Cyclodextrins are cyclic oligosaccharides obtained by bacterial decomposition of starch, thus being a highly sustainable product. α-CD forms the smallest ring of six glucose molecules, whereas β-CD consists of seven, and γ-CD of eight glucose molecules. The glucose units are arranged to form a conical cylinder, generating a cavity with approximately 174, 262, and 427 Å³, for α- to γ-CD, respectively. The cavity enables the formation of inclusion complexes and makes them therefore viable for drug delivery applications. However, this three-dimensional structure is stabilized by an intramolecular hydrogen bonding belt of the secondary hydroxyl groups at the base of the truncated cone (with larger cavity diameter). The primary hydroxyl groups located at the “entrance” of the smaller cavity diameter along with the ether linkages of the glycosidic bonds pointing inside of the frustum elucidate the hydrophobic character of the inner cavity. The hydrogen bonds of the secondary hydroxyl groups are most stable in β-CD resulting in a rigid structure and rather poor water solubility and therefore limiting its potential applications. Improving the solubility of β-CD has been of scientific interest for a long time and various modifications of its structure have been investigated, including amination, esterification or etherification of the respective primary and/or secondary hydroxyl groups. The rigidity of the secondary hydroxyl groups aggravates the selective functionalization, whereas the primary hydroxy groups are more reactive due to their nucleophilic character. In detail, primary and/or secondary OH-groups of β-CDs are tosylated for further functionalization towards amino, azide, thio, thiocyanate or halo-derivatives. For example, the synthesis of mono 6-(p-toluenesulfonyl)-β-CD could be improved by the application of ultrasound and p-toluenesulfonyl imidazole as starting material, leading to a yield of 55%. However, the formation of a 6-amonoamino-6-monodeoxy-β-CD requires two additional synthesis steps. In general, multistep syntheses are often necessary when introducing new functionalities into β-CDs. As in the formerly mentioned example, the hydroxy group is typically first converted to a more reactive functional group, such as a tosylate or an azide, and then further functionalized. For instance, applying an azide-functionalized β-CD, a Staudinger-Aza-Wittig reaction could be performed and an isocyanate, which could be later transferred to the desired urea-functionalized β-CD, was obtained. In a similar manner, cyclodextrins were crosslinked with toluene diisocyanate forming carbamate-functionalized cyclodextrins. The resulting films were insoluble in water but soluble in organic solvents. But also water-soluble were prepared: Polyethylene glycol (PEG)-modified hydrogels were obtained by cycloadition of the formerly mentioned azide-functionalized β-CD and α,ω-dialkyne-PEG. Twofold iodine-functionalized β-CDs can be converted with an amino-acid derivative and subsequently difunctionalized PEG-molecules yielding linear water-soluble polymers. A direct modification of β-CD was performed with diphenyl carbonate. In this way, a crosslinked material with carbonate linkages between the cyclodextrins is obtained. Since the material was insoluble, it was tested as sequestering agent. Further directly modified, water-soluble β-CD-polymer were synthesized by crosslinking with epichlorohydrin.
Within this study, a multicomponent reaction (MCR) approach is introduced for the functionalization of cyclodextrins. Using the Ugi-SCR, a carbamate function can be implemented into cyclodextrins in a straightforward and direct fashion.\textsuperscript{[16]} The Ugi-SCR is a variation of the well-known Ugi-four-component reaction (Ugi-4CR), which requires a primary amine, a carbonyl functional group, an acid, and an isocyanide.\textsuperscript{[17]}

In the Ugi-SCR, the acid component is replaced by carbon dioxide and an alcohol, which also serves as solvent.\textsuperscript{[16]} So far, mostly methanol was investigated as alcohol in the Ugi-SCR, giving excellent yields.\textsuperscript{[18]} While the Ugi-4CR was applied in various polymer syntheses and the modification of polysaccharides,\textsuperscript{[19]} the Ugi-SCR found little application so far.\textsuperscript{[20]}

To our knowledge, the Ugi-SCR was not yet applied for the modification of carbohydrates. Previously, the use of different alcohols was reported by our group.\textsuperscript{[20]} As mentioned before, the Ugi-SCR performs especially well with methanol as alcohol component. However, with allyl alcohol and 1,4-butanediol, Ugi products with yields of 49\% and 52\%, respectively, could be obtained. Interestingly, in these reactions, carbon dioxide serves as carbon source, which can be considered as inexhaustible and sustainable feedstock. Thus, polyurethanes with a molar carbon dioxide content of up to 13\% were synthesized via the Ugi-SCR.\textsuperscript{[24]} Herein, we describe a synthesis protocol for modifying \(\beta\)-CDs in a direct one-pot fashion via the Ugi-SCR. No pre-modification towards intermediates is necessary and the reaction does not require the use of any catalyst, making the reported procedure simple and straightforward.

In the Ugi-SCR, usually the respective alcohol is used as solvent and reactant at the same time in an excessive amount.\textsuperscript{[16,18,20]} For methanol, the excess can be limited to 10 equivalents (equiv.),\textsuperscript{[18]} for allyl alcohol and 1,4-butanediol, however, approximately 130 and 70 equiv. were applied, respectively.\textsuperscript{[20]} However, using carbohydrates as alcohol component, other solvent systems have to be considered due to solubility issues. Dimethyl sulfoxide (DMSO), \(N,N\)-dimethylformamide (DMF) and \(N,N\)-dimethylacetamide (DMAc) are excellent solvents for \(\beta\)-CD and do not contain hydroxyl groups, which could potentially undergo a side reaction.\textsuperscript{[21]}

Since excess of the alcohol component is not possible in this particular case, the other components have to be added in excess. A high-pressure laboratory reactor with 10 bar carbon dioxide pressure guarantees the excess of the respective gas. A first set of reactions (Table S1, Supporting Information, V1) was thus performed at room temperature with 2.7 equiv. \(n\)-butylamine (1a), 2.7 equiv. isobutyraldehyde (2a) and 2.7 equiv. tert-butyl isocyanide (3a) per hydroxyl group in 3.6 mol*10\textsuperscript{-2}L\textsuperscript{-1} DMSO, with respect to \(\beta\)-CD. The reaction mechanism of the Ugi-SCR is proposed in Scheme 1.

The conversion was the same for reactions run over the weekend and overnight. Therefore, all the following approaches were conducted for 24 hours. The mixture was precipitated in various solvents like acetone, \(n\)-hexane, dichloromethane, and diethyl ether. A short screening revealed that precipitation in cold diethyl ether is best suited to remove the unreacted reagents.

According to \(^1\)H nuclear magnetic resonance (NMR) spectroscopy, this first set of experiments (V1, see supporting information Table S1) gave a degree of substitution (DS) of 0.06. Since 21 hydroxy groups can be functionalized (3 OH groups for each glucose moiety), the maximum DS = 3. Statistically, a DS of 1/7 = 0.14 would therefore correspond to one functionalization per \(\beta\)-CD molecule, and the initial DS of 0.06 correlates to approximately one modification in every second \(\beta\)-CD molecule. The DS was determined by comparison of a reference signal in \(\beta\)-CD at 3.40–3.80 ppm with the isolated aliphatic signals of the newly attached moieties. The reference signal comprised the peak of the only CH\(_2\) group and the two axial protons of the glucose unit pointing downwards in \(\beta\)-CD and was therefore normalized to a value of “4.00” (compare Figure 1).\textsuperscript{[22]}

In order to improve the initial DS of the first reactions, lower (1.3 equiv. V2, supporting information Table S1) and higher amounts (5.4 equiv. V3, supporting information Table S1) of the different components were investigated next. With only 1.3 equiv. excess of the components, experiments yielded a lower substitution of the \(\beta\)-CDs. As the Ugi-SCR usually requires excessive amount of the alcohol (> 10 equiv.), which we cannot apply here, we assume that reducing the reagents leads to lower yields (equal to reducing the amount of alcohol in other Ugi-SCR). Interestingly, the DS seems to correlate with the added amount of the components since halving the excess of the components led to a DS of 0.03. Thus, doubling the components to 5.4 equiv. should have resulted in higher substituted \(\beta\)-CDs. However, the reaction mixture could not be precipitated in any organic solvent or in water. Possibly, the formed, higher substituted \(\beta\)-CDs show an excellent solubility behavior. Besides, a side reaction following decomposition could have happened as well.

Further improvement of the Ugi-SCR was achieved by performing the reaction in DMF instead of DMSO, while keeping the reaction conditions identically (V4, supporting
After precipitation in cold diethyl ether, the suspension was centrifuged, and the precipitate dried in vacuum oven. An improved DS of 0.36 was observed by $^1$H NMR spectroscopy.

The product was separated from native $\beta$-CD by column chromatography with a mixture of acetonitrile/water = 3:1, increasing the DS to 0.42, while decreasing the yield to 80 mg. The $^1$H NMR spectrum of the purified product P1 is depicted in Figure 1. The new signals appearing in the higher field indicate the successful modification to P1, as the ratio of the aliphatic signals matches to the corresponding protons a and b (ratio 13:9). Signal b includes nine protons from three CH$_3$ groups originating from isobutyraldehyde and $n$-butylamine and signal a includes 13 protons from three CH$_3$ groups resulting from tert-butyl isocyanide and two CH$_3$ groups resulting from $n$-butylamine. Moreover, signal 3 clearly decreased in P1 compared to native $\beta$-CD, indicating a substitution of the primary hydroxyl groups. Integration of signal 3 gives a decrease of about 35%, indicating a DS of approximately 0.35. Thus, both DS calculations are in good agreement to each other, especially considering the often poor resolution of proton spectra of carbohydrates.$^{(19g,23)}$

Modified $\beta$-CD P1 was further analyzed by fast atom bombardment mass spectrometry (FAB-MS) (compare Figure 2). The masses of mono-, di-, and tri-substituted $\beta$-CD could be clearly assigned, confirming the successful modification. Furthermore, no remaining native $\beta$-CD ([M + H]$^+$ = 1135.38, [M + Na]$^+$ = 1157.36) was detected in the purified mixture. Hence, a DS in the range of 0.35 for P1, as determined by $^1$HNMR spectroscopy, is reasonable. Statistically, two functionalizations per $\beta$-CD would result in a DS = 2/7 = 0.28, three in DS 3/7 = 0.43. Since FAB-MS spectra cannot be quantified, but still indicate that di-modified $\beta$-CD is more present than mono and tri-substituted $\beta$-CD, the DS should be in the range of di-substituted $\beta$-CD, which is the case.

Changing the components in MCRs allows fine-tuning the structure and properties of the obtained products. Therefore, further amines, aldehydes and isocyanides were chosen for directly modifying $\beta$-CD (compare Table 1) with the formerly established reaction conditions. After the reaction, the crude product was always purified by column chromatography with acetonitrile/water (3:1). Table 1 summarizes all different investigated combinations for the modification of $\beta$-CD. Only one combination of reactants (Table 1, entry 3) was unsuccessful.

**Figure 1.** $^1$H NMR spectrum of P1 (black, compare Table 1) and $\beta$-CD (grey) in DMSO-$d_6$, including assigned signals ($\beta$-CD signals 1–5 in grey and signals a and b resulting in broad absorptions due to the different protons from the moiety in blue). According to this spectrum, the primary hydroxyl groups are modified since they are more easily accessible. In general, the modification broadens the signals of the sugar backbone protons, since they are differently shielded and additionally, their rotation might be restricted due to the functionalization. The signals around 3 ppm are traces of DMF.
An overview of the $^1$H NMR spectra of the modifications 2–6 and β-CD is depicted in Figure 3 (for the respective individual NMR and FAB-MS spectra, please see Supporting Information).

In modification P2, benzyl isocyanide (3 b) was incorporated instead of tert-butyl isocyanide (3 a). Additional signals in the low field at 7.20–7.50 ppm verify the incorporation of aromatic rings into the β-CD. According to the $^1$H NMR spectrum, a DS of 0.41 was achieved. Furthermore, the masses of the mono-, di-, and tri-substituted β-CD could be assigned via FAB-MS also in this case. Due to the successful incorporation of aromatic compounds, we tested further aromatic components, such as benzaldehyde (2 c, entry P3) and benzylamine (1 b, entry P4). However, in case of benzaldehyde, native β-CD was obtained after filtration (Figure 3, entry P3 with DMF residues at 8.03, 2.92, and 2.75 ppm) and when incorporating benzylamine (entry P4), substituted β-CD was obtained, however, with a low DS of 0.16. This corresponds again well to the FAB-MS result, where only masses of the mono- and di-substituted β-CD could be assigned.

Probably, sterically demanding aromatic aldehydes hinder further reaction progress. If the isocyanide has an aromatic function, enough spacing to the CD ring is guaranteed and the reaction can proceed as usual. During polymerizations with Ugi-derived acrylamide monomers, similar difficulties have been observed. Aromatic benzaldehydes, anilines, and benzylamines blocked the polymerization process because of steric reasons.24

Substituting isobutyaldehyde with isovaleraldehyde (2 b, entry P5) resulted in a DS of 0.37 and thus a straightforward direct modification. Moreover, we also proved the successful incorporation of an allyl group, namely allyl amine (1 c, entry P6). The DS was calculated to 0.28 and the respective mono-, di-, and tri-substituted masses were also identified by FAB-MS.

The modifications P1, P2, P4, P5 and P6 were further analyzed by attenuated total reflection infrared (ATR-IR) spectroscopy (compare Figure 4).

Three new absorptions emerged in the spectra of the modified products, compared to native β-CD, in the range of 2955–2960, 2870–2875 and 1540–1560 cm$^{-1}$. The signals at 2955 and 2870 cm$^{-1}$ correspond to symmetric and asymmetric stretching vibrations from the CH$_2$ groups. The signal at 2920–2930 cm$^{-1}$, which is also present in β-CD can be reducible to asymmetric stretching vibration from the CH$_3$ and CH groups. The absorption at 1540 cm$^{-1}$ can be assigned to secondary

$^\text{[a]}$ Determined after column chromatography.

Table 1. Results of variations of the Ugi-5CR applying different amines (1a–b), aldehydes (2a–c), different isocyanides (3a–b) and β-CD. DMF was used as solvent with a concentration of 3.6 10$^2$ mol L$^{-1}$ with respect to the hydroxyl groups in β-CD. 200 mg of β-CD was applied and the reagents were added in excess of 2.7 equiv.

| sample | amine | aldehyde | isocyanide | calculated DS$^\text{[a]}$ | Yield [mg]$^\text{[a]}$ |
|--------|-------|----------|------------|--------------------------|----------------------|
| P1     | butyl | isobuty | tert-butyl | 0.35–0.42                | 80.0                 |
| P2     | butyl | isobuty | benzyl     | 0.41                    | 115                  |
| P3     | butyl | benzyl  | tert-butyl | –                       | 0                    |
| P4     | benzyl| isobuty | tert-butyl | 0.16                    | 73.9                 |
| P5     | butyl | isovaler| tert-butyl | 0.37                    | 63.2                 |
| P6     | allyl | isobuty | tert-butyl | 0.28                    | 112                  |

Figure 2. FAB spectrum of P1. The three peaks correspond to the respective mono- (calculated [M + Na]$^+$ = 1411.56 Da), di- (calculated [M + Na]$^+$ = 1665.76 Da), and tri- (calculated [M + Na]$^+$ = 1919.96 Da) substituted β-CD with Na$^+$ (see Figure 1 for structure).

Figure 3. $^1$H NMR spectra of modifications P2, P3, P4, P5, P6 and pristine β-CD (top to bottom) in DMSO-d$_6$. Signals of DMF can be detected in P3 (8.03, 2.92, 2.75 ppm) and to a minor extent in P4 and P5. According to the NMR spectrum, P3 is pure β-CD with DMF impurities, but the other approaches were more successful. The broad signals of the carbohydrate backbone in P2 might indicate an interaction of the benzyl moiety and the β-CD cavity. In P4, the aromatic moiety is covalently too close to the cavity and an interaction is not possible. Therefore, the carbohydrate signals are sharper as in P2. The NMR spectrum of P6 displays an inferior signal-to-noise ratio. The approach was repeated several times, but the quality of the spectrum could not be improved but P6 was confirmed via FAB-MS (see Supporting Information). The broader signal at 0.8 ppm, arising from the isobutyl moiety, can be explained due to the vicinity to the allyl group which results in a different chemical surrounding.
The significant increase of the intensity at 1640 cm\(^{-1}\) compared to \(\beta\)-CD spectrum indicates C=O stretching vibrations originating from the amide as well. Furthermore, compound P4 showed lower signal intensities for these new signals when compared to the other modifications P1, P2, P5 and P6, which is in accordance with its lower DS. The integrals of the \(^1\)H NMR spectrum therefore correlate not only with the FAB-MS, \(^1\)H NMR and IR spectroscopy. Furthermore, a different solubility of the modified cyclodextrins in alcohols is indicated. This could offer a wider application and the incorporation of polar compounds lead to a better water solubility of \(\beta\)-CDs, which is of interest for pharmaceutical research. Further investigations concerning the solubility is needed. Additionally, the synthesis procedure itself might be improved, by applying a switchable solvent system, which was recently introduced in the Passerini-four-component reaction.\(^{[15]}\) In this way, higher yields and enhanced DS might be obtained.

**Supporting Information Summary**

The experimental section including materials and instruments is provided in Supporting Information. Detailed characterization data is provided as well.

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**Conflict of Interest**

The authors declare no conflict of interest.

**Keywords:** \(\beta\)-cyclodextrin · Ugi-five component reaction · one-pot synthesis · carbon dioxide · solubility

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