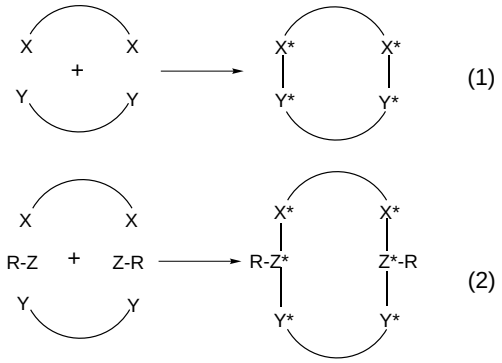


Scheme 1. Schematic representation of cyclodimerization [Eq. (1)] and multicomponent (ABC_2) synthesis [Eq. (2)] of macrocycles.

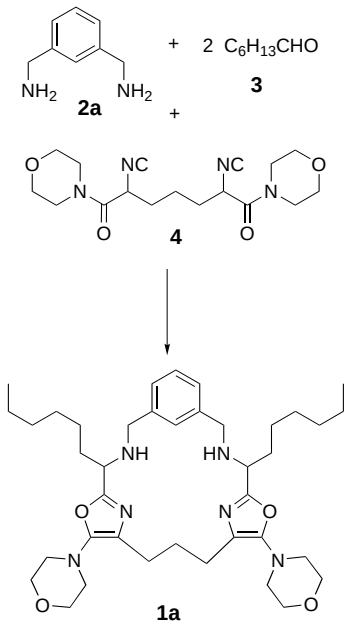
Functional Symmetric Cyclophanes

A One-Pot Four-Component (ABC_2) Synthesis of Macrocycles**

*Pierre Janvier, Michèle Bois-Choussy, Hugues Bienaymé, and Jieping Zhu**

Macrocycles, by virtue of their widespread occurrence in nature and their intrinsic three-dimensional structure, have found numerous applications in areas such as drug development, material science, and supramolecular chemistry.[1] Not surprisingly, the challenging problem of macrocyclization has attracted attention of synthetic chemists and provided impetus for the development of new technologies.[2] Among many existing methodologies, one-step synthesis of targeted macrocycles is a particularly attractive strategy.[3] Indeed, the cyclodimerization of two bifunctional monomers ([Eq. (1)], Scheme 1) has been successfully developed and applied in the synthesis of natural products[4] as well as non-natural molecules.[5] We report herein a novel four-component (ABC_2) synthesis of symmetric cyclophanes (see schematic representation in Equation (2) in Scheme 1).

Multicomponent reactions (MCRs) are based on a cascade of bond-forming events that are kinetically favored when the reaction is performed at high concentration.[6] On the other hand, macrocyclization has to be generally carried out at high dilution for it involves entropically disfavored end-to-end cyclization.[7] The projected transformation shown in Equation (2) in Scheme 1 comprises a sequence of one three-component process, one bimolecular reaction, and finally one intramolecular reaction. To help circumvent the problems associated with concentration and to make the overall process successful, we decided to incorporate a structural unit that could reduce the conformational mobility of the linear precursor, which assembles in situ during the MCR. The rigidifying effect of aromatic heterocycles is well known, we therefore considered that the recently developed three-component synthesis of oxazole[8] might be applicable for the synthesis of macrocycles **1** according to Scheme 2.



Scheme 2. A four-component (ABC_2) synthesis of macrocycle **1a**. Variations of the reaction conditions are given in Table 1.

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Interestingly, double Ugi-4CR (formally one intermolecular and one intramolecular Ugi-4CR)[9] has been observed as an undesired side reaction during a search for macrocyclization substrates based on the cyclization strategy pioneered by Ugi and co-workers.[10]

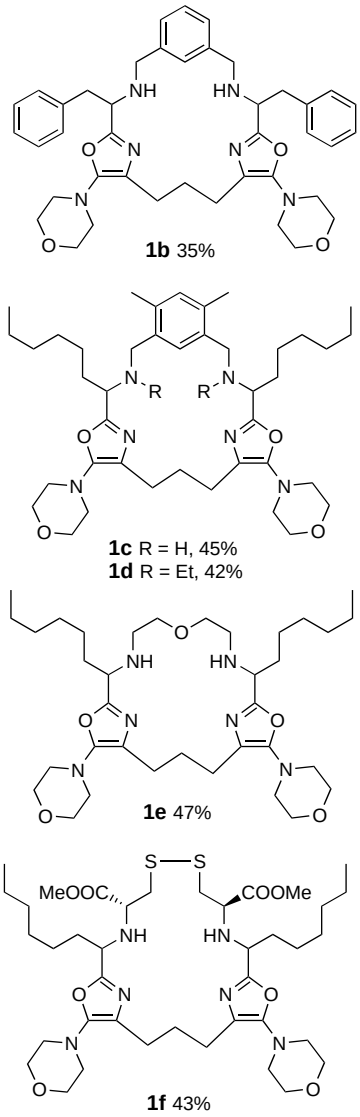
Initial experiments employed *m*-xylylenediamine (**2a**), *n*-heptanal (**3**), and 2,6-diisocyanoheptanedioic acid bismorpholinylamide (**4**).[11] Stirring a solution of **2a** and **3** (molar ratio 1/2, 0.01M) in toluene for 30 min in the presence of lithium bromide followed by addition of **4** provided **1a** (70 °C, 4 h) in 15% yield as a mixture of inseparable diastereomers. Although only one set of peaks was observed in the ^{1}H NMR spectrum of **1a**, the presence of two diastereomers (*dl* and *meso* forms in a 1:1 ratio) of the purified material is readily seen from the ^{13}C NMR spectrum.

These promising results prompted a more detailed examination of the reaction conditions (Table 1). Methanol was found to be a better solvent than toluene leading to **1a** in an improved yield of 31% (Table 1, entry 2). Interestingly, increasing the concentration from 0.01M to 0.1M further improved the yield of **1a** (52%, Table 1 entry 3).[12] The template effect was examined by adding various salts to the reaction mixture.[13] However, it was observed that none of the salts used, including antimony methoxide,[14] led to an improved yield for this multicomponent process (Table 1, entries 5–7).

Table 1: Survey of reaction conditions for the one-pot four-component synthesis of macrocycle **1**.[a]

Entry	Solvent	*T*	Additive	Conc. [M]	Yield [%][b]
1	toluene	70 °C	LiBr	0.01	15
2	MeOH	reflux	non	0.01	31
3	MeOH	reflux	non	0.1	52
4	MeOH	reflux	CSA[c]	0.1	48
5	MeOH	reflux	LiBr	0.1	29
6	MeOH	reflux	NaBr	0.1	35
7	MeOH	reflux	$Sb(OMe)_3$	0.1	43

[a] Reaction time: 4 h. [b] Yield of isolated product. [c] CSA = camphorsulfonic acid.



Scheme 3. Structures of macrocycles synthesized.

With these results in hand, the potential and generality of this one-pot multicomponent synthesis of macrocycles were examined under optimized conditions (MeOH, 0.1M, reflux). We initially focused on the structural tolerance of the diamine employed since a wider variety of this component was more readily available than derviatives of the bis(isonitrile) **4**, and it was considered the diamine would have more impact than the aldehyde **3** on the outcome of the reaction. To examine whether the steric buttressing effect[15] as well as intramolecular hydrogen bonds[16] could have any effect on the macrocyclization step, 1,3-bis(aminomethyl)-4,6-dimethylbenzene (**2c**) and its *N,N′*-diethyl derivative (**2d**) were synthesized[17] and submitted to the MCR conditions. The yields of resulting macrocycles **1c** and **1d** (Scheme 3) were similar to that of **1a**, indicating that both effects are minimal, if they exist at all. In the case of **1d**, two diastereomers (1:1 ratio) were isolated and characterized, although their relative stereochemistry remained unknown. Besides the rigid *m*-xylylenediamine, aliphatic diamines such as 1,5-diamino-3-oxapentane (**2e**) and cystine dimethyl ester (**2f**) were shown to participate in this process leading to the macrocycles **1e** and **1f**, respectively (Scheme 3). The formation of macrocycles at such a high concentration (0.1M) is unique and intriguing. It may indicate that the intermediate, assembled in situ by MCR, was preorganized into a folded conformer that is conducive to cyclization.[18]

Although compound **1** is of interest in its own right (e.g., as a pincer ligand for metal complex),[19] it could also serve as a useful chemical platform for the production of new structures by taking advantage of the rich chemistry of oxazole.[8,20] One such example is shown in Scheme 4. Hydrolysis of **1a** under standard conditions (THF–H_2O–TFA (8/2/1))[21] afforded the corresponding macrocyclic amide **5** in over 85% yield. All six possible diastereomers were readily separated and identified by LC/MS. Interestingly, the retention time of these diastereomers differed

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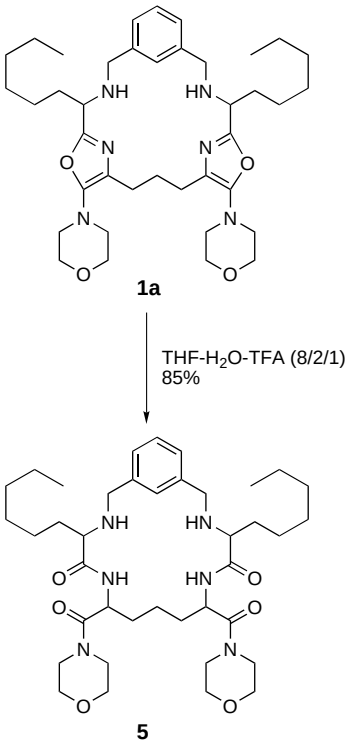

Scheme 4. Transformation of cyclophane **1a**: selective hydrolysis of oxazole groups to give **5**.

significantly, ranging from 2.2 min to 26.3 min (column: Symmetry C-18, gradient H_2O/MeCN = 2/3, then MeCN). This result confirmed the earlier observation that stereochemistry can have an impact on the hydrophobicity and consequently, may modulate the pharmacological properties of small bioactive molecules.[22]

In summary, we have developed a novel one-pot multicomponent synthesis that delivers at least three elements of diversity into the final macrocycles. The overall process leads to the creation of six chemical bonds with the concomitant formation of two oxazole groups as part of a new macrocycle, and thus involves a large increase in molecular complexity.[23] The synthesis is ecologically benign and atom economic since only two molecules of water are lost in this rather complex bond-forming process.[24]

Experimental Section

Typical procedure: A solution of diamine **2a** (95.0 μmol) and aldehyde **3** (209.0 μmol, 2.2 equiv) in anhydrous methanol (0.45 mL) was stirred at room temperature for 30 min. The diisocyanide **4** (114.0 μmol, 1.2 equiv) in anhydrous methanol (0.5 mL) was added and the reaction mixture was heated to reflux. When the reaction was deemed complete by TLC analysis (typically 4 h), the reaction mixture was cooled to room temperature and the volatile components were removed under reduced pressure. The crude reaction mixture was purified by either preparative TLC (silica gel) or flash chromatography (alumina gel). Compound **1a** (pale yellow oil, yield 52%, two diastereomers, preparative TLC on silica gel, eluent: CH_2Cl_2/MeOH = 95/5). IR ($CHCl_3$): $\tilde{\nu}$ = 3692, 3438, 3017, 2957, 2929, 2859, 1666, 1603, 1455, 1376, 1264, 1212, 1115, 910 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.40–7.27 (m, 4H), 3.83 (m, 8H), 3.65 (q, J = 7.1 Hz, 2H), 3.54 (m, 4H), 3.07 (m, 8H), 2.51 (m, 4H), 2.09 (m, 4H), 1.74 (m, 4H), 1.25 (m, 16H), 0.86 ppm (t, J = 6.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 162.1 (161.8), 151.5 (151.3), 140.1 (139.9), 131.3 (131.1), 128.9 (128.8), 128.2 (128.1), 126.1 (125.9), 67.4, 57.0 (56.7), 52.8 (52.6), 51.8, 35.4 (35.1), 32.0, 29.4, 29.0 (28.9), 26.3, 25.2 (25.1), 22.9, 14.4 ppm; MS (ES, positive mode): m/z $[M+H]^+$ 677.

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