There have recently been several studies of nuclear tunneling.[57,58] The overall degree of nuclear tunneling is not easily experimentally accessible at room temperature, but it can be evaluated theoretically. In the high-temperature limit the problem becomes classical, and so a nuclear tunneling factor may be defined as $\Gamma_n = k(T)/k(T = \infty)$.[59] Calculations of the Fe^{2+}/Fe^{3+} exchange have led to $\Gamma_n = 3.5$ at 300 K, while for Co^{2+}/Co^{3+} a $\Gamma_n \sim 10$ was found. A simple expression due to Holstein[60] relates the classical activation barrier ΔG_{i}^* to the barrier corrected for nuclear tunneling $\Delta G^*_{\mathrm{i,tun}}$[57]

$$\Delta G^*_{\mathrm{i,tun}} = \Delta G_{\mathrm{i}}^* \left(\frac{4RT}{Nh\nu_{\mathrm{in}}}\right) \tanh \left(\frac{Nh\nu_{\mathrm{in}}}{4RT}\right) \qquad (23)$$

where ν_{in} is the average vibrational frequency for the two oxidation states. Since two vibrational modes contribute to the activation barrier for triatomic molecules, eq 23 is applied as a correction to both terms in eq 21. Table VI shows the results of these corrections. In the case of the ClO_2/ClO_2^- exchange, the correction is substantial, while the correction for the NO_2/NO_2^- case is much greater. Since the correction is effectively a reduction of the inner-sphere barrier, the solvent reorganization barrier is correspondingly larger. Molecular radii calculated from eq 22, also listed in Table VI, are smaller than in the classical model, and are closer to expected radii. Note that r_1^* for the NO_2/NO_2^- couple is significantly less than r_1^* for the ClO_2/ClO_2^- couple in contrast with the classical result. This observation lends support to the semiclassical model. The nuclear tunneling correction is equivalent to $\Gamma = 79$ for the NO_2/NO_2^- system; nuclear tunneling can be much more important for reactions of bent triatomic molecules than for octahedral complexes because of the greater vibrational frequencies. A similar degree of nuclear tunneling has recently been calculated for the isomerization of 1,3-cyclobutadiene to 2,4-cyclobutadiene.[61]

Summary

The kinetics studies of outer-sphere electron-transfer reactions involving the ClO_2/ClO_2^- couple are consistent with the cross relationship for a series of reactions spanning 14 orders of magnitude in equilibrium constant and 7 orders of magnitude in self-exchange rate constants, and involving a diversity of coordination complexes. The classical model of vibrational activation has been found useful in rationalizing the effective self-exchange rate constants for the ClO_2^-/ClO_2, NO_2^-/NO_2, and SO_2^-/SO_2 redox couples. Corrections for nuclear tunneling are substantial and correlate the data even better.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We are also pleased to acknowledge support from the Robert A. Welch Foundation and the Research Corporation. This material is based upon work supported by the National Science Foundation under Grant No. CHE-8215501. Professor T. J. Meyer is thanked for his encouragement in the analysis of nuclear tunneling effects.

Registry No. $[Co(terpy)_2]^{2+}$, 18308-16-2; $IrCl_6^{2-}$, 16918-91-5; $IrBr_6^{2-}$, 16919-98-5; ClO_2, 10049-04-4; ClO_2^-, 14998-27-7.

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[57] (a) Siders, P.; Marcus, R. A. *J. Am. Chem. Soc.* **1981**, *103*, 741. (b) Newton, M. D. *Int. J. Quantum Chem., Quantum Chem. Symp.* **1980**, *14*, 363. (c) Buhks, E.; Bixon, M.; Jortner, J.; Navon, G. *J. Phys. Chem.* **1981**, *85*, 3759. (d) Chapters by N. Sutin and B. S. Brunschwig, M. D. Newton and N. S. Hush In "Mechanistic Aspects of Inorganic Reactions"; Rorabacher, D. B.; Endicott, J. F. Eds. American Chemical Society: Washington, D.C. 1982; A.C.S. Symp. Ser. No. 198.

[58] (a) Weaver, M. J.; Li, T. T.-T. *J. Phys. Chem.* **1983**, *87*, 1153. (b) Buhks, E.; Bixon, M.; Jortner, J. *Ibid.* **1981**, *85*, 3763.

[59] Brunschwig, B. S.; Logan, J.; Newton, M. D.; Sutin, N. *J. Am. Chem. Soc.* **1980**, *102*, 5798.

[60] Holstein, T. *Philos. Mag.* **1978**, *37*, 49.

[61] Carpenter, B. K. *J. Am. Chem. Soc.* **1983**, *105*, 1700.

CO Insertion into the Iron–Carbon σ Bond in Optically Active CpFe(CO)(L)R. Solvent Dependence and Acid Catalysis

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Abstract: The insertion of CO into the iron–carbon bond in optically active organoiron complexes $CpFe(CO)(PPh_3)Et$ (Cp = η^5-C_5H_5) (**1**) and $CpFe(CO)(mtpb)Et$ (mtpb = $P(OCH_2)_3CMe$) (**3**) in the presence of CO yields $CpFe(CO)(PPh_3)COEt$ (**2**) and $CpFe(CO)(mtpb)COEt$ (**4**), and in the presence of cyclohexyl isocyanide (chi) yields $CpFe(chi)(PPh_3)COEt$ (**5**) and $CpFe(chi)(mtpb)COEt$ (**6**), respectively. In nitroethane or nitromethane under CO pressure **2** and **4** are formed highly stereospecifically, and in MeCN with much reduced stereospecificity, but all with formal alkyl migration. In HMPA, Me_2SO, DMF, or propylene carbonate the optical purity is moderate to low, and the configuration corresponds to formal CO migration. Mixed-solvent studies, cyclic voltammetry, and UV–vis spectra suggest that a special charge- or electron-transfer mechanism in nitroalkane solvent is unlikely. Use of ^{13}C-labeled CO results in the expected incorporation of label only in the terminal CO position of **2**. Strong catalysis results from $BF_3 \cdot Et_2O$ addition, but with no change in stereochemistry. Insertion in the presence of chi yields **5** and **6** with formal alkyl migration in either nitroethane or HMPA (the configurational assignment of the latter is highly tentative) but with reduced % ee. Operation of the usual reversible first-order insertion followed by second-order ligand uptake in the presence of chi is confirmed by a kinetics study of **1** with chi in Me_2SO with $k_1 = 4.9 \times 10^{-4}$ s^{-1}, and $k_2/k_{-1} = 0.54$ L M^{-1}. No intermediates could be detected by IR or NMR in nucleophilic solvents. Possible mechanisms are discussed, including the likely presence of an (η^2-acyl)iron intermediate in rapid equilibrium with an unsaturated (η^1-acyl)iron species.

The path of the insertion of CO into the metal–carbon σ bond is well-known to proceed in most cases as shown in eq 1.[1] The stereochemistry of this important reaction has been a subject of considerable interest and has been extensively reviewed.[1-3] While

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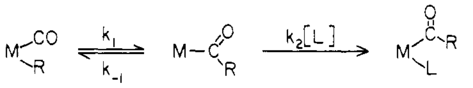

(1)

$$M(CO)R \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} M{-}C(O)R \xrightarrow{k_2[L]} M(L)C(O)R \quad (1)$$

the insertion is virtually always stereospecific with retention at carbon, the stereochemistry at the metal has been shown to be quite variable. The central question concerning metal stereochemistry is whether the CO group moves to the alkyl site in the coordination sphere of the metal, whether the alkyl group moves to the CO site, or whether the intermediate has any sterochemical memory at all (Scheme I). In practice, trans effects in intermediates arising from octahedral starting materials can lead to overall stereochemistry which corresponds to an extensive reorganization of ligands, rather than to either a simple CO or alkyl migration. Thus, the inherent stereochemical preference at the metal center may not be evident.

Similar to the extensively studied $MeMn(CO)_5$,[4] optically active pseudotetrahedral systems of the type CpM(CO)(L)R (Cp = η^5-C_5H_5) should have an advantage over other octahedral systems for the study of metal-centered stereochemistry. Trans effects with their complicating cis–trans isomerizations should be absent. Only formation of one enantiomer or the other (Scheme I) or some degree of racemization should result from CO insertion.

Some studies of such systems have been reported. Photochemical decarbonylation of species of the type CpFe(CO)(PPh_3)(COR) have been reported by Wojcicki to proceed with greater than 85% stereospecificity,[5] and the stereochemistry was shown first by Davison[6] and later by Wojcicki[7] to be formal alkyl migration to CO. We recently reported[3] the preparation of some new chiral organoiron complexes, CpFe(CO)(mtpb)X (mtpb = $P(OCH_2)_3CMe$, X = CH_2Omenthyl, Et, $S(O)_2$Et, COEt), and their resolution and optical assay. The stereochemistry of the insertion of CO induced by CO and by isonitriles into CpFe(CO)(PPh_3)Et and CpFe(CO)(mtpb)Et was reported. Under CO atmosphere in nitroalkanes the insertion was found to proceed highly stereospecifically with formal alkyl migration, while in HMPA moderate stereospecificity was found, but in this case, formal CO migration was observed. At the same time, Brunner and co-workers[8] reported that BF_3 catalyzes the insertion of CO into the Fe–C bond of CpFe(CO)(PPh_3)Me and several CpFe(CO)(PPh_2NRR')Me below 0 °C in toluene with high stereospecificity and formal alkyl migration.

In this paper we report further data on the CO insertion into the iron–carbon bond of CpFe(CO)(PPh_3)Et (**1**) and CpFe(CO)(mtpb)Et (**3**) induced by CO and by cyclohexyl isocyanide (chi), including more extensive data on the solvent dependence of the stereochemistry, and on acid catalysis, kinetics of the chi-induced insertion, and ^{13}CO labeling.

Results

Materials. The syntheses and optical assay of optically active complexes **1**–**6**[9] have been reported previously.[3,10–12] The absolute configurations of **1**, **2**, and **3** are known.[3,10–12] The configurational assignments of **4** and **5** are based on correlations of circular dichroism spectra,[3] and we consider their correctness to be highly probable. The configurational assignment of **6**[3] is much less reliable and is assumed here for the sake of internal consistency.

Scheme I

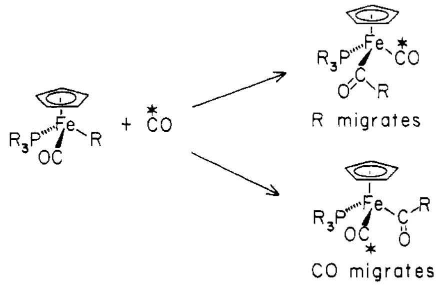
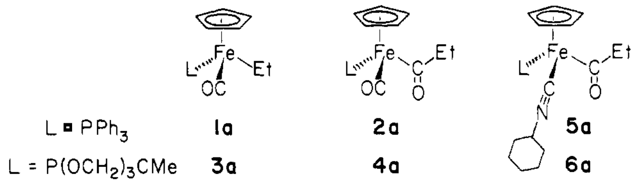


Table I. CO Insertions into (*S*)-**1a** in Various Solvents with $P_{[CO]}$ = 1 atm

expt	solvent[a]	product	% yield	% ee[b]
1	MeCN	(*R*)-**2b**	20	16
2	DMF	(*S*)-**2a**	7	4
3	Me_2SO	(*S*)-**2a**	4	23

[a] Ambient temperature, 70 h. [b] In all cases, recovered starting material was totally racemic.



Insertions under CO Atmosphere. Solvent Dependence. The insertion of CO into **1** and **3** has been carried out in a variety of solvents with use of several CO pressures. Stereochemical results which are reproducible but highly variable were obtained. Table I shows that at 1 atm not only is the reaction of CO very slow but the stereospecificity is quite low as well. Recovered starting material was racemic in all three reactions. In these reactions is also seen the general result that a change of solvent can result in a reversal of the predominant stereochemistry—MeCN yields "alkyl migration",[13] while DMF or Me_2SO yields "CO migration".

Reactions have been carried out at up to 1500 psi of CO. In general, it was found that good rates and stereochemistry could be obtained at the more convenient pressure of 50 psi, so that these reactions are reported here. The results of experiments 4–12 given in Table II are typical. Rates of insertion vary substantially depending on two factors—solvent and phosphorus ligand. Pseudo-first-order half-lives for **1** and **3**, each in $EtNO_2$, at 50 psi of CO and ambient temperature (experiments 4 and 11), would be ca. 7 and 240 h, respectively, indicating a large effect of the phosphorus ligand. Also, pseudo-first-order half-lives for **1** in $EtNO_2$ and in HMPA, both at the same temperature and CO pressure (experiments 1 and 10), whould be ca. 7 and 480 h, respectively. Qualitatively, the rates as a function of solvent appear to be $EtNO_2 \sim MeNO_2 >$ MeCN > DMSO ~ DMF ~ PDC > HMPA. Indeed, reaction of **3** in HMPA was so slow that Me_2SO was used instead, and this at 40 °C and under 1180 psi of CO, in order to observe product formation. It was assumed

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(1) Reviews concerning the CO insertion in general: (a) Wojcicki, A. *Adv. Organomet. Chem.* **1973**, *11*, 87. (b) Calderazzo, F. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 299. (c) Kuhlman, E. J.; Alexander, J. J. *Coord. Chem. Rev.* **1980**, *33*, 195–225.

(2) Flood, T. C. *Top. Stereochem.* **1981**, *12*, 37.

(3) Flood, T. C.; Campbell, K. D.; Downs, H. H.; Nakanishi, S. *Organometallics* **1983**, *28* 1590–1595.

(4) (a) Noack, K.; Calderazzo, F. *J. Organomet. Chem.* **1967**, *10*, 101. (b) Flood, T. C.; Jensen, J. E.; Statler, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 4410–4414.

(5) (a) Attig, T. G.; Wojcicki, A. *J. Organomet. Chem.* **1974**, *82*, 397. (b) Reich-Rohrwig, P.; Wojcicki, A. *Inorg. Chem.* **1974**, *13*, 2457.

(6) Davison, A.; Martinez, N. *J. Organomet. Chem.* **1974**, *74*, C17.

(7) Attig, T. G.; Teller, R. G.; Wu, S.-M.; Bau, R.; Wojcicki, A. *J. Am. Chem. Soc.* **1979**, *101*, 619.

(8) Brunner, H.; Hammer, B.; Bernal, I.; Draux, M. *Organometallics* **1983**, *2*, 1595–1603.

(9) The conventions for configurational designations used in this paper are those of Stanley and Baird: Stanely, K.; Baird, M. C. *J. Am. Chem. Soc.* **1975**, *97*, 6598. Minor changes in structure can lead to a reversal of *R–S* designation without a change in configuration. Therefore, in order to reduce confusion, this paper has taken the convention of designating all species of the configuration corresponding to (*S*)-**1** as the "a" series, and the species enantiomeric to this at iron as the "b" series.

(10) Staler, J. A.; Flood, T. C., to be submitted.

(11) Flood, T. C.; Disanti, F. J.; Miles, D. L. *Inorg. Chem.* **1976**, *15*, 1910.

(12) Chou, C.-K.; Miles, D. L.; Bau, R.; Flood, T. C. *J. Am. Chem. Soc.* **1978**, *100*, 7271.

(13) Throughout the remainder of this paper, the stereochemical path will be characterized as "alkyl migration", or "CO migration". It should be borne in mind that these are *formal* designations only, and are not meant to convey mechanistic information.

Table II. CO Insertions in Various Solvents in the Presence of CO

expt	reactant[a]	product	solvent	time (h)	product % yield	product % ee	% ee recov. reactant	material balance[b]
4	(*S*)-1a	(*R*)-2b	$EtNO_2$	18	82	95	90	92
5	(*S*)-1a	(*R*)-2b	$MeNO_2$	20	99	81		99
6	(*S*)-1a	(*R*)-2b	MeCN	12	15	28	10	90
7	(*S*)-1a	(*S*)-2a	PDC[c]	18	15	20	89	90
8	(*S*)-1a	(*S*)-2a	DMF[d]	22	90	38		90
9	(*S*)-1a	(*S*)-2a	Me_2SO	22	15	35	20	90
10	(*S*)-1a	(*S*)-2a	HMPA	36	5	73	71	86
11	(*S*)-3a	(*R*)-4b	$EtNO_2$	118	29	>95	>95	90
12	(*S*)-3a	(*S*)-4a	Me_2SO[e]	135	2	8	20	45
13	(*S*)-1a	(*R*)-2b	$EtNO_2$[f]	16	22	8		87
14	(*S*)-1a	(*R*)-2b	$MeNO_2$[g]	15 min	85	77		85
15	(*S*)-3a	(*R*)-4b	$MeNO_2$[h]	15	16	>95	>95	99

[a] [FeR] between 2×10^{-2} and 1×10^{-3} M, ambient temperature, $P_{[CO]} = 50$ psi, unless otherwise noted. [b] Recovered starting material plus product, both isolated from column chromatography. [c] Propylene carbonate. [d] $P_{[CO]} = 1600$ psi. [e] At 40 °C, $P_{[CO]} = 1180$ psi. [f] In the presence of 1 M HMPA. [g] Solution was 2.2×10^{-3} M in [FeR] and 1.4×10^{-4} M in $BF_3{\cdot}Et_2O$. [h] Solution was 8.1×10^{-2} M in [FeR] and 7.0×10^{-4} M in $BF_3{\cdot}Et_2O$.

Table III. CO Insertions in the Presence of Cyclohexyl Isocyanide

expt	reactant[a]	product	solvent	time (h)	product % yield	product % ee	% ee recov. reactant	material balance[b]
16	(*S*)-1a	(*S*)-5b	$EtNO_2$	24	71	41	87	78
17	(*S*)-1a	(*S*)-5b	HMPA	32	35	20	87	70
18	(*S*)-3a	(*S*)-6b[c]	$EtNO_2$[d]	190	47	20	64	89
19	(*S*)-3a	(*S*)-6b[c]	MeCN[d]	214	46	8	32	98
20	(*S*)-3a	(*S*)-6b[c]	Me_2SO[d]	219	27	16	18	91

[a] [FeR] between 6 and 8×10^{-3} M, [CNR] = 1 M, ambient temperature. [b] Recovered starting material plus product, both isolated from column chromatography. [c] Highly tentative configurational assignment. [d] At 39 °C.

that elevated temperatures in general would give extensive racemization by phosphine dissociation, at least in the case of **1**.[14]

Methylene chloride solvent yielded extensive decomposition and racemization of the reactants and products. No product formation was observed at all over several days in ether, THF, or arene solvents.

It may be noted from Table II that as the solvent is varied, the stereochemistry of the insertion reaction is *reversed.* the solvents can be divided into two groups—those giving alkyl migration which are relatively soft and/or weakly coordinating or noncoordinating ($EtNO_2$, $MeNO_2$, MeCN) and those giving CO migration which are relatively hard and good at complexing (HMPA, Me_2SO, DMF, PDC). Stereospecificity was high only in the nitroalkanes, and was relatively high in HMPA. In all other cases the stereospecificity was moderate to quite low. In general, the optical purity of the recovered starting material paralleled that of the product in any given experiment.

Reaction of **1a** in $EtNO_2$ which was 1 M in HMPA (experiment 13) resulted in a significant drop in stereospecificity, to the point that product **2** was nearly racemic. Nevertheless, CD spectra allowed the unequivocal assignment of the configuration of the predominant enantiomer. The qualitative rate of reaction was that expected from interpolation from experiments 4 and 10 assuming a linear dependence of rate on the mole fractions of the solvents.

Attempts to observe solvated intermediates under insertion conditions were uniformly unsuccessful. NMR observation of **1** in Me_2SO-d_6 or in 1:1 HMPA/CD_2Cl_2 revealed no resonances other than those of starting material even after long times, and no acyl stretching bands could be detected by IR in such solutions.

Insertion under ^{13}CO. When insertion into **1** was conducted in $CD_3NO_2/EtNO_2$ under ^{13}CO, the ^{13}C NMR spectrum of product **2** exhibited only a signal characteristic of a terminal CO. No signal for an acyl resonance was visible.

Acid Catalysis. At the beginning of our study, use of nitroalkanes distilled directly from P_2O_5 as solvents in insertion reactions led to varying qualitative rates of reaction. When these solvents were treated with Na_2CO_3 and then alumina prior to use, the rates were quite reproducible. These observations led us to attempt acid catalysis. Complex **1a** under CO atmosphere in the presence of $BF_3{\cdot}Et_2O$ (experiment 14, approximate molar ratios of 1:7:0.06, respectively) showed complete reaction in less than 15 min, while a very qualitative pseudo-first-order half-life of the uncatalyzed reacton (experiment 4) would be 7 h. Product **2b** still exhibited alkyl migration stereochemistry, but had suffered some racemization in comparison to the uncatalyzed reaction (77% ee vs. 95%).

Similarly, **3a** underwent reaction under CO atmosphere in the presence of $BF_3{\cdot}Et_2O$ (experiment 15, approximate molar ratios 1:10:0.009, respectively) at a significantly accelerated rate. A pseudo-first-order rate plot of the reaction showed linear behavior for ca. 2 h after which strong deceleration was observed. The pseudo-first-order half-life for the linearly catalyzed portion of the reaction was ca. 16 h, as compared with the uncatalyzed reaction which had a half-life of 240 h. In this case, the insertion was completely stereospecific with formal alkyl migration.

Electrochemistry and UV–vis Spectra. The cyclic voltammetry of **1** was very briefly examined in $EtNO_2$ solution with $N(n\text{-}Bu)_4PF_6$ as electrolyte. A solvent/electrolyte blank showed the onset of reduction below −1.2 V (SCE). Complex **1** showed three quasireversible oxidation peaks, the lowest in energy at $^1/_2(E_{1/2}(\text{ox}) + E_{1/2}(\text{red}))$ ca. 0.26 V.[15]

UV–vis spectra of **1** (ca. 4×10^{-4} M) were very similar in the region of 350–600 nm in toluene, HMPA, and $EtNO_2$, so that no charge-transfer interaction in $EtNO_2$ was evident.

Insertions in the Presence of Cyclohexyl Isocyanide. Solvent Dependence. Insertion of CO in **1** in the presence of 1 M cyclohexyl isocyanide (chi) in nitroethane to produce **5** proceeded at qualitatively the same rate as did the insertion in the presence of CO in this solvent. Insertion into **3** to form **6** was much slower

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(14) Reger, D. L.; Culbertson, E. C. *J. Am. Chem. Soc.* **1976**, *98*, 2789–94.

(15) The electrochemical oxidation of CpFe(CO)(PPh_3)Me has been reported to be reversible: (a) Magnuson, R. H.; Zulu, S.; T'sai, W.-M.; Giering, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 6887–8. For other electrochemical investigations see: (b) Treichel, P. M.; Wagner, K. P.; Mueh, H. J. *J. Organomet. Chem.* **1975**, *86*, C13–C16. (c) Rogers, W. N.; Page, J. A.; Baird, M. C. *Inorg. Chim. Acta* **1979**, *37*, L539–L540.

than for **1**. In the isocyanide-induced insertions, however, the stereospecificity was much less than in the CO-induced reactions (see Table III). The lower optical purity of **5** and **6** was not due to racemization after their formation, since no racemization of **5** (expected to be the more labile of the two) was detected upon its resubmission to reaction conditions, and rechromatography led to only ca. 5% racemization. Unlike the CO-induced insertions, even though the optical purity of **5b** was not high in experiments 16 and 17, recovered starting material had only undergone slight racemization.

As anticipated, when the isocyanide-induced insertions were carried out on **1** in HMPA and on **3** in Me_2SO, the rates were retarded over the same reactions in nitroethane, and the stereospecificity was similarly not high. Complex **1** in either nitroethane or HMPA yielded **5** with overall alkyl migration. The configuration of **6** has not been reliably assigned,[3] but its tentative assignment as **6b** would be internally consistent with the other results reported herein.

Kinetics of chi-Induced Insertion. The kinetics of the chi-induced insertion of **1** were determined by NMR in Me_2SO-d_6 at 35 °C under pseudo-first-order conditions where the isocyanide was always in excess. Pseudo-first-order plots of these reactions are shown in Figure 1. A plot (not shown) of $1/k_{\mathrm{obsd}}$ vs. $1/[\mathrm{chi}]$ yielded a good line with slope = 3.76×10^3 s M L^{-1} and intercept = 2.03×10^3 s.

Discussion

It is abundantly clear from the stereochemical data presented above that the simple mechanism of eq 1 cannot be an adequate description of the detailed path of the CO insertion reaction. While it is not presently possible to construct a compelling argument for a unique detailed path, some conclusions can be drawn, and some possibilities can be outlined.

It has been demonstrated in several cases already[1] that the inserting CO must first be coordinated to the metal. Nevertheless, for the sake of rigor, we have established this in the present system as well through the use of ^{13}CO as described above.

That there is at least one intermediate in this reaction is likely, since the kinetics of $CpFe(CO)_2R$ and a number of related systems have been shown to have a nonlinear dependence on the concentration of the incoming ligand.[1,16] As mentioned above and discussed below, we have confirmed this point in our system in the case of the isocyanide-induced insertion.

According to extended Hückel calculations,[17] an intermediate such as A (Scheme II) would be expected to be pyramidal (chiral), as shown, rather than quasi-trigonal (achiral), and to possess a finite barrier to inversion. Therefore, we thought that a stereospecific insertion reaction might take place in these molecules. This system should have the same advantage as $MeMn(CO)_5$ in being a stereochemically "pure" system having no complications from trans effects. This additional case would test the generality of alkyl migration as observed in the manganese system.

Alkyl migration was indeed observed upon CO insertion into **1a** under CO atmosphere in nitroalkanes and in acetonitrile (experiments 4–6), the highest stereospecificity being observed in nitroethane. From our work on insertions in $MeMn(CO)_5$,[4b] we anticipated that a change of solvent from nitroalkanes to donor solvents such as Me_2SO or HMPA might result in formation of racemic product. We were astonished to observe upon moving from use of nitroalkanes to donor solvents that the stereochemistry was actually reversed. The net stereochemical outcome was formal CO migration in DMF, Me_2SO, PDC, and HMPA, with the highest ee in the last solvent. It is noteworthy that in all cases except for nitroalkane solvents and DMF (where the CO pressure was much higher) the reaction was very much slower, and the conversion only 5–15%. Still, in Me_2SO, MeCN, and even HMPA where the conversion to product was only 5% the starting material was largely racemized. Thus, at 4 atm of CO at larger conversions, the product would surely have been essentially racemic, as originally anticipated.

A long-standing concern of ours in the use of these PPh_3-substituted systems was the helical and therefore chiral nature of this ligand's dominant conformation. It is possible, for example, that the chirality at Fe in **1a** could induce a highly favored sense of chirality at the PPh_3 center, thereby generating a predominant conformational diastereomer. If the intermediate in the CO insertion were quasiflat, or if it were pyramidal but rapidly inverting, and if rotation of the phenyl groups in the PPh_3 moiety were slow with respect to the lifetime of the intermediate,[18] then any stereospecificity of the insertion reaction might derive from asymmetric induction by the PPh_3 ligand and not from its inherent stereochemical properties. Furthermore, the favored conformation of **1a** would conceivably be solvent dependent, perhaps leading to the kind of solvent-dependent results which we were observing. For these reasons, we decided to prepare the mptb-substituted series of molecules wherein such conformationally based effects would be impossible.

Significantly, **3**, although much less reactive, behaved stereochemically in parallel with **1** (experimental 11 and 12). This clearly rules out any large contribution from chiral conformations of PPh_3 to the behavior of **1** in this context.

If a species such as A (Scheme II) were the sole intermediate from, say, **1a**, it is possible that nucleophilic solvents might somehow cause inversion of stereochemistry, for example, by complexation of A to form B and then attack by CO causing a Walden inversion at iron. As unlikely as this might seem, if it were true, then the trapping of A more rapidly by a better nucleophile than CO might obviate the solvent effect. Treatment of **1a** with chi does lead to predominant formation of **5b** with alkyl migration whether in $EtNO_2$ or HMPA (experiment 16 and 17), and similarly, **3** leads predominantly to the same enantiomorphic form of **6** (probably **6b**) whether in $EtNO_2$, MeCN, or Me_2SO (experiments 18–20). Another intersting observation intrudes here, however. While **1** and **2** both undergo highly stereospecific insertion under CO in $EtNO_2$, products **5** and **6** are both formed in only modest ee in $EtNO_2$ (41 and 20%, respectively). As mentioned above, these optical purities are kinetic since **5**, expected to be the more labile of the two, is stable to reaction and workup conditions.

Numerous kinetics studies have dealt with the nonlinear dependence of insertion rates on incoming ligand concentrations in various systems,[1,16] including $CpFe(CO)_2R$.[1,16a,b,d] Insertions with strictly second-order kinetics are known for a number of related systems, although generally in nonpolar solvents in the presence of good nucleophiles, such as phosphines.[1] Nevertheless, the possibility exists that the use of isocyanide with these phosphine-substituted iron complexes might result in a change of

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(16) (a) Green, M.; Westlake, D. J. *J. Chem. Soc. A* **1971**, 367–371. Some more recent examples follow: (b) Cotton, J. D.; Crisp, G. T.; Latif, L. *Inorg. Chim. Acta* **1981**, *47*, 171–176. (c) Cotton, J. D.; Crisp, G. T.; Daly, V. A. *Ibid.* 165–169. (d) Nicholas, K.; Raghu, S.; Rosenblum, M. *J. Organomet. Chem.* **1974**, *7*, 133–137. (e) Wax, M. .; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 7028–7030.

(17) Hofmann, P. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 536.

(18) It is not possible to accurately judge the likelihood of this situation, but some highly qualitative guesses can be made. Faller and Johnson[19] have estimated an upper limit for the barrier to P–C rotation in $CpFe(CO)(PPh_3)(CN)$ at −20 °C to be ca. 8 kcal/mol. Assuming that $\Delta S^{\ddagger}$ is 0, this extrapolates to $k = 10^7\ s^{-1}$ at ambient temperature. It is possible that the corresponding rate in the very different **7** might be of this magnitude, or even slower. Ligand uptake rates for unsaturated species such as **7** are not known, but complexation of $M^0(CO)_5$ (M = Cr, Mo, W) by a variety of ligands exhibits rates which are rather insensitive to the nature of the incoming ligand, with constants in the range of 3×10^6 to 2×10^8 L $mol^{-1}\ s^{-1}$.[20] Taking the latter value as an approximation, and the maximum likely [CO] in these solvents at 4 atm as 5×10^{-2} M,[21] then $k_2[CO]$ might be as fast as $10^7\ s^{-1}$. While it is unlikely that all of the limiting values assumed in this discussion would actually apply, it is nevertheless possible that rotation within the PPh_3 ligand could be slow with respect to the lifetime of the intermediate.

(19) Faller, J. W.; Johnson, B. V. *J. Organomet. Chem.* **1975**, *96*, 99–113.

(20) Dobson, G. R.; Rousche, J.-C. *J. Organomet. Chem.* **1979**, *179*, C42 and references therein.

(21) Bunsen coefficients for CO in a wide variety of solvents at 25 °C vary little, probably as a result of its very small dipole moment, with values ranging from 0.23 to 0.047. Gjaldbaek, J. C.; Andersen, E. K. *Acta Chem. Scand.* **1954**, *8*, 1398–1413. Battino, R.; Clever, H. L. *Chem. Rev.* **1966**, *66*, 395–463.

$$\underset{\mathbf{1}}{CpFe(CO)(PPh_3)Et} + CN\text{-}C_6H_{11} \xrightarrow[35\,°C]{DMSO} \underset{\mathbf{5}}{CpFe(CN\text{-}C_6H_{11})(PPh_3)(COEt)}$$

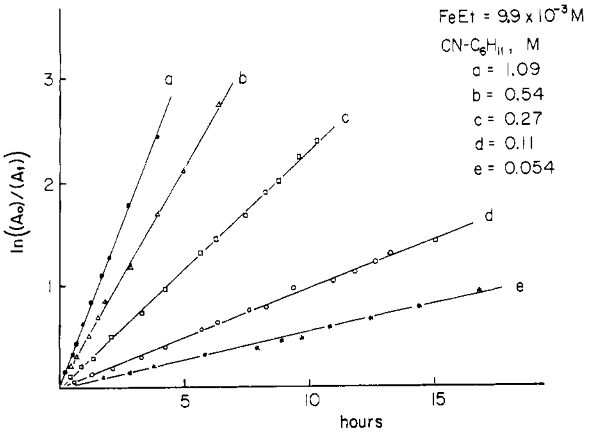


Figure 1. Pseudo-first-order plots of the chi-induced CO insertion of **1** to form **5** in Me$_2$SO at 35 °C at several chi concentrations.

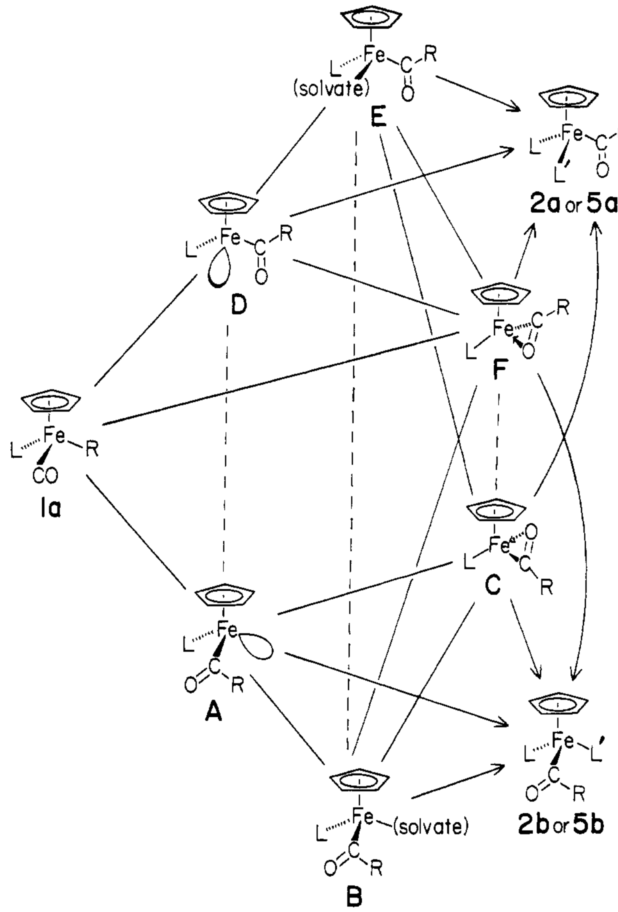
mechanism, and that this new mechanism might account for the loss of the solvent dependence of insertion stereochemistry, as well as for the lower stereospecificity. for this reason, we determined the kinetics of the reactions of **1** with chi in Me$_2$SO as described above and in the Experimental Section.

Applying the steady-state assumption and standard kinetic analysis of the mechanism of eq 1[1,16] leads one to conclude from a plot of $1/k_{obsd}$ (from Figure 1) vs. 1/[chi] that the slope = k_{-1}/k_1k_2 and the intercept = $1/k_1$. Thus, $k_1 = 4.9 \times 10^{-4}$ s^{-1} and $k_2/k_{-1} = 0.54$ M^{-1}. The fit in this plot was quite good (R = 0.9998), while a simple second-order plot of the data was highly nonlinear. The k_1 obtained is somewhat faster than those found for CpFe(CO)$_2$Et (0.22×10^{-4} at 29 °C,[16b] 1.3×10^{-4} at 47.5 °C[16a]), probably a case of steric acceleration[16b] from the presence of the bulky PPh$_3$ ligand in **1**.

It is to be noted from k_2/k_{-1} that even at [chi] = 1 M, the intermediate will revert to starting material twice as fast as it will proceed to product. When the trapping ligand is CO, k_2 may be significantly smaller, and CO at 4 atm in any of these solvents would have a maximum concentration of ca. 5×10^{-2} M. Thus, k_{-1}/k_2[CO] would have a value at least as high as 40, probably much higher, and the intermediate in the insertion must have very good configurational stability during its lifetime in EtNO$_2$. This observation underlines the question of why the chi-induced insertion is of such low stereospecificity. In any event, it is clear that the change in stereochemical behavior between CO and chi as trapping ligands is not the result of a change in the initial step of the reaction.

It is possible that in nitroalkane solvents some special charge-transfer or redox interaction of solvent with substrate might take place. This different mechanism might account for the alkyl migration in these solvents, as opposed to the CO migration observed in most of the other solvents. We believe this is not likely to be the case, based on several lines of reasoning. First, the cyclic voltammograms show that reduction of bulk EtNO$_2$ and the lowest energy oxidation of **1**, which should be more easily oxidized than **3**, are separated by more than a volt. This should render the concentration of an electron-transfer intermediate too small to be important. Second, the possibility of a special interaction, such as charge transfer, between EtNO$_2$ and **1** which might lead to a more rapid reaction and special stereochemistry seems unlikely since the spectrum of **1** is essentially unchanged in hexane, benzene, and EtNO$_2$. Third, as mentioned above, with 1 M HMPA (ca. 17% by volume) in EtNO$_2$ as solvent, a proportionate decrease in rate is observed compared to that in pure EtNO$_2$, but the stereospecificity of the reaction decreases substantially. This suggests that the properties of HMPA are causing the change in stereochemistry and not those of EtNO$_2$. Finally, it is to be noted that MeCN also yielded net alkyl migration, and this solvent is not anticipated to be a species prone to charge-transfer or electron-transfer interactions.

Scheme II



A reasonably complete set of mechanistic possibilities is shown in Scheme II, and any plausible mechanism is likely to be a subset of this diagram.[22] For clarity, only **1**, **2**, and **5** have been included in the scheme and in the following discussion, but all the comments would apply to **3**, **4**, and **6** as well. Direct solvent-assisted (bimolecular) insertion (such as **1a** → B) has been convincingly demonstrated recently by Wax and Bergman[16e] in the case of CpMo(CO)$_3$R in THF. Nicholas et al., on the other hand, have concluded that direct solvent participation in the transition state for acyl formation in CpFe(CO)$_2$(CH$_2$-c-C$_6$H$_{11}$) is not likely.[16d] They found that a solvate, CpFe(CO)(COR)(Me$_2$SO), was formed in Me$_2$SO solvent, and yet the rate of insertion in the presence of PPh$_3$ was rather insensitive to bulk solvent properties. In particular, Me$_2$SO showed no special accelerating effect. Furthermore, the rate definitely did not correlate with the "donicity number, DN(SbCl$_5$)"[26] of the solvent. We have found that, very qualitatively, the rates of insertion *decrease* with increasing

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(22) Of course there are still other processes which one can envisage. For example, an alkyl migration to the Cp ring would have analogy in recent iron hydride chemistry,[23] as would the reverse, a migration of an alkyl group from the ring to iron.[24] The "slipage" of the Cp ring to a lower coordination is also possible.[25] To invoke such mechanisms does not particularly help to explain our data, however. Recent electrochemical work with CpFe(CO)$_2$R reveals extremely large accelerations of the CO insertion upon one-electron oxidation.[15a] It is possible that much of CO insertion chemistry in general is in reality driven by trace quantities of catalytically active oxidized impurities, and we cannot strictly rule out this possibility here. Nevertheless, the facts that (1) intentionally added O$_2$ has no effect on the rate or stereochemistry of our insertion and (2) these reactions are quite reproducible seem to suggest that such an oxidatively catalytic path is not likely here.

(23) Davies, S. G.; Hibberd, J.; Simpson, S. J. *J. Organomet. Chem.* **1983**, *246*, C16–C18.

(24) Eilbracht, P.; Dahler, P. *Chem. Ber.* **1980**, *113*, 542.

(25) Casey, C. P.; Jones, W. D. *J. Am. Chem. Soc.* **1980**, *102*, 6154–56.

(26) Gutmann, V. "Coordination Chemistry in Non-Aqueous Solutions"; Springer Verlag: New York, 1968; Chapter II.

donicity of the solvent. Also, all attempts to observe solvates in HMPA or Me_2SO have failed. For these reasons, we consider the direct solvent-induced paths unlikely, and they have been omitted from the diagram.

In contrast, the stereospecificity of the insertion reaction in various solvents at low conversion does roughly parallel the solvent DN($SbCl_5$), Table IV. The correlation is not perfect, at least in part because in DMF the conversion was high and the CO pressure was very high. Furthermore, the DN are the enthalpy of complexation of various solvents to $SbCl_5$ and so are not kinetic numbers and they are not determined for species at all resembling the present iron system. Nevertheless, there is a rough parallel wherein the smaller DN solvents have yielded **2b**, and higher DN solvents have yielded more **2a**. Furthermore, it is to be noted that there is no particular relationship between the qualitative reaction rates or the % ee of product and the Taft solvatochromic π values which are thought to be a reflection of the bulk solvating ability of a given solvent over a wide range of reactions[27] (Table IV). It thus does appear that the solvent dependence of the stereochemistry of the insertion reaction has more to do with the nucleophilicity than the general polar properties of the solvent.

The simplest possible paths from **1a** to **2a** or **2b** in Scheme II are (1) direct formation of A with A and B as the only intermediates and (2) direct formation of F with F and E as the only intermediates. Dihaptoacyl metal complexes have been well precedented for some time,[29] with one recent example involving ruthenium.[29c] In some cases these have been shown to have a significant barrier to rotation around the metal–ligand bond.[29d] Thus, intermediate C or F could well be configurationally stable. Formation of D and E as the only intermediates seems unlikely since it would fail to explain the production of **2b** as the only product in poorly coordinating $EtNO_2$. Also, direct formation of C would be geometrically highly improbable.

Mechanisms 1 and 2 could each explain many of the experimental observations, but each has some drawbacks. In the case of (1), presumably only intermediate A would be important in nitroalkanes, while in good coordinating solvents B would be predominant. This requires that CO function as a nucleophile, inducing a Walden inversion upon attack on B. It seems unlikely to us that CO would function as a nucleophile in this way, or that displacement of solvent would involve inversion at all. We have been unable to find clear-cut stereochemical precedents for true associative or interchange displacement (A, I_A, or I_D) of coordinated solvent at octahedral 18-electron centers. Nevertheless, the bulk of work on substitutions in octahedral carbonyl complexes[28] strongly suggests that retention is a more likely path. Furthermore, the substantial decrease in stereospecificity of the insertion induced by chi in $EtNO_2$ must be explained by an inversion component in the attack of chi on A or on a presumably very weak $EtNO_2$ solvate, B. Again, we can find no precedent to substantiate such a path or any reason to prefer it.

Mechanism 2 would require that CO and "hard" nucleophilic solvents each attack intermediate F from opposite sides. Presumably chi would exhibit intermediate properties and attack from both sides. However, such stereospecificity based on the characteristics of the nucleophile seems unlikely to us as well.

An alternative path might be to invoke a rapid equilibrium between A and C (and D and F) (mechanism 3). In noncoordinating solvents such as nitroalkanes, intermediate A would be captured by CO to form product **2b**. Intermediates B and E would be unimportant. However, in HMPA, for example, attack by the nucleophilic solvent on both A to give B and C to give E might be important. Bimolecular substitution on B and E by CO with *retention* of configuration, presumably by an approximately I_d mechanism,[28] would yield **2b** and **2a**, respectively. For this scheme to explain the net formation of **2a** in donor solvents, additional requirements would be that the conversion of A to C must be competitive with capture of A by solvent, C must be highly favored in the A–C equilibrium, and attack by solvent on C would need to be fast. These all seem plausible to us.

It is problematic that mechanism 3 requires solvent to attack at the face adjacent to the carbonyl carbon, which would be the more sterically encumbered. Nevertheless, intermediate C would possess a quasi-trigonal structure (about the metal) such as in CpRh(CO)(ethylene), and to this extent should have better accessibility at the face adjacent to the alkyl group than would A. Mechanism 1 would require Walden inversion by attack at the extremely hindered face of A in preference to an open coordination site, as mentioned above. Mechanism 2 would also require attack by the larger nucleophile at the more hindered face of C and by the smaller CO at the less hindered face. None of these possibilities is entirely satisfactory.

The reduction of stereospecificity upon attack by chi in $EtNO_2$ might be explained by the tendency of chi, which should be signficiantly more nucleophilic than CO, to attack C and proceed directly to **5a**. The fact that **5b** is the predominant product even in HMPA could result from the fact that A → **5b** has become the dominant kinetic term;[31] k_{A5b} should be inherently larger for chi than CO, and chi was used at much higher concentrations than CO.

In mechanism 3, starting material racemization in more donating solvents would be rationalized by the overall reversibility of formation of the intermediates, which in the case of the presence of E would result in formation of **1b**. The fact that MeCN exhibits net formation of **2b** would suggest that while MeCN ought to be a very good ligand for iron in these molecules,[30] it may not be a good enough nucleophile to attack C as rapidly as the "harder" solvents.

The decrease in rate as a function of solvent donicity poses a problem for any of the above mechanisms. For example, having an additional path in a donor solvent for reaction of A as in mechanism 3 would not lead to rate retardation unless there were to be a buildup of a new intermediate. As noted above, we were not able to detect any intermediates. That the same variation in rate as a function of solvent was observed for both the CO and chi reactions argues more for a difference in the rate of the initial insertion step as a function of bulk solvent properties. Taft π values in Table IV, however, do not reveal such a trend. It is possible that there is some specific solvent effect which is a special property of the CO insertion reaction which simply is not accounted for in the π values. Other than this, we have no explanation for the solvent effects on rates.

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[27] Abboud, J. L.; Kamlet, M. J.; Taft, R. W. *J. Am. Chem. Soc.* **1977**, *99*, 8325–27.

[28] (a) Darensbourg, D. J. *Adv. Organomet. Chem.* **1982**, *21*, 113–150. (b) Dobson, G. R. *Acc. Chem. Res.* **1978**, *9*, 300–306.

[29] (a) Fachinetti, G.; Fochi, G.; Floriani, C. *J. Chem. Soc., Dalton Trans.* **1977**, 1946–50. (b) Fagan, P. J.; Manriquez, J. M.; Marks, T. J.; Day, V. W.; Vollmer, S. H.; Day, C. S. *J. Am. Chem. Soc.* **1980**, *102*, 5393–96. (c) Roper, W. R.; Taylor, G. E.; Waters, J. M.; Wright, L. J. *J. Organomet. Chem.* **1979**, *182*, C46–C48. (d) Erker, G.; Rosenfeldt, F. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 605–6. (e) Very recently, carefully measured IR spectra of photochemically generated CpFe(CO)(COMe) in CH_4 at 12 K have revealed a doublet for the acetyl stretching mode at 1602.0 and 1564.7 cm^{-1} [Hitam, R. B.; Narayanaswamy, R.; Rest, A. J. *J. Chem. Soc., Dalton Trans.* **1983**, 615–619]. These data could be consistent with two conformations of a species analogous to A, or to single conformations of a mixture of analogues of A and C. In any event, two speecies in rapid equilibrium with one another at ambient temperature (even with a rate constant as large as 10^8 s^{-1}) would have completely rigid structures at 12 K. Thus, either of the above interpretations could be consistent with mechanisms 2 or 3 here.

[30] Johnson, E. C.; Meyer, T. J.; Winterton, N. *J. Chem. Soc., Chem. Commun.* **1970**, 934–35.

[31] We have carried out limited kinetics modeling with the use of "CHEMK", a numerical analysis program written by G. Z. Whitten and H. Hogo. All of the essential features of our observations can be reproduced by mechanism 3 in these calculations. For example, the results of experiment 9 in Me_2SO (Table II; after 22 h, 50% **11a**, 33% **1b**, 6% **2b**, and 12% **2a**; no buildup of intermediate in the absence of CO) were reproduced by using the rate constants and concentrations: $k_{1aA} = 5 \times 10^{-4}$, $k_{A1a} = 10^6$,$k_{AC} = 10^7$, $k_{CA} = 1$, $k_{AB} = 10^5$, $k_{BA} = 0.1$, $k_{CE} = 1$, $k_{EC} = 10$, $k_{E2a} = 0.05$, $k_{A2b} = 10^7$, $[CO] = 0.01$, $[Me_2SO] = 14$. In the case of trapping by isocyanide, both experiments 16 and 17 (Table III) are reproduced well by using $[CNR] = 1$, and $k_{C5a} = 1$. Naturally, since this scheme has 20 rate constants (22 in the case of the isocyanide reaction) and far fewer experimental parameters, the above solution is by no means unique, and may well not be the best solution. Nevertheless, these calculations do serve to establish that the mechanistic scheme is reasonable.

Table IV. Stereospecificity of the CO Induced Insertion Into **1a** at Low Conversion[a] and Solvent Properties

solvent	$MeNO_2$	MeCN	PDC	DMF	Me_2SO	HMPA
$DN(SbCl_5)$[b]	2.7	14.1	15.1	26.6	29.8	38.8
% ee of **2**[c]	>80 (b)[d]	28 (b)	20 (a)	38 (a)[e]	35 (a)	73 (a)
Taft π[f]	0.85	0.86		0.88	1.00	(0.87)[g]

[a] As outlined in Table III, at 4 atm CO, to 5–15% conversion. [b] Reference 22. [c] Configuration of **2** in parentheses. [d] At 100% conversion, 81% ee. [e] At 90% conversion, 1600 psi CO. [f] Reference 27. [g] This number is stated not to be reliably general from one chemical system to another; ref 27.

A reasonable mechanism of BF_3 catalysis of the insertion reaction would include complexation of either the metal[32,33] or the oxygen of the CO[33] by BF_3. This would render the metal center and/or the carbonyl carbon more electron deficient, thus accelerating the reaction. Analogous effects have been found upon electrochemical[15] and chemical[34] oxidation of $CpFe(CO)_2R$ systems, and upon treatment of $CpFe(CO)_2Me$ with $AlBr_3$.[35] In the case where BF_3 would be complexed to intermediate A, this complex would probably be of structure $\mathrm{Cp\overline{Fe[C(O{-}B}FF_2)Et]}$-(CO), in analogy with the known $\mathrm{Cp\overline{Fe[C(O{-}AlB}rBr_2)Me]}$-(CO).[35] It would be quite unlikely that a dihaptoacyl intermediate could form under these circumstances. Rapid ligand uptake should still afford product with potentially substantial stereospecificity. The loss of catalysis in reaction 15 might result from mutual destruction of the catalyst and iron substrate, or from the fact that the complex $CpFe(CO)(L)[C(O{-}BF_3)Et]$, in analogy with the known $CpFe(CO)_2[C(O{-}AlBr_3)Me]$,[35] might be so stable that the catalyst is effectively removed from the reaction as the concentration of product builds up.

Experimental and Section

NMR spectra were recorded on a Varian XL-100 FT spectrometer; chemical shifts are reported in ppm downfield from tetramethylsilane for both ^1H and ^{13}C spectra; all coupling constants are reported in Hz. Infrared spectra were recorded with a Perkin-Elmer 337 spectrometer. UV–vis spectra were recorded with a Beckman ACTA MVI spectrometer and are reported over the range of ca. 300–600 nm. Cyclic voltammetry was performed with a Princeton Applied Research (PAR) Model 175 Universal Programmer and a PAR Model 173 Potentiostat/Galvanostat with an Omnigraphyic 2000 recorder. Reactions above 1 atm of pressure were carried out in a 1-L Parr Instruments Co. autoclave with fittings to allow venting, sample removal, and repressuring without admission of air; a 125-mL Erienmeyer flask served as a reaction vessel inside the bomb. Reactions in the bomb were stirred magnetically.

All reactions involving organometallic compounds were carried out under an atmosphere of nitrogen purified over reduced copper catalyst, and in flamed-out glassware. All reactions and samples, including those for NMR, CD, and optical rotations, were always kept totally in the dark. Chromatography columns were wrapped in aluminum foil. THF, benzene, and toluene were distilled from purple solutions of disodium benzophenone dianion. Nitroethane, nitromethane, and acetonitrile were distilled from P_4O_{10}, treated with anhydrous sodium carbonate, and passed through a column of active alumina. Me_2SO, DMF, and HMPA were distilled under nitrogen atmosphere at reduced pressure from CaH. PDC (1,2-propanediol cyclic carbonate) was distilled at reduced pressure under nitrogen atmosphere. The synthesis, analysis of optical purity, and configurational assignment of all materials mentioned herein have been reported previously.[3,10-12] The CO was CP grade specified to contain less than 600 ppm of O_2. Alumina for column chromatography was Brockmann grade IV (deactivated with 10% H_2O).

In all cases, care was taken to use homogeneous samples for optical analysis in order to give accurate determinations of enentiomeric excesses.

General CO Insertion Procedure. (a) Reactions at 1 atm. First, a 250-mL, foil-covered flask containing ca. 0.2 mmol of **1** was evacuated and refilled several times with CO at 1 atm. Then 25 mL of the appropriate solvent was added, and the solution was stirred vigorously for 70 h. The solvent was removed at reduced pressure, and the residue was submitted to column chromatography (alumina). Elution with 25% ether–hexane afforded two bands, first **1** and then **2**. Recovered **1** was treated with SO_2 in CH_2Cl_2, this product was purified by chromatography on alumina, and optical assay was conducted with optically active EuL_3 NMR shift reagents and NMR spectroscopy as described previously.[3,11] Product **2** was submitted directly to the same type of shift reagent/NMR analysis. The results of these experiments are tabulated in Table I.

(b) Reactions at Elevated Pressure. The Parr high-pressure apparatus was assembled, including the internal Erlenmeyer flask, and this was evacuated and refilled with a CO atmosphere. A solution of iron alkyl (typically 50–100 mg, ca. 0.16–0.32 mmol, in 25 mL of solvent) was injected via a septum-sealed valve into the Erlenmeyer flask, and the pressure was increased to 50 psi of CO. Progress of the reaction was followed by venting excess CO pressure, removing samples via the valve, and repressuring the system. For workup, reaction mixtures were removed by forced syphon (cannula) from the reactor, and the solvent was removed at reduced pressure. The residue was chromatographed on alumina, resulting in isolation of unreacted starting material and product. Optical analysis of these was conducted as described just above. Reaction conditions, yields, and optical yields are given in Table II.

Insertions in the Presence of chi. A solution generally ca. 6–8 × 10^{-3} *in iron alkyl and 1 M in cyclohexyl isocyanide (chi) in ca. 25 mL of a* specific solvent was allowed to react as specified in Table III. Workup consisted of removal of the solvent under reduced pressure and chromatography of the residue on alumina. In the case of **1**/**5**, two bands were eluted with 25% ether–hexane. In the case of **3**/**6**, starting material was eluted with 25% ether–hexane and product with acetonitrile. Optical yields were determined as above and are reported in Table III.

Kinetics of Insertion into 1 in the Presence of chi. A solution of 17.4 mg (0.040 mmol) of **1** in 2.0 mL of Me_2SO-d_6 was prepared and 0.25 mL added to each of five septum-covered amber NMR tubes. Volumetrically prepared solutions of cyclohexyl isocyanide in the same solvent were added to these to bring the total volume to 2.0 mL, the final [FeEt] to 9.9 × 10^{-3}, and the [chi] to (a) 1.09, (b) 0.54, (c) 0.27, (d) 0.11, and (e) 0.054 M. Solutions were stored at −20 °C during preparation and were then warmed to 35 ± 1 °C in a constant-temperature water bath. Progress was followed by NMR integration of the Cp resonances (δ 4.26 for **1** and 4.07 for **5**). Error limits were estimated to be ±5%. A plot of the data is shown in Figure 1 which yields pseudo-first-order rate constants of (all × 10^5) (a) 16.8, (b) 11.7, (c) 6.32, (d) 2.75, and (e) 1.40 s^{-1}, all with correlation coefficients of 0.993 or better. A plot of $1/k_{obsd}$ vs. 1/[chi] (not shown) gave a slope of 3.76 × 10^3, intercept of 2.03 × 10^3, correlation coefficient of 0.9998, $k_1 = 4.9 \times 10^{-4}\ s^{-1}$, and $k_2/k_{-1} = 0.54\ L\ M^{-1}$.

Insertion in the Presence of ^{13}CO. A solution of 20 mg of **1** in 2 mL of CD_3NO_2 and 2 mL of $EtNO_2$ in a 12-mm NMR tube was placed under 30 psi (in ca. 16 mL) of 90% ^{13}C CO and the tube was sealed. After 8 h of vigorous shaking, only peaks for solvent and terminal CO (δ 222.4, $J_{PC} = 31.5$) were visible (signal/noise = 10 for the latter). No peak was visible for the acyl carbon (δ 271.1, $J_{PC} = 23$).

Electrochemical Measurements. Nitroethane solutions 0.10 M in $N(n\text{-}Bu)_4\ PF_6$ were used. Cyclic voltammetry of the solvent/electrolyte alone showed reduction below −1.2 V (SCE). The cyclic voltammogram of a 1 × 10^{-3} M solution of**1** at 200 mV/sec was quasireversible at best and contained oxidation peaks at approximately $E_{1/2} = 0.29$, 0.40, and 0.75 V, with reduction at 0.23, 0.33, and 0.66 V.

$BF_3 \cdot Et_2O$ Catalysis. (a) Complex 1. First, 0.5 mL of a 7.0 × 10^{-3} M solution of freshly distilled $BF_3 \cdot Et_2O$ in $EtNO_2$ was added to 25 mg of **1a** in 25 mL of the same solvent. After reaction for 1 h at 50 psi of CO, only product **2b** could be isolated (85% yield). NMR/shift reagent analysis showed this to be of 78% ee. A very similar sample of **1** and BF_3 ethereate was prepared under a 70 psi of CO in a sealed NMR tube, and after 15 min only product **2** could be detected by NMR.

(b) Complex 3. A solution of 13.3 mg (4.0 × 10^{-2} mmol) of **3** and 5 μL of a 7.0 × 10^{-2} M toluene solution of $BF_3 \cdot Et_2$ in 0.5 mL of CD_3NO_2 in an NMR tube was frozen, evacuated, and refilled with CO and sealed with a resultant CO pressure of 65 psi (ca. 0.3 mmol). The tube was shaken vigorously at ambient temperature. Progress of the reaction was followed by integration of the NMR resonances of the Cp groups (δ 4.52 for **3** and 4.65 for **6**) with respect to one another and to the toluene internal standard. A plot of ln ($[\mathbf{3}]_0/[\mathbf{3}]_t$) vs. time was linear for about 2 h (ca. 10% conversion) after which strong curvature appeared. The linear component of the curve yielded a pseudo-first-order rate constant of 1.2 × 10^{-5} s^{-1} (correlation coefficient = 0.983), with a "$t_{1/2}$" of 16 h.

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(32) Complexation of Lewis acids to metal centers in electron-rich complexes is well known: (a) Flood, T. C.; Rosenberg, E.; Sarhangi, A. *J. Am. Chem. Soc.* **1977**, *99*, 4334–40. (b) Edgar, K.; Johnson, B. F. G.; Lewis, J.; Wild, S. B. *J. Chem. Soc. A* **1968**, 2851.

(33) Shriver, D. F. *J. Organomet. Chem.* **1975**, *94*, 259–71.

(34) (a) Roesnblum, M. *Acc. Chem. Res.* **1974**, *7*, 122. (b) Johnson, M. D. *Ibid.* **1978**, *11*, 57–64.

(35) Butts, S. B.; Strauss, S. H.; Holt, E. M.; Stimson, R. E.; Alcock, N. W.; Shriver, D. F. *J. Am. Chem. Soc.* **1980**, *102*, 5093–5100.

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After 15 h, the sample was worked as usual with the results recorded in Table II.

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Registry No. (*S*)-**1a**, 53318-85-7; (*S*)-**2a**, 53403-10-4; (*R*)-**2b**, 87069-62-3; (*S*)-**3a**, 87040-83-3; (*S*)-**4a**, 87069-63-4; (*R*)-**4b**, 87040-79-7; (*S*)-**5b**, 87040-80-0; (*S*)-**6b**, 87069-66-7; CO, 630-08-0; cyclohexyl isocyanide, 931-53-3.

Crystal and Molecular Structure of the Ferrous Ion Complex of A23187

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Abstract: The 1:2 ferrous ion complex of the ionophorous antibiotic A23187 has been prepared, and its structure has been determined by single-crystal X-ray diffraction techniques. Crystals of the compound formed in the orthorhombic space group $P2_12_12_1$ with unit cell dimensions $a = 24.174$ (11) Å, $b = 17.642$ (12) Å, and $c = 14.947$ (9) Å, and with one molecule of the complex and two disordered molecules of solvent ethanol per asymmetric unit. They are isomorphous with crystals of the corresponding 6-coordinate calcium complex. The structure was refined by blocked-matrix least-squares methods to an R_F of 0.10 based on the 2256 observations with $|F_o| > 3\sigma(|F_o|)$. Coordination to the ferrous ion is approximately octahedral through a carboxyl oxygen, the nitrogen of the benzoxazole ring system, and the carboxyl oxygen of each ligand with the two A23187 moieties being disposed so that the molecule as a whole exhibits pseudo-2-fold symmetry. The Fe–O distances range from 2.01 to 2.19 Å while the Fe–N distances are both 2.22 Å.

The ionophorous antibiotic A23187 (Figure 1) is a monocarboxylic acid which has been shown to transport divalent cations (e.g., Mn^{2+}, Ca^{2+}, Mg^{2+}) across natural and artificial membranes.[2–5] It is unique among ionophores in that its specificity pattern is similar to those of divalent cation pumps in natural membranes.[5] The high selectivity shown by A23187 is a consequence of charge interactions, ion solvation energies, ionic radii, and the small number of ligating atoms available from a single ionophore molecule.[5]

Recent studies have shown that iron is also transported by A23187 across liposomes,[6,7] red blood cells,[6,7] and hepatocytes membranes.[8,9] Hence it is a useful experimental tool for investigating the mechanism of iron transport across biological membranes and may have clinical potential in iron mobilization in diseases associated with iron overload, such as thalassemia.[8,9] A major restriction to the clinical use of A23187, however, is its relatively high toxicity due primarily to its ability to transport calcium ions. Any modification of its structure which resulted in an increase of its affinity for iron relative to that for calcium would therefore increase its potential as an iron mobilizing agent for use in "mixed ligand chelation therapy".[10]

The exact nature of the iron complex with A23187 is not known. The structure of the free acid of A23187 has been determined by chemical methods and by X-ray crystallographic techniques (Figure 1).[11] More recently two different crystal structures of the 1:2 calcium:ionophore complex have been elucidated.[12,13] In both complexes the calcium ion is coordinated to each A23187 molecule through a carboxyl oxygen atom, the nitrogen atom of the benzoxazole ring system, and a carbonyl atom in such a manner that the complexes as a whole exhibit pseudo-2-fold symmetry, the axes passing through the calcium ions. In one structure a water molecule is also bound to the calcium ion, whose coordination number in this case is thus 7.[13,14] To accommodate this extra ligand the geometry surrounding the calcium ion in this complex is considerably different from that in the other nearly octahedral molecule; the calcium–ligand bond lengths, for example, are all 0.2–0.3 Å longer. In both structures the complex molecules are stabilized by head-to-tail hydrogen bonding between the two A23187 molecules.

The work described here was undertaken (1) to determine whether the putative ferrous ion–ionophore complex could be crystallized in stable form, (2) to analyze the chemical nature and detailed structure of the iron complex, and (3) to investigate the feasibility of designing an analogue of A23187 having enhanced specificity for iron transport through biological membranes.

Experimental Section

Single crystals of the iron–A23187 complex were prepared from ethanol under strictly anaerobic conditions. A23187 (5 mg) dissolved in 4 mL of 95% ethanol (pH 4) was warmed to 50 °C, gassed with nitrogen for 5 min, and then mixed with a freshly prepared solution of $FeSO_4$ (equimolar in iron) in 0.1 M ascorbic acid (pH 3.0). After further gassing with nitrogen for 5 min the resulting solution was tightly stoppered and allowed to stand at room temperature. Yellow, elongated

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(1) (a) Department of Physiology. (b) Crystallography Centre.

(2) Reed, P. W.; Lardy, H. A. *J. Biol. Chem.* **1972**, *247*, 6970–6977.

(3) Caswell, A. H.; Pressman, B. C. *Biochem. Biophys. Res. Commun.* **1972**, *49*, 292–298.

(4) Deber, C. M.; Pfeiffer, D. R. *Biochemistry* **1976**, *15*, 132–141.

(5) Pfeiffer, D. R.; Reed, P. W.; Lardy, H. A. *Biochemistry* **1974**, *13*, 4007–4014.

(6) Young, S.; Baker, E.; Gomperts, B. D.; Huehns, E. R. "Proteins of Iron Storage and Transport in Biochemistry and Medicine"; Crichton, R. R., Ed.; North-Holland: Amsterdam, 1975; 417–426.

(7) Young, S. P.; Gomperts, B. D. *Biochem. Biophys. Acta* **1977**, *469*, 281–291.

(8) Young, S. P.; Baker, E.; Huehns, E. R. *Br. J. Haematol.* **1979**, *41*, 357–363.

(9) Baker, E.; Vicary, F. R.; Huehns, E. R. *Br. J. Haematol.* **1981**, *47*, 493–504.

(10) Jacobs, A. *Br. J. Haematol.* **1979**, *43*, 1–4.

(11) Chaney, M. O.; Demarco, P. V.; Jones, N. D.; Occolowitz, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 1932–1933.

(12) Chaney, M. O.; Jones, N. D.; Debono, M. *J. Antibiot.* **1976**, *29*, 424–427.

(13) Smith, G. D.; Duax, W. L. *J. Am. Chem. Soc.* **1976**, *98*, 1578–1580.

(14) Smith, G. D.; Duax, W. L. "Metal-Ligand Interactions in Organic Chemistry and Biochemistry", Part I; Pullman, B.; Goldblum, N., Eds.; D. Reidel: Dordrecht-Holland; 1977, 291–315.

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