On the other hand, when **5b** was treated with hydrochloric acid, the butyrolactone derivative **6b** was obtained with 84% yield and 53% de. When a solution of **5b** was treated with 1% TFAA as described for **5b** except using toluene, **6b** having a maximum de of 71% was obtained quantitatively. In dichloromethane, **6b** with 54% de was formed quantitatively. However, this reaction did not proceed in EtOH or THF. The de of **6b** was determined with HPLC and ^{1}H NMR (200 MHz) monitoring of the methine protons (δ 3.90–4.09 for the *R* isomer and δ 4.27–4.43 for the *S* isomer). Alcohol **10b** ($[\alpha]^{25}_D$ −24.0° (*c* 0.58, EtOH)) was derived from **6b** with 47% de according to Scheme II. The ee of **10b** was determined to be 47% according to Jones,[11] which agreed well with the de of **6b**. Consequently, the *R* configuration of the lactone moiety of **6b** was established based on the *S* configuration of (−)-**10b**.[2e]

Contrary to our hypothetical transition state predicting attack upon the pro-*S* carbonyl group of **5b** as **5a**, the pro-*R* carbonyl group of **5b** was preferentially attacked. The unexpected direction of the asymmetric bias in **5b** could be rationalized by distortion of the ring resulting in a highly strained bicyclic transition state. Consideration using a CPK model shows that the pro-*R* amide group is oriented out of the plane of the distorted naphthyl ring in **5b**. In such a conformation, stereochemical requirements are fulfilled by an intramolecular approach of the hydroxyl group to the pro-*R* carbonyl group.

Acknowledgment. We acknowledge a Grant-in-Aid for Scientific Research on Priority Areas, Advanced Molecular Conversion.

Supplementary Material Available: Experimental details about preparation of **5a,b** lactonization and stereochemical correlation of **6a,b** and spectral data of all the compounds herein (9 pages). Ordering information is given on any current masthead page.

(11) The alcohol **10b** was treated with *tert*-butyldimethylsilyl chloride and triethylamine to give the protected lactone (95%), which was analyzed according to the following report. See: Jakovac, I. J.; Jones, J. B. *J. Org. Chem.* **1979**, *44*, 2165.

Extension of Chromatographically Derived Molecular Recognition Concepts to First-Order Asymmetric Transformations

William H. Pirkle* and Daniel S. Reno

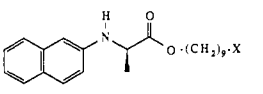
School of Chemical Sciences, University of Illinois Urbana, Illinois 61801

Received May 4, 1987

The equilibration of diastereomeric species in solution has been defined as a first-order asymmetric transformation.[1,2] Processes under kinetic rather than thermodynamic control are excluded from this definition and are termed stereodifferentiating reactions.[2] Interconversion and equilibration of *covalent* diastereomers, *intramolecular* asymmetric induction, is relatively common, mutarotation of glucose being a prime example of such a process. Interconversion and equilibration of noncovalent diastereomeric species, a somewhat less common process, is exemplified by the "Pfiffer effect", an alteration of the 1:1 equilibrium ratio of interconverting enantiomers of certain metal ion complexes by the presence of chiral solvents or other chiral species.[3] Typically, first-order asymmetric transformations of enantiomers do not proceed with extreme stereochemical bias nor are they amenable to mechanistic rationalization. In this communication, we describe a first-order asymmetric transformation which is both effective and readily explained by a chiral recognition model recently advanced to account for the chromatographic separation of enantiomers on a chiral stationary phase.[4] This mechanistic picture should enable one to predictably extend such asymmetric transformations to other systems.

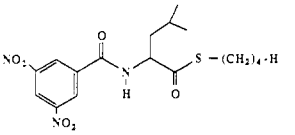
By altering the usual 1:1 equilibrium ratio of interconverting enantiomers, one is, in essence, performing a deracemization.[5] For a thermodynamically controlled deracemization to occur, several conditions must be fulfilled: (1) to eliminate the energetic degeneracy of the enantiomers, it is necessary, but not necessarily sufficient, that the transformation solvent be either chiral nonracemic or contain a species which is chiral nonracemic; (2) the chiral nonracemic species must be stereochemically stable under the transformation conditions; (3) the species to be deracemized must be stereochemically labile.

Immobilization of **1** onto silica affords chiral stationary phase **1a**. This phase exhibits highly enantioselective behavior toward the enantiomers of esters and amides of *N*-(3,5-dinitrobenzoyl) amino acids.[4a] Similar behavior occurs with the corresponding



1 X= CH═CH$_2$

1a X= CH$_2$– CH$_2$– Si≡



2

thioesters, and since "the acidifying effect of a thioalkyl substituent is substantial",[7] it was anticipated that the differential complexation of **1** with the enantiomers of a thioester such as **2** coupled with base-promoted interconversion of the thioester enantiomers would afford first-order asymmetric transformation of the racemic thioester. Indeed, deracemization of racemic **2** occurs in the presence of triethylamine and (*R*)-**1**.

A 3:1 cyclohexane/methylene chloride solution 0.045 M in **2**, 0.18 M in triethylamine, and 0.20 M in (*R*)-**1** was periodically examined by HPLC using a column packed with chiral stationary phase **1a**. This column effectively separates all components of the mixture. After a period of 28 days, equilibrium was achieved with a 78% ee of (*R*)-**2**. The equilibrium position of deracemization is dependent upon the conditions employed. In general, more polar solvents reduce enantiomeric enrichment while lower temperatures increase the extent of enrichment. An increase in the concentration of the complexing agent, **1**, increases the enantiomeric enrichment, albeit, with diminishing return, evidence of a saturation effect. The concentration of triethylamine, necessary as a basic catalyst to promote interconversion of the enantiomers, affects the rate of deracemization but has little effect upon the ultimate extent of enrichment over the range 0.05–0.30 M.

Differential complexation of **1** with the enantiomers of the thioester supplies the energetic driving force for the deracemization in solution. The sense and degree of differential complexation are rationalized simply by application of the previously reported chromatographically derived chiral recognition mechanism.[4] In this mechanism, three simultaneous attractive interactions are proposed to occur during the complexation of (*R*)-**1** with the (*R*) thioester. These are (1) a hydrogen bond between the amino

(1) Turner, E.; Harris, M. *Q. Rev., Chem. Soc.* **1947**, 299.

(2) Izumi, Y.; Tai, A. *Stereodifferentiating Reactions*; Academic: New York, 1977; pp 178–179.

(3) Mason, S. F. *Molecular Optical Activity and the Chiral Discriminations*; Cambridge University Press: Cambridge, 1982; pp 208–211.

(4) (a) Pirkle, W.; Pochapsky, T.; Mahler, G.; Corey, D.; Reno, D.; Alessi, D. *J. Org. Chem.* **1986**, *51*, 4991. (b) Pirkle, W.; Pochapsky, T. *J. Am. Chem. Soc.* **1986**, *108*, 5627. (c) Pirkle, W.; Pochapsky, T. *J. Am. Chem. Soc.*, in press.

(5) This term has been applied by Duhamel and Duhamel[6] to the asymmetric protonation of achiral enolates, a kinetically controlled process and hence not a first-order asymmetric transformation. We view the term "deracemization" as being sufficiently broad to cover any process in which a racemate is made nonracemic by increasing the quantity of one enantiomer at the expense of the other. The process may be under either thermodynamic or kinetic control and does not preclude a phase change.

(6) Duhamel, L.; Duhamel, P.; Launay, J.; Plaquevent, J. *Bull. Soc. Chim. Fr.* **1984**, 11–421.

(7) Douglas, K. *Acc. Chem. Res.* **1986**, *19*, 186.

0002-7863/87/1509-7189$01.50/0

proton of **1** and the C-terminal carbonyl oxygen of **2**, (2) a hydrogen bond between the dinitrobenzoyl amide proton of **2** and the carbonyl oxygen of **1**, and (3) a π-donor–acceptor interaction between the naphthyl system of **1** and the dinitrobenzoyl system of **2**. The complex derived from the (*S*) thioester cannot achieve all of these bonding interactions simultaneously and is consequently of lesser stability. This model is supported by a recently reported study of intermolecular nuclear Overhauser effects in a closely related system.[4b,c]

The effects of solvent and temperature are easily rationalized by the complexation model. Polar solvents decrease the extent of complexation by providing competitive solvation of the uncomplexed species. Not surprisingly, the extent of complexation increases as the temperature is lowered.

In addition to differential complexation, interconversion of the enantiomers is requisite for deracemization. Both diazabicyclooctane (Dabco) and triethylamine are sufficiently basic to promote the interconversion of thioester enantiomers; pyridine is not. The amidine bases 1,5-diazabicyclo[4.3.0]non-5-ene and 1,8-diazabicyclo[5.4.0]undec-7-ene, still stronger bases, induce decomposition of the dinitrobenzoyl portion of the thioester, thus precluding their use for deracemization of the ester and amide analogues of **2**. These fail to undergo deracemization with triethylamine owing to insufficient acidity of their α-hydrogens.

In summary, we have demonstrated a highly selective deracemization process in which the mechanism of differentiation is similar to that which occurs in analogous chiral HPLC processes. Further applications of chromatographic data to the development of first-order asymmetric transformation processes are in progress.

Acknowledgment. This work was supported by grants from the National Science Foundation and from Eli Lilly and Co.

Models for Iron–Oxo Proteins: A Mixed-Valence Iron(II)–Iron(III) Complex

A. S. Borovik, B. P. Murch, and L. Que, Jr.*

Department of Chemistry
University of Minnesota, Minneapolis, Minnesota 55455

V. Papaefthymiou and E. Münck*

Gray Freshwater Biological Institute
University of Minnesota, Navarre, Minnesota 55392

Received June 1, 1987

Mixed-valence iron clusters in the active sites of metal–oxo proteins are characterized by EPR signals with $g_{av} \sim 1.7$–1.8 which arise from the antiferromagnetic coupling of high-spin Fe(II) and Fe(III) ions.[1-4] Such sites have been found in the semimet forms of hemerythrin[1] and the reduced forms of the purple acid phosphatases[2] and may also be present in methane monooxygenase[3] and the early stages of ferritin core formation.[4] Efforts to model such sites by one-electron reduction of analogues for methemerythrin which have (μ-oxo)bis(μ-carboxylato)diiron(III) core structures have been unsuccessful because of the instability of the Fe(II)–Fe(III) core.[5] A strategy for circumventing the instability problem is the use of a binucleating ligand to hold the two metal centers together. One such Fe(II)–Fe(III) complex has been characterized by elemental analyses, near-IR spectroscopy, and magnetic susceptibility measurements from 80 to 300 K.[6] We have also adopted the binucleating ligand strategy to model the mixed-valence forms of iron–oxo proteins and report herein the properties of the Fe(II)–Fe(III) complex of *N,N'*-(2-hydroxy-5-methyl-1,3-xylylene)bis[*N*-(carboxymethyl)glycine] (HXTA).[7]

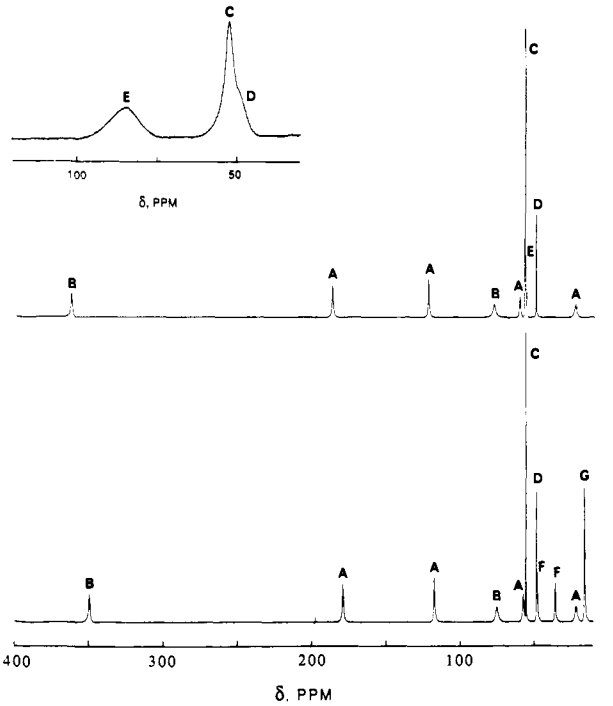


Figure 1. NMR spectra of $[Fe^{II}Fe^{III}(HXTA)(OAc)_2]^{2-}$ (top), $[Fe^{II}Fe^{III}(HXTA)(OPr)_2]^{2-}$ (bottom), and $[Fe^{III}Fe^{III}(HXTA)(OAc)_2]^{-}$ (insert) in CD_3OD with 0.050 M NaO_2CR/HO_2CR. Assignments (integration): (A) NCH_2COO^- (2); (B) $ArCH_2N$ (2); (C) *p*-$ArCH_3$ (3); (D) *m*-ArH (2); (E) $^-OAcCH_3$ (6); (F) $^-OPrCH_2$ (2); (G) $^-OPrCH_3$ (6).

The diferric complex $[Me_4N][Fe_2(HXTA)(OAc)_2]$ (**1**) has been crystallographically characterized to have a (μ-phenoxo)bis(μ-acetato)diiron(III) core structure.[8] Cyclic voltammetry of **1** in DMF shows a reversible wave centered at −286 mV vs SCE, which corresponds to the Fe(III)Fe(III)/Fe(II)Fe(III) couple.[9] Thus the treatment of a methanolic solution of **1** in the presence of 50 mM NaOAc/50 mM HOAc[8] with β-mercaptoethanol and excess Me_4NCl under nitrogen results in a one-electron reduction of **1** and yields a dark crystalline complex, $[Na][Me_4N][Fe_2(HXTA)(OAc)_2]\cdot 3H_2O$ (**2**).[10]

The electronic absorption spectrum of **2** exhibits a broad band at 470 nm (ϵ 800 M^{-1} cm^{-1}) which corresponds to phenolate-to-Fe(III) charge-transfer transitions. Two additional features are observed at 840 nm (ϵ 190 M^{-1} cm^{-1}) and 1275 nm (ϵ 200 M^{-1} cm^{-1}), which have extinction coefficients that are significantly higher than those normally expected for ligand field transitions.[11] We assign these bands as predominantly intervalence charge-transfer transitions between the two iron centers. These results suggest that **2** is a type II mixed-valence complex in the Robin–Day classification.[12]

As illustrated in Figure 1, the NMR spectra of **2** and its propionate derivative (**3**) exhibit sharp well-resolved signals which span 400 ppm in chemical shift. The significant decrease in the

(1) Wilkins, R. G.; Harrington, P. C. *Adv. Inorg. Biochem.* **1983**, *5*, 51–85.
(2) Antanaitis, B. C.; Aisen, P. *Adv. Inorg. Biochem.* **1983**, *5*, 111–136.
(3) Woodland, M. P.; Dalton, H. *J. Biol. Chem.* **1984**, *259*, 53–59.
(4) Chasteen, N. D.; Aisen, P. *J. Biol. Chem.* **1985**, *260*, 2926–2929.
(5) Armstrong, W. H.; Spool, A.; Papaefthymiou, G. C.; Frankel, R. B.; Lippard, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 3653–3667.
(6) Suzuki, M.; Uehara, A. *Inorg. Chim. Acta* **1986**, *123*, L9–L10.
(7) Schwarzenbach, G.; Anderegg, R.; Sallman, R. *Helv. Chim. Acta* **1952**, *35*, 1785–1793.
(8) Murch, B. P.; Bradley, F. C.; Que, L., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 5027–5028.
(9) $E°'$ for the ferricinium/ferrocene couple was found to be +519 mV vs SCE under the experimental conditions employed (Pt working electrode, 0.1 M tetrabutylammonium tetrafluoroborate in DMF using a BAS100 electrochemical analyzer).
(10) Elemental Anal. Calcd for $C_{25}H_{41}Fe_2N_3NaO_{14}$: C, 38.78; H, 5.35; Fe, 14.42; N, 5.42. Found: C, 38.73; H, 4.97; Fe, 14.70; N, 5.48. We have also isolated the corresponding propionate derivative, $[Me_4N]_2[Fe_2(HXTA)(OPr)_2]$. Anal. Calcd for $C_{31}H_{51}Fe_2N_4O_{13}$: C, 46.57; H, 6.44; N, 7.00. Found: C, 46.21; H, 6.69; N, 7.15.
(11) Loehr, J. S.; Loehr, T. M.; Mauk, A. G.; Gray, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 6992–6996.
(12) Robin, M. B.; Day, P. *Adv. Inorg. Chem. Radiochem.* **1967**, *10*, 247–422.

0002-7863/87/1509-7190$01.50/0