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Synthesis of upper rim calix[4]arene divalent glycoclusters via amide bond conjugation

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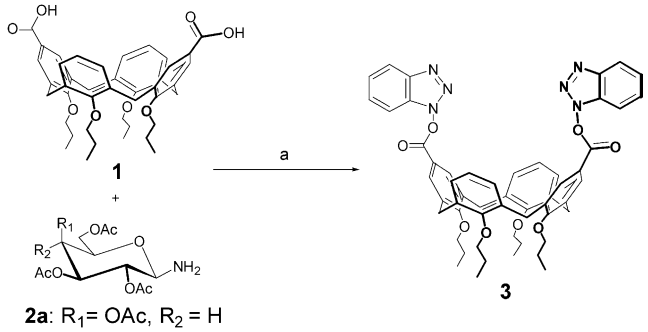
Abstract—Synthetic routes for linking two sugar units at the upper rim of cone calix[4]arenes, through the formation of amide bonds, have been explored. Steric effects prevent the coupling of calix[4]arene dicarboxylic acid with simple aminoglycosides, whereas the corresponding reaction with carbohydrates bearing a two or three carbon atoms spacer, terminating with a primary amino group, allows the synthesis of several difunctionalized calix[4]arene neoglycoconjugates, attractive in chemical glycobiology and supramolecular chemistry.

1. Introduction

Carbohydrate clusters are becoming interesting targets as model systems for studying protein–sugar[1] and sugar–sugar[2] interactions, which play a central role in glycobiology.[3] Neoglycoconjugates based on cyclodextrin and calixarene cores[4] have been used for this purpose and they are also attractive as potential molecular delivery systems.[5] For this purpose, the presence of binding groups in addition to the sugar units is useful in order to complex substrates to be delivered to a specific target. In the case of calix[4]arenes, the sugar moieties were almost exclusively attached at the lower or upper rim through the formation of ether bonds or carbon–carbon bonds[6] exploiting trimethylsilyl triflate[7a] and copper(II) triflate[7b] mediated glycosylation reactions on bis- and tetrahydroxymethylcalix[4]arenes, a Suzuki type reaction using calix[4]arene di- and monoboronic acid derivatives[7d] and Wittig reactions[7c,e] on formylated calix[4]arenes. Only a couple of examples of thiourea containing glycocalixarenes are known where the hydrogen bonding spacer is able to complex anionic species.[8] The dicarboxylic acid **1** is a well known cone calix[4]arene intermediate[9] and has been used for the synthesis of cleft-like[10] and macrobicyclic[11] N-linked peptidocalix[4]arenes and other molecular receptors.[12] We therefore explored the possibility of using compound **1** as a starting material for the synthesis of novel upper rim calix[4]arene glycoconjugates through amide bond formation, where the amide group could be exploited for the binding of acidic and/or basic substrates, and report in this paper the synthetic results obtained. An amide bond has been used to synthesize lower rim calix[4]arene–monosaccharide conjugates,[13] but to the best of our knowledge the synthesis of upper rim derivatives has never been reported.

2. Results and discussion

Reaction of the calix[4]arene diacid **1**[9] with 2,3,4,6-tetra-*O*-acetyl-β-D-galactosamine **2a**[14] and 2,3,4,6-tetra-*O*-acetyl-β-D-glucosamine **2b**[14] in the presence of *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) and triethylamine (TEA) at rt (Scheme 1) did not give a glycosylated calixarene, but the benzotriazole ester **3**, which was isolated in yields higher than 70% and characterized since it is quite stable. Heating compound **3** with these monosaccharides overnight in presence of an excess of base in acetonitrile led to the complete



Scheme 1. (a) HBTU, TEA, CH_2Cl_2, rt, 5 h.

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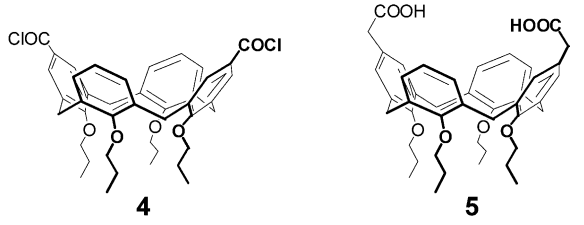
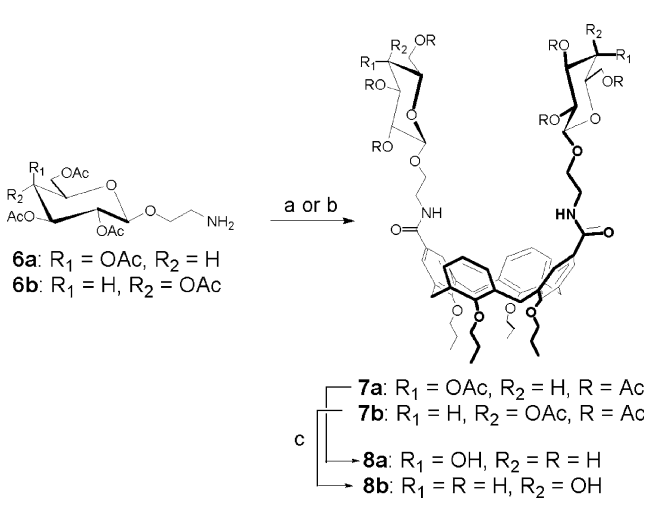
decomposition of **3** without forming any coupling product with glycosamines **2a**,**b**. Similarly, when the acid chloride **4**[11] was reacted with glycosylamines **2a**,**b** using TEA as base, the calix[4]arene acid **1** and the sugar were found after aqueous work-up and no coupling product could be detected.



Suspecting that failure in the coupling reaction between **2a**,**b** and **3** or **4** could be mainly ascribed to repulsive steric interactions between the reacting partners, we decided to introduce a spacer either on the calixarene or on the sugar moiety. Nevertheless, the condensation reaction of calix[4]-arene–acetic acid derivative **5**[15] with galactosamine **2a** was unsuccessful in a variety of conditions. On the other hand, the reaction of the calix[4]arene dicarboxylic acid **1** with the galactosamine derivative **6a**,[16] having a two methylene unit spacer between the sugar moiety and the amine group, in the presence of HBTU and an excess of base (pH > 12) at 80 °C in acetonitrile, led to the synthesis of the coupling product **7a** (Scheme 2). Comparable results were obtained using glucosamine **6b** as glycosyl donor to obtain **7b**, and also reacting at rt the two glycosylamines **6a** and **6b** with the calixarene diacylchloride **4**. Deprotection of **7a**,**b** with triethylamine in aqueous methanol gave the amide-linked glycoconjugates **8a**,**b** in 30–33% overall yield. The ^{1}H NMR spectra of derivatives **7a**,**b** in $CDCl_3$ show sharp signals, which allow the exclusion of intermolecular aggregation phenomena. It is well known[17] that calix[4]arenes difunctionalized at the upper rim with hydrogen bonding donor and acceptor groups can experience intramolecular H-bonding in apolar solvents, which stabilize a closed flattened cone conformation (Fig. 1) with respect to the open flattened cone conformation, which is more stable in strong donor solvents. Usually, these conformational preferences can be recognized very clearly by inspecting the aromatic region of the ^{1}H NMR spectra of these compounds. In the case of glycocalixarenes **7a**,**b**, the aromatic protons of the unsubstituted aromatic rings resonate at $\delta \sim 6.30$ and those of the substituted ones at $\delta \sim 7.35$, thus confirming that these compounds exist mainly in the open flattened cone conformation, in $CDCl_3$.



Scheme 2. (a) **1**, HBTU, TEA, CH_3CN, 80 °C, 12 h, 35–37%; (b) **4**, TEA, CH_2Cl_2, rt; (c) TEA, MeOH, H_2O, rt, 16 h, 96–98%.

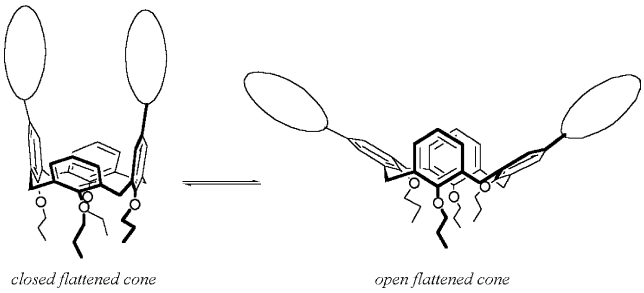


Figure 1. The two possible flattened cone conformers of a upper rim difunctionalised tetrapropoxycalix[4]arene.

Therefore, no intramolecular hydrogen bonding is taking place between the two amide groups in compounds **7a**,**b** which could be ascribed to the intrinsic weakness of the noncovalent interaction or to steric repulsion between the two protected sugar units. The ^{1}H NMR spectra of the deprotected glycocalixarenes **8a**,**b** in the same solvent give very broad signals, which tend to sharpen upon dilution, thus indicating extensive intermolecular aggregation due to the large number of free OH groups. In CD_3OD, the spectra show sharp signals instead. The relative position of the signals of the aromatic protons in this solvent indicates again a preference for the open flattened cone conformation also for compounds **8a**,**b**. Both for the protected and the deprotected compounds **7a**,**b** and **8a**,**b** no splitting could be observed for the signals of the *ortho* aromatic and of the axial and equatorial protons of the calixarene Ar–CH_2–Ar methylene bridge, which is indeed typical for other calix[4]arene derivatives bearing chiral units at the upper rim.[7b,10,11] Evidently, because of the spacer, the carbohydrate chiral units are too far away from the calixarene skeleton to influence its NMR signals.

The second approach we investigated was the formation of an amide bond with an amino acid spacer. This constitutes an attractive route to build up a novel type of hybrid sugar–peptidocalix[4]arene receptors to be used in the recognition of biologically relevant substrates. We focused our attention on aspartic acid as spacer, because of its wide use in natural and synthetic peptides for the linkage of sugar units, and on glucose as saccharide unit, because of its higher solubility in water in comparison with other neutral monosaccharides, which could lead to water soluble glycocalixarenes. L-Aspartic acid dimethyl ester hydrochloride was then reacted with the calix[4]arene diacid **1** giving **9** and, after hydrolysis, **10** in moderate overall yields. The reaction of compound **10** with glucosamine **2b** in the presence of HBTU (Scheme 3) gave a complex mixture of products in which the sugar–peptide conjugate **11** was detected by ESI-MS but could not be isolated. Significantly better results were obtained through the alternative synthetic route consisting in the condensation of the sugar–amino acid derivative **13** with calix[4]arene dicarboxylic acid **1** or diacylchloride **4** (Scheme 3). In these cases, the protected