Flipping the shape of a sugar through molecular machinery

The lectin protein receptors that are present at the surface of cell membrane are very interesting targets for drugs in order to recognize and penetrate into specific cells. Indeed, sugar moieties are able to specifically bind some lectins, before being internalized in the cell. Hence, and as in all kind of recognition phenomenon, the shape of the ligand, here the sugar moietiy, is crucial for an optimal binding. The aim of our research is to synthesize a glucidic ligand (more precisely a mannopyranose ligand), that is able to change its own shape, with a high control, depending on a pH *stimulus* that could be delivered closed to the recognition site. If well designed, this kind of compounds could act as ligands with controllable recognition (for example, on or off) depending on the acidity of the middle. In our recent paper, we studied the possibility, in an interlocked molecule (a so called rotaxane), to flip the chair-like conformation (*i.e.* the chair-like shape) of the mannopyranose through the switching on or off of an effect called reverse anomeric effect (Fig. 1). We particularly studied the chemical variation of the molecular station (*i.e.* site of recognition for the macrocycle) that is close to the sugar group (in purple).

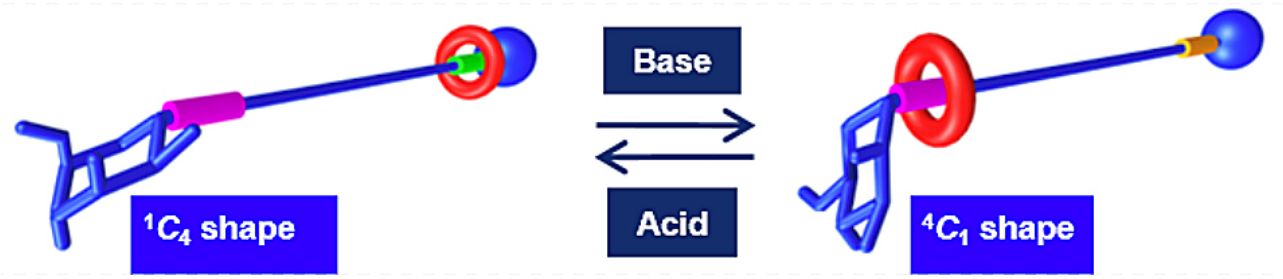

Fig. 1. Cartoon representation of the flipping of the chair-like sugar moiety (left blue extremity) depending on the location of the macrocycle (in red)

For one of the obtained molecules, the tremendous change of shape of the sugar extremity was observed through the shuttling of the macrocycle (the “wheel”, in red) along the glucidic thread (in blue), which was triggered by a pH *stimulus*. The shape of the sugar moiety appeared completely different when the macrocycle is located far away from it or close to it, because of induced effects of the macrocycle on the sugar in only one of the two locations of the macrocycle. This example highlights the possibility to distort the glucidic extremity of an encircled molecular thread through the deprotonation of the other extremity of the molecule (*i.e.* the green site), thanks to the induced large-amplitude gliding motion of the macrocycle. To the best of our knowledge, this example that combines an interlocked sugar-containing encircled molecule and an accurate control of the shape variation of a sugar is unique to date. It opens the way to appealing potential applications in the selective targeting of lectins.

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