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Examiner's report on the Ph.D. thesis

Examiner: Prof. Ing. Vladimír Šindelář, Ph.D.

Ph.D. student: **Ing. Gábor Benkovics**

Title of the thesis: **Selectively substituted cyclodextrins for analytical and pharmaceutical applications**

This thesis reports on the synthesis of selectively modified cyclodextrins, describes some supramolecular properties of the prepared macrocyclic derivatives and also shortly demonstrate applications of these derivatives. It is clear that there is a lot of work behind the presented results and also that the preparation and isolation of the selectively substituted macrocycles required very good synthetic skills. Entire thesis is written with good English. The theoretical part is quite extensive but some specific examples given in the text are difficult to follow as they are not accompanied with figures. The part "Results and Disscusion" is difficult to follow in several places. It does not represent compact scientific text but rather a composition of separate chapters which, in the addition, lack of some important discussion or additional results. I believe that this is caused by copying long parts of the thesis from the scientific papers of the student while leaving it without important additional text which would mount these parts together. For example, in the chapter 4.4.2 very different UV-Vis spectra of unbound fluorescein and the one appended to β-CD are presented without any explanation. Next chapter 4.4.3 presents eosin (as different xanthene fluorophore) appended to β-CD but discusses an aggregation of this conjugate without any mentioning its spectroscopic characteristics, which are however discussed in following chapter. Aggregation of fluorescein-appended-β-CD is not discussed although it may be possible explanation for the behavior presented in the chapter 4.4.2.

In conclusion, I like the science discussed in the thesis as it represents significant original contribution to the field of organic and supramolecular chemistry. However, I would appreciate its better presentation within the thesis. After reading the thesis, I went through several student's publications and were surprised to find answers to some of my questions which were raised during my examination of the thesis. However, there are still some important questions left to be satisfactorily answered. After that, I would recommend the thesis for the award of the Ph.D. degree.

Questions:

1) Almost entire chapter 4.3 (pages 54 – 67) is based on the article named "New synthetic strategies for xanthene-dye-appended cyclodextrins" (*Beilstein J. Org. Chem.* **2016,** *12*, 537–548)

and the student is only coauthor of this paper. The student should specify his personal contribution on this part of thesis.

2) The preparation of α-CDs bearing a cinnamyl substituent in positions 2 and 3 is claimed to be significantly improved in comparison with the reported procedure, but the advantages of the newly reported method are discussed rather scarcely. Please compare old and new procedures regarding the yields, consumed time, and product isolation.

3) Please explain the difference in ability of 2-*O*-Cin-α-CD and 3-*O*-Cin-α-CD to aggregate in the MeOH/water mixture.

4) How do you explain that addition of α-CD into the solution of 3-*O*-Cin-α-CD does not inhibit the formation of the supramolecular polymer?

5) For which purpose rhodamine B and fluorescein-appended-β-CD were prepared? Did these compounds fulfill the expectations?

6) The first sentence on page 74 seems to be incorrect. What is shown in Figure 36b?

7) The first sentence on page 76 stays: "Carboxymethylated CDs usually separate the enantiomers effectively in the pH range where the carboxylates are partially protonated…". I suppose this sentence means "…in the range where only some from carboxylates are protonated…"? How this is in agreement with the observation that the separation of the tadalafil and tapentadol enantiomers is better at pH 7 than at pH 4.5? Was the same trend observed also in the separation of dapoxetines enantiomers?

Brno, June 7, 2018.

Vladimír Šindelář