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Self-Sorting under Solvent-Free Conditions: One-Pot Synthesis of a Hetero[3]rotaxane

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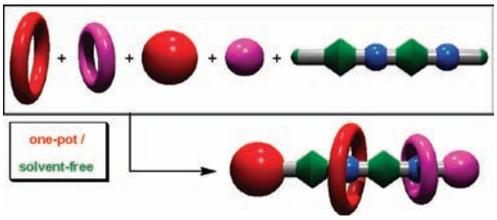
ABSTRACT



The one-pot synthesis of a hetero[3]rotaxane, assembled from five different molecular components under solvent-free conditions, through "self-sorting" of the bead and stopper units during the threading and stoppering processes, is reported.

The growing realization that mechanically interlocked molecules, such as rotaxanes, can be used to develop mesoscale devices and artificial molecular machinery on the nanoscale has drawn much attention to their syntheses.[1] In Nature, important biomolecules (e.g., pairs of DNA strands forming double helices) assemble through selective recognition (e.g., of A–T and C–G base pairs); the same "self-sorting" concept also allows the efficient, selective self-assembly of non-natural systems (e.g., in rotaxane-like systems, the threading of two different macrocyclic components onto a single thread-like unit in solution).[2] The classical "threading-followed-by-stoppering" approach for rotaxane synthesis generally involves noncovalent threading of bead(s) onto a rod and then sealing the assembly through covalent attachment of stopper units.[3] We wished to test whether we could realize the self-sorting concept in both steps—threading and stoppering—to form a hetero[3]rotaxane from five different molecular components (one thread, two beads, two stoppers) through selective assembly in a simple stepwise one-pot reaction (Figure 1). Because the use of less-hazardous substances and the generation of lower amounts of waste are important issues in organic synthesis,[4] we sought to take the challenge to the next level by assembling such a hetero[3]rotaxane under solvent-free conditions; that is, we wanted the self-sorting processes in both the threading and stoppering steps to occur in the absence of solvent molecules. Herein, we report the one-pot synthesis of a hetero[3]rotaxane, assembled from five different molecular components under solvent-free conditions, through "self-sorting" of the bead and stopper units during the threading and stoppering processes.

Although concentrating a solution containing a mixture of a single thread and two macrocycles can result in

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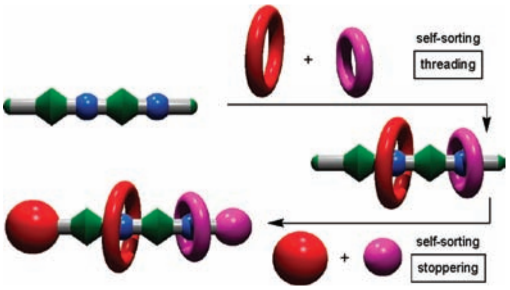
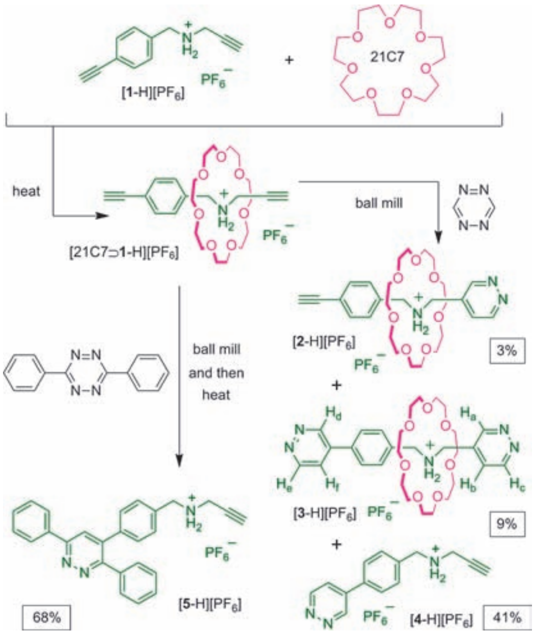


Figure 1. Using two sequential self-sorting steps to construct a hetero[3]rotaxane.

isolation of the corresponding hetero[3]pseudorotaxane in solid form,[5] this approach does not fit into the strict definition of solvent-free "self-sorting." Instead, we turned our attention to the melting approach, reported more than a decade ago, for the synthesis of slippage [2]rotaxanes,[6] expecting that self-sorting in the threading process would proceed smoothly upon melting a mixture of a single thread and two different macrocycles. To avoid possible decomposition of these components at their high melting temperatures, we chose to employ one of the recognition components that is naturally a liquid at room temperature to improve the degree of contact between the components and thereby ensure that the threading process would proceed at relatively lower temperatures. With regard to a solvent-free self-sorting stoppering process, we required two different stoppers to be placed selectively at their appropriate termini, adjacent to the two well-organized macrocycles, in the absence of solvent molecules. Although using two orthogonal stoppering reactions would likely solve this problem, we sought the challenge of using the same types of chemical functionalities but controlling their relative reactivities under solvent-free conditions. We have previously demonstrated that the Diels–Alder reactions between propargyl and tetrazine units occur smoothly when grinding the corresponding solid mixtures; the same reactions between para-substituted phenylacetylene and diphenyltetrazine units, however, require heating and do not proceed under the same grinding conditions.[7] Therefore, we selected these components to realize self-sorting stoppering in the solid state.

To begin our quest toward the one-pot synthesis of a hetero[3]rotaxane under solvent-free conditions, we performed some model reactions on simple two-component systems. We selected the solid thread-like salt **1**-H$\cdot$PF$_6$ and the liquid macrocycle 21C7 as a model to investigate the possibility of forming a [2]pseudorotaxane when heating their mixture in the absence of solvent and then tested the selectivities of the two terminal alkyne units toward tetrazine derivatives under solid-to-solid grinding conditions (Scheme 1). We heated a neat mixture of the solid **1**-H$\cdot$PF$_6$ and the liquid 21C7 at 323 K while mixing with a spatula until the sample solidified completely. We presumed that this solid contained predominantly the corresponding [2]pseudorotaxane [21C7$\supset$**1**-H][PF$_6$], which we used directly in the ball-milling process. Grinding an equimolar mixture of this solid [2]pseudorotaxane and solid tetrazine for 6 h gave a mixture of the [2]rotaxanes **2**-H$\cdot$PF$_6$ and **3**-H$\cdot$PF$_6$ and the ammonium salt **4**-H$\cdot$PF$_6$ (Figure 2), suggesting that both the passage of 21C7 onto the thread-like salt **1**-H$\cdot$PF$_6$ and the Diels–Alder reactions at its termini proceeded efficiently through this sequential treatment process, albeit with poor reaction selectivity of tetrazine toward the two terminal alkyne units. A similar ball-milling reaction of a mixture of solid tetrazine and the solid [2]pseudorotaxane obtained after concentrating an equimolar mixture of 21C7 and **1**-H$\cdot$PF$_6$ in CH$_3$NO$_2$ gave almost identical results to those from our heating/mixing/grinding approach. Therefore, we suspected that [2]pseudorotaxane formation from **1**-H$\cdot$PF$_6$ and 21C7 occurred during the heating-and-mixing process performed in the absence of solvent, encouraging us to investigate the self-sorting of two different macrocycles onto a single thread-like salt using such a solvent-free heating-and-mixing method.

Scheme 1



Next, we evaluated the reactivities of tetrazine and alkyne units so that we could position appropriate stoppers during the grinding process. To ensure a difference in reactivity of the two terminal alkyne units of the thread-like salt **1**-H$\cdot$PF$_6$, we performed the grinding reaction using an equimolar mixture of solid diphenyltetrazine and the solid [2]pseudorotaxane [21C7$\supset$**1**-H][PF$_6$] obtained after heating and mixing. As expected, the reaction did not proceed, even after 6 h of ball-milling; in contrast, heating this ground solid mixture at 373 K

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(5) A similar method has been used to generate pseudorotaxanes as solids for the efficient syntheses of [2]- and [4]rotaxanes; see: Hsueh, S.-Y.; Cheng, K.-W.; Lai, C.-C.; Chiu, S.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4436.

(6) Händel, M.; Plevoets, M.; Gestermann, S.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1199.

(7) (a) Hsu, C.-C.; Chen, N.-C.; Lai, C.-C.; Liu, Y.-H.; Peng, S.-M.; Chiu, S.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7475. (b) Hsu, C.-C.; Lai, C.-C.; Chiu, S.-H. *Tetrahedron* **2009**, *65*, 2824.

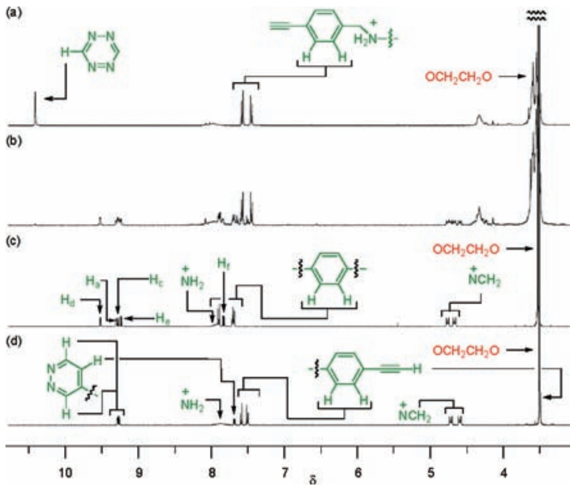
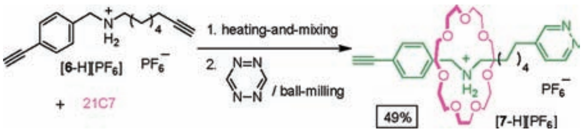


Figure 2. Partial ^{1}H NMR spectra (400 MHz, CD$_3$CN, 298 K) of (a) an equimolar (40 mM) mixture of 21C7, **1**-H$\cdot$PF$_6$, and tetrazine; (b) the crude product after solid state ball-milling for 6 h of an equimolar mixture of tetrazine and the [2]pseudorotaxane [(21C7$\supset$**1**-H)$\cdot$PF$_6$] formed by heating and mixing; (c) purified **3**-H$\cdot$PF$_6$; and (d) purified **2**-H$\cdot$PF$_6$.

for 72 h gave the ammonium salt **5**-H$\cdot$PF$_6$ as the predominant product. This result suggested that the phenylacetylene terminus of the [2]pseudorotaxane was more reactive toward diphenyltetrazine than was the propargyl terminus during this solid-to-solid heating process. Initially, we suspected that the difference in selectivity of tetrazine and diphenyltetrazine toward the two different terminal alkynes was due to their reactivity—with the more-reactive tetrazine providing poorer selectivity. Grinding an equimolar solid mixture of the thread-like salt **1**-H$\cdot$PF$_6$ and tetrazine, however, gave predominantly the salt **4**-H$\cdot$PF$_6$, suggesting that tetrazine does react selectively with the phenylacetylene terminus when the NH$_2^+$ unit is not encircled by a 21C7 unit.

The reaction of an electron-deficient tetrazine with an alkyne most likely occurs between the lowest unoccupied molecular orbital (LUMO) of the diene and the highest occupied molecular orbital (HOMO) of the dienophile.[8] Therefore, we suspect that the improved selectivity of tetrazine toward the phenylacetylene unit in **1**-H$\cdot$PF$_6$ in the absence of complexation to 21C7 arose from the greater electron-withdrawing effect of the NH$_2^+$ unit, thereby decreasing the HOMO energy level of the propargyl unit (decreasing its reactivity toward tetrazine and resulting in greater selectivity). This result suggested that if we could decrease the inductive effect of the NH$_2^+$ unit even more, we might have a chance to reverse the reactivity of the two alkyne units by having tetrazine react selectively with the propargyl group under the grinding conditions. The product of the reaction of tetrazine with a propargyl unit—a pyridazine—is an efficient stopper for a 21C7 unit in a rotaxane; therefore, we designed our one-pot, solvent-free synthesis of a hetero[3]rotaxane such that the smaller tetrazine would react with the propargyl terminus, leaving the phenylacetylene end to react with diphenyltetrazine. The resulting pyridazine and diphenylpyridazine stoppers would both be of sufficient size to interlock their adjacent crown ether units.

Scheme 2



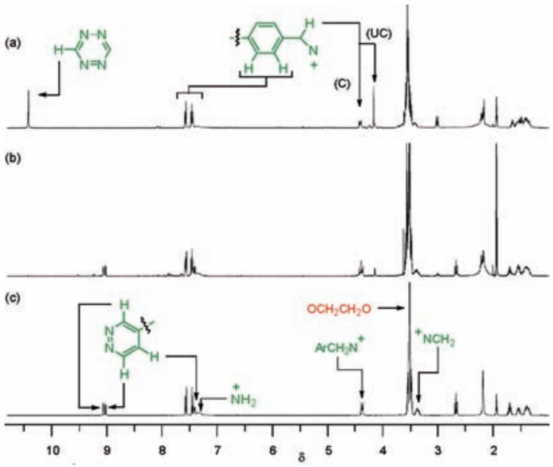


Figure 3. ^{1}H NMR spectra (400 MHz, CD$_3$CN, 298 K) of (a) an equimolar (40 mM) mixture of 21C7, **6**-H$\cdot$PF$_6$, and tetrazine; (b) the crude product after solid state ball-milling for 9 h of an equimolar mixture of tetrazine and the [2]pseudorotaxane [(21C7$\supset$**6**-H)][PF$_6$] formed by heating and mixing; and (c) purified **7**-H$\cdot$PF$_6$. The descriptors "c" and "uc" refer to complexed and uncomplexed states, respectively, of the components.

One approach toward minimizing the inductive effect of the NH$_2^+$ center on the propargyl unit would be to distance the acetylene group farther from the positive charge. Therefore, we synthesized the thread-like salt **6**-H$\cdot$PF$_6$ (see the Supporting Information), which features an oct-7-ynyl group in place of the propargyl group in **1**-H$\cdot$PF$_6$ (Scheme 2). Gratifyingly, grinding an equimolar mixture of tetrazine and the solid [2]pseudorotaxane [21C7$\supset$**6**-H][PF$_6$] (obtained after heating and mixing a 1:1 mixture of the thread-like salt **6**-H$\cdot$PF$_6$ and 21C7) led to reaction of the oct-7-ynyl unit in preference to the phenylacetylene unit with a selectivity as high as 9:1, based on integration of pertinent signals in ^{1}H NMR spectra (Figure 3).[9]

Encouraged by this result, we synthesized the bis(ammonium) thread-like salt **8**-H$_2$$\cdot$2PF$_6$, expecting its

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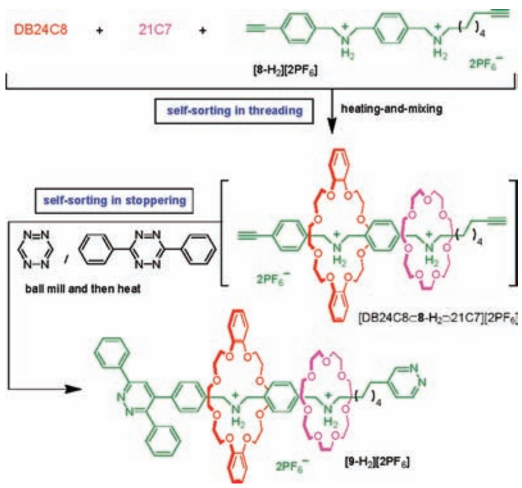
[8] (a) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. (b) Hamasaki, A.; Ducray, R.; Boger, D. L. *J. Org. Chem.* **2006**, *71*, 185. (c) Blackman, M. L.; Royzen, M.; Fox, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 13518.

[9] We recovered 21% of the thread-like salt **6**-H$\cdot$PF$_6$ during the purification process, possibly because of the loss of tetrazine through sublimation under the reaction conditions.

Scheme 3



corresponding [3]pseudorotaxane [DB24C8$\subset$**8**-$H_2$$\supset$21C7][2$PF_6$] to be generated selectively through solvent-free heating and mixing (because a phenyl group is an efficient stopper for 21C7,[7a] this crown ether could encircle only the NH_2^+ center adjacent to the oct-7-ynyl terminus, leaving the other NH_2^+ center free for complexation with a DB24C8 unit). We also anticipated that the oct-7-ynyl terminus of **8**-$H_2\cdot 2PF_6$ would react selectively with tetrazine under solid-to-solid grinding conditions, leaving its less-reactive phenylacetylene terminus to react with diphenyltetrazine in the subsequent heating process. If so, we would obtain a hetero[3]rotaxane, featuring interlocked macrocyclic and stopper units placed precisely, under solvent-free conditions through sequential self-sorting processes in both the threading and stoppering steps.

We heated an equimolar mixture of the thread-like dicationic salt **8**-$H_2\cdot 2PF_6$ and the crown ethers DB24C8 and 21C7 at 373 K while mixing with a spatula until the sample completely solidified to form, presumably, primarily the [3]pseudorotaxane [DB24C8$\subset$**8**-$H_2$$\supset$21C7][2$PF_6$] in the first self-sorting process (Scheme 3). The ^{1}H NMR spectrum of the solid obtained after grinding an equimolar mixture of the solid [3]pseudorotaxane, tetrazine, and diphenyltetrazine for 9 h revealed the absence of the signal of tetrazine together with the appearance of signals for the alkylpyridazine (Figure 4b). The presence of signals for the relatively intact diphenyltetrazine after grinding, but their significant decrease after heating the solid mixture at 373 K for 72 h, indicated the success of the second Diels–Alder reaction. The new signals that formed were similar to those in the ^{1}H NMR spectrum of the salt **5**-H·PF_6, suggesting that diphenyltetrazine had reacted with the phenylacetylene unit to form a stopper under these conditions. Purification of the resulting solid mixture afforded the hetero[3]rotaxane **9**-$H_2\cdot 2PF_6$ in 9% yield.[10]

Therefore, applying two self-sorting processes sequentially—one for threading and the other for stoppering—allowed five different molecular components to assemble precisely into a hetero[3]rotaxane in one pot under completely solvent-free conditions. This hetero[3]rotaxane contains the same types of bead-like (crown ether) and stopper (pyridazine) units; therefore, judicious selection of the components was necessary to prevent the production of a messy mixture of products.

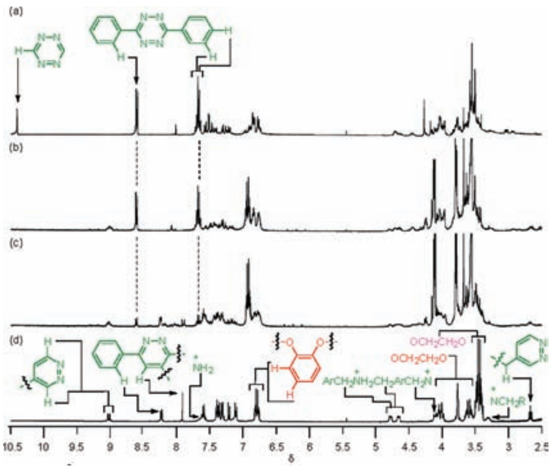


Figure 4. ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K) of (a) an equimolar (10 mM) mixture of 21C7, DB24C8, **8**-$H_2\cdot 2PF_6$, diphenyltetrazine, and tetrazine; (b) the crude product obtained after subjecting the neat mixture of compounds in (a) to a one-pot heating/mixing/grinding (9 h) process; (c) the crude product obtained after heating the mixture in (b) for 72 h at 373 K; and (d) purified **9**-$H_2\cdot 2PF_6$.

We have achieved the selective synthesis of a hetero[3]rotaxane from five discrete components by applying the concept of self-sorting to sequential threading and stoppering processes in the absence of solvent molecules. Thus, the power of self-sorting can be extended into solvent-free conditions, allowing future integration of many molecular components through selective transformations to form complicated functional molecules in a simple, efficient, and waste-free manner.

Acknowledgment. We thank the National Science Council (Taiwan) for financial support (NSC-98-2113-M-002-004-MY3).

Supporting Information Available. Synthetic procedures and characterization data for the hetero[3]rotaxane **9**-$H_2\cdot 2PF_6$. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The tedious purification process of the hetero[3]rotaxane **9**-$H_2\cdot 2PF_6$ appeared to significantly decrease its isolated yield. Using CH_2Br_2 as an external reference in a coaxial insert NMR tube, we estimated the yield of **9**-$H_2\cdot 2PF_6$ in the crude product to be 13%. Similarly, we determined the yield of **9**-$H_2\cdot 2PF_6$ to be 18% in the crude product obtained from sequential ball-milling and heating of diphenyltetrazine and tetrazine with the solid formed after concentrating an equimolar mixture of 21C7, DB24C8, and **8**-$H_2\cdot 2PF_6$ in CH_3NO_2. Thus, the efficiency of the passage of the macrocycles around the threadlike component in the solid state should not be significantly lower than that in solution. We did not observe signals corresponding to **9**-$H_2\cdot 2PF_6$ after heating an equimolar (50 mM) mixture of 21C7, DB24C8, **8**-$H_2\cdot 2PF_6$, diphenyltetrazine, and tetrazine in CD_3NO_2 at 373 K for 48 h. We did, however, observe (^{1}H NMR) decomposition of the pyridazine unit generated from the reaction of tetrazine with the oct-7-ynyl terminus in CD_3NO_2 at 373 K. Therefore, thermal decomposition might also be a factor responsible for the low yields under solvent-free conditions.