the corresponding imine, $PhC(CH_3)=NCH(CH_3)Ph$, which gives acetophenone only in limited amounts due to the higher stability of the Schiff base. Tribenzylamine is inert as may have been expected due to the absence of a hydrogen at the nitrogen blocking the potential dehydrogenation pathway. In contrast to the situation found for alcohols, primary aliphatic amines, Table IV, are effectively dehydrogenated, e.g., cyclohexylamine to cyclohexanone, octylamine to octaldehyde and octanoic acid, and phenylethylamine to phenylacetic acid. Significant amounts of acid are formed with primary acyclic amines as substrates because aliphatic aldehydes undergo oxidation much more easily than their aromatic counterparts. On the other hand, a simple secondary aliphatic amine such as di-*n*-butylamine is inert as is aniline, which lacks the required α-hydrogen. For the aliphatic amines no Schiff-base intermediates were formed (too unstable); thus, the overall reaction to the carbonyl compound is faster although the oxidative dehydrogenation reaction itself is slower than in the benzylamine case.

An active-carbon-supported molybdenum-vanadium heteropolyanion salt has been shown to be an effective and selective catalyst for the aerobic oxidative dehydrogenation of alcohols and amines. Further kinetic and spectroscopic research is under way in our laboratory in order to decipher the mechanism of these and similar reactions.

Experimental Section

Materials and Instruments. All reagents and solvents used were obtained commercially and were used without further purification. The activated carbon (Merck Catalog No. 2186) used was a fine powder. GLC measurements were made with a HP-5890 equipped with a FID detector and helium carrier gas. Peaks were quantified by a HP-3396 integrator after calibration with known reference compounds, except for the Schiff bases (see below). Mass spectra were taken on a HP5790 and ^1H NMR on a Brucker WP-200-SY spectrometer.

Catalyst Preparation. The $Na_5PV_2Mo_{10}O_{40}$ heteropolyanion salt was prepared by the common literature procedures.[13] The catalyst is in fact a hydrated mixture of stereoisomers and was identified by its ^{51}V NMR as previously described.[10] The heteropolyoxometallate was wet-impregnated onto the active carbon support by dissolving 1 gm of metalate in water and adding 9 gm of active carbon. The mixture was stirred for 30 min, and then the excess water was evaporated under reduced pressure. The catalyst was dried overnight in a vacuum oven (0.01 atm) at 80 °C. Karl Fisher titration showed that the 10% PVMo/C catalysts contained about 0.2 wt % water.

Typical Procedure for the Oxidative Dehydrogenation Reactions. The supported PVMo/C catalyst (0.04 mmol, 800 mg) was added to a solution of 4 mmol of benzyl alcohol in 12 mL of toluene in a magnetically stirred 25-mL flask. The mixture was heated to 100 °C in a thermostated oil bath and kept under a constant pressure of 1 atm of air by continuous flow air through the solution. Aliquots were removed from the reaction mixture and directly analyzed by GLC using a 10-m cross-linked (fused silica) FFAP megabore (i.d. 530 μm) column. Products and reactants were generally determined on a relative basis; however, to cross-check for noneluted products (none were indicated), bromobenzene was used as an external standard.

The identity of the Schiff bases was confirmed by isolation from the reaction mixture by catalyst filtration and solvent evaporation. For example, for benzylamine: MS 195, M (15), 194, M - 1 (17), 91, C_7H_7 (100); ^1H NMR at 200 MHz in $CDCl_3$ δ 8.35 (s, 1 H), 7.74 (m, 2 H), 7.32 (m, 8 H), 4.85 (s, 2 H).

Acknowledgement. We thank the Wolfson Foundation for Scientific Research for their support.

Registry No. $PMo_{10}V_2O_{40}$, 58071-93-5; PhCH=NH, 16118-22-2; $C_6H_5CH_2NH_2$, 100-46-9; $4\text{-}MeOC_6H_4CH_2NH_2$, 2393-23-9; $4\text{-}ClC_6H_4CH_2NH_2$, 104-86-9; $C_6H_5CH{=}NCH_2C_6H_5$, 780-25-6; $(C_6H_5CH_2)_2NH$, 103-49-1; $C_6H_5CH_2NHCH_3$, 103-67-3; $C_6H_5CH(CH_3)NH_2$, 98-84-0; $(C_6H_5CH_2)_3N$, 620-40-6; $4\text{-}MeOC_6H_5CH{=}NCH_2$, 3261-60-7; $C_6H_5CH{=}NCH_3$, 622-29-7; $C_6H_5C(CH_3){=}NCH(CH_3)C_6H_5$, 25102-87-8; $4\text{-}ClC_6H_4CH{=}NCH_2C_6H_4Cl$, 31264-06-9; $c\text{-}C_6H_{11}NH_2$, 108-91-8; $CH_3(CH_2)_7NH_2$, 111-86-4; $C_6H_5CH_2CH_2NH_2$, 64-04-0; $(CH_3CH_2CH_2CH_2)_2NH$, 111-92-2; $C_6H_5NH_2$, 62-53-3; $c\text{-}C_6H_{10}O$, 108-94-1; $CH_3(CH_2)_6CHO$, 124-13-0; $CH_3(CH_2)_6COOH$, 124-07-2; $C_6H_5CH_2COOH$, 103-82-2; benzyl alcohol, 100-51-6; 4-bromobenzyl alcohol, 873-75-6; 4-nitrobenzyl alcohol, 619-73-8; 4-methoxybenzyl alcohol, 105-13-5; 2-hydroxybenzyl alcohol, 90-01-7; 4-hydroxybenzyl alcohol, 623-05-2; 1-phenylethanol, 98-85-1; benzaldehyde, 100-52-7; 4-bromobenzaldehyde, 1122-91-4; 4-nitrobenzaldehyde, 555-16-8; 4-methoxybenzaldehyde, 123-11-5; acetophenone, 98-86-2; 2-octanol, 123-96-6; 3-heptanol, 589-82-2; cyclohexanol, 108-93-0; 2-phenylethanol, 60-12-8; 1-octanol, 111-87-5.

Kinetics and Mechanism of Ni(II) Ion Retarded Schiff-Base Hydrolysis of 2,2'-Dipyridylmethylideneaniline

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Received January 17, 1991

Nitrogen atoms of Schiff bases (imines) are weak bases and readily coordinate to metal ions. Imine bonds formed from amines and carbonyl compounds in the presence of metal ions are utilized as cyclizing linkages in a large number of macrocyclic complexes.[1]

Effects of metal ions acting as Lewis acid catalysts on organic reactions have been extensively investigated.[2-4] Although imines are labile and readily hydrolyzed, metal ions stabilize imine bonds present on macrocyclic rings. Whether metal ions stabilize or activate imine bonds in general, however, has not been systematically investigated. In this regard, we have performed kinetic studies on the hydrolysis of 2,2'-dipyridylmethylideneaniline (1), a non-macrocyclic imine, in the presence of Ni(II) ion.

Results and Discussion

In the absence of Ni(II) ion, pseudo-first-order kinetics were observed for the hydrolysis of 1, and the pseudo-first-order rate constants (k_o) measured therein at pH 2.3-5.2 are illustrated in Figure 1. Analysis of the pH profile according to Scheme I led to the values of pK_a = 3.40 and k_{lim} = 0.29 s^{-1}.

Scheme I

$$1 \underset{K_a}{\overset{H^+}{\rightleftharpoons}} 1H^+ \xrightarrow{k_{lim}} \text{products}$$

In the presence of Ni(II) ion, however, biphasic kinetics were observed with the relatively fast formation of an intermediate (spectrum b of Figure 2) from the substrate (spectrum a of Figure 2) and the subsequent slow conversion of the intermediate into the hydrolysis products (spectrum c of Figure 2). The addition of Ni(II) ion changes the UV-vis spectrum of 1 considerably. The spectrum of 1 (6×10^{-5} M), however, was identical in the presence of either 1 or 12 mM Ni(II), indicating that 1 is

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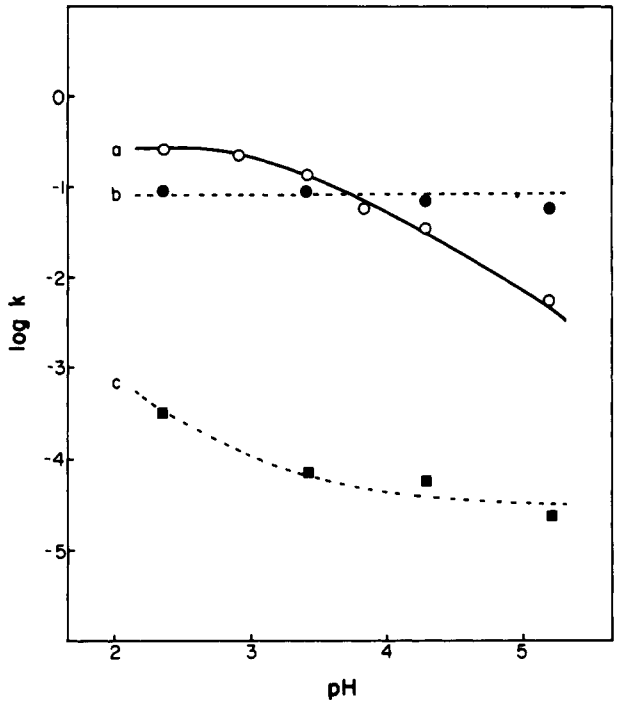


Figure 1. pH profiles of logarithms of rate constants (in s^{-1}): (a) k_o for the spontaneous hydrolysis of 1, (b) k_A for Ni(II)1, (c) k_B for Ni(II)1.

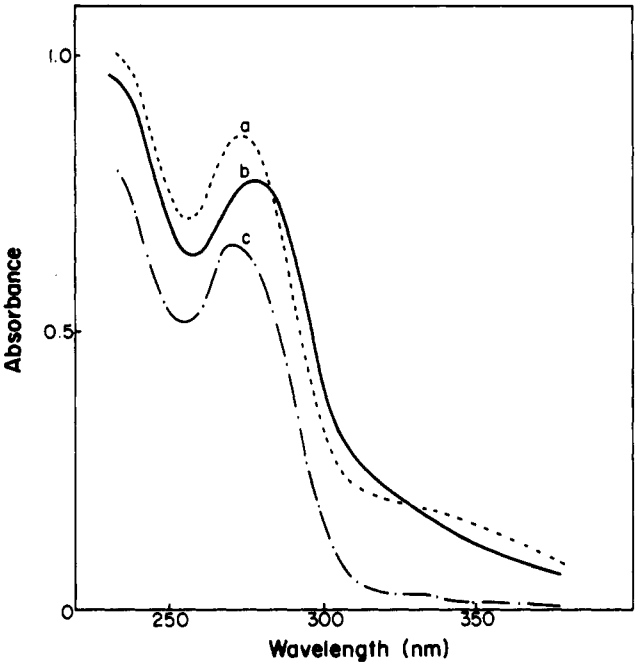
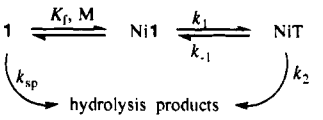


Figure 2. Spectra of 1 (curve a), the accumulating intermediate (curve b), and the reaction product (curve c) measured in the presence of Ni(II) ion at pH 5.2. Initially added concentration of 1 was 6×10^{-5} M and that of Ni(II) was 6×10^{-4} M. Curve a was obtained immediately after mixing 1 with Ni(II). Curve b was measured after the accumulation of the intermediate was complete.

completely bound to Ni(II) ion even with 1 mM Ni(II). As [Ni(II)] was raised, the k_o values for both the formation and the breakdown steps of the intermediate rapidly changed from the k_o of the spontaneous hydrolysis to constant values. Thus, the k_o values reached saturation values that were independent of [Ni(II)] at sufficiently large (2–5 mM) Ni(II) concentrations. This saturation behavior is consistent with complex formation between the substrate and the metal ion. The formation constant (K_f) for the complex may be estimated from the dependence of the rate constant on [Ni(II)]. In order to estimate K_f values, however, kinetic data should be measured accurately at very low ($<10^{-4}$ M) Ni(II) concentrations due to the very large K_f values. Therefore, K_f values were not estimated. The saturation values of k_o (k_A for the first step and k_B for the second step) measured in the presence of Ni(II) ion are illustrated in Figure 1. The value of k_A is independent of pH ($k_A = 0.080\ s^{-1}$). Analysis of the pH dependence (curve c of Figure 1) of k_B led to $k_B = 3.5 \times 10^{-5} + (7.7 \times 10^{-2})[H^+]\ s^{-1}$. The ionization of 1 would be reflected in the pH dependence of K_f but does not directly affect the pH dependence of k_A and k_B. This is because k_A and k_B are affected by the ionization of the Ni(II) complex of 1 instead of that of 1.

Scheme II



The saturation kinetic behavior and biphasic absorbance changes observed for the reaction of 1 in the presence of Ni(II) is consistent with Scheme II. Rate expressions for the limiting values of k_o (k_A; pseudo-first-order rate constant for equilibration between Ni1 and NiT, k_B; pseudo-first-order rate constant for conversion of the equilibrium mixture of Ni1 and NiT into the hydrolysis products) for the accumulation and the breakdown steps of the intermediate achieved at large Ni(II) concentrations are derived as eqs 1 and 2 from this scheme. Here, K_T is the

$$k_A = k_1 + k_{-1} = k_1(1 + 1/K_T) \quad (1)$$

$$k_B = k_2(1 + 1/K_T) \quad (2)$$

equilibrium constant (k_1/k_{-1}) for the formation of NiT from Ni1. Since the saturation value (k_A) of the k_o for the accumulation step of the intermediate is attained at 1 mM [Ni(II)], K_f is greater than 5000 M^{-1}. Curve a of Figure 2 stands for the spectrum of Ni1, whereas curve b is that of the equilibrium mixture of Ni1 and NiT. Although the exact value of K_T is not calculated as the spectrum of NiT is not known, K_T is estimated as >0.3 based on the absorbance values of curves a and b at 350 nm.

Kinetics and mechanisms of the hydrolysis of imines have been extensively investigated, indicating the intermediacy of carbinolamines formed by addition of a water molecule to the imines and cleavage of C–N bond in the N-protonated form (HT) of the carbinolamine intermediate.[5-7] The spontaneous hydrolysis of 1 would follow the same mechanism, and it is likely that the hydrolysis of 1 in the presence of Ni(II) ion also involves the carbinolamine intermediate.

Three nitrogen atoms are present in 1. Thus, 1 may form a chelate ring by using either the two pyridyl nitrogen atoms as illustrated by 2 or the imine nitrogen and one of the two pyridyl nitrogen atoms as illustrated by 3. Whether the reaction path leading to the products involves 2 or 3, however, is not necessarily related to the relative thermodynamic stability of 2 and 3. On the basis of the kinetic stability of the intermediate revealed by the present study, which will be discussed below, the accumulating intermediate is assigned as carbinolamine 4, which is formed by the hydration of 3. The pH independence of

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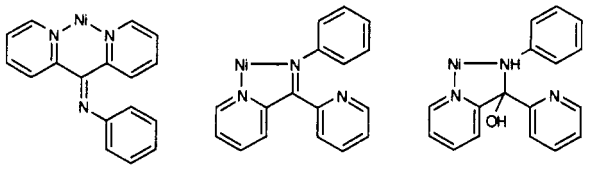


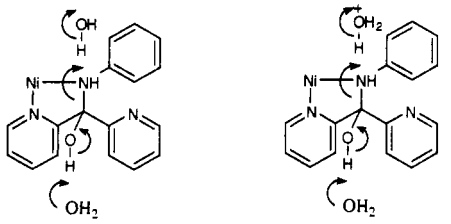
2 3 4

k_A measured in the presence of Ni(II) ion supports addition of water molecule to the Ni(II) complex of 1 to form 4.

The resistance of the carbinolamine to breakdown in the presence of Ni(II) ion indicates the kinetic stability of the Ni(II) complex of the carbinolamine. The spontaneous hydrolysis of 1 involves C–N bond cleavage in HT, the N-protonated form of the carbinolamine, as mentioned above. The rate constant for the breakdown of HT is not smaller than the observed value of k_{lim} (0.29 s^{-1}). Comparison of this value with the rate constant for the breakdown of NiT (3.5×10^{-6} s^{-1}) indicates that breakdown of NiT is slower than that of HT by more than 10^4 times.

If the amine moiety is expelled from the neutral form, instead of the protonated form, of the carbinolamine intermediate, amide anion becomes the leaving group and the activation energy is raised greatly. Even when the leaving amide anion is bound by a metal ion, it would be expelled with a great difficulty. When the amine nitrogen of the carbinolamine intermediate is bound to a metal ion, protonation of the amine would be inhibited. This would lead to the very slow breakdown of 4. In addition, expulsion of the amine moiety from 4 might be accompanied by an increase in the strain of the chelate ring in the transition state and this might be partly responsible for the slow rate.

If the carbinolamine intermediate is converted into the product through the breakdown of 4 in the presence of Ni(II) ion, expulsion of the amine moiety requires assistance from general acids such as water as indicated by 5 or hydronium ion as indicated by 6. The pH dependence of curve c in Figure 1 indicates that the expulsion of amine from the Ni(II)-bound intermediate is partially assisted by hydronium ion at low pHs.



5 6

In conclusion, Ni(II) ion exerts two opposite effects on the stability of 1. The metal ion bound to the imine nitrogen atom polarizes the imine bond facilitating the nucleophilic attack by water molecule at the imine carbon atom. On the other hand, blockade by the metal ion of the protonation of the leaving nitrogen atom greatly retards the breakdown of the carbinolamine, leading to overall inhibition of the hydrolysis of the Schiff base.

Some macrocycle complexes retain imine bonds even in water,[8] although the carbinolamine form is quite stable in the case of the Ni(II) complex of 1. The stability of a chelate ring containing an imine bond relative to that with a carbinolamine linkage or in comparison with the hydrolysis products would be governed by many structural elements. The present study suggests that the blockade of the protonation of the leaving amines in the carbinolamine intermediates by metal ions is one of the factors contributing to the extraordinary stability of imine bonds included in macrocyclic metal complexes.

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Experimental Section

Compound 1 was prepared by refluxing the solution of 2,2′-dipyridyl ketone (3 g) and concd HCl (0.3 ml) in 10 mL of aniline for 30 min and was purified by separation on a silica gel column by eluting with 2:3 ethyl acetate–hexane and recrystallization from ethyl acetate; mp 147–149 °C. Anal. Calcd for $C_{17}H_{13}N_3$: C, 78.74; H, 5.05; N, 16.20. Found: C, 78.92; H, 5.02; N, 16.38. Water was distilled and deionized prior to use in kinetic studies. Nickel chloride was prepared according to the general method reported previously.[9] Reaction rates were measured with a Beckman Model DU-64 UV–vis spectrophotometer. Temperature was controlled at 25 ± 0.1 °C with a Haake E52 circulator. Ionic strength was adjusted to 1.0 M with NaCl. Buffers (0.01 M) used were chloroacetate (pH 2–3.5) and acetate (pH 3.6–5.2). The reaction mixture for kinetic runs contained 0.8 % (v/v) acetonitrile, which was used as the solvent for the stock solutions of 1.

Acknowledgment. This work was supported by the Basic Sciences Research Program (1990) of the Ministry of Education, Republic of Korea.

Registry No. 1, 100288-61-7; 4, 135192-18-6; Ni, 7440-02-0; $PhNH_2$, 62-53-3; 2,2′-dipyridyl ketone, 19437-26-4.

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Crambescidins: New Antiviral and Cytotoxic Compounds from the Sponge *Crambe crambe*[1]

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Received February 13, 1991

Crambescidins 816 (1), 830 (2), 844 (3), and 800 (4), a family of complex pentacyclic guanidines linked by a linear ω-hydroxy fatty acid to a hydroxyspermidine, have been obtained by bioassay-guided isolation, involving solvent partition and chromatography on Sephadex LH-20, cyano, and C-18 columns, from extracts of the red, encrusting sponge *Crambe crambe* (Order Poecilosclerida, Family Esperiopsidae). In assays on board the *R/V Garcia del Cid* during a 1988 Pharma Mar, S.A., expedition to the Western Mediterranean, extracts of *C. crambe* were regularly active vs *Herpes simplex* virus, type 1 (HSV-1), and cytotoxic to L1210 murine leukemia cells. Compounds 1, 3, and 4 inhibit HSV-1 completely, with diffuse cytotoxicity, at 1.25 μg/well and are 98% effective against L1210 cell growth at 0.1 μg/mL. The crambescidins' pentacyclic guanidine moiety has been isolated only once before,[2] and a hydroxyspermidine unit from a marine source is unprecedented.[3]

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