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Bisamidoximes: Synthesis and Complexation with Iron(III)

James E. Johnson,[A,E] *Carol Carvallo,*[A] *Debra D. Dolliver,*[B] *Natalia Sanchez,*[A]
Vilma Garza,[A] *Diana C. Canseco,*[A] *Gordon L. Eggleton,*[C]
and Frank R. Fronczek[D]

[A]Department of Chemistry and Physics, Texas Woman's University, Denton, TX 76204-5859, USA.
[B]Department of Chemistry and Physics, Southeastern Louisiana University, Hammond, LA 70402, USA.
[C]Department of Physical Sciences, Southeastern Oklahoma University, Durant, OK 74701-0609, USA.
[D]Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803, USA.
[E]Corresponding author. Email: jjohnson@mail.twu.edu

Bisamidoximes have been synthesized by the reaction of 4-methylbenzohydroximoyl chloride with 1,2-diaminoethane, 1,3-diaminopropane, 1,4-diaminobutane, and 3,3′-diamino-*N*-methyl-dipropylamine. A monoamidoxime and a trisamidoxime were also prepared in the present work by the reaction of 4-methylbenzohydroximoyl chloride with *N*,*N*-dimethylethylenediamine and tris(2-aminoethyl)amine. Single crystal X-ray structures of three of the bisamidoximes have shown that the two amidoxime moieties have the *Z* configuration in all three compounds. Job's method of continuous variations showed that three of the bisamidoximes prepared in this work form 1:1 complexes with iron(III) and therefore are acting as tetradentate ligands.

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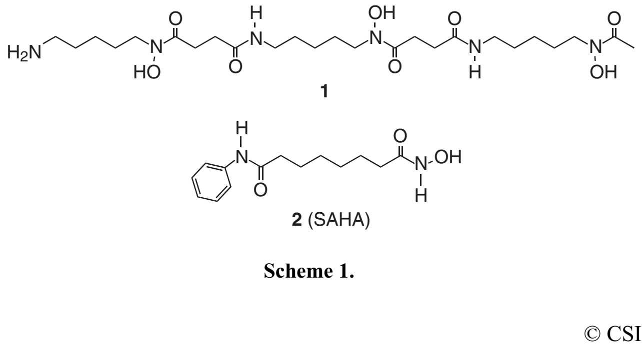
Introduction

Although iron is essential for most forms of life, the low solubility of ferric hydroxide in water has necessitated sophisticated mechanisms for the transport and management of iron(III) in biological systems. Microorganisms often use low molecular weight chelators (siderophores) to solubilize and transport ferric ion. Siderophores commonly contain the hydroxamic acid functional group, which forms hexacoordinate, octahedral complexes with ferric ion.[1,2]

Humans have developed a complex iron storage and recycling process to supply the ferric ion necessary for proper cell function. Unfortunately, humans afflicted with certain genetic disorders, such as thalassemia and aplastic anemia, must receive periodic transfusions, which lead to excess iron in the body.[3] Excess iron in this closed metabolic loop leads to chronic overload and to peroxidative tissue damage. For these iron overload syndromes, the treatment of choice has been chelation therapy. Specifically, an open-chain siderophore (desferrioxamine B, **1**, DFO, Scheme 1), which forms a 1:1 hexacoordinate, octahedral complex with iron(III), has been the primary chelator used to rid the body of iron in these overload syndromes.[4] Although it has been proved to be effective and to display good long-term tolerability, it is expensive and relatively inefficient.[3–5]



Scheme 1.

Recently, it has been discovered that hydroxamic acids can be used as histone deacetylase (HDAC) inhibitors. These compounds have antiproliferative activity and have been shown to be useful therapeutic agents.[6–8] Octanedioic acid hydroxyamide phenylamide (**2**, suberoylanilide hydroxamic acid, SAHA, Scheme 1) has recently received US Food and Drug Administration approval for the treatment of advanced cutaneous T-cell lymphoma.[8b] An important feature of the HDAC inhibitors is their ability to complex the zinc ion in the active site.[8d]

It is apparent then that other types of metal chelators should be investigated as alternative therapies for the removal of ferric ion in iron overload syndromes and as potential HDAC inhibitors. The present paper reports on a new and improved route for the synthesis of bisamidoximes (**3d**–**g**, Scheme 2). Whereas **3a** and **3b** have been previously synthesized through a seven-step route,[9] the procedure described herein is a relatively simple three-step route that begins with 4-methylbenzaldehyde. As amidoximes are known to form coloured complexes with transition metals including iron(III),[10,11b] the ability of these bisamidoximes to complex with iron(III) has also been investigated.

Results and Discussion

The bisamidoximes were synthesized by treating various diamines with a benzohydroximoyl chloride (**4**, Scheme 2). The hydroximoyl chloride was prepared by reaction of a benzaldoxime with *N*-chlorosuccinimide according to a literature procedure.[12]

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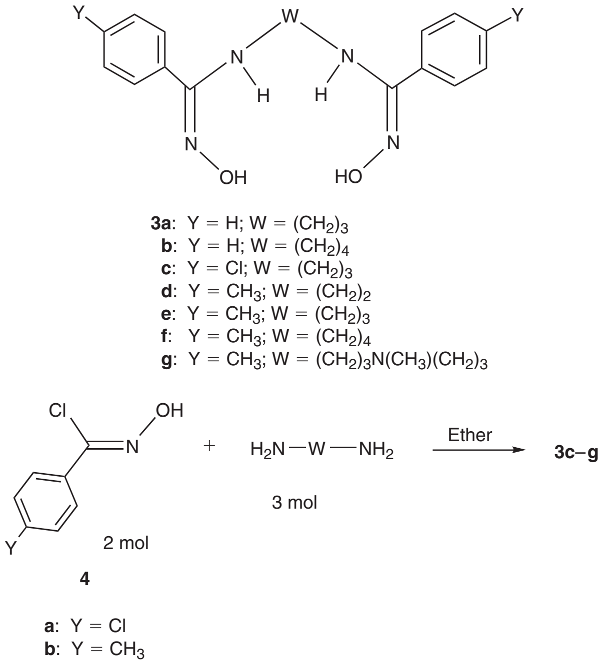
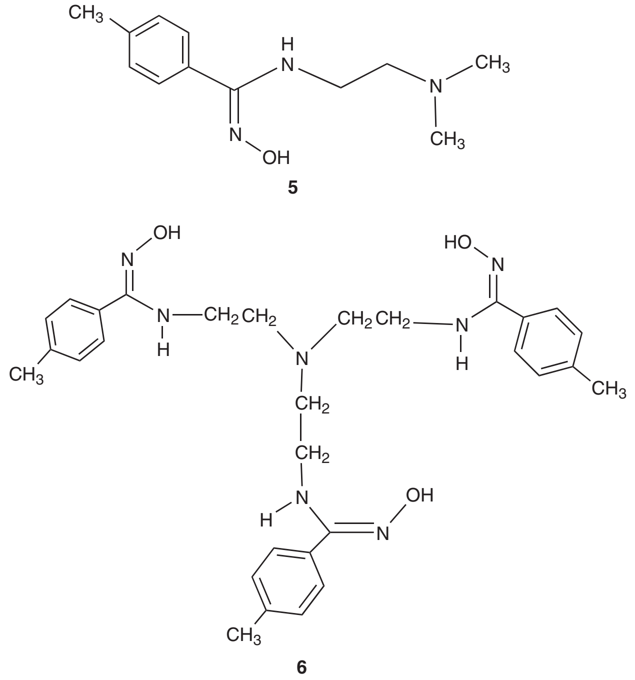


Scheme 2.



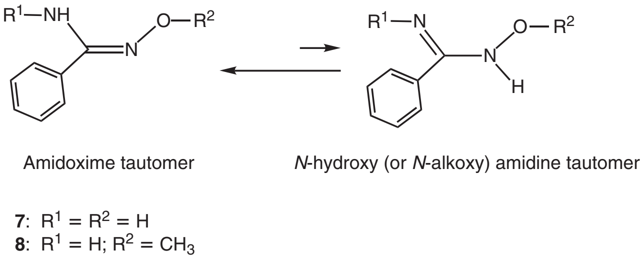
Scheme 3.

In the initial work on the present project, 4-chlorobenzohydroximoyl chloride **4a** was treated with 1,3-diaminopropane to give the bisamidoxime. The bisamidoxime **3c** proved to be highly insoluble and could not be recrystallized and further steps at purification were abandoned. When the reaction was carried out with 4-methylbenzohydroximoyl chloride **4b**, the products were considerably more soluble and could be purified by recrystallization. Reactions of 1,2-diaminoethane, 1,3-diaminopropane, 1,4-diaminobutane, and 3,3′-diamino-*N*-methyl-dipropylamine with 4-methylbenzohydroximoyl chloride **4b** gave the bisamidoximes **3d**–**g** (Scheme 2). The reaction requires a 2:3 mol ratio of hydroximoyl chloride to diamine. Two moles of the diamine act as a base and form the diamine hydrochloride.

Two other amidoximes (Scheme 3) were prepared in the present work by the reaction of *N*,*N*-dimethyl-1,3-diaminoethane and tris(2-aminoethyl)amine with **4b** to give the monoamidoxime **5** and the trisamidoxime **6**, respectively.

Amidoximes that have at least one hydrogen on the amide nitrogen are capable of existing in two tautomeric forms (Scheme 4). It is generally accepted that the oxime tautomer is favoured.[11] It is possible to isolate the *Z* and *E* isomers of amidoximes when the amide nitrogen is disubstituted (**10** and **11**, Scheme 5 for example).[13,14]

Single crystal X-ray structures of **3d**, **3e**, and **3f** have shown that in the crystalline state these compounds are in the amidoxime tautomeric form. The two amidoxime moieties in each of these compounds have the *Z* configuration, with N–C=N–O torsion angles −4.10(15)° in **3d**, 1.2(3)° and −4.1(3)° in **3e**, and 4.62(13)° in **3f**. Compound **3d** (Fig. 1) lies on an inversion centre in the crystal, and thus has its central N–$(CH_2)_2$–N group fully extended. Both **3e** (Fig. 2) and **3f** (Fig. 3) have their central N–$(CH_2)_n$–N groups folded, with approximate C_2 symmetry for **3e** and exact crystallographic C_2 symmetry for **3f**.



Scheme 4.

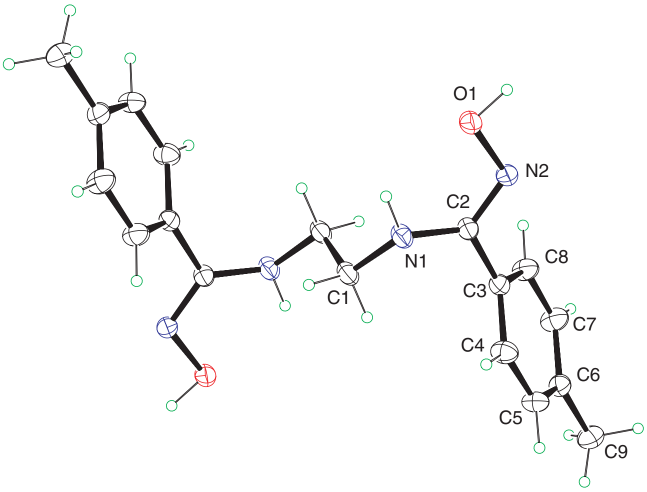


Fig. 1. ORTEP drawing of **3d**, with 50% ellipsoids, showing the numbering scheme.

To determine the structural requirements for complexation of amidoximes, qualitative tests (Table 1) with iron(III) chloride were carried out on some amidoximes synthesized in the present work and some other amidoximes prepared in previous work in our laboratory (**7**–**9**, **10*Z*** and **10*E***, Schemes 4 and 5).

Benzamidoxime **7**, as has been previously reported, gave a burgundy colour with alcoholic ferric chloride.[11b]

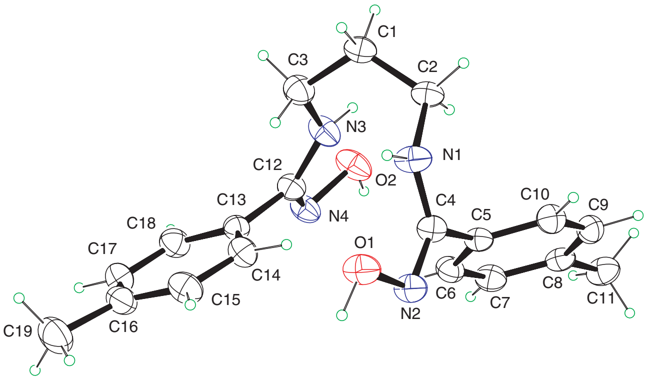


Fig. 2. ORTEP drawing of **3e**, with 50% ellipsoids, showing the numbering scheme.

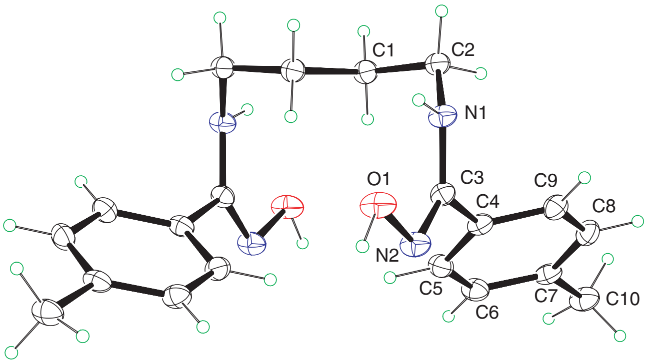


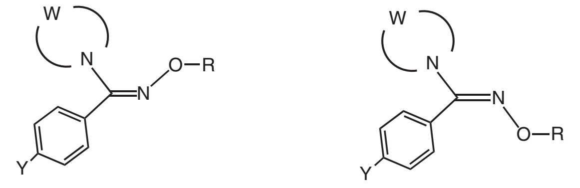
Fig. 3. ORTEP drawing of **3f**, with 50% ellipsoids, showing the numbering scheme.

Table 1. Complex formation of amidoximes with iron(III) chloride

Amidoxime	Colour test with alcoholic iron(III) chloride
7	Positive
8	Negative
9	Negative
10*Z*	Positive
10*E*	Negative

O-Methylbenzamidoxime[14] **8**, which has also been reported in the literature,[11b] gave a negative test result. This is similar to alkyl hydroxamates, which also do not form complexes with ferric ion.[11b] Recent calculations[8d] on hydroxamic acids show that a hydroxamic acid can act as bidentate ligand only when the hydroxylamine oxygen is deprotonated. The coordination sites are the carbonyl oxygen and the deprotonated hydroxylamine oxygen. It seems reasonable to assume that in amidoximes, the oxime oxygen must be deprotonated for it to act as a bidentate ligand. The other site for coordination is likely to be the amide nitrogen atom.

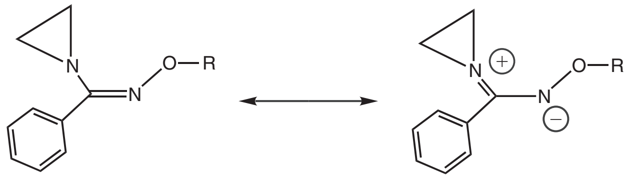
To determine the role of the amide nitrogen in complexation with iron(III), two compounds with the amide nitrogen incorporated into a three-membered or a six-membered ring system were tested (Scheme 5). When the amide nitrogen was part of a three-membered ring (an aziridine ring)[13] (**9*Z*** and **9*E***), the compound did not produce a colour with iron(III). When the amide nitrogen was a part of a six-membered ring (morpholine)[15] (**10*Z***), a burgundy colour was produced with iron(III).



9*Z*: W = $CH(CH_3)CH_2$; Y = R = H
10*Z*: W = $(CH_2)_2O(CH_2)_2$; Y = Cl; R = H
11*Z*: W = $(CH_2)_2$; Y = H; R = CH_3

10*E*: W = $(CH_2)_2O(CH_2)_2$; Y = Cl; R = H
11*E*: W = $(CH_2)_2$; Y = H; R = CH_3

Scheme 5.



9*Z*: R = H
11*Z*: R = CH_3

Scheme 6.

Two factors can be considered in causing this apparent difference in the ability of the amide nitrogen to complex with iron: resonance with the imine bond and the inherent basicity of the amide nitrogen. In previous work, we suggested that poor overlap of the nitrogen unbonded electron pair in the aziridine ring with the p-orbital on the oxime carbon atom is responsible for the extraordinary resistance of **11*Z*** and **11*E*** to thermal *Z*/*E* isomerization.[13b]

We suggested that the zwitterionic resonance structure (Scheme 6) in amidoximes **11*Z*** (and **11*E***) does not make as large a contribution as it does in amidoximes with larger rings (**10*Z*** for example). It has been suggested[16] that the downfield chemical shift of the α-vinyl proton in *N*-alkenyl aziridines compared with enamines derived from simple amines is due to the decreased importance of the zwitterionic resonance form. Poor overlap in **9*Z***, however, should make the electron pair on the amide nitrogen of **9*Z*** more available for coordination. We conclude that poor overlap of the amide nitrogen lone pair is not a significant factor in determining metal ion complexation.

It is well established[17] that incorporation of a nitrogen atom into a three-membered ring decreases the basicity of the nitrogen atom. Aziridine has a pK_b of 5.99 and the pK_b of morpholine is 5.67.[18] Theoretical calculations have indicated that the decrease in basicity of aziridine is due to an increase in the pyramidalization around the nitrogen atom.[19] It is likely that the decrease in basicity of the nitrogen in the aziridine ring in **9*Z*** is responsible for the inability of this amidoxime to form a complex with iron(III).

Another area to consider when looking at complexes of amidoximes with transition metals is stereochemical effects. The result of the ferric chloride test on the *Z* isomer of morpholino-4-chlorobenzamidoxime (**10*Z***)[15] was positive, whereas the *E* (**10*E***) failed to give a colour.

In summary, the qualitative tests of these amidoximes with iron(III) chloride show that the following requirements must be met in order for an amidoxime to act as a chelating agent: (i) the hydroxylamine oxygen must be unsubstituted; (ii) the amidoxime must be in the *Z* configuration; and (iii) the amide nitrogen of the amidoxime cannot be incorporated into a three-membered ring.

Job's method of continuous variations, a commonly used method for determining compositions of complexes in solution,[20] was used to determine the stoichiometry of the complexes formed by the reaction of amidoximes with iron(III). The method is carried out in a batch mode by mixing aliquots of two equimolar stock solutions of metal and ligand. The solutions are prepared in such a manner that the total molar concentration of metal plus ligand is kept constant while the ligand-to-metal ratio varies from flask to flask, that is:

$$\mathrm{C_M} + \mathrm{C_L} = k,$$

where $\mathrm{C_M}$ and $\mathrm{C_L}$ are the analytical concentrations of metal and ligand, respectively, and k is a constant. The corrected absorbance, the measured absorbance at a given wavelength minus the absorbance of the metal in the absence of ligand, is plotted as a function of mole fraction of ligand. The resulting curves (Job's plots) show a maximum absorbance that yields the ligand-to-metal ratio of the complex in solution.[20] Job's plots for benzamidoxime **7**[10f] have been reported for cobalt(II), but to our knowledge, no other reports on continuous variation studies of amidoximes have been reported.

The continuous variations data, obtained at 533 nm in dimethylformamide (DMF), is given for benzamidoxime **7** with iron(III) in tables 12S and 13S in the Accessory Publication. When the data is plotted (figs 12S and 13S in the Accessory Publication), an absorbance maximum appears at a ligand mole fraction of 0.67, which indicates a 2:1 ligand-to-metal ratio in the complex. This result suggests that benzamidoxime is acting as a bidentate ligand. The fact that the plot is a curve rather than two intersecting straight lines is an indication that the formation constant for this complex is not high ($K_f < 1.4 \times 10^2$).[20]

Tables in the Accessory Publication give the continuous variations data obtained in DMF for the other bisamidoximes prepared in the present work. Table 2 contains a summary of the continuous variation experiments carried out on benzamidoxime and the new amidoximes prepared in the present work. Three of the bisamidoximes (**3d**, **3f**, and **3g**) prepared in this work form complexes in a 1:1 ligand-to-metal ratio. This indicates that the bisamidoximes **3d**, **3f**, and **3g** are acting as tetradentate ligands.

Table 2. Ratios of ligand to iron(III) from Job's plots in acetonitrile

C, curved plot; I, intersecting lines

Ligand	Total conc. of ligand and iron(III) [M]	Job's plot max. (ratio of ligand to iron(III))	Type of plot	λ_{max} [nm]
5	0.0040	0.67 (2:1)	C	533
5	0.0020	0.67 (2:1)	C	533
3d	0.0040	0.50 (1:1)	C	520
3d	0.0020	0.50 (1:1)	C	520
3e	0.0016	0.67 (2:1)	C	500
3e	0.0020	0.67 (2:1)	C	500
3f	0.0020	0.50 (1:1)	C	525
3f	0.00080	0.50 (1:1)	C	525
3g	0.0020	0.67 (2:1)	C	550
3g	0.00080	0.50 (1:1)	C	550
5	0.0020	0.50 (1:1)	I	540
5	0.00080	0.50 (1:1)	I	540
6	0.00160	0.67 (2:1)	I	465

Conclusions

A relatively simple three-step synthesis from 4-methylbenzaldehyde has been developed for the preparation of bisamidoximes. Four new bisamidoximes have been prepared using this method. Single crystal X-ray structure determinations on three of the bisamidoximes shows that both amidoxime moieties exist in the *Z* configuration. The structural requirements for complex formation with iron(III) have been determined. One trisamidoxime and one new monooxime containing an amine functional group also have been prepared in the present work. Job's method of continuous variations has shown that three of the bisamidoximes act as tetradentate ligands with iron(III).

Experimental

General Procedures

Melting points were determined in a Mel-Temp capillary melting point apparatus and are uncorrected. Proton and carbon NMR spectra were determined on a Varian Mercury 300 MHz or a Varian EM 390 90 MHz spectrometer. High-resolution mass spectra were determined on a BioTOF II ESI Instrument. Midwest Microlab (LLC, Indianapolis, IN, USA) performed the elemental analysis of the new compounds. All chemicals used in this work were purchased from Aldrich Chemical Co., and were at least 98% pure.

Crystal Structure Determinations

The structures of compounds **3d**, **3e**, and **3f** were determined, using data collected at low temperature with $\mathrm{Mo_{K\alpha}}$ radiation (λ 0.71073 Å) on a Nonius KappaCCD diffractometer. Crystal data for **3d**: $C_{18}H_{22}N_4O_2$, MW 326.40, monoclinic, space group $P2_1/n$, a 5.6466(5), b 8.5760(10), c 17.919(2) Å, β 98.997(7)°, V 857.06(16) Å^3, Z 2, T 110 K, D_x 1.265 g cm^{-3}, μ 0.85 cm^{-1}, colourless needle with dimensions 0.50 × 0.25 × 0.23 mm^3, 23 244 measured data with θ <30.8°, 2667 unique data used in refinement, R 0.046 for 2135 observed data, 116 refined parameters. Crystal data for **3e**: $C_{19}H_{24}N_4O_2$, MW 340.42, monoclinic, space group $P2_1/c$, a 18.220(6), b 7.185(3), c 14.269(5) Å, β 108.92(2)°, V 1767.0(11) Å^3, Z 4, T 220 K, D_x 1.280 g cm^{-3}, μ 0.85 cm^{-1}, colourless plate with dimensions 0.47 × 0.22 × 0.12 mm^3, 9260 measured data with θ <25.4°, 3215 unique data used in refinement, R 0.046 for 2072 observed data, 241 refined parameters. Cooling to lower temperatures led to destruction of the crystal, an apparent result of a phase change. Crystal data for **3f**: $C_{20}H_{26}N_4O_2$, MW 354.45, monoclinic space group $C2/c$, a 19.854(2), b 7.1601(10), c 13.514(2) Å, β 106.463(9)°, V 1842.3(4) Å^3, Z 4, T 110 K, D_x 1.278 g cm^{-3}, μ 0.85 cm^{-1}, colourless blade fragment with dimensions 0.50 × 0.50 × 0.12 mm^3, 18 500 measured data with θ <30.6°, 2793 unique data used in refinement, R 0.042 for 2284 observed data, 126 refined parameters. The X-ray crystallographic data have been deposited in CIF format as CCDC-637298, 637299, 637300, available from the Cambridge Crystallographic Data Centre.

Synthetic Experimental Procedures

4-Methylbenzohydroximoyl Chloride *4b*

4-Methylbenzaldehyde oxime (15.0 g, 0.111 mol) was dissolved in DMF (90 mL) at 25–30°C followed by the addition of

1/5 of the solid *N*-chlorosuccinimide (15.0 g, 0.112 mol) while stirring. The reaction was then kept below 35°C by the rate of the addition of the *N*-chlorosuccinimide and intermittent cooling in an acetone/dry ice bath. Completion of the reaction was noted by the cessation of the exotherm. The solution was poured into four volumes of ice water and extracted with ether (2 × 200 mL). The combined ether extracts were then washed with ice-cold water (2 × 200 mL). The organic layer was dried over magnesium sulfate and the ether removed by rotary evaporation at aspirator pressure to yield pale yellow crystals (17.0 g, 0.100 mol, 90%). The crude hydroximoyl chloride was used for the conversion to the bisamidoxime without further purification: mp 70–72°C (68–71°C).[12] δ_H (90 MHz, $CDCl_3$) 2.35 (3H, s), 7.18 (2H, d), 7.70 (2H, d), 9.05 (1H, s).[12]

*1,2-Bis[*N′*-(*Z*)-4-methylbenzene-*N*-hydroxycarboximidamido]ethane* **3d**

1,2-Diaminoethane (1.77 g, 0.0295 mol) in anhydrous ether (100 mL) was stirred in an ice bath at <5°C during the dropwise addition of 4-methylbenzohydroximoyl chloride (5.00 g, 0.0295 mol) dissolved in ether (40 mL). After completion of the addition, the solution was then stirred at room temperature for 1 h, and during this time a colourless precipitate formed. The solution was filtered and the solid was recrystallized from ethanol/water (1.87 g, 60%). mp 204°C (dec.). (Found: C 66.2, H 6.9, N 17.1. $C_{18}H_{22}N_4O_2$ requires C 66.2, H 6.8, N 17.2%). δ_H (300 MHz, d_6-DMSO) 2.33 (6H, s), 2.89 (br d, *J* 6, 4H), 5.74 (br t, *J* 7, 2H), 7.17 (8H, s), 9.68 (2H, s). δ_C (300 MHz, d_6-DMSO) 20.9, 44.0, 128.0, 128.7, 129.6, 138.2, 154.5. ν_{max} (KBr)/cm^{-1} 3380, 3119, 1651. λ_{max} (ethanol)/nm 255 (8.54).

*1,3-Bis[*N′*-(*Z*)-4-methylbenzene-*N*-hydroxycarboximidamido]propane* **3e**

1,3-Diaminopropane (4.40 g, 0.0593 mol) in anhydrous ether (100 mL) was stirred in an ice water bath at <5°C during the dropwise addition of 4-methylbenzohydroximoyl chloride (5.00 g, 0.0260 mol) dissolved in ether (40 mL). After completion of the addition, the solution was then stirred at room temperature for 1 h and during this time a colourless precipitate formed. The mixture was then filtered and the colourless solid was recrystallized from ethanol/water (1.23 g, 25%). mp 110–112.5°C. (Found: C 66.5, H 7.2, N 16.4. $C_{19}H_{24}N_4O_2$ requires C 67.0, H 7.1, N 16.5%). δ_H (300 MHz, d_6-DMSO) 1.37 (quintet, *J* 6.7, 2H), 2.30 (s, 6H), 2.86 (4H, q, *J* 6.7), 5.66 (1H, t, *J* 6.6), 7.16 (4H, d, *J* 8), 7.23 (4H, d, *J* 8), 9.62 (2H, s). δ_C (300 MHz, d_6-DMSO) 20.9, 32.7, 40.3, 127.9, 128.8, 129.8, 138.2, 154.7. ν_{max} (KBr)/cm^{-1} 3405, 3254, 1638. λ_{max} (ethanol)/nm 258 (3.83).

*1,4-Bis[*N′*-(*Z*)-4-methylbenzene-*N*-hydroxycarboximidamido]butane* **3f**

1,4-Diaminobutane (4.00 g, 0.0454 mol) in anhydrous ether (100 mL) was stirred in an ice bath at <5°C during the dropwise addition of 4-methylbenzohydroximoyl chloride (5.10 g, 0.0301 mol) dissolved in ether (40 mL). After completion of the addition, the solution was stirred at room temperature for 1 h, and during this time a colourless precipitate formed. The solution was then filtered and the solid was isolated and recrystallized from ethanol/water (4.10 g, 77%). mp 186.5–187°C. (Found: C 67.7, H 7.5, N 15.8. $C_{20}H_{26}N_4O_2$ requires C 67.8, H 7.4, N 15.8%). δ_H (300 MHz, d_6-DMSO) 1.23 (4H, br s), 2.32 (6H, s), 2.82 (4H, d with shoulders, *J* 6), 5.57 (2H, t, *J* 6.6), 7.24 (4H, d, *J* 8), 7.18 (4H, d, *J* 8), 9.65 (2H, s). δ_C (300 MHz, d_6-DMSO) 20.9, 27.9, 42.7, 127.9, 128.8, 129.9, 138.2, 154.9. ν_{max} (KBr)/cm^{-1} 3395, 3243, 1638.

*1,7-Bis[*N′*-(*Z*)-4-methylbenzene-*N*-hydroxycarboximidamido]-*N*-methyl-4-azaheptane* **3g**

3,3′-Diamino-*N*-methyldipropylamine (4.88 g, 0.0336 mol) in anhydrous ether (100 mL) was stirred in an ice bath at <5°C during the dropwise addition of 4-methylbenzohydroximoyl chloride (3.80 g, 0.0224 mol) dissolved in ether (40 mL). After completion of the addition, the solution was stirred at room temperature for 1 h, during which time a beige semi-solid formed. Enough water was added to the solution to dissolve the precipitate. An open Erlenmeyer flask containing the ether/water mixture was allowed to stand in the hood until dense crystals formed at the interface and fell to the bottom of the flask. The liquid was then decanted from the crystals and they were recrystallized from an ethanol/water solution to yield colourless crystals (1.43 g, 17%). mp 118–119.5°C. (Found: C 67.1, H 8.0, N 17.0, $M^{+\bullet} + H$ 412.270. $C_{23}H_{33}N_5O_2$ requires C 67.1, H 8.1, N 17.0%, $M^{+\bullet} + H$ 412.2707). δ_H (300 MHz, $CDCl_3$) 1.53 (4H, quintet, *J* 7), 2.09 (3H, s), 2.29 (4H, t, *J* 7), 2.36 (6H, s), 3.04 (4H, s with shoulders), 5.65 (2H, br s), 7.17 (4H, d, *J* 8), 7.35 (4H, d, *J* 8). δ_C (300 MHz, $CDCl_3$) 21.3, 28.4, 41.8, 42.2, 55.2, 128.4, 128.8, 129.0, 139.3, 156.8. ν_{max} (KBr)/cm^{-1} 3374, 3214, 1620. λ_{max} (ethanol)/nm 258 (3.81).

*(*Z*)-*N*-Hydroxy-*N′*-(2-*N*,*N*-dimethylaminoethyl)-4-methylbenzenecarboximidamide* **5**

N,*N*-Dimethyl-1,3-diaminoethane (5.20 g, 0.0590 mol) in anhydrous ether (100 mL) was stirred in an ice/water bath at <5°C during the dropwise addition of the 4-methylbenzohydroximoyl chloride (5.00 g, 0.0295 mol) dissolved in ether (40 mL). After completion of the addition, the solution was then stirred at room temperature for 1 h; during this time a colourless precipitate formed. The solution was then filtered, and the filtrate was decolourized with activated charcoal yielding a colourless solution. The ether solution was allowed to sit overnight to concentrate the solution, yielding large colourless crystals, which were then recrystallized from ether/hexanes (5.34 g, 82%). mp 97–98°C. (Found C 65.1, H 8.6, N 19.0. $C_{12}H_{19}N_3O$ requires C 65.1, H 8.7, N 19.0%). δ_H (300 MHz, d_6-DMSO) 2.07 (6H, s), 2.24 (2H, t, *J* 6), 2.32 (3H, s), 2.96 (2H, q, *J* 6), 5.70 (1H, t, *J* 6), 7.21 (2H, d, *J* 8), 7.31 (2H, d, *J* 8), 9.65 (1H, s). δ_C (300 MHz, d_6-DMSO) 20.8, 40.8, 45.0, 59.4, 128.0, 128.7, 129.9, 138.3, 154.6. ν_{max} (KBr)/cm^{-1} 3347, 2955, 1632. λ_{max} (ethanol)/nm 257 (3.66).

Synthesis of the Trisamidoxime **6**

Tris(2-aminoethyl)amine (3.60 g, 0.0245 mol) in anhydrous ether (75 mL) was stirred in an ice bath at <5°C during the dropwise addition of 4-methylbenzohydroximoyl chloride (3.00 g, 0.0177 mol) dissolved in ether (30 mL). After completion of the addition, the solution was stirred at room temperature for 1 h, during which time a solid formed. The ether was then decanted from the precipitate and the precipitate was recrystallized from an ethanol/water solution to yield colourless crystals (0.54 g, 17%). mp 178–179°C. (Found: C 66.2, H 7.2, N 17.9, $M^{+\bullet} + H$ 546.3204. $C_{30}H_{39}N_7O_3$ requires C 66.0, H 7.2, N 18.0%, $M^{+\bullet} + H$ 546.3187). δ_H (300 MHz, d_6-DMSO) 2.17 (6H, t, *J* 6.3), 2.32 (9H, s), 2.77 (6H, q, *J* 6.3), 5.63 (3H, t, *J* 6.6), 7.18, 7.23 (12H, dd, *J* 8.4), 9.63 (3H, s). δ_C (300 MHz, d_6-DMSO), 20.9, 41.0, 54.9, 127.9, 128.8, 129.8, 138.2, 154.5. ν_{max}(Nujol)/cm^{-1} 3396, 3355, 3106(br), 1634. λ_{max} (ethanol)/nm 258 (3.81).

(*Z*)-Morpholino-4-chlorobenzamidoxime **10Z**

4-Chlorobenzohydroximoyl chloride (5.0 g, 0.03 mol) in dry benzene was added to dry morpholine (5.2 g, 0.06 mol) also in dry benzene at 0–5°C. After stirring for 30 min, the precipitated morpholine hydrochloride was filtered off and washed with dry benzene until colourless. The combined benzene washings were evaporated under vacuum at room temperature and the resultant yellow solid was recrystallized from chloroform/pentane at room temperature (5.54 g, 85%). mp 132–137°C (110–112°C).[15]

(*E*)-Morpholino-4-chlorobenzamidoxime **10E**

Crystals of **10*Z*** were allowed to stand at room temperature for several days to ensure complete isomerization to the *E* isomer. mp 132–137°C (lit.[14] 110–112°C).

Accessory Publication

Accessory publications for the Job's plots are available from the authors or from the *Australian Journal of Chemistry* until September 2011.

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