INSIGHT INTO THE THREE-DIMENSIONAL STRUCTURE OF CYCLODEXTRINS/FOLIC ACID NONCOVALENT COMPLEXES BY ION MOBILITY MASS SPECTROMETRY TECHNIQUE

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Introduction

The inclusion complexes of cyclodextrins (CDs) with active compounds have become very attractive for pharmaceutical applications due to the increase the solubility, stability and bioavailability of an included guest molecule in the host–guest complexes.

The aim of our study was to determine the three-dimensional structure of the cyclodextrins/folic acid complexes using ion mobility mass spectrometry (IM-MS).

In the previous study we showed that noncovalent complexes of folic acid (FA) and cyclodextrins (α-, β- and γ-CDs) differ significantly in their gas-phase stability. It was found that these differences are due to different structures of cyclodextrins/folic acid noncovalent complexes, i.e., formation of inclusion and exclusion complexes.[1] **(Figure 1)**

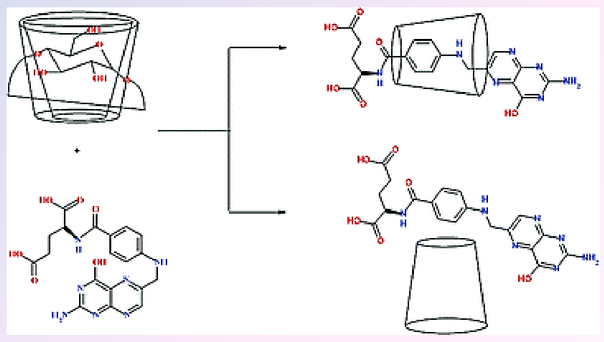

Fig. 1. The formation a) inclusion complex b) exclusion complex

Methods

IM-MS measurements were performed on a quadrupole ion mobility time-of-flight instrument (Synapt G2-S HDMS, Waters). Typically, water/methanol (1:1) solution served as the spray solvent and ca. 0.7 mM solutions of the studied complexes were used. The samples were analyzed in negative ion mode with a capillary voltage at 3.63 kV and source temperature at 80 °C. For optimal ion mobility separation, the traveling wave velocity and pulse height were set at 623 m/s and 40 V, respectively. T-Wave ion mobility was calibrated using polyalanine. Optimized structures of CDs/FA were generated at the PM6-DH2 level of theory.[2] Theoretical collision cross-sections of α-, β- and γ-CDs/FA complexes were calculated using the open source program MOBCAL.[3] The Trajectory Method (TM) implemented in MOBCAL was used to calculate the theoretical collision cross sections of the studied complexes.

Results

- The complexes formed between FA salt and α-, β- and γ-CDs were subjected to IMS analysis. The results show significant differences in measured drift times between α-, β- and γ-CDs/FA complexes (**Figure 2**).

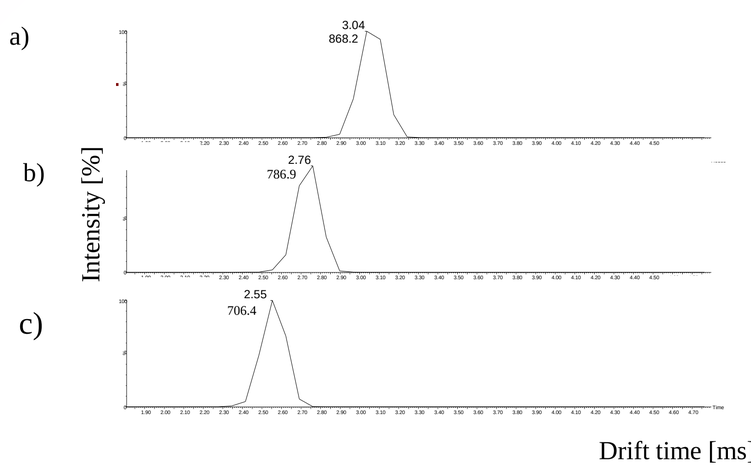

Fig. 2. Ion mobility spectra of a) γ-CD/FA b) β- CD/FA c) α-CD/FA

- Theoretical collision cross-sections are calculated for the various types of complexes and are compared with the experimentally derived values. (**Table 1**). The cross-sections of α-, β- and γ-CDs and their complexes with folic acid are shown in **Table 2.**

Table 1. Collision cross-sections of the α-, β- and γ-CDs /FA complexes .

	m/z	z	Ω [Å2] measured	Ω [Å²] theoretical (Trajectory Method)	Δ [%]
α-CD/FA	706.4	-2	288.20	288.62	0.15
β- CD/FA	786.9	-2	294.35	293.87	0.16
γ-CD/FA	868.2	-2	307.36	317.71	3

Table 2. Collision cross-sections of the α-, β- and γ-CDs and their complexes.

	m/z	z	Ω [Å²] Theoretical Trajectory Method	increase ccs (%)
α-CD	485.5	-2	215.00	34.24
α-CD/FA	706.4	-2	288.62	
β-CD	566.34	-2	257.32	14.20
β-CD/FA	786.9	-2	293.87	
γ-CD	647.34	-2	286.86	10.75
γ-CD/FA	868.2	-2	317.71	

- The semi-empirical theoretical calculations (PM6-DH2 method) yield the optimized structures of complexes that differ in type (inclusion and exclusion complexes) and position of negative charges **(Figure 3)**.

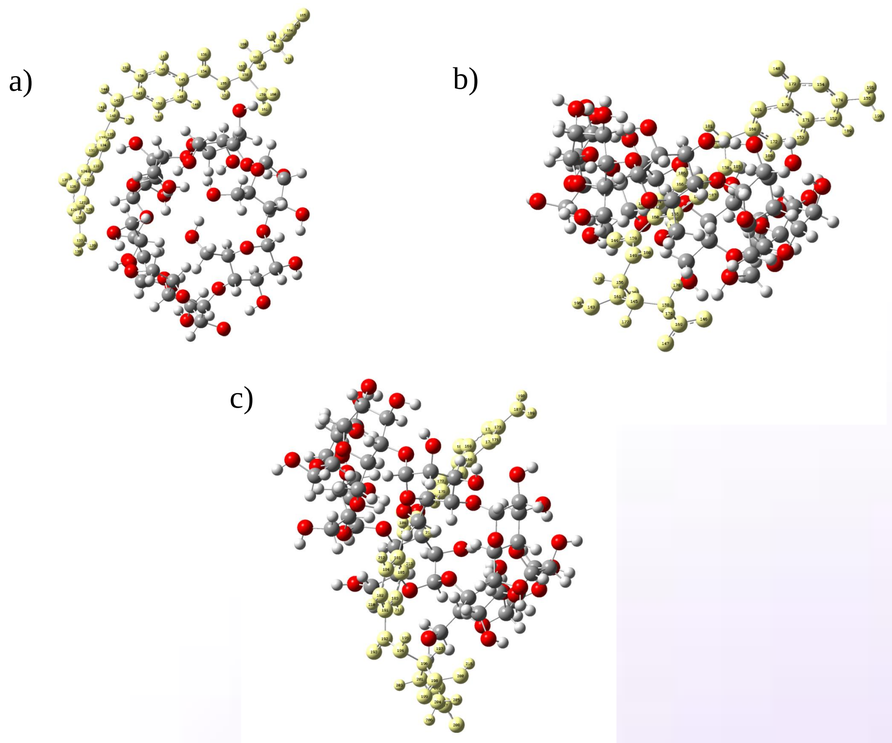

Fig. 3. Proposed structures of a) α-CD/FA, b) β- CD/FA and c)) γ-CD/FA complexes (yellow-folic acid)

Conclusions

We show that IM-MS method can yield useful structural information about cyclodextrins/folic acid complexes. The results obtained within this work are consistent with NMR, differential scanning calorimetry and thermogravimetric analyses.

Bibliography

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2 Riley, K.E.; Jurecka P., Pitonak M, Hobza P, Chem Rev 2010, 110, 5023–5063.

3. http://www.indiana.edu/~nano/software.html