Interplay of Interactions Governing the Dynamic Conversions of Acyclic and Macrocyclic Helicates

Victoria E. Campbell,[a] Xavier de Hatten,[b] Nicolas Delsuc,[b] Brice Kauffmann,[b] Ivan Huc,*[b] and Jonathan R. Nitschke*[a]

Abstract: A rigid, helical macrocycle that contains two copper(I) ions has been synthesized through subcomponent self-assembly. Although it does not obey the “rule of coordinative saturation”, this macrocycle could be prepared through subcomponent substitution starting from a tri(copper(I)) helicate, in a reaction in which copper(I) was ejected. The macrocycle was observed to readily participate in a sequence of transformations between helical structures mediated by the electronic effects of substituents, entropic effects, the conformational preferences of organic building blocks, and the coordinative preferences of the metal ion. The thermodynamic parameters governing the interconversion of an “open” helicate and the “closed” macrocycle were determined through van ’t Hoff analysis, allowing quantification of the entropic driving force for macrocyclization.

Keywords: dynamic covalent chemistry · macrocyclization · self-assembly · substitution · systems chemistry

Introduction

The creation and transformation of complex structures under thermodynamic control requires a nuanced understanding of the rules, or “programming instructions”, governing the self-assembly processes of interest. Intricate self-assembled structures have been created using the interplay of different kinds of interactions, such as circular helicates and cages (metal coordination + guest templation), Borromean and Solomon links (metal coordination + π-stacking + dynamic covalent (imine bond formation), triply interpenetrated catenanes (metal coordination + π-stacking), strained grids (metal coordination + hydrophobic interactions + dynamic covalent bonds), and multicomponent cycles and rotaxanes (metal coordination + boronate ester formation + imine bond formation). Herein we build upon these prior examples by showing how four types of interactions may act together not only upon a single structure but within a system of structures.[10] We were able to describe the evolution of this system following the addition of a subcomponent, allowing multiple sequential transformations to be executed between acyclic and macrocyclic helicates.

Results and Discussion

The products expressed by our system were observed to depend upon interactions mediated by 1) the electronic effects of substituents, 2) entropic effects, 3) the conformational preferences of organic building blocks, and 4) the coordinative preferences of copper(I). All of these effects were important, but none taken alone could allow the prediction of the product observed from a given set of building blocks.

We have previously described the self-assembly of trinuclear double helicates similar to 4, which formed (Scheme 1) from 2,9-diformyl-1,10-phenanthroline (2 equiv), copper(I) was ejected. The macrocycle was observed to readily participate in a sequence of transformations between helical structures mediated by the electronic effects of substituents, entropic effects, the conformational preferences of organic building blocks, and the coordinative preferences of the metal ion. The thermodynamic parameters governing the interconversion of an “open” helicate and the “closed” macrocycle were determined through van ’t Hoff analysis, allowing quantification of the entropic driving force for macrocyclization.

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formation of a stable product structure 2 (Scheme 1), wherein all ligand nitrogen atoms were not bound to metal ions. This demanding subcomponent could be introduced and removed quantitatively following selection rules based upon substituent electronic effects,[12,13] allowing the system to be switched back and forth between obeying and disobeying the rule of coordinative saturation. This rule,[14] which postulates that the most stable structure will have all ligand donor atoms bound to a metal ion and all metal ions coordinatively saturated, has been broken in exceptional cases,[15] but its expression has not previously been switched on and off within a system.

Even though only four of the six ligand nitrogen atoms of macrocycle 2 are bound to copper(I) ions, we observed no tendency for the subcomponents of 2 to form coordinatively saturated structures. No changes to the 1H NMR spectrum of 2 were noted following either the addition of excess copper tetrafluoroborate (4 equiv) or excess 1 (4 equiv) followed by heating to 393 K for 12 h. The reaction of helicate 4 (1 equiv) with 1 (2 equiv) resulted in quantitative conversion to 2 upon addition of 1 (4 + 2·1 → 1 + 4·3 + CuI).

Examination of the coordination vectors[16] of the unbound nitrogen atoms of 2 revealed that they are not well situated either to chelate or bridge. The degrees of freedom available to the system are limited by the rigidity of subcomponent 1 and the preferred trans-orientation of the carbonyl and N-phenyl vectors of its tertiary amide groups.[17] Operating within these constraints, we infer that the system of diformylphenanthroline, 1, and CuI, minimizes strain and maximizes entropy by breaking the rule of coordinative saturation in generating 2.

Bis(aminouquinoline) 1 was observed to react with helicate 5[12] (Scheme 2), with the equilibrium not strongly favoring either side. This system was thus more amenable to thermodynamic analysis than the transformation of 4 into 2 (Scheme 1), where the equilibrium lay strongly on the side of 2. Van ‘t Hoff analysis of the system of Scheme 2 provided quantitative insight as to the effects of entropy and enthalpy on substitution reactions involving 2. The equilibrium composition of the product mixture of the reaction between 1 and helicate 5 was measured from 373 K to 403 K, and a linear least-squares fit of ln(K) versus T−1 (see the Supporting Information) yielded the values of ΔH° = 81 kJ mol−1 and ΔS° = 0.193 kJ mol−1 K−1. The system of Scheme 2 is thus balanced between enthalpy, which favors incorporation of the p-toluidine subcomponent during the formation of 5, and entropy, which favors the increase in number of parti-
cles during the formation of macrocycle 2 (three species going to five). Similar effects presumably govern the formation of 2 from 4 (Scheme 1), although this system is more complicated to analyze because the equilibrium lay strongly on the side of 2 and because of potential interactions between liberated CuI and the solvent and with liberated 3.

In prior work[12] we had investigated how substituent effects can generate an enthalpic driving force for imine exchange. The Hammett equation[18] was observed to quantitatively predict the degree to which a less electron-rich amine residue was displaced by a more electron-rich amine within the imine ligands of a metal complex. Although the Hammett equation appears an unsuitable tool to quantify the behavior of the systems incorporating diamines because of the importance of entropy in these equilibria, we reasoned that the balanced nature of the equilibrium between 5 and 2 would allow 1 to displace electron-poor anilines that p-toluidine (Hammett $\sigma_{\text{para}} = -0.17$)[18] is able to displace[12] and that 1 would in turn be displaced by electron-rich anilines that displace p-toluidine.

We thus designed the sequence of transformations shown in Scheme 3. Each step was observed to occur in >95% yield and the entire sequence could be carried out within the same reaction flask. The corresponding NMR spectra are presented in Figure 2. The presence of additional CuI did not result in the formation of products incorporating 1 that obeyed the rule of coordinative saturation.

Scheme 2. Equilibrium between helicate 5 and macrocycle 2 ($2 \cdot 1 + 5 \rightleftharpoons 4 \cdot p$-toluidine $\rightleftharpoons 2$).

Scheme 3. Four-stage subcomponent substitution sequence incorporating 2 ($6 + 2 \cdot 1 \rightarrow 2 + 4 \cdot p$-chloroaniline; $2 + 4 \cdot p$-methoxyaniline $\rightarrow 7 + 2 \cdot 1 + 2$ (ethylenedioxy)bis(ethylamine) $\rightarrow 8 + 4 \cdot p$-methoxyaniline).
The substantial geometrical changes required during the conversion of 6 to 2 and 2 to 7 are reflected in the slower kinetics of these transformations (\( t_{1/2} = \text{12 h at 393 K} \)) than in the transformation of 7 to 8 (\( t_{1/2} = \text{ca. 5 min at 393 K} \)). We attribute this difference in activation energy to the extensive rearrangement necessary—involving the breakage and reforming of six nitrogen-copper linkages—to convert the coordination environments of 6 to 2 or 2 to 7.

With the exception of 2, all of the products shown in Schemes 1–3 obey the rule of coordinative saturation, having four ligand nitrogen atoms per copper ion. The presence of subcomponent 1 thus causes this “rule” to be broken upon its incorporation, only to be reinstated following this subcomponent’s ejection. Thus, to determine whether the system will follow this rule, it is necessary to know not only whether 1 is present, but also whether another subcomponent is present with a greater affinity for complex formation (such as 4-methoxyaniline). The first condition must be true, and the second false, for the system to exist in the state of coordinative unsaturation exemplified by 2.

**Conclusions**

The system encompassing helicates 2, 4, 5, 6, 7, and 8 is thus governed by substituent and entropic effects, acting together to determine which subcomponent will be incorporated into the favored product. The rule of coordinative saturation[14] dictates the structure of this product, except when this product incorporates 1: the preferred geometry of this subcomponent then favors the structure of 2. We are currently investigating new structures built around the novel dicopper double-helicate core of 2, as well as developing new ways to use linear free energy relationships to quantitatively predict the outcome of reassembly reactions involving diamines and higher-order multitopic amines.

**Experimental Section**

**General:** All reactions were carried out in dry glassware with an argon overpressure. Unless otherwise noted, all reagents were purchased from Aldrich or Acros and used without further purification; 1,10-phenanthroline (1.07 mg, 4.78 mmol), 1,10-phenanthroline (1.07 mg, 4.78 mmol), [Cu(CH3CN)]BF4 (2.26 mg, 7.18 mmol), CD-CN (0.1 mL), and CDCl3 (0.4 mL) were added. The tube was sealed and the solution was purged of dioxygen by three vacuum/argon-fill cycles, and heated for 12 h at 393 K, after which 2 and p-chloroaniline were the only species observed in solution by 1H NMR spectroscopy. p-Methoxyaniline (1.10 mg, 8.94 mmol) was added to this solution and the tube was purged of dioxygen by three vacuum/argon-fill cycles. The solution was heated to 191 K for five days, after which 7 and 1 were the only products observed by NMR spectroscopy. To this solution 2.2'-ethylenedioxybis(ethylene) (1.32 mg, 8.94 mmol) was added. The tube was sealed and the solution was purged of dioxygen by three vacuum/argon-fill cycles, and heated for 5 min at 393 K, to afford 8, p-methoxyaniline and 1 as the unique products observed by 1H NMR spectroscopy.

**Synthesis of 4:** To a Teflon-capped NMR tube, 2,2-diformyl-1,10-phenanthroline (1.87 mg, 7.94 mmol), 3 (5.55 mg, 15.9 mmol), [Cu(CH3CN)]BF4 (3.75 mg, 11.9 mmol), CD-CN (0.1 mL), and CDCl3 (0.4 mL) were added. The tube was sealed and the solution was purged of dioxygen by three vacuum/argon-fill cycles. The dark brown solution was left at 323 K overnight, resulting in the formation of 3 in quantitative yield, as observed by 1H NMR spectroscopy. 

**Synthesis of 2 from 4:** To a Teflon-capped NMR tube, 2,2-diformyl-1,10-phenanthroline (1.87 mg, 7.94 mmol), 3 (5.55 mg, 15.9 mmol), [Cu(CH3CN)]BF4 (3.75 mg, 11.9 mmol), CD-CN (0.1 mL), and CDCl3 (0.4 mL) were added. The tube was sealed and the solution was purged of dioxygen by three vacuum/argon-fill cycles. The dark brown solution was left at 323 K overnight, resulting in the formation of 4 in quantitative yield, as observed by 1H NMR spectroscopy.

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(4.01 mg, 6.61 mmol) was added into the NMR tube. The solution was purged of dioxygen again, then heated at 323 K for 2.5 h, after which all volatiles were removed under dynamic vacuum and CD$_2$CN (0.2 mL) and [D$_6$]DMSO (0.2 mL) were added. The reaction was heated at 353 K for five days, then at 393 K for seven days, after which the reaction came to completion. The reaction was monitored by $^1$H NMR spectroscopy and ESI-MS. $^1$H NMR (400 MHz, 300 K, CD$_2$CN/[D$_6$]DMSO, referenced to TMS peak, the reaction was considered to be at equilibrium when the integrations of the imine peaks did not change over time with respect to the TMS peak, the reaction was considered to be at equilibrium.

Equilibrium between 5 and 2: Into a Teflon-capped NMR tube, 5 (3.39 mg, 3.55 mmol), 1 (4.39 mg, 7.10 mmol), CD$_2$CN (0.1 mL), and [D$_6$]DMSO (0.4 mL) were added. The tube was sealed and the solution was purged of dioxygen by three vacuum/argon-fill cycles. The temperature was increased from 373 K to 403 K in 10 degree intervals, being kept for 96 h at each interval. The reaction was monitored by $^1$H NMR spectroscopy; when the imine peaks did not change over time with respect to the TMS peak, the reaction was considered to be at equilibrium.

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