Table I. Forward Rates and Equilibrium Constants for 1 ⇌ 2

temp, °C	$10^4 k_1$, s^{-1} [a,b]	$K = [2]/[1]$ [c]
25	2.0	0.702
30	2.6	0.714
40	5.7	0.728
45	10.2	0.739
50		0.750

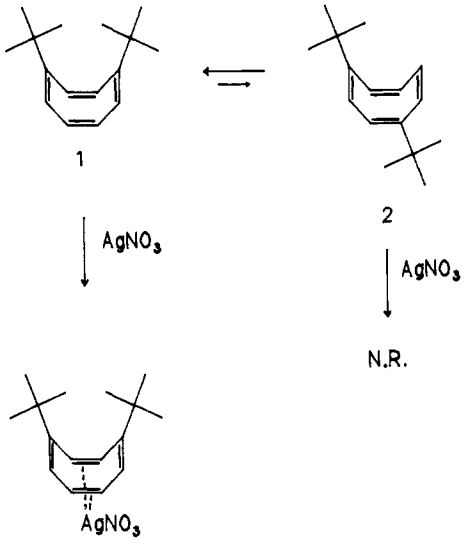
[a] Estimated error is 10%. [b] $\Delta H^{\ddagger} = 15.5$ kcal mol^{-1}, $\Delta S^{\ddagger} = -23.6$ eu. [c] $\Delta H^{\circ} = 0.48$ kcal mol^{-1}, $\Delta S^{\circ} = 0.92$ eu.

clearly evident in the 250-MHz spectrum. The olefinic region of **1** consists of a singlet (H 7, 8) at δ 6.05 and two broadened singlets (H 2, 3, 4, 5) at δ 5.78 and 5.63, while that of **2** consists of a singlet (H 7, 8) at δ 5.66 and a broadened AB quartet (H 5, 6, 7, 8) centered at δ 5.89 and 6.03, $J = 10.4$ Hz. This pattern is consistent with a very small coupling between H2 and H3 of **1** which are nearly orthogonal and a 10-Hz coupling between the cis olefinic H5 and H6 of **2**.

Integration gives a 1:2 ratio of **1**:**2** at 25 °C; that is, the 1,6 isomer in which both *tert*-butyl groups extend from the same side of the tub COT is actually more stable, despite the steric interactions between such *tert*-butyl groups indicated by models. Measurement of the equilibrium constant, $K = [2]/[1]$, by NMR integration at several temperatures gives the results summarized in Table I. Isomer **1** is more stable by $\Delta H^{\circ} = 0.48$ kcal mol^{-1}, but a small entropy change of $\Delta S^{\circ} = 0.92$ eu favors isomer **2**. Rotational entropy (symmetry number) and entropy of mixing (**2** exists as enantiomer pairs) contributions to the equilibrium cancel; hence, the experimental ΔS° change indicates slightly greater freedom of motion for **2**.

Why is **1**, the apparently more congested isomer, also the more stable? The only reasonable explanation is that the *tert*-butyl groups in **1** are actually positioned just at the edge of steric repulsion and intramolecular van der Waals attraction dominates. van der Waals forces are certainly important in chemistry but have rarely been implicated as a significant intramolecular effect in nonmacromolecular organic compounds.[3]

Treatment of the mixture of isomers with excess hot alcoholic silver nitrate gives a single crystalline adduct, mp 151 °C, having a satisfactory analysis.[4] The 250-MHz NMR spectra is simple, δ ($CDCl_3$) 6.31 (s, 2 H), 5.99 (br s, 2 H), 5.72 (br s, 2 H), 1.10 (s, 18 H), and is consistent only with the $AgNO_3$ complex of **1**. In **2** both faces of the tub COT are blocked by the *t*-Bu groups and adduct formation is not expected. Such an adduct would be expected to show six different olefin and two different *t*-Bu signals.



A $CDCl_3$ solution of the adduct in an NMR tube was quenched with aqueous NH_3 and produced signals associated with **1**. The NMR spectrum changed gradually to that of the equilibrium mixture of **1** and **2**. The reaction followed first-order kinetics, and the kinetic results at several temperatures are summarized in Table I. The activation energy is typical of other double bond isomerizations of substituted COTs,[5] but the magnitude of the entropy of activation, $\Delta S^{\ddagger} = -23.6$ eu, is unusually high for a unimolecular process. Even the isomerizations of 1,2,3-trimethyl ($\Delta S^{\ddagger} = -12$ eu) and 1,2,3,4-tetramethylcyclooctatetraenes ($\Delta S^{\ddagger} = -13.3$ eu) as reported by Paquette et al.,[6] and in which vicinal butressing effects dominate, have lower entropy demands. Evidently, in the planar [8]annulene transition state, the relatively large internal angle of the octagon (135°) results in sufficient interaction between *tert*-butyl and adjacent ring hydrogens that the *tert*-butyl motions are severely encumbered.

These results prompt additional questions concerning disubstituted cyclooctatetraenes which are currently under study in our laboratory.[7]

Acknowledgment. This work was supported in part by NSF Grant CHE 78-24084 and the Division of Nuclear Sciences, Office of Basic Energy Services, U.S. Department of Energy, under Contract W-7405-Eng-48.

(3) One example of the incursion of the effect appears to occur in 1,3,5-trineopentylbenzene: Carter, R. E.; Nilsson, B.; Olsson, K. *J. Am. Chem. Soc.* **1975**, *97*, 6155. Another example may well be in the unusual conformations preferred by 2,2-dimethyl-4-phenyl-3-pentanols: Kodama, Y.; Nishihata, K.; Zushi, S.; Nishio, M.; Uzawa, J.; Sakamoto, K.; Iwamura, H.; *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2661.

(4) Analysis by Analytical Services Laboratory, University of California, Berkeley. Anal. Calcd for $C_{16}H_{24}{\cdot}AgNO_3$: C, 49.76; H, 6.26; N, 3.63. Found: C, 50.29; H, 6.24; N, 3.69.

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(7) After submission of this paper we learned that Professor Pacquette has independently prepared the compound and observed the transformation of **1** and **2**.

Catalysis of Ester Aminolysis by Divalent Metal Ions

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A number of reactions involving a variety of organic substrates possessing metal ion coordinating or -chelating sites proximate to the reactive center have been shown to be susceptible to catalysis by divalent metal ions. Such reactions include hydrolysis of nitriles,[1] esters,[2,3] amides,[4] and acetals,[5] hydration of aldehydes,[6] and formation of Schiff bases.[7] In most cases such studies, often carried out as models of enzymatic processes, have involved reactions of a hydrolytic nature; few such metal-ion-catalyzed reactions leading to more complex products have been studied, and among the exceptions,[8] the potential synthetic value lacks generality.

One class of synthetically useful reactions of considerable importance is amide bond formation; the repetitive generation of amide bonds in peptide synthesis is an obvious example of that importance. Since a variety of acyl substitution processes have been shown to be susceptible to catalysis by metal ions coordinated

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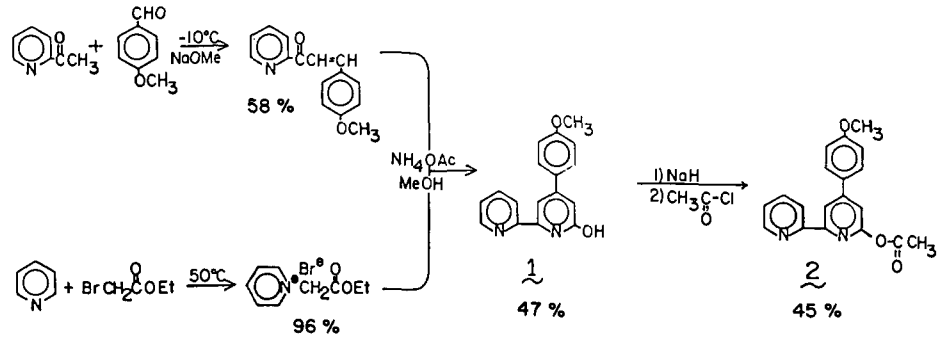
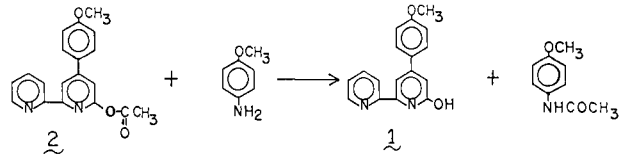
(8) For example, as in the Schiff base formation described in ref 7.

0002-7863/81/1503-3233$01.25/0

Scheme I



Scheme II



near the substrate carbonyl group,[9] this type of strategy might provide an expedient means of accelerating amide bond forming processes, including those of interest in the synthesis of peptides. As an initial step in that direction, we have examined the metal ion catalyzed aminolysis of an ester containing a chelating site in the leaving group, as an example of a potentially general procedure for facilitating the formation of amide bonds.

The preparation of 6-hydroxy-4-(4-methyoxyphenyl)-2-(2-pyridyl)pyridine (**1**) is summarized in Scheme I.[10] Treatment of **1** with 1 equiv of sodium hydride in tetrahydrofuran, followed by addition of 1 equiv of acetyl chloride and workup yielded the corresponding acetyl ester (**2**).[11] Aminolysis of **2** by reaction with 4-methoxybenzenamine (*p*-anisidine) in dimethyl sulfoxide occurs cleanly to give *N*-(4-methoxyphenyl)acetamide (Scheme II); the progress of the reaction can be conveniently followed by either proton NMR or infrared spectroscopy. The observed ready reactivity of **2** as an acylating agent is expected in view of its structural similarities to the 2-pyridyl esters used in peptide synthesis.[12] Proton acids and a wide variety of metal ions catalyze the aminolysis of **2**.[13] For the reaction of **2** with *p*-anisidine in the presence of metal ion and *p*-anisidinium acetate, the kinetic data obtained for reaction at 29 °C in dimethyl sulfoxide provide a satisfactory fit to the rate expression

$$d[amide]/dt = (k + k_a[acid] + k_{cat}[metal])[ester][amine] \quad (1)$$

The second-order rate coefficient k obtained for this reaction in the absence of catalysis is found to be 1.5×10^{-1} M^{-1} s^{-1}. For reaction of 0.05 M **2** with 1 equiv of catalyst and a fivefold excess of amine, addition of anisidinium ion, Mg^{2+}, Pb^{2+}, or Cd^{2+} all lead to modest increases in the rate of aminolysis. The rate of the reaction in the presence of 0.05 M anisidinium ion is 1.4 times

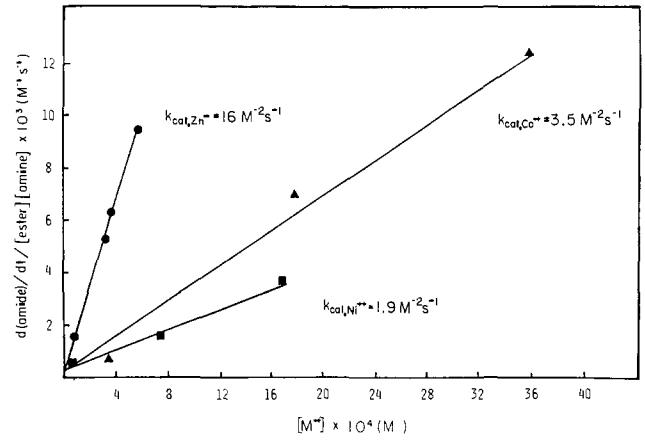


Figure 1. Determination of catalytic rate coefficients for the reaction of *p*-anisidine with **2** in Me_2SO at 29 °C as catalyzed by Zn^{2+} (●), Co^{2+} (▲), and Ni^{2+} (■).

that of the uncatalyzed reaction, whereas under comparable conditions a fivefold enhancement was observed for Pb^{2+}, the most effective of the nontransition metals. A study of the dependence of reaction rates on *p*-anisidinium ion concentration yielded a value of 1.4×10^{-3} M^{-2} s^{-1} for k_a of eq 1. Addition of alkali metal ions, even at high ionic strength (i.e., 0.15 M K^+), resulted in no significant change in rate of aminolysis.

In contrast to the relatively modest effects discussed above, the presence of a number of divalent transition-metal ions leads to a pronounced enhancement of the rate of aminolysis of **2**. The dependence of this reaction rate on the concentration of Zn^{2+}, Co^{2+}, and Ni^{2+} is shown in Figure 1. These data yield values for the catalytic rate constant, k_{cat}, where k_{cat} is found to be 1.9 M^{-2} s^{-1} for Ni^{2+}, 3.5 M^{-2} s^{-1} for Co^{2+}, and 16 M^{-2} s^{-1} for Zn^{2+}. The order of reactivity observed ($Zn^{2+} > Co^{2+} > Ni^{2+}$) is the same as that found by Fife for the catalytic effect of these metals in the hydroxide-catalyzed hydrolysis of 8-quinolyl hydrogen glutarate.[14] This order of reactivity is opposite the order of stability for the corresponding complexes of the ions with 1,10-phenanthroline in water[15] (as noted by Fife) and 2,2'-bipyridine in Me_2SO.[16] The catalytic effect of these metal ions on the aminolysis of **2** is substantial;[17] k_{cat} for Zn^{2+} is more than 10^4 times as large as the acid-catalyzed rate constant term, k_a, found in eq 1. Analogous effects in the hydrolysis reactions discussed previously[1-5] have yielded rate accelerations by these transition metals in the order of a millionfold or more.

It is clear from these results that one can prepare acylating agents whose reactivity can be "switched on" by addition of transition-metal catalysts. Furthermore, since the metal-chelating

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(10) This procedure was modeled on that described in the literature for the 4-nitrophenyl analogue of **1**: Krohnke, F.; Schalke, K.-E.; Zecher, W. *Chem. Ber.* **1970**, *103*, 322.

(11) Compound **2** was isolated as a white crystalline solid, mp 145–146.5 °C, and was characterized by ^1H NMR, ^{13}C NMR, and IR spectra and elemental analysis, all of which were fully consistent with the proposed structure.

(12) For a description of the reactivity of the 2-pyridyl esters of *N*-acyl amino acids, see: Dutta, A. S.; Morley, J. S. *J. Chem. Soc. C.* **1971**, 2896.

(13) This is in contrast to the reactivity of the acetyl ester of 2-(2-hydroxyphenyl)-4-phenyl-6-(2-pyridyl)pyridine, the rate of aminolysis of which is strongly catalyzed by Ni^{2+}, but is significantly less catalyzed by other divalent transition metals, and is only weakly affected by proton acids or nontransition metals: Puckette, J. G.; Roper, D. J.; Trzupek, L. S. Southeast–Southwest Regional Meeting of the American Chemical Society, New Orleans, LA, Dec., 1980.

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(17) In contrast, we have found that Zn^{2+}, as an example, has only an inhibiting effect on the aminolysis of an ester lacking a metal-coordinating site (i.e., as in the reaction of benzylamine with phenyl acetate).

site in compounds such as **2** is built into the leaving group, this sort of strategy can in principle provide catalytic rate enhancement for the formation of amides by reaction of esters with widely varying acyl structures. Whether this generality will extend to structurally sensitive analogues of **2**, such as those required in peptide synthesis, ultimately depends on the mechanism of the reactions discussed above. Three types of mechanisms have been proposed for metal ion catalyzed acyl substitution processes;[9] all three have been postulated or demonstrated for several of the reactions studied in detail.[1-7] Mechanisms involving activation at the carbonyl oxygen or leaving-group oxygen of substrates such as **2** would likely lead to racemization of amino acid or peptide analogues of **2**.[18,19] On the other hand, a mechanism involving intracomplex transfer of a coordinated amine to the ester moiety should be less conducive to such racemization. With these considerations in mind, we are continuing study of **2**, as well as related compounds.

Acknowledgment. Support of this research by Research Corporation and the Furman University Research and Professional Growth Committee is gratefully acknowledged.

(18) A number of groups have described aminolyses of amino acid esters coordinated at Co(III) through the ester carbonyl oxygen. See, for example: Buckingham, D. A.; Dekkers, J.; Sargeson, A. M. *J. Am. Chem. Soc.* **1973**, *95*, 4173. Lability of the α hydrogens of such coordinated amino acid esters is a serious complication in their potential synthetic utility: Collman, J. T.; Kimura, E. *J. Am. Chem. Soc.* **1967**, *89*, 6096.

(19) Metal-ion catalysis of the enolization of 2-acetylpyridine is thought to involve coordination of the carbonyl oxygen of that substrate: Cox, B. G. *J. Am. Chem. Soc.* **1974**, *96*, 6823.

Homogeneous Asymmetric Catalysis: Structural Studies of Catalytic Intermediates Using Extended X-ray Absorption Fine Structure

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Optically active rhodium complexes function as very effective catalysts for the asymmetric hydrogenation of prochiral olefins such as α-acyl- or α-(benzoylamino)cimmamic acid.[1-7] In recent years, a number of cationic rhodium complexes with various phosphine ligands have been prepared, and, when employed as catalysts, they have been reported to yield products with enantiomeric excesses as high as 99%.[6c] Conjointly with studies of the catalytic chemistry of these systems, a number of groups have been investigating the mechanistic aspects of the asymmetric hydrogenation reactions.[2-8] Our most recent efforts have focused on the mechanism of asymmetric induction for systems of the general formulations $Rh(P\text{–}P)L^+X^-$[9] and $Rh(P)_2L^+X^-$[9] by using X-ray crystallography, ^{13}C and ^{31}P solution NMR spectroscopy, and solid-state ^{13}C NMR spectroscopy.[10] Our work combined with that of others has yielded the proposed mechanism for asymmetric hydrogenation[10a] shown in Figure 1. The present report describes our recent work using X-ray absorption spectroscopy and, in particular, the extended X-ray absorption fine structure (EXAFS) to investigate under simulated reaction conditions the various intermediate catalytic species depicted in Figure 1.

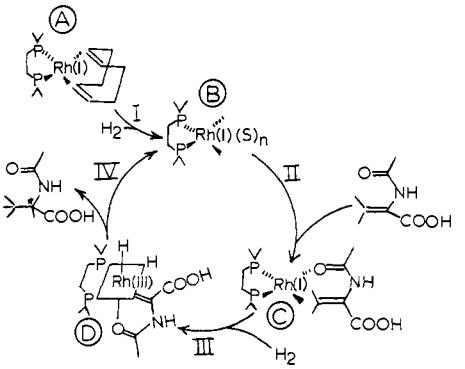

Figure 1. Proposed catalytic cycle for asymmetric hydrogenation.

Our interest in using EXAFS to study these homogeneous catalysts is twofold. First, we want to obtain structural information about the various intermediate species shown in Figure 1. EXAFS is a remarkable technique in its capability to provide this direct structural information on molecules in solution. This would allow us to compare the detailed crystallographic description of the material isolated in the solid state with the species actually present in its catalytically active phase, i.e., solution. Secondly, we want to evaluate the general potential of EXAFS for studying chemical reactions in solution. We are interested in determining the sensitivity of EXAFS to differing species in solution, present separately and concurrently, and the accuracy of the structural parameters derived from solution EXAFS. While there are numerous literature reports on EXAFS studies of heterogeneous catalysts[11] and reports on studies of single species in solution,[12] the present report describes the first attempts to study homogeneous catalysis, i.e., the identification of intermediate species

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(9) Ligand abbreviations: P–P is diPAMP = (*R,R*)-1,2-ethanediylbis-[(*o*-methoxyphenyl)phenylphosphine], DIOP = (*R,R*)-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane, diPHOS = bis(1,2-diphenylphosphino)ethane, *cis*-ethylene = *cis*-bis(diphenylphosphino)ethylene; P is CAMP = (*R*)-*o*-anisylmethylcyclohexylphosphine; L = 1,5-cyclooctadiene or bicyclo[2.2.1]heptadiene.

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