Flavosemiquinone Model Systems. Part 2.[1] Methyl-substituted Quinoxaline Radical Ions

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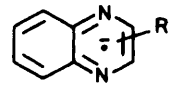
2,3-Dimethyl-, 6,7-dimethyl-, and 2,3,6,7-tetramethyl-quinoxaline were reduced in aprotic (THF) and acidic media (DMF–$HClO_4$) to yield the corresponding quinoxaline radical anions and 1,4-dihydroquinoxaline radical cations. Analysis of their e.s.r. spectra was accomplished by computer simulation; a consistent assignment of coupling constants in quinoxaline radical ions could be made on the basis of the methyl substitution pattern. The hyperfine splitting is in agreement with Hückel MO correlations and may be used to explain the spin distribution in flavosemiquinones.

The quinoxaline radical anion (**1**) has frequently been the subject of e.s.r. spectroscopic studies[2-8] and of theoretical calculations.[3-10] Early assignments of the three triplet couplings from 3 × 2 equivalent hydrogen atoms have been contradictory;[5,7,9,10] the work by Pedersen and Muus[6] on two dimethyl derivatives (**2**) and (**3**) seemed to have settled this question. However, the e.s.r. spectrum of (**2**)-K^+ shown in this paper is not fully compatible with the computer simulation displayed, and although the authors have tried to explain this disagreement with linewidth variations,[6] we have reinvestigated this radical and related species (**2**)—(**4**) in order to obtain unambiguous results.

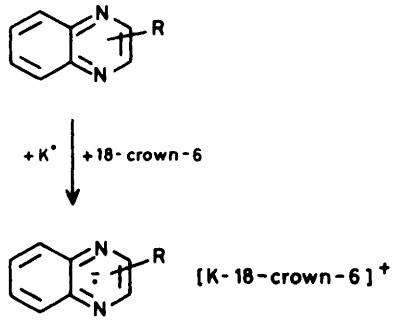
Alkali-metal ion pairing, which had created complicated hyperfine splitting,[6] was prevented in our experiments by using a complexing crown ether.[11] In acidic media, 1,4-diazines are reduced to 1,4-dihydro-1,4-diazine radical cations such as (**5**)—(**8**).[12,13]

Our interest in methyl-substituted quinoxaline radical ions (**2**)—(**4**) and (**6**)—(**8**) is derived from their possible function as models for the flavosemiquinones (**9**)—(**11**). E.s.r. and e.n.d.o.r. (electron nuclear double resonance) studies[14-16] of flavosemiquinones have suggested that the spin density in these biologically important species[17] is almost exclusively confined to the π system in the quinoxaline part of the molecule.

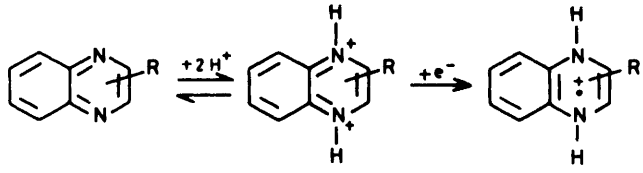
We have, for both of the reasons indicated, prepared the radical anions (**2**)—(**4**) and 1,4-dihydro radical cations (**6**)—(**8**) of 6,7-dimethyl-, 2,3-dimethyl-, and 2,3,6,7-tetramethyl-quinoxaline and studied these species by high-resolution e.s.r. spectroscopy.



(**1**) R = H
(**2**) R = 6,7-Me_2
(**3**) R = 2,3-Me_2
(**4**) R = 2,3,6,7-Me_4



Scheme 1.



(**5**) R = H
(**6**) R = 6,7-Me_2
(**7**) R = 2,3-Me_2
(**8**) R = 2,3,6,7-Me_4

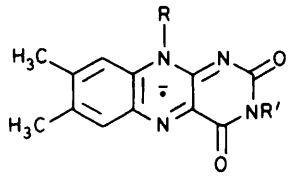
Scheme 2.

Results and Discussion

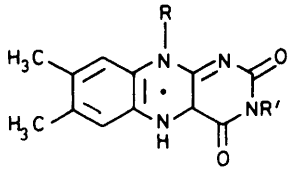
The quinoxaline radical ions (**2**)—(**4**) and (**6**)—(**8**) were obtained at room temperature *via* the routes shown in Schemes 1 and 2, respectively. The radicals could be characterized by well resolved e.s.r. spectra which were analysed with computer simulation techniques (Figures 1 and 2). The Table summarizes the coupling constants derived from computer simulations and shows also data for the related radicals (**1**), (**5**), and (**9**)—(**11**).

The first result concerns the hyperfine splitting of the radical anion (**2**). In contrast to Pedersen and Muus,[6] we did not observe a potassium splitting (Scheme 1). Analysis of the spectrum gave couplings very similar to those reported[6] with the exception of the ^{14}N splitting constant which proved to be substantially higher.

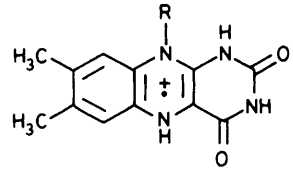
The Table shows a consistent pattern of the a_N and a_H values for the quinoxaline ions and demonstrates that methyl substitution causes only minor spin redistributions in the π system. Three aspects may be noted. (i) Methyl splittings are significantly larger in the cations than in the corresponding anions, an effect which is well established for hydrocarbon radical ions.[18] (ii) A comparison of anions with corresponding cations also exhibits a change in the overall spin distribution which may be explained on the basis of Hückel MO calculations. The transition from anions to 1,4-dihydro cations is reproduced by increasing the nitrogen Coulomb integral parameter h_N in the HMO procedure; correlations shown by Barton and Fraenkel[12] are in good agreement with the trends



(9)



(10)



(11)

R = methyl : lumiflavin
R = ribityl : riboflavin (vitamin B_2)

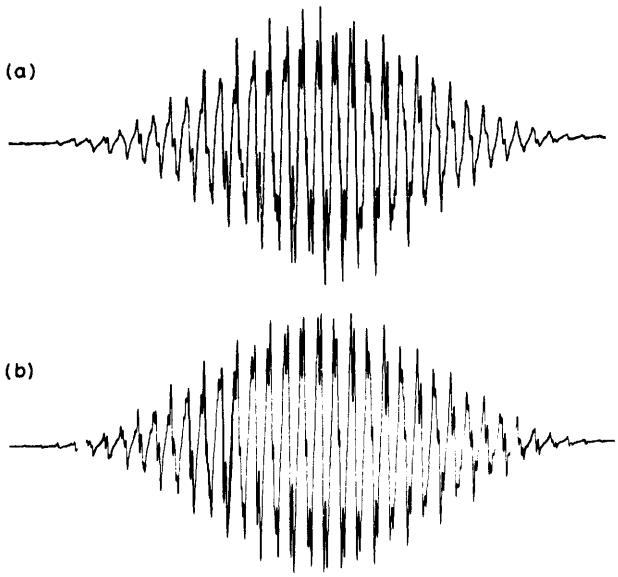


Figure 1. Experimental (a) and computer-simulated (b) e.s.r. spectrum of the 2,3,6,7-tetramethylquinoxaline radical anion (**4**) at 300 K in THF, counter-ion: K^+. Linewidth for computer simulation 12 μT, 735 theoretical lines

evident in the Table: $a_{H_{2,3}}^{(+\bullet)} > a_{H_{2,3}}^{(-\bullet)}$, $a_{H_{5,8}}^{(+\bullet)} < a_{H_{5,8}}^{(-\bullet)}$, $a_{H_{6,7}}^{(+\bullet)} \sim a_{H_{6,7}}^{(-\bullet)}$. This agreement again confirms the assignments made for the quinoxaline radical ions. (iii) A neighbouring group effect through methyl substitution is evident (Table): 2,3-dimethyl substitution causes a decrease of $a_{N_{1,4}}$ by *ca.* 10%, 6,7-dimethyl substitution leads to a reduction of $a_{H_{5,8}}$.

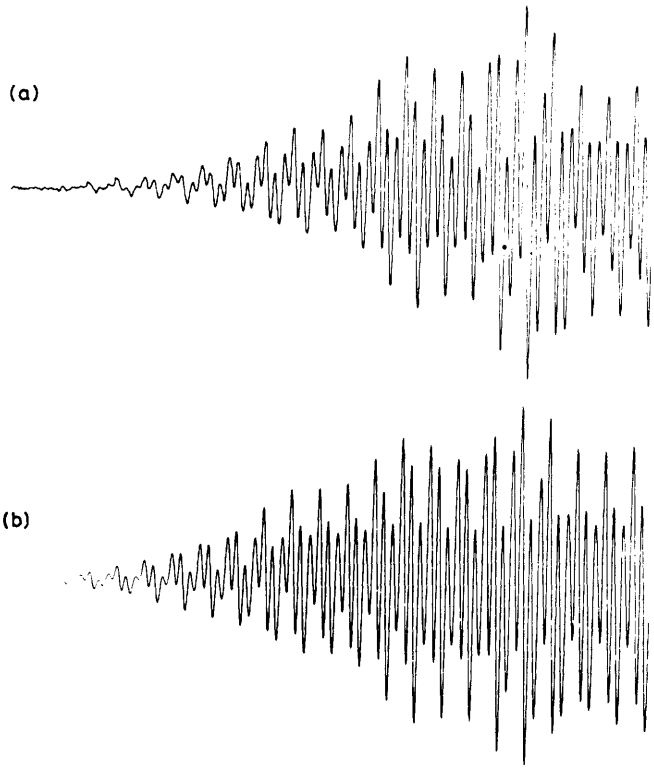


Figure 2. Experimental (a) and computer-simulated (b) e.s.r. spectrum (low field section) of the 1,4-dihydro-6,7-dimethylquinoxaline radical cation (**6**) at 300 K in DMF–1M-$HClO_4$. Linewidth for computer simulation 33 μT, 945 theoretical lines.

E.s.r. coupling constants a_X(μT) for quinoxaline radical anions (**1**)—(**4**), 1,4-dihydroquinoxaline radical cations (**5**)—(**8**), and lumiflavin semiquinones (**9**)—(**11**)[a]

Radical	$a_{N_{1,4}}$	$a_{H_{1,4}}$	$a_{H_{2,3}}$	$a_{H_{5,8}}$	$a_{H_{6,7}}$	Solvent	
(**1**)	570		333	238	145	DMF	ref. 7
(**2**)	578		319	217	141[b]	THF	*c*
(**3**)	513		270[b]	243	140	THF	*cf.* ref. 7
(**4**)	522		259[b]	229	138[b]	THF	
(**5**)	665	717	399	78	138	DMF	ref. 12
(**6**)	662	712	375	53	165[b]	DMF	
(**7**)	612	660	397[b]	78	128	DMF	*cf.* ref. 12
(**8**)	611	662	374[b]	52	148[b]	DMF	
(**9**)[d,e]	525			220	200[f]	DMF	ref. 14
(**10**)[e,g]	580			85	120	$CHCl_3$	ref. 15
(**11**)[e]	606			(−)45	162	C_6H_5Me–CF_3CO_2H	ref. 16

[a] *g* Values of (**2**)—(**4**): 2.0033 ± 0.0001, *g* values of (**6**)—(**8**): 2.0031 ± 0.0001. [b] Methyl proton coupling constant. [c] Ref. 6: a_N 469 μT, a_H 326, 212, and 140 μT. [d] R′ = $CH_2CO_2^-$. [e] R = CH_3, averaged values from $a_{N_{5,10}}$, $a_{H_{6,9}}$, and $a_{H_{7,8}}$ (flavin numbering system). [f] Large experimental error. [g] R′ = CH_2CO_2H.

The main objective of this work was to determine whether the quinoxaline radical π system can serve as a model for the biologically significant[17] flavosemiquinones (**9**)—(**11**). It has to be considered that the isoalloxazine ring system contains two methyl groups in positions 6 and 7 and a pyrimidinedione ring, condensed to positions 2 and 3 of the quinoxaline moiety. The

latter perturbation was simulated here by introduction of methyl at C-2 and C-3; however, this transformation does not take account of the symmetry reduction $C_{2v} \longrightarrow C_s$ introduced by the pyrimidinedione ring. In order to make a comparison possible, the non-equivalent coupling constants in (**9**)—(**11**) were averaged in the Table with the result that the relevant coupling constants $a_{N_{1,4}}$, $a_{H_{5,8}}$, and $a_{H_{6,7}}$ are virtually identical for (i) the 2,3,6,7-tetramethylquinoxaline radical anion (**4**) and a 3-alkylated lumiflavine radical anion (**9**; R′=$CH_2CO_2^-$),[14] and for (ii) the 1,4-dihydro-2,3,6,7-tetramethylquinoxaline radical cation (**8**) and the lumiflavine cation radical (**11**).[16] The neutral lumiflavin semiquinone (**10**; R′=CH_2CO_2H)[15] takes an intermediate position.

This almost perfect agreement suggests that these particular quinoxaline radical ions are indeed very valuable models for the flavosemiquinone system. Although strong dissymetry is introduced through perturbation from the pyrimidinedione ring system,[1] it does not affect the average spin distribution that prevails in the quinoxaline moiety.

Experimental

2,3-Dimethylquinoxaline and starting materials were purchased from Aldrich. 6,7-Dimethyl- and 2,3,6,7-tetramethyl-quinoxaline were prepared according to published methods.[19,20] 2,3,6,7-Tetramethylquinoxaline had δ_H (60 MHz; $CDCl_3$) 2.47 (6 H, s, 6,7-Me_2), 2.70 (6 H, s, 2,3-Me_2), and 7.72 (2 H, s, 5,8-H_2). Radical anions (**2**)—(**4**) were obtained in sealed glass systems by reacting the quinoxaline in a THF–1M-18-crown-6 solution with a freshly prepared potassium mirror under high vacuum.

Radical cations (**6**)—(**8**) were generated by cathodic reduction (*ca.* 1 V) of solutions of the quinoxaline in DMF–1M-$HClO_4$ at a mercury electrode.

E.s.r. instrumentation and spectra analysis have been described before.[1]

Acknowledgements

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