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ELECTRON SPIN RESONANCE STUDIES OF AZASEMIQUINONE FREE RADICAL INTERMEDIATES IN THE OXIDATION OF HYDROXYPYRIDONES

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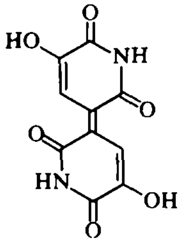
Abstract—The oxidation of hydroxy-2-pyridones by a number of one-electron oxidants has been studied, and intermediate free radicals observed by ESR spectroscopy. In alkaline media, azasemiquinones arising from electron transfer, solvation and oxidative coupling processes have been detected. The ESR hyperfine splittings are assigned with the aid of Me substitution, and the spin densities can be understood by considering the perturbation of the N atom within the semiquinone nucleus. In acid solution, the protonation of nitrogen produces structural changes in the semiquinone nucleus, which greatly affect the spin density distributions. The apparent lifetimes of the various radical species can be correlated with their expected tendencies to direct free radical dimerisation.

Azaquinonoid structures have become firmly established for a group of blue bacterial pigments found chiefly in species of *Pseudomonas* and *Arthrobacter.*[1] Certain members of the group can be readily produced by bacterial oxidation, using nutrients containing pyridine substrates, for example nicotine and pyridinols.[2,3] In order to investigate possible biosynthetic routes to these pigments, and to develop methods of structure determination, the general chemistry of azaquinones has recently received a good deal of attention, particularly by Knackmuss and his group.[1] These workers have shown[4,5] that the stable azaquinones formed by chemical oxidation of hydroxypyridones, possess the diazadiphenoquinone structure **1** found in the bacterial pigments, rather than the simple "pyridoqunone" structures **2** and **3** previously suggested.[6] In fact, as a result of the facile solvation of the -CH=N- group, only azaquinones such as **4**, in which the C atoms adjacent to nitrogen are substituted by oxygen, are known.[1]



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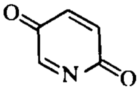

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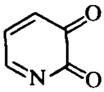

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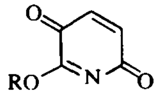

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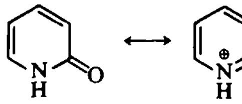
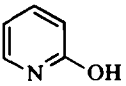
Many of the previous oxidation studies with hydroxypyridones have employed well known one-electron oxidants such as ferricyanide ion and manganese dioxide. The possibility of detectable free radical intermediates being involved in these processes has recently been confirmed by ESR spectroscopy,[7] with the observation of azasemiquinones during oxidation of 3-hydroxy- and 5-hydroxy-2-pyridone. This has now led us to a more detailed study of the structure and formation of azasemiquinone radicals, with particular reference to the effect of the N atom on certain properties of the quinonoid nucleus.

One important effect of nitrogen in azaquinones and pyridinols, compared to their benzenoid counterparts, is the introduction of tautomerism, which has been the subject of many spectroscopic studies involving IR, UV and NMR.[8] Taking 2-pyridone as an example, the spectral data shows that it exists almost entirely as the pyridone tautomer **5** in solution, rather than the pyridinol **6**. 2-Pyridone, however, behaves as an aromatic compound, suggesting a considerable contribution from the dipolar structure **5b**. Azaquinones such as **7**, also appear to exist largely in the tautomeric imide form, with the proton residing on nitrogen.[1]



a **5** **b**



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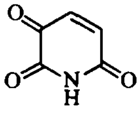

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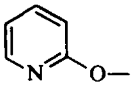

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Since much of the work described here was carried out in alkaline solution, the structures of anionic forms are very relevant to the present discussion. Some IR and NMR data have demonstrated that the anion of 2-pyridone, for example, is best represented by structure **8**, in which the charge resides chiefly on oxygen.[8]

EXPERIMENTAL

Materials. 3-Hydroxy-2-pyridone, 6-hydroxy-2-pyridone and 2,6-dihydroxyisonicotinic acid were obtained from commercial sources.

5-Hydroxy-2-pyridone and the 3-Me, 4-Me and 6-Me derivatives were synthesised by hydroxylation of the corresponding 2-pyridones with potassium persulphate in alkaline soln, according to the method of Berhrman and Pitt.[9] The 2-pyridones were prepared from the corresponding aminopyridines, via the benzenediazonium salts, according to the procedure of Adams and Schrecker.[10] 3-Hydroxy-5-methyl-2-pyridone was obtained from 2-amino-5-methylpyridine in the same way.

3-Hydroxy-6-methyl-2-pyridone was prepared by reaction of 2-iodo-3-hydroxy-6-methylpyridine with NaOMe in a sealed tube at

150°, followed by hydrolysis with 48% HBr, according to the method of Loth and Hempel.[11] The iodo compound was prepared by direct iodination of 3-hydroxy-6-methylpyridine.

Identical samples of the pigment 2,2′,5,5′-tetrahydroxy-3,3′-diaza-4,4′-diphenoquinone were obtained (a) by oxidation of 5-hydroxy- and 3-hydroxy-2-pyridones with potassium bromate in strongly acidic soln, using the method of Boyer and Kruger,[12] and (b) by bacterial oxidation of 2-pyridone by *Arthrobacter crystallopoietes*, and extraction of pigment from the cell mass as described by Kuhn *et al.*[3]

Oxidation and ESR studies. The ESR spectra were recorded using a Varian E-3 instrument, and the oxidations were carried out using both flow and static methods.[7]

The flow method consisted of the pyridone (0·01M in a suitable solvent; water, aq. acetone or aq. alcohol) being mixed with potassium ferricyanide (0·01M in 0·1M NaOH) or ceric sulphate (0·01M in 1M H_2SO_4), the solns being driven by means of a peristatic pump. The mixture could be examined at any time in excess of several milliseconds after mixing.

The static method employed potassium ferricyanide, lead dioxide or manganese dioxide as oxidant in mildly alkaline soln, only a few mg of pyridone being required in this case. Reductions of pigment was carried out in the static cell, by addition of a few drops of alkaline sodium dithionite solution to a few ml of a soln of pigment in dimethylformamide.

The hydroxy-2-pyridones are autoxidised only very slowly in alkaline solution and no ESR signals were detected in each case. Old samples which had been exposed to air for some time often gave unanalysable signals on autoxidation, probably due to the presence of polyhydroxylated products. The pyridones were therefore purified by crystallization shortly before the oxidation studies were carried out.

RESULTS

Primary azasemiquinones. In our preliminary work on the oxidation of 5-hydroxy-2-pyridone (2,5-pyridinediol),[7] we observed only secondary radicals arising from addition of solvent at some stage to the pyridine nucleus. We have since succeeded in obtaining spectra of the primary azasemiquinone under fast flow conditions with ferricyanide ion (alkaline media) and ceric ion (acidic media) as oxidants (Table 1). The radicals are very short-lived, and oxidation of the 3-Me and 4-Me derivatives gave even weaker spectra due to the increased number of lines, and these have not been analysed.

The 6-Me derivative, on the other hand, gave rise to a very intense spectrum (Fig. 1a), which remained for a considerable time in a static system, with lead dioxide or manganese dioxide as oxidants in mildly alkaline media. The nitrogen splittings for both the unsubstituted and 6-Me substituted radicals were apparently within the line-widths for the aqueous media employed, but for the latter, became discernable on changing the solvent to 50% aqueous DMF (Fig. 1b). The variation of solvent has proved valuable in resolving related problems in the case of benzosemiquinone radicals.[13]

Fig. 1. (a) Complete ESR spectrum of the primary radical from 5-hydroxy-6-methyl-2-pyridone in aqueous alkaline solution. (b) Wing of the spectrum from the same radical in 50% aqueous DMF, showing small splitting from nitrogen.

Table 1. Hyperfine splitting constants of primary azasemiquinone radicals from hydroxy-2-pyridones

2-Pyridone	Hyperfine Splitting Constants (Gauss).[c]					
		a_3	a_4	a_5	a_6	a_N
3-Hydroxy-	A		5.90	0.25	8.90	1.50
	B		2.60	2.60	6.50	0.95
3-Hydroxy-6-methyl-	A	[d]				
	B		2.90	2.90	6.50 (Me)	0.85
5-Hydroxy-	A	1.90	1.60		9.90	$\sim$0.0
	B	2.60	0.80		5.90	$\sim$0.0
5-Hydroxy-6-Methyl	A	[d]				
	B	2.95	1.02		4.95 (Me)	$\sim$0.0 (0.05)[e]
6-Hydroxy-	A	12.30	2.95	12.30		1.00
	B	[d]				
6-Hydroxy-4-carboxyl-	A	12.30		12.30		0.90
	B	12.10		12.10		0.60

A: Aqueous acidic solution

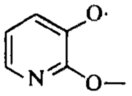
B: Aqueous alkaline solution

[c] Recorded at 25°C

[d] No analysable spectra obtained

[e] Solvent 50% aqueous DMF

When 3-hydroxy-2-pyridone and the 5-Me derivative were oxidised under the fast flow conditions, only the former gave readily analysable ESR spectra corresponding in alkaline solution, to the primary semiquinone **9**. A spectrum originally ascribed to this radical,[7] now shows, on improvement, a 1:4:7:7:4:1 pattern ($a_N = a_{Me} =$ 1·32 G), rather than a 1:2:2:1 pattern ($a_N = a_H$) previously suggested.[7] This spectrum may have arisen from an impurity in the pyridone formed during crystallization from methanol. 3-Hydroxy-2-pyridone recrystallized several times from ethanol, gives only the primary spectrum of **9** in aqueous media, while the spectrum corresponding to radical **10** is obtained when the oxidation is carried out in aqueous methanolic solution, and the time of observation is increased to several seconds after mixing.



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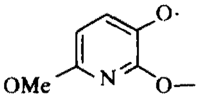

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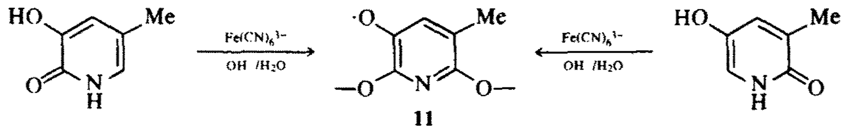
3-Hydroxy-6-methyl-2-pyridone (like the 5-hydroxy isomer) gave a very intense spectrum of the primary azasemiquinone in alkaline solution with lead or manganese dioxide as oxidant. Clearly, the lifetimes of the primary azasemiquinones are considerably increased in the absence of a replaceable proton at the 6-position of the pyridone ring.

The 6-hydroxy-2-pyridones (Table 1) gave spectra corresponding to the primary radicals only under the fast flow conditions, their spin density distributions and apparent lifetimes being very similar to those of the related meta-benzosemiquinones.[14]

Secondary and tertiary azasemiquinones. With the flow system so designed as to make the time of observation several seconds after mixing, intense spectra of secondary species were obtained during ferricyanide oxidation of hydroxypyridones possessing a replaceable proton at C-6 (Table 2). These secondary azasemiquinones were relatively long-lived and the best spectra could be obtained in a static system, where line-broadening is minimised. Their observation can be readily understood in terms of addition of solvent at the reactive C=N bond[1,7] of the pyridone ring, and in some cases the radical structures (e.g. **11**) are confirmed by production from different isomeric starting materials (Scheme 1, Table 2). The secondary radicals are mostly products of hydroxylation, but in two cases addition of methanol was effected by carrying out the oxidations in largely methanolic solutions (Table 2).

In our preliminary work,[7] we described the tertiary species observed during oxidation of 3-hydroxy- and 5-hydroxy-2-pyridones, i.e. the radical-anion of 2,2′,5,5′-



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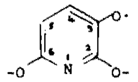
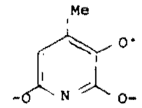
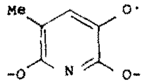
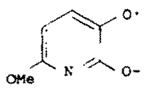
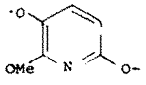
Scheme 1.

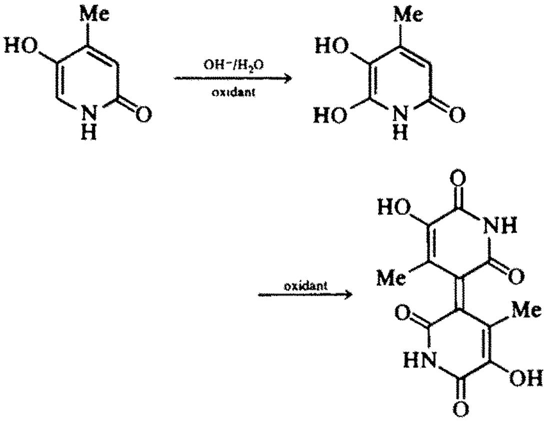
Table 2. Hyperfine splitting constants of secondary azasemiquinone radicals from hydroxy-2-pyridones in alkaline solution

Radical-anion	Hyperfine Splitting Constants (Gauss)[b]				
	a_3	a_4	a_5	a_6	a_N
	[c]	0.91	4.92		1.55
	[d]	0.35 (Me)	5.20		1.34
	[c]	0.18	6.10 (Me)		1.20
	[e]	1.57	4.52	1.32 (OMe)	1.32
	[e]4.58	0.78		1.18 (OMe)	0.78

[b] Recorded at 25°C. [c] Obtained from both the 3- and 5-hydroxy-2-pyridones.

[d] Obtained from 5-hydroxy-4-methyl-2-pyridone. [e] Obtained from the hydroxy-2-pyridone in aqueous methanolic solution.

tetrahydroxy-3,3′-diaza-4,4′-diphenoquinone. A comparable example might be expected to arise during the oxidation of 5-hydroxy-4-methyl-2-pyridone which leads to the dimeric azaquinone **12** (Scheme 2).[1,5] We have, however failed to detect the radical-anion of **12**, which may be produced so slowly (due to steric inhibition of the coupling process by the Me groups), that concentrations insufficient for detection are present.



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Scheme 2.

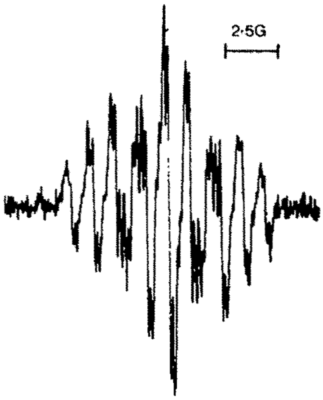


Fig. 2. ESR spectrum of the 2,2′-bipyridyl radical-anion from 5-hydroxy-2-pyridone in D_2O.

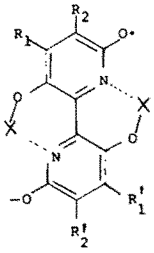
2,2′-Bipyridyl radical-anions. The blue pigments produced by chemical and bacterial oxidation of pyridinols and pyridones invariably contain the 3,3′-bipyridyl skeleton.[1] We have however, obtained intense ESR spectra ascribed to the 2,2′-bipyridyl radical-anions **13** (Table 3), during the oxidation of concentrated solutions of 5-hydroxy-2-pyridones (>0·1M) which have a replaceable proton at C-6. The best spectra are obtained using lead dioxide as oxidant in a mildly alkaline mixture of DMF (80%)–water (20%). The parent radical from 5-hydroxy-2-pyridone, shows hyperfine splittings due to 2 equivalent nitrogens and 3 pairs of equivalent protons, one pair of which is absent in DMF-D_2O (Table 3, Fig. 2). The presence of this pair of tightly bound protons is consistent with the 2,2′-bipyridyl structure **13**, and in fact, the probable precursor of this radical, 3,3′,6,6′-tetrahydroxy-2,2′-bipyridyl, has been identified[15] together with the diazadiphenoquinone pigment (**1**), as a product of oxidation of 5-hydroxy-2-pyridone with peroxidase-hydrogen peroxide. Presumably, the presence of the hydroxypyridone in high concentrations favours the coupling of some primary species rather than the solvation step[1,7] which leads to the secondary and tertiary species observed in less concentrated solutions. This idea also accounts for the fact that the best solvent media for observing the 2,2′-bipyridyls have a low percentage of water.

DISCUSSION

Structure and ESR spectra. The ESR spectra of semiquinone-type radicals have been the subject of much study and discussion, and a variety of theoretical treatments have been applied to the problem of rationalising the hyperfine splitting data obtained.[13,16–21] The complexity of this problem is considerably increased as a result of extensive solvation and protonation of the radicals, and in the case of azasemiquinones is further complicated by the presence of an additional type of

Table 3. Hyperfine splitting constants of 3,3′,6,6′-tetrahydroxy-2,2′-bipyridyl radical-anions from 5-hydroxy-2-pyridones

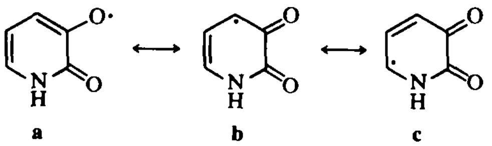
Radical-Anion (XIII)	Hyperfine Splitting Constants (Gauss)[b]			
R = R′	a_4	a_5	a_N	a_{other} (X)
$R_1 = R_2 = X = H$	0.20	2.40	1.03	$a_H = 0.27$
$R_1 = R_2 = H$, $X = D$	0.20	2.40	0.98	$a_D \sim 0.0$
$R_1 = Me$, $R_2 = X = H$	0.16 (Me)	2.08	0.96	$a_H = 0.32$
$R_2 = Me$, $R_1 = X = H$	0.20	2.39 (Me)	1.07	$a_H = 0.30$



[b] Recorded at 25°C

heteroatom in the semiquinone nucleus. We can, however, gain at least some qualitative understanding of the relationships between structure and spin density distribution in azasemiquinones, by extending our knowledge of benzosemiquinones to include the influence of the N atom.

The OH group of 3-hydroxy-2-pyridone is known to exhibit the usual phenolic properties,[8] and the oxidation of this pyridone in acidic solution with ceric ion might be expected to correspond to a one-electron phenolic oxidation. The neutral free radical produced is best represented in Valence Bond terms by structures **14a–c**, with predicted high spin density at two ring positions, as is observed (Table 1). A very rapid intermolecular exchange of the enolizable -NH- proton occurs in solutions of pyridones,[8] and a similar exchange in radical **14** would account for the apparent lack of hyperfine coupling with this proton. The acid oxidation of the isomeric 5-hydroxy-2-pyridone gives another short-lived radical, which can be represented by only two important resonance structures **15a** and **15b**. In this case only a single large ring proton splitting is predicted, and this is again observed (Table 1).



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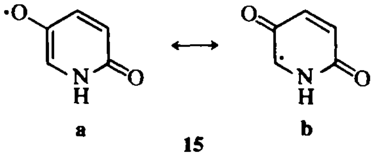

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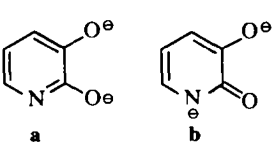
In alkaline solution, where the enolizable proton of the pyridone is lost, the anions are known to carry the negative charge chiefly on the O atom,[22,23] so that the corresponding anion of 3-hydroxy-2-pyridone is best represented by **16a** rather than **16b**. The oxidation of this species is more comparable to that of quinol anions[24] than the monohydric phenol oxidation already discussed for the acidic media. The radical-anion formed in alkaline solution can be thought of as a true semiquinone, and like the *o*- and *p*-benzosemiquinones, can be represented in V.B. terms by a large number of important resonance structures which place spin density on all atoms, e.g. **17a–e**, etc. For this reason, the V.B. treatment offers little help in obtaining a simple qualitative picture of relative magnitudes of spin densities in semiquinone anions. The simple Molecular Orbital methods are more helpful in this respect, and considerable success has been achieved for substituted semiquinones using an inductive model to change only the coulomb integral of the ring carbon atom to which the substituent is attached.[18] We can use the same model in the case of azasemiquinones, by choosing a suitable coulomb integral for the nitrogen heteroatom which reflects its greater electronegativity.



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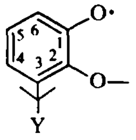
The actual evaluation of spin densities for *ortho*-semiquinone radicals has not proved particularly successful, due to the difficulty of finding a consistent set of C–O parameters for a suitably wide range of substituted radicals.[25] However, calculations at least predict a high spin density at the ring C atom (C–4) adjacent to the position bearing a strongly electron-withdrawing group Y (which increases α_{C-3}), in radical **18**. In the azasemiquinone **19** (where $\alpha_N > \alpha_C$), we expect a similar situation, with high spin density in this case at C–6. The results of Table 1 are in line with this expectation.



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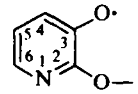

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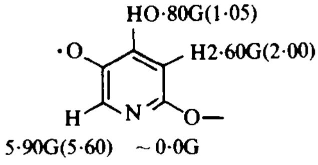
The simple inductive model has had much more success for the quantitative evaluation of spin densities in the case of *para*-semiquinones. Using the C–O parameters of Fairbourn and Lucken,[18] and a generally acceptable value for the coulomb integral of nitrogen ($\alpha_N = \alpha_C + 0{\cdot}09\beta_{CC}$),[26] we obtain fairly good agreement with experimental hyperfine splittings for the radical anion **20** of 5-hydroxy-2-pyridone (calculated values in parenthesis). The calculation is rather crude, but the good agreement somewhat justifies the treatment of this radical as a true *para*-semiquinone.



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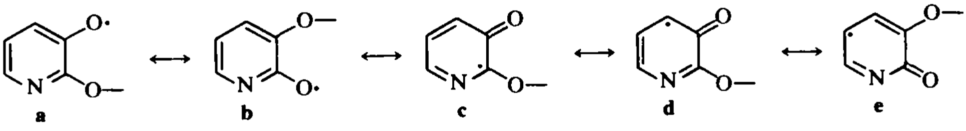
The one-electron oxidation products of 6-hydroxy-2-pyridones give ESR spectra with rather similar hyperfine splitting constants in acidic and alkaline conditions. The N atom has also apparently little effect on spin densities since the ring splittings are close to those of the corresponding "*meta*-semiquinones", formed from resorcinols.[14] The important V.B. structures in acid (**21**) and alkaline (**22**) solutions account for the large coupling of protons at C–3 and C–5. In addition, MO calculations on the resorcinol derivative **23**, predict that while large



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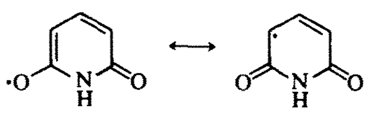

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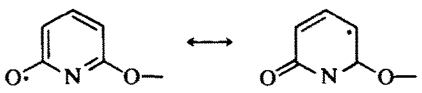

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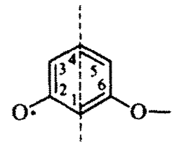


23

splittings are expected at C-3 and C-5, the non-bonding orbital has an effective node through C-1 and C-4,[27] as shown. In this case, the replacement of a CH group by nitrogen in the nodal plane, is expected to have only a small effect on the overall spin density distribution.

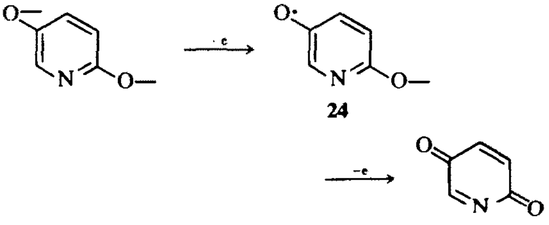
The secondary radicals (Table 2), which are derived from 3,6-dihydroxy-2-pyridones, also have spin density distributions closely similar to those of the corresponding benzosemiquinone anions from 1,2,4-trihydroxybenzenes.[24] In such highly oxygenated radicals, the nature of the non-bonding orbital is apparently dominated by the CO groups.

In the bipyridyl radical anions, the spin is shared equally between the two rings and the overall distribution is not too different from that of the corresponding radicals obtained from hydroxylated biphenyls.[28,29] In the 2,2′-bipyridyls, the tendency is probably more towards coplanarity of the two rings due to the presence of the strong H-bonds.

In the discussion of spin densities in the various types of azasemiquinone radicals, the assignment of hyperfine splittings was made possible with the substitution of aromatic ring protons by Me groups. As with the related benzosemiquinones, the perturbing effect of the Me group with regard to the overall spin distribution is small, and the observed splittings of a proton and a methyl group in the same position are roughly equal.[16,24]

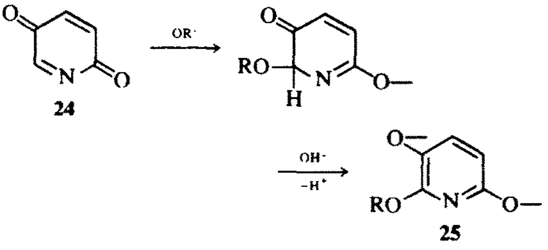
Formation of azasemiquinones

We shall consider firstly the oxidation of hydroxy-2-pyridones in alkaline solution, since the reactions, and the types of radical species involved, appear to be closely analogous to those occurring in the well-known alkaline oxidations of benzoquinols.[24,30] The primary species are presumably formed in the same way as the hydroquinone and catechol semiquinones, by simple electron transfer from the pyridone anion to the oxidant (Scheme 3). The monohydroxy-2-pyridone anions, unlike those of hydroquinone and catechol, are rather resistant to autoxidation, probably reflecting the increased electronegative character of the ring due to the presence of nitrogen. A similar resistance to milder oxidising agents is observed for hydroquinones containing strongly electron-withdrawing substituents, e.g. NO_2, CHO, COMe, and again semiquinone formation requires the use of lead and manganese dioxides.[31]



Scheme 3.

The transfer of a second electron in Scheme 3, completes the primary oxidation to azaquinone **24**, which, however, undergoes a rapid solvation at the C=N bond in hydroxylic media[1] (Scheme 4), to form the pyridone anion **25** (R = H, Me). The secondary radicals can then be formed by further oxidation, and since dihydroxypyridones are easily autoxidised,[1] this process presumably accompanies that due to the added oxidant. Solvation, and secondary radical formation, can only occur in this way if a replaceable proton is present at C-6 of the azaquinone **24**. Solvation at the C=C bond of a 6-methylazaquinone is apparently much less favourable, and no secondary radicals corresponding to such a process have been observed (Table 2). Solvation at the C=C bonds of benzoquinones leads to mixtures of secondary radicals,[24] and although the reaction schemes appear to be closely parallel for the formation of secondary benzo- and azasemiquinones, the chief divergence is that in the latter case any solvation appears to occur exclusively at one ring position, i.e. C-6.



Scheme 4.

In view of obtaining very intense and stable ESR spectra of 2,2′- and 3,3′-bipyridyl radical anions from hydroxypyridone oxidations, it appears that, under certain conditions, coupling processes are particularly favourable. The formation of the 2,2′-bipyridyl radicals from 5-hydroxy-2-pyridones is almost certainly in competition with further oxidation to give secondary products, and not unexpectedly, is favoured by high concentrations of pyridone, low hydroxylic content of solvent and an oxidant (Pbo$_2$) which is known to promote phenolic coupling reactions.[32]

With regard to the actual mechanism of coupling, a direct radical dimerisation[32] through the position of high spin density in each case, would seem to be most attractive for several reasons. The 2,2′-bipyridyls and the 3,3′-bipyridyl are symmetrical dimers, the coupling site being that of high spin density in the monomer radical. The dimerisation of such primary azasemiquinones is apparently greatly enhanced by use of the heterogeneous lead dioxide system, but these types of coupling reactions, which are thought to occur at the metal oxide surface, are not well understood.[32]

The possibility of coupling between a nucleophilic phenoxy anion and an azaquinone, although perhaps a less likely mechanism, cannot be ruled out. However, substantial amounts of C–O coupling might be expected in this case, and, in addition to observing no corresponding radical species, product studies point to a predominance of C–C coupling.[15]

In the ferricyanide oxidation of 5-hydroxy-2-pyridone

(Results), the hydroxylic solvent conditions favour secondary radical formation (Scheme 4), rather than the coupling reaction, in the initial stages. However, further hydroxylation of the ring is much less favourable than that at the C=N bond, and the coupling of secondary radicals apparently becomes the predominant reaction leading to the 3,3'-bipyridyl structure of the bacterial pigments.

Diazadiphenosemiquinone formation is, of course, only observed, when the expected coupling site bears a replaceable proton, and it is noteworthy that the apparent lifetimes of the monomeric azasemiquinones can be readily understood in terms of their expected rate of destruction, by direct dimerisation through the position of maximum spin density. For example, the semiquinones of 3-hydroxy- and 5-hydroxy-2-pyridone are difficult to observe even under fast flow conditions, while the 6-methyl derivatives give very intense, stable spectra in a static system. Similarly, although all the secondary radicals can be observed in a static system, those containing a methyl group at the ring position of high spin density (C-5) are by far the most long-lived. The observation of large concentrations of radicals in such cases, does of course imply that the chemical processes involving azasemiquinones are not merely side reactions, but make up the major reaction pathway.

The reactions of hydroxy-2-pyridones in acid solution with ceric ion appear to correspond more closely to monohydric phenol oxidations, the primary process leading to species of the phenoxy radical type. The likely fate of these radicals is destruction by dimerisation,[32] on account of the sites of very high spin-density present in the ring. The inability to detect any secondary processes occurring is due chiefly to the short-lifetimes of phenoxy and semiquinone radicals under such conditions of acidity.[20]

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