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Methyl-triclosan binding to human serum albumin: Multi-spectroscopic study and visualized molecular simulation

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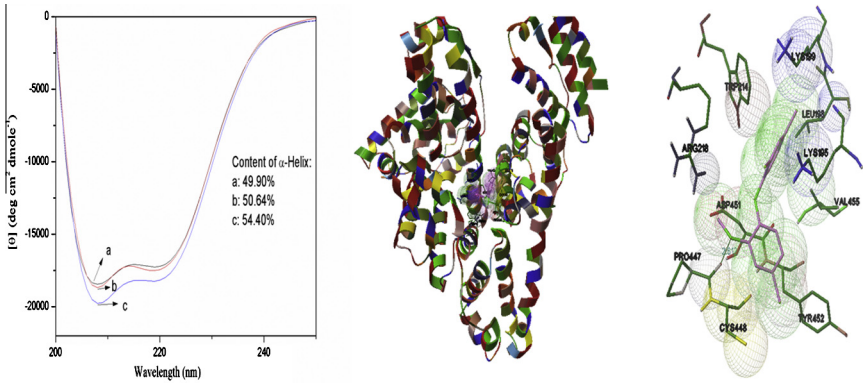
HIGHLIGHTS

- Potential toxicity of methyl-triclosan (MTCS) at the protein level was evaluated.
- Binding mechanism of human serum albumin (HSA) with MTCS was discussed in detail.
- Binding distance between MTCS and HSA was provided.
- Visualized binding details were shown clearly by molecular simulation method.

GRAPHICAL ABSTRACT



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ABSTRACT

Methyl-triclosan (MTCS), a transformation product and metabolite of triclosan, has been widely spread in environment through the daily use of triclosan which is a commonly used anti-bacterial and anti-fungal substance in consumer products. Once entering human body, MTCS could affect the conformation of human serum albumin (HSA) by forming MTCS–HSA complex and alter function of protein and endocrine in human body. To evaluate the potential toxicity of MTCS, the binding mechanism of HSA with MTCS was investigated by UV–vis absorption, circular dichroism and Fourier transform infrared spectroscopy. Binding constants, thermodynamic parameters, the binding forces and the specific binding site were studied in detail. Binding constant at room tempreture (T = 298 K) is 6.32 × 10^3 L mol^{-1}; ΔH^0, ΔS^0 and ΔG^0 were 22.48 kJ mol^{-1}, 148.16 J mol^{-1} K^{-1} and −21.68 kJ mol^{-1}, respectively. The results showed that the interactions between MTCS and HSA are mainly hydrophobic forces. The effects of MTCS on HSA conformation were also discussed. The binding distance (r = 1.2 nm) for MTCS–HSA system was calculated by the efficiency of fluorescence resonance energy transfer. The visualized binding details were also exhibited by molecular modeling method and the results could agree well with that from the experimental study.

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1. Introduction

Personal care products and pharmaceutical (PCPP) agents such as soaps, toothpastes, body washes and medical disinfectants, which contain up to 2% (w/w) of triclosan (2,4,4′-trichloro-2′-hydroxydiphenyl ether, TCS) in their formula (Sabaliunas et al., 2003; Halden and Paull, 2004), enter the municipal waste stream from large amount of household use (Kolpin et al., 2002; McClellan

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and Halden, 2010). And the literature shows some of these chemicals are not readily removed by sewage treatment (Yu et al., 2011). In most cases, triclosan is not removed completely by sewage treatment, but appears in the outflow discharge water at concentrations from 0.01 to 2.7 $\mu g\,L^{-1}$ and is sequestered in sewage sludge, or biosolids (McAvoy et al., 2002; Heidler and Halden, 2007). Actually, TCS has been detected in 57.6% of the water bodies across 30 states of the USA with a maximum level of 2.3 $mg\,mL^{-1}$ (Kolpin et al., 2002). Analysis of freshwater bed sediment samples from 12 WWTPs in Minnesota revealed TCS concentration of up to 85 $ng\,g^{-1}$ dry weights (Venkatesana et al., 2012). The highest concentrations for TCS were 478 $ng\,L^{-1}$ in surface water and 1329 $ng\,g^{-1}$ in the sediment from Shijing River, Guangzhou, South China (Zhao et al., 2010).

Methyl-triclosan (MTCS) is a biomethylated transformation product of triclosan formed through some biochemical pathways and conditions for instance during wastewater treatment (Canosa et al., 2008; Chen et al., 2011). The molecular structures of TCS and MTCS are displayed in Fig. 1. Studies have also shown that bacteria can convert TCS to MTCS, which has been detected in rivers, ponds, sewage sludge, and river and estuarine sediments downstream from sewage treatment plants (Lindstrom et al., 2002; Balmer et al., 2004; Bester, 2005; Grabic et al., 2010; Fernandes et al., 2011). Concentrations of MTCS are generally higher in WWTP effluent than influent, indicating formation of this transformation product in the treatment process (Bester, 2003; Balmer et al., 2004). MTCS, with a calculated log octanol:water coefficient ($\log P$) of 5.1 is slightly more lipophilic and environmentally persistent than TCS, which has a calculated $\log P$ of 4.8 (McAvoy et al., 2002). Based only on their higher lipid than aqueous solubility, both compounds would be predicted to bioaccumulate in plants and animals (Golding et al., 2008; Zarate et al., 2012) and transfer into human body through food chain and induce harm finally. TCS, as well as MTCS, are known as endocrine disrupting contaminants (EDCs), and several authors have reported their estrogenic activity (Silva et al., 2002; Farré et al., 2008). The effects of TCS and other EDCs on the structure change of macrobiomolecules such as proteins have been discussed (Chen et al., 2012; Gredell et al., 2012). These findings have led to a renewed interest in the safety of MTCS, especially its safety to human body. Thus, a good understanding of the potential bioeffect of MTCS in human body is needed.

As the major soluble protein constituent of circulatory system, human serum albumin (HSA) has many physiological and pharmacological functions. For instance, it contributes to maintain of the blood osmotic pressure. Furthermore, it can bind and transport various endogenous substances such as fatty acids, hormones and drugs (Peters, 1985). Studying interactions of small molecules to proteins is crucial for understanding many biological processes at the molecular level. The binding of chemicals to protein will change the macromolecular conformation, and thus affect physiological function of protein. Consequently, the study of the interaction between MTCS and HSA will be helpful to observe the effect of MTCS on HSA stability and secondary structure and understand the disposition, transportation and potential toxicity of MTCS at the protein molecular level.

The aim of this work was to probe the binding mechanism of MTCS to HSA by multispectroscopic, fluorescence resonance energy transfer and molecular modeling methods. The binding mechanism was investigated and the binding details together with the conformational changes of HSA were presented. The results reported are expected to provide some useful information for further discussing the toxicology of MTCS.

2. Materials and methods

2.1. Materials

MTCS was purchased from the Dr. Ehrenstorfer GmbH (Germany). HSA was obtained from Beijing Deweina biotechnology Co., Ltd. and used without further purification; the molecular weight of 66 500 was assumed to be to calculate the molar concentrations of HSA. All HSA solutions were prepared in 0.9% NaCl solution and HSA stock solution ($1.5 \times 10^{-5}\,mol\,L^{-1}$) was kept in the dark at 277 K. Tris (0.05 M)–HCl (0.1 M) buffer solution was used to keep the pH of the solution at 7.40. Dilutions of the HSA stock solution in 0.9% NaCl were prepared immediately before use. Stock solutions of MTCS were prepared at a concentration of $4.18 \times 10^{-3}\,mol\,L^{-1}$ in anhydrous methanol. All other reagents were of analytical reagent grade and distilled water was used throughout the experiments. All pH values were checked with a PHS-3B acidity meter (Shanghai precision and scientific Co., Ltd.).

2.2. Apparatus and measurements

2.2.1. Fluorescence measurements

All fluorescence spectra were performed on a RF-5301PC Spectrofluorometer (Shimadzu, Japan) with a 1 cm quartz cell. Both excitation and emission bandwidths were set at 5 nm. The excitation wavelength was 286 nm, and the emission wavelength was read at 220–500 nm with a maximum observed at 334 nm.

2.2.2. UV–vis absorption measurements

UV–vis absorption spectroscopy was recorded on a TU-1810 UV–vis absorption spectrophotometer (Beijing, China) equipped with 1.0 cm quartz cells. The range of wavelength was from 190 to 500 nm.

2.2.3. Circular dichroism (CD) measurements

CD measurements were measured using an Olis DSM 1000 automatic recording spectrophotometer in a 1 mm quartz cell at room temperature. CD spectra were recorded in the range of 200–260 nm. The slit width was set at 5 nm, and the speed of scanning was 30 $nm\,min^{-1}$.

2.2.4. Fourier transform infrared(FT-IR) spectroscopy

FT-IR measurements were carried out at room temperature on a VERTEX 70 V (Bruker optics.Inc.) FT-IR spectrometer equipped

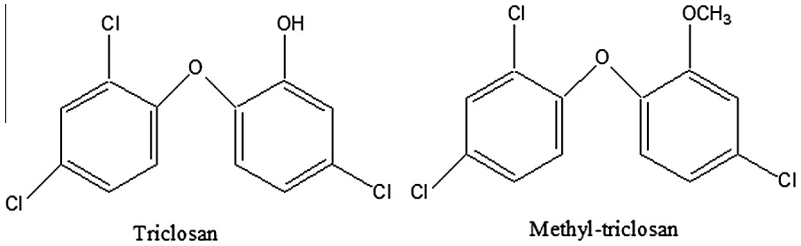

Fig. 1. Molecular structrues of TCS and MTCS.

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