

Synthesizing Macrocycles under Thermodynamic Control – Dynamic Combinatorial Libraries and Templates

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Abstract

An effective way to synthesize macrocycles using a dynamic combinatorial library is demonstrated for the reaction of pyridine-2,6-dicarbaldehydes with several long diamines. According to the template ions present, a given library can be shifted towards several macrocycles as desired.

The Beilstein encyclopaedia distinguishes between acyclic and cyclic compounds. Macrocycles are a subclass of the cyclic compounds, and only a smaller number of macrocycles exist in nature. Therefore it is necessary to develop effective routes for their synthesis.

In contrast to the formation of five- or six-membered rings,¹ cyclic organic compounds of other sizes are more difficult to synthesize. Due to ring strain, small rings and medium size rings are less stable than five- or six-membered rings, and thus they are more difficult to obtain. However, most macrocycles are unstrained and thus their enthalpy of formation is comparable to that of five- or six-membered rings (when calculated per subunit, e.g., per CH₂ group). There are no thermodynamic arguments against the formation of an unstrained macrocycle. But the kinetics for the formation of a macrocycle are different. Entropic reasons make it more difficult to synthesize large rings because the remote ends of a long chain (A and B) have to find each other.

Cyclization is an intramolecular process, which competes with the intermolecular reactions of the reactive ends of the linear precursor. Such intermolecular reactions lead to oligomers and polymers. In order to circumvent these side reactions, macrocyclizations are often carried out in high dilution to favour the intramolecular first-order cyclization over the intermolecular second order oligo- or polymerization.

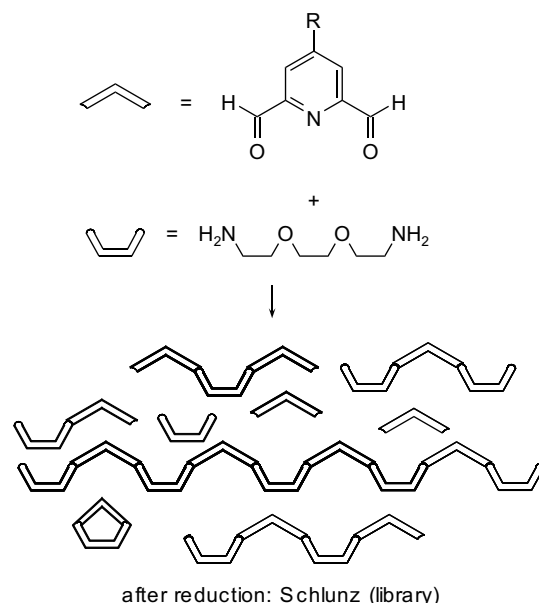
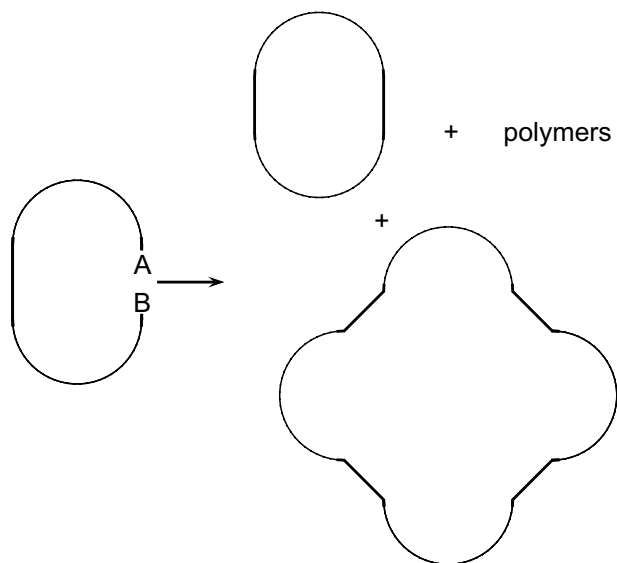
However, the high dilution principle is only effective if the macrocyclization reaction is an irreversible reaction: once a macrocycle is formed, it remains a macrocycle. In contrast to this kinetic approach, all products are in equilibrium in a thermodynamically controlled reaction. The relative stabilities of all products, macrocyclic or acyclic, polymeric or not, determine the product distribution. If by chance the macrocycle is the most stable compound, it will be formed in good

yield. Indeed, some examples exist where macrocycles are formed as the most stable products in a reversible reaction. Besides others, such a reaction is for instance the cyclization of tetraalkenyl-substituted diaryl-1,10-phenanthrolines by ring closing metathesis (RCM) to give bimacrocyclic concave 1,10-phenanthrolines [2, 3]. In only moderately diluted solutions, the bimacrocycles are formed in excellent yield and can be isolated after the Grubbs catalyst is filtered off. However, if the solution is concentrated with the catalyst still present, the products polymerize.

But in most cyclization mixtures, macrocycles, oligomers and polymers will be of comparable thermodynamical stability and therefore, all of them will exist in the mixture, and all of them will be interconverted into one another. In other words, dynamic combinatorial libraries are formed [4–6].

The synthetic challenge is now, to ‘make’ the macrocycle the most stable compound. This can be done by molecular recognition. The building blocks for the macrocycle and its oligo- and polymers are the same, but a macrocycle possesses a well-defined internal surface. If a guest can be found which binds complementarily into this cavity, a supermolecule will be formed which is more stable than its components. If macrocycle and template match best, this combination will be much more favoured than a supermolecule between the template and any of the other molecules of the dynamic library. Due to the thermodynamic control and the interconversion of all components of the dynamic library, all products will be interconverted eventually, ending up in the most stable, desired supermolecule.

This strategy has been exploited for some decades and is known as the template effect. In addition to mixtures in equilibrium, the template effect can also be useful in kinetically controlled reactions when the

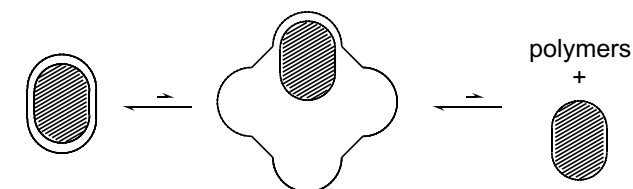


template facilitates the intramolecular reaction by a proper prearrangement of the reactive ends.

If a macrocycle was to be synthesized from two bifunctional molecules like a dialdehyde and a diamine for instance, the resulting library would contain the desired macrocyclic diimine, oligomeric cyclic diimines and linear oligo- and polymers. This mixture can be analyzed after reduction with sodium borohydride.

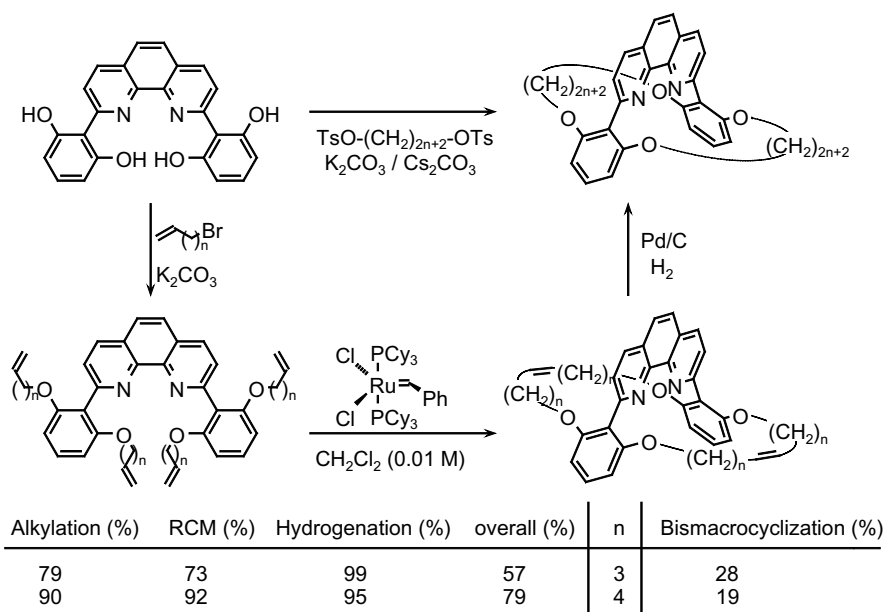
Addition of the proper template to the mixture of dialdehyde and diamine enhances the yields of the 1 + 1-macrocycle. This has been exploited in the synthesis of macrocyclic diamines as intermediates on the route to concave pyridines [7–9] and concave 1,10-phenanthrolines [10]. In these cases, the proper templates are alkaline earth metal ions.

Unsaturated crown ethers have been obtained using ring closing metathesis and employing the proper metal ions as templates [11]. Using organic templates, other



classes of macrocyclic oligomers could be obtained from the respective monomers, for instance by hydrazone formation [12].

More complicated dynamic libraries would be formed when several divalent building blocks are mixed, for instance when more than one diamine is present in the above-discussed mixture of diimines. In Figure 1, the diamines of different lengths are symbolized by v-, u- and similarly shaped units. Then, all of them may react



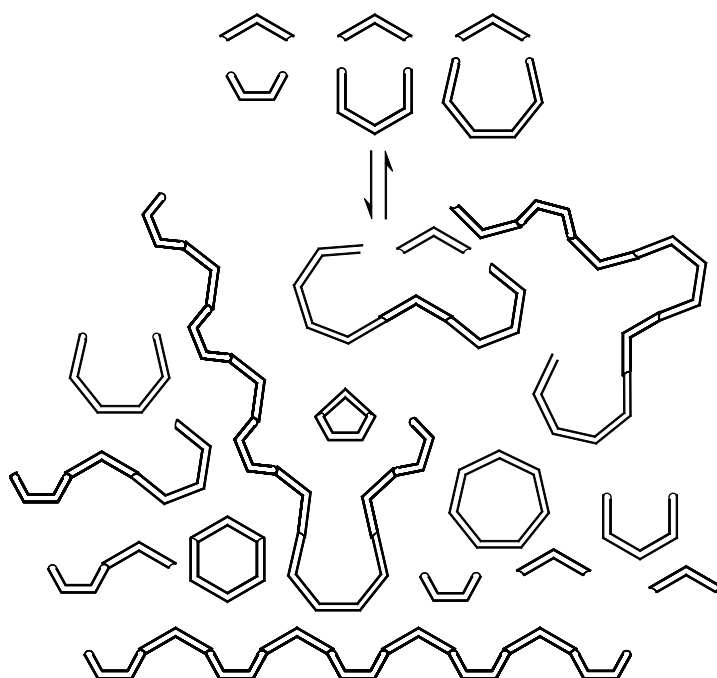
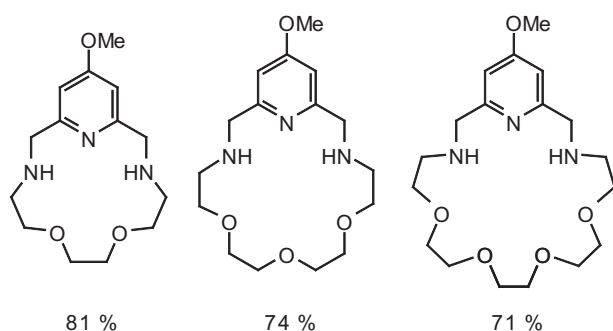


Figure 1. When a pyridine-2,6-dialdehyde, symbolized by the roof-shaped object, is mixed with diamines of different lengths (u-shaped objects), a huge dynamic combinatorial library consisting of various macrocycles, oligomers and polymers will be formed.



with the roof-shaped dialdehyde and a huge combinatorial library will be formed. Due to the reversibility of imine formation, the library is dynamic.

This dynamic combinatorial library has the potential to form several products, which may be present or not in the mixture. Therefore this type of library has also been named virtual combinatorial library (VCL) [5].

Adding one template will stabilize one product, adding another template may stabilize a second product. We have mixed a pyridine-2,6-dicarbaldehyde with oligoethyleneglycol-based diamines of different lengths. When adding magnesium ions, the smallest macrocycle, a 15-membered ring is formed, while calcium ions or barium ions stabilize larger macrocycles, respectively. The predominant formation of one macrocyclic diimine-alkaline earth metal complex can be followed by ESI mass spectrometry, and the respective products can be isolated as reduced macrocyclic diamines when the reaction mixtures are quenched by sodium borohydride. Thus the same combinatorial library can be the source

of different products – only the template determines which one will be formed! [13].

By using all the selective templates simultaneously, the combinatorial library can also be used to form several macrocycles in parallel. Thus a 15-, an 18-, and a 21-membered macrocyclic diamine were formed simultaneously from a library, which contained all three diamines and all three template ions in better than 70% yield each [13].

Other examples of dynamic combinatorial libraries which start from more than two molecules and use different templates for the generation of several macrocycles from one mixture have been described recently [4, 14, 15]. In these cases, the reversible reactions were the formations of disulfide bridges [14, 15] and hydrazones [4], respectively.

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Note

¹ The third 'Schiementz'scher Hauptsatz der Organischen Chemie' (third fundamental law of organic chemistry) states: Wherever five- and six-membered rings may form, they will; see [1].

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