residues (V36, V39, V40) are located in a β-sheet region of the aggregate, whereas the terminal residues, L34 and I41 (and A42) and the central residues, G37 and G38, are probably not part of an idealized β-sheet.

An analogue of β34-42 in which Gly38 was replaced by Pro (H_2N-LMVGPVVIA-CO_2H) was synthesized with the intention of disrupting the amyloid-forming structure (ϕ38 is restricted to $-60° \pm 20°$).[16] This peptide formed fibrils[17] but was more soluble than β34-42. A film formed from LMVGPVVIA contained β-sheet (1638 cm^{-1}) and β-turn or random coil structure (ca. 1665 cm^{-1}, see Figure 1). Labeling at V40 led to a significant shift in the ^{12}C amide I band (1638 to 1648 cm^{-1}), whereas labeling of the G37 amide did not result in a similar shift (see Figure 1), suggesting that the V40 amide carbonyl is involved in the β-sheet structure and G37 is not.

These studies demonstrate that FTIR can be used to locate β-sheet (strongly coupled) structure in fibrillar proteins. Isotopic substitution within a β-sheet region reduces TDC, leading to a shift of the ^{12}C amide I absorption band to higher frequency. This shift is diagnostic for β-sheet structure; other structures do not produce this effect. The differences in the position of the ^{13}C amide I bands of the labeled β34-42 analogues are due to deviations from idealized β-sheet structure and to intermolecular ^{13}C-^{13}C dipole coupling. The latter effect could be exploited in order to elucidate the intermolecular interactions which drive aggregation.

Acknowledgment. We thank Dr. Lee Walters for stimulating our interest in FTIR and isotope labeling. We are grateful to Dr. Isao Noda, Dr. Tony Dowrey, Dr. Curt Marcott, Prof. Bob Field, Prof. Bob Silbey, Dr. Todd Miller, and Prof. Samuel Krimm for their insight and suggestions concerning this manuscript. This work was supported by Alzheimer's Disease Research (a program of the American Health Assistance Foundation, Rockville, MD), the Whitaker Health Sciences Fund, the National Institutes of Health (R01-AG08470-02), the National Science Foundation (Presidential Young Investigator Award), Merck & Co. (Faculty Development Grant), and the Camille and Henry Dreyfus Foundation (New Faculty Award).

Supplementary Material Available: The IR spectra discussed in this communication (6 pages). Ordering information is given on any current masthead page.

Electronic Tuning of Asymmetric Catalysts

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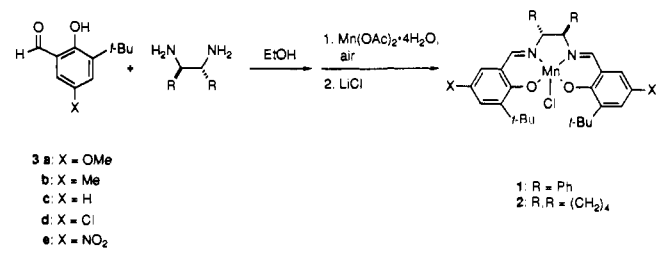
Received May 22, 1991

Although stereoelectronic control of π-facial diastereoselectivity has been recognized and evaluated in model systems,[1] this concept has not been successfully applied to the design of synthetically useful asymmetric catalysts. Indeed, the stereoselectivity of known

Scheme I



chiral reagents and catalysts is generally interpreted solely in terms of steric considerations. To our knowledge, the effect of varying the electronic properties of chiral catalysts has never been systematically assessed in practical systems,[2] although this is largely because known effective chiral catalysts tend not to be synthetically or structurally well-suited to electronic tuning. In contrast, chiral Mn^{III}salen epoxidation catalysts recently developed in our labs[3] consist of a rigid and kinetically nonlabile ligand template wherein steric and electronic properties of the metal center may be tuned in a synthetically straightforward manner. We have taken advantage of this system to study substituent effects on alkene epoxidation, and we report examples of remarkable electronic control of enantioselectivity. This result may carry general implications for the design of new catalysts for reactions of unfunctionalized substrates.

Two series of catalysts were prepared from 1,2-diaminocyclohexane (catalysts **1a-e**) and from 1,2-diamino-1,2-diphenylethane (catalysts **2a-e**), respectively. Condensation of either of these diamines with the appropriate 5-substituted *tert*-butyl salicylaldehyde derivatives **3a-e** followed by insertion of the Mn(III) center as described previously[3b] led to the requisite catalysts in excellent yield (Scheme I).[4]

We selected three model substrates for this study: 2,2-dimethylchromene (**4**), a member of a synthetically important class of olefins that is epoxidized with particularly high enantioselectivities with certain Mn^{III}salen catalysts;[3c,5] *cis*-β-methylstyrene (**5**), an aryl-substituted alkene which has served as a model substrate for a variety of enzymatic and nonenzymatic epoxidation processes;[6] and *cis*-2,2-dimethyl-3-hexene (**6**), an example of an aliphatically substituted alkene. As noted previously, cis disubstituted alkenes are generally the best substrates for chiral salen and porphyrin epoxidation catalysts.[2a,3]

Each catalyst/substrate combination was examined under our previously described epoxidation conditions,[7] and the results with catalyst **1** are presented in Hammett plots in Figure 1. In all cases the same trend was observed, with electron-donating groups on the catalyst leading to higher enantioselectivities in epoxidation. The effect is small with **6**, which is generally epoxidized with only marginal selectivity (26-37% enantiomeric excess), but it is particularly striking with **4**, where enantioselectivities (ee's) range from 22% with **1e** to 96% for **1a**. This corresponds to a remarkable selectivity difference $\Delta\Delta G^{\ddagger}$ of 2.0 kcal/mol. Catalysts **2a-e**

(1) (a) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447. (b) Halterman, R. L.; McEvoy, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 6690. (c) Chung, W.-S.; Turro, N. J.; Srivastava, S.; Li, H.; le Noble, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 7882.

(2) Electronic properties of substrate that have been shown in certain cases affect enantioselectivity with a given catalyst system. See, for example: (a) Groves, J. T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628. (b) Naruta, Y.; Tani, F.; Maruyama, K. *Chem. Lett.* **1989**, 1269.

(3) (a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (b) Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2296. (c) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* In press. See, also: Irie, R.; Noda, K.; Ito, Y.; Katsuki, T. *Tetrahedron Lett.* **1991**, *32*, 1055.

(4) All catalysts exhibited satisfactory analytical data (C, H, N, Cl, Mn).

(5) Lee, N. H.; Muci, A. R.; Jacobsen, E. N. *Tetrahedron Lett.* In press.

(6) (a) Ortiz de Montellano, P. R.; Fruetel, J. A.; Collins, J. R.; Camper, D. L.; Loew, G. H. *J. Am. Chem. Soc.* **1991**, *113*, 3195. (b) O'Malley, S.; Kodadek, T. *J. Am. Chem. Soc.* **1989**, *111*, 9116. See, also, refs 2a and 3b.

(7) Epoxidations were carried out at room temperature with aqueous commercial NaOCl buffered to pH 11.3 as the stoichiometric oxidant.[3b] All ee's were determined by capillary GC chromatography of crude reaction mixtures with a commercially available Cyclodex-B column (J & W Scientific, Folsom, CA 95630, 30 m × 0.25 mm i.d., 0.25 μm film).

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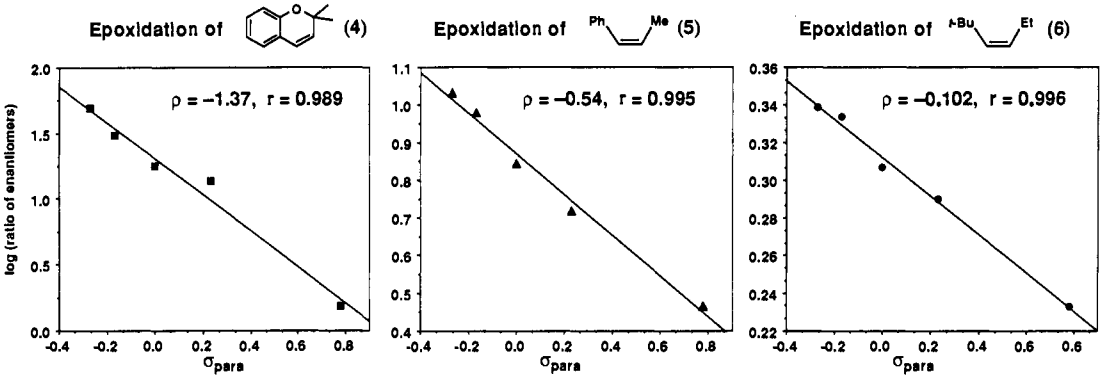

Figure 1. Hammett plots depicting enantiomeric composition of epoxides generated by oxidation of the indicated alkenes by catalysts **1a-e**. Enantiomeric excess ranges: **4**, 22-96%; **5**, 49-83%; **6**, 26-37%.

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.

Acknowledgment. This work was supported in part by the National Institutes of Health (GM-43214-01A1), a National Science Foundation PYI Award (CHE-9057740) to E.N.J., and by generous contributions from ICI Pharmaceuticals, Merck, and Rohm & Haas.

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(9) Nugent, W. A.; Mayer, J. M. *Metal-Ligand Multiple Bonds*; Wiley: New York, 1988; pp 148-152.

(10) The more electron-deficient Mn center in the NO_2-substituted case might be expected to result in a shorter Mn-oxo bond length, leading to an increase, rather than a reduction in selectivity in oxo transfer to alkenes.

(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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Received May 15, 1991

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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