HIGH ENERGY IONIZING RADIATION INDUCED DEGRADATION OF ß-BLOCKERS IN AQUEOUS SOLUTIONS

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Abstract
Degradation reactions of two beta-blockers, atenolol and propranolol were studied using high energy ionizing irradiation interpreting the outcome of the ongoing radical reactions on the degradation efficiency, oxidation and mineralization processes and toxicity. Under appropriate conditions both hydroxyl radical ($^{\bullet}OH$) and hydrated electron (e_{aq}^{-}) take part in degradation reactions. Propranolol showed higher reactivity under both oxidative end reductive conditions than atenolol. Thus it is not surprising that the oxidation and mineralization reactions take place more rapidly due to its condensed ring having higher electron density on the aromatic ring in propranolol. During removal of propranolol toxic products, hydroxylated naphthalene derivatives form. Using appropriate doses the starting molecules can be degraded and the toxic character of the end-products can be eliminated.

Introduction
Beta-blockers are applied for treatment of cardiovascular diseases. These molecules contain an aromatic ring and an oxypropanolamine side chain. Both beta-blockers and their metabolites can be detected in wastewater effluents and surface waters in ng-µg dm^{-3} concentration level [1-2]. Their elimination has been already investigated by a wide range of Advanced Oxidation Processes [3-5].
In this study the removal efficiency and degradation mechanism of two frequently used beta-blockers, atenolol and propranolol was investigated in details supplemented by monitoring the change of the organic content and the toxicity.

Experimental
Atenolol and propranolol dihydrochloride were obtained from Sigma-Aldrich. *Tert*-butanol was produced by Molar Chemicals, it was used in order to remove the hydroxyl radicals from the system when the hydrated electron reactions were studied. In pulse radiolysis experiments buffer solution was used from K_2HPO_4 and KH_2PO_4. Purified water with a conductivity of 0.055 µS cm^{-1} and total organic content of < 2 ppb was provided by an Adrona B30 system. The solutions were air equilibrated or bubbled with N_2 or N_2O continuously during the measurements depending on the reaction investigated.
Pulse radiolysis experiments were performed using 4 MeV accelerated electrons with electron pulse length of 800 ns and an optical system with 1 cm path length cell [6-7]. The measurements were performed in 0.1 mmol dm^{-3} atenolol and propranolol solutions at pH 7. The formation and decay of the transient intermediates were monitored in the reactions of atenolol and propranolol under oxidative and reductive conditions. The rate constants for these reactions were measured by transient kinetic measurements.
The γ-radiolysis experiments were carried out in a panoramic type ^{60}Co γ-chamber with a dose rate of 10 kGy h^{-1} at room temperature. The reactions of various reactive intermediates from water radiolysis were studied under specific reaction conditions. In N_2 saturated solutions all

the three radical intermediates of water radiolysis, hydroxyl radical, hydrated electron and hydrogen atom are reacting agents. In the presence of *tert*-butanol e_{aq}^- is the main reaction partner, but there is a small contribution from the H$^\bullet$ reactions. In the presence of O_2, i.e., in air equilibrated solutions e_{aq}^- and H$^\bullet$ transform to the low reactivity $O_2^{\bullet-}/HO_2^\bullet$ pair (pK_a = 4.8). Hydroxyl radical reactions are generally investigated in N_2O saturated solutions [8-9].
The end-products were featured by ultraviolet–visible (UV–Vis) measurements, chemical oxygen demand (COD), total organic carbon (TOC) and toxicity. The un-irradiated solutions and solutions irradiated under different conditions were measured by a JASCO 550 UV-Vis spectrophotometer in 1 cm cell. In COD and TOC measurements a Behrotest TRS 200 COD system and a Shimadzu TOC-LCSH/CSN equipment was applied. In acute toxicity tests *Vibrio fischeri* luminescent bacteria was used as test organism detecting the changes in the luminescence of the bacteria, caused by the chemicals tested.

Results and discussion

Pulse radiolysis

In N_2O saturated solutions (c = 0.1 mmol dm^{-3}) the reactions of $^\bullet$OH with atenolol and propranolol were studied, respectively (Fig. 1, A and B). In the case of atenolol a wide, double band with maxima at 310 and 325 nm was observed. For propranolol a more narrow, sharp peak appeared at $\lambda_{max} \approx 325$ nm with a shoulder at the longer wavelength side and a wide and a flat band at 380 nm. Similar transient absorption spectra with two bands at 320 and 370 nm were measured in aqueous naphthalene solution [10-11]. The transient absorbances in Fig. 1 decayed on the several times 100 µs timescale, during the decay no major changes in the shapes of the spectra were observed. In the reaction between aromatic molecules and $^\bullet$OH several hydroxycyclohexadienyl isomers form, these intermediates exhibit light absorption in the of 300-400 nm range.

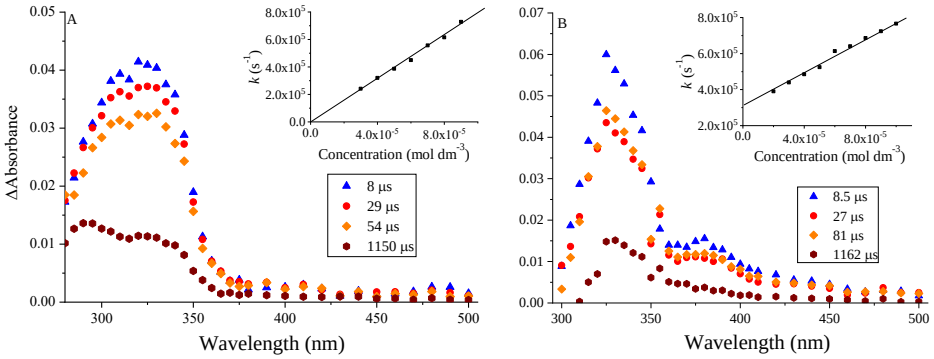

Figure 1. Absorption spectra of transient intermediates of $^\bullet$OH reactions in N_2O saturated, 0.1 mmol dm^{-3} atenolol (A) and propranolol (B) solutions, respectively. Insets: concentration dependence of pseudo-first-order rate constant of product build-up at 325 nm for both molecules.

The e_{aq}^- reactions were also studied for both beta-blockers (not shown). For atenolol very weak absorbances were measured in the 300-350 nm range, whereas a strong absorption spectrum can be observed at 325 nm and 380 nm appeared in the e_{aq}^- + propranolol reaction, similar to that obtained in the $^\bullet$OH + propranolol reaction (Fig. 1 B). Protonation of electron adduct is expected to give similar radical intermediate that also forms in H-atom addition to the naphthalene unit.
Kinetic measurements were carried out to determine the rate constant of $^\bullet$OH and e_{aq}^- reactions. In $^\bullet$OH reactions the second-order rate constants were found to be 4.80×10^9 and 7.55×10^9 mol^{-1} dm^3 s^{-1} for atenolol and propranolol, respectively (Fig. 1 Insets). This

difference can be interpreted by the chemical structure of the two molecules: propranolol possesses a condensed ring with higher electron density and more vulnerable sites than atenolol having a simple aromatic ring. In e_{aq}^- reactions the rate constants of 5.8×10^8 mol^{-1} dm^3 s^{-1} and 8.6×10^9 mol^{-1} dm^3 s^{-1} were measured for atenolol and propranolol, respectively.

UV-Vis measurements

The effect of different reaction conditions on the degradation efficiency was followed up by UV-Vis measurements (Figures 2 and 3). In the UV spectra there are two absorption bands for atenolol: one at 225 nm, and a second one (the typical wide aromatic band) is between 250 and 290 nm. In the case of propranolol both bands are wider, they are at 221 nm and between 250 and 320 nm. When ˙OH participated as a reacting agent in the degradation (in air, N_2 and N_2O saturated solutions) slight shifts of the absorbance maxima were observed to the longer wavelengths. This shift can imply the presence of forming hydroxylated products in irradiated solutions having absorbance maxima at longer wavelengths than the initial molecule. In such solutions increase in the baseline was also marked due to the light scattering in the presence of some badly soluble products. When ˙OH is the main initiating radical about 1 kGy dose is sufficient to degrade practically all the initial atenolol or propranolol molecules.

In N_2 saturated solutions containing *tert*-butanol (reaction partner e_{aq}^-) different changes can be observed. The hydrated electrons practically do not degrade atenolol. By contrast, abatement and shift of the band between 250 and 320 nm to lower wavelengths can be observed in the case of propranolol. This degradation is almost as intensive as in the case of ˙OH reaction.

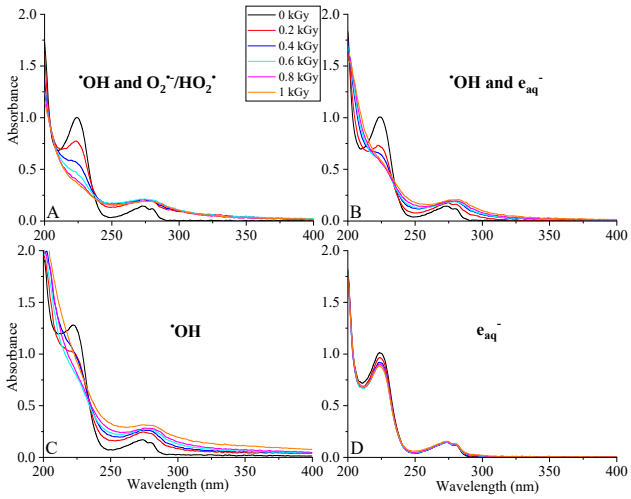

Figure 2. UV-Vis absorption spectra in 0.1 mmol dm^{-3} irradiated atenolol solutions under different conditions in the 0-1 kGy dose range: ˙OH and $O_2^{\bullet-}$/$HO_2^{\bullet}$ (A), ˙OH and e_{aq}^- (B), ˙OH (C) and e_{aq}^- (D).

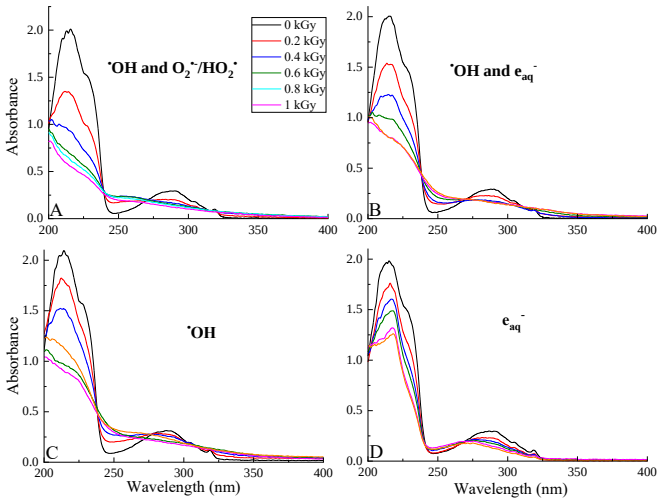

Figure 3. UV-Vis absorption spectra in 0.1 mmol dm^{-3} irradiated propranolol solutions under different conditions in the 0-1 kGy dose range: $^{\bullet}OH$ and $O_2^{\bullet-}/HO_2^{\bullet}$ (A), $^{\bullet}OH$ and e_{aq}^- (B), $^{\bullet}OH$ (C) and e_{aq}^- (D).

Oxidation and mineralization

In the presence of O_2 the solutes gradually transform to more and more oxidized molecules (oxidation), finally they end up as inorganic species, H_2O, CO_2, etc. (mineralization). The oxidation and mineralization are often followed up by the changes in the dissolved O_2 and organic carbon atom contents of the solutions using chemical oxygen demand (COD, mg O_2 dm^{-3}) and total organic carbon (TOC, mg C dm^{-3}) measurements (Fig. 4). Both the COD and TOC values decrease with the increasing dose. The initial rates of oxidation were 8 and 13 mg dm^{-3} kGy^{-1} in atenolol and propranolol solutions. At the early stage of the degradation mainly the initial compound and its slightly transformed products are present in the solution which oxidize more readily than the small molecular fragments (aldehydes, carboxylic acids, etc.) dominating the organic content present at higher doses [12]. At 10 kGy, 58.8 and 65.4% COD decline was observed in aerated solutions for atenolol and propranolol, respectively.

The TOC values decrease almost linearly in the dose range investigated. The mineralization rates were 0.9 and 1.4 mg C dm^{-3} kGy^{-1} for atenolol and propranolol, respectively, the processes were more effective in the case of propranolol.

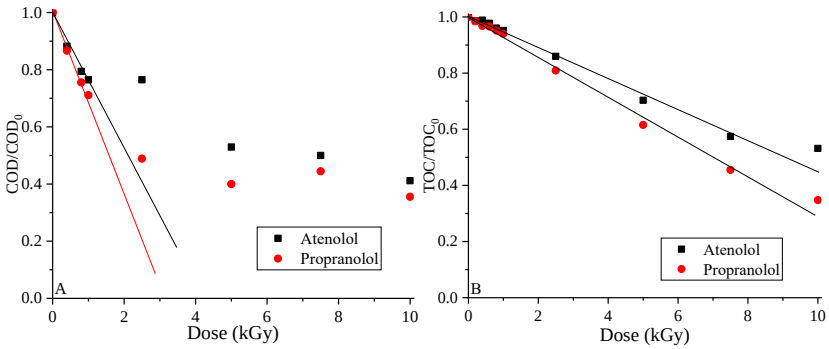

Figure 4. The dose dependence of the oxidation and mineralization in aerated, 0.1 mmol dm^{-3} atenolol and propranolol solutions.

Toxicity assays

Vibrio fischeri bioluminescence toxicity assays were applied to follow up the change of toxicity in irradiated solutions equilibrated with air. The initial concentration was 0.1 mmol dm^{-3} similar

to the former measurements. Neither atenolol, nor propranolol did show toxic effect in the initial concentration in agreement with their published high EC_{50} values, 5 and 0.3 mmol dm^{-3} for *Vibrio fischeri* [13]. In the case of atenolol luminescence inhibition of the degradation products was below 10% in the entire dose range. The products of propranolol were more toxic than the products of atenolol. In propranolol solutions irradiated with 0.4 kGy dose ~80% inhibition was observed. At higher doses the toxicity of products decreased below 15%.

Conclusion

Both atenolol and propranolol degrade *via* radiolytic processes in which $^{\bullet}OH$ may predominantly react with the aromatic ring in 0.1 mmol dm^{-3} aqueous solutions. Due to the presence of the condensed ring propranolol has higher reactivity towards both $^{\bullet}OH$ and e_{aq}^{-} than atenolol, thus the oxidation and mineralization reactions proceed also with higher rates in the case of propranolol. In the case of propranolol the end-products with high toxicity may also form at low doses as highly toxic hydroxylated naphthalene derivatives may evolve in $^{\bullet}OH$ reactions. Removal of atenolol and propranolol, as well as abolishment of the toxicity can be achieved using appropriate doses.

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