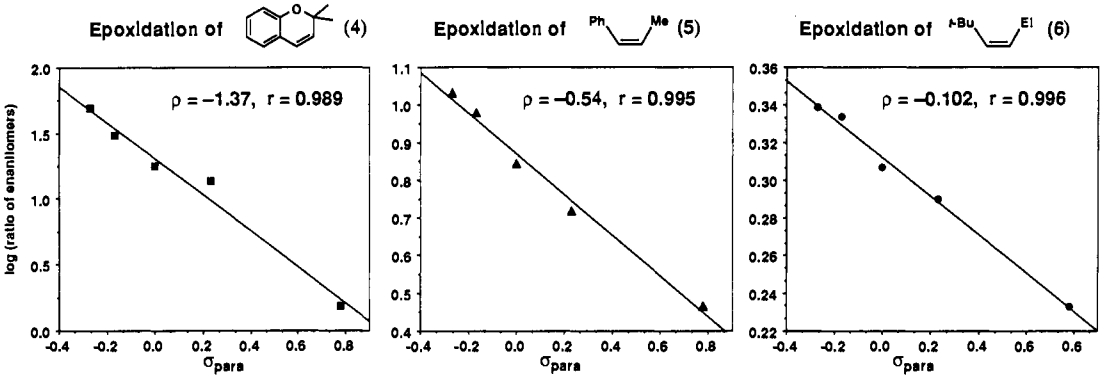

Figure 1. Hammett plots depicting enantiomeric composition of epoxides generated by oxidation of the indicated alkenes by catalysts **1a–e**. Enantiomeric excess ranges: **4**, 22–96%; **5**, 49–83%; **6**, 26–37%.

generally afford slightly higher selectivity (66% ee for **2e**, 98% ee for **2a**, $\Delta\Delta G^{\ddagger}$ = 1.8 kcal/mol).

These sizeable electronic effects may be attributed to several factors. The substituent X may induce significant conformational changes in the reactive Mn(V)–oxo intermediates.[8] This possibility is difficult to assess in detail without structural data on these intermediates, but given the relative lack of flexibility of the salen ligand system such conformational effects would not be predicted to play a very important role. The substituents probably also provoke changes in Mn–oxo bond length in the active species, resulting in different substrate/ligand nonbonded interactions in the ee-determining transition structures. However, such effects on metal–oxo bond distance are usually very small,[9] and the observed effects on ee run contrary to what one would predict from this hypothesis.[10]

An alternate explanation, which we consider most plausible, is that effects on enantioselectivity result from changes imparted by the substituents on the reactivity of the oxo intermediates. Electron-withdrawing groups on the catalysts increase the rate of epoxidation (e.g., k_{rel} for **1e**/**1a** = 4 in the epoxidation of **5**), and preliminary kinetic studies indicate that these rate differences arise from the epoxidation step.[11] A milder oxidant is expected to transfer oxygen to alkene via a more product-like transition state, resulting in more specific nonbonded interactions. With oxo transfer as the irreversible ee-determining step in a purely bimolecular process (i.e., no substrate precoordination), more reactive oxidants should proceed via a more reactant-like ee-determining transition state, with greater separation between substrate and catalyst and concomitantly poorer steric differentiation of diastereomeric transition structures. This argument should hold whether the ee-determining event is the first step of a stepwise process or if it is a concerted oxygen-atom-transfer from metal to alkene.[12]

The manipulation of electronic properties of remote substituents provides a new handle on the optimization of epoxidation catalysts through ligand modification. If changes in enantioselectivity are interpreted according to a simple Hammond postulate argument, this also raises an important general consideration for catalyst design. Regulation of electronic effects should be important especially for asymmetric transformations where selectivity relies purely on nonbonded interactions. Such bimolecular reactions will benefit from late (product-like) transition states in order to maximize stereochemical communication between the chiral catalyst and the substrate.

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(11) A complete kinetic study of the catalytic cycle will be reported in a forthcoming full paper.

(12) Indeed, the mechanisms of epoxidation may be different for aryl- and alkyl-substituted olefins: Fu, H.; Look, G. C.; Wong, C.-H.; Zhang, W.; Jacobsen, E. N. Submitted for publication.

Ligand-Selection Rules in the Classical Zinc Finger Motif

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The Zn finger motif,[1] a class of peptide metal-binding sites with characteristic structure,[2-5] consists of appropriately spaced cysteine and histidine residues ($CX_{2,4}CX_3FX_5LX_2HX_{3-5}H$[6]) involved in tetrahedral coordination of Zn^{2+}.[7] Analogue studies indicate that thiol and imidazole participation in Zn^{2+} binding are specific requirements for proper folding;[8] domain stability is further regulated by conserved "framework" residues in the hydrophobic core.[9] An interesting problem is posed by "ambiguous" Zn finger sequences that contain multiple possible ligands. Are there rules that predict in such cases which cysteine and histidine residues will be selected as ligands? May ligand selection be presumed by analogy to related but "unambiguous" sequences? These questions are of general interest in relation to deciphering the informational content of protein sequences.[10] Here we consider a particularly striking example of an ambiguous Zn finger sequence and define its coordination scheme by peptide mutagenesis. Interestingly, ligand selection in this case is *not as expected on the basis of immediate sequence homologies* but instead appears

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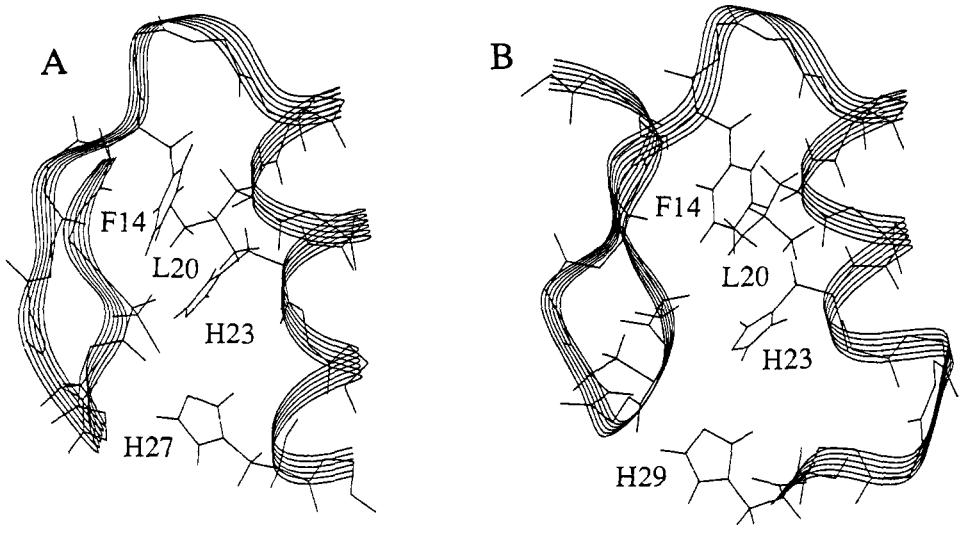

Figure 1. 2D NMR structures of (A) an HX_3H Zn finger (Xfin-31[3]) with N-terminal β-hairpin and C-terminal α-helix with 3_{10} extension and (B) an HX_5H Zn finger (EBP-1[5]), which contains a nonstandard loop between histidines. Selected internal side chains are shown; for clarity, the numbering scheme is as defined in the text and differs from that used in the original studies.[3,5]

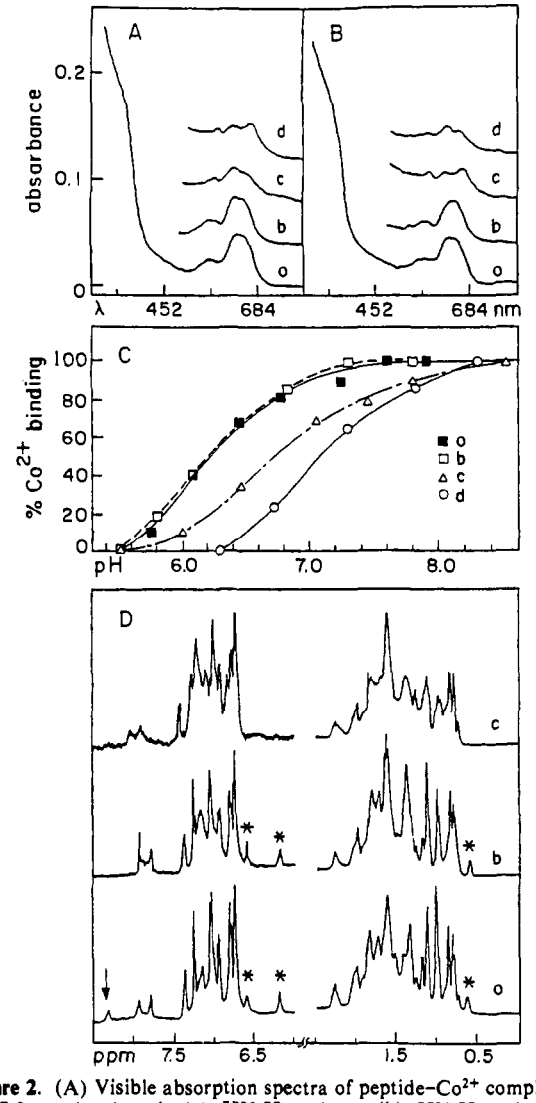

Figure 2. (A) Visible absorption spectra of peptide-Co^{2+} complexes at pH 7.8: native domain (a), HX_3H analogue (b), HX_5H analogue (c), and HXH analogue (d). (B) Corresponding data at pH 7.0. (C) pH dependence of d–d bands: native domain (a), HX_3H analogue (b), HX_5H analogue (c), and HXH analogue (d). (D) 500 MHz ^1H NMR spectra: native domain (a), HX_3H analogue (b), and HX_5H analogue (c) at 25 °C in 50 mM deuterated Tris-DCl (pD 6.5). Asterisks indicate upfield-shifted resonances, which are similar in spectra a and b; arrow indicates H_ϵ resonance of H29 in native spectrum.

to be determined by optimal formation of peptide hydrogen bonds in the metal-binding site.

The majority of Zn finger sequences contain the C-terminal sequence pattern HX_3H,[1] which folds as an α-helix with 3_{10} extension.[3] Variant HX_4H and HX_5H domains are also observed.[11-13] In this study we focus on a family of HX_5H sites[13] that recognize specific DNA control sequences in vertebrate genes.[14] The structure of a representative HX_5H domain has been determined[5] and exhibits a distinctive looplike structure—rather than classical α or 3_{10} helix—between histidines (Figure 1A,B); the structure is otherwise similar to that of a standard Zn finger.[3] In the course of analyzing sequence patterns in this gene family, we noticed that one putative HX_5H site (R_1ERPYPCVTC_{10}-GFSFKTKSNL$_{20}$YKH_{23}KKSH_{27}AH_{29}TIK$_{32}$; potential ligands in boldface) also conforms to the HX_3H consensus: the sequence is ambiguous.

Because resolution of this ambiguity may provide general insights into the design of such metal-binding sites, this peptide and three analogues have been synthesized.[15] Each analogue contains

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single H → K substitutions to give unambiguous HX_3H (H29 → K), HX_5H (H27 → K), or HXH (H23 → K) metal-binding sites (the latter does not correspond to a pattern observed in nature). The metal-binding properties of these peptides were investigated by visible absorption (Co^{2+} complexes) and ^1H NMR (Zn^{2+} complexes) spectroscopy as follows. (i) The tetrahedral Co^{2+} ligand fields of the native and HX_3H peptides are identical, as indicated by d–d and thiolate charge-transfer transitions in their visible absorption spectra; these transitions differ from those of the HX_5H and HXH peptides (Figure 2A,B). (ii) Analysis of the thermodynamic stabilities of the peptide/Co^{2+} complexes by optical pH titration (Figure 2C) demonstrates that the native and HX_3H analogue are equally stable (pH midpoint approximately 6.2); the HX_5H analogue is significantly less stable (pH midpoint 6.8). The nonnative HXH analogue is least stable (pH midpoint 7.1) and is not to be considered further. (iii) The ^1H NMR spectrum of the native domain is essentially identical to that of the HX_3H analogue, whereas marked differences are observed in the ^1H NMR spectrum of the HX_5H analogue (Figure 2D). These results demonstrate that EBP-1 adopts an HX_3H structure rather than the HX_5H structure expected on the basis of sequence homologies.[13]

The Zn finger motif[1] provides a model of a sequence "template" that encodes a characteristic structure.[2-5] To define rules that relate sequence to structure, we and others have undertaken comparative studies of variant domains.[8,9] In this communication we have focused on alternative ligand spacings HX_3H and HX_5H, which (upon binding Zn^{2+}) encode a helical or looplike structure, respectively (Figure 1). The "ambiguous" metal-binding site (HX_3HXH) in a HX_5H gene family[13] is shown to follow the general Zn finger consensus (HX_3H) rather than that of homologous HX_5H domains. Ligand selection in this case may be rationalized by the presence of three peptide hydrogen bonds in a presumed HX_3H-associated 3_{10} helix that are absent or attenuated in the HX_5H-associated loop, as inferred from detailed comparison of representative NMR structures (Figure 1[16]). Such a mechanism would reflect the general thermodynamic coupling between metal binding and peptide folding.

Acknowledgment. We thank P. E. Wright for the coordinates of ref 3 and G. M. Glore and A. M. Gronenborn for the coordinates of ref 5. This work was supported by grants to M.A.W. from the NIH, the American Cancer Society, and Pfizer Scholars Program. M.A.M. is an NSF Predoctoral Fellow.

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Efficient Low-Temperature Thermal Functionalization of Alkanes. Transfer-Dehydrogenation Catalyzed by $Rh(PMe_3)_2Cl(CO)$ in Solution under a High Pressure Dihydrogen Atmosphere

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The ability of soluble, low valent transition metal complexes to activate alkane carbon–hydrogen bonds has attracted intense interest for the past decade.[1,2] While numerous systems have been developed that undergo stoichiometric reactions with C–H bonds, progress toward the goal of catalytic alkane functionalization has been much more limited.[2] Dehydrogenation systems involving sacrificial hydrogen acceptors (transfer-dehydrogenation) represent one of the few reported classes of homogeneous alkane functionalization catalysts; however, they have hitherto displayed limited efficiency (under 70 turnovers) and have required severe reaction conditions (e.g., several days at 150 °C) to yield more than ca. 10 turnovers.[3-5]

Recently it was reported that $RhL_2Cl(CO)$ (**1**; L = PMe_3) photochemically catalyzes alkane dehydrogenation with unprecedented efficiency.[6-8] Ford has shown that the major photoreaction of **1** is loss of CO and that the resulting fragment, RhL_2Cl, inserts into alkane C–H bonds.[9] Our photokinetic investigation of this system revealed that CO loss is the *only* photochemical step driving this uphill reaction; subsequent steps are thermal (nonphotochemical) and may be expressed as eqs 2a and 2b (each equation represents a multistep process).[7] The enthalpy of eq

$$RhL_2Cl(CO) \xrightarrow{h\nu} RhL_2Cl + CO \qquad (1)$$

$$RhL_2Cl + \text{alkane} = RhL_2ClH_2 + \text{alkene} \qquad (2a)$$

$$RhL_2ClH_2 + CO = RhL_2Cl(CO) + H_2 \qquad (2b)$$

2 is the difference between the enthalpy of alkane dehydrogenation and that of Rh–CO bond dissociation. Given that disruption enthalpies of bonds between second-row transition metals and CO are less than 40 kcal/mol,[10] it might be expected that eq 2 is only slightly exothermic and therefore significantly reversible.[17] This

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