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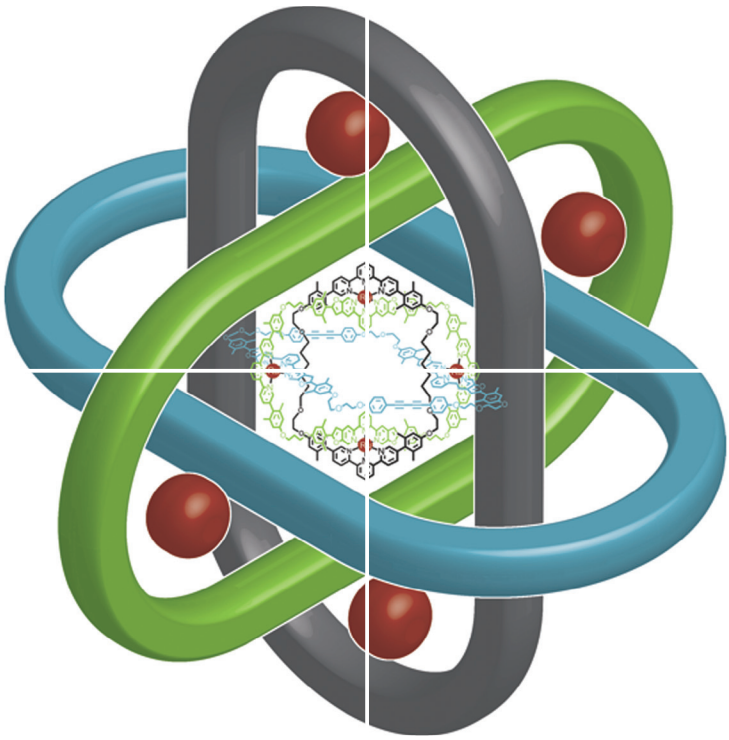

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Towards the molecular Borromean link with three unequal rings: double-threaded ruthenium(II) ring-in-ring complexes†

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This study describes synthetic efforts towards the molecular Borromean link consisting of three unequal rings. The design and strategy involve step by step construction of a ruthenium(II) templated ring-in-ring complex doubly threaded with endocyclic ligands ready for the macrocyclization. The control over the topology is achieved by using specially designed directional building blocks based on 2,2′:6′,2″-terpyridine. Preliminary macrocyclization attempts utilizing the copper-mediated Eglington reaction provide the mass spectrometric evidence consistent with the ruthenium(II) complex of the molecular Borromean link.

Introduction

The Borromean link comprises three topologically interlocked rings with the remarkable property that no two loops are mutually linked and the cleavage of any one loop results in separation of the other two.[1] Such links[2] have long fascinated chemists as a complex synthetic target.[3] The knotted DNA superstructure[4] with the Borromean topology, the Borromean networks,[5] and the thermodynamic assembly of the molecular Borromean links consisting of equal rings[6] have been reported. When all rings are either oriented or unequal the topological symmetry becomes a factor; thus, a directed synthesis of a molecular Borromean link controlling the nature of the three rings would be of special interest;[7] however, despite several attempts, the synthesis involving three unequal rings remains a challenge.[2b,8,9] In this context, ring-in-ring complexes[8,10,11] may serve as strategic intermediates towards this goal.

A classic ring-in-ring strategy involves starting from the complexation of a macrocycle **A**, possessing endocyclic coordination sites, with the heteroleptic metal complex **B** to form an *endo*,*endo*-threaded macrocycle **C** (Fig. 1(a)).[8] Subsequent coupling of **C** with linker **D** would afford a ring-in-ring complex **E**. If **E** contains endocyclic coordination sites, then threading with another complex **F** would give a double threaded ring-in-ring structure **G**. The closure of the final ring with linker **H** would form the Borromean link metal complex **I**. This strategy has led to the synthesis of Ru(II) ring-in-ring complexes having two 2,2′-bipyridine (bipy)[8a] or 2,2′:6′,2″-terpyridine (terpy)[8b] pockets in the internal ring, which are topologically equivalent structures to **E**. All attempts to perform threading of the ring-in-ring complexes **E** with **F** have so far been unsuccessful, presumably because of an unfavorable strain inhibiting the necessary change of the bipy confor-

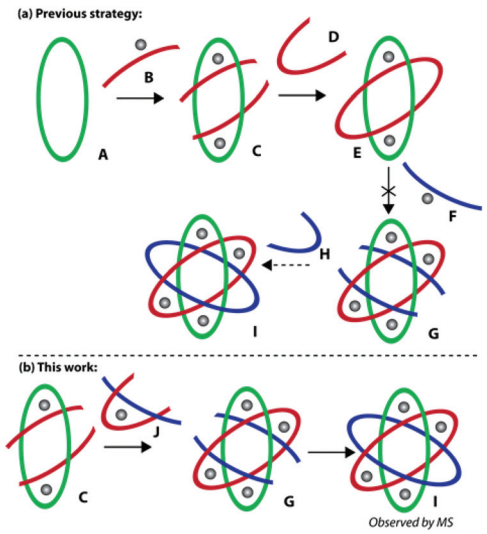

Fig. 1 Towards the molecular Borromean link comprising unequal rings.

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†Electronic supplementary information (ESI) available: Full experimental synthesis procedures and characterization data, including ^{1}H NMR and ^{13}C NMR spectra of all new compounds and CIF files. CCDC 1431458 and 1431459. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6qo00025h

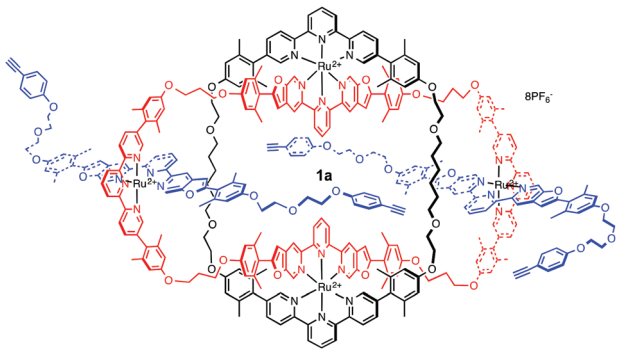


Fig. 2 The double threaded macrocyclic ruthenium(II) ring-in-ring complex **1a**.

mation upon complexation or the limited cavity available for the incoming motif **F**. This motivated a detailed structural study of the conformational flexibility of large macrocycles and ring-in-ring complexes, which supports the necessity for new strategies.[8b]

A modified approach implementing preformed Ru(II)-templated cap **J** combined with the threaded ring **C** could be used to afford directly a **G** analog (Fig. 1(b)). If cap **J** would already contain linkers suitable for the macrocyclization then it would take one step to convert **G** into the Borromean link **I**. Herein we report a successful synthesis of a double threaded ring-in-ring ruthenium(II) complex **1a** (Fig. 2), which is the topological equivalent of **G**. This molecule contains linkers functionalized with terminal acetylenes, suitable for the macrocyclization to form the final third ring. The macrocyclization attempts provided mass spectrometric detection of the Borromean link Ru(II) complex.

Our molecular design involves the use of directional building blocks from a set of 2,2′:6′,2″-terpyridine (terpy)[12] based ligands (Fig. 3), which mimic the linear-rod geometry of 5,5′-substituted 2,2′-bipyridine ligands – "linear bilateral extended terpy"[13] – the missing unit for the construction of extended terpy based structures. For example, "V-terpy" is handy for the 60° turn motifs with respect to its coordination vector, but "extended terpy" is useful for orthogonal motifs, moving substituents further away from one another. The proper combination of such building blocks allows one to control how the molecular strands inter-weave in **1a** (*cf.* Fig. 2).

Results and discussion

Synthesis of the necessary ligands starts from diiodoterpyridine **2** (Scheme 1),[13] which couples to the corresponding acetylene **3** (**a** or **b**) *via* the Sonogashira reaction,[14] to give either bromo- or methoxy-substituted bis-ethynyl terpyridines **4**. A one-pot methoxymethyl (MOM) deprotection and cycloisomerization affords "linear bilateral extended terpy" ligands **5**.[13] The methoxy substituted ligand **5b** was further converted to bis-hydroxy-substituted "extended terpy" **5c**, which could be alkylated readily with 2-(2-chloroethoxy)ethan-1-ol to give ligand **5d**.

Independent functionalization of bis-methoxy substituted "V-terpy" ligand **6a**[15] with appropriate linkers (Scheme 2) is achieved in a good yield by cleaving the methoxy groups of **6a** under microwave irradiation in the presence of pyridine hydrochloride to obtain **6b**, which is then alkylated with 3-chloropropan-1-ol to afford bis-alcohol **6c**.

Pretemplated Ru(II) caps of structure-type **J** (Fig. 1) come from the complexation of "extended terpy" ligands **5a** or **5c** with $RuCl_3{\cdot}3H_2O$ to furnish the ligand–ruthenium(II)Cl_3 complexes **7a**/**b** (Scheme 2). Further complexation of **7a**/**b** with "extended terpy" ligands **5a** and **5d**, or "V-terpy" ligand **6c** in EtOH and *N*-ethylmorpholine[16] as a base provides the heteroleptic ligand complexes **8a**, **9a**, or **10a**, accordingly. The ^1H and ^{13}C NMR spectra along with mass spectrometry (ESI) support the formation of 1 : 1 mixed ligand Ru(II) complexes. Slow diethyl ether vapor diffusion into an acetonitrile solution of the complex **9a** gave red crystals, for which the crystal structure was solved in space group $P2_1/n$, revealing the coordination of two different ligands around the ruthenium(II) center, as anticipated from the solution NMR and MS data (Fig. 4A).[17]

Next, complexes **8a** and **10a** were functionalized with the linkers containing terminal acetylene groups suitable for the

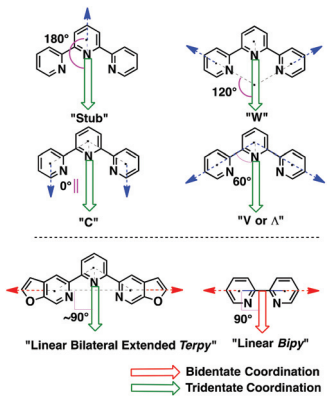
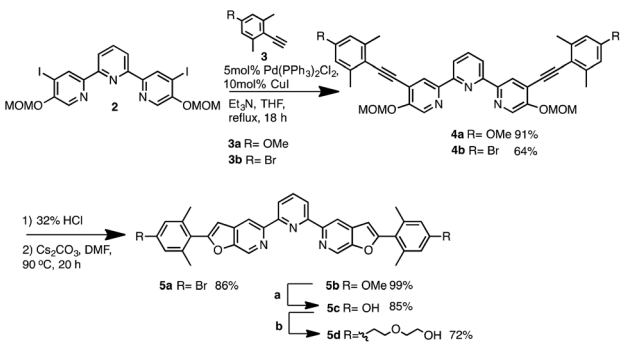
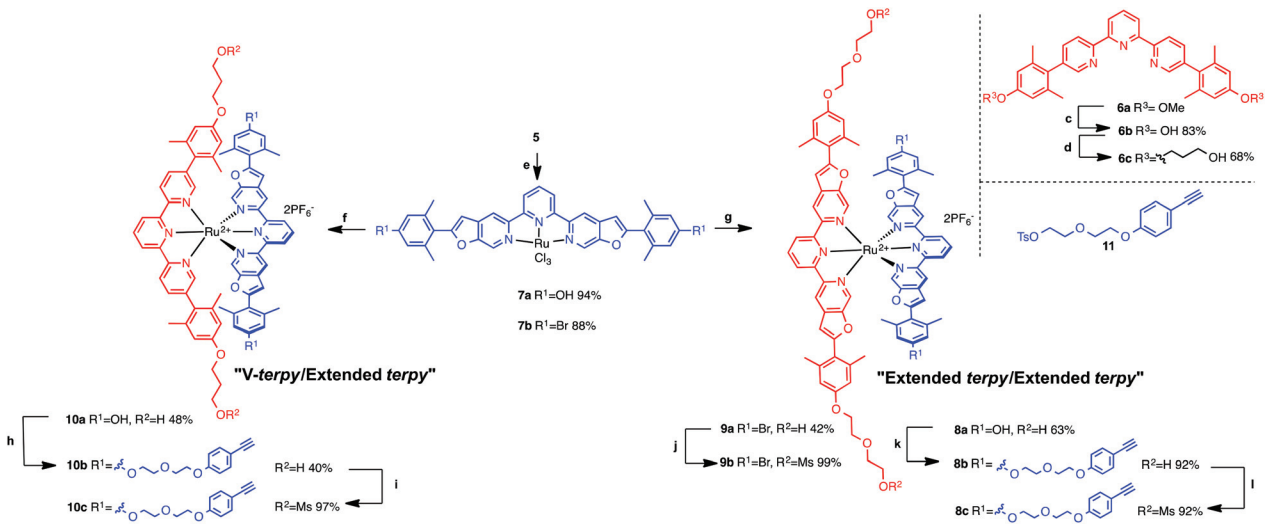


Fig. 3 Terpy-based motifs as the topological control element.



Scheme 1 Conditions: (a) **5b** (1 eq.), Py·HCl (50 eq.), MW, 190 °C, 2 × 2 min; (b) **5c** (1 eq.), 2-(2-chloroethoxy)ethan-1-ol (2.9 eq.), Cs_2CO_3 (3 eq.), DMF, 100 °C, 18 h.



Scheme 2 Conditions: (c) **6a** (1 eq.), Py·HCl (19 eq.), MW, 190 °C, 10 min; (d) **6b** (1 eq.), 3-chloropropan-1-ol (2.2 eq.), Cs_2CO_3 (3.0 eq.), DMF, 100 °C, 20 h; (e) **5** (1 eq.), $RuCl_3{\cdot}3H_2O$ (1 eq.), EtOH, reflux, 18 h; (f) **7a** (1 eq.), **6c** (1.1 eq.), *N*-ethylmorpholine (2.3 eq.), EtOH, N_2, reflux, 24 h, then aq. KPF_6; (g) **7a** (1 eq.) or **7b** (1 eq.), **5d** (1 eq.), *N*-ethylmorpholine (2.3 eq.), EtOH, N_2, reflux, 20–24 h, then aq. KPF_6; (h) **10a** (1 eq.), **11** (2.55 eq.), Cs_2CO_3 (3 eq.), DMF, N_2, 75 °C, 5 h; (i) **10b** (1 eq.), Et_3N (70 eq.), MsCl (36 eq.), THF/MeCN (20 : 3), rt, 1.5 h; (j) **9a** (1 eq.), Et_3N (40 eq.), MsCl (20 eq.), THF/MeCN (7 : 3), rt, 1 h; (k) **8a** (1 eq.), **11** (2.2 eq.), Cs_2CO_3 (3 eq.), DMF, N_2, 80 °C, 9.5 h; (l) **8b** (1 eq.), Et_3N (60 eq.), MsCl (30 eq.), THF/MeCN (6 : 1), rt, 2 h. Py = pyridine, MW = microwave irradiation, Ms = methanesulfonyl.

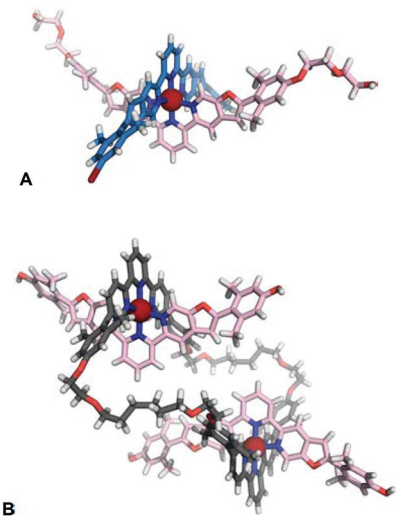


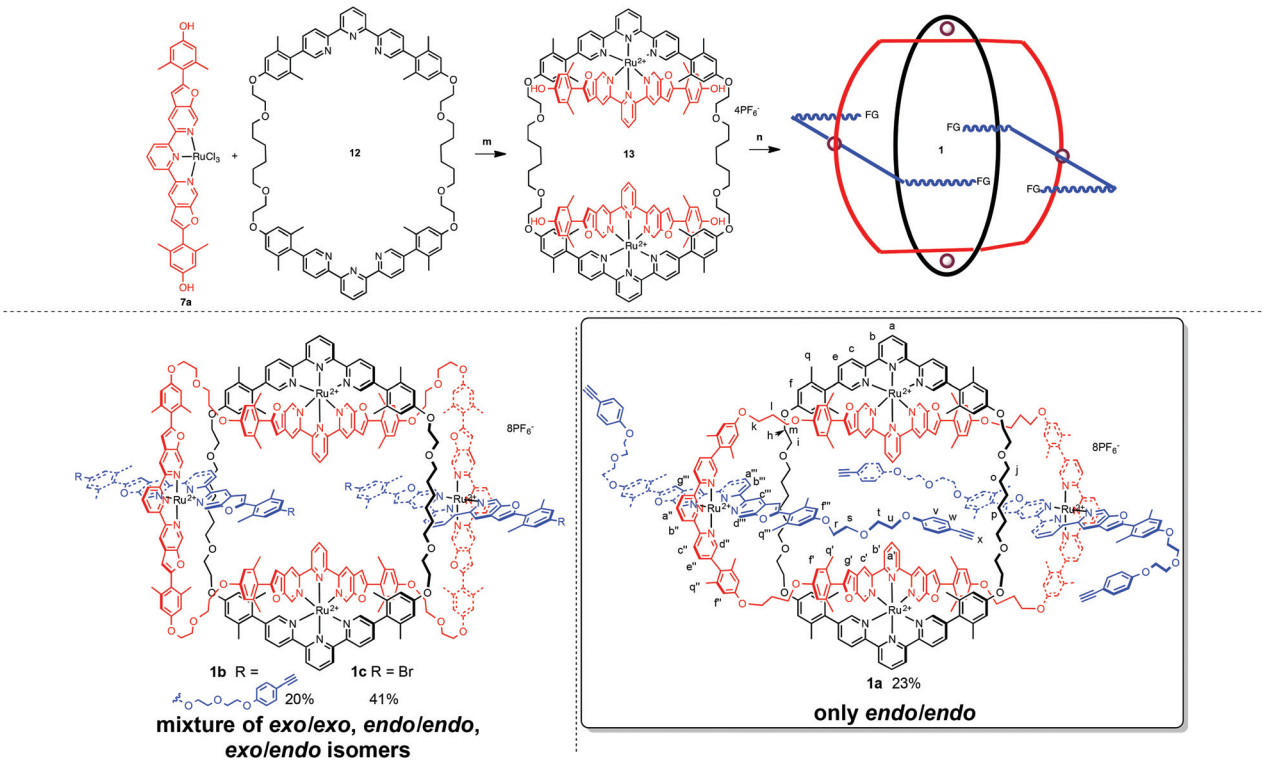
Fig. 4 The molecular structures of: (A) the heteroleptic ruthenium(II) complex **9a**; (B) the *endo*,*endo*-double threaded ruthenium(II) complex **13**. (Solvent molecules and PF_6^- omitted for clarity.)

final macrocyclization. The heteroleptic complexes **8a** and **10a** have two pairs of chemically distinct –OH groups, thus no alcohol protection was necessary to perform bis-alkylation with linker **11** (Scheme 2). The phenolic hydroxy groups are more reactive, exclusively affording products **8b** or **10b**. Further, the treatment of corresponding complexes with methanesulfonyl chloride resulted in bis-mesylate complexes **8c**, **9b**, and **10c**.

The reaction of **12**,[8a] with "extended terpy" Ru(II)Cl_3 complex **7a** furnished *endo*,*endo*-double threaded ruthenium(II) complex **13** (Scheme 3) – a topological equivalent of **C** (Fig. 1). Slow solvent Et_2O/MeCN diffusion afforded red block-like crystals of **13**, for which the crystal structure was solved in space group $P\bar{1}$ (Fig. 4B). Both threaded ligands have the expected endocyclic conformation necessary for the synthesis of the Borromean link. It reveals that the distance between both flanking hydroxy groups on the opposing ligands is 19.242(7) Å – twice as much as for the similar previously reported bis-"W-terpy"/macrocycle Ru(II) complex (~8.3 Å).[8b] The distance between the –OH groups of the same ligands is 23.084(9) Å, providing a significant void for the incorporation of the third ring.

Further, attempts were made to combine the threaded macrocycle **13** with the pretemplated caps **8c**, **9b**, or **10c** by intermolecular alkylation to form the double threaded ring-in-ring complexes **1**. This turned out to be challenging because of competing decomposition and polymerization pathways. After investigating various reaction parameters, it was identified that the best result for the synthesis of ring-in-ring complexes **1** was reached when the reaction was performed in high dilution using DMF as a solvent, K_2CO_3 as a base, and activated 4 Å molecular sieve powder as an additive (Scheme 3).

This reaction is extremely sensitive to temperature variations. The temperature must be increased gradually from 70 to 80 °C over the course of the reaction. Higher temperatures (80–83 °C) caused polymerization and decomposition of the starting materials giving only traces of the products **1**. Heating at lower temperature (70 °C) resulted in an extremely slow conversion of the starting materials and accumulation of partially alkylated/cyclized intermediates, but it helped to decrease the rate of decomposition.



Scheme 3 Conditions: (m) **12** (1 eq.), **7a** (3 eq.), *N*-ethylmorpholine (1.6 eq.), EtOH, N_2, reflux, 24 h, yield 31%; (n) **13** (1 eq.), **8c** (2.7 eq.), or **9b** (2.3 eq.), or **10c** (2.2 eq.), K_2CO_3 (25 to 28 eq.), 4 Å molecular sieve powder, DMF, Ar, 70 to 80 °C, 2 to 4 days.

Three reaction pathways could take place, depending on how the orthogonal caps approach the macrocyclic complex **13** (Fig. 5), and three different stereochemical outcomes are foreseen – D_{2h} symmetric *exo*,*exo*-, C_{2v} symmetric *endo*,*exo*-, or the desired D_{2h} symmetric *endo*,*endo*-structures.

When heteroleptic complexes **8c** or **9b** consisting of only "extended terpy" ligands were used (Scheme 3), complex mixtures of ring-in-ring stereoisomers **1b** or **1c** appear to be obtained, as suggested by the low symmetry observed in the ^{1}H and ^{13}C NMR spectra (see ESI,† pages S58 to S64). The significant overlap of the NMR signals prevented unambiguous determination of an exact ratio and geometry of these isomeric species. The expected composition of the complexes **1b** or **1c** was supported by HRMS-ESI.

When the mixed "V-shaped/extended terpy" cap **10c** was used for grafting onto the threaded macrocycle **13**, the ^{1}H and ^{13}C NMR spectra showed the formation of a product of high symmetry (D_{2h}). As expected, the ^{1}H NMR spectrum of the putative **1a** appears as a superimposition of the corresponding building blocks **10c** and **13** (Fig. 6). The phenolic –OH signals observed for **13** and the –OMs signals of **10c** disappear in the product's spectra. In addition, the $-CH_2$ signal corresponding to the *m*-protons is shifted upfield in the product in comparison to **10c**, supporting the formation of ether bonds (Fig. 6 and Scheme 3). HRESI-MS data support the expected composition, charge (8+) and isotope pattern of the desired complex **1a** (see ESI† and Fig. 7). The geometry of "V-shaped terpy" and relatively short 3-carbon linkers should prevent the *exo*-approach (Fig. 5) favoring the formation of an *endo*,*endo*-

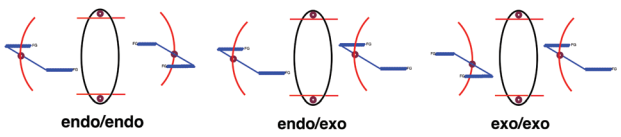


Fig. 5 Three theoretical trajectories of orthogonal caps towards the threaded macrocycle leading to *endo*- and *exo*-isomerism.

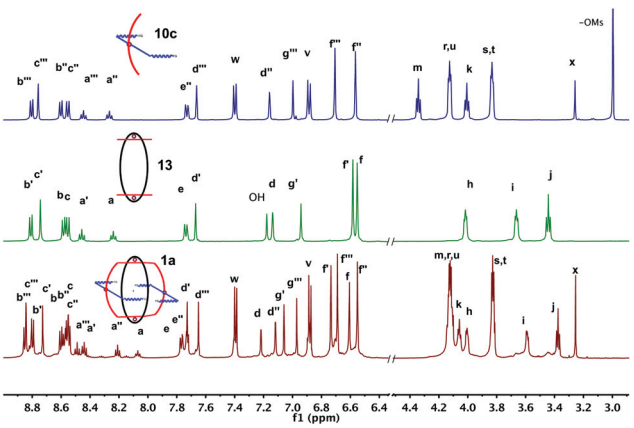


Fig. 6 Selected regions of the ^{1}H NMR spectra of the building blocks **10c**, **13**, and the threaded ring-in-ring complex **1a**.

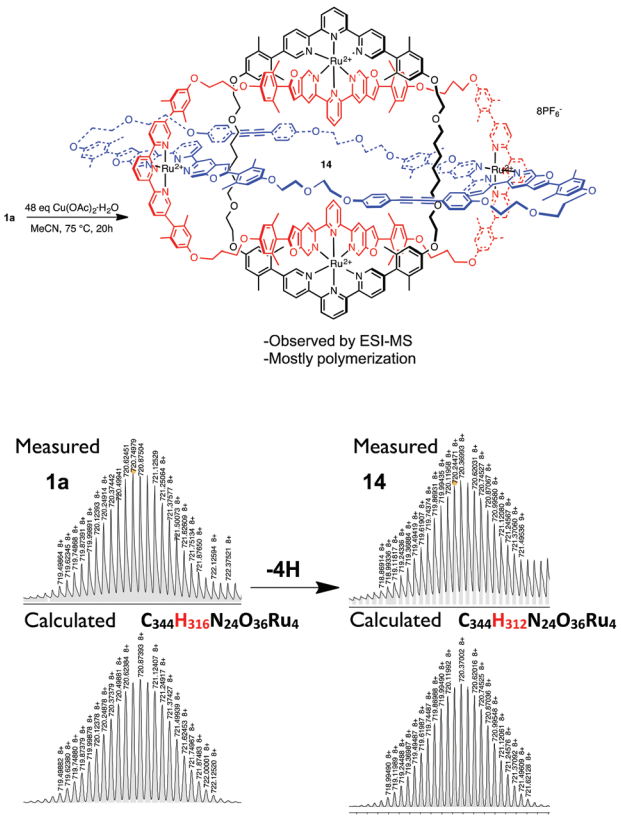


Fig. 7 Mass spectrometric support for the intramolecular macrocyclization of **1a**.

complex **1a**. Thus, the product obtained seems to have the required threading analogous to intermediate **G** (Fig. 1) on the way towards the Borromean link consisting of three unequal rings.

When complex **1a** was subjected to the copper-mediated Eglington reaction to facilitate macrocyclization by acetylene homocoupling,[18] mostly insoluble material formed, which presumably arises from the intermolecular polymerization reaction (Fig. 7). However, mass spectrometry (HRESI-MS) supports the formation of a molecular ion with the loss of four mass units and a composition consistent with the desired intramolecular macrocyclization product **14**, providing hope that the Borromean link Ru(II) complex forms, albeit in minute quantities.

These results provide a new departure point for future investigations towards the synthesis of the molecular Borromean link consisting of three unequal rings. We anticipate that the optimization of the structure **1**, with emphasis on the linker lengths, should provide the desired product in synthetically practical yields.

Conclusions

In conclusion, the *endo*,*endo*-double threaded ruthenium(II) ring-in-ring complex **1a** was successfully prepared in a stepwise synthesis by grafting preformed heteroleptic terpy cap **10c** with double-threaded macrocycle ruthenium(II) complex **13**. The shape of the directional terpy based ligands can be a defining control element for the *exo*-,*endo*-conformation of the metal-templated threaded macrocyclic architectures. The mass spectrometric evidence suggests that the herein described strategy towards the molecular Borromean link consisting of three unequal rings is conceptually feasible. In the future, optimization of the building blocks and linkers should provide the desired product in synthetically useful quantities.

Acknowledgements

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