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Electron Transfer Initiated Reactions Photoinduced by Pterins

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Abstract

Interest in the photochemistry and photophysics of pterins has increased since the participation of this family of compounds in different photobiological processes has been suggested or demonstrated in recent decades. Pterins participate in relevant biological processes, such as metabolic redox reactions, and can photoinduce the oxidation of biomolecules through both electron transfer mechanisms (Type I) and singlet oxygen production (Type II). This article describes recent findings on electron transfer-initiated reactions photoinduced by the triplet excited state of pterins and connects them in the context of photosensitized processes of biological relevance.

Key words: pterins, electron transfer, photosensitization, superoxide anion

Introduction

Pterins are present in biological systems in multiple forms and play different roles ranging from pigments to enzymatic cofactors for numerous redox and one-carbon transfer reactions (1,2). The most common pterin derivatives are 6-substituted compounds (Figure 1). According to the molecular weight and the functional groups of these substituents, pterins can be divided into two groups: (1) *unconjugated pterins*, containing substituents with one carbon atom or a short hydrocarbon chain, and (2) *conjugated pterins*, with larger substituents containing a *p*-aminobenzoic acid (PABA) moiety. Pterins can exist in living systems in different redox states and may be classified into three classes according to this property: fully oxidized (or aromatic) pterins, and dihydro and tetrahydro derivatives. Finally they behave as weak acids in aqueous solution. The dominant equilibrium at pH > 5 involves the lactam group (pyrimidine ring) (Figure 1). The pK_a of this equilibrium is *ca*. 8 for the aromatic pterins and *ca.* 10 for dihydropterin derivatives.

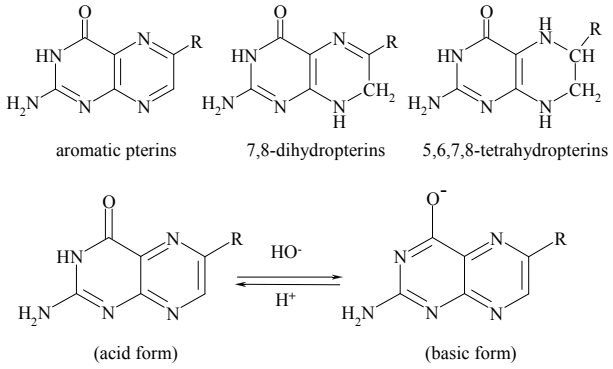

Figure 1. Molecular structures of pterin derivatives and the acid-base equilibrium in aqueous solution.

Pterins have a profuse and amazing photochemistry: under UV-A excitation (320-400 nm), these biomolecules can fluoresce, undergo photooxidation to produce different products and generate reactive oxygen species (ROS) such as singlet oxygen ($^1O_2$) (3,4). The interest in the photochemical properties of pterin derivatives has been increasing steadily during the past decades, as more evidence of their implication in pho-

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tobiological processes became available. For instance, the participation of pteridines in photoreception in *Phycomyses* (5), *Neurospora* (6), *Euglena* (7) and superior plants (8) has been suggested. 5,10-Methenyltetrahydrofolate is a light-harvesting chromophore of DNA photolyases (9), enzymes involved in DNA repair processes that take place after UV irradiation.

In addition, dihydrobiopterin (H_2Bip), biopterin (Bip) and other pterin derivatives accumulate in the skin of patients affected by vitiligo, a chronic depigmentation disorder (10). These patients express a characteristic fluorescence in their white skin patches upon Wood's light examination. This emission results from the accumulation of oxidized unconjugated pterins (11), compounds with high fluorescence quantum yields (12). In the tissues affected by this disease, the cells undergo oxidative stress, deactivation of enzymes of the melanin biosynthesis takes place and the protection of the skin against UV radiation fails because of the lack of melanin. Therefore, the photochemistry of pterins is of particular interest to this disease. Moreover, 6-carboxypterin (Cap), a product of the photolysis of Bip (*vide infra*) that is not synthesized in the skin cells, has been isolated from the affected skin, thus proving that photooxidation of pterins occurs *in vivo* under pathological conditions (13).

The photochemical reactivity of pterins became relevant when it was demonstrated that these compounds generate reactive oxygen species, in particular singlet oxygen ($^1O_2$), upon UV-A irradiation. After Kritsky *et al.* reported in 1996 the quantum yields of $^1O_2$ production (Φ_Δ) by 6,7-dimethylpterin and 6-tetrahydroxybutylpterin (14), several works were published on the capability of pterins to generate photochemically this reactive oxygen species (15,16,17). It was shown that, in general, aromatic unconjugated pterins produce significant amounts of $^1O_2$, both in their acid and basic forms. Although values of Φ_Δ for the basic forms are higher than those for the corresponding acid forms, Φ_Δ of these compounds are mainly affected by the 6-substituent on the pterin moiety. Therefore, aromatic unconjugated pterins could contribute to photodynamic processes *in vivo*. Interestingly, biologically active pterin derivatives (aromatic conjugated pterins and reduced pterins) do not produce $^1O_2$. The very low Φ_Δ values ($\leq$0.02) for the conjugated derivatives, such as folic acid (the most important aromatic pterin in mammalians), was explained by the efficient radiationless deactivation of the singlet excited state of the pterin moiety by the large 6-substituent (PABA), acting as an internal fluorescence quencher (18).

Besides $^1O_2$ production by energy transfer of the triplet excited states of pterins to O_2, electron transfer processes have been shown to play a dominant role in the formation of other ROS, such as superoxide anion ($O_2^{\cdot -}$) and H_2O_2, in the photosensitization of DNA and nucleotides, in the photodegradation of folic acid and in the photoreduction of pterins themselves. Main results relevant for the biological implications of pterin derivatives are summarized and discussed in this review.

Production of Superoxide Anion and Hydrogen Peroxide

UV-A irradiation of aqueous solutions containing aromatic pterins results in the production, not only of $^1O_2$, but also of $O_2^{\cdot -}$ and H_2O_2. Since these latter species participate in the physiopathology of many diseases (19), the photochemical production of these species by pterins is biologically relevant. Aromatic pterins are able to generate $O_2^{\cdot -}$ and H_2O_2 through two different photochemical mechanisms:

a) In neutral or slightly acidic aqueous solutions, *photoinduced electron transfer* from the pterin moiety itself (Pt), to the triplet excited state of Pt (^{3}Pt*) may initiate a series of reactions leading to the formation of $O_2^{\cdot -}$ and H_2O_2 (20). The main results supporting this mechanism are: EPR analysis in the presence of the spin trap DMPO shows the characteristic signal of the adduct between DMPO and $O_2^{\cdot -}$; the formation of H_2O_2 has been proven by a colorimetric method and its amount increased in the presence of superoxide dismutase (SOD) which catalyzes the $O_2^{\cdot -}$ disproportionation; it also increased with the pterin concentration and decreased when the O_2 concentration increased.

b) *Oxidation of 5,8-dihydroderivatives* has been shown to be also a source of H_2O_2. Hence, it was demonstrated that Bip, neopterin (Nep) or 6-hydroxymethylpterin (Hmp) exposed to UV-A radiation form 6-formyl-5,8-dihydropterin, generated in an O_2-independent process (Figure 2) (21,22,23). This red intermediate is rapidly oxidized on admission of O_2 to yield 6-formylpterin (Fop) and $O_2^{\cdot -}$, the latter being disproportionated to form H_2O_2. Finally, Fop is photolyzed to Cap, producing more H_2O_2 in the process. The mechanism proposed in Figure 2 is in agreement with the suggestion that Bip may be a source for H_2O_2 generation in vitiligo (13).

Photosensitization of DNA and nucleotides

Solar radiation induces modifications to genomic DNA and is implicated in the generation of human skin cancers (24,25). UV radiation is the most mutagenic and carcinogenic component of the solar radiation. UV-B radiation (280-320 nm) damages DNA through

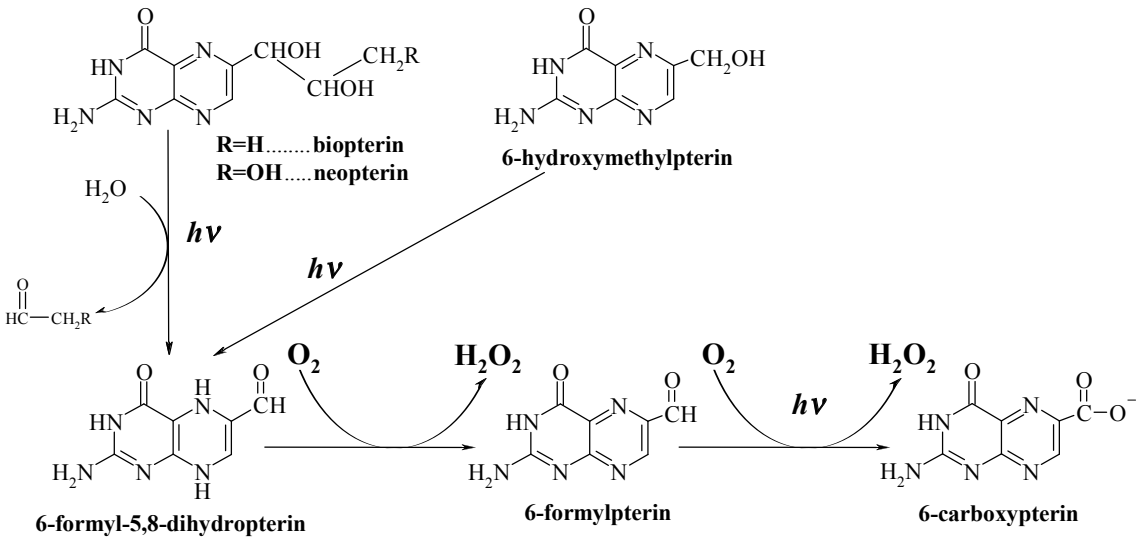

Figure 2. Formation of H_2O_2 in the photooxidation of biopterin, neopterin, 6-hydroxymethylpterin and 6-formylpterin in aqueous solution.

the direct excitation of the nucleobases (26). Although nucleobases absorb very weakly above 300 nm, both UV-B and UV-A radiations can induce modifications in DNA through photosensitized reactions (27). This indirect action may be mediated by endogeneous or exogenous sensitizers. The chemical changes in DNA and its components resulting from photosensitized reactions can take place through different mechanisms. Energy transfer from the triplet state of the photosensitizer to pyrimidine bases leads to the formation of pyrimidine dimers (28,29). Photosensitized oxidations also contribute to DNA damage induced by UV-A radiation. These processes involve the generation of radicals (type I mechanism), *e.g. via* electron transfer or hydrogen abstraction, and/or the production of ***singlet molecular oxygen*** ($^1O_2$) (type II mechanism) (27,30).

In agreement with the capability of aromatic unconjugated pterins to produce $^1O_2$, it was demonstrated that, upon excitation with UV-A radiation, pterins are able to photoinduce DNA damage (31,32,33). However, taking into account indirect evidence, it was suggested that these compounds may be able to act as photosensitizers of DNA not only through the production of $^1O_2$, but also *via* electron-transfer-initiated processes.

This hypothesis was confirmed in studies performed using 2'-deoxyadenosine 5'-monophosphate (dAMP), an interesting substrate for studying photosensitized reactions via type I mechanism because adenine is not oxidized by $^1O_2$ (34) (actually the rate constant of the chemical reaction is extremely low (35)). Therefore if a given photosensitizer produces $^1O_2$, its presence in the media does not interfere with the analysis of the electron-transfer process. In addition, dAMP is highly soluble in H_2O and is easily quantified by chromatographic methods.

The mechanism involved in the oxidation of dAMP photosensitized by pterin (Ptr) in aqueous solutions is summarized in Figure 3 (35). After UV-A excitation of Ptr and formation of its triplet excited state (^{3}Ptr*), three reaction pathways compete for the deactivation of the latter: intersystem crossing to singlet ground state, energy transfer to O_2 leading to the regeneration of Ptr and the production of $^1O_2$, and electron transfer between dAMP and ^{3}Ptr* yielding the corresponding pair of radical ions ($Ptr^{\cdot-}$ and $dAMP^{\cdot+}$). In the following step, the electron transfer from $Ptr^{\cdot-}$ to O_2 regenerates Ptr and forms $O_2^{\cdot-}$, which undergoes disproportionation into H_2O_2 and O_2. Finally a group of processes that might include the reactions of $dAMP^{\cdot+}$ (and/or deprotonated $dAMP^{\cdot+}$) with O_2 and H_2O, leads to the formation of products.

Two products of the photosensitized oxidation of dAMP were characterized by mass spectrometry. One of them is 8-oxo-7,8-dihydro-2'-deoxyadenosine 5'-monophosphate (8-oxo-dAMP, Figure 3). This finding is in agreement with the proposed mechanism initiated by an electron transfer from dAMP to excited Ptr because 8-oxo-7,8-dihydro 2'-deoxyadenosine (8-oxo-dAdo) has been proposed as a product of the photosensitized oxidation of 2'-deoxyadenosine (dAdo) in DNA *via* a type I mechanism (36). Moreover, the efficient conversion of the radical cation of dAdo into 8-oxo-dAdo has been reported (37). The other product would be a tetracyclic compound (8-P-dAMP, Figure 3) with a –OP(=O)(OH)O– bridge formed between the deoxyribose phosphate substituent and the C-8 of the adenine moiety.

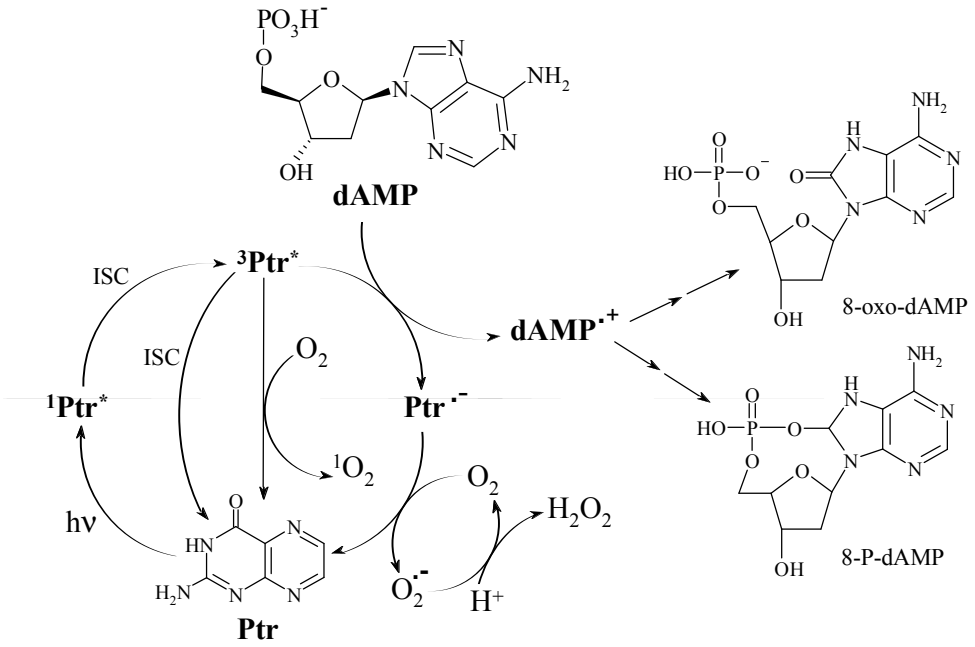

Figure 3. Mechanism of the oxidation of dAMP photosensitized by pterin (Ptr)

In contrast to dAMP, the oxidation of 2'-deoxyguanosine 5'-monophosphate (dGMP) photosensitized by Ptr occurs through two competing mechanisms: (1) electron transfer between dGMP and ^{3}Ptr* (type I) and (2) reaction of dGMP with $^1O_2$ produced by Ptr (type II) (38). The first mechanism is similar to that describe for dAMP (Figure 3), but in this case the photoproducts have not been characterized yet. The oxidation via $^1O_2$, summarized in Figure 4, takes place because Ptr is a relatively good $^1O_2$ sensitizer (*vide supra*) and this reactive oxygen species oxidizes guanine (Gua) very fast. Actually Gua is the only DNA constituent that significantly reacts with $^1O_2$ (39).

In this case, Type I and type II mechanisms are competitive and contribute in different proportions depending on the pH. In alkaline media, where Φ_Δ of Ptr and the rate constant of the chemical reaction between dGMP and $^1O_2$ (k_r) are higher than those in acidic media (38), the main mechanism involves $^1O_2$ as the reactive intermediate. On the other hand, under acidic

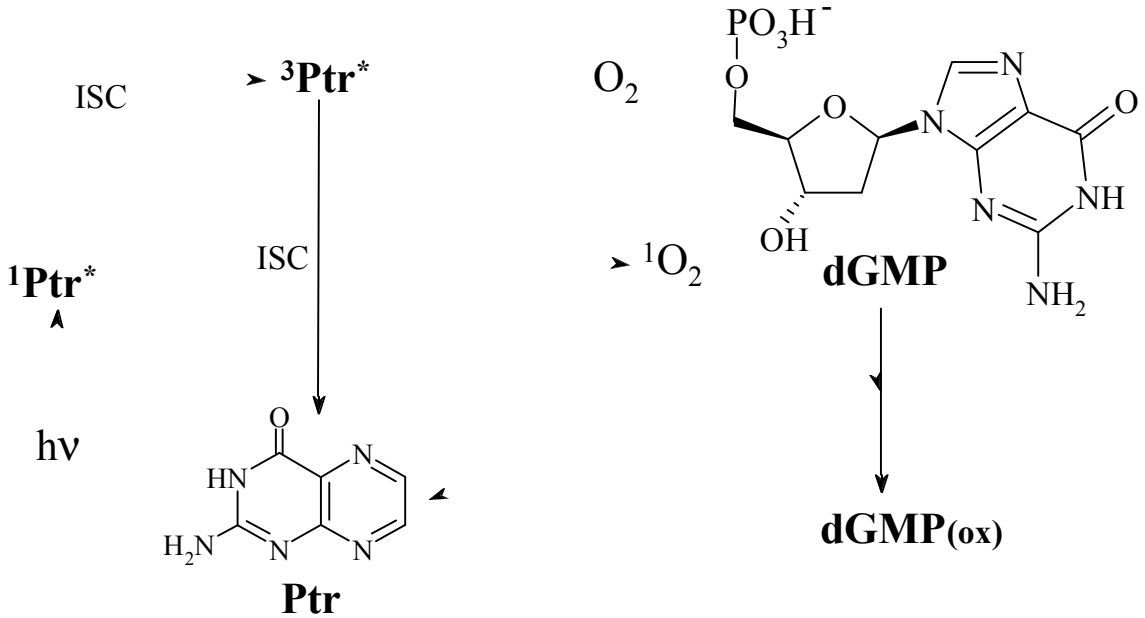

Figure 4. Oxidation of dGMP photosensitized by pterin (Ptr) through a type II mechanism.

or neutral conditions, where the reaction with $^1O_2$ is much slower and the initial electron transfer is likely to be more efficient, the type I mechanism is the main pathway. Since this is the situation at physiological pH, it can be inferred that electron transfer should be the main mechanism responsible for oxidation of nucleotides photosensitized by Ptr in biological systems.

Autocatalytic photooxidation of folic acid

Folic acid, or pteroyl-L-glutamic acid (PteGlu), is a conjugated pterin widespread in biological systems. Coenzymes derived from PteGlu facilitate the transfer of one-carbon units from donor molecules in metabolic pathways leading to the biosynthesis of nucleotides and amino acids (40). PteGlu deficiency has been related to many diseases. The photosensitivity of PteGlu has been known since the late 1940s (41). In 1978, Branda and Eaton proposed that one of the main functions of skin pigmentation is to avoid photolysis of folate (42). Recent reports indicate that both *in vitro* and *in vivo* exposure of human blood to UV-A radiation leads to photodegradation of folate (43,44).

In the absence of oxygen, PteGlu is photostable. However, upon UV-A excitation in air-equilibrated aqueous solutions, PteGlu undergoes photooxidation to yield 6-formylpterin (Fop) and *p*-aminobenzoyl-L-glutamic acid (PABA-Glu). The rate of this process increases with irradiation time due to an "photo-autocatalytic" effect that involves a photosensitized reaction wherein one of the products (Fop) formed in the process photoinduces the oxidation of PteGlu. This process, in which no excitation of PteGlu is needed, also takes place with other pterins as photosensitizers (Pt = Sens), thus revealing a general mechanism.

Recently an electron transfer-initiated mechanism was proposed for the autocatalytic photooxidation of PteGlu (45) (Figure 5). In this case the electron transfer process takes place from the PABA unit of PteGlu to ^{3}Pt* (^{3}Sens*) to form the corresponding radical ions, $Pt^{\cdot -}$ ($Sens^{\cdot -}$) and $PteGlu^{\cdot +}$. The autocatalytic photochemical process described in Figure 5 could contribute significantly to the photodegradation of PteGlu in a plethora of relevant biological systems. Moreover, many endogenous or exogenous photosensitizers might cause the degradation of PteGlu, upon UV, or even visible, irradiation.

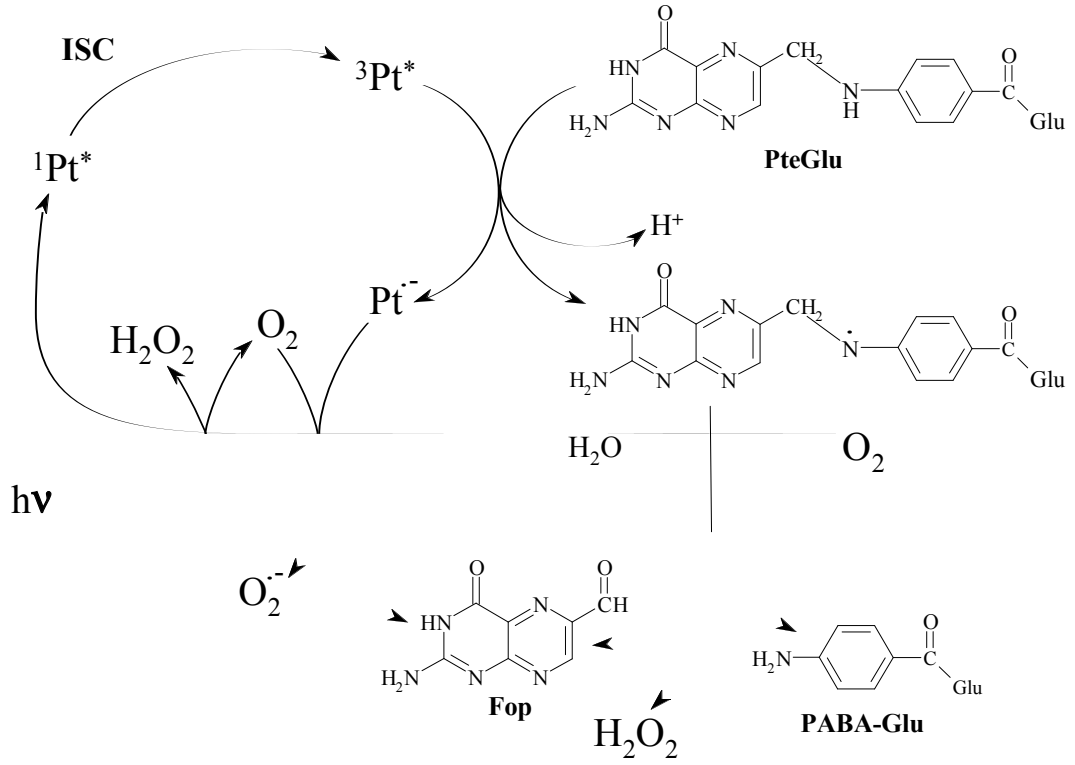

Figure 5. Mechanism of the photooxidation of folic acid (PteGlu).

Photoreduction of pterins

Electron transfer-initiated mechanisms were also proposed for the autocatalytic photooxidation of 7,8-dihydrobiopterin (46) and for the photosensitization of nucleotides by lumazine (47,48), a compound chemically related to pterins. Therefore this type of mechanism might be a general pathway of photosensitization of biomolecules by pterins and related heterocycles.

However, it was demonstrated that some pterins in the presence of electron donors undergo photoreduction, yielding the corresponding dihydropterin derivative, which in turn is reduced to a tetrahydropterin (49,50). Although, an electron transfer process must be involved in the photoreduction of pterins, the overall mechanism should be different from that proposed for the photosensitized oxidation of nucleotides. In a very recent work it was explained why, in some cases, photooxidation of a substrate take place without photosensitizer (Pt) consumption, whereas in other cases photoreduction of pterins occurs (20).

Under anaerobic conditions and in the presence of ethylenediaminetetraacetic acid (EDTA) as an electron donor, the reduction of pterins (Ptr, 6-methylpterin (Mep)) to the corresponding 7,8-dihydropterin was detected. Taking into account the behaviour using nucleotides as substrates, wherein no consumption of photosensitizer was reported, it seems that, under anaerobic conditions, substrates with very low ionization potential, such as EDTA ($E_{(EDTA^{\cdot+}/EDTA)}$=0.4V *vs*. NHE) (51) induce the photoreduction of pterins, whereas this process does not take place with oxidizable substrates with higher ionization potential, such as purine nucleotides (NT) ($E_{(NT^{\cdot+}/NT)}$ > 1.33 V *vs*. NHE) (52).

On the other hand, in air-equilibrated solutions and in the presence of different EDTA concentrations, no photoreduction was detected and no consumption of Ptr or Mep was registered. In these experiments, H_2O_2 was formed and its concentration increased as a function of irradiation time. These results suggest that the pterin radical anion reacts with dissolved O_2 regenerating the pterin and yielding $O_2^{\cdot-}$, which in turn gives H_2O_2 as measurable product.

Based on the results obtained for the photolysis of Mep in the presence of EDTA, the mechanistic pathways may be described by the Scheme presented in Figure 6. In both deaerated and aerated solutions, the radical anion of a given aromatic pterin ($Pt^{\cdot-}$) and the radical cation of EDTA ($D^{\cdot+}$) are formed by electron transfer from EDTA to the pterin triplet state ($^3Pt^*$). $Pt^{\cdot-}$ and $D^{\cdot+}$ are in equilibrium with their corresponding neutral forms: Pt(H)• and D(-H)•, respectively. Alternatively, these neutral radicals may be formed by a proton transfer between the radical ions pair within the solvent cage. Then, the following reactions depend on the O_2 concentration:

a) *Under anaerobic conditions*, a hydrogen transfer between the neutral radicals D(-H)• and Pt(H)• may lead to the formation of the reduced pterin (H_2Pt) and the oxidized donor D(-2H) (in the case of EDTA, ethenediaminetetraacetic acid should be formed).

b) *In air-equilibrated solutions*, trapping of $Pt^{\cdot-}$ by O_2 to yield Pt and $O_2^{\cdot-}$ competes with the reduction of $Pt^{\cdot-}$. Although in air-equilibrated solutions both reactions are possible, the former one appears to be predominant since no consumption of Pt, but an efficient production of H_2O_2 resulting from $O_2^{\cdot-}$ disproportionation, was observed. In addition, it has been reported for amines, including EDTA, that the corresponding radicals formed after one electron oxidation and deprotonation ($D(-H)^{\cdot}$) are able to reduce O_2 to $O_2^{\cdot-}$ (53,54).

c) *In O_2-saturated solutions*, the formation of H_2O_2 was slower than in air-equilibrated conditions. This result suggests that competitive quenching processes of $^3Pt^*$ by O_2 decrease the relative efficiency of the electron transfer reaction between the electron donor (in this case EDTA) and $^3Pt^*$, reaction at the origin of the formation of $Pt^{\cdot-}$ and thus of $O_2^{\cdot-}$ and H_2O_2.

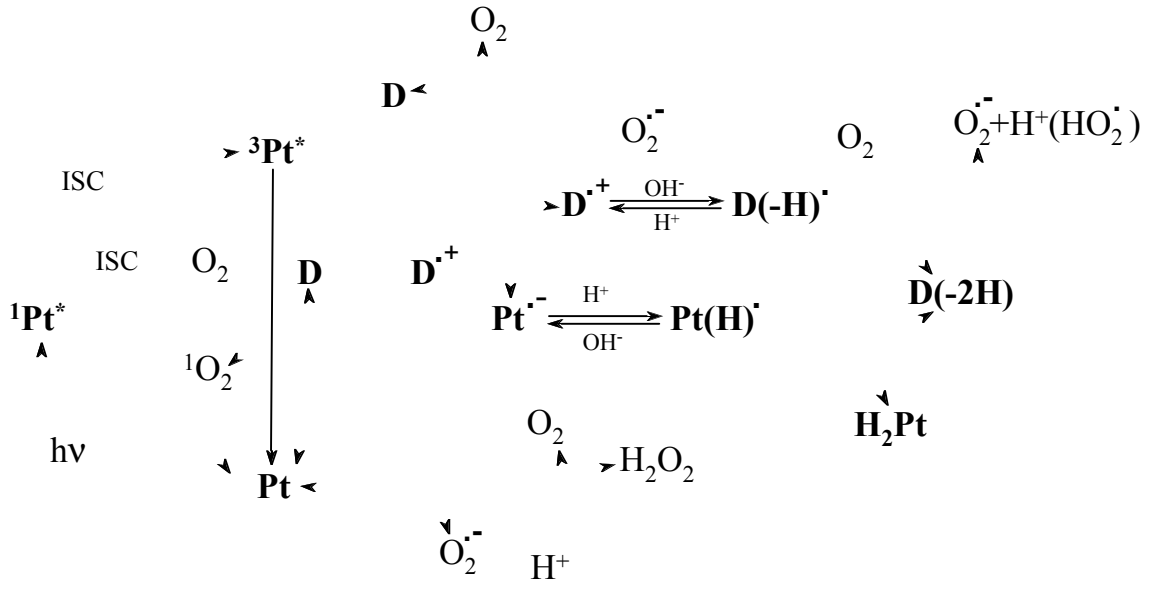

Figure 6. Overall mechanism of electron transfer processes photoinduced by pterins (Pt) (D = electron donor).

Conclusions

Taking into account all the results reported so far, an overall mechanism can be proposed (Figure 6). Besides intersystem crossing to the ground state, triplet state of pterins (^{3}Pt*) can be deactivated by dissolved O_2. Alternatively, ^{3}Pt* can react with an electron donor (D), which can be Pt itself or a different compound (nucleotides, EDTA, etc). Three different pathways are possible for the resulting radical anion ($Pt^{\cdot -}$): back electron transfer to $D^{\cdot +}$ (main reaction in the absence of O_2 and of a strong electron donor (EDTA)), electron transfer to O_2 or reaction with $D^{\cdot +}$ to yield a dihydroderivative (main reaction in the presence of the electron donor EDTA under anaerobic conditions). Finally, $O_2^{\cdot -}$ can react with $D^{\cdot +}$ or undergo disproportionation yielding H_2O_2 and O_2 as final products.

Acknowledgements

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