An artificial hydrogen bond relay in a supramolecular capsule enables highly selective β-glycosylation

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Carbohydrates are of central importance in biology. Their selective chemical synthesis, however, and in particular the selective formation of the thermodynamically labile β-glycosidic bond still pose a challenge in various cases. The Tiefenbacher group recently demonstrated that a hexameric molecular capsule catalyzes the selective formation of globally protected β-glycosides independent of the substrate's substitution pattern and configuration.[1,2] Interestingly, the proposed mechanism involves synchronized activation of the glycosyl donor and acceptor inside the supramolecular capsule via a relay involving seven hydrogen bonds. While such activation is known for enzymes, it is unprecedented for man-made catalysts. The state-of-the-art mechanistic picture is that the capsule-catalyzed pyranosylation exclusively proceeds through a loose S_N2 transition state while furanosyl donors additionally allow the transformation in a highly β-selective S_N1 fashion. Glycosyl donors are very suitable electrophiles for the proton-wire catalyzed reaction mode. Although analogous substitutions can also be performed with non-glycosidic electrophiles such as allylic, propargylic, and aryl halides, the yields are generally low. The main limit of this methodology is due to the confined space inside the molecular capsule, which naturally limits the reaction scope concerning the size of reactants. A detailed investigation revealed that approaching the maximum cavity packing, the β-selectivity of glycosylation reactions remains generally very good. Further, the production of glycosides can be performed utilizing solvents obtained from renewable sources, improving its applicability as compared to the toxic and petroleum-based solvents previously known for this catalyst.

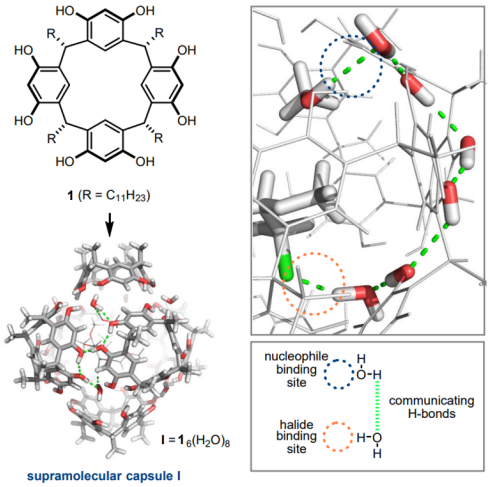

Figure 1. Capsule **I** self-assembles in apolar solvents from six resorcinarene units and eight water molecules forming a network of sixty hydrogen bonds. This catalyst facilitates glycosylation reactions by synchronizing both reaction partners through a proton relay (depicted as green dotted lines).

[1] T.-R. Li, F. Huck, G. M. Piccini, K. Tiefenbacher, *Nat. Chem.*, **2022**, 14 (9), 985–994.
[2] T.-R. Li, Piccini, G., K. Tiefenbacher, *J. Am. Chem. Soc.*, **2023**, 145, 7, 4294–4303