# CYCLODEXTRIN-BASED "FRUSTRATED" AMPHIPHILES: ONE-COMPONENT, CELL-SELECTIVE NUCLEIC ACID DELIVERY SYSTEMS

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Prior research has identified carbohydrates, specifically cyclodextrins (CDs), as promising candidates in the development of non-viral vectors for gene therapy.[1] The precise structure and versatility of these molecules, encompassing aspects such as sequence, spatial relationships, and functionality, provide a foundation for investigating the intricate interplay of diverse molecular factors involved in the stepwise assembly processes responsible for creating CD-nucleic acid nanocomplexes (CDplexes). Our earlier studies have shown how subtle adjustments in molecular architecture can yield distinct assembly behaviors, resulting in a spectrum of nanocomplex topologies with specific affinities for particular organs and cells.[2,3] Notably, the majority of reported instances typically display a Janus-type configuration, characterized by separate cationic and lipophilic domains. In the context of this investigation, we introduce an innovative prototype for nucleic acid delivery, which relies on βCD. In this prototype, the conventional segregation of hydrophilic and lipophilic components is deliberately depressed due to geometric constraints, leading to "geometrically frustrated amphiphiles" (GFAs). This communication covers the development, synthesis, and supramolecular properties of sequence-defined βCD-based cationizable GFAs. Computational simulations (MM and MD), as well as transmission electron microscopy (TEM), have been harnessed to scrutinize the preferred modes of interaction. Furthermore, our in vitro transfection experiments underscore the potential of βCD-based ionizable GFAs to surpass the conventional Janus archetype in encoding topological information, underscoring their suitability for advancing cell-selective nucleic acid therapeutics, e.g., targeting macrophages (Figure 1).

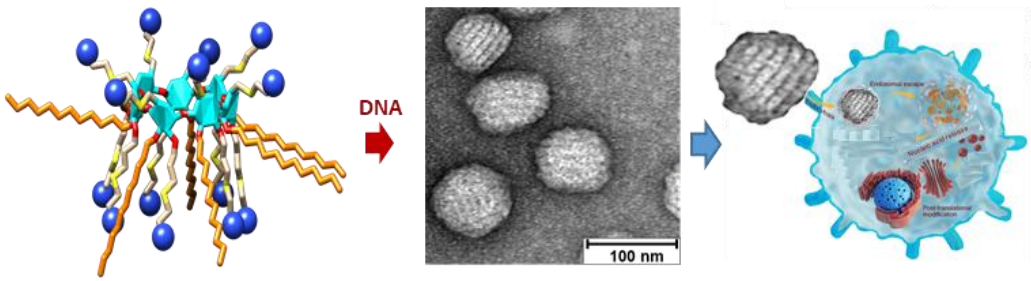


**Figure 1**. Representation of a βCD-based GFA (left, blue spheres represent cationic groups and orange segments lipid tails), characteristic TEM image of pDNA CDplexes (middle) and cartoon of their preferred uptake by macrophages (right).

## References

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