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DERIVATIVE SPECTROPHOTOMETRIC DETERMINATION OF PARTITION COEFFICIENT OF HYDROCHLOROTHIAZIDE BETWEEN CETYLTRIMETHYLAMMONIUM BROMIDE MICELLES AND WATER

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Abstract

The interaction of hydrochlorothiazide (HCT), benzothiadiazine diuretic, with cationic surfactant cetyltrimethylammonium bromide (CTAB) was studied as a model system for drug/membrane interactions. From the dependence of first order derivative amplitude $^1D_{250.1}$ on CTAB concentration, by using mathematical models based on the partition of the drug between micellar and aqueous pseudo-phase, CTAB/water partition coefficient K_p was calculated.

Introduction

Drug interactions with heterogeneous media (micelles, lipid bilayer vesicles, biomembranes) induce changes in some physicochemical properties of the drugs (solubility, spectroscopic and acid-base properties) [1]. By monitoring these changes it is possible to quantify the degree of drug/micelle interaction which is expressed as micelle/water partition coefficient, K_p. The elucidation of K_p is important for the understanding of interactions with biomembranes and for the quantitative structure-activity relationship of drugs, as well as for the use of surfactants in HPLC or MEKC in drug quality control.

In this work, the effect of cationic micelles of cetyltrimethylammonium bromide, CTAB, on the spectroscopic properties of benzothiadiazine diuretic hydrochlorothiazide (6–chloro–3, 4–dihydro–2H–1, 2, 4–benzothiadiazine–7–sulfonamide–1, 1–dioxide), HCT is described. The derivative spectrophotometry was used to quantify the partition coefficient of HCT by applying the mathematical model [2] that considers partitioning of the drug between CTAB micellar and aqueous pseudo-phase.

Experimental

Spectrophotometric measurements used to calculate derivative spectra were performed on a GBC Cintra 20 spectrophotometer with 1.0 cm quartz cuvettes. The optimized operating conditions were: wavelength range 230 – 260 nm; slit width 1.0 cm; scan speed 100 nm min^{-1}; data interval 0.32 nm. The first-order derivative spectra were calculated using Savitzky-Golay algorithm with smoothing of 7 points. Stock solutions of 10 mM hydrochlorothiazide (Gödecke GmbH, Freiburg, Germany) were prepared by dissolving the compound in methanol.

Results and Discussion

The absorption spectra of HCT at pH=5 and pH=10.5, both in aqueous and CTAB micellar solutions, were measured. The effect of cationic micelles on the absorption spectrum of HCT is observed only in basic solutions. Hence it was concluded that electrostatic interaction between positively charged micelle surface and HCT dianion (pK_a^{HCT} are 7.0 and 9.2 [3]) is crucial for the micelle/drug binding.

The first order derivative spectra calculated from the absorption spectra of 0.42 mM HCT at pH=10.5 in the wavelength spectral range from 230 nm to 260 nm as a function of various concentrations of CTAB (c_{CTAB}=0.1-2 mM) are depicted in Figure 1. It is evident that a hipsochromic shift exists as a consequence of HCT binding to CTAB micelles, i. e. the drug exists in two states, free and micelle-bound, that have different derivative spectra. Two characteristic wavelengths are 250.1 nm and 242.1 nm being zero-crossing points of free and micelle-bound HCT, respectively. Hence, the concentration of free and/or micelle-bound HCT can be calculated from the values of $^1D_{242.1}$ and $^1D_{250.1}$, respectively, since the derivative intensity is proportional to solute concentration $^1D_\lambda = E_{\lambda *}c$. From the calibration curves of $^1D_{242.1}$ and $^1D_{250.1}$ versus c_{HCT} (concentration range 0.02 – 0.5 mM) measured in aqueous and micellar solutions (c_{CTAB}=3 mM) respectively, the molar derivative intensity for free HCT $E_{242.1}^w$= -185.4 ± 1.5 M^{-1} cm^{-1} (r=0.999) and micelle-bound HCT $E_{250.1}^m$= 143.7 ± 1.8 M^{-1} cm^{-1} (r=0.999) were obtained.

The addition of increasing concentrations of CTAB to the aqueous solutions of HCT resulted in the corresponding hyperbolic binding isotherm ($^1D_\lambda$ vs. c_{CTAB}, inset of Fig. 1), representing the disappearance of free HCT ($^1D_{242.1}$) and the formation of micelle-bound HCT ($^1D_{250.1}$). The values of $^1D_{242.1}$ and $^1D_{250.1}$ are constant in the concentration range of c_{CTAB}=0-0.2 mM assuming that it is the premicellar region, i. e. CMC_{CTAB} = 0.2 mM under experimental conditions used.

The partition coefficient K_p defined as the ratio of the mole fractions of HCT in micellar and aqueous phase was determined from $^1D_{250.1}$ values by using the equation [2]

$$\frac{1}{{}^1D_{250.1}} = \frac{1}{{}^1D_{250.1}^{\infty}} + \frac{1}{K_c \cdot {}^1D_{250.1}^{\infty} \cdot (c_{HCT} + c_{CTAB} - CMC)}$$

where $^1D_{250.1}^{\infty}$ is derivative intensity at infinite concentration of CTAB and $K_c = K_p / n_w$ (n_w = 55.5 M is the molarity of water). By measuring $^1D_{250.1}$ in five series (n=5) containing HCT (c = 0.42 mM) and increasing concentrations of CTAB (0.1-2.0 mM) and plotting $1/^1D_{250.1}$ versus $1/(c_{HCT} + c_{CTAB} - CMC)$ the values obtained for partition coefficients were K_c = 985 ± 100 M^{-1} and K_p = 54668 ± 5550.

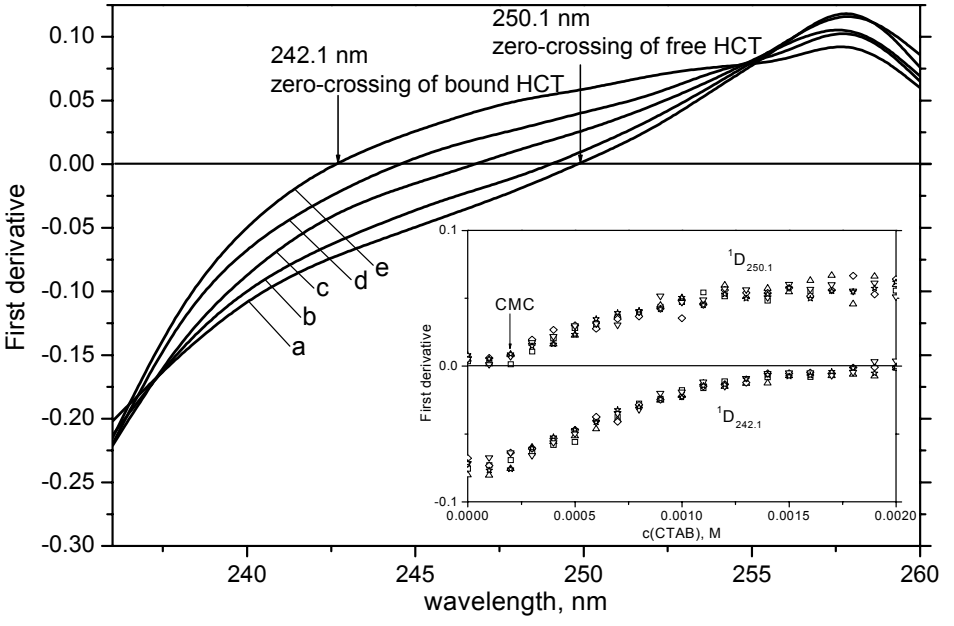

Figure 1. First order derivative spectra of 0.42 mM HCT at pH=10.5 containing various amounts of CTAB (mM): a) 0; b) 0.3; c) 0.6; d) 0.9; e) 2.0. Inset: First order derivative intensity at 242.1 nm and 250.1 nm of 0.42 mM HCT as a function of CTAB concentration.

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