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Photochemical Fate of Carbamazepine in Surface Freshwaters: Laboratory Measures and Modeling

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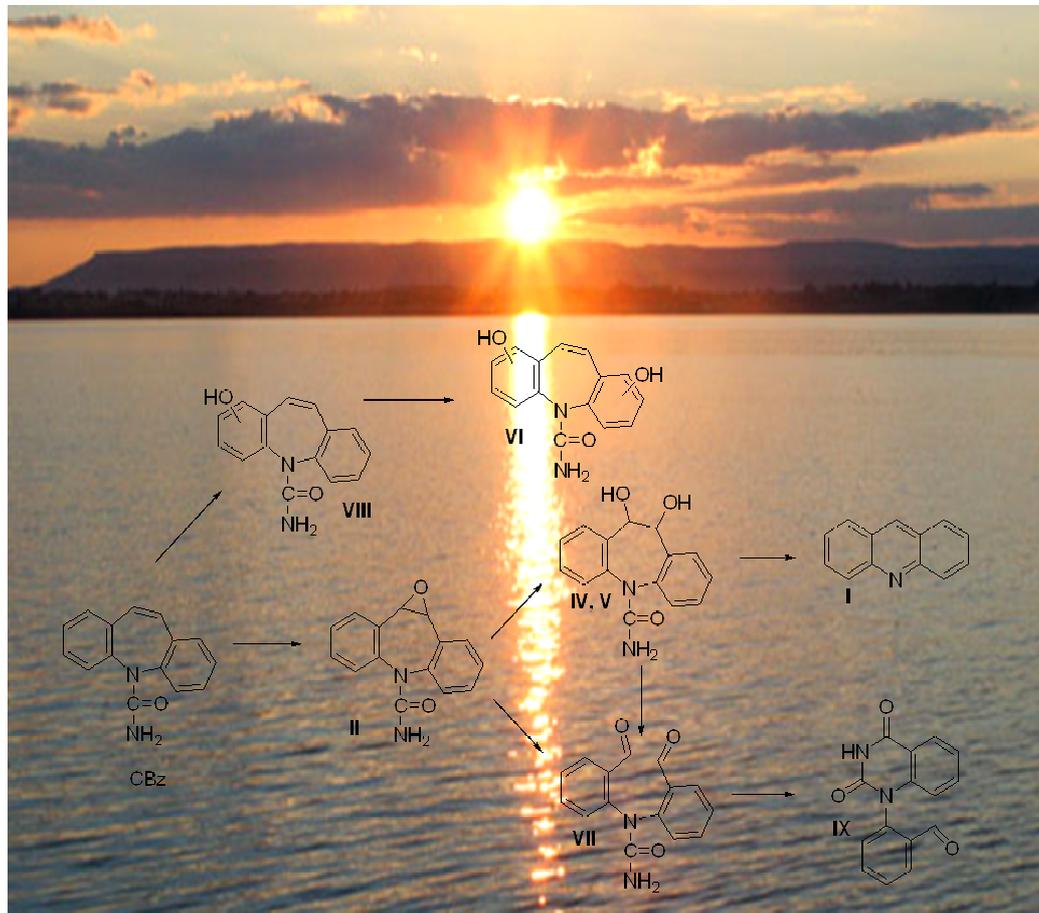
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ABSTRACT

It is shown here that carbamazepine (CBZ) would undergo direct photolysis and reaction with $\bullet\text{OH}$ as main phototransformation pathways in surface waters. Environmental lifetimes are expected to vary from a few weeks to several months, and predictions are in good agreement with the available field data. Acridine (**I**) and 10,11-dihydro-10,11-trans-dihydroxy-CBZ (**V**) are the main quantified phototransformation intermediates upon direct photolysis and $\bullet\text{OH}$ reaction, respectively. The photochemical yield of mutagenic **I** from CBZ is in the 3-3.5% range and, being similar for both direct photolysis and $\bullet\text{OH}$ reaction, it would undergo limited variation with environmental conditions. In contrast, the yield of **V** would vary in the 4-8.5% range depending on the conditions, because **V** is formed from CBZ by $\bullet\text{OH}$ (9.0% yield) more effectively than upon direct photolysis (1.4% yield). Other important photointermediates, mostly formed from CBZ upon $\bullet\text{OH}$ reaction are an aromatic-ring-dihydroxylated CBZ (**VI**) and N,N-di(2-carboxyphenyl)urea (**VII**). Compounds **VI** and **VII** are formed by photochemistry and are not reported as human metabolites, thus they could be used as tracers of CBZ phototransformation in surface waters. Interestingly, **VI** has recently been detected in river water.

INTRODUCTION

Carbamazepine (CBZ) is an antiepileptic drug that is highly metabolized in the human body and is excreted both as parent compound and its metabolite forms. Two key metabolic pathways have been listed, with the main route being the formation of carbamazepine-10,11-epoxide, a pharmacologically active compound with anticonvulsant properties. CBZ-Epoxide is further metabolized into 10,11-dihydro-10,11-trans-dihydroxycarbamazepine (DiOH-CBZ or **V**), acridine and acridone. A second minor metabolic route involves the production of hydroxylated compounds, 2-hydroxycarbamazepine and 3-hydroxycarbamazepine.¹ CBZ and DiOH-CBZ are compounds of high environmental relevance because they show almost no elimination in wastewater treatment plants (WWTPs).^{2,3} Studies have reported their occurrence,^{2,3} in surface water up to $\mu\text{g/L}$ levels,^{3,4} in groundwater up to 50 ng/L,⁵ and in drinking water up to 20 ng/L.^{6,7}

Photochemical reactions are important transformation processes of xenobiotics in surface waters, particularly for compounds like CBZ that are refractory to biodegradation.⁸ Photoinduced processes can be divided into direct photolysis and sensitized phototransformation, the latter involving transients produced by so-called photosensitizers under irradiation. The main photosensitizers are chromophoric dissolved organic matter (CDOM), nitrate, nitrite, and possibly also H_2O_2 and Fe compounds. The most important photogenerated transients are $\bullet\text{OH}$, $\text{CO}_3^{\bullet-}$, $^1\text{O}_2$ and the triplet states of CDOM, $^3\text{CDOM}^*$.⁹ Irradiated CDOM yields $^3\text{CDOM}^*$, $^1\text{O}_2$ and $\bullet\text{OH}$,¹⁰⁻¹³ the latter also produced by nitrate and nitrite. The radical $\text{CO}_3^{\bullet-}$ is formed by reaction between $\bullet\text{OH}$ and HCO_3^- or CO_3^{2-} , and upon CO_3^{2-} oxidation by $^3\text{CDOM}^*$.¹⁴ Together with direct photolysis

(operational for sunlight-absorbing molecules), sensitized reactions can be involved in the removal of xenobiotics from surface waters, but sometimes also in the formation of harmful intermediates.^{15,16}

Several studies have addressed the issue of CBZ photodegradation under natural conditions or upon application of advanced technologies for water treatment.^{e.g.,17-24} Despite this, many knowledge gaps still exist concerning the photochemical fate of CBZ in environmental waters. Earlier works did not try to calculate reaction rate constants and quantum yields, which strongly limits data applicability beyond the particular experimental set-up used. Moreover, only very limited attempts have been made so far to relate water chemistry with CBZ fate. Even the most thorough previous studies usually gave a single or few half-life time(s) for CBZ in surface waters, which is of limited use. Indeed, half-life times may vary by orders of magnitude for the same compound, depending on water chemical composition and column depth.^{25,26} Moreover, while most studies were concentrated on CBZ direct photolysis and $\bullet\text{OH}$ reaction, contrasting results can be found in the literature concerning the role of CDOM on its photodegradation. While some authors suggest that CDOM occurrence would inhibit CBZ direct photolysis by an inner-filter effect,^{18,23,24} others underline the key role of CDOM as photosensitizer, although the reactive species involved in CDOM photosensitization were not reported.^{17,19-21} Additionally, and perhaps most importantly, despite the many studies aimed at identifying CBZ phototransformation intermediates under a wide variety of environmentally or technologically significant conditions,^{e.g.,27-30} there has been no attempt so far to predict or model the formation kinetics of intermediates in the environment, let alone under variable conditions of water chemical composition and depth. Finally, because of the large overlap between CBZ biotransformation and phototransformation metabolites/intermediates, the same compounds are produced by quite different processes.^{1,27-31} Largely out of this reason, to date there is no indication of which intermediates could be used as reliable markers of CBZ phototransformation in the environment. Therefore, it is presently not possible to distinguish between human metabolism, the (however limited) WWTP processing and photochemistry, as sources of CBZ intermediates in surface waters.

The present work aims at filling up all the knowledge gaps cited before. To this purpose, it addresses the quantitative assessment of the photochemical fate of CBZ, relevant to surface waters. This substrate was chosen because it is biologically refractory and its irradiation yields mutagenic acridine, which is a compound of considerable concern.³² Moreover, many potential phototransformation intermediates of CBZ are commercially available as standards. The approach we followed involves laboratory studies of CBZ photoactivity *via* different transformation pathways (direct photolysis and reaction with $\bullet\text{OH}$, $\text{CO}_3^{\bullet-}$, $^1\text{O}_2$ and $^3\text{CDOM}^*$), including the formation yields of photointermediates. The aim is to provide input data for a photochemical model that predicts the kinetics of CBZ phototransformation and intermediate formation as a function of water chemical composition and column depth. The model has been able to successfully predict the transformation kinetics of xenobiotics in surface waters^{25,26} and was here implemented to include the formation of

intermediates. To our knowledge, this is the very first attempt to address the photochemical formation of intermediates with such an approach.

MATERIALS AND METHODS

CBZ phototransformation kinetics. The kinetic parameters relevant to the phototransformation of CBZ (direct photolysis quantum yield and second-order rate constants with the reactive transients) were determined following an experimental protocol already reported.²⁶ Direct photolysis was studied upon UVB irradiation, reactivity with $\bullet\text{OH}$ upon nitrate photolysis adopting competition kinetics with 2-propanol, and reactivity with $\text{CO}_3^{\bullet-}$ upon irradiation of nitrate and bicarbonate.³³ Furthermore, irradiated Rose Bengal was used as $^1\text{O}_2$ source and anthraquinone-2-sulphonate (AQ2S) as triplet sensitizer (CDOM proxy). Reactivity of CBZ with irradiated riboflavin (RF) was also investigated, using both laser flash photolysis and steady-state irradiation. Details of all these experiments are reported as Supporting Information (hereafter SI). The relevant parameters were determined in neutral solution, but additional runs showed that they would not vary significantly in the pH range 4-9 (see Figure S11, SI). This is in agreement with CBZ not undergoing protonation or deprotonation under such conditions.

Identification of CBZ phototransformation intermediates. Intermediate identification was carried out following CBZ transformation *via* the pathways that would be most significant for surface waters (direct photolysis and reaction with $\bullet\text{OH}$, as shown by combination of reactivity data and photochemical modeling). Irradiation was carried out in a cylindrical immersion-type glass photoreactor (0.5 L, Heraeus TQ 150) equipped with a water-cooled, medium-pressure Hg lamp. The whole assembly was wrapped with aluminum foil. The lamp irradiance between 290 and 400 nm was 220 W m^{-2} and the incident photon flux in solution was $1.0 \cdot 10^{-4} \text{ Einstein L}^{-1} \text{ s}^{-1}$, actinometrically determined. The radiation path length inside the reactor was 2 cm. The emission spectrum of the lamp, as well as the absorption spectra of CBZ and nitrate are reported in Figure S1 (SI). After irradiation, aliquots were removed at selected time intervals and processed by HPLC-MS. A BetaBasic $150 \times 2 \text{ mm}$ C-18 endcapped column ($3 \mu\text{m}$ particle size) equipped with a $10 \times 2 \text{ mm}$ guard column containing the same material was used, at a flow rate of 0.2 mL min^{-1} . The mobile phase was a mixture of methanol (A) and 0.1% HCOOH in water (B); gradient was operated from 5% to 100% A for 30 min and back to the initial conditions in 5 min. Mass spectrometry was performed on an Esquire 6000 ion trap system (Bruker, Bremen, Germany), equipped with an electrospray interface and operated in positive ionization mode. Operating conditions of the source were: capillary voltage, 4000 V; nebulizer pressure, 45 psi; drying gas flow, 10 L/min at a temperature of 365°C .

Molecular weight of CBZ phototransformation intermediates was assigned on the basis of the m/z values of the quasi-molecular ions $[\text{M}+\text{H}]^+$. Structures were tentatively elucidated according to the MS/MS fragmentation patterns, using the quasi-molecular ions as precursor ions. Confirmatory

methods were also used, including authentic standards when available and matching the fragmentation patterns with those reported in published mass spectra.

Kinetic data treatment. The experimental time trend of CBZ was fitted with pseudo-first order equations $C_t = C_o \cdot e^{-k_{CBZ} t}$, where C_t is CBZ concentration at the time t , C_o its initial concentration and k_{CBZ} the transformation rate constant. The time evolution of the intermediates was fitted with $I_i = k_i' C_o (k_i'' - k_{CBZ})^{-1} (e^{-k_{CBZ} t} - e^{-k_i'' t})$, where C_o and k_{CBZ} are as above, I_i is the concentration of the intermediate i at the time t , k_i' the rate constant of i formation from CBZ, and k_i'' the rate constant of i transformation. The initial rate of CBZ disappearance is $R_{CBZ} = k_{CBZ} C_o$, that of i formation is $R_i = k_i' C_o$. The errors on the rates were derived from the scattering of the experimental data around the fit curve. Reproducibility of repeated runs was in the range of 10-15%.

The photochemical model. The model predicts the half-life time and the pseudo-first order phototransformation rate constant of an organic compound in surface waters, based on environmental variables (water column depth and chemical composition) and substrate reactivity parameters (direct photolysis quantum yield and reaction rate constants with photoreactive transients).³⁴ The latter are derived by laboratory measures that quantify reaction kinetics rather than simulating the environment, a task that is extremely difficult at the very least. The link between reaction kinetics and the environment is provided by the model. With this approach, very good agreement with available field data has been obtained for 2,4-dichloro-6-nitrophenol and the herbicide MCPA in lagoon water,^{25,35} as well as ibuprofen and several pesticides in lake water.^{26,36} The model uses as time unit a conventional Summer Sunny Day (SSD) that is equivalent to a fair-weather 15 July at 45°N. It also hypothesizes consistent good weather,³⁶ and meteorological issues should be considered separately.

For CBZ the model yielded the pseudo-first order transformation rate constants k_{CBZ}^p , where p is a photochemical process (photolysis or reaction with $\bullet\text{OH}$, $\text{CO}_3^{\bullet-}$, $^1\text{O}_2$ and $^3\text{CDOM}^*$). The overall rate constant of phototransformation is $k_{CBZ} = \sum_p k_{CBZ}^p$. The model was also implemented to obtain the formation rate constants of CBZ photointermediates. In the process p , CBZ could produce the intermediate i with yield η_i^p , experimentally determined as the ratio between the initial formation rate of i and the initial transformation rate of CBZ. The pseudo-first order rate constant of i formation in the process p is $(k_i^p)' = \eta_i^p k_{CBZ}^p$. The production of i from CBZ could take place *via* more than one process. Therefore, the overall rate constant of i formation is:

$$(k_i)' = \sum_p (k_i^p)' = \sum_p (\eta_i^p k_{CBZ}^p) \quad (1)$$

One can also obtain the overall yield of i formation from CBZ (η_i), as:

$$\eta_i = (k_i)'(k_{CBZ})^{-1} = \frac{\sum_p (\eta_i^p k_{CBZ}^p)}{\sum_p k_{CBZ}^p} \quad (2)$$

Note that the model in the present version would mainly deal with freshwater, while the foreseen extension to saline systems (*e.g.* brackish waters)¹² should for instance include bromide as $\bullet\text{OH}$ scavenger. In brackish systems (*e.g.* estuaries or saline lakes), the decrease of the importance of $\bullet\text{OH}$ -induced transformation because of scavenging by bromide would be partially offset by CBZ reaction with halogen-containing transients, which could yield CBZ halogenoderivatives.²³

The model adopts a Lambert-Beer approximation that neglects radiation scattering by particles as well as particle photoreactivity. While the model could not work well in highly turbid systems, there is evidence that particles are much less important than CDOM in photochemical processes in most surface waters and particularly in lake water.³⁷

RESULTS AND DISCUSSION

CBZ phototransformation kinetics. The measurement of the quantum yield of CBZ direct photolysis and of the second-order reaction rate constants with $\bullet\text{OH}$, $^1\text{O}_2$ and $^3\text{AQ2S}^*$ ($^3\text{CDOM}^*$ proxy) was carried out following an already reported procedure.²⁶ Significant reactivity between CBZ and $\text{CO}_3^{\bullet-}$ could be excluded by means of a semi-quantitative screening method.³³ The relevant experimental data are reported and discussed as SI. The obtained parameters of photochemical interest (Φ_{CBZ} , $k_{\text{CBZ},\bullet\text{OH}}$, $k_{\text{CBZ},^1\text{O}_2}$, $k_{\text{CBZ},^3\text{AQ2S}^*}$, $k_{\text{CBZ},^3\text{RF}^*}$) are listed in Table 1. The use of AQ2S under irradiation as proxy of CDOM is motivated by (*i*) the occurrence of quinones in CDOM, that would account for a fraction of CDOM fluorescence,³⁸ and (*ii*) the well-known photochemistry of AQ2S, which produces $^3\text{AQ2S}^*$ but not $\bullet\text{OH}$ or $^1\text{O}_2$ ³⁹⁻⁴¹ and allows kinetic parameters of triplet-state reactivity to be easily obtained. An alternative CDOM proxy is riboflavin (RF),²⁶ and the reactivity of its triplet state with CBZ was also tested. The reaction rate constants of CBZ with triplet RF and triplet AQ2S are comparable (see Table 1).

Note that the value of $k_{\text{CBZ},\bullet\text{OH}}$ obtained in this study was a factor of ~ 2 higher compared to previous work.¹⁹ Competition kinetics was used in both studies but, differently from our approach, previous work followed the time evolution of both CBZ and $\bullet\text{OH}$ competitor (*p*-chlorobenzoic acid), so that the $\bullet\text{OH}$ rate constant could be determined with just one run (with some replicates).¹⁹ Such a time-saving procedure has the disadvantage that data points at elevated reaction times have the highest weight in the calculation of the $\bullet\text{OH}$ rate constant. A reaction system tends to become more complex as the reaction progresses: therefore, it could become substantially different from the initial one. Analytical errors would also be higher on low-concentration data points at elevated reaction time, which have the most important role in defining the $\bullet\text{OH}$ rate constant. Our approach required 11 runs with 5-6 data points each (see Figure S3), but it has the advantage of giving more weight to early-time data, in the measurement of the initial degradation rates. Another issue with previous work is that H_2O_2 at different concentration values was used as $\bullet\text{OH}$ source, but the

reaction between H_2O_2 and $\bullet\text{OH}$ was not taken into account.¹⁹ Unfortunately, H_2O_2 concentrations were not reported, which precludes prediction of the importance of the related $\bullet\text{OH}$ -consumption process.

Very variable literature values are available for the photolysis quantum yield of CBZ.^{18,19} In one case, calculation details are unfortunately not reported.¹⁹ In the other, CBZ photolysis was studied under real sunlight, obtaining a considerably lower photolysis quantum yield than ours.¹⁸ Radiation sources (sun *vs.* UVB lamp) are unlikely to explain the difference, because CBZ mostly absorbs UVB radiation with a single absorption band, which should feature a constant photolysis quantum yield.⁴² Sunlight irradiance in the previous study was not actually measured, it was rather calculated from literature data.¹⁸ Therefore, disturbing effects due to haze/cloud cover, UV absorption by air pollutants (*e.g.* O_3 , NO_2) and absorption by glassware have not been taken into account. Considering that the cited factors would decrease sunlight irradiance, most notably in the UVB region where CBZ absorbs sunlight,⁴³ irradiance overestimation and photolysis quantum yield underestimation are quite probable.

An additional issue is that, in some cases, substrate-metal complexes play an important role in direct photolysis, in particular with Fe(III)⁴⁴ and somewhat less for Cu(II).⁴⁵ CBZ phototransformation in the presence of Fe(III) in acidic solution was accounted for by $\bullet\text{OH}$ photoproduction by FeOH^{2+} , not by photolysis of Fe(III)-CBZ complexes.²³ Therefore, Fe(III) complexation would not be important for CBZ photochemistry (and FeOH^{2+} would not be relevant in the typical pH range of surface waters).¹²

Comparison between model predictions and field data. An initial survey was made of the relative importance of different CBZ phototransformation processes, under a set of conditions (water chemical composition and column depth) that would be relevant to most surface waters. Reactivity parameters reported in Table 1 were incorporated into our photochemical model,^{25,26} which indicated that reaction with $\bullet\text{OH}$ and direct photolysis would be the main CBZ phototransformation pathways. Reaction with ${}^3\text{CDOM}^*$ would play a secondary to minor role, independently of the use of reactivity data derived from AQ2S or RF. Quinones such as AQ2S produce quite reactive triplet states.⁴⁶ Therefore, it is highly unlikely that average ${}^3\text{CDOM}^*$ are more reactive than ${}^3\text{AQ2S}^*$ and cause significant CBZ phototransformation in surface waters. Still lower reactivity is expected for CDOM formed by in-water biological processes (autochthonous) or for CDOM derived by atmospheric deposition.⁴⁷ Moreover, processes involving ${}^1\text{O}_2$ would be unimportant. Such considerations hold as well under conditions characterized by high DOM concentration, because organic matter is a source as well as a sink of $\bullet\text{OH}$.¹²

Note that the model takes into account competition for sunlight irradiance between the different light-absorbing species in solution, substrate (CBZ) included.^{25,26,34-36} Moreover, the laboratory use of nitrate as a reasonably “clean” $\bullet\text{OH}$ source to study the reaction kinetics of CBZ does not imply that it is the main $\bullet\text{OH}$ source in the environment. Indeed, nitrite and CDOM are usually more

important than nitrate as $\bullet\text{OH}$ sources in surface waters, but they are less suitable for laboratory studies.^{12,34,36}

The fact that direct photolysis and $\bullet\text{OH}$ reaction are the main CBZ phototransformation pathways agrees well with previous studies.^{18,19,24} It also allows exclusion of $^3\text{CDOM}^*$ as important reactive species for CBZ phototransformation in humic waters.²⁰ The most likely explanation for the contrasting literature findings about CDOM/humic acids and CBZ phototransformation, is that CDOM produces $\bullet\text{OH}$ along with triplet states.^{13,48,49} CDOM samples that produce more $\bullet\text{OH}$ could account for CBZ photodegradation enhancement, those producing less would account for the opposite effect.

Field data of CBZ persistence that allow comparison with the model have been reported for Lake Greifensee, Switzerland.⁵⁰ The field monitoring campaign has been carried out in late summer and yielded a pseudo-first order rate constant of CBZ attenuation of $0.011 \pm 0.002 \text{ day}^{-1}$ in the lake epilimnion, of which 0.006 day^{-1} accounted for by outflow and the remaining $0.005 \pm 0.002 \text{ day}^{-1}$ by other processes. Chemical transformation not involving light, gas partitioning and sedimentation could be excluded (the latter because CBZ is polar and rather hydrophilic),⁵⁰ while biotransformation seems little likely for CBZ.^{2,51}

With data relevant to the epilimnion of Lake Greifensee (5 m depth, 0.1 mM nitrate, 3.5 mg C L⁻¹ DOC, 2 mM bicarbonate, 10 μM carbonate^{14,52}) and Table 1 parameters, our model derives $k_{\text{CBz}}^{\bullet\text{OH}} = 0.009 \pm 0.002 \text{ SSD}^{-1}$ for transformation with $\bullet\text{OH}$ and $k_{\text{CBz}}^{\text{Phot}} = 0.003 \pm 0.001 \text{ SSD}^{-1}$ for the direct photolysis. As far as the equivalence between SSD and outdoor days is concerned, meteorology issues in the study period suggested to roughly halve the rates of photochemical reactions.²⁸ Therefore, 1 SSD would approximately equal 2 days. With this consideration, our model gives $k_{\text{CBz}}^{\bullet\text{OH}+\text{Phot}} \approx 0.006 \pm 0.002 \text{ day}^{-1}$. This value is very near the field rate constant of CBZ attenuation after exclusion of the outflow, and suggests that photochemistry could play a role in the loss of CBZ in Lake Greifensee epilimnion. Here the photochemical half-life time would be 55 SSD \approx 110 days, which makes CBZ a fairly persistent pollutant as far as phototransformation is concerned. However, CBZ phototransformation could be significantly faster under different conditions (*e.g.* shallow lagoons that collect water draining agricultural areas), where light-induced processes could be more important.¹²

CBZ phototransformation intermediates. Intermediates **I-V** (see Table 2), for which commercial standards are available were monitored upon CBZ transformation *via* both reaction with $\bullet\text{OH}$ (produced by nitrate irradiation) and direct photolysis, which are the two main processes that CBZ is expected to undergo in surface waters. Intermediates **I**, **II**, **IV** and **V** were identified as acridine, CBZ-10,11-epoxide, 10,11-dihydro-10,11-*cis*-dihydroxy-CBZ and 10,11-dihydro-10,11-*trans*-dihydroxy-CBZ, respectively, by comparing their chromatographic and mass spectrometric behavior with that of authentic standards. The *trans* and *cis* stereoisomers (**IV**, **V**) were distinguished on the basis of the retention time of individual standards. Intermediate **III** was never detected in our experimental conditions. It was included among standards because of its detection in

previous work,²³ although it was not very clear whether it was formed from hydrolysis or photochemistry. Lack of **III** in this study suggests possible formation by hydrolysis. HPLC-MS/MS data for standards, obtained by selecting the quasi-molecular ion $[M+H]^+$ as precursor ion are reported in Table 2.

Figure 1a shows the time trend of 90 μ M CBZ and intermediates **I-V** upon irradiation of 0.10 M nitrate, Figure 1b shows the corresponding trend upon direct photolysis of 90 μ M CBZ alone. An alternative representation of intermediate evolution vs. CBZ percent transformation is provided as SI, Figure S12. **I** and **V** were the intermediates formed with the highest initial rates, **I** upon direct photolysis and **V** upon \bullet OH reaction. As far as direct photolysis is concerned, assuming R_{CBZ}^{Phot} as the initial transformation rate of CBZ and R_i^{Phot} as the initial formation rate of the intermediate i ($i = \mathbf{I-V}$), the yield of i from CBZ is given by the ratio of the initial rates, $\eta_i^{Phot} = R_i^{Phot} \cdot (R_{CBZ}^{Phot})^{-1}$. In the case of nitrate irradiation, the direct photolysis could be operational to some extent and its contribution should be considered, while additional processes would be unimportant (see SI). Figure 1 shows that the time scales of the two experiments were quite different (irradiation time up to 6 h for nitrate vs. 72 h for the direct photolysis), which justifies the choice of experimental conditions including nitrate concentration. Therefore, minor contribution of the direct photolysis is expected in CBZ transformation with nitrate. Anyway, the role of direct photolysis can be taken into account by calculating the photon flux absorbed by CBZ in the two cases.

The procedure to calculate radiation absorption by CBZ alone and in mixture with nitrate, as well as its implications for yield calculation is reported as SI. Table 1 reports the calculation results, namely values of η_i^{Phot} and $\eta_i^{\bullet OH}$ for intermediates **I-V**. Note that $\sum_{i=1}^V \eta_i^{\bullet OH} = 0.140 \pm 0.014$ and $\sum_{i=1}^V \eta_i^{Phot} = 0.069 \pm 0.0012$, thus other important non-quantified intermediates could be formed (*vide infra*). In both cases, the yield of mutagenic acridine **I** was around 3-3.5%. The fact that the same intermediates, although with different yields, were observed upon both direct photolysis and reaction with \bullet OH could be accounted for by the fact that CBZ photolysis proceeds *via* photoionization followed by reaction between the resulting carbocation and water.²³ Such a process would simulate reaction with \bullet OH and yield the same radical intermediates in the primary reaction step. The photoionization/hydrolysis pathway would for instance explain the formation of hydroxyderivatives upon CBZ direct photolysis.

Apart from **I-V**, four additional relevant intermediates (**VI-IX**, see Scheme 1) were tentatively identified on the basis of their MS/MS fragmentation patterns (SI, Figure S13), upon direct photolysis and \bullet OH reactivity. The MS/MS spectrum of **VII** was characterized by losses of 17 (m/z 252) and 43 (m/z 226) mass units, due to respective losses of NH_3 and $CONH_2$, which supports the preservation of the $CONH_2$ lateral chain. The lack of the product ion at m/z 180, which accounts for the unmodified heterocyclic ring structure of acridine, suggests that the heterocyclic ring was modified. Additional fragment ions at m/z 224 ($-CONH_3$) and m/z 196 ($-COCONH_3$) might reveal the formation of two aldehyde moieties. A detailed mechanism of ring closure of **VII** by an

intramolecular reaction to a quinazoline moiety **IX** is provided elsewhere.⁵³ **IX** eluted as two peaks due to the hindered rotation of the partial double bond character of the phenyl-N bond, yielding two stereoisomers. Intermediate **VIII** has a MS/MS spectrum depicting fragment ions at m/z 236 (OH loss) and m/z 210 (CONH₂ loss). It would probably derive from \bullet OH attack on a C₆ aromatic ring, and was assigned the structure of hydroxycarbamazepine. **VIII** was further transformed into the dihydroxylated derivative **VI**. On the basis of these chemical structures, a photochemical transformation pathway could be suggested (see Scheme 1). CBZ would thus undergo two competitive oxidation pathways. The first involves hydroxylation of the aromatic rings, the second implies formation of an epoxyde that could either evolve into a diol (**IV**, **V**), or undergo heterocyclic ring opening (**VII**). The diol further undergoes ring contraction to yield acridine, as previously described.²³

Intermediate identification and quantification was also carried out in the presence of 1 mM AQ2S under irradiation. Intermediates **II**, **V**, **VII** and **VIII** were identified, and the former two also quantified (Figure S14). The relevant yields of **II** and **V** formation from CBZ are extremely low (Table 1). Therefore, considering that reaction with ³CDOM* only plays a secondary role in CBZ phototransformation, the formation of **II** and **V** *via* ³CDOM* could be neglected under environmental conditions.

Note that **I**, **II**, **IV**, **V**, **VI**, **VIII** have also been detected with TiO₂/UV,^{28,30} **II** and **VIII** with H₂O₂/UV,^{19,29} **I** upon direct photolysis,²³ and **I**, **VIII** upon UV irradiation of FeOH²⁺ (yielding \bullet OH).²³

Modeling of intermediates photogeneration. Intermediates **I**, **II**, **IV**, **V** are formed from CBZ *via* direct photolysis and reaction with \bullet OH, with different yields depending on the process (see Table 1). The parameters of Table 1 can be used as input data to model the formation kinetics of the relevant compounds, expressed as pseudo-first order formation rate constants (k_i)' (see equation 1 with $i = \mathbf{I-V}$), as a function of environmental variables (water chemical composition and column depth d). The trends of the rate constants for CBZ transformation and intermediate formation (SSD⁻¹ units) are reported in SI, Figures S15-S19 (0.2 μ M nitrite, 2 mM bicarbonate, 0-6 mg C L⁻¹ dissolved organic carbon (DOC), 1-100 μ M nitrate, 1-100 μ M carbonate, $d=0-5$ m). Additionally, Figure S20 reports the corresponding steady-state [\bullet OH], [¹O₂] and [³CDOM*], for a sunlight UV irradiance of 22 W m⁻².

The rate constants (k_i)' are expected to increase with increasing nitrate and nitrite as \bullet OH sources. In contrast, (k_i)' would decrease with increasing d (the poorly illuminated bottom layers of a deep water body are hardly favorable to photochemistry) and increasing carbonate and bicarbonate as \bullet OH scavengers. Increasing DOC would decrease (k_i)', because high-DOC waters contain elevated DOM and usually also CDOM.⁵⁴ DOM (both CDOM and non-chromophoric material) is a \bullet OH scavenger and CDOM a \bullet OH source, with variable offset of opposite effects, but radiation-absorbing CDOM would inhibit the direct photolysis of CBZ. Figures S15-S19 also

suggest that the kinetics of CBZ transformation and intermediate formation would vary by orders of magnitude depending on environmental conditions.

The model can also be used to derive the formation yields η_i of intermediates from CBZ, as a function of environmental parameters (equation 2, with η_i^p values from Table 1). Figure 2 shows the predicted trend of the yields of the main quantified photointermediates, **I** (mutagenic acridine) and **V**, as a function of d , nitrate, carbonate and DOC. The yield η_I is not expected to change much, because it is quite similar for both $\bullet\text{OH}$ and the direct photolysis (Table 1). The trends of η_V are opposite to η_I and the corresponding variations are more important, in the 0.04-0.085 range, because the **V** yield from $\text{CBZ} + \bullet\text{OH}$ is about six times higher than for direct photolysis. The decrease of η_V with increasing DOC and the increase with d suggest that: (i) low DOC would inhibit $\bullet\text{OH}$ transformation (mostly by $\bullet\text{OH}$ scavenging) more than it inhibits direct photolysis (the latter *via* radiation absorption by CDOM); (ii) depth would favor $\bullet\text{OH}$ vs. direct photolysis, because the $\bullet\text{OH}$ sources CDOM, nitrate and nitrite absorb a larger fraction of the sunlight spectrum than CBZ. Carbonate as $\bullet\text{OH}$ scavenger would enhance the relative role of the direct photolysis, and the opposite would take place with nitrate as $\bullet\text{OH}$ source. Moreover, nitrite is expected to behave like nitrate, and bicarbonate like carbonate.

Modeling the time trends of CBZ and acridine (I) in surface waters. Figure 2 shows the formation rate constants of intermediates **I** and **V**, but it is also interesting to model the time evolution of both CBZ and its intermediates. This issue requires consideration of degradation rate constants of the intermediates, in addition to those of CBZ transformation and intermediate formation from CBZ. We will consider here the case of mutagenic acridine (**I**), both because it has the highest environmental concern, and because literature data are available for reaction rate constant with $\bullet\text{OH}$ ($9.7 \cdot 10^9 \text{ M}^{-1} \text{ s}^{-1}$)⁵⁵ and photolysis quantum yield under sunlight ($3.93 \cdot 10^{-5}$)⁵⁶. The absorption spectrum of **I** is reported in Figure S21. Direct photolysis and reaction with $\bullet\text{OH}$ will provide a reasonable lower limit for **I** photodegradation kinetics in environmental waters. Figure 3 reports the trends of the modeled pseudo-first order degradation rate constants, k_{CBZ} and $(k_I)'$, as a function of depth and DOC. The model also yielded the pseudo-first order formation rate constant of **I** from CBZ ($(k_I)''$, data not shown). Availability of such data allows the modeling of the time evolution of, *e.g.*, 10^{-8} M CBZ and **I** for definite values of water chemical composition and depth (four sample points 1-4 are considered in Figure 3). First-order equations (3) and (4) can be used for CBZ and **I**, respectively (here it was $[\text{CBZ}]_0 = 10^{-8} \text{ M}$ and $[\text{I}]_0 = 0$, implying a CBZ spike with no further emission until complete disappearance: of course, it is a simplified case).

$$[\text{CBZ}]_t = [\text{CBZ}]_0 e^{-k_{\text{CBZ}} t} \quad (3)$$

$$[\text{I}]_t = \frac{(k_I)' [\text{CBZ}]_0}{(k_I)'' - k_{\text{CBZ}}} (e^{-k_{\text{CBZ}} t} - e^{-(k_I)'' t}) + [\text{I}]_0 e^{-(k_I)'' t} \quad (4)$$

The model suggests that **I** would be slightly more persistent than CBZ in surface waters ($(k_I)^{0.5} = 0.65-0.85 k_{CBZ}$), but it would reach quite low concentration values. Under conditions of Figure 3, direct photolysis and $\bullet\text{OH}$ would play a comparable role in **I** degradation, while $\bullet\text{OH}$ would dominate CBZ transformation. Direct photolysis is thus expected to play a more important role for **I** than for CBZ. Note that the time scale to achieve comparable transformation is modified from 10 to 200 SSD, when passing from $d = 1$ m and $\text{DOC} = 0.5 \text{ mg C L}^{-1}$ to $d = 4$ m and $\text{DOC} = 4 \text{ mg C L}^{-1}$.

Environmental implications. Direct photolysis and reaction with $\bullet\text{OH}$ are the main expected phototransformation processes of CBZ in surface waters. The photochemical half-life time would vary in the range of weeks to several months or more, depending on environmental conditions. CBZ phototransformation would be faster in shallow and DOC-poor water bodies, rich in nitrate and nitrite. The relative importance of direct photolysis vs. $\bullet\text{OH}$ reaction as CBZ transformation pathways is expected to increase with DOC and carbonate/bicarbonate and to decrease with depth, nitrate and nitrite.

Among the quantified intermediates, **I** (mutagenic acridine) and **V** are those formed in higher yield. The yield of **I** (3-4.5%) is similar for both direct photolysis and $\bullet\text{OH}$ reaction. It is of some concern, given the relevant health effects. Intermediates **II**, **VIII** and most notably **V** are important human CBZ metabolites, which have often been detected at the inlet and outlet of wastewater treatment plants.^{57,58} Therefore, they could hardly be used as unequivocal indicators of CBZ phototransformation. Some evidence of formation by human metabolism exists for **I** as well.¹

Based on peak areas one can infer that compounds **VI** and **VII**, which are not produced by human metabolism, would be major intermediates of CBZ phototransformation, most notably upon reaction with $\bullet\text{OH}$. Therefore, their possible environmental occurrence could be used as an index of CBZ phototransformation in general, and of $\bullet\text{OH}$ reaction in particular. Trends of their photogeneration kinetics in surface waters would be similar to those reported for **V**. Interestingly, **VI** has been identified in the water of river Po, near Turin (NW Italy).⁵⁹

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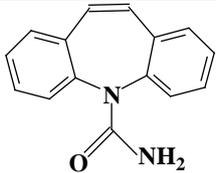
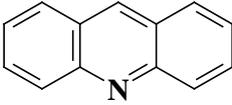
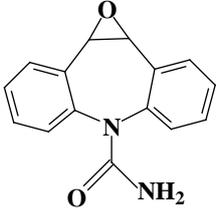
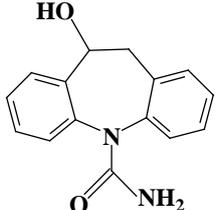
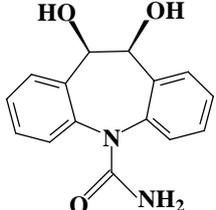
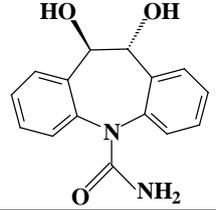
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Table 1. Photochemical reactivity parameters of CBZ: reaction kinetic constants of CBZ in the main photochemical reactions relevant to surface waters, and formation yields of the intermediates **I-V** via the main CBZ phototransformation processes (Phot = direct photolysis). The reaction between CBZ and $\text{CO}_3^{\bullet-}$ in surface waters can be neglected (see SI). Intermediate **III** was not detected in the irradiation experiments.

<i>Parameter</i>	<i>Value</i>	
Φ_{CBZ}	$(7.8 \pm 1.8) \cdot 10^{-4}$	
$k_{\text{CBZ},\bullet\text{OH}}$	$(1.8 \pm 0.2) \cdot 10^{10} \text{ M}^{-1} \text{ s}^{-1}$	
$k_{\text{CBZ},\text{IO}_2}$	$(1.9 \pm 0.1) \cdot 10^5 \text{ M}^{-1} \text{ s}^{-1}$	
$k_{\text{CBZ},3\text{AQ2S}^*}$	$(7.0 \pm 0.2) \cdot 10^8 \text{ M}^{-1} \text{ s}^{-1}$	
$k_{\text{CBZ},3\text{RF}^*}$	$(8.2 \pm 0.4) \cdot 10^8 \text{ M}^{-1} \text{ s}^{-1}$	
$\bullet\text{OH}$	$\eta_{\text{I}}^{\bullet\text{OH}}$	0.031 ± 0.010
	$\eta_{\text{II}}^{\bullet\text{OH}}$	0.014 ± 0.003
	$\eta_{\text{III}}^{\bullet\text{OH}}$	<i>Not detected</i>
	$\eta_{\text{IV}}^{\bullet\text{OH}}$	0.004 ± 0.002
	$\eta_{\text{V}}^{\bullet\text{OH}}$	0.090 ± 0.007
Phot	$\eta_{\text{I}}^{\text{Phot}}$	0.036 ± 0.009
	$\eta_{\text{II}}^{\text{Phot}}$	0.019 ± 0.006
	$\eta_{\text{III}}^{\text{Phot}}$	<i>Not detected</i>
	$\eta_{\text{IV}}^{\text{Phot}}$	0.006 ± 0.001
	$\eta_{\text{V}}^{\text{Phot}}$	0.014 ± 0.002
AQ2S	$\eta_{\text{I}}^{\text{AQ2S}}$	<i>Not detected</i>
	$\eta_{\text{II}}^{\text{AQ2S}}$	$(2.25 \pm 0.08) \cdot 10^{-5}$
	$\eta_{\text{III}}^{\text{AQ2S}}$	<i>Not detected</i>
	$\eta_{\text{IV}}^{\text{AQ2S}}$	<i>Not detected</i>
	$\eta_{\text{V}}^{\text{AQ2S}}$	$(1.34 \pm 0.01) \cdot 10^{-4}$

Table 2. Structures and HPLC-MS/MS data for carbamazepine (CBZ) and its detected or potential phototransformation intermediates, for which standards were available (**I**: acridine; **II**: CBZ-10,11-epoxide; **III**: 10-hydroxy-10,11-dihydroxy-CBZ; **IV**: 10,11-dihydro-10,11-*cis*-dihydroxy-CBZ; **V**: 10,11-dihydro-10,11-*trans*-dihydroxy-CBZ). The mass spectrometer was run in multiple reaction monitoring (MRM) mode. The protonated molecule was isolated and subjected to collision-induced dissociation, to produce full-scan MS/MS spectra. The trap parameters were set in ion-charge control, with a target of 30 000 and a maximum accumulation time of 200 ms at *m/z* from 50 to 1000. The cut-off and the autotune fragmentation amplitude were set for all compounds at one third of the mass of the precursor ion and to 1 V, respectively. Normalized collision energy of 30% was selected, which offers informative spectra without any stable molecular ions and good isolation yield. Bold face values indicate the product ion used for quantification.

<i>Acronym</i>	<i>Structure</i>	<i>Precursor ion</i>	<i>MS/MS ions</i>	<i>Remarks</i>
CBZ		237 [M+H] ⁺	220 , 194	Detected
I		180 [M+H] ⁺	152	Detected
II		253 [M+H] ⁺	236 , 180	Detected
III		255 [M+H] ⁺	237	Not detected
IV		271 [M+H] ⁺	253 , 236, 228, 210	Detected
V		271 [M+H] ⁺	253 , 236, 228, 210	Detected

Captions to Figures and Schemes

Figure 1. Time evolution of CBZ and intermediates **I-V** upon irradiation under neutral conditions of:

- a) 90 μM CBZ and 0.1 M nitrate;
- b) 90 μM CBZ.

Figure 2. Formation yields from CBZ of intermediates **I (a, b)** and **V (c, d)**, as a function of important water parameters: nitrate and depth (**a, c**), and carbonate and DOC (**b, d**). When not varying, water parameters were set at the following values: 5 m depth, 0.1 mM nitrate, 0.2 μM nitrite, 2 mM bicarbonate, 10 μM carbonate, 3.5 mg C L⁻¹ DOC.

Figure 3. Modeled transformation rate constants of CBZ (**a**) and of intermediate **I (b, acridine)**, as a function of DOC and depth. Other parameters: 0.1 mM nitrate, 1 μM nitrite, 2 mM bicarbonate, 10 μM carbonate. The insets ①-④ report the modeled time trends of CBZ and **I** under different conditions, based on the transformation rate constants of CBZ and **I**, and on the formation rate constant of **I** from CBZ. The percentage yields $\eta_{\text{I}} = 100 (k_{\text{I}})' (k_{\text{CBZ}})^{-1}$ of **I** formation from CBZ are also reported for ①-④. SSD = Summer Sunny Day, equivalent to 15 July at 45°N.

Scheme 1. Proposed phototransformation pathways of CBZ into the observed intermediates.

Figure 1

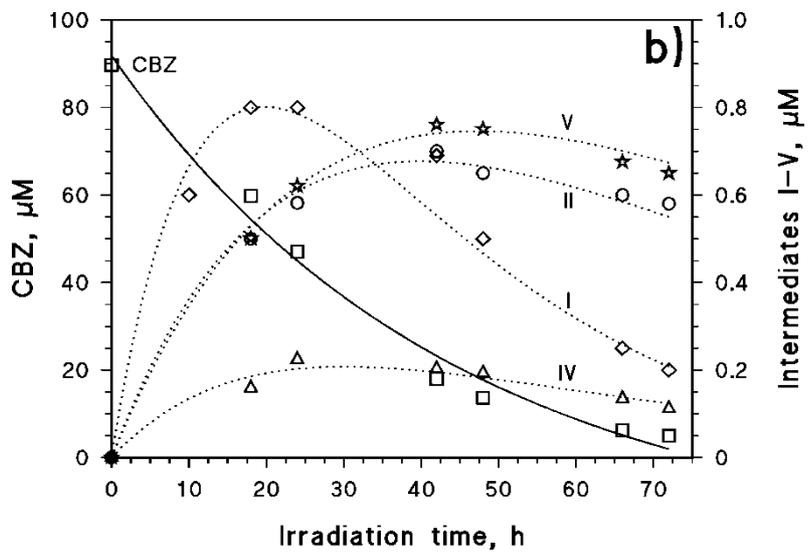
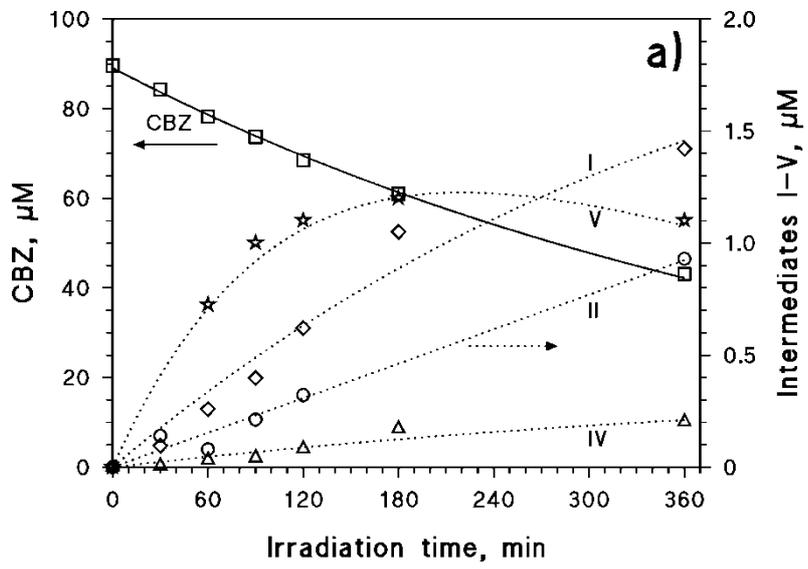


Figure 2

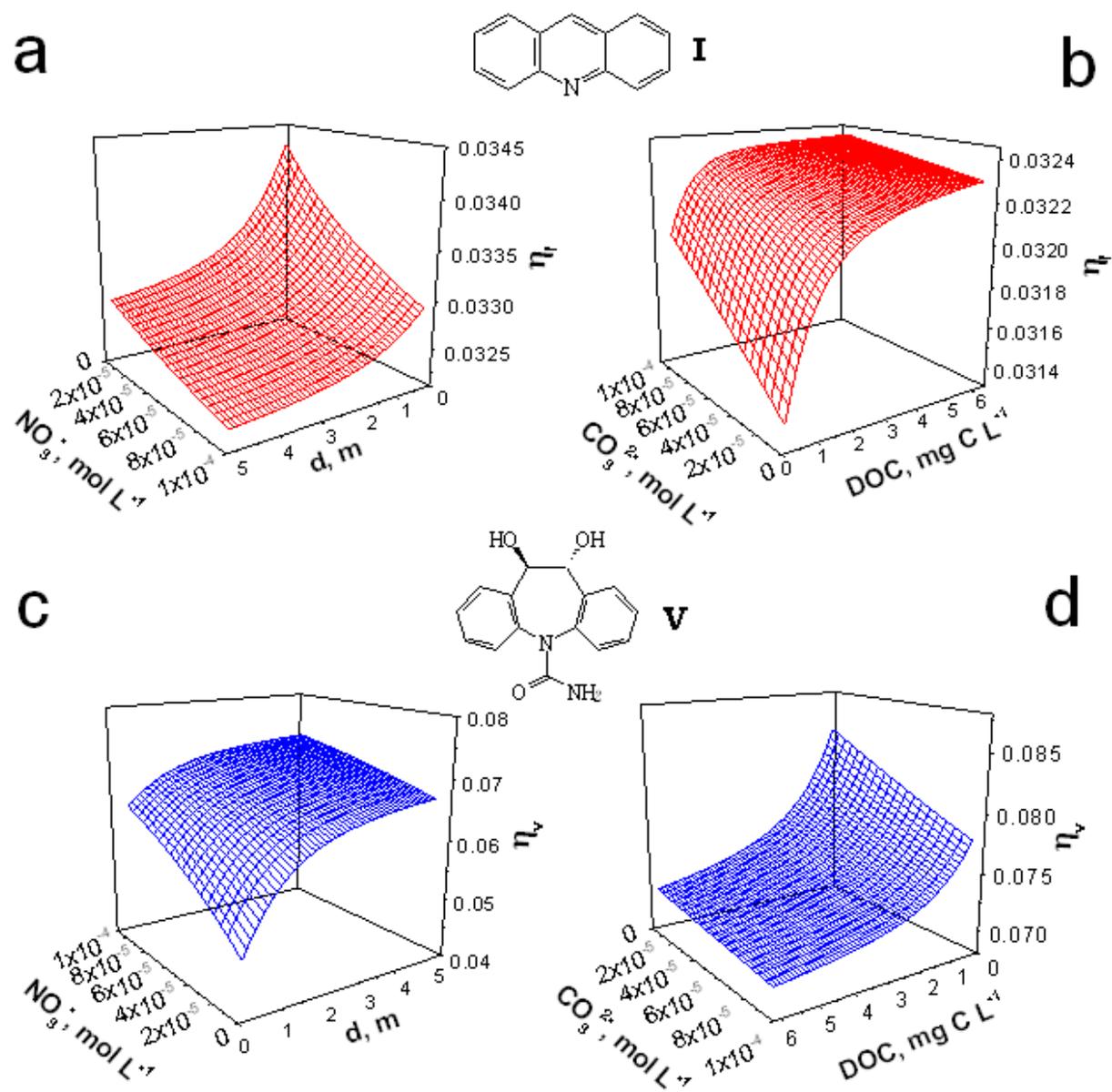
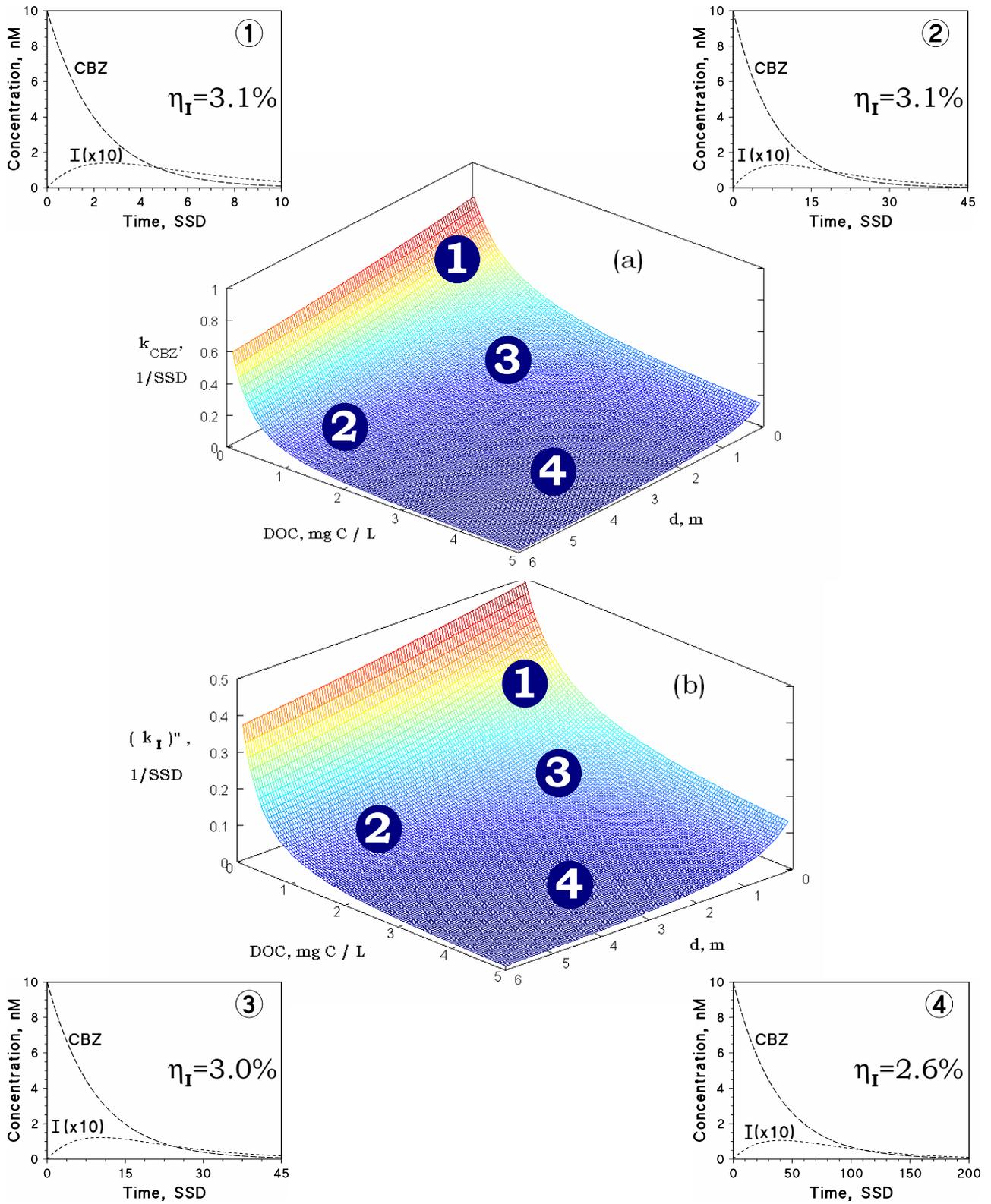


Figure 3



Scheme 1

