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Novel zinc(II)/chitosan-based composite: ultrasound-assisted synthesis, catalytic and antibacterial activity

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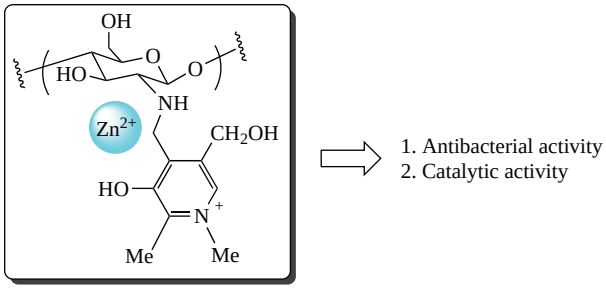
Ultrasonic treatment of the reaction between chitosan and aromatic aldehyde, 4-formyl-3-hydroxy-5-hydroxymethyl-1,2-dimethylpyridin-1-ium iodide, resulted in its significant acceleration and increase in degree of derivatization. The CH=N bond of the prepared Schiff base was reduced, and the formed polymeric material was converted into the corresponding zinc(II) composite by treatment with $ZnCl_2$ and NaOH. The obtained composite is non-toxic, possesses high antibacterial activity and can be employed as the catalyst in the Mannich reaction between benzaldehyde, phenylacetylene and piperidine.



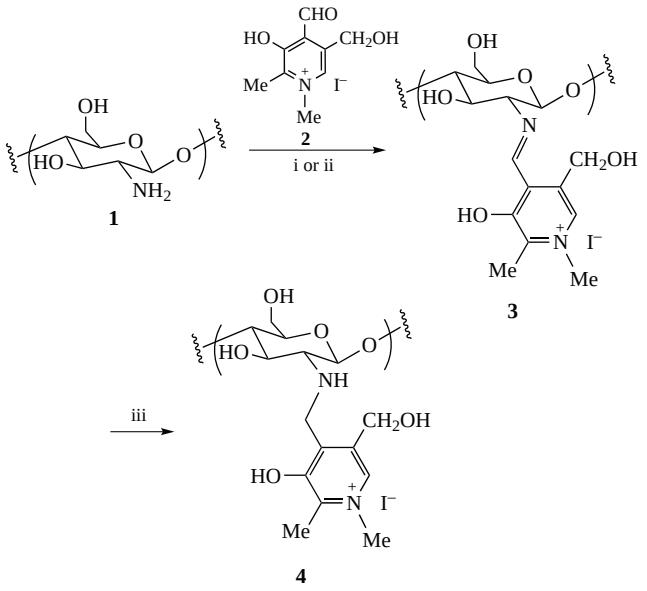
Keywords: chitosan, zinc(II) complexes, antibacterial activity, catalytic activity, Mannich reaction, propargylic amines, pyridoxal.

Preparation of multifunction chitosan-based materials is an important area of green chemistry, since chitosan is bio-condensatum characterized by biocompatibility, biodegradability and low toxicity.[1–7] Chemical modification of chitosan provides novel derivatives with attractive physicochemical properties.[8–10] Recently, using ultrasonic-assisted dipolar cycloaddition, we have prepared dual function chitosan materials which can serve as efficient catalysts for monoesterification of glycerol as well as possess high antibacterial effect.[11] Coordination of various metal centers to polymer matrix of chitosan or its derivatives often results in reinforcement of the chitosan-based materials and improvement of their physicochemical and biological properties.[12,13]

Being inspired by these facts and in view of our previous progress in ultrasound-assisted chemical modification of chitosan,[14–17] in this study, we employed ultrasonic derivatization of chitosan amino group with *N*-methylpyridoxal iodide (4-formyl-3-hydroxy-5-hydroxymethyl-1,2-dimethylpyridin-1-ium iodide) as the aldehyde component. The thus obtained material was further modified and converted into zinc complex whose properties were found promising. Reaction between chitosan and aromatic aldehydes giving Schiff bases is a powerful means for chitosan derivatization.[18] On the other hand, such type of Ad_N-E reactions can be efficiently accelerated by ultrasound providing yield improvement and reduction in excess of aldehyde used.[19–23] However, to the best of our knowledge, ultrasound assistance for Ad_N-E reactions in chitosan chemistry were not documented to date. For the complex preparation, we chose zinc(II) since it is known for pronounced antibacterial effect and catalytic activities in Mannich-type synthesis of propargylic amines.[24]

The target chitosan derivatives were prepared from chitosan **1** and aldehyde **2** (Scheme 1). The first step of obtaining the Schiff base was performed under both ultrasonic and common conditions (see Online Supplementary Materials). Screening of ultrasonic conditions showed frequency of 80 kHz, output power 250 W, and a reaction time of 10 min as the optimum ones. These conditions dramatically accelerate the reaction and save integrity of the polysaccharide backbone (the control experiment showed that sonication of chitosan solution at 80 kHz and 250 W for 10 min reduced its viscosity by less than 2%). Moreover, ultrasound allows one to decrease the amount of the used aldehyde to reach the same degree of derivatization as compared with common protocol. We have revealed that to achieve 0.6 (60%) degree of derivatization under common conditions at 25 °C, 1.8 equiv. of aldehyde and *ca*. 3 h reaction time were needed, while under ultrasonic conditions the reaction takes only 10 min and requires only 0.7 equiv. of the aldehyde at the same temperature. The resulting Schiff base **3** was reduced into the corresponding amine **4** (see Scheme 1) with sodium borohydride.

Assuming that chitosan-supported zinc(II) can possess higher catalytic activity for the synthesis of propargylic amines than free salts, we prepared zinc(II) complexes of chitosan (Zn@**1**) and its derivative **4** (Zn@**4**). For this purpose, aqueous solutions of polymers **1** or **4** were treated with 1% $ZnCl_2$ followed by addition of 50% NaOH, which caused precipitation of white-



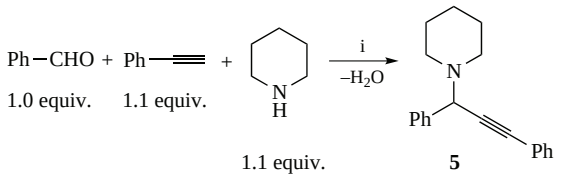
Scheme 1 *Reagents and conditions*: i, aq. HCl (0.1 M), ultrasound, 25 °C, 10 min; ii, aq. HCl (0.1 M), 25 °C, 3 h; iii, $NaBH_4$, H_2O.

coloured composites (for details, see Online Supplementary Materials). The starting chitosan **1** and derivatives **4**, Zn@**1**, and Zn@**4** were characterized by FTIR spectroscopy, scanning electron microscopy (SEM), thermogravimetric analysis (TGA) and powder X-ray diffraction analysis. Water-soluble material **4** was also characterized by ^{1}H NMR spectroscopy. The corresponding data and their short discussion are presented in Online Supplementary Materials.

Catalytic studies on the Mannich-type reaction between benzaldehyde, piperidine and phenylacetylene affording propargylic amine **5** (Scheme 2) were carried out in the presence of new complexes Zn@**1** and Zn@**4**. For comparison, inorganic zinc(II) compounds were also tested (see Table S2, Online Supplementary Materials).

In fact, various inorganic zinc(II) compounds have the similar catalytic effects on the reaction, while chitosan-supported ones demonstrates higher catalytic activity. The most effective catalyst proved to be Zn@**4**, the most suitable solvent was toluene. We have found that complex Zn@**4** could be reused 6 times without decrease in its catalytic activity. High catalytic activity of Zn@**4** compared to Zn@**1** and reusability of Zn@**4** can be explained by its high thermal stability caused, most probably, by its higher crystallinity (TGA data, see Online Supplementary Materials, Figures S3–S6). Our results are among the best ones so far reported (see review[25]). Importantly, the related $Zn(NO_3)_3$/chitosan catalyst is less effective in the same Mannich reaction.[26]

Antibacterial *in vitro* activity against *E. coli* and *S. aureus* of the obtained complexes Zn@**1** and Zn@**4** was studied and compared with those of starting chitosan **1**, **4**, $ZnCl_2 \cdot 6H_2O$, $Zn(OH)_2$, ZnO, and commercially available antibiotics Ampicillin and Gentamicin. Complex Zn@**4** demonstrated high antibacterial effect compared to that of the reference antibiotics. It can be explained by symbatic effect of (i) increased cationic density of Zn@**4** compared with the starting chitosan and (ii) the



Scheme 2 *Reagents and conditions*: i, zinc(II)-based catalyst (8–10 wt%), solvent, 78–110 °C, 10 h.

presence of zinc(II) in polymeric matrix of the composite. Toxicity of the tested antibacterial compounds (**1**, **4**, Zn@**1**, Zn@**4**, $ZnCl_2 \cdot 6H_2O$, $Zn(OH)_2$, ZnO, Ampicillin and Gentamicin) was evaluated *in vitro* by conventional MTT-test. At concentrations of less than 700 ng μl^{-1}, compounds **4**, Zn@**1** and Zn@**4**, within the margin of error, showed a toxicity similar to that of the starting chitosan **1**. At the same concentrations, $ZnCl_2 \cdot 6H_2O$, $Zn(OH)_2$, ZnO, Ampicillin and Gentamicin demonstrated twofold and higher toxicity.

In conclusion, using effective ultrasonic approach, we have prepared new cationic chitosan derivative which efficiently coordinates zinc(II) center to give complex Zn@**4** with higher thermostability (as compared with both the starting chitosan and its zinc(II) complex Zn@**1**). This complex turned to be a promising catalyst for the Mannich-type synthesis of propargylic amines. Antibacterial activity of Zn@**4** was found to be comparable with that of Ampicillin and Gentamicin, while toxicity of Zn@**4** is much lower. It would be very intriguing to compare zinc(II) complexes of chitosan derivatives based on other aldehydes with regard to their catalytic and antibacterial activity to clarify specific structure–property relationships, and this project is underway in our group.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.09.030.

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