Indirect Photodegradation of Amine Drugs in Aqueous Solution under Simulated Sunlight

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Received November 24, 2008. Revised manuscript received January 18, 2009. Accepted February 23, 2009.

The photodegradation of the widely used amine drugs including primary amine (mexiletine), secondary amine (propranolol, phenytoin), and tertiary amine (diphenhydramine, antipyrine) were investigated in the presence of nitrate and humic substances under simulated sunlight. All of the amine drugs were photodegraded by nitrate due to the attack of hydroxyl radicals ($\cdot\text{OH}$). The bimolecular rate constants for the reaction between each amine drug and $\cdot\text{OH}$ ranged from $(2.1 \pm 0.2) \times 10^9$ to $(8.7 \pm 0.3) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$. In contrast, only mexiletine, propranolol, and diphenhydramine were selectively photodegraded in the presence of humic substances (HS). Fulvic acid was a more efficient sensitizer than humic acid throughout. The HS triplet states were verified to be main reactive species in the photochemical reaction. Furthermore, an electron transfer mechanism for the reaction with the HS triplet states was proposed on the basis of all information obtained under a series of experiments. The electron transfer from the nonbonding electrons on nitrogen (N-electrons) of the amine drugs to the excited ketone of the HS occurred. The availability of N-electrons and presence of hydrogen on carbon α of amine (α -hydrogen) were two key factors for the electron-transfer interaction. Moreover, the photoproducts were identified by GC-MS and the degradation pathways were proposed. The results strongly suggest the impact of humic substances on the photochemical fate of amine drugs in the natural waters.

Introduction

Pharmaceuticals and personal care products (PPCPs) are the subject of increasing concern and scientific interest (1, 2). There are numerous reports concerning the occurrence of PPCPs in the wastewater treatment plants (WWTP), surface water, groundwater, and drinking water every year. Although they were generally detected in the ng– $\mu\text{g/L}$ range, the continual infusion into the aquatic environment leads to the chronic exposure of nontarget organisms in the waters with largely unknown consequences (3, 4). As one subset of the PPCPs pollutant class, the amine drugs have been widely used and repeatedly found at concentration ranging from 0 to 2.5 $\mu\text{g/L}$ (5–12). The structures of the amine drugs are shown in Figure 1. Until recently, except that direct pho-

todegradation of propranolol was documented (13), fairly little is known about the environmental fate of these amine drugs.

Recent studies have demonstrated that certain pharmaceuticals are susceptible to photodegradation in the aquatic environment (14–16). Therefore, direct and indirect photochemical reactions may contribute to the transformation of these compounds in sunlit surface waters. The numerous studies have identified humic substances (HS) and NO_3^- as significant participants in the indirect photodegradation of pollutants (17, 18). Both of them can photogenerate the highly reactive, nonselective $\cdot\text{OH}$ thereby limiting the persistence of many pollutants that degrade relatively slowly by direct photolysis (19, 20). Additionally, photolysis of HS leads to the formation of other reactive species, including $^1\text{O}_2$ (21), $\text{O}_2^{\cdot-}/\text{HO}_2^{\cdot}$ (22), H_2O_2 (23), e_{aq}^- (24), and the reactive HS triplet states ($^3\text{HS}^*$), of which $\text{O}_2^{\cdot-}/\text{HO}_2^{\cdot}$, H_2O_2 , and e_{aq}^- may play a minor role in the sunlit surface waters (25). Direct reactions between $^3\text{HS}^*$ and organic substrates are likely to occur. They can be classified as energy, electron or hydrogen atom transfer reactions (25). Although there have been many studies proving the enhancement effects of HS on photolysis of the substrates (26), the photochemical mechanism underlying the degradation is still not well understood. To date, most of the concerns were the phenolic compounds for the enhanced degradation mediated by HS (17, 26–28), and some phenols have been demonstrated to be degraded via electron transfer mechanism (28).

In this work, a class of amine drugs including primary, secondary, and tertiary amines was selected for study based on the likelihood that they would undergo photodegradation due to their structural moieties in the presence of HS. The photodegradation mechanism was elucidated in detail. The relationship between structure and activity for the reaction of amine drugs with HS was preliminarily examined in order to predict the propensity of various amines toward photo-oxidation in the sunlit surface waters. Major degradation products were identified by GC-MS analysis. The bimolecular rate constants (reaction with $\cdot\text{OH}$ and $^1\text{O}_2$) and apparent quantum yields of the indirect photodegradation for amine drugs were determined to predict the photochemical fate of amine drugs in the natural waters.

Experimental Section

Materials. Mexiletine (99%), propranolol (99%), diphenhydramine (99%), phenytoin (dilantin, 99+%), and antipyrine (phenazone, 99%) were purchased from Acros. Acetophenone (99.9+%), 2-propanol (99+%), and humic acid sodium (HA) were purchased from Aldrich. Fulvic acid (FA) was obtained from Henan ChangSheng Corporation. Ferrous sulfate ($\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$), Rose Bengal, furfural alcohol (FFA), potassium nitrate were obtained from Beijing Chemicals Corporation. All chemicals used were of purity at least analytical-reagent grade.

Photolysis Experiments. The photochemical experiments were performed in a 60 mL capped cylindrical Pyrex vessel (40 mm i.d., containing 50 mL of solution). The light source was a 150 W Xenon Short Arc Lamp. The light of wavelengths less than 300 nm was filtered with the Pyrex glass to simulate the sunlight. Lamp output was monitored over time by ferrioxalate actinometry (29). The deoxygenated condition was achieved by bubbling nitrogen into the solution. In general, 5 μM substrates were irradiated in phosphate (10 mM) buffered solutions in the presence of HA and FA (5 mg/L DOC). Inhibition experiments were carried out with addition of 10 mM 2-propanol. Aliquots of samples (~300

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FIGURE 1. Molar extinction coefficients and molecular structures of amine drugs: (a) mexiletine; (b) propranolol; (c) diphenhydramine; (d) phenytoin; (e) antipyrine.

μL) were withdrawn at various intervals and substrate decay was measured by high performance liquid chromatography.

Analytical Procedures. UV-vis spectra were recorded on a Hitachi U3100 spectrophotometer. Phosphorescence spectrum of diphenhydramine was measured in a methanol-ethanol glass at 77 K on a Hitachi F-4500 FL spectrophotometer. The excitation wavelength was set at 235 nm. The triplet state energy corresponds to the highest energy band maximum in the phosphorescence spectrum. The concentration of each amine drug was measured by HPLC, Agilent 1200 equipped with a UV-absorbance detector and a Zorbax SB-C18 column ($5\ \mu\text{m}$, $250 \times 4.6\ \text{mm}$). The mobile phase was a mixture of acetonitrile and pH 2.5 KH_2PO_4 buffer with a ratio of 35:65 for all amine drugs except phenytoin (60:40). The flow rate of was 1.0 mL/min and the detection wavelength was 220 nm. GC-MS analysis procedures were shown in the Supporting Information.

Determination of Rate Constant. $\cdot\text{OH}$ and $^1\text{O}_2$ reactions rate constants for each amine drug were determined using Fenton's reagent and Rose Bengal, respectively (30, 31). The detailed procedures were shown in the Supporting Information.

Results and Discussion

Reactions with $\cdot\text{OH}$ and $^1\text{O}_2$. The bimolecular rate constant for the reaction between each amine drug and $\cdot\text{OH}$ was determined by competition kinetics according to eq 1:

$$k_{\text{OH}}^{\text{S}} = \frac{\ln([S]_t/[S]_0)}{\ln([R]_t/[R]_0)} k_{\text{OH}}^{\text{R}} \quad (1)$$

where S is the substrate and R is the reference compound acetophenone with a known rate constant for reaction with $\cdot\text{OH}$ ($k_{\text{OH}} = 5.9 \times 10^9\ \text{M}^{-1}\ \text{s}^{-1}$) (32). The plots of $\ln([S]_t/[S]_0)$ versus $\ln([R]_t/[R]_0)$ for the amine drugs were shown in Figure S1 of the Supporting Information. The $\cdot\text{OH}$ reaction rate constants for the amine drugs range from $(2.1 \pm 0.2) \times 10^9$ to $(8.7 \pm 0.3) \times 10^9\ \text{M}^{-1}\ \text{s}^{-1}$ (Table S1 of the Supporting Information).

The determination of rate constants for reaction between each amine drug and $^1\text{O}_2$ was conducted in the Rose Bengal solution (Figure S2 of the Supporting Information). The depletion of substrate upon reaction with $^1\text{O}_2$ was simultaneously monitored alongside the reaction of a reference compound FFA, with a known rate constant for reaction with $^1\text{O}_2$ ($1.2 \times 10^8\ \text{M}^{-1}\ \text{s}^{-1}$) (33). The light below 400 nm was removed by a filter ($\lambda > 400\ \text{nm}$, Shanghai Seagull Colored Optical Glass Co., Ltd.) to avoid the direct photodegradation. The results indicated that the amine drugs did not react with $^1\text{O}_2$ significantly except propranolol with a low rate constant (Table S1 of the Supporting Information).

TABLE 1. Photodegradation of Amine Drugs in the Presence of Natural Environmental Substances^a

compound	systems ^b	$k_{\text{obs}}(\text{h}^{-1})$	$t_{1/2}(\text{h})$	$\phi_{\text{amine}}^{\text{c}}$ ($\times 10^5$)
mexiletine	light control	nd ^d	nd	nd
	HA	0.003	231	0.1
	FA	0.029	23.9	0.83
	NO_3^-	0.020	34.6	nm ^e
propranolol	light control	0.069	10	222 ^f
	HA	0.033 ^g	21	1.2
	FA	0.230 ^g	3	6.6
	NO_3^-	0.066	10.5	nm
diphenhydramine	light control	nd	nd	nd
	HA	0.008	86.6	0.29
	FA	0.128	5.4	3.7
	NO_3^-	0.055	12.6	nm
phenytoin	light control/HA/FA	nd	nd	nd
	NO_3^-	0.057	12.2	nm
antipyrine	light control/HA/FA	nd	nd	nd
	NO_3^-	0.042	16.5	nm

^a Results are the means of triplicate measurements in pH 8 phosphate (10 mM) buffered solutions in the air atmosphere except NO_3^- system ($n = 2$). ^b Concentrations of HA and FA were 5 mg/L (DOC), respectively; the nitrate concentration was 1 mM; no dark reaction was observed. ^c Apparent quantum yields obtained over the wavelength range above 300 nm, $I_0 = 2.5 \times 10^{-7}\ \text{einstein/min}$. ^d nd, Not detected. ^e nm, Not measured. ^f Taken from ref 34. ^g Value was obtained by subtracting direct photolysis from the total degradation according to the fraction of absorbed light by propranolol.

Kinetics of Photodegradation. Photodegradation of amine drugs in the presence of humic substances and nitrate under simulated sunlight were shown in Table 1. The pseudofirst-order rate constants were obtained after 14 h irradiation of the amine drugs in the air-saturated aqueous solutions. It was expected that the degradation of each amine drug occurred in the nitrate solution and was positively correlated with the k_{OH} , since the bimolecular rate constants for reactions with $\cdot\text{OH}$ approach diffusion-controlled limits. In contrast, only mexiletine, propranolol, diphenhydramine could be degraded in the presence of HA and FA, while the depletion of phenytoin and antipyrine was negligible under the same conditions. Except propranolol, no direct photodegradation was observed for the other four amine drugs due to no appreciable light absorption over $\lambda > 300\ \text{nm}$ (Figure 1). The direct photolysis of propranolol was comparable to the indirect photodegradation in the presence of nitrate and HA, but much slower compared with the degradation in the presence of FA. The indirect photolysis rate of the amine drugs in the HS solution was in the order: propranolol > diphenhydramine > mexiletine. The reaction rate constants were about 10-fold higher in the presence of FA than in the presence of HA, which was in agreement with the photodegradation of 2, 4, 6-trimethylphenol and phenylurea derivatives under polychromatic light (27, 35). This was partly ascribed to the slightly higher molar extinction coefficient of FA compared with HA (Figure S3 of the Supporting Information). Additionally, it was suggested that there were more reactive chromophoric groups in FA than that of HA contributing to the photodegradation. To assess the photodegradation efficiency of each amine drug in the HS solution, the average apparent quantum yield of photodegradation (ϕ_{amine}) was measured under irradiation ($\lambda > 300\ \text{nm}$) by dividing the rate of amine

drugs depletion (r_{amine}) by the photon flux rate absorbed by HS (27). It was written as

$$\phi_{\text{amine}} = \frac{r_{\text{amine}}}{(I_0/V) \times \sum F_{\lambda}(1 - 10^{-\varepsilon_{\lambda}bc})} \quad (2)$$

where V is the volume of the reaction solution, (I_0/V) is the photon flux rate expressed in Einstein $\text{L}^{-1}\text{s}^{-1}$ and obtained by actinometry, F_{λ} is the spectral distribution of the light emitted by the lamp, ε_{λ} is the molar extinction coefficient at specific wavelength, b is the path length. The apparent quantum yields of amine drugs, which were dependent on the light absorption rate of HS and the reaction rate of substrates, were listed in Table 1.

Reaction Mechanism with the HS Triplet States. The kinetic experiments showed that all of the amine drugs were degraded in the nitrate solution for the high reaction rate constants with $\cdot\text{OH}$. However, in the presence of HA and FA, both phenytoin and antipyrine were not depleted, while the degradation of mexiletine, propranolol, and diphenhydramine occurred, indicating that $\cdot\text{OH}$ was not the primary specie responsible for the latter reactions. The role of $^1\text{O}_2$ could be excluded in the HS-mediated photodegradation due to the unappreciable or too weak reactions between the amine drugs and $^1\text{O}_2$.

It is well-known that oxygen is the quencher of most triplet states of organic compounds (27, 36). Figure 2 shows the contrast of photodegradation for the three drugs in the air-saturated and deoxygenated aqueous HS solutions. Obviously, the reactions of mexiletine, propranolol, and diphenhydramine were drastically enhanced in the deoxygenated solutions. For example, the photodegradation rate increased 42-fold and 50-fold for diphenhydramine in the HA and FA solution after removing the oxygen, respectively. Furthermore, the addition of the $\cdot\text{OH}$ inhibitor 2-propanol did not

FIGURE 2. Comparison of pseudofirst-order rate constants for the photodegradation of the amine drugs in the presence of HA (a) and FA (b) at air and nitrogen atmospheres (with and without 10 mM 2-propanol). Error bars indicate 95% confidence intervals for $n = 3$.

FIGURE 3. Relationship between photolysis of amine drugs in the presence of the model sensitizer acetophenone (a), HA (b), and FA (c) and their deprotonated forms (d) in deoxygenated aqueous solutions with various pH: (■) mexiletine, (●) propranolol, and (▲) diphenhydramine. Initial conditions: 5.0 μM amine drugs, 85 μM acetophenone, 5 mg/L (DOC) HA and FA, respectively. The fraction of deprotonated form of each amine drug was calculated according to the pK_a of the amine drugs (mexiletine, 9.2; propranolol, 9.5 and diphenhydramine, 9.0, see ref 40). Error bars indicate 95% confidence intervals for $n = 3$.

suppress the depletion of the three amine drugs in the HA and FA solutions (Figure 2a and b). Therefore, the contributions of primarily HS derived reactive photooxidants including $\cdot\text{OH}$ and $^1\text{O}_2$ were of negligible importance for the photodegradation of mexiletine, propranolol and diphenhydramine in the HS solution. These results verified that the amine drugs reacted almost exclusively with $^3\text{HA}^*$ and $^3\text{FA}^*$ in the aqueous solutions.

The mean value of triplet state energy for HS was estimated to be 170–180 kJ/mol, and a significant fraction of HS triplet states was found to be above 250 kJ/mol (28). The triplet state energies of the amine drugs for diphenhydramine and propranolol were estimated to be 341 and 266 kJ/mol, according to the phosphorescence spectrum in this study (Figure S4 of the Supporting Information) and elsewhere (37). The triplet state energies were much higher than that of HS. Accordingly, direct reaction for diphenhydramine and propranolol following energy transfer from the excited triplet states ($^3\text{HA}^*$ and $^3\text{FA}^*$) to amine drugs could not occur.

Nevertheless, the electron transfer mechanism was possibly responsible for the photodegradation of amine drugs in the HS solution. It has been well established that the photoreaction between photoexcited aromatic ketones and amines proceeds by initial rapid charge-transfer interaction from the N-electrons of the amines to the excited aromatic ketone, followed either by transfer of α -hydrogen and formation of radicals, or by charge destruction and quenching (38). If α -hydrogen is not present in the structure, the amines only act as quenchers (39). Accordingly, the photodegradation of amines in the presence of aromatic ketone depends on

FIGURE 4. The proposed pathway for the indirect photodegradation of propranolol in the HS solution.

FIGURE 5. The proposed pathway for the indirect photodegradation of diphenhydramine in the HS solution.

two factors: the presence of α -hydrogen and the availability of N-electrons of amines.

In this experiment, some representative amine drugs were chosen to obtain a better insight into the intrinsic mechanism for the reactions with the triplet excited ketones of HS, including primary amine (mexiletine), secondary amine (propranolol, phenytoin), and tertiary amine (diphenhydramine, antipyrine) with and without α -hydrogen (phenytoin). The results of kinetic experiments were in good accordance with the electron transfer mechanism mentioned above. The lack of α -hydrogen for phenytoin rendered it to be inert in the HS solution. Although antipyrine has the potentially transferable α -hydrogen, it resembled phenytoin rather than the other amine drugs and was not photodegraded under otherwise identical conditions. This may be attributed to the p - π conjugation of C—N bond in the penta-heterocycle of antipyrine (Figure 1). The conjugation effect made the N-electrons of antipyrine become less available. Moreover, the reaction rate for the three drugs in the deoxygenated aqueous HS solution was in the order: diphenhydramine > propranolol > mexiletine (Figure 2). This was in satisfactory agreement with the common reaction order, namely, tertiary amine > secondary amine > primary amine for the photooxidation of amines by ketones sensitizer in various deoxygenated organic solutions (39). It has been demonstrated that the p - π conjugation effect was unfavorable to the photooxidation of the amine drugs. Equally, hydrogen bonding to the N-electrons was postulated to hinder the N-electrons transfer, thereby inhibiting the photodegradation of the three amine drugs. As shown Figure 3a, in the presence of model sensitizer acetophenone, the photodegradation of the three drugs increased with increasing pH, corresponding to the increasing fraction of deprotonated form of each amine drug (Figure 3d). In the tested pH range, the form of acetophenone kept constant, thus the quantum yield of triplet state acetophenone did not vary within the pH range. Therefore, the increase of the photodegradation for the three drugs was attributed to the increasing deprotonated form of them. The similar results were obtained in the HA and FA solutions (Figure 3b and c).

This result verified again the electron transfer mechanism for the photodegradation of mexiletine, propranolol and diphenhydramine in the HS solution.

Photodegradation Products and Pathway. To obtain a further insight into the mechanism of the reactions and the photochemical fate of the amine drugs, the main photodegradation products for different substrates in the nitrate and HS solutions were identified by GC-MS, respectively. In the presence of nitrate, for propranolol, diphenhydramine and phenytoin, most of the intermediates were identified as aliphatic acid, alcohol and aromatic acid (Table S2a–c of the Supporting Information). The results showed that the photodegradation in the nitrate solution proceeded by the cleavage of the branching chain and the heterocyclic part of the parent compounds, followed by the opening of part phenyl rings into the hydroxylation production. No nitration or nitrosation products were identified for all samples. Differently, in the HS solution, there were not products to be detected from the cleavage of the phenyl rings. For propranolol, the photoproducts included naphthalen-1-ol and 2-hydroxypropionic acid. Moreover, for diphenhydramine, the photoproducts were diphenylmethane, diphenylmethanol and benzophenone (Table S3a and b of the Supporting Information).

Combined the main intermediates identified by GC-MS with the electron transfer mechanism, the photodegradation pathways for propranolol and diphenhydramine in the HS solution were proposed. For propranolol, the first step was the charge-transfer interaction between the excited HS and the N atom of the amine drug (process a), followed by a rapid transfer of α -hydrogen to form a carbon radical intermediate (process b). The subsequent cleavage of C—O bond of propranolol led to naphthalen-1-ol (Figure 4). For diphenhydramine, after the similar processes to propranolol (process a and b), a dislocated π bond was suggested to be generated (process c), and simultaneously decomposed into diphenylmethane, diphenylmethanol and benzophenone (process d, Figure 5).

Environmental Significance. The data strongly suggest the impact of HS triplet states on the environmental fate of mexiletine, propranolol and diphenhydramine in the sunlit

surface waters. The other degradation pathways such as reaction with $\cdot\text{OH}$ and $^1\text{O}_2$ (if possible) are of less important due to the low concentrations of these reactive species in the natural waters and thus comparatively long half-lives for the amine drugs (Table S4 of the Supporting Information). In this study, FA is a more efficient sensitizer for photodegradation compared with HA. Accordingly, the composition of the HS, along with the season and latitude exerts great influence on the photodegradation of the three amine drugs. For phenytoin and antipyrine, the degradation was primarily due to reaction with $\cdot\text{OH}$ in the natural waters with half-lives ranging from 25 to 3700 h. This appeared to explain that phenytoin and antipyrine was repeatedly detected in the natural waters (6–9).

The structurally similar amine drugs, especially the tertiary and secondary amines, were expected to be degraded in the presence of HS. The reaction may be related to the steric structure of amines. The presence of transferable α -hydrogen was necessary for the reaction with triplet states of HS. The reaction rate will be dependent on the availability of the N-electrons of the amines. The results presented here demonstrated that HS could be a key factor to account for the fate of amines in the natural waters.

Acknowledgments

This work was supported by the National 863 Project of China (Grant No. 2006AA06Z304).

Supporting Information Available

Four figures and seven tables on the determination of radical rate constants, molar extinction coefficients of HS, phosphorescence spectrum of diphenhydramine and reaction products in both nitrate and humic acid solutions. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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ES803325J