**Оригинальная статья / Original article**
**УДК 547.245/246 + 547.79 + 542.91**
**http://dx.doi.org/10.21285/2227-2925-2019-9-3-366-375**

# Interaction of β-cyclodextrin with tosyl chloride in an aqueous alkaline medium

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***Abstract:*** *The regioselective functionalisation of the cyclodextrin matrix provides the possibility of purposefully altering the ability of cyclodextrins to form inclusion compounds, as well as to ensure their solubility, thus expanding the scope of their practical application [1, 2]. The most significant and promising trend in the selective modification of β-cyclodextrins consists in the preparation of tosyl derivatives, given that the substitution of such nucleophilic reagents as iodide, azide, thioacetate, hydroxylamine, alkylamide or polyalkylamide for the tosyl group results in the corresponding monosubstituted derivatives. In this study, we implemented a method for the synthesis of mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin, which was improved by β-cyclodextrin reacting with tosyl chloride in an aqueous medium in the presence of a base. The reaction of β-cyclodextrin with tosyl chloride in an aqueous alkaline medium produced a 58% yield of mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin not requiring additional purification. The optimal concentrations of β-cyclodextrin and tosyl chloride were found to be 0.0032 mol/l and 0.0015 mol/l, respectively. It was shown that a decrease in the rate of filtering the unreacted tosyl chloride out of the reaction mixture is accompanied by an increase in the proportion of ditosyl derivatives and mono(3,6-anhydro)-β-cyclodextrin resulting from the intramolecular cyclisation of mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin at room temperature under alkaline conditions. The structure of the obtained mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin was confirmed using Proton NMR Spectroscopy. The proton NMR spectrum of the product resulting from the reaction of β-cyclodextrin with tosyl chloride contains signals corresponding to a tosyl radical: a singlet (2.42 ppm) and two doublets (7.41–7.43 ppm) produced by hydrogens of the benzene ring having radicals in the para position. Monosubstitution was confirmed by comparing the integrated intensities of signals produced by the protons of the cyclodextrin skeleton and the protons from the aromatic part of the reaction product. Their ratio indicated that only one of the seven primary hydroxyl groups of β-cyclodextrin was substituted.*

***Keywords:*** *β-cyclodextrin, tosyl chloride, mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin, Proton NMR Spectroscopy*

**Acknowledgements:** The work is executed within the framework of state task of Department of education and science of Russia (№ 4.5867.2017/8.9) and with the use of equipment of the Baikal analytical center of the collective use.

**Information about the article:** Received November 30, 2018; accepted for publication September 5, 2019; available online September 30, 2019.

**For citation:** Novokshonov V.V., Nguyen Thi Thu Xuan, Shaglaeva N.S., Podgorbunskaya T.A., Bayandin V.V. Interaction of β-cyclodextrin with tosyl chloride in an aqueous alkaline medium. *Izvestiya Vuzov. Prikladnaya Khimiya i Biotekhnologiya* [Proceedings of Universities. Applied Chemistry and Biotechnology]. 2019, vol. 9, no. 3, pp. 366–375. (In Russian). DOI: 10.21285/2227-2925-2019-9-3-366-375

# Взаимодействие β-циклодекстрина с толуолсульфохлоридом в водно-щелочной среде

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***Резюме:*** *Региоселективная функционализация циклодекстриновой матрицы позволяет целенаправленно изменить способность циклодекстринов к образованию соединений включения, а также их растворимость, расширяя тем самым спектр их практического применения. Важнейшим и перспективным направлением в области селективной модификации β-циклодекстринов является получение тозильных производных, так как замещение тозильной группы такими нуклеофильными реагентами, как йодид, азид, тиоацетат, гидроксиламин, алкил- или полиалкиламид, приводит к соответствующим монозамещенным производным. В данной работе реализован метод синтеза моно[6-О-(4-толилсульфонил)]-β-циклодекстрина, усовершенствованный путем взаимодействия β-циклодекстрина с тозилхлоридом в водной среде в присутствии основания. Реакцией β-циклодекстрина с тозилхлоридом в водной среде в присутствии щелочи получен моно[6-О-(4-толилсульфонил)]-β-циклодекстрин с выходом 58% с чистотой, не требующей дополнительной очистки продукта. Установлено, что оптимальная концентрация β-циклодекстрина и тозилхлорида составляет 0,0032 моль/л и 0,0015 моль/л соответственно. Показано, что снижение скорости отфильтровывания непрореагировавшего тозилхлорида от реакционной смеси сопровождается возрастанием доли дитозильных производных и моно(3,6-ангидро)-β-циклодекстрина, образующегося в результате внутримолекулярной циклизации моно[6-О-(4-толилсульфонил)]-β-циклодекс-трина в щелочной среде при комнатной температуре. Структура полученного моно[6-О-(4-толилсульфонил)]-β-циклодекстрина подтверждено методом ПМР-спектроскопии. В ПМР-спектре продукта реакции β-циклодекстрина с тозилхлоридом появляются сигналы тозильного радикала при 2,42 м.д. и два дублета от водородов бензольного кольца с радикалами в пара-положении в области 7,41–7,43 м.д. Монозамещение доказано сопоставлением интегральных интенсивностей сигналов протонов циклодекстринового каркаса и протонов ароматической части продукта реакции, при этом их соотношение свидетельствовало о том, что только одна из семи первичных гидроксильных групп β-циклодекстрина была замещена.*

***Ключевые слова:*** *β-циклодекстрин, тозилхлорид, моно[6-О-(4-толилсульфонил)]-β-циклодекстрин, ПМР-спектроскопия*

**Благодарности**: Работа выполнена в рамках государственного задания Министерства образования и науки России (№ 4.5867.2017/8.9) и гранта РФФИ (№ 19-08-00342) и с использованием оборудования Байкальского аналитического центра коллективного пользования.

**Информация о статье:** Дата поступления 30 ноября 2018 г.; дата принятия к печати 5 сентября 2019 г.; дата онлайн-размещения 30 сентября 2019 г.

**Для цитирования:** Новокшонов В.В., Нгуен Тхи Тху Суан, Шаглаева Н.С., Подгорбунская Т.А., Баяндин В.В. Взаимодействие β-циклодекстрина с толуол-сульфохлоридом в водно-щелочной среде // *Известия вузов. Прикладная химия и биотехнология.* 2019. Т. 9, N 3. С. 366–375. DOI: 10.21285/2227-2925-2019-9-3-366-375

## INTRODUCTION

Cyclodextrins are cyclic oligosaccharides built from D-glucopyranose units joined by α-1,4 glycosidic bonds. Cyclodextrin molecules possess a truncated cone structure having a hydrophilic outer surface and a more hydrophobic cavity. Primary and secondary hydroxyl groups are located on the narrow and wide rims of the truncated cone, respectively. Due to this structure, cyclodextrins can be molecularly recognised, providing the possibility of selectively capturing organic and inorganic molecules or ions [1, 2]. The correspondence of the cyclodextrin cavity and the guest molecule in terms of their geometric characteristics constitutes a necessary condition for the formation and stability of such inclusion complexes.

The regioselective functionalisation of the cyclodextrin matrix allows the purposeful alteration of the capacity of cyclodextrins to form inclusion compounds, as well as to ensure their solubility, thus expanding the scope of their practical application [1, 2]. However, the synthesis of regioselectively substituted cyclodextrin derivatives constitutes an experimentally challenging task due to cyclodextrin having a large number of spatially close hydroxyl groups similar in terms of reactivity and the presence of a cavity resulting in the tendency to form inclusion compounds with reagents [3, 4].

The increased interest in basic and applied research pertaining to α-, β- and γ-cyclodextrins – especially β-cyclodextrin (β-CD) and its derivatives –

is determined by the unique ability of cyclodextrins to form inclusion complexes.

The β-CD molecule contains three types of hydroxyl groups (each comprising seven hydroxyl groups) that can participate in a modification reaction: primary groups in Position 6, as well as secondary groups in Positions 2 and 3 in each of the seven glucopyranose units (Fig. 1).

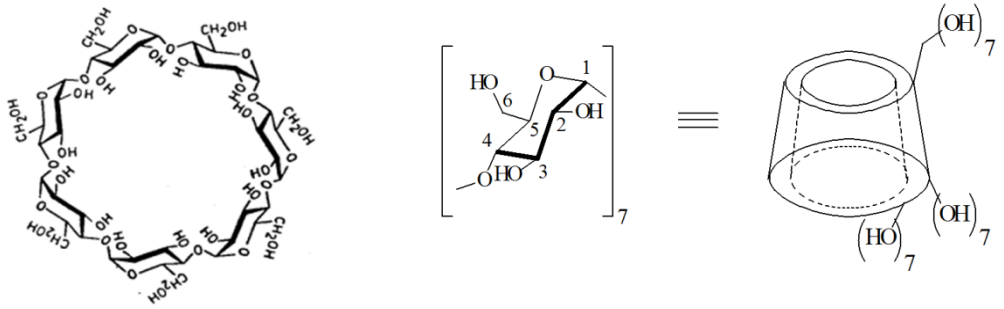

***Fig. 1. Structure of β-cyclodextrin***

***Рис. 1. Структура β-циклодекстрина***

Modified β-CD molecules are used as enzyme simulators for targeted drug delivery in the human body using substituted functional groups, which participate in molecular recognition [5, 6], as well as having applications in analytical chemistry [2, 7–11].

Given that mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin is a precursor for the preparation of β-CD derivatives monosubstituted in Position 6, a significant and promising trend in the selective modification of β-CDs consists in the preparation of tosyl derivatives. The substitution of such nucleophilic reagents as iodide, azide, thioacetate, hydroxylamine, alkylamide or polyalkylamide for the tosyl group results in the corresponding monosubstituted derivatives [2, 12–14].

The reaction of β-CD with tosyl chloride under aqueous alkaline conditions produces an 11–43% yield of mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin [15–17]. In non-aqueous media and in the presence of sodium hydride, tosylation occurs at the secondary hydroxyl group in position 2, with the yield of mono-2-O-(p-toluenesulphonyl)-β-cyclodextrin coming to 42% [18]. In terms of experimental setup, aqueous alkaline conditions are simple and convenient; however, a wide variation in the target product yield obtained using various versions of the method indicates the necessity for improving the process.

The substitution of p-toluenesulfonic acid anhydride (1.5-fold excess) for tosyl chloride allows the yield of the monotosylated product to be increased up to 61% [19]. However, the use of this reagent is impractical due to its high cost and difficulty of procurement.

In [20], it is proposed to use 1-(p-toluenesulphonyl)imidazole as a tosylating reagent under aqueous alkaline conditions. In comparison with p-toluenesulfonic acid anhydride, the advantage of this reagent consists in its better water solubility and greater resistance to hydrolysis at room temperature. In the above-mentioned work, mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin was isolated from the solution by means of precipitation, giving a yield of approximately 40%.

When using a complex based on β-CD and $Cu^{2+}$ ions, an increase in the yield of mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin up to 48% is observed. The reaction occurs in an aqueous alkaline medium, with tosyl chloride acting as the tosylating agent [21]. While an indisputable advantage of this method consists in the regioselectivity of tosylation (functionalisation of only primary hydroxyl groups), its main disadvantages include excessive use of p-toluenesulphonyl chloride (up to 8 equiv), the necessity of freezing a large volume of the aqueous phase in order to isolate the target product and the problem of managing copper-containing waste.

In [22], an 84.6% yield of mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin was obtained through the reaction of β-CD with p-toluenesulphonyl chloride in aqueous acetonitrile and in the presence of sodium hydroxide. However, following multiple attempts to repeat this procedure and calculate the material balance of the process, the researchers concluded that the yield of the tosylated product is proportional to the amount of β-CD that enters into the reaction.

The present work is aimed at improving the method for producing mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin through the interaction of β-CD with tosyl chloride in an aqueous alkaline medium. The procedure presented in [16] was selected as the basis of the experimental work.

## EXPERIMENTAL PART

$^1$H NMR spectra were recorded in DMSO-$d_6$ using a BrukerDPX-400 (400 MHz).

*Synthesis of mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin according to the procedure presented in* [16]. 10 g (0.008 mol) of β-CD and 100 ml of $H_2O$ were mixed in a 500 ml three-neck flask.

Next, NaOH was added in the amount of 1.6 g (0.04 mol). After cooling the reaction mixture to 0 °C, powdered dry tosyl chloride – 7 g (0.037 mol) at a time – was sprinkled into the mixture for 7 minutes. The reaction mixture was then stirred for 30 min at 0 °C. Excess tosyl chloride was isolated from the solution via filtration using a Buchner funnel equipped with a vacuum water pump. Next, the isolated p-toluenesulphonyl chloride was placed in a freezer for a short time. The filtrate was slightly acidified with an HCl solution to pH = 5–6 and stirred for 1 h at 0–2 °C. The white precipitate was filtered out using a Buchner funnel and then washed twice with 10 ml of $H_2O$. Following dessication under a vacuum, 3.88 g (38%) of the target product was obtained. Following the addition of NaOH to the filtrate in the amount of 1.6 g (0.04 mol), the synthesis was repeated using the previously isolated tosyl chloride. Following a similar procedure, 4.49 g (44%) of mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin was obtained in total. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm, (*J*, Hz): 2.42 (s, 3H); 3.20–3.65 (m, 40H); 4.15–4.20 (m, 1H); 4.30-4.38 (m, 2H); 4.44–4.57 (m, 2H); 4.51 (br. s, 3H); 4.76 (br. s, 2H); 4.83 (br. s, 4H); 5.62–5.83 (m, 14H); 7.42 (d, 2H, *J* = 8.1 Hz); 7.73 (d, 2H, *J* = 8.1 Hz).

*Synthesis of mono-6-deoxy-(p-toluenesulphonyl)]-β-cyclodextrin in an aqueous acetonitrile solution.* 10 g (0.008 mol) of β-CD and 100 ml of $H_2O$ were mixed in a 500 ml three-neck flask, with the subsequent addition of NaOH in the amount of 1.6 g (0.04 mol). After the resulting mixture was cooled to 0 °C, 7 g (0.037 mol) of tosyl chloride dissolved in 5 ml acetonitrile was added dropwise for 4 minutes. The reaction mixture was stirred for 30 min at 0 °C. Then the excess tosyl chloride was promptly isolated from the solution via filtration using a Buchner funnel equipped with a water pump. The isolated p-toluenesulphonyl chloride was temporarily placed in the freezer. The filtrate was slightly acidified with an HCl solution (3 ml $HCl_{conc}$ in 10ml of water, pH = 5–6) and stirred for 1 h at 0 – +2 °C. The white precipitate was filtered out using a Buchner funnel equipped with a vacuum water pump, washed with 10 ml of water and then air-dried. Following one more addition of NaOH to the filtrate in the amount of 1.6 g (0.04 mol), the synthesis was repeated using the previously isolated tosyl chloride. After completing a similar procedure, the total mono-6-deoxy-(p-toluenesulphonyl)]-β-cyclodextrin amounted to 1.66 g (a yield of 15%). The characteristics of this NMR spectrum are completely identical to those mentioned above.

*Synthesis of mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin using a modified procedure.* 10 g (0.016 mol) of β-CD and 40 ml of $H_2O$ were mixed in a 500 ml three-neck flask. Then 1.6 g (0.04 mol) of NaOH dissolved in 10ml of water was added. After cooling the resulting mixture to 0 °C, powered dry tosyl chloride – 7 g (0.074 mol) at a time – was sprinkled into the mixture for 7 minutes. The reaction mixture was stirred for 30 min at 0 °C. Then the excess tosyl chloride was promptly isolated from the solution via filtration using a Buchner funnel equipped with a water pump. The isolated p-toluenesulphonyl chloride was temporarily placed in the freezer. The filtrate was slightly acidified with an HCl solution to pH = 5–6 and stirred for 1 h at 0 °C. The white precipitate was filtered out using a Buchner funnel or separated by centrifugation and washed 2 times with 10 ml of $H_2O$, followed by the air-drying and then drying under vacuum. After adding 1.6 g (0.04 mol) of NaOH to the total filtrate, the synthesis was repeated again using the previously isolated tosyl chloride. Following the completion of a similar procedure, the total mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin amounted to 5.98 g (a yield of 58%). The characteristics of this NMR spectrum are completely identical to the ones mentioned above.

## RESULTS AND DISCUSSION

According to the basic procedure, the synthesis of mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin is achieved by 10 g of β-CD (8 mmol) reacting with 7 g of tosyl chloride (37 mmol, 4.5 equiv.) in the presence of 1.6 g NaOH (40 mmol) in 100 ml of water at a temperature no higher than 0–2 °C for 30 min and the subsequent (if possible) prompt filtering out of the unreacted p-toluenesulphonyl chloride. The yield of the target product amounts to 38% (Table 1, Experiment 1). The reuse of the isolated unreacted tosyl chloride in the reaction with the recently acidified filtrate following the isolation of the target product (Reaction Cycle 2) results in increasing the total yield of mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin to 44% (Table 1, Experiment 2). It should be noted that the obtained mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin is characterised by high purity, so it can be used without additional purification. It is established that a decrease in the rate of filtering the unreacted tosyl chloride out of the reaction mixture results in it heating up to room temperature and a consequent decrease in the purity of mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin. This occurs due to an increase in the proportion of ditosyl derivatives and mono(3,6-anhydro)-β-cyclodextrin, which is formed as a result of the intramolecular cyclisation of mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin in an alkaline medium at room temperature.

An increase in the reaction temperature lowers the target product yield to 11% (Table 1, Experiment 3). When the solvent is replaced by acetonitrile, the yield of mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin rises to 15% (Table, Experiment 4).

***Table***

***Conditions for the reaction of β-cyclodextrin with tosyl chloride***

***Таблица***

***Условия реакции β-циклодекстрина с тозилхлоридом***

| Experiment No. | Reagent amount, mol | | | Reaction conditions | | | Yield β-CD-Tos, % |
|---|---|---|---|---|---|---|---|
| | β-CD | TosCl | NaOH | Solvent | T, °C | Time, min | |
| 1 | 0.08 | 0.037 | 0.008 | $H_2O$, 100 ml | 0–2 | 30 | 38 |
| 2 | 0.08 | 0.037 | 0.008 (cycle 1)<br>0.008 (cycle 2) | $H_2O$, 100 ml | 0 | 30 | 44 |
| 3 | 0.08 | 0.037 | 0.008 | $H_2O$, 100 ml | 23 | 120 | 11 |
| 4 | 0.08 | 0.037 | 0.008 (cycle 1)<br>0.008 (cycle 2) | $H_2O$/MeCN<br>100 ml / 5 ml | 0 | 30 | 15 |
| 5 | 0.08 | 0.037 | 0.008 (cycle 1)<br>0.008 (cycle 2) | $H_2O$, 50 ml | 0 | 30 | 58 |
| 6 | 0.16 | 0.074 | 0.008 (cycle 1)<br>0.008 (cycle 2) | $H_2O$, 50 ml | 0 | 30 | 58 |

In order to further improve the procedure for producing mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin in an aqueous alkaline medium, we studied the possibility of increasing the target product yield by assuming that an increase in the concentration of reagents (with their ratio being kept the same as in the basic procedure) will result in a higher yield of mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin. An increase in the concentration of reagents was achieved by reducing the volume of water being used for the same experiment duration (30 min) at lower reaction temperatures (~0 °C). Given that the rate of by-product formation depends on the content of gradually accumulating mono-6-O-(p-toluenesulphonyl)-β-cyc-lodextrin rather than on the concentration of the starting β-CD, we also assumed that the optimised concentrations of reacting components would not increase the proportion of by-products during a quick reaction. All other things being equal, performing the reaction at a temperature not higher than 0 °C, halving the volume of water being used and reusing the unreacted tosyl chloride resulted in an increase in the yield of mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin to 58% without sacrificing product quality (Table 1, Experiment 5). However, no further increase in the concentration of the starting substances led to an additional increase in the target product yield.

As indicated above, a β-CD molecule contains three types of hydroxyl groups (each including 7 hydroxyl groups) in Positions 2, 3 and 6 (see Fig. 1). The molecular structure of β-CD has the form of a truncated cone. Unlike hydroxyl groups attached to the second and sixth carbon atoms, the hydroxyl group attached to the third carbon atom (OH-3) is oriented into the cavity of the cone and is thus not available for substitution reactions with tosyl chloride. The reaction of β-CD with tosyl chloride is schematically shown in Figure 2.

A comparison of proton NMR spectra for the starting β-CD and the product of its reaction with tosyl chloride determines the structural orientation in the reaction (Fig. 3).

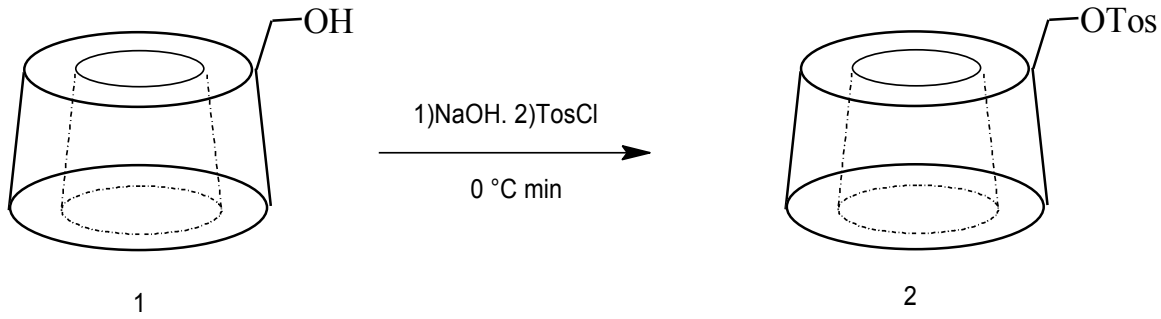


***Fig. 2. Reaction of β-CD with tosyl chloride***

***Рис. 2. Реакция β-CD с тозилхлоридом***

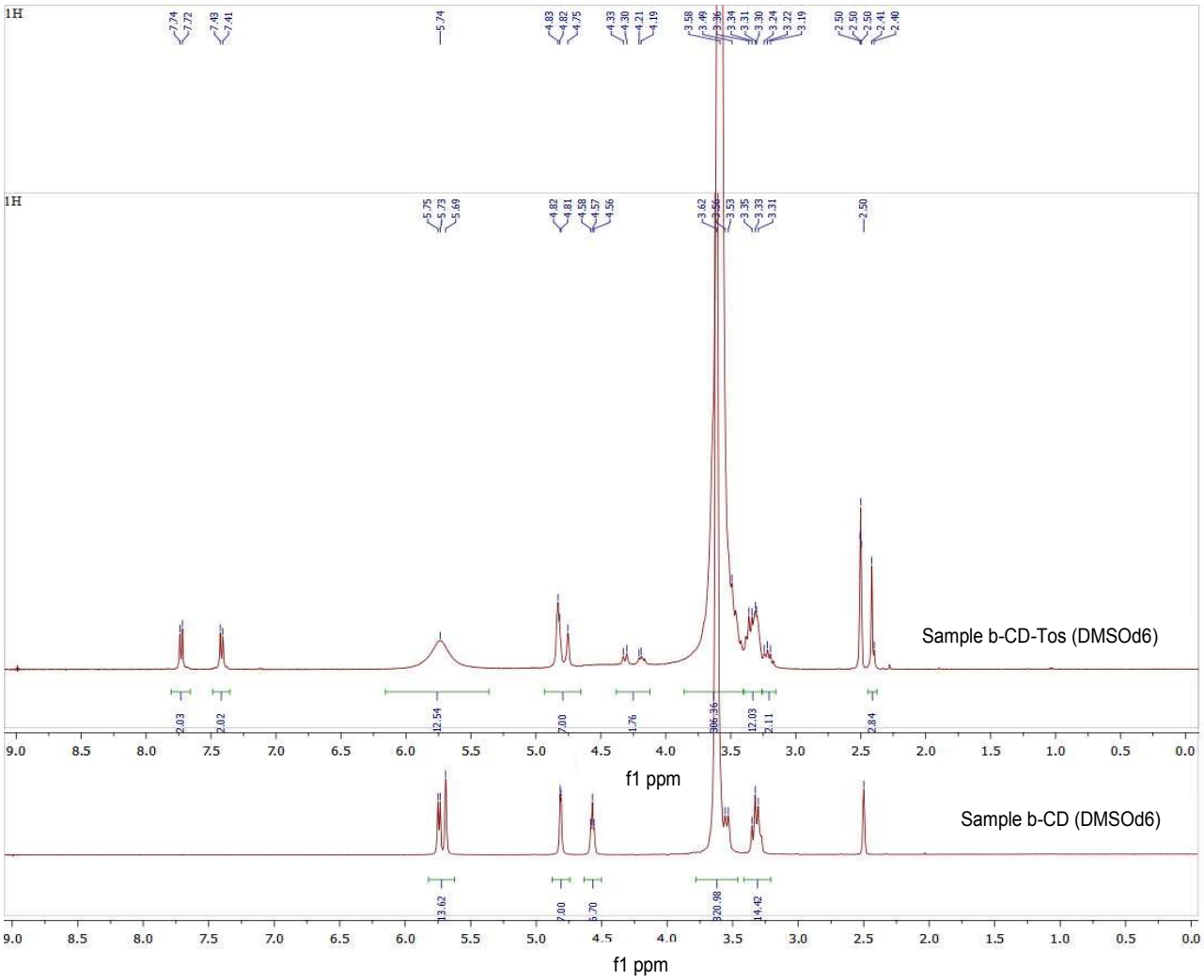


***Fig. 3 $^1$H NMR spectrum for the starting β-cyclodextrin and mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin***

***Рис. 3 Спектр $^1$H ЯМР исходного β-циклодекстрина и моно[6-О-(4-толилсульфонил)]-β-циклодекстрина***

The proton NMR spectrum for β-CD shows a doublet (5.73–5.75 ppm) corresponding to the hydroxyl group attached to the second carbon atom (OH-2), a singlet (5.69 ppm) corresponding to the hydroxyl group attached to the third carbon atom (OH-2), a doublet (4.81–4.82 ppm) corresponding to the H-1 proton, a triplet (4.56–4.58 ppm) corresponding to the hydroxyl group attached to the sixth carbon atom (OH-6) and a multiplet (3.29–3.35 ppm) produced by H-2 and H-4 protons [23]. Other signals of β-CD are obscured by the intense signal produced by water molecules.

Figure 3 shows that the proton signals of β-CD are split in a ratio of 6:1 and that the integrated intensity for every two protons from the aromatic ring of the tosyl radical equals 2, whereas the intensity of signals corresponding to a hydrogen atom of one β-CD unit comes to 7. Given that a β-CD molecule contains seven D-glucopyranose units, the reaction results in the formation of a monosubstituted product.

It was assumed that the introduction of a tosyl radical would significantly change the position of signals produced by the hydrogen protons attached to the carbon atom that is bound to the tosyl radical, shifting them to the weak-field region, whereas the remaining protons of β-CD would only shift to an insignificant extent. Indeed, the proton NMR spectrum for the product (result of β-CD reacting with tosyl chloride) shows signals of a tosyl radical: a singlet at 2.42 ppm (-$CH_3$) and two doublets (7.41–7.43 ppm and 7.72–7.74 ppm) produced by the hydrogens of the benzene ring having radicals in the para position.

In the proton NMR spectrum, the signals of the H-2 and H-4 hydrogen atoms split slightly at 3.30–3.36 ppm and 3.18–3.24 ppm (see Fig. 3). Signals observed at 3.30–3.36 ppm were pro-

duced by the hydrogen atoms of the unsubstituted β-CD; whereas signals observed at 3.18–3.24 ppm correspond to the hydrogen atoms of the substituted β-CD. These results indicate that the tosyl radical is not bound to the second β-CD carbon atom. However, two multiplets having centres at 4.19 ppm and 4.30 ppm appear in the proton NMR spectrum for the substituted reaction product, which can be attributed to nonequivalent hydrogens attached to the 6th carbon atom (H-6a, H-6b) that is bound to the tosyl radical. Signals produced by the same protons, but from the unsubstituted β-CD units, are obscured by a wide water peak. This means that the reaction of β-CD with tosyl chloride occurs at the hydroxyl group attached to the sixth carbon atom of β-CD.

Thus, the analysis of the proton NMR spectra for the starting and substituted β-CD indicates that the reaction of β-CD with tosyl chloride occurs only at the hydroxyl group attached to the sixth carbon atom of β–CD, with the formation of a monosubstituted β-CD product.

## CONCLUSION

The improvement of a known procedure for obtaining mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin in an aqueous alkaline medium [16] by doubling the concentration of reagents and using unreacted tosyl chloride in the second reaction cycle resulted in an increase of the yield of mono-6-O-(p-toluenesulphonyl)-β-cyclodextrin up to 58% with no need for additional purification.

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### *Contribution*

Vladimir V. Novokshonov, Nguyen Thi Thu Xuan, Nina S. Shaglaeva, Tatiana A. Podgorbunskaya, Victor V. Bayandin carried out the experimental work, on the basis of the results summarized the material and wrote the manuscript. Vladimir V. Novokshonov, Nguyen Thi Thu Xuan, Nina S. Shaglaeva, Tatiana A. Podgorbunskaya, Victor V. Bayandin have equal author's rights and bear equal responsibility for plagiarism.

### *Conflict of interests*

The authors declare no conflict of interests regarding the publication of this article.

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### *Критерии авторства*

Новокшонов В.В., Нгуен Тхи Тху Суан, Шаглаева Н.С., Подгорбунская Т.А., Баяндин В.В. выполнили экспериментальную работу, на основании полученных результатов провели обобщение и написали рукопись. Новокшонов В.В., Нгуен Тхи Тху Суан, Шаглаева Н.С., Подгорбунская Т.А., Баяндин В.В. имеют на статью равные авторские права и несут равную ответственность за плагиат.

### *Конфликт интересов*

Авторы заявляют об отсутствии конфликта интересов.

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