

Supramolecularly Assisted Synthesis of Pseudopeptidic Macrocyclic Compounds

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Topic:Beyond the Elements: building Nano- and Bio-materials

Macrocyclic compounds are often bioinspired structures characterized by their ability to display strong binding and selectivity towards specific substrates in a competitive environment. The main driving force for the tight binding with the substrate is the decrease in the degrees of conformational freedom, with the macrocycle providing a higher preorganization and functional density than open-chain analogues.¹ These receptors can display solvent-excluded cavities, in particular for cage-like systems, able to interact with the target molecule through non-covalent forces.² Nevertheless, one of the main bottlenecks for their use is the laborious experimental procedure often required for their preparation. Generally, reaching high purity products involve multi-step coupled reactions and complex and lengthy separation/purification protocols. Hence, promoting their assisted and controlled synthesis is crucial in order to modify the selectivity towards one of the many possible products.³

In this work the synthesis of new pseudopeptidic macrocycles **3** has been attained in excellent yields. These cyclic pseudopeptides contain a more rigid cavity and preorganization than previous related systems.⁴ The process involves four coupled S_N2 reactions between bisaminoamides **1** and tetrakis(bromomethyl)benzene **2** competing efficiently with the analogous intermolecular processes leading to oligomers.

The kinetic outcome of each reaction was followed using $^1\text{H-NMR}$ spectroscopy, and the experimental data were rationalized with the help of conformational searches at the MMFF level of theory. The effect of the different structural parameter and environmental stimuli has been analysed in detail.

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