

Dynamic nanoscale Borromean links†

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Employing halogen atom labels on one of the ligand precursors, the lability of at least some of the 30 dative and 12 imine bonds stabilizing and constituting the three rings of a metallo-Borromean linked compound are scrambled in acidic methanolic solution.

Early interest in the mechanical bond¹ and topological chemistry² has led to the advent of molecular catenanes, rotaxanes, and knots.³ In addition, the Borromean Rings (BRs), a unique class (Fig. 1) of nontrivial links⁴ have captivated the imaginations of mathematicians,⁵ physicists,⁶ biologists,⁷ and chemists,⁸ encouraging them to unveil examples that illustrate and emulate this form. In a wholly synthetic chemical context, the synthesis of molecular BRs at the nanoscale level has only just been achieved recently⁹ by an ‘all-at-once’ strategy, wherein the virtues of reversibility, proof-reading, and error-checking processes associated with supramolecular,¹⁰ metal–ligand inorganic,¹¹ and dynamic covalent¹² chemistry (DCC), are coupled to the geometrical precision that characterises¹³ coordination chemistry.

Because of its reliance on thermodynamic control, DCC has advantages when it comes to the synthesis of compounds where a large number of weak interactions are incorporated cooperatively within their molecular frameworks. Examples of the use of DCC in synthesis include the formation of labile coordinative bonds associated with certain metal–ligand interactions^{11,14} and olefin metathesis reactions,¹⁵ in addition to covalent bond forming reactions that rely on the production, for example, of imines,¹⁶ oximes,¹⁷ hydrazones,¹⁸ esters,¹⁹ borazaaromatic anhydrides,²⁰ acetals,²¹ and disulfides.²²

The synergism that exists between molecular recognition,²³ self-assembly,²⁴ and dynamic covalent¹² processes in the realm of imine bond formation and exchange, has been given strong practical expression in the preparation of mechanically interlocked compounds,¹⁶ as well as in the generation of dynamic

combinatorial libraries²⁵ (DCLs) under thermodynamic control. The marriage of these processes with the phenomenon of transition metal ion complexation^{13,14} has led²⁶ to the defining of U-turn scaffolds, based on the gathering of tridentate bis-Schiff base ligands around metal templates. These U-turn scaffolds have subsequently been incorporated successfully into a class of interlocked catenanes²⁷ and rotaxanes,^{16a-e} as well as in the near-quantitative production of a BR complex.^{9a}

Here, we describe the results of an investigation we have carried out to probe the structural integrity of BR complexes by assessing the reversible nature of the 30 dative and 12 imine bonds, in addition to the 12 π – π stacking interactions between π -donating and π -accepting aromatic rings that are essential in assembling cooperatively and holding together the three rings around the six octahedrally disposed zinc(II) ions in the nanoscale structure shown in Fig. 1b and represented graphically in Fig. 1c. Structural integrity is significant when contemplating whether, after their isolation, BR complexes can participate in dynamic equilibrium processes‡ or whether these structures inhabit a deep thermodynamic well on the energy landscape, and for all intents and purposes are kinetically trapped?

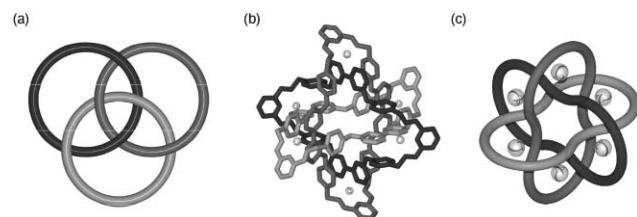
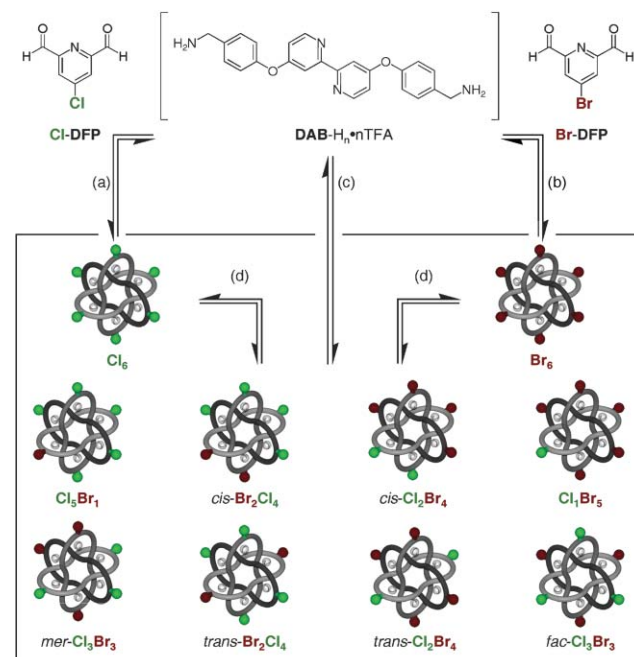


Fig. 1 Borromean Rings depicted as (a) a Venn diagram, (b) the X-ray crystal structure of the parent BRs and (c) a graphical representation.



Scheme 1 Products formed when mixtures (each 38 mM) of Cl-DFFP : DAB-H_n·nTFA : Br-DFFP : Zn(OAc)₂ are reacted under the following conditions. (a) 1.0 : 1.0 : 0.0 : 1.0, *i*-PrOH, 60 °C, 12 h. (b) 0.0 : 1.0 : 1.0 : 1.0, *i*-PrOH, 60 °C, 12 h. (c) 0.5 : 1.0 : 0.5 : 1.0, *i*-PrOH, 60 °C, 12 h. (d) 1 : 1 mixture (2 mM) of homo-Cl₆ : homo-Br₆, cat. TFA, MeOH, 60 °C, 5 d.

† Electronic supplementary information (ESI) available: experimental details relating to the preparation of the homo-Cl₆·12TFA, homo-Br₆·12TFA, and hetero-Cl₆–Br₆·12TFA BR complexes. See <http://www.rsc.org/suppdata/cc/b5/b503717d/index.sht>
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In order to answer this question, we have synthesised separately (routes a and b, respectively, Scheme 1), using 4-chloro- and 4-bromo-2,6-diformylpyridine (**DFP**) as the starting aldehydes, the pure hexachloro- and hexabromo- derivatives of the homo-BR complexes, **homo-Cl₆** and **homo-Br₆**, respectively, in reactions with the TFA salt of the diaminobipyridine (**DAB**) ligand with Zn(OAc)₂ in *i*-PrOH at 60 °C for 12 h. Similarly, the statistical mixture of the 10 BR complexes displayed in Scheme 1 was prepared in high yield (route c) by reaction of 1.0 molar equivalents of **DAB-H_n-nTFA** and Zn(OAc)₂ with 0.5 molar equivalents of **Cl-DFP** and **Br-DFP**. Any thermodynamic differences in the reactivities of the **Cl-DFP** and **Br-DFP** can be assumed to be minor and therefore should not influence significantly the outcome of the equilibration process. From a structural viewpoint, the positions of the six peripheral halogen atoms on the 4-positions of the pyridine rings in the eight **hetero-Cl_{6-x}Br_x** BR complexes can be correlated with the configurational isomers of an octahedral complex. An ¹H NMR spectroscopic investigation (Fig. 2) of the isolated statistical mixture did not reveal the presence of the 10 products but instead showed what appeared to be an equimolar mixture of **homo-Cl₆** and **homo-Br₆**. This observation is not at all surprising since the six coordination centres are well separated (at least 1.3 nm) from each other. Hence, we turned our attention towards characterising the statistical mixture using electrospray ionisation (ESI) mass spectrometry since the atomic weights and isotopic distributions of chlorine and bromine atoms are significantly different: the only limitation of the technique is the inability to determine the difference between the two pairs of disubstituted *cis*- and *trans*-, and the two trisubstituted *mer*- and *fac*-isomeric BR products.

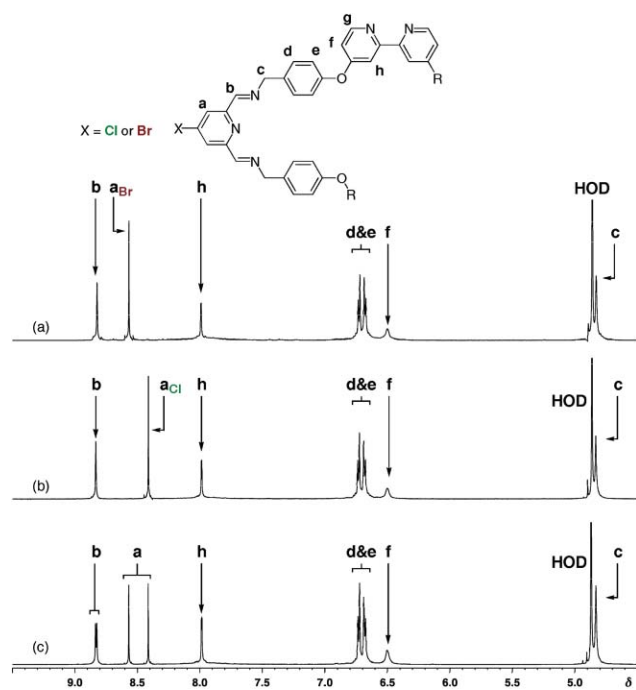


Fig. 2 Partial ¹H NMR (600 MHz, CD₃OD, 25 °C) spectra of the (a) **homo-Br₆**·12TFA, (b) **homo-Cl₆**·12TFA, and (c) **hetero-Cl_{6-x}Br_x**·12TFA BR derivatives. The letters a to h are defined with respect to appropriate protons on the inset structural formula.

It was found that complete scrambling of the halogen atoms, starting with an equimolar mixture of **homo-Cl₆** and **homo-Br₆** occurs within 5 days§ in methanolic solution at 60 °C, provided a few drops of CF₃CO₂H are added¶ to the reaction mixture. The relative intensities of the packets of peaks for the seven distinguishable tetracationic species [**homo-Cl₆**·8TFA]⁴⁺, [**hetero-Cl₅Br**·8TFA]⁴⁺, [**hetero-Cl₄Br₂**·8TFA]⁴⁺, [**hetero-Cl₃Br₃**·8TFA]⁴⁺, [**hetero-Cl₂Br₄**·8TFA]⁴⁺, [**hetero-ClBr₅**·8TFA]⁴⁺ and [**homo-Br₆**·8TFA]⁴⁺ are centered on *m/z* 1122, 1133, 1144, 1155, 1167, 1178, and 1189, respectively, in the case of both (Fig. 3b and 3c) the control and scrambling experiments. It is possible to calculate, using the factorial combination (ⁿC_r) of placing either one, two, or three chloro- or bromo-substituents (*r* = 1, 2, or 3) into any of the six (*n* = 6) possible positions of an extended octahedral array, the expected distribution of the tetracationic [**homo/hetero-Cl_{6-x}Br_x**·8TFA]⁴⁺ products in the mass spectrum: see Fig. 3a. The agreement with experiment is excellent.

Although, until more experiments have been performed, the precise mechanism of exchange is open to debate, the enabling role of trifluoroacetic acid is not. Presumably, the coordinative bond between the imine nitrogen atom and the zinc ion is weakened in this acidic medium. Furthermore, protonation of the imine activates it toward nucleophilic attack, by, in this case, methanol, resulting in a single-site cleavage of one of the rings of the BRs. The fate of this species is perhaps most often one in which the ring

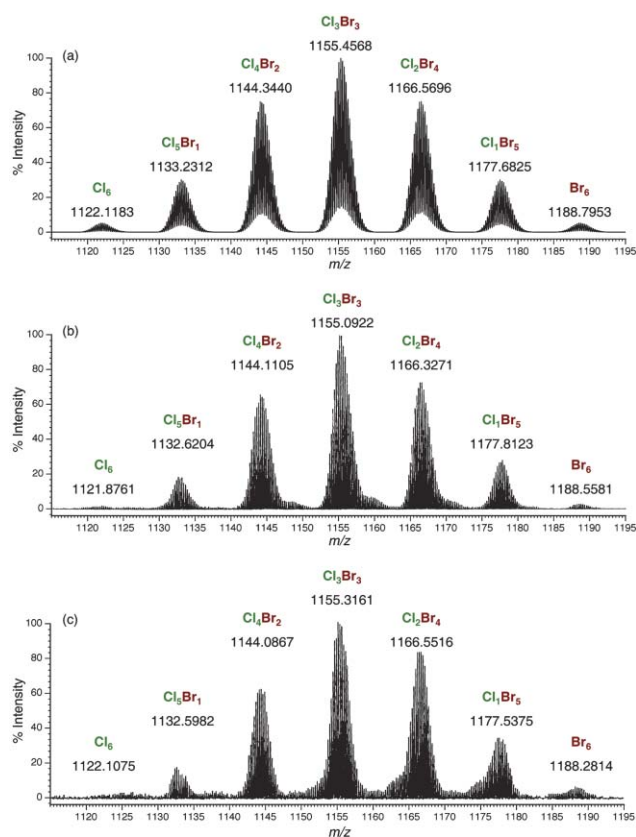


Fig. 3 A comparison of (a) the calculated distributions for all the possible tetracationic products with (b) the control experiment starting with **Cl-DFP** : **DAB-H_n-nTFA** : **Br-DFP** : Zn(OAc)₂ (0.5 : 1.0 : 0.5 : 1.0), and (c) after scrambling the **homo-Cl₆** with the **homo-Br₆** in reagent grade MeOH at 60 °C in the presence of CF₃CO₂H for 5 days.

simply snaps back shut again. On occasion, however, subsequent cleavage of the adjacent imine bond releases into solution the halopyridine fragment which can then be incorporated into any other partially opened BR complex, resulting in the observed halogen scrambling. In such a cooperatively organised system, it is unlikely that each BR structure entirely disassembles and then statistically reassembles since the energy barriers would be too great, and moreover, no BR fragments are observed in the ESI-MS analysis.

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† To our knowledge, the largest number of imine bonds in a molecule and its complex, where exchange reactions have been performed, are in dynamic hemicarcerands and hemicarceplexes. See S. Ro, S. J. Rowan, A. R. Pease, D. J. Cram and J. F. Stoddart, *Org. Lett.*, 2000, **2**, 2411–2414.

§ In a separate experiment, a methanolic solution containing an equimolar mixture of **homo-Cl₆** and **homo-Br₆** was stirred at room temperature in the absence of CF₃CO₂H. After a period of 2 weeks under these conditions, ESI-MS analysis of the sample produced spectra with only peaks that corresponded to the **homo-Cl₆** BR derivative at *m/z* 1122 and the **homo-Br₆** BR derivative at *m/z* 1188 in the tetracationic region. This observation suggests that the BR compounds are kinetically nonlabile and thermodynamically stable under neutral conditions at room temperature. To this sample, five drops of CF₃CO₂H were added and stirring was continued. After two weeks of stirring, the reaction was studied by ESI-MS. The mass spectrum revealed no significant changes in the intensities and distributions for the parent peaks for the **homo-Cl₆** BR and the **homo-Br₆** BR derivatives. However, sampling the solution after stirring for an additional 5 weeks indicated that the two **homo-BR** derivatives were completely scrambled. This observation suggests that the BR compounds are kinetically labile and thermodynamically activated under acidic conditions at room temperature.

¶ In a separate experiment, a methanolic solution containing an equimolar mixture of **homo-Cl₆** and **homo-Br₆** was heated under reflux in the absence of CF₃CO₂H. After 4 days under these conditions, ESI-MS analysis of this sample gave a spectrum containing only two peaks, corresponding to the **homo-Cl₆** BR compound at *m/z* 1122 and the **homo-Br₆** BR compound at *m/z* 1188. This observation suggests that, under these conditions over several days, these BR compounds are kinetically inert and thermodynamically stable.

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