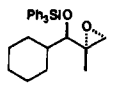
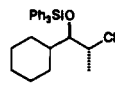
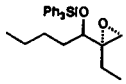
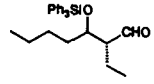
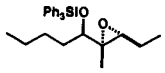
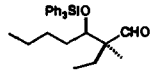
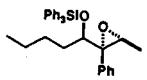
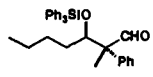
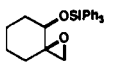
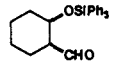
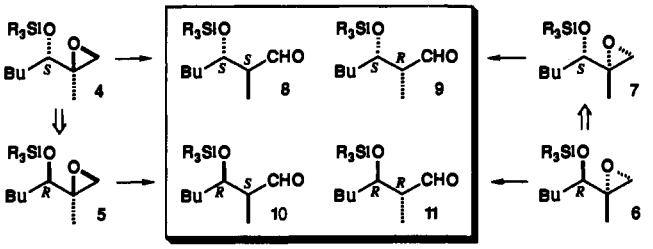
Table II. Stereoselective Rearrangement of Epoxy Silyl Ethers with MABR[a]

entry	substrate	conditions (°C, h)	major isomer of siloxy aldehyde	yield, %[b] (*erythro*/*threo*)[c]
1		-78, 1; -40, 1.5		92 (1:6)
2		-78, 1; -40, 2[d]		88 (1:100)
3		-78, 1; -40, 0.5		86 (1:6)
4		-78, 2; -40, 2[d]		82 (1:30)
5		-40, 2; -20, 0.5		67 (1:100)
6		-40, 2; -20, 2		47 (4:1)
7		-40, 2; -20, 2[d]		64 (200:1)
8		-78, 0.5		83 (0:1)
9		-40, 2; -20, 2[d]		85 (1:0)

[a] Unless otherwise stated, the rearrangement was carried out in CH_2Cl_2 with 2 equiv of MABR under the indicated conditions. [b] Isolated yield. [c] Determined by 200-MHz ^1H NMR or HPLC analysis. [d] Use of toluene as solvent.

$CHCl_3$)) on treatment with MABR gave threo β-siloxy aldehydes **8** (R = Ph; >98% ee, $[\alpha]^{22}_D$ +38.5° (*c* 1.00, $CHCl_3$)) almost exclusively (**8**:**9** (R = Ph) = 40:1). It should be noted that reaction of erythro epoxy silyl ether **4** (R = Ph) with conventional Lewis acids such as $TiCl_4$ and $BF_3{\cdot}OEt_2$ gave none of the desired β-siloxy aldehydes.[10]



Selected results of the rearrangement of erythro epoxy silyl ethers **4** with MABR to β-siloxy aldehydes **8** and **9** are summarized in Table I and show the following characteristic features. Apparently, the observed stereoselectivity reflects the marked electronic effect of silyl substituents rather than their steric effect (entries 1-5), and the more electron withdrawing triphenylsilyl group exhibited better selectivity than the more sterically hindered *tert*-butyldiphenylsilyl group (entry 5 vs 4).[11] The even more hindered triisopropylsilyl group did not significantly alter the selectivity (entry 1). The stereoselectivity of the phenylsilyl series (i.e., $PhMe_2Si$, Ph_2MeSi, and Ph_3Si groups) increases with increasing electronegativity of the silyl groups (entries 2, 3, and 5). Furthermore, rearrangement of a dimethylphenylsilyl system bearing an electron-withdrawing fluoro group at the para position exhibited higher selectivity [R_3 = (p-FC_6H_4)Me_2, 75% (**8**:**9** = 2:1)] relative to the unsubstituted system (entry 2). This rearrangement proceeded with anti migration of the hydride to the epoxide moiety. Use of nonpolar toluene showed higher selectivity than use of CH_2Cl_2 [R_3 = $PhMe_2$, 60% (**8**:**9** = 3.5:1) in toluene]. Notably, the stereoselectivity was markedly decreased with less bulky dimethylaluminum 4-bromo-2,6-di-*tert*-butylphenoxide or methylaluminum bis(4-bromo-2,6-diisopropylphenoxide). The similar electronic effect of silyl groups was observed in the rearrangement of optically active threo epoxy silyl ether **5** to erythro β-siloxy aldehyde **10** [R_3 = *t*-$BuMe_2$, 68% (**10**:**11** = 2.2:1); R_3 = $PhMe_2$, 42% (2.6:1), R = Ph, 81% (12:1)].[9]

Since enantiomeric erythro epoxy silyl ether **6** and its threo isomer **7** are readily accessible by the Sharpless asymmetric epoxidation using (-)-DIPT as a chiral auxiliary,[7,9] this method allows the practical asymmetric synthesis of four possible aldol isomers **8**-**11**. Other examples with triphenylsilyl substituents are illustrated in Table II. β-Siloxy aldehydes possessing an asymmetric quaternary α-carbon, hitherto not obtainable by ordinary asymmetric aldol reactions, can be readily synthesized with virtually complete stereoselectivity (entries 7 and 8).

(10) For example, $TiCl_4$ showed totally different behavior for the substrate **4** (R = Ph) resulting in formation of 2-methyl-2-[(triphenylsiloxy)methyl]-hexanal and 2-methyl-1-(triphenylsiloxy)-3-heptanone in 68% yield.

(11) For the steric and electronic nature of Si-O interactions, see: (a) Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgenson, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697. (b) Stern, A. J.; Swenton, J. S. *J. Org. Chem.* **1989**, *54*, 2953. See also: Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 6130.

Design and Characterization of a Ligand-Binding Metallopeptide

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The design of peptides that mimic the structural and/or functional features of naturally occurring proteins or that have novel properties is an area of much current interest.[1] The incorporation of metal binding sites into designed peptides presents an opportunity to use the structural, spectroscopic, and chemical properties of metal ions to advantage. Initial results with designed metallopeptides have been reported[2,3] although the ability of such peptides to bind or activate ligands has not been demonstrated. We report here a strategy to convert a peptide with a structural site in which all of the ligands are provided by the peptide to one that has an open coordination position for substrate binding and potential activation. Our approach involves truncation of a metal-binding peptide to remove one of the ligands with the hope that such a truncated peptide will still bind metal ions.

Our initial studies have used a prototypical zinc finger peptide, CP1, which has the sequence ProTyrLys*Cys*ProGlu*Cys*GlyLysSerPheSerGlnLysSerAspLeuValLys*His*GlnArgThr*His*ThrGly.[4] CP1 binds Co^{2+} with a dissociation constant of 50 nM[4] and also binds a variety of other metal ions.[5] An attempt to create a peptide with a Cys-His-His coordination site by truncation of the first five amino acids proved unsuccessful; treatment of this amino terminal truncated peptide with Co^{2+} yielded no spectral indications of tetrahedral metal coordination even when a 10-fold excess of Co^{2+} had been added. In contrast to these results, truncation of the last four amino acids produced a peptide, termed CP1-C4, that binds Co^{2+} in a tetrahedral site with high affinity. The absorption spectrum of the complex formed between this peptide and Co^{2+} is shown in Figure 1. This is similar to but distinct from spectra of Co^{2+} complexes of zinc finger peptides that have two cysteinate and two histidine coordination sites. The intensity of the d-d bands in the visible region ($\epsilon > 500$ M^{-1} cm^{-1}) strongly suggests tetrahedral coordination. Metal ion titration data[6] could be fit with a dissociation constant for the 1:1 CP1-

(1) DeGrado, W. F. *Adv. Protein Chem.* **1988**, *39*, 51.
(2) Handel, T.; DeGrado, W. F. *J. Am. Chem. Soc.* **1990**, *112*, 6710.
(3) Regan, L.; Clarke, N. D. *Biochemistry* **1990**, *29*, 10878.
(4) Krizek, B. A.; Amann, B. T.; Kilfoil, V. J.; Merkle, D. L.; Berg, J. M. *J. Am. Chem. Soc.*, in press.
(5) Krizek, B. A.; Berg, J. M., submitted for publication.

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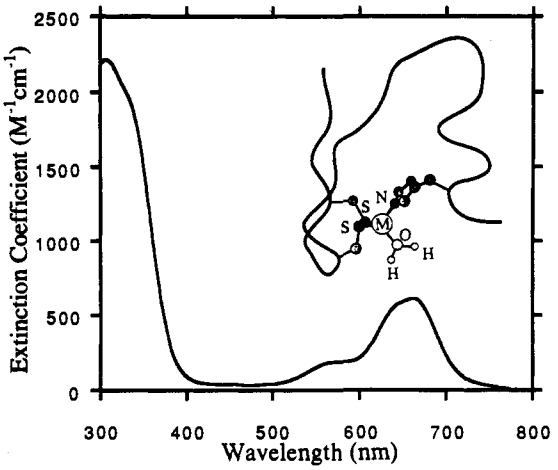

Figure 1. The absorption spectrum of the one-to-one complex between the truncated zinc finger peptide CP1-C4 and cobalt(II) in 50 mM HEPES, 50 mM NaCl buffer, pH 7.0. This spectrum is similar to that for complexes of intact zinc finger peptides although it is slightly broader and somewhat red-shifted due to the replacement of one histidine by a coordinated water. The schematic structure shown is supported by nuclear magnetic resonance studies of the parent CP1-Zn^{2+} complex.[4] This and all other experiments were performed under an atmosphere of 95% dinitrogen/5% dihydrogen.

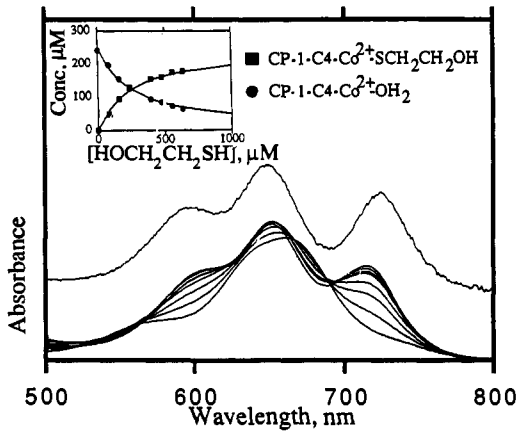

Figure 2. Titration of the cobalt(II) complex of CP1-C4 with β-mercaptoethanol. The absorption spectra upon addition of various amounts of β-mercaptoethanol are shown. The offset curves is from the cobalt(II) complex of the CP1 sequence variant in which the final histidine was replaced by cysteine.[5] This spectrum is very similar to the CP1-C4-Co^{2+} spectra in the presence of saturating β-mercaptoethanol. The inset shows the experimental data from spectral deconvolution and the fit using a β-mercaptoethanol dissociation constant of 2×10^{-4} M. These experiments were performed in 50 mM HEPES, 50 mM NaCl, pH 8.0 buffer.

C4-Co^{2+} complex in the range $5 \times 10^{-8} - 2 \times 10^{-7}$ M. These values are less than 1 order of magnitude greater than that for the untruncated CP1-Co^{2+} complex. The stability of this complex was foreshadowed by the discovery of a low-pH form of the CP1-Zn^{2+} complex that has the latter of the histidines protonated and dissociated from the metal.[5]

The existence of an available coordination site on CP1-C4-Co^{2+} has been demonstrated by the availability of this complex to bind externally provided ligands. Titration of a solution of the peptide-Co^{2+} complex with β-mercaptoethanol resulted in series of spectra with isosbestic points as shown in Figure 2. The final spectrum is very similar to that obtained for the Co^{2+} complex of a sequence variant of CP1 in which the final histidine has been replaced with cysteine[4] (also shown in Figure 2), providing strong support for the assignment of a three-thiolate, one-imidazole coordination sphere. A dissociation constant of 2×10^{-4} M at pH 8.0 was obtained from the titration data. Other ligands will also bind to CP1-C4-Co^{2+}. Titration with *N*-methylimidazole produced a complex that has a spectrum nearly identical with that for the parent CP1-Co^{2+} complex that forms with a dissociation constant of 8×10^{-4} M at pH 8.0. Chloride will also bind although it does so rather weakly. Titration of an initially chloride free sample of the peptide-Co^{2+} complex with NaCl resulted in development of a somewhat red-shifted spectrum. The spectral changes could be fit with a dissociation constant of 0.8 M for chloride. Proof that chloride binding is weak is important since the other studies had been performed in the presence of ca. 50 mM Cl^- as part of the buffer solutions used. Control experiments with intact CP1 revealed no spectral changes with these ligands.

Thus, the truncation strategy has allowed the generation of a novel metallopeptide that has a coordination site available for the binding of externally added ligands. This site appears to be occupied by water in the absence of added ligands on the basis of the absence of any pH dependence of the spectrum up to pH 9 and consistent with the expected high pK_a for water bound to such a thiolate-rich site.[7] The site is quite similar to the catalytic site in liver alcohol dehydrogenase,[8] which is also capable of binding exogenous ligands. Initial attempts to demonstrate catalysis of reactions such as acetaldehyde hydration and *p*-nitrophenylacetate hydrolysis of Co^{2+} or Zn^{2+} complexes of CP1-C4 have not been successful. This lack of reactivity may be due to the apparent high pK_a of the coordinated water. Clearly more sophisticated design of a coordinatively unsaturated metal-based catalytic site will be required. Studies with other reactions and attempts to modify the properties of the peptide-metal complexes are in progress.

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(6) Metal ion titrations revealed the presence of a two peptide to one cobalt(II) complex that formed under conditions of high peptide-to-metal ratios. Deconvolution techniques allowed determination of the equilibrium constants for the formation of this species as well as the one-to-one complex. These results will be described in more detail in a subsequent publication (Schmidt, M. H.; Krizek, B. A.; Berg, J. M., manuscript in preparation).

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Effect of Chain Length on the Energy Gap in Radical Ions of Oligomeric *p*-Phenylene[1]

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A dramatic increase in conductivity in poly(*p*-phenylene) (PPP), polythiophene, polypyrrole and other polyaromatics, upon oxidation or reduction (doping), is associated with the formation of charged defects (radical ions, diions)[2,3] in the polymer matrix. Theoretical models[4] predict the formation of radical ions (polarons) at low

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