

Inclusion-dependent mechanism of modification of cyclodextrins with heterocycles

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Abstract: Mono(6-deoxy-dimethylpyridinium)- β -cyclodextrins have been synthesized in reaction of mono (p-toluenesulfonyl) derivative of β -cyclodextrin with the appropriate lutidine under microwave irradiation and conventional conditions. The results indicate that the mechanism consists of inclusion complex formation.

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1 Introduction

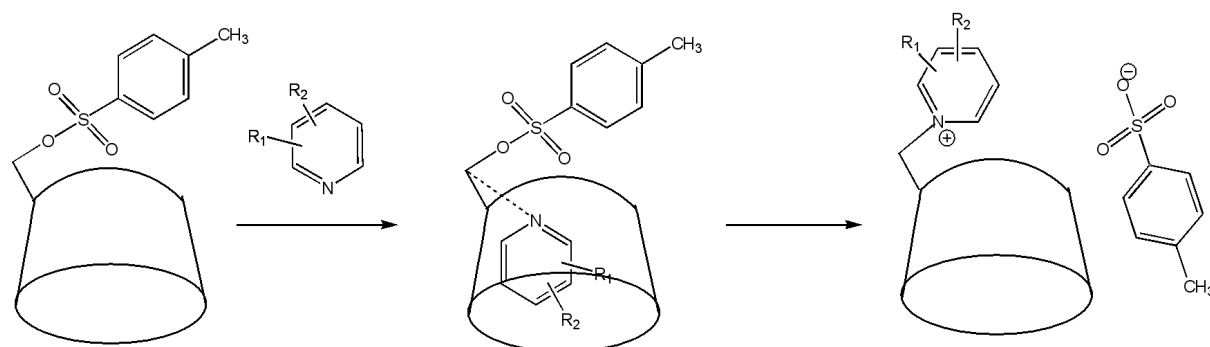
Cyclodextrins (CD) as well as their derivatives and polymers have gained high popularity in the last years because of their industrial importance [1-3]. Their abilities to complex a wide variety of organic and inorganic compounds are broadly utilized. CD derivatives may form chemoreceptors for different guests [4,5]. Interestingly, similar structures could be used as carriers to increase bioavailability of water insoluble drugs [6,7]. Many new possibilities have been discovered with new, microwave-assisted protocols for synthesis of such structures [8-11]. This prompted us to present our preliminary observations regarding to new procedure facilitating synthesis of new monomodified, water soluble β -CD derivatives, containing heterocyclic moieties. These could be of great importance in understanding the reactivities of cyclodextrins under both conventional and solid state,

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microwave assisted conditions [12].

2 Results and discussion

In our experience, an efficient way of obtaining water soluble monofunctionalized cyclodextrins is through the formation of monotosyl derivatives. There are a number of methods of monotosylation of CDs [13,14]. We performed this using simple and easy to monitor protocol [12]. We synthesized p-toluenesulfonyl salts of β -cyclodextrin functionalized with dimethylpyridine moieties as shown in Scheme 1. The microwave-assisted synthesis affords lower yields than conventional heating; however, this technique is much faster and very convenient. Table 1 shows the results obtained by conventional and microwave-assisted synthesis in comparison to similar compounds described in the literature.



Scheme 1 Synthesis of monomodified of β -CD.

Products obtained this way need no further purification by column chromatography. Use of equimolar amounts of substrates reduces the waste and additional chemicals necessary in synthesis (e.g. solvents). Microwave-assisted synthesis in solid state reported here matches well with the aims of “green chemistry”.

Unexpectedly, we observed that there was no product in the cases of 2,6-dimethylpyridine, 3,5-dimethylpyridine, and 2,4,6-collidine. An explanation of this observation may be an effect of steric disturbances during the formation of inclusion complexes, as shown in Scheme 2. This implicates that these reactions are undergoing a two-step mechanism. First, the molecule of substituted pyridine is complexed into the β -CD cavity, then the proper substitution takes place. In cases of structurally extended compounds the inclusion complex is formed in the “tail first” manner that prevents the next step and product formation.

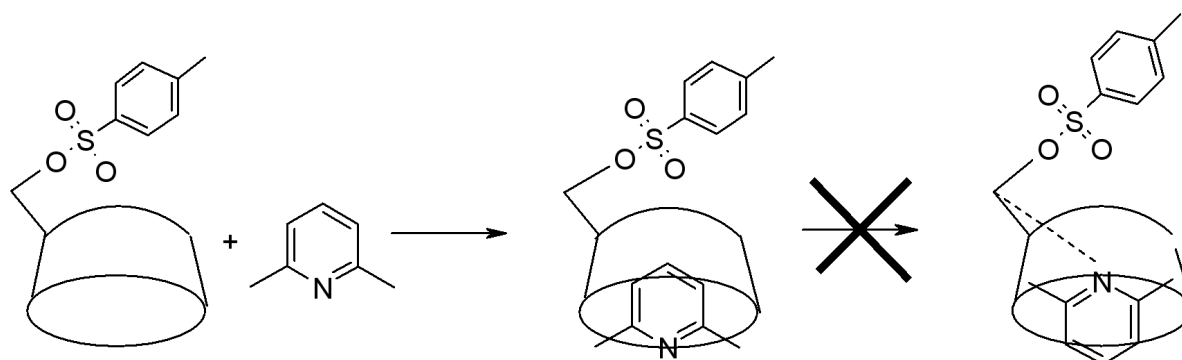
3 Experimental section

All ^1H NMR and 2D NMR spectra were recorded on Bruker NMR 300 MHz instrument in DMSO- d_6 ; diffuse signals from easily exchangeable protons were not listed. For

Compound	Procedure	
	Microwave	Conventional
Pyridine	–	12h/18 % [15]
3-methyl-pyridine	–	12h/91 % [12]
4-methyl-pyridine	–	12h/89 % [12]
2,3-dimethyl-pyridine	2min/47 %	2h/90 %
2,4-dimethyl-pyridine	2min/65 %	2h/93.5 %
3,4-dimethyl-pyridine	2min/65 %	2h/94 %
2,6-dimethyl-pyridine	–	–*
3,5-dimethyl-pyridine	–	–*
2,4,6-trimethyl-pyridine	–	–*

* After 12h reflux or 2min irradiation the product was not formed.

Table 1 Traditional and microwave assisted synthesis of mono[6-(lutidinyl)-6-deoxy]- β -cyclodextrins



Scheme 2 Inclusion complex dependent mechanism of modification of β -CD

better visualization, examples of ^1H NMR and 2D NMR (in COSY experiment) spectra of mono(6-deoxy-6-(2,3-dimethylpyridinium)- β -cyclodextrin tosylate are shown in Supporting Information (www.cesj.com/chemistry/files/13-paper-Support-SI1-SI3.pdf). Traditional reactions were carried out in a standard oil bath and microwave assisted synthesis were carried out using a Sharp domestic microwave oven. IR spectra were recorded on a Nexus Nicloet FTIR apparatus (KBr). TLC experiments were done on SiO_2 precoated plates with UV indicator (butanol/ethanol/water in proportions 3/5/3 was used as a mobile phase).

3.1 Materials

For the reason that β -cyclodextrin forms very stable complex with six molecules of water [2], β -CD, after recrystallization from water was dried under low pressure for 12 hours at 100 °C. Pyridine was dried with solid NaOH and then fractionally distilled. Commercially

available p-toluenesulfonyl chloride (Anal. purity) and pyridine derivatives were used without further purification.

MTs- β -CD was synthesized as described before [8]. Crude MTs- β -CD was recrystallized from water and dried under low pressure at 90 °C. Monomodification was verified by liquid chromatography followed by ^1H NMR spectroscopy, yield 5 g, 22 % [12].

3.2 General procedure A

0.5 g of MTs- β -CD was added into 30 ml of lutidine and the solution was refluxed under nitrogen atmosphere for 2 hours. Next the precipitate was extracted with acetone in a Soxhlet apparatus, dissolved in a small amount of water and after filtering, precipitated with acetone and centrifuged, filtered and dried under vacuum at 60 °C. When it was necessary the product was purified by column chromatography on Sephadex G25.

3.3 General procedure B

0.5 g of MTs- β -CD and 3 ml of lutidine were mixed with 5 g of Al_2O_3 Montmorillonite and put into the open reactor. Then the mixture was subjected to microwave irradiation for 2 minutes (4 x 0.5 minutes with 2-minute intervals) at output power level 850 W. After the reaction the mixture was added to a small amount of water, filtered and the product precipitated with an excess of acetone. Next the precipitate was centrifuged and dried under vacuum at 60 °C.

Mono(6-deoxy-6-(2,3-dimethyl)pyridinium)- β -cyclodextrin tosylate, was obtained as a light brown solid.

^1H NMR (DMSO- d_6) (δ ppm) 2.082(s, 3H); 2.286(s, 3H); 2.497(s, 3H); 3.20–5.12(m, 42H); 6.28(s 7H); 7.10(d, $J=7.8\text{Hz}$ 2H). IR(neat, cm^{-1}); 3374, 2928, 1646, 1558, 1417, 1367, 1300, 1156, 1080, 1032, 950–530.

Mono(6-deoxy-6-(2,4-dimethyl)pyridinium)- β -cyclodextrin tosylate, was obtained as a light brown solid.

^1H NMR (DMSO- d_6) (δ ppm) 2.25 (s, 3H); 2.375 (s, 3H); 2.475 (s, 3H); 2.875–5.125 (m, 42H); 5.75 (s, 7H); 7.075 (d, $J=7.5\text{Hz}$, 2H); 7.475 (d, $J=7.5\text{Hz}$, 2H); 7.69–7.95 (m, 1H); 8.25 (d, $J=6.25\text{Hz}$, 1H); 8.65–8.875 (m, 1H). IR(neat, cm^{-1}); 3374, 2928, 1643, 1573, 1412, 1367, 1300, 1156, 1080, 1031, 950–530.

Mono(6-deoxy-6-(3,4-dimethyl)pyridinium)- β -cyclodextrin tosylate, was obtained as the yellow solid.

^1H NMR (DMSO- d_6) (δ ppm) 2.079 (s, 3H); 2.29 (s, 3H); 2.5 (s, 3H); 2.9–5.1 (m, 42H); 5.76 (s, 7H); 7.14 (d, $J=7.8\text{Hz}$, 2H); 7.5 (d, $J=8.3\text{Hz}$, 2H); 7.76–8.1 (m, 1H); 8.16–8.37 (m, 1H); 8.52–8.9 (m, 1H). IR (neat, cm^{-1}); 3374, 2928, 1642, 1576, 1412, 1367, 1300, 1156, 1080, 1032, 950–530.

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