UNIVERSITY OF CHEMISTRY AND TECHNOLOGY PRAGUE

Dissertation evaluation report

Title of thesis: SELECTIVELY SUBSTITUTED CYCLODEXTRINS FOR ANALYTICAL AND PHARMACEUTICAL APPLICATIONS

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Review:

The above-mentioned doctoral Thesis represents an interesting contribution, from the group of Doc. Jindřich Jindřich (Charles University, Prague), based on the supramolecular chemistry of cyclodextrines.

Thesis adopts common form and is logically divided into several chapters. The first part (Theoretical overview) deals with a short introduction of the cyclodextrin (CD) family and its most common applications in pharmaceutical and analytical chemistry. This chapter gives a detailed description of the inclusion phenomenon and methods that can be used for the characterization of host-guest chemistry of CDs. This chapter also provides a short overview of the chemical modifications of basic cyclodextrin skeletons.

Another topic is represented by the synthesis of CDs, bearing the corresponding fluorophore moiety (Rhodamine B, Fluorescein, Eosin B and Eosin Y), and thorough characterisation of their structures and the aggregation behaviour. Finally, some of prepared compounds were used as chiral resolving agents in chiral capillary electrophoresis, thus showing the application potential of these derivatives.

The thesis itself is clearly and perceivably written, with a minimum number of linguistic errors and misprints. In my opinion, the thesis contains interesting findings from the area of supramolecular chemistry of cyclodextrines. The results are scientifically sound and the thesis contributes to the field of the host-guest chemistry and applications of CD derivatives.

Nevertheless, there are some weak spots and conceptual imperfections, which should be mentioned here:

Remarks and notes:

Mono-6-*O*-cinnamyl-α-cyclodextrin (**2**) was prepared in 6% yield by direct alkylation of α-CD with cinnamyl bromide. Hence, a question arises as what is the rest of the reaction mixture? Did you consider the application of the corresponding monotosylate (which is accessible in more than 30% yield) and cinnamyl alcohol? I would expect a much better yield under such conditions.

Figure 12: The temperature dependence for the aggregates of 2-*O*-Cin-α-CD and 3-*O*-Cin-α-CD is dramatically different. Do you have any explanation for this phenomenon?

Figure 20, showing the possible intermolecular inclusion mode of Rho-β-CD in solution, does not correspond to the experimental data. In my opinion, the number of signals in the NMR for such a dimer should be twice the number reported because of the lower symmetry of the whole assembly.

How did you assess the quantitative values of the compounds based on TLC (e.g. p 64: 5–10% based on TLC evaluation)?

Very low quality of some Figures (e.g. Figs 27, 28) obscures their full meaning, which makes the corresponding discussion rather painful to follow.

p. 74: How did you predict the corresponding pK_a values of your compounds?

The substantial part of the thesis is based on a discussion of very sophisticate NMR experiments. Contrary to this, the NMR spectra given in the Experimental part of the thesis are mostly poorly presented and possess many imperfections. Missing coupling constants can be detected in almost every ^{1}H NMR spectrum. If you write "d" (doublet) you must add the corresponding coupling constant, if you write "dd" (doublet of doublets), two values must follow!
The ^{1}H NMR spectra of compounds **6** and **7** are fully unassigned (no coupling constants at all)! Moreover, the description like "7.83-7.82 (d, 1H)" is obviously nonsense as the doublet cannot be "from-to" but instead, it should be reported with the corresponding chemical shift and the coupling constant (more than 25 cases in two spectra).
The chemical shifts in the ^{1}H NMR spectra should be given with only two decimal places (not with three as can be seen in compounds **8**, **9**, **11** and **12**).
Moreover, the ^{13}C NMR spectrum of compound **8** should contain 14 signals, while only 10 signals are reported in the Experimental part. It would deserve some explanation. The same is truth for the spectrum of **9** where one can find only 9 signals reported (out of 14)?!
In my opinion, all these errors shed a bad light on all the above-mentioned sophisticated discussions and indicate that this part of theses was completed rather carelessly.

Recommendation: I have to stress that most of the above-written remarks are more or less marginal. Despite some weaknesses mentioned above, the thesis still contains interesting findings, mostly dealing with a supramolecular behaviour of selected guests. Finally, I recommend this thesis for the defence and subsequent awarding of the academic degree PhD. to Ing. Gábor Benkovics.

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in Prague, 6th June 2018

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