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CHEMICALLY INDUCED PARKINSON'S DISEASE II:+ INTERMEDIATES IN THE OXIDATION AND REDUCTION REACTIONS OF THE 1-METHYL-4-PHENYL-2,3-DIHYDROPYRIDINIUM ION AND ITS DEPROTONATED FORM

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The one-electron reduction product of 1-methyl-4-phenyl-2,3-dihydropyridinium ion has been generated by pulse radiolysis and its absorption spectrum recorded. This radical was found to decay by second-order kinetics ($2k=9.5\times10^8$ $M^{-1}s^{-1}$) to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and 1-methyl-4-phenyl-2,3-dihydropyridinium ion. Reactions of the above radical species and that formed by one-electron reduction of 1-methyl-4-phenylpyridinium ion, which can also be generated by one-electron oxidation of 1-methyl-4-phenyl-1,2-dihydropyridine, with a number of molecules of biochemical interest have been studied. The one-electron reduction product of oxidised nicotinamide adenine dinucleotide efficiently reduced 1-methyl-4-phenyl-2,3-dihydropyridinium ion ($k=2.2\times10^9$ $M^{-1}s^{-1}$). The relevance of these results in relation to redox cycling, a possible mechanism for 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine neurotoxicity, is discussed.

INTRODUCTION. It is established that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP(H_3)) causes Parkinson's disease in humans and some animals (1-5). It is accepted that the conversion of MPTP(H_3) to 1-methyl-4-phenylpyridinium ion (MPP^+) via 1-methyl-4-phenyl-2,3-dihydropyridinium ion ($MPDP(H_2)^+$) initiated by the enzyme monoamine oxidase, is of pivotal importance for the neurotoxic effect. A scheme for the metal-catalysed conversion of MPTP(H_3) to MPP^+ involves the conversion of MPTP(H_3) to $MPDP(H_2)^+$ via two separate one-electron (1-e) oxidation steps and subsequent further oxidation via MPP· to MPP^+ (6). We described (7) the use of pulsed radiation techniques to generate

+Part I of this series is Biochem. Biophys. Res. Comms., (1987), 144, 957-964.

Abbreviations: DA, dopamine; DASQ, dopamine semiquinone; DAQ, dopamine quinone; ϵ, extinction coefficient; GSH, reduced glutathione; GSSG, oxidised glutathione; lfp, laser flash photolysis; MPTP(H_3), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; $MPDP(H_2)^+$, 1-methyl-4-phenyl-2,3-dihydropyridinium ion; MPDP(H), 1-methyl-4-phenyl-1,2-dihydropyridine; MPP^+, 1-methyl-4-phenylpyridinium ion; NAD^+, oxidised nicotinamide adenine dinucleotide; PQ^{2+}, paraquat; pr, pulse radiolysis; 1-e, one-electron.

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and characterise the radical species involved in this oxidative sequence and to study, by kinetic spectrophotometry, the rates of reaction of these radicals with species of biological interest. Thus we reported the absorption spectrum of MPP• and also that of the product of $MPTP(H_3)$ 1-e oxidation. This latter species was attributed to either $MPTP(H_3)^{\bullet+}$ or its deprotonated form. Also, we reported a kinetic study of the reactivity of this latter species, and of MPP• with dopamine (DA) and of MPP• with oxygen (O_2). We now discuss a further characterisation of the oxidation/reduction intermediates in the $MPTP(H_3)/MPP^+$ scheme based on pulse radiolysis studies of the $MPDP(H_2)^+$ ion. We report, for the first time, what we now believe to be the authentic the absorption spectrum of $MPDP(H_2)^{\bullet}$ (termed X• by Poirier *et al* (6)) and also the direct measurement of the reactivity of this radical and the species MPP• (termed Y• by Poirier *et al* (6)) with several molecules of biological relevance.

METHODS. The perchlorate salt of $MPDP(H_2)^+$ was obtained from Research Biochemicals Inc. Reduced glutathione (GSH) and the sodium salt of linoleic acid were from Sigma Chem. Co., oxidised glutathione (GSSG), ascorbic acid, dopamine and cysteine were from Aldrich Chemical Co., and oxidised nicotinamide adenine dinucleotide (NAD^+), sodium azide and sodium formate were from BDH Chemicals Ltd. The pulse radiolysis (pr) apparatus has been described previously (8) and typically 20ns pulses of 10-12Mev electrons and quartz capillary cells of optical path 2.5cm were used. In water N_2O flushed solutions of sodium azide were used to achieve an oxidising environment and sodium formate to achieve reducing conditions as described in part I (7) and in more detail in reference (9). The extinction coefficients (ϵ) were calculated via KCNS dosimetry using the appropriate primary yield of OH• and ϵ $(CNS)_2^{\bullet-}$ (10). The laser flash photolysis (lfp) system uses a neodymium YAG laser which gives 12ns pulses of the frequency quadrupled 266nm light and a ruby laser which gives 20ns pulses of frequency doubled 347nm light. This equipment has also been described previously (11). For some experiments it was necessary to exclude rigorously the presence of trace amounts of O_2 and this was achieved with an O_2 filter purchased from Chrompack.

RESULTS. In the present work we have considered both the oxidative and reductive reactions of $MPDP(H_2)^+$ (figure 1).

(i) Reduction of $MPDP(H_2)^+$. $MPDP(H_2)^+$ was reduced by both e^-_{aq} and the $CO_2^{\bullet-}$ radical with rate constants of 2.4×10^{10} and 5.8×10^9 $M^{-1}s^{-1}$ respectively, to give the species with the absorption profile given in Figure 2. This species formed by (1) and (2) below, was assigned to that termed X• by Poirier *et al* (6)

$MPDP(H_2)^+ + e^-_{aq} \rightarrow MPDP(H_2)^{\bullet}$ ..(1) $MPDP(H_2)^+ + CO_2^{\bullet-} \rightarrow MPDP(H_2)^{\bullet} + CO_2$ ..(2)

As can be seen from figure 2 the λmax of the difference spectrum is at 390nm ($\Delta\epsilon$=12300$M^{-1}cm^{-1}$) with a much weaker band at ≃ 520nm $\epsilon=\Delta\epsilon$=800 $M^{-1}cm^{-1}$. After correction for $MPDP(H_2)^+$ absorption, the λmax for $MPDP(H_2)^{\bullet}$ is at 370nm with an extinction coefficient of 17300 $M^{-1}cm^{-1}$. This species was found to decay with second-order kinetics ($2k=9.5\times10^8$ $M^{-1}s^{-1}$) probably to $MPDP(H_2)^+$ and $MPTP(H_3)$, via the disproportionation:

$$2\ MPDP(H_2)^{\bullet} \xrightarrow{H^+} MPDP(H_2)^+ + MPTP(H_3) \quad ..(3)$$

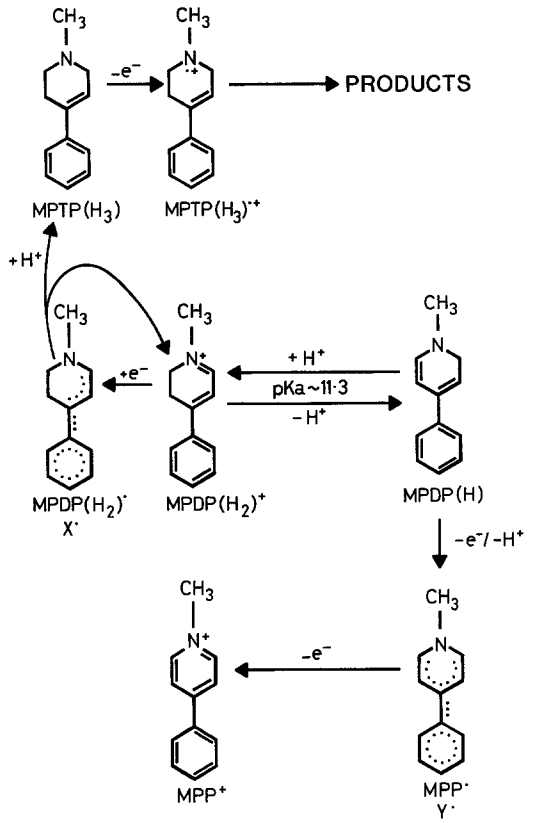


Figure 1. Reaction scheme summarising laser flash photolysis and pulse radiolysis results.

Evidence in favour of this reaction was obtained by careful measurement of the stoichiometry of the decay of $MPDP(H_2)^{\cdot}$ (or X·). $MPDP(H_2)^{+}$ was first reduced to X· and the amount of $MPDP(H_2)^{+}$ then reformed by the subsequent decay of X· was estimated at 350nm. This was achieved by measuring the bleaching at 350nm (ϵ=17000 M^{-1} cm^{-1} (12)) on a long time scale such that all of X· had decayed. On a shorter time scale we estimated the amount of X· formed (at 390nm using the extinction coefficient as given above). The ratio of $MPDP(H_2)^{+}$ lost, as measured by the bleaching, to X· formed was found to be 1/1.9, consistent with a disproportionation. As $MPDP(H_2)^{+}$ was found to be photosensitive in these experiments an interference filter was used to minimise unwanted reactions.

(ii) Oxidation Reactions. $MPDP(H_2)^{+}$ exists in equilibrium with its deprotonated form 1-methyl-4-phenyl-1,2-dihydropyridine (MPDP(H)). We have attempted to determine the pKa for this equilibrium. However, both forms are rather unstable to O_2 and light so that our value can only be regarded as approximate. Using spectrophotometric titrations we obtained a pKa value of about 11 for this process:

$$MPDP(H_2)^{+} \underset{}{\overset{pKa\approx11}{\rightleftharpoons}} MPDP(H) + H^{+} \quad .....(4)$$

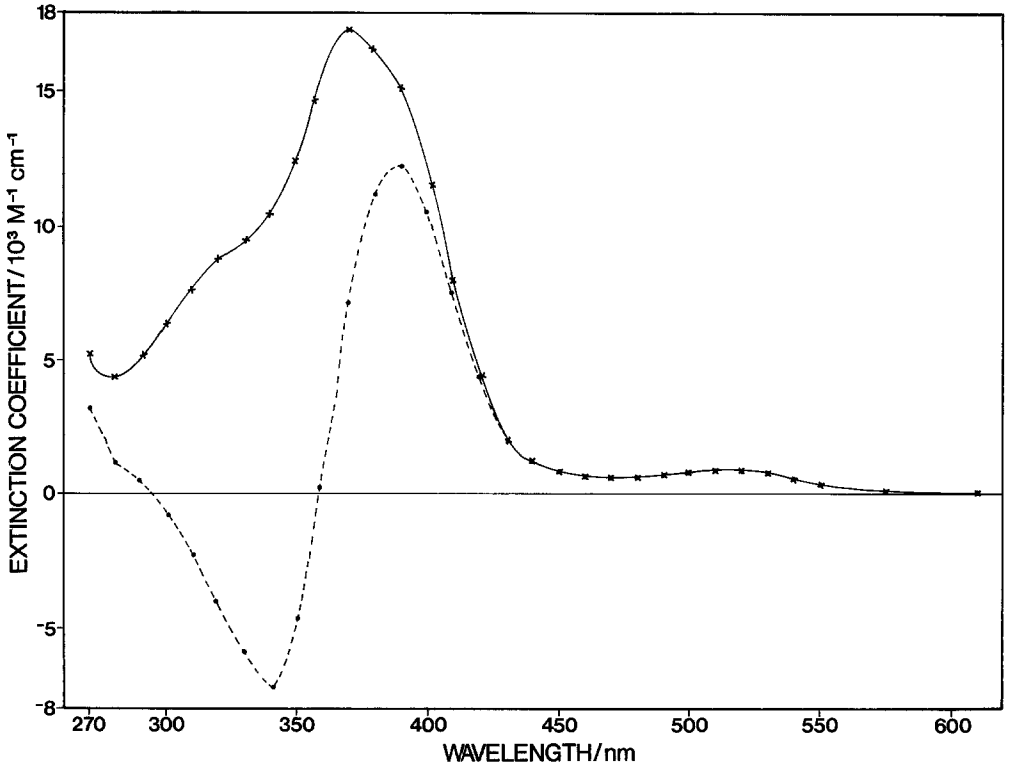


Figure 2. ---- Difference spectrum ($\in MPDP(H_2)^{\cdot} - \in MPDP(H_2)^{+}$), —— corrected absorption spectrum of $MPDP(H_2)^{\cdot}$ measured 44 μs after pulse radiolysis of an argon-saturated solution of 2.2×10^{-5} M $MPDP(H_2)^{+}$ containing 10^{-1} M sodium formate and 10^{-1} M phosphate buffer (pH 7.0).

Studies of the acid form by both pulse radiolysis using $N_3^{\cdot}$ or $Br_2^{\cdot -}$ radicals as oxidants and lfp with 347 nm excitation showed that this species could not be easily oxidised. However, the deprotonated form MPDP(H) is readily oxidised both by pr and lfp although we have only studied in detail oxidation by pr. $N_3^{\cdot}$ and $Br_2^{\cdot -}$ radicals were found to oxidise MPDP(H) ($k=1.2 \times 10^9$ and 7.6×10^8 M^{-1} s^{-1} respectively) to a species which showed absorption bands at 360 and 540nm consistent with those we have previously reported for MPP$^{\cdot}$ (7), but also to a species absorbing at 290nm. With increasing time after the pulse the MPP$^{\cdot}$ bands at 360 and 540nm decrease in intensity and that at 290nm increases as shown in figure 3. The band at 290nm is assigned to MPP^{+} formed from MPP$^{\cdot}$. However, we previously found MPP$^{\cdot}$ to be stable over seconds when formed by 1-e reduction of MPP^{+} (7), thus an apparent kinetic inconsistency arises in that MPP$^{\cdot}$ produced from oxidation of MPDP(H) decays over a few milliseconds whereas that produced from reduction of MPP^{+} is quite stable on this time scale. The possibility that this apparent difference in behaviour was due to different amounts of O_2 impurities in the nitrous oxide and argon gases used for the

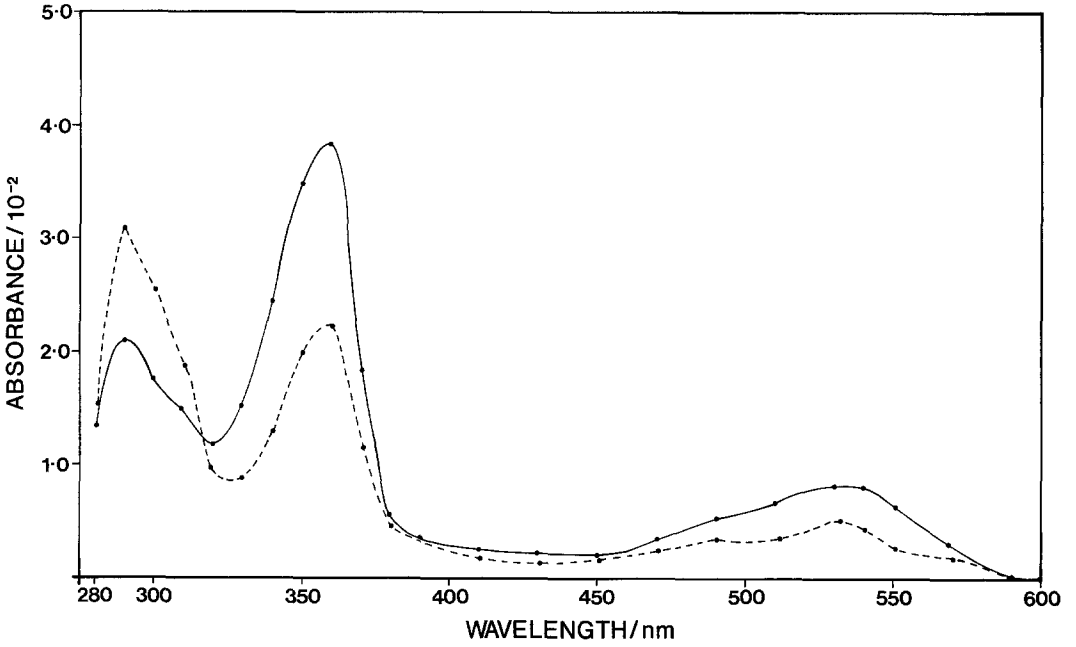


Figure 3. Absorption spectrum of the species obtained by one-electron oxidation of MPDP(H). The band at 290nm is assigned to MPP^+ and those at 360 and 540nm to MPP•. Spectrum measured: ——, 120 μs; ----, 1.01 ms after pulse radiolysis of a nitrous oxide saturated solution of $3.3x10^{-5}$ M $MPDP(H_2)^+$ containing $5x10^{-2}$ M sodium azide and 10^{-1} M sodium hydroxide (pH 13).

oxidising and reducing conditions, respectively, was ruled out by the use of an O_2 filter. The apparent variation in kinetic decay of MPP• was found to be due to a reaction between $MPDP(H_2)^+$ and MPP• producing MPP^+ and $MPDP(H_2)$• ie.

$$MPDP(H_2)^+ + MPP• \rightarrow MPDP(H_2)• + MPP^+ \ldots.(5).$$

We estimated the second-order rate constant for (5) at pH 7.0 by adding known amounts of $MPDP(H_2)^+$ to MPP• formed from MPP^+ and obtained a k of $2.1x10^9$ $M^{-1}s^{-1}$. We have also measured this rate constant when MPP• is obtained by oxidation of MPDP(H) at pH 11.0. At this pH we were able to estimate the residual $MPDP(H_2)^+$ and hence evaluate k for the above reaction, $k=1.9x10^9$ $M^{-1}s^{-1}$, in good agreement with the above value. The reactivity towards O_2 of the species formed on 1-e oxidation of MPDP(H) ($k=5.8x10^9$ $M^{-1}s^{-1}$, at pH 13) was consistent with that we have found previously for MPP• (7). At pH 7 $MPDP(H_2)^+$ was found to react with hydroxyl radicals and several products such as adducts as well as MPP• may be formed ($k=9.2x10^9$ $M^{-1}s^{-1}$).

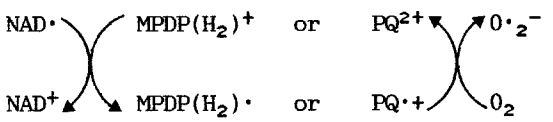
(iii) Reactivity of the Radicals $MPDP(H_2)$• and MPP•. We have studied the interaction of $MPDP(H_2)$• and MPP• with a number of antioxidants of biochemical relevance (reactions 6-11), and the sodium salt of linoleic acid (reactions 12 and 13), and the reactivity of $MPDP(H_2)$•, with DA (reaction 14) and with O_2 (MPP• reaction with O_2 has been reported in part I.)

$MPP^{\cdot}$ + GSSG → products.....(6) $MPP^{\cdot}$ + GSH → products.....(7)
$MPDP(H_2)^{\cdot}$ + GSH → products.....(8) $MPP^{\cdot}$ + cysteine → products.....(9)
$MPDP(H_2)^{\cdot}$ + cysteine → products...(10) $MPP^{\cdot}$ + Ascorbic acid → products.....(11)
$MPP^{\cdot}$ + Na linoleate → products....(12) $MPDP(H_2)^{\cdot}$ + Na linoleate → products.(13)
$MPDP(H_2)^{\cdot}$ + DA → products.....(14) $MPDP(H_2)^{\cdot} + O_2 \rightarrow MPDP(H_2)^{+} + O_2^{\cdot -}$...(15)

Our results show that none of the reactions (6-14) occur in an efficient manner, thus we could only measure upper limits for the reaction rate constants; these are given in the Discussion section. The second-order rate constant for reaction (15) was obtained as 1.8×10^9 $M^{-1}s^{-1}$. We have also studied the reaction of the 1-e reduction product of NAD^+, ie the radical $NAD^{\cdot}$, with $MPDP(H_2)^+$ that is: $NAD^{\cdot} + MPDP(H_2)^{+} \rightarrow NAD^{+} + MPDP(H_2)^{\cdot}$ .....(16)
For this interaction we have obtained a second-order rate constant of 2.2×10^9 $M^{-1}s^{-1}$. The relevance of this result in relation to redox cycling as a possible mechanism of $MPTP(H_3)$ toxicity is discussed below. Some literature reports have also suggested the interaction of MPP^+ with dopamine semiquinone (reaction (17)) to be involved in the neurotoxicity of $MPTP(H_3)$ (13). We also tested the equivalent reaction when $MPDP(H_2)^+$ is used instead of MPP^+ (reaction (18)).
$MPP^{+} + DASQ^{\cdot} \rightarrow MPP^{\cdot} + DAQ$ ..(17) $MPDP(H_2)^{+} + DASQ^{\cdot} \rightarrow MPDP(H_2)^{\cdot} + DAQ$ ..(18)
At neutral pH no interaction of either MPP^+ or $MPDP(H_2)^+$ with dopamine semiquinone could be detected (for both reactions, $k \leq 1 \times 10^6$ $M^{-1}s^{-1}$).

DISCUSSION. We will discuss our pr studies and the intermediates in the overall $MPTP(H_3)/MPP^+$ interconversion in terms of the scheme given in Figure 1 as our current "working model" for this reaction sequence. In part I (7) we reported the 1-e oxidation of $MPTP(H_3)$ and assigned the product as either the radical cation $MPTP(H_3)^{\cdot +}$ or the deprotonated species $MPDP(H_2)^{\cdot}$. We have now unambiguously generated $MPDP(H_2)^{\cdot}$ by 1-e reduction of $MPDP(H_2)^+$. The spectrum of $MPDP(H_2)^{\cdot}$ is given in Figure 2, and is quite different from that we reported earlier for the oxidation product of $MPTP(H_3)$. Clearly, this oxidation does not lead to $X^{\cdot}$ but perhaps to the radical cation and the second-order decay of this radical cation also does not lead to $MPDP(H_2)^+$ and must therefore lead to some other species (maybe a dimer) which may not be of biochemical relevance. The formation of $X^{\cdot}$ from $MPDP(H_2)^+$ leads to a subsequent disproportionation of $X^{\cdot}$ which produces $MPTP(H_3)$ and $MPDP(H_2)^+$ as shown in figure 1. Thus if enzymic conversion of $MPTP(H_3)$ to $MPDP(H_2)^{\cdot}$ occurs, a subsequent (non-enzymic) disproportionation to give $MPDP(H_2)^+$ is likely to follow. The conversion of $MPDP(H_2)^+$ to MPP^+ also requires further oxidation. However, it was not possible to readily oxidise the species $MPDP(H_2)^+$ but it was possible to oxidise its conjugate base MPDP(H). As noted previously the product of this oxidation was identical to that found from the reduction of MPP^+ (Figure 3).

This species (MPP•) formed from either route, was found to react with $MPDP(H_2)^+$ to give MPP^+ and $MPDP(H_2)$• . Thus while the conversion of MPP• to MPP^+ could simply involve reaction with O_2, the "recycling" second-order process (5) cannot be ruled out. Furthermore $MPDP(H_2)$• itself (but not MPP•) could be involved in further "recycling processes" with O_2 as discussed below. Several reports have suggested a relation between, Parkinson's disease and decreased levels of natural antioxidants (14-17), and lipid peroxidation has been considered as one of the possible mechanisms of $MPTP(H_3)$ neurotoxicity (18-19). Thus using pr we have undertaken the direct study of the interactions 6-13. Under our experimental conditions, we could not monitor any reaction of MPP• with either oxidised or reduced glutathione (reaction 6 and 7, $k \leq 1x10^4$ $M^{-1}s^{-1}$ and $k \leq 5x10^3$ $M^{-1}s^{-1}$ respectively). Similarly no reaction of $MPDP(H_2)$• with reduced glutathione could be detected (reaction 8, $k \leq 1x10^6$ $M^{-1}s^{-1}$). No interaction of either MPP• or $MPDP(H_2)$• with cysteine could be monitored (reactions 9 and 10, $k \leq 8x10^3$ M^{-1} s^{-1} and $k \leq 8x10^5$ $M^{-1}s^{-1}$ respectively). These results suggest that if such interactions occur in either chemically-induced or idiopathic Parkinson's disease, their rates are too slow to explain the reported depletion of reduced glutathione levels. The observed decrease in glutathione levels in the *substantia nigra* region may be due to excessive consumption of glutathione in other detoxification processes as suggested by Yong *et al* (17). Ascorbic acid has been reported to attenuate the neurotoxic effects of $MPTP(H_3)$ (20-22). Our results (reaction 11, $k \leq 10^4$ $M^{-1}s^{-1}$) show that the direct interaction of MPP• with ascorbic acid is unlikely to be involved in such a protective process. The results obtained for reactions (12) and (13) are consistent with the recent findings of Corongui *et al* (23), and Ekstrom *et al* (24), that is lipid peroxidation does not play a major role in the cytotoxicity of these neurotoxins. Redox cycling has been discussed as a possible mechanism of action of $MPTP(H_3)$ (25-29). In this hypothesis an intermediate of $MPTP(H_3)/MPP^+$ oxidation would be seen to act in a similar way as has been proposed to explain the cytotoxicity of paraquat (PQ^{2+}) in animals (30, 31). Thus such intermediates must be reduced at physiological pH to a sufficiently stable radical which can then react with O_2 to generate superoxide radical. Cytotoxicity then results from the production of $O_2^{\bullet -}$, •OH and H_2O_2 species coupled with the depletion of NADH/NADPH levels, the coenzymes acting as bioreductants. The following schemes can be envisaged:



We now have shown that NAD• does react very efficiently with $MPDP(H_2)^+$ to yield $MPDP(H_2)$• which in turn can react efficiently with oxygen. While this does not prove the biochemical importance of the above cycling reactions, is at least

consistent with such processes, and shows a parallel to the possible harmful effects of paraquat. For the reaction between NAD$^{\cdot}$ and PQ^{2+} we obtained a second-order rate constant of 1.6×10^9 $M^{-1}s^{-1}$ which is very similar to that we have found for the NAD$^{\cdot}$/MPDP$(H_2)^+$ reaction. However, in assessing the significance of the possible role that MPDP$(H_2)^+$ may play in redox cycling, O_2 sensitivity and the lifetime of the compound in the tissue must be taken in consideration.

Regarding reactions (14), (17) and (18); the lack of reactivity observed does not support the involvement of such interactions in the neurotoxicity of MPTP(H_3) as proposed by Kopin (13). This is not surprising in view of the relative redox potentials involved.

In conclusion, we have demonstrated that (i) The MPDP$(H_2)^{\cdot}$ radical can be generated by pr, disproportionates to MPTP(H_3) and MPDP$(H_2)^+$, and shows little reactivity with biosubstrates such as reduced glutathione, cysteien, linolic acid and dopamine, even though some such interactions have been suggested in the literature in relation to MPTP(H_3) toxicity. (ii) If the radical NAD$^{\cdot}$ were to be generated *in vivo*, our *in vitro* results suggest that such species would react very efficiently with MPDP$(H_2)^+$ to generate MPDP$(H_2)^{\cdot}$, which we have now shown reacts with O_2 presumably to produce $O_2^{\cdot-}$. Thus redox cycling involving MPDP$(H_2)^{\cdot}$ could play a role in MPTP(H_3) cytotoxicity. (iii) The 1-e oxidation of MPDP(H) yields the radical MPP$^{\cdot}$ which we have previously characterised (7). (iv) In view of the marked O_2 and in some cases light sensitivity of the species MPDP$(H_2)^+$, MPDP$(H_2)^{\cdot}$ and MPDP(H), extreme care should be taken, particularly in steady state studies, to avoid excessive exposure to light and air.

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