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A facile access to ureido sugars. Synthesis of urea-bridged β-cyclodextrins

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Abstract—The preparation of a urea-bridged β-cyclodextrin dimer and of a 6-monodeoxy-6-mono[3-(β-D-glucopyranos-2-yl)ureido]-β-cyclodextrin has been developed, using triphosgene as the isocyanation agent in an aqueous two-phase system. Per-*O*-acetylated β-D-gluco and mannopyranosylamines and 2-amino-2-deoxy-α- and β-D-glucose were also transformed into the corresponding isocyanates and converted in situ into ureas by coupling with aromatic and aliphatic amines.

Compounds containing the urea functionality are of biological interest as antimycobacterial[1] and anti-trypanosomal agents,[2] and as inhibitors of HIV protease.[3] These compounds are also used as plant growth regulators and agrochemicals.[4] The urea moiety is also found in artificial receptors useful in supramolecular chemistry.[5]

In the carbohydrate field, a series of glycosylureas have been shown to be α-glucosidase inhibitors[6] and *N*-acyl-*N*′-β-D-glucopyranosyl ureas exhibit strong inhibition against glycogen phosphorylase,[7] and can be useful as antidiabetic agents.[8]

Cyclodextrins have been extensively used in different applications, such as drug delivery, enzyme mimics and chiral chromatography.[9] Much effort has been devoted to the synthesis of cyclodextrin dimers,[10] using a variety of functional tethers[11] including the urea bridge,[12] in order to improve the binding properties of the parent cyclodextrin.

For the preparation of sugar ureas, one of the most widely used methods involves the treatment of glycosylamines or amino sugars with alkyl or aryl isocyanates.[13] The formation of sugar-derived ureas using alkyl isocyanates has been reported to fail[14] in aqueous solvents due to the hydrolysis of the isocyanate and the subsequent formation of the *N*,*N*′-dialkyl urea as the major by-product. Another approach involves the preparation of sugar isocyanates from *O*-protected amino sugars and phosgene under anhydrous conditions.[15]

We now report a novel access to the urea-linked-β-cyclodextrin dimer **4**[16] (Scheme 1) by the transformation of the peracetylated 6^A-amino-6^A-deoxy-β-D-cyclodextrin **2** into the isocyanate **3**, which reacts with another equivalent of **2** to yield **4**. The method developed by us consists of an unprecedented procedure for the synthesis of sugar-derived ureas in which the two steps (isocyanation of an amine and coupling with the same or a different amine) are carried out in a one-pot fashion in a vigorously stirred CH_2Cl_2-saturated aqueous $NaHCO_3$ mixture using triphosgene,[17] as an easily handled and stable substitute for phosgene, as the isocyanation agent. It is remarkable that both the isocyanates and triphosgene can be used in the presence of water despite the expectation that they would hydrolyse rapidly.[17]

The amine **2** was prepared by hydrogenation of the azido derivative **1**,[18] and used without further purification for the isocyanation reaction. The overall yield for the synthesis of the dimer **4** from **1** was 49%, which is comparable with the recently described procedure[19] using a polymer-bound triphenylphosphine, carbon dioxide and azide **1**.

We have also extended our method to the synthesis of the hitherto unknown per-*O*-acetylated 6-monodeoxy-6-mono[3-β-D-glucopyranos-2-yl)ureido]-β-cyclodextrin **15**, starting from peracetylated 2-amino-2-deoxy-β-

Keywords: cyclodextrin; triphosgene; sugar ureas; sugar isocyanates; aqueous two-phase system.
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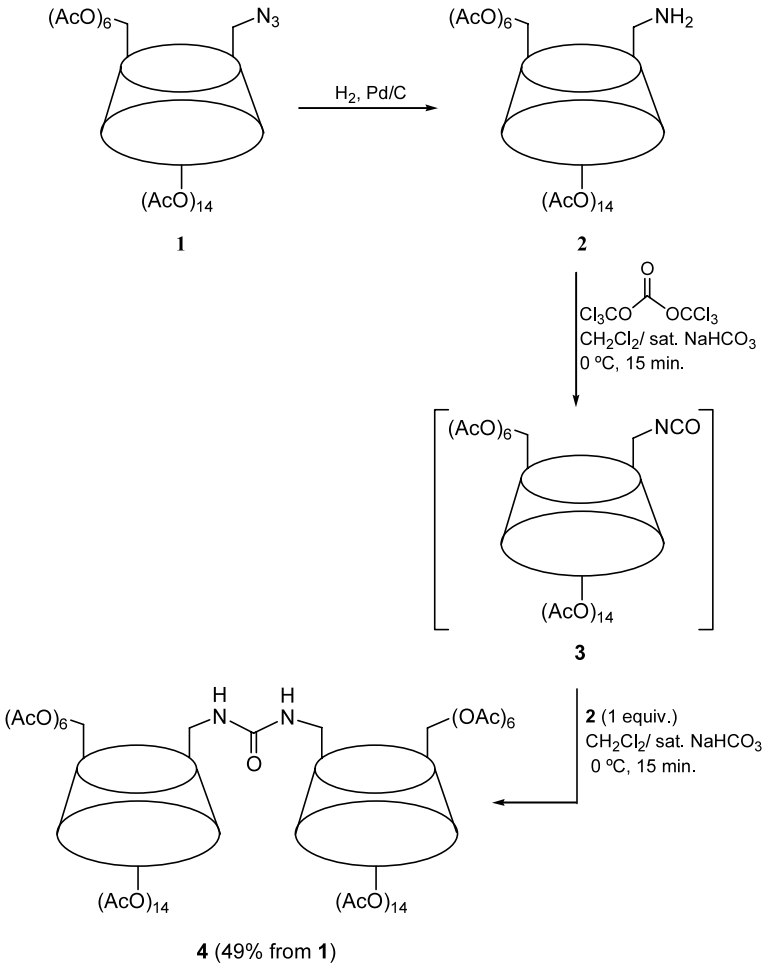
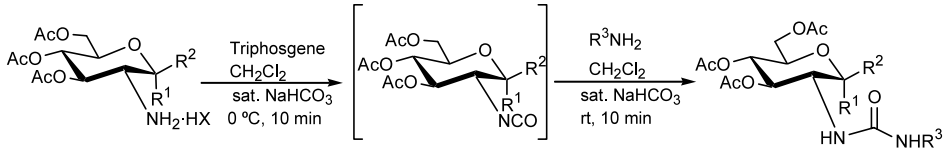
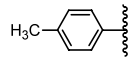
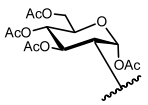
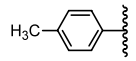
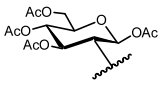
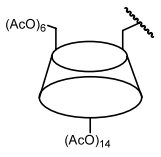


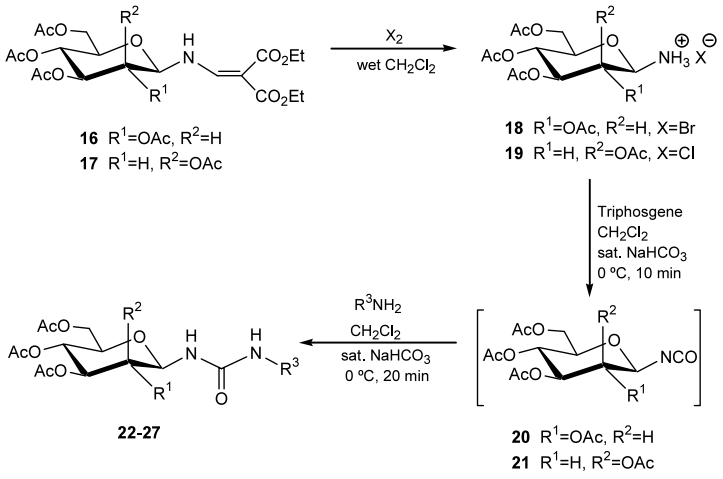
Scheme 1.

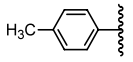
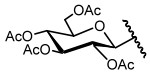
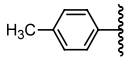
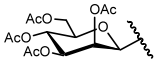


5 R^1=OAc, R^2=H, X=Br
6 R^1=H, R^2=OAc, X=Cl
7 R^1=OAc, R^2=H
8 R^1=H, R^2=OAc
9-15

Compound	R^1	R^2	R^3	Yield (%)
9	OAc	H	*n*-Bu	73
10	OAc	H		63
11	OAc	H		82
12	H	OAc	*n*-Bu	86
13	H	OAc		86
14	H	OAc		78
15	H	OAc		46

Scheme 2.



Compound	R^1	R^2	R^3	Yield (%)
22	OAc	H	*n*-Bu	63
23	OAc	H		66
24	OAc	H		99
25	H	OAc	*n*-Bu	71
26	H	OAc		58
27	H	OAc		69

Scheme 3.

D-glucopyranose hydrochloride **6**[20] (Scheme 2). Compound **6** was treated with triphosgene[21] as described above for amine **2**, to give isocyanate **8** which was in situ coupled with amine **2** (1.0 equiv.); this gave urea **15**[22] in 46% yield, calculated from azide **1**.

The preparation of the 2-ureido-α- and β-D-glucopyranoses **9**, **10**, **12** and **13**, and symmetrical pseudodisaccharides **11** and **14** (Scheme 2) was also achieved starting from per-*O*-acetylated 2-amino-2-deoxy-α-D-glucopyranose hydrohalide **5**[23] and its β-isomer **6** in good yields (63–86%).

Furthermore, per-*O*-acetylated glucopyranosylamine hydrobromide **18** could be transformed into symmetrical and unsymmetrical glucopyranosyl ureas **22**–**24** (63–99% yield) via the transient glycosyl isocyanate **20** (Scheme 3). Crystalline hydrobromide **18** was synthesised[24] from the readily available β-D-glucopyranosylamine[25] by removal of the enamino group of **16** with bromine in moist dichloromethane.

Finally, as hydrohalide **19** could not be obtained as a crystalline product, the mannopyranosylureas **25**–**27** were obtained from enamine **17**[26] by adding aliquots of a saturated solution of Cl_2 in CH_2Cl_2 at 0°C until disappearance of the starting material by TLC. After concentration, the residue was directly used for the next two steps (Scheme 1). This gave ureas **25**–**27**[27] in 58–71% overall yields for the three steps, showing that the by-products from the chlorolysis do not interfere with the isocyanation reaction. No anomerisation under the reaction conditions was observed by ^1H NMR analysis for ureas **25**–**27**, in contrast with the reported behaviour for the analogous mannopyranosyl thioureas.[26]

In conclusion, we have developed a novel one-pot, two-step method to prepare urea-bridged cyclodextrin derivatives including dimer **4** and 6-monodeoxy-6-mono[3-(β-D-glucopyranos-2-yl)ureido]-β-cyclodextrin **15** via transient sugar isocyanates. Other unsymmetrical *N*,*N*′-disubstituted sugar-derived ureas and symmetrical pseudodisaccharides containing a (1→1) or (2→2) urea tether starting from *O*-protected glycopyranosyl amines and D-glucosamine were also obtained by this method.

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16. A solution of 6^{A}-azido-6^{A}-deoxy-β-D-cyclodextrin **1** (260 mg, 0.13 mmol) in methanol (10 mL) was hydrogenated at atmospheric pressure by stirring with 10% Pd(C) catalyst for 2.5 h at rt. After filtration of the mixture through a Celite pad, the filtrate was concentrated to dryness to afford the crude amine **2** and divided into two equal portions. One portion was dissolved in an 1:1 CH_2Cl_2–satd aqueous $NaHCO_3$ mixture (12 mL), cooled to 0°C in an ice bath and treated with solid triphosgene in a single portion (6.5 mg, 0.022 mmol). After 15 min of vigorous stirring the other portion of amine **2** was added and the stirring was maintained at rt for 15 min. Conventional work-up and column chromatography afforded cyclodextrin dimer **4** (127 mg, 49%). $[\alpha]_D^{26}$ +117 (*c* 1.1, CH_2Cl_2); IR 3300, 1748, 1541, 1433, 1371, 1233, 1042 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.32–5.25 (m, 7H, H-$3^{A–G}$), 5.17 (d, 1H, $J_{1,2}=3.5$ Hz, H-1^{A}), 5.14–5.11 (m, 1H, NH), 5.10–5.05 (m, 6H, H-$1^{B–G}$), 4.87–4.71 (m, 7H, H-$2^{A–G}$), 4.58–4.49 (m, 6H, H-$6a^{B–G}$), 4.31–4.23 (m, 6H, H-$6b^{B–G}$), 4.18–4.11 (m, 6H, H-$5^{B–G}$), 3.98–3.94 (m, 1H, H-5^{A}), 3.88–3.82 (m, 1H, H-$6a^{A}$), 3.76–3.64 (m, 7H, H-$4^{A–G}$), 3.46–3.41 (m, 1H, H-$6b^{A}$), 2.14–2.03 (20 s, 60H, 20Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 170.65–170.33, 169.57–169.32 (CH_3CO), 158.20 (CO urea), 96.90–96.67 (C-$1^{A–G}$), 77.85–76.46 (C-$4^{A–G}$), 71.24–69.37 (C-$2^{A–G}$, C-$3^{A–G}$, C-$5^{A–G}$), 62.88–62.36 (C-$6^{B–G}$), 40.40 (C-6^{A}), 20.80–20.60 (CH_3CO) ppm. MALDITOF-MS, *m*/*z* 3980 $[M+H]^+$.
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21. General procedure for the preparation of sugar ureas: to a vigorously stirred solution of the hydrohalides **5**, **6**, **18**, **19** (0.6 mmol) in a 1:1 mixture of CH_2Cl_2 and saturated aqueous $NaHCO_3$ (12 mL) at 0°C in an ice bath was added solid triphosgene (0.22 mmol) in a single portion. After 10 min of stirring, butylamine, *p*-toludine, or the corresponding hydrohalides **5**, **6**, **18**, **19** (0.66 mmol) were added in a single portion. For the preparation of D-glucosamine derived ureas **9**–**14** the coupling with the amines was performed at rt for 10 min; for the preparation of glycopyranosyl ureas **22**–**27** the coupling of the isocyanate with the amines was carried out at 0°C for 20 min. Conventional work-up and column chromatography afforded ureas **9**–**14** and **22**–**27**.
22. For the preparation of **15**: the above described procedure (Ref. 21) was carried out starting from hydrochloride **6** (0.13 mmol). Azide **1** (260 mg, 0.13 mmol) was transformed into amino cyclodextrin derivative **2** as described above (Ref. 16) which was added to the crude isocyanate **8**, and the coupling reaction took place at rt for 15 min. Conventional work-up and column chromatography afforded **15** (140 mg, 46%). $[\alpha]_D^{26}$ +101 (*c* 1.0, CH_2Cl_2); IR 3295, 1746, 1520, 1456, 1366, 1221 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.80 (d, 1H, $J_{1',2'}=8.9$ Hz, H-1′), 5.35–5.21 (m, 8H, H-$3^{A–G}$, H-3′), 5.14 (d, 1H, $J_{1,2}=3.5$ Hz, H-1), 5.15–5.12 (m, 1H, NH), 5.10 (t, 1H, $J_{3',4'}=10.0$ Hz, $J_{4',5'}=10.0$ Hz, H-4′), 5.09–5.06 (m, 5H, H-$1^{B–F}$), 4.98 (d, 1H, $J_{1,2}=3.0$ Hz, H-1), 4.94–4.91 (m, 1H, N*H*-CH_2), 4.89 (dd, 1H, $J_{1,2}=4.5$, $J_{2,3}=8.5$ Hz, H-2), 4.84 (dd, 1H, $J_{1,2}=4.0$, $J_{2,3}=9.7$ Hz, H-2), 4.81 (dd, 1H, $J_{1,2}=3.5$, $J_{2,3}=10.0$ Hz, H-2), 4.80 (dd, 1H, $J_{1,2}=3.5$, $J_{2,3}=9.5$ Hz, H-2), 4.77 (dd, 1H, $J_{1,2}=4.1$, $J_{2,3}=9.5$ Hz, H-2), 4.75 (dd, 1H, $J_{1,2}=3.6$, $J_{2,3}=9.5$ Hz, H-2), 4.67 (dd, 1H, $J_{1,2}=3.5$, $J_{2,3}=10.0$ Hz, H-2), 4.65–4.47 (m, 6H, H-$6a^{B–G}$), 4.33–4.22 (m, 7H, H-$6b^{B–G}$, H-6a′), 4.18–4.07 (m, 8H, H-$5^{B–G}$, H-2′, H-6b′), 4.01–3.97 (m, 1H, H-5^{A}), 3.94–3.89 (m, 1H, H-5′), 3.76–3.59 (m, 8H, H-$4^{A–G}$, H-$6a^{A}$), 3.47–3.42 (m, 1H, H-$6b^{A}$), 2.16–1.99 (24 s, 72H, 24Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 171.50, 170.94–170.29, 169.55–169.32 (CH_3CO), 157.73 (CO urea), 97.38, 96.96, 96.92, 96.87, 96.76, 96.51, 96.48 (C-$1^{A–G}$), 92.79 (C-1′), 78.41 (C-4^{A}), 77.25-76.14 (C-$4^{B–G}$), 72.81 (C-5′), 72.44 (C-3′), 71.46-69.02 (C-$2^{A–G}$, C-$3^{A–G}$, C-$5^{A–G}$), 68.14 (C-4′), 63.05,

62.79, 62.78, 62.54, 62.45, 62.18 (C-6^{B-G}), 61.81 (C-6′), 53.99 (C-2′), 40.94 (C-6^{A}), 20.85-20.60 (CH_3CO) ppm. FAB-MS, m/z 2370 (29%, $[M+Na]^+$).

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27. Selected data for **27**: $[\alpha]_D^{25}$ −24 (c 0.3, CH_2Cl_2); IR ν_{max} 3352, 1746, 1537, 1227 cm^{-1}; mp: 154–156°C (EtOH); ^1H NMR (500 MHz, $CDCl_3$): δ 5.45 (d, 1H, $J_{1,NH}=9.6$ Hz, NH), 5.41 (s, 1H, $J_{1,2}\approx 0.0$ Hz, H-1); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 153.8 (CO urea), 77.4 (C-1) ppm. Anal. calcd for $C_{29}H_{40}N_2O_{19}\cdot H_2O$: C, 47.16; H, 5.73; N, 3.79. Found: C, 47.26; H, 5.61; N, 3.83.