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AN ELECTRON SPIN RESONANCE STUDY OF STRUCTURE AND CONFORMATION IN SEMIQUINONE RADICALS FORMED DURING THE AUTOXIDATION OF HYDROXYLATED COUMARINS

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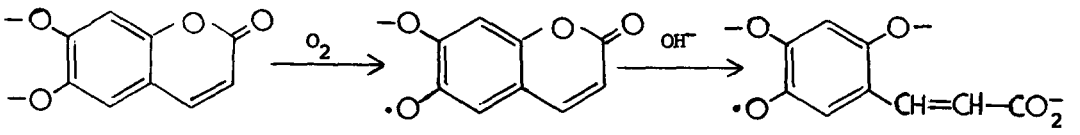
In the course of our studies on free radical oxidation processes of some natural products, our attention has turned towards coumarins, particularly the hydroxylated derivatives which are widely distributed throughout the plant kingdom[1]. We have found that coumarins containing hydroxyl groups in the aromatic ring are readily autoxidised in aqueous alkaline solution, forming relatively stable semiquinone radicals, which can be studied by electron spin resonance (esr) spectroscopy.

Some of these semiquinones are formed by straightforward autoxidation[2] (where the aromatic ring contains two ortho hydroxy groups), but the opening of the pyrone ring under the alkaline conditions employed, invariably leads to secondary species. Esculetin(6,7-dihydroxycoumarin), for example, in dilute alkaline solution and in the presence of air, gives rise initially to an



A B

esr spectrum ascribed to radical A. On standing however, this spectrum decays and is gradually replaced by that due to radical B. That this radical is the semiquinone of 2,4,5-trihydroxy-cinnamic acid, is confirmed by autoxidation of the latter compound, whereupon an identical esr spectrum is obtained (see Table).

With coumarins containing a single hydroxyl substituent in the aromatic ring, semiquinones are formed only as a result of pyrone ring opening. 6-Hydroxycoumarins give spectra in dilute alkali, arising from the semiquinones of 2,5-dihydroxycinnamic acid derivatives (Figure 1 and Table). In stronger alkali, further base-catalysed hydroxylation[3] occurs readily to give the 2,4,5-trihydroxycinnamic acid semiquinones. In the case of 7-hydroxycoumarins, ring opening leads to resorcinol derivatives which form no stable semiquinones. If hydrogen peroxide is added to the alkaline solution, however, hydroxylation of the resorcinol can occur,[4] to again give the 2,4,5-trihydroxycinnamic acid semiquinones. The structures of the radicals obtained by pyrone ring-opening are thus confirmed by obtaining identical esr spectra from different starting materials (Table).

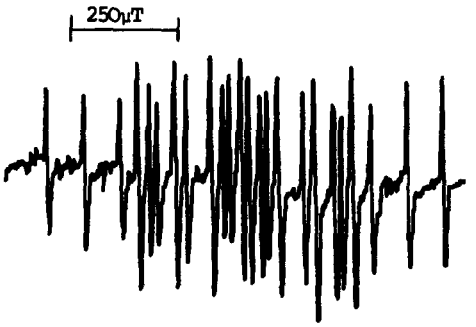
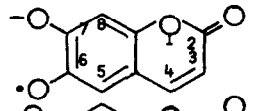
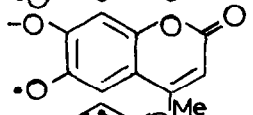
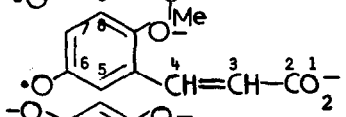
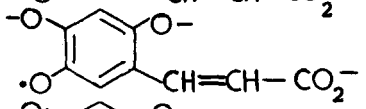
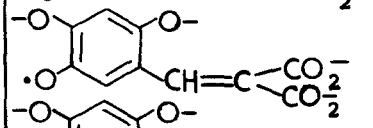
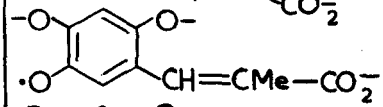
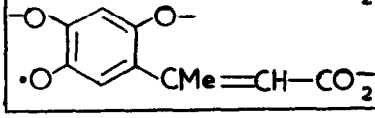


Figure 1. Esr spectrum of primary radical from 6-hydroxycoumarin

Spin densities and conformation. The assignments of hyperfine splittings for the aromatic ring protons are quite straightforward, with the aid of previous data on substituted semiquinones. In the cinnamic acid semiquinones,

Table. H.f.s. constants of Radicals from Autoxidation of Hydroxycoumarins

Radical	Coumarin Source	Hyperfine Splittings (μT) a_3	a_4	a_5	a_7	a_8
	6,7-diOH-	338	106	234	-	47
	6,7-diOH-4-Me-	278	58 (Me)	220	-	45
	6-OH-	85	170	213	213	240
	6-OH- 6,7-diOH- (2,4,5-triOH cinnamic acid)	175	283	132	-	44
	6-OH-3-CO_2H-	-	250	125	-	40
	6-OH-3-Me	259 (Me)	320	69	-	47
	6-OH-4-Me- 7-OH-4-Me- 6,7-diOH-4-Me	24	~0 (Me)	96	-	47

the effect of the side chain is evidently quite small, being comparable to that of a methyl or phenyl group[3,5]. Aromatic proton splittings for the coumarin semiquinones (pyrone ring intact) are expected to be determined chiefly by the much stronger electronic effect of the -O-CO- grouping. From our data this effect appears to be comparable to that of a methoxy substituent.[6] Since the aromatic proton splittings in both types of radical are governed mainly by the oxygens attached to the ring, any effects of methyl or carboxyl substituents in the side chain or the pyrone ring on these splittings, are found to be small (see Table).

Methyl and carboxyl substituents at the 3-position have, as we might expect, only a small effect on the hyperfine splitting of the adjacent proton on C_4, thus enabling the distinction of splittings from protons at these two positions. The splittings of protons in the side chain of the cinnamic acid semiquinones are, on the other hand, very dependent on substitution at C_4, and the ratio $a_3^H:a_4^H$ changes drastically on opening the pyrone ring. These observations appear to reflect conformational changes at the C-C bond joining the aromatic ring and the remaining fragment, and can be rationalised in terms of σ-π-delocalisation.

Since the side chain of a cinnamic acid semiquinone has little influence on spin densities in the aromatic ring, it can be treated, to a good approximation, as a simple substituent drawing spin density from the pπ-orbital of the aromatic ring carbon to which it is attached. For the coumarin semiquinones, the problem is the same since the -O-CO- grouping is expected to effectively form a barrier to any spin transfer from its neighbouring aromatic ring carbon atom, and the value of ρ_{C_r} (the spin density in the pπ-orbital of C_r) is expected to be approximately the same in both cases (see Figure 2). The problem is thus reduced to that of an allylic fragment, and spin can be transmitted from C_r by both π- and σ-delocalisation (hyperconjugation) to degrees dependent on the dihedral angle (θ) between the pπ- orbitals on C_r and C_4.[5,7]

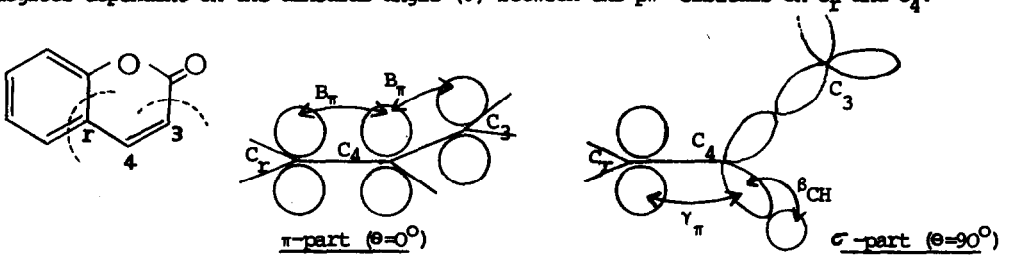


Figure 2. Major orbital interactions responsible for π- and σ-spin delocalisation.

For the π-contribution we can use the simplified model of Huckel coefficients for an allylic fragment, placing high spin density on C_3 but zero spin density on C_4. This π-delocalisation, depending on pπ-pπ overlap, (Figure 2) varies directly with $\cos^2\theta$. For the σ-contribution, spin density is transmitted by overlap of the pπ - orbital of C_r with the carbon σ-orbitals (which have $^2/_3$ p character). For the present discussion the effect is significant only for a proton on C_4 (Figure 2), falling off rapidly for methyl group and C_3 protons. Maximum σ-overlap occurs when $\theta = 90^o$, the effect following a $\sin^2\theta$ relation.

With this simple approach we can see how the hyperfine splittings of the allylic fragment reflect conformation changes (the angle of twist, θ) at the C_r-C_4 bond as the pyrone ring is opened and substituents are added at C_4. With the pyrone ring closed, π-delocalisation is

clearly very important ($a_3^H > a_4^H$), and a 4-methyl substituent causes only a small reduction in the spin density reaching C_3. When the constraints of near-planarity are removed by pyrone ring-opening, σ-delocalisation becomes more important with the increasing angle of twist ($a_4^H > a_3^H$), and a 4-methyl group in this case has the huge effect of reducing a_3^H to a value approaching zero ($\theta \rightarrow 90^o$). Comparisons of proton and methyl group splittings at C_3 and C_4 also reflect their dependence on the mechanism of spin transfer, i.e. $a_4^{Me} < a_4^H$, $a_3^{Me} \sim a_3^H$.

In view of the fact that substituents on C_3 have little effect on spin density distribution in the radicals, the conformational changes occurring at the C_r-C_4 bond appear to arise only from steric interactions between the substituent on C_4 and some group on the aromatic ring, probably the adjacent oxygen atom. In this case the conformational changes discussed will be independent of any tendency towards rigid cis or trans configuration of the cinnamic acid radicals with respect to the C_3-C_4 bond. However, in view of the fact that identical esr spectra are obtained from pyrone ring-opening and from the trans-cinnamic acid derivative (see Table), it would appear that either rapid interconversion of the cis and trans forms occurs (due to the allylic nature of the side chain) or that pyrone ring opening is followed by rapid conversion to the more stable trans form[1]. In either case, the essential relation between spin delocalisation and the dihedral angle θ at the C_r-C_4 bond remains the same.

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