Selectively substituted cyclodextrins for analytical and pharmaceutical applications

Abstract

This thesis is focused on the selective modification of cyclodextrins, and its primary aim is the preparation and characterization of mono- and persubstituted derivatives of cyclodextrins in a regioselective and straightforward manner. The work is divided into two main parts describing synthetic strategies and applications of modified cyclodextrins with one or several substituents, respectively.

The first section deals with the introduction of a single chromophoric moiety on the cyclodextrin scaffold such as cinnamyl, rhodaminyl, fluoresceinyl and eosinyl groups.

The complete set of monocinnamyl-α-cyclodextrin regioisomers has been prepared by direct alkylation, and the self-assembling properties of the corresponding regioisomers were thoroughly investigated by dynamic light scattering and NMR experiments. These investigations revealed that the different isomers (mono-6-*O*-, mono-2-*O*- and mono-3-*O*-cinnamyl-α-cyclodextrin) form distinct supramolecular species through intermolecular association. A fast method for the unambiguous identification of the pure regioisomers has also been developed based on a series of 2D NMR measurements.

Xanthene-modified β-cyclodextrins, other representatives of monosubstituted cyclodextrins, have been synthesized. A new synthetic strategy for the green and mild coupling reaction between mono(6-deoxy-6-amino)-β-cyclodextrin and the xanthene dyes has been developed. Spectroscopic investigations showed that fluorescein- and rhodamine B-appended β-cyclodextrin can be used as pH-sensitive fluorescent sensors, while the eosin Y-tagged β-cyclodextrin can be used for the photogeneration of singlet-oxygen and applicable in photodynamic therapy. Similarly to the cinnamylated derivatives xanthene-cyclodextrins also showed a tendency to self-associate and this phenomenon clearly influences their photophysical properties. For this reason, a great emphasis was placed on the study of the supramolecular behavior of xanthene-modified β-cyclodextrins.

The second part of the thesis is discussing the perfunctionalization of β- and γ-cyclodextrin with methyl and carboxymethyl groups. The developed synthetic strategy is based on primary-side selective protection, secondary-side methylation and deprotection-carboxymethylation of the primary side, resulting in two-faced derivatives fully methylated on their secondary side and carboxymethylated on their primary side. The prepared derivatives were exploited as chiral selectors in capillary electrophoresis for the enantioseparation of pharmacologically significant molecules, and they represent the first single-isomer carboxymethylated cyclodextrins applied in this field.

Keywords: Cyclodextrins, Monosubstitution, Persubstitution, Regioselectivity, Supramolecular aggregates, Fluorophore labeling, Chiral separation, Photodynamic therapy, Capillary electrophoresis