

Review report on PhD thesis of

M.Sc. Jelica Kovačević

**Study of Adamantane-based Supramolecular Cross-linkage Agents for
Cyclodextrin Modified Biopolymers**

The reviewed PhD thesis is devoted to the intermolecular interactions between macrocyclic host molecule (cyclodextrins) and guest molecules that consist of cationic part (quaternary imidazole or benzimidazole) covalently bound by non-polar moiety (adamantane or bicyclo [2,2,2]octane). The author presents very interesting and current material research problem connected with the development of novel organic compounds with the potential application in the biomedicine. The thesis is written on 106 pages and divided into these sections: Theoretical background, Aims of the doctoral study, Experimental section, Results and Discussion, Conclusions and References.

In the theoretical background the author collected information on cyclodextrins (their properties, modifications, their complexes with adamantane) chitosan (physicochemical properties, chemical modification) hyaluronic acid (biosynthesis, enzymatic degradation, metabolism, and bulk gels). Special interest is focussed on host guest systems, particularly formation of cyclodextrin-based complexes, their determination and characterisation. Finally, hydrogels, their classification, techniques for hydrogel preparation and applications are also mentioned.

In the experimental section are mentioned following analytical methods (NMR, IR, ESI-MS, SEC, ITC). Synthetic procedures for preparation of 1-(3-(1-adamantyl)propyl)-3-methylbenzimidazoliumbromide, 1,4-bis(3-methylbenzimidazoliummethyl)bicyclo[2,2,2]octane diiodide and 1,4-bis(3-n-butylbenzimidazoliummethyl)bicyclo[2,2,2]octane diiodide are presented and received intermediates and target products are confirmed by above mentioned analytical methods. Synthesis of B-cyclodextrins modified with reactive groups (p-toluenesulfonyl-, azido-, formylphenyl-) and hyaluronic acid (modified with propargylamino- group) are described. Moreover, B-cyclodextrin-hyaluronan and B-cyclodextrins-chitosan polymers are prepared. Both polymers were characterized with ¹H NMR and IR spectra.

In the section Results and Discussions, experience and knowledge received on target compounds synthesis are discussed. Also results of measurement of intermolecular interactions of six guest molecules: 1-(1-adamantylalkyl)-3-methyl(benz)imidazolium salts with three host molecules: B-cyclodextrin, CB[7] and CB[8] by ITC. Results of supramolecular study of B-cyclodextrin-

hyaluronic acid and B-cyclodextrin-chitosan were discussed. The study revealed that B-cyclodextrin units on B-cyclodextrin-hyaluronic acid polymer form 1 : 1, 1 : 2 and 1 : 3 supramolecular aggregates in a host-guest manner with one-, two- and three- binding sites adamantane-based guest motifs. Similar properties showed B-cyclodextrin-chitosan polymer.

I have following comment to data presented in the thesis:

chapter 7.3.4 page 60

Bicyclo[2,2,2]octane-1,4-dicarboxylic acid CAS No 711-02-4 can be prepared by more straightforward way from dimethyl 1,4-cyclohexane dicarboxylate (Merck 1590 Kč/ 25 g) by reaction with 2-bromoethylchloride (Synthetic Commun. Vol 37(8), 1267-72)

chapter 7.4.1 page 63

Reaction of p-TsCl with water is highly exothermic, the most of p-TsCl is decomposed and adjustment of reaction conditions (water: B-cyclodextrin ratio), (p-TsCl : B-cyclodextrin ratio) speed of stirring, speed of p-TsCl addition is crucial for synthesis of intermediate having one toluenesulfonyl- group per molecule of B-cyclodextrin and important for reproducibility of the experiment.

chapter 8.3 page 72

It was observed (page 72) that intermediate after reaction of 1-adamantane-1-carboxaldehyde and Wittig reagent is unstable, aldehyde is released from dioxolane group. The reason may be presence of water in acidic silica on chromatography purification. Addition of some triethylamine to mobile phase (methanol : chloroform 2 : 98) could prevent it.

For the better understanding of presented results, I have these questions related to the PhD thesis:

1. Why 0.48 equivalent of triphenylphosphine were used in procedure 7.2.6, while 3.3 equivalents of triphenylphosphine were used in previous procedure 7.2.5?
2. Quaternization of 1-alkylimidazoles with methyl iodide (page 74). Could proceed this reaction more selectively if methyl iodide is used at lower temperature? What about alkylation with dimethyl sulphate?
3. Preparation 7.3.4 What reaction vessel was used for reaction with Raney nickel at 80°C, an autoclave?

4. Preparation 7.4.1 What amount of 0.4 M NaOH was charged?
5. Preparation 7.4.2: How the reaction mixture was worked up to get the crude product?
6. Preparation 7.4.4 Is it possible to recrystallize oxidized hyaluronic acid from water?
7. Is carbonyl group in oxidized hyaluronic acid stable and does not react with hydroxy groups of neighbouring molecules by glycosidic bounds?

One remark to Doctoral Thesis Summary

Scheme 8 on the page 20, switch methyl benzimidazole with imidazole

Despite of my critical remarks M.Sc. Jelica Kovačević proved to carry out research on supramolecular and organic chemistry. She elaborated research study on cyclodextrin modified biopolymers from 249 references. Then she prepared target molecules including synthesis of 6 newly prepared intermediates and final products. With these compounds she studied interaction in host-guest manner by measurement of their physical properties with $^1\text{H-NMR}$, DOSY spectra and ITC.

The author of the dissertation thesis has demonstrated the ability to work independently and creatively in the specific field. The thesis meets the standard requirements imposed on the dissertation thesis in the field. Therefore, **I recommend** its acceptance.

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