Electrochemical Properties of Pyrazinothiadiazoles

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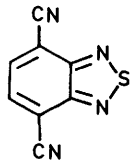
The reduction properties of some pyrazinothiadiazoles have been measured by cyclic voltammetry and pulse radiolysis. Variation in substitution on the pyrazine ring has given compounds with half-peak reduction potentials varying between −280 and −1 100 mV (*versus* Ag–AgCl) in 3:1 methanol–water. Some of these compounds act as Photosystem I electron acceptors at a concentration lower than 10^{-6} mol dm^{-3}. MNDO calculations have been used to help in the understanding of the redox processes involving this class of molecules.

The bipyridinium herbicides, in particular paraquat and diquat, exert their herbicidal effect by accepting an electron from Photosystem I (PSI),[1] in direct competition with the natural substrate ferredoxin and giving rise to a bipyridyl cation radical, $PQ^{\bullet+}$. The latter species reacts rapidly with oxygen (k 7.7×10^8 dm^3 mol^{-1} s^{-1})[2] to give superoxide, $O_2^{\bullet-}$, *via* reaction (1), with regeneration of the bipyridinium cation, PQ^{2+}. The

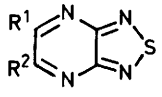
$$PQ^{\bullet+} + O_2 \longrightarrow PQ^{2+} + O_2^{\bullet-} \qquad (1)$$

superoxide anion radical itself is not considered to be toxic to the chloroplast system. However, this species is thought to convert into other toxic species such as the $HO^{\bullet}$ radical or H_2O_2 by Fenton-type reactions.[3] Interaction of these reactive oxygen species with allylic hydrogens of galactolipid material both in the thylakoid and the chloroplast envelope and other outer membranes forming the leaf system leads initially to the formation of unstable hydroperoxides and eventually to the destruction of the plant.

Recently we described the synthesis and the electrochemical properties of a number of neutral molecules, namely the dioxathiadiazaheteropentalenes,[4] which interact with the chloroplast in a similar manner to the bypyridinium herbicides.[5,6] We also reported a detailed study of the one-electron reduction of another PSI electron acceptor, namely 2,1,3-benzothiadiazole-4,7-dicarbonitrile (**1**) in aqueous solution.[7] Compound (**1**)



(**1**)



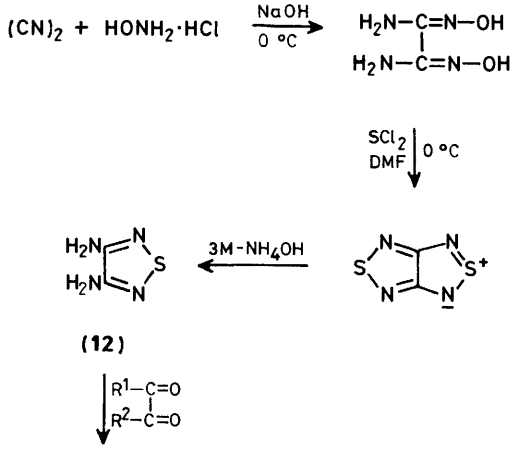
(**2**)

unlike the parent compound 2,1,3-benzothiadiazole (E_7^1 < −1 000 mV) is reduced at a potential of −490 mV, which is within the range characteristic of PSI electron acceptors. This difference in reduction potential between the two compounds is due to the electron-withdrawing effect of the cyano groups in (**1**).[7]

As part of our continued effort to discover novel PSI electron acceptors, we have replaced the benzene moiety in (**1**) by a pyrazine ring to give compounds of general structure (**2**) where R^1 and R^2 are shown in Scheme 1. In this paper we detail some electrochemical properties of these molecules studied by cyclic voltammetry and pulse radiolysis. We have also performed MNDO calculations on (**1**) and (**2**) and their corresponding radical anions in order to evaluate the likely effect of R^1 and R^2 on the reduction properties of these molecules.

Experimental

Compounds (**3**)—(**11**) were provided by the Organic Chemistry Division at Sittingbourne Research Centre. The preparation of (**3**)—(**9**) involved reaction of 3,4-diamino-1,2,5-thiadiazole (**12**) with the corresponding glyoxal as shown in Scheme 1.



(**3**) $R^1 = R^2 = H$
(**4**) $R^1 = R^2 = CH_3$
(**5**) $R^1 = H$, $R^2 = C_6H_5$
(**6**) $R^1 = R^2 = C_6H_5$
(**7**) $R^1 = R^2 = C_4H_4O$
(**8**) $R^1 = OH$, $R^2 = C_6H_5$
(**9**) $R^1 = R^2 = C_5H_4N$
(**10**) $R^1 = C_5H_4N$, $R^2 = C_5H_4NO$
(**11**) $R^1 = C_5H_4N$, $R^2 = C_5H_4N^+CH_3$

Scheme 1.

Compound (**11**) was prepared from (**9**) by quaternisation with methyl iodide in dimethylformamide (DMF). Oxidation of (**9**) with *m*-chloroperbenzoic acid in methylene dichloride at room temperature yields the *N*-oxide derivative (**10**). Full details of these operations can be found in ref. 8.

Cyclic voltammetry was carried out using the conditions outlined in ref. 4, except that in the present study the scan rate

Table. Reduction potentials for compounds (3)—(11)

Compound	$-E_{p/2}$/mV* (±10 mV)	$-E_7^1$/mV† (±10 mV)
(3)	620	
(4)	780	
(5)	610	
(6)	630	
(7)	530	374
(8)	1 100	
(9)	490	286
(10)	460	253
(11)	280	

* $E_{p/2}$ *versus* Ag–AgCl reference electrode (electrochemical determination). † Benzyl viologen used as standard (E_7^1 −354 mV).[1] Potential as determined using pulse radiolysis at pH 7 (NHE scale).

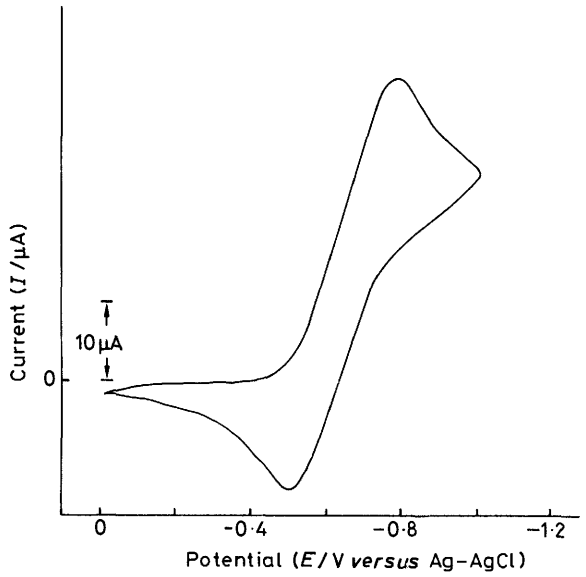


Figure 1. Cyclic voltammogram of (3) in methanol–water (3:1) at a scan rate of 50 mV s^{-1}

was 50 mV s^{-1} and compounds were dissolved in methanol–water (3:1 v/v) at a concentration varying between 5×10^{-4} and 5×10^{-5} mol dm^{-3}. Potassium nitrate (0.05 mol dm^{-3}) was used as the support electrolyte. For the pulse radiolysis measurements the experimental procedure was as described previously.[7,9] The solutions were buffered at pH 7.0 and contained 0.2 mol dm^{-3} propan-2-ol.

MNDO calculations on the electronic features of the parent molecules and the corresponding radicals generated by one-electron reduction were performed by using MNDO/AM1 geometry optimisation procedure.[10] These calculations were carried out on the VAX 11-780 computer at Sittingbourne. Molecules were displayed on the Evans and Sutherland Multi Picture System.

Results and Discussion

The Table reports the reduction potentials of the pyrazinothiadiazoles (3)—(11). With the exception of compounds (4) and (8), which are electrochemically irreversible, the derivatives are 'quasi' reversible on the timescale of the cyclic voltammogram, *i.e.* the separation of the anodic and cathodic peak potentials is greater than 58 mV. The irreversibility of the dimethyl (4) and the hydroxy(phenyl) (8) derivatives may be due

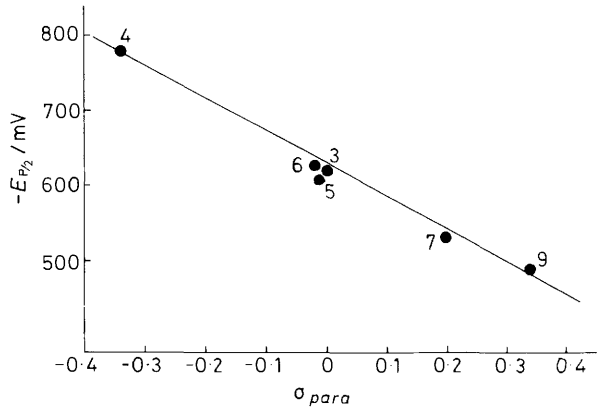
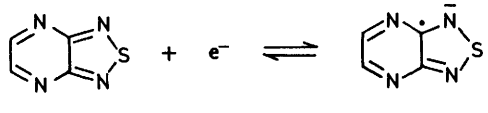


Figure 2. Plot of half-peak reduction potential ($E_{p/2}$) *versus* the Hammett substituent parameter σ_{para}

to the fact that these compounds are reduced at a more negative potential, where more reactive radical anions could be formed; the irreversibility of (8) may also be due to the acidity of this compound. The cyclic voltammogram of the unsubstituted pyrazinothiadiazole (3) is shown in Figure 1 and most probably represents the occurrence of the one-electron redox process, whereby (13) represents one of the possible canonical forms of the anion radical.



(3) (13)

The reversibility of an electrode process is affected appreciably by the degree of charge transfer control relative to diffusion control. As the present cyclic voltammetry experiments were only run at a sweep rate of 50 mV s^{-1}, it is not known which of these two components dominates the electrode process occurring with the pyrazinothiadiazole derivatives. It is also possible that ohmic error contributes to the displacement of the cathodic and anodic peaks.

Changing the nature of the substituents R^1 and R^2 has allowed variation of the half-peak reduction potentials, $E_{p/2}$, by over 800 mV. Electron-donating substituents such as CH_3 and OH render the resulting molecules more difficult to reduce than those molecules which have electron-attracting substituents. The extent to which the electronic nature of R^1 and R^2 affects the reduction of these compounds is seen in Figure 2, which shows a linear correlation of $E_{p/2}$ with the sum of the Hammett σ_{para} constants[11,12] for R^1 and R^2.

Compounds (10) and (11) were not included in the foregoing analysis as no δ_{para} values could be found in the literature for either pyridine *N*-oxide or *N*-methylpyridinium. Compound (8) has also been omitted as the pK_a of the hydroxy group in this molecule has not been determined. Moreover, it is difficult to interpret the reduction potential for this molecule as it is not known to what extent it is in equilibrium with its keto form under the conditions of the cyclic voltammetry.

The Table includes the one-electron redox potentials, E_7^1, determined by pulse radiolysis for compounds (7), (9), and (10) and are related to the NHE scale. These values are less negative than the corresponding ones measured by cyclic voltammetry in 3:1 methanol–water. $E_{p/2}$ and E_7^1 are also linearly correlated. This finding is similar to that with other redox molecules,[5] provided the cyclic voltametric wave is shown to be reversible, and is convenient as it allows approximate values of E_7^1 in an

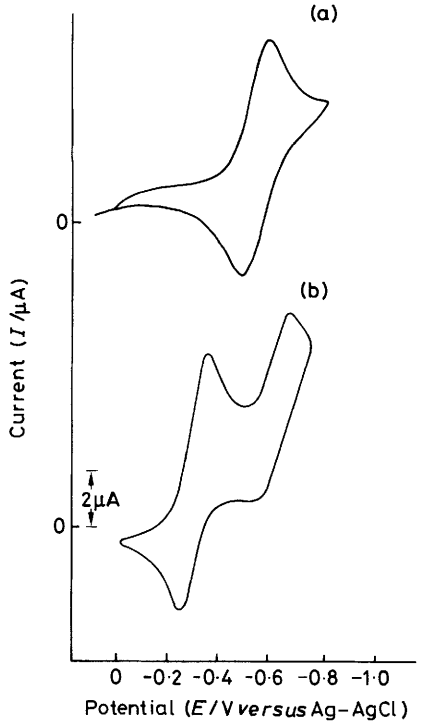
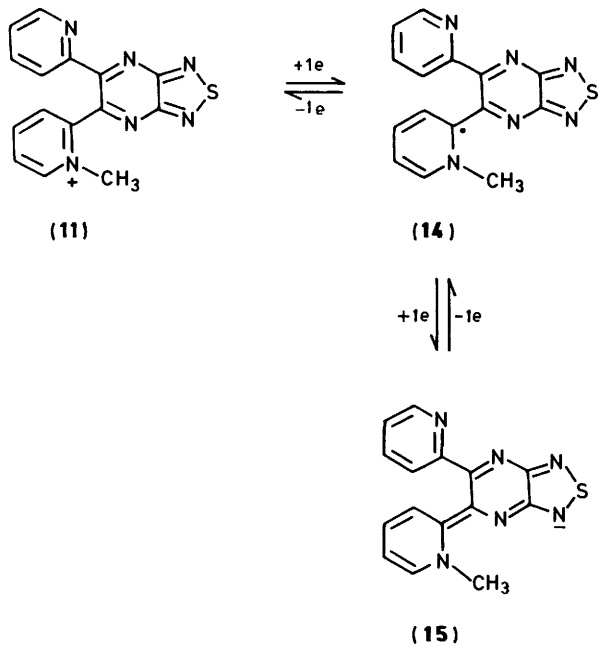


Figure 3. Cyclic voltammograms of (a) (**9**) and (b) (**11**) in methanol–water (3:1) at a scan rate of 50 mV s^{-1}

aqueous environment to be determined from cyclic voltammetry measurements in methanol–water.

The cyclic voltammogram of (**11**) (Figure 3) was found to be dissimilar to that of the other pyrazinothiadiazole derivatives considered in this study. It shows the occurrence of two consecutive one-electron redox processes. These processes can be represented by the equilibria in Scheme 2, where the intermediate radical shown is one of several canonical forms that may be written for this species.



Scheme 2.

If is of interest that the second redox process has a half-peak reduction potential which is of the same order of magnitude as that of the uncharged dipyridine derivative (**9**) (Figure 3). In fact when the pyridinium entity of (**11**) accepts an electron the electron-withdrawing power of the 'bipyridyl' substituents in (**14**) should not differ substantially from that in the uncharged molecule (**9**).

A requisite step in the toxic action of PSI electron-acceptor molecules is reaction of the resultant radical with oxygen producing, as an intermediate species, superoxide anion, $O_2^{\bullet -}$. This process regenerates the original acceptor molecule which can then undergo further oxidation–reduction cycling. The extent to which the pyrazinothiadiazoles (**3**)—(**11**) react with oxygen was determined using isolated chloroplast thylakoid fragments, illuminated in the chamber of a Clark-type oxygen electrode.[6] Compounds (**3**)—(**7**) and (**9**)—(**11**) are good electron acceptors at concentrations as low as 5×10^{-7} mol dm^{-3}. Using pulse radiolysis, the rate constants for the reaction of oxygen with the anion radicals derived from (**7**) and (**10**) have been measured to be 1.8×10^8 and 2.1×10^7 dm^3 mol^{-1} s^{-1}, respectively. These values are consistent both with the E_7^1 values measured for these two compounds (Table) and with the reduction potential for oxygen (E_7^1 −155 mV pH 7).[13] The lower reduction potential of (**8**) makes this compound a poor PSI electron acceptor; the concentration required by (**8**) to accept an electron from 'broken' thylakoids is lower than 1×10^{-4} mol dm^{-3}.

To examine further the likely effect that the substituents R^1 and R^2 may have on the reduction of the pyrazinothiadiazole ring system, MNDO was used to calculate the residual electron densities of the unsubstituted molecule (**3**) and of the dimethyl derivative (**4**). The distribution of charge for these two molecules is shown in Figures 4 and 5. Both the electron density values and the 'dot' surface algorithm[14] show that one of the effects of the methyl groups is to make the sulphur atom in (**4**) less positive than that in the parent molecule (**3**). Moreover, the degree of negative charge in (**4**) is greater than that in (**3**) as is shown schematically by the larger density of blue dots in the former molecule. These features are in agreement with the more negative reduction potential of (**4**) in comparison to that at which molecule (**3**) is reduced. Moreover, the MNDO-calculated LUMO energy values for (**3**) and (**4**) are 88 and 198 kcal mol^{-1}, respectively. These values reflect the trend in the reduction potentials of these two molecules.

From the electron density values in Figures 4 and 5 it appears that, on reduction, it is the sulphur atom on the pyrazinothiadiazole ring system that accepts an electron. Using CNDO the superdelocalisability indices[15] on the sulphur atoms of (**3**) and (**4**) have been calculated as 98 and 54. The higher the value of such an index, the higher is the susceptibility of a particular atom to nucleophilic attack or electrochemical reduction. Thus, the indices calculated for (**3**) and (**4**) are again in agreement with the ease with which the sulphur atom in these molcules accepts an electron.

The residual electron densities of the resultant anion radicals derived from molecles (**3**) and (**4**) are also shown in Figures 4 and 5. These values indicate that, after the sulphur atom accepts an electron, negative charge 'tunnels' to the rest of the pyrazinothiadiazole ring system. During this process the nitrogen atoms of the five-membered ring retain the highest negative charge density.

In conclusion, the combined use of techniques such as cyclic voltammetry, pulse radiolysis, and molecular modelling has allowed the design of pyrazinothiadiazoles with redox properties that can be varied, over an appreciable range, by altering the nature of substitution. Work is in progress to incorporate some of these molecules in artificial photosynthetic schemes for the transport of electrons across lipid membranes.

Acknowledgements

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