

# CYCLODEXTRIN – LACTIDE OLIGOMERS. MOLECULAR LEVEL CHARACTERIZATION

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## Introduction

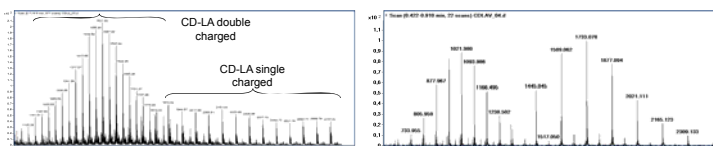
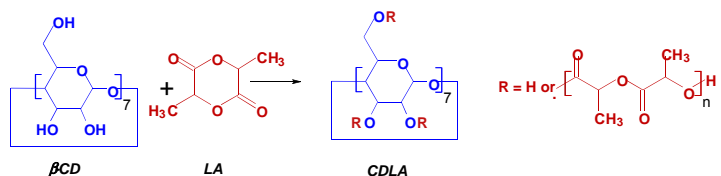
Cyclodextrins (CD) ability to form inclusion complexes and hence to alter the physical-chemical properties of guest molecules has been exploited in order to increase the water mixing properties of hydrophobic drugs. To optimize the physical inclusion of specific guests, the polarity of native CD molecules should be adjusted. Generally this is achieved by attaching small alkyl or hydroxyalkyl substituents through ether linkages.

Mass spectrometry is known to be an easy and fast method to achieve cyclodextrin derivatives characterization. In fact, ESI mass spectrometry has been used to characterize CD derivatives obtained through ring opening oligomerization of  $\beta$ -butyrolactone [1,2], D,L-lactide [3], and other cyclic esters [4]. Therefore, we considered useful the investigation of esterified cyclodextrins through tandem MS [5]. The present study shows that depending on the chosen parent ion type, the cyclodextrin-lactide derivatives can be selectively cleaved at the level of the semiacetal junction or at the level of the ester bonds. This distinct behavior in CID fragmentation conditions allows a direct access at the modified cyclodextrin substitution pattern.

## Results

The compounds used for this study are a standard commercial sample, triacetyl- $\beta$ -cyclodextrin (TABCD), and a random esterified  $\beta$ -cyclodextrin with oligolactide (CDLA), synthesized in our laboratory. The tandem MS experiments, performed on a Q TOF instrument, revealed distinct fragmentation patterns according to the type of adduct submitted to CID fragmentation similar to previous studies [5]. For TABCD, the proton charged parent ions were cleaved at both semiacetal (M1) and ester bond levels (M2a & M2b). In the case of CDLA sample the observed fragments issued from the cleavage of the semiacetal bonds. The  $\text{Na}^+$  cationized samples yielded fragments at the level of the ester bonds for both considered compounds. This study reveals the substitution pattern of esterified CDs, first due to the direct observation of the intact substituted glycoside units and secondly due to the clear evidence of the esterified functions, and demonstrates that a fast evaluation of this type of compounds is possible through tandem MS.

ESI MS and MS/MS experiments were conducted using the AGILENT 6520 LC QTOF mass spectrometer equipped with an dual ESI source. The data were analyzed using the Mass Hunter software. The MS/MS experiments were performed in the collision cell using the nitrogen as collision gas. Samples were infused via autosampler system, bypassing the column and using  $\text{H}_2\text{O}/\text{MeCN}$  solvents.



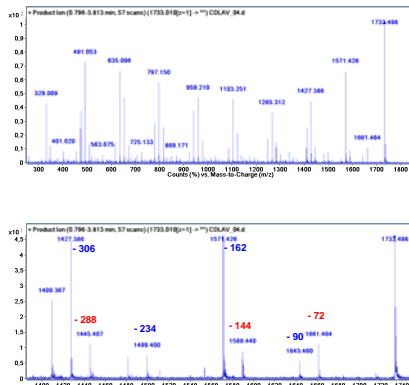
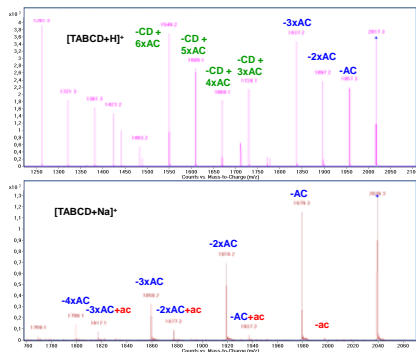
CDLA obtained through ROP of LA catalyzed by (-)-Sparteine, in DMSO. Mn~3000 Da and average SD = 26. Double charged  $\text{NH}_4^+$  ions-1521 = 1134 + 26x72 + 2x18. High transesterification proved by 72 Da sequence.

CDLA obtained through ROP of LA catalyzed by DMF. Mn~2000 Da, average SD = 12. Double charged  $\text{Na}^+$  ions-1022 = 1134 + 12x72 + 2x23. Almost no transesterification proved by 144 Da sequence.

TABCD – MS/MS

CDLA – MS/MS:  $\text{Na}^+$  parent ions

Rationalization of MS/MS spectra

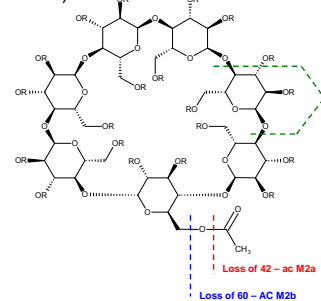


CDLA	1	2	3	4	5	6	7
0	185	347	509	671	833	995	1157
1	287	449	611	773	935	1097	1259
2	389	551	713	875	1037	1199	1361
3	491	653	815	977	1139	1301	1463
4	593	755	917	1079	1241	1403	1565
5	695	857	1019	1181	1343	1505	1667
6	797	959	1121	1283	1445	1607	1769
7	899	1061	1223	1385	1547	1709	1871
8	1001	1163	1325	1487	1649	1811	1973

CDLA – copolymer composed of glycoside (CD) with mass of 162 Da and lactide (LA) with mass of 72 Da. Then, 1733 = 162x7 + 72x8 + 23. The table contains the observed mass values for the most important fragments (highlighted).

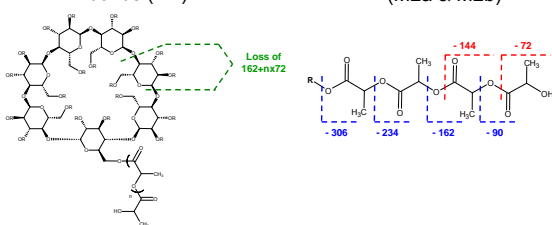
### Fragmentation mechanisms:

- > [TABCD+H]<sup>+</sup>: Cleavage of oligosaccharide bonds (M1) and ester bonds (M2b)
- > [TABCD+Na]<sup>+</sup>: Cleavage of ester bonds (M2a & M2b)

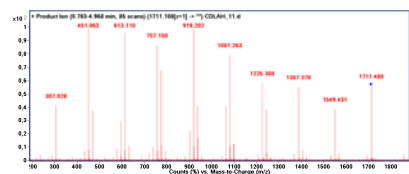


Cleavage of oligosaccharide bonds (M1)

Cleavage of ester bonds (M2a & M2b)



CDLA – MS/MS:  $\text{H}^+$  parent ions



CDLA	1	2	3	4	5	6	7
0	185	347	509	671	833	995	1157
1	287	449	611	773	935	1097	1259
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7	899	1061	1223	1385	1547	1709	1871
8	1001	1163	1325	1487	1649	1811	1973

There are no fragments resulted from the side chain cleavage. Similarly, 1711 = 162x7 + 72x8 + 1. The table contains the observed mass values for the most important fragments (highlighted). One glycoside unit can be substituted with 2 to 8 LA units.

## Conclusions

ESI MS can reveal information on the Mn and substitution degree of esterified CDs. However, structural details like the attachment of monomer units as single chain or multiple chains can't be answered. MS/MS spectra of fully esterified CD (TABCD commercial sample) show that Na cationized parent ions are fragmented at the side chain while protonated parent ions are fragmented predominantly at the semiacetalic bonds, thus allowing to observe intact glycosides. The CDLA sample was found to behave in a similar way, the Na parent ions being cleaved at the side LA chain but also at the level of GL bonds. The cleavage of GL units is due perhaps to lower substitution degree as compared to TABCD. Thus, Na parent ions allowed direct observation of lactide chains attached to CD. The attachment is random, as multiple LA chains with variable chain length were exposed. This conclusion is supported by the observation of the protonated ion species which allowed direct observation of intact glycoside rings together with their substitution pattern. E.g. one glycoside unit can be substituted with 2 to 8 LA units. This study may be expanded to various esterified CDs in order to elucidate the nature of substitution.

## References

1. Peptu, C., Nicolescu, A., Peptu, C.A., Harabagiu, V., Simionescu, B.C., Kowalczyk, M. Journal of Polymer Science, Part A: Polymer Chemistry Volume 48, Issue 23, 1 December 2010, Pages 5581-5592.
2. Peptu, C., Kwicielec, I., Harabagiu, V. Cellulose Chemistry and Technology Volume 48, Issue 1-2, January 2014, Pages 1-10.
3. Shen, J., Hao, A., Du, G., Zhang, H., Sun, H. Carbohydrate Research Volume 343, Issue 15, 13 October 2008, Pages 2517-2522.
4. Miao, Y., Zinck, P. Polymer Chemistry Volume 3, Issue 5, May 2012, Pages 1119-1122.
5. Peptu, C., Harabagiu, V. Digest Journal of Nanomaterials and Biostructures Volume 8, Issue 4, 2013, Pages 1551-1561