Conformational behaviour of hydroxamic acids: *ab initio* and structural studies

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The conformational behaviour of a series of monohydroxamic acids, *p*-$RC_6H_4CONR'OH$ (R = Me, R' = H, Me; R = MeO, R' = H, Me; R = NO_2, R' = H), and a series of dihydroxamic acids, $(CH_2)_n(CONR'OH)_2$ (n = 3–8, 10, R' = H and n = 7, R' = Me), in methanol, DMSO and chloroform and in the solid state has been examined using IR and NMR spectroscopy. X-Ray crystal structure determinations of *p*-$MeC_6H_4CONMeOH$ and the monohydrate of glutarodihydroxamic acid (n = 3) together with *ab initio* molecular orbital calculations for several hydrated and unhydrated hydroxamic acids have been performed. Hydrogen bonding effects are shown to be important in both the solid state and solution. The *cis*(*Z*) conformation of the hydroxamate group(s) (CONHOH) is preferentially stabilized by hydrogen bonding with water molecules.

Introduction

Hydroxamic acids are very important bioligands.[1] Naturally occurring hydroxamic acids (siderophores) are involved in the microbial transport of iron[2] and consequently have therapeutic uses in iron-related conditions.[3] They are also inhibitors of urease activity[4] and have been used therapeutically in the treatment of hepatic coma.[5] Much of their biological activity[4] is related to their ability to form very stable chelates with a range of metals and most especially with iron.[2] In the vast majority of metal chelates formed by hydroxamic acids, coordination occurs by deprotonation of the OH group and subsequent (O,O) coordination of the carbonyl oxygen and deprotonated OH [Scheme 1(*c*)] as in [$Fe(RCONHO)_3$]. This mode of bonding has been confirmed by X-ray crystallography in a wide range of metal complexes. No examples have yet been observed of (N,O) coordination by normal hydroxamic acids which would involve deprotonation of the NH group [Scheme 1(*d*)] despite recent experimental and theoretical studies[6,7] which, at least for RCONHOH (R = H, CH_3), support the idea that these monohydroxamic acids are *N* acids in the gas phase. However, aminohydroxamic acids such as glycinehydroxamic acid (2-aminoacetohydroxamic acid), $NH_2CH_2CONHOH$, provided the first example of (N,N) coordination in [$Ni(NH_2CH_2CONHO)_2$][8] and subsequent examples include the glycinehydroxamic acid complexes of Co^{III}[9] and Cu^{II}.[10] There is now good evidence for a number of aminohydroxamic acids showing different coordination behaviour, that is (N,N), (N,O) and (O,O), depending on the metal being complexed and on the pH of solution.[11]

In the case of the normal (O,O) coordination mode, the hydroxamate groups of a siderophore must be in the prearranged *cis*(*Z*) conformation [Scheme 1(*a*)] in order to chelate the metal ion (M) [Scheme 1(*c*)] effectively. However all secondary hydroxamic acids (RONR'OH) studied to date by X-ray crystallography occur in the *trans* (*E*) conformation [Scheme 1(*b*)], so clearly the solvent in which metal complexation takes place plays an important role in facilitating the required conformation changes necessary for (O,O) coordination.†

This paper is concerned with the variation of conformation (*Z*/*E*) in solution and in the solid state for a number of mono- and di-hydroxamic acids.

Results and discussion

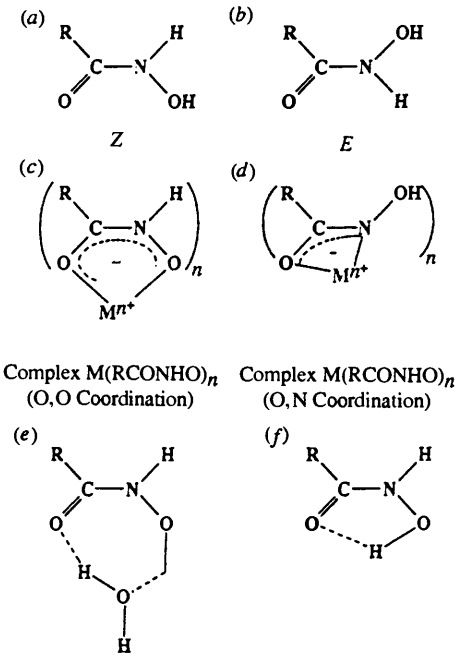
Conformational changes in solution (DMSO, $CHCl_3$ and CH_3OH) were studied by IR, ^1H and ^{13}C NMR spectroscopy for four series of hydroxamic acids: Series A, the primary *para*-substituted benzohydroxamic acids, *p*-$RC_6H_4CONHOH$ (R = Me, MeO, NO_2); Series B, the corresponding *N*-methyl secondary hydroxamic acids, *p*-$RC_6H_4CONMeOH$ (R = Me, MeO); Series C, the primary dihydroxamic acids, $(CH_2)_n(CONHOH)_2$ (n = 3–8, 10) and finally Series D, comprising only one compound, the secondary *N*-methyldihydroxamic acid, $(CH_2)_7(CONMeOH)_2$ (*N*',*N*'-dimethylazelaodihydroxamic acid). X-Ray crystal structures are reported for *p*-$MeOC_6H_4CONMeOH$ (MOTH) and glutarodihydroxamic acid monohydrate ($GHA{\cdot}H_2O$). Standard *ab initio* molecular orbital calculations were performed for glutarodihydroxamic acid and its mono- and di-hydrates using the Gaussian 92 program.

Solid state infrared spectra (KBr)

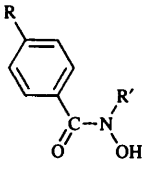
For diagnostic purposes, the most important infrared absorption bands are those due to the N–H, C=O and O–H stretching vibrations of the hydroxamate group, –CONHOH, as shown in Table 1, which also include solution values for comparison.

In all four series, ν(CO) lies in the range 1570–1666 cm^{-1}, considerably lower than the typical ketonic ν(CO) of 1715 cm^{-1}. This lowering of ν(CO) together with the broad ν(OH) bands in the range 2750–3152 cm^{-1} may be attributed to intermolecular hydrogen bonding as proven in the case of glutarodihydroxamic acid dihydrate by the X-ray crystal structure (Fig. 1). In general, ν(NH) occurs as a sharp absorption in the range 3254–3293

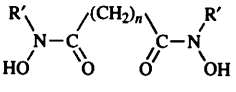
† Throughout this paper the stereodescriptors *E* and *Z* are used to describe the *trans* and *cis* orientation of the OH and C=O groups of the hydroxamic acid, respectively.



Scheme 1 Conformations of hydroxamic acids and metal complexes



Series A: R′ = H; R = Me (**1**), R = MeO (**2**), R = NO_2 (**3**),
Series B: R′ = Me; R = Me (**4**), R = MeO (**5**)



Series C: R′ = H; n = 3 (**6**), n = 4 (**7**), n = 5 (**8**), n = 6 (**9**), n = 7 (**10**), n = 8 (**11**), n = 10 (**12**),
Series D: R′ = Me; n = 7 (**13**)

cm^{-1} although slightly lower for the shorter chain dihydroxamic acids (**6–8**). In many cases ν(CO) occurs as a doublet in the solid state. The effect of *N*-methyl substitution is clearly shown on ν(CO) which in both series B and D (1570–1608 cm^{-1}) lies lower than in the corresponding primary acid in series A and C (1600–1666 cm^{-1}) thus suggesting increased electron donation by the *N*-methyl group; however, ν(OH) rather than decreasing as expected from this argument actually increases relative to the unsubstituted compound.

Solution infrared spectra

It was not possible to obtain satisfactory solution infrared spectra for series A because of their poor solubility in both polar and non-polar solvents, whilst for series C the effect of concentration on ν(CO) could only be studied satisfactorily in polar solvents such as DMSO and CH_3OH. The *N*-methyl series (B and D) presented no such problems. In the series C and D, ν(CO) increased considerably in both DMSO and CH_3OH over the corresponding solid state values (Table 1). As suggested previously,[12] such shifts in polar solvents are probably due to the replacement of strong intermolecular H-bonds in the solid state (see Fig. 1 for example) by weaker and more entropically favoured intramolecular H-bonds [Scheme 1(*f*)] and/or H-bonding to the solvent *e.g.* CH_3OH or to water in the solvent [Scheme 1(*e*)], an explanation which is supported by the absence of concentration effects on the ν(CO) frequencies (Table 1) and by the NMR studies below.

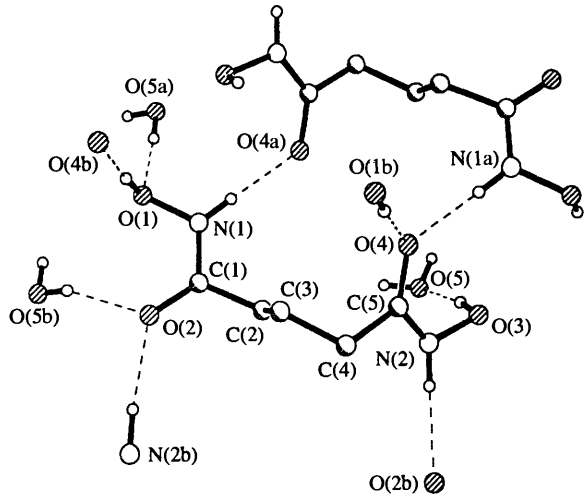


Fig. 1 Molecular structure and hydrogen bonding scheme of GHA·H_2O (**6**)

Comparison between compound **13**, series D, and the corresponding unsubstituted compound **10** (n = 7) in Series C shows considerably lower ν(CO) values for **13** compared with the unsubstituted dihydroxamic acid **10** (n = 7), as in the monohydroxamic acid series A and B.

^{1}H and ^{13}C NMR spectra

NMR studies for Series A and C were limited to [$^2H_6$]DMSO because of their poor solubilities, whereas series B and D could also be studied in $CDCl_3$.

Series A and C. Series A (**1–3**) and C (**6–12**) showed contrasting behaviour in [$^2H_6$]DMSO. Series A showed a single set of characteristic peaks in both the ^{1}H and ^{13}C NMR spectra at room temperature, consistent with the presence of only one conformer (Table 2) whereas series C showed two sets of ^{1}H singlets in the region 8.0–11.0 ppm, one set significantly more intense than the other. By analogy with our previous studies of [^{15}N]acetohydroxamic acid,[13] the major peaks at *ca.* 10.3 and 8.7 ppm of series C are assigned to the NH and OH protons of the (*Z*)-hydroxamate groups and those of the minor component of series C at *ca.* 9.7 and 9.0 ppm to the *E* conformation. This is in accord with the fact that protons *trans* to a carbonyl group are more deshielded than *cis*.[14] In all cases in Series C, the *Z*:*E* ratio is in the range 12–16:1 but there is no general trend with chain length in contrast to the monohydroxamic acids where the proportion of *Z* isomer increases with increasing alkyl chain length.[15] The ^{13}C NMR spectra of Series C confirm the above conclusions since two ^{13}C carbonyl resonances occur, the more intense at *ca.* 169 ppm being assigned to the *Z* isomer and the less intense at *ca.* 176 ppm to the *E* isomer (Table 2). The backbone carbons for both *Z* and *E* isomers are identical in all cases. In the case of series A (**1–3**), it was assumed that the *Z* isomer was the only one present and this conclusion is supported by the ^{13}C NMR spectra which all show a single ^{13}C carbonyl signal at *ca.* 164 ppm (Table 2) and also by the fact

Table 1 Effect of solvent and concentration on IR carbonyl stretching frequencies, ν(CO)/cm^{-1}

Compound	Solid state (KBr)	Solvent: $CHCl_3$			
		0.03 M		0.06 M	
1	1652, 1611				
2	1651, 1646				
3	1651, 1600				
4	1608, 1591	1618		1618	
5	1608, 1570	1610		1611	
		Solvent: CH_3OH		Solvent: DMSO	
		0.02 M	0.04 M	0.02 M	0.04 M
6	1616, 1657	1659	1659	1679	1679
7	1625	1657	1657	1679	1679
8	1631	1657	1657	1679	1679
9	1620, 1665	1657	1657	1678	1678
10	1620, 1665	1657	1657	1677	1676
11	1621, 1666	1657	1657	1678	1673
12	1623, 1665	1657	1658	1679	1679
		0.015 M	0.030 M	0.015 M	0.030 M
13	1608	1630	1631	1644	1644

that limited concentration studies gave no evidence for shifts consistent with the presence of intramolecular H-bonding expected for the *Z* isomer [Scheme 1(*f*)] in contrast to intermolecular H-bonding which is more probable for the *E* isomer than the *Z* isomer [Scheme 1(*g*)].

Series B and D, [$^2H_6$]DMSO. As for the corresponding primary acids (**1–3**, Series A) in [$^2H_6$]DMSO, series B (**4** and **5**) also shows a single set of characteristic peaks in the ^1H and ^{13}C spectra measured in [$^2H_6$]DMSO at room temperature (Table 2) assigned by analogy with series A to the *Z* isomer. In contrast, whereas the primary dihydroxamic acids (Series C) show clear evidence for both *Z* and *E* conformers in [$^2H_6$]DMSO, the secondary compound (Series D, **13**) shows only a single OH resonance at 9.72 ppm (Table 2) integrating for two protons and similarly for the single NMe signal at 3.07 (6 H) which is identical with the NMe resonance in *N*-methylacetohydroxamic acid.[15] The ^{13}C spectrum also shows a single carbonyl resonance at 172.9 ppm. Accordingly, we conclude that in [$^2H_6$]DMSO, *N*,*N*′-dimethylazelaodihydroxamic acid exists as only the *Z* isomer.

Series B and D, $CDCl_3$. In contrast to [$^2H_6$]DMSO, Series D (**13**) shows a doubling of the ^1H NMR resonances even at room temperature in $CDCl_3$ (Table 2). The NCH_3 peak at 3.35 ppm (major component) is attributed to the *Z* isomer and the minor component at 3.27 ppm to the *E* isomer, due to the anisotropy of the diamagnetic susceptibility of the carbonyl group as discussed previously.[15] Similarly the major OH peak at 8.50 ppm is assigned to the *Z* isomer and the minor peak at 9.40 ppm to the *E* isomer.[13] Clearly the solvent effect is important for the secondary dihydroxamic acids and results in considerable stabilisation of the *E* isomer relative to the *Z* isomer in $CDCl_3$ with the proportion of *E* isomer increasing considerably on lowering the temperature (*Z*/*E* = 1.2 at 25 °C and 0.7 at 0 °C), consistent with intermolecular H-bonding occurring between *E* isomers. The OH region in **13** (8.00–11.00 ppm) changed on lowering the temperature to 0 °C with the formation of four peaks in **13** apparently due to a splitting of both the *Z*(OH) and *E*(OH) peaks observed at 25 °C. This could arise if the intermolecular H-bonding occurs in such a way that the two hydroxamate groups are oriented differently with respect to each other. The ^{13}C NMR spectra give further confirmation of the occurrence of *Z* and *E* isomers at room temperature with respective CO peaks at 167.5 and 174.9 ppm (Table 2). In $CDCl_3$, series B, in contrast to series D, shows only one set of ^1H NMR resonances at room temperature, *e.g.* in **4** the N–Me resonance is observed at 3.34 ppm and assigned to the *Z* isomer because on lowering the temperature to −50 °C, the N–Me resonance of **4** splits into a minor peak at 3.20 ppm and a major peak at 3.34 ppm assigned to the *E* and *Z* conformers respectively as discussed above for series D.

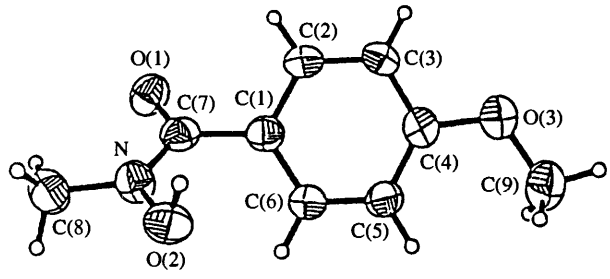


Fig. 2 Molecular structure of MOTH (**5**)

The ^{13}C NMR spectra confirmed these conclusions, since at the lower temperature two sets of N–Me peaks appeared at 36.8 and 40.2 ppm for **4** and 37.0 and 40.2 ppm for **5** assigned to the minor (*E*) component and the major (*Z*) component, respectively, for each compound. The carbonyl carbon resonances gave further support to this assignment (Table 2).

X-Ray structural studies

Full structural determinations of two of the above hydroxamic acids were made, *vis* $(CH_2)_3(CONHOH)_2$ (GHA, **6**) with one water molecule coordinated and *p*-$MeOC_6H_4CONMeOH$ (MOTH, **5**). The molecular structures are shown in Figs. 1 and 2, respectively. Selected bond lengths and angles are presented in Tables 3 and 4.

Fig. 1 shows that in the solid state both hydroxamic acid groups of GHA·H_2O are in the *Z* conformation and form an extensive hydrogen bonding network. Each GHA molecule is hydrogen bonded to five neighbouring GHA and three water molecules as presented in Fig. 2 and Table 5. The surroundings of the hydroxamic acid moieties are slightly different and this is reflected in their planarity and in the C=O bond lengths. Most bond lengths of the hydroxamic acid moieties are equal and similar to those found[12] in *N*,*N*′-dihydroxy–*N*,*N*′-diisopropylhexanediamide (PAH) which posseses the *E* conformation, as observed in all secondary hydroxamates reported in the solid state to date.

The molecular structure of unhydrated *N*-methyl-*p*-methoxybenzohydroxamic acid (MOTH, **5**) is presented in Fig. 2. The acid moiety assumes the *E* conformation. A strong O(2)–H···O(1) hydrogen bond links molecules to each other forming infinite chains similar to *N*-methyl-*p*-toluohydroxamic

Table 2 NMR (^{1}H and ^{13}C) chemical shifts (ppm) of *p*-$RC_6H_4CONR'OH$ (Series A and B) and $(CH_2)_n(CONR'OH)_2$ (Series C and D)

Comp.	R	R'	Nucleus	Chemical shift/ppm R Z(E)	R Z(E)	OH Z(E)	CO Z(E)
Series A							
1[a]	Me	H	^{1}H	2.34	11.2	9.02	—
			^{13}C	21.04	—	—	164.4
2[a]	MeO	H	^{1}H	3.78	11.1	8.94	—
			^{13}C	55.2	—	—	163.9
3[a]	NO_2	H	^{1}H	—	11.6	9.40	—
			^{13}C	—	—	—	163.1
Series B							
4[a]	Me	Me	^{1}H	2.32	3.24	9.96	—
			^{13}C	20.85	37.31	—	168.5
4[b]	Me	Me	^{1}H	2.36	3.34	9.02	—
			^{13}C	21.4	38.4	—	167.5
4[c]	Me	Me	^{1}H	2.40 (2.35)	3.40 (3.20)	10.60 (br)	—
			^{13}C	21.6	40.2 (36.8)	—	167.6 (170.3)
5[a]	MeO	Me	^{1}H	3.78	3.23	9.93	—
			^{13}C	55.2	37.5	—	168.5
5[b]	MeO	Me	^{1}H	3.83	3.38	8.95	—
			^{13}C	55.3	38.6	—	167.4
5[c]	MeO	Me	^{1}H	3.87 (3.82)	3.45 (3.21)	10.36 (10.31)	—
			^{13}C	55.4 (55.3)	40.2 (37.0)	—	167.3 (169.7)
Series C	*n*						
6[a]	3		^{1}H		10.4 (9.76)	8.68 (9.02)	—
		H	^{13}C		—	—	168.6 (175.1)
7[a]	4		^{1}H		10.3 (9.74)	8.67 (9.01)	—
		H	^{13}C		—	—	169.0 (175.7)
8[a]	5		^{1}H		10.3 (9.71)	8.66 (8.99)	—
		H	^{13}C		—	—	169.0 (175.7)
9–12[a]	6–8, 10		^{1}H		10.3 (9.71)	8.66 (8.99)	—
		H	^{13}C		—	—	169.1 (175.7)
Series D							
13[a]	7		^{1}H		3.07	9.72	—
		Me	^{13}C		35.6	—	172.9
13[b]	7		^{1}H		3.35 (3.27)	8.50 (9.40)	—
		Me	^{13}C		36.2 (35.9)	—	167.5 (174.9)

[a] [$^2H_6$]DMSO; room temperature. [b] $CDCl_3$; room temperature. [c] $CDCl_3$; −50 °C.

Table 3 Selected bond lengths (Å) for mono- and di-hydroxamic acids with esd values in parentheses

	GHA[a]	PAH[b]	MOTH[a]	MTH[c]
N1–C8	—	1.461(2)	1.443(4)	1.456(2)
N1–O1	1.399(2)	1.396(2)	1.394(3)	1.405(2)
N2–O3	1.400(2)	—	—	—
N1–C1	1.326(2)	1.328(2)	1.337(4)	1.339(2)
N2–C5	1.324(2)	—	—	—
C1–O2	1.243(2)	1.241(2)	1.241(4)	1.244(1)
C5–O4	1.251(2)	—	—	—
C1–C2	1.513(2)	1.502(2)	1.487(4)	1.494(2)
C5–C4	1.515(2)	—	—	—
C2–C3	1.526(2)	1.502(2)	—	—
C4–C3	1.536(2)	—	—	—

[a] Present work. [b] Ref. 12. [c] Ref. 16.

Table 4 Selected bond angles (°) for mono- and di-hydroxamic acids with esd values in parentheses

	GHA[a]	PAH[b]	MOTH[a]	MTH[c]
O1–N1–C1	118.8(1)	120.1(1)	121.0(3)	119.1(1)
O3–N2–C5	119.4(1)	—	—	—
N1–C1–C2	122.4(1)	119.5(1)	120.0(3)	119.0(1)
N2–C5–O4	123.0(1)	—	—	—
N1–C1–C2	114.6(1)	119.7(2)	118.1(3)	120.9(1)
N2–C5–C4	114.8(1)	—	—	—
O2–C1–C2	122.9(1)	120.8(2)	122.0(3)	120.1(1)
O4–C5–C4	122.2(1)	—	—	—

[a] Present work. [b] Ref. 12. [c] Ref. 16.

acid, the respective hydrogen bond parameters are: O(2)···O(1) = 2.667 and 2.642 Å, O(2)–H = 0.91 and 0.92 Å, H···O(1) = 1.76 and 1.74 Å, and the angle O(2)–H···O(1) = 167 and 170° for the present compound and *N*-methyl-*p*-toluohydroxamic acid, respectively. Furthermore in both compounds the corresponding bond lengths are approximately equal as shown in Table 3 but the average deviation of 0.043 Å for the O(2), N, C(7) and O(1) atoms from their mean plane in the present compound is about half of that (0.094 Å) found in *N*-methyl-*p*-toluohydroxamic acid (MTH). In other secondary hydroxamic acids the planarity of the acid group depends on the nature of the N- or C-substituent.[16] In the present compound MOTH **5** the C(1)–C(7) bond length of 1.487[4] Å is a single C–C bond between sp^2 hybridized carbon atoms since the dihedral angle between the hydroxamate moiety and the benzyl ring is 54.1°.

Theoretical studies

Ab initio molecular orbital calculations were carried out on the isolated formohydroxamic acid and glutarodihydroxamic acid molecules at the Hartree–Fock level using the 6-31G* basis sets and the Gaussian 92 program.[17] Similar optimized calculations were also carried out on formohydroxamic acid and glutarodihydroxamic acid monohydrates and glutarodihydroxamic acid dihydrate. To test the reliability of the 6-31G* computations, formohydroxamic acid and formohydroxamic acid monohydrate were optimized at the MP2(FC)/6-31G* level. The results are shown in Fig. 3 for the various conformations. The *E* and *Z* conformers of isolated formohydroxamic acid are predicted to be equally stable at the MP2(FC)/6-31G** level while at the 6-31G* level the *Z* conformer is less stable by 8.1 kJ mol^{-1}.

Table 5 Interatomic distances (Å) and angles (°) for GHA·H_2O with esd values in parentheses

X–H···Y	Bond distances/Å X–H	H···Y	X···Y	Bond angles (°) < X–H···Y
O1–H1···O4a	0.90 (2)	1.77 (2)	2.664 (2)	174 (1)
N2–H9···O2b	0.89 (2)	1.97 (2)	2.856 (2)	172 (1)
N1–H2···O4a	0.90 (2)	2.01 (2)	2.900 (2)	172 (1)
O1–H12···O5a	0.87 (2)	2.03 (2)	2.890 (2)	172 (1)
O2–H11···O5b	0.84 (2)	2.06 (2)	2.862 (2)	160 (1)
O3–H10···O5	0.88 (2)	1.76 (2)	2.640 (2)	171 (1)

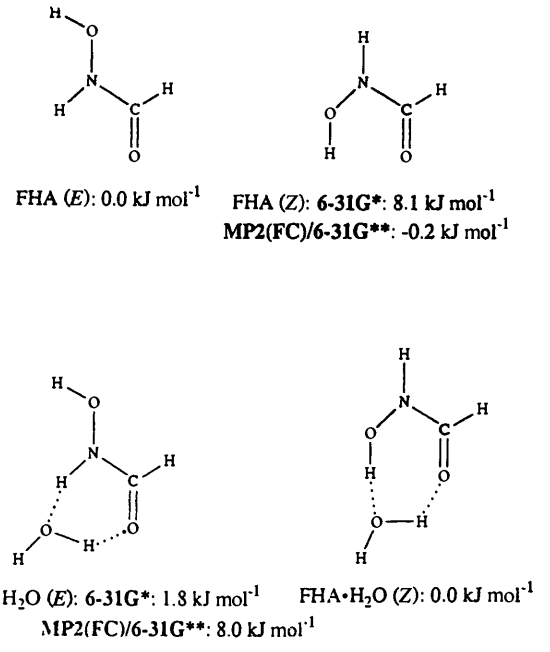


Fig. 3 Structures and calculated relative energies of conformers of FHA and FHA·H_2O

However, in contrast to the calculations on the isolated molecules, the addition of a water molecule makes the *Z* conformer more stable than the *E* conformer at all the levels employed.

In the case of free glutarodihydroxamic acid (GHA), the *ZZ* conformer is 15.1 kJ mol^{-1} (6-31G*) less stable than the *EE* conformer (Fig. 4). However, addition of one water molecule results in a considerable lowering of the energy difference between the *EE* and *ZZ* conformers to only 4.5 kJ mol^{-1} (6-31G*) (Fig. 4). Finally, addition of a further water molecule results in the conformation with both hydroxamate groups *cis* (*ZZ*), through formation of H-bonds between the water molecules and the CONHOH groups, now being the preferred structure with the *EE* conformer being 5.2 kJ mol^{-1} (6-31G*) higher in energy than the *ZZ* conformer. These theoretical results are in good agreement with previous calculations on both acetohydroxamic acid and its hydrate[18] where again the *E* conformer was the stable structure in the absence of a water molecule, whereas addition of a water molecule causes the hydroxamate group to take up the *Z* conformation as observed in the crystal structure of acetohydroxamic acid.[19] Our theoretical results are also in accord with the X-ray crystal structure of GHA·H_2O (Fig. 1) where clearly the water molecules are partly responsible for the hydroxamate groups taking up the *Z* conformation.

Conclusions

X-Ray crystallography and *ab initio* molecular orbital calculations show that the effect of water on glutarodihydroxamic acid is preferentially to stabilize the *Z* conformation of the CONHOH hydroxamate groups. In contrast, the X-ray crystal structure of the unhydrated *p*-MeC_6H_4NMeOH shows only the *E* conformation. IR and NMR solution studies show in $CHCl_3$, in general, both *Z* and *E* conformers may occur, whereas in DMSO the *Z* isomer generally predominates.

Experimental

General

NMR spectra, using tetramethylsilane (TMS) as reference, were obtained on a JEOL GX270Hz spectrometer in the NMR Centre, Department of Chemistry, University College Dublin. Infrared spectra were recorded using a 0.1 mm CaF_2 cell or as KBr discs (2%) on a Perkin-Elmer 1720 FTIR spectrometer linked to a Perkin-Elmer 3700 data station. Analyses were performed by the Microanalytical Laboratory of the Chemical Services Unit of University College Dublin.

Atomic coordinates, bond lengths and angles and thermal parameters for GHA(**6**)·H_2O and MOTH (**5**) have been deposited at the Cambridge Crystallographic Data Centre (CCDC).‡ Intensity measurements were made on a Nicolet R3M diffractometer using graphite-monochromatized Mo-Kα radiation (λ = 0.710 73 Å), ω-scan mode with a scan width of 1.50 and a variable scan speed of 2.00–29.3° min^{-1}. The data sets were corrected for Lorentz and polarization factors.

The crystal structures were determined by direct methods and subsequent Fourier synthesis using the SHELXTL program package.[20] Non-hydrogen atoms were refined anisotropically. For GHA, hydrogen atoms were located from difference Fourier maps and refined isotropically using all 2075 independent reflections measured. For MOTH, hydrogen atoms were placed at calculated positions with fixed isotropic thermal parameters (C–H = 0.96 Å and U = 0.06 $Å^2$) except for those attached to oxygen (O2) of the hydroxamic group which were located from a difference Fourier map and not refined. Refinement of the enantiomeric model of MOTH did not change the *R* factors.

Syntheses

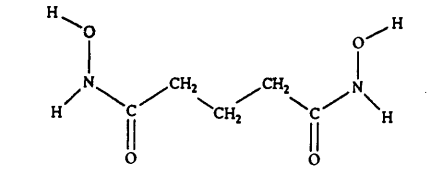
Substituted benzohydroxamic acids (Series A and B). Series A was prepared by standard procedures from the corresponding carboxylic ester and hydroxylamine.[21] Series B was prepared similarly from the corresponding acid chloride and *N*-methylhydroxylamine in a mixed methanol–diethyl ether (30:70) solvent.

Series A.—*p*-Methylbenzohydroxamic acid **1** (Found: C, 63.6; H, 6.00; N, 9.22. $C_8H_9NO_2$ requires C, 63.6; H, 5.96; N, 9.27%); ν_{max}(KBr)/cm^{-1} 3293 (NH), 2753 (OH), 1562 (CN), 904 (NO).

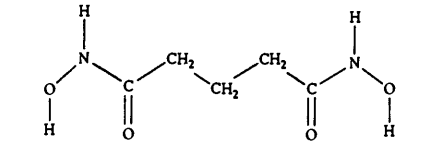
p-Methoxybenzohydroxamic acid **2** (Found: C, 57.5; H, 5.39; N, 8.27. $C_8H_9NO_3$ requires C, 57.5; H, 5.43; N, 8.38%); ν_{max}(KBr)/cm^{-1} 3288 (NH), 2760 (OH), 1562 (CN), 904 (NO).

p-Nitrobenzohydroxamic acid **3** (Found: C, 46.2; H, 3.24; N, 15.32. $C_7H_6N_2O_4$ requires C, 46.2; H, 3.29; N, 15.4%); ν_{max}(KBr)/cm^{-1} 3256 (NH), 2857 (OH), 1562 (CN), 904 (NO).

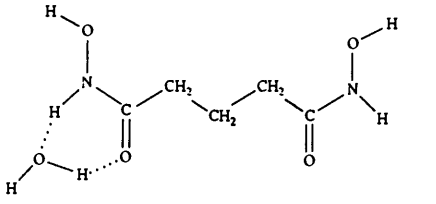
‡ For details of the deposition scheme, see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 2*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and reference number 188/28.



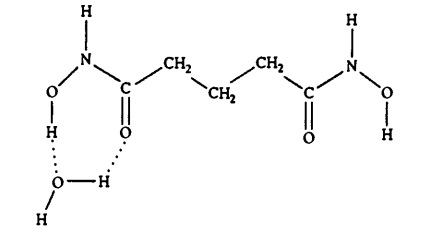
GHA (*E,E*): 0.0 kJ mol^{-1}



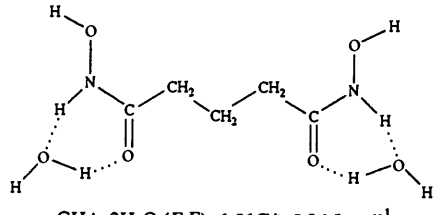
GHA (*Z,Z*): **6-31G***: 15.1 kJ mol^{-1}



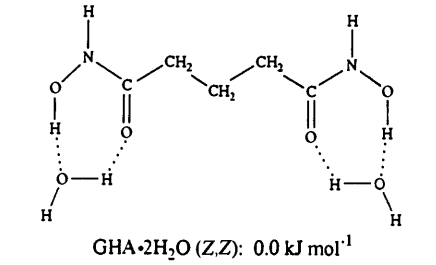
GHA·H_2O (*E,E*): 0.0 kJ mol^{-1}



GHA·H_2O (*Z,Z*): **6-31G***: 4.5 kJ mol^{-1}



GHA·$2H_2O$ (*E,E*): **6-31G***: 5.2 kJ mol^{-1}



GHA·$2H_2O$ (*Z,Z*): 0.0 kJ mol^{-1}

Fig. 4 Structures and relative energies of conformers of GHA, GHA·H_2O and GHA·$2H_2O$

Series B.—*N,p*-Dimethylbenzohydroxamic acid **4** (Found: C, 65.6; H, 6.77; N, 8.42. $C_9H_{11}NO_2$ requires C, 65.4; H, 6.71; N, 8.48%); ν_{max}(KBr)/cm^{-1} 3089 (OH), 2867 (N–CH_3), 1560 (CN), 913 (NO).

p-Methoxy-*N*-methylbenzohydroxamic acid **5** (Found: C, 60.0; H, 6.19; N, 7.79. $C_9H_{11}NO_3$ requires C, 59.7; H, 6.12; N, 7.73%); ν_{max}(KBr)/cm^{-1} 3144 (OH), 2845 (N–CH_3), 1570 (CN), 917 (NO).

Dihydroxamic acids (Series C and D). These were prepared according to the method previously developed in these laboratories[22] in which the corresponding dicarboxylic acid was first treated with *N,N'*-carbonyldiimidazole with formation of the diimidazolide which is then reacted with hydroxylamine (or *N*-methylhydroxylamine) to give the desired dihydroxamic acid. A typical preparation is as follows for glutarohydroxamic acid. Glutaric acid (0.011) mol was stirred overnight with a suspension of *N,N'*-carbonyldiimidazole (0.022 mol) in THF (40 ml) with a gas outlet fitted to the reaction flask. Filtration and drying gave glutarodiimidazolide (77% yield). Free hydroxylamine in methanol was prepared by slowly adding methanolic KOH [0.072 mol in methanol (20 ml)] to a stirred solution of hydroxylamine hydrochloride (0.022) in methanol (15 ml) and stirred at room temperature for 30 min. After cooling for 30 min in ice, KCl was filtered off and the resulting solution added dropwise to the glutarodiimidazolide and the mixture stirred overnight at room temperature. Recrystallization from a water–acetone mixture (1:1) gave white monoclinic crystals (25% yield). Series D was prepared similarly using *N*-methylhydroxylamine in place of the hydroxylamine above; however the crystallization procedure was different because of the greater solubility of series D in methanol. In this case, the methanol was first removed under vacuum and hot ethyl acetate was added to the residual yellow oil until dissolution was complete. Shining white crystals formed on cooling (yield ~25%).

Series C: $(CH_2)_n(CONHOH)_2$.—Glutarodihydroxamic acid monohydrate **6** ($n = 3$) (Found: C, 33.5; H, 6.69; N, 15.6. $C_5H_{12}N_2O_5$ requires C, 33.3; H, 6.72; N, 15.6%); ν_{max}(KBr)/cm^{-1} 3181 (NH), 2871 (OH), 1551 (CN), 977 (NO).

Adipodihydroxamic acid dihydrate **7** ($n = 4$) (Found: C, 34.4; H, 7.78; N, 13.1. $C_6H_{16}N_2O_6$ requires C, 34.0; H, 7.60; N, 13.1%); ν_{max}(KBr)/cm^{-1} 3212 (NH), 2889 (OH), 1510 (CN), 974 (NO).

Pimelodihydroxamic acid **8** ($n = 5$) (Found: C, 44.7; H, 7.61; N, 14.7. $C_7H_{14}N_2O_4$ requires C, 44.2; H, 7.42; N, 14.7%); ν_{max}(KBr)/cm^{-1} 3166 (NH), 2867 (OH), 1558 (CN), 976 (NO).

Suberodihydroxamic acid **9** ($n = 6$) (Found: C, 47.4; H, 8.08; N, 13.6. $C_8H_{16}N_2O_4$ requires C, 47.1; H, 7.90; N, 13.7%); ν_{max}(KBr)/cm^{-1} 3254 (NH), 2754 (OH), 1567 (CN), 979 (NO).

Azelaodihydroxamic acid **10** ($n = 7$) (Found: C, 49.4; H, 8.32; N, 12.7. $C_9H_{18}N_2O_4$ requires C, 49.5; H, 8.31; N, 12.8%); ν_{max}(KBr)/cm^{-1} 3257 (NH), 2750 (OH), 1573 (CN), 970 (NO).

Sebacodihydroxamic acid **11** ($n = 8$) (Found: C, 51.6; H, 9.15; N, 11.6. $C_{10}H_{20}N_2O_4$ requires C, 51.7; H, 8.68; N, 12.1%); ν_{max}(KBr)/cm^{-1} 3256 (NH), 2755 (OH), 1568 (CN), 967 (NO).

Dodecanodihydroxamic acid **12** ($n = 10$) (Found: C, 55.5; H, 9.42; N, 10.4. $C_{11}H_{22}N_2O_4$ requires C, 55.4; H, 9.29; N, 10.8%); ν_{max}(KBr)/cm^{-1} 3254 (NH), 2761 (OH), 1568 (CN), 969 (NO).

Series D: $(CH_2)_7(CONCH_3OH)_2$.—*N,N'*-Dimethylazelaodihydroxamic acid **13** (Found: C, 53.3; H, 9.31; N, 11.5. $C_{11}H_{22}N_2O_4$ requires C, 53.7; H, 9.00; N, 11.4%); ν_{max}(KBr)/cm^{-1} 3152 (OH), 1608 (CN).

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