatomic bond lengths/Å			
N(12)–C(2)	1.411(3)	N(12)–C(7)	1.348(3)
O(9)–C(8)	1.316(3)	O(9)–C(10)	1.464(3)
O(13)–C(7)	1.213(3)	O(14)–C(8)	1.195(3)
O(15)–C(1)	1.358(3)	O(15)–C(16)	1.426(4)
C(1)–C(2)	1.403(4)	C(1)–C(6)	1.384(4)
C(2)–C(3)	1.379(4)	C(3)–C(4)	1.387(4)
C(4)–C(5)	1.362(5)	C(5)–C(6)	1.385(5)
C(7)–C(8)	1.541(4)	C(10)–C(11)	1.490(5)
Bond angles (°)			
C(2)–N(12)–C(7)	128.8(2)	C(8)–O(9)–C(10)	114.9(2)
C(1)–O(15)–C(16)	118.0(2)	O(15)–C(1)–C(2)	114.7(2)
O(15)–C(1)–C(6)	125.5(3)	C(2)–C(1)–C(6)	119.8(3)
N(12)–C(2)–C(1)	115.6(2)	N(12)–C(2)–C(3)	124.4(3)
C(1)–C(2)–C(3)	119.9(3)	C(2)–C(3)–C(4)	119.5(3)
C(3)–C(4)–C(5)	120.6(3)	C(4)–C(5)–C(6)	120.9(3)
C(1)–C(6)–C(5)	119.3(3)	N(12)–C(7)–O(13)	127.2(3)
N(12)–C(7)–C(8)	109.7(2)	O(13)–C(7)–C(8)	123.1(3)
O(9)–C(8)–O(14)	125.7(3)	O(9)–C(8)–C(7)	111.3(2)
O(14)–C(8)–C(7)	123.0(2)	O(9)–C(10)–C(11)	106.1(3)
Torsion angles (°)			
O(14)–C(8)–C(7)–O(13)	−170.2	H(121)–N(12)–C(2)–C(1)	−7.6
H(121)–N(12)–C(7)–C(8)	6.4	H(31)–C(3)–C(2)–N(12)	2.0
O(14)–C(8)–C(7)–N(12)	8.7	O(13)–C(7)–N(12)–C(2)	1.7

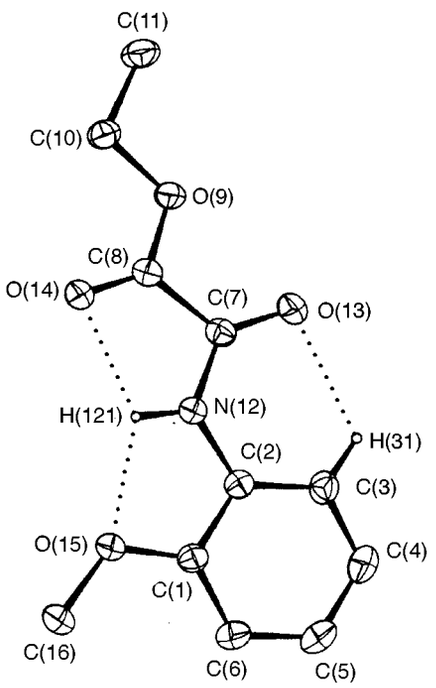


Fig. 3 The molecular structure of **11** showing the three-center hydrogen bonding interaction [N(12)–H(121)···O(15)–Me = 2.15(3) Å] and [N(12)–H(121)···O(14) = 2.22(3) Å]

bonding forming one five-(N···H = 2.20–2.22 Å) and one six-membered ring (NH···OC = 1.62–2.00 Å).[18]

Molecular structures of **1** and **11** showed that the carbonyl amide group N–CO is in an *endo* conformation, pointing towards the aromatic ring and in the plane of the molecule with values of the angles O(8)–C(7)–N(9)–C(2) of −0.3(4)° and O(13)–C(7)–N(12)–C(2) of 1.72(2)°. This conformation favours the formation of a second intramolecular hydrogen interaction between C(7)–O(8)···H(31)–C(3) [2.216(2) Å] in **1** and C(3)–H(3)···O(13)–C(7) [2.35(3) Å] in **11**, forming a six-membered ring in each molecule.

The combined effect of the three-center hydrogen bond O···H···O and the simpler one NH···OC confers on these molecules the full planar arrangement observed in the solid state. This structure is strong enough to be the predominant form in solution as was found by NMR spectroscopy.[10] Therefore it is confirmed that in the solid state compound **1** and **11** have the same conformation as in solution.

Conclusions

The present NMR and crystallographic studies have shown that compounds **1**–**11** have the same conformation in the solid state and in solution. The planar structure of **1**–**3**, **6**, **10** and **11** compounds is stabilized by an intramolecular three-center hydrogen bond forming two five-membered rings. In compound **4** the hydrogen bond forms two six-membered rings; this arrangement is less strong than the five-membered one. Also worth noting is the stability difference with the hydrogen bonding in compound **5** where three coordinated hydrogen bonding is not possible. In the non-symmetric oxamines **7**–**9** only the phenolic part of the molecule presents strong three-centered hydrogen bonding. The role of variable temperature ^{1}H NMR studies as a tool in the study of hydrogen bonding has been confirmed.

The three-center hydrogen bonding interaction is favored by formation of at least two coplanar rings (five- or six-membered rings). This planar structure is stable enough to remain the principal conformer in solution.

Experimental

All solvents were freshly distilled and dried before use according to established procedures. Melting points were measured on a Gallenkamp apparatus and are uncorrected. The IR spectra were recorded in KBr discs using a Perkin-Elmer 16F PC IR spectrophotometer. Elemental analyses were performed in a Fisons Instruments EA 1108 elemental analyzer CHNS-0. The NMR spectra were obtained on a JEOL GXS-270 spectrometer in [$^2H_6$]DMSO solution. ^{1}H and ^{13}C NMR spectra were measured with $SiMe_4$ as internal reference. Variable temperature experiments were performed with a temperature controller to keep the temperature constant within 0.3 °C. A microprogram was used to change the temperature automatically in fixed increments, with a delay of 5 min for temperature stabilization. Each spectrum was obtained with 32 scans.

^{15}N NMR spectra were obtained with neat nitromethane as standard set to 0 ppm. All signals are upfield from nitromethane and chemical shifts are negative. ^{15}N spectra were recorded at 27.25 MHz using a multinuclear 5 mm probe and approximately 0.3 mmol of each compound was dissolved in 0.5 cm^3 of [$^2H_6$]DMSO. The refocused INEPT pulse sequence was used to detect the ^{15}N signal. The values of t_D were set to 2.7 ms in instances where the average $^1J(^{15}N–^1H)$ value was 93 Hz (t_D = 1/4, $^1J(^{15}N–^1H)$. A spectral width of 16 400 Hz with a digital resolution of 0.5 Hz was used; the pulse delay was 5 s with an acquisition time of 0.999 s.

The X-ray diffraction studies were performed on an Enraf-Nonius CAD4 diffractometer ($\lambda_{MoK\alpha}$ = 0.710 69 A, monochromator: graphite, T = 293 K, ω-2θ scan). Cell parameters were determined by least squares refinement on diffractometer angles for 24 automatically centred reflections. Absorption correction was not necessary; corrections were made for Lorentz and polarization effects. Solution and refinement: direct methods (SHELXS-86) for structure solution. The CRYSTALS (version 9, 1994)[19] and SHELXL (Sheldrick)[20] software packages were used for refinement and data output. All hydrogen atoms were found and refined in the case of structure **11**; in the case of structure **1** hydrogen atoms were refined as riding atoms. Structure **1** has a C_2 axis and structure **11** has no symmetry axes. No intermolecular hydrogen bonding interactions were found in either

Table 6 Crystallographic data of compounds **1** and **11** at room temperature

Compound	**1** [a]	**11** [b]
Formula	$C_{14}H_{12}N_2O_4$	$C_{11}H_{13}NO_4$
F_w/g mol^{-1}	272.2	223.23
Space group	$P2_1/n$	$P\bar{1}$
Crystal size/mm^3	0.28 × 0.27 × 0.15	0.30 × 0.39 × 0.42
a/Å	5.289(10)	8.2168(5)
b/Å	5.316(10)	11.3201(5)
c/Å	21.495(4)	12.3648(5)
α/°	90.00(3)	80.245(4)
β/°	92.81(3)	81.839(4)
γ'/°	90.00(3)	81.666(4)
V/Å^3	603.6(2)	1113.4(1)
Z	2	4
Linear abs. coeff./μ mm^{-1}	0.112	0.095
D_c/g cm^{-3}	1.50	1.33
θ limits/°	2–24	2–27
Octants collected	0, 6; −6, 6; −24, 24	−10, 0; −14, 14; −15, 15
No. of data collected	1775	5202
No. of unique data collected	940	4311
No. of unique data used	726 [$(F) > 4\sigma(F)$]	3125 [$F_o > 3\sigma(F_o)$]
Intensity variation (σ)	>4	>3
R	0.0415	0.0430
R_w	0.1143	0.0440 $w = 1/\sigma^2$
Goodness of fit s	0.675	1.17
No. of variables	91	368
$\Delta\rho_{min}$/e A^{-3}	−0.28	−0.21
$\Delta\rho_{max}$/e A^{-3}	0.24	0.17

[a] Program for structure solution and refinement: SHELXL (1993).[20] [b] Program for structure solution and refinement: CRYSTALS.[19]

structures **1** or **11**. The experimental parameters are listed in Table 6.†

***N*,*N*′-Bis(2-hydroxyphenyl)oxamide 1**
Compound **1** was prepared as reported.[10]

***N*,*N*′-Bis(5-*tert*-butyl-2-hydroxyphenyl)oxamide 2**
2-Amino-4-*tert*-butylphenol (2.0 g, 12.10 mmol) in tetrahydrofuran (THF) (20 ml) was treated dropwise under vigorous stirring with oxalyl chloride (0.769 g, 6.06 mmol, 0.5 equiv.) at 25 °C. After stirring for an additional 1 h at 25 °C, the solid was removed and washed with 95% ethanol to give **2** (1.27 g, 56.6%) as beige solid. ν_{max}(KBr)/cm^{-1} 3358, 1654, 1558, 1540, 1458, 1362, 1264, 1122, 820, 668 and 472 (Found: C, 68.35; H, 7.26; N, 7.27. Calc. for $C_{22}H_{28}N_2O_4$: C, 68.75; H, 7.29; N, 7. 29%); mp 288–289 °C.

***N*,*N*′-Bis(3,5-dimethyl-2-hydroxyphenyl)oxamide 3**
6-Amino-2,4-dimethylphenol (2.0 g, 14.59 mmol) in THF (20 ml) was treated dropwise under vigorous stirring with oxalyl chloride (0.926 g, 7.29 mmol, 0.5 equiv.) at 25 °C. After stirring for an additional 1 h at 25 °C, the solid was removed and washed with 95% ethanol to give **3** (2.1 g, 87.8%) as a beige solid. ν_{max}(KBr)/cm^{-1} 3488, 1670, 1654, 1558, 1540, 1458, 1420, 1338, 1208, 1026, 668 and 506 (Found: C, 65.11; H, 5.97; N, 8.27. Calc. for $C_{18}H_{20}N_2O_4$: C, 65.85; H, 6.09; N, 8.53%); mp 262–264 °C.

***N*,*N*′-Bis(2-hydroxybenzyl)oxamide 4**
2-Aminobenzyl alcohol (2.0 g, 16.26 mmol) in THF (15 ml) was treated dropwise under vigorous stirring with oxalyl chloride (1.032 g, 8.13 mmol, 0.5 equiv.) at 25 °C. After stirring for an additional 1 h at 25 °C, the solid was removed and washed with 95% ethanol to give **4** (2.24 g, 92.1%) as a white solid. ν_{max}(KBr)/cm^{-1} 3470, 1682, 1592, 1558, 1526, 1456, 1302, 1260, 1188, 1014, 748, 668 and 500 (Found: C, 63.74; H, 5.52; N, 9.17. Calc. for $C_{16}H_{16}N_2O_4$: C, 64.00; H, 5.30; N, 9.30%); mp 206–208 °C.

***N*,*N*′-Diphenethyloxamide 5**
Phenethylamine (2.0 g, 16.52 mmol) in CH_2Cl_2 (10 ml) and triethylamine (0.82 g, 1.14 ml) were treated dropwise under vigorous stirring with oxalyl chloride (1.049 g, 8.26 mmol, 0.5 equiv.) at 25 °C. After stirring for an additional 2 g at 25 °C, the solid was filtered and washed with water (20 ml) to give **5** (2.1 g, 86.0%) as white solid. ν_{max}(KBr)/cm^{-1}, 3305, 1653, 1520, 1495, 1224, 1189, 740 and 697 (Found: C, 72.94; H, 7.22; N, 9.97. Calc. for $C_{18}H_{20}N_2O_2$: C, 72.94; H, 6.80, N 9.45%), mp 184–185 °C.

***N*-(2-Hydroxyphenyl)-*N*′-(2-methoxyphenyl)oxamide 6**
Ethyl *N*-(2-hydroxyphenyl)oxalamate **10** (1.0 g, 4.78 mmol) in THF (10 ml) was treated under vigorous stirring with *ortho*-anisidine (0.587 g, 4.78 mmol) at 25 °C. After refluxing for 18 h, the solid was filtered and washed with THF (2 ml) to give **6** (0.72 g, 52.2%) as a beige solid. ν_{max}(KBr)/cm^{-1} 3370, 3314, 1670, 1615, 1596, 1528, 1457, 1287, 1196, 1100, 1018, 744, 696 and 512 (Found: C, 63.39; H, 5.23; N, 9.68. Calc. for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.92; N, 9.78%); mp 230–231 °C.

***N*-(2-Hydroxyphenyl)-*N*′-phenethyloxamide 7**
The oxalamate **10** (1.0 g, 4.78 mmol) in THF (10 ml) was treated under vigorous stirring with phenylethylamine (0.578 g, 4.78 mmol) at 25 °C. After refluxing for 18 h, the solid was filtered and washed with THF (2 ml) to give **7** (0.82 g, 60.7%) as white solid. ν_{max}(KBr)/cm^{-1}, 3314, 3148, 1663, 1597, 1527, 1457, 1361, 1281, 1104, 747, 698 and 529 (Found: C, 68.01; H, 5.98; N, 10.09. Calc. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85%); mp 183–185 °C.

† Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 2*, available *via* the RSC Web pages (http://chemistry.rsc.org/rsc/plpifa.htm). Any request to the CCDC for this material should quote the full literature citation and the reference number 188/114.

_N_-(2-Hydroxyphenylcarbamoylcarbonyl)-(1_S_,2_R_)-(−)-norephedrine 8

The oxalamate **10** (1.0 g, 4.78 mmol) in anhydrous ethanol (20 ml) was treated dropwise under vigorous stirring with (1*S*,2*R*)-(−)-norephedrine (0.721 g, 4.78 mmol) at 25 °C. After refluxing for 12 h, the solvent was removed under vacuum. Recrystallization from ethyl acetate gave **8** (0.915 g, 61.8%) as a beige solid. ν_{max}(KBr)/cm^{-1} 3383, 1670, 1560, 1522, 1458,1386, 1258, 1104, 1044, 750, 702 and 518 (Found: C, 65.13; H, 5.80; N, 8.76. Calc. for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.76; N, 8.90%); mp 154–156 °C.

_N_-(2-Hydroxyphenylcarbamoylcarbonyl)-(1_R_,2_S_)-(−)-norephedrine 9

The oxalamate **10** (1.0 g, 4.78 mmol) in anhydrous ethanol (20 ml) was treated dropwise under vigorous stirring with (1*R*,2*S*)-(−)-norephedrine (0.721 g, 4.78 mmol) at 25 °C. After refluxing for 5 h, the solvent was removed under vacuum. Recrystallization from ethyl acetate gave **9** (0.7 g, 47.3%) as a beige solid, ν_{max}(KBr)/cm^{-1} 3304, 1652, 1600, 1524, 1456, 1480, 1384, 1240, 1102, 1042, 756, 696 and 518 (Found: C, 65.47; H, 5.88; N, 9.01. Calc. for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.76; N, 8.90%); mp 202–203 °C.

Ethyl _N_-(2-hydroxyphenyl)oxalamate 10

o-Aminophenol (2.0 g, 18.34 mmol) in THF (25 ml) was treated dropwise under vigorous stirring with ethyl oxalyl chloride (2.49 g, 18.8 mmol, 1.0 equiv.) at 5 °C. After stirring for an additional 1 h at 25 °C the solid was filtered. Recrystallization from ethyl acetate gave **10** (2.75 g, 71.9%) as a beige solid. ν_{max}(KBr)/cm^{-1}: 3362, 1654, 1596, 1544, 1464, 1350, 1292, 1106, 1026, 752, 744 and 504 (Found: C, 57.90; H, 5.54; N, 6.96. Calc. for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.69%); mp 179–181 °C.

Ethyl _N_-(2-methoxyphenyl)oxalamate 11

o-Anisidine (2.0 g, 16.26 mmol) in THF (10 ml) was treated dropwise under vigorous stirring with ethyl oxalyl chloride (2.21 g, 16.26 mmol, 1 equiv.) at 5 °C. After stirring for an additional 1 h at 25 °C, the solid was filtered and washed with water (50 ml) and dried in vacuum to give **11** (2.48 g, 68.9%) as beige solid. ν_{max}(KBr)/cm^{-1} 3378, 1704, 1534, 1463, 1296, 1168, 1018, 936 and 754 (Found: C, 59.65; H, 6.22; N, 6.63. Calc. for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87; N, 6.27%); mp 82–83 °C.

Acknowledgements

This work was supported by CONACYT-México. M. T. and E. G. thank CONACYT-México for scholarships, Dr Armando Ariza-Castolo for some of the ^{15}N NMR spectra and Dr Noráh Barba-Behrens for the elemental analysis facilities.

References

1 L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, Ithaca, N.Y, 1960.
2 S. M. Reutzel and M. C. Etter, *J. Phys. Org. Chem.*, 1992, **5**, 44.
3 Y. A. Ovchinnikov and V. T. Ivanov, *Tetrahedron*, 1975, **31**, 2177.
4 E. S. Stevens, N. Sugawara, G. M. Bonora and C. Tionolo, *J. Am. Chem. Soc.*, 1980, **102**, 7048.
5 G. P. Dado and S. H. Gellman, *J. Am. Chem. Soc.*, 1994, **116**, 1054.
6 T. Ishida, Y. In, A. Fujikawa, H. Urata, M. Inouse, K. Akai, K. Takesako and I. Kato, *J. Chem. Soc., Chem. Commun.*, 1992, 1231.
7 C. Huang, L. A. Cabell and E. A. Anslyn, *J. Am. Chem. Soc.*, 1994, **116**, 2778.
8 S. Subramanian and M. J. Zaworotko, *Coord. Chem. Rev.*, 1994, **137**, 357.
9 C. B. Aakeröy and K. R. Seddon, *Chem. Soc. Rev.*, 1993, 397.
10 F. J. Matínez-Martínez, A. Ariza-Castolo, H. Tlahuext, M. Tlahuextl and R. Contreras, *J. Chem. Soc., Perkin Trans 2*, 1993, 1481.
11 G. P. Dado and S. H. Gellman, *J. Am. Chem. Soc.*, 1994, **116**, 1054.
12 S. H. Gellman, B. R. Adam and G. P. Dado, *J. Am. Chem. Soc.*, 1990, **112**, 460.
13 S. Provera, C. Marchioro, S. Davailli and N. Case, *Magn. Reson. Chem.*, 1997, **35**, 342.
14 H. Kessler, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 2177.
15 G. A. Webb, *Ann. Rep. NMR Spectrosc.*, 1981, **113**, 112.
16 G. Verardo, A. G. Giumanini, F. Gorassini, M. Tolazzi and P. Strazzolini, *Tetrahedron*, 1993, **49**, 10 609.
17 J. E. Huheey, *Inorganic Chemistry*, Harper International SI edn., 1983, p. 258.
18 Y. Hamuro, S. J. Geib and A. D. Hamilton, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 446.
19 D. J. Watkin, J. R. Carruthers and P. W. Betteridge, *CRYSTALS, An Advanced Chrystallographic Program System*, Chemical Chrystallography Laboratory, University of Oxford, Oxford, 1988.
20 G. W. Sheldrick, SHELXTL 93, University of Göttingen, 1993.

Paper 7/04640E
Received 1*st July* 1997
Accepted 15*th October* 1997