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Characterization and application of single-isomer cyclodextrin derivatives

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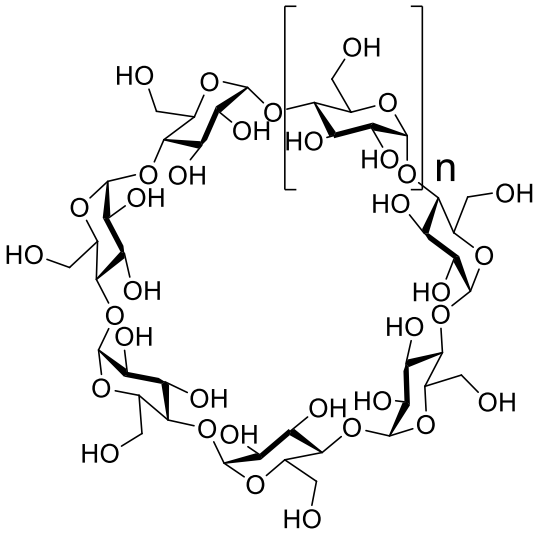
Cyclodextrins



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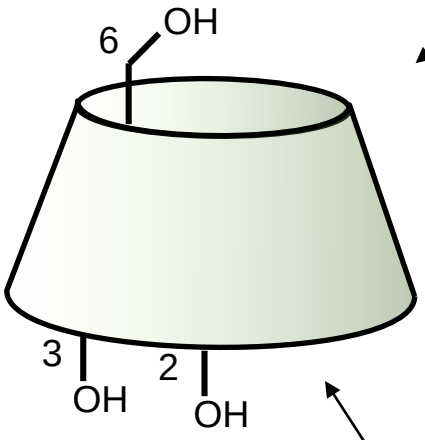

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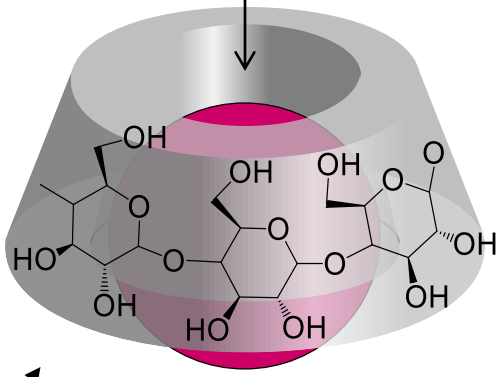


primary side

hydrophobic cavity

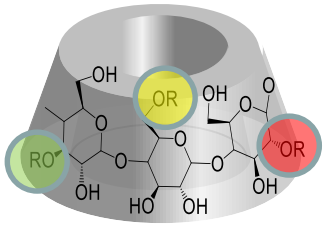
secondary side

hydrophilic outer surface

CD	Number of glucose units
α	6
β	7
γ	8

Isomerism in cyclodextrin derivatization

Random/statistical substitution

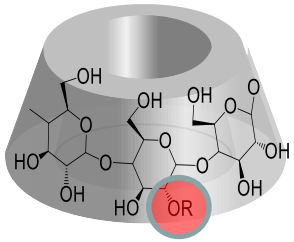


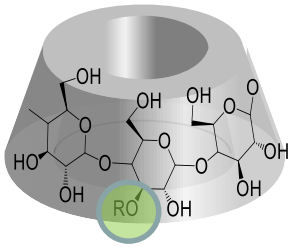
position 2-*O*

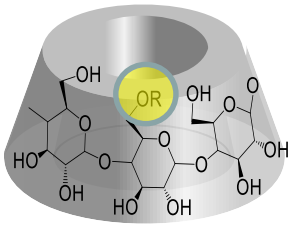
position 3-*O*

position 6-*O*

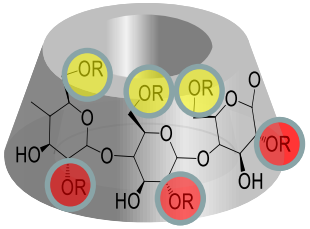
Monosubstitution

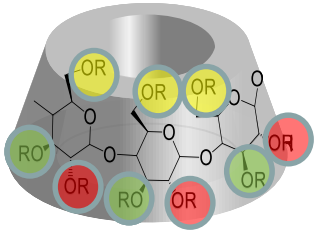


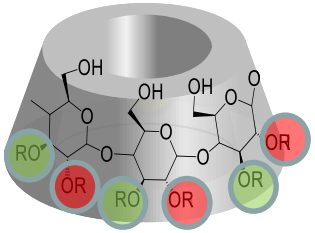




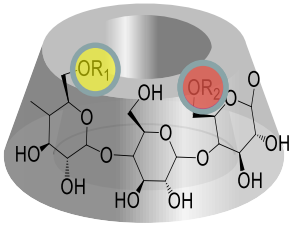
Persubstitution



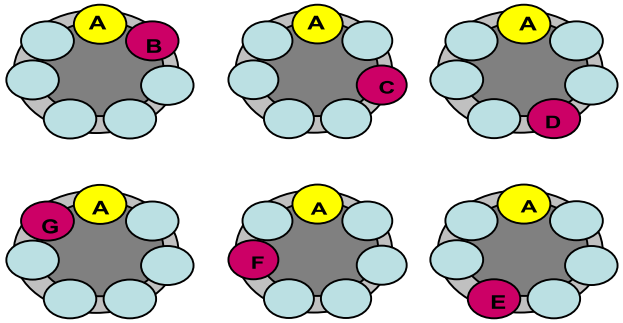




Disubstitution

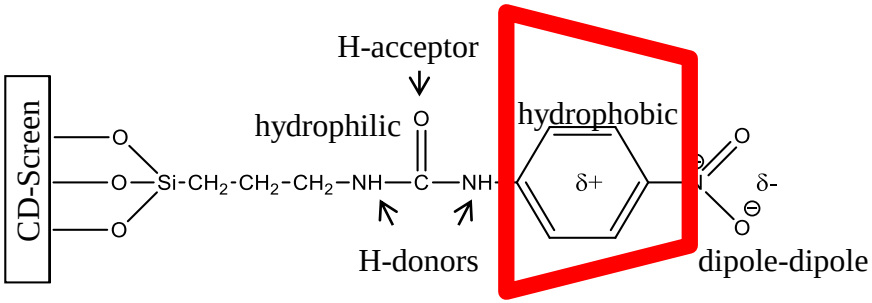


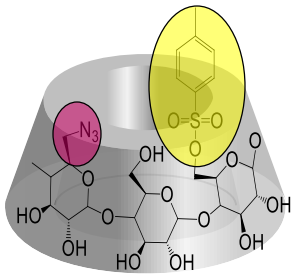
‘Top’ view for β-CD

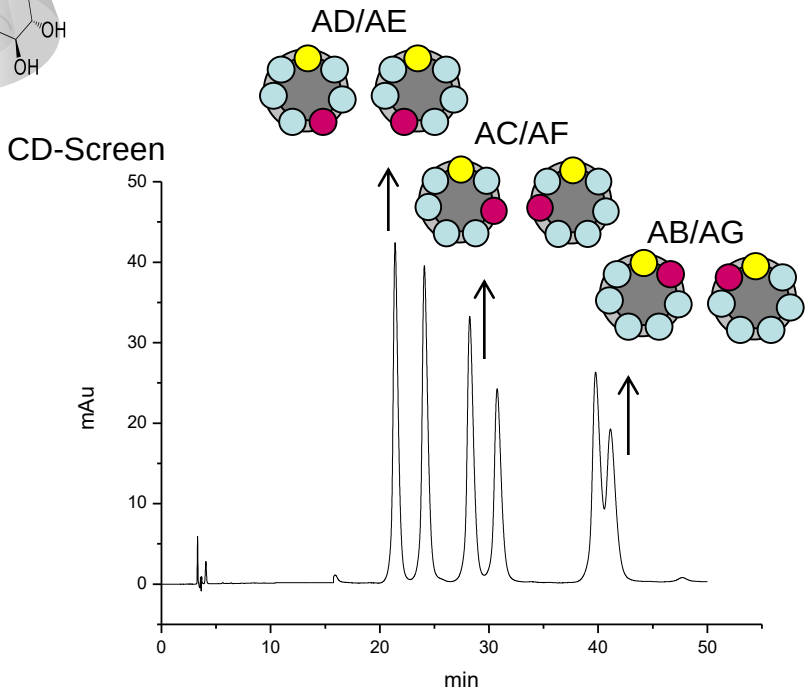


pseudoenantiomers

Inclusion-assisted liquid chromatography
CD-Screen columns

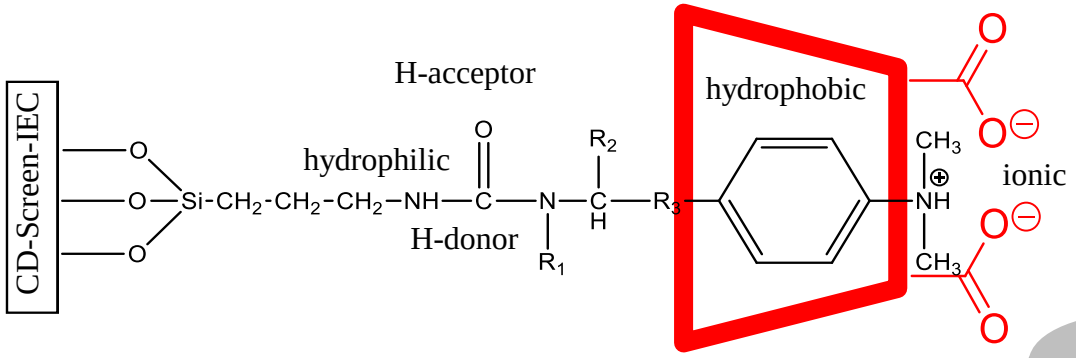


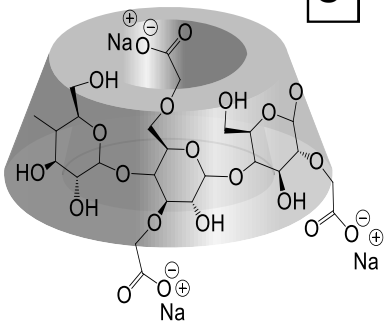


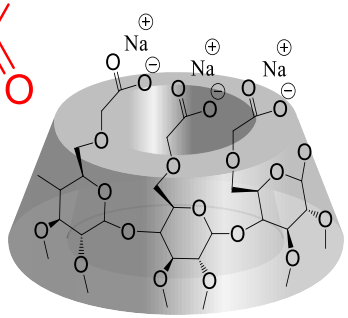


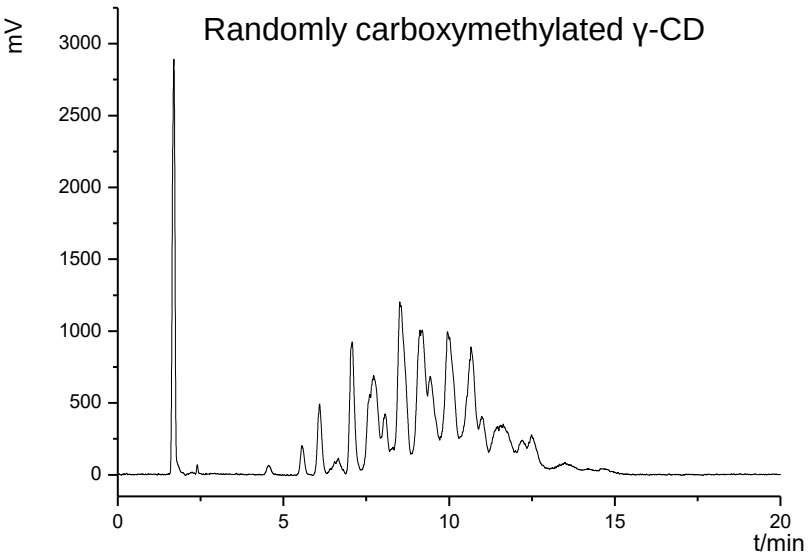
1. Benkovics et al. *Int. J. Pharm* **2017**, *Ahead of print*

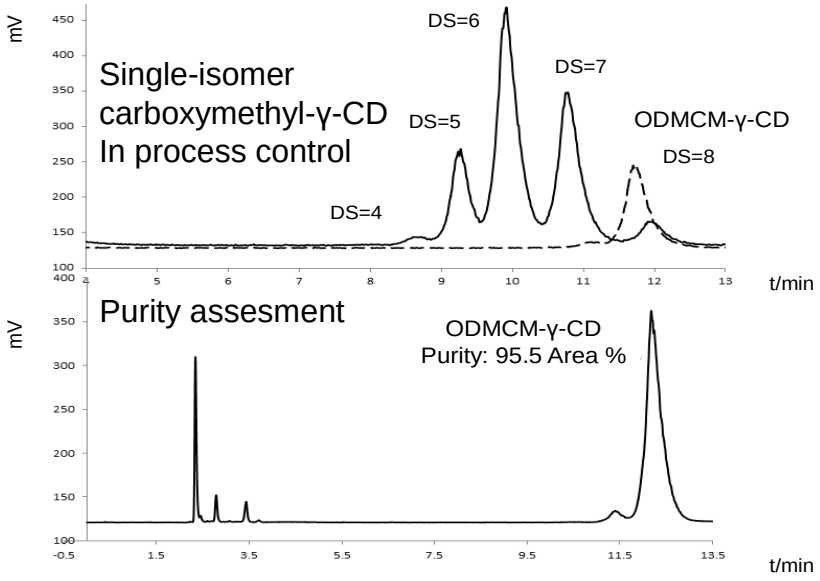
Inclusion-assisted ion-exchange chromatography (CD-Screen-IEC columns)





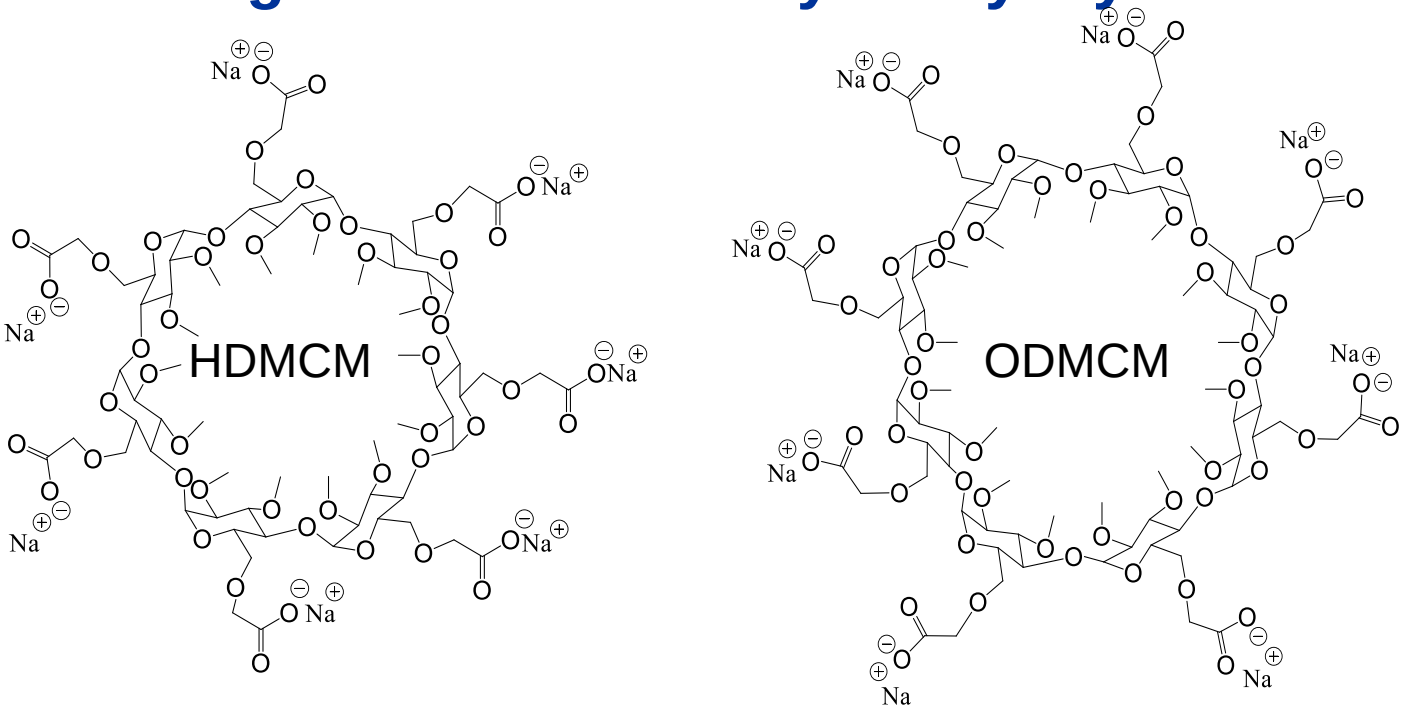






HPLC conditions: CD-Screen-IEC stationary phase, ammonium acetate (pH 4.0), gradient with ACN, ELS detection

Single-isomer carboxymethyl cyclodextrins



heptakis-(2,3-di-*O*-methyl-6-*O*-carboxymethyl)-β-cyclodextrin (HDMCM)
octakis-(2,3-di-*O*-methyl-6-*O*-carboxymethyl)-γ-cyclodextrin (ODMCM)

Preparation:

- 4-step synthesis from native CDs in 52 % (HDMCM) and 48 % (ODMCM) total yield

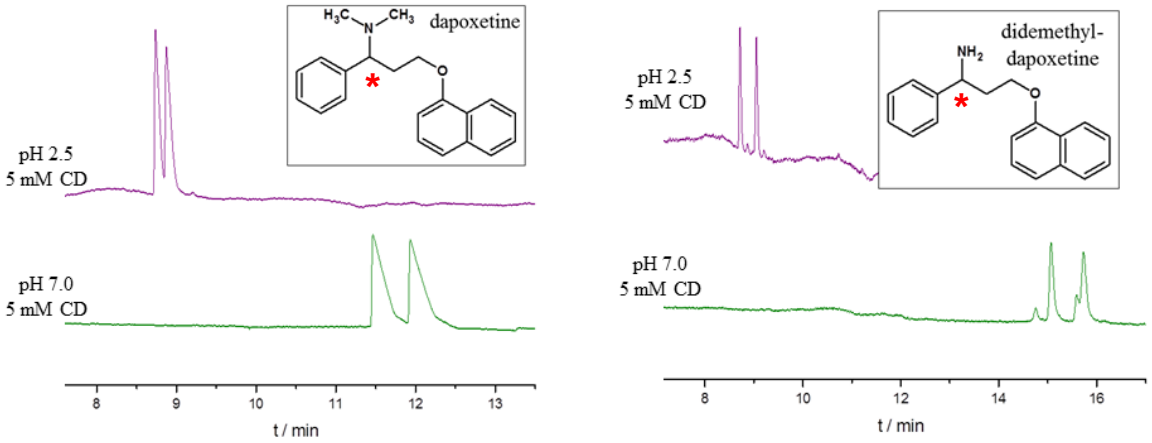
Characterization:

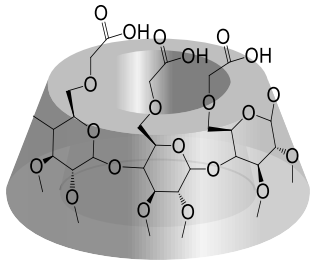
- HPLC - inclusion-assisted ion-exchange chromatography (CD-Screen-IEC columns) with ELS detection
- Capillary electrophoresis with indirect UV detection
- ^{1}H NMR titration

1. Fejős et al. *Electrophoresis* **2017,** *Ahead of print*
2. Benkovics et al. *J. Chromatogr. A.* **2016,** *1467*, 445-453

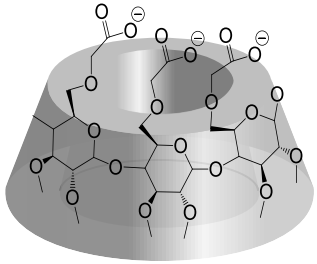
Single-isomer carboxymethyl cyclodextrins (application)

- pH tunable ionic interactions on a well-defined position





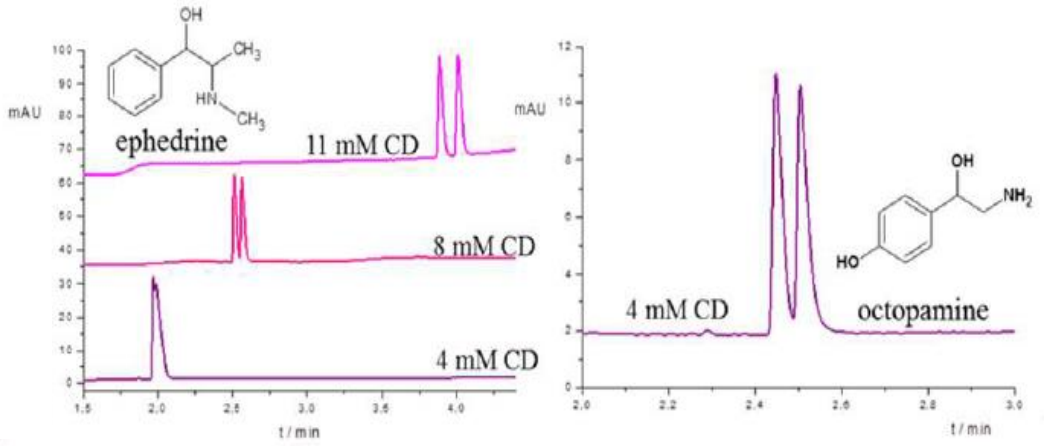
electroneutral



octaanionic

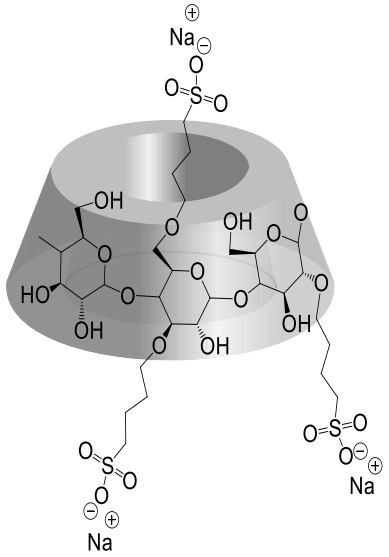
CE electropherograms applying ODMCM as chiral selector

- applicability in aqueous as well as in non-aqueous capillary electrophoresis (NACE)

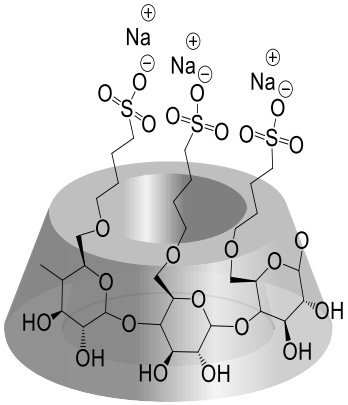


NACE electropherograms applying HDMCM as chiral selector

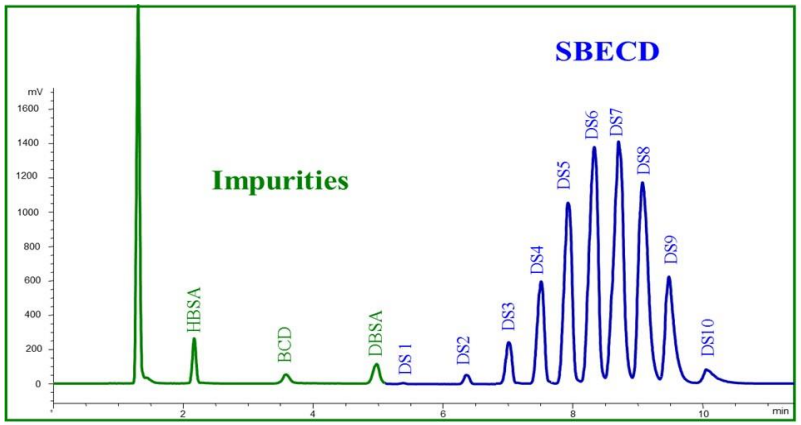
Single-isomer sulfobutyl-β-cyclodextrin

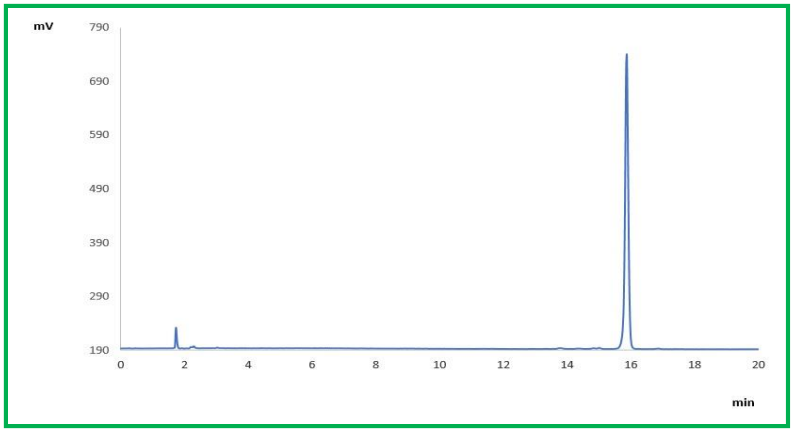


Sulfobutylated β-CD (DS=6.4)
(Dexolve™, Captisol™)



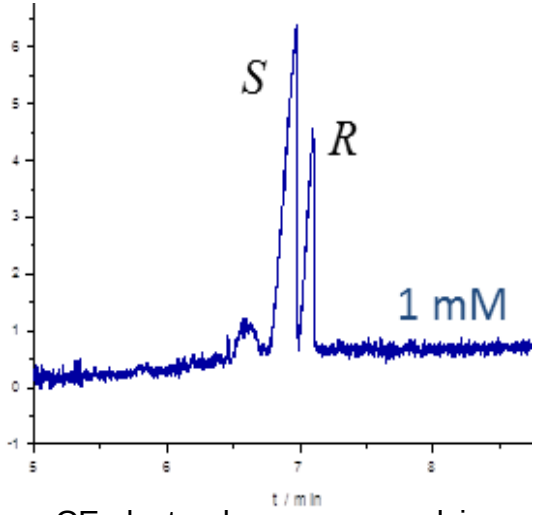
Heptakis-(6-*O*-sulfobutyl)-β-CD (DS=7.0)
6-$(SB)_7$-β-CD



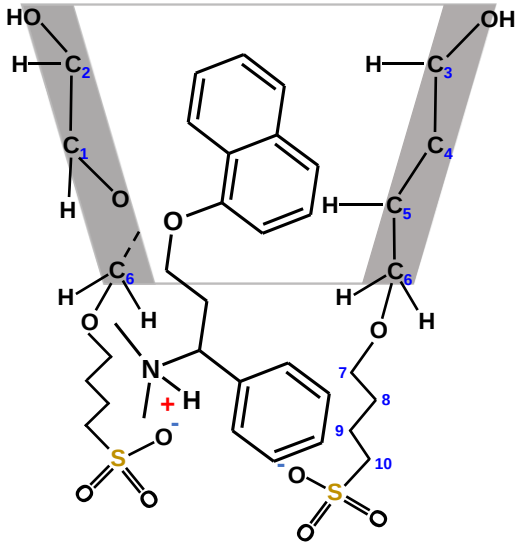


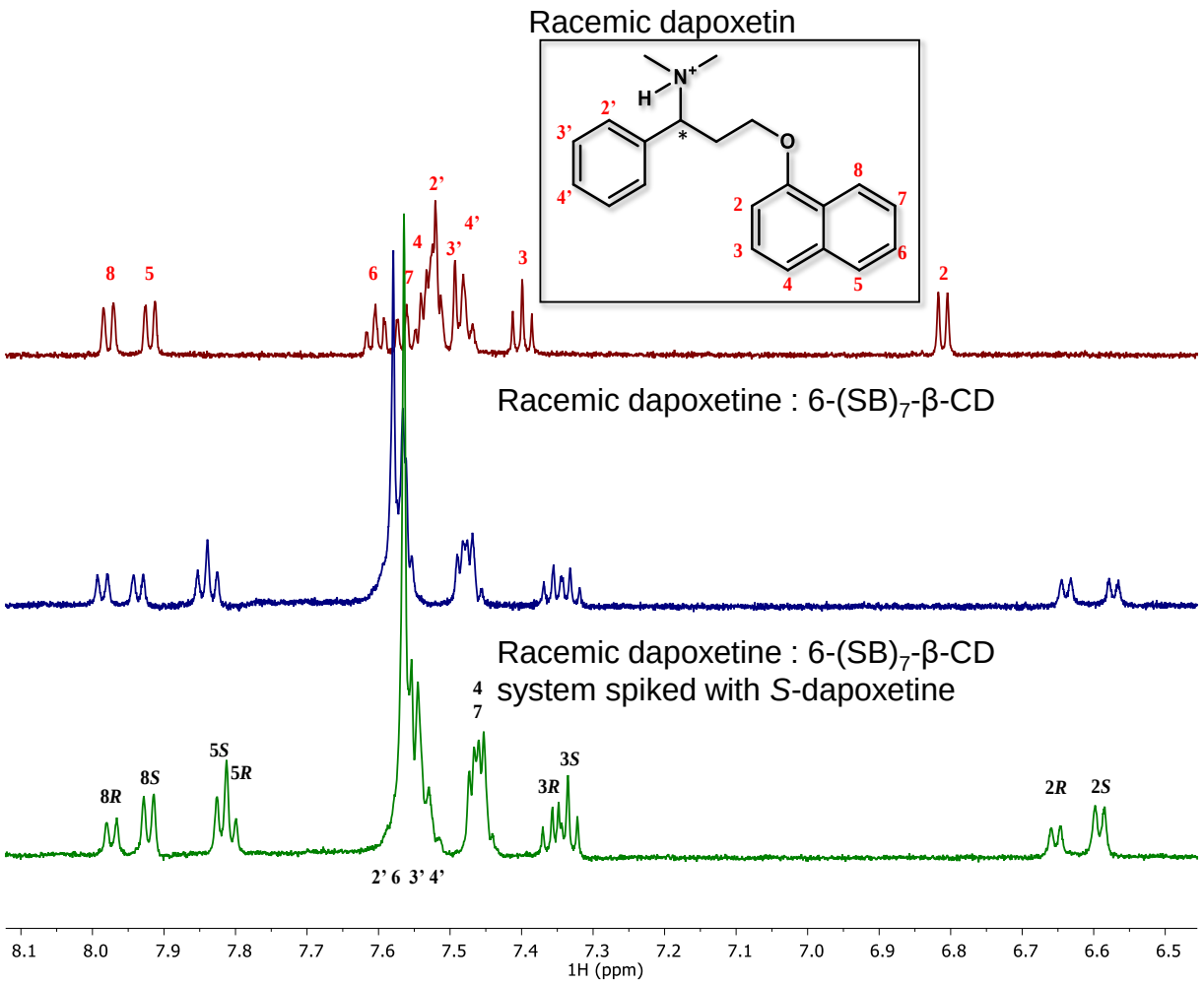
HPLC conditions: CD-Screen-IEC stationary phase, solvent gradient of 1.5% triethylamine-formate (pH 4.5) with ACN, ELS detection

Single-isomer sulfobutyl β-cyclodextrin



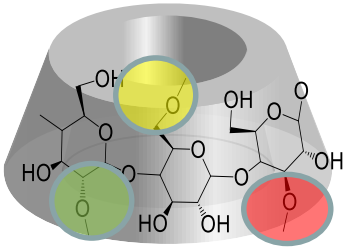
CE electropherograms applying 6-(SB)$_7$-β-CD as chiral selector



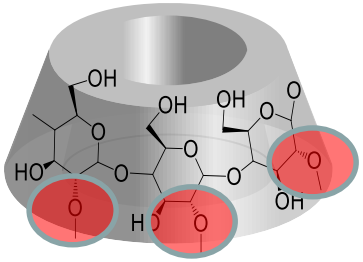


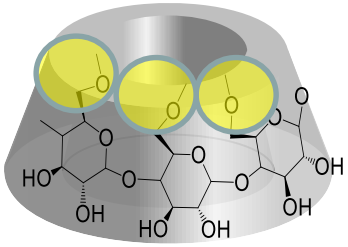
Malanga et al. *J. Chromatogr. A.* **2017**, *1514*, 127-133.

Beyond enantiomer separation: Methylated cyclodextrins

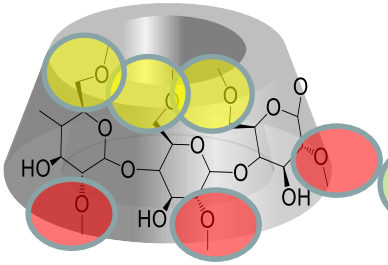


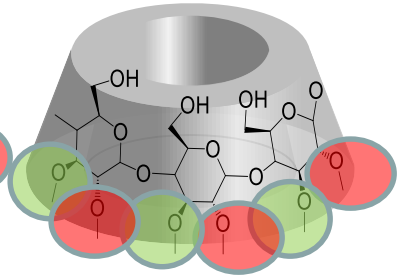
randomly-methylated β-cyclodextrins (RAMEB, CRYSMEB)



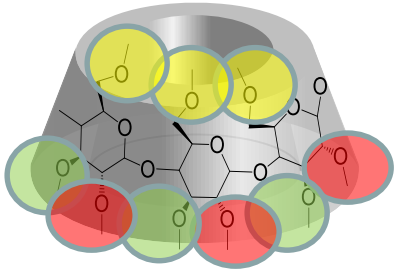


heptakis-(6-*O*-methyl)-β-cyclodextrin (SIXMEB)
heptakis-(2-*O*-methyl)-β-cyclodextrin (TWOMEB)





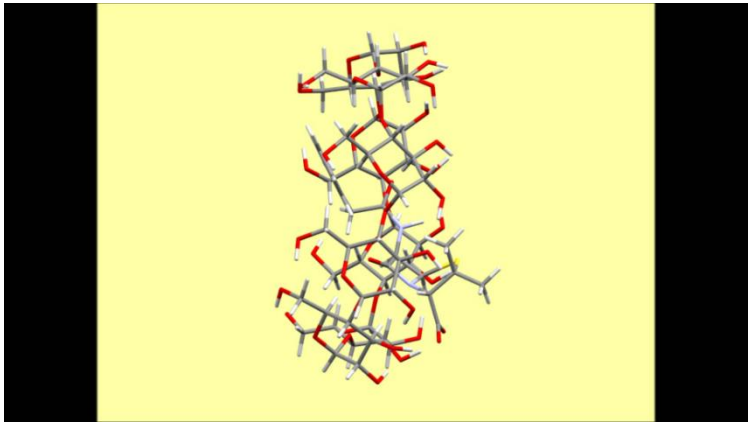
heptakis-(2,6-di-*O*-methyl)-β-cyclodextrin (2,6-DIMEB)
heptakis-(2,3-di-*O*-methyl)-β-cyclodextrin (2,3-DIMEB)

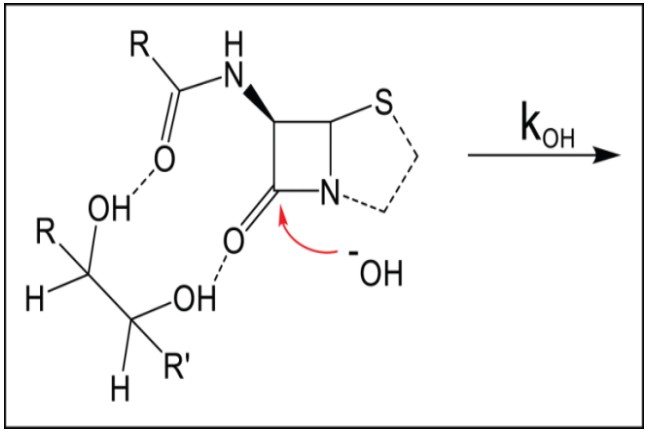


heptakis-(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TRIMEB)

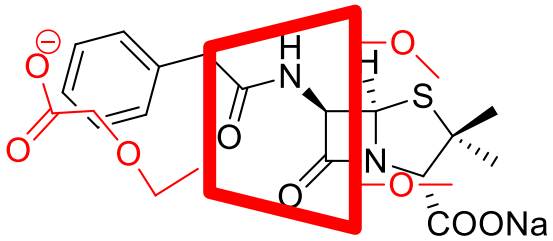
Beyond enantiomer separation

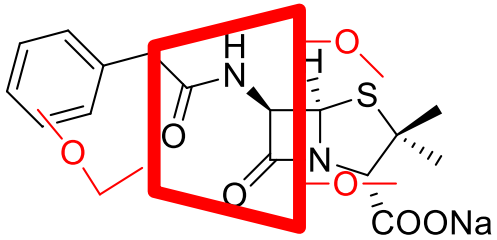
- Nanocarriers for the delivery of antimicrobials to fight resistance mechanisms
- Cyclodextrin-penicillin interactions





- ODMCM, HDMCM and TRIMEB are able to protect the β-lactam ring from catalytic degradation





Popielec *et al. Pharmazie* **2016**, *71*, 68–75.
Popielec *et al. Int. J. Pharm* **2017**, *Ahead of print*

Summary

- New negatively charged single-isomer CDs have been synthesized:
ODMCM , HDMCM (carboxymethylated)
6-SB_7-β-CD (sulfoalkylated)

- Chiral resolution properties of these derivatives have been studied with a wide set of test racemates applying aqueous and non-aqueous capillary electrophoresis

- The synthesized library of single-isomer carboxymethylated and methylated CD derivatives helped us to understand the inclusion phenomenon between CDs and β-lactam antibiotics

- ODMCM, HDMCM and TRIMEB are the first CD derivatives showing stabilization effect of the β-lactam ring

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Prof. Gyula Vígh

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The Cyclodextrin Company

Thank you for your kind attention!

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