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Dynamic Covalently Bonded Rotaxanes Cross-Linked by Imine Bonds between the Axle and Ring: Inverse Temperature Dependence of Subunit Mobility**

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Establishing methods to control submolecular movements of rotaxane components is a prerequisite for the development of artificial devices that function through translational and rotational motion at the molecular level. During the last decade, many systems capable of controlling interactions among components through external stimuli, such as metal binding, change in pH value, electrochemistry, light, or temperature, have been developed to realize on/off switching

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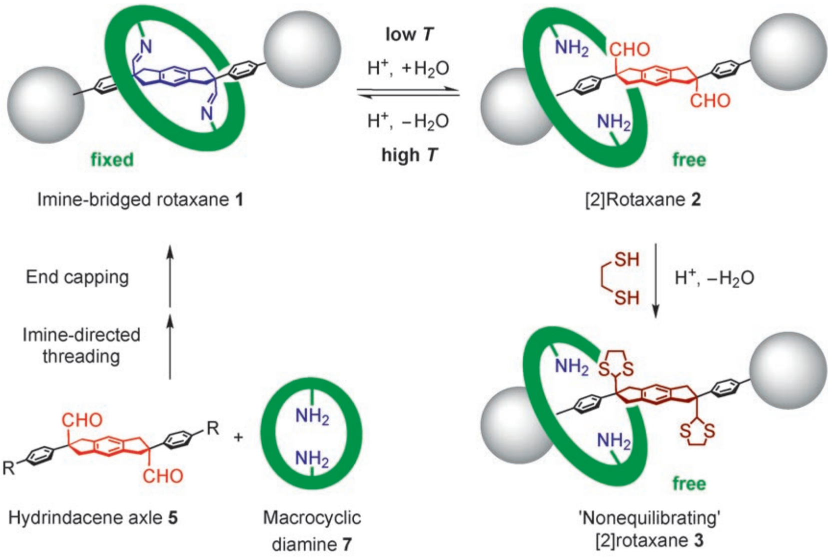
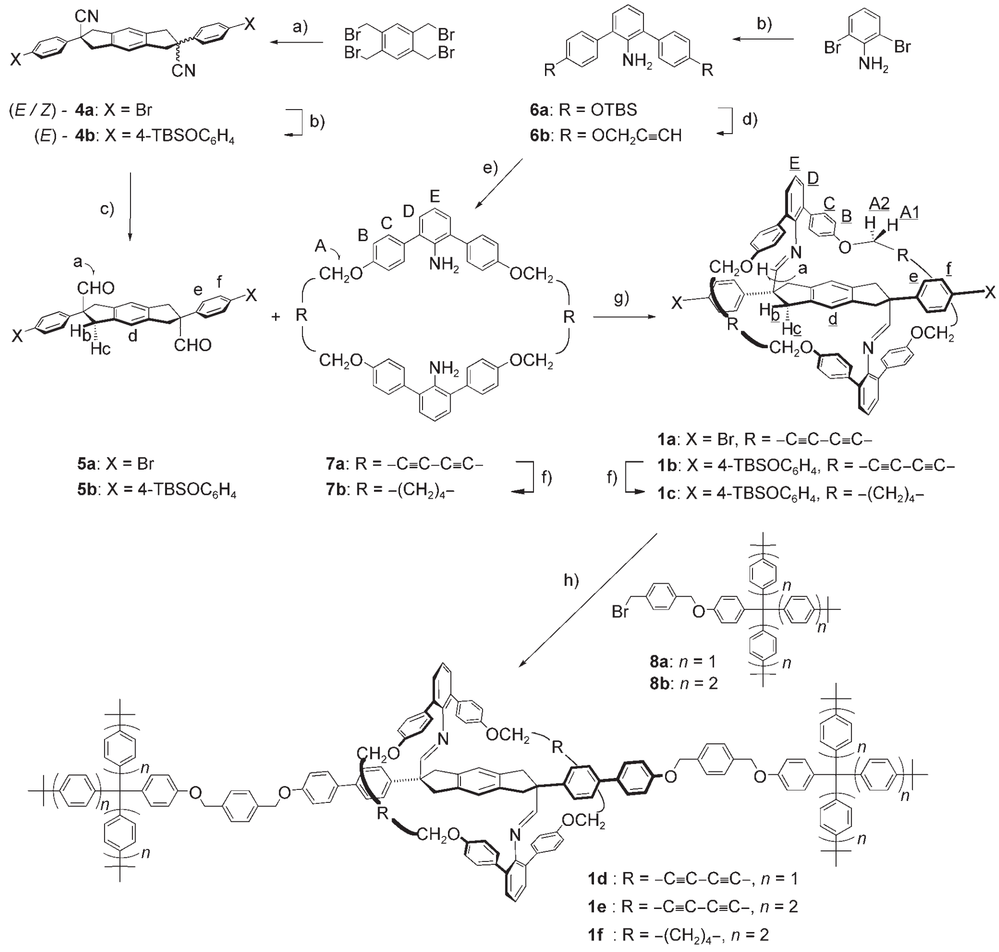
of subunit mobility or change in the position of the ring on the axle in rotaxanes (molecular shuttles).[1]

The use of dynamic covalent bonds,[2] which can be formed and broken reversibly under mild conditions, to link components seems promising for this purpose. There are no precedents for the use of the imine bond[3] as a cross-linkable/cleavable motif between the axle and ring components of rotaxanes,[4] yet we found it very useful for constructing interlocked compounds able to control the subunit mobility. The imine compounds in general can be equilibrated with the corresponding amine–aldehyde pair under hydrolytic conditions. Accordingly, the novel assembly can adopt the imine-bridged rotaxane (strictly, [1]rotaxane[5]), in which the ring is covalently fixed on the axle, or the [2]rotaxane, in which the ring can freely move on the axle (Scheme 1). Furthermore, the [2]rotaxane



Scheme 1. Dynamic formation of [2]rotaxanes **2** from imine-bridged rotaxanes **1** under acidic hydrolysis/dehydration conditions, and the transformation of **2** into [2]rotaxane **3** by dithioacetalization of the formyl groups.



Scheme 2. Synthesis of imine-bridged rotaxanes **1**: a) 4-$BrC_6H_4CH_2CN$, cat. $PhCH_2NEt_3Cl$, PhMe/40% NaOH, 65 °C (19 and 28% for (*E*)- and (*Z*)-**4a**, respectively); b) 4-$TBSOC_6H_4B(OH)_2$, $[Pd(PPh_3)_4]$, PhH/EtOH/2 M Na_2CO_3, 80 °C (98% for (*E*)-**4b**; 97% for **6a**); c) DIBAL, PhH (for **5a**) or CH_2Cl_2 (for **5b**), 25 °C (94% for **5a**, 84% for **5b**); d) TBAF, then Cs_2CO_3, propargyl bromide, THF, 25 °C (87%); e) $Cu(OAc)_2$, CH_3CN, 80 °C (79%); f) H_2, 10% Pd/C, THF, 25 °C (>99% for **7b**; >99% for **1c**); g) TFA, 4-Å ms, PhH, reflux (>99% for **1a**; 95% for **1b**); h) TBAF, then Cs_2CO_3, **8a** or **8b**, THF/DMF, 25 °C (68% for **1d**; 52% for **1e**, 69% for **1f**). DIBAL = diisobutylaluminum hydride, TBAF = tetrabutylammonium fluoride, TFA = trifluoroacetic acid, 4-Å ms = 4-Å molecular sieves, DMF = dimethylformamide, TBS = *tert*-butyldimethylsilyl.

2 generated by hydrolysis could be transformed to another [2]rotaxane **3** by protection of the functional groups, thus preventing its participation in the dynamic regeneration of the imine-bridged rotaxane. In this way, we expected that the independent mobility of the axle and ring components in this novel type of rotaxane can be regulated based on the controllable reversibility of the dynamic covalent bond.

Herein, we report the preparation of novel assembly **1** by threading an axle bearing two formyl groups into a macrocyclic diamine, directed by cross-linking imine bond formation,[6] and attaching bulky end groups. We also report that [2]rotaxane **2** is successfully generated in equilibrium with **1** in an acidic medium, in which the relative abundance of **2** increases with decreasing temperature, and that **2** is trapped by ethanedithiol to afford "nonequilibrating" [2]rotaxane **3**.

The axle molecule **5** was designed by exploiting the well-defined geometrical features of the hydrindacene (1,2,3,5,6,7-hexahydro-*s*-indacene) skeleton.[7] The less-bulky carbaldehyde groups at the 2,6-positions preferentially occupy the pseudoaxial positions, and so can work as linkers with the amino groups of macrocycle **7** at opposing sides of the molecular plane. The bromo-terminated dicarbaldehyde axle **5a** and TBSO-terminated axle **5b** were prepared from 1,2,4,5-tetrakis(bromomethyl)benzene (Scheme 2). Macrocyclic diamine **7a** was prepared from 2,6-diarylaniline **6a** by oxidative coupling.

Upon mixing equimolar amounts of **5a** and macrocycle **7a** in $CDCl_3$ at 298 K, the ^1H NMR spectrum showed a new set of resonances just after the addition of a catalytic amount of TFA or silica gel. The newly generated species resonated at a higher field than most of the protons of both components (Figure 1). Signals that arose from **5a** and **7a** remained detectable for several hours. However, the addition of 4-Å ms to this sample or azeotropic refluxing in benzene led to the quantitative formation of doubly bridged pseudorotaxane **1a**.

Imine-bridged pseudorotaxane **1a** was isolated intact by column chromatography on alumina or gel-permeation chromatography (GPC). X-ray analysis of the THF solvate unambiguously revealed the threading of the hydrindacene axle through the macrocycle to create C_i-symmetric **1a** (Figure 2).[8] An imine-directed threading of a longer axle **5b** into **7a** quantitatively afforded **1b**. Imine-bridged pseudorotaxane **1c** with its flexible macrocycle was quantitatively obtained by hydrogenation of **1b** over 10% Pd/C. Finally, end groups were attached to **1b** and **1c** by one-pot desilylation–benzylation reactions with **8a** or **8b** to afford imine-bridged rotaxanes **1d**, **1e**, or **1f** (see Figure 3b and the Supporting Information[9]).

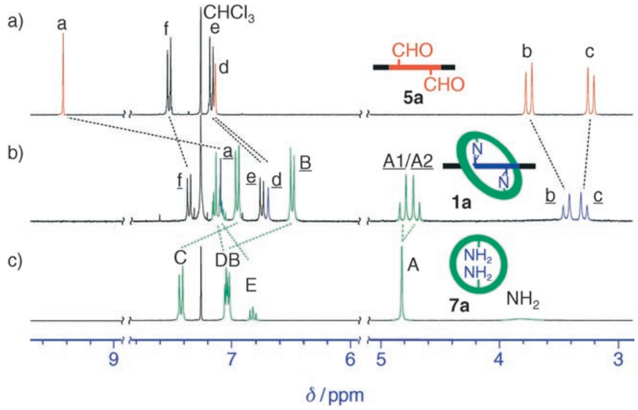


Figure 1. ^1H NMR spectra (300 MHz, $CDCl_3$) of a) hydrindacene axle **5a**, b) imine-bridged pseudorotaxane **1a**, and c) macrocycle **7a**. The lettering corresponds to the assignments shown in Scheme 2.

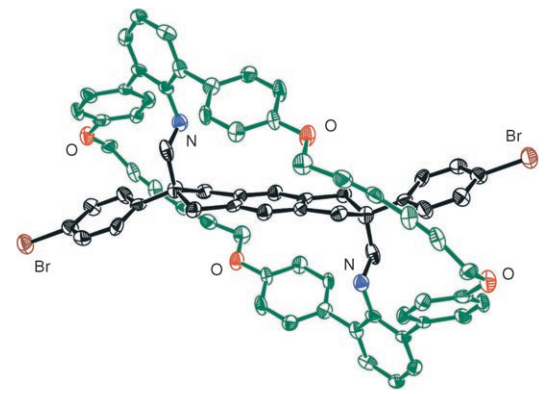


Figure 2. X-ray structure of imine-bridged pseudorotaxane **1a** in a THF solvate. Hydrogen atoms and solvents are omitted for clarity.

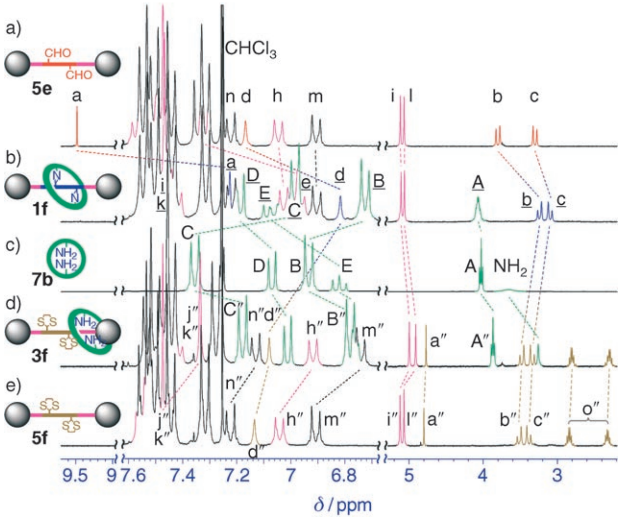
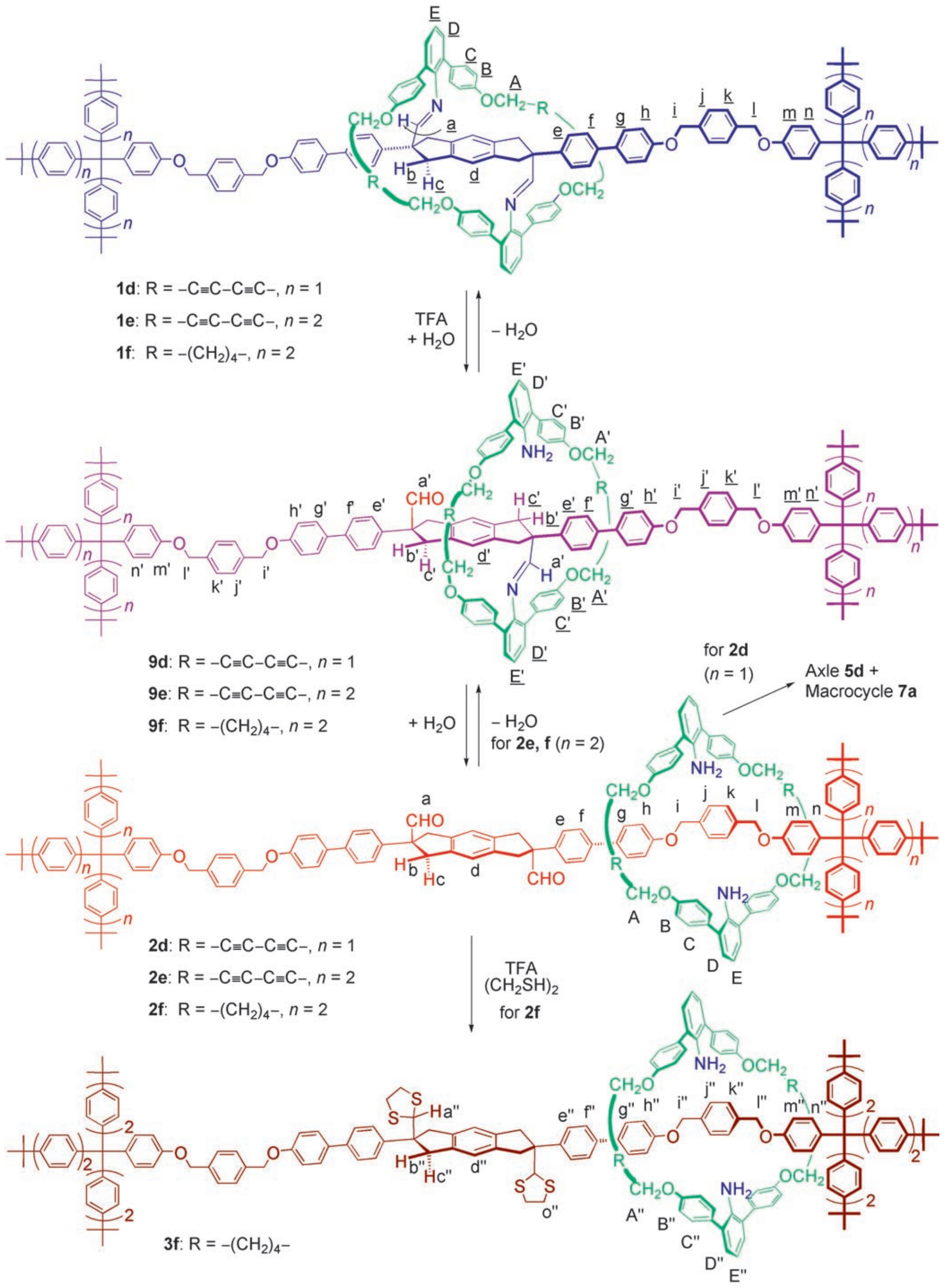


Figure 3. ^1H NMR spectra (300 MHz, $CDCl_3$, 298 K) of a) axle **5e**, b) imine-bridged rotaxane **1f**, c) macrocycle **7b**, d) dithioacetalized [2]rotaxane **3f**, and e) dithioacetalized axle **5f**. The lettering correspond to the assignments shown in Scheme 3.

With these imine-bridged rotaxanes in hand, we studied the dynamic generation of the [2]rotaxanes **2** under acidic hydrolysis conditions. The addition of TFA to a solution of **1a** or **1b** in wet $CHCl_3$ led to the quantitative (> 95%) formation of the axle, **5a** or **5b**, and the macrocycle **7a**. Similar hydrolysis and dethreading was observed for **1d** with 4-[tris(4′-*tert*-butylphenyl)methyl]phenoxy end groups (Scheme 3). These results obviously indicate the lability of the imine bonds in **1** toward acidic hydrolysis and the ready dethreading of the resultant pseudorotaxanes with the insufficiently bulky end groups.



Scheme 3. Generation of [2]rotaxanes **2** from the imine-bridged rotaxanes **1** by acidic hydrolysis and transformation to the "nonequilibrating" [2]rotaxane **3**.

In striking contrast, compound **1f** exhibited dynamic behavior in its hydrolysis. Thus, a new set of resonances, including a C*H*O signal at $\delta = 9.4$ ppm, appeared upon addition of TFA to **1f** in $CDCl_3$ at 298 K. Another set of resonances was observed when the spectrum was recorded at 258 K, and interestingly both new sets of signals enhanced in intensity at the expense of those from **1f** as the recording temperature was lowered (see Figure 4 and the Supporting Information). The scrutiny of those sets of spectra revealed that the former spectrum was of a species low in symmetry and was consistent with the structure of the partially hydrolyzed monoimine **9f**, whereas the latter was simpler and in good agreement with that expected for the desired [2]rotaxane **2f** (see the Supporting Information).[10] The upfield shifts of the xylylene CH_2 protons in **2f**, but not in **9f**, relative to **1f** suggest relocation of the macrocycle toward the end group from the central hydrindacene moiety. The observed temperature dependence of the equilibrated ratios indicates that the dynamic generation of **2f** and **9f** by hydrolysis of the imine bonds are enthalpy-driven processes, whereas the reverse

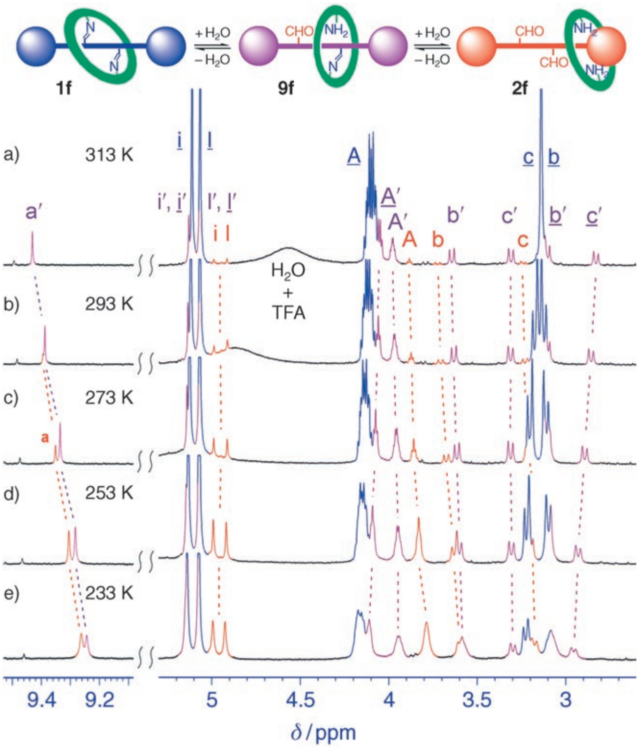


Figure 4. ^1H NMR spectra (600 MHz, 0.08% TFA/$CDCl_3$ (v/v)) of the hydrolyzed mixture containing imine-bridged rotaxane **1 f**, monoimine **9 f**, and [2]rotaxane **2 f**. An equilibrated ratio of **1 f**/**9 f**/**2 f** is shown in parenthesis at a) 313 K (81:18:≈1), b) 293 K (72:24:4), c) 273 K (64:30:6), d) 253 K (52:34:14), and e) 233 K (42:36:22). The lettering corresponds to the assignments shown in Scheme 3.

formation of the imine bonds are entropy driven. The release of water molecules upon the intramolecular condensation in **2 f** and **9 f** may contribute to the gain in entropy in those steps. Importantly, the increasing ratio of **2 f** at low temperature signifies that the submolecular mobility in this system (that is, the translational and rotational movement of macrocycle with respect to the axle) is enhanced as the temperature decreases. This thermosetting behavior is in sharp contrast to that of ordinary rotaxanes restricted by noncovalent interactions, in which the submolecular mobility is suppressed at lower temperature.

We could obtain the "nonequilibrating" [2]rotaxane **3 f** from the imine-bridged rotaxane **1 f** in good yield (75%) through the dithioacetalization of the formyl groups (ethanedithiol, TFA, wet $CHCl_3$) in situ. The [2]rotaxane structure of **3 f** was supported by field-desorption mass-spectrometric and ^1H NMR spectroscopic analysis (Figure 3 d). The ^1H NMR spectrum of **3 f** in $CDCl_3$ revealed that the xylylene protons (CH_2; $H_{i'',1''}$) of the tether groups of **3 f** ($\delta = 4.91$ and 5.00 ppm) were shielded relative to those of **1 f** ($\delta = 5.06$ and 5.11 ppm) or the dithioacetalized axle **5 f** ($\delta = 5.07$ and 5.12 ppm), and no peak-splitting was observed over a temperature range of 188–298 K in CD_2Cl_2. The central hydrindacene part of **3 f** ($\delta = 3.48$ ($H_{b''}$), 3.34 ($H_{c''}$), and 7.08 ppm ($H_{d''}$)) was not magnetically shielded, and their resonances appear in the similar region to those of **5 f** ($\delta = 3.51$, 3.38, and 7.13 ppm). These results indicate that the macrocycle of **3 f** preferentially resides around the tether groups and rapidly shuttles between the two xylylene spacers, as in the case of [2]rotaxane **2 f**.

In summary, by using diformylhydrindacene **5** as a synthetic platform, we have demonstrated the validity of a novel threading method directed by imine-bond formation. From the resultant imine-bridged [2]rotaxane **1**, two types of [2]rotaxane **2** and **3** were generated through the imine-bond cleavage, that is, acidic hydrolysis that leads to a dynamic mixture containing **2** and thioacetalization of **2** to give **3** in situ. More importantly, the submolecular mobility in this novel assembly could be regulated by the imine-bond formation/cleavage between the macrocycle and axle: the imine-bond formation allows control over the ability of the macrocycle to be able to move over the axle or not. This restriction of motion must be important for "ratcheting",[11] a crucial requirement for the preparation of molecular machines that are more complex than simple switchable molecular shuttles. Another outstanding feature of the present system is the temperature dependence of a proportion of **2** under the hydrolytic equilibration: as the temperature is lowered, the proportion of **2** relative to **1** is increased. Increasing submolecular mobility as a bulk with lowering of temperature is unusual, and we are investigating the exploitation of this peculiar behavior.

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[8] X-ray crystal structural data for **1a**·4THF (collected at 103 K): $C_{90}H_{82}Br_2N_2O_8$, $M_r = 1479.45$, triclinic $P\bar{1}$, $a = 11.185(5)$, $b = 12.645(3)$, $c = 14.799(7)$ Å, $\alpha = 67.08(5)$, $\beta = 82.55(6)$, $\gamma = 68.39(5)^\circ$, $V = 8461.0(1)$ Å^3, $\rho_{calcd}(Z{=}1) = 1.370\ \mathrm{g\,cm^{-3}}$, $\mu = 1.196\ \mathrm{cm^{-1}}$, 7611 independent reflections ($R_{int} = 0.131$) and 509 parameters, $R1(F^2) = 0.092$ ($I > 2\sigma I$), $wR2(F^2) = 0.244$ (all data). Estimated standard deviations for bond lengths and angles are 0.009–0.02 Å and 0.6–1.0° for non-hydrogen atoms. CCDC-252150 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] See the Supporting information.

[10] As **1e** has more rigid macrocycles than **1f**, most of the ^{1}H NMR signals, except for those of the end groups, broadened under the hydrolytic conditions, thus suggesting that the hydrolysis that generates **9e** and **2e** might proceed to some extent; however, the expected C*H*O signals were not clearly discernible and the propargyl methylene protons on the macrocycle remained nonequivalent to each other. Thus, the equilibration among **1e**, **9e**, and **2e** seems to be heavily in favor of **1e** under the hydrolytic conditions, and as a result the preorganization of the macrocycle favors imine formation.

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