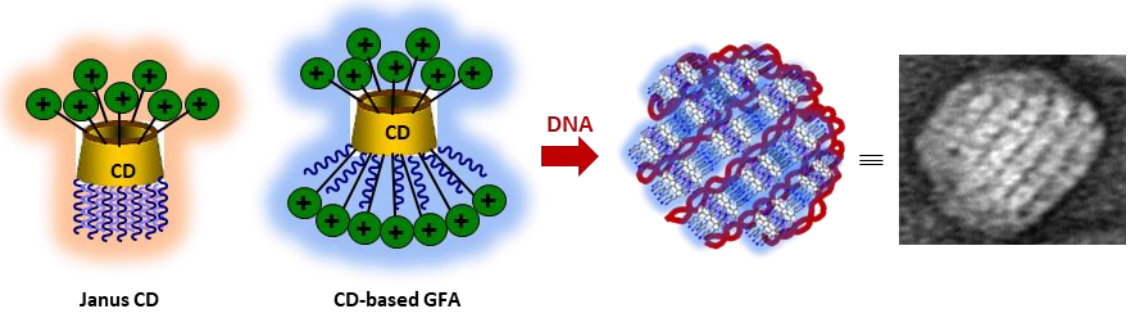
β-Cyclodextrin-Based Geometrically Frustrated Amphiphiles: Synthesis, Self-Assembly and DNA Delivery Capabilities

José M. García Fernández,[1] Gonzalo Rivero-Barbarroja,[2] José López-Fernández,[1] Inmaculada Juárez-Gonzálvez,[3] Carlos Fernández-Clavero,[4] Christophe Di Giorgio,[5] Itziar Vélaz,[6] María J. Garrido,[3] Juan M. Benito,[1] Carmen Ortiz Mellet,[2] Francisco Mendicuti,[4] Conchita Tros de Ilarduya[3]

[1] *Institute for Chemical Research (IIQ), CSIC – University of Seville, 41092 Sevilla, Spain*
[2] *Department of Organic Chemistry, Faculty of Chemistry, University of Seville, 41012 Sevilla, Spain*
[3] *Department of Pharmaceutical Sciences, School of Pharmacy and Nutrition, University of Navarra, Spain*
[4] *Departamento de Química Analítica, Química Física e Ingeniería Química and Instituto de Investigación Química "Andrés del Rio", Universidad de Alcalá, Spain*
[5] *Institut de Chimie Nice,UMR 7272, Université Côte d'Azur, Nice F-06108, France*
[6] *Department of Physical Chemistry, School of Sciences, University of Navarra, Spain*

jogarcia@iiq.csic.es

In this study, we introduce a novel approach to nucleic acid delivery using a β-cyclodextrin (βCD) framework, termed "geometrically frustrated amphiphiles (GFAs)," showcasing remarkable ability in encoding topological data. These molecular vectors feature a uniform distribution of cationic centers at both the βCD primary O6 and secondary O2 positions, with hydrophobic tails anchored at the seven O3 positions. This strategic arrangement of functional components disrupts the conventional sharp separation of cationic and lipophilic domains typically seen in Janus architectures.[1] The aim of this communication is to present the design, synthesis, and supramolecular characteristics of βCD-based GFAs, including self-assembly and co-assembly with DNA. Transfection experiments further demonstrate their potential utility in formulating site-specific nucleic acid therapeutics.



[1] Neva, T.; Carbajo-Gordillo, A. I.; Benito, J. M.; Lana, H.; Marcelo, G.; Ortiz Mellet, C.; Tros De Ilarduya, C.; Mendicuti, F.; García Fernández, J. M. Tuning the topological landscape of DNA-cyclodextrin nanocomplexes by molecular design. *Chem.-Eur. J.* **2020**, *26,* 15259-15269.