# Bioinspired approaches to the synthesis of pseudopeptidic macrocycles: combination of experimental and in-silico technologies

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Nature is always an inspiring source for organic chemists. Many complex structures are synthesized by living beings in a very efficient and under green conditions. Synthesis of large multifunctional macrocycles is always a real synthetic challenge that, very often, need to be carried out through a complex synthetic sequence involving low yields, use of protecting groups, tedious and solvent consuming purification steps and so on.

Two bioinspired strategies can be used for this purpose: the conformational/configurational preorganization of the components (Alfonso *et. al.*, 2008, Bru *et. al.*, 2005). and the forced preorganization trough the use of a template (Bru *et. al.*, 2006, Bolte *et. al.*, 2008).

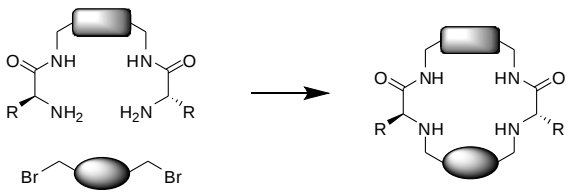


Fig. 1 – General scheme for a [1+1] macrocyclization

Simple [1+1] macrocyclization of $C_2$ pseudopeptidic systems has been reported to be favored by the preorganization of the chain with a folded conformation (Becerril *et. al.*, 2003). In the light of our recent results an anion template synthesis, we have undertaken a study on the effects of anions on this process, revealing that some anions can act as templates for the transition state of the ciclyzation reaction being able to accelerate the reaction. If we accelerate the cyclization reaction, we avoid the formation of side products. As a result of this improvement of the macrocyclization reaction we can simplify the purification steps and we can reduce the reaction time for the completion of the reaction.

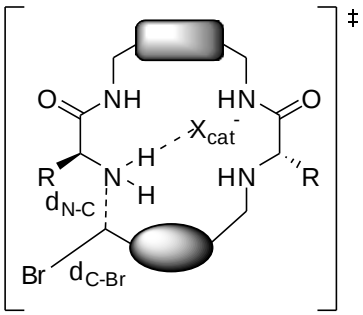


Fig. 2 – General structure for the transition state of a [1+1] macrocyclization

The study has been made trough a combination of experimental and in-silico tools. The use of computational techniques does not only help to rationalize the results out to successfully predict the best suited anion for this propose. Moreover this methodology opens a new way to predict the best reaction conditions for the synthesis of new macrocycles with the aid of computational chemistry. It's to say, by using chemical modeling we are able to predict if a cyclization reaction will take place or not. As a result we can reduce the number of experiments to optimize the reaction in the laboratory using less solvents and reagents, and therefore we make the synthesis more green.

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