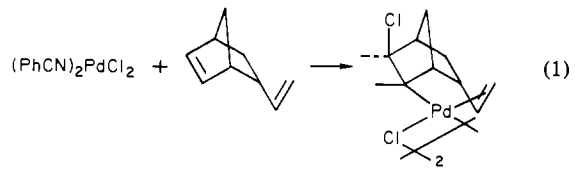

(1)

bornadiene and 1,5-cyclooctadiene, base is essential in order to obtain the analogous methoxy complexes.[1f] Since the norbornadiene·$PdCl_2$ complex is relatively unreactive, there must be some source of activation other than just the relief of strain in the norbornene systems. Models show that a metal complex of 5-vinylnorbornene would require the norbornene double bond to be even more seriously tilted than in the case of the dicyclopentadiene·$PdCl_2$ complex. The two double bonds in 5-vinylnorbornene are even less parallel, and when the less substituted vinyl group binds to the metal in a normal perpendicular manner, the norbornene double bond is forced to bind in an extremely unsymmetrical manner.

Thus, we conclude that deformation from the symmetrical η^2-π complex plays a dominant role in directing the attack of nucleophiles on activated double bonds.

Acknowledgment. Support for this work from the National Science Foundation (Grant CHE-7822691), the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the University of California Intramural Research Fund is gratefully acknowledged.

Registry No. Dichloro(*endo*-dicyclopentadiene)palladium(II), 12294-98-3.

Supplementary Material Available: Fractional coordinates and thermal parameters (Table I), bond lengths (Table II), and structure factors (Table III) (10 pages). Ordering information is given on any current masthead page.

Nickel(II)-Promoted Ethanolysis and Hydrolysis of *N*-(2-Pyridylmethyl)urea. A Model for Urease

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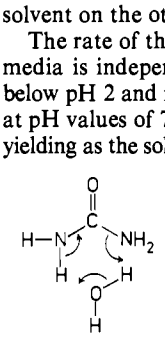
Received September 21, 1981

Experiments are reported which establish that O-coordination of the title urea to nickel(II) promotes nucleophilic attack of solvent on the otherwise unreactive carbonyl group of the urea.

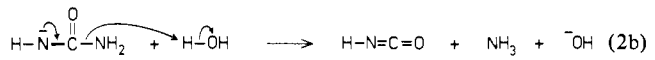
The rate of the nonenzymatic degradation of urea in aqueous media is independent of pH between pH 2 and pH 12, falling below pH 2 and rising above pH 12.[1,2] It has been demonstrated at pH values of 7, 13, and 14 that the reaction is an *elimination*, yielding as the sole products ammonia and cyanic acid (eq 1). The



$\longrightarrow$ H-N=C=O + NH_3 + H_2O (1)

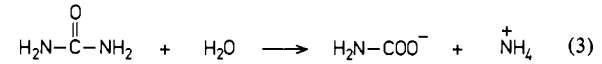
data support an invariant mechanism of degradation over the entire pH range (eq 1),[3] the falloff below pH 2 being reasonably ascribed to the protonation of urea and the dependence on [$^-$OH] above pH 12 being ascribed to specific base catalysis of the elimination reaction (eq 2a,b).[4] The latter chemistry is adequately supported by a variety of models.[5-7]

(2a)



(2b)

Urease catalyzes the *hydrolysis* of urea to form carbamate ion (eq 3).[8] At pH 7.0 and 38 °C, the *urease-catalyzed hydrolysis*



(3)

of urea must be at least 10^{14} times as fast as the *spontaneous hydrolysis* of urea which has never been observed.[9] On the balance of available evidence from model studies,[10] and especially from consideration of the structures of molecules which are and are not substrates for urease,[7] we recently postulated that *all* substrates for urease (thus far, urea, *N*-hydroxyurea,[8,11] *N*-methylurea,[7] semicarbazide,[7,12] formamide,[7,13] and acetamide[7]) are activated toward nucleophilic attack on carbon by virtue of O-coordination to an active-site Ni(II) ion as in I. The detailed mechanism[7] arising from this postulate was without precedent in the chemistry of ureas or amides.

Hydroxamic acids reversibly inhibit urease from all sources that have been tested.[14] Wherever the dependence of urease on metal

Table I. Ethanolysis and Hydrolysis of *N*-(2-Pyridylmethyl)urea in the Presence of 0.39 M $NiCl_2$[a]

temp, °C	$[1]_0$, M	$[H_2O]$, M	$10^5 k_{obsd}$,[b] s^{-1}	$\frac{[3]_\infty}{[1]_0}$[c]	$10^5 k'_{EtOH}$, s^{-1}	$10^5 k'_{H_2O}$, s^{-1}
80.25	0.025	0.78	17.7	0.064	16.6	1.1
80.25	0.050	0.78	17.1	0.067	15.9	1.1
80.25	0.100	0.78	17.8	0.078	16.4	1.4
80.25	0.050	1.67	20.3	0.100	18.3	2.0
80.25	0.050	3.00	23.1	0.185	18.8	4.3
80.25	0.050	5.22	27.7	0.269	20.2	7.5
70.04	0.050	0.78	5.10	0.086	4.66	0.44
60.02	0.050	0.78	1.50	0.089	1.36	0.134
50.00	0.085	0.78	0.409	0.091	0.372	0.037

[a] $NiCl_2 \cdot 6H_2O$ was partially dehydrated at 82 °C in vacuo. The concentration of $NiCl_2$ was determined spectrophotometrically at 395 nm in 1 M HCl. Distilled ethanol was dried over 4A molecular sieves. [b] ±4% (2 standard errors); from loss of 1. [c] 1 = *N*-(2-Pyridylmethyl)urea; 3 = (2-Pyridylmethyl)amine.

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(4) Reported values of the pK'_a of urea range from 13.7 to 14.3 while those of its conjugate acid (urea·H^+) range from 0.1 to 0.2: Woolley, E. M.; Hepler, L. G. *Anal. Chem.* **1974**, *44*, 1520-1523.
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(9) The value of k_{cat} for the urease-catalyzed hydrolysis of urea (eq 3) is 5.87×10^3 s^{-1} at pH 7.00 and 38 °C.[7] The rate constant k for the pH-independent degradation of urea (eq 1) at 38 °C is 6.1×10^{-9} s^{-1} where $k = Ae^{-E_a/RT}$, $A = 5.77 \times 10^{14}$ s^{-1} and $E_a = 32.7$ kcal/mol.[2,3a]
(10) N-Coordination of carboxylic acid amides with Cu(II) (Nakon, R.; Angelici, R. J. *J. Am. Chem. Soc.* **1973**, *95*, 3170-3174) and Co(III) (Buckhingham, D. A.; Foster, D. M.; Sargeson, A. M. *J. Am. Chem. Soc.* **1969**, *91*, 3451-3456) does *not* produce activation toward alkaline hydrolysis. In contrast, O-coordination of *N*,*N*-dimethylformamide to pentaminecobalt(III) activates the amide by a factor of $\sim 10^4$ toward alkaline hydrolysis: Buckingham, D. A.; Harrowfield, J. MacB.; Sargeson, A. M. *J. Am. Chem. Soc.* **1974**, *96*, 1726-1729.
(11) Fishbein, W. N.; Winter, T. S.; Davidson, J. D. *J. Biol. Chem.* **1965**, *240*, 2402-2406.
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(13) Fishbein, W. N. *Biochim. Biophys. Acta* **1977**, *484*, 433-442.

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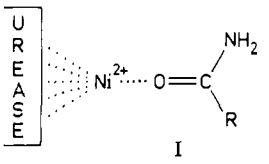


I

(R = NH_2, NHOH, $NHCH_3$, $NHNH_2$, H, CH_3)

ions has been determined, nickel has been found to be involved. We may confidently expect, therefore, that all hydrolytic ureases will be nickel metalloenzymes. In this communication we describe a model system containing Ni(II) and urea, which successfully mimics elements of the enzyme-catalyzed reaction.

In aqueous ethanol in the presence of excess $NiCl_2$, *N*-(2-pyridylmethyl)urea[15] (**1**) undergoes ethanolysis to give ethyl *N*-(2-pyridylmethyl)carbamate[16] (**2**) and hydrolysis to give (2-pyridylmethyl)amine (**3**) in accordance with eq 4.[17-19] The

$$R{-}NH{-}\overset{O}{\overset{\|}{C}}{-}NH_2 + EtOH \longrightarrow R{-}NH{-}\overset{O}{\overset{\|}{C}}{-}OEt + NH_3 \quad (4a)$$

$$R{-}NH{-}\overset{O}{\overset{\|}{C}}{-}NH_2 + H_2O \longrightarrow R{-}NH_2 + H_2CO_3 + NH_3 \quad (4b)$$

(R = 2-pyridylmethyl)

disappearance of **1** and the appearance of products (from measurements on **3**) are both first order, with virtually identical rate constants. Values of k_{obsd} (Table I) are essentially independent of the initial concentration of **1** but increase linearly with the concentration of water.

Equation 4a,b describes parallel pseudo-first-order reactions[20] for which $k_{obsd} = k'_{EtOH} + k'_{H_2O}$ and $k'_{H_2O} = k_{obsd}[3]_\infty/[1]_0$. Values of k'_{EtOH} have a slight dependence on $[H_2O]$ (Table I), and linear extrapolation to zero $[H_2O]$ gives a limiting value, $k'^{lim}_{EtOH} = 1.60 \times 10^{-4}$ s^{-1} at 80.25 °C.[21] A calculated second-order rate constant for reaction with ethanol may be defined as $k_{EtOH} = k'^{lim}_{EtOH}/[EtOH]$ and has the value 9.4×10^{-6} M^{-1} s^{-1} based on the molarity of pure ethanol (17.0 M at 25 °C). Values of k'_{H_2O} are directly proportional to $[H_2O]$, leading to a calculated second-order rate constant, k_{H_2O}, of 1.45×10^{-5} M^{-1} s^{-1} at 80.25 °C.

In ethanol, nickel chloride displays the three electronic absorption peaks in the visible and near infrared regions which are characteristic of octahedral coordination[22] (Figure 1). The

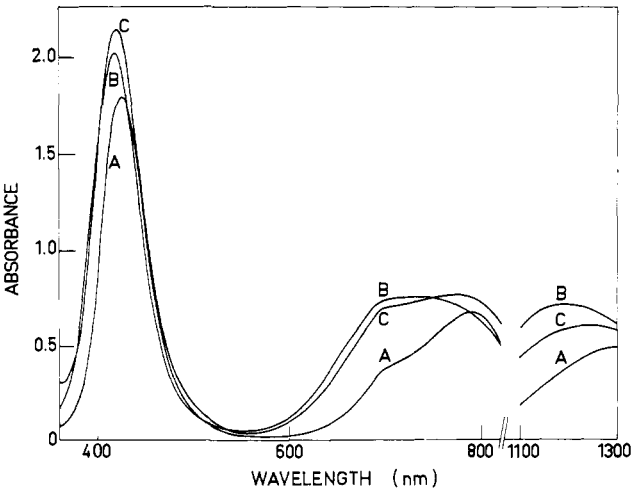
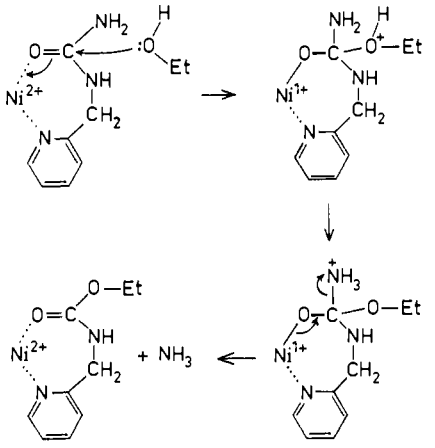


Figure 1. Absorption spectra of 0.16 M $NiCl_2$ in ethanol which contains ≤0.04 M H_2O: (A) $NiCl_2$ only; (B) $NiCl_2$ + equimolar *N*-(2-pyridylmethyl)urea (**1**); (C) $NiCl_2$ + equimolar ethyl *N*-(2-pyridylmethyl)-carbamate (**2**). λ_{max} (nm), ϵ_{max} (M^{-1} cm^{-1}): (A) 426, 10.9; 787, 4.1; 1310, 3.0; (B) 418.5, 12.2; 730, 4.6; 1190, 4.4; (C) 421, 13.1; 772, 4.65; 1250, 3.7.

Scheme I



spectrum is slightly but significantly altered by addition of **1** or of **2** in equimolar amounts, establishing that an octahedral complex of Ni(II) is formed by each. The spectral differences between nickel(II) and the nickel(II)–*N*-(2-pyridylmethyl)urea complex near 400 nm are unchanged between 0.16 and 0.019 M. This indicates that the dissociation constant of the complex in ethanol must be less than ~0.01 M. It follows that **1** exists almost completely as a Ni(II) complex under the conditions of the kinetic studies.

Application of transition-state theory to k'_{EtOH} leads to $\Delta H^\ddagger = 27.5 \pm 0.3$ kcal mol^{-1} and $\Delta S^\ddagger = 1.45 \pm 0.06$ cal mol^{-1} K^{-1}. For k'_{H_2O}, $\Delta H^\ddagger = 25.2 \pm 1.5$ kcal mol^{-1}. The similarity in $\Delta H^\ddagger$ for k'_{EtOH} and k'_{H_2O} strongly implies that the two reactions have the same mechanism. This is supported by similar values of the corresponding second-order rate constants ($k_{EtOH}/k_{H_2O} = 0.65$ at 80.25 °C).

Spontaneous degradation of **1** in anhydrous ethanol at 80.25 °C in the presence of 1 mM 8-hydroxyquinoline is undetectable in 1200 h, which indicates a rate constant less than 2.3×10^{-9} s^{-1}. The rate enhancement (eq 4a) due to coordination of **1** to Ni(II) is therefore greater than 7×10^4.

Salts which promote the ethanolysis of **1** are $NiCl_2$, $CoCl_2$, and $MnCl_2$ in order of decreasing efficiency. Ethanolysis does not appear to be promoted by $MgCl_2$ or $CaCl_2$. Several salts ($FeCl_2$, $CuCl_2$, $ZnCl_2$) could not adequately be tested because of insolubility of the complex with **1**.

A reasonable mechanism for the $NiCl_2$-promoted ethanolysis of **1** is shown in Scheme I.[23] In essence, the Ni^{2+} ion acts as a

(14) The sources include bacteria, plants, and invertebrates. Hydroxamic acids reversibly chelate nickel ion in jack bean urease. Dixon, N. E.; Hinds, J. A.; Fihelly, A. K.; Gazzola, C.; Winzor, D. J.; Blakeley, R. L.; Zerner, B. *Can. J. Biochem.* **1980**, *58*, 1323-1334.

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(16) Winterfield, K.; Schüler, H. *Arch. Pharm.* (*Weinheim*) **1960**, *293*, 203-210.

(17) A preparative scale reaction in ethanol [0.1 M **1**, 0.39 M $NiCl_2$, 0.78 M H_2O] was carried out at 50 °C in a large glass ampule. The ethanol was removed under reduced pressure. The residue was taken up in buffer (0.05 M 2-morpholinoethanesulfonate, pH 6.0, 0.05 M in EDTA), and **2** was extracted into chloroform; yield 80%. (2-Pyridylmethyl)amine was identified in 12% yield.[18]

(18) Progress was monitored with a Cary 17 spectrophotometer by addition of an aliquot (250 μL) from each ampule to 2.0 mL of 1.0 M HCl which contained 1.17% (w/v) 4-(dimethylamino)cinnamaldehyde (recrystallized from ethanol and sublimed). Compound, $\Delta\epsilon$ (M^{-1} cm^{-1}) at 530 nm and 25 °C in 11.1% (v/v) ethanol at the time of mixing: **1**, 85; **2** <0.5; **3** <0.5; ethyl carbamate, 28; urea, 112. Under these conditions, **3** reacts with a half-life of 0.9 min. [**3**] was determined from the absorbance change at 500 nm ($\Delta\epsilon$ = 135 M^{-1} cm^{-1}) between the time of mixing and 10 half-lives by using the method of Guggenheim for extrapolation.

(19) Under the conditions, both **2** and ethyl carbamate are stable, and **3** does not react with either **1**, **2**, or ethyl carbamate. An acid-soluble precipitate which forms in the course of the reaction does not contain **1** or **3**.

(20) Frost, A. A.; Pearson, R. G. "Kinetics and Mechanism", 2nd Ed.; Wiley: New York, 1961.

(21) Using $NiCl_2$ dried at 200-300 °C under high vacuum, the yield of **3** from 0.05 M **1** was only 3.7%, and k_{obsd} was 1.46×10^{-4} s^{-1} at 80.25 °C in the presence of 0.51 M $NiCl_2$ and ≤0.12 M H_2O.

(22) Rosenberg, R. C.; Root, C. A.; Gray, H. B. *J. Am. Chem. Soc.* **1975**, *97*, 21-26.

superacid[24,25] to promote nucleophilic attack of ethanol on the carbonyl group of the urea to form a tetrahedral intermediate. After a prototropic shift, ammonia is ejected to form the Ni(II) complex of the product. An analogous nucleophilic attack by a water molecule would account for the formation of **3**, since the initially produced carbamate ion would decarboxylate in the acidic assay system.[18]

The activation parameters found here for k'_{EtOH} may be compared with those for k_{cat} of the urease-catalyzed hydrolysis of urea ($\Delta H^{\ddagger} = 6.07 \pm 0.27$ kcal mol^{-1}, $\Delta S^{\ddagger} = -21.8$ cal mol^{-1} K^{-1}).[7] The rate constants k'_{EtOH} and k_{cat} both refer to reactions of a urea which is O-coordinated to a nickel ion. A markedly lower $\Delta H^{\ddagger}$ in the enzymatic system overcomes the less favorable enzymatic $\Delta S^{\ddagger}$ to produce the $\sim 10^{10}$-fold factor by which k_{cat} exceeds k'_{EtOH} at 38 °C. We are continuing to investigate the mechanism of both systems.

Acknowledgment. We thank the Australian Research Grants Committee and the University of Queensland for financial support.

Registry No. 1, 36226-31-0; **2**, 80145-75-1; **3**, 3731-51-9; Ni, 7440-02-0.

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Differentiation between Reaction Pathways in the Photoaddition of Guest *p*-Fluoroacetophenone to Host Deoxycholic Acid via X-ray Analysis of a Complex Undergoing a Single-Crystal-to-Single-Crystal Transformation[1]

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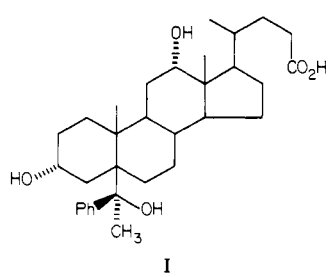
Received August 25, 1981

In a previous communication,[2] we demonstrated that crystalline channel inclusion complexes of DCA may serve as appropriate matrices for elucidation of reaction pathways. Irradiation of the complex DCA–acetophenone yielded a single diastereomeric photoaddition product (**1**) with an absolute configuration *S* at the newly generated chiral carbon, opposite to the configuration ex-



I

pected from the host–guest packing at the reaction site.[3] By virtue of the fact that DCA–acetophenone maintained its crystalline integrity[4] on photoconversion, the photoaddition reaction pathway was monitored by determination of the crystal structures before and after reaction. That study showed that on photoexcitation the acetyl group of acetophenone underwent a net rotation of 180° prior to bond formation to the steroid. This unusual molecular reaction pathway made it imperative to design a crystalline DCA–substituted acetophenone complex whose host–guest packing would yield a product analogous to **1** but with absolute configuration *R* at the newly generated chiral carbon. In order to obtain this product it is necessary to modify the observed guest packing (Figure 1a) in the channel so that the acetophenone molecule G would occupy a new position approximately 1.5–2 Å removed along the $-c$ direction.[5] It appeared that such a change might possibly be achieved by para substitution of the guest phenyl ring or by extension of the alkyl side chain of the ketone. We chose *p*-fluoroacetophenone as an appropriate guest. The structure of DCA–*p*-fluoroacetophenone was determined via low-temperature (−170 °C) X-ray diffraction.[6] Two independent guest molecules G and G′ were located in the channel. The molar guest–host ratios

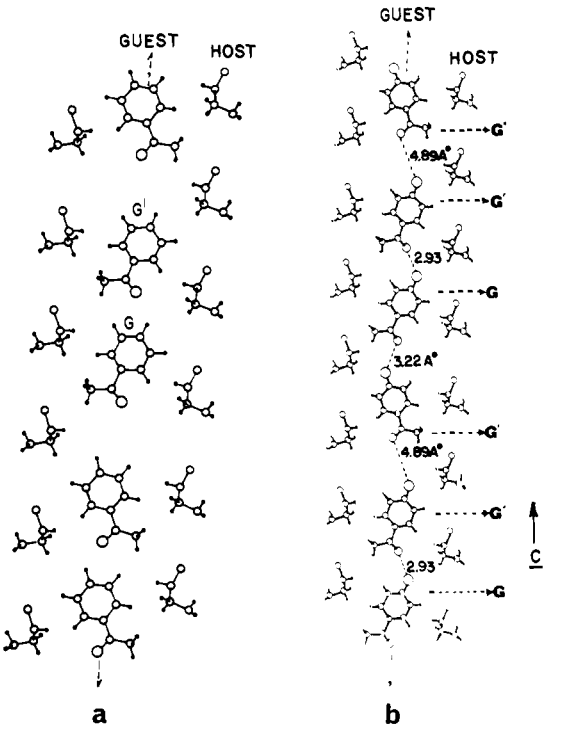


Figure 1. (a) Packing arrangement of acetophenone G and G′ molecules in the channel as viewed perpendicular to the plane of the guest molecule. The two independent guest molecules G and G′ of a close-packed pair are related by pseudotranslation of $C + \Delta C$, where $\Delta C = 0.8$ Å. The sides of the guest molecules are bracketed by the steroid channel wall comprising the side-chain atoms [HO_2C]–CH_2–CH_2–CH–C(methyl). (b) *p*-Fluoroacetophenone packing motif in the channel as viewed perpendicular to the plane of the guest molecule. The guest molecules form chains comprising close-packed triplets G′GG′. . .G′GG′. . .G′, etc., yielding a superstructure with a translation repeat of 4C. The molecules G and G′ expose opposite faces of their acetyl groups to C_5–H_5 of the steroid. G and G′ are related by a pseudotranslation of $C + \Delta C$ where $\Delta C = 1.64$ Å.

(1) This paper should be considered as "Reactions in Molecular Inclusion Complexes". 5. For part 4, see: Popovitz-Biro, R.; Tang, C. P.; Chang, H. C.; Shochet, N. R.; Lahav M.; Leiserowitz L. *Nouv. J. Chim.*, in press.

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(4) Nakanishi, N.; Jones, W.; Thomas, J. M.; Burshouse, H. B.; Maltevalli, M. *J. Chem. Soc., Chem. Commun.* **1980**, 611. Ohashi, Y.; Yanagi, K.; Kurihara, T.; Sasada, Y.; Ohgo, Y. *J. Am. Chem. Soc.* **1981**, *103*, 5805.

(5) This point will be elucidated in a full paper (Chang, H. C.; Tang, C. P.; Popovitz-Biro, R.; Lahav, M.; Leiserowitz, L., to be submitted for publication).

(6) The cell constants at −170 °C are $a = 25.270$ (7) Å, $b = 13.579$ (8) Å, $c = 7.198$ (3) Å, space group $P2_12_12_1$. The diffraction data were measured on a CAD-4 diffractometer using Mo Kα radiation filtered with a graphite monochromator; 10 280 reflections were measured to a maximum value of $\sin\theta/\lambda = 0.91$ to yield 4916 independent "observed" reflections.

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