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Carbohydration of 1,4,8,11-tetraazacyclotetradecane (cyclam): synthesis and binding properties toward concanavalin A

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Dedicated to Dr. Hartmut Spies in memoriam

Abstract—Two novel glycocluster ligands with cyclam core bearing thiourea-linked D-glucose and 2-acetamido-2-deoxy-D-glucose at the periphery have been synthesized. The interaction with concanavalin A has been studied by isothermal titration microcalorimetry for characterizing protein-ligand interactions. The sugar-containing multivalent ligands showed higher association affinity compared to the sugar monomers, which is attributed to an entropy driven glycoside clustering effect.

Radiopharmaceuticals based on the metallic radionuclides $^{64/67}$Cu, ^{99m}Tc, $^{186/188}$Re and ^{90}Y are often used for diagnostic and therapeutic purposes.[1] Cyclam and its derivatives are one of the most important ligands for the radionuclides mentioned above.[2] Regarding to radiopharmaceutical applications radiometal complexes of cyclam derivatives with hydrophilic surface groups are attractive candidates. Recently, we could show that a star-like cyclam ligand appended with four PEG-arms rapidly forms stable copper(II) complexes.[3] Besides the pegylation the carbohydration of radio-labelled compounds is of considerable interest to improve the pharmacokinetics and tumor accumulation.[4] In this perspective, carbohydrate clusters are gaining in importance as interesting targets.[5] Thus, sugar-containing dendritic wedges show both unique cell uptake behavior and specific carbohydrate–protein interaction.[6,7] However, only a couple of examples of glycoclusters with metal complexing units are known. In connection with the work to be presented in this Letter, upper rim calyx[4]arene divalent glycoclusters have to be mentioned.[8] Glycosylated macrocyclic amphiphiles with cyclam as core element show unique self-aggregation properties and have the potential for use in enantioselective metal-catalyzed reactions.[9] Roy and Kim described dendritic bipyridyl-glycoclusters whereby particularly the corresponding Cu(II)-complexes show enhanced efficacy to inhibit the binding of asialoglycoprotein to the lectin VVA-HRP.[10] Recently, glycoconjugates possessing dendritic wedges with 12 glucose or galactose groups linked to a central gadolinium complex have been developed in view of MRI applications.[11]

Currently, we are focusing our attention on the development of dendritic ligands having both enhanced complex stability and improved bio-availability. In this perspective, the synthesis of two glycoclusters with a cyclam core modified with thiourea-linked sugar residues at the periphery of the molecules is presented. D-glucose and 2-acetamido-2-deoxy-D-glucose have been chosen as sugar moieties. The interaction of these sugar-containing ligands with concanavalin A has been studied using isothermal titration microcalorimetry to characterize protein-ligand interaction and possible cluster effects.

The glycocluster ligands **6** and **7** were prepared by glycosylation of the tetraamino-functionalized cyclam core predecessor **1**[3] using the *O*-acetyl-protected glucosyl isothiocyanates **2**[12] and **3**[13] (Scheme 1). The reaction course

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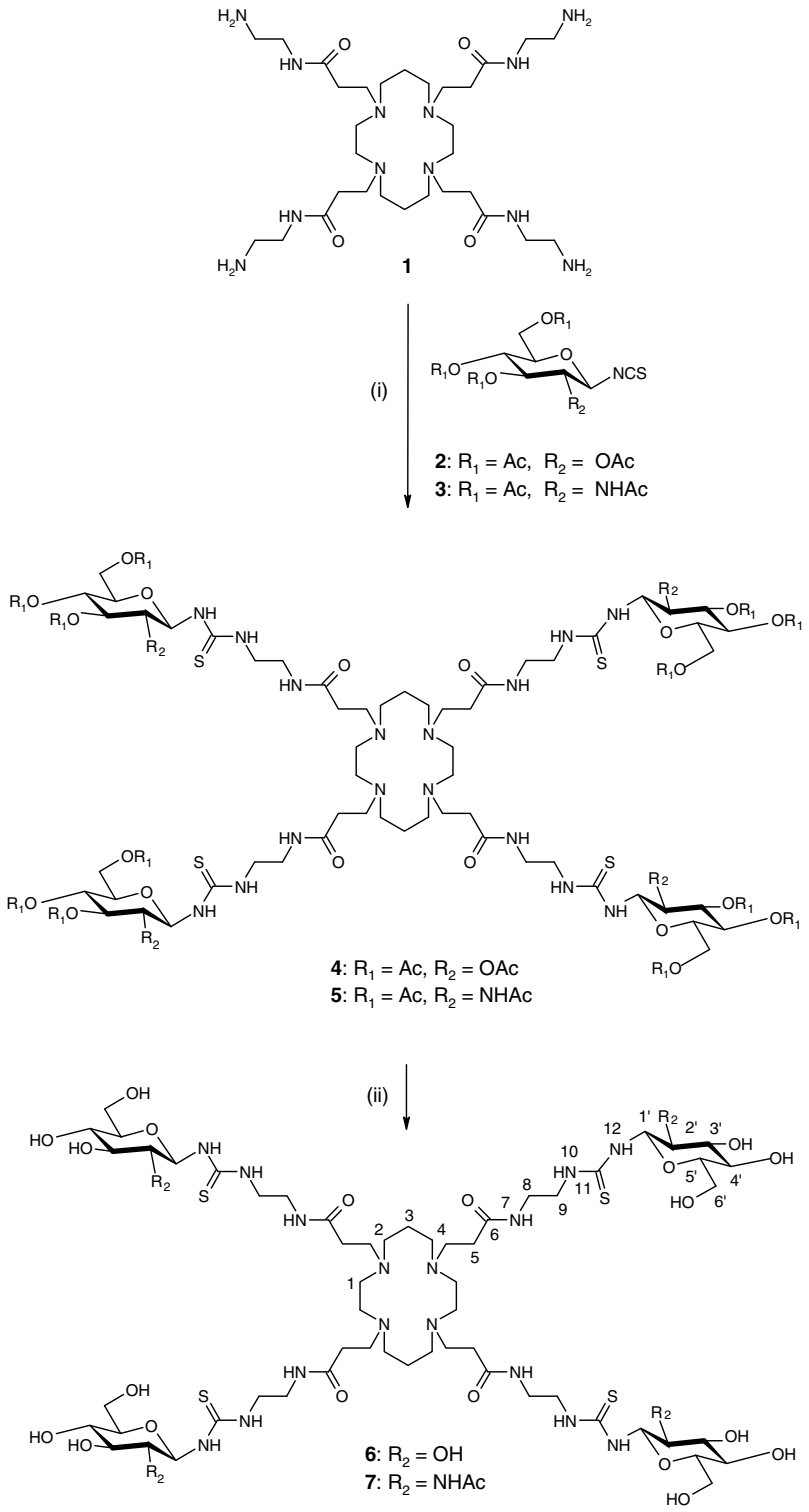

Scheme 1. Synthesis of **6** and **7**. Reagents and conditions: (i) excess of **2** and **3**, $CHCl_3$ (MeOH), rt, 6 days, Al_2O_3, $CHCl_3$/MeOH (12:1), (**4**: 85 %), 1 day (**5**: >50%); (ii) NaOMe/MeOH, pH 8–9, rt, 2 h, neutralization with DOWEX 50WX8, SEC (**6**: 69%; **7**: 37%).

was studied by thin layer chromatography [neutral alumina plates, methanol, $R_f = 0$ (**1**), $R_f = 0.92$ (**2**, **3**), $R_f = 0.33$ (**4**, **5**)]. The reaction was completed after 6 days for **4** and 1 day for **5**. The purification of the O-acetylated products was not trivial. Due to irreversible sorption of **4** and **5** on silica gel, flash chromatography failed. The replacement of acetyl- by benzoyl-protecting groups for the glucosyl isothiocyanates led to highly lipophilic cluster compounds allowing the purification by silica gel chromatography.

However, thiourea-bridging reaction of **1** with 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl isothiocyanate proved to be rather slow and low yielding. Therefore,