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Asymmetric Homogeneous Hydrogenation Catalyzed by a Cobalt Complex. High Enantiomeric Excess via Statistically Designed Experiments and Mechanistic Studies

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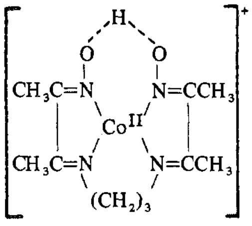
This study describes the asymmetric homogeneous hydrogenation of a variety of keto substrates by $[Co^{II}(BDM1,3pn)]^+$. (The quadridentate, mononegative ligand $(BDM1,3pn)^-$ is formed by the condensation of 2,3-butanedione monooxime and 1,3-propanediamine in a 2:1 molar ratio.) The use of a 2^n factorial experimental design and statistical analyses of the results in conjunction with mechanistic studies resulted in the presently highest percent enantiometric excess (% S − % R) published for a cobalt catalyst. The maximum 79% enantiomeric excess was obtained in the reduction of benzil ($C_6H_5COCOC_6H_5$) to benzoin ($C_6H_5CHOHCOC_6H_5$).

Introduction

Asymmetric homogeneous catalytic hydrogenation reactions, in which chiral catalysts are used to produce an excess of one entantiomer over the other, have been primarily carried out with rhodium catalysts.[1-3] The quality of an asymmetric reaction is measured by the percent enantiomeric excess (% ee), for example, % S − % R. Rhodium catalysts have resulted in reactions of nearly 100% ee. Unfortunately, the most effective catalysts are synthesized from very expensive metals of the second and third transition series. For this reason and because of the lack of data on cobalt systems we are studying the reactions of a cobalt(II) catalyst $[Co^{II}(BDM1,3pn)]^+$ (structure I).[4]



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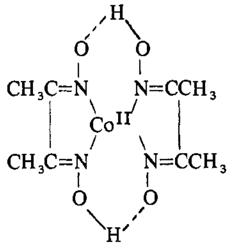


II

Although there have been no previous studies on the $[Co^{II}(BDM1,3pn)]^+$ system, the $Co^{II}(dmg)_2$ system (structure II)[4] has been thoroughly studied by Ohgo and co-workers.[5-10] In the presence of quinine and related chiral bases (Figure 1) they effected the asymmetric reduction of the α-diketone benzil ($C_6H_5COCOC_6H_5$) to the α-hydroxy ketone benzoin ($C_6H_5COCHOHC_6H_5$). The maximum % ee obtained by Ohgo and co-workers was 78.[10] They obtained the high % ee with the aid of a mechanistic study. Another group obtained a maximum 70% ee using as a catalyst a bis complex of cobalt(II) and a camphor dioxime.[11] Our preliminary communication[12] has a 65% maximum ee for the $[Co^{II}(BDM1,3pn)]^+$ system with the benzil substrate.

We approached our goal of obtaining the highest % ee for the reduced substrates in the $[Co^{II}(BDM1,3pn)]^+$ system from two points of view. (1) We realized that a random or intuitive varying of the many experimental variables would be ineffectual and that statistically designed and analyzed experiments would be necessary. (2) The statistical analysis would be most effective in conjunction with a mechanistic study.

A statistical technique to the study of these catalytic reductions was chosen for five reasons. (1) The complexity of the system caused meaningless results when only one variable at a time was changed. (2) The different variables must be examined without personal bias. (3) Statistically designed experiments furnish the greatest amount of information for the fewest number of experiments performed. (4) Significant effects may be separated from insignificant ones. (5) The effect of a variable on other variables may be measured. A qualitative discussion of the statistical design of experiments is given in the Appendix.

Experimental Section

Materials. Organic and inorganic compounds were used as purchased from VWR, Aldrich, Eastman, or Fisher. Discolored liquids were distilled to remove the colored impurities. Solvents were dehydrated and distilled by published methods.[13]

Gas–Liquid Phase Chromatography. A Varian Aerograph Series 1860-1 gas chromatograph was used to identify products of some reductions. A flow rate of 20 mL of N_2/min was used with a 6-ft × $^1/_8$-in. column packed with 10% QF-1 on Chromosorb W (80–100 mesh) at 175 °C to separate components of the reductions. When used for quantitative analysis, samples of known volume and concentration were injected into the instrument to generate a graph of instrument response vs. concentration for each compound being analyzed.

Proton Magnetic Resonance Spectra. Proton magnetic resonance spectra were obtained using a JEOL JNM-MH 100 nuclear magnetic resonance spectrometer. Tetramethylsilane was used as an internal standard. D_2O was shaken with alcohol samples after the initial spectra were taken to remove the OH peak.

Optical Rotations. Optical rotations were measured on a Zeiss Photoelectric Precision polarimeter (0.005°) using 50- and 100-mm glass polarimeter cells. The calculation of the specific rotation of the reduced substrate at the sodium D line (α_D) was done in the usual fashion.[13] The % ee was calculated according to eq 1 in which $[\alpha]_D$

$$\%\,ee = \%S - \%R = \frac{\alpha_D}{[\alpha]_D} \times 100 \qquad (1)$$

is the specific rotation for the pure enantiomer at the sodium D line. The $[\alpha]_D$ values of the reduced substrates are as follows: $C_6H_5CHOHCO_2CH_3$, +252°;[14] $C_6H_5COCHOHC_6H_5$, +118°;[15] $CH_3CHOHCO_2CH_3$, +8.2°.[16] At and above the 50% ee level replicate values are within ±3%.

Reduction and Isolation Procedures. All the reductions were carried out in a similar manner. In a typical reduction, benzylamine (0.129 g, 0.131 mL, 0.0012 mol) was dissolved in 100 mL of deoxygenated benzene–methanol (9:1 v/v). $CoCl_2 \cdot 6H_2O$ (0.286 g, 0.0012 mol), H(BDM1,3pn)[17] (0.288 g, 0.0012 mol), quinine (1.233 g, 0.0036 mol), and benzil (5.046 g, 0.024 mol) were added to the flask. The system was flushed with H_2 at atmospheric pressure, warmed to 38 °C, and cooled to the desired temperature. After 12 h the flask was opened and the product isolated by method 1 (see below). The chemical yield, as determined by an acylation method,[18] was 99.8%. The % ee was 35.

The products were separated by two methods. **Method 1** was used for water-insoluble substrates and products (benzoin and mandelic acid). The reaction mixture (usually 100 mL) was diluted with an equal volume of solvent and then extracted twice with equal volumes (200 mL) of H_2O, 10% aqueous HCl, saturated aqueous $NaHCO_3$, and H_2O. The organic solvent was dried over anhydrous $MgSO_4$ and removed on a rotary evaporator. **Method 2** was used for methyl lactate because it is water soluble. This reduced substrate was vacuum-distilled

Table I. Substrates Reduced in the $[Co^{II}(BDM1,3pn)]^+$ System

Substrate	Products	% yield	Max % ee
$C_6H_5COCO_2CH_3$	$C_6H_5CHOHCO_2CH_3$[a]	93	48
$C_6H_5COCOC_6H_5$	$C_6H_5COCHOHC_6H_5$	99	79
$C_6H_5COCF_3$	$C_6H_5CHOHCF_3$	65	0
CH_3COCO_2H	$CH_3CHOHCO_2H$	Trace	*b*
$C_2H_5CO_2CHCH_3COCO_2C_2H_5$	*c*	≃70	*b*
$CH_3COCO_2CH_3$	$CH_3CHOHCO_2CH_3$	97	48

[a] Unknown racemic product in unknown yield also observed. [b] % ee not calculated. [c] Nature of reduced product unknown.

Table II. Variable Settings for the Four Factorial Experiments

Factorial expt	Variable	Variable settings[a] High	Low
6-factor	[Cat], M	0.012	0.008
	Quinine:cobalt	3	1
	Benzylamine:cobalt	1	0
	Substrate:cobalt	20	10
	Temp, °C	30	7
	Reaction time, h	12	6
1st 2-factor[b]	[Cat], M	0.020	0.010
	Quinine:cobalt	4	2
3-factor[c]	[Cat], M	0.016	0.010
	Substrate:cobalt	25	15
	Reaction time, h	24	12
2nd 2-factor[d]	% methanol in benzene	20	10
	Ligand:cobalt	1.2	1.0

[a] The center settings are halfway between the high and low settings. [b] Constant settings: benzylamine:cobalt = 1, substrate:cobalt = 20, temperature 30 °C, reaction time 11 h. [c] Constant settings: quinine:cobalt = 3, benzylamine:cobalt = 1, temperature 30 °C. [d] Constant settings: [Cat] = 0.010 M, quinine:cobalt = 3, benzylamine:cobalt = 1, substrate:cobalt = 20, temperature 30 °C, time 12 h.

from the reaction mixture. The distillate was then carefully distilled again to obtain a solvent-free product.

Once the product was obtained free of the solvent, chemical and optical yields were determined without any further attempt to purify the product. This prevents changes in optical yield during purification. Recrystallization of benzoin, for example, results in lowered optical activity in the solid and increased optical activity in the mother liquor.[8]

Reaction Conditions Investigated. We studied a total of ten variables in attempts to achieve the highest % ee. Some of the variables and their ranges are temperature (−10 to +30 °C), time (3–72 h), quinine:cobalt (1–4), base:cobalt (0–1), H(BDM1,3pn):cobalt (1–1.2), substrate:cobalt (6–25), and catalyst concentration (0.008–0.020 M). In addition we used several axial bases including $(n\text{-Bu})_3P$, Ph_3P, Et_3N, and $PhCH_2NH_2$ and a variety of solvents including dioxane, acetic acid, benzene–methanol, toluene–methanol, and toluene–2-propanol. Table I shows the substrates studied along with their percent chemical yield and their maximum percent ee.

Factorial Experiments. Four factorial experiments were performed: a six-factor screening experiment, two two-factor experiments, and one three-factor experiment. The values of the variables studied in the factorial experiments are in Table II.

Racemization of Benzoin. Optically active benzoin (5 g) was placed in 100 mL of 9:1 benzene–methanol (v/v), and H_2 was placed over the solution. Samples were withdrawn at 6-h intervals and placed in a polarimeter to check optical rotation. No loss of optical rotation was noted. After 48 h and at 48-h intervals, the following substances were added: benzylamine (0.129 g, 0.131 mL, 0.0012 mol), quinine (1.233 g, 0.0036 mol), $CoCl_2\cdot 6H_2O$ (0.286 g, 0.0012 mol), and H(BDM1,3pn) (0.288 g, 0.0012 mol). The optical rotation remained constant until $CoCl_2\cdot 6H_2O$ was added. At this point, there was slow loss in optical rotation until H(BDM1,3pn) was added.

Addition of CH_3I to the Reduction Mixture. A typical hydrogenation was initiated and allowed to run to 50% completion (1 h). Then excess methyl iodide was added and the hydrogenation quickly ceased. After 45 min the solution was extracted with water, and a quantitative amount of $[CH_3Co(BDM1,3pn)]^+$ was determined by spectrophotometric analysis at 460 nm (ε 2120 M^{-1} cm^{-1}).[19]

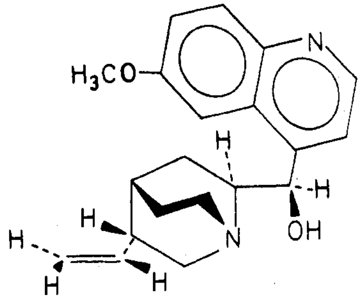


Figure 1. The chirality of quinine.

Formation and Reactions of $[HCo^{III}(BDM1,3pn)]^+$. $Co^{III}(BDM1,3pn)Br_2$ was suspended in deoxygenated methanol. $NaBH_4$ in methanol (pH 13 by addition of NaOH) was slowly added until the solution just remained blue, indicating the formation of $Co^{I}(BDM1,3pn)$. $[HCo^{III}(BDM1,3pn)]^+$ was formed by careful addition of 1 M $HClO_4$ until the color of the solution changed from blue to yellow (eq 2). The addition of NaOH reversed the equilibrium,

$$Co^{I}(BDM1,3pn) + H^+ \rightleftharpoons [HCo^{III}(BDM1,3pn)]^+ \qquad (2)$$

re-forming $Co^{I}(BDM1,3pn)$. The cobalt(I) complex was identified by its $[CH_3Co(BDM1,3pn)]^+$ product upon addition of methyl iodide.[19,20]

Deuterium Experiments. Experiments were run with D_2 and/or CH_3OD under the following conditions: [catalyst] = 0.01 M, quinine:cobalt = 3, benzylamine:cobalt = 1, substrate:cobalt = 20, temperature 30 °C, reaction time 6 h, and solvent 10% methanol in benzene. Three experiments in which $C_6H_5COCOC_6H_5$ was the substrate were run. Experiment 1 with CH_3OD and H_2 and experiment 2 with CH_3OD and D_2 both resulted in about 50% D on the alcohol carbon of the reduced substrate. Experiment 3 with CH_3OH and D_2 resulted in 5% D. The analyses were done by NMR.

Results and Discussion

Scope of the System. In a typical experiment benzylamine, cobalt(II) chloride hexahydrate, H(BDM1,3pn), quinine (Figure 1), and a substrate were dissolved in a deoxygenated benzene–methanol solvent. Then hydrogen at atmospheric pressure was added. The benzylamine coordinates trans to the active site thus increasing the rate of the reaction and preventing trans coordination of the chiral molecule quinine.[10]

The prochiral substrates reduced by the $[Co^{II}(BDM1,3pn)]^+$ system, their chemical yield, and their highest % ee are given in Table I. Based on these results, we decided to emphasize benzil ($C_6H_5COCOC_6H_5$) in the research. We did this primarily because the reduction product benzoin is easy to separate from the reaction mixture, is not readily racemized during the reaction, and is easily analyzed by acylation.[18] In addition its absolute configuration is known.[21]

Factorial Experiments. Because the $[Co^{II}(BDM1,3pn)]^+$ catalytic system is so complex with so many potentially important variables, attempts to improve the % ee by changing one variable at a time lead to erroneous conclusions. A large number of variables were considered important (see Experimental Section), but experimental considerations forced us to choose six for a screening experiment. They are catalyst concentration ([Cat]), quinine:cobalt ratio (Q:B), benzylamine:cobalt ratio (BA:Co), substrate:cobalt ratio (S:Co), reaction temperature, and reaction time.

Initially a half-fractional six-factor screening experiment of 40 reductions was run with the above six variables at the settings shown in Table II. The % ee ranged from 6.4 to 59.7. The highest value was obtained for [Cat] = 0.010 M, Q:Co = 3, BA:Co = 1, S:Co = 20, temperature 7 °C, and reaction time 12 h. However, the goal of the screening experiment was not to obtain the highest % ee but to evaluate the importance of the individual variables and their interactions. The calculated *F* statistic shows that the Q:Co ratio is clearly the most important variable, followed by the temperature. The results show predictably that a high Q:Co and a low temperature enhance the % ee. After the above two single variables, the most important effect is the two-factor interaction between the [Cat] and time. The positive sign of the effect suggests that both variables should be set at high (or low) values. On the basis of the statistical analyses of the six-factor experiment, we predicted optimum reaction conditions of [Cat] = 0.008 M, Q:Co = 2, BA:Co = 1, S:Co = 20, temperature 8 °C, and time 6 h. The calculated % ee based on these conditions would be 64.6. Details of the statistical analysis of the factorial experiments are available.[22]

On the basis of the results of the six-factor screening experiment, we did ten reductions for a first two-factor experiment (Table II) with the variables [Cat] (0.010–0.020 M) and Q:Co (2–4). We chose these variables because both were significant in the six-factor screening experiment and they did not strongly interact. In addition, the [Cat] was chosen because of ambiguity in the six-factor experiment with respect to its high or low setting. The results of this set of experiments demonstrated that Q:Co should be at a high setting and [Cat] at a low one.

Next a three-factor experiment of 12 reductions was run. The variables (Table II) chosen were [Cat] (0.010–0.016 M), S:Co (15–25), and time (12–24 h). We chose these variables primarily because each of their two-factor interactions were important in the six-factor screening experiment, but their optimum settings were unclear. In this experiment only the reaction time and the [Cat]–S:Co interaction were significant. Both effects are equally important and negative; the signs of the effects mean that low [Cat], short reaction time, and high S:Co will lead to the highest % ee.

A second two-factor experiment of ten reductions was done using two previously unstudied variables (Table II): the percent methanol in benzene (% MeOH, 10–20%) and the H(BDM1,3pn):Co (L:Co, 1–1.2) ratio. The second variable was chosen because there was a negative effect of time in the three-factor experiment and because we knew that free Co^{2+} caused racemization of the chiral benzoin (see Experimental Section). The % MeOH variable was chosen because previous experiments in the $Co^{II}(dmg)_2$ system[5,8] showed a low-polarity solvent enhanced the % ee. The results of this set of experiments showed that both variables and their interaction are significant. The highest % ee was obtained with 10% methanol in benzene and a 20% excess of ligand. The latter result confirms our observation that free Co^{2+} catalyzes the racemization of the product. The % MeOH is low for the highest % ee because the polarity of the solvent and/or its acidity adversely affect the asymmetric syntheses. The solvent effect is further considered below.

The four factorial experiments indicate that the conditions shown in Table III (second column) should result in a high % ee. The optimum settings of all variables were not determined exactly, but the direction in which to change them is indicated. The factorial experiments not only direct the researcher toward the specific goal of increasing the % ee but also give insights into the reaction mechanism. The factorial method shows what variables are important and how the variables interact with one another. The significant variables and interactions may then give clues about the mechanism that might be missed if only one variable at a time were changed.

Table III. Predicted and Observed Reaction Conditions to Maximize % ee in the $[Co^{II}(BDM1,3pn)]^+$ System

Variable	Conditions	
	Predicted[a]	Obsd[b]
[Cat], M	0.01 or lower	0.010
Quinine:cobalt	4 or higher	4
Benzylamine:cobalt	1	1
Substrate:cobalt	20 or higher	20
Temp, °C	As low as possible	−8
Time, h	As short as possible	24
Solvent	Nonpolar, nonacidic	10% 2-propanol in toluene
Ligand:cobalt	1.2	1.2

[a] Predicted by the four factorial experiments. [b] For maximum 79% ee with the benzil substrate. Chemical yield is 99.3%; a 12-h reaction resulted in 88.0% chemical yield and similar % ee.

The combination of the 72 reductions run during the four factorial experiments and mechanistic studies (see below) resulted in the presently highest % ee in a cobalt system. The maximum 79% ee for the reduction of benzil to (*S*)-(+)-benzoin occurred under the conditions of the third column of Table III.

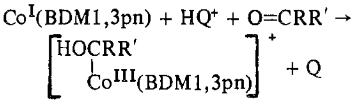
Mechanism of the Reaction. The rhodium catalysts utilized for homogeneous asymmetric hydrogenation typically contain a nondissociating chiral ligand, which imparts chirality to the catalytic rhodium site.[1-3] Thus, in most rhodium systems a chiral ligand, a substrate, and hydrogen are simultaneously coordinated. Because of the nonlabile macrocyclic ligand in $[Co^{II}(BDM1,3pn)]^+$, the substrate, the chiral quinine, and hydrogen probably have available only one coordination site. This assumes that the benzylamine coordinates trans to the active site, which it does in the $Co^{II}(dmg)_2$ system,[10] and that 6 is the maximum coordination number of cobalt. The mechanism suggested below, which is similar to the one proposed for the $Co^{II}(dmg)_2$ system,[10] will first be presented; then evidence in its support will be discussed.

The proposed mechanism (eq 3) consists of six steps (Q is

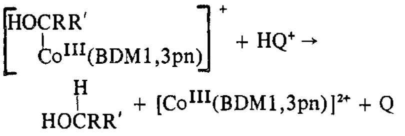
$$H_2 + 2[Co^{II}(BDM1,3pn]^+ \rightleftharpoons 2[HCo^{III}(BDM1,3pn]^+ \quad (3a)$$

$$2[HCo^{III}(BDM1,3pn)]^+ \rightleftharpoons 2H^+ + 2Co^{I}(BDM1,3pn) \quad (3b)$$

$$2H^+ + 2Q \rightleftharpoons 2HQ^+ \quad (3c)$$



$$Co^{I}(BDM1,3pn) + HQ^+ + O{=}CRR' \rightarrow \left[\begin{array}{l} HOCRR' \\ \quad | \\ \quad Co^{III}(BDM1,3pn) \end{array}\right]^+ + Q \quad (3d)$$



$$\left[\begin{array}{l} HOCRR' \\ \quad | \\ \quad Co^{III}(BDM1,3pn) \end{array}\right]^+ + HQ^+ \rightarrow \begin{array}{c} H \\ | \\ HOCRR' \end{array} + [Co^{III}(BDM1,3pn)]^{2+} + Q \quad (3e)$$

$$Co^{I}(BDM1,3pn) + [Co^{III}(BDM1,3pn)]^{2+} \rightarrow 2[Co^{II}(BDM1,3pn)]^+ \quad (3f)$$

quinine). Equation 3a is the cleavage of H_2 by the cobalt(II) catalyst to produce the cobalt(III) hydride. The hydride then ionizes to form a proton and the cobalt(I) complex in eq 3b. The proton reacts in eq 3c with the strongly basic nitrogen on the quinuclidine ring of the quinine (Figure 1). The fourth step (eq 3d), which determines the stereochemistry of the product, consists of activation of the substrate by protonated quinine as the cobalt(I) to carbonyl carbon bond is formed and the proton is transferred from the quinine to the carbonyl oxygen. Protonated quinine then attacks as an electrophile in eq 3e to displace the cobalt(III) complex by backside attack. Finally, in eq 3f, the second cobalt(I) complex produced in eq 3b combines with this cobalt(III) complex to regenerate the 2 mol of the cobalt(II) complex. Evidence in support of this mechanism follows.

Homolytic activation of H_2 (eq 3a) is known for many catalytic cobalt systems, including $[Co^{II}(CN)_5]^{3-}$ [1-3] and $Co^{II}(dmg)_2$,[23,24] and is undoubtedly responsible for the formation of the catalytically active Co^{I}(BDM1,3pn) (see below). Heterolytic cleavage of H_2 is not reasonable because the unlikely complexes $[HCo^{IV}(BDM1,3pn)]^{2+}$ and/or HCo^{II}(BDM1,3pn) would be formed. Nor could traces of $[Co^{III}(BDM1,3pn)]^{2+}$ or Co^{I}(BDM1,3pn) account for the heterolytic activation of H_2, because these complexes do not react with H_2 under the reaction conditions.

The cobalt(III) hydride formed in eq 3a is not the active catalyst. This was shown by in situ preparation of the hydride,[12] its interconversion (eq 3b) with the cobalt(I) analogue, and its nonreactivity toward a variety of substrates including benzil. In contrast we have several reasons that Co^{I}(BDM1,3pn) is the active catalyst. For example, the observation that just after the reaction is initiated at 38 °C, the orange-red reaction mixture color darkens is suggestive of the formation of deep blue Co^{I}(BDM1,3pn).

Better evidence for the cobalt(I) complex as the active species is provided by the addition of methyl iodide to the reaction mixture.[12] When methyl iodide is added to the reaction mixture while benzil is being reduced, the hydrogenation reaction quickly stops and $[CH_3Co(BDM1,3pn)]^+$ is formed quantitatively within 45 min. These results are in agreement with the rapid reaction of Co^{I}(BDM1,3pn) (formed in eq 3b) with methyl iodide.[25]

The Co^{I}(BDM1,3pn) must be nucleophilic to act as a catalyst via formation of a cobalt–carbon bond with the substrate. Strong π-acceptor ligands reduce the nucleophilicity of cobalt(I) complexes.[25] If we add sufficient tri-*n*-butylphosphine to the reaction mixture, the reduction stops entirely. The resulting blue-green color is due to the cobalt(I) complex. Pyridine also acts to stabilize Co^{I}(BDM1,3pn), but not as well as a phosphine. The reaction mixture turns blue, but reduction takes place at a slow rate. By performing these reactions in the presence of an excess of the base quinine, eq 3b is shifted toward Co^{I}(BDM1,3pn).

Additional evidence that indicates Co^{I}(BDM1,3pn) is the active species is the blue color of the reaction mixture when all of the substrate has been reduced. The reaction mixture retains the blue color of the cobalt(I) complex for 5–30 min when H_2 uptake stops and then turns orange-brown due to the hydrogenation of the ligand system as observed with $Co^{II}(dmg)_2$.[23,26]

The concomitant nucleophilic attack of Co^{I}(BDM1,3pn) on the carbonyl carbon of the substrate and the acceptance of a proton from quinine by the carbonyl oxygen are shown in eq 3d. This step and eq 3e are responsible for the stereoselectivity. The origin of the stereoselectivity is the bidentate hydrogen-bonded interaction between quinine and the substrate (Figure 2). Space-filling models show that quinine can bond to only one face of the substrate molecule while retaining the correct geometry for addition of the proton to the carbonyl oxygen. If quinidine, which has the opposite chirality of quinine, is used in place of quinine, the opposite *R*-(–) enantiomer of benzoin is produced with approximately the same % ee. This result occurs with quinidine because the opposite face of the substrate molecule becomes the correct one for addition of the proton.

We believe that initially the quinine associates with the substrate making it more susceptible to nucleophilic attack by the cobalt(I) complex. If activation of the substrate by quinine and concurrent addition of a proton to the carbonyl oxygen were not conditions for reduction, then there would be no obvious reason for the high % ee. The excess substrate would have a greater probability of being attacked with the result being an approximately racemic product. Thus there must be a concerted reaction in which the substrate is activated by quinine which donates a proton as the carbon–cobalt bond forms. The alternate mechanism of the racemic, coordinated alcohol being stereoselectively cleaved by protonated quinine cannot be completely dismissed. However, this mechanism is less likely because the apparent necessity of difunctional substrates like α-diketones, α-keto esters, etc. agrees with the substrate–quinine interaction shown in Figure 2. For example, $C_6H_5COCF_3$ was reduced to the alcohol with no enantiomeric excess (Table I).

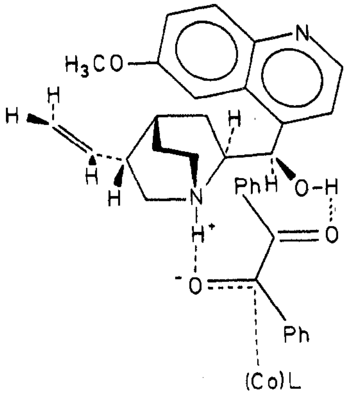


Figure 2. The quinine-coordinated benzil interactions that result in the stereoselective formation of benzoin. ---(Co)L = $[---Co^{III}(BDM1,3pn)(NH_2CH_2C_6H_5)]^+$.

Step 5 (eq 3e) in the reduction mechanism is the cleavage of the cobalt–carbon bond to form the reduced substrate and $[Co^{III}(BDM1,3pn)]^{2+}$. At least three potential reactants for the bond cleavage are present: Co^{I}(BDM1,3pn), H_2, and H^+. One group[24] suggested for the $RCo^{III}(dmg)_2$ system (R = α-styryl) that nucleophilic attack by $[Co^{I}(dmg)_2]^-$ with formation of an R^- carbanion occurs. This is not possible in the system being discussed here, because the carbanion would racemize. The cleavage of the cobalt–carbon bond by H_2 is excluded by deuteration experiments discussed below. The backside attack of H^+ from quinine, which was suggested for the $Co^{II}(dmg)_2$ system,[10] is in agreement with the (*S*)-(+)-benzoin product formed in the presence of quinine as well as the (*R*)-(–)-benzoin product formed in the presence of quinidine.

If achiral components of the reaction mixture were able to donate both protons (eq 3d and 3e), there would be nothing to direct the formation of one enantiomer over the other, and a racemic product would form. In an extreme case the addition of the strong base triethylamine considerably decreases the % ee. More subtle effects are due to the acidic proton of methanol which may be abstracted by the carbonyl oxygen as the carbon–cobalt bond forms. To investigate this possibility several experiments were run with 2-propanol to determine if the pK_a of the hydrogen on the alcohol had an effect on the observed % ee. Methanol and 2-propanol have approximate pK_a values (relative to water) of 16 and 18, respectively.[27] Under conditions of 10% alcohol in toluene that produce 65% ee with methanol[12] our highest ee, 79%, is produced with 2-propanol (Table III). Unfortunately, the alcohol cannot be entirely omitted or the catalyst will not dissolve.

Deuteration experiments were run to determine the source of the cobalt–carbon bond-breaking proton when benzoin is the reduced substrate. After extraction by method 1, the H:D

Table IV. Variable Settings and % ee Results of the Second Two-Factor Experiment[a,b]

Run[c]	% methanol[d] (level)	Ligand:cobalt[e] (level)	% ee
1, 6	20 (+)	1.2 (+)	42.0, 42.4
2, 7	10 (−)	1.2 (+)	49.7, 48.2
3, 8	20 (+)	1.0 (−)	16.2, 18.4
4, 9	10 (−)	1.0 (−)	38.2, 40.4
5, 10	15 (0)	1.1 (0)	36.3, 28.2

[a] High, center, and low variable settings are +, 0, and − level, respectively. [b] Constant settings: [Cat] = 0.010 M, quinine:cobalt = 3, benzylamine:cobalt = 1, substrate:cobalt = 20, temperature 30 °C, time 12 h. [c] For purposes of description the order of the runs is not randomized. [d] Percent methanol in benzene. [e] Ligand = H(BDM1,3pn).

ratio on the hydroxyl carbon was determined by NMR. We did experiments under three conditions: (1) MeOD and H_2, (2) MeOD and D_2, and (3) MeOH and D_2.

Experiments 1 and 2 yield approximately 50% D on the hydroxyl carbon of benzoin, while experiment 3 results in only about 5% of the deuterated product. Although these results are not straightforward, some useful conclusions can be made.

(1) The results with MeOD and H_2 and those with MeOD and D_2 are about the same because H_2 or D_2 exchanges with the acidic alcoholic proton by eq 3a and 3b. (2) The surprisingly high 50% H on the hydroxyl carbon of benzoin in the D_2–CH_3OD experiment must be due to the exchangeable ligand protons[28] and to the alcohol methyl group protons, which are known to exchange in various catalytic reactions.[29] (3) Any direct attack by D_2 in eq 3e would lead to a predominantly deuterium product, which was not observed in the D_2–MeOD experiment in agreement with the previous discussion about electrophilic proton attack. (4) Extensive exchange on the hydroxylic carbon of the reduced substrate benzoin must be ruled out, because such a process would lead to a racemic product. All of these results are in agreement with the previous discussion of the mechanism in eq 3.

The final step in the reduction is the reaction between $[Co^{III}(BDM1,3pn)]^{2+}$ and $Co^{I}(BDM1,3pn)$ to form 2 mol of the starting material $[Co^{II}(BDM1,3pn)]^{+}$. We proved that reaction 3f can occur because equal amounts of the cobalt(I) and cobalt(III) complexes combine in methanol to form the red cobalt(II) complex in a fast reaction.

This proposed mechanism accounts for all aspects of the reduction including the initial activation of H_2, the stereoselectivity of the reduction, and the regeneration of the starting cobalt(II) complex. The mechanism is unusual for synthetic systems because the chirality-determining site is attached not to the metal catalyst but to the substrate. Such a situation is similar to many reactions that take place in biological systems where the site that determines the stereochemistry of the reaction is separated from the active catalytic site.

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Appendix

The use of a 2^n factorial design[22,30] allows one to simultaneously investigate a number of different factors, termed independent variables. When there are *n* factors to be considered, 2^n experiments are necessary for all combination of factors, with each factor set at a high and a low value. When the required number of experiments are completed, all factors and their combinations may be ranked in the order of their effect on the response (or dependent) variable, which is the % ee in this paper. An analysis of variance (ANOVA) will then tell the experimentalist which factors and combinations have a significant effect on the response variable.

The first step in setting up a 2^n factorial design it to list all factors that may have an effect on the response variable. Next, factor settings should be chosen in a manner that will adequately cover a range that is normally encountered by the experiment. For example, if one normally uses reagents in 0.01 M concentration, a concentration factor set at 0.10 M would lie outside the normally encountered range, so results from the factorial experiment would not be applicable to the usual experimental conditions.

Once the factor settings are established, the high level is coded + and the low level −. The setting halfway between the two may be coded 0. Table IV shows the experimental plan for a 2^n factorial with two factors in a typical experiment. A total of $2^2 = 4$ experiments must be run to obtain the peripheral points (runs 1–4). A center point is also run to detect a maximum or minimum at the center of the experimental space (run 5). Runs 6–10 represent a duplicate set of experiments. The variables 20% MeOH and 1.2:1 L:Co are coded +, and 10% MeOH and 1:1 L:Co are coded −.

In order to avoid any bias, the order in which the experiments are performed is randomized. With a repetitious operation, the order of experiments may be important for two reasons. A learning process may be involved that makes later operations more efficient, or carelessness may have an opposite effect on later operations. The aging of reagents could also affect experimental results. Such systematic bias can be avoided by randomizing the order of the experiments by use of a random number table. The experiments are then run in this random order. More complete discussions of factorial experiments are available.[22,30]

Registry No. $[Co^{II}(BDM1,3pn)]^{+}$, 26221-16-9; $C_6H_5COCO_2CH_3$, 614-20-0; $C_6H_5COCOC_6H_5$, 134-81-6; $C_6H_5COCF_3$, 434-45-7; CH_3COCO_2H, 127-17-3; $C_2H_5CO_2CHCH_3COCO_2C_2H_5$, 759-65-9; $CH_3COCO_2CH_3$, 600-22-6; $C_6H_5CHOHCO_2CH_3$, 771-90-4; $C_6H_5COCHOHC_6H_5$, 119-53-9; $C_6H_5CHOHCF_3$, 340-04-5; $CH_3CHOHCO_2H$, 50-21-5; $CH_3CHOHCO_2CH_3$, 547-64-8; quinine, 130-95-0.

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Solvent Effects on the Coordination of Nd^{3+} in Concentrated $NdCl_3$ Solutions

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Nd^{3+} is, on the average, eight-coordinated in very concentrated solutions when anhydrous $NdCl_3$ is dissolved into 10 N hydrochloric acid or methanol as well as water. However, the extent to which $NdCl_3$ dissociates upon dissolution is dependent upon the solvent, with $NdCl(H_2O)_7{}^{2+}$, $NdCl_2(CH_3OH)_6{}^{+}$, and $Nd(H_2O)_8{}^{3+}$ being the average inner-sphere solute species in these three solutions. The inner-sphere Nd–O and Nd–Cl contact distances are ca. 2.41 and ca. 2.78 Å, respectively, and the ion-pair Nd···Cl distance is ca. 4.9 Å in each solution.

Introduction

In previous papers[1-5] it has been shown that lanthanide cations are, on the average, eight-coordinated in some concentrated solutions. These include solutions where the solvent is water and the solute is anhydrous LnX_3 (Ln = La, Nd, Gd; X = Cl, Br). In these aqueous solutions, $Ln(H_2O)_8{}^{3+}$ is the predominant solute species. However, extensive inner-sphere Ln–X bonding can occur when the solvent is methanol, and solute association appears to occur in an $LaCl_3$ solution.[3] Extensive Gd–Cl inner-sphere bonding also occurs in concentrated solutions where 10 N hydrochloric acid is the solvent;[2] but in an exactly equivalent solution where $LaCl_3$ is the solute, no inner-sphere La–Cl bonding occurs.[1]

Because differences in the extent of Ln–X inner-sphere bonding have been found in our previous investigations, we have examined two additional solutions of $NdCl_3$ with methanol and 10 N hydrochloric acid as solvents. The purpose of this investigation is to determine the following: (a) the coordination sphere details of the resulting solute complexes, (b) the extent to which Nd–Cl inner-sphere bonding occurs, (c) the extent to which Nd–Cl and/or Nd–O bonding is affected by the solvent, and (d) additional information for the development of a unifying theory regarding lanthanide–ligand interactions.

For each of the solutions examined, the mole fraction of Nd^{3+} is 0.010. The results of this investigation are compared to the results obtained from a similar study of aqueous $NdCl_3$ solutions. The solutions were examined by x-ray diffraction methods.

Experimental Section

Solutions were prepared by weight from predried anhydrous $NdCl_3$. Densities were measured with a specific gravity bulb. Solution compositions are shown in Table I, and for convenience one of the aqueous $NdCl_3$ solutions[4] is also included as solution C. Each solution was loaded into a Teflon sample holder, which had a window covered by a 1.0-mil Mylar film, and an x-ray diffraction pattern was obtained using the reflection method.[6] Scattered intensities were collected using our θ–θ diffractometer[2] as counts per preset time as a function of the scattering angle in the range $s = 1.23$–15.09 Å^{-1} ($s = 4\pi\lambda^{-1}\sin\theta$) at increments in θ of 0.25°. At least three runs over the entire angular range were made for each solution. The average intensity at each scattering point was used in subsequent calculations. For these solutions the maximum value of $\sigma < 1\%$,[7] and σ is significantly lower at most of the 219 data points at which data were collected.

Table I. Solution Compositions

	Solution		
	A	B	C
Solvent	10 N HCl	Methanol	Water
Molality	1.54	1.95	1.73
Density, g/L	1.29	1.08	1.26
Mole fractions			
Nd	0.010	0.010	0.010
Cl	0.060	0.030	0.030
O	0.300	0.160	0.320
H	0.630	0.640	0.640
C		0.160	

Table II. Summary of the ARDF'S

	Soln A	Soln B	Soln C
Peak location, Å			
C–O peak		1.48	
P1	2.49	2.56	2.41
P2	3.3	3.2	3.2
P3	4.1	4.1	3.8, 4.1
P4	4.8	4.9	4.5, 4.9
P5		5.6	6.2
P6	6.8	6.8	6.7
P7			
P8			
Area under 1st peak, e^2	101	119	83
Area/Nd^{3+}, e^2	10 100	11 900	8300
Width at half-maximum, Å	0.46	0.54	0.36

The scattered intensity was corrected for background (ca. 5 cpm), polarization,[8] sample penetration,[9] multiple scattering,[10] and, after inclusion of a monochromator discrimination function, Compton scattering.[11] The corrected intensity, e.g., the coherent intensity curve $I(s)$, was then tentatively computer fitted to $\sum x_i f_i^2(s)$,[12] according to the methods of Lawrence and Kruh.[13] Final fitting of $I(s)$ to $\sum x_i f_i^2(s)$ was performed by a method similar to that used by Konnert and Karle.[14] Atomic radial distribution functions (ARDF's) were calculated at increments in Δr of 0.01 and 0.05 Å by

$$D(r) = 4\pi r^2\rho_0 + (2r/\pi)\int[\mathrm{si}(s)]\,[M(s)]\,[\sin sr]\ ds$$