

# Synthesis of cyclodextrin derivatives for practical applications

## Abstract

The first part of this PhD thesis is focused on the synthesis of a series of monosubstituted tetraalkylammonium cyclodextrin (CD) derivatives. The emphasis was placed on the possible applicability of the synthetic process to multigram or even industrial scale. Monotosylation of the native cyclodextrins ( $\alpha$ -,  $\beta$ -,  $\gamma$ -) on the primary side of the macrocycle afforded the starting materials. Derivatives with one cationic group were prepared by the reaction with aqueous trimethylamine. The reaction of the mono-Ts-CD with neat *N,N,N'*-trimethylethane-1,2-diamine or *N,N,N'*-trimethylpropane-1,3-diamine and subsequent methylation led to derivatives with the substituent bearing two cationic groups (PEMEDA- and PEMPDA- $\beta$ -CD). Analogs bearing a moiety with three tetraalkylammonium sites were synthesized by reaction of mono-Ts-CD with bis(3-aminopropyl)amine with subsequent methylation. 1,3-Dipolar cycloaddition of mono-6-azido- $\beta$ -CD with diaminoacetylenes followed by methylation led to analogs with a variable distance of the charged substituent from the CD core. Majority of the presented reactions are straightforward, relatively high-yielding and the workup does not require chromatographic steps.

The second part of the work is dealing with the determination of properties of the selected prepared derivatives. Thermal stability of the two charged analogs PEMEDA- $\beta$ -CD and PEMPDA- $\beta$ -CD, which differ in the substituent linker length (ethylene and propylene respectively) was studied by  $^1\text{H}$  NMR experiment. The measured kinetics of the Hofmann degradation proved PEMPDA- $\beta$ -CD to have higher thermal stability and was selected as the most suitable host molecule for further measurements. The inclusion capabilities of permanently charged PEMPDA- $\beta$ -CD in aqueous solution with three model aromatic guests (salicylic acid, *p*-methoxyphenol and *p*-nitroaniline) were determined by isothermal titration microcalorimetry (ITC) and the obtained values of stability constants ( $K_s$ ) compared to the ones of native  $\beta$ -CD. Permanently charged cationic CD derivatives were successfully deposited on the anionic solid surface of polymeric Nafion<sup>®</sup> 117 membrane via electrostatic interactions. Deposition kinetics and coverage of the surface were determined by ELSD. The ability of the ionic assembly on the solid surface to encapsulate aromatic compounds from aqueous solution was measured by UV/Vis spectrometry.

The results indicate that prepared cationic derivatives maintain the ability to form inclusion complexes with a suitable guest in solution and also when deposited on an anionic surface.

**Keywords:** Cyclodextrins, Tetraalkylammonium derivatives, Cationic, Monosubstitution, Regioselectivity, Host-guest complex, Thermal stability, Solid surface, Inclusion properties