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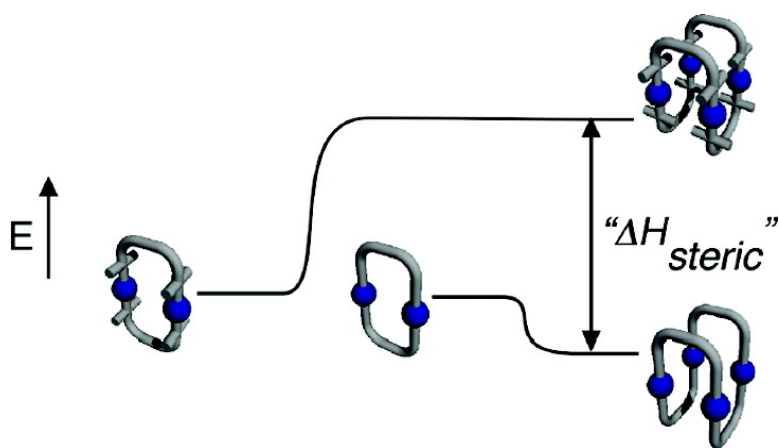
How Bulky Is a Bulky Ligand: Energetic Consequences of Steric Constraint in Ligand-Directed Cluster Assembly and Disassembly

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How Bulky Is a Bulky Ligand: Energetic Consequences of Steric Constraint in Ligand-Directed Cluster Assembly and Disassembly

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Steric effects are important determinants in many chemical reactions. The shapes and spatial orientations of molecular fragments often dictate individually weak but collectively strong interactions.[1] This is well exemplified by the self-assembly of noncovalently linked structures, in which thermodynamically the most stable structure evolves from multiple, competing species.[2] Understanding the energetic consequences of steric bulk in shaping the reaction coordinates of such process is critical to rational molecular design in supramolecular chemistry. Exploiting the kinetic lability and stereochemical promiscuity associated with the d^{10} metal system, we have explored solution dynamics of copper(I) clusters built on amidinate ligands. Tetramer−dimer and dimer−dimer interconversion displayed by this system immediately suggest a means to experimentally quantify energies that are associated with steric bulk.[3−7]

$$(1)$$
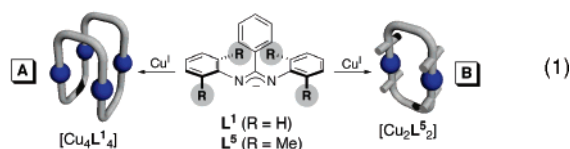
We have recently reported the use of ligand steric controller groups to direct the assembly of discrete copper(I) tetramers (**A**) and dimers (**B**) from a homologous set of amidinate ligands (eq 1).[8] On the basis of a number of X-ray structures obtained, we tentatively concluded that the 2,6-substituents on the ligand *N*-aryl groups play a key role in determining the cluster nuclearity: less bulky ligand L^1 can support crowded **A**, whereas bulky L^5 favors less crowded **B**.[9] This intuitive explanation, however, was immediately challenged by the realization that L^1, while being able to support structurally congested tetramer, did not afford a dimer in solid state, even though the dimer apparently has alleviated steric demands compared with the tetramer. A simple steric consideration was thus inadequate to rationalize this observation, prompting us to reconsider our initial view on this ligand-directed self-assembly.

A dynamic solution process involving copper dimers and tetramers was initially hinted by ^{1}H NMR studies. To install spectroscopic handles well-resolved from the complicated aromatic region, the phenyl "wings" of the parent ligand L^1 were replaced with *p*-anisyl to furnish L^2-L^4 (Scheme 1). Metalation followed by recrystallization afforded corresponding tetracopper(I) complexes (Scheme 1).[10] At 25 °C, CDCl$_3$ solution samples of $[Cu_4L^2_4]$ (**2**) display two methyl ^{1}H NMR signals, the relative intensities of which changed reversibly as a function of the temperature as well as the solution concentration (Figure S1). Increasing the temperature or diluting the sample resulted in a build-up of the resonance at 3.67 ppm, which cleanly correlated with diminution of the signal at 3.63 ppm.[11] Similar observations were made in toluene-d_8. These findings are consistent with solution equilibrium between two distinctive species, rather than ligand fluxionality within **2**. Mass spectra

Scheme 1. Synthetic Routes to Tetrameric and Dimeric Copper(I) Clusters, and Solid-State Structures of $[Cu_4(L^2)_4]$ (**2**) and $[Cu_2(L^6)_2]$ (**6**) Generated Using X-ray Coordinates
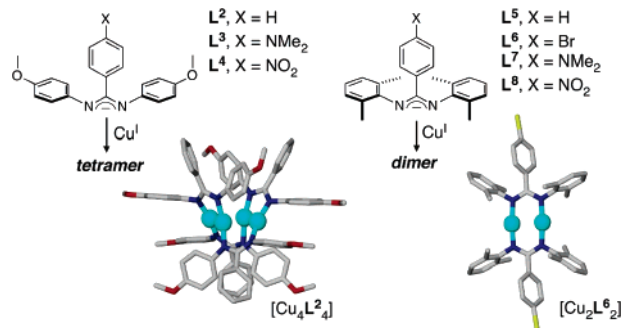
(MALDI-TOF) of solution samples of **2** comprise peaks from the $[Cu_2L^2_2]^+$ cation ($m/z = 788.1$) in addition to the $[Cu_4L^2_4]$-derived $[Cu_4L^2_3]^+$ ($m/z = 1245.2$) ion (Figure S2), which points toward tetramer−dimer equilibrium in solution (eq 2). A van't Hoff plot could be constructed from variable-temperature (25−60 °C) ^{1}H NMR data to afford $\Delta H = 5.4 \pm 0.1$ kcal mol^{-1} and $\Delta S = 10.8 \pm 0.3$ cal mol^{-1} K^{-1} (Figure S3). Similar results were obtained for copper(I) clusters supported by L^3 or L^4 (Table S1).

$$(2)$$
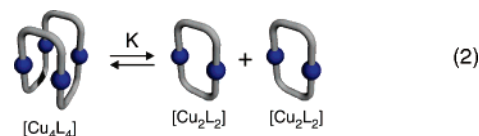
This facile tetramer−dimer interconversion of copper(I) complexes supported by L^2-L^4 prompted us to investigate whether a similar process is operative for systems built on their bulkier homologues L^5-L^8 (Scheme 1). These ligands have 2,6-dimethylphenyl wing groups and consistently furnished dimeric structures in the solid state (Scheme 1).[10] Consistent with its local D_{2h} symmetry, the ^{1}H NMR spectrum of $[Cu_2L^5_2]$ (**5**)[8] in CDCl$_3$ displays a single methyl resonance at 2.34 ppm. No other L^5-containing species were detected even upon heating the solution to 60 °C. This apparent thermodynamic stability of **5**, however, belies its inherent kinetic lability. Upon mixing equimolar amounts of **5** and $[Cu_2L^6_2]$ (**6**) in CDCl$_3$ at 25 °C, a pair of new methyl ^{1}H NMR signals appeared (Figure 1a). These two peaks simultaneously built up with concomitant decrease of the signals from **5** and **6**, reaching an equilibrium peak ratio of ~1:1:1:1. Mass spectrometric analysis (CI-MS) of this mixture revealed peaks corresponding to a $[Cu_2L^5L^6]^+$ ion ($m/z = 858.1437$), in addition to those of $[Cu_2L^5_2]^+$ ($m/z = 780.2272$) and $[Cu_2L^6_2]^+$ ($m/z = 936.0456$) ions (Figure 1b). The relative intensities of the three peaks approximate 1:2:1, which fully supports the assignment of the two new methyl ^{1}H NMR signals (Figure 1a) to the heteroleptic $[Cu_2L^5L^6]$ complex. The equilibrium constant K for the ligand metathesis reaction (Figure
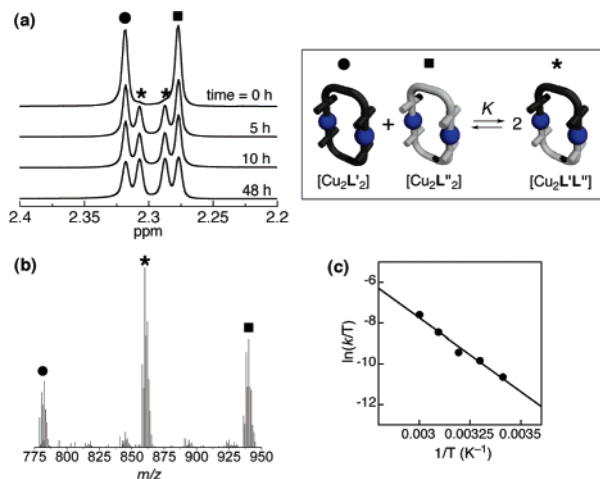
Figure 1. (a) ^{1}H NMR spectra of an equimolar mixture of $[Cu_2\mathbf{L'}_2]$ (●) and $[Cu_2\mathbf{L^6}_2]$ (■) in CDCl$_3$ at 25 °C. Methyl proton signals from the heteroleptic $[Cu_2\mathbf{L^5L^6}]$ complex (∗) build up over time with concomitant diminution of those from ● and ■. (b) CI-MS of the solution sample of (a) after 48 h. (c) An Eyring plot for ligand metathesis reaction between $[Cu_2\mathbf{L^7}_2]$ and $[Cu_2\mathbf{L^8}_2]$.

1) could readily be obtained from integrated methyl ^{1}H NMR resonances. Four independent sets of $[Cu_2\mathbf{L'}_2] + [Cu_2\mathbf{L''}_2]$ afforded K values ranging 3.5−4.2 (Table S2), which are close to the statistical mixing entropy term of 4. The essentially isoenthalpic nature of this metathesis reaction shown in Figure 1 allowed us to use ligand scrambling between differently substituted copper dimers ($\mathbf{L'} \neq \mathbf{L''}$) to approximate kinetic parameters dictating genuine self-exchange ($\mathbf{L'} = \mathbf{L''}$).

To attain baseline resolutions of methyl ^{1}H NMR signals, compounds $[Cu_2\mathbf{L^7}_2]$ (**7**) and $[Cu_2\mathbf{L^8}_2]$ (**8**) were deployed in our kinetic studies. Under pseudo-first-order conditions ($[\mathbf{8}] > 12[\mathbf{7}]$), the formation kinetics of $[Cu_2\mathbf{L^7L^8}]$ cleanly correlates with the decay kinetics of both **7** and **8**, with a second-order rate constant of $k = (7.0 \pm 0.3) \times 10^{-3}$ M^{-1} s^{-1} at 20 °C. From an Eyring plot (Figure 1c) constructed from temperature-dependent measurements (Figure S4), activation parameters of $\Delta H^{\ddagger} = 14.5 \pm 1.2$ kcal mol^{-1} and $\Delta S^{\ddagger} = -19.3 \pm 3.9$ cal mol^{-1} K^{-1} could be obtained. The negative activation entropy is consistent with an associative mechanism, in which formation of the mechanistically required tetrameric intermediate becomes rate-determining. An alternative pathway requiring complete dissociation of free ligand from the dicopper(I) complex is less likely, considering the high energy required for complete charge separation as well as the positive activation entropy anticipated for this scenario, which is inconsistent with the experimental observation.

From the thermodynamic and kinetic studies described above emerges a unifying energy diagram (Scheme 2). The equilibrium constants of $K \approx 4$ determined for the metathesis of bulky ligands indicate no enthalpic preference for either reactants' or products' side, therefore indicating a symmetric reaction coordinate with the tetrameric intermediate **C** in the middle (Scheme 2, right side). The experimentally determined activation barrier leading to **C**, $\Delta H^{\ddagger}_{\text{metathesis}}$, is the upper limit of the dimer−tetramer energy difference for the bulky ligand system. The corresponding dimer−tetramer energy difference in the unsubstituted "less-bulky" system (Scheme 2, left side), $\Delta H_{\text{dimer−tetramer}}$, is measured from the thermodynamics of dimer−tetramer equilibrium. Without steric constraint, the enthalpic gain ($\Delta H \approx -5$ kcal mol^{-1}) associated with the formation of interlinked and thus mechanically more robust $[Cu_4L_4]$ structure overrides the entropic cost ($\Delta S \approx -10$ cal mol^{-1} K^{-1}) of dimerizing two $[Cu_2L_2]$ units. With bulky ligands that introduce a total of 16

Scheme 2. Energetics of Dimer−Tetramer Interconversion
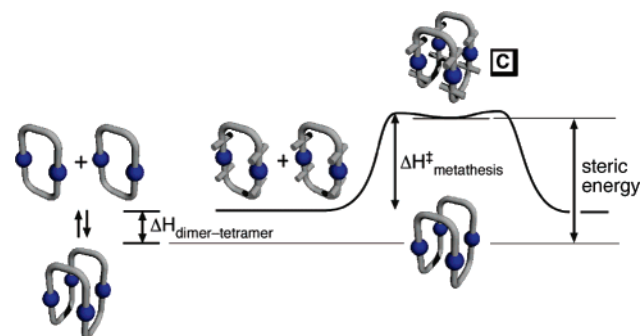
methyl groups onto this $[Cu_4L_4]$ platform, however, the collective steric energy builds up to ~ 20 kcal mol^{-1} ($= \Delta H_{\text{dimer−tetramer}} + \Delta H^{\ddagger}_{\text{metathesis}}$),[12] which is large enough to invert this inherent preference for tetramer over dimer (Scheme 2).

In sum, a delicate interplay between steric constraint and mechanical stability shapes the energy landscape of self-assembly, which could be mapped out using thermodynamic and kinetic parameters of metathesis reactions. As a bonus, steric energies dictating such ligand-directed assembly and disassembly could be quantified without resorting to empirical parameters or computational methods.[3]

Supporting Information Available: Experimental details (PDF) and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(3) Absolute steric energy associated with any substituent needs to be quantified within the context of its interactions with a specific molecular entity, making its generalization less than straightforward. Empirical scales have been commonly used to assess "steric effects" instead, which include: (a) Taft parameter, $E_s = \log(k/k_o)$, based on the relative rate ratios of acid-catalyzed ester hydrolysis with methyl as the standard group;[4] (b) Winstein−Holness A value, which is the free energy difference, $-\Delta G°$, between axial and equatorial isomers of monosubstituted cyclohexanes;[5] (c) cone angle, θ, defined as the internal angle of an enveloping cone of a metal-bound PR$_3$ ligand with M−P distance of 2.28 Å.[6] Computational studies have complemented such efforts.[7]
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(10) See Supporting Information.
(11) Unless otherwise noted, ^{1}H NMR peaks are referenced to (Me$_3$Si)$_2$O, which also served as an internal standard in quantitation.
(12) This estimation assumes that 2,6-dimethyl substitutions in $\mathbf{L^5}$−$\mathbf{L^8}$ induce negligible interligand steric congestion at the dimer level, and therefore, the two dicopper(I) species in Scheme 2 are of comparable energy. In support of this notion, X-ray structures of **5**−**8** show no van der Waals contacts between adjacent methyl groups.[10]

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