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Spectrophotometric studies on the photostability of some thiazide diuretics in ethanolic solution

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Abstract

First derivative and dual-wavelength spectrophotometric methods were used in the quantum yield determination of the photochemical decomposition reactions of three thiazide diuretics (chlorothiazide, hydrochlorothiazide and trichloromethiazide) in ethanolic solution. The radiation absorbed by the compounds was measured using iron(III) oxalate actinometry based on absorption spectrophotometry. An apparatus is described in which the drugs were irradiated in quartz cuvettes cooled by water in a stand built on a magnetic stirrer. The wavelength region available to the reaction cuvette was restricted to 313 nm with chemical potassium chromate filter solutions and a Corning filter plate. Chlorothiazide proved to be more photostable than hydrochlorothiazide and trichloromethiazide in ethanol.

Keywords: Thiazide diuretics; Photodecomposition; Spectrophotometry; Quantum yield

1. Introduction

Chlorothiazide (CT), hydrochlorothiazide (HCT) and trichlormethiazide (TCMT) are important diuretic drugs which are decomposed in ethanolic solutions under UV irradiation yielding several products [1,2]. The maxima of the UV spectra of the main products and of the product mixtures are at shorter wavelengths than those of the parent compounds. Depending on the spectrum of the product mixture first-derivative spectrophotometry or dual wavelength spectrophotometry gave comparable results to HPLC in the determination of the parent compounds in reaction mixtures where the decomposition degree was between 0 and 30% [3,4]. In this work I have studied the photostability of these compounds by using these spectrophotometric methods for the determination of the parent compounds and iron(III) oxalate actinometry based on absorption spectrophotometry for the measurement of the irradiation intensity.

2. Experimental

The parent compounds were obtained and investigated as previously described [3]. They were dissolved in 96% ethanol (Oy Alko, Helsinki, Finland). All other chemicals were of analytical-reagent grade. A Philips PU 8740 UV-vis spectrophotometer with derivative, dual-lambda and

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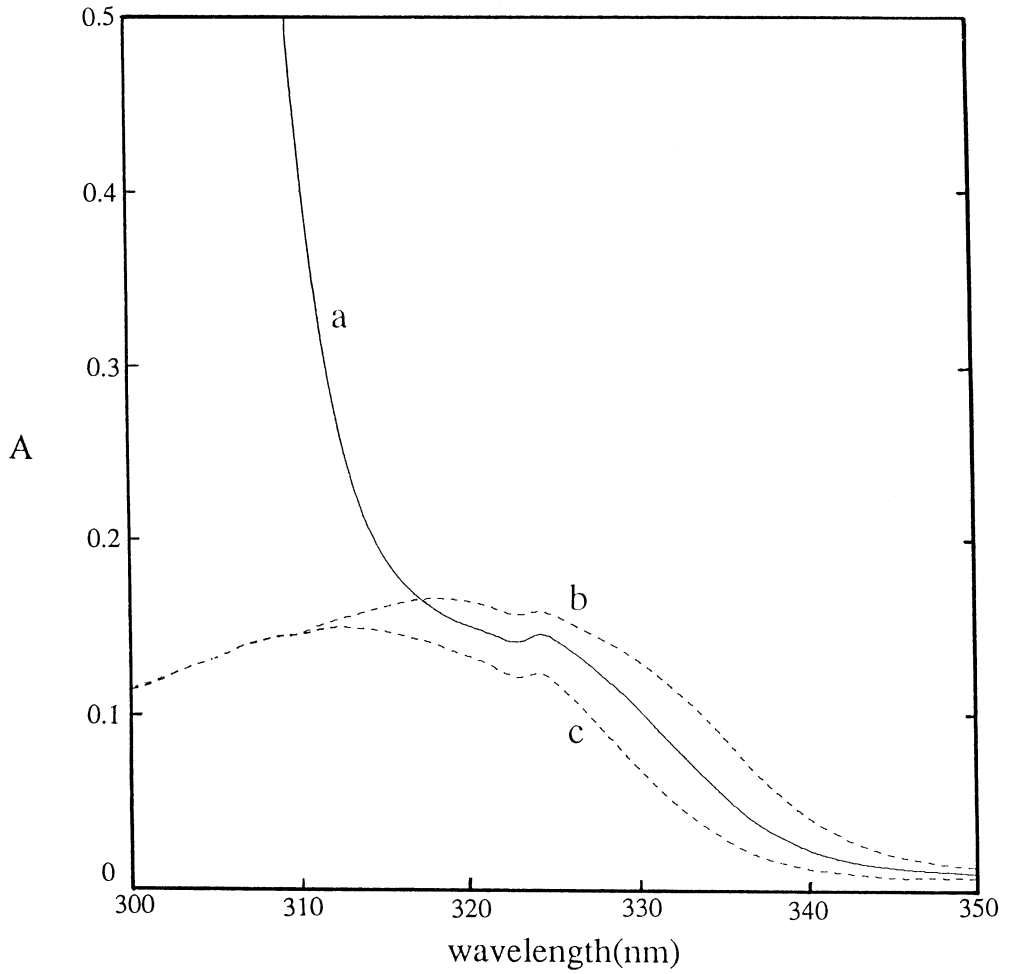


Fig. 1. UV absorption spectra of (a) CT, (b) HCT and (c) TCMT in the region 300–350 nm. The reference was 96% ethanol.

fixed lambda programs was used in the quantitative analyses. The slit width was 1.0 nm, the scan speed in the first-derivative analyses 125 nm min^{-1} and the smoothing setting was medium. Quartz cuvettes (10 mm i.d.) were used in the measurements and as reaction vessels. The irradiations were carried out at 313 nm, the main emission of the high-pressure mercury lamp (Original Hanau TQ-718 at 500 W) in the UV-B region near an absorption maximum of HCT and TCMT (Fig. 1). The 313 nm wavelength was isolated with a potassium chromate-Corning CS-7-54 filter combination [3]. A metallic stand inside of which cooling water circulated was built on a magnetic stirrer (Fig. 2). The flow-rate of the cooling water was adjusted so that the temperature of the solution to be irradiated was $+19 \pm 1$°C during the irradiations. A Corning filter plate was placed in front of the stand and of the light path and three quartz cuvettes closed with a cap aligned inside the stand according to the experimental arrangement presented by Moore [5]. The size of the rectangular opening behind the Corning filter was 8 mm × 25 mm and the inner sides of the stand were blackened in order to prevent reflections. The first cuvette contained the potassium chro-

mate filter solution, the second one the solution to be irradiated or ethanol and the third one an iron(III) oxalate solution. A small magnetic bar was placed into the second and third cuvettes. The stand was covered in order to prevent radiation from above. The distance of the stand from the lamp was varied by moving the stand along a support so that the extent of the photolysis reaction of the compounds was between 7 and 15%. For the CT solution the optimal distance was 10–15 cm and for the HCT and TCMT solutions 30–40 cm. The concentrations of the parent compounds were chosen so that the absorbance of the initial solutions was approximately 0.2 and was 0.05 mM for HCT and TCMT

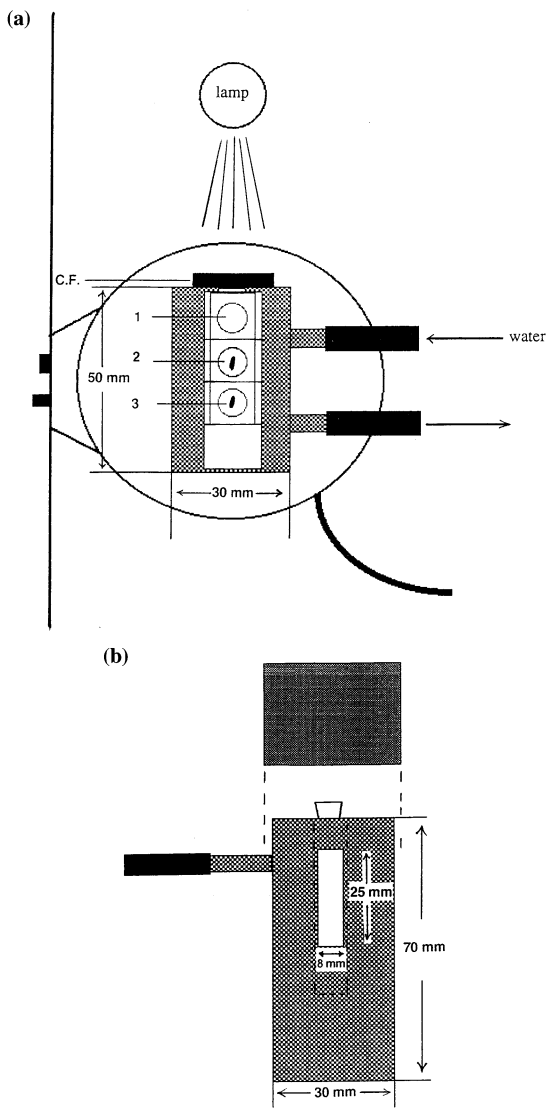
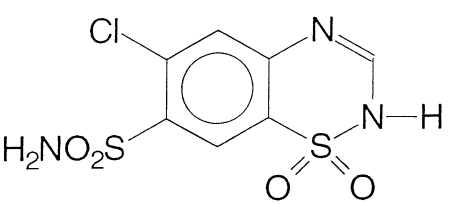
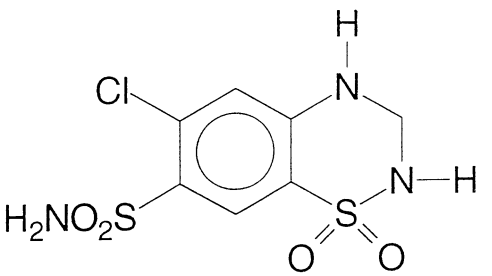


Fig. 2. Schematic representation of the irradiation apparatus used (a) from above and (b) from the front. C.F., Corning filter CS-7-54; (1) potassium chromate solution (5×10^{-4} M); (2) reaction cuvette; (3) iron(III) oxalate solution.

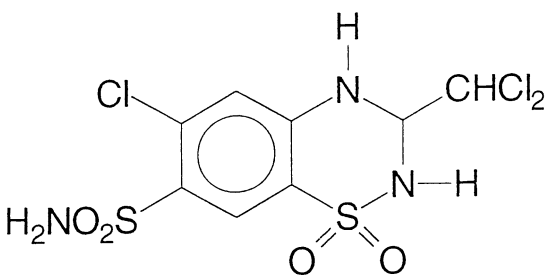
CT



HCT



TCMT



and 0.5 mM for CT. The absorbance of the 0.05 mM CT solution was only about 0.02 and the absorbed radiation could not be determined reproducibly. The concentrations of HCT were calculated based on the first-derivative values of the

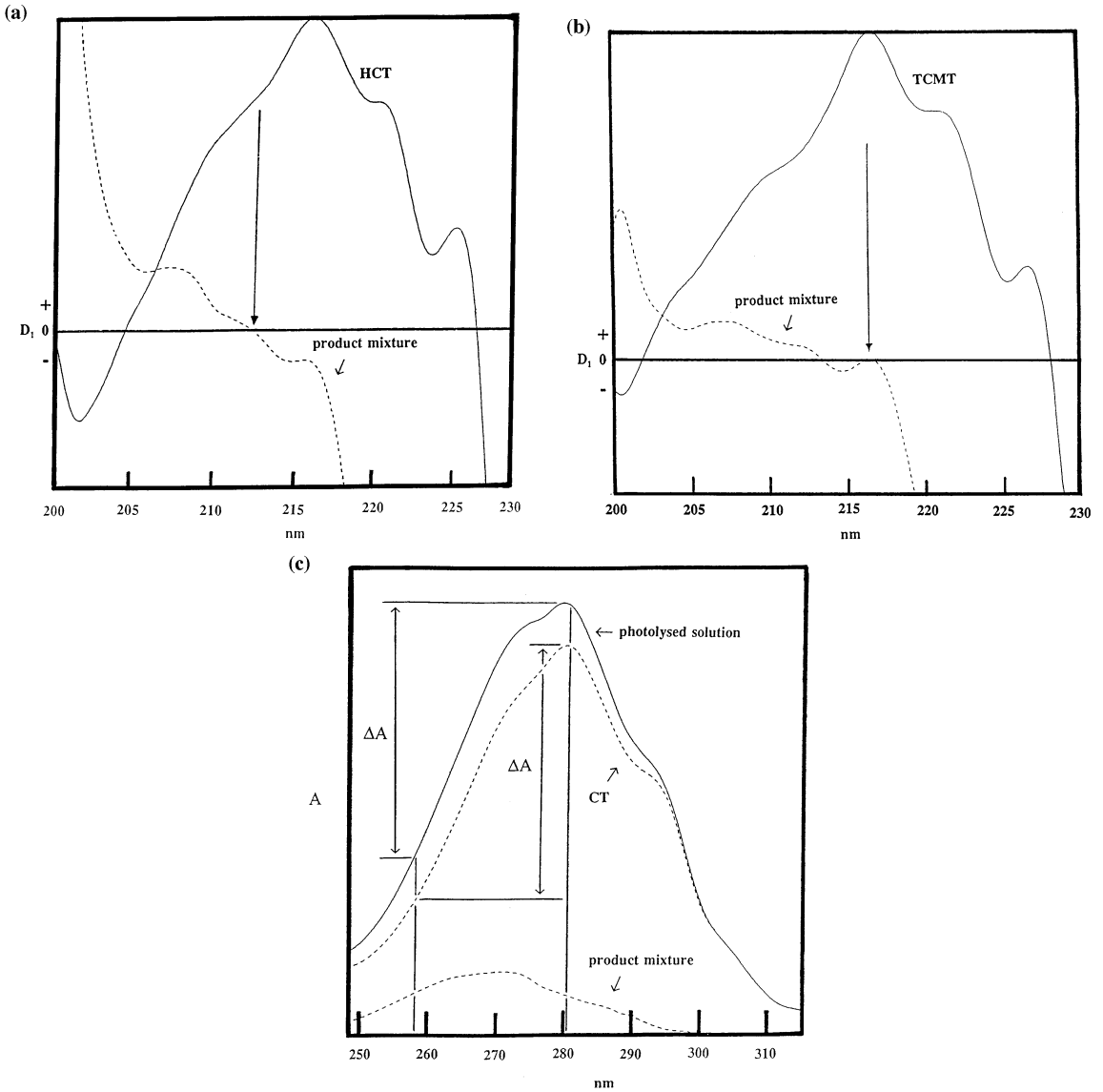


Fig. 3. First-derivative spectra of (a) HCT, (b) TCMT and of their product mixtures and (c) absorption spectra of CT and of its product mixture and of the photolysed CT solution.

photolysed solutions at the zero-crossing point of the product mixture, which was 213 nm and those of TCMT at 216 nm. HCT and TCMT were also investigated at a concentration of 0.15 mM. The absorbance of these solutions was about 0.5. For the determination of the parent compounds 2.5 ml of these solutions was diluted to 10.0 ml. The 0.5 mM CT solutions were first diluted 10-fold and the concentrations of the parent compound were determined based on the absorbance difference $A_{280.5} - A_{258}$ of the photolysed solutions (Fig. 3).

The preparation of the iron(III) oxalate actinometer and the measurement of the irradiation intensity was carried out in a dark room according to Kuhn et al. [6]. When the lamp was started, a shield was kept in front of the stand for 15 min.

Thereafter, when the lamp had reached constant intensity, the shield was removed and the solutions were irradiated for 4–20 min. 3 ml of the 0.006 M actinometer solution was placed into cuvette 3. The difference between the irradiation intensities when cuvette 2 was filled with 3.0 ml ethanol and when the same cuvette was filled with 3.0 ml of the thiazide solution represents the radiation absorbed by the drug. 1 ml of the actinometer solution was transferred into a 10 ml volumetric flask containing a mixture of 0.1% *o*-phenanthroline solution (4.0 ml) and a buffer solution (0.5 ml). The solution was diluted to volume with water and the absorbance of the complex between phenanthroline and iron(II) ions formed was measured after 30 min against a blank containing 1.0 ml iron(III) oxalate solution which had not been irradiated. The quantum yields were calculated as follows:

$$\Phi = \frac{\text{number of molecules decomposed s}^{-1}}{\text{number of photons absorbed s}^{-1}}$$

3. Results and discussion

The photodecomposition of the 0.5 and 0.05 mM solutions of the compounds appears to proceed according to first-order kinetics (unpublished results). In this work HCT was studied at the 0.05 mM concentration level in the intensity range of 2.0×10^{14}–8.7×10^{14} photons s^{-1} 3 ml^{-1} and at the concentration level 0.15 mM in the range of 6.8×10^{14}–9.0×10^{14} photons s^{-1} 3 ml^{-1}. For TCMT the corresponding ranges were 2.3×10^{14}–8.7×10^{14} photons s^{-1} 3 ml^{-1} and 6.2×10^{14}–1.1×10^{15} photons s^{-1} 3 ml^{-1}. Because of greater photostability of the 0.5 mM CT solution a sufficient reaction velocity was achieved at intensities 3.3×10^{15}–6.6×10^{15} photons s^{-1} 3 ml^{-1}. The quantum yields are presented in Table 1. The values of TCMT are slightly higher than those of HCT at both concentration levels studied and more than triple compared to the 0.5 mM CT solution. Although CT was not irradiated in the same molar concentrations as the other two compounds, and thus any possible concentration effect is not known, it is obvious that the difference between CT and the others can mainly be explained by the different nature of the decomposition reactions of these compounds. The main products of HCT [1] and TCMT [2] are formed after dechlorination of the parent molecules, while the aromatic $-SO_2NH_2$ group of the CT molecule is replaced by a hydrogen atom [1].

Table 1
Quantum yields ($\pm$ S.D.) for decomposition of CT, HCT and TCMT at 313 nm in 96% ethanol

Compound	C (mM)		
	0.05 ($n = 6$)	0.15 ($n = 4$)	0.5 ($n = 6$)
CT			0.019 ± 0.001
HCT	0.051 ± 0.004	0.052 ± 0.004	
TCMT	0.064 ± 0.004	0.067 ± 0.003	

n, Number of experiments.

Experiments with triplet sensitizers suggest that the reactions arise from different excited states, dechlorination from the triplet state and photofragmentation in the $-SO_2NH_2$ group from the singlet state [1,7]. The photochemical decomposition of HCT had earlier been studied in methanol and water and the quantum yields for the chloride ion production on irradiation through Pyrex glass determined (0.18 ± 0.05) [8,9]. Thus the values obtained in this study for the decomposition of HCT in ethanol are lower, but the quantum yields are dependent on the solvent.

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