Intramolecular Electron Transfer between Tyrosine and Tryptophan Photosensitized by a Chiral π,π* Aromatic Ketone

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Abstract: The photochemical reaction of Trp and Tyr and related peptides with Suprofen (SUP) as sensitizer in H_2O/CH_3CN (28:1 *v*/*v*) solutions has been studied by time-resolved spectroscopy. The results show that SUP induces oxidation of both Trp and Tyr, as well as intramolecular-ET reactions in the related peptides. The influence of photosensitizer configuration on the involved processes has been studied by using the enantiomerically pure compounds. A significant chiral recognition is observed in which the concentration of the radicals formed after triplet quenching depends on the configuration of the chiral center; the quenching process is higher when using the (*R*)-SUP enantiomer.

Keywords: chiral recognition · electron transfer · ketones · photochemistry

Introduction

It has been proposed and in some cases also demonstrated that intramolecular electron transfer (intra-ET) between tyrosine (Tyr) and oxidized tryptophan (Trp) occurs in native biological reactions.[1] Thus, it has been shown that intraprotein electron transfer between Tyr and Trp in DNA photolyase from *Anacystis nidulans* leads to the catalytically competent state of the flavin adenine dinucleotide.[1b] It has also been suggested that electron transfer between tyrosine and tryptophan is involved in the activation of voltage-sensitive ion channels.[1c] The feasibility of such an ET process has been evidenced both in aqueous and in non-aqueous solvents, by using model peptides or proteins, after artificial oxidation of Trp.[2]

On the other hand, amino acids Tyr and Trp are photooxidized by non-steroidal antiinflammatory drugs such as tiaprofenic acid (TPA) and Suprofen (SUP). This reaction results in a high photoallergic activity of these drugs, as a result of the formation of adducts between amino acids and Suprofen, which are the relevant species in the drug–protein photobinding.[3] Time-resolved studies have shown that the lowest-lying triplet state (π,π*) of 2-benzoylthiophene (BT), the common chromophore of both drugs, is quenched by phenol and indole leading to the BT ketyl plus phenoxy or indolyl radicals.[4] Moreover, recent experimental and theoretical (DFT) studies[4,5] support the formation of encounter complexes during the quenching of BT by phenol or indole. The involvement of this type of species appears to be an essential condition for the asymmetry observation in emission quenching or photosensitization.[6]

Therefore, it was considered of interest to study the capability of SUP as a photosensitizer for the intra-ET reactions in Trp-Tyr and Trp-Gly-Tyr peptides as simple models of proteins (see below). Moreover, because of the potential importance of drug chirality in the photooxidation of proteins and related biological reactions, special attention would have to be drawn to the possible influence of the photosensitizer configuration on the involved processes when employing enantiomerically pure compounds.

Herein, we report that excitation of SUP in H_2O/CH_3CN (28:1 *v*/*v*) solutions induces oxidation of both Tyr and Trp, as well as intra-ET reactions in peptides. A significant chiral recognition has been observed related to the configuration-dependent concentration of radicals formed after triplet quenching.

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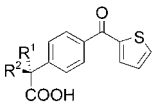
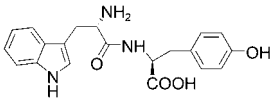
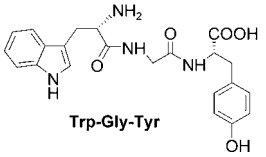


(*R*)-SUP: $R^1 = CH_3$, $R^2 = H$
(*S*)-SUP: $R^1 = H$, $R^2 = CH_3$



Trp-Tyr



Trp-Gly-Tyr

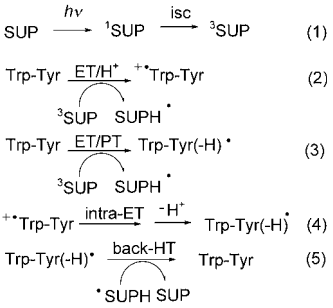
Results and Discussion

Transient species in the reaction of Trp-Tyr peptides with triplet Suprofen: Time-resolved experiments were performed in deaerated H_2O/CH_3CN (28:1 *v*/*v*) solutions, as these conditions allow a compromise between solubility of all the components, control of the pH of the media and similarity to biological environment. A pH value of 3.8 was chosen, because it is close to pK_a of the Trp-Tyr dipeptide.[7] The transient absorption spectrum of SUP triplet excited state (λ_{max} at 350 and 600 nm)[8] was observed after 355 nm laser excitation of (*S*)-SUP (0.64 mM) in deaerated solutions with a 10 ns Nd/YAG laser pulse (Figure 1a). To obtain the spectrum corresponding to the SUP ketyl radical (SUPH$^\bullet$) and Tyr(-H)$^\bullet$ radical, similar experiments were performed in the presence of *N*-Boc-tyrosine (3.5 mM), both in the absence and in the presence of air. After a sufficiently long delay (20 μs), no triplet should be left, due its quenching by the protected amino acid. While in dearated media both species would be present, under aerated conditions the carbon-centered ketyl radical would not be detectable, due to its fast reaction with oxygen in the timescale of the experiment. Thus, the only observable transient absorption under air corresponded to the tyrosinyl radical (Figure 1e, λ_{max} at 385 and 410 nm)[9] Hence, the "isolated" spectrum of the SUP ketyl radical (SUPH, λ_{max} at 350 and 580 nm)[4,10] was obtained by subtraction of the spectra in deaerated and aerated solution (Figure 1b).

On the other hand, upon 355 nm laser excitation of (*S*)-SUP in the presence of Trp three transient species should be formed: SUPH$^\bullet$ radical, Trp$^{+\bullet}$ cation radical and the Trp-derived skatolyl radical. Only the cation radical would exhibit low reactivity towards oxygen; therefore its spectrum (λ_{max} at 345 and 500–650 nm)[11] was obtained under aerated conditions (Figure 1f). It is known that skatolyl radicals are formed from 3-methylindole upon photosensitization by BT.[12a] In order to detect the possible formation of this type of oxygen-quencheable species in the present experiments, the spectra obtained 0.1 μs after the laser pulse in the presence and absence of oxygen (Figure 1g) were subtracted. As a result, the transient spectrum of this long-lived, C-centered radical (λ_{max} at 340 nm and no significant absorption beyond 400 nm)[12] was indeed observed (Figure 1h).

It is known that, under neutral conditions, 2-benzoylthiophene triplet is quenched by phenolic and indolic derivatives leading to phenoxy or indolyl radicals (arising from deprotonation of indole cation radical with a pK_a 4.9)[13] through a concerted electron-proton transfer (ET/PT).[4] In the acid media employed, the reaction of SUP triplet with Trp-Tyr should proceed to give Trp$^{+\bullet}$ and Tyr(-H)$^\bullet$, as the pK_a for Trp$^{+\bullet}$ is 4.3[13c,d] in the free amino acid (compared with a value of −1 for Tyr$^{+\bullet}$)[13e] and increases in the dipeptide.[13b] Actually, a value of 6.2 has been reported for Trp$^{+\bullet}$ in the Trp-Tyr dipeptide.[14] These data justify the observation of Trp$^{+\bullet}$ cation radical and Tyr(-H)$^\bullet$ radical at pH 3.8.

Formation of Tyr(-H)$^\bullet$ in Trp-Tyr was observed at 410 nm, where the SUP ketyl radical does not possess a significant absorption,[4] with a biphasic kinetics. The main part of this signal was formed "instantaneously" on the nanosecond time scale, while the remainder showed a delayed increase (curve a in Figure 2). This suggests the involvement of two different Tyr radical precursors: ^{3}SUP and Trp$^{+\bullet}$ [Eqs. (3) and (4)].



Intra-ET in the reaction of Trp-Tyr peptides with triplet Suprofen: Kinetic measurements were performed at 510 nm, where the Trp$^{+\bullet}$ absorbs significantly and the contribution of the SUP ketyl radical is very low. The decay at 510 nm was concomitant with the increase of Tyr(-H)$^\bullet$ radicals at 410 nm (Figure 2); the latter occurred with a rate constant around $1.6\times10^6\ s^{-1}$, similar to the value ($1\times10^6\ s^{-1}$) previously found for the intra-ET in aqueous solution of Trp-Tyr at pH 3.4.[2f] Furthermore, the growth rate constant dropped by a factor of about 3 when one glycine spacer was inserted between Tyr and Trp (Figure 3). According to the literature,[2c,f] this is in agreement with the intra-ET from Tyr to the Trp$^{+\bullet}$ [see Eq. (4)] which occurs predominately through direct nonbonding interactions between aromatic chains.

Stereodifferentiation in the reaction of Trp-Tyr peptides with triplet Suprofen: Next, we focused our interest on the possible influence of the photosensitizer configuration on

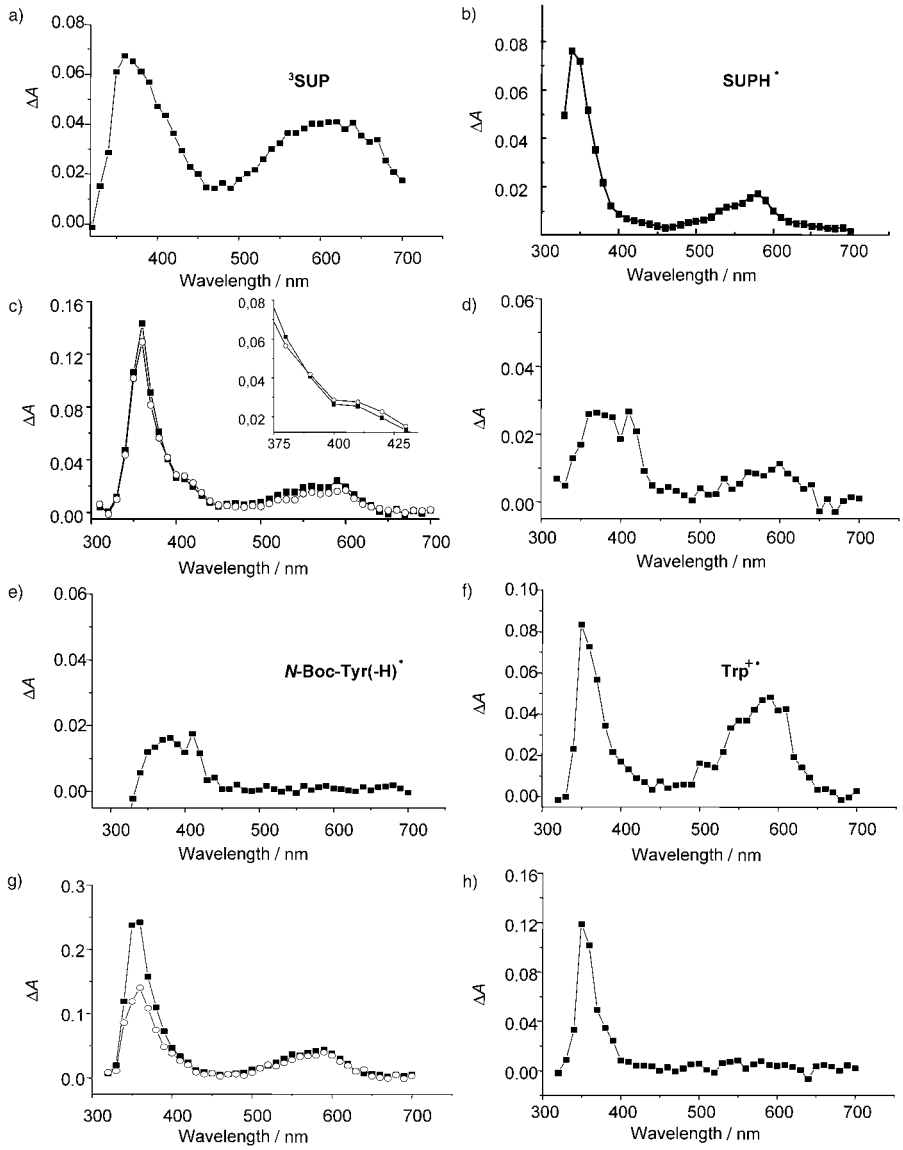


Figure 1. a) Transient absorption spectrum of a deaerated H_2O/CH_3CN (28:1) solution of (*S*)-SUP (0.64 mM) recorded 0.16 μs after laser excitation (355 nm). b) Transient absorption spectrum of a H_2O/CH_3CN (28:1) solution of (*S*)-SUPH recorded 20 μs after laser excitation (355 nm). The spectrum was obtained from the subtraction of spectra in deaerated and aerated solution of SUP (0.64 mM) and *N*-Boc-(*S*)-tyrosine (3.5 mM). c) Transient absorption spectra of a deaerated H_2O/CH_3CN (28:1) solution of (*S*)-SUP (0.64 mM) and dipeptide (5.12 mM) recorded 0.16 μs (■) and 2.0 μs (○) after the laser pulse (355 nm). Magnification of the spectra between 375 and 425 nm. d) Transient absorption spectrum of an aerated H_2O/CH_3CN (28:1) solution of (*S*)-SUP (0.64 mM) and dipeptide (5.12 mM) recorded 1 μs after laser pulse (355 nm). e) Transient absorption spectrum of a deaerated H_2O/CH_3CN (28:1) solution of (*S*)-SUP (0.64 mM) and *N*-Boc-Tyr (3.5 mM) recorded 20 μs after the laser pulse (355 nm). f) Transient absorption spectrum of an aerated H_2O/CH_3CN (28:1) solution of (*S*)-SUP (0.64 mM) and tryptophan (5.12 mM) recorded 0.5 μs after laser pulse (355 nm). g) Transient absorption spectra of a deaerated (■) and aerated (○) H_2O/CH_3CN (28:1) solution of (*S*)-SUP (0.64 mM) and dipeptide (5.12 mM) recorded 0.1 μs after laser excitation (355 nm). h) Skatolyl radical obtained from the difference between the transient absorption spectrum of a deaerated and aerated H_2O/CH_3CN (28:1) solution of (*S*)-SUP (0.64 mM) and dipeptide (5.12 mM) recorded 0.1 μs after the laser pulse (355 nm).

the efficiency of all the occurring processes; this was performed with enantiomerically pure (*S*)- and (*R*)-Suprofen.

The quantum yields for the formation of Tyr(-H)$^\bullet$ and Trp$^{+\bullet}$ were determined by a comparative method, taking into account the molar absorption coefficients of the species involved (see Experimental Section). The yields found for Tyr(-H)$^\bullet$ were not very different from those found for Trp$^{+\bullet}$ (between 0.2 and 0.3), in spite of the lower oxidation potential of indole compared with phenol.[4,13b,15]

The "initial" concentration of the Tyr(-H)$^\bullet$ radicals was dependent on the photosensitizer configuration, and was higher when using the (*R*)-enantiomer (Figure 4a, Table 1). A parallel stereodifferentiation was observed for SUPH$^\bullet$ radical and Trp$^{+\bullet}$ cation radical formation (Figure 4b, Table 1).

On the other hand, the growth of Tyr(-H)$^\bullet$ and the concomitant decay of the Trp$^{+\bullet}$ were not strongly configuration dependent (Figure 4); this is in agreement with the intra-ET nature of the involved process.

Comparative experiments with the isolated amino acids: Similar experiments were performed by using the natural amino acids as quenchers of the enantiomeric ^{3}SUP triplets, in H_2O/CH_3CN (28:1 *v*/*v*) solutions at a pH value of 2.3.[16] The bimolecular rate constants found for (*S*)-Trp were slightly higher than those determined for (*S*)-Tyr or *N*-(*tert*-butoxycarbonyl)-L-tyrosine [*N*-Boc-(*S*)-Tyr] [$(3.3\pm0.1)\times10^9\,M^{-1}s^{-1}$ for Trp, $(2.00\pm0.06)\times10^9\,M^{-1}s^{-1}$ for Tyr and $(2.35\pm0.05)\times10^9\,M^{-1}s^{-1}$ for *N*-Boc-(*S*)-Tyr]. The same species were observed when using the Trp-Tyr peptide: Trp$^{+\bullet}$ (pK_a 4.3) and skatolyl or Tyr(-H)$^\bullet$, together with SUPH$^\bullet$.[17,18]

The quantum yields determination showed that Trp$^{+\bullet}$ formation was somewhat more efficient with (*R*)-SUP than with (*S*)-SUP (see Table 1). A higher effect compared with the Trp$^{+\bullet}$ was found for Tyr$^\bullet$ formation in the quenching of SUP enantiomers by (*S*)-Tyr (see Figure 5 and Table 1).

Under the experimental conditions SUP is essentially present as the free carboxylic acid (pK_a 4.9),[19] while 50%

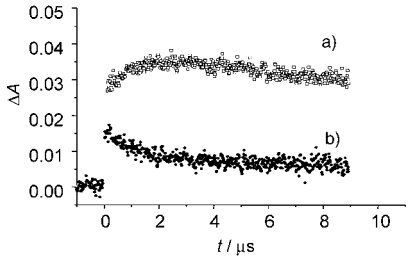


Figure 2. Transient kinetic traces observed at a) 410 nm and b) 510 nm after laser flash photolysis (355 nm) of a deaerated H_2O/CH_3CN (28:1) solution of (*S*)-SUP (0.64 mM) containing Trp-Tyr (5.12 mM).

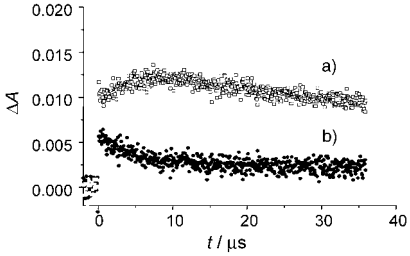


Figure 3. Transient kinetic traces observed at a) 410 nm and b) 510 nm after laser flash photolysis (355 nm) of a deaerated H_2O/CH_3CN (28:1) solution of (*S*)-SUP (0.64 mM) and Trp-Gly-Tyr (5.12 mM).

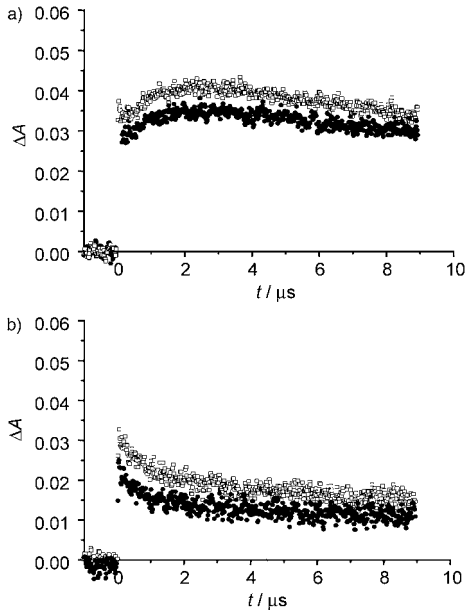


Figure 4. a) Transient kinetic traces observed at 410 nm after laser flash photolysis of a deaerated H_2O/CH_3CN (28:1) solution of Trp-Tyr (5.12 mM) and (*S*)-SUP (□, 0.64 mM) or (*R*)-SUP (●, 0.64 mM). b) Transient kinetic traces observed at 580 nm after laser flash photolysis of a deaerated H_2O/CH_3CN (28:1) solution of Trp-Tyr (5.12 mM) and (*S*)-SUP (●, 0.64 mM) or (*R*)-SUP (□, 0.64 mM). In all the experiments, the laser energy was the same (11 mJ per pulse).

Table 1. Quantum yields and relative efficiencies of radical formation in the quenching of photoexcited (*R*)- or (*S*)-SUP by Trp-Tyr, Trp, Tyr and *N*-Boc-Tyr.

		$Trp^{\bullet+}$	$Tyr(-H)^{\bullet}$[a]	$SUPH^{\bullet}$
Trp-Tyr[b]	(*R*)-SUP	0.32	0.27	0.61
pH 3.8	(*S*)-SUP	0.27	0.22	0.52
	(*R*)-/(*S*)-SUP	1.2	1.2	1.2
Trp[b]	(*R*)-SUP	0.45	–	0.70
pH 2.3	(*S*)-SUP	0.40	–	0.64
	(*R*)-/(*S*)-SUP	1.1	–	1.1
Tyr[b]	(*R*)-SUP	–	0.68	0.69
pH 2.3	(*S*)-SUP	–	0.58	0.59
	(*R*)-/(*S*)-SUP	–	1.2	1.2
N-Boc-Tyr[c]	(*R*)-SUP	–	0.60	0.62
pH 3.4	(*S*)-SUP	–	0.55	0.58
	(*R*)-/(*S*)-SUP	−1.1	1.1	

[a] Initial concentration. [b] H_2O/CH_3CN 28:1. [c] H_2O/CH_3CN 28:2.

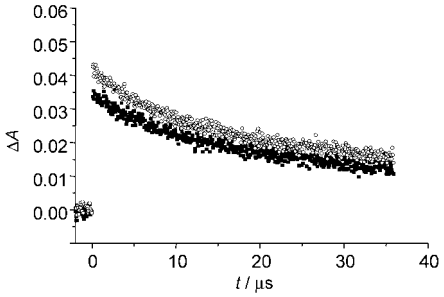


Figure 5. Transient kinetic traces observed at 410 nm after laser flash photolysis of a deaerated H_2O/CH_3CN (28:1) solution of (*S*)-tyrosine (5.12 mM) and (*S*)-SUP (●, 0.64 mM) or (*R*)-SUP (□, 0.64 mM). In both experiments, the laser energy was the same (11 mJ per pulse).

of the quencher is in its zwitterionic form. Hence, the hydrogen-bonding interactions between the amino acid carboxylate group and the carboxylic acid of the photosensitizer could be reason for the observed chiral recognition. To check this hypothesis, triplet quenching of (*R*)- and (*S*)-SUP by Trp-Tyr was performed at pH 2.3; under these conditions, where the amount of zwitterion is strongly decreased, no stereodifferentiation was detected (data not shown). Moreover, when *N*-Boc-(*S*)-Tyr was used as quencher, (at pH 3.4 close to its pK_a)[20] chiral recognition (measured as $Tyr(-H)^{\bullet}$ formation) was also observed, although to a lower degree. Finally, no chiral recognition was observed when *N*-Boc-(*S*)-Tyr methyl ester was used as quencher at pH 3.8.

Conclusion

The non-steroidal drug Suprofen not only photosensitizes the oxidation of Tyr and Trp, but also induces intramolecular electron transfer between Tyr and Trp in model peptides, that is Trp-Tyr and Trp-Gly-Tyr. By using the enantiomerically pure compounds, a stereodifferentiation effect is observed in the formation of radicals arising from quenching of the SUP triplet excited state. Comparative studies with the natural amino acids show a decreased, though parallel,

chiral recognition. These data agree with the involvement of encounter complexes in the quenching of the photosensitizer by the amino acids and related peptides. The fact that higher radical formation yields are obtained when using the (*R*)-enantiomer suggests stereodifferentiation in the efficiency of the electron transfer process.

Experimental Section

Chemicals: Both enantiomers of [4-(thien-2-ylcarbonyl)phenyl]propanoic acid (Suprofen, SUP) were obtained by resolution of commercially available racemic Suprofen by using chiral HPLC chromatography (Kromasil 100 TBB, 5 μm 250×10 mm): a 60:40 solution of hexane/*tert*-butyl methyl ether (containing 0.1% of acetic acid) as eluent.

Laser flash photolysis: The solutions were prepared by using distilled water and acetonitrile (HPLC grade). The pH of the Tyr and Trp solutions was lowered to 2.3 by adding HCl; it did not change after the experiments. The time-resolved experiments were carried out using a pulsed Nd/YAG Spectrum laser system instrument. The single pulses were about 10 ns duration and the energy was about 11 mJ per pulse. A Xenon lamp was employed as detecting light source. The laser flash photolysis apparatus consisted of the pulsed laser, the Xe lamp, a monochromator, a photomultiplier (PMT) system made up of side-on PMT, PMT housing and a PMT power supply. The output signal from the oscilloscope was transferred to a personal computer for study. Samples were contained in 7×7 mm cells made of Suprasil quartz and were deaerated with dry nitrogen prior to the experiments. Compounds concentration was adjusted to yield an absorbance of 0.3 at 355 nm.

Rate constants for the intermolecular quenching of SUP by (*S*)-Trp were determined in deaerated solutions by monitoring the decay of the SUP T–T absorption spectra at 650 nm, where neither $SUPH^{+\cdot}$ nor $Trp^{+\cdot}$ absorb significantly. In the case of Tyr(-H)$^{\cdot}$ measurements were performed at 630 nm, where $SUPH^{\cdot}$ does not interfere and ^3SUP has still a significant molar absorption coefficient. The bimolecular rate constants were determined from plots of the ketone triplet decay versus quencher concentration [Q] according to the following Equation:

$$k_{decay} = k_0 + k_q\,[Q] \tag{6}$$

where k_0 is the pseudo-first-order rate constant in the absence of quencher.

The values found for (*S*)-Trp were slightly higher than those determined for (*S*)-Tyr or *N*-Boc-(*S*)-Tyr (ca. $3\times10^9\,M^{-1}s^{-1}$ for Trp and $2\times10^9\,M^{-1}s^{-1}$ for Tyr compounds).

Molar absorption coefficients of SUP ketyl radical (SUPH)$^{\cdot}$ were determined by a comparative method, by using two solutions with the same absorbance (0.3) at 355 nm: BP in MeCN and SUP (6.4×10^{-4} M) containing *p*-cresol (19.0×10^{-3} M) in H_2O/CH_3CN (28:1 *v*/*v*) (ca. 90% of SUP triplet quenching). The quantum yield for formation of the aryloxy radical (φ_{ArO}) was calculated by using Equation (7):

$$\phi_{ArO} = \phi_{isc}^{BP} \times \Delta A_{410}^{ArO} \times \varepsilon_{525}^{BP}/\Delta A_{525}^{BP} \times \varepsilon_{410}^{ArO} \tag{7}$$

where ΔA_{410}^{ArO} and ε_{410}^{ArO} ($3200\,M^{-1}\,cm^{-1}$) are the net absorbance and the molar absorption coefficient of aryloxy radical at 410 nm. Thus, for φ_{ArO} a value of about 0.90 was calculated. Considering that $\phi_{ArO} = \phi_{SUPH}$ Equation (8) allowed for the calculation of the molar absorption coefficients of the $SUPH^{\cdot}$:

$$\phi_{SUPH} = \phi_{isc}^{BP} \times \Delta A_{580}^{(SUPH)} \times \varepsilon_{525}^{BP}/\Delta A_{525}^{BP} \times \varepsilon_{580}^{(SUPH)} \tag{8}$$

where ΔA_{580} refers to the net absorbance of the ketyl radical at 580 nm. Thus, the SUPH molar absorption coefficient was found to be about $1510\,M^{-1}\,cm^{-1}$ at 580 nm.

For the case of Trp-Tyr, the quantum yield for the formation of $Trp^{+\cdot}$ and $SUPH^{\cdot}$ were calculated taking into account their contribution to the 580 nm absorption band, as well as the fast decay of $Trp^{+\cdot}$. The quantum yield for the formation of Tyr(-H) was obtained from the initial net absorbances at 410 nm. In all these cases Equation (9) was used to determine the quantum yield (ϕ_j) of the considered species. The following molar absorption coefficients ($M^{-1}cm^{-1}$) were employed: $\varepsilon_{410}^{Tyr^{\cdot}(-H)} = 3200$,[22] $\varepsilon_{580}^{Trp^{+\cdot}} = 2885$,[11] $\varepsilon_{580}^{SUPH} = 1510$, $\varepsilon_{600}^{^3SUP} = 2900$[4]. The triplet yield for ^3SUP is taken to be 1.[21]

$$\phi_j = \phi_{isc}^{SUP} \times \Delta A_\lambda^j \times \varepsilon_{600}^{SUP}/\Delta A_{600}^{SUP} \times \varepsilon_\lambda^j \tag{9}$$

By the same methodology the quantum yields for the formation of the species in the intermolecular studies were calculated by using Equation (9).

Acknowledgements

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