between ligand cavity size and cation size was offered as a possible explanation of the observed trends.[19] Sandwich formation rates were observed to decrease across the first row from Ti^+ to Fe^+, becoming much slower for the smaller ions Co^+, Ni^+, and Cu^+, which presumably fit within the ligand cavity. Valence electron count arguments were alternatively suggested. We can be confident that electronic effects are not responsible for the patterns in our data, since the alkali metal cations are closed-shell species isoelectronic with the noble gases. This suggests that the size argument may be correct for the cyclotriynes as well.

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Template-Mediated Synthesis of Metal-Complexing Polymers for Molecular Recognition

Pradeep K. Dhal and Frances H. Arnold*

Division of Chemistry and Chemical Engineering 210-41
California Institute of Technology
Pasadena, California 91125
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The design of synthetic molecules capable of recognizing given chemical entities in a specific and predictable manner is of great fundamental and practical importance.[1] The principal paradigm of the molecular design of such materials involves the preorganization of binding sites of the host system (receptor) around complementary binding sites of the guest molecule (substrate).[2] Wulff and co-workers devised a novel approach to synthesizing substrate-selective polymers that consists of covalent linking of polymerizable groups around a template molecule and subsequent cross-linking polymerization of the resulting assembly.[3] The orientations of the binding sites of the template molecules sculpt the substrate-selective architecture of the templated polymers. Here we report a novel variation of this template polymerization technique to synthesize rigid macroporous polymers containing strategically distributed Cu(II)-iminodiacetate (Cu^{II}IDA) complexes. The resulting polymers exhibit selectivity for bisimidazole "protein analogues" that are not distinguishable by reverse-phase HPLC.

Various groups have synthesized imprinted polymers using both covalent[3] and noncovalent hydrogen bonding and electrostatic interactions[4] as the basis for recognition. Although noncovalent interactions provide polymers that exhibit faster rebinding kinetics, the recognition capabilities are limited by the weak nature of individual interactions. Due to their relative strength and selectivity, metal-ligand coordination is well-suited to molecular recognition of biological molecules, as exemplified by metal-affinity chromatographic purification of proteins.[5] We propose that very high affinity and selectivity can be achieved in polymer matrices containing metal ions strategically positioned to match the distribution of metal-coordinating groups on the surface of the molecule of interest.

Formation of the polymerizable template assembly was promoted by slow addition of 1 molar equiv of the methanolic solution

Scheme I

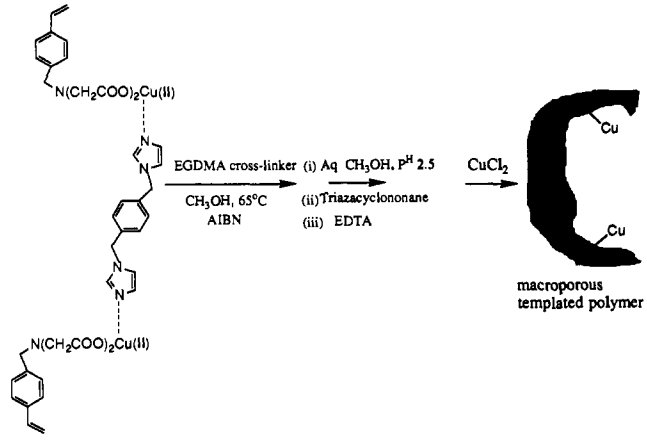
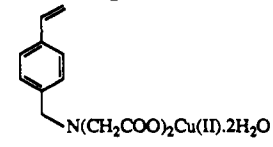


Table I. Polymerization Recipe and Workup of Templated Chelating Polymers[a]

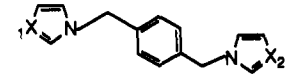
entry	polymer	Cu(II) in polymerizatn mixture, mmol/g	template type and concn in polymerizatn mixture, mmol/g	recovery of Cu(II), mmol/g	recovery of template, mmol/g
1	P-1	0.52		0.49	
2	P-2	0.52	(**2a**) 0.26	0.47	0.26
3	P-3	0.53	(**3a**) 0.27	0.49	0.26

[a] Polymerization reactions were carried out in the presence of EGDMA cross-linker having a molar ratio of **1** to EGDMA of 5:95.

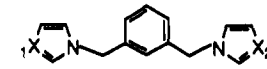
of the appropriate bisimidazole derivative (**2a** or **3a**) to 2 equiv of Cu^{II}IDA-derivatized vinyl monomer (**1**) in methanol. Deepening of the blue coloration of the resulting solution and shifting of the 778-nm band of the Cu^{II}IDA complex to 665 nm (a consequence of a ligand-to-metal charge-transfer band for copper-coordinated imidazole derivatives[6]) is indicative of complex formation. UV titration experiments suggest the stoichiometry of the Cu(II)-monomer:template complex is 2:1, with an association constant of $\sim$8800 M^{-1}. The template assemblies were copolymerized at 60 °C with ethylene glycol dimethacrylate (EGDMA) as cross-linker and methanol as porogenic agent using azobis(isobutyronitrile) (AIBN) as initiator (Scheme I).



1



2a: $X_1 = X_2 = N$; 1,4-diimidazol-1-ylxylene
b: $X_1 = X_2 = CH$; 1,4-dipyrrol-1-ylxylene
c: $X_1 = N$, $X_2 = CH$; 1-imidazol-1-yl-4-pyrrol-1-ylxylene



3a: $X_1 = X_2 = N$; 1,3-diimidazol-1-ylxylene
b: $X_1 = X_2 = CH$; 1,3-dipyrrol-1-ylxylene

After extraction with methanol for 24 h to remove any unpolymerized and soluble contaminants (<1%), the blue macroporous polymers were treated with acidified 50% aqueous methanol (pH 2.5) at 37 °C for 36 h to remove the bisimidazole templates. A two-step procedure involving treatment with methanolic tria-

* To whom correspondence should be addressed.

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Table II. Summary of Rebinding Studies of Templated Copper-Complexing Copolymers

entry	polymer	original template	rebinding substrate	substrate bound,[a,b] mmol/g of polymer	rel substrate selectivity in competitive binding[b,c]
1	P-1		2a	0.42	
2	P-1		3a	0.43	
3	P-1		2a + 3a		$\alpha_{3a/2a}$ = 1.02
4	P-2	2a	2a	0.33	
5	P-2	2a	3a	0.22	
6	P-2	2a	2b	0.016	
7	P-2	2a	2a + 3a		$\alpha_{2a/3a}$ = 1.17
8	P-2 (Cu free)	2a	2a + 3a		$\alpha_{2a/3a}$ = 1.04
9	P-3	3a	3a	0.24	
10	P-3	3a	2a	0.17	
11	P-3	3a	3b	0.014	
12	P-3	3a	2a + 3a		$\alpha_{3a/2a}$ = 1.15
13	P-3 (Cu free)	3a	2a + 3a		$\alpha_{3a/2a}$ = 1.04

[a] Saturation binding studies: >5-fold molar excess of substrate over theoretical binding sites. [b] Amounts bound determined from analysis of unbound substrates after equilibration, using 500-MHz ^{1}H NMR and an internal reference of known concentration (single substrate binding) or relative peak intensities (for competitive binding). [c] Competitive binding: equimolar mixtures of substrates used. α_{ij} is the ratio of i to j in the bound state.

zacyclononane (0.025 M) followed by aqueous EDTA (0.1 M, pH 7.0) removed more than 95% of the bound copper. The copper ions can be reloaded quantitatively by treating the polymers with aqueous $CuCl_2$. The polymerization process and subsequent workup are illustrated in Scheme I, and results are summarized in Table I.

Substrate recognition and selective binding abilities of the templated polymers were determined by both saturation rebinding and competitive rebinding experiments with substrates **2** and **3** (Table II). While the templated polymers exhibit selectivity for their templates over the close structural analogue (entries 7 and 12 in Table II), polymer P-1 prepared without template exhibits essentially no selectivity (entry 3). The separation factors of 1.15–1.17 for the templated polymers are significant in view of the fact that substrates **2a** and **3a** are indistinguishable by reverse-phase HPLC and ligand-exchange chromatography on Cu^{II}IDA. One can expect significantly higher selectivities for less similar substrates.

It is not clear whether orientation of the binding sites (multiple-site binding) or shape selectivity governs the binding selectivities of imprinted polymers.[7] To obtain insights into the origin of the observed substrate selectivity of these metal-coordinating templated polymers, rebinding experiments were performed on both copper-loaded and copper-free polymers using substrates **2a**, **2b**, **3a**, and **3b**. As can be seen from Table II, the inability of copper-free polymers to bind their templates (entries 8 and 13) and the low binding of substrates **2b** and **3b** having no imidazole ϵ-nitrogen (entries 6 and 11) rule out the possibility that simple shape selectivity is the primary source of binding selectivity. Furthermore, when templated polymer P-2 was used, the maximum capacities (Q_{max})[8] for substrates **2a**, **2c** (a pseudotemplate having a single imidazole residue), and *N*-benzylimidazole were found to be 0.33, 0.30, and 0.55 mmol/g of polymer, respectively. That nearly twice as many sites are available to *N*-benzylimidazole as to **2a** and that the capacities for **2a** and **2c** are similar are consistent with the view that two copper ions are closely spaced in the binding cavities. The order of apparent Langmuir binding constants (K_L)[8] for the substrates is **2a** (3800 M^{-1}) > *N*-benzylimidazole (2800 M^{-1}) > **2c** (1700 M^{-1}). The higher binding constant for **2a** compared to those for the substrates containing only one imidazole nitrogen may partly reflect interactions by the favorably disposed metal ions in the templated polymers toward the bifunctional template substrates, although one would expect a larger differential in the binding affinities for two-point versus one-point binding. Direct spectroscopic determination of the template binding configuration will be required to determine the extent to which two-point binding contributes to selectivity.

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Supplementary Material Available: Experimental details for the synthesis of bisimidazoles **2a** and **3a** (1 page). Ordering information is given on any current masthead page.

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Cyclization Reactions of Chromium Dienylcarbene Complexes. Entry to Ortho-Substituted Aromatic Alcohols via a Designed Photoreaction

Craig A. Merlic* and Daqiang Xu

Department of Chemistry and Biochemistry
University of California
Los Angeles, California 90024-1569

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The benzannulation reaction based on alkyne cycloaddition to chromium carbene complexes, reported by Dötz in 1975,[1] has become the most studied reaction[2] of Fisher carbene complexes and the most useful for synthesis of natural products.[3] It is uniquely suited for the synthesis of *p*-alkoxyphenols and, by oxidation thereof, 1,4-quinones. However, the large number of natural products, in particular antitumor agents, that possess *o*-alkoxyphenol or *o*-quinone[4] type structures argues for the development of chromium carbene based strategies that will provide access to substitution patterns other than para.

Consideration of a simplified mechanism[5,6] for the Dötz benzannulation reaction (Scheme I) suggests that an alternative pathway to ortho-substituted products is feasible. They key intermediate is the dienylcarbene complex I, resulting from metathesis of an alkyne, which inserts carbon monoxide to form a dienylketene complex II, which can then undergo an electrocyclization reaction. If this is a reasonable mechanistic pathway,[7] then *starting with a dienylcarbene complex, without added alkyne, should lead to ortho-substituted phenolic products* (Scheme II). Added support for this proposal comes from the recent work of

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