A molecular construction set: template-directed synthesis of large macrocycles

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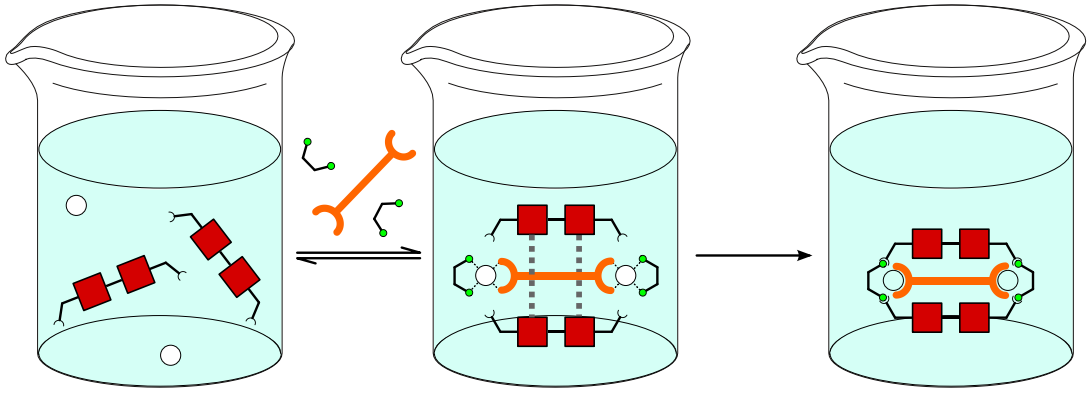
Abstract:

Large, highly symmetrical cyclic molecules (macrocycles) have recently received increasing attention, thanks to their promise in applications such as the construction of chemical sensors, and as building blocks for functional organic materials. These molecules, however, are intrinsically hard to make through conventional synthetic methods.

We intend to explore routes to simplify their synthesis by using a) molecular templates to pre-arrange the reactive precursors, and b) reversible reactions to form the new bonds, in order to provide some degree of error correction. Once the desired structures have been obtained, the reversible linkages can be eliminated: this step "freezes" the configuration of the final products and allows their isolation and handling.

We will explore multiple choices of building blocks and templates, and their effect on the distribution of the products formed. The nature and strength of the interaction between the molecular templates and the building blocks is particularly important, so it will be investigated in detail. Throughout the study, we will compare our approach to traditional synthetic methods.



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Marco Bonizzoni 02/25/2013

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02/25/13

Kevin Shaughnessy Chair, Department of Chemistry

Formation of large cyclic structures (macrocycles) held together by covalent bonds from non-cyclic precursors is inherently difficult:[1] in the example of a long, flexible, linear precursor, forming a ring structure entails that the two ends of the chain must find themselves close enough to react with each other, which in turn requires the molecule to fold up on itself. Such a specific geometrical conformation is only one of very many that the molecule can assume, so the process is at least statistically unlikely, if not downright unfavorable energetically.[2]

Molecular recognition tools may be used to preorganize reactive species for a chemical reaction.[3] Chemical templates are used to bring the precursors' reactive sites closer together, facilitating the desired chemical transformation.[4] Such templates must have chemical recognition sites that interact with complementary regions in the precursors, so that these can "wrap around" the template (Figure 1). The template can be later removed to free up the desired product.

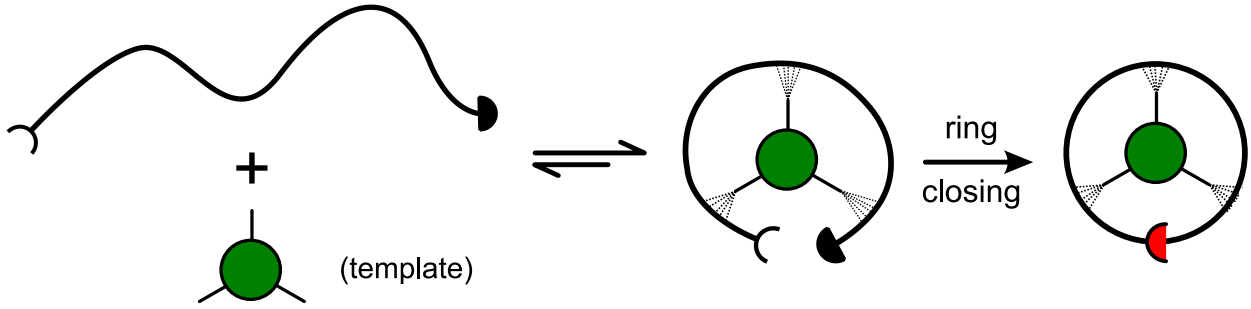


Figure 1 Macrocyclic ring closure is facilitated by the presence of a chemical template around which the linear precursor can wrap. The reactive ends of the precursor are thus brought closer together, which makes them more likely to undergo a reaction to form a new chemical bond.

The chemical template approach is still error-prone, because most synthetic techniques form irreversible chemical bonds: once formed, these bonds cannot be easily broken. This is often a desirable feature, affording stable compounds that are easy to handle. In some cases, however, the preferred product is not likely to be the one formed first, and the synthesis can get irreversibly stuck.[5] To tackle these difficult cases, we intend to combine the use of **chemical templates with reactions that form reversible (i.e. "breakable") covalent bond**.[6]

Reversible bonds are capable of **error correction**:[7] even if less stable products are formed first, such products can be broken down, so that more stable ones can then be accessed. Eventually, the most stable products will be formed preferentially. Such systems show excellent promise in allowing the formation of thermodynamically stable products that are otherwise difficult to access, thanks to this molecular-level refinement process. We propose here a set of versatile building blocks for the templated dynamic synthesis of large structures (Figure 2).

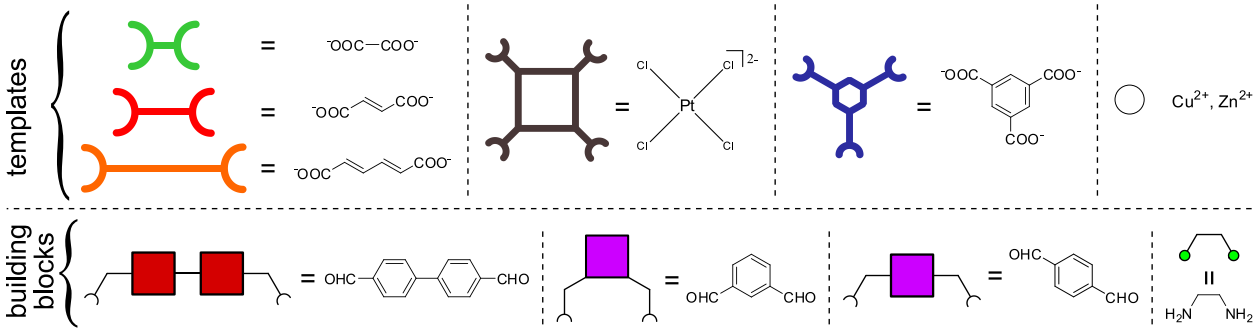
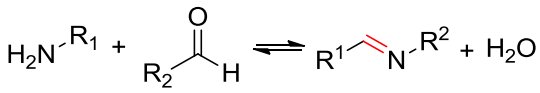


Figure 2 Structures and cartoon representations of building blocks proposed for the dynamic combinatorial library.

We intend to use **imines** as dynamic covalent linkages (see scheme on right; the bond highlighted in red is the reversible imine linkage).[8] Furthermore, the template will organize the building blocks around itself by forming coordination bonds with transition metal ions, another family of dynamic, "breakable" bonds. We have identified a set of building blocks of varying shapes and rigidity that should allow us to span a wide range of shapes and sizes in the product of their reactions. Additionally, we have identified a number of rigid structures to use as templates, allowing us to form **different products from the same starting materials** (Figure 2).



The permanence of non-reversible structures, however, is still attractive: therefore, once a product has been prepared, it is desirable to be able to **lock in the final product**. The imine linkage will prove handy in this respect as well, since it can be chemically transformed into a

non-dynamic amine moiety in a variety of minimally invasive ways,[9] thereby turning the reversible linkage into a permanent one and locking the desired product in a fixed, non-reversible form that is easy to handle for further use.

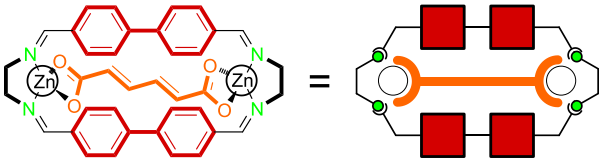


Figure 3 A templated macrocyclic structure (left) and its cartoon representation (right).

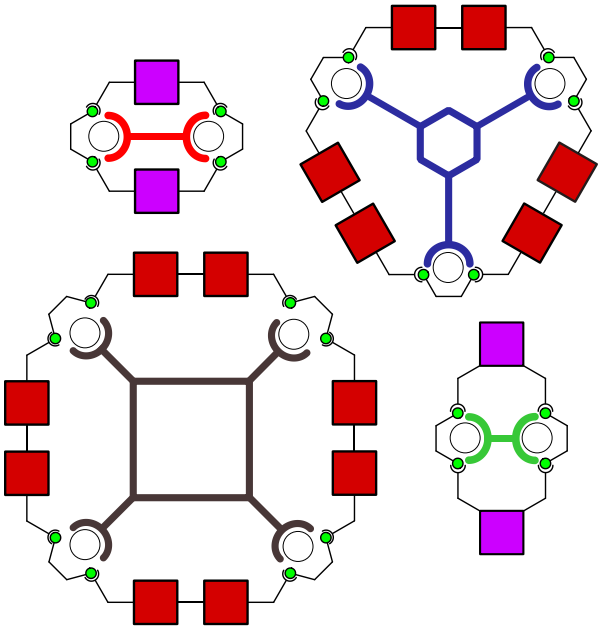


Figure 4 Examples of other macrocycles obtainable from the same set of building blocks by changing the templating agents.

Figure 3 presents the actual and cartoon structures of one of the macrocycles that we intend to prepare. Figure 4 presents a few of the structures accessible through the method described here: it is important to notice that **the same building blocks** can form **different products** depending simply on the **shape and size of the template**.

The experimental methods involved are relatively simple, so this project is well suited to involve **undergraduate students** in the research right from the start. If funded, we plan to recruit a team of at least two undergraduates to start work on the project in the Summer 2013. After initial supervision from current graduate students, I expect the undergraduate researchers to take ownership and work on the project independently.

Success will be gauged by the achievement of the following aims: a) establishment of a proof of feasibility; b) dissemination of results at regional venues, such as the American Chemical Society's annual South-Eastern Regional Meeting (SERMACS), and at national meetings; c) publication of at least **one communication** on the results obtained.

Budget request and justification:

Personnel (0.5 Graduate Research Assistant over Summer 2013)	**$**	**3,055.00**
Salary, 3 months, based on yearly salary ($21,640) x 0.5	$	2,705.00
GRA fringe benefits (7.7%), health insurance ($283/student x 0.5)	$	350.00
Supplies (prices from Sigma-Aldrich catalog, as of 02/10/13)	**$**	**1,189.00**
Templates:	$	249.00
Square template (potassium tetrachloroplatinate, 1 g)	$	84.00
Trigonal template (1,3,5-benzenetricarboxylic acid, 50 g)	$	70.00
Linear templates, (oxalic, muconic and fumaric acid, gram scale)	$	95.00
Macrocycle building blocks:	$	440.00
Benzenedialdehydes, *meta*- and *para*- isomers, 5 g each	$	79.00
Ethylenediamine, 250 mL	$	60.00
Starting materials to make biphenyl-4,4'-dialdehyde (5-7 g yield expected)	$	198.00
Zinc(II) and copper(II) trifluoromethanesulfonate salts, 5 g each	$	103.00
Solvents, consumables (estimated over the course of 12 months)	$	500.00
Product characterization (ESI-MS user fees, estimated 100 hrs @ $5 / hr)	**$**	**500.00**
Total funds requested	**$**	**4,744.00**

Personnel: Undergraduate researchers will work for academic credit. In the project's initial stages it will be expeditious to have one graduate student dedicate effort (50% FTE) to oversee their first steps. This will provide the impetus to establish initial results. From then on, the undergraduate researchers will take full ownership of the project.

Supplies: The initial cost to procure the necessary building blocks is high enough that we would be unable to devote any current funds to this high-risk / high-reward attempt without CARSCA support. Product characterization will make heavy use of electrospray mass spectrometry (ESI-MS), which is available to us through the Chemistry Department facilities: user fees covering 100 hr of instrument time over the course of the project were included in the budget.

Timeline:

- Overall project period: 12 months.
- Initial phase: familiarization, synthesis of the non-commercial building blocks (3 months).
- Background work for comparison: attempts to synthesize the macrocycles *in the absence of templates*; characterization of results (linear, trigonal, square planar) (2 months)
- Characterization of template effects: binding constants, nature of interactions (3 months)
- Templated syntheses, characterization; establishing reversibility (3 months)
- Product "lock-in" protocols: elimination of reversible linkage in finished products (1 month)
- Data interpretation, preparation of dissemination material: as the project proceeds.

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Formation:

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- Doctorate in Chemistry
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  Advisor: Prof. Luigi Fabbrizzi
  Dissertation title: Anion recognition through metal-ligand and hydrogen-bonding interactions
  October 2003 – September 2006
- B.S. in Chemistry Summa cum laude (five year degree)
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Selected publications:

- Marco Bonizzoni, S. Reid Long, Chance Rainwater, Eric V. Anslyn. PAMAM dendrimer-induced aggregation of 5(6)-carboxyfluorescein. *Journal of Organic Chemistry*, **2012**, *77*(3), 1258-1266
- Tianzhi Zhang, Nicola Y. Edwards, Marco Bonizzoni, Eric V. Anslyn. The use of differential receptors to pattern peptide phosphorylation. *Journal of the American Chemical Society*, **2009**, *131* (33), 11976–11984
- Michela Allevi, Marco Bonizzoni, Luigi Fabbrizzi. Homo- and hetero-dinuclear anion complexes. *Chemistry - A European Journal*, **2007**, *13* (13), 3787-3795
- Marco Bonizzoni, Luigi Fabbrizzi, Angelo Taglietti, Federico Tiengo. Benzylideneamine-thioureas: chromogenic interactions with anions and N-H deprotonation. *European Journal of Organic Chemistry*, **2006**, *16*, 3567-3574
- Valeria Amendola, Marco Bonizzoni, David Esteban-Gomez, Luigi Fabbrizzi, Maurizio Licchelli, Felix Sancenon, Angelo Taglietti. Some guidelines for the design of anion receptors. *Coordination Chemistry Reviews*, **2006**, *250* (11-12), 1451-1470

- Marco Bonizzoni, Luigi Fabbrizzi, Giulio Piovani, Angelo Taglietti. Fluorescent detection of glutamate with a dicopper(II) polyamine cage. *Tetrahedron*, **2004**, *60* (49), 11159-11162
- Massimo Boiocchi, Marco Bonizzoni, Luigi Fabbrizzi, Giulio Piovani, Angelo Taglietti. A dimetallic cage with a long ellipsoidal cavity for the fluorescent detection of dicarboxylate anions in water. *Angewandte Chemie, Int. Ed.* **2004**, *43* (29), 3847-3852

Prior external funding: none

Presentations at conferences and meetings:

- Marco Bonizzoni, Ashley M. Jolly, Alie M. Mallet. Molecular assembly onto water-soluble dendritic polyelectrolytes. Poster communication presented at the *Macromolecular Materials* Gordon Research Conference, Ventura, CA, January 6th-11th **2013**.
- Marco Bonizzoni, Eric V. Anslyn. Towards multicomponent assembly on dendritic scaffolds. Oral presentation at the *ACS Spring National Meeting* in San Francisco, CA, March 21st-25th **2010**
- Marco Bonizzoni, Eric V. Anslyn. A pattern-based recognition approach to the discrimination of protein kinase enzymes. Poster communication presented at the *III International Symposium on Macrocyclic and Supramolecular Chemistry* (ISMSC), Las Vegas, NV, July 13th-18th **2008**

Synergistic activities:

- Professional development and service:
    - Manuscript reviewing for the *Journal of Organic Chemistry*
    - National Institutes of Health *Early Career Reviewer Program*: July 2011 – ongoing
      The program identifies and educates qualified scientists without prior review experience to develop well trained critical reviewers, and at the same time to benefit the young reviewers' careers through exposure to the peer review process.

- Teaching:
    - Spring 2012, Fall 2012: Instructor for Organic Chemistry I
    - Fall 2010, Spring 2011, Spring 2013: Instructor for Organic Chemistry II
    - *Using technology for student assessment* seminar: February – March 2013
    - *Learner – Centered Initiative Workshop*: College of A&S Oct. – Nov. 2010 Workshop focusing on the processes by which a student gains knowledge and understanding, and exploring active involvement in the learning experience.