DX

91304

TITLE CHEMISTRY AND BIOLOGICAL ACTIVITY OF IRON QUINONEOXIMIC COMPLEXES

AUTHOR NAVIN DEEPAL PATHIRANA

INSTITUTION and DATE C.N.A.A. 1990 NORTH. LONDON. POLYTECHNIC

CHEMISTRY AND BIOLOGICAL ACTIVITY OF IRON QUINONEOXIMIC COMPLEXES

A thesis submitted to the Council for National Academic Awards in partial fulfilment of the requirements for the Degree of Doctor of Philosophy.

by

NAVIN DEEPAL PATHIRANA

The Polytechnic of
North London in
collaboration with
MRC Clinical Research Centre
and Beecham Pharmaceuticals

March 1990

Dedicated to my parents

and my sisters

Declaration

Whilst registered as a candidate for this degree the author has not been registered as a candidate for any other award.

N. D. Pathirana

Navin Deepal Pathirana

CHEMISTRY AND BIOLOGICAL ACTIVITY OF IRON QUINONEOXIMIC COMPLEXES

ABSTRACT

The synthesis and structure of 1,2-quinone mono-oximes have been reviewed. The reaction of 3-hydroxyphenol, 3-hydroxy-2-methylphenol, 3-hydroxy-5-methylphenol and N-acetyl-3-aminophenol with amyl nitrite/M(OEt) (M = Na or K) has been systematically examined. It has been found that the complex formed depends on the reaction temperature and phenol/M(OEt) ratio. Infra-red spectroscopic studies have shown that in the solid state 5-hydroxy-1,2-benzoquinone 2-oxime ($hqoH_2$), 5-hydroxy-3-methyl-1,2-benzoquinone 2-oxime ($3\text{-}MehqoH_2$), 5-hydroxy-6-methyl-1,2-benzoquinone 2-oxime ($6\text{-}MehqoH_2$) and N-acetyl-5-amino- 1,2-benzoquinone 2-oxime (N-AcqoH) and their sodium and potassium complexes exist in the oximic form rather than the nitroso form. Nuclear magnetic resonance studies have also shown that in d_6-DMSO solution $hqoH_2$, $3\text{-}MehqoH_2$ and $6\text{-}MehqoH_2$ and their sodium complexes exist in one form only which is oximic in character. However, in D_2O the results for the sodium complexes of $hqoH_2$ and $6\text{-}MeqoH_2$ indicate the presence of at least two species. In the case of the sodium 5-hydroxy-6-methyl-1,2-benzoquinone 2-oximate these species are oximic in character. An X-ray crystallographic study of $6\text{-}MehqoH_2$ has shown that in the solid state this compound exists in the 1,4- rather than the 1,2-quinone 2-oximic form.

The synthesis of iron(II) complexes of $hqoH_2$, $3\text{-}MehqoH_2$ and $6\text{-}MehqoH_2$ using the direct and the nitrosation methods was examined. The direct method gave rise to the complexes $Fe(hqoH)_2 \cdot 3H_2O$, $Fe(3\text{-}MehqoH)_2 \cdot 2H_2O$ and $Fe(6\text{-}MehqoH)_2 \cdot 2H_2O$ whereas the nitrosation method gave rise to ill-defined solids. $Na[Fe(N\text{-}Acqo)_3] \cdot 4H_2O$ was obtained by nitrosation of N-acetyl-3-aminopnenol in the presence of iron(II) ammonium sulphate. Mossbauer and magnetic studies indicate that $Na[Fe(N\text{-}Acqo)_3] \cdot 4H_2O$ is a low spin iron(II) complex whereas the bischelates have properties indicative of the S = 1 spin state.

In-vivo assesment of the iron chelating ability of $hqoH_2$, $3\text{-}MehqoH_2$, $6\text{-}MehqoH_2$, N-AcqoH , N,N-dimethyl-5-amino-1,2-benzoquinone 2-oxime and violuric acid was carried out using a normal rat model. The chelators $hqoH_2$ and $6\text{-}MehqoH_2$ were found to be effective in removing iron when administered intra-muscularly but they also caused the excretion of magnesium. Their activity was lower than that of desferrioxamine and neither was effective when administered orally.

Acknowledgements

I wish to express my thanks to my supervisors, Prof. J. Charalambous and Prof. L. I. B. Haines, for their guidance and encouragement throughout the course of this work.

My thanks are also due to Prof. M. J. Pippard of University of Dundee for help and advise specially with regard to the *in-vivo* studies.

Finally, my thanks to Prof. P. C. Christidis of University of Thessaloniki for help with the X-ray crystallographic study, and Dr. M. Campbell and Dr. E. A. Vidgeon for making Mössbauer and n.m.r. facilities available at Thames Polytechnic.

Abbreviations

DF	desferrioxamine
Fig.	figure
h	hour(s)
$hqoH_2$	5-hydroxy-1,2-benzoquinone 2-oxime
H_3Va	violuric acid
i.r.	infra-red
i.v.	intravenous
$3\text{-}MehqoH_2$	5-hydroxy-3-methyl-1,2-benzoquinone 2-oxime
$6\text{-}MehqoH_2$	5-hydroxy-6-methyl-1,2-benzoquinone 2-oxime
m.p.	melting point
N-AcqoH	N-acetyl-5-amino-1,2-benzoquinone 2-oxime
$N\text{-}Me_2qoH$	N,N-dimethyl-5-amino-1,2-benzoquinone 2-oxime
n.m.r.	nuclear magnetic resonance
py	pyridine
qoH	any 1,2-quinone mono-oxime
Ref.	reference (s)
t.l.c.	thin layer chromatography

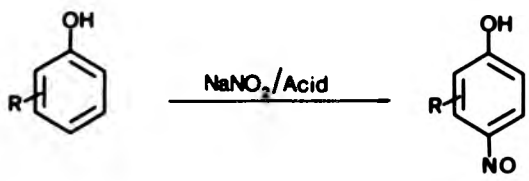
CONTENTS

CHAPTER 1

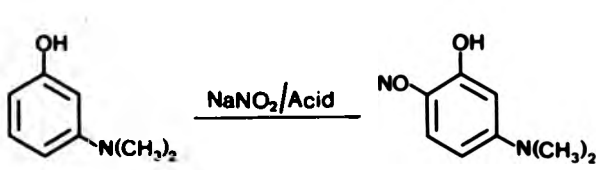
SYNTHESIS AND PROPERTIES OF 3-HYDROXY-1,2-BENZOQUINONE MONO-OXIMES, N-ACETYL-5-AMINO-1,2-BENZOQUINONE 2-OXIME AND SOME OF THEIR GROUP I AND GROUP II METAL COMPLEXES

1.1 Introduction

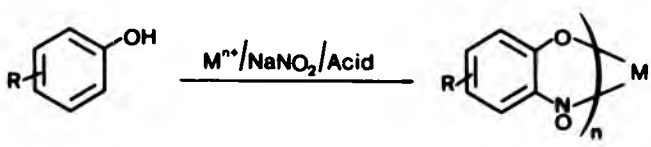
Ring nitrosation of aromatic compounds is difficult unless activating groups are attached to the aromatic ring, e.g. hydroxy or amino. The hydroxy group is ortho/para directing and theoretically nitrosation of phenols can yield a mixture of 2- and 4-isomers. In practice for most phenols the predominant product of nitrosation with sodium nitrite/acid is the 4-isomer (Reaction 1.1) and the 2-isomer is only formed in a few cases, e.g. N,N-dimethyl-3-aminophenol (Reaction 1.2).[1-3] In marked contrast nitrosation in the 2-position occurs readily in the presence of a transition metal salt (Reaction 1.3).[4,5] In this case the 2-nitrosophenol is obtained in the form of its metal complex. Significantly, using this approach nitrosation in the 2-position has been accomplished even in the case of phenols which do not afford the 2-nitrosated product on treatment with sodium nitrite/acid.



Reaction 1.1



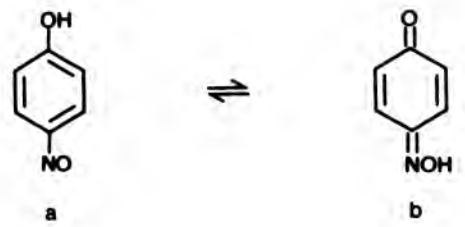
Reaction 1.2



Reaction 1.3

4-Nitrosophenol has been isolated in two forms.[6] One of these forms has been assigned a nitrosophenolic structure (Fig. 1.1a) and the other a quinone oximic structure (Fig. 1.1b). A tautomeric equilibrium between these two forms has been suggested to exist in solution. Two forms, yellow crystals and white fibers, have also been isolated in the case of 2-chloro-

5-methyl-4-nitrosophenol.[7,8] An X-Ray crystallographic study of the yellow crystals has revealed it has quinone oximic structure with the OH of the NOH group *syn* to the chlorine (Fig. 1.2a).[7] From chemical evidence and the knowledge of the structure of the *syn* form, an *anti* quinone oximic structure (Fig. 1.2b) has been suggested for the white fibers.[8] This agrees with the observed powder diagrams of the white fibers.[8] Similar proposals have been made for 5-bromo-5-methyl-1,4-benzoquinone 4-oxime which has also been isolated in a yellow crystalline form and as white fibers.[8]



a b

Fig. 1.1

a b

Fig. 1.2

As in the case of 4-nitrosophenol some 2-nitrosophenols have also been isolated in two forms. Initially these were assigned nitrosophenolic (Fig 1.3a) and quinone oximic structures (Fig. 1.3b) and considered to be tautomeric in solution. However, X-ray crystallographic studies have demonstrated that in the solid state both forms are quinone oximic in character and that the isolation of two forms relates to the possibility of the oximic species existing in a *syn* or *anti* configuration (Fig. 1.4). For example, 5-methoxy-2-nitrosophenol was found to crystalise as green rectangular plates from benzene and as red needles from ethanol.[9] Initially, the quinone oximic structure was assigned to the red form (α-form) and the nitrosophenolic structure to the green form (β-form). An X-ray crystallographic study of the α-form showed it to have quinone oximic structure with the OH of the NOH group *anti* to the CO group.[10] In the case of the 5-propoxy-2-nitrosophenol which also exists in α- and β-forms, X-ray studies showed the latter to be quinone oximic rather than nitrosophenolic.[11] However, in this case the compound has the OH of the NOH group *syn* to the CO group. The significance of the oximic structure has also been demonstrated by the finding that all 2-nitrosophenols characterised by X-ray crystallography have quinone oximic structures in the solid state (see Chapter 2).

a b

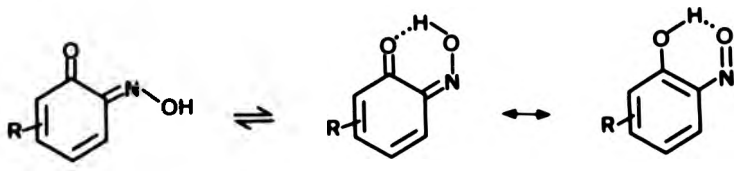
Fig 1.3

syn *anti*

Fig. 1.4

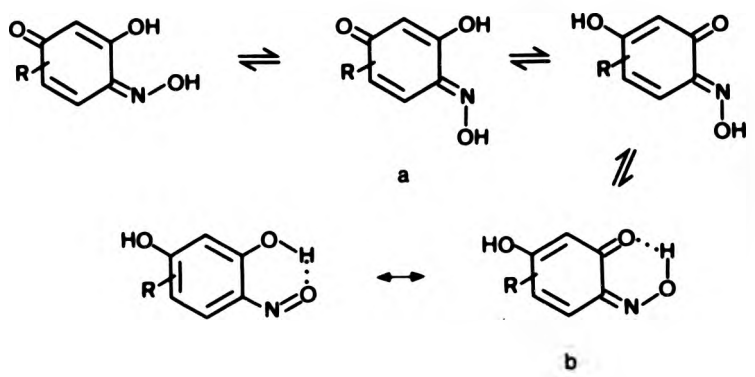
In solution, i.r., u.v. and n.m.r. studies have indicated the presence of an equilibrium between quinone oximic and nitrosophenolic species, (also see Section 1.5).[12-16]

In view of the above the 2-nitrosophenol/1,2-quinone mono-oxime system may be represented as shown in Scheme 1.1. Because of the important contribution from the oximic forms, in this thesis the compounds will, hereafter be referred to as quinone mono-oximes.



Scheme 1.1

In the case of 5-hydroxy-1,2-benzoquinone mono-oximes additional contribution from the 1,4-quinone 4-oxime isomers is also a possibility (Scheme 1.2). An X-ray crystallographic investigation carried out during the present study has shown that the product arising from the nitrosation of 3-hydroxy-2-methylphenol exists in the 1,4-quinone 4-oxime form ((a) in Scheme 1.2) rather than in the 1,2-quinone 2-oxime form ((b) in Scheme 1.2). However, for the sake of convenience quinone mono-oximes derived from 3-hydroxyphenols will be referred to as 5-hydroxy-1,2-benzoquinone mono-oximes in this thesis.



Scheme 1.2

1.2 Synthesis of 1,2-Quinone Mono-oximes

A variety of direct and indirect methods for the synthesis of 1,2-quinone mono-oximes have been reported. In the direct methods the 1,2-quinone mono-oxime itself is obtainable from the reaction. In the case of the indirect methods a metal complex of the 1,2-quinone mono-oxime is first formed from which the free oxime may be isolated. The isolation of the free oxime is achievable by acidification of the complex or by passing a solution of the complex over an ion exchange resin. In the case of selected Lewis base adducts of copper(II) 1,2-quinone mono-oximato complexes the isolation of the free oxime has also been achieved by treating their methanolic solutions with silica.

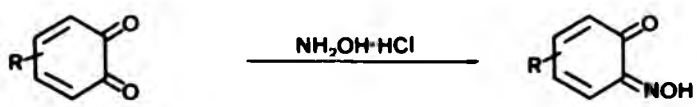
Direct Methods

Nitrosation of phenols using sodium nitrite/acid

This method involves the reaction of a phenol, an acid (usually acetic acid) and sodium nitrite. Several 1,2-quinone mono-oximes derived from 3-substituted phenols (e.g. Reaction 1.2) have been obtained by this method but in some cases the 4-isomer is also formed.[1,2] Nitrosation of other phenols does not lead to the 2-isomer even when the 4-position is substituted. The reasons for this have not been established but instability of the 2-substituted product towards acids may be a cause.

Reaction of hydroxylamine hydrochloride with a quinone

A very limited number of 1,2-quinone mono-oximes have been synthesized by heating hydroxylamine hydrochloride with the corresponding quinone (Reaction 1.4).[17]

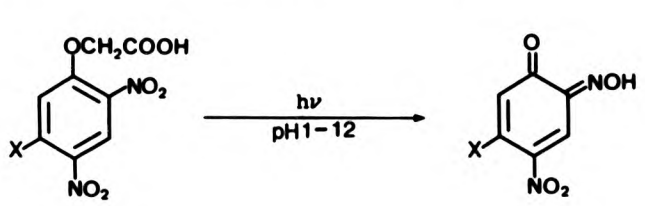


Reaction 1.4

Photochemical synthesis

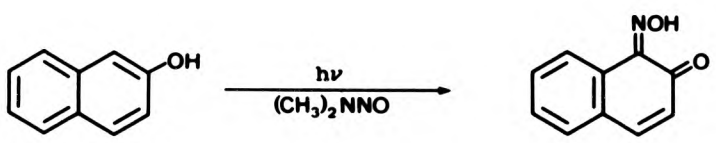
Two methods for the photochemical synthesis of 1,2-quinone mono-oximes have been described. The first

method involves the photolysis of 2-nitrophenoxyacetic acids (Reaction 1.5).[18] The second method, which has only been applied to the synthesis of 1,2-naphthoquinone 1-oxime involves the photolysis of 1-naphthol and N-nitrosodimethylamine (Reaction 1.6).[19]



X=H or RO

Reaction 1.5



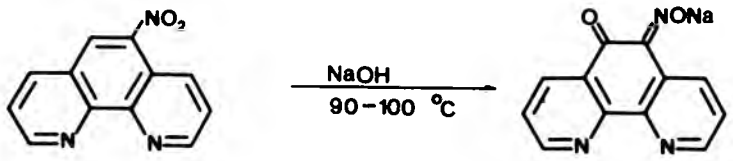
Reaction 1.6

Indirect Methods

Acidification of metal complexes of 1,2-quinone 2-oxime

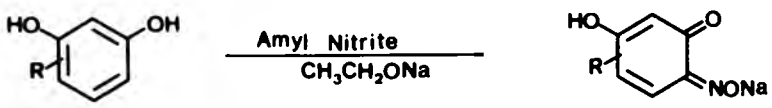
Quinone mono-oximes such as the mono-oximes of 3-hydroxyphenols and 1,2-naphthoquinones can be prepared by acidification of their metal complexes.

The quinone mono-oxime of 1,10-phenanthroline has been prepared by the acidification of its sodium complex which is obtainable by the alkali induced rearrangement of 5-nitro-1,10-phenanthroline (Reaction 1.7).[20]



Reaction 1.7

In the case of alkali metal complexes of 3-hydroxy-1,2-benzoquinone mono-oximes, which are obtainable by the action of sodium alkoxide and alkyl nitrite on a 3-hydroxyphenol (Reaction 1.8),[21] acidification affords the free ligand but in the 1,4-tautomeric form (see Chapter 2).



Reaction 1.8

Recent studies have shown that potassium or sodium complexes of 1,2-naphthoquinone 1-oxime (1-nqoH) and

1,2-naphthoquinone 2-oxime (2-nqoH) can be obtained by reacting their complexes, $M(1\text{-nqo})_2$, $M(2\text{-nqo})_2$ ($M = Cu^{2+}$ or Ni^{2+}) $Cu(2\text{-nqo})_2.dipy$ or $Cu(2\text{-nqo})(Ph_3P)_2$ with potassium or sodium cyanide.[22] This route to potassium and sodium complexes has a potentially wide range of applicability.

The preparation of 1,2-quinone mono-oximes by the acidification of their transition metal complexes has also been reported by several workers.[23-25] Generally these reports lack experimental details. In this procedure the metal complex is treated with an aqueous acid and the resultant oxime is extracted with an organic solvent. Solutions of several 1,2-quinone mono-oximes have been prepared but isolation of the oxime from the solution has only been accomplished in very few cases.

Use of ion exchange resins

This approach which is essentially a modification of the above method has been used to obtain 1,2-quinone mono-oximes in high yield and purity from their metal complexes.[22] The technique has proved applicable to the preparation of N-acetyl-5-amino-1,2-benzoquinone 2-oxime (N-AcqoH) from its nickel complex. Significantly, this oxime cannot be prepared by acidification of its metal complexes or by the direct nitrosation of N-acetyl-3-aminophenol (see later).

Reaction of $Cu(qo)_2X$ (X = dipy or phen) adducts on silica

Recently a limited number of 1,2-quinone mono-oximes have been prepared by stirring methanolic solutions of bis(1,2-quinone mono-oximato)copper(II) adducts of 1,10-phenanthroline or 2,2'-dipyridyl with silica. The liberated ligand is isolated by removing the methanol from the reaction mixture and extracting the residue with an organic solvent (Reaction 1.9).[22]

$$Cu(qo)_2 \cdot X \xrightarrow[\text{Methanol}]{\text{Silica}} Cu(qo) \cdot X' + qoH$$

Reaction 1.9

1.3 Behaviour of 3-Hydroxyphenols and N-Acetyl-3-aminophenol Towards Nitrosation

The nitrosation of 3-hydroxyphenols has been investigated by several workers.[21,24,26-29] These compounds can undergo mono- and/or di-nitrosation, depending on the nature and position of the substituents and the method of nitrosation employed.[24,27] 3-Hydroxyphenol itself can be dinitrosated by amyl nitrite/sodium ethoxide at room temperature as well as by sodium nitrite/acetic acid (Reaction 1.10). Mono-nitrosation can be achieved by using amyl nitrite/sodium ethoxide at -10 °C.[26] In the case of 2-methyl-3-hydroxyphenol the mono-nitrosated product is

formed irrespective of the method of nitrosation.[24] The nature of the alkali metal complexes arising from the reactions involving amyl nitrite (Reaction 1.8) has not been systematically investigated. Such a complex may be mono-metallic or di-metallic.

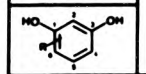
Reaction 1.10

In this study the behaviour of 3-hydroxyphenol, of its homologues 3-hydroxy-2-methylphenol and 3-hydroxy-5-methylphenol, and of the related compound N-acetyl-3-aminophenol towards nitrosation by sodium nitrite/acid and amyl nitrite/base has been studied in greater detail.

The studies have confirmed previous results of nitrosation reactions involving sodium nitrite/acid (Table 1.1).

In the case of reactions involving amyl nitrite/base, it can be concluded that the nature of the product is primarily dependent on the reaction temperature and the molar ratio of the reactants. The nature of the base used i.e. sodium hydroxide or sodium ethoxide, has no

Table 1.1 Products Arising from the Nitrosation of 3-Hydroxyphenols

Phenol 	M	Product[1]						$NaNO_2$/acid[3]	Temp./ °C
		Molar ratio of Amyl nitrite to MOH[2]			Molar ratio of Amyl nitrite to EtOH[2]				
		1:1	1:1.4	1:2	1:1	1:1.4	1:2		
R = H	Na	Na(hqoH)	Na(hqoH) + Na_2(hqo)	Na_2(hqo)	Na(hqoH)	Na(hqoH) + Na_2(hqo)	Na_2(hqo)	-	-10
	Na	Na(dnrH)	-	-	Na(dnrH)	-	-	$dnrH_2$	20
	K	K(hqoH)	-	K_2(hqo)	K(hqoH)	-	K_2(hqo)	-	-10
R = 2-Me	Na	Na(6-MehqoH)	-	Na_2(6-Mehqo)	Na(6-MehqoH)	-	Na_2(6-Mehqo)	-	-10
	Na	Na(6-MehqoH)	-	Na_2(6-Mehqo)	Na(6-MehqoH)	-	Na_2(6-Mehqo)	6-$MehqoH_2$	20
	K	K(6-MehqoH)	-	-	K(6-MehqoH)	-	-	-	-10
R = 5-Me	Na	Na(3-MehqoH)	-	Na_2(3-Mehqo)	Na(3-MehqoH)	-	Na_2(3-Mehqo)	-	-10
	Na	Na(5-MednrH)	-	-	Na(5-MednrH)	-	-	5-$MednrH_2$	20
	K	K(3-MehqoH)	-	-	K(3-MehqoH)	-	-	-	-10

1=Water of crystallization is omitted 2=This work 3=Repeat of work in ref.26

effect on the nature of the product but affects the yield.

In the case of the 3-hydroxyphenol it has now been established that, contrary to a previous report,[26] the reaction involving sodium hydroxide and amyl nitrite at -10 °C affords a mixture of the mono- and di-sodium derivatives of the mono-nitrosated phenol when a 1:1.4 phenol to sodium hydroxide ratio is used. The mono-sodium derivative is obtained using a 1:1 phenol to sodium hydroxide ratio whereas the disodium by using a 1:2 ratio. Analogous behaviour is shown by 3-hydroxy-2-methylphenol and 3-hydroxy-5-methylphenol.

When the reaction of the 3-hydroxyphenols with amyl nitrite/sodium ethoxide involving 1:1 phenol to sodium ethoxide ratio is carried out at room temperature 3-hydroxyphenol and 3-hydroxy-5-methylphenol afford the mono-sodium derivative of the dinitrosated phenol. In contrast, the analogous reaction of 3-hydroxy-2-methylphenol affords the mono-sodium derivative of the mono-nitrosated phenol.

N-Acetyl-3-aminophenol afforded a mixture of products on treatment with sodium nitrite/acid or amyl nitrite/sodium ethoxide. However, neither of the mixtures had the ability to chelate iron(II) suggesting that N-acetyl-5-amino-1,2-benzoquinone 2-oxime is not a

product of these reactions. This oximic ligand was successfully isolated from its nickel complex $[Ni(N\text{-}Acqo)_2]\cdot 4H_2O$ by using the ion exchange method (see Section 1.2). The sodium complex of the ligand was synthesized by reacting it with sodium ethoxide.

Acidification with acetic acid at 0 °C of the alkali metal complexes of the oximes synthesized during this study and listed below afforded the respective ligand. Hydrochloric acid (4 M) could also be used, however this gave lower yields.

$Na(6\text{-}MehqoH)\cdot H_2O$ $Na_2(6\text{-}Mehqo)$ $K(6\text{-}MehqoH)\cdot H_2O$	—Acid→	$6\text{-}MehqoH_2\cdot H_2O$
$Na(3\text{-}MehqoH)\cdot 2H_2O$ $Na_2(3\text{-}Mehqo)$ $K(3\text{-}MehqoH)$	—Acid→	$3\text{-}MehqoH_2\cdot H_2O$
$Na(hqoH)\cdot H_2O$ $Na_2(hqo)\cdot 0.5H_2O$ $K(hqoH)$ $K_2(hqo)$	—Acid→	$hqoH_2$

Table 1.2 Formulations and Thermal Gravimetric Analysis of 3-Hydroxy-1,2-benzoquinone mono-oximes, N-Acetyl-5-amino-1,2-benzoquinone 2-oxime and their Metal Complexes

Formulation	Wt. of Sample/mg	Weight Loss /mg		Temperature of Loss of Water/ °C	Decomposition Temperature/ °C
		Found	Calc		
6-MehqoH$_2$·H$_2$O	214.8	21.0	22.6	100 - 110	135
Na(6-MehqoH)·H$_2$O	189.3	17.0	18.7	100 - 120	210
Na$_2$(6-Mehqo)	170.0	-	-	-	200
K(6-MehqoH)·H$_2$O	203.3	19.6	21.4	100 - 110	200
Ca(6-Mehqo)$_2$	160.0	-	-	-	280
3-MehqoH$_2$·H$_2$O	187.0	20.0	19.7	100 - 110	130
Na(3-MehqoH)·2H$_2$O	191.4	32.0	32.7	100 - 110	220
Na$_2$(3-Mehqo)	169.1	-	-	-	225
K(3-MehqoH)	231.0	-	-	-	215
Ca(3-Mehqo)$_2$	169.0	-	-	-	270
hqoH$_2$	201.2	-	-	-	135
Na(hqoH)·H$_2$O	189.2	19.0		100 - 130	215
Na$_2$(hqo)·0.5H$_2$O	189.2	8.4	8.9	105 - 120	220
K(hqoH)	153.0	-	-	-	225
K$_2$(hqo)	197.9	-	-	-	220
N-AcqoH	182.0	-	-	-	140
Na(N-Acqo)	108.3	-	-	-	195

The formulations and the t.g.a. results for the free ligands as well as the sodium, potassium and calcium complexes are presented in Table 1.2.

1.4 Group I and Group II Metal Compounds of 1,2-Quinone Mono-oximes

Previously, very few studies on Group I metal compounds of 1,2-quinone mono-oximes have been carried out.[26,30-35] Almost all the studies have involved either 1,2-naphthoquinone 1-oxime or 1,2-naphthoquinone 2-oxime. In the case of Group II metals only one complex, $Ca(4\text{-Meqo})_2$, has been reported.[36] From Table 1.3, which summarises all the previous studies, it can be seen that there are three main types of Group I metal compounds of 1,2-quinone mono-oximes:

(i) Compounds of type $M(qo)B_n$ (n = 0, 1, 2), which contain anionic quinone oximato and neutral ligands (e.g. B = H_2O).

(ii) Compounds of type $M(qo)(qoH)(B)_n$ (n = 0, 1; B = e.g. H_2O) which contain an anionic quinone oximato ligand as well as a neutral quinone oximic ligand.

(iii) Compounds of type M(L)(qoH) which contain a neutral quinone oximic ligand together with a anionic ligand L such as the anion of 2-nitrophenol.

During the present study 11 sodium and potassium complexes of the oximes 6-MehqoH$_2$, 3-MehqoH$_2$, hqoH$_2$ and N-AcqoH were prepared. Each of the complexes, except Na(N-Acqo), was prepared by the direct reaction of the ligand with metal ethoxide and by the nitrosation of the respective phenol with amyl nitrite/metal ethoxide. Only the former method was used for the synthesis of Na(N-Acqo). In all cases the products were of the type M(qo) or M(qo)(B)$_n$ (where B = H_2O, n = 0 or 1). All attempts to synthesize complexes of the type M(qo)(qoH) failed. Thus for example when the complexes Na(3-MehqoH) and Na(6-MehqoH) were stirred with the corresponding free ligand in methanol no adduct formation occurred and the starting materials were recovered quantitatively.

The calcium complexes of 3-MehqoH$_2$ and 6-MehqoH$_2$ were prepared by stirring an excess of the ligand in methanol-water (4:1) with calcium hydroxide. The excess ligand was removed by washing the crude product with diethyl ether. Elemental analysis indicate that in both cases the anhydrous complex is formed. In the case of hqoH$_2$, the reaction led to the decomposition of the ligand and hence no calcium complex was obtained.

Table 1.3 Alkali Metal Complexes of 1,2-Quinone Mono-oximes

1,2-qoH	Complex	Data Reported	Ref.
1-nqoH	Li(1-nqo)	el., A,	30
	Li(1-nqo)(1-nqoH)·B	X-ray, el., A	31
	Li(1-nqo)(1-nqoH)	el., A	31
	Na(1-nqo)	el., m.p., A	30
	Na(1-nqo)(phen)	el., t.t.	32
	Na(1-nqoH)(hbza)	el., t.t., A	33
	Na(1-nqoH)(nph)	el., t.t., A	33
	K(1-nqo)	el., m.p., A	30
	K(1-nqo)(1-nqoH)	el., t.t., A	30
	K(1-nqo)(phen)	el., t.t.	32
	K(1-nqo)(iapH)	el., t.t., A	33
	K(1-nqo)(hquH)	el., t.t., A	33
	K(1-nqoH)(nph)	el., t.t., A	33
	K(1-nqoH)(hbza)	el., t.t., A	33
	Rb(1-nqo)	el., m.p., A	30
	Rb(1-nqo)(1-nqoH)	el., t.t., A	30
	Rb(1-nqo)(iapH)	el., t.t., A	33
	Rb(1-nqo)(hquH)	el., t.t., A	33
	Rb(1-nqoH)(hbza)	el., t.t., A	33
	Rb(1-nqoH)(nph)	el., t.t., A	33
	Cs(1-nqo)	el., m.p., A	30

Table 1.3 Continued

1,2-qoH	Complex	Data Reported	Ref.
1-nqoH	Cs(1-nqo)(1-nqoH)	el., t.t., Λ	30
	Cs(1-nqo)(iapH)	el., t.t., Λ	33
	Cs(1-nqoH)(hbza)	el., t.t., Λ	33
	Cs(1-nqoH)(nph)	el., t.t., Λ	33
2-nqoH	Li(2-nqo)(2-nqoH)	el., t.t.	34
	Na(2-nqo)(2-nqoH)	el., t.t.	34
	K(2-nqo)(2-nqoH)	el., t.t.	34
	Rb(2-nqo)(2-nqoH)	el., t.t.	34
	Cs(2-nqo)(2-nqoH)	el., t.t.	34
	$Cs(2\text{-}nqo)(2\text{-}nqoH)_2$	el., t.t.	34
phenqoH	$Na(phenqo)\cdot 2H_2O$	el.	20
4-ClqoH	K(4-Clqo)	X-ray	35
$hqoH_2$	$Na_2(hqo)$	el.	26
4-MeqoH	$Ca(4\text{-}Meqo)_2$	-	36

1-nqoH=1,2-Naphthoquinone 1-oxime; 2-nqoH=1,2-Naphthoquinone 2-oxime; E=Ethanol; phen=1,10-Phenanthroline; hbzaH=2-Hydroxybenzoic acid; nphH=2-Nitrophenol; iapH=Isonitrosoacetophenone; hquH=8-Hydroxyquinoline;

el.=Elemental analysis; Λ=Conductivity; m.p.=Melting point; t.t.=Transition temperature (after this temperature a solid remains which melts at the same temperature as ML, see Ref.34).

1.5 Properties and Structural Studies of $hqoH_2$, 3-$MehqoH_2$, 6-$MehqoH_2$, N-AcqoH and Their Sodium, Potassium and Calcium Complexes

1.5.1 General Properties

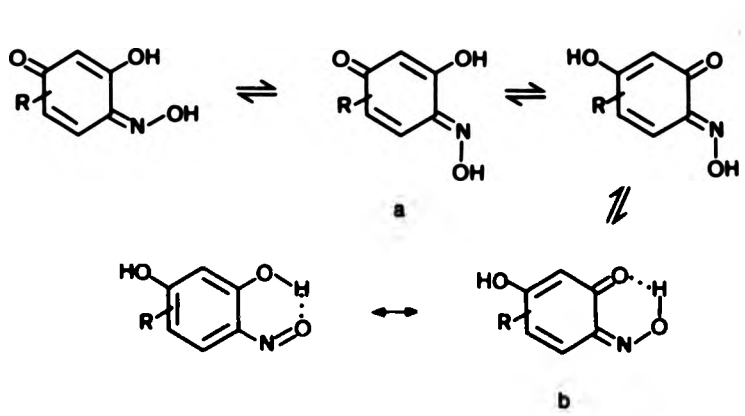
The quinone mono-oximes synthesized during this study were coloured solids which decomposed on heating between 130 - 140 °C. Generally, they were appreciably soluble in organic solvents (e.g. ethanol) and also showed some solubility in water.

All the sodium, potassium and calcium complexes of the oximes were coloured compounds which had limited solubility in ethyl acetate but were very soluble in methanol and water. Generally, the alkali metal complexes decomposed on heating at a temperature *ca.* 75 °C higher than that of the respective ligands, (Table 1.2). The calcium complexes showed even greater thermal stability, e.g. $Ca(6\text{-}MehqoH)_2$ decomposed at 280 °C whereas the decomposition temperature of 6-$MehqoH_2$ was 135 °C.

1.5.2 Infra-red Spectra

As noted earlier 3-hydroxy-1,2-quinone mono-oximes can exhibit a number of isomeric and tautomeric structures. Scheme 1.2 which demonstrates this is presented again

here for the convenience of the reader. An X-ray crystallographic structure determination of the mono-oxime derived from 2-methyl-3-hydroxyphenol (see Chapter 2) has shown that in the solid state the compound has the 1,4- structure, i.e. it exists as 3-hydroxy-2-methyl-1,4-benzoquinone 4-oxime ((a) in Scheme 1.2).



Scheme 1.2

The i.r. spectrum of four quinone mono-oximes and nine complexes have been recorded and all show a strong band between 1615 - 1660 cm^{-1} (Table 1.4). In accord with the crystallographically established structure, 6-MehqoH_2 shows a band at 1647 cm^{-1} assignable to νCO. This is in the region (*ca.* 1618 - 1668 cm^{-1}) previously reported for the νCO absorption of quinone mono-oximes.[14] The other ligands investigated during this study, i.e. 3-MehqoH_2, hqoH_2 and N-AcqoH also show similar νCO

bands in this region. Thus it can be concluded that they too exist in the quinone oximic form in the solid state.

Table 1.4 The νCO Band Assignments for 3-Hydroxy-1,4-benzoquinone Mono-oximes and some of their Metal Complexes

Compound	νCO /cm^{-1}
6-MehqoH$_2$·H$_2$O	1647
Na(6-MehqoH)·H$_2$O	1620
K(6-MehqoH)·H$_2$O	1622
Ca(6-Mehqo)$_2$	1618
3-MehqoH$_2$·H$_2$O	1642
Na(3-MehqoH)·2H$_2$O	1632
K(3-MehqoH)	1645
Ca(3-Mehqo)$_2$	1633
hqoH$_2$	1638
Na(hqoH)·H$_2$O	1625
K(hqoH)	1626
N-AcqoH	1649
Na(N-Acqo)	1638

A strong band in the 1615 - 1660 cm^{-1} region assignable to νCO is also shown by all complexes of 6-MehqoH$_2$,

3-MehqoH$_2$ and hqoH$_2$ studied (Table 1.4). In all cases, except K(3-MehqoH), this band appears at a lower frequency relative to the νCO band of the respective ligand.

The shift to lower frequency observed in the majority of the complexes suggests that the CO group is involved in the bonding to the metal. Possible structures involving bonding of the CO group are shown in Figs. 1.5 - 1.7. In these structures the ligand may be chelating or bridging and may have 1,2- or 1,4-quinone character. X-Ray crystallographically established examples of structures depicted in Fig. 1.5 and Fig. 1.6 have been reported previously. For example in the compound shown in Fig. 1.8 the sodium ion is chelated.[37] In contrast, in the case of potassium 4-chloro-1,2-benzoquinone 2-oximate, the ligand has 1,2-quinone character and bridges two potassium ions (Fig. 1.9).[35]

In the case of K(3-MehqoH), where the νCO absorption occurs at a higher frequency than in the free ligand, the quinone CO is not involved in bonding. Examples of complexes in which the CO group is not bonded to the metal are known, e.g. the UO_2^{2+} complex derived from nqoH shown in (Fig. 1.10).[38]

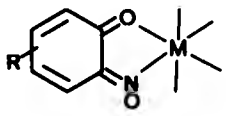


Fig. 1.5

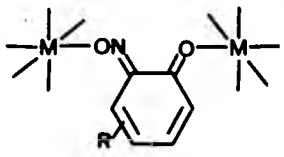


Fig. 1.6

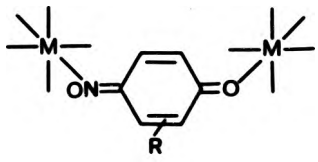


Fig. 1.7

The calcium complexes of 6-MehqoH$_2$ and 3-MehqoH$_2$ are most likely to be bis-chelates, in which case the observed lowering of the νCO band suggests 1,2-quinone character for the ligands (Fig. 1.11). Polymeric structures involving ligands with 1,2- or 1,4-quinone character are also possible but are not compatible with

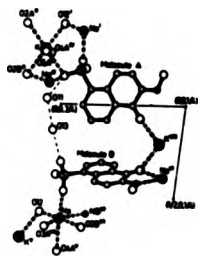


Fig. 1.8

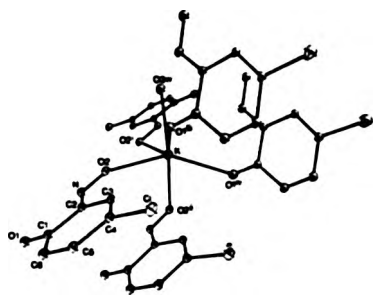


Fig. 1.9

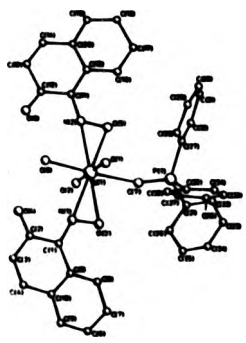
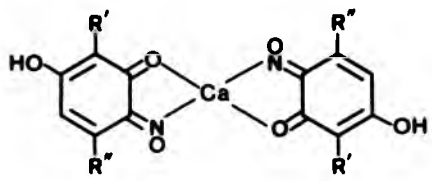


Fig. 1.10

the relatively high solubility of the complex in methanol.



$R' = H$, $R'' = CH_3$ or
$R'' = H$, $R' = CH_3$

Fig. 1.11

1.5.3 Investigation of Quinone Mono-oximes and their Metal Complexes by Nuclear Magnetic Resonance Spectroscopy

The possibility of nitroso - oximino tautomerism in quinone mono-oximes has been investigated using n.m.r. techniques by several workers.[15,16,27,39] The compounds investigated as well as their suggested structures in solution are shown in Table 1.5. All compounds investigated, except 1,4-benzoquinone 4-oxime and 1,2-naphthoquinone 2-oxime, exist in the oxime form irrespective of the solvent. 1,4-Benzoquinone 4-oxime is phenolic in DMSO and oximic in chloroform, whereas in dioxan and diethyl ether both forms coexist.[39] In the case of 1,2-naphthoquinone 2-oxime, a mixture of the two forms was found in DMSO/acetic acid (5%), but only the

Table 1.5 Nuclear Magnetic Resonance Studies of Quinone Mono-oximes

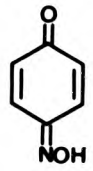
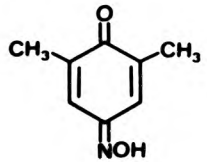
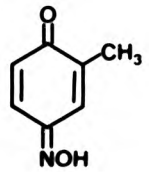
Compound	Solvent	Tautomer Observed	Reference
	Dimethyl sulphoxide	Phenol	39
	Chloroform	Oxime	39
	Dioxan	Oxime (83%) Phenol (17%)	15
	Diethyl ether	Oxime (84%) Phenol (16%)	15
	Dimethyl sulphoxide	Oxime	15,39
	Chloroform	Oxime	15
	Dioxan	Oxime	15

Table 1.5 Continued

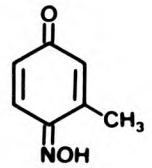
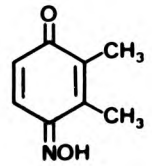
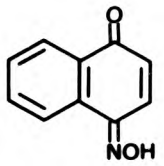
Compound	Solvent	Tautomer Observed	Reference
	Dioxan	Oxime	15
	Dioxan	Oxime	15
	Dimethyl sulphoxide	Oxime	15

Table 1.5 Continued

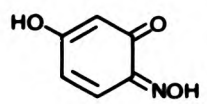
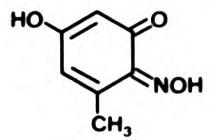
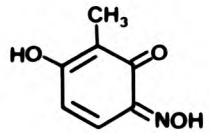
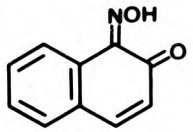
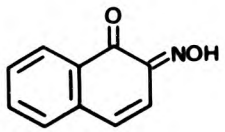
Compound	Solvent	Tautomer Observed	Reference
	Dimethyl sulphoxide	Oxime	27 and this study
	Dimethyl sulphoxide	Oxime	27 and this study
	Dimethyl sulphoxide	Oxime	27 and this study

Table 1.5 Continued

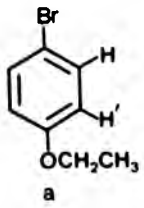
Compound	Solvent	Tautomer Observed	Reference
	Dimethyl sulphoxide	Oxime	16
	Hexamethylphosphoramide	Oxime	16
	Chloroform	Oxime	16
	Dioxane	Oxime	16
	Dimethyl sulphoxide/Acetic acid (5%)	Oxime	16
	Dimethyl sulphoxide	Oxime	16
	Dimethyl sulphoxide/Dioxane	Oxime (80%) Phenol (20%)	16
	Dimethyl sulphoxide/Acetic acid (5%)	Oxime (80%) Phenol (20%)	16

oxime form was found in several other solvents investigated.[16]

In this study $hqoH_2$, $3\text{-}MehqoH_2$, $6\text{-}MehqoH_2$, N-AcqoH and some of their metal complexes were investigated by n.m.r. spectroscopy. The complexes were studied both in d_6-dimethylsulphoxide (d_6-DMSO) and deuterium oxide (D_2O). The free ligands were only studied in d_6-DMSO because of their poor solubility in water.

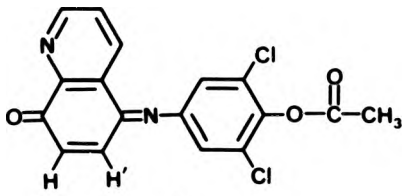
The ^1H n.m.r.spectra (Table 1.6) obtained for $hqoH_2$ and $6\text{-}MehqoH_2$ agree with those reported previously.[27] Evidence that the compounds exist as quinone mono-oximes comes from the fact that two hydroxyl protons are observed. If the compounds have a nitroso phenol structure then both the acidic protons would be very similar and hence have similar chemical shifts. However, for these compounds two acidic protons are observed at *ca.* 10.5 ppm and *ca.* 13.5 ppm (Table 1.6), suggesting the presence of two different OH groups and hence of an oximic structure. In the case of 1,4-naphthoquinone 4-oxime, the hydrogen of the oxime group has been observed at 13.45 ppm.[39] By analogy the peak at *ca.* 13.5 ppm observed in the spectra of $hqoH_2$ and $6\text{-}MehqoH_2$ is assigned to the oximic hydrogen and the peak observed at *ca.* 10.5 ppm is assigned to the phenolic hydrogen. Further evidence for the quinone oximic structure is provided by consideration of the

values of ortho coupling constants (J_{ortho}). Aromatic carbon-carbon bonds have less double bond character than carbon-carbon double bonds in quinone type compounds, and hence are longer. As a result the ortho coupling constant is less for a benzenoid system (e.g. Fig. 1.12a) than for a quinonoid system (e.g. Fig. 1.12b).[40,41] Typically, the value for J_{ortho} for a benzenoid system is *ca.* 8 Hz., whereas for a quinonoid system it is *ca.* 10 Hz. The coupling constants observed for 6-MehqoH_2 and hqoH_2 are *ca.* 9.9 Hz suggesting that in these compounds the bonds are of quinonoid character.



a

$J_{H,H'}$ = 8.0 Hz



b

$J_{H,H'}$ = 10.5 Hz

Fig. 1.12

3-MehqoH_2 shows a single broad peak between 9-15 ppm. The broadness of this peak most probably arise because of the coalescence of the two OH peaks as a result of the rate of exchange of these protons. Therefore a quinonoid structure is also suggested for this compound.

Table 1.6 ^{1}H Nuclear Magnetic Resonance Spectral Assignments for $hqoH_2$, 6-$MehqoH_2$ and 3-$MehqoH_2$

Compound	Assignment	Multiplicity (J/Hz)	δ/ppm
	1 (broad)	s	13.55
	2	d ($J_{2,3}$ = 9.9)	7.42
	3	dd ($J_{2,3}$ & $J_{3,5}$)	6.19
	4 (broad)	s	10.98
	5	d ($J_{3,5}$ = 2.2)	5.69
	1 (broad)	s	13.43
	2	d ($J_{2,3}$ = 9.9)	7.45
	3	d ($J_{2,3}$ = 9.9)	6.27
	4 (broad)	s	9.96
	5	s	1.78
	1,4 (v. broad)	s	9-14
	2	d ($J_{2,3}$ = 1.3)	2.33
	3	m	6.40
	5	d ($J_{3,5}$ = 2.4)	5.81

d=Doublet; dd=Doublet of doublets; s=Singlet; m=Multiplet

N.m.r. Spectra of Na(hqoH), Na(3-MehqoH) and Na(6-MehqoH) in DMSO

The ^{1}H n.m.r. spectra obtained for Na(hqoH), Na(6-MehqoH) and Na(3-MehqoH) in d_6-DMSO are shown in Figs. 1.13 - 1.15 together with suggested assignments. The ^{13}C n.m.r. data for the above compounds are given in Table 1.7. In all cases the spectra show that only a single species exists in d_6-DMSO. Although the compounds are presented as having 1,2-quinonoid structures both in Figs. 1.13 - 1.15 and Table 1.7, it should be stressed that the n.m.r. data are also compatible with 1,4-quinonoid structures. As in the case of the i.r. results, the n.m.r. data do not allow the distinction between 1,2- and 1,4-quinonoid character.

The values of ortho coupling constants observed for the ^{1}H spectra of Na(hqoH) and Na(6-MehqoH) in d_6-DMSO (see Fig. 1.13- 1.14) suggest that these compounds exist in the quinonoid form. Further evidence for this is obtained from the ^{13}C n.m.r. spectra which are presented in Table 1.7 together with proposed assignments. For these compounds as well as for Na(3-MehqoH), ^{13}C n.m.r. data indicate the presence of a quinonoid (>C=O) and an oximic (>C=N) carbon (Fig. 1.16). The peaks for quinonoid and oximic carbons were assigned by comparison with chemical shift data observed for similar compounds. Hence, the peak at *ca.* 183 ppm was assigned to the quinonoid carbon in comparison with 9,10-anthroquinone[42]

Fig. 1.13 ^{1}H Nuclear Magnetic Resonance Spectrum of Na(hqoH) in d_6-DMSO

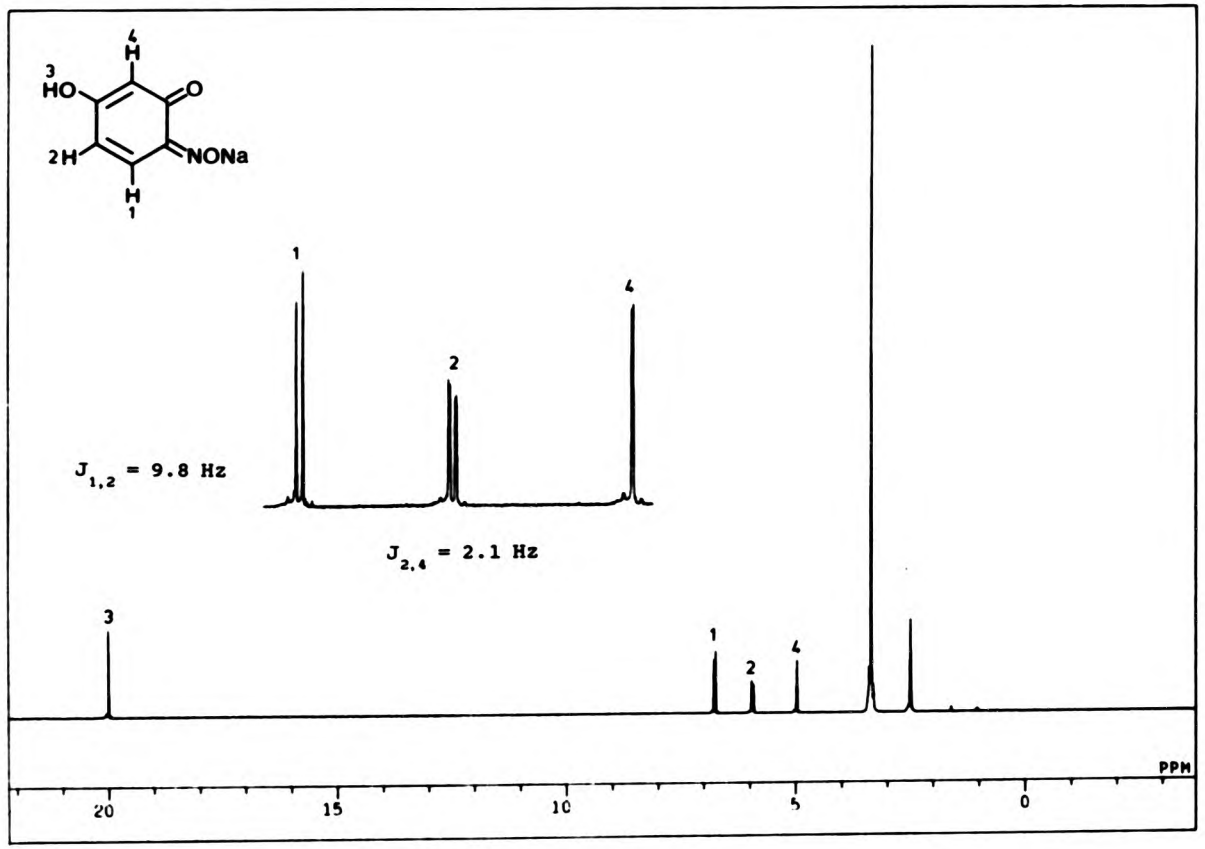


Fig. 1.14 ^{1}H Nuclear Magnetic Resonance Spectrum of Na(6-MehqoH) in d_6-DMSO

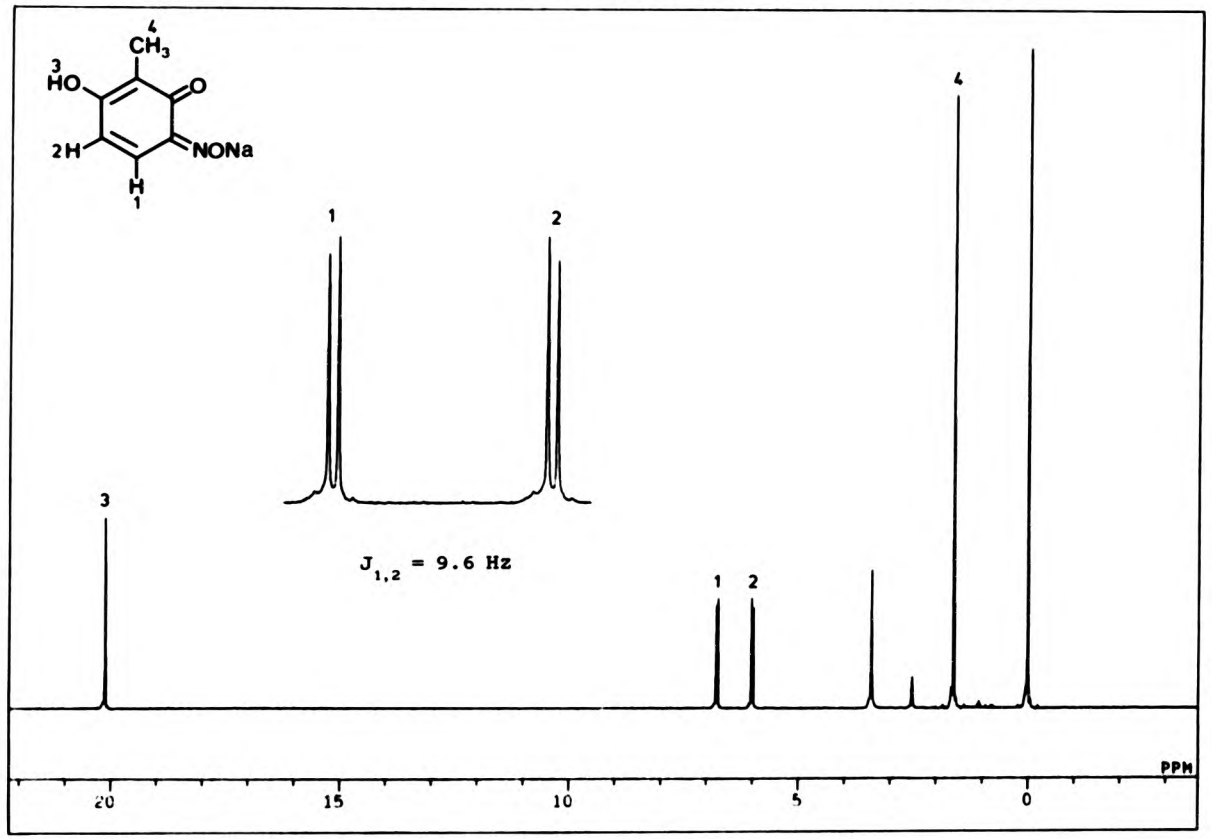
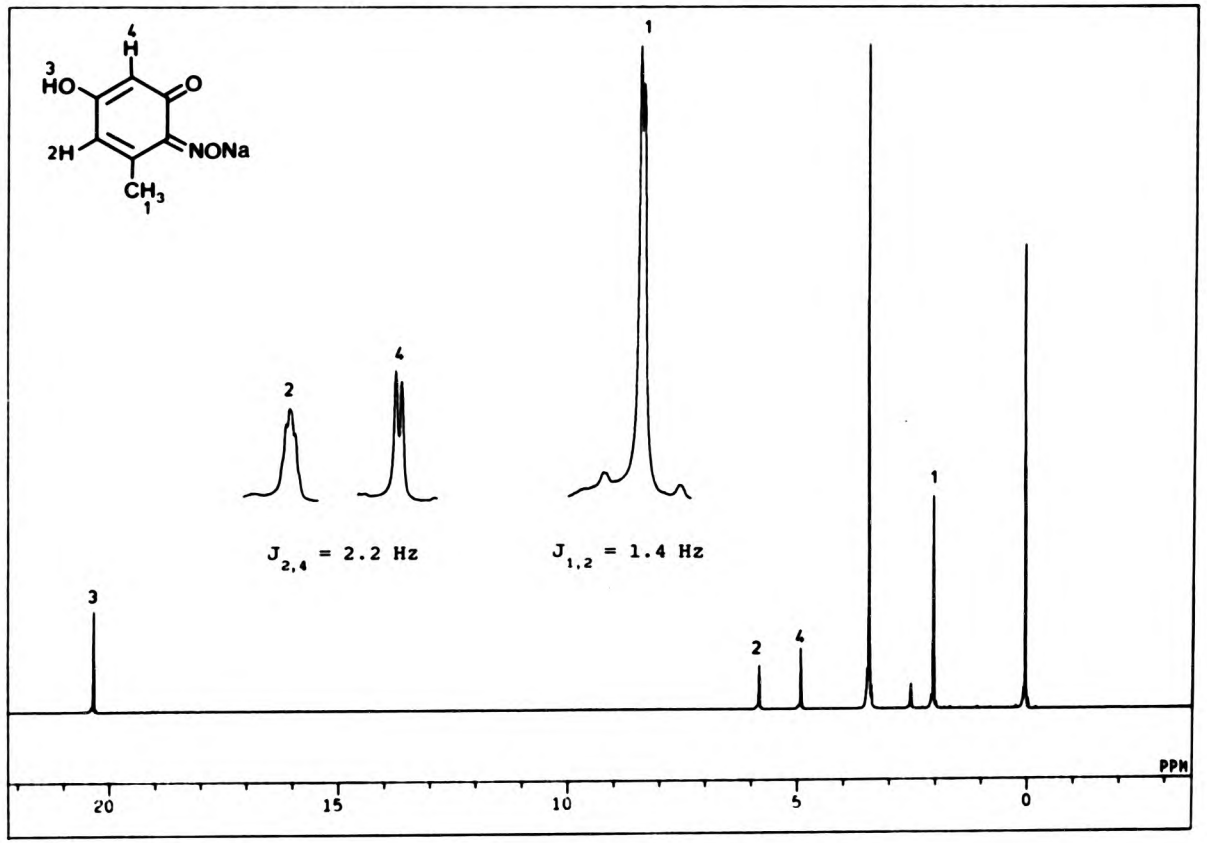


Fig. 1.15 ^{1}H Nuclear Magnetic Resonance Spectrum of Na(3-MehqoH) in d_6-DMSO



in which the quinonoid carbons are observed at 183 ppm. The peak observed at *ca.* 167 ppm was assigned to the oximic carbon in comparison with ketoximes in which the oximic carbon is observed in the range *ca.* 155 - 170 ppm, e.g. in 4,4-dimethylpentan-3-one oxime the oxime carbon is observed at 168.1 ppm.[43]

In the ^{1}H n.m.r. spectra of all compounds, a noteworthy feature is a singlet at *ca.* 20 ppm due to the hydrogen of the OH group. Such a high value is unusual and indicates very strong hydrogen bonding.

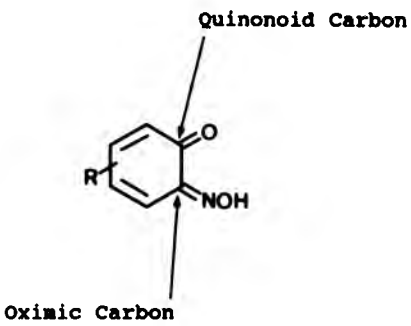
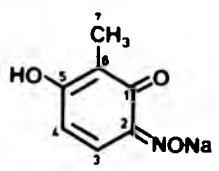
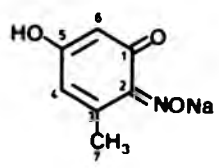


Fig. 1.16

Table 1.7 ^{13}C Nuclear Magnetic Resonance Spectral Assignments for Na(hqoH), Na(6-MehqoH) and Na(3-MehqoH)

Compound*	Assignment	δ/ppm
	1 (C=O)	183.99
	2 (C=NOH)	169.86
	3 (C-H)	132.25
	4 (C-H)	127.71
	5 (C-OH)	149.29
	6 (C-H)	102.25
	1 (C=O)	182.81
	2 (C=NOH)	164.97
	3 (C-H)	131.27
	4 (C-H)	126.21
	5 (C-OH)	148.77
	6 (C-H)	107.82
	7 (CH_3)	7.12
	1 (C=O)	184.56
	2 (C=NOH)	170.84
	3 (C-H)	139.59
	4 (C-H)	126.55
	5 (C-OH)	148.62
	6 (C-H)	101.31
	7 (CH_3)	16.65

*=Although 1,2-quinonoid structure is shown, the n.m.r. data are also compatible with 1,4-quinonoid structure (see text page 37).

N.m.r. Spectra of of Na(hqoH), Na(3-MehqoH) and Na(6-MehqoH) in D_2O

As stated above the ^1H n.m.r. spectrum of Na(hqoH) in d_6-DMSO shows that only a single species is present and its structure is compatible with that of Na(hqoH). In contrast, the spectrum of Na(hqoH) in D_2O (Fig. 1.17) was fundamentally different to that observed in d_6-DMSO, and did not allow any conclusions to be made regarding the structure of the compound in this solvent. The spectrum in D_2O was also recorded at different concentrations and temperatures, and double resonance decoupling experiments were carried out, but again no meaningful conclusions could be made.

The ^1H n.m.r. spectrum of Na(3-MehqoH) in D_2O as well as the proposed assignments are shown in Fig. 1.18. This spectrum is very similar to that obtained in d_6-DMSO (Fig. 1.15) and shows the presence of only one species.

The ^1H n.m.r. spectrum of Na(6-MehqoH) in D_2O is shown in Fig. 1.19. The spectrum contain two peaks at *ca.* 1.7 ppm and *ca.* 1.8 ppm assignable to the methyl hydrogen, indicating the presence of two species. In the aromatic region seven peaks are observed. If two species, both with 2 aromatic hydrogens are present, eight peaks (4 doublets) are expected. However, it is clear from the integration ratio that the three peaks at *ca.* 6 ppm result from the partial overlap of two

Fig. 1.17 ^{1}H Nuclear Magnetic Resonance Spectrum of Na(hgoH) in D_2O

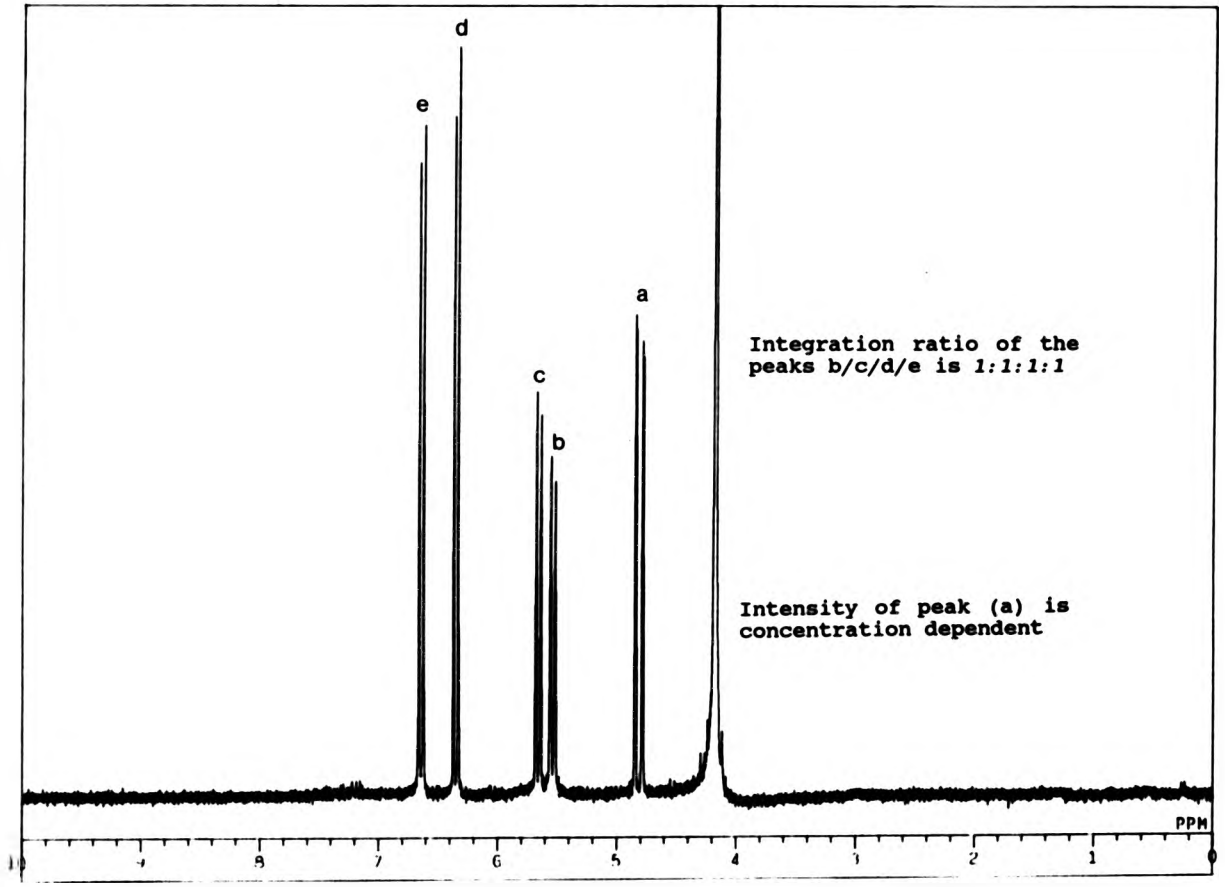
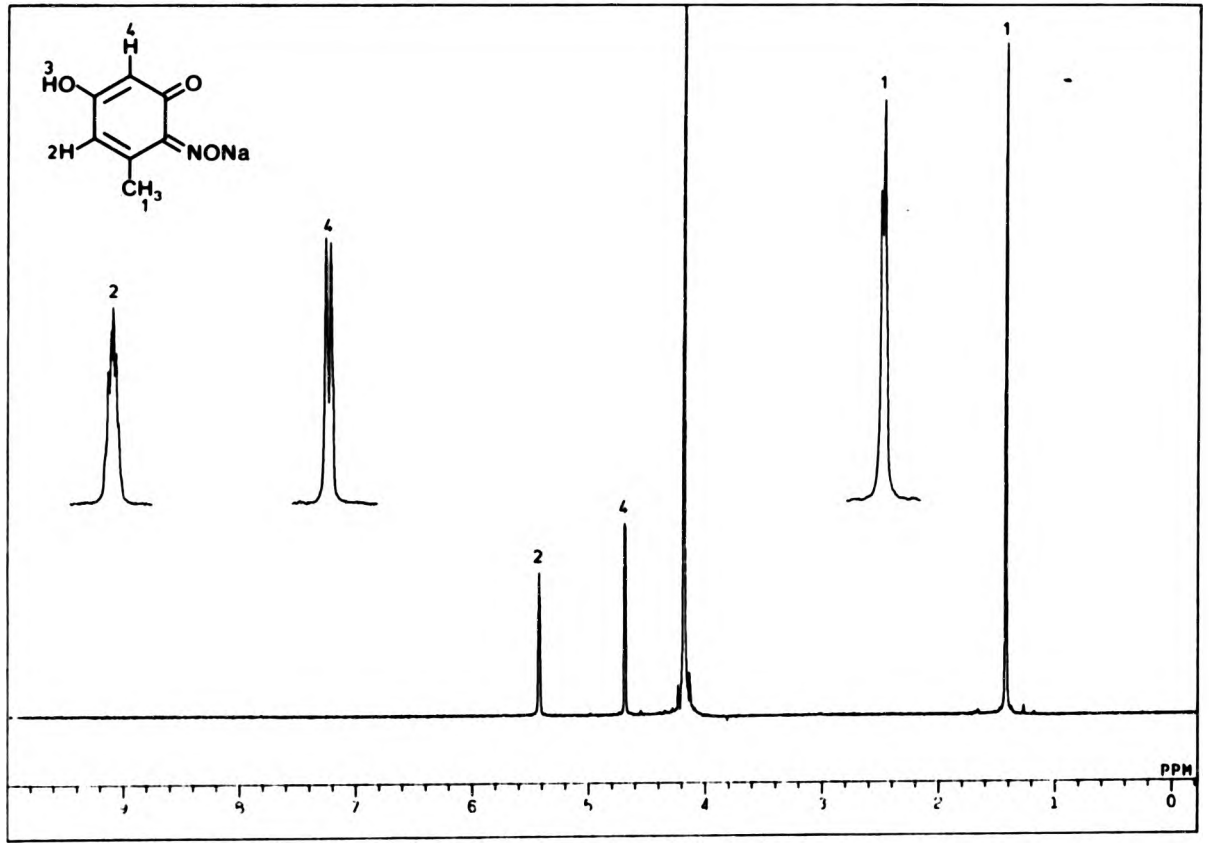


Fig. 1.18 ^{1}H Nuclear Magnetic Resonance Spectrum of Na(3-MehqoH) in D_2O



doublets. This was confirmed by running a spectrum at a higher temperature. On increasing the temperature the chemical shift of the peaks alter slightly revealing the hidden peak and the true pattern expected for two species is observed (Fig. 1.20). The coupling constants of all pairs of peaks are identical. The value of the constants (9.9 Hz) indicate that both species have a quinonoid structure. Furthermore, the integration ratio suggest that the two species are present in the ratio of 1:6.

The broad band decoupled ^{13}C spectrum (Fig. 1.21) also shows the presence of two species, since a total of 12 peaks can be observed instead of the 7 peaks expected for a single species. This spectrum shows two peaks assignable to quinonoid carbons at 186.8 ppm and 186.1 ppm. Although two quinonoid carbons are observed, only one oximic (166.0 ppm) and one hydroxylic (148.8 ppm) carbon is observed. This suggest that the chemical shifts of the quinonoid and oximic carbons of the two species are identical. The observation of two quinonoid carbon peaks suggest that both species are oximic in character. As noted in Scheme 1.2 there are 3 possible oximic isomers for 5-hydroxy-6-methyl-1,2-benzoquinone 2-oxime. On the basis of the available information it is not possible to define the exact structures of these isomers. However, the presence of two oximic isomers is novel. Previously

Fig. 1.19 ^{1}H Nuclear Magnetic Resonance Spectrum of Na(6-MehgoH) in D_2O at 20 °C

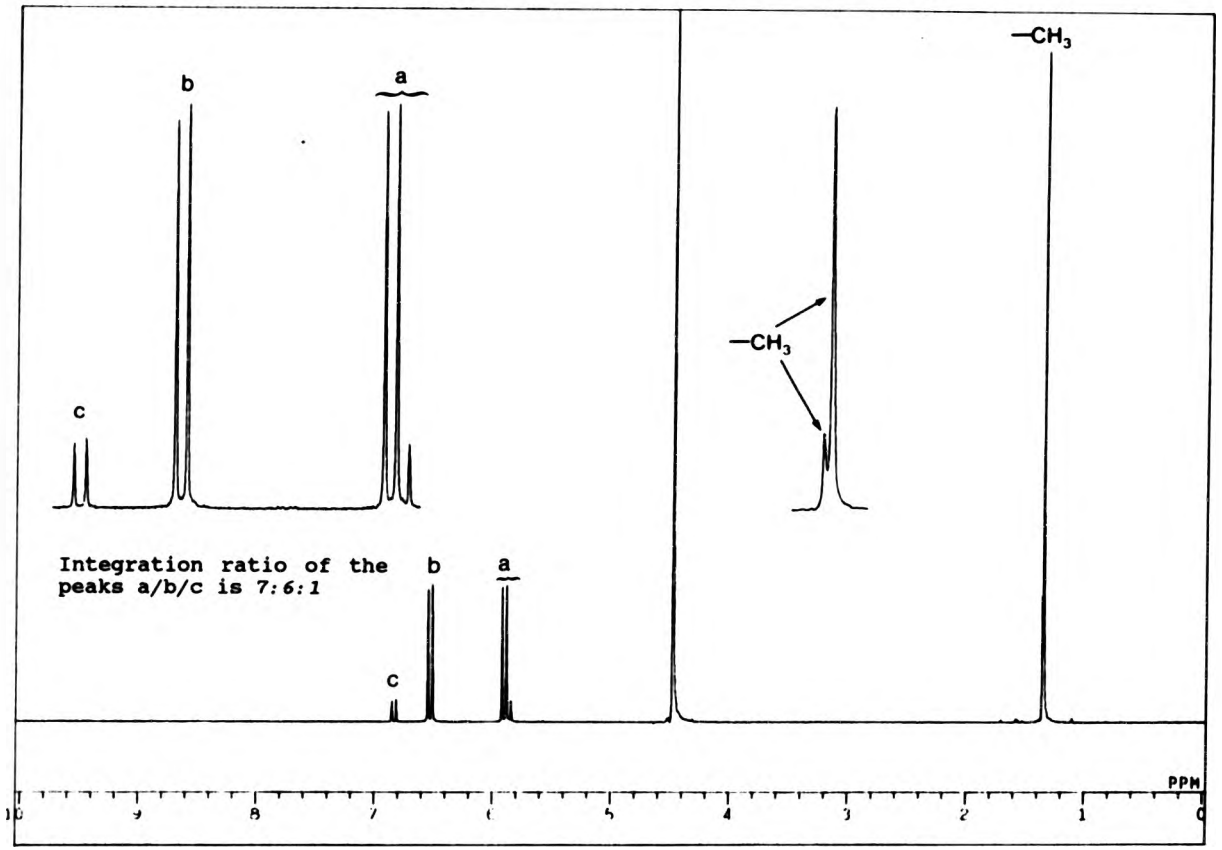
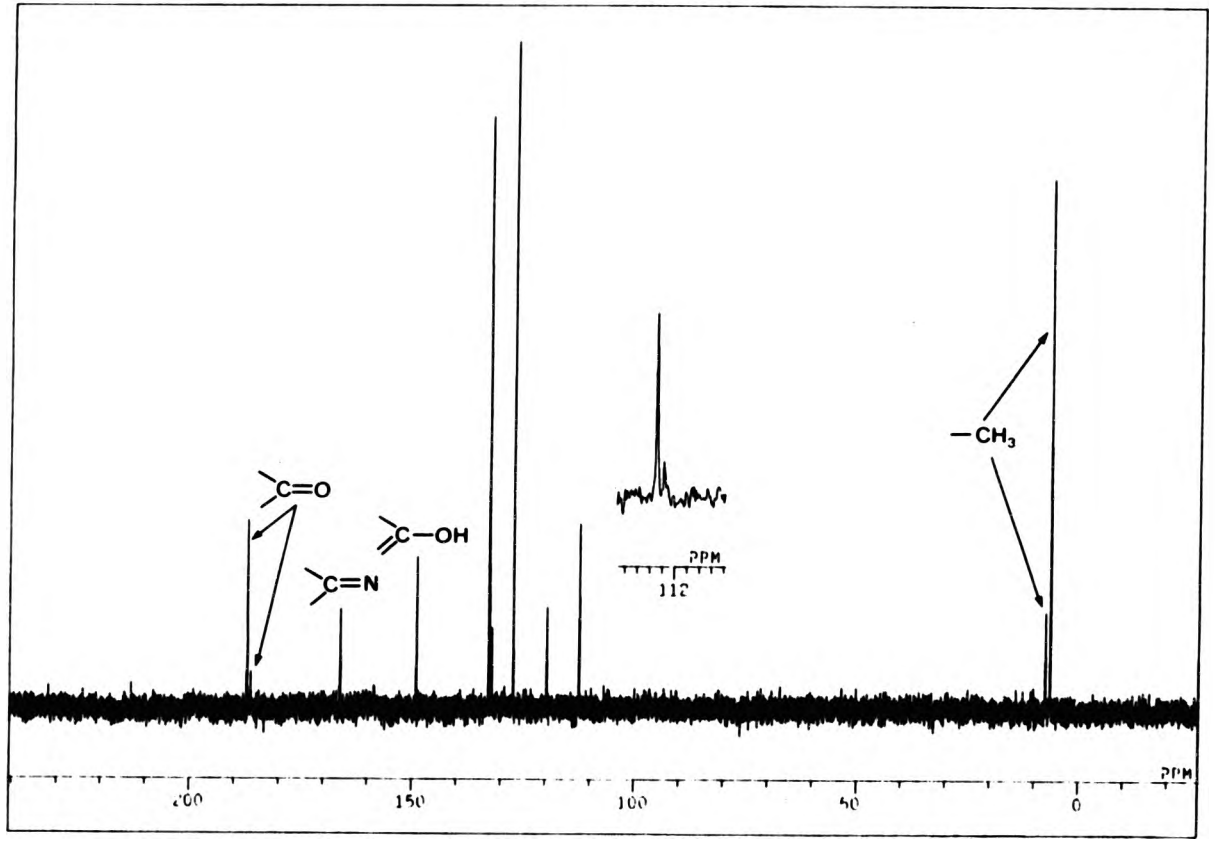


Fig. 1.20 ^{1}H Nuclear Magnetic Resonance Spectrum of Na(6-MehgoH) in D_2O at 60 °C

Fig. 1.21 ^{13}C Nuclear Magnetic Resonance Spectrum of Na(6-MehqoH) in D_2O



two isomers have been detected in the solution spectra of 1,4-benzoquinone 4-oxime and 1,2-naphthoquinone 2-oxime but in both cases it was suggested that one of the isomers was oximic and the other nitrosophenolic.

1.6 References

1 H. H. Hodgson, *J. Chem. Soc.*, 1931, 1494.

2 H. H. Hodgson and F. H. Moore, *J. Chem. Soc.*, 1923, 2499.

3 H. H. Hodgson and A. Kershaw, *J. Chem. Soc.*, 1929, 1553.

4 J. Charalambous, M. J. Frazer, and F. B. Taylor, *J. Chem. Soc. (A)*, 1969, 2787.

5 J. Charalambous, M. J. Frazer, and F. B. Taylor, *J. Chem. Soc. (A)*, 1971, 602.

6 I. L. Finar, 'Organic Chemistry, Vol. 1,' Longman, Essex, 6th edition, 1973.

7 C. Romers and E. Fischmann, *Acta Crystallogr.*, 1960, 13, 809.

8 E. Fischmann, C. Romers, and A. J. H. Umans, *Acta Crystallogr.*, 1960, 13, 885.

9 F. Henrich and H. Eisenach, *J. Prakt. Chem.*, 1904, 70, 332.

10 G. W. R. Bartindale, M. M. Crowder, and K. A. Morley, *Acta Crystallogr.*, 1959, 12, 111.

11 C. Romers, *Acta crystallogr.*, 1964, 17, 1287

12 A. Burawoy, M. Cais, J. T. Chamberlain, F. Liversedge, and A. R. Tompson, *J. Chem. Soc.*, 1955, 3727.

13 H. S. French and D. J. Perkins, *J. Am. Chem. Soc.*, 1937, 59, 1182

14 D. Hadzi, *J. Chem. Soc.*, 1956, 2725.

15 R. K. Norris and S. Sternhell, *Aust. J. Chem.*, 1966, 19, 841.

16 T. Shono, Y. Hayashi, and K. Shinra, *Bull. Chem. Soc. Jpn.*, 1971, 44, 3179.

17 H. Goldschmidt, *Ber.*, 1884, 17, 213.

18 P. H. McFarlane and D. W. Russel, *J. Chem. Soc., Chem. Commun.*, 1969, 475.

19 Y. L. Chow and Z. Z. Wu, *J. Am. Chem. Soc.*, 1985, 107, 3338.

20 R. D. Gillard, R. P. Houghton, and J. N. Tucker, *J. Chem. Soc., Dalton Trans.*, 1980, 2102.

21 T. Teshigawara, Jap. Pat. 13,918, Jul. 17, 1964. (Chem. Abs. no. 62:7688b).

22 K. W. P. White, Ph.D. Thesis, 1988, The Polytechnic of North London.

23 G. Chronheim, *J. Org. Chem.*, 1947, 12, 7.

24 R. G. Cawthorne, J. Charalambous, W. M. Shutie, F. B. Taylor, and A. Betts, *Inorg. Chim. Acta*, 1979, 37, 245.

25 O. Baudisch, *Naturwissenschaften*, 1939, 27, 768.

26 W. M. Shutie, Ph.D. Thesis, 1981, The Polytechnic of North London.

27 Z. Iqbal, M.Phil. Thesis, 1986, The Polytechnic of North London.

28 F. Henrich, *Ber.*, 1902, 35, 4191.

29 W. R. Orndorff and M. L. Nicholls, *J. Amer. Chem.*

Soc., 1923, 45, 1538.

30 A. K. Banerjee, A. J. Layton, R. S. Nyholm, and M. R. Truter, *J. Chem. Soc. (A)*, 1969, 2536.

31 P. Gaganatsou, Ph.D. Thesis, 1987, The Polytechnic of North London.

32 A. J. Layton, R. S. Nyholm, A. K. Banerjee, D. E. Fenton, C. N. Lestas, and M. R. Truter, *J. Chem. Soc. (A)*, 1970, 1894.

33 A. K. Banerjee, A. J. Layton, R. S. Nyholm, and M. R. Truter, *J. Chem. Soc. (A)*, 1970, 292.

34 A. K. Banerjee, D. Prakash, and S. K. Roy, *J. Indian chem. Soc.*, 1976, 53, 773.

35 C. B. Castellani, O. Carugo, and A. Coda, *Acta Crystallogr.* 1988, C44, 265.

36 E. Y. Belyaev, L. M. Gornostaev, V. A. Levdanskii, *Khim. Geterotsikl. Soedin.*, 1975, 11, 1571

37 M. Näsäkkälä, H. Saarinen, J. Korvenranta, and E. Näsäkkälä, *Finn. Chem. Lett.*, 1977, 234.

38 R. Graziani, U. Casellato, P. A. Vigato, S. Tamburini and M. Vidali, *J. Chem. Soc. Dalton Trans.*, 1983, 697.

39 A. Fischer, R. M. Golding, and W. C. Tennant, *J. Chem. Soc.*, 1965, 6032.

40 L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon Press, London, 2nd edition, 1969.

41 D. H. Williams and I. Fleming, 'Spectroscopic Methods in Organic Chemistry,' Mcgraw-Hill Book Company, Maidenhead, 3rd edition, 1980.

42 A. Arnone, G. Fronza, R. Mondelli, and J. St. Pyrek, *J. Magn. Reson.*, 1977, **28**, 69.

43 G. E. Hawkes, K. Herwig, and J. D. Roberts, *J. Org. Chem.*, 1974, **39**, 1017.

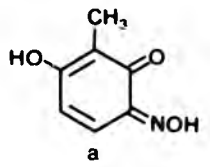
CHAPTER 2

SINGLE CRYSTAL X-RAY STRUCTURE OF

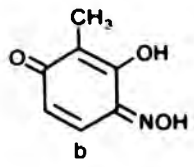
3-HYDROXY-2-METHYL-1,4-BENZOQUINONE 4-OXIME

2.1 Introduction

As discussed in Chapter 1 quinone mono-oximes can have various structures and in solution may exhibit nitrosophenol/quinone oxime tautomerism. In the past a number of 1,2- and 1,4-quinone mono-oximes have been studied by X-ray crystallography.[1-7] However, the present investigation is the first study of a quinone mono-oxime which could exist either as a 1,2- or a 1,4-quinone mono-oxime (Fig. 2.1a and 2.1b respectively).



a



b

Fig. 2.1

2.2 Crystal Data for 3-Hydroxy-2-methyl-1,4-benzoquinone 4-Oxime

$C_7H_7NO_3 \cdot H_2O$, M = 171.09, a = 3.931(2), b = 13.741(3), c = 14.214(3), $\alpha = \gamma = 90.00^\circ$, $\beta = 92.08^\circ$, U = 767.27 Å^3, F(000) = 320.00, μ(Mo-K_α) = 4.84 cm^{-1},

$Z = 4$, $D_c = 1.32\ gcm^{-3}$.

2.3 Crystal Preparation and Data Collection

5-Hydroxy-3-methyl-1,4-benzoquinone 4-oxime was synthesized by nitrosation of 3-hydroxy-2-methylphenol using amyl nitrite/sodium ethoxide followed by acidification of the resultant sodium complex. The precipitate obtained from the acidification reaction was recrystalised from methanol/water (2:1). The crystal selected for the X-ray study had dimensions of 0.40 X 0.24 X 0.24 mm. The data was collected on a Philips PW1100 diffractometer in the θ-range 3 - 25°, with a scan width of 0.8°. Using a graphite monochromated Mo-K_α radiation source, a total of 1353 unique reflections with $I > 3\sigma(I)$ were collected. The intensity relationship $I_{hkl} = I_{\bar{h}kl} = I_{h\bar{k}l} = I_{\bar{h}\bar{k}l}$ observed for selected strong reflections confirmed the presence of a primitive monoclinic crystal system. The data was corrected for Lorentz and polarization effects but not for absorption.

2.4 Structure Solution and Refinement

Systematic absences in the data of the type: *0k0*; $k = 2n + 1$ and *h0l*; $l = 2n + 1$ indicated that the crystal had crystallized in the centrosymmetric space

group $P2_1/c$. This was subsequently confirmed by complete structure solution in this space group. The structure was solved by direct methods using the MULTAN 77 program.[8] This initially involved using the observed structure factors to statistically calculate several electron density maps. Careful study of these maps enabled the location of all the non-hydrogen atoms, while successive difference Fourier synthesis revealed the positions of all but the two hydrogen atoms of the water molecule. A full-matrix least-squares refinement minimising $\Sigma w(F_o - F_c)^2$ was then performed using the SHELX 77 program.[9] All non-hydrogen atoms were refined anisotropically and all hydrogen atoms isotropically using $w = 2.6734/[\sigma^2(F) + 0.000787F^2]$ as the weighting scheme. At convergence R and R_w were 0.065 and 0.068 respectively.

2.5 Discussion

All atomic co-ordinates, temperature factors, structure factors, bond lengths and intra bond angles are given in Appendix 1.

Selected bond lengths and bond angles for 3-hydroxy-2-methyl-1,4-benzoquinone 4-oxime are shown in Fig. 2.2 and Fig. 2.3 respectively. Molecular packing is shown in Fig. 2.4.

Fig. 2.2 Selected Bond Lengths (Å) in 3-Hydroxy-2-methyl-1,4-benzoquinone 4-Oxime

Fig. 2.3 Selected Bond Angles (°) in 3-Hydroxy-2-methyl-1,4-benzoquinone 4-oxime

Fig. 2.4 Molecular Packing in 3-Hydroxy-2-methyl-1,4-benzoquinone 4-Oxime

Comparison of the bond length of the CO group in the structure of 3-hydroxy-2-methyl-1,4-benzoquinone 4-oxime (Fig. 2.2) to those tabulated for compounds with established quinone mono-oxime structures in Table 2.1 shows that the bond C(4) - O(3) [1.247(5) Å] is within the range quoted for compounds (I - V). The bond length of N - O(1) [1.364(6) Å] is also very similar to those reported previously. The C=N bond length of 1.284(6) Å appears to be in the upper range of bond distances reported for the related structures shown in Table 2.1. Furthermore, the C=N and N-O bond distances are similar to those found in oximes, e.g. acetoxime[10] (C=N, 1.29 Å; N-O, 1.36 Å) whereas the C=O bond is similar to those in quinones, e.g. 1,4-naphthoquinone[11] (1.21 Å). The single bond character in the bond C(2) - O(2) [1.341(5) Å] is apparent with this bond being 0.094 Å longer than the bond C(4) - O(3).

The C-C bond distances of the ring show that two C-C bonds are markedly shorter than the remaining four C-C bonds (Fig. 2.2). The short bonds are C(2) - C(3) and C(5) - C(6). The mean bond length of these two short bonds (1.327 Å) is 0.122 Å shorter than the mean of the four remaining C-C bonds within the ring. This indicates that the bonds C(2) - C(3) and C(5) - C(6) have more double bond character than the remaining ring C-C bonds. Interestingly, these data show that the double bonds are

Table 2.1 Bond Lengths of 1,2-Quinone Mono-oximes from Previous X-Ray Studies

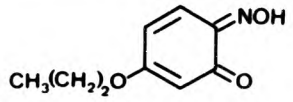
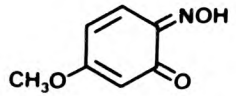
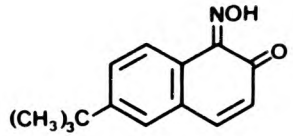
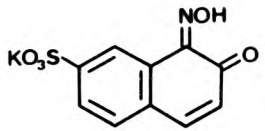
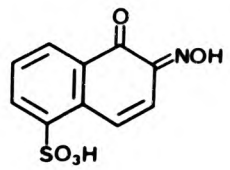
Quinone mono-oxime		Bond length (Å)					Reference
		C-O	C-N	N-O	C-C†	C-C‡	
	(I)	1.27	1.32	1.35	1.35	1.45	1
	(II)	1.23	1.22	1.36	1.34	1.46	2
	(III)	1.24	1.30	1.36	1.37	1.47	3

Table 2.1 cont.

Quinone mono-oxime		Bond length (Å)					Reference
		C-O	C-N	N-O	C-C†	C-C‡	
	(IV)	1.22	1.31	1.39	1.31	1.47	4
	(V)	1.24	1.30	1.38	1.33	1.46	5

†=Average bond length of the 2 short bonds ‡=Average bond length of the 4 long bonds

1,4 with respect to each other rather than 1,2 as observed for compounds I - V listed in Table 2.1.

The Fig. 2.4 shows the molecular packing of the crystal. Two kinds of intermolecular hydrogen bonds [O(1)-H(O1)···O(3) and O(2)-H(O2)···O(W)] have been confirmed in the structure (See Appendix 1, Table 5). In addition the short contact distances, O(W)···N and O(W)···O(3) [2.981(6) and 2.844(6) Å respectively] indicate the involvement of the water molecule in the formation of the hydrogen bonds O(W)-(H)···N and O(W)-H···O(3), which contribute further to the stabilization of the structure.

From Table 2.2 it can be seen that in 3-hydroxy-2-methyl-1,4-benzoquinone 4-oxime all non-hydrogen atoms except O(1) are planar to within 0.02 Å. However O(1) lies at a small but significant distance out-side the least square plane. This can be attributed to the involvement of this atom in the hydrogen bond O(1)-H(O1)···O(3) (See Appendix, Table 5).

Table 2.2 Least Squares Plane for 3-Hydroxy-2-Methyl-1,4-Benzoquinone 4-Oxime

C(1)	-0.002(4)
C(2)	-0.006(4)
C(3)	0.009(4)
C(4)	-0.005(4)
C(5)	-0.002(4)
C(6)	0.005(4)
C(7)*	0.017(9)
N*	0.012(8)
O(1)*	0.036(9)
O(2)*	-0.001(7)
O(3)*	0.003(7)

*=Atoms not included in the calculation of the plane

The results show that the compound has quinone oximic rather than nitrosophenolic character. Additionally, the compound has the 1,4- rather than the 1,2-quinone oxime structure. In summary, this is indicated by the following:

(i) A hydrogen atom is bonded to the oxygen of the NO group but no hydrogen is bonded to O(3).

(ii) Two short [C(2)-C(3), C(5)-(C6)] and four long carbon-carbon bonds.

(iii) Short CO and CN bond distances.

2.6 References

1 C. Romers, *Acta Crystallogr.*, 1964, 17, 1287.

2 G. W. R. Bartindale, M. M. Crowder, and K. A. Morley, *Acta Crystallogr.*, 1959, 12, 111.

3 J. C. A. Boeyens, *J. Cryst. Mol. Struct.*, 1976, 6, 217.

4 H. Saarinen, J. Korvenranta, and E. Näsäkkälä, *Acta Chem. Scand., Ser. A*, 1977, 31, 213.

5 H. Saarinen, J. Korvenranta, and M. Näsäkkälä, *Finn. Chem. Lett.*, 1977, 47.

6 C. Romers and E. Fischmann, *Acta Crystallogr.*, 1960, 13, 809.

7 J. W. L. van Oijen and C. Romers, *Acta Crystallogr.*, 1966, 20, 169.

8 P. Main, L. Lessinger, M. M. Woolfson, G. Germain and J. P. Declerq, 'A system of computer programs for the automatic solution of crystal structures from X-ray diffraction data,' Universities of York, England, and Louvain-La-Neuve, Belgium, (1977).

9 G. M. Sheldrick, 'Program for crystal structure determination,' University of Cambridge, England, (1976).

10 A. Chakravorty, *Coord. Chem. Rev.*, 1974, 13, 1.

11 P. J. Gaultier and C. Hauw, *Acta Crystallogr.*, 1965, 18, 179.

CHAPTER 3

IRON COMPLEXES OF 3-HYDROXY-1,2-BENZOQUINONE MONO-OXIMES AND N-ACETYL-5-AMINO-1,2-BENZOQUINONE 2-OXIME

3.1 Introduction

Iron complexes of 1,2-quinone mono-oximes have been known for a considerable length of time. These chelating agents have been used as analytical reagents for the determination of iron[1,2] and their iron complexes have been used as dyes.[3,4] A naturally occurring iron complex of the 1,2-quinone mono-oxime, 4-ethenylphenyl 4-hydroxy-3-nitrosobenzoate, known as ferroverdin[5,6] has been isolated from *Streptomyces* sp. strain Wak. A-305 (see Chapter 4).

3.2 Preparation of Iron Complexes of 1,2-Quinone Mono-oximes

There are three main methods for the preparation of iron complexes of 1,2-quinone mono-oximes:

(i) Direct method

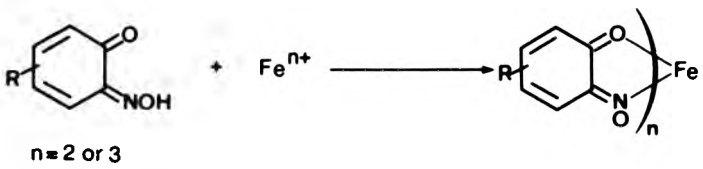
(ii) Nitrosation method

(iii) Metal carbonyl method

Direct Method

This method involves the reaction of a 1,2-quinone mono-oxime with an iron(II) or an iron(III) salt

(Reaction 3.1).[7-9] The applicability of the method is limited by the small number of 1,2-quinone mono-oximes which are readily available. Generally the reaction with iron(III) salts leads to mixtures of iron(II) and iron(III) complexes. The reaction with iron(II) salts, affords only iron(II) complexes.



n=2 or 3

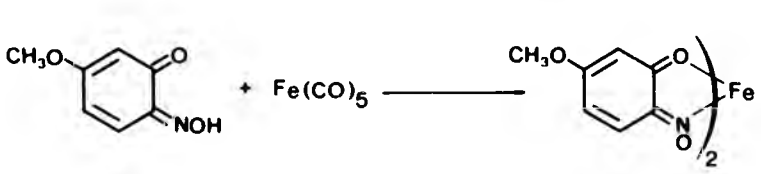
Reaction 3.1

Nitrosation Method

As noted earlier transition metal complexes of 1,2-quinone mono-oximes are readily obtainable by the reaction of phenols with sodium nitrite/acid in the presence of a transition metal salt. This route has proved useful for the synthesis of a variety of iron complexes such as $Fe(2\text{-nqo})_3$, $Fe(3\text{-MeOqo})_2$ and $Na[Fe(3,4\text{-DiMeqo})_3]$.[10] Generally the reaction leads to mixtures of iron(II) and iron(III) complexes irrespective of the oxidation state of the iron salt used.[10,11]

Metal Carbonyl Method

This method has been used to synthesize complexes of iron(II) derived from 5-methoxy-1,2-benzoquinone 2-oxime and the mono-oximes of 1,2-naphthoquinone (e.g. Reaction 3.2).[10,12,13]

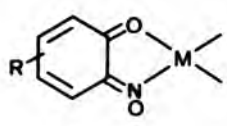


Reaction 3.2

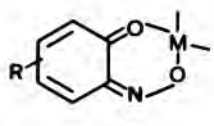
3.3 The Structure of Iron Complexes of 1,2-Quinone Mono-oximes

The donor atoms in 1,2-quinone mono-oximes can bond to a metal ion in several ways. Chelation may involve the quinone oxygen and either the nitrogen (Fig. 3.1a) or the oxygen (Fig. 3.1b) of the NO group. Another possibility is for the metal to co-ordinate via the oxygen and the nitrogen of the NO group (Fig. 3.1c). Examples of complexes whose structures have been determined by X-ray crystallography are shown in Table 3.1. In all cases except the uranyl complexes of 1,2-naphthoquinone 2-oxime and 1,2-naphthoquinone 1-oxime, the bonding involves chelation through the

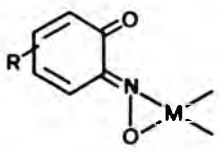
oxime nitrogen and the quinone oxygen, (Fig. 3.1a). In the case of the uranyl complexes the bonding occurs through the NO group only (Fig. 3.1c). To-date, co-ordination via the oxygen of the NO group and the quinone oxygen (Fig. 3.1b) has not been observed.



a



b



c

Fig. 3.1

Metal chelates derived from 1,2-quinone mono-oximes have been represented in valence bond terms as a resonance system (e.g. Fig. 3.2) involving nitrosophenolic (Fig. 3.2a) and quinone oximic (Fig. 3.2b) structures. However, the complexes are essentially quinone mono-oximic in character as indicated by X-ray crystallographic studies of several metal complexes. Selected bond lengths for some complexes are shown in Table 3.1. The observed pattern of two short and four long carbon-carbon bond distances show that the quinone oximic form makes a significant contribution. Further

Table 3.1 Bond Lengths of Metal Complexes of 1,2-Quinone Mono-oximes

Complex (qoH)	Bond length (Å)					Ref.
	C-O	C-N	N-O	C-C†	C-C‡	
$Na[Fe(qo)_3]$ (4-ethenylphenyl 4-hydroxy-3-nitrosobenzoate)	1.29	1.40	1.25	-	-	5
$Cu(qo)_2 \cdot py$ (4-methyl-1,2-benzoquinone 2-oxime)	1.27	1.35	1.25	1.35	1.43	14
$K[Ni(qo)_3] \cdot (CH_3)_2CO$ (4-chloro-1,2-benzoquinone 2-oxime)	1.25	1.33	1.27	1.35	1.45	15
$[UO_2(qo)_2(H_2O)_2] \cdot 2CHCl_3$ (1,2-napthoquinone 2-oxime)	1.23	1.30	1.34	1.32	1.45	16
$[pyH][Ir(qo)(py)Cl_3]$ (1,2-napthoquinone 1-oxime)	1.30	1.35	1.27	1.35	1.44	17

† = Average length of the 2 short C-C bonds ‡ = Average length of the 4 long C-C bonds

evidence for quinone oximic contribution can be obtained from consideration of the C-N and C-O bond lengths. The C-N and C-O bond lengths of these complexes are comparable to those found in complexes containing oximino[18] (C=N; *ca.* 1.40 Å) or carbonyl[19] (C=O; 1.28 Å) groups respectively. This is indicative of the contribution from the quinone oximic structure. Similar features can be observed in the ferroverdin complex.

Fig. 3.2

3.4 Previous Work on Iron Complexes of 1,2-Quinone Mono-oximes

A survey of the literature shows that a range of iron complexes of 1,2-quinone mono-oximes have been synthesized. These complexes and the methods used for their preparation and characterisation are presented in Table 3.2.

Complexes of type $Fe(qo)_3$ have been prepared by the direct reaction of iron(III) chloride with 1,2-quinone

Table 3.2 Previously Reported Iron Complexes of 1,2-Quinone Mono-oximes

Quinone mono-oxime	Proposed Formulation	Method of Preparation	Data Reported	Ref.
1,2-Naphthoquinone 1-oxime	$Fe(qo)_3$	D	Fe, el., μ, m.p., Mö., M.	7
"	"	D	Fe	20
"	"	D	i.r.	21
"	"	D	el., i.r.	9
"	"	D	el., μ, Mö.	8
"	$Fe(qo)_2$	D	i.r.	21
"	-	D	colour	22
"	"	D	Fe, el., i.r., μ, Mö.	11
"	"	C	Fe, el., μ, Mö.	13
"	$Fe(qo)_2 \cdot H_2O$	D	el., μ, Mö.	8
"	$Fe(qo)_2Cl$	1, 2	Fe, el., μ, M.	7

Table 3.2 continued

Quinone mono-oxime	Proposed Formulation	Method of Preparation	Data Reported	Ref.
1,2-Naphthoquinone 1-oxime	$Fe(qo)_2 \cdot 2py$	3	Mö	23
"	$Fe(qo)_2 \cdot 2py$	4	Fe, el., μ, Mö.	13
"	$K[Fe(qo)_3]$	5	Fe, el., μ.	7
"	$Na[Fe(qo)_3]$	5	el., Mö.	7
"	$K[Fe(qo)_3] \cdot 2H_2O$	5	el., Mö.	8
4-Hydroxy-1,2-naphthoquinone 2-oxime	-	D	u.v.	2
7-Hydroxy-1,2-naphthoquinone 2-oxime	-	D	u.v.	2
1,2-naphthoquinone 2-oxime 6-sulphonic acid	-	D	u.v.	2
1,2-Naphthoquinone 2-oxime	$Fe(qo)_3$	D	el., i.r., u.v.	9

Table 3.2 Continued

Quinone mono-oxime	Proposed Formulation	Method of Preparation	Data Reported	Ref.
1,2-Naphthoquinone 2-oxime	$Fe(qo)_3$	D	Fe, el., μ, m.p., M.	7
"	$Fe(qo)_2$	D	Fe, el., μ, Mö.	10
"	$Fe(qo)_2$	C	Fe, el., μ, Mö.	13
"	$Fe(qo)_2 \cdot 2py$	5	Fe, el., μ, Mö.	13
Phenanthrene-9,10-quinone 10-oxime	$Fe(qo)_3$	D	Fe, el., μ, m.p.	7
4-Ethenylphenyl 4-hydroxy-3-nitrosobenzoate	$Na[Fe(qo)_3]$	6	Fe, el., X-ray	5
5-Methoxy-1,2-benzoquinone 2-oxime	$Fe(qo)_3$	D	μ, Mö., M., m.s.	7
"	$Fe(qo)_3$	D	Fe	24

Table 3.2 Continued

Quinone mono-oxime	Proposed Formulation	Method of Preparation	Data Reported	Ref.
5-Methoxy-1,2-benzoquinone 2-oxime	$Fe(qo)_2(OH)$	D	Fe	24
"	$Fe(qo)_2$	D	Fe, el., μ, M.	10
"	$Fe(qo)_2$	C	Fe, el., μ, Mö, M.	10
"	$Fe(qo)_2 \cdot 2py$	4	Fe, el., μ, Mö. M.	10
"	-	D	none	2
3-Chloro-5-methoxy-1,2-benzo-quinone 2-oxime	$Fe(qo)_3$	D	Cl	24
"	$Fe(qo)_2(OH)$	D	Cl	24
5-Ethoxy-1,2-benzoquinone 2-oxime	$Fe(qo)_2$	D	Fe, el.	25
5-Hydroxy-1,2-benzoquinone 2-oxime	$Fe(qo)_3 \cdot 3H_2O$	D	Fe, el., μ, Mö.	26

Table 3.2 Continued

Quinone mono-oxime	Proposed Formulation	Method of Preparation	Data Reported	Ref.
5-Hydroxy-1,2-benzoquinone 2-oxime	-	D	u.v.	2
4-Methyl-1,2-benzoquinone 2-oxime	-	D	none	2
"	$Na[Fe(qo)_3]\cdot S$	N	Fe, el., Mö., Λ	27
"	$K[Fe(qo)_3]\cdot S$	N	Fe, el., Mö., Λ	27
5-Methyl-1,2-benzoquinone 2-oxime	$Fe(qo)_3$	D	Fe, el., m.p., Mö., M.	7
3,4-Dimethyl-1,2-benzoquinone 2-oxime	$Na[Fe(qo)_3]$	N	Fe, el., Mö.	10
"	$K[Fe(qo)_3]$	N	Fe, el., Mö.	10
"	$Na[Fe(qo)_3]\cdot S$	N	Fe, el., Mö.	10
"	$K[Fe(qo)_3]\cdot S$	N	Fe, el., Mö.	10

Table 3.2 Continued

Quinone mono-oxime	Proposed Formulation	Method of Preparation	Data Reported	Ref.
3,4-Dimethyl-1,2-benzoquinone 2-oxime	$Fe(qo)_3$	N	Fe, el.,	10
4,5-Dimethyl-1,2-benzoquinone 2-oxime	$Fe(qo)_3$	N	Fe, el., m.p., Mö., M.	7
"	$Fe(qo)_2Cl$	1	μ, M.	7
N,N-Dimethyl-5-amino-1,2-benzo-quinone 2-oxime	-	D	u.v.	2
"	-	D	u.v.	2

D=Direct reaction; N=Nitrosation reaction; C=Iron pentacarbonyl reaction. S=Acetone

1=Interaction of $Fe(qo_3)$ with HCl. 2=Interaction of a Na complex of 1-nqoH with $FeCl_3$.

3=Interaction of $Fe(qo)_3$ with pyridine. 4=Interaction of $Fe(qo)_2$ pyridine.

5=Interaction of $Fe(qo)_3$ with MI (M=Na or K). 6=Naturally occurring.

Fe=Iron analysis; el.=C,H,N analysis; m.p.=Melting point; M=Relative molecular mass;

Mo.=Mossbauer spectrum; μ=Magnetic moment; Cl=Chlorine analysis; m.s.=Mass spectrum

i.r.=Infra-red spectrum; u.v.=Ultra-violet spectrum

mono-oximes and by the nitrosation of phenols in the presence of iron(III) chloride. The compounds obtained by both routes were shown to have identical X-ray powder diffraction patterns and i.r. spectra as well as similar elemental analysis.[7] It was also shown that these iron(III) chelates react with alkali metal iodides (Reaction 3.3), sodium acetate (Reaction 3.4) or sodium nitrite (Reaction 3.5) to give iron(II) compounds of type $Fe(qo)_2$ or $M[Fe(qo)_3]$ where M = Na or K.[10,11] Generally the iron(III) chelates are brown in colour whereas the iron(II) compounds are green in colour.

$$2Fe(qo)_3 + 2MI \xrightarrow{MeOH} 2M[Fe(qo)_3] + I_2$$

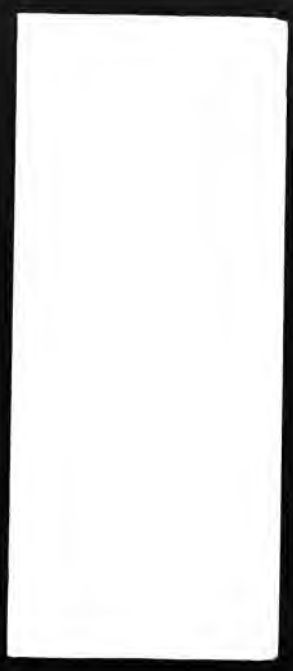
(M = Na or K)

Reaction 3.3

$$Fe(qo)_3 + C_2H_5CO_2M \xrightarrow{MeOH/H_2O} M[Fe(qo)_3] + [C_2H_5CO_2]^-$$

(M = Na or K)

Reaction 3.4

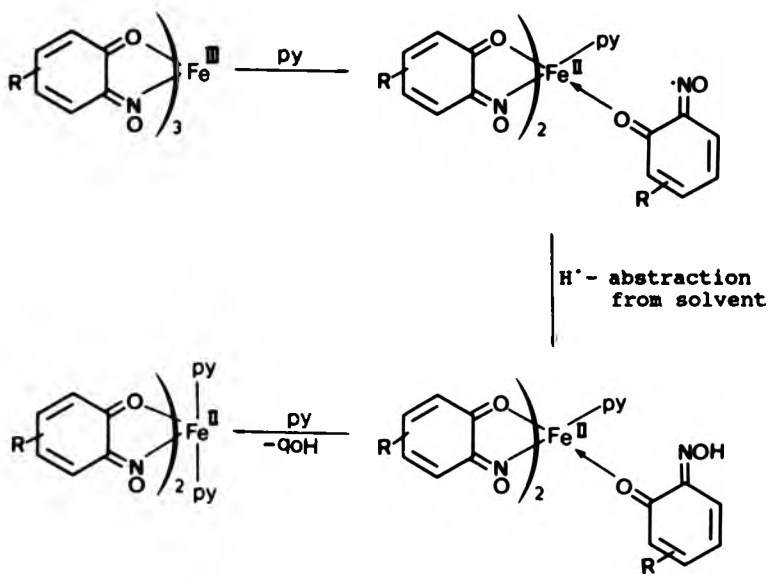


$$Fe(qo)_3 + NaNO_2 \xrightarrow{MeOH/H_2O} Fe(qo)_2 + Na(qo) + [NO_2]^{\cdot}$$

Reaction 3.5

It has been shown that iron(III) chelates react readily with pyridine to form iron(II) pyridine adducts of type $Fe(qo)_2 \cdot 2py$. This observation has been rationalised in terms of an internal redox reaction (Scheme 3.1).[12] Later work showed that other Lewis bases such as dimethylsulphoxide and acetone are also capable of inducing internal redox behaviour.[28]

Iron(II) complexes have been synthesized by both the direct and nitrosation methods. Two types of iron(II) complexes have been isolated from the nitrosation reactions. These are complexes of the types $Fe(qo)_2$ or $Na[Fe(qo)_3]$. The direct method usually leads to complexes of type $Fe(qo)_2$ but in certain cases some iron(III) complexes of type $Fe(qo)_3$ is also formed.[10,11]



Scheme 3.1

3.5 Iron Complexes Derived from the Mono-oximes of 3-Hydroxyphenols and N-Acetyl-3-aminophenol

3.5.1 Introduction

In this study several new quinone oximic iron complexes were prepared using the nitrosation method from N-acetyl-3-aminophenol, 3-hydroxyphenol, 3-hydroxy-2-methylphenol and 3-hydroxy-5-methylphenol. Complexes have also been prepared by the direct reaction of iron(II) with 3-hydroxy-1,2-benzoquinone mono-oximes.

3.5.2 Reaction of 3-Hydroxy-1,2-benzoquinone Mono-oximes with Ammonium Iron(II) Sulphate

The reaction of 5-hydroxy-1,2-benzoquinone 2-oxime ($hqoH_2$), 5-hydroxy-3-methyl-1,2-benzoquinone 2-oxime ($3\text{-}MehqoH_2$) and 5-hydroxy-6-methyl-1,2-benzoquinone 2-oxime ($6\text{-}MehqoH_2$) with ammonium iron(II) sulphate resulted in dark green solids of composition $Fe(hqoH)_2 \cdot 3H_2O$, $Fe(3\text{-}MehqoH)_2 \cdot 2H_2O$ and $Fe(6\text{-}MehqoH)_2 \cdot 2H_2O$ respectively. The suggested formulations are based on analytical evidence and are supported by t.g.a. results (Table 3.3). The green colour of the complexes is in accord with the presence of iron in the oxidation state II. The magnetic moments (Table 3.3) fall in the range 3.61 - 3.94 BM and are

Table 3.3 Thermal Gravimetric Analysis and Room Temperature Magnetic Moments of $Fe(hqoH)_2 \cdot 3H_2O$, $Fe(3\text{-}MehqoH)_2 \cdot 2H_2O$ and $Fe(6\text{-}MehqoH)_2 \cdot 2H_2O$

Formulation	Wt. of Sample /mg	Weight Loss /mg		Temperature of Loss of Water/ °C	Decomp. Temp./ °C	μ_B
		Found	Calc			
$Fe(hqoH)_2 \cdot 3H_2O$	231.5	32.0	32.4	100 - 120	190	3.61
$Fe(3\text{-}MehqoH)_2 \cdot 2H_2O$	157.2	15.0	14.3	105 - 120	160	3.94
$Fe(6\text{-}MehqoH)_2 \cdot 2H_2O$	223.5	19.0	20.3	105 - 115	155	3.77

Fig. 3.3 Mössbauer Spectrum of $Fe(hqoH)_2 \cdot 3H_2O$ at 20 °C

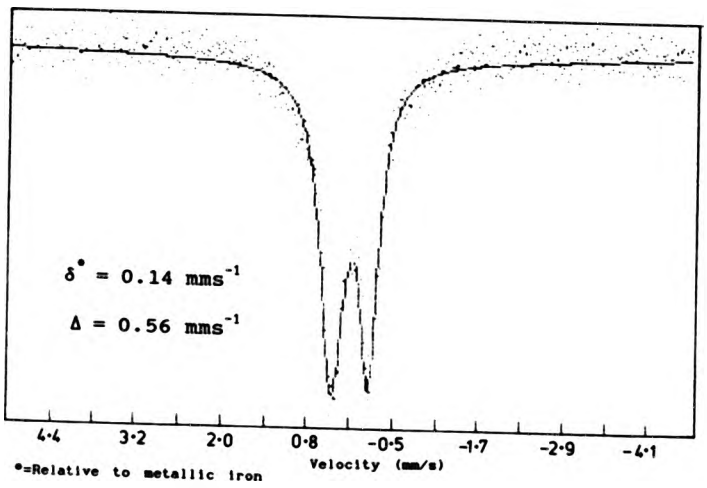


Fig. 3.4 Mössbauer Spectrum of $Fe(hqoH)_2 \cdot 3H_2O$ at -196 °C

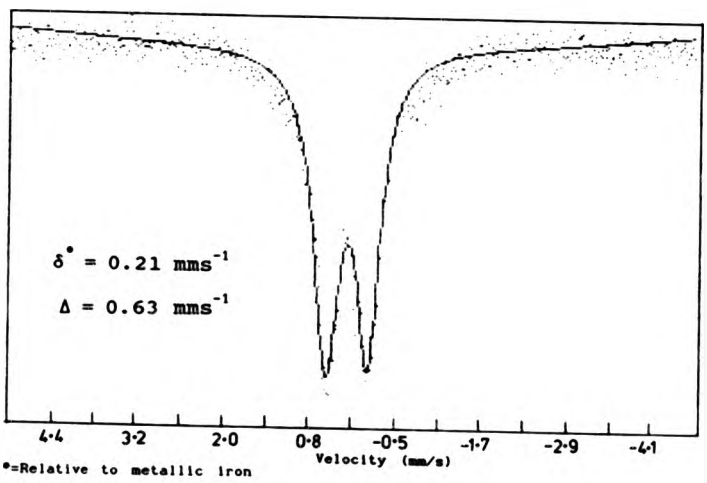
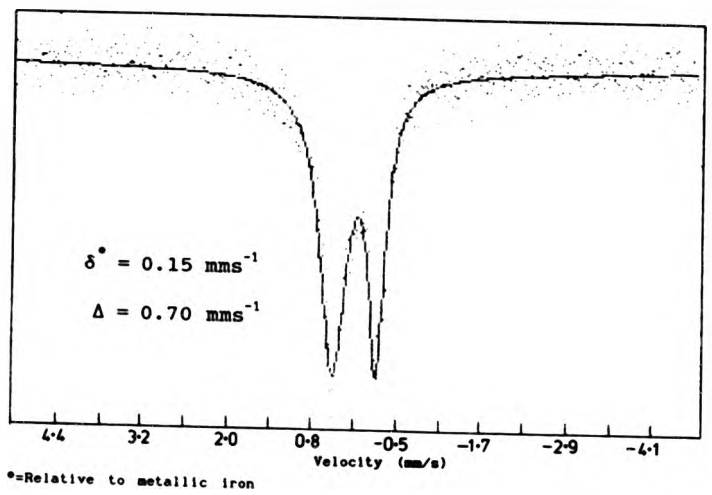
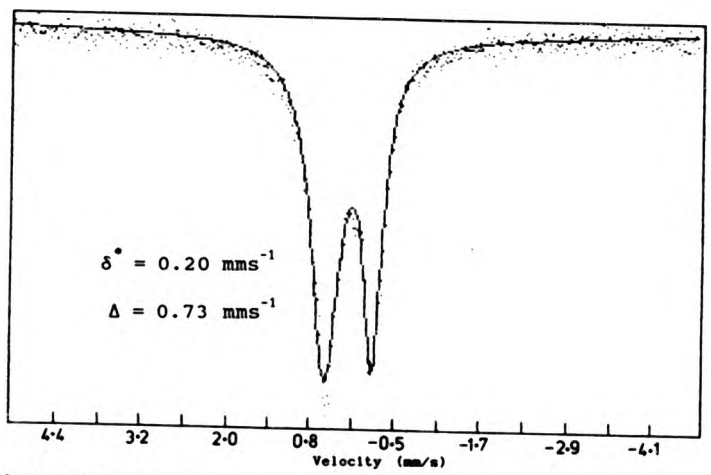


Fig. 3.5 Mössbauer Spectrum of $Fe(3\text{-MehqoH})_2 \cdot 2H_2O$ at 20 °C



*=Relative to metallic iron

Fig. 3.6 Mössbauer Spectrum of $Fe(3\text{-MehqoH})_2 \cdot 2H_2O$ at -196 °C



*=Relative to metallic iron

Fig. 3.7 Mössbauer Spectrum of $Fe(6\text{-MehqoH})_2 \cdot 2H_2O$ at 20 °C

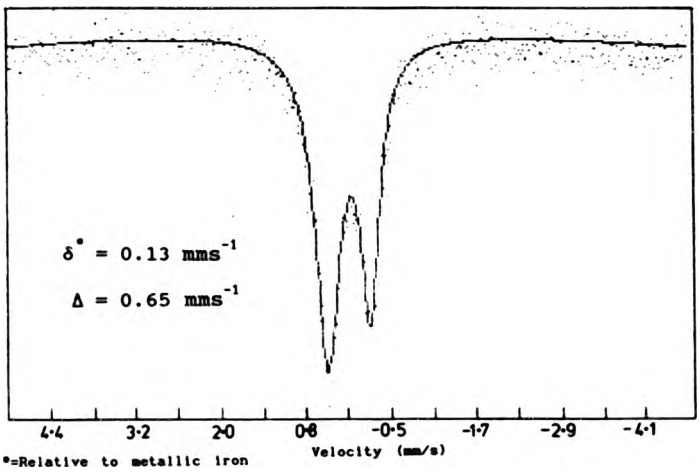
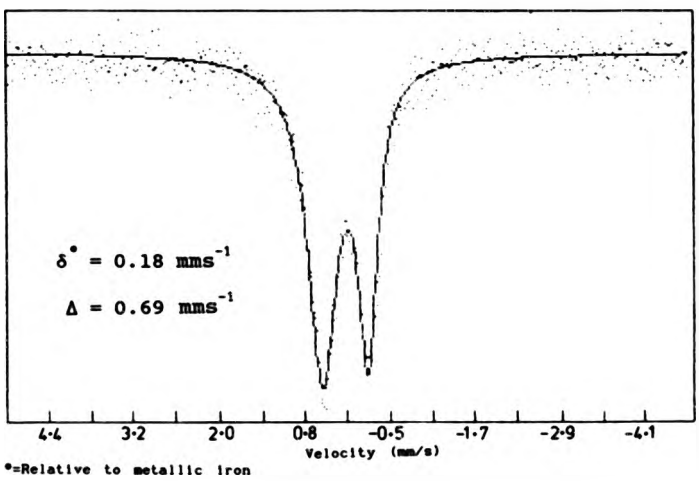


Fig. 3.8 Mössbauer Spectrum of $Fe(6\text{-MehqoH})_2 \cdot 2H_2O$ at -196 °C



lower than expected for high spin iron(II). However, they preclude the possibility of low spin iron(II). The Mössbauer spectra (Figs. 3.3 - 3.8) of all three compounds show a single pair of quadrupole split peaks indicating that for any given compound there is only one type of iron site.

Previously low magnetic moments were observed for the complexes $Fe(1\text{-nqo})_2$, $Fe(2\text{-nqo})_2$ and $Fe(5\text{-Meqo})_2$ which were also green in colour.[10,13,23] However, the Mossbauer spectra of these complexes contained two doublets (Table 3.4). During the course of the study the reaction between 1,2-naphthoquinone 1-oximes and ammonium iron(II) sulphate was repeated several times.[10,13] In each case the composition of the product closely corresponded to $Fe(1\text{-nqo})_2$. The room temperature magnetic moments varied from sample to sample, but each product reacted with pyridine to give the diamagnetic iron(II) complex Fe(1-nqo)·2py. All samples of the pyridine adduct lost pyridine quantitatively on heating at *ca.* 0.1 mm/120 °C to give residues of composition $Fe(1\text{-nqo})_2$ which were similar to the product of the reaction between ammonium iron(II) sulphate and 1,2-naphthoquinone 1-oxime. Again the magnetic properties of the residues varied from sample to sample, the Mössbauer spectra showed two doublets, and each sample reacted readily with pyridine to reform the

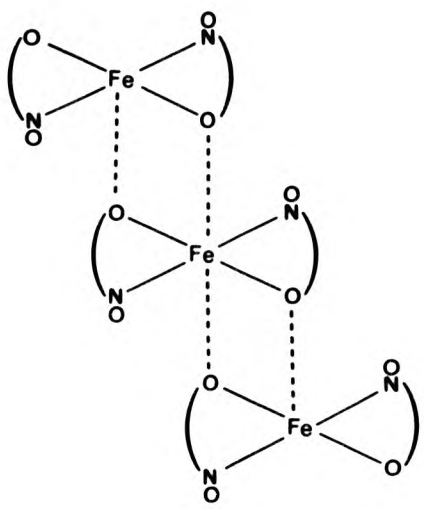
complex $Fe(1\text{-}nqo)_2 \cdot 2py$.

These observations were explained in terms of an oligomeric structure for $Fe(1\text{-}nqo)_2$ (Fig. 3.9).[23] The outer pair of peaks in the Mössbauer spectrum of this complex was assigned to the terminal 5 co-ordinated high spin iron(II) and the inner pair to the six co-ordinated low spin iron(II). The variation of the magnetic moments from sample to sample was explained as due to the differences in the average chain length of the oligomer. Similar observations and suggestions were made for the products $Fe(2\text{-}nqo)_2$ and $Fe(5\text{-}MeOqo)_2$ arising from the reaction of iron(II) with 1,2-naphthoquinone 2-oxime and 5-methoxy-1,2-benzoquinone 2-oxime respectively.[23]

Table 3.4 Room Temperature Mössbauer Parameters and Magnetic Moments of $Fe(qo)_2$ Complexes

Complex	δ^*/mm s^{-1}	Δ/mm s^{-1}	μ_B	Ref.
$Fe(1\text{-}nqo)_2$	0.08	0.79	3.08	13
	1.22	4.00		
$Fe(2\text{-}nqo)_2$	0.05	0.71	3.04	13
	1.22	3.99		
$Fe(5\text{-}MeOqo)_2$	0.12	0.60	2.78	10
	1.05	3.74		

* Relative to metallic iron



O NO = qo⁻

Fig. 3.9

From the above it is evident that the complexes prepared during this study must have different structures from those proposed for $Fe(1\text{-nqo})_2$, $Fe(2\text{-nqo})_2$ and $Fe(5\text{-MeOqo})_2$. Further evidence for this is provided by the behaviour of $Fe(hqoH)_2 \cdot 3H_2O$, $Fe(3\text{-}MehqoH)_2 \cdot 2H_2O$ and $Fe(6\text{-}MehqoH)_2 \cdot 2H_2O$ towards pyridine which is different from that established for $Fe(1\text{-nqo})_2$, $Fe(2\text{-nqo})_2$ and $Fe(5\text{-MeOqo})_2$. None of the complexes under investigation afforded a pyridine adduct of type $Fe(qo)_2 \cdot 2py$ on refluxing with pyridine. In all cases the reaction with pyridine led to the decomposition of the complexes.

The room temperature magnetic moments of $Fe(hqoH)_2 \cdot 3H_2O$, $Fe(3\text{-}MehqoH)_2 \cdot 2H_2O$ and $Fe(6\text{-}MehqoH)_2 \cdot 2H_2O$ are too low for the iron to exist as high spin iron(II). However $^5T_2$-$^1A_1$ spin crossover or antiferromagnetic coupling of a high spin iron(II) system can reduce the room temperature magnetic moment. These possibilities are precluded by the Mossbauer results as discussed below.

Iron(II) complexes normally have either the $^5T_2$ (S = 2, high spin) or the $^1A_1$ (S = 0, low spin) configurations. If the energies of these two states are similar then both forms can coexist. A magnetic moment in between the values expected for high spin (4.9 - 5.3 BM) and low spin (0 BM) will be observed at the vicinity of the crossover temperature. When the crossover temperature coincides with the temperature chosen for magnetic moment measurements then, the magnetic moment will be low but the Mossbauer spectra at the same temperature should show iron sites due to both spin states. However no such effect is observed for the complexes under discussion. Hence their abnormal magnetic moments cannot be due to $^5T_2$-$^1A_1$ spin crossover.

Antiferromagnetic coupling of a high spin iron(II) species is also unlikely since the Mossbauer spectra do not show such a coupling at the temperatures examined. Furthermore, the Mossbauer parameters do not correspond

to those expected for high spin iron(II) compounds.

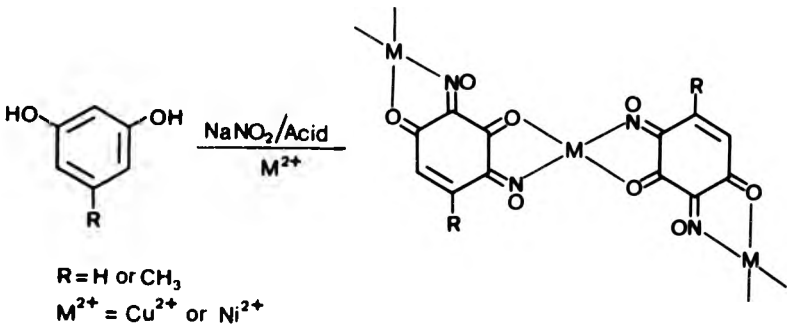
The most likely explanation for the observed magnetic moments and Mössbauer spectra is that these compounds are iron(II) complexes in which the iron(II) exists in the S = 1 state.

When the symmetry is close to octahedral iron(II) complexes adopt either S = 2 or S = 0 electronic configurations. However, when the symmetry is low the intermediate S = 1 state can be adopted[29] and has been observed in complexes such as $[Fe(L_2)F_2 \cdot 4H_2O]$ and $[FeL_2(ox) \cdot 5H_2O]$ (L = 1,10-phenanthroline and oxH_2 = oxalic acid).[30-32] Significantly the room temperature magnetic moments of such complexes[32] (*ca.* 3.8 - 4.2 BM at 293 K) are very similar to those found for the complexes under discussion.

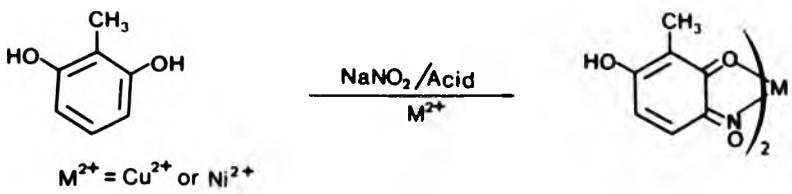
3.6 Reaction of 3-Hydroxyphenols with Sodium Nitrite/Acid in the Presence of Ammonium Iron(II) Sulphate

The synthesis of iron complexes derived form 5-hydroxy-1,2-benzoquinone mono-oximes was also attempted using the nitrosation method. Previously it has been established that 3-hydroxyphenol and 3-hydroxy-5-methylphenol undergo di-nitrosation in the

presence of nickel(II) or copper(II) salts.[33,34] In both cases, polymeric materials of type $M(dnr)\cdot xH_2O$ ($M = Ni^{2+}$ or Cu^{2+}) are formed (Reaction 3.6). However, in the case of 3-hydroxy-2-methylphenol mono-nitrosation occurs and complexes of type $M(6\text{-Mehqo})_2\cdot xH_2O$ ($M = Ni^{2+}$ or Cu^{2+}) are obtained (Reaction 3.7). In all cases the ligand could be liberated by acidification of the complex.



Reaction 3.6



Reaction 3.7

The nitrosation of 3-hydroxyphenols in the presence of ammonium iron(II) sulphate afforded highly insoluble

black solids whose i.r. spectra were ill-defined. In all cases elemental analysis of the solids indicated the presence of both iron and sodium, but no meaningful formulations could be deduced. Thermal gravimetric analysis showed these compounds to be thermally unstable with a decomposition temperature of *ca.* 80 °C. Attempts to isolate the ligands by acidification of the complexes failed.

3.7 Reaction of N-Acetyl-3-aminophenol with Sodium Nitrite/Acid in the Presence of Ammonium Iron(II) Sulphate

In contrast to the behaviour of the 3-hydroxyphenols, N-acetyl-3-aminophenol reacted smoothly with sodium nitrite/acid in the presence of ammonium iron(II) sulphate to give two iron complexes and an organic product. Thus when N-acetyl-3-aminophenol was treated with sodium nitrite/acid in the presence of ammonium iron(II) sulphate a brown mixture resulted which changed into green after *ca.* 1-2 h. This crude green product contained three components, one yellow and two green, which were separated by column chromatography. The yellow product which was eluted with ethylacetate was identified as N-acetyl-3-amino-1,4-benzoquinone 4-oxime. The first green product eluted with methanol was the major product and was characterised as sodium

tris(N-acetyl-3-amino-1,2-benzoquinone 2-oximato)-ferrate(II) tetrahydrate. The second green component was eluted with methanol after leaving the column filled with pyridine for 12 h. This component was characterised as bis(N-acetyl-3-amino-1,2-benzoquinone 2-oximato)-iron(II) dipyridine. On the basis of the characteristic colours previously reported for iron complexes of 1,2-quinone mono-oximes, i.e. brown for iron(III) and green for iron(II),[7,10] it is reasonable to assume that the above reaction initially leads, at least in part to the formation of iron(III) complexes which subsequently change to iron(II) complexes. As mentioned in Section 3.4, such reduction involving complexes of type $Fe(qo)_3$ has been observed earlier and lead either to complexes of types $Fe(qo)_2$ or $M[Fe(qo)_3]$.[10]

Both complexes, $Na[Fe(N\text{-}Acqo)_3]\cdot 4H_2O$ and $Fe(N\text{-}Acqo)_2\cdot 2py$ obtained from this reaction were diamagnetic. This agrees with previous results obtained for similar complexes. The n.m.r. spectra and the assignments for N-Acetyl-3-amino-1,4-benzoquinone 4-oxime and $Na[Fe(N\text{-}Acqo)_3]\cdot 4H_2O$ are shown in Figs. 3.10 - 3.11. The room temperature Mossbauer spectra of $Na[Fe(N\text{-}Acqo)_3]\cdot 4H_2O$ and $Fe(N\text{-}Acqo)_2\cdot 2py$ are shown in in Fig. 3.12 and Fig. 3.13 respectively. Mossbauer parameters for analogous iron(II) complexes obtained in previous studies are given in Table 3.5 and are similar

Fig. 3.10 ^{1}H Nuclear Magnetic Resonance Spectrum of N-Acetyl-3-amino-1,4-benzoquinone 4-oxime in d_6-DMSO

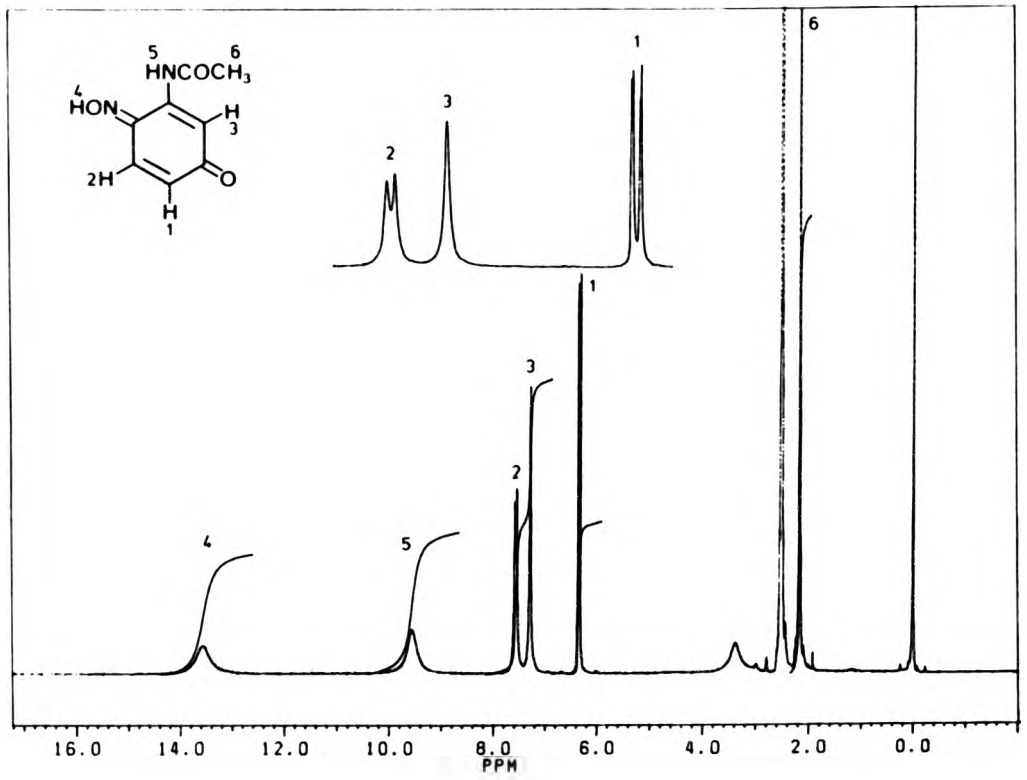


Fig. 3.11 ^{1}H Nuclear Magnetic Resonance Spectrum of $Na[Fe(N\text{-}Acgo)_3]\cdot 4H_2O$ in d_6-DMSO

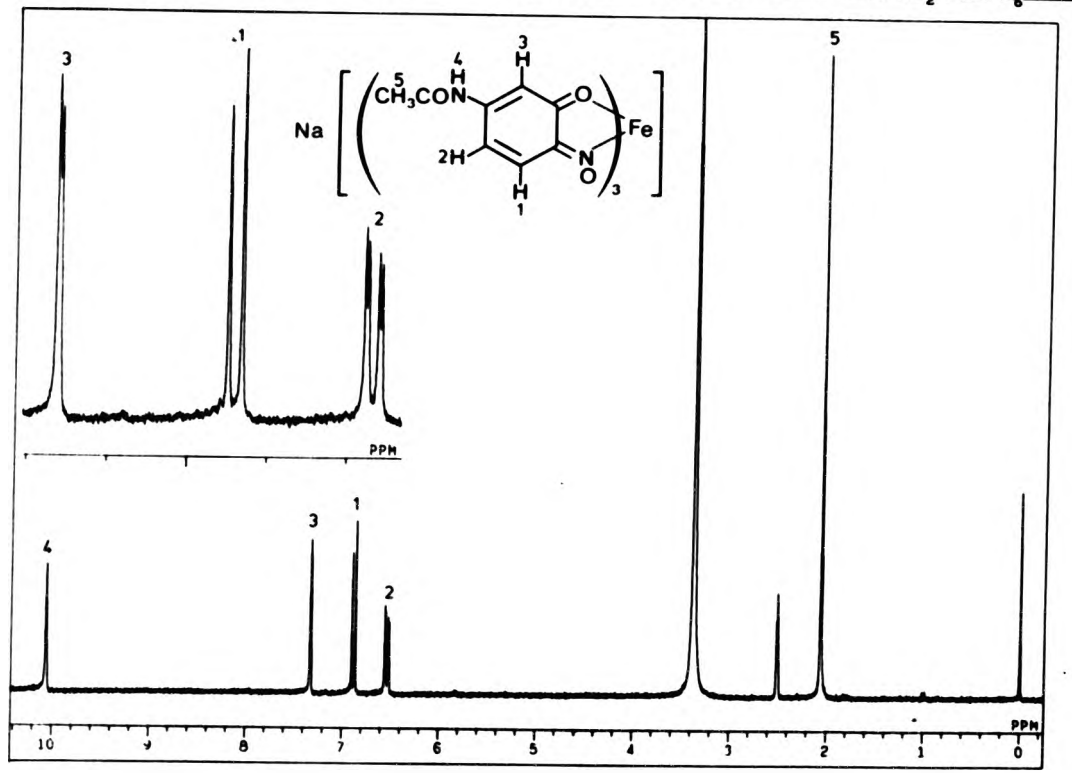


Table 3.5 Mössbauer Parameters of M[Fe(qo)$_3$] (M = Na or K) and Fe(qo)$_2$·py Complexes

Complex	Temp./K	δ^{*}/mm s^{-1}	Δ/mm s^{-1}	Reference
Na[Fe(1-nqo)$_3$]	300	0.14	0.82	11
	77	0.23	0.87	
Na[Fe(3,4-Meqo)$_3$]	77	0.08†	0.70	10
Na[Fe(3,4-Meqo)$_3$]·(CH$_3$)$_2$C=O	300	0.13†	0.68	10
K[Fe(3,4-Meqo)$_3$]	77	0.10†	0.69	10
K[Fe(3,4-Meqo)$_3$]·(CH$_3$)$_2$C=O	300	0.05†	0.65	10
	77	0.14†	0.70	
Na[Fe(4-Meqo)$_3$]	293	0.29	0.85	27
K[Fe(4-Meqo)$_3$]	293	0.29	0.76	27
Fe(1-nqo)$_2$·2py	293	0.19	0.92	12
Fe(2-nqo)$_2$·2py	293	0.20	0.88	12
Fe(5-MeOqo)$_2$·2py	293	0.10†	0.65	10

* Relative to metallic iron

† In the original reference values reported were relative to stainless steel. The figure was converted by adding -0.161 mm/s to the original value.

Fig. 3.12 Mössbauer Spectrum of $Na[Fe(N\text{-}Acgo)_4]\cdot 4H_2O$ at 20 °C

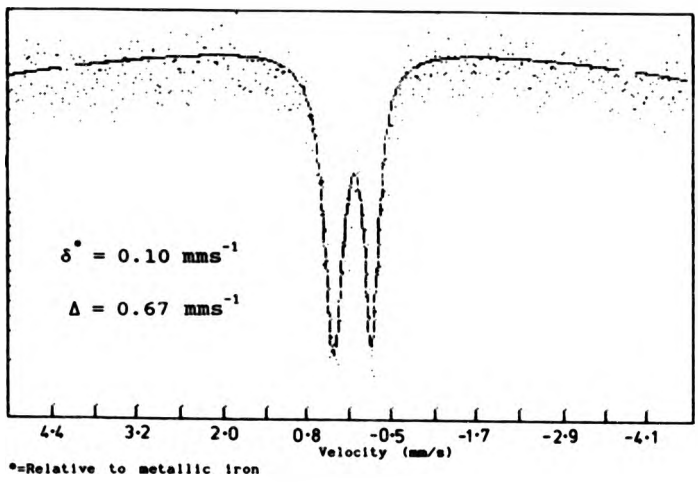
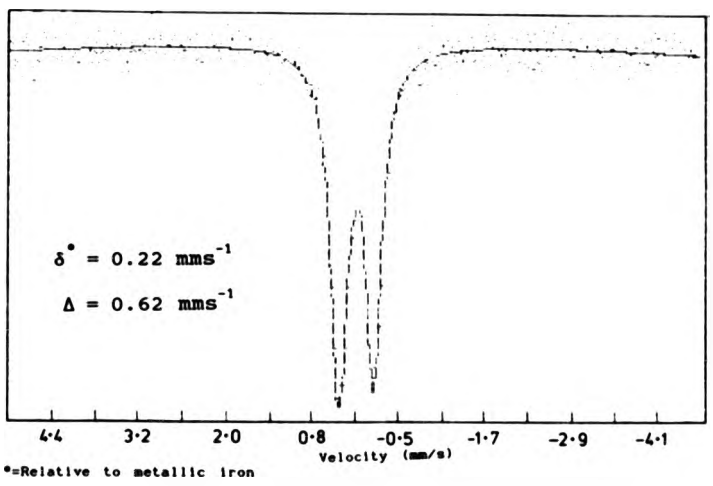
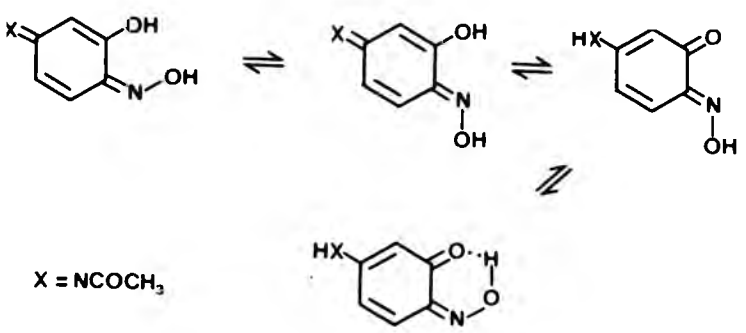


Fig. 3.13 Mössbauer Spectrum of $Fe(N\text{-}Acgo)_2\cdot 2py$ at 20 °C



to those obtained during the present study for the above two complexes.

As in the case of 3-hydroxy-1,2-benzoquinone mono-oximes, N-acetyl-3-amino-1,2-benzoquinone 2-oxime can also exist in the 1,2- or 1,4- forms (Scheme 3.2). The structure of the complex and especially the structure of the ligand in the complex is important with regard to the stability and other characteristics of the complex. This is because of the different ligand field effects of the chelated 1,2- and 1,4- forms. As noted above the magnetic moment, Mossbauer parameters and the colour of the iron(II) complexes of N-acetyl-3-amino-1,2-benzoquinone 2-oxime agree with those previously observed for iron(II) complexes of 1,2-quinone mono-oximes such as 1,2-naphthoquinone 2-oxime which has no corresponding 1,4-form. Hence, it is likely that N-acetyl-3-amino-1,2-benzoquinone 2-oxime also exist in the 1,2-form in its iron complexes.



Scheme 3.2

3.8 References

1 W. H. Shipman, S. C. Foti, and W. Simon, *Anal. Chem.*, 1955, 27, 1240.

2 K. Toei, S. Motomizu and T. Korenaga, *Analyst*, 1975, 100, 629.

3 W. Federkiel, H. Pfitzer, and H. Baumann, U.S. 2, 726, 920 Dec. 13. 1955.
Chem. Abs.; 50:7471f

4 J. Eisele and W. Federkiel, Ger. 936, 503, Dec. 15, 1955.
Chem. Abs. 52:19154a.

5 S. Candeloro, D. Grdenic, N. Taylor, B. Thompson, M. Viswamitra, and D. C. Hodgkin, *Nature*, 1969, 224, 589.

6 C. Yang and J. Leog, *J. Bacteriol.*, 1982, 149, 381.

7 J. Charalambous, M. J. Frazer and R. Sims, *Inorg. Chim. Acta*, 1976, 18, 247.

8 M. Takada and H. Sano, *Bull. Chem. Soc. Jpn.*, 1974, 47, 2341.

9 S. Gurrieri and G. Siracusa, *Inorg. Chim. Acta.*, 1971, 5, 650.

10 M. H. Johri, Ph.D. Thesis, 1979, The Polytechnic of North London.

11 R. Sims, Ph.D. Thesis, 1974, University of London.

12 J. S. Morgan, Ph.D. Thesis, 1985, The Polytechnic of North London.

13 J. Charalambous, L. I. B. Haines, J. S. Morgan, D. S. Peat, M. J. M. Campbell, and J. Bailey, *Polyhedron*, 1987, 6, 1027.

14 M. McPartlin, *Inorg. Nucl. Chem. Lett.*, 1973, 9, 1207.

15 P. W. Carreck, J. Charalambous, M. J. Kensett, M. McPartlin, and R. Sims, *Inorg. Nucl. Chem. Lett.*, 1974, 10, 749.

16 R. Graziani, U. Casellato, P. A. Vigato, S. Tamburini, and M. Vidali, *J. Chem. Soc., Dalton Trans.*, 1983, 697.

17 J. Charalambous, K. Henrick, Y. Musa, R. G. Rees, and R. N. Whiteley, *Polyheron*, 1987, 6, 1509.

18 L. L. Merritt Jr, C. Guare, and A. E. Lessor Jr, *Acta Crystallogr.*, 1956, 9, 253.

19 D. Hall, A. J. McKinnon, and T. N. Waters, *J. Chem. Soc.*, 1965, 425.

20 F. Jaccard, D. Monnier, and P. E. Wenger, *Helv. Chim. Acta.*, 1950, 33, 1458.

21 Y. A. Barbalat and V. M. Pashkova, *Vestn. Mosk. Univ., Khim.*, 1972, 13, 78.
Chem. Abs. 77:11742j.

22 S. Lal and S. N. Srivastava, *J. Chem. Educ.*, 1967, 44, 482.

23 D. K. Allen, J. Charalambous, M. H. Johri, R. Sims, *Inorg. Chim. Acta.*, 1978, 29, L235.

24 H. H. Hodgson and W. E. Batty, *J. Chem. Soc.*, 1935, 1617.

25 N. F. Mody and C. M. Desai, *Acta Ciencia Indica*, 1977, **4**, 310.

26 W. M. Shutie, Ph.D. Thesis, 1981, The Polytechnic of North London.

27 N. A. Nasset, M. Phil. Thesis, 1978, The Polytechnic of North London.

28 D. Baluch, Ph.D. Thesis, 1987, The Polytechnic of North London.

29 N. N. Greenwood and T. C. Gibb, 'Mossbauer Spectroscopy,' Chapman and Hall Ltd., London, 1971.

30 B. W. Dale, R. J. P. Williams, C. E. Johnson, and T. L. Thorp, *J. Chem. Phys.*, 1968, **49**, 3441.

31 B. W. Dale, R. J. P. Williams, P. R. Edwards and C. E. Johnson, *J. Chem. Phys.*, 1968, **49**, 3445.

32 E. König and K. Madeja, *Inorg. Chem.*, 1968, **7**, 1848.

33 R. G. Cawthorne, J. Charalambous, W. M. Shutie, F. B. Taylor, and A. Betts, *Inorg. Chim. Acta*, 1979, **37**, 245.

34 J. Charalambous, C. W. Newnham, F. B. Taylor, M. J. Whelehan, K. W. P. White, and I. G. H. Wilson, *Polyhedron*, 1987, **6**, 1033.

CHAPTER 4

THE IN-VIVO STUDY OF 1,2-BENZOQUINONE MONO-OXIMES AS IRON CHELATORS

4.1 Introduction

Generally, a total of 26 elements are believed to be essential for animal life.[1] The elements carbon, hydrogen, oxygen, nitrogen, sulphur, calcium, phosphorus, potassium, sodium, chlorine and magnesium are classified as major elements as they are required in large amounts. The remaining 15 elements (iron, iodine, copper, manganese, zinc, cobalt, molybdenum, selenium, chromium, nickel, tin, silicon, vanadium, arsenic and fluorine) are classified as trace elements. However the necessity and/or physiological function of the last 6 elements has not been identified with any great certainty. Out of the 15 trace elements 10 are metals. With the exception of sodium, potassium, calcium, magnesium and tin, all the other essential metals are transition metals.

The amount of essential metals within living systems is controlled by two parameters, (i) external availability and (ii) internal physiological control mechanisms. The control mechanisms have the capability of maintaining the amounts of metals in the living system to within fine limits. If as a result of the diet or other external function, or as a result of malfunction of a control mechanism, the concentration of an essential

metal becomes abnormal, then the well-being of the organism is affected.

Metal Deficiency Disorders

In man, the most common metal deficiency is probably that of iron deficiency anaemia. It has been estimated that in developed countries, the incidence of iron deficiency in children under 3 years and women during child bearing years is between 20% and 30%.[2] In developing countries, this figure is at least doubled as a result of poor diet and blood loss due to intestinal parasitism. Clinical signs associated with anaemia are paleness, lethargy, decreased growth, behavioural changes, and an increase in vulnerability to infections. Iron deficiency anaemia can be easily corrected in most individuals by oral administration of iron(II) sulphate, sometimes together with ascorbic acid to aid absorption.

Deficiency disorders related to manganese, copper and zinc are also known. The occurrence of manganese and copper deficiency is rather rare.[1] Zinc deficiency disorders are however quite common and are widespread both in developed and the developing countries. Deficiency can result from either dietary factors that reduce zinc absorption, or as a result of the rare inherited disorder acrodermatitis enteropathica,[3] which causes a partial block of dietary zinc absorption. Zinc deficiency has been associated with various clinical features including from disturbances of normal growth

patterns, skin rashes and abnormal sensory perception to behavioural abnormalities.

Metal Over-load Disorders

The concentration of trace metal ions in the body can increase as a result of: (i) poisoning, (ii) breakdown of the regulatory mechanism, and (iii) side effect of certain medical treatments. Such increases can lead to disorders which are referred to as metal over-load disorders.

Metal poisoning may arise because of dietary factors, pollution or as a result of exposure to metal compounds. A well known example of this type of metal poisoning has been observed in the African Bantu,[4] where a high incidence of iron over-load especially in adult males results from the preparation of food and alcoholic drinks in iron containers. Alcoholics can also suffer from mild degrees of iron over-load. This is because of the iron content of some alcoholic drinks and because of the alcohol-stimulated absorption of iron. Lead and mercury are also known to cause poisoning as a result of consuming food or water contaminated with these metals. Lead poisoning can arise in localities where the drinking water is soft and the water supply pipes are made of lead.[5] A well documented case of mercury poisoning occurred in Minamata, Japan.[6] This resulted from mercury released into Minamata bay from an industrial plant. The metal was concentrated along the

food chain, and on eating the contaminated fish humans developed mercury poisoning.

Increase in metal concentration due to the breakdown of a regulatory mechanism occurs for example, in patients suffering from Wilson's disease.[7] In Wilson's disease the natural mechanism for the control of copper concentrations is disrupted, resulting in the accumulation of free copper ions in the liver, brain and kidneys. Up to one hundred times greater than average concentrations of copper have been observed in some patients. The symptoms of Wilson's disease include hepatic cirrhosis, lack of co-ordination, severe tremors, and progressive mental deterioration. Another disorder that falls within this category is primary or idiopathic haemochromatosis.[4] This is a genetically determined disease of iron metabolism which results in a increase in iron absorption. Patients suffering from the disease have a positive iron balance in the order of 2 mg/day. This results in the accumulation of 20 to 30 g of iron during 40 years prior to occurrence of symptomatic disease in later life. This includes cirrhosis of the liver, pituitary, adrenal, and thyroid failure, and eventually cardiac failure.

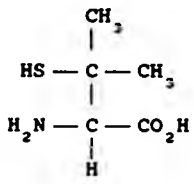
Occurrence of metal over-load as a secondary effect of medical treatment is only applicable to aluminium and iron. Over-load involving aluminium and iron occurs in patients undergoing long term dialysis treatment[8] and

those receiving multiple blood transfusions[9] respectively.

Multiple blood transfusions are needed in a variety of inherited and acquired forms of anaemia, of particular importance are the haemoglobinopathies, including thalassaemia and to a lesser extent sickle cell anaemia.[10] In man, there is no physiological system for iron excretion.[11] Iron balance is maintained by regulation of iron absorption. Each unit of transfused blood contain about 200 mg of iron and hence, the body iron content (normally about 4 g in an adult) is increased with each transfusion.

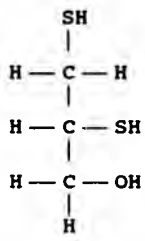
Generally the only method of treating metal over-load is by chelation therapy. This involves the administering of a chelating agent which binds with the harmful metal and the metal complex is then excreted from the body in urine and/or faeces. For example, in the treatment of copper poisoning in Wilson's disease, the chelating agent D-penicillamine (Fig. 4.1a) is used.[7] Other examples of chelating agents are 2,3-dimercaptopropanol (British Anti-Lewisite, BAL) (Fig. 4.1b) and ethylenediaminetetraacetic acid (EDTA) (Fig.4.1c) and its disodiumcalcium(II) complex. BAL has been used for the treatment of poisoning by arsenic, mercury, cadmium, gold, thallium and bismuth, and EDTA and its calcium complex for the treatment of lead poisoning. The use of the calcium complex of EDTA is preferred to counter the

effect of calcium removal by the acid.[7]



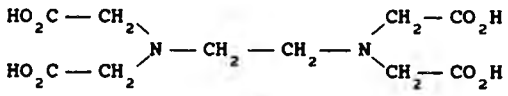
a

D-Penicillamine



b

2,3-Dimercaptopropanol

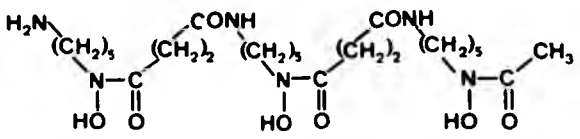


c

Ethylenediaminetetraacetic acid

Fig. 4.1

In the case of iron over-load arising due to primary haemochromatosis an alternative method to chelation therapy is available. The accepted treatment for patients suffering from this disease is venesection.[12] However for thalassaemic patients venesection is not practical because of the inherent anaemia. Hence in these patients the only method of removing iron is by chelation therapy. At present the main drug used for iron chelation therapy is desferrioxamine (Fig. 4.2).[9]



Desferrioxamine

Fig. 4.2

Thalassaemia Syndromes

Thalassaemias are an inherited group of disorders of haemoglobin, which are characterised by a reduced rate of synthesis of one or more of the globin chains of haemoglobin.[9] This leads to a reduction in the amount of haemoglobin synthesized as well as to unbalanced globin chain synthesis, with the resultant precipitation of those chains which are produced in excess. Thalassaemias can be classified according to which particular globin chain is synthesized ineffectively, i.e. into α, β, $\delta\beta$, δ, and $\gamma\delta\beta$ thalassaemias. Additionally they can also be classified according to their clinical phenotypes. Usually the clinical and molecular classifications are combined. Thus homozygues β-thalassaemia usually gives rise to a severe transfusion dependent form of β-thalassaemia called β-thalassaemia major, but a proportion of homozygotes have a less severe but symptomatic form called β-thalassaemia intermedia. The asymptomatic heterozygous carrier state is called

β-thalassaemia trait.[9]

Thalassaemia has a world-wide distribution. It is especially common in the Mediterranean region, parts of the Middle-East, India, Pakistan, and in South-East Asia, and particularly Thailand. The reason for the high incidence of β-thalassaemia genes in some populations is not fully understood, although there is some evidence to show that carriers are more resistant to *Plasmodium falciparum* malaria infection.[10] The percentage of the population who are carriers of thalassaemia vary from country to country. It is estimated that world-wide about 100,000 severely affected homozygotes are born each year,[13] and thalassaemia is a major public health problem in the Mediterranean regions and particularly in South-East Asia. Application of molecular biological techniques to antenatal diagnosis combined with antenatal screening and counselling is leading to a dramatic decrease in new homozygote births in several European countries. However, large numbers of patients will continue to require regular blood transfusions with inevitable increase in their iron load.

4.2 Chelators for the Treatment of Iron Over-load

Before proceeding further it should be noted that ideally, a chelator used in the treatment of metal over-load should have the following properties:

(i) low toxicity,

(ii) chemical stability,

(iii) ability to form a stable, non-toxic complex with the target metal which can be excreted rapidly in urine and/or faeces,

(iv) activity after oral administration,

(v) specificity for the target metal, i.e. must not cause the excretion of other essential metals,

(vi) ability to penetrate into the tissue deposits of the target metal.

Desferrioxamine, the main drug used at the present time for the treatment of iron over-load was introduced in 1960.[14] It is a siderophore produced by the yeast *Streptomyces pilosus*. Desferrioxamine was first used in the treatment of acute iron toxicity that results from accidental ingestion of iron tablets. In the 1970's it was shown that intra-muscular injections of this drug slows down iron accumulation in thalassaemic patients.[15] It was also found that administration of ascorbic acid to these patients could substantially increase the quantity of urinary iron excretion caused by desferrioxamine.[16] It was also established that for maximal iron excretion, prolonged intra-venous infusion of desferrioxamine is necessary. However, this technique was found to be impractical on a daily basis and a method of subcutaneous infusion by use of a micro-pump was introduced.[17]

With a few exceptions, only minimal toxicity has been

observed with desferrioxamine. Minor side effects that have been observed include abdominal pain, lowering of blood sugar, diarrhoea and fever. In some instances however, particularly when large doses of desferrioxamine have been infused into patients with only modest degrees of iron over-load, serious ocular and auditory toxicity have been observed.[18-20]

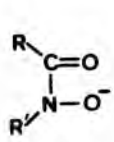
There are two major disadvantages to the use of desferrioxamine. These are (i) ineffectiveness of the drug when given orally and (ii) high expense of the drug. The need for daily subcutaneous infusions leads to high non-compliance, especially amongst teenagers. Efforts to modify desferrioxamine so as to make it orally active have been unsuccessful. The high cost of the drug is also a problem, especially in developing countries. For example, it has been estimated on the basis of 1983 prices that to supply the drug to 300 patients in the U.K. would cost $ 1.6 million for the purchase of the drug alone.[21] However additional expenses for micro-pumps, syringes and other disposables increase the cost substantially.

Another possible disadvantage of desferrioxamine relates to its specificity towards iron. As noted earlier ideally, a chelating agent used in the treatment of iron over-load should only cause the excretion of iron since excretion of other biologically essential metals can lead to harmful effects. In the case of desferrioxamine

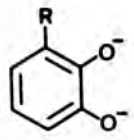
there have been contradictory reports about its effect on the excretion of biologically important metals other than iron.[22-25] It has been suggested that the ocular toxicity of desferrioxamine may arise as a result of chelation of copper.[18]

Because of the disadvantages of desferrioxamine there is a need for an alternative drug. A new drug for the treatment of iron over-load should comply with the general criteria listed earlier and in particular should be: (i) orally active, (ii) non-toxic, and (iii) cheap.

Several research groups are currently involved in the synthesis and study of alternative drugs for the treatment of iron over-load. Most of the compounds studied are modelled on naturally occurring siderophores but other simple chelating agents have also been investigated. Siderophores are iron chelators excreted by microbes under conditions of iron deficiency.[26] The siderophores have been developed by micro-organisms to counteract the high insolubility of iron hydroxide ($K_{sp} \approx 10^{-38}$) at physiological pH. The micro-organisms synthesize and excrete siderophores into the surrounding environment where they complex with iron. Various methods have been developed by micro-organisms to up-take these iron(III) siderophore complexes.[27]



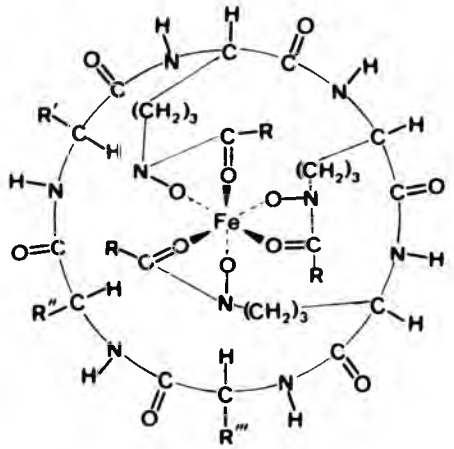
a



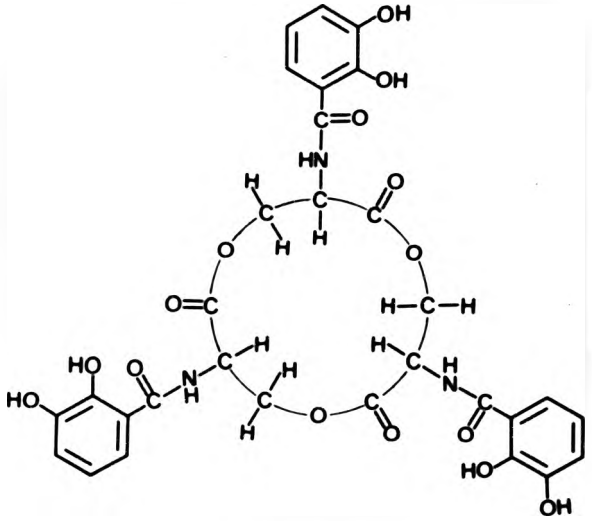
b

Fig. 4.3

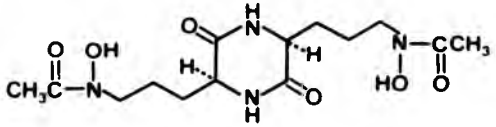
Although there are considerable variations in the siderophores, the donor atoms are usually oxygen belonging to the hydroxamate (Fig. 4.3a) or catecholate (Fig. 4.3b) groups.[7,26] However, there are several exceptions which utilise mixed forms of co-ordination.[26] Generally the catecholates are utilised by bacteria whereas the hydroxamates are utilised by higher organisms such as yeasts and fungi. Examples of different types of siderophores are illustrated in Fig. 4.4. Most of the naturally occurring hydroxamic acid siderophores have three hydroxamic groups per molecule and hence form neutral iron(III) complexes with an iron to ligand ratio of 1:1. Examples of this type are the ferrichromes and the ferrioxamines. Ferrichromes consist of a cyclic peptide moiety with three hydroxamic acid side chains, while in ferrioxamines the hydroxamic groups are part of a linear or cyclic molecule. Rhodotorulic acid is also a hydroxamic acid siderophore. However this compound has two hydroxamic groups per molecule and forms 2:3 (metal:ligand) complexes with iron(III) at pH 7.[26] Examples of catecholate siderophores are itoic acid and enterobactin. Enterobactin forms a negatively charged 1:1 iron(III)



Ferrichromes

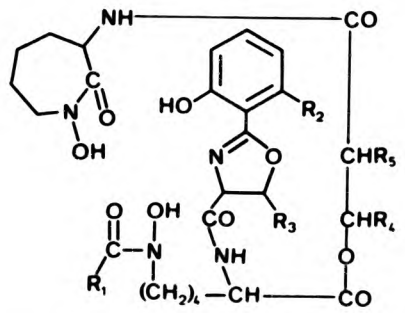


Enterobactin



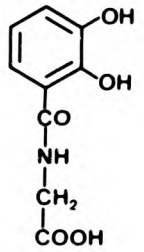
Rhodotorulic Acid

Fig. 4.4

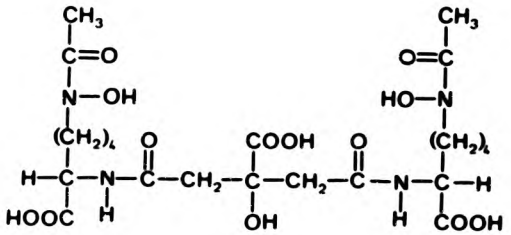


$R_1 = C_nH_m$, $R_2 = R_5 = CH_3$, $R_3 = C_2H_5$, $n \geq 12$

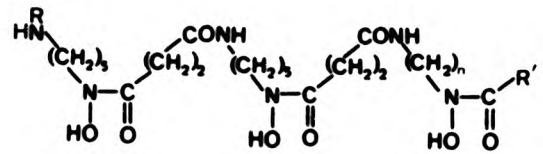
Mycobactin



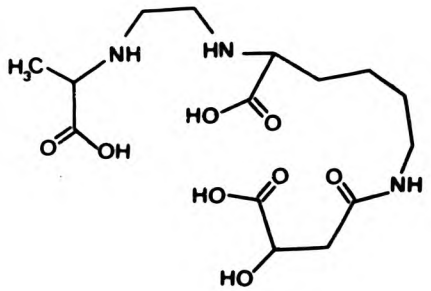
Itoic Acid



Aerobactin



Linear Desferrioxamines



Rhizobactin

Fig. 4.4 (cont.)

complex. Mycobactin and aerobactin are examples of siderophores which utilise mixed forms of co-ordination. Mycobactin co-ordinates via two hydroxamate groups, a phenolate group and an oxazoline nitrogen, whereas in aerobactin two hydroxamate groups and a α-hydroxycarboxylate group are utilised. Recently it has been shown that in rhizobactin (Fig. 4.4) a siderophore produced by the bacterium *Rhizobium meliloti* DM4, the metal is co-ordinated via the ethylenediaminedicarboxylate and α-hydroxycarboxylate moieties. Hence uniquely contain neither hydroxamate nor catecholate groups.[28]

To date, a considerable number of compounds have been tested for their suitability as orally active iron chelators. A large portion of the these compounds are either naturally occurring siderophores or synthetic siderophore analogues. A selection of chelators that have been tested on humans and/or animals are listed in Table 4.1. 2,3-Dimercaptopropanol (BAL), disodium N-hydroxyethyl(ethylenediaminetriacetate) (Na_2HEDTA), and ethylenediaminetriacetic acid (EDTA) were found to cause very little iron excretion.[23,29] In addition, for EDTA toxic effects were observed. The quantity of iron excreted as a result of intravenous infusion of ethylenediamine-N,N´-bis(2-hydroxyphenylglycine) (EHPG) was in excess of that required to maintain iron balance.[30,31] The only side effect reported in humans was polyurea,[31] however in animals other side effects

Table 4.1 A Selection of Chelators that have been Tested on Humans and /or Animals

Compound	Toxic Effects	Comments	Reference
Chelators tested on humans			
2,3-Dimercaptopropanol (BAL)	none reported	low excretion of Fe	23, 29
Disodium N-hydroxyethyl(ethylene-diaminetriacetate) (Na_2HEDTA)	none reported	low excretion of Fe	29
Ethylenediamine-N,N'-bis(2-hydroxy-phenylglycine) (EHPG)	polyurea (weight loss, anaemia, pulmonary and renal toxicities)[1]	orally inactive	30-32
Ethylenediaminetetraacetic acid (EDTA)	headache, fever, malaise, potential renal tubular damage	low excetion of Fe	23
Diethylenetriaminepentaacetic acid (DTPA)	diarrhea, vomiting, nausea, skin rash, coma, death	None selective for Fe. Increases the urinery excretin of Zn	31, 39, 40
N,N-Dihydroxyethylglycine (DHEG)	none reported	low excretion of Fe	29
5-Hydroxy-2-formylpyroxidine thiosemicarbazone (5-HP)	nausea, vomiting, muscle and abdominal pains		46
Cholylhydroxamic acid (CHA)	transient diarrhea		30
2,3-Dihydroxybenzoic acid (2,3-DHB)	gastrointestinal complaints	orally active rate of Fe excretion too low	33-36

Table 4.1 cont.

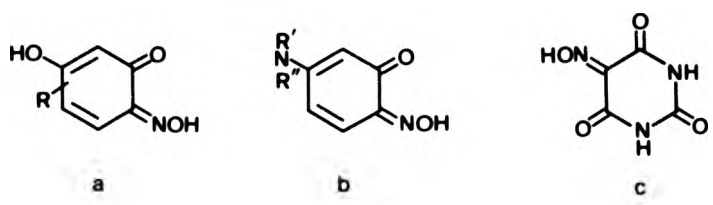
Compound	Toxic Effects	Comments	Reference
Chelators tested on humans			
Rhodotorulic acid (RA)	intense pain at site of injection	causes excretion of Zn	37, 38
1,2-Dimethyl-3-hydroxypyrid-4-one (CP 20 or L1)	agranulocytosis and thrombocytopenia observed in 1 patient	orally active under further investigation	41-45
Chelators tested only in animals			
Tropolone	variable LD_{50}	orally active	42
Pyridoxal isonicotinoyl hydrazone (PIH)	inhibits DNA synthesis	orally active	48-50
2,2-Dipyridyl	toxic, specific effects not reported	Fe(II) chelator	37
1,10-Phenanthroline	toxic, specific effects not reported	Fe(II) chelator	37

1=These toxic effects were observed in animals

have been observed.[30,32] 2.3-Dihydroxybenzoic acid (2,3-DHB), although orally active and of low toxicity causes too little iron excretion to have any effect on the rate of iron build-up in the liver.[33-36] In contrast rhodotorulic acid causes higher rates of iron excretion than desferrioxamine, however it has a number of serious disadvantages. These are increased urinary excretion of zinc, intense pain and swelling at the site of injection, and ineffectiveness when administered orally.[37,38] Similarly diethylenetriaminepentaacetic acid (DTPA) was also found to be orally inactive as well as being non-selective for iron.[31,39,40] This compound causes the excretion of calcium, magnesium, zinc, manganese and copper. Despite these side effects DTPA has been used in cases where the patients are allergic to desferrioxamine. Recently 1,2-dimethyl-3-hydroxypyrid-4-one has been tested as an iron chelator in man.[41] The compound was found to be orally active. However, toxic effects have been observed in animals and in man. Toxic effects observed in animals are hypersalivation, ocular toxicity and reduction in white cell count.[42-44] In addition, agranulocytosis and thrombocytopenia have been observed in a female patient undergoing treatment with this compound.[45] Other derivatives of 3-hydroxypyrid-4-ones which are less toxic (e.g. 1-ethyl-2-methyl-3-hydroxypyrid-4-one) are also under investigation.[43]

4.3 In-vivo Screening of Potential Iron Chelators

4.3.1 Types of Chelators Investigated

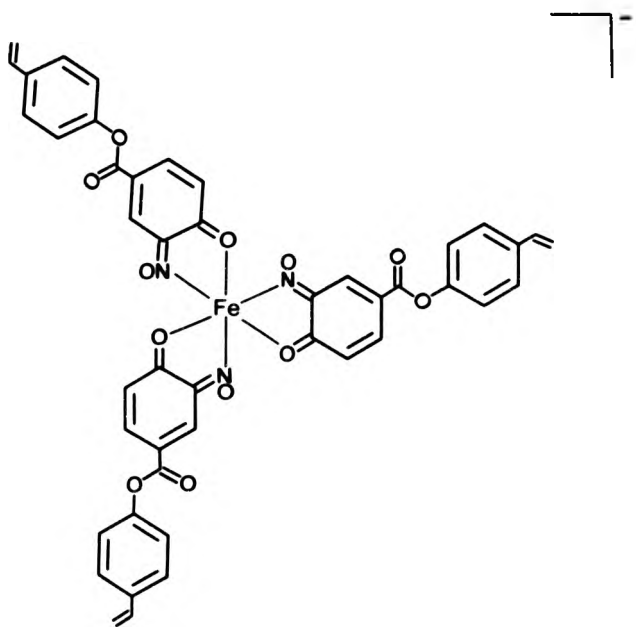


a b c

Fig. 4.5

In this study three related types of quinone mono-oximic chelators (Fig. 4.5a-c) were investigated with regard to their ability to remove iron *in-vivo*. These chelators were selected because such compounds are known to have a strong affinity for iron. A compound containing this type of chelator is found in the naturally occurring ferroverdin (Fig. 4.6). This is produced by *Streptomyces* sp. strain Wak. A-305.[51-53] A further reason for the choice of quinone mono-oximes for this study was the ability of these compounds to chelate iron(II). Although quinone mono-oximes form chelates with both iron(II) and iron(III), their affinity for iron(II) is greater. To-date most compounds that have been tested have been iron(III) chelators. Two iron(II) chelators that have been tested, 2,2'-dipyridyl and 1,10-phenanthroline, cause moderate amounts of iron excretion, suggesting the possible existence of an accessible pool of iron(II).[37]

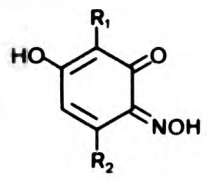
The chelators (Fig. 4.7) were administered in the form

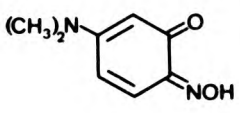


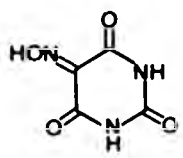
Anion of Ferroverdin

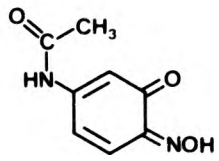
Fig. 4.6

of sodium complexes except in the case of N,N-dimethyl-5-amino-1,2-benzoquinone 2-oxime where the hydrochloride salt was used. These derivatives rather than the free ligands were used because of their higher solubility in water.









hqoH: $R_1=R_2=H$
3-MehqoH: $R_1=H$, $R_2=CH_3$
6-MehqoH: $R_1=CH_3$, $R_2=H$

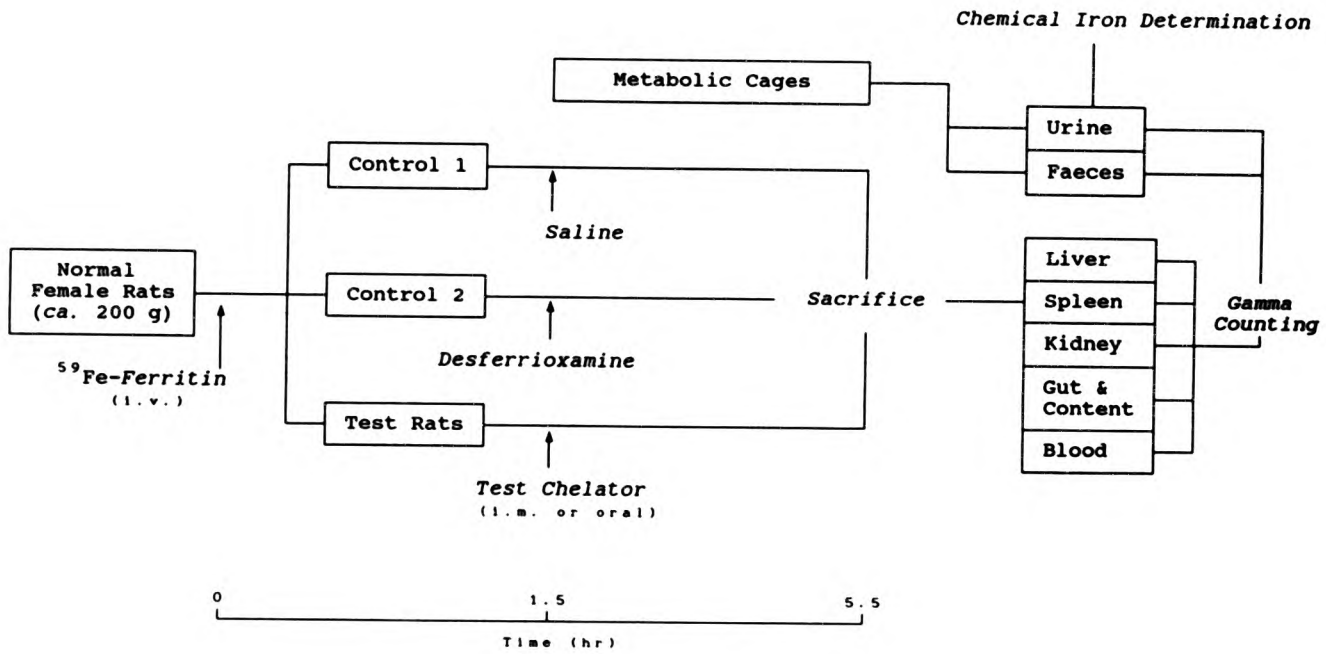
Fig. 4.7

4.3.2 In-vivo Evaluation of the Oximic Iron Chelators

In earlier studies both *in-vivo* and *in-vitro* methods have been used for the assessment of iron chelators. Two *in-vitro* models that have been proposed are the hepatocyte culture[43] and the Chang liver cell culture[54] models. The hepatocyte culture model involves trace labelling of primary hepatocyte cultures from male Wistar rats with ^{59}Fe-transferrin followed by incubation

of these cells with the test chelator. The effectiveness of the chelator is determined by the amount of iron mobilised into the culture medium. In the Chang liver cell culture model the effectiveness of the chelator is determined by measuring the inhibition of iron uptake and ferritin synthesis by the cells. In addition an *in-vitro* model based on heart cell cultures has also been proposed.[55]

A number of *in-vivo* animal models have also been proposed. These models are based on either iron loaded[33,56-58] or normal animals.[23,59] The main disadvantages of the *in-vitro* models are their inability to assess the oral activity and the iron selectivity of the test chelator. However *in-vivo* models based on iron loaded animals involve prolonged and inherently inaccurate iron balance studies. Hence a normal iron replete animal model[59] was chosen for this study. The protocol for this model is illustrated in Scheme 4.1. The rats were first injected with ^{59}Fe-ferritin through the lateral tail vein. After 1.5 h the test chelator was administered, either orally or as an intra-muscular injection. The urine and faeces were collected separately for 4 h. At the end of this period, the animals were sacrificed by exsanguination followed by perfusion with normal saline prior to removal of the organs. Gamma counting was carried out on various organs as well as on blood, urine and faeces to determine the amount of ^{59}Fe present. The urine was further analysed


Chemical Iron Determination
Metabolic Cages
Urine
Faeces
Control 1
Saline
Normal Female Rats (ca. 200 g)
Control 2
Sacrifice
Liver
Spleen
Kidney
Gut & Content
Blood
Gamma Counting
59Fe-Ferritin
(i.v.)
Desferrioxamine
Test Rats
Test Chelator
(i.m. or oral)
0
1.5
5.5
Time (hr)

Scheme 4.1

by atomic absorption spectroscopy for magnesium, calcium, iron, copper, and zinc.

It has been shown that the 7.5 µg dose of ferritin radio iron used in this model is cleared rapidly from blood and that after 2 h. about 94 % of the ^{59}Fe was in the liver.[59] It has also been shown that there is a "time window" of maximal availability of ^{59}Fe to the chelator. The "time window" is between 2-6 h after the injection of ^{59}Fe-ferritin. To account for this observation it has been suggested that the iron is available to the chelators while in transit within the hepatocyte and that once the iron is incorporated into endogenous ferritin it becomes relatively unavailable.[59] The ratio between ^{59}Fe and total iron excreted (the specific activity) in bile was constant irrespective of the wide range of total iron excretion produced by different doses of desferrioxamine. Furthermore in iron loaded rats, the specific activity was lower than in normal rats. This indicate that the ^{59}Fe-ferritin is uniformly labelling a pool of chelatable iron within the hepatocyte.[59]

The results of the ^{59}Fe-ferritin study are presented in Table 4.2. These indicate that:

(i) None of the test chelators are successful in causing iron excretion when administered orally.

Table 4.2 Distribution of ^{59}Fe after Administration of Desferrioxamine and the Test Compounds

Substance Administered†	Route of Administration (no. of rats)	^{59}Fe (% of injected counts)						
		Liver	Spleen	Kidney	Gut & Faeces	Urine	Blood	Carcass
Control	- (6)	93.40	0.39	0.04	2.32	0.00	1.00	2.84
DF (20 mg)	i.m. (6)	49.62	0.33	0.06	45.50	0.85	0.54	3.10
DF (40 mg)	i.m. (6)	51.19	0.09	0.04	44.67	0.62	0.47	2.91
Na(hqoH)	i.m. (3)	77.51	0.23	0.07	17.72	0.14	0.79	3.54
Na(hqoH)	p.o. (3)	92.27	0.20	0.06	3.26	0.02	0.78	3.45
Na(3-MehqoH)	i.m. (3)	93.42	0.23	0.07	2.11	0.03	0.92	3.24
Na(3-MehqoH)	p.o. (3)	92.85	0.27	0.09	2.26	0.02	0.73	3.70
Na(6-MehqoH)	i.m. (3)	59.31	0.57	0.14	33.48	0.07	1.43	5.00
Na(6-MehqoH)	p.o. (3)	90.51	0.18	0.06	4.44	0.05	1.05	3.72
Na(N-Acqo)	i.m. (3)	93.00	0.35	0.13	1.72	0.07	1.62	3.11
Na(N-Acqo)	p.o. (3)	91.85	0.23	0.26	3.19	0.10	1.78	2.60
$N\text{-}Me_2qoH\cdot HCl$	i.m. (3)	90.13	0.44	0.10	6.03	0.24	0.59	2.48
$N\text{-}Me_2qoH\cdot HCl$	p.o. (3)	88.17	0.38	0.16	7.67	0.19	1.32	2.22
NaH_2Va	i.m. (3)	91.89	0.47	0.00	1.74	0.22	1.36	4.32
NaH_2Va	p.o. (3)	84.71	0.36	0.20	1.86	3.19	4.86	4.82

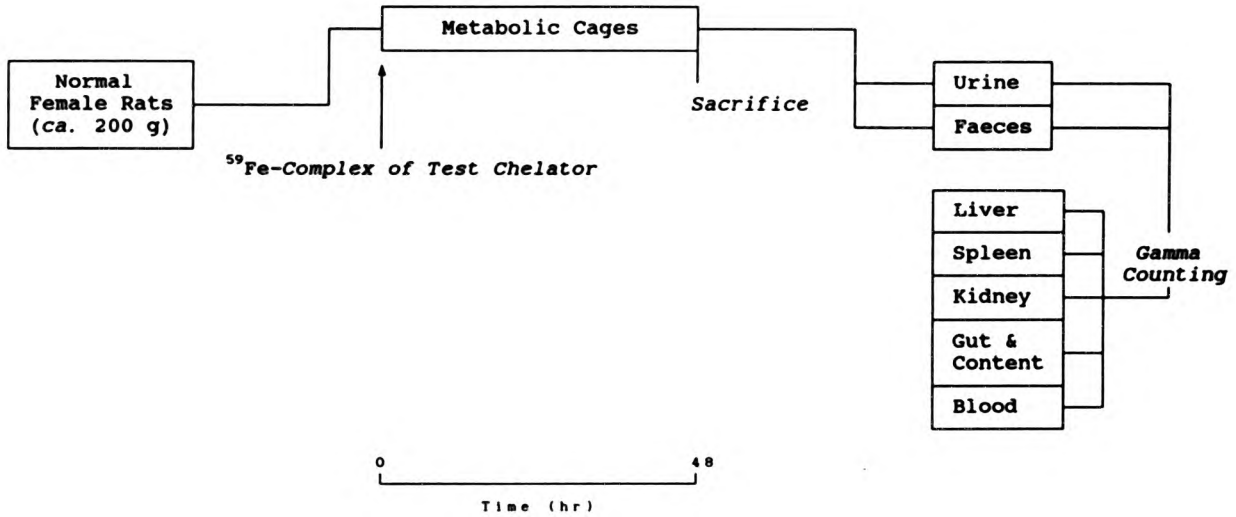
†=Dose of test compounds is equivalent to the iron binding capacity of 20 mg of desferrioxamine

(ii) With the exception of Na(hqoH) and Na(6-MehqoH), none of the chelators cause iron excretion when administered intra-muscularly.

(iii) Na(6-MehqoH) causes more iron excretion than Na(hqoH) when administered by intra-muscular injection, though less than in the case of desferrioxamine.

Iron content determination in urine (Fig 4.8) by atomic absorption showed similar results to urine ^{59}Fe determination experiments. This indicates that the chelators are not causing the urinary excretion of iron from an iron pool which has not been labelled by ^{59}Fe.

In separate experiments, the $^{59}Fe(III)$-chelates were administered to rats by stomach tube (Scheme 4.2). The purpose of these experiments was to investigate whether the chelate would be absorbed in the gut. If a chelator is to successfully remove iron from the body by excretion of the iron complex in faeces then the complex must not be reabsorbed during its passage through the gut. The results (Table 4.3) indicate that in all the cases over 80% of the administered complex is found in the gut and faeces after 48 h. The highest absorption occurs in the case of sodium 5-hydroxy-6-methyl-1,2-benzoquinone 2-oximate Na(6-MehqoH). The absorbed iron appears in the blood and the carcass. In general, it can be concluded that for


Metabolic Cages
Normal Female Rats (ca. 200 g)
59Fe-Complex of Test Chelator
Sacrifice
Urine
Faeces
Liver
Spleen
Kidney
Gut & Content
Blood
Gamma Counting
0
48
Time (hr)

Scheme 4.2

Table 4.3 Distribution of ^{59}Fe after Oral Administration of ^{59}Fe Complexes of 6-MehqoH$_2$, N-AcqoH, N-MeqoH and H_3Va

Test Ligand†	^{59}Fe (% of injected counts)						
	Liver	Spleen	Kidney	Gut & Faeces	Urine	Blood	Carcass
6-MehqoH$_2$	1.86	0.13	0.12	82.02	0.09	6.72	9.02
N-AcqoH	0.50	0.05	0.05	94.04	0.20	0.78	4.38
N-Me$_2$qoH	1.11	0.07	0.10	91.14	2.24	2.03	3.13
H_3Va	1.49	0.11	0.12	94.00	0.06	3.02	1.20

†=2 Animals per group

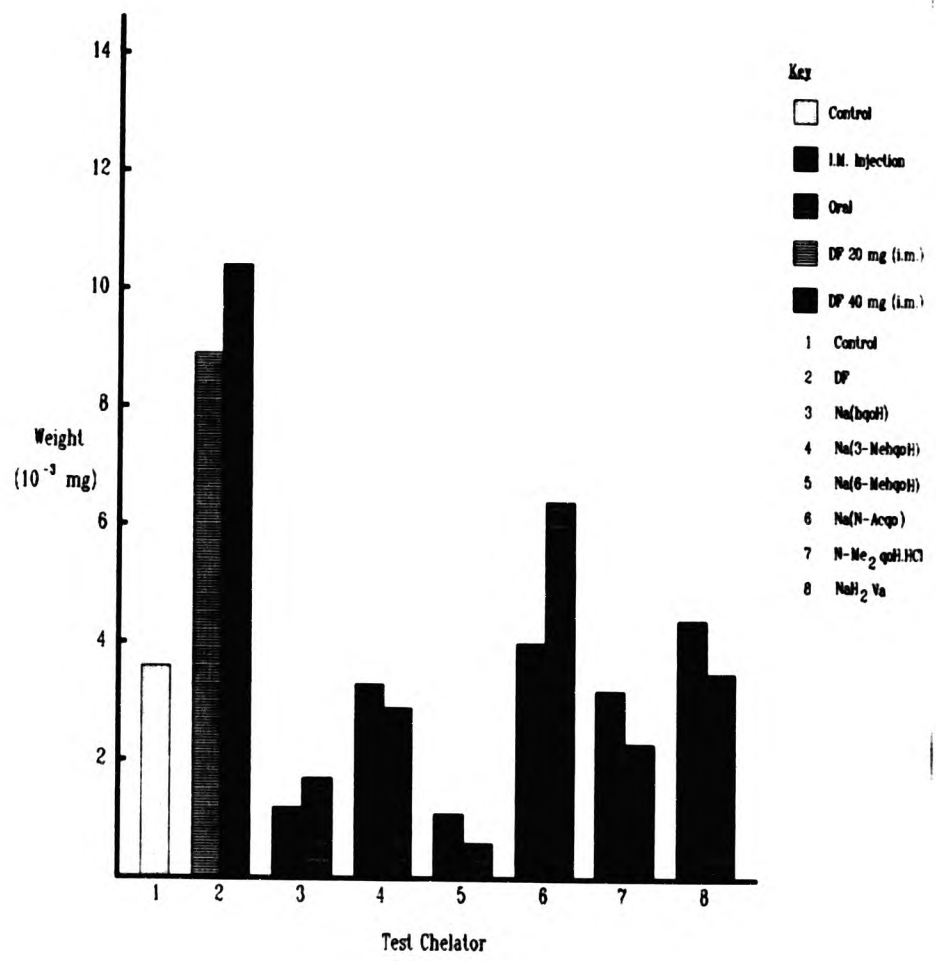
Note: Dose of iron administered = 10 mg per animal

the ligands tested no major absorption of the Fe(III)-chelate occurs.

The results of the urinary excretion of magnesium, calcium, copper and zinc are presented in Fig. 4.9-4.12. Except for the case of intra-muscularly injected N-Me_2qoH.HCl, the charts indicate the total weight of metal excreted during the 4 h urine collection (Scheme 4.1). Since the animals died within 1 h of injecting N-Me_2qoH.HCl, the metal excreted up to the time of death is presented. The results show that magnesium excretion is increased for all test chelators irrespective of the route of administration. In contrast all test chelators caused the retention of calcium. It has been reported that desferrioxamine causes the retention of magnesium and calcium in rats.[33] During the present study a similar effect was observed for calcium both at the 20 mg and 40 mg dose levels, but no alteration of the magnesium excretion was observed. Zinc retention was observed for all the test chelators except N-AcqoH for which normal levels of excretion was observed. No alteration of the urinary excretion of copper or zinc was observed for desferrioxamine. The copper excretion was normal for all test chelators.

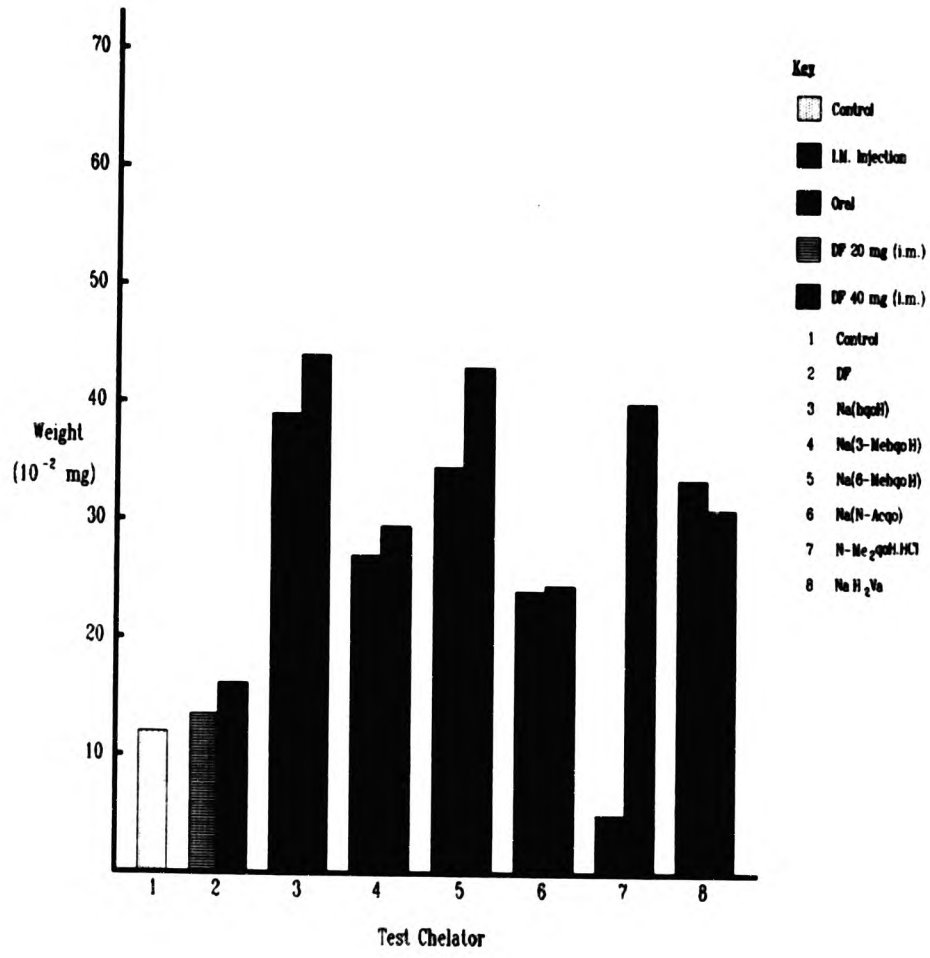
Although no systematic assessment of the toxicity of the chelators were carried out the results allow some conclusion to be drawn regarding their relative toxicity. No toxic effects were observed for Na(N-Acqo),

Fig. 4.8 Total Weight of Iron in Urine



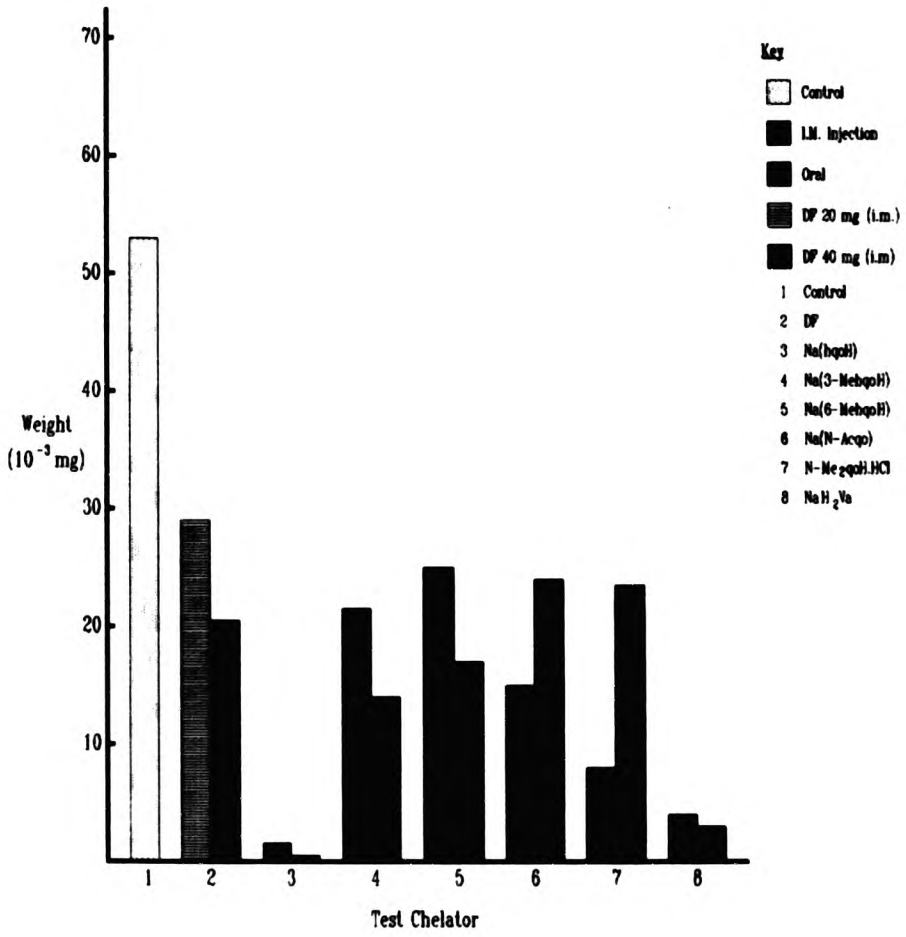
Note: See Table 4.2 for number of animals in each group.

Fig.4.9 Total Weight of Magnesium in Urine



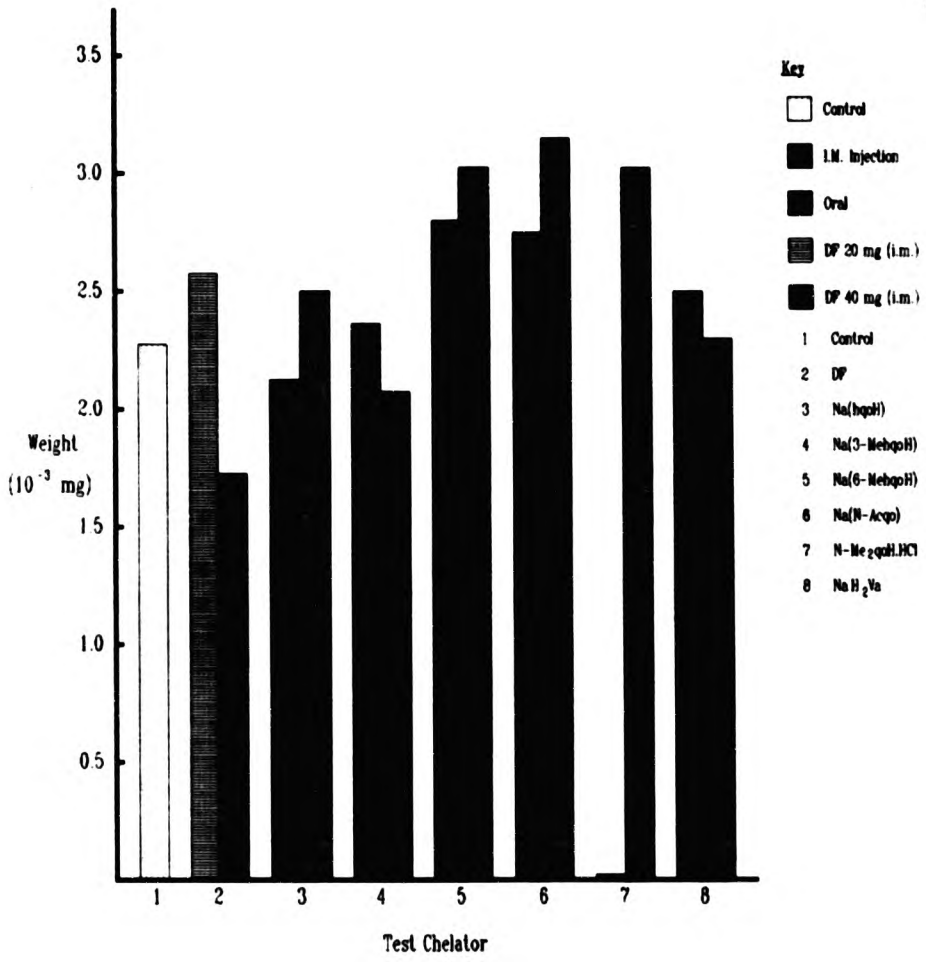
Note: See Table 4.2 for number of animals in each group.

Fig. 4.10 Total Weight of Calcium in Urine



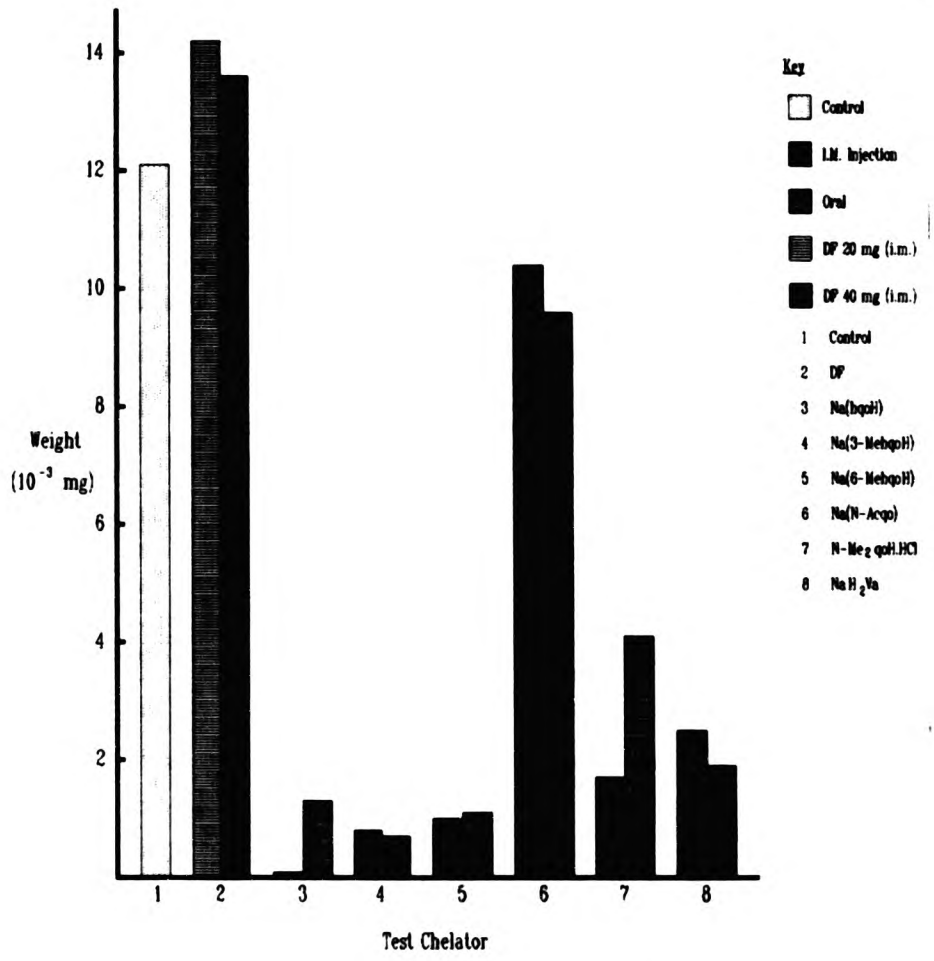
Note: See Table 4.2 for number of animals in each group.

Fig. 4.11 Total Weight of Copper in Urine



Note: See Table 4.2 for number of animals in each group.

Fig. 4.12 Total Weight of Zinc in Urine



Note: See Table 4.2 for number of animals in each group.

NaH_2Va and Na(3-MehqoH) except stomach distension in cases where Na(3-MehqoH) was administered orally. The compounds Na(hqoH), Na(6-MehqoH) and N-Me_2qoH.HCl caused hypersalivation. However in the case of Na(hqoH) this effect was only observed when it was administered intra-muscularly. This phenomenon has also been observed in the case of 1,2-dimethyl-3-hydroxypyrid-4-one which as mentioned previously causes hypersalivation in rats.[42]

N-Me_2qoH.HCl was the most toxic of the chelators tested. Within 0.5 h of administering the drug, hypersalivation occurred. The intra-muscularly injected rats started to convulse within 0.75 h of injection and died within an hour.

Addition of iron(II) sulphate to a aliquot of urine from rats administered with Na(hqoH), Na(3-MehqoH), Na(N-Acqo), or N-Me_2qoH.HCl gave a green colouration. Urine of rats administered with NaH_2Va gave a blue colouration. These colours are characteristic of the iron(II) complexes of these chelators and is indicative of the presence of unmetabolized chelators in urine. Additionally, the presence of the unmetabolized chelators were further established by comparative thin layer chromatography.

From the chelators tested, the only compound that caused the excretion of iron to any great extent was

Na(6-Mehqo). However the compound is only active when administered intra-muscularly and the amount of iron excreted is less than for desferrioxamine. Although Na(6-Mehqo) has the advantage that it can be synthesized easily, oral inactivity and magnesium excretion are serious drawbacks.

4.4 REFERENCES

1 'Trace Element Deficiency: Metabolic and Physiological Consequences'. The Royal Society of London, London, 1981.

2 N. J. Smith and E. Rios, 1974, *Adv. Pediatr.*, 21, 239.

3 E. J. Moynahan, *Lancet*, 1974, ii, 399.

4 E. R. Hughes, in 'Metal Ions in Biological Systems,' Vol. 7, H. Sigel (Ed.), Marcel Dekker, New York, 1978, chap. 9.

5 C. Walker, 'Environmental Pollution by Chemicals,' Hutchinson and Co., London, 2nd edition, 1974, Chap. 4.

6 J. H. Ottaway, 'The Biochemistry of Pollution,' Edward Arnold, London, 1980, Chap. 1.

7 M. N. Hughes, 'The Inorganic Chemistry of Biological Processes,' John Wiley and Sons, Chichester, 1981.

8 A. C Alfrey, G. R. Legendre, and W. D. Kaehny, *N. Engl. J. Med.*, 1976, **294**, 184.

9 D. J. Weatherall and J. B. Clegg, in 'Blood and its Disorders,' R. M. Hardisty and D. J. Weatherall (Eds.) Blackwell Scientific Publications, London, 2nd edition, 1982, Chap. 9.

10 D. J. Weatherall and J. B. Clegg, 'The Thalassaemia Syndromes,' Blackwell Scientific Publications, London, 3rd edition, 1981.

11 R. A. McCance and E. M. Widdowson, *Lancet*, 1937, i, 680.

12 A. Jacobs and M. Worwood, 'Iron in Biochemistry and Medicine,' Academic press, London, 1974.

13 Bulletin of the World Health Organization, 1983, 61, 63.

14 H. Bickel, E. Gaumann, W. Keller-Schierhein, V. Prelog, E. Vischer, A. Wettstein, and H. Zahner, *Experientia*, 1960, 16, 129.
Chem. Abs.:55:23684e

15 B. Modell and J. Beck, *Ann. N. Y. Acad. Sci.*, 1974, 232, 201.

16 R. J. O'Brien, *Ann. N. Y. Acad. Sci.*, 1974, 232, 211.

17 R. D. Propper, B. Cooper, R. R. Rufo, A. W. Nienhuis, W. F. Bunn, A. Rosenthal, and D. G. Nathan, *N. Engl. J. Med.*, 1977, 297, 418.

18 S. C. Davis, R. E. Marcus, J. L. Hugerford, M. H. Miller, J. Arden, and E. R. Huehns, *Lancet*, 1983, ii, 181.

19 N. F. Olivieri, J. R. Buncic, E. Chew, T. Gallent, R. V. Harrison, N. Kennan, N. Logan, D. Mitchell, G. Ricci, B. Skark, M. Taylor, and M. H. Freedman, *N. Engl. J. Med.*, 1986, 314, 869.

20 M. Rubinstein, P. Dupont, J. P. Doppee, C. Dehon, J. Ducobu, and J. Hainaut, *Lancet*, 1985, i, 817.

21 E. B. Brown, *Progr. Clin. Biol. Research*, 1983, 127, 33.

22 E. C. Zaino in 'Chelation Therapy in Chronic Iron Overload,' E. C. Zaino and R. H. Roberts (Eds.), Symposia Specialists Inc., Miami, 1977, Page 95.

23 A. Jacobs in 'Development of Iron Chelators for

Clinical Use,' A. E. Martell, W. F. Anderson, and D. G. Badman (Eds.), Elsevier North Holland, New York, 1981, Page 39.

24 H. Keberly, *Ann. N. Y. Acad. Sci.*, 1961, 119, 758.

25 S. de Virgiliis, M. Congia, M. P. Turco, F. Frau, C. Dessi, F. Argiolu, R. Sorcinelli, A. Sitzia and A. Cao, *Arch. Dis. Child.*, 1988, 63, 250.

26 K. N. Raymond, G. Müller and B. F. Matzanke, *Top. Curr. Chem.*, 1984, 123, 49.

27 R. C. Hider, *Struc. and Bonding*, 1984, 58, 25.

28 M. J. Smith, J. N. Shooley, B. Schwyn, I. Holden, and J. B. Neilands, *J. Am. Chem. Soc.*, 107, 1739.

29 H. S. Waxman and E. B. Brown in 'Progress in Hematology,' E. B. Brown and C. V. More (Eds.), Grune and Stratton Inc., New York, 1969, Volume VI, Page 338.

30 A. Cerami, R. W. Grady, C. M. Peterson, and K. K. Bhargava, *Ann. N. Y. Acad. Sci.*, 1980, 344, 425.

31 F. Cleton, A. Turnbull, and C. A. Finch, *J. Clin. Invest.*, 1963, 42, 327.

32 J. B. Porter, E. R. Huehns, and R. C . Hider in 'Bailliére's Clinical Haematology,' Vol.2/No.2, April 1989. References therein.

33 J. H. Graziano, R. W. Grady, and A. Cerami, *J. Pharmacol. Exp. Ther.*, 1974, 190, 570.

34 C. M. Peterson, J. H. Graziano, R. W. Grady, R. L. Jones, H. V. Vlassara, V. C. Canale, D. R. Miller, and A. Cerami, *Br. J. Haematol.*, 1976,

33, 477.

35 C. M. Peterson, J. H. Graziano, R. W. Grady, R. L. Jones, A. Markenson, U. Lavi, V. Canale, G. F. Gray, A. Cerami, and D. R. Miller, *Exp. Hematol.*, 1979, 7, 74.

36 C. M. Peterson and R. L. Jones, *Birth Defects, Orig. Artic. Ser.*, 1976, 12, 187.

37 R. W. Grady, J. H. Graziano, H. A. Akers, and A. Cerami, *J. Pharmacol. Exp. Ther.*, 1976, 196, 478.

38 R. W. Grady, C. M. Peterson, R. L. Jones, J. H. Graziano, K. K. Bargava, V. A. Berdoukas, G. Kokkini, D. Loukopoulos, and A. Cerami, *J. Pharmacol. Exp. Ther.*, 1979, 209, 342.

39 J. L. Fahey, C. E. Rath, J. V. Princiotto, I. B. Brick and M. Rubin, *J. Lab. Clin. Med.*, 1961, 57, 436.

40 U. Müller-Eberhard, M. E. Erlandson, H. E. Ginn, and C. H. Smith, *Blood*, 1963, 22, 209.

41 G. J. Kontohiorghes, M. A. Aldouri, A. V. Hoffbrand, J. Barr, B. Wonke, T. Kourouclaris, and L. Sheppard, *Br. Med. J.*, 1987, 295, 1509.

42 G. J. Kontoghiorghes, L. Sheppard, A. V. Hoffbrand, J. Charalambous, J. Tikerpae, and M. J. Pippard, *J. Clin. Pathol.*, 1987, 40, 404.

43 E. R. Huehns, J. B. Porter, and R. C. Hider, *Heamoglobin*, 1988, 12, 593.

44 J. B. Porter, K. P. Hoyes, R. Abeysinghe, E. R. Huehns, and R. C. Hider, *Lancet*, 1989, ii, 156.

45 A. V. Hoffbrand, A. N. Bartlett, P. A. Veys,

N. T. J. O' Connor, and G. J. Kontoghiorghes, *Lancet*, 1989, ii, 457.

46 C. B. Hyman, J. A. Ortega, G. Costin, B. Landing, J. Lazerson, S. Leimbrock, and P. Lurie *Birth Defects, Orig. Artic. Ser.*, 1976, 12, 43.

47 R. W. Grady, J. H. Graziano, G. P. White, A. Jacobs, and A. Cerami, *J. Pharmacol. Exp. Ther.*, 1978, 205, 757.

48 P. Ponka, J. Borova, J. Neuwirt, O. Fuchs, and E. Necas, *Biochim. Biophys. Acta*, 1979, 586, 278.

49 M. Cikrt, P. Ponka, E. Necas, and J. Neuwirt, *Br. J. Haematol.*, 1980, 45, 275.

50 D. K. Johnson, M. J. Pippard, T. B. Murphy, and N. J. Rose, *J. Pharmacol. Exp. Ther.*, 1982, 221, 399.

51 A. Ballio, H. Bertholdt, A. Carilli, E. B. Chain, V. Di Vittorio, A. Tonolo, and L. Vero-Barcellona, *Proc. R. Soc. London, Ser. B*, 1963, 158, 71.

52 S. Candeloro, D. Grdenic, N. Taylor, B. Thompson, M. Viswamitra, and D. C. Hodgkins, *Nature*, 1969, 224, 589.

53 C. Yang and J. Leong, *J. of Bacteriol.*, 1982, 149, 381.

54 G. P. White, R. Bailey-Wood, and A. Jacobs, *Clin. Sci. Mol. Med.*, 1976, 50, 145.

55 C. V. Sciortino, B. R. Byers, and P. Cox, *J. Lab. Clin. Med.*, 1980, 96, 1081.

56 C. G. Pitt, G. Gupta, W. E. Estes, H. Rosenkrantz, J. J. Metterville, A. L. Crumbliss, R. A. Palmer, K. W. Nordquest, K. A. Sprinkle Hardy,

D. R. Whitcomb, B. R. Byers, J. E. L. Arceneaux, C. G. Gaines and C. V. Sciortino, *J. Pharmacol. Exp. Ther.*, 1979, **208**, 12.

57 M. Gyparaki, J. B. Porter, S. Hirani, M. Streater, R. C. Hider, and E. R. Huehns, *Acta Haematol.*, 1987, **78**, 217.

58 G. J. Kontoghiorghes and A. V. Hoffbrand, *Br. J. Haematol.*, 1986, **62**, 607.

59 M. J. Pippard, D. K. Johnson, and C. A. Finch, *Blood*, 1981, **58**, 685.

CHAPTER 5

EXPERIMENTAL

5.1 Reagents and General Techniques

The reagents and solvents employed were obtained commercially and used without further purification. The silica gel absorbent used in the chromatography columns was Merck silica gel 60 (70 - 230 mesh) and the ion exchange resin used was Dowex 50W-X8(H) supplied by BDH Chemicals Limited. Thin layer chromatography was performed using commercially supplied silica coated alumina plates.

5.2 Analytical Techniques

Magnesium, calcium, iron, copper and zinc in urine was determined quantitatively by the method of atomic absorption spectrometry, using a Pye-Unicam SP9 atomic absorption spectrometer. After centrifugation to remove any urinary sediment present a known volume of urine was warmed in a mixture of concentrated nitric acid/perchloric acid /sulphuric acid (3:1:1) (ca. 4 cm^3) and 30% hydrogen peroxide (ca. 1 cm^3). After allowing the mixture to digest, the inorganic residue was diluted to a known volume with water.

Sodium, potassium, calcium and iron in samples of metal complexes were also determined by the method of atomic

absorption spectrometry. A kown mass (ca. 0.2 g) of the material under investigation was warmed with concentrated sulphuric acid (ca. 1 cm^3), concentrated nitric acid (ca. 2 cm^3) and hydrogen peroxide (ca. 1 cm^3). After allowing the mixture to digest, the inorganic residue was diluted to a known volume with water.

Carbon, hydrogen and nitrogen analysis were carried out on a Carlo Erba 1106 elemental analyser.

5.3 Physical Techniques

Infra-red Spectroscopy. — Infra-red spectra in the region 4000 - 400 cm^{-1} were recorded on a BIO-RAD FTS40 spectrometer. The samples were prepared as pressed potassium bromide discs.

Nuclear Magnetic Resonance Spectroscopy. — Fourier transform ^1H and ^{13}C n.m.r. spectra were recorded on a Bruker AM250 or on a Joel 270 MHz spectrometer. Trimethylsilane was used as an internal standard for spectra recorded in d_6-DMSO and it was used as an external standard in the case of spectra recorded in D_2O.

Magnetic Measurments. — Room temperature magnetic moments were recorded using a Johnson Matthey magnetic

susceptibility balance. The instrument was calibrated with a solution of manganese(II) chloride. Magnetic moments were corrected for the diamagnetic effect of the metal and the ligands.[1]

Mossbauer Spectra. — A Cryophysics Mössbauer spectrometer with a ^{57}Co/(rhodium) source and a CO_2/Xe detector was used to record the Mössbauer spectra at 20 °C and -196 °C.

Thermal Gravimetric Analysis. — Thermal gravimetric analysis was carried out on a Stanton HT-SM Thermobalance.

5.4 Reactions

5.4.1 Reaction of 3-hydroxyphenols (1 mol equiv) with amyl nitrite and sodium ethoxide (1 mol equiv) at -10 °C

Sodium (4.60 g, 200 mmol) was dissolved in dry ethanol (200 cm^3) and the solution was cooled to -10 °C. To this solution 3-hydroxyphenol (22.00 g, 200 mmol) was added, followed by portionwise addition of amyl nitrite (25.74 g, 220 mmol) over a period of 1 h. The reaction mixture was allowed to reach 20 °C over a period of 2 h and then filtered to give orange *sodium 5-hydroxy-1,2-benzoquinone 2-oximate monohydrate* (31.83 g, 89%) which was washed with ice cold water

(30 cm^3), ethanol (30 cm^3), light petroleum (b.p. 30 - 40 °C) (6 X 50 cm^3) and dried at 0.1 mm/50 °C.

Similarly, 3-hydroxy-2-methylphenol (24.80 g, 200 mmol) gave *sodium 5-hydroxy-6-methyl-1,2-benzoquinone 2-oximate monohydrate* (32.85 g, 85%) and 3-hydroxy-5-methylphenol (24.80 g, 200 mmol) gave *sodium 5-hydroxy-3-methyl- 1,2-benzoquinone 2-oximate dihydrate* (38.40 g 91%). (See Table 5.1 for elemental analysis).

5.4.2 Reaction of 3-hydroxyphenols (1 mol equiv) with amyl nitrite and sodium ethoxide (2 mol equiv) at -10 °C

Sodium (3.45 g, 150 mmol) was dissolved in dry ethanol (150 cm^3) and the solution was cooled to -10 °C. To this solution 3-hydroxyphenol (8.25 g, 75 mmol), was added, followed by portionwise addition of amyl nitrite (9.65 g, 82 mmol) over a period of 1 h. The reaction mixture was allowed to reach 20 °C over a period of 2 h and then filtered to give orange *disodium 5-hydroxy-1,2-benzoquinone 2-oximate hemihydrate* (11.97 g, 83%) which was washed with ice cold water (20 cm^3), ethanol (20 cm^3), light petroleum (b.p. 30 - 40 °C) (6 X 50 cm^3) and dried at 0.1 mm/50 °C.

Similarly, 3-hydroxy-2-methylphenol (9.30 g, 75 mmol)

gave *disodium 5-hydroxy-6-methyl-1,2-benzoquinone 2-oximate* (12.85 g, 87%) and 3-hydroxy-5-methylphenol (9.30 g, 75 mmol) gave *disodium 5-hydroxy-3-methyl-1,2-benzoquinone 2-oximate* (14.10 g, 95%). (See Table 5.1 for elemental analysis).

5.4.3 Reaction of 3-hydroxyphenols (1 mol equiv) with amyl nitrite and sodium hydroxide (1 mol equiv) at -10 °C

Sodium hydroxide (6.00 g, 150 mmol) was dissolved in dry ethanol (250 cm^3) and the solution was cooled to -10 °C. To this solution 3-hydroxyphenol (8.25 g, 75 mmol) was added, followed by portionwise addition of amyl nitrite (9.65 g, 82 mmol) over a period of 1 h. The reaction mixture was allowed to reach 20 °C over a period of 2 h and then filtered to give orange *sodium 5-hydroxy-1,2-benzoquinone 2-oximate monohydrate* (7.38 g, 55%) which was washed with ice cold water (20 cm^3), ethanol (20 cm^3), light petroleum (b.p. 30 - 40 °C) (6 X 50 cm^3) and dried at 0.1 mm/50 °C.

Similarly, 3-hydroxy-2-methylphenol (9.30 g, 75 mmol) gave *sodium 5-hydroxy-6-methyl-1,2-benzoquinone 2-oximate monohydrate* (6.77 g, 47%) and 3-hydroxy-5-methylphenol (9.30 g, 75 mmol) gave *sodium 5-hydroxy-3-methyl- 1,2-benzoquinone 2-oximate dihydrate*

(9.60 g, 61%). (See Table 5.1 for elemental analysis).

5.4.4 Reaction of 3-hydroxyphenols (1 mol equiv) with amyl nitrite and sodium hydroxide (2 mol equiv) at -10 °C

The procedure is similar to that described in Section 5.4.3 except that a greater quantity of sodium hydroxide (12.00 g, 300 mmol) was used. 3-Hydroxyphenol gave *disodium 5-hydroxy-1,2-benzo-quinone 2-oximate hemihydrate* (6.36 g, 44%). 3-Hydroxy-2-methylphenol gave *disodium 5-hydroxy-6-methyl-1,2-benzoquinone 2-oximate* (8.46 g, 57%). 3-Hydroxy-5-methylphenol gave *disodium 5-hydroxy-3-methyl-1,2-benzoquinone 2-oximate* (8.57 g, 58%). (See Table 5.1 for elemental analysis).

5.4.5 Reaction of 3-hydroxyphenols (1 mol equiv) with amyl nitrite and sodium ethoxide (1 mol equiv) at 20 °C

The procedure is similar to that described in Section 5.4.1 except that the reaction was carried out at 20 °C. 3-Hydroxyphenol gave sodium 1,2,3,4-benzoquinone 2,4-oximate (14.94 g, 72%). 3-Hydroxy-5-methylphenol gave sodium 5-methyl-1,2,3,4-benzoquinone 2,4-oxime (17.21 g, 77%). 3-Hydroxy-2-methylphenol gave *sodium 5-hydroxy-6-methyl-1,2-benzoquinone 2-oximate monohydrate* (31.42 g, 81%). (See Table 5.1 for elemental

analysis).

5.4.6 Reaction of 3-hydroxy-6-methylphenol (1 mol equiv) with amyl nitrite and sodium ethoxide (2 mol equiv) at 20 °C

The procedure is similar to that described in Section 5.4.2 except that the reaction was carried out at 20 °C. The product obtained was *disodium 5-hydroxy-6-methyl-1,2-benzoquinone 2-oximate* (12.35 g, 84%). (See Table 5.1 for elemental analysis).

5.4.7 Reaction of 3-hydroxyphenols (1 mol equiv) with amyl nitrite and sodium hydroxide (1 mol equiv) at 20 °C

The procedure is similar to that described in Section 5.4.3 except that the reaction was carried out at 20 °C. 3-Hydroxyphenol gave sodium 1,2,3,4-benzoquinone 2,4-oximate (3.72 g, 48%). 3-Hydroxy-5-methylphenol gave sodium 5-methyl-1,2,3,4-benzoquinone 2,4-oxime (3.72 g, 44%). 3-Hydroxy-2-methylphenol gave *sodium 5-hydroxy-6-methyl-1,2-benzoquinone 2-oximate monohydrate* (7.24 g, 50%). (See Table 5.1 for elemental analysis.)

Table 5.1 Elemental Analysis of $hqoH_2$, 3-$MehqoH_2$, 6-$MehqoH_2$ and Their Alkali Metal Derivatives

Compound	Found (%)					Required (%)				
	C	H	K	Na	N	C	H	K	Na	N
$hqoH_2$	52.3	3.9	-	-	9.8	51.8	3.6	-	-	10.1
$Na(hqoH)\cdot H_2O$	39.8	3.3	-	12.6	7.6	40.2	3.4	-	12.8	7.8
$Na_2(hqo)\cdot 0.5H_2O$	37.8	2.3	-	12.1	7.5	37.5	2.1	-	12.0	7.3
K(hqoH)	40.8	2.4	22.4	-	7.8	40.7	2.3	22.1	-	7.9
$K_2(hqo)$	33.8	1.6	36.9	-	6.6	33.5	1.4	36.3	-	6.5
Na(dnrH)	38.1	1.7	-	12.2	14.7	37.9	1.6	-	12.1	14.7
$Na_2(dnr)$	33.9	1.0	-	22.0	13.0	34.0	0.9	-	13.2	21.7
$3\text{-}MehqoH_2\cdot H_2O$	49.5	5.7	-	-	8.0	49.1	5.3	-	-	8.2
$Na(3\text{-}MehqoH)\cdot 2H_2O$	39.9	4.4	-	11.0	6.6	39.8	4.7	-	10.9	6.6
$Na_2(3\text{-}Mehqo)$	42.5	2.4	-	23.2	7.3	42.6	2.5	-	23.4	7.1
K(3-MehqoH)	43.4	3.2	20.5	-	7.0	44.0	3.1	-	20.5	7.3
Na(3-Mednr)	41.2	2.5	-	11.4	14.0	41.2	2.5	-	11.3	13.7
$Na_2(3\text{-}Mednr)$	37.3	1.9	-	20.0	12.6	37.2	1.8	-	20.4	12.4
$6\text{-}MehqoH_2\cdot H_2O$	49.3	5.2	-	-	8.2	49.1	5.3	-	-	8.2
$Na(6\text{-}MehqoH)\cdot H_2O$	44.1	4.4	-	11.6	7.2	43.5	4.1	-	11.9	7.3
$Na_2(6\text{-}Mehqo)$	42.6	2.7	-	23.7	7.4	42.6	2.5	-	23.4	7.1
$K(6\text{-}MehqoH)\cdot H_2O$	40.5	3.8	18.2	-	6.8	40.2	3.8	18.7	-	6.7

5.4.8 Reaction of 3-hydroxy-6-methylphenol (1 mol equiv) with amyl nitrite and sodium hydroxide (2 mol equiv) at 20 °C

The procedure is similar to that described in Section 5.4.3 except that a greater quantity of sodium hydroxide (12.00 g, 300 mmol) was used and the reaction was carried out at 20 °C. The product obtained was *disodium 5-hydroxy-6-methyl-1,2-benzoquinone 2-oximate* (8.30 g, 56%). (See Table 5.1 for elemental analysis).

5.4.9 Reaction of 3-hydroxyphenols (1 mol equiv) with amyl nitrite and potassium ethoxide (1 mol equiv) at -10 °C

The procedure is similar to that described in Section 5.4.2 except that sodium was replaced by potassium (2.93 g, 75 mmol). 3-Hydroxyphenol gave *potassium 5-hydroxy-1,2-benzoquinone 2-oximate* (10.80 g, 81%). 3-Hydroxy-2-methylphenol gave *potassium 5-hydroxy-6-methyl-1,2-benzoquinone 2-oximate monohydrate* (12.07 g, 77). 3-Hydroxy-5-methylphenol gave *potassium 5-hydroxy-3-methyl-1,2-benzoquinone 2-oximate* (11.85 g, 83%). (See Table 5.1 for elemental analysis).

5.4.10 Reaction of 3-hydroxyphenols (1 mol equiv) with amyl nitrite and potassium hydroxide (1 mol equiv) at -10 °C

The procedure is similar to that described in Section 5.4.2 except that sodium was replaced by potassium hydroxide (4.21 g, 75 mmol). 3-Hydroxyphenol gave *potassium 5-hydroxy-1,2-benzoquinone 2-oximate* (7.89 g, 59%). 3-Hydroxy-2-methylphenol gave *potassium 5-hydroxy-6-methyl-1,2-benzoquinone 2-oximate monohydrate* (8.72 g, 56%). 3-Hydroxy-5-methylphenol gave *potassium 5-hydroxy-3-methyl-1,2-benzoquinone 2-oximate* (9.14 g, 64%). (See Table 5.1 for elemental analysis).

5.4.11 Reaction of 3-hydroxyphenol (1 mol equiv) with amyl nitrite and potassium ethoxide (2 mol equiv) at -10 °C

The procedure is similar to that described in Section 5.4.2 except that sodium was replaced by potassium (5.87 g, 150 mmol). The product obtained was dipotassium 5-hydroxy-1,2-benzoquinone 2-oximate (12.75 g, 79%). (See Table 5.1 for elemental analysis).

5.4.12 Reaction of 3-hydroxyphenol (1 mol equiv) with amyl nitrite and potassium hydroxide (2 mol equiv) at -10 °C

The procedure is similar to that described in Section 5.4.2 except that sodium was replaced by potassium hydroxide (6.00 g, 150 mmol). The product obtained was dipotassium 5-hydroxy-1,2-benzoquinone 2-oximate (9.97 g, 62%). (See Table 5.1 for yield and elemental analysis).

5.4.13 Reaction of 3-hydroxyphenol (1 mol equiv) with amyl nitrite and sodium hydroxide (1.4 mol equiv) at -10 °C

Sodium hydroxide (5.60 g, 140 mmol) was dissolved in dry ethanol (250 cm^3) and the solution was cooled to -10 °C. 3-Hydroxyphenol (11.00 g, 100 mmol), was added to the ethanolic sodium hydroxide. Amyl nitrite (12.87 g, 110 mmol) was added portionwise over a period of 1 h. The reaction mixture was allowed to reach 20 °C over a period of 2 h and filtered to obtain an orange coloured solid. The solid was washed with ice cold water (30 cm^3), ethanol (30 cm^3), light petroleum (b.p. 30 - 40 °C) (6 X 75 cm^3) and dried at 0.1 mm/50 °C. (Found: C, 38.7; H, 2.3; Na, 16.8; N, 7.4).

5.4.14 Reaction of 5-hydroxy-6-methyl-1,2-benzoquinone 2-oxime monohydrate with calcium hydroxide

5-Hydroxy-6-methyl-1,2-benzoquinone 2-oxime monohydrate (2.50 g, 15 mmol) in methanol (50 cm^3) was added to a suspension of calcium hydroxide (0.40 g, 5 mmol) in water (10 cm^3). The reaction mixture was stirred at 20 °C for 48 h and filtered to obtain a mauve coloured solid. This solid was washed with water (2 X 25 cm^3), methanol (25 cm^3), diethyl ether (6 X 30 cm^3) and dried at 0.1 mm/20 °C to obtain *bis(5-hydroxy-6-methyl-1,2-benzoquinone 2-oximato)calcium(II)* (1.13 g, 61%) (Found: C, 49.0; H, 3.3; Ca, 11.5; N, 8.3. $C_{14}H_{12}CaN_2O_6$ requires C, 48.8; H, 3.5; Ca, 11.5, N, 8.1%); N.m.r.:^{1}H[$(CD_3)_2SO$] (80 MHz), δ 1.61 (3H, s, CH_3), 5.99 (H, d, aromatic), 6.77 (H, d, aromatic), 20.04 p.p.m.(H, s, OH).

5.4.15 Reaction of 5-hydroxy-3-methyl-1,2-benzoquinone 2-oxime monohydrate with calcium hydroxide

5-Hydroxy-3-methyl-1,2-benzoquinone 2-oxime monohydrate (2.50 g, 15 mmol) in methanol (50 cm^3) was added to a suspension of calcium hydroxide (0.40 g, 5 mmol) in water (20 cm^3). The reaction mixture was stirred at 20 °C for 48 h and filtered to obtain an orange coloured solid. This solid was washed with water (2 X 25 cm^3), methanol (25 cm^3), diethyl ether (6 X 30 cm^3) and dried

at 0.1 mm/20 °C to obtain *bis(5-hydroxy-3-methyl-1,2-benzoquinone 2-oximato)calcium(II)* (1.41 g, 76%) (Found: C, 48.4; H, 3.3; Ca, 11.8; N, 8.2. $C_{14}H_{12}CaN_2O_6$ requires C, 48.8; H, 3.5; Ca, 11.5, N, 8.1%); N.m.r.:[$(CD_3)_2SO$] (250 MHz), δ 2.03 (3H, s, CH_3), 4.96 (H, d, aromatic), 5.85 (H, d, aromatic), 20.26 (H, s, OH).

5.4.16 Reaction of 5-hydroxy-1,2-benzoquinone 2-oxime with calcium hydroxide

5-Hydroxy-1,2-benzoquinone 2-oxime (2.09 g, 15 mmol) in methanol (50 cm^3) was added to a suspension of calcium hydroxide (0.40 g, 5 mmol) in water (20 cm^3). The reaction mixture was stirred at 20 °C for 48 h. T.l.c. indicated that the reaction solution consisted of at least 4 components. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. However, separation of the components was not acheved.

5.4.17 Synthesis of N-acetyl-5-amino-1,2-benzoquinone 2-oxime

Bis(N-acetyl-5-amino-1,2-benzoquinone 2-oximato)-nickel(II) tetrahydrate (2.00 g, 4 mmol) was dissolved in methanol (300 cm^3). The solution was added to an ion exchange column (15 cm X 4.5 cm, 'Dowex' 50W - X8(H) ion

exchange resin) and eluted with methanol/water (4:1). The solvent was removed under reduced pressure to obtain *N-acetyl-5-amino-1,2-benzoquinone 2-oxime* (1.28 g, 87%) (Found:C, 53.0; H, 4.1; N, 15.4. $C_8H_8N_2O_3$ requires C, 53.3; H, 4.4; N, 15.6%).

5.4.18 Synthesis of sodium N-acetyl-5-amino-1,2-benzoquinone 2-oximate

N-Acetyl-5-amino-1,2-benzoquinone 2-oxime (6.00 g, 33 mmol) in ethanol (100 cm^3) was added to a solution of sodium ethoxide (1.90 g, 28 mmol) in ethanol (50 cm^3). The reaction solution was stirred at 20 °C for 1 h and the solvent was removed under reduced pressure. The residue was washed with ethyl acetate (4 X 50 cm^3), diethyl ether (4 X 50 cm^3) and dried at 0.1 mm/20 °C to obtain *sodium N-acetyl-5-amino-1,2-benzoquinone 2-oximate* (5.43 g, 96%) (Found: C, 47.7; H, 3.3; Na, 11.0; N, 14.0. $C_8H_7NaN_2O_0$ requires C, 47.5; H, 3.5, Na, 11.4, N, 13.9%).

5.4.19 Acidification of alkali metal complexes of 5-hydroxy-1,2-benzoquinone mono-oximes

Glacial acetic acid (*ca.* 50 cm^3) was slowly added with stirring to a mixture of the alkali metal complex (100 mmol) and crushed ice (*ca.* 50 g). The mixture was left standing for 1 h and filtered. The solid was washed

with water (3 X 30 cm^3) and dried at 0.1 mm/50 °C. (See Table 5.1 for elemental analysis).

5.4.20 Interaction of sodium or potassium 5-hydroxy-1,2-benzoquinone mono-oximes with their corresponding free ligand

Sodium 5-hydroxy-1,2-benzoquinone 2-oximate monohydrate, (1.79 g, 10 mmol) was digested with the corresponding free ligand, i.e. 3-hydroxy-1,2-benzoquinone 2-oxime (1.39 g, 10 mmol) in refluxing methanol (50 cm^3). After 1 h the solution was cooled and the solvent was removed under reduced pressure. Comparitive t.l.c. of the residue indicated that only the starting materials were present. This was confirmed by extraction of the residue with diethyl ether. The free ligand dissolved in diethyl ether where as the sodium complex did not (identified by i.r.).

Sodium 5-hydroxy-3-methyl-1,2-benzoquinone 2-oximate dihydrate, sodium 5-hydroxy-6-methyl-1,2-benzoquinone 2-oximate monohydrate and the potassium derivates of these compounds behaved similarly.

5.4.21 Reaction of 5-hydroxy-3-methyl-1,2-benzoquinone 2-oxime monohydrate with ammonium iron(II) sulphate hexahydrate

Ammonium iron(II) sulphate hexahydrate (9.80 g, 25 mmol) in water (70 cm^3) was added to a solution of 5-hydroxy-3-methyl-1,2-benzoquinone 2-oxime monohydrate (8.55 g, 50 mmol) in methanol (150 cm^3). The reaction mixture was stirred at 20 °C for 48 h and filtered to give a dark green solid. This solid was washed with water (75 cm^3), methanol (50 cm^3), ethyl acetate (100 cm^3), and dried at 0.1mm/60 °C to give *bis(5-hydroxy-3-methyl-1,2-benzoquinone 2-oximato)iron(II) dihydrate* (7.62 g, 77%) (Found: C, 42.3; H, 3.9; Fe, 13.9; N, 7.1. $C_{14}H_{16}FeN_2O_8$ requires C, 42.4; H, 4.0; Fe, 14.1; N, 7.1%).

5.4.22 Reaction of 5-hydroxy-1,2-benzoquinone 2-oxime with ammonium iron(II) sulphate hexahydrate

Ammonium iron(II) sulphate hexahydrate (19.60 g, 50 mmol) in water (150 cm^3) was added to a solution of 5-hydroxy-1,2-benzoquinone 2-oxime (13.90 g, 100 mmol) in methanol (400 cm^3). The reaction mixture was stirred at 20 °C for 48 h and filtered to obtain a dark green solid. This solid was washed with water (150 cm^3), methanol (100 cm^3), and finally extracted (Soxhlet) with ethyl acetate. The residue was dried at 0.1mm/60 °C to

give *bis(5-hydroxy-1,2-benzoquinone 2-oximato)iron(II) trihydrate* (11.62 g, 60%) (Found: C, 37.1; H, 3.4; Fe, 14.1; N, 7.0. $C_{12}H_{14}FeN_2O_9$ requires C, 37.3; H, 3.6; Fe, 14.5; N, 7.3%).

5.4.23 Reaction of 5-hydroxy-6-methyl-1,2-benzoquinone 2-oxime monohydrate with ammonium iron(II) sulphate hexahydrate

Ammonium iron(II) sulphate hexahydrate (9.80 g, 25 mmol) in water (70 cm^3) was added to a solution of 5-hydroxy-6-methyl-1,2-benzoquinone 2-oxime monohydrate (8.55 g, 50 mmol)in methanol (150 cm^3). The reaction mixture was stirred at 20 °C for 48 h and filtered to obtain a dark green solid. This solid was washed with water (75 cm^3), methanol (50 cm^3), and finally extracted (Soxhlet) with ethyl acetate. The residue was dried at 0.1mm/60 °C to give *bis(5-hydroxy-6-methyl-1,2-benzoquinone 2-oximato)iron(II) dihydrate* (5.4 g, 55%) (Found: C, 42.7; H, 3.6; Fe, 13.9;, N, 7.0. $C_{14}H_{16}FeN_2O_8$ requires C, 42.4; H, 4.0; Fe, 14.0; N, 7.1%).

5.4.24 Interaction of bis(3-hydroxy-1,2-quinone mono-oximato)iron(II) hydrates with pyridine

The bis(5-hydroxy-1,2-benzoquinone mono-oximato)iron(II) hydrate (2.00 g) was refluxed in

pyridine for 2 h and filtered hot. The residue was washed with diethyl ether (5 X 50 cm^3) and dried at 0.1 mm/20 °C. (See Table 5.2 for yields and elemental analysis).

5.4.25 Reaction of 3-hydroxyphenol with sodium nitrite/acetic acid in the presence of ammonium iron(II) sulphate hexahydrate

Sodium nitrite (25.00 g) in water (50 cm^3) was added dropwise with stirring to a solution of 3-hydroxyphenol (11.01 g, 100 mmol), ammonium iron(II) sulphate hexahydrate (19.61 g, 50 mmol), acetic acid (45 cm^3) and sodium acetate trihydrate (45.00 g) in ethanol/water (1:1) (600 cm^3) at 0 °C. The reaction mixture was stirred at 20 °C for 24 h and then filtered to obtain a black solid. The solid was washed with water (3 X 100 cm^3), ethanol (3 X 50 cm^3), diethyl ether (2 X 50 cm^3) and dried at 0.1 mm/50 °C to give a black solid (solid S1) (21.20 g) (Found: C, 27.9; H, 2.4; Fe, 14.5; Na, 3.9; N, 11.2%). (See Table 5.3 for Mossbauer and t.g.a. results).

5.4.26 Interaction of solid S1 with pyridine

The solid S1 (5.00 g) was digested in pyridine (150 cm^3) at 50 °C for 2 h and filtered hot. The solid was washed with ethanol (50 cm^3), light petroleum (b.p. 30 - 40 °C)

Table 5.2 Products Obtained by the Interaction of Bis(5-hydroxy-1,2-benzoquinone mono-oximato)iron(II) Hydrates with Pyridine

REACTANT		PRODUCT				
Complex	Wt. Used/g	Yield/g	Found % Fe			
			C	H	Fe	N
$Fe(hqoH)_2 \cdot 3H_2O$	2.00	1.87	44.7	3.1	9.6	8.4
$Fe(3\text{-}MehqoH)_2 \cdot 2H_2O$	2.00	1.39	54.0	3.4	5.3	5.1
$Fe(6\text{-}MehqoH)_2 \cdot 2H_2O$	2.00	1.76	54.4	4.1	9.9	10.2

(6 X 75 cm^3). The residue was dried at 0.1 mm/20 °C to obtain a solid (solid S2) (4.68 g) (Found: C, 33.0; H, 2.6; Fe, 12.4; Na, 3.3; N, 11.9%). (See Table 5.3 for Mössbauer and t.g.a. results).

5.4.27 Reaction of 3-hydroxy-5-methylphenol monohydrate with sodium nitrite/acetic acid in the presence of ammonium iron(II) sulphate hexahydrate

Sodium nitrite (25.00 g) in water (50 cm^3) was added dropwise with stirring to a solution of 3-hydroxy-5-methylphenol monohydrate (14.20 g, 100 mmol), ammonium iron(II) sulphate hexahydrate (19.61 g, 50 mmol), acetic acid (45 cm^3) and sodium acetate trihydrate (45.00 g) in ethanol/water (1:1) (500 cm^3) at 0 °C. The reaction mixture was stirred at 20 °C for 48 h and then filtered to give a solid. The solid was washed with water (3 X 100 cm^3), ethanol (3 X 50 cm^3), diethyl ether (2 X 50 cm^3) and dried at 0.1 mm/50 °C to give a black solid (solid S3) (20.40 g) (Found: C, 31.3; H, 2.8; Fe, 12.2; Na, 2.4; N, 11.2%). (See Table 5.3 for Mossbauer and t.g.a. results).

5.4.28 Interaction of solid S3 with pyridine

The solid S3 (5.00 g) was digested in pyridine (150 cm^3) at 50 °C for 2 h and filtered hot. The solid was washed with ethanol (50 cm^3), light petroleum (b.p. 30 - 40 °C)

(6 X 75 cm^3). The residue was dried at 20 °C/0.1 mm to give a black solid (solid S4) (4.60 g) (Found: C, 37.7; H, 2.9; Fe, 10.3; Na, 2.2; N, 11.9%). (See Table 5.3 for Mossbauer and t.g.a. results).

5.4.29 Reaction of 3-hydroxy-2-methylphenol with sodium nitrite/acetic acid in the presence of ammonium iron(II) sulphate hexahydrate

Sodium nitrite (25.00 g, 36 mmol) in water (50 cm^3) was added dropwise with stirring to a solution of 3-hydroxy-2-methylphenol monohydrate (12.40 g, 100 mmol), ammonium iron(II) sulphate hexahydrate (19.61 g, 50 mmol), acetic acid (45 cm^3) and sodium acetate (26.00 g) in ethanol/water (1:1) (400 cm^3) at 0 °C. The reaction mixture was stirred at 20 °C for 48 h and then filtered to obtain a solid. The solid was washed with water (3 X 100 cm^3), and methanol (3 X 50 cm^3) followed by extraction (Soxhlet) with ethyl acetate. The residue was dried at 0.1 mm/50 °C to obtain a black solid (solid S5) (11.60 g) (Found: C, 44.8; H, 3.7; Fe, 11.3; Na, 2.55; N, 8.0%). (See Table 5.3 for Mossbauer and t.g.a. results).

5.4.30 Interaction of solid S5 with pyridine

The solid S5 (1.20 g) was digested in pyridine (50 cm^3) at 50 °C for 2 h and filtered hot. The solid was washed

Table 5.3 Mössbauer Parameters and Decomposition Temperatures for Solids S1-S6

Solid	Mossbauer Parameters				Decomposition Temperature†/ °C
	20 / °C		-196 / °C		
	δ*/mms^{-1}	Δ /mms^{-1}	δ*/mms^{-1}	Δ /mms^{-1}	
S1	0.23	0.71	0.24	0.74	110
S2	0.16	0.74	0.22	0.84	115
S3	0.15	0.64	0.28	0.82	70
S4	0.20	0.78	0.24	0.83	90
S5	0.16	0.75	0.23	0.76	125
S6	0.10	0.72	0.15	0.77	130
	0.19	1.82	0.24	1.84	

*=Relative to metallic iron †=From thermal gravimetric analysis

with ethanol (50 cm^3), ethyl acetate (50 cm^3), light petroleum (b.p. 30 - 40 °C) (6 X 50 cm^3). The residue was dried at 20 °C/0.1 mm to obtain solid (solid S6) (1.15 g) (Found: C, 47.5; H, 3.7; Fe, 9.3; Na, 2.1; N, 9.3%). (See Table 5.3 for Mössbauer and t.g.a. results).

5.4.31 Reaction of N-acetyl-3-aminophenol with sodium nitrite/acetic acid in the presence of ammonium iron(II) sulphate hexahydrate

Sodium nitrite (14.00 g, 203 mmol) in water (60 cm^3) was added dropwise with stirring to a solution of ammonium iron(II) sulphate hexahydrate (29.40 g, 75 mmol), N-acetyl-3-aminophenol (22.65 g, 150 mmol) acetic acid (45 cm^3) and sodium acetate in ethanol/water (1:1) (600 cm^3) at 0 °C. The mixture was set aside at 20 °C for 72 h and then filtered to obtain a dark green solid. A portion (2.50 g) of this solid was chromatographed on silica gel. Elution with ethyl acetate gave *N-acetyl-3-amino-1,4-benzoquinone 4-oxime* (0.30 g) m.p. 187 - 190 °C (decomp.) (Found: C, 53.3; H, 4.5; N, 15.6. $C_8H_8N_2O_3$ requires C, 53.3, H, 4.4; N, 15.6%); *m/z* 180 (M^+). Elution with methanol gave *sodium tris(N-acetyl-5-amino-1,2-benzoquinone 2-oximato)ferrate(II) tetrahydrate* (1.36 g) (Found: C, 41.7, H, 4.3;, Fe, 8.2; Na, 3.1; N, 12.0. $C_{24}H_{29}FeNaN_6O_{13}$ requires C, 41.9; H, 4.2; Fe, 8.1; Na, 3.3; N, 12.2%). Pyridine was then added to the chromatographey column. Elution with methanol after

1 h yielded *bis(N-acetyl-5-amino-1,2-benzoquinone 2-oximato)iron(II) dipyridine* (0.69 g) (Found: C, 54.9; H, 4.3; Fe, 9.6; N, 14.7. $C_{26}H_{24}FeN_6O_6$ requires C, 54.6; H, 4.2; Fe, 9.8; N, 14.7%).

5.5 References

1 A. Earnshaw, 'Introduction to Magnetochemistry', Academic Press, London, 1968.

APPENDIX

Details of The Crystal Structure of 3-Hydroxy-2-methyl-1,4-benzoquinone 4-oxime monohydrate

Table 1 Atomic coordinates and thermal parameters ($Å^2$) for the non-hydrogen atoms in 3-Hydroxy-2-methyl-1,4-benzoquinone 4-oxime monohydrate

Atom	x	y	z	U_{eq}
C(1)	0.4151(13)	0.2417(3)	0.1996(3)	0.0371(16)
C(2)	0.3384(12)	0.3310(3)	0.2500(3)	0.0359(15)
C(3)	0.1796(12)	0.3307(3)	0.3318(3)	0.0370(16)
C(4)	0.0755(15)	0.2378(3)	0.3688(3)	0.0400(17)
C(5)	0.1525(15)	0.1486(4)	0.3182(4)	0.0463(19)
C(6)	0.3135(14)	0.1505(3)	0.2388(3)	0.0419(18)
C(7)	0.1000(17)	0.4209(4)	0.3855(4)	0.0474(20)
N	0.5747(11)	0.2536(3)	0.1232(3)	0.0428(15)
O(1)	0.6475(10)	0.1687(3)	0.0784(2)	0.0571(14)
O(2)	0.4374(9)	0.4157(2)	0.2130(2)	0.0504(13)
O(3)	-0.0746(10)	0.2317(3)	0.4444(2)	0.0547(14)
O(W)	0.7510(11)	0.0561(3)	0.5369(3)	0.0783(17)

Table 2 Atomic coordinates and thermal parameters ($Å^2$) for the hydrogen atoms in 3-Hydroxy-2-methyl-1,4-benzoquinone 4-oxime monohydrate

Atom	x	y	z	U
H(O1)	0.733(15)	0.199(5)	0.023(4)	0.087(21)
H(O2)	0.521(17)	0.410(5)	0.152(5)	0.111(25)
H1(C7)	0.190(14)	0.413(4)	0.454(4)	0.070(17)
H2(C7)	0.159(17)	0.475(5)	0.344(5)	0.099(22)
H3(C7)	-0.123(23)	0.431(7)	0.400(6)	0.158(37)
H(C5)	0.084(12)	0.096(4)	0.342(3)	0.049(15)
H(C6)	0.351(11)	0.093(3)	0.206(3)	0.042(13)

Table 3 Bond Lengths (Å) for 2-Methyl-3-hydroxy-1,4-benzoquinone 4-oxime monohydrate

C(1) - C(2)	1.458(6)	C(3) - C(7)	1.495(7)
C(2) - C(3)	1.340(6)	C(4) - O(3)	1.247(5)
C(3) - C(4)	1.445(6)	C(5) - H(C5)	0.84(5)
C(4) - C(5)	1.458(7)	C(6) - H(C6)	0.93(5)
C(5) - C(6)	1.314(7)	C(7) - H1(C7)	1.03(6)
C(6) - C(1)	1.434(6)	C(7) - H2(C7)	0.98(6)
C(1) - N	1.284(6)	C(7) - H3(C7)	0.92(9)
N - O(1)	1.364(6)	O(1) - H(O1)	0.96(6)
C(2) - O(2)	1.341(5)	O(2) - H(O2)	0.94(7)

Table 4 Bond Angles (°) for 2-Methyl-3-hydroxy-1,4-benzoquinone 4-oxime monohydrate

C(6)	- C(1) -	C(2)	118.6(4)
C(6)	- C(1) -	N	126.3(4)
C(2)	- C(1) -	N	115.1(4)
C(1)	- C(2) -	C(3)	122.4(4)
C(1)	- C(2) -	O(2)	118.0(4)
C(3)	- C(2) -	O(2)	119.6(4)
C(2)	- C(3) -	C(4)	117.8(4)
C(2)	- C(3) -	C(7)	123.6(4)
C(4)	- C(3) -	C(7)	118.6(4)
C(3)	- C(4) -	C(5)	119.8(4)
C(3)	- C(4) -	O(3)	121.5(4)
C(5)	- C(4) -	O(3)	118.8(4)
C(4)	- C(5) -	C(6)	121.5(5)
C(5)	- C(6) -	C(1)	120.0(5)
C(1)	- N -	O(1)	113.8(4)
C(4)	- C(5) -	H(C5)	116(3)
C(6)	- C(5) -	H(C5)	122(3)
C(5)	- C(6) -	H(C6)	120(3)
C(1)	- C(6) -	H(C6)	120(3)
C(3)	- C(7) -	H1(C7)	109(3)
C(3)	- C(7) -	H2(C7)	105(4)
C(3)	- C(7) -	H3(C7)	117(6)
H1(C7)	- C(7) -	H2(C7)	125(5)

Table 4 cont.

H1(C7)	- C(7) -	H3(C7)	96(6)
H2(C7)	- C(7) -	H3(C7)	105(7)
N	- O(1) -	H(O1)	96(4)
C(2)	- O(2) -	H(O2)	114(4)

Table 5 Intermolecular Distances Less than the Sum of the Corresponding Van Der Waals Radii

N	··· $O(3)^{II}$	2.942(5)	O(W)	··· $O(W)^{V}$	2.687(6)
N	··· $O(W)^{III}$	2.981(6)	O(W)	··· $O(W)^{VI}$	2.731(6)
O(1)	··· $O(3)^{II}$	2.616(5)	C(4)	··· $H(O1)^{VII}$	2.75(6)
O(2)	··· $O(W)^{III}$	2.856(5)	O(3)	··· $H(O1)^{VII}$	1.67(6)
O(3)	··· $O(W)^{I}$	2.844(6)	O(W)	··· $H(O2)^{IV}$	1.95(7)

Symmetry Code:

I: -1+x, y, z
II: 1+x, 1/2-y, -1/2+z
III: x, 1/2-y, -1/2+z
IV: x, 1/2-y, 1/2+z
V: 1-x, -y, 1-z
VI: 2-x, -y, 1-z
VII: -1+x, 1/2-y, 1/2+z

Table 6 Anisotropic temperature coefficients ($Å^2$ X 10^4) for 3-hydroxy-2-methyl-1,4-benzoquinone 4-oxime monohydrate

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	413(31)	386(28)	318(24)	4(25)	57(24)	24(22)
C(2)	405(29)	287(24)	384(25)	-10(24)	7(24)	55(22)
C(3)	413(31)	295(25)	404(27)	6(23)	50(25)	19(21)
C(4)	423(33)	391(29)	388(28)	35(24)	47(27)	-11(22)
C(5)	616(38)	268(28)	514(32)	-31(27)	140(30)	44(24)
C(6)	536(35)	304(28)	426(28)	32(27)	127(27)	-26(23)
C(7)	561(40)	387(30)	486(33)	21(30)	167(32)	-66(26)
N	542(29)	341(23)	410(23)	-30(21)	137(23)	-47(19)
O(1)	820(29)	406(20)	507(22)	-17(20)	281(22)	-89(19)
O(2)	693(27)	301(19)	532(22)	-38(18)	203(20)	26(17)
O(3)	725(28)	471(22)	466(20)	-28(19)	305(20)	0(16)
O(W)	1050(35)	541(24)	780(27)	88(24)	333(25)	40(20)

Table 7 Observed and Calculated Structure Factors

H	K	L	F(O)	F(C)	H	K	L	F(O)	F(C)	H	K	L	F(O)	F(C)
1	0	0	16.4	16.6	1	13	0	6.6	6.0	-2	6	1	5.3	4.1
2	0	0*	2.5	1.7	2	13	0*	2.8	2.3	-1	6	1	14.8	15.2
3	0	0*	0.7	2.0	0	14	0	4.2	3.5	0	6	1	12.8	11.5
4	0	0	7.7	9.9	1	14	0	5.4	6.4	1	6	1	16.3	16.0
1	1	0	31.9	31.7	2	14	0*	0.8	1.8	2	6	1	13.1	12.9
2	1	0	7.7	8.2	1	15	0	9.9	8.8	3	6	1*	2.8	0.9
3	1	0	3.6	3.0	0	16	0*	2.0	3.7	4	6	1*	2.4	0.3
4	1	0*	0.8	0.1	-4	1	1*	0.8	0.8	-4	7	1*	2.1	1.5
1	2	0	3.4	3.1	-3	1	1	5.8	6.1	-3	7	1	5.1	5.5
2	2	0	16.0	15.5	-2	1	1	10.8	10.6	-2	7	1*	1.9	2.5
3	2	0	4.5	5.4	-1	1	1	3.8	2.6	-1	7	1	6.5	6.8
4	2	0	4.2	5.9	1	1	1	14.1	13.9	0	7	1	22.8	23.5
1	3	0	14.0	15.7	2	1	1	3.0	2.0	1	7	1	9.1	9.2
2	3	0*	1.4	0.6	3	1	1	8.0	7.7	2	7	1	3.2	3.2
3	3	0	12.7	12.1	4	1	1*	1.9	3.9	3	7	1*	0.7	0.1
4	3	0*	2.3	1.2	-4	2	1*	1.6	0.4	4	7	1*	0.8	1.0
0	4	0*	0.6	0.4	-3	2	1	7.8	7.9	-4	8	1*	0.8	1.4
1	4	0	10.2	10.3	-2	2	1	25.3	24.2	-3	8	1*	2.6	3.3
2	4	0	26.0	23.3	-1	2	1	3.5	4.9	-2	8	1*	2.7	3.0
3	4	0*	0.7	0.3	0	2	1	18.4	18.0	-1	8	1	5.2	4.8
4	4	0*	0.8	0.0	1	2	1	22.1	20.8	0	8	1	12.2	12.4
1	5	0	34.0	34.8	2	2	1	7.6	7.0	1	8	1	16.9	17.8
2	5	0	9.1	7.8	3	2	1*	3.1	2.7	2	8	1*	2.2	1.1
3	5	0	9.3	9.1	4	2	1*	0.8	0.1	3	8	1	5.1	6.1
4	5	0*	0.8	0.6	-4	3	1*	0.8	0.5	4	8	1*	2.3	0.8
0	6	0	33.7	33.9	-3	3	1	4.9	4.5	-3	9	1*	1.8	1.6
1	6	0*	1.5	0.9	-2	3	1	6.0	6.6	-2	9	1	10.7	11.2
2	6	0	35.5	33.6	-1	3	1	28.9	30.2	-1	9	1	3.8	4.1
3	6	0	6.9	6.4	0	3	1	26.7	26.9	0	9	1	15.0	14.9
4	6	0*	2.6	0.2	1	3	1	11.9	12.8	1	9	1	13.0	13.3
1	7	0*	2.2	2.4	2	3	1	18.9	20.0	2	9	1*	0.7	1.2
2	7	0	7.1	6.7	3	3	1*	2.1	1.9	3	9	1	4.9	4.5
3	7	0	3.7	3.3	4	3	1*	1.8	0.7	-3	10	1*	3.5	4.0
4	7	0*	2.0	1.1	-4	4	1*	2.3	1.9	-2	10	1	10.1	10.7
0	8	0	5.1	4.6	-3	4	1	3.8	2.5	-1	10	1*	2.3	0.1
1	8	0*	1.7	3.1	-2	4	1	5.6	5.6	0	10	1	26.1	26.1
2	8	0	14.9	14.6	-1	4	1	21.4	22.4	1	10	1*	2.6	1.7
3	8	0*	1.9	0.7	0	4	1	46.6	46.9	2	10	1	5.2	6.1
4	8	0*	1.7	0.7	1	4	1	34.0	35.5	3	10	1*	0.8	0.6
1	9	0*	2.4	0.6	2	4	1	13.9	13.3	-3	11	1*	2.4	4.7
2	9	0*	2.5	2.9	3	4	1*	2.4	0.6	-2	11	1*	1.8	3.3
3	9	0	4.8	5.2	4	4	1*	3.1	3.0	-1	11	1	7.3	8.4
0	10	0	39.3	38.1	-4	5	1*	2.2	1.0	0	11	1	22.0	20.7
1	10	0*	0.7	1.3	-3	5	1	7.3	7.1	1	11	1	26.5	25.2
2	10	0	5.0	5.6	-2	5	1	11.0	10.3	2	11	1	4.5	4.4
3	10	0*	0.8	1.7	-1	5	1	28.3	29.6	3	11	1*	3.0	4.4
1	11	0	9.1	9.2	0	5	1*	1.5	1.8	-3	12	1*	0.8	0.2
2	11	0	4.2	4.5	1	5	1	13.9	14.4	-2	12	1*	1.6	0.3
3	11	0*	3.2	3.1	2	5	1	7.0	5.5	-1	12	1*	2.9	2.8
0	12	0	39.3	38.8	3	5	1	6.9	6.6	0	12	1	14.5	13.7
1	12	0	10.4	9.9	4	5	1*	0.8	1.9	1	12	1	7.5	6.6
2	12	0	4.6	3.9	-4	6	1*	0.8	0.9	2	12	1*	1.6	2.3
3	12	0*	0.9	0.2	-3	6	1*	0.7	0.3	3	12	1*	2.2	1.1

*=Unobserved reflections

Table 7 (cont.)

H	K	L	F(O)	F(C)	H	K	L	F(O)	F(C)	H	K	L	F(O)	F(C)
1	3	3	23.9	25.1	2	9	3*	2.6	2.9	3	1	4*	3.1	2.7
2	3	3	4.2	4.3	3	9	3*	2.8	2.7	4	1	4*	0.9	1.5
3	3	3*	1.8	0.2	-3	10	3*	2.9	4.4	-4	2	4*	0.8	1.1
4	3	3*	0.8	0.2	-2	10	3	7.7	8.6	-3	2	4	5.6	4.8
-4	4	3	6.7	8.1	-1	10	3	17.7	18.7	-2	2	4	20.3	19.1
-3	4	3*	3.1	2.2	0	10	3	7.2	7.0	-1	2	4	28.8	27.6
-2	4	3	21.8	21.0	1	10	3	26.0	26.1	0	2	4	26.2	26.2
-1	4	3	35.7	35.9	2	10	3	13.6	12.6	1	2	4	6.4	5.9
0	4	3	42.9	43.7	3	10	3*	1.9	3.1	2	2	4	29.9	26.3
1	4	3	3.0	3.9	-3	11	3*	3.0	4.7	3	2	4	4.6	4.2
2	4	3*	1.8	1.1	-2	11	3*	2.1	0.8	4	2	4*	3.6	1.8
3	4	3	9.3	9.2	-1	11	3	7.0	6.8	-4	3	4	4.2	4.7
4	4	3*	1.8	1.4	0	11	3	3.5	2.8	-3	3	4*	0.7	2.0
-4	5	3*	0.9	2.5	1	11	3	10.5	11.0	-2	3	4	8.2	7.3
-3	5	3*	1.7	1.0	2	11	3	5.9	5.4	-1	3	4	29.6	30.4
-2	5	3	3.1	4.3	3	11	3*	0.8	2.2	0	3	4	20.5	21.2
-1	5	3*	0.6	1.2	-3	12	3*	2.1	0.8	1	3	4	9.5	10.1
0	5	3	15.0	14.7	-2	12	3*	1.6	2.2	2	3	4*	1.7	1.0
1	5	3	12.2	11.4	-1	12	3*	2.7	1.6	3	3	4*	0.7	0.2
2	5	3	9.0	8.8	0	12	3	6.9	6.9	4	3	4*	0.8	2.4
3	5	3	3.9	4.8	1	12	3	13.6	13.5	-4	4	4	4.8	7.1
4	5	3*	1.8	2.4	2	12	3	11.2	11.2	-3	4	4*	0.7	0.5
-4	6	3*	3.1	4.4	3	12	3*	1.6	0.5	-2	4	4	5.7	5.1
-3	6	3*	3.3	4.7	-2	13	3*	2.7	1.8	-1	4	4	16.8	18.0
-2	6	3	3.0	2.8	-1	13	3	5.2	6.6	0	4	4	26.9	27.5
-1	6	3	5.9	5.1	0	13	3*	1.9	1.8	1	4	4	14.0	13.7
0	6	3	8.7	9.0	1	13	3	4.4	4.3	2	4	4	4.4	4.4
1	6	3	10.4	10.4	2	13	3*	2.6	3.0	3	4	4	6.6	5.5
2	6	3*	2.8	1.9	-2	14	3*	0.8	1.2	4	4	4*	0.8	4.1
3	6	3*	0.7	1.4	-1	14	3*	2.6	1.6	-4	5	4	12.4	17.5
4	6	3*	0.9	2.0	0	14	3	9.8	8.6	-3	5	4*	1.8	1.3
-4	7	3*	2.6	0.3	1	14	3	4.8	2.9	-2	5	4	4.4	4.9
-3	7	3	3.7	1.6	2	14	3*	0.8	2.4	-1	5	4	21.0	21.3
-2	7	3	7.6	7.9	-1	15	3*	1.9	0.5	0	5	4	48.1	47.3
-1	7	3*	2.1	1.0	0	15	3*	2.7	1.8	1	5	4	19.1	19.8
0	7	3	7.6	8.1	1	15	3*	1.8	0.4	2	5	4	10.2	10.2
1	7	3	21.6	22.1	0	16	3	8.7	7.6	3	5	4	4.7	5.6
2	7	3	13.5	13.2	-4	0	4	4.9	4.9	4	5	4*	0.9	5.5
3	7	3	4.4	3.5	-3	0	4	10.2	9.1	-4	6	4	8.4	12.7
4	7	3*	1.7	2.1	-2	0	4	38.4	32.1	-3	6	4	8.9	8.3
-4	8	3*	0.9	2.1	-1	0	4	55.5	51.6	-2	6	4	4.6	5.2
-3	8	3	4.1	3.9	0	0	4	4.2	5.2	-1	6	4	16.3	15.7
-2	8	3	3.4	3.9	1	0	4	14.4	14.2	0	6	4	19.2	17.7
-1	8	3	4.7	4.7	2	0	4	60.4	55.7	1	6	4	5.9	6.6
0	8	3	5.9	5.4	3	0	4	12.0	11.8	2	6	4*	1.9	1.1
1	8	3	8.1	8.5	4	0	4*	0.8	1.0	3	6	4	4.2	4.4
2	8	3*	2.0	4.3	-4	1	4*	1.8	1.9	4	6	4*	1.9	4.1
3	8	3*	2.1	1.6	-3	1	4	6.4	5.4	-4	7	4	8.1	11.7
-3	9	3*	1.9	1.6	-2	1	4	22.1	18.6	-3	7	4*	2.1	1.9
-2	9	3	8.5	9.5	-1	1	4	10.9	12.0	-2	7	4	4.7	4.6
-1	9	3*	1.3	0.6	0	1	4*	1.2	1.6	-1	7	4	7.3	7.1
0	9	3	8.6	9.4	1	1	4	17.2	19.4	0	7	4	49.2	46.4
1	9	3	3.5	3.2	2	1	4	61.6	55.4	1	7	4	4.1	4.3

Table 7 (cont.)

H	K	L	F(O)	F(C)	H	K	L	F(O)	F(C)	H	K	L	F(O)	F(C)
1	3	3	23.9	25.1	2	9	3*	2.6	2.9	3	1	4*	3.1	2.7
2	3	3	4.2	4.3	3	9	3*	2.8	2.7	4	1	4*	0.9	1.5
3	3	3*	1.8	0.2	-3	10	3*	2.9	4.4	-4	2	4*	0.8	1.1
4	3	3*	0.8	0.2	-2	10	3	7.7	8.6	-3	2	4	5.6	4.8
-4	4	3	6.7	8.1	-1	10	3	17.7	18.7	-2	2	4	20.3	19.1
-3	4	3*	3.1	2.2	0	10	3	7.2	7.0	-1	2	4	28.8	27.6
-2	4	3	21.8	21.0	1	10	3	26.0	26.1	0	2	4	26.2	26.2
-1	4	3	35.7	35.9	2	10	3	13.6	12.6	1	2	4	6.4	5.9
0	4	3	42.9	43.7	3	10	3*	1.9	3.1	2	2	4	29.9	26.3
1	4	3	3.0	3.9	-3	11	3*	3.0	4.7	3	2	4	4.6	4.2
2	4	3*	1.8	1.1	-2	11	3*	2.1	0.8	4	2	4*	3.6	1.8
3	4	3	9.3	9.2	-1	11	3	7.0	6.8	-4	3	4	4.2	4.7
4	4	3*	1.8	1.4	0	11	3	3.5	2.8	-3	3	4*	0.7	2.0
-4	5	3*	0.9	2.5	1	11	3	10.5	11.0	-2	3	4	8.2	7.3
-3	5	3*	1.7	1.0	2	11	3	5.9	5.4	-1	3	4	29.6	30.4
-2	5	3	3.1	4.3	3	11	3*	0.8	2.2	0	3	4	20.5	21.2
-1	5	3*	0.6	1.2	-3	12	3*	2.1	0.8	1	3	4	9.5	10.1
0	5	3	15.0	14.7	-2	12	3*	1.6	2.2	2	3	4*	1.7	1.0
1	5	3	12.2	11.4	-1	12	3*	2.7	1.6	3	3	4*	0.7	0.2
2	5	3	9.0	8.8	0	12	3	6.9	6.9	4	3	4*	0.8	2.4
3	5	3	3.9	4.8	1	12	3	13.6	13.5	-4	4	4	4.8	7.1
4	5	3*	1.8	2.4	2	12	3	11.2	11.2	-3	4	4*	0.7	0.5
-4	6	3*	3.1	4.4	3	12	3*	1.6	0.5	-2	4	4	5.7	5.1
-3	6	3*	3.3	4.7	-2	13	3*	2.7	1.8	-1	4	4	16.8	18.0
-2	6	3	3.0	2.8	-1	13	3	5.2	6.6	0	4	4	26.9	27.5
-1	6	3	5.9	5.1	0	13	3*	1.9	1.8	1	4	4	14.0	13.7
0	6	3	8.7	9.0	1	13	3	4.4	4.3	2	4	4	4.4	4.4
1	6	3	10.4	10.4	2	13	3*	2.6	3.0	3	4	4	6.6	5.5
2	6	3*	2.8	1.9	-2	14	3*	0.8	1.2	4	4	4*	0.8	4.1
3	6	3*	0.7	1.4	-1	14	3*	2.6	1.6	-4	5	4	12.4	17.5
4	6	3*	0.9	2.0	0	14	3	9.8	8.6	-3	5	4*	1.8	1.3
-4	7	3*	2.6	0.3	1	14	3	4.8	2.9	-2	5	4	4.4	4.9
-3	7	3	3.7	1.6	2	14	3*	0.8	2.4	-1	5	4	21.0	21.3
-2	7	3	7.6	7.9	-1	15	3*	1.9	0.5	0	5	4	48.1	47.3
-1	7	3*	2.1	1.0	0	15	3*	2.7	1.8	1	5	4	19.1	19.8
0	7	3	7.6	8.1	1	15	3*	1.8	0.4	2	5	4	10.2	10.2
1	7	3	21.6	22.1	0	16	3	8.7	7.6	3	5	4	4.7	5.6
2	7	3	13.5	13.2	-4	0	4	4.9	4.9	4	5	4*	0.9	5.5
3	7	3	4.4	3.5	-3	0	4	10.2	9.1	-4	6	4	8.4	12.7
4	7	3*	1.7	2.1	-2	0	4	38.4	32.1	-3	6	4	8.9	8.3
-4	8	3*	0.9	2.1	-1	0	4	55.5	51.6	-2	6	4	4.6	5.2
-3	8	3	4.1	3.9	0	0	4	4.2	5.2	-1	6	4	16.3	15.7
-2	8	3	3.4	3.9	1	0	4	14.4	14.2	0	6	4	19.2	17.7
-1	8	3	4.7	4.7	2	0	4	60.4	55.7	1	6	4	5.9	6.6
0	8	3	5.9	5.4	3	0	4	12.0	11.8	2	6	4*	1.9	1.1
1	8	3	8.1	8.5	4	0	4*	0.8	1.0	3	6	4	4.2	4.4
2	8	3*	2.0	4.3	-4	1	4*	1.8	1.9	4	6	4*	1.9	4.1
3	8	3*	2.1	1.6	-3	1	4	6.4	5.4	-4	7	4	8.1	11.7
-3	9	3*	1.9	1.6	-2	1	4	22.1	18.6	-3	7	4*	2.1	1.9
-2	9	3	8.5	9.5	-1	1	4	10.9	12.0	-2	7	4	4.7	4.6
-1	9	3*	1.3	0.6	0	1	4*	1.2	1.6	-1	7	4	7.3	7.1
0	9	3	8.6	9.4	1	1	4	17.2	15.4	0	7	4	49.2	46.4
1	9	3	3.5	3.2	2	1	4	61.6	55.4	1	7	4	4.1	4.3

Table 7 (cont.)

H	K	L	F(O)	F(C)	H	K	L	F(O)	F(C)	H	K	L	F(O)	F(C)
2	7	4	3.9	3.0	-1	1	5	16.2	16.4	-2	7	5*	1.9	1.7
3	7	4*	2.1	1.6	0	1	5	40.3	40.1	-1	7	5	3.4	4.1
4	7	4*	3.2	5.2	1	1	5	3.8	3.9	0	7	5	3.9	4.2
-3	8	4*	0.7	0.6	2	1	5	10.8	10.0	1	7	5	3.5	3.3
-2	8	4*	1.6	0.0	3	1	5	6.4	6.2	2	7	5*	1.5	0.2
-1	8	4	20.0	20.9	4	1	5*	0.8	1.6	3	7	5*	0.8	2.5
0	8	4	13.2	14.3	-4	2	5*	1.8	2.9	-3	8	5	3.9	2.5
1	8	4*	0.6	1.6	-3	2	5	10.4	9.8	-2	8	5	4.0	4.1
2	8	4	5.6	5.0	-2	2	5	10.1	10.5	-1	8	5	17.7	18.8
3	8	4*	2.0	2.0	-1	2	5	3.6	2.4	0	8	5*	2.4	1.6
-3	9	4	5.2	4.5	0	2	5	2.9	3.3	1	8	5*	3.1	2.4
-2	9	4	3.6	4.2	1	2	5	8.8	8.1	2	8	5	6.3	6.7
-1	9	4	7.1	7.4	2	2	5	9.6	9.0	3	8	5*	0.8	0.1
0	9	4	3.8	3.9	3	2	5	5.4	5.8	-3	9	5*	0.8	1.5
1	9	4	3.7	4.1	4	2	5*	0.8	1.4	-2	9	5	10.8	11.0
2	9	4	3.8	3.1	-4	3	5*	3.2	1.6	-1	9	5	9.2	10.1
3	9	4*	2.3	2.2	-3	3	5	7.1	7.0	0	9	5	14.4	14.9
-3	10	4*	3.8	6.8	-2	3	5	5.1	4.4	1	9	5*	3.2	4.4
-2	10	4*	0.7	1.8	-1	3	5	11.9	12.7	2	9	5	12.1	11.8
-1	10	4*	0.7	1.9	0	3	5*	2.3	2.6	3	9	5	4.1	2.1
0	10	4*	1.8	2.2	1	3	5	16.4	17.6	-3	10	5*	2.6	2.6
1	10	4*	2.9	1.2	2	3	5	4.8	5.3	-2	10	5*	1.5	1.4
2	10	4	15.6	15.4	3	3	5	4.6	3.4	-1	10	5*	1.5	0.7
3	10	4*	3.4	2.9	4	3	5*	0.8	3.9	0	10	5*	2.7	3.2
-3	11	4*	2.2	3.4	-4	4	5*	2.2	2.4	1	10	5	4.3	4.4
-2	11	4	8.8	9.6	-3	4	5	10.3	9.8	2	10	5*	0.7	1.4
-1	11	4*	1.9	0.4	-2	4	5*	0.6	0.1	3	10	5	6.0	7.4
0	11	4	5.0	5.1	-1	4	5	17.0	17.7	-3	11	5*	0.8	2.1
1	11	4	9.2	9.2	0	4	5	33.0	32.9	-2	11	5*	3.9	5.6
2	11	4	20.0	20.1	1	4	5	8.4	8.4	-1	11	5*	2.0	3.9
3	11	4*	0.8	1.4	2	4	5	11.2	10.8	0	11	5	11.4	11.4
-3	12	4*	2.2	1.0	3	4	5	3.7	2.9	1	11	5	8.7	8.6
-2	12	4	8.4	9.1	4	4	5*	0.8	1.3	2	11	5	16.5	16.7
-1	12	4	8.7	8.9	-4	5	5	5.7	6.3	3	11	5*	0.9	4.5
0	12	4	6.2	5.4	-3	5	5	10.4	9.6	-2	12	5	7.1	6.5
1	12	4	5.7	4.9	-2	5	5	8.5	8.4	-1	12	5*	2.0	0.3
2	12	4	10.7	10.4	-1	5	5	9.1	9.7	0	12	5*	1.1	0.8
-2	13	4	6.6	7.0	0	5	5	25.2	24.9	1	12	5*	1.6	1.6
-1	13	4*	2.0	2.8	1	5	5	7.9	8.4	2	12	5*	2.2	2.7
0	13	4	3.0	2.3	2	5	5	4.9	4.9	-2	13	5*	2.3	2.7
1	13	4	6.7	6.9	3	5	5*	2.4	1.0	-1	13	5	4.0	3.0
2	13	4	10.9	10.6	4	5	5*	2.4	2.9	0	13	5*	2.5	3.1
-2	14	4*	2.1	1.4	-4	6	5*	0.9	0.2	1	13	5*	3.3	0.6
-1	14	4*	1.8	2.1	-3	6	5	3.9	3.8	2	13	5*	3.8	1.7
0	14	4	5.6	4.6	-2	6	5	4.9	6.0	-2	14	5*	0.8	0.5
1	14	4	4.1	4.1	-1	6	5	3.3	2.1	-1	14	5*	0.7	1.3
2	14	4*	0.8	2.1	0	6	5*	1.1	1.8	0	14	5	5.3	4.3
-1	15	4*	1.9	0.9	1	6	5	11.6	11.9	1	14	5*	2.1	2.3
0	15	4	3.8	2.9	2	6	5	7.2	7.6	-1	15	5*	0.8	2.6
1	15	4*	3.3	3.4	3	6	5*	3.1	1.7	0	15	5	5.1	4.8
-4	1	5*	1.7	2.3	4	6	5*	2.0	1.6	1	15	5	6.5	5.8
-3	1	5	5.0	4.6	-4	7	5*	1.9	2.5	-4	0	6*	1.8	2.9
-2	1	5	4.2	3.3	-3	7	5*	3.5	3.5	-3	0	6	10.3	10.6

Table 7 (cont.)

H	K	L	F(O)	F(C)	H	K	L	F(O)	F(C)	H	K	L	F(O)	F(C)
-2	0	6	6.9	6.8	-3	6	6	36.4	37.4	1	14	6*	2.7	0.4
-1	0	6	38.4	35.1	-2	6	6	6.0	6.0	0	15	6*	2.9	2.4
0	0	6	21.8	23.2	-1	6	6	4.2	3.7	-4	1	7*	0.8	1.5
1	0	6	3.0	3.1	0	6	6	6.9	7.2	-3	1	7	5.2	5.0
2	0	6	6.2	6.0	1	6	6	35.5	35.1	-2	1	7	9.9	10.1
3	0	6	36.0	32.6	2	6	6*	2.0	1.3	-1	1	7	14.9	14.7
4	0	6*	2.0	0.9	3	6	6*	2.6	3.2	0	1	7	6.8	7.2
-4	1	6*	3.7	3.8	-3	7	6	4.7	3.7	1	1	7	11.8	12.5
-3	1	6*	3.1	3.9	-2	7	6	8.7	8.6	2	1	7*	1.7	2.6
-2	1	6	17.7	15.6	-1	7	6	3.6	3.3	3	1	7	4.9	5.6
-1	1	6	25.8	25.3	0	7	6	2.8	2.9	4	1	7*	2.4	1.2
0	1	6	14.7	14.6	1	7	6*	1.7	1.0	-4	2	7*	3.2	0.5
1	1	6	4.4	4.1	2	7	6*	1.5	0.4	-3	2	7	7.5	6.4
2	1	6	10.5	11.0	3	7	6*	1.6	0.6	-2	2	7	18.9	18.6
3	1	6	6.3	6.6	-3	8	6	7.3	8.1	-1	2	7*	2.2	1.4
4	1	6*	3.2	5.6	-2	8	6*	2.8	2.5	0	2	7*	1.3	0.7
-4	2	6*	2.5	1.2	-1	8	6	6.3	6.5	1	2	7	15.3	15.2
-3	2	6*	0.8	0.9	0	8	6	6.4	5.9	2	2	7*	0.7	2.2
-2	2	6*	2.3	2.0	1	8	6	17.3	16.4	3	2	7*	2.9	3.0
-1	2	6	28.4	28.5	2	8	6	4.5	4.9	4	2	7*	2.7	4.7
0	2	6	12.2	11.9	3	8	6*	1.7	1.4	-4	3	7*	2.7	1.9
1	2	6	13.5	13.9	-3	9	6*	1.6	0.9	-3	3	7	3.6	3.8
2	2	6*	1.5	3.2	-2	9	6	10.4	10.8	-2	3	7*	2.5	2.8
3	2	6	15.6	14.7	-1	9	6*	3.2	1.7	-1	3	7	8.4	8.6
4	2	6*	0.8	0.2	0	9	6	15.4	15.9	0	3	7	12.2	12.6
-4	3	6*	0.8	1.9	1	9	6	5.4	6.0	1	3	7	12.9	12.8
-3	3	6	4.1	3.4	2	9	6*	2.1	0.4	2	3	7	6.3	5.9
-2	3	6	6.0	5.9	3	9	6	4.9	5.9	3	3	7	7.5	6.8
-1	3	6	4.8	3.7	-3	10	6*	0.8	0.8	4	3	7*	0.8	0.9
0	3	6	42.7	43.0	-2	10	6*	1.6	2.1	-4	4	7*	2.9	1.6
1	3	6	15.3	15.2	-1	10	6	4.6	5.7	-3	4	7	9.9	8.5
2	3	6	3.5	3.4	0	10	6*	1.1	0.9	-2	4	7*	1.5	0.8
3	3	6	5.5	5.4	1	10	6	4.5	4.2	-1	4	7	7.6	7.3
4	3	6*	2.3	0.1	2	10	6	6.0	4.9	0	4	7	7.0	7.2
-4	4	6*	0.8	1.7	3	10	6	7.9	9.6	1	4	7	4.9	4.9
-3	4	6	24.7	22.9	-3	11	6*	2.0	0.6	2	4	7*	2.9	2.8
-2	4	6*	2.0	1.4	-2	11	6	4.8	5.6	3	4	7*	1.5	0.6
-1	4	6	5.2	5.7	-1	11	6	3.7	2.2	4	4	7*	2.5	0.8
0	4	6	7.5	8.2	0	11	6	7.3	7.3	-4	5	7*	2.2	1.1
1	4	6	26.0	26.4	1	11	6	3.8	3.0	-3	5	7	4.1	3.7
2	4	6	3.6	4.6	2	11	6	5.4	5.0	-2	5	7	16.8	17.2
3	4	6*	2.4	2.5	-2	12	6*	2.2	2.9	-1	5	7	9.3	9.4
4	4	6*	0.8	0.6	-1	12	6	13.9	15.4	0	5	7	13.0	13.1
-4	5	6	5.8	7.2	0	12	6	6.7	6.6	1	5	7	16.9	16.6
-3	5	6	7.0	5.8	1	12	6*	2.1	2.0	2	5	7	5.4	5.9
-2	5	6	4.0	2.4	2	12	6*	0.8	3.4	3	5	7*	0.8	1.1
-1	5	6	8.4	8.8	-2	13	6*	2.8	2.7	-3	6	7	7.4	7.3
0	5	6	18.5	17.4	-1	13	6*	2.3	3.5	-2	6	7	10.0	10.9
1	5	6*	1.9	0.8	0	13	6*	2.4	1.9	-1	6	7*	1.5	2.2
2	5	6	9.1	9.5	1	13	6	4.2	3.1	0	6	7*	1.8	1.0
3	5	6*	2.0	1.1	2	13	6*	3.5	3.6	1	6	7	5.3	4.5
4	5	6*	2.0	3.0	-1	14	6*	0.8	2.6	2	6	7*	1.8	0.1
-4	6	6*	3.7	3.5	0	14	6*	3.1	0.1	3	6	7*	0.8	0.2

Table 7 (cont.)

H	K	L	F(O)	F(C)	H	K	L	F(O)	F(C)	H	K	L	F(O)	F(C)
-3	7	7*	0.8	1.4	4	0	8*	2.9	3.5	2	7	8	13.1	13.4
-2	7	7*	2.8	0.4	-4	1	8	10.9	11.9	3	7	8*	0.8	2.3
-1	7	7*	1.8	1.1	-3	1	8*	2.0	2.5	-3	8	8*	3.1	2.6
0	7	7	13.2	13.3	-2	1	8	10.6	10.0	-2	8	8*	2.3	1.1
1	7	7	6.8	7.8	-1	1	8	3.4	3.1	-1	8	8*	0.7	2.0
2	7	7*	2.4	2.2	0	1	8	32.1	32.4	0	8	8	3.8	2.8
3	7	7*	2.1	3.1	1	1	8	13.6	13.6	1	8	8	6.3	6.3
-3	8	7	4.1	3.0	2	1	8*	2.1	2.2	2	8	8*	2.5	1.3
-2	8	7	5.0	4.9	3	1	8*	2.4	0.4	3	8	8*	1.6	1.1
-1	8	7	6.8	7.0	4	1	8	7.9	10.5	-3	9	8*	2.2	2.8
0	8	7	11.2	11.6	-4	2	8*	2.4	2.8	-2	9	8*	1.9	1.0
1	8	7	3.6	4.0	-3	2	8*	0.8	1.2	-1	9	8*	3.4	3.2
2	8	7	4.8	4.6	-2	2	8	6.7	6.2	0	9	8*	2.3	2.5
3	8	7*	1.9	2.1	-1	2	8	6.8	6.6	1	9	8	7.4	7.6
-3	9	7*	2.3	1.6	0	2	8	3.1	2.6	2	9	8*	3.1	3.2
-2	9	7*	1.8	0.8	1	2	8	12.4	12.6	3	9	8	4.1	3.3
-1	9	7	11.7	11.7	2	2	8*	3.2	2.9	-3	10	8*	2.1	5.9
0	9	7	3.3	4.0	3	2	8*	2.9	4.3	-2	10	8*	1.6	1.4
1	9	7	5.1	4.2	-4	3	8*	3.9	4.6	-1	10	8	10.4	11.8
2	9	7*	1.9	2.0	-3	3	8*	0.8	1.5	0	10	8*	1.8	1.8
3	9	7*	3.9	4.6	-2	3	8	11.6	10.8	1	10	8*	2.8	0.6
-3	10	7*	2.1	3.8	-1	3	8	9.6	10.1	2	10	8*	3.5	2.5
-2	10	7*	2.4	2.4	0	3	8	8.6	8.7	-2	11	8*	2.1	1.1
-1	10	7	8.9	10.3	1	3	8	11.2	11.8	-1	11	8*	2.8	0.8
0	10	7	3.5	3.5	2	3	8	12.2	11.9	0	11	8	9.3	9.6
1	10	7	9.6	9.1	3	3	8*	0.8	1.3	1	11	8	6.5	5.9
2	10	7*	0.8	0.1	-4	4	8*	2.6	1.2	2	11	8*	0.8	0.2
3	10	7	7.1	8.0	-3	4	8	7.6	7.2	-2	12	8*	1.8	1.3
-2	11	7*	1.8	1.4	-2	4	8	5.4	4.4	-1	12	8*	0.8	0.9
-1	11	7	5.6	4.9	-1	4	8*	1.3	2.3	0	12	8	4.2	3.0
0	11	7	3.8	4.5	0	4	8	2.9	2.3	1	12	8*	3.2	2.3
1	11	7	4.0	4.3	1	4	8*	2.3	2.4	2	12	8*	2.1	0.6
2	11	7	4.1	4.0	2	4	8*	1.9	0.1	-1	13	8	4.0	2.3
-2	12	7	5.3	4.3	3	4	8*	2.3	3.0	0	13	8	9.1	9.5
-1	12	7	7.3	7.6	-3	5	8*	0.8	0.0	1	13	8*	2.8	3.1
0	12	7*	1.3	1.9	-2	5	8	48.4	50.0	-1	14	8*	0.8	0.4
1	12	7*	2.4	1.3	-1	5	8	4.6	5.4	0	14	8*	1.4	0.9
2	12	7*	2.7	2.8	0	5	8	10.5	10.6	-4	1	9*	2.1	0.9
-2	13	7*	2.3	3.9	1	5	8*	0.7	0.1	-3	1	9*	1.6	0.2
-1	13	7*	1.9	2.1	2	5	8	14.5	15.1	-2	1	9	12.1	11.5
0	13	7*	2.1	0.9	3	5	8*	0.8	0.7	-1	1	9	20.5	21.0
1	13	7*	2.7	0.3	-3	6	8	10.3	11.2	0	1	9	2.9	3.5
-1	14	7*	2.0	0.0	-2	6	8	16.5	16.7	1	1	9*	2.9	3.5
0	14	7	4.8	4.8	-1	6	8	3.4	2.5	2	1	9*	2.2	1.4
1	14	7*	2.5	0.1	0	6	8	4.4	4.9	3	1	9*	0.8	2.0
-4	0	8	6.7	5.9	1	6	8	9.2	9.7	-4	2	9*	2.5	1.3
-3	0	8	8.6	8.5	2	6	8	6.1	7.1	-3	2	9*	3.4	2.7
-2	0	8	3.3	3.9	3	6	8*	0.8	3.1	-2	2	9	5.6	5.7
-1	0	8	26.6	26.5	-3	7	8*	0.8	1.6	-1	2	9*	0.6	1.4
0	0	8	6.3	6.9	-2	7	8	28.8	30.0	0	2	9	13.8	14.4
1	0	8	12.2	12.7	-1	7	8	10.7	10.7	1	2	9*	0.7	1.0
2	0	8*	0.7	0.3	0	7	8	3.8	3.2	2	2	9	3.8	3.9
3	0	8	7.5	7.6	1	7	8	4.3	3.0	3	2	9*	0.8	0.7

Table 7 (cont.)

H	K	L	F(O)	F(C)	H	K	L	F(O)	F(C)	H	K	L	F(O)	F(C)
-3	3	9	4.3	3.9	-2	11	9*	2.4	0.2	3	5	10*	2.8	4.3
-2	3	9	3.8	3.0	-1	11	9*	2.0	0.4	-3	6	10*	3.0	4.1
-1	3	9*	2.8	3.1	0	11	9	9.0	9.4	-2	6	10*	3.0	4.3
0	3	9*	1.0	1.0	1	11	9*	3.1	2.5	-1	6	10	32.3	34.3
1	3	9*	1.5	1.6	2	11	9*	3.3	1.6	0	6	10	10.9	10.8
2	3	9*	3.1	2.8	-2	12	9*	2.0	1.9	1	6	10	3.4	3.7
3	3	9*	0.8	2.6	-1	12	9*	2.0	0.9	2	6	10*	2.0	3.1
-3	4	9*	1.7	0.6	0	12	9*	0.8	1.6	3	6	10	4.3	5.3
-2	4	9	10.8	11.0	1	12	9*	0.8	2.1	-3	7	10*	2.6	2.6
-1	4	9	8.8	9.1	-1	13	9	5.8	6.4	-2	7	10	8.8	10.0
0	4	9	7.5	7.5	0	13	9	3.8	3.9	-1	7	10	20.1	21.8
1	4	9	10.4	9.8	1	13	9*	3.6	3.8	0	7	10*	2.2	1.5
2	4	9	9.6	10.6	-3	0	10	13.2	11.6	1	7	10*	3.2	2.9
3	4	9*	2.3	2.6	-2	0	10*	2.3	0.2	2	7	10*	0.8	1.5
-3	5	9*	0.7	1.1	-1	0	10	8.8	8.9	3	7	10*	3.2	4.2
-2	5	9	9.0	9.1	0	0	10	8.6	8.4	-3	8	10	5.3	6.1
-1	5	9	5.5	5.8	1	0	10	15.6	16.2	-2	8	10*	0.8	0.9
0	5	9*	2.3	1.5	2	0	10	10.5	10.4	-1	8	10	10.1	10.7
1	5	9	4.1	4.0	3	0	10*	2.3	0.3	0	8	10*	2.8	2.9
2	5	9*	1.5	0.4	-3	1	10	16.6	15.2	1	8	10*	1.7	2.2
3	5	9*	0.8	1.1	-2	1	10	7.3	7.5	2	8	10*	3.8	4.0
-3	6	9*	2.1	1.6	-1	1	10	4.4	5.1	-2	9	10*	2.1	3.1
-2	6	9	8.6	8.5	0	1	10	12.5	12.2	-1	9	10*	1.9	2.0
-1	6	9	12.4	13.2	1	1	10	5.5	6.5	0	9	10	5.6	5.2
0	6	9	5.6	5.3	2	1	10*	1.8	0.1	1	9	10*	3.0	1.3
1	6	9*	1.9	0.4	3	1	10*	2.1	0.3	2	9	10*	0.8	1.2
2	6	9*	1.7	1.0	-3	2	10	10.8	10.6	-2	10	10	4.1	4.5
3	6	9*	1.8	1.6	-2	2	10*	3.0	3.2	-1	10	10*	1.5	1.1
-3	7	9*	2.3	0.2	-1	2	10	6.7	7.4	0	10	10	5.8	5.0
-2	7	9	4.8	5.6	0	2	10	8.0	7.9	1	10	10*	3.6	2.7
-1	7	9	13.2	14.4	1	2	10	11.5	11.9	2	10	10*	2.9	0.1
0	7	9*	2.2	0.8	2	2	10*	2.8	1.9	-2	11	10*	3.9	3.9
1	7	9	6.9	7.2	3	2	10*	3.4	3.4	-1	11	10*	3.3	2.0
2	7	9*	1.9	4.0	-3	3	10	3.6	3.2	0	11	10	5.3	5.4
3	7	9*	2.1	1.7	-2	3	10	3.8	3.8	1	11	10	4.1	4.7
-3	8	9	3.8	4.3	-1	3	10*	2.9	2.2	-1	12	10*	0.8	1.1
-2	8	9*	2.5	2.9	0	3	10	4.0	3.6	0	12	10*	3.0	1.3
-1	8	9*	2.9	2.8	1	3	10*	1.5	1.7	1	12	10	4.9	5.5
0	8	9	11.4	11.1	2	3	10	3.6	1.1	0	13	10	3.8	0.4
1	8	9*	3.1	2.2	3	3	10*	2.6	0.4	-3	1	11*	3.0	4.2
2	8	9*	2.4	2.2	-3	4	10	5.8	4.7	-2	1	11*	2.9	1.8
3	8	9*	0.8	0.4	-2	4	10*	1.9	3.3	-1	1	11*	0.7	0.9
-3	9	9*	2.5	1.3	-1	4	10	27.8	29.7	0	1	11	6.8	6.8
-2	9	9	6.6	7.1	0	4	10	2.9	2.6	1	1	11	4.7	5.1
-1	9	9*	2.9	0.6	1	4	10	3.8	2.4	2	1	11*	0.8	2.0
0	9	9*	2.5	2.3	2	4	10*	2.8	3.1	3	1	11*	2.0	1.3
1	9	9	5.1	4.8	3	4	10	4.3	6.1	-3	2	11*	2.3	3.2
2	9	9*	2.5	3.2	-3	5	10*	0.8	0.2	-2	2	11	4.3	3.8
-2	10	9*	2.5	2.1	-2	5	10	10.0	10.0	-1	2	11	12.6	12.7
-1	10	9*	1.8	1.0	-1	5	10	32.7	33.8	0	2	11	9.9	10.0
0	10	9	5.7	6.3	0	5	10*	2.0	2.1	1	2	11	4.8	4.6
1	10	9*	3.1	2.4	1	5	10*	1.6	0.5	2	2	11*	2.0	2.2
2	10	9	4.6	4.6	2	5	10*	2.1	3.9	3	2	11*	2.0	0.5

Table 7 (cont.)

H	K	L	F(O)	F(C)	H	K	L	F(O)	F(C)	H	K	L	F(O)	F(C)
-3	3	11	5.4	4.9	-2	0	12	23.4	23.2	2	8	12*	0.9	1.3
-2	3	11*	2.4	1.5	-1	0	12	7.8	8.3	-2	9	12	7.4	6.9
-1	3	11	7.3	8.0	0	0	12	9.1	9.0	-1	9	12	4.6	4.0
0	3	11*	1.1	1.5	1	0	12	7.1	6.7	0	9	12	4.0	4.8
1	3	11	7.4	6.9	2	0	12	5.0	6.9	1	9	12*	2.2	1.9
2	3	11*	2.5	3.2	3	0	12*	0.9	1.2	-1	10	12*	2.6	3.3
3	3	11*	0.8	1.9	-3	1	12*	3.6	4.4	0	10	12*	1.5	0.5
-3	4	11*	2.3	0.1	-2	1	12	4.4	3.9	1	10	12*	0.9	2.3
-2	4	11	4.8	4.8	-1	1	12*	1.4	1.0	-1	11	12	4.6	3.4
-1	4	11*	2.7	2.0	0	1	12*	2.3	1.6	0	11	12*	2.4	1.7
0	4	11	10.2	10.5	1	1	12	6.9	6.6	-3	1	13	5.3	3.8
1	4	11*	0.7	0.5	2	1	12*	3.4	3.7	-2	1	13	7.3	7.0
2	4	11*	3.3	2.4	3	1	12*	2.6	2.7	-1	1	13*	1.6	1.9
3	4	11*	1.9	1.8	-3	2	12*	1.9	0.9	0	1	13	4.7	4.8
-3	5	11	7.8	8.2	-2	2	12	16.1	15.8	1	1	13	3.7	1.8
-2	5	11*	1.8	1.5	-1	2	12*	1.8	0.9	2	1	13*	3.0	2.3
-1	5	11	15.3	15.7	0	2	12*	1.1	0.4	-3	2	13*	0.8	1.9
0	5	11	5.0	4.7	1	2	12*	0.7	1.0	-2	2	13*	2.1	0.3
1	5	11	4.3	4.7	2	2	12	4.8	4.9	-1	2	13*	2.6	2.1
2	5	11*	0.8	0.8	3	2	12*	0.8	1.6	0	2	13*	1.2	0.2
3	5	11	3.9	3.0	-3	3	12	6.2	6.7	1	2	13	4.2	3.3
-3	6	11*	1.8	0.2	-2	3	12	8.8	8.5	2	2	13*	1.9	2.4
-2	6	11*	2.7	0.4	-1	3	12	3.6	4.3	-2	3	13*	2.0	0.1
-1	6	11	4.4	3.6	0	3	12	13.6	14.0	-1	3	13	4.6	4.1
0	6	11*	1.4	1.3	1	3	12	3.4	2.0	0	3	13	9.0	8.9
1	6	11*	2.5	0.2	2	3	12*	2.9	2.0	1	3	13*	2.1	2.6
2	6	11*	2.6	0.3	3	3	12*	0.9	0.1	2	3	13*	3.4	3.0
-3	7	11	3.9	2.6	-3	4	12*	1.9	2.4	-2	4	13	10.2	9.6
-2	7	11*	2.3	0.3	-2	4	12*	3.1	2.5	-1	4	13*	3.8	3.1
-1	7	11*	1.9	1.9	-1	4	12	5.6	5.9	0	4	13	9.4	9.1
0	7	11	12.9	12.4	0	4	12	19.9	19.4	1	4	13	4.6	4.4
1	7	11	4.0	2.6	1	4	12*	1.7	2.0	2	4	13*	1.9	3.1
2	7	11*	0.8	1.5	2	4	12*	0.8	0.4	-2	5	13	4.7	4.7
-2	8	11*	0.8	0.9	-3	5	12*	2.8	3.2	-1	5	13	3.7	2.4
-1	8	11	8.6	9.6	-2	5	12*	2.6	2.9	0	5	13	5.6	5.3
0	8	11	6.1	6.6	-1	5	12	5.7	6.3	1	5	13	5.2	5.0
1	8	11*	3.1	3.1	0	5	12	13.8	13.8	2	5	13*	2.0	1.1
2	8	11	3.7	2.9	1	5	12	4.6	4.7	-2	6	13*	1.6	1.8
-2	9	11	9.4	8.4	2	5	12*	1.9	1.9	-1	6	13*	2.8	2.9
-1	9	11*	0.8	0.0	-2	6	12	3.9	3.5	0	6	13	6.9	7.4
0	9	11*	1.9	2.0	-1	6	12	7.3	7.7	1	6	13	5.1	5.7
1	9	11	6.5	6.9	0	6	12	33.5	32.7	2	6	13*	0.8	0.8
2	9	11*	2.6	1.1	1	6	12*	2.6	4.0	-2	7	13*	0.9	0.8
-2	10	11*	3.8	5.1	2	6	12*	0.8	0.2	-1	7	13*	1.6	1.1
-1	10	11*	3.0	2.7	-2	7	12	5.2	4.4	0	7	13	7.3	6.8
0	10	11*	2.9	2.0	-1	7	12	5.8	6.4	1	7	13*	0.8	0.3
1	10	11*	1.7	1.5	0	7	12	7.1	7.4	2	7	13*	0.9	2.1
-1	11	11	4.3	3.4	1	7	12	7.1	6.2	-2	8	13*	3.3	1.6
0	11	11*	2.4	0.9	2	7	12*	0.8	0.2	-1	8	13*	3.0	3.0
1	11	11*	2.7	3.1	-2	8	12	4.8	4.2	0	8	13*	2.5	1.3
-1	12	11*	2.8	3.7	-1	8	12*	3.1	3.4	1	8	13	7.2	7.7
0	12	11	4.1	3.0	0	8	12	8.6	8.7	-1	9	13*	4.1	5.6
-3	0	12*	3.5	2.6	1	8	12*	2.8	2.3	0	9	13	6.7	5.9

Table 7 (cont.)

H	K	L	F(O)	F(C)	H	K	L	F(O)	F(C)	H	K	L	F(O)	F(C)
1	9	13*	0.8	0.5	2	4	14*	2.2	2.2	0	3	15	4.7	4.6
-1	10	13	5.1	3.9	-2	5	14	7.0	5.9	1	3	15*	1.7	1.0
0	10	13*	2.2	1.6	-1	5	14*	1.7	2.2	-1	4	15	7.2	6.6
-2	0	14	8.8	8.0	0	5	14*	3.2	2.9	0	4	15*	1.9	1.5
-1	0	14	7.6	6.7	1	5	14	18.8	18.6	1	4	15	7.0	7.4
0	0	14	3.8	4.2	2	5	14*	3.1	2.2	-1	5	15	4.0	3.0
1	0	14*	3.4	2.8	-2	6	14*	3.2	2.1	0	5	15*	0.8	0.4
2	0	14	4.5	4.2	-1	6	14*	1.7	0.1	1	5	15*	3.1	3.5
-2	1	14*	1.9	0.0	0	6	14	7.5	7.3	-1	6	15*	1.8	1.4
-1	1	14	17.4	17.9	1	6	14*	0.9	3.2	0	6	15*	0.8	1.5
0	1	14*	2.1	2.1	-1	7	14	5.1	4.8	1	6	15*	0.8	0.5
1	1	14*	2.2	2.6	0	7	14*	0.8	2.0	0	7	15*	1.3	1.5
2	1	14*	0.9	0.2	1	7	14	13.8	13.3	-1	0	16	3.9	3.5
-2	2	14*	1.8	2.6	-1	8	14	4.8	4.4	0	0	16	9.6	9.3
-1	2	14*	0.8	0.9	0	8	14*	1.5	2.6	1	0	16*	0.8	0.8
0	2	14*	2.1	1.4	1	8	14*	1.8	0.9	-1	1	16*	2.4	2.9
1	2	14	5.1	4.2	0	9	14*	1.5	0.5	0	1	16	7.3	6.8
2	2	14*	2.1	1.4	-2	1	15*	2.7	2.7	1	1	16*	2.8	1.3
-2	3	14	4.2	3.6	-1	1	15*	3.4	2.3	-1	2	16*	2.2	3.4
-1	3	14	10.7	10.6	0	1	15*	0.8	1.8	0	2	16	11.0	9.9
0	3	14*	2.0	2.6	1	1	15*	2.0	0.4	1	2	16*	1.7	0.9
1	3	14	7.7	8.3	-2	2	15	4.3	3.2	-1	3	16*	0.8	0.7
2	3	14*	0.9	1.8	-1	2	15	5.4	6.0	0	3	16*	1.3	0.4
-2	4	14*	2.5	2.9	0	2	15*	2.7	1.2	1	3	16	4.0	3.3
-1	4	14	4.7	3.9	1	2	15	4.7	4.7	-1	4	16*	0.8	0.4
0	4	14	5.9	5.6	-2	3	15*	3.0	3.2	0	4	16	5.1	4.7
1	4	14*	2.7	3.9	-1	3	15	4.4	4.6		5	16*	2.6	0.3

TITLE CHEMISTRY AND BIOLOGICAL ACTIVITY OF IRON QUINONEOXIMIC COMPLEXES

AUTHOR NAVIN DEEPAL PATHIRANA

INSTITUTION and DATE CNAA 1990 NORTH LONDON POLYTECHNIC

DX

91304