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Model Compounds for Microbial Iron-transport Compounds. Part V. Substituent Effects in the Catechol/$FeCl_3$ System

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Titration data are reported for a number of substituted catechol molecules with ferric chloride. The data are interpreted in terms of the complexes formed and their stabilities. The pH's at which one complex transforms to another have been shown to have a linear relationship to modified Hammett substituent constants. It is demonstrated that this approach can be used to forecast approximate stabilities of complexes formed with iron, if the Hammett substituent constant of the ligand is known.

Introduction

Catecholic chelating agents have aroused considerable interest, both as analytical reagents and as models for siderophores [1–12]. In the course of our work on models for microbial iron transport we have carried out extensive studies on iron(II) and iron(III) complexes of phenolic [7, 8] and catecholic systems [9–12]. Mössbauer spectroscopy provided unambiguous data for the assignment of iron oxidation states, in both the iron/catechol [9] and the related iron/pyridinol systems [11].

Previous work [9] has demonstrated the existence of four distinct coloured complexes in the catechol:iron(III) chloride system. These were shown by Job's plots and Mössbauer spectroscopy to be a green, iron(II):catechol, 1:1 complex; a blue, iron(II):catechol 1:3 complex; a purple, iron(III):catechol, 2:4 complex and a red iron(III):catechol, 1:3 complex.

Similar behaviour was also found for both 2,3-dihydroxybenzaldehyde and for 2,3-dihydroxybenzoic acid, with the exception that a green species was not observed with the acid. This led to the general conclusion that, in aromatic systems containing an *ortho* dihydroxy entity, complexes with iron which were green or blue contained iron(II) and purple or red complexes contained iron(III). This conclusion was found to hold true for systems containing a heterocyclic nitrogen atom [11] *i.e.* 2,3-dihydroxypyridine and 2-mercapto-3-pyridinol.

The mechanism for the reduction of iron is dependent on the formation of a catecholic radical species [9]. Such a species will result from the donation of an electron to the iron(III) ion from the catecholic moiety [9, 11, 12]. As this species will only donate an electron if its affinity for it will be less than that of the iron(III) ion, this affinity will differ from one substituted catechol to another. The reaction should be susceptible to the presence of electron donating or withdrawing substituent groups. In principle therefore this permits the application of the well known Hammett equation:

$$\log \frac{k}{k_o} = \rho\sigma$$

where ρ = reaction constant, σ = substituent constant, which has been finding increasing use in its application to systems of inorganic interest [13].

A similar study [14] has recently been reported for the reduction of cytochrome *c* by catecholic and quinolic molecules.

We report here studies on iron-catecholic (substituted with various electron withdrawing and donating groups) systems and compare these to the original catechol:ferric chloride system. We also discuss the effects of these substituents on the stability of the resulting iron-species formed. In this work we report new titration data for iron ligand systems where the

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ligand is 4-nitrocatechol, 4-methylcatechol, 4-tertiarybutylcatechol, 3-methylcatechol, 4-chlorocatechol, tetrabromocatechol and tetrachlorocatechol.

Experimental

Materials

Catechol (SLR Fisons); 2,3-dihydroxybenzoic acid (Aldrich); 4-nitrocatechol (Aldrich); 2,3-dihydroxybenzaldehyde (Sigma); 4-*t*-butylcatechol, 4-methylcatechol, 3-methylcatechol and 4-chlorocatechol, tetrabromocatechol and tetrachlorocatechol (P. C. Barnard) were all recrystallised before use. Anhydrous iron(III) chloride (SLR Fisons) was used without further purification. Solutions were prepared by dissolving weighed amounts of the reagents in deionised water and were stored under an oxygen free nitrogen atmosphere.

pH Titration in Aqueous Solution

Iron (10^{-3} mol dm^{-3}) was used throughout with the ligand concentration set to (3×10^{-3} mol dm^{-3}). Additions of NaOH (1 mol dm^{-3}) or HCl (1 mol dm^{-3}) were achieved under nitrogen. A digital WPA model CD60 was used for pH measurements and the values of C_B/C_M where C_B is the analytical metal concentration, were corrected for increasing volume during titrations. The pH of the colour transitions were determined by taking the mid point of the transitory period, *i.e.* from when the solution was definitely one colour to when it was definitely another. The pH of the colour transitions were further clarified by taking visible spectra of the species on a Beckman instruments DU-7 spectrophotometer. All measurements were taken at 25 °C.

Calculation of Stability Constants and Formation Curves

These were obtained from titration curves using the method of Albert and Sergeant [15] using a Sinclair ZX81 computer and a PDP-10 mainframe computer. The programs both used a minimum least squares iteration to produce stability constant values.

Curve Fitting

Straight lines were fitted by linear regression analysis using a program modified for the PDP-10 from ref. 16.

Results

The new systems reported here were found to behave in a similar manner to the ferric chloride-catechol system [9]; in general green, blue, purple and red complexes are observed on titration with ferric chloride.

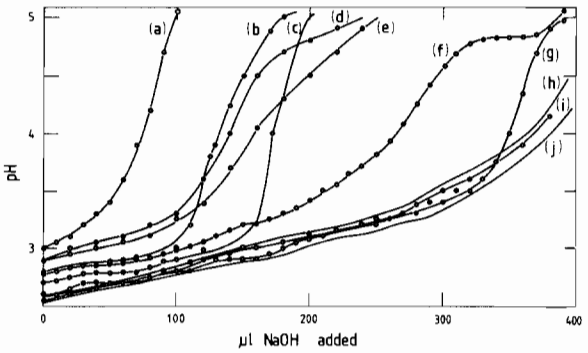


Fig. 1. pH titration curves for substituted catechol/$FeCl_3$ systems where substituted catechol = (a) 3-methylcatechol, (b) 4-*t*-butylcatechol, (c) 4-chlorocatechol, (d) catechol (unsubstituted), (e) 2,3-dihydroxybenzaldehyde, (f) 4-nitrocatechol, (g) 4-methylcatechol, (h) 2,3-dihydroxybenzoic acid, (i) tetrachlorocatechol, (j) tetrabromocatechol.

The pH titration curves in the pH range 2 to 5 are presented in Fig.1. To avoid possible interference these solutions contained no additional buffers. As a consequence, the starting pH varies, and is dependent on the individual pK_a values of the particular substituted catechol. Each species shows a different titration curve. The green/blue transition for the catechol/iron system occurs at about 1.5 equivalents of alkali, whereas for 4-nitrocatechol, this transition occurs at about 3.5 equivalents of alkali. Hence this reflects the initial starting pH values (caused by the different substituted catechols) for the systems studied.

However, the pH ranges over which the colour changes occur show a marked trend which reflects the change in pK_a of the hydroxyl group with change of other substitutents on the aromatic ring (Table I).

For the 4-*t*-butylcatechol, the green complex was observed up to pH 4.0, the blue species up to pH 9.0 and the red species only appearing after pH 11.0, (Table I). Similar effects were observed with 4-methyl catechol with the green complex being present up to pH 4.77, the blue to pH 8.2 and the red again appearing after pH 11.0.

4-chlorocatechol with the green present until pH 4.2, the blue present until pH 6.7 and the red species being dominant over pH 9.40 was also in agreement with this trend in pH of the transitions between the species.

Unlike the iron(III) chloride/2,3-dihydroxybenzaldehyde and 2,3-dihydroxybenzoic acid system which we have reported previously [9], the 3-methyl

TABLE I. The pH Dependence of Coloured Complexes Found in the Iron Chloride:Ligand Systems.

pH	a	b	c	d	e	f	g	h	i	j	k
1	—	—	—	—	—	—	—	—	—	—	—
2	Green	Green	Green	Green	Green	Green	Blue	Green	Blue	Blue	Blue
3	//	//	//	//	//	//	//	//	//	//	//
4	—	—	—	—	—	—	—	—	—	—	—
5	Blue	Blue	Blue	Blue	Blue	Blue	Purple	—	—	—	—
6	//	//	//	//	//	//	//	—	—	—	—
7	—	—	—	—	—	—	—	Red-wine	—	—	—
8	—	—	—	—	—	—	—	—	—	—	—
9	Purple	Purple	Purple	Purple	Purple	Purple	Red-wine	—	Purple	Purple	Purple
10	//	//	//	//	//	//	//	—	//	//	//
11	—	—	—	—	—	Red-wine	—	—	Red-wine	Red	Red
12	Red-wine	Red-wine	Red-wine	Red-wine	Red-wine	—	—	—	—	—	—

where ligand = [a]catechol, [b]4-*t*-butylcatechol, [c]4-methylcatechol, [d]4-chlorocatechol, [e]3-methylcatechol, [f]2,3-dihydroxybenzaldehyde, [g]2,3-dihydroxybenzoic acid, [h]4-nitrocatechol, [i]2,3-dihydroxypyridine, [j]tetrachlorocatechol, [k]tetrabromocatechol.

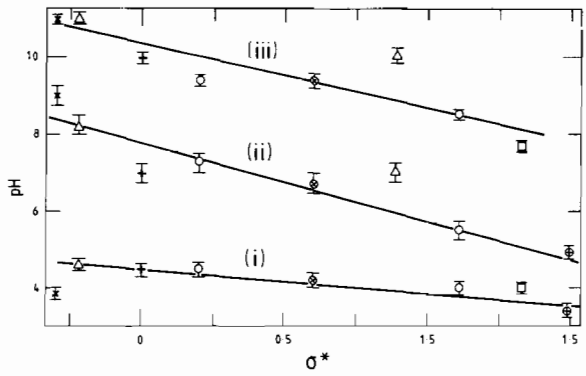


Fig. 2. Hammett plot of the three observed colour transitions for the substituted catechol:$FeCl_3$ systems against, σ^*, X = 4-*t*-butylcatechol; 1, △ = 4-methylcatechol; 2, + = catechol; 3, ○ = 3-methylcatechol; 4, ⊛ = 4-chlorocatechol, 5, ⍙ = 2,3-dihydroxypyridine; 6, ⍜ = 2,3-dihydroxybenzaldehyde; 7, □ = 2,3-dihydroxybenzoic acid; 8, ⊕ = 4-nitrocatechol. (i) green/blue transition standard error on slope = 0.172, coefficient of determination = 0.914, coefficient of correlation = 0.956; (ii) blue/purple transition standard error on slope = 0.768, coefficient of determination = 0.791, coefficient of correlation = 0.889; (iii) purple/red transition standard error on slope = 1.121, coefficient of determination = 0.687, coefficient of correlation = 0.828.

catechol system is more in keeping with the 4-substituted catechol systems. The green species is present up to pH 4.5, the blue to pH 7.4 and the purple to pH 9.4. Tetrachlorocatechol and tetrabromocatechol, however, display a blue species until pH 5.00 (pH 4.00 for the tetrabromocatechol), a purple species until pH 10.00 and a red complex thereafter despite the titration being carried out in methanol/water, 1:1, volume/volume, due to the low solubility of these ligands in water.

The notable exception for the colours of the complexes present is the 4-nitrocatechol system, where the green is present to pH 3.4, after which the solution takes on a reddish hue becoming completely red at pH 4.9. This system (though complicated by the fact that the ligand itself shows pH dependent colours being green at pH 1.1 and below, yellow to pH 5.5, orange up to pH 9.0 and red to pH 12.0), still shows colours that are obviously due to the presence of iron in the complexes.

Enterobactin [2, 9], where the ligand is designed to favour the red 3:1 species, also only shows two species but in this system the species found below pH 5.0 is blue.

The positions of these analogous colour transitions will be dependent on the equilibrium constant for each complex. These colour transitions can be plotted against the Hammett substituent constant σ to provide a means of correlating the equilibrium constants.

TABLE II. pK_a and σ^* Values for Substituted Catechols.

	pK_{a_1}	pK_{a_2}	σ^*	ref.
catechol	9.37	12.8	0.00	*
4-*t*-butylcatechol	9.70	12.8	−0.30	a
4-methylcatechol	9.70	12.8	−0.24	*
4-chlorocatechol	8.43	11.54	+0.60	c
2,3-dihydroxybenzaldehyde	8.05	11.5	+1.11	a
2,3-dihydroxybenzoic acid	8.60	10.0	+1.32	a
4-nitrocatechol	6.70	10.9	+1.49	b
2,3-dihydroxypyridine	8.60	–	+0.88	a
3-methylcatechol	9.28		+0.22	b
Tetrachlorocatechol	5.80	10.1	–	*
Tetrabromocatechol	6.00	11.0	–	a

*Values taken from ref. 20. [a]Values taken from our titration data. [b]Values taken from ref. 22. [c]Values taken from ref. 23.

To achieve such a plot it is first necessary to discuss which substituent effects must be considered. Substituents in position 4(a) are *meta* to one hydroxyl group and *para* to the other. As both hydroxyl groups are used in iron binding, σ^* in this case is best represented as the sum of σ *meta* and σ *para i.e.*

$$\sigma^* = (\sigma \textit{ meta} + \sigma \textit{ para})$$

Substituents in position 3 are *ortho* to one hydroxyl and *meta* to the other. Again a sum is indicated and is calculated in this case using values for *ortho* substi-

$$\sigma^* = (\sigma \textit{ meta} + \sigma \textit{ ortho})$$

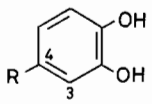
tuents from Charton [17] and all other σ values are taken from Barlin and Perrin [18] and Clark [19]. The adopted procedure with *ortho* substituents is only valid in the absence of steric or hydrogen bonding effects which could occur with some of the 3-substituents.

A plot of the pH of the colour transitions against σ^* is shown in Fig. 2.

Discussion

The Hammet correlation holds well for the green/blue transition, with only the 4-*t*-butylcatechol species showing significant deviation. As this transition is a measure of the change from the green 1:1 species to the blue 3:1 species, from purely entropic considerations, the increased steric bulk of the *t*-butyl species would make this proportionately more difficult to occur.

The 3 methyl species which might be expected to be an exception because *ortho* substituents often



(a)

upset Hammett correlations due to steric effects or hydrogen bonding complications also fits the line using this approach. A linear relationship is also obtained with the other two colour transitions, the *t*-butyl species showing much less deviation from the line as the concentration of fully deprotonated species increases with pH, resulting in a greater probability of the iron(III) complexes forming due to the double charge on the ligand.

The exact position of the color change could be confused in some of these species because of the presence of black precipitates [6, 9, 11], arising from radical association. This mainly occurs in the region of the blue and purple complexes [9] and may be a consequence of the iron(II) to iron(III) interconversion. Evidence in favour of this explanation is that this behaviour is most pronounced in the case of 2,3-dihydroxypyridine [11] which is rather more oxygen sensitive than the corresponding catechol. To avoid confusion in the position of these colour changes (where such precipitates occur) the pH ranges over which they occur have been extended to regions in which there is no doubt of the colour of the species present, (Fig. 2).

A validification of this application of the Hammett equation is that the 4-methyl and 4-*t*-butyl substituents have similar values of σ^*. Hence similarity of their properties is to be expected and is indeed found using the values shown in Table II and Fig. 2.

The pK_as of 2,3-dihydroxypyridine and 2,3-dihydroxybenzoic acid are also similar but do not fall

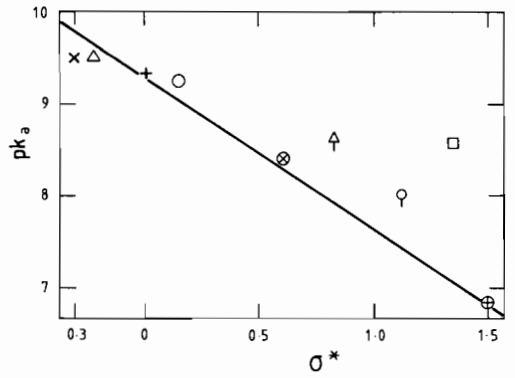


Fig. 3. Plot of pK_{a_1}'s for ligands against their σ^* values, standard error on slope = 7.89×10^{-2}, coefficient of determination = 0.997, coefficient of correlation = 0.998. The ligands 2,3-dihydroxybenzoic acid and 2,3-dihydroxypyridine though appearing on the plot were not included in the linear regression analysis fit.

on the line shown in Fig. 3, which is a linear regression fit of the pK_a's of the other substituted catechols against σ^* (Table II). It is interesting to note that a green 1:1 complex has not been detected in either of these compounds, a blue complex being present instead [9, 11].

From Fig. 3, it appears that as the pK_a's of the hydroxy groups fall, then their ability to reduce iron falls (Fig. 2). This may appear to be surprising, as the compounds need to lose one proton to form the radical species [9, 12], but it must be remembered that the iron would induce the formation of a doubly deprotonated species if the second pK_a was low enough, thus preferentially forming the purple and red iron(III) species.

The slope of Fig. 3 yields a ρ value of -1.85 and hence by knowing the σ^* value for a substituted catechol in the 4-position it should be possible to calculate the pK_{a_1} of the substituted catechols using eqn. I.

$$pK_{a_1} = -1.85\,\sigma^* + 9.37 \qquad (I)$$

(where 9.37 is the first pK_a of catechol)

Unfortunately as it is difficult to measure pK_a s in excess of pH 11.0 accurately because of the effect of Na^+ ions on glass electrodes, it was not thought expedient to try a similar treatment for the pK_{a_2}. The footnote given as reference 50 in reference 6 is worth reading on this point.

Stability constants were calculated (by previously published methods [15]) for the 1:1 complexes (such constants cannot be easily calculated for the other complexes for catechol and substituted catechols, as experimental evidence [9] in these systems shows that the other complexes do not form by a simple stepwise addition).

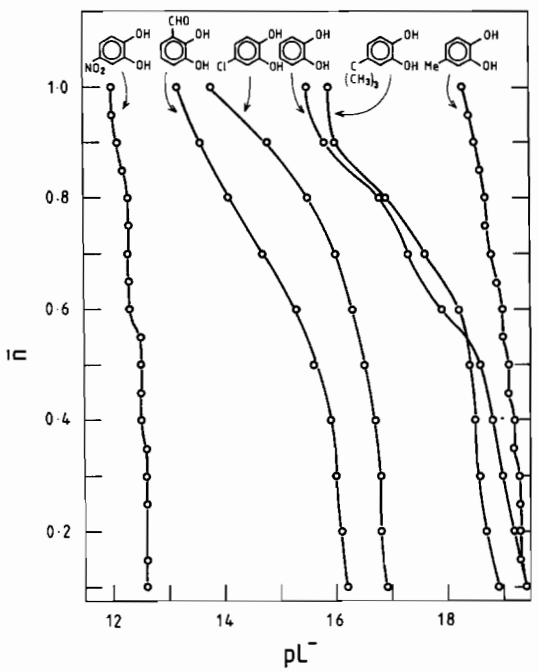


Fig. 4. Graph of $\bar{n}$ (average number of ligand molecules bound) against pL^- (log of the deprotonated (and bindable) ligand concentration).

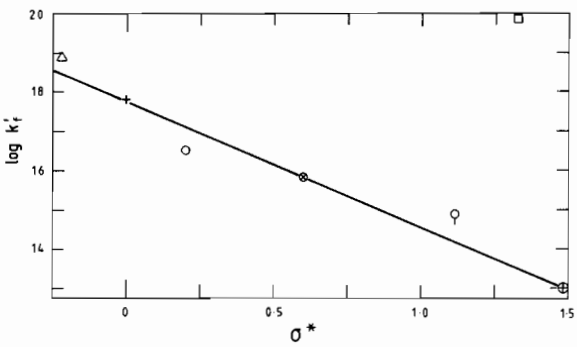


Fig. 5. Plot of log stability constant for the 1:1 complex against σ^* assuming two ionizable hydrogens. Standard error on slope = 0.824, coefficient of determination = 0.923, coefficient of correlation = 0.961. Values for 2,3-dihydroxybenzoic acid and 2,3-dihydroxypyridine again not included in regression analysis.

If a plot of the formation curves is considered (Fig. 4, assuming two protons released per ligand on complexation with iron) it can be observed that up to $\bar{n} = 1$ (the average number of ligand molecules bound), pL^- (the concentration of free *i.e.* bindable ligand) is in the order 4-Me > 4-*t*-Butyl > catechol > 4-chlorocatechol > 2,3-dihydrozybenzaldehyde > 4-nitro which is also the order of electron affinities

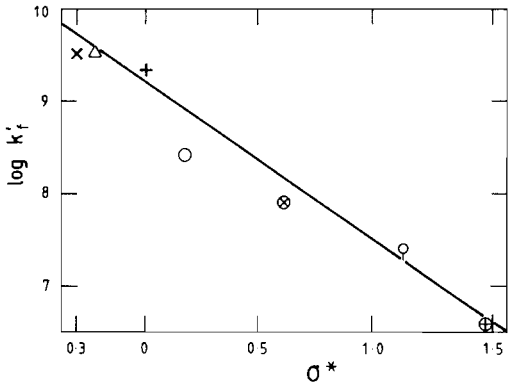


Fig. 6. Plot of log stability constant for the 1:1 complex against σ^* assuming one ionizable proton, standard error on slope = 0.171, coefficient of determination = 0.985, coefficient of correlation = 0.992, 2,3-dihydroxybenzoic acid and 2,3-dihydroxypyridine not included in regression analysis.

as manifest in the order shown in Fig. 1, Tables I and II. Hence a plot of their formation constants (which are the overall equilibrium constants for the reaction under study) should give a straight line against σ^*, (Fig. 5).

A straight line is achieved but the 4-*t*-butyl stability constant and the 4-methyl are off the line. Again, the 2,3-dihydrozybenzaldehyde is off the line with the 2,3-dihydroxybenzoic acid significantly off the line. (This point will be explained later in the text.) These stability constant calculations were performed assuming two ionisable hydrogen ions removed from the catecholic molecules in these low pH ranges and the resulting values of log k_1 are around those reported by other workers [6]. However, from the pK_a values and σ^* values for 4-methylcatechol and 4-*t*-butylcatechol (Table II), similar stability constants are to be expected but are not found (Fig. 5) and will be explained below.

In competition reactions between catechol and ascorbic acid for complexation with iron(III) no green species is observed [9], and the formation constant [12] for an ascorbic acid iron complex is of the order of 10^{10}. We have recently reported [12] a stability constant for the green iron catechol complex of $10^{9.3}$ when the catechol ligand is still monoprotonated. Such small stability constants resulting from monoprotonated ligand iron complexes would produce a different result (Fig. 6) to that of Fig. 5.

Here the deviations from the line are much less marked including 2,3-dihydroxybenzaldehyde. Also the stability constants for 4-methyl-catechol/iron and 4-*t*-butylcatechol/iron are almost coincident as predicted from their σ^* values and similar pK_{a_1} values.

This treatment also leads to a log k_1 for 2,3-dihydroxybenzoic acid of around 8 which is similar to that reported for 2,3-dihydroxypyridine [11]. In the 2,3-dihydroxypyridine/iron complex there is only one proton available for release [11].

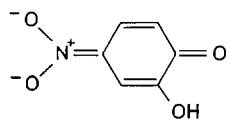
The slope of the line in Fig. 6 is negative giving a ρ of -1.85 indicating the reduction to be favoured by electron donation. This also allows the calculation of 1:1 stability constants for other unstudied 4-substituted catechols with iron by using equation (II) and knowing the σ^* value for the substituted catechol

$$\log k_{f_1} = -1.85\ \sigma^* + 9.37 \qquad \text{(II)}$$

Tetrachlorocatechol and tetrabromocatechol also agree with this treatment. Their low pK_a values of approximately 6.00 (Table II) indicating that they are strongly electron withdrawing, more positive σ^* values than 4-nitro catechol are indicated from Fig. 3. This is confirmed by plotting the position of the blue/purple transition on Fig. 2. Hence the green complexes are much too unstable to exist, accounting for the formation of the blue 3:1 complexes at acidic pH's.

Conclusions

From this Hammett procedure it can be inferred that substituent effects on the reduction of iron(III) by substituted catechols are essentially inductive in origin, with the availability of the electron for reduction showing a good correlation with the distribution of the electron cloud in the aromatic ring. Therefore electron withdrawing substituents tend to remove electrons from the ring leading to decreased stability of the green 1:1 species *e.g.* 4-chlorocatechol log K'_{f_1} = 7.9 whereas catechol log K'_{f_1} = 9.36. This behaviour is most marked with substituents like 4-nitrocatechol and as mentioned by Saleem and Wilson [14] structures like (b).



(b)

where the electron residues on the substituent (b), can be considered to dominate, leaving little electron density for radical formation. This is exemplified in the low pK_a values of 4-nitrocatechol and the low stability of the 1:1 complex (log K'_{f_1} = 6.56) making it only able to exist at acidic pH's.

By contrast, substituents like 4-methyl and 4-*t*-butyl which are electron donating $\sigma(m + p) = -0.24$ and -0.30 respectively, greatly enhance the formation of radicals enabling the green 1:1 complex

to exist up to pH 4.77, and enhance its stability log K'_{f_1} (4-methyl) = 9.56. It is therefore possible to 'design' substituted catechols to maximise reduction of iron using substituents that are strongly electron donating.

On comparing eqns. I and II and Figs. 3 and 6. it can be seen that there is an almost linear relationship between the first pK_a of the substituted catechol, and the stability constant of the 1:1 complex formed. Hence effectively

$$\log K'_{f_1} = pK_{a_1}$$

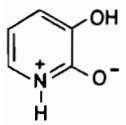
These lower values of the stability constants for the iron(II) complexes agree with the general rule that when a transition metal shows different valencies with the same ligand, the complexes of higher valency are nearly always the most stable due to the greater charge forming a stronger attraction [21].

The inductive dependency of the reaction is further qualified by the similar behaviour of the sterically bulky *t*-Butyl moiety as compared to the less sterically hindered 4-Methyl group. This may extend as far as the occurrence of substituents of small steric bulk in the 3 position *e.g.* 3-Methyl and 2,3-dihydroxybenzaldehyde.

The higher pK_a's of 2,3-dihydroxybenzoic acid and 2,3-dihydroxypyridine inevitably lead to higher values for K'_{f_1} by this treatment, but it is interesting to note that of all the systems studied, only these two show a blue 1:1 complex instead of a green, in water.

From Fig. 8 it can be seen that the pK_a's of these two species fall above the line indicating an increase in the stability of these compounds over the 4-substituted derivatives. This is most pronounced in the case of 2,3-dihydroxypyridine where the blue complex is dominant over most of the pH range.

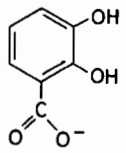
The ability of pyridines to tautomerize allows the contribution of canonical forms like (c)



(c)

where the electron withdrawing properties of the ring nitrogen are much reduced. Such a species can be considered to be a good ligand for iron reduction. Similarly the electron withdrawing properties of the carboxylate group could be neutralised by virtue of the low pK_a of the carboxylate group in 2,3-dihydroxybenzoic acid (2.91) from [20].

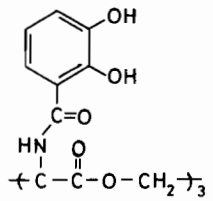
Hence at pH 2.0, at least 10% of the carboxylate protons would be ionized, allowing the contribution of structures like (d) which is of course electron donating. The *ortho* group has been given a σ value of −0.91 [17] and this combined with the σm value



(d)

of −0.1 would account for the abnormally high pK_a of this compound and thereby its large stability constants.

In enterobactin the three catechol groups are linked to the body of the molecule by an *ortho* −C=O group as in (e)



(e)

This gives a similar structure to 2,3-dihydroxybenzoic acid and thus is highly electron donating, facilitating both the reduction of iron and the transport across the bacterial membrane under suitable conditions [8, 9].

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