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COMMUNICATION

# Hypervalent Iodine Based Reversible Covalent Bond in Rotaxane Synthesis

Markéta Kandrnálová, Zoran Kokan, Václav Havel, Marek Nečas, and Vladimír Šindelář*

**Abstract:** Reversible covalent bonds play a significant role in achieving the high-yielding synthesis of mechanically interlocked molecules. Still, only a handful of such bonds have been successfully employed in synthetic procedures. Herein, we introduce a novel approach for the fast and simple preparation of interlocked molecules, combining the dynamic bond character of bis(acyloxy)iodate(I) anions with macrocyclic bambusuril anion receptors. The proof of principle was demonstrated on rotaxane synthesis, with near-quantitative yields observed in both the classical and "in situ" approach. The rotaxane formation was confirmed in the solid state and solution by the X-ray and NMR studies, respectively. Our novel approach could be utilized in the fields of dynamic combinatorial chemistry, supramolecular polymers, or molecular machines, as well inspire further research on molecules that exhibit dynamic behavior, but due to their high reactivity, have not been considered as constituents of more elaborate supramolecular structures.

Successful design of chemical systems with targeted functions/properties relies heavily on novel approaches for governing the molecular assembly. Alongside non-covalent interactions, reversible covalent bonds[1,2] have been frequently utilized in the design and synthesis of numerous functional molecules, with applications in materials chemistry,[3] catalysis,[4] recognition,[5] sensing,[6] cargo delivery,[7] as well as flourished in the field of dynamic combinatorial chemistry.[8] Moreover, due to their dynamic nature, reversible covalent bonds facilitate the high-yielding synthesis of mechanically interlocked molecules[9–12] such as catenanes, rotaxanes, and knots, representing important components of molecular machines.[12] Despite the obvious synthetic advantages, a limited number of reversible covalent bonds have been utilized in this manner. This is especially true for the rotaxane synthesis, as only a few approaches have been used up to now. These include the ring closing metathesis,[13,14] formation of imine[15–17] and disulfide[18,19] bonds, and reversible metal-organic bonds,[20–24] which highlight the need for novel approaches to rotaxane synthesis.

Bis(acyloxy)iodate(I) anions are a class of hypervalent iodine compounds that are gaining increasing attention in synthetic organic chemistry as iodination reagents.[25] Their synthetic utility is a consequence of the labile I–O bonds, the breaking of which results in the formation of reactive hypoiodite species. Possibly for this reason, the dynamic nature of bis(acyloxy)iodate(I) O–I bond has not been recognized as a reversible covalent bond in a constitutive sense. We, however, have hypothesized that the complexation with a macrocyclic anion receptor could contribute to the stability of the bond and its use as a constitutive element of more elaborate structures such as rotaxanes. In this respect, we have considered using neutral bambusuril receptors[26–28] – the barrel-like, $D_3$-symmetric macrocyclic molecules (Figure 1), that form strong supramolecular complexes with many anions, in both aqueous and organic media. Bis(acyloxy)iodates(I), possess favorable geometry of the O–I–O moiety in terms of linearity and bond length, which makes them perfect candidates as threads for the bambusuril macrocycle. In further support of this, iodide anions are known to bind in the center of the bambusuril cavity and form especially strong 1:1 complexes ($K \approx 10^{10}$ M$^{-1}$),[29] as the carboxylates can form 2:1 complexes,[30] with two anions bound at the opposite sides of a bambusuril. It is worth noting that bambusuril anion receptors are unprecedented as interlocked molecules. Furthermore, in comparison to the number of rotaxanes prepared by metal cation and pi-pi (donor-acceptor interactions) templation, not many have been prepared with the help of an anion template.[31,32] These examples include enolate-capture strategy for the preparation of rotaxanes with a neutral axle and a neutral wheel by Vögtle,[33,34] rotaxanes of anionic axle and neutral wheel by Schalley,[35,36] and Flood,[37,38] and neutral or positively charged interlocked molecules by Beer,[39–42] which assembled due to the presence of small inorganic anions.

Herein, we present a novel approach for the high-yielding synthesis of rotaxanes, based on the reversible covalent bond of bis(acyloxy)iodates(I) and the bambusuril macrocycle (Figure 1).

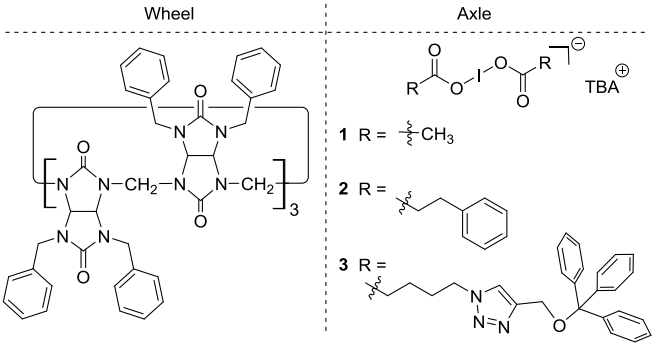


**Figure 1.** Constitutive parts of the compounds, **BU**·**1**–**3**, described in this work.

The compounds (**BU**·**1**–**3**) were prepared in a straightforward manner, just after minutes of mixing the equimolar amounts of dodecabenzylbambus[6]uril macrocycle (**BU**) and bis(acyloxy)-iodate(I) axles (**1**–**3**) as tetrabutylammonium (TBA) salts in chloroform, followed by the solvent evaporation (see SI). Alternatively, the rotaxanes were synthesized "in situ" from the iodate(III) precursor and a TBA salt of iodide complex with **BU**

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(see SI). Both approaches showed the near-quantitative yields of the rotaxanes with no apparent decomposition even after several months of storage in a closed vial.

X-ray single crystal structures of **BU·1** and **BU·2** confirmed the formation of inclusion complexes (Figure 2). Axles **1** and **2** are threaded through the **BU**, with iodine atoms occupying the center of the macrocycle with an average distance from the methine hydrogen atoms of 3.48 and 3.44 Å, respectively. The complexes are further stabilized by the C–H···O interactions between the methine hydrogen atoms of the macrocycle and oxygen atoms of the guests. The O–I bonds are 2.20 Å long, as found for other bis(acyloxy)iodates(I).[25] The two oxygen atoms bound at the iodine are 4.40 Å apart, accounting for only a 0.23 Å shorter distance from the center of the **BU** cavity in comparison to the 2:1 **BU** complexes with carboxylates.[30] These observations highlight the high compatibility of the bambusurils and bis(acyloxy)iodates(I) for the rotaxane formation.

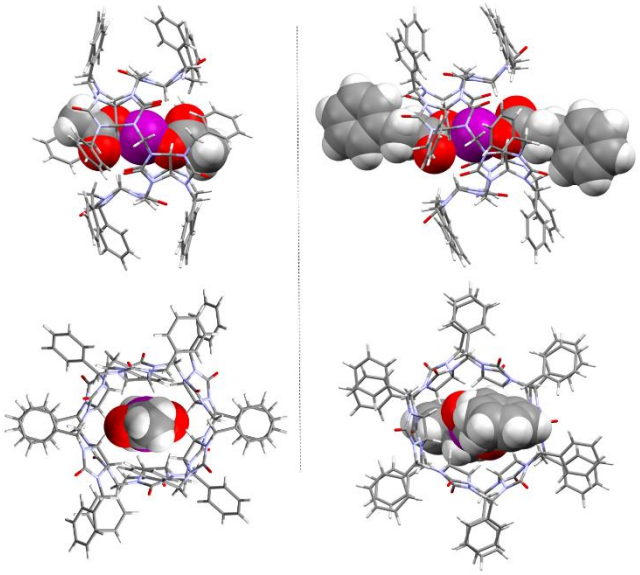

**Figure 2.** Side and top views of single crystal X-ray structures of the rotaxanes **BU·1** (left) and **BU·2** (right). Solvent molecules and counter ions are omitted for clarity. Only one out of two symmetrically independent molecules is shown for the **BU·2**.

$^1$H NMR spectroscopy performed in chloroform-D revealed that the rotaxane formation induces similar chemical shift changes in the spectra for all the axles **1**–**3** (Figure 3, S33-S35). For instance, addition of **2** into the **BU** solution resulted in a downfield shift of **BU** methine signals H(*B*), from 5.16 to 5.68 ppm, indicating anion encapsulation inside the macrocycle. The signals H(*1*) and H(*2*) of the axle **2** were shifted upfield, compared to its original position, indicating the guest inclusion inside electropositive cavity of **BU**. At non-equimolar host-guest ratio, the signals of bound and free forms of both components were present in the spectra. This indicates the formation of highly stable inclusion complexes with a 1:1 stoichiometry, as well that the exchange between the bound and the free forms is slow on the NMR time scale.

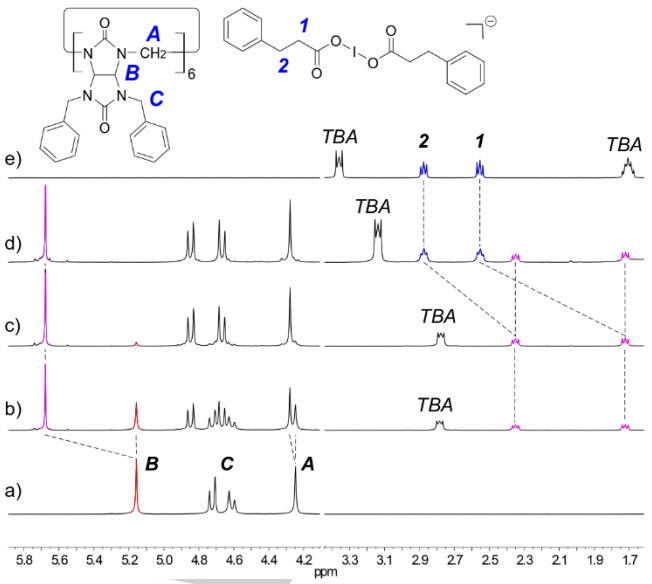


**Figure 3.** $^1$H NMR spectra (500 MHz, $CDCl_3$, 30 °C) of **BU** in the absence (a) and in the presence of 0.60 (b), 0.95 (c), and 2.50 equivalents (d) of **2**, and pure axle **2** (e).

The association constants of **BU·1**–**3** in chloroform-D were determined by the NMR competition experiments (Figures S38–41), using anions with known binding affinity[29] towards the **BU** (i.e. hexafluorophosphate or methanesulfonate). The constants were calculated using the integrated values of the **BU** methine proton signals, attributed to the rotaxanes and those of the competing anion complex. As expected, the obtained values indicated very high stability of **BU·1**–**3**, and were determined $1.4\times10^7$, $2.5\times10^6$, and $2.9\times10^6$ $M^{-1}$ respectively (Table S1).

The dynamic nature of the complexes **BU·1**–**3** was investigated by the $^1$H NMR in chloroform-D. For example, when the **BU**, **1**, and **2** were mixed together, three distinct sets of signals were observed. Namely, those of the **BU·1**, **BU·2**, and the "mixed-axle" complex in which the axle comprises both the acetate and 3-phenylpropanoate moieties (Figure S42), strongly supported by the NMR measurements. Moreover, upon adding acetic or 3-phenylpropanoic acid to the **BU·2** or **BU·1**, respectively, the same sets of signals are evident (Figures S43,44). The ROESY measurements indicated chemical exchange between the "mixed-axle" complex and **BU·1**, but not with **BU·2** (Figure S51, suggesting that the axles containing acetate more readily dissociate from the **BU**. Furthermore, using a large excess of the acids, equilibria could be pushed to a greater extent towards the **BU** complex with respect to the added acid, which could then be reversed by adding an even greater excess of another acid, reverting the equilibrium towards the starting rotaxane (Figures S43,44). In addition, the rotaxanes can also exchange their components by using the corresponding TBA carboxylates (Figures S46–48). However, investigating such systems is complicated as the equilibria also involves carboxylate binding to the **BU**, where 1:1 and 1:2 carboxylate complexes are formed,[30] exhibiting both the slow and fast exchange on the NMR timescale (Figures S36,37). Nevertheless, the dynamic nature of the

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compounds **BU·1–3** was undoubtedly shown as they easily exchanged components using three distinct approaches – either by simple mixing of the axles, different carboxylic acids or their corresponding TBA salts, important for applications in dynamic combinatorial chemistry.

The reactivity of the rotaxanes was probed in the oxidation reaction of 3,4-dihydro-2*H*-pyran (Figure 4), a model substrate for the iodane(I) reagents.[43] Without the **BU**, axles **1–3** fully transformed the model substrate within several minutes, as evidenced by $^1$H NMR (Figures S52–54). In sharp contrast, **BU·1–3** exhibited remarkably lower reactivity where, even after 3 days, only approximately half of the starting material was consumed in all the reactions (Figures S55–57). The reaction kinetics seems not to depend on the axles' bulkiness. The obtained results further support the high stabilization of the reactive bis(acyloxy)iodates(I) by the complexation with **BU**. Furthermore, we tested whether competitive anion binding to the **BU** could be used as chemical stimuli to modulate the reactivity of the system (Figure 4c). Indeed, the reactions performed in the presence of hexafluorophosphate exhibited increased kinetics to a varying extent, following the order **BU·1**>**BU·2**>**BU·3** (Figures S58-60). In the case of **BU·1**, the reaction was done within 15 minutes as for the **BU·2** and **BU·3** it took several hours. These results seem to follow the bulkiness of the axles, in contrast to the experiments performed only with **1–3**, suggesting that the hexafluorophosphate may be explicitly involved in the axle dissociation from the **BU**.

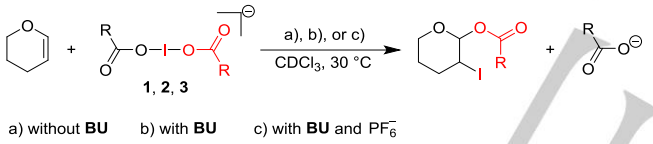


**Figure 4.** Oxidation reaction of 3,4-dihydro-2*H*-pyran with axles **1–3** under different conditions.

Although the mechanistic investigations of dynamic supramolecular systems are far from trivial, we have proposed a tentative mechanism for the rotaxane (dis)assembly, based on the aforementioned experimental and literature data, which includes the breaking and forming of the labile O–I bond inside the **BU** (Figure 5). The bis(acyloxy)iodates(I) are known to be in a fast equilibrium with their neutral hypoiodite and charged carboxylate counterparts,[44] as the **BU** are exceptionally strong anion receptors.[28] Therefore, the first step prior to complexation very likely involves the breaking of the labile O–I bond, followed by the carboxylate binding to **BU** (rather than the neutral hypoiodite counterpart), and subsequent reforming of the O–I bond within the **BU**. It should be noted that the small axle **1**, could potentially slip through the **BU** without the O–I bond breaking, thus falling into the category of pseudo-rotaxanes. However, the rotaxane formation with rods **2** and **3** unambiguously supports the proposed mechanism, as their substituents are too bulky to slip through the small **BU** cavity. It is worth noting that the system presented herein is one of the few examples of reagent-less rotaxane preparations.[20,45–48]

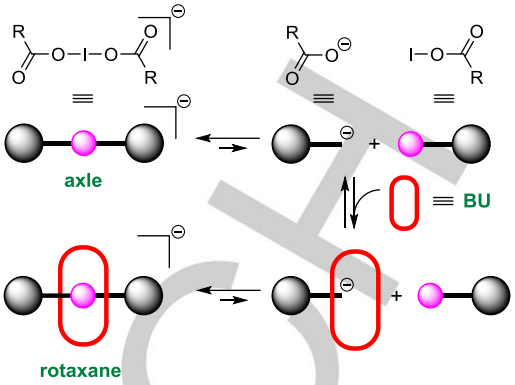


**Figure 5.** The proposed mechanisms of rotaxane formation.

In conclusion, we have presented a novel approach in the synthesis of mechanically interlocked molecules by means of stabilizing a reactive reversible covalent bond via the host-guest interactions. We have used highly reactive anionic hypervalent iodine(I) compounds, possessing a reversible covalent bond, and bambusuril macrocyclic anion receptor, in the synthesis of rotaxanes. The compounds were prepared in a fast, easy, and near-quantitative way, by simple mixing of the bis(acyloxy)iodate(I) axles **1–3** and the bambusuril macrocycle **BU**, in chloroform. Component exchange experiments further supported the dynamic behavior of the system, where the axles within the **BU** readily exchanged their carboxylate counterparts. On the basis of these results and the available literature, the mechanism for the (dis)assembly of the rotaxanes was suggested, incorporating the breaking and forming of the labile O–I bond within the **BU**. The findings presented in this work may be utilized in the high-yielding preparation of interlocked molecules, relevant to the fields of dynamic combinatorial chemistry, supramolecular polymers, and molecular machines. It is worth disclosing that the compounds described herein may as well present a boundary case for using the rotaxane terminology, as the high stability of the assemblies may be a result of strong noncovalent interactions rather than mechanical bonds. Yet, they can only dissociate as the weakest of the covalent bonds is broken (e.g. a dynamic covalent bond). We hope that this approach will also serve as a motivation for others to investigate reactive dynamic systems and the means of stabilization thereof, for the utilization in a constitutive sense in more elaborate supramolecular assemblies.

## Acknowledgements

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**Keywords:** dynamic covalent bond • bambusurils • rotaxanes • anion receptors • macrocycles

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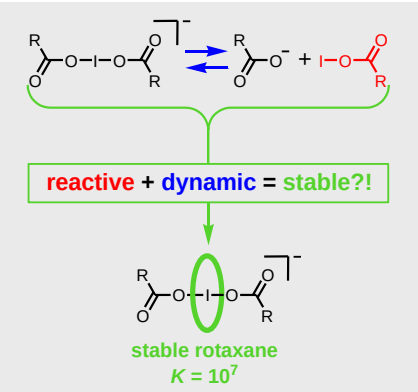
## Entry for the Table of Contents

COMMUNICATION

Reactive hypervalent iodine species possessing dynamic covalent bonds were utilized in a constitutive sense for the near quantitative rotaxane synthesis via the stabilization by the bambusuril anion receptor.

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