Alcoholysis of Urea Catalyzed by Palladium(II) Complexes

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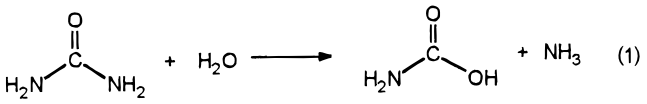
The palladium(II) aqua complex *cis*-$[Pd(en)(H_2O)_2]^{2+}$ catalyzes the alcoholysis of urea into alkyl carbamate and ammonia. The observed rate constants for the ester formation fall in the range from 1.8×10^{-5} to 5.9×10^{-1} min^{-1} at 313 K and pH 3.3, depending on the alcohol. This catalyzed reaction is at least 10^5 times faster than the uncatalyzed alcoholysis of urea under the same conditions. This is the first example of catalytic, nonhydrolytic cleavage of the amide bond in urea. The following steps in the mechanism of the methanolysis reaction are studied quantitatively: binding of urea to the catalyst in the presence of various alcohols or various concentrations of water, direct methanolysis of O-bound and N-bound urea, formation of carbamic acid (NH_2COOH) coordinated to palladium(II) via the nitrogen atom, methanolysis of this intermediate, and the fast dissociation resulting in free methyl carbamate. Ammonia, a product of alcoholysis, inhibits this reaction by binding to palladium(II). When, however, ammonia is sequestered by the silver(I) cation, alcoholysis becomes relatively fast, and catalytic turnover is achieved. Various alcohols are compared in their reactivity toward urea. The effects of nucleophilicity, steric bulk, size, and additional hydroxyl groups (in diols) are examined. The intramolecular alcoholysis in the 2,6-dithia-1,8-octanediol complex *cis*-$[Pd(C_6H_{14}O_2S_2)(H_2O)_2]^{2+}$ results in at least 100-fold rate enhancement relative to the intermolecular alcoholysis by *cis*-$[Pd(en)(H_2O)_2]^{2+}$. Alkyl carbamates do not hydrolyze further into carbamic acid and alcohol. Aryl carbamates do hydrolyze further, and this reaction requires the palladium(II) aqua complex as a catalyst. Carbamic acid then spontaneously decomposes into carbon dioxide and ammonia. Observed rate constants for the appearance and disappearance of aryl carbamates agree with the relative nucleophilicities of aryl alcohols. This study of the catalysis by a metal complex may contribute to the understanding of the metalloenzyme urease. We propose a new method, alcoholysis, for cleaving amide bonds in peptides and proteins.

Introduction

The enzyme urease contains nickel(II) ions and catalyzes the hydrolysis of urea to ammonia and carbamic acid (eq 1).[1] Because carbamic acid spontaneously decomposes into ammonia and carbon dioxide (eq 2), the overall hydrolysis reaction is usually written as a sum of eqs 1 and 2. Because uncatalyzed



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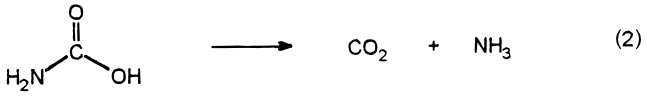

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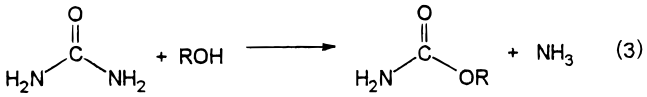
hydrolysis of urea has not been reported, the catalytic power of urease can only be estimated; the enzymatic rate enhancement is at least 10^{14}-fold at pH 7 and 311 K.[2]

Examination of coordination compounds for their ability to catalyze these and similar reactions could be important in assessing the roles of nickel(II) ions in enzymatic decomposition of urea. Several models of urease have previously been reported, among them rhodium(III) and platinum(II) complexes that promote decomposition of urea.[3−10] Because the reaction in eq 2 does not require a catalyst, we were more interested in the hydrolysis or solvolysis of urea resulting in the amide bond cleavage, as shown in eq 1. Alcohols have basic and nucleophilic properties similar to those of water and are potential reagents for the cleavage of the amide bond in urea, as shown in eq 3.[11] The resulting carbamate esters are more stable than



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carbamic acid and do not decompose further.[12] Some etha-

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(12) Our unpublished results show that in the absence of the palladium(II) complex, methyl carbamate and phenyl carbamate are stable for at least 3 days in wet acetone that is made 0.1 M in $HClO_4$ at 318 K. The estimated observed rate constant for their hydrolysis is, therefore, lower than 7×10^{-7} min^{-1}.

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nolysis of *N*-(2-pyridylmethyl)urea in the presence of an excess $NiCl_2$ has been observed.[13] The activating interaction between the carbonyl oxygen of urea and nickel(II) ion was reinforced by the strong coordination of the pyridyl nitrogen atom to the same nickel(II) ion.

We recently studied hydrolytic decomposition of urea into carbon dioxide and ammonia catalyzed by palladium(II) aqua complexes.[14] These catalysts enhance the reaction rate as much as 10^5-fold. Now we report that the same palladium(II) aqua complexes, especially *cis*-$[Pd(en)(H_2O)_2]^{2+}$, catalyze alcoholysis of urea to yield carbamate esters and ammonia, according to eq 3. Although the simple palladium(II) complexes differ from the nickel(II) complex at the active site of urease,[15] hydrolysis of urea catalyzed by both complexes involves carbamic acid as an intermediate. Kinetic and mechanistic studies of hydrolysis and alcoholysis by metal compounds may contribute to the understanding of the mechanisms of enzymatic hydrolysis.

Because urea is an amide, its alcoholysis is of some practical interest. Cleavage of amide bonds in proteins has long been one of the most important procedures in analytical biochemistry.[16] The amide bond is extremely unreactive—uncatalyzed hydrolysis of peptides by water occurs with half-lives of 250−600 years.[17] Proteolytic enzymes widely used in sequencing cleave proteins by hydrolysis of amide bonds.[16,18] Few transition-metal complexes have been applied so far to this task, and most of them effect hydrolytic cleavage.[19] Various conceivable types of nonhydrolytic cleavage of amide bonds are yet to be explored. Alcoholytic cleavage of the phosphoester bond promoted or catalyzed by transition-metal complexes has been known for some time.[20] To our knowledge, however, catalytic alcoholysis of amides has not been reported before.

Experimental Section

Chemicals. The deuterium-containing compounds D_2O, $DClO_4$, and NaOD and the salts $K_2[PdCl_4]$, $PdCl_2$, and $AgClO_4 \cdot H_2O$ were obtained from Sigma Chemical Co. and Aldrich Chemical Co. Anhydrous $AgClO_4$ (caution, strong oxidant!) was obtained from G. Frederich Smith Chemical Co. All of the aliphatic and aromatic alcohols and amino alcohols were obtained from Aldrich Chemical Co., except *tert*-butyl alcohol, which was obtained from Fisher Scientific. The ligand 3,6-dithia-1,8-octanediol ($C_6H_{14}O_2S_2$) was obtained from Aldrich Chemical Co. The isotopomers urea-^{13}C (99%), urea-$^{15}N_2$ (98%), and urea-^{13}C,$^{15}N_2$ (^{13}C 99%, ^{15}N 98%) and also acetone-d_6, methanol-d_4, and dimethylformamide-d_7 were obtained from Cambridge Isotope Laboratories. The esters methyl carbamate and phenyl carbamate were obtained from Aldrich Chemical Co. Trifluoroacetic acid was obtained from Fisher Scientific Co. These and all other chemicals were of reagent grade.

Palladium(II) Complexes. The palladium(II) complex *cis*-$[Pd(en)Cl_2]$ was prepared by the published procedure.[21] The chloro ligands were aquated by stirring a solution of this complex and 2 equiv of anhydrous $AgClO_4$ or $AgClO_4 \cdot H_2O$ in acetone-d_6 or methanol-d_4 for 1 h at 25 °C in the dark. The solid AgCl was filtered off in the dark, and a fresh solution of the aqua complex was used in further experiments. The salt *cis*-$[Pd(en)(H_2O)_2](ClO_4)_2$ had an absorption maximum at 360 nm, as reported before.[21] The complex *cis*-$[Pd(PhCN)_2Cl_2]$ was prepared by the published procedure.[22] Complexes *cis*-$[Pd(en)(H_2O)(NH_2(CH_2)_nOH)]^{2+}$ (**5**) and *cis*-$[Pd(en)(NH_2(CH_2)_nOH)_2]^{2+}$ (**6**), in which $n = 2-4$, were prepared in situ from *cis*-$[Pd(en)(H_2O)_2]^{2+}$ in acetone-d_6 by adding, respectively, 1 or 4 equiv of the corresponding amino alcohol $NH_2(CH_2)_nOH$, in which $n = 2-4$. Addition of 4 equiv of an amino alcohol ensured formation of the disubstituted complex. The following ^1H and ^{13}C chemical shifts were referenced to an internal standard, tetramethylsilane (TMS) at 0.00 ppm. ^1H NMR in acetone-d_6 at 293 K: *cis*-$[Pd(en)(H_2O)(NH_2(CH_2)_2OH)]^{2+}$ δ 3.96 and 3.93 (t, CH_2), 7.55 (t, NH_2); *cis*-$[Pd(en)(NH_2(CH_2)_2OH)_2]^{2+}$ δ 3.80 and 3.75 (t, CH_2), 7.55 (t, NH_2); *cis*-$[Pd(en)(H_2O)(NH_2(CH_2)_3OH)]^{2+}$ δ 3.85 and 3.72 (t, CH_2), 1.95 (tt, CH_2), 7.55 (m, NH_2); *cis*-$[Pd(en)(H_2O)(NH_2(CH_2)_4OH)]^{2+}$ δ 3.64 and 3.57 (t, CH_2), 1.85 (tt, CH_2), 1.62 (tt, CH_2), 7.62 (m, NH_2). In complexes **5** and **6**, $\delta = 2.9$ (br s, CH_2 of en); integration showed all four protons. The complex *cis*-$[Pd(C_6H_{14}O_2S_2)Cl_2]$, designated **7**, was prepared from *cis*-$[Pd(PhCN)_2Cl_2]$ and 1 equiv of 3,6-dithia-1,8-octanediol in benzene at room temperature. The mixture was stirred overnight, and the yellow precipitate was filtered off. The solid was soluble in dimethylformamide and acetone. Anal. Calcd. for *cis*-$[Pd(C_6H_{14}O_2S_2)Cl_2]$: C, 20.04; H, 3.92. Found: C, 20.53; H, 3.91. ^{13}C NMR at 293 K in DMF-d_6: δ 60.5 (CH_2), 41.0 (CH_2), 40.6 (CH_2), 39.3 (CH_2), 39.0 (CH_2). ^{13}C NMR in DMF-d_7 at 313 K: δ 60.5 (CH_2), 40.8 (CH_2), 39.15 (CH_2). The chloride ligands in complex **7** were aquated by stirring a solution of **7** and 2 equiv of anhydrous $AgClO_4$ or $AgClO_4 \cdot H_2O$ in acetone-d_6 for 1 h at 25 °C in the dark. The solid AgCl was filtered off in the dark, and a fresh solution of the aqua complex was used. ^{13}C NMR of *cis*-$[Pd(C_6H_{14}O_2S_2)(H_2O)_2]^{2+}$ in acetone-d_6 at 313 K: δ 59.5 (CH_2), 41.6 (CH_2), 39.2 (CH_2).

Carbon-13 Relaxation Times. Longitudinal relaxation times (T_1) in the presence of 0.040 M paramagnetic complex $[Cr(acac)_3]$ were determined by the inversion−recovery method, with a Bruker DRX-400 spectrometer, at 298 and 313 K. The solvent was either acetone-d_6 or methanol-d_4. The results are given in Table 1. The three palladium(II) complexes and the carbamate esters included there were obtained in situ, after 2 h at 313 K, in a solution that was initially 0.30 M in *cis*-$[Pd(en)(H_2O)_2]^{2+}$, 0.30 M in urea-^{13}C, and 0.9−3.6 M in an alcohol. The concentrations of the compounds in Table 1 fell in the range 0.0030−0.15 M. All the experiments in the presence of $[Cr(acac)_3]$ involved 30 scans with 20 s delays between them, to prevent saturation.

Carbon-13 NMR Spectra. These spectra were recorded with Varian VXR-300 and Bruker DRX-400 spectrometers. The chemical shifts (δ) are given in ppm downfield from the methyl resonance of the solvent, which was acetone-d_6 or methanol-d_4. The internal reference in the kinetic experiments performed in acetone-d_6 was the carbonyl resonance of this solvent because its chemical shift is similar to the shifts of urea and of the carbamate esters. The quality of the

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Table 1. Longitudinal Relaxation Times of ^{13}C Nuclei in the Presence of the Paramagnetic Relaxation Agent $[Cr(acac)_3]$[a]

compound	T_1, s	
	298 K	313 K
$(CH_3)_2CO$	not determined	0.65 ± 0.01[b]
$(NH_2)_2CO$	0.21 ± 0.01	0.33 ± 0.01[b]
cis-$[Pd(en)(OC(NH_2)_2)(H_2O)]^{2+}$	not determined	0.17 ± 0.01[b]
cis-$[Pd(en)(NH_2C(O)NH_2)(H_2O)]^{2+}$	not determined	0.19 ± 0.02[b]
cis-$[Pd(en)(NH_2C(O)OH)(H_2O)]^{2+}$	not determined	0.54 ± 0.01[b]
CO_2	not determined	1.6 ± 0.1[b]
$NH_2C(O)OCH_2CH_2CH_3$	1.3 ± 0.1	1.6 ± 0.1
$NH_2C(O)OCH(CH_3)_2$	1.2 ± 0.1	1.5 ± 0.2
$NH_2C(O)O(CH_2)_4OH$	0.64 ± 0.02	0.91 ± 0.01
$NH_2C(O)O(CH_2)_6OH$	0.46 ± 0.03	0.68 ± 0.02
$NH_2C(O)OCH_2CH(OH)CH_3$	0.47 ± 0.01	0.74 ± 0.02
$NH_2C(O)OCH_3$	1.2 ± 0.2	1.32 ± 0.1
	0.58 ± 0.02[c]	0.86 ± 0.03[c]

[a] The concentration of $[Cr(acac)_3]$ is 0.040 M. [b] From ref 14. [c] The solvent is methanol-d_4. In all other cases the solvent is acetone-d_6.

^{13}C NMR spectra was improved by their acquisition in narrow windows. In all of the quantitative experiments, the solution was made 0.040 M in $[Cr(acac)_3]$. The delay between the pulses was longer than $5T_1$ for the slowest-relaxing species, CO_2; each scan took 9.35 s. Usually 30 scans of the enriched samples, and as many as 3000 scans of the unenriched ones, were taken. Spectra were recorded with and without proton decoupling. In quantitative experiments, in which accurate relative intensities were needed, decoupling was not used. The resonances were integrated with an estimated error of ±5%. Concentrations of the compounds were determined on the basis of these integrals, the initial concentrations of urea, and the known concentration of ^{13}C nuclei in the known volume of the solvent, which was acetone-d_6 or methanol-d_4. Equilibrium constants, rates, and rate constants were calculated from the known concentrations of the reactants and products, with an estimated error of 10−20%.

Binding of Urea to Palladium(II). These experiments were performed by ^{13}C NMR spectroscopy. In each experiment, the solution was initially 0.30 M in *cis*-$[Pd(en)(H_2O)_2]^{2+}$, 0.30 M in urea-^{13}C, and 1.5 M in H_2O; the solvent was methanol-d_4. In the experiments with alcohols, their initial concentrations were 0−3.6 M, and the solvent was acetone-d_6. The equilibrium constants are average results of several experiments.

Kinetics of Alcoholysis. The following solvents were used: methanol-d_4 in experiments concerning the reaction mechanism; acetone-d_6 (which was ca. 0.6 M in adventitious water) in experiments concerning the reactivity of various alcohols; and either methanol-d_4 or a 4.5 M solution of methanol-d_4 in acetone-d_6 in experiments concerning catalytic turnover. In experiments concerning acid effects, the solvent methanol-d_4 was made 3.7 M in H_2O. In experiments concerning ionic strength effects, the solvent was 3.6 M methanol-d_4 in acetone-d_6. The temperature was always 313 ± 0.5 K, except in experiments concerning the catalytic turnover, when it was 333 ± 0.5 K. The reactions in eqs 1−3 were followed by ^{13}C NMR spectroscopy. In a typical experiment, to a solution of a freshly prepared complex were added solid $[Cr(acac)_3]$, sometimes other chemicals, and finally solid urea, to start the reaction. Acquisition of the spectra began as soon as possible. The variable chemical was an alcohol, an acid ($HClO_4$ or CF_3COOH), or H_2O. The final concentrations of $[Cr(acac)_3]$ and H_2O were 0.040 and 1.5 M, respectively. Other concentrations were variously adjusted.

The initial rates were determined in experiments in which only the first 3−5% of the reaction was followed. The observed rate constants were determined from the initial rates. The microscopic rate constants were obtained by fitting the ^{13}C NMR integrals for at least 5 half-lives to the appropriate equations.

The acidity was adjusted with either $HClO_4$ or CF_3COOH. Both methods gave the same kinetic results, within the experimental error. The acid concentration was corrected for the contribution from the stock solution of *cis*-$[Pd(en)(H_2O)_2]^{2+}$, for which the first pK_a is 5.6 at ionic strength 0.10 M in H_2O at 25 °C.[21]

Composition of the Reaction Mixtures. The reactant was urea, an intermediate was carbamic acid N-bound to palladium(II), and the products were carbon dioxide, ammonia, ammonium ion, and various carbamate esters. All carbamate esters except methyl carbamate were obtained in the protio form. Methyl carbamate was obtained as $NH_2C(O)OCD_3$; for the sake of consistency, it is shown as $NH_2C(O)OCH_3$ in all schemes and figures. All of these compounds were detected by ^{13}C NMR spectroscopy. The assignments of the resonances were confirmed by spiking the reaction mixture with the pure chemical of interest, if this chemical was commercially available. The chemical shifts could deviate from the stated values by up to 0.10 ppm, depending on the composition of the reaction mixture and other conditions.

Results and Discussion

Use of ^{13}C NMR Spectroscopy in Kinetics. Alcoholysis of urea is conveniently followed by ^{13}C NMR spectroscopy. Because the signal intensity depends on differential relaxation and the nuclear Overhauser effect (NOE), concentrations are not accurately obtained from the routine spectra.[23] Precautions must be taken if ^{13}C NMR spectroscopy is to be used in quantitative experiments.

We determined relaxation times T_1 of the ^{13}C nuclei in various compounds at 298 and 313 K. The results are given in Table 1. The undetermined T_1 times are too long in the absence of the paramagnetic relaxation agent, $[Cr(acac)_3]$, but they were conveniently determined in its presence.[24] The T_1 values generally increase as the number of ^1H and ^{14}N nuclei in the molecule decreases. The carbonyl ^{13}C nuclei in carbamate esters have similar relaxation times, which do not depend on the solvent composition. As expected, T_1 increases with temperature.[25]

Differential relaxation was avoided because the delay time between the pulses was greater than $5T_1$ of the slowest-relaxing nucleus, that in CO_2. In the presence of $[Cr(acac)_3]$, the delay time between the pulses became sufficiently short for practical work.[24]

The NOE problem disappeared when all the spin−spin couplings were preserved, i.e., when decoupling was not used.[24] Evidently, ^{13}C NMR spectroscopy can be a reliable tool in quantitative analysis if precautions are taken. We know of few other quantitative studies by ^{13}C NMR spectroscopy.[14,26−32]

Binding of Urea to Palladium(II) in the Presence of Various Alcohols. The most common modes of urea coordination to transition metals are shown in Chart 1.[33] There are no precedents for bidentate urea.[10,14] The ^{13}C NMR spectra of mixtures containing urea-^{13}C, *cis*-$[Pd(en)(H_2O)_2]^{2+}$, and various alcohols show the resonances at 162.8, 165.5, and 158.0 ppm for free urea and for the O-bound and N-bound ligands, respectively. These values agree with those reported previously by us and others.[10,14]

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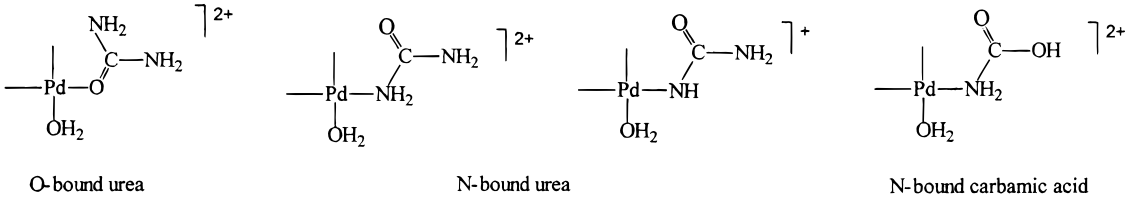
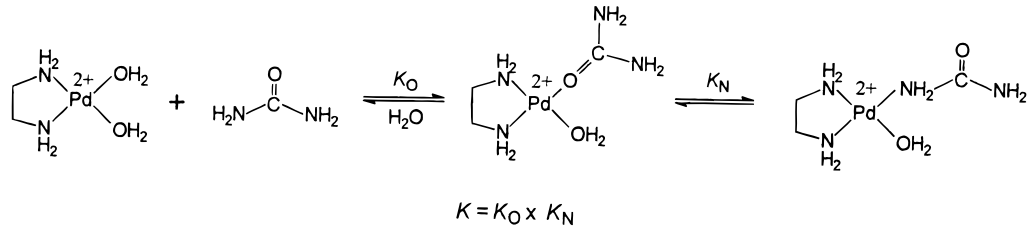
Chart 1. Coordination Modes



Scheme 1. Coordination of Urea



$K = K_O \times K_N$

Table 2. Equilibrium Constants[a] at 313 K for Urea Binding to *cis*-$[Pd(en)(H_2O)_2]^{2+}$ in the Presence of Various Alcohols

alcohol (conc)	K_O, M^{-1}	K_N	K, M^{-1}
none	23	0.056	1.3
CH_3OH (3.6 M)	31	0.020	0.63
CH_3OH (neat, 22.6 M)[b]	18	0.013	0.23
CH_3CH_2OH (1.5 M)	31	0.016	0.49
CFH_2CH_2OH (1.5 M)	34	0.056	1.9
CF_3CH_2OH (1.5 M)	42	0.055	2.3
$CH_3CH_2CH_2OH$ (1.5 M)	28	0.015	0.41
$CH_3CH(OH)CH_3$ (1.5 M)	26	0.015	0.40
$CH_3CH(OH)CH_2CH_3$ (1.5 M)	26	0.017	0.44
$HOCH_2CH_2OH$ (0.9 M)	36	0.023	0.83
$HOCH_2CH_2CH_2OH$ (0.9 M)	32	0.029	0.92
$HOCH_2CH(OH)CH_2OH$ (0.9 M)	39	0.020	0.77

[a] Defined in Scheme 1. [b] The solvent is methanol-d_4. In all other cases the solvent is acetone-d_6.

Urea initially displaces an aqua ligand in *cis*-$[Pd(en)(H_2O)_2]^{2+}$ to yield the O-bound isomer. It then converts into the N-bound isomer, which is thermodynamically more stable. In the 1,5-dithiacycloocta-3-ol complex *cis*-$[Pd(dtco\text{-}OH)(H_2O)_2]^{2+}$, this process occurs over approximately 1 h, but further decomposition of N-bound urea into ammonia and carbon dioxide precluded quantitative determination of the rate constants.[14]

The three equilibrium constants are defined in Scheme 1. Their values, which are average results of multiple experiments by ^{13}C NMR spectroscopy, are given in Table 2. The O-bound isomer is much more abundant than the N-bound isomer. Because N-bound urea is ca. 10^7 times more acidic than O-bound urea,[5] the observed equilibrium between them depends strongly on pH. When pH is lowered, K_N decreases.[14] The three equilibrium constants do not change significantly when various alcohols are added to the solution of *cis*-$[Pd(en)(H_2O)_2]^{2+}$ and urea in acetone-d_6. The values obtained in methanol-d_4 solutions are slightly lower than those obtained in acetone-d_6 solutions. Because urea is much better than alcohol as a ligand for the palladium(II) ion, the presence of various alcohols at the concentrations used (as high as 3.6 M) does not detectably affect urea coordination.

The equilibrium for urea coordination is affected by the presence of water, as Table 3 shows. The concentration of bound urea decreases as the concentration of H_2O increases, because these two ligands compete for binding to palladium(II). The increase of K_N with increasing concentration of water is evidence that N-bound urea is thermodynamically more stable than O-bound urea in the more polar medium.[10,34]

Table 3. Effects of Water Concentration on Equilibrium Constants[a] for Urea Binding to *cis*-$[Pd(en)(H_2O)_2]^{2+}$ at 313 K in Methanol-d_4 Solution

conc of H_2O, M	K_O	K_N	K, M^{-1}
0.0	18	0.019	0.34
1.5	12	0.022	0.26
3.7	3.1	0.036	0.11
7.4	0.61	0.066	0.040
11.1	0.32	0.094	0.030

[a] Defined in Scheme 1.

Table 4. Observed Rate Constants for the Formation of Carbamate Esters (NH_2COOR) and Their Carbon-13 Carbonyl Chemical Shifts[a] in the Presence of *cis*-$[Pd(en)(H_2O)_2]^{2+}$

alcohol	$k_{obs} \times 10^4$, min^{-1}	^{13}C chemical shift, ppm
CH_3OH	5.12 ± 0.29	158.38
CH_3CH_2OH	1.46 ± 0.12	158.51
$CH_3CH_2CH_2OH$	1.68 ± 0.12	158.47
$CH_3(CH_3)CHOH$	0.620 ± 0.070	157.94
$CH_3CH_2(CH_3)CHOH$	0.930 ± 0.130	158.53
$(CH_3)_3COH$	0.230 ± 0.010	157.56
$(CH_3)_2CHCH_2CH_2OH$	2.30 ± 0.16	158.47

[a] The solvent is acetone-d_6, the temperature is 313 K, and the concentration of *cis*-$[Pd(en)(H_2O)_2]^{2+}$ is 0.30 M.

Products of Urea Alcoholysis. In the absence of palladium(II) complexes, urea does not react with either water or alcohols. In the presence of palladium(II) complexes, urea undergoes solvolysis to give carbon dioxide, various carbamate esters, NH_3, and NH_4^+ ion. These products were readily detected by their NMR chemical shifts listed in Tables 4−8 and those published previously.[10] Carbon dioxide, a product of urea hydrolysis, a side reaction, was observed only in the acetone-d_6 solution, which was ca. 0.6 M in adventitious water. This undesirable product was not detected in the methanol-d_4 solutions, in which urea was selectively converted to carbamate esters and ammonia.

Kinetic Effects of Methanol. As Figure 1 shows, methanolysis shows first-order kinetics with respect to methanol at low concentrations of methanol-d_4. At high concentrations of methanol-d_4 in acetone-d_6 and also in neat methanol-d_4, the initial rate of methyl carbamate formation decreases, as shown

(33) Fairlie, D. P.; Jackson, W. G. *Inorg. Chim. Acta* **1988**, *150*, 81.
(34) *Handbook of Chemistry and Physics*; Lide, R. D., Ed.; CRC Press: New York, 1996−1997; pp 6−151.

Table 5. Constants pK_a for Alcohols, the Observed Rate Constants for the Formation of Carbamate Esters (NH_2COOR), and Their Carbon-13 Carbonyl Chemical Shifts[a] in the Presence of *cis*-$[Pd(en)(H_2O)_2]^{2+}$

alcohol	pK_a	$k_{obs} \times 10^4$, min^{-1}	^{13}C chemical shift, ppm
CH_3CH_2OH	15.9	1.46 ± 0.18	158.51
CFH_2CH_2OH	14.3	1.08 ± 0.06	157.87
CF_3CH_2OH	12.4	0.180 ± 0.010	158.12

[a] The solvent is acetone-d_6, the temperature is 313 K, and the concentration of *cis*-$[Pd(en)(H_2O)_2]^{2+}$ is 0.30 M.

Table 6. Observed Rate Constants for the Formation of Hydroxyalkyl Carbamate Esters (NH_2COOR) and Their Carbon-13 Carbonyl Chemical Shifts[a] in the Presence of *cis*-$[Pd(en)(H_2O)_2]^{2+}$

polyol	chain length[b]	$k_{obs} \times 10^4$, min^{-1}	^{13}C chemical shift, ppm
$HOCH_2CH_2OH$	2	2.01 ± 0.13	158.52
$HOCH_2(CH_3)CHOH$	2	0.970 ± 0.060	158.35
cis-1,2cyclohexanediol	2	$< 9 \times 10^{-3}$	not determined
$HOCH_2CH_2CH_2OH$	3	3.22 ± 0.10	158.62
$HOCH_2CH_2CH_2CH_2OH$	4	3.11 ± 0.12	158.62
$HOCH(CH_3)CH_2CH_2CH_2OH$	4	2.22 ± 0.20	157.92
$HOCH_2CH_2CH_2CH_2CH_2OH$	5	2.62 ± 0.20	158.50
$HOCH_2CH_2CH_2CH_2CH_2CH_2OH$	6	4.08 ± 0.10	158.50
$HOCH_2(OH)CHCH_2$**OH**[c]		0.610 ± 0.040	158.67
$(HOCH_2)_2CH$**OH**[d]		0.460 ± 0.020	158.05

[a] The solvent is acetone-d_6, the temperature is 313 K, and the concentration of *cis*-$[Pd(en)(H_2O)_2]^{2+}$ is 0.30 M. [b] Number of carbon atoms in the diol. [c] Glycerol reacts as a primary alcohol, via the highlighted hydroxyl group. [d] Glycerol reacts as a secondary alcohol, via the highlighted hydroxyl group.

Table 7. Coordination of Urea to *cis*-$[Pd(en)(H_2O)_2]^{2+}$ in the Presence of Amino Alcohols,[a] Observed Rate Constants for the Formation of Aminoalkyl Carbamate Esters (NH_2COOR), and Their Carbon-13 Carbonyl Chemical Shifts[b]

amino alcohol	K_O	K_N	K	$k_{obs} \times 10^4$, min^{-1}	^{13}C chemical shift, ppm
$NH_2(CH_2)_2OH$	8.9	0.13	1.2	2.56 ± 0.20	158.00
$NH_2(CH_2)_3OH$	0.70	0.25	0.20	0.43 ± 0.13	157.53
$NH_2(CH_2)_4OH$	5.8	0.25	1.5	4.07 ± 0.53	158.20

[a] The concentration of amino alcohols is 0.30 M. [b] The solvent is acetone-d_6, the temperature is 313 K, and the concentration of *cis*-$[Pd(en)(H_2O)_2]^{2+}$ is 0.30 M.

Table 8. Carbon-13 Carbonyl Chemical Shifts of Aryl Carbamates, Formed (k_f)[a] from Urea and Aryl Alcohols and Decomposed (k_d)[a] in the Reactions[b] Catalyzed by *cis*-$[Pd(en)(H_2O)_2]^{2+}$

ArOH	pK_a	^{13}C chemical shift, ppm	$k_f \times 10$, min^{-1}	$k_d \times 10^3$, min^{-1}
4-$CH_3O-C_6H_4OH$	10.2	158.56	5.9 ± 1.6	5.18 ± 0.29
4-$NO_2-C_6H_4OH$	7.16	158.52	4.7 ± 0.8	16.3 ± 0.9

[a] Defined in Scheme 6. [b] The concentration of *cis*-$[Pd(en)(H_2O)_2]^{2+}$ is 0.30 M, the solvent is acetone-d_6, and the temperature is 313 K.

in the inset in Figure 1. This decrease in the rate is consistent with the result in Table 2. Evidently, urea coordination is less favorable in neat methanol-d_4 than in a 3.6 M solution of methanol-d_4 in acetone-d_6.

As Figure S1 in the Supporting Information shows, the initial rate of carbon dioxide formation decreases as the concentration of methanol-d_4 in the solvent (acetone-d_6) is raised. In neat methanol-d_4, the formation of carbon dioxide ceases, and urea is selectively converted to methyl carbamate and ammonia. Because in neat methanol-d_4 the side reaction (urea hydrolysis) does not occur, a simplified kinetic scheme can be used.

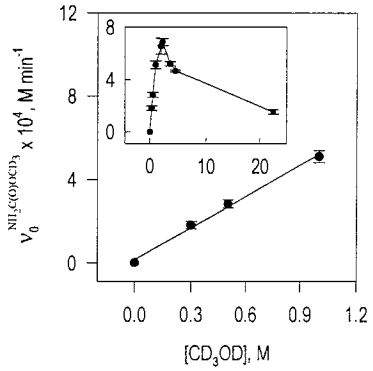
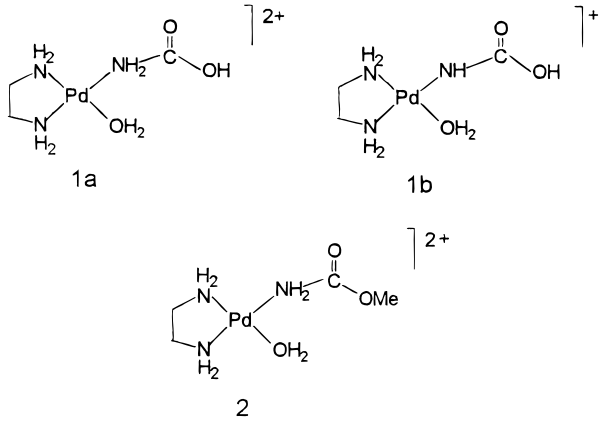


Figure 1. Initial rate of methyl carbamate formation depends on the initial concentration of methanol-d_4. Initial concentrations of the catalyst, *cis*-$[Pd(en)(H_2O)_2]^{2+}$, and of urea were 0.30 M each; the temperature is 313 K; and the solvent is acetone-d_6.

Therefore, the experiments concerning the methanolysis mechanism were conveniently performed in neat methanol-d_4, and this solvent acted as the reagent.

An Intermediate in Alcoholysis. An intermediate is consistently observed in both acetone-d_6 and methanol-d_4 solutions. Isocyanate coordinated to platinum(II) has been recently observed as an intermediate in the noncatalytic decomposition of urea, promoted by the complex $[Pt(dien)(acetone)]^{2+}$.[10] This reaction, evidently, is an elimination. In our study, which involves palladium(II) complexes, neither the ^{15}N nor the ^{13}C NMR spectrum is consistent with the NCO^- ion. We did not observe the characteristic resonances of this ion, either free or coordinated to palladium(II).[14] Neither spectrum is consistent with N,N- or N,O-bidentate urea as a ligand on palladium(II).[14]

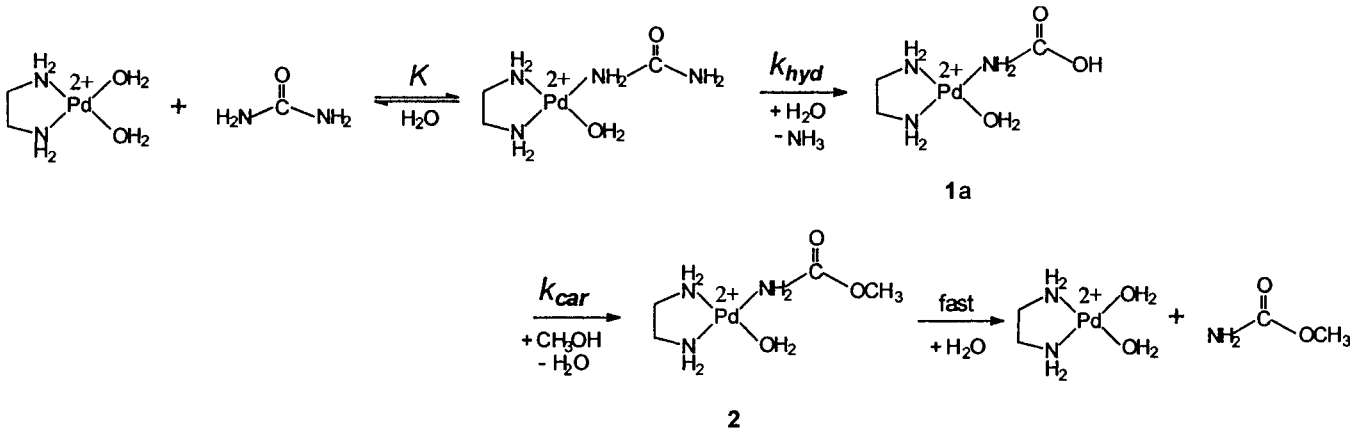
Carbamic Acid as an Intermediate in Alcoholysis. Both the ^{13}C and ^{15}N NMR spectra of the intermediate are consistent with N-coordination of carbamic acid (**1a**) or of its conjugate base (**1b**).[14] When urea is enriched only in ^{13}C, the resonances



of the intermediate at 174.3 ppm in acetone-d_6 and at 173.0 ppm in methanol-d_4 are singlets. When urea is enriched in both ^{13}C and ^{15}N, the ^{13}C resonance of the intermediate in acetone-d_6 is a doublet of broad triplets, owing to coupling to one ^{15}N nucleus ($J_{CN}^1 = 21.8$ Hz) and to two equivalent protons ($J_{CH}^2 = 3.7$ Hz). This ^{13}C resonance appears as a broad doublet when the solvent is methanol-d_4, owing to H−D exchange with this solvent. Carbamic acid N-bound to metal ions is relatively acidic, with the pK_a value in the range 6−7, depending on the metal ion.[35] Since in all kinetic experiments acid concentration

(35) Dixon, N. E.; Sargeson, A. M. In *Zinc Enzymes*; Spiro, T. G., Ed.; Wiley: New York, 1983; p 253.

Scheme 2. Indirect Methanolysis of Urea, via Carbamic Acid as an Intermediate



was at least 0.5 mM, the concentration of **1b** is expected to be undetectably low. In acetone-d_6, the ^{1}H resonance at 4.95 ppm corresponding to the NH protons in the intermediate is a broad doublet of doublets, owing to coupling to one ^{15}N nucleus and one ^{13}C nucleus. Integration of this resonance shows two protons bound to nitrogen, a structure consistent with **1a**. The iminol tautomers of **1a** and **1b** are unlikely because urea and carbamic acid exist mostly in the amide form.[33] In a very recent study of urea decomposition, a ^{13}C NMR resonance at 173 ppm, in acetone-d_6 as a solvent, was attributed to a "minor carbamate species" but this species was not invoked as an intermediate in the reaction.[10]

In the absence of an alcohol, N-bound carbamic acid decomposes completely into carbon dioxide and ammonia.[14] In the presence of an alcohol, this intermediate is esterified to form the corresponding free carbamate ester. In methanol-d_4 solution, in which carbon dioxide does not form, N-bound carbamic acid is completely converted to free methyl carbamate, probably via N-bound methyl carbamate (**2**), as shown in Scheme 2. Complex **2** was not observed by ^{13}C NMR spectroscopy in the actual reaction mixture. Our attempts to prepare a complex containing either O-bound or N-bound methyl carbamate from *cis*-$[Pd(en)(H_2O)_2]^{2+}$ and $NH_2C(O)OCH_3$ in acetone-d_6 solutions failed. Evidently, methyl carbamate does not detectably bind to palladium(II). Similar to urea and carbamic acid, methyl carbamate is expected initially to bind to palladium(II) via its carbonyl oxygen atom.[10,14] In the case of urea, the kinetically favored O-bound isomer then converts to the thermodynamically favored N-bound isomer.[10,14] The presence of the methoxy group in methyl carbamate, however, may lower the nucleophilicity of the carbonyl oxygen and suppress its coordination. Complexes **1a** and **2** in Scheme 2 should have nearly identical thermodynamic stabilities. Complex **1a** accumulates and complex **2** does not, because **1a** forms from N-bound urea more rapidly than **2** forms from **1a**. Methanolysis of **1a** and dissociation of **2** preclude their isolation. Because methyl carbamate is produced from N-bound urea indirectly, via N-bound carbamic acid, this pathway of methyl carbamate production is termed the indirect methanolysis.

Kinetic Effect of Acid and Base. The initial rates of formation of carbon dioxide and methyl carbamate do not depend on the ionic strength of the acetone-d_6 solution; $v_0^{CO_2} = (1.80 \pm 0.06) \times 10^{-5}$ M min^{-1} and $v_0^{NH_2C(O)OCH_3} = (5.19 \pm 0.17) \times 10^{-4}$ M min^{-1} when the ionic strength varies in the range 0.9−2.9 M. Evidently, moderate amounts of acids and bases may be added to the reaction mixture in acetone-d_6 or in methanol-d_4 without adjusting the ionic strength.

Addition of 0.05 M NaOH lowers the initial rate of methyl carbamate formation to $(3.58 \pm 0.09) \times 10^{-4}$ M min^{-1}. The slight inhibition of the methanolysis reaction is attributed to partial deprotonation of the observed intermediate **1a** to yield the stable form **1b**, which neither decomposes into ammonia and carbon dioxide nor undergoes methanolysis.[14]

The initial rate of methyl carbamate formation slightly decreases upon addition of acid, as Figure S2 in the Supplementary Information shows. Our previous studies showed that an increase in the solution acidity inhibits coordination of urea to palladium(II) but favors the O-bound over the N-bound isomer in the diminishing fraction of urea that is coordinated. On an equimolar basis, however, O-bound urea is less reactive than N-bound urea in hydrolysis, forming bound carbamic acid.[14] Now we find that, similarly, O-bound urea is less reactive than N-bound urea in alcoholysis, forming carbamate ester. Catalysis of methanolysis by the hydroxo ligand as a general base is suppressed at the acid concentrations that we used. For these two reasons, the initial rate of methyl carbamate formation decreases when the concentration of acid is raised.

Kinetic Profile of the Intermediate, a Complex of Carbamic Acid, in the Indirect Methanolysis of Urea. Concentration of the intermediate **1a** in Scheme 2, determined by ^{13}C NMR spectroscopy, was fitted to eq 4, and rate constants k_{hyd} and k_{car} were obtained. Because the intermediate **1a** is formed

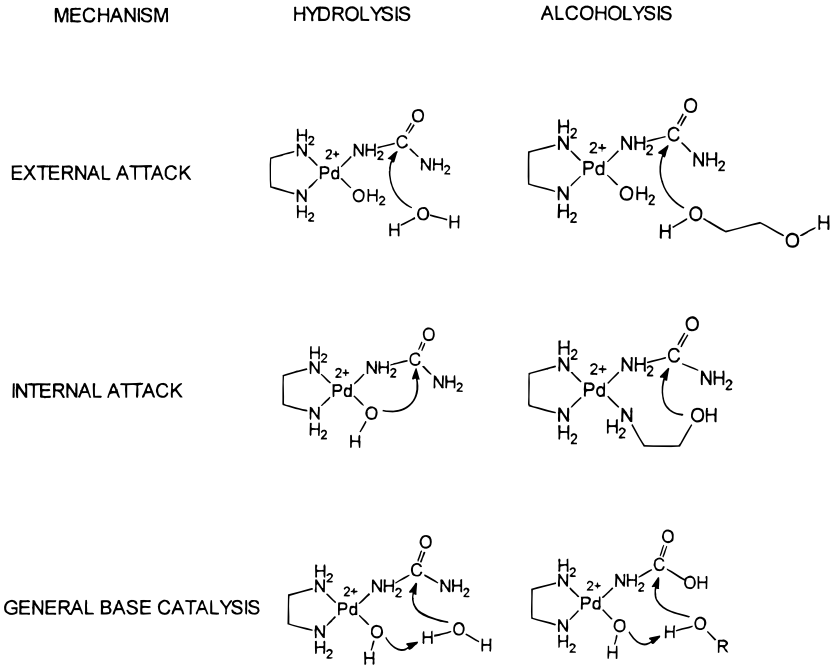
$$[Pd(en)(H_2O)(NH_2C(O)OH)^{2+}] = \frac{k_{hyd}K[Pd(en)(H_2O)_2{}^{2+}]_0[NH_2C(O)NH_2]_0}{k_{car} - k_{hyd}}[\exp(-k_{hyd}t) - \exp(-k_{car}t)] \quad (4)$$

from the N-bound urea ligand, whose concentration is relatively low, the rate constant for the formation of **1a** must be relatively high. The initial rate of methyl ester formation is similar to the rate of the disappearance of the intermediate **1a** and much lower than the rate of appearance of the intermediate **1a**. For these reasons, the larger rate constant, k_{hyd}, is assigned to the formation of the intermediate and the smaller one, k_{car}, to its conversion into methyl carbamate, as in Scheme 2.

Both of these rate constants are composite quantities, which depend on the concentrations of acid and of water. Analysis of these dependences gave several microscopic rate constants for individual steps in the reaction mechanism. These rate constants are discussed in the next two subsections.

Rate Constant k_{hyd}. This rate constant was determined by monitoring the appearance of **1a** in Scheme 2. The nucleophilic

Scheme 3. Mechanisms of Nucleophilic Attack in Hydrolysis and Alcoholysis of Coordinated Urea



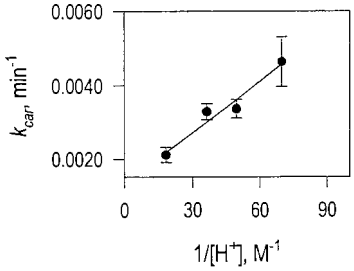


Figure 2. Rate constant k_{car} in Scheme 2 for the esterification of coordinated carbamic acid depends on the concentration of trifluoroacetic acid. Initial concentrations of the catalyst, *cis*-$[Pd(en)(H_2O)_2]^{2+}$, and of urea were 0.30 M each; the temperature is 313 K; and the solvent is methanol-d_4.

attack of water at the carbon atom of N-bound urea can occur by one of the three mechanisms shown in Scheme 3. That *cis*-$[Pd(en)(H_2O)(OH)]^+$ is ca. 1500 times more effective than *cis*-$[Pd(en)(H_2O)_2]^{2+}$ in catalyzing the nucleophilic attack (the respective k_{hyd} values are 460 and 0.3 min^{-1}) is consistent with either internal attack or general base catalysis.[14,36] Independence of k_{hyd} of water concentration in the range 1.5−11.1 M, shown in Figure S3 in the Supporting Information, supports the internal-attack mechanism for the formation of N-bound carbamic acid.

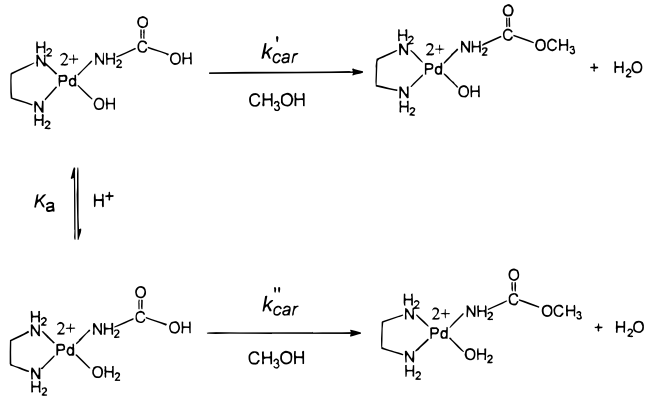
Rate Constant k_{car}. This rate constant was determined by monitoring the disappearance of **1a** in Scheme 2. The coordinated carbamic acid reacts with methanol to yield N-bound methyl carbamate. As this ligand dissociates, the catalyst, *cis*-$[Pd(en)(H_2O)_2]^{2+}$, is released. Because methanolysis of **1a** is faster than its decarboxylation, decarboxylation is not observed in methanol-d_4 solution.

Although the experimental results in Figure 2 span relatively narrow intervals of acidity and of k_{car}, they were fitted to eq 5, derived from Scheme 4. The equilibrium constant K_a could

$$k_{car} = \frac{k'_{car}K_a}{[H^+]} + k''_{car} \qquad (5)$$

not be determined experimentally because complex **1a** in Scheme 2 is reactive and because water and carbamic acid as

Scheme 4. Effect of Acid on the Methanolysis of Coordinated Carbamic Acid



ligands probably have a similar acidity. With an estimated value of $K_a = 1 \times 10^{-6}$ M,[14,21] the slope and the intercept in Figure 3 yielded the rate constants $k'_{car} = 48$ min^{-1} and $k''_{car} = 1.4 \times 10^{-3}$ min^{-1}. The ratio k'_{car}/k''_{car} for methanolysis of N-bound carbamic acid is 3.4×10^4. The hydroxo complex is more reactive than the "parent" aqua complex in alcoholysis, as it is in hydrolysis; see the discussion of k_{hyd} in the preceding subsection. This feature of alcoholysis is consistent with either internal attack or general base catalysis, shown in Scheme 3.[36]

Interestingly, methanolysis of N-bound carbamic acid is enhanced by water, as Figure 3 shows. Because the methanolyis is first order with respect to methanol, the effect of water is consistent only with the intermolecular methanolysis catalyzed by the hydroxo ligand as a general base, depicted in Scheme 3. From the intercept and the slope of the plot in Figure 3, the water-independent and the water-dependent rate constants for the methanolysis of N-bound carbamic acid are $(1.37 \pm 0.09) \times 10^{-3}$ min^{-1} and $(1.88 \pm 0.22) \times 10^{-4}$ M^{-1} min^{-1}, respectively.

Direct Methanolysis of Urea. Both N-bound urea in *cis*-$[Pd(en)(H_2O)(NH_2C(O)NH_2)]^{2+}$ and O-bound urea in *cis*-

(36) Kim, J. H.; Britten, J.; Chin, J. *J. Am. Chem. Soc.* **1993**, *115*, 3618.

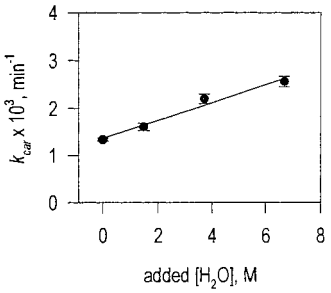


Figure 3. Rate constant k_{car} in Scheme 2 for the esterification of coordinated carbamic acid depends on the concentration of added water. Initial concentrations of the catalyst, *cis*-$[Pd(en)(H_2O)_2]^{2+}$, and of urea were 0.30 M each; the temperature is 313 K; and the solvent is methanol-d_4.

$[Pd(en)(H_2O)(OC(NH_2)_2)]^{2+}$ react with methanol to give the corresponding N-bound and O-bound methyl carbamate ligands. As these ligands dissociate, the catalyst, *cis*-$[Pd(en)(H_2O)_2]^{2+}$, is released. These two pathways, which do not involve carbamic acid as an intermediate, are called the direct methanolysis of urea. Coordinated methyl carbamate does not accumulate because it disappears more rapidly than it forms, as discussed above. Because of partial overlap between the ^{13}C NMR resonances for free and O-bound urea at 313 K, the initial rates for the direct methanolysis of O-bound and N-bound urea cannot be determined from the ^{13}C NMR spectra. The sum of these two initial rates was deduced from the known initial rates for methanolysis of carbamic acid and for the formation of free methyl carbamate. On average, ca. 80% of methyl carbamate is produced in the two direct pathways; ca. 20% is produced in the indirect pathway, via N-bound carbamic acid.

The overall initial rate for methyl ester formation is a composite of the two direct and one indirect pathways for urea methanolysis, as eq 6 shows. The initial rate for the two direct

$$\frac{\partial[NH_2C(O)OCH_3]}{\partial t} = k_O[Pd(en)(H_2O)(OC(NH_2)_2)^{2+}] + k_N[Pd(en)(H_2O)(NH_2C(O)NH_2)^{2+}] + k_{car}[Pd(en)(H_2O)(NH_2C(O)OH)^{2+}] \quad (6)$$

pathways in eq 7 is expressed in terms of the equilibrium constant K_N and the concentration of O-bound urea, both of which are conveniently determined from ^{13}C NMR spectra. The

$$\frac{\partial[NH_2C(O)OCH_3]}{\partial t} = (k_O + k_N K_N)[Pd(en)(H_2O)(OC(NH_2)_2)^{2+}] + k_{car}[Pd(en)(H_2O)(NH_2C(O)OH)^{2+}] \quad (7)$$

observed rate constant for the two direct pathways is defined in eq 8. The second term in eq 7 is easily calculated from the

$$k_{obs}{}^{dir} = k_O + k_N K_N \quad (8)$$

known k_{car} and the concentration of N-bound carbamic acid. Both $k_{obs}{}^{dir}$ and K_N at different concentrations of water can be determined directly from the integration of ^{13}C NMR spectra. The equilibrium constant K_N and the rate constant $k_{obs}{}^{dir}$ each approximately double when the concentration of water is doubled, as shown in Table 3, Figure S4 in the Supporting Information, and Figure 4. Therefore, k_O and k_N in eq 8 do not markedly depend on the water concentration.

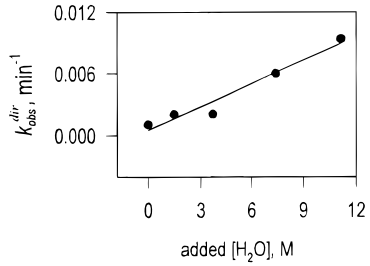


Figure 4. Observed rate constant $k_{obs}{}^{dir}$ in eq 8 for the formation of methyl carbamate by direct alcoholysis of urea depends on the concentration of added water. Initial concentrations of urea and the catalyst, *cis*-$[Pd(en)(H_2O)_2]^{2+}$, were 0.30 M each; the temperature is 313 K; and the solvent is methanol-d_4.

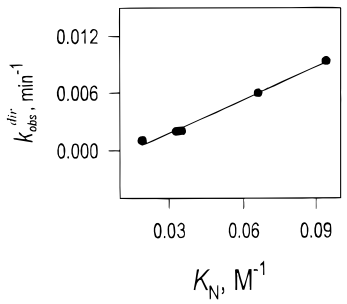


Figure 5. Observed rate constant $k_{obs}{}^{dir}$ in eq 8 for the formation of methyl carbamate by direct alcoholysis of urea depends on the equilibrium constant K_N. Initial concentrations of urea and the catalyst, *cis*-$[Pd(en)(H_2O)_2]^{2+}$, were 0.30 M each; the temperature is 313 K; and the solvent is methanol-d_4.

The experimental results in Figure 5 were fitted to eq 8. The slope yielded the microscopic rate constant for the direct methanolysis of N-bound urea: $k_N = (1.15 \pm 0.06) \times 10^{-1}$ min^{-1}. The intercept is too close to the origin to yield an accurate microscopic rate constant for the direct methanolysis of O-bound urea; the estimated value is $k_O = 1 \times 10^{-4}$ min^{-1}. In methanolysis, N-bound urea is much more reactive than O-bound urea.

We cannot rule out internal attack of MeOH at urea when both are coordinated to palladium(II) because individual rate constants for the disappearance of O-bound and N-bound urea could not be determined directly from ^{13}C NMR spectra. We reasonably suppose that palladium(II)-bound urea undergoes methanolysis similarly to palladium(II)-bound carbamic acid (**1a)**, namely by intermolecular attack of MeOH catalyzed by the hydroxo ligand. This mechanism was documented in the subsection concerning the rate constant k_{car}.

Kinetic Effect of Water. The virtual independence on water concentration of the initial rate for methyl carbamate formation, seen in Figure S5 in the Supporting Information, is a result of a compensation of two factors. As eqs 7 and 8 show, this rate is a composite quantity. As water concentration increases, $k_{obs}{}^{dir}$ and k_{car} increase (Figures 3 and 4) while the concentrations of O-bound urea and N-bound carbamic acid decrease (Table 3).

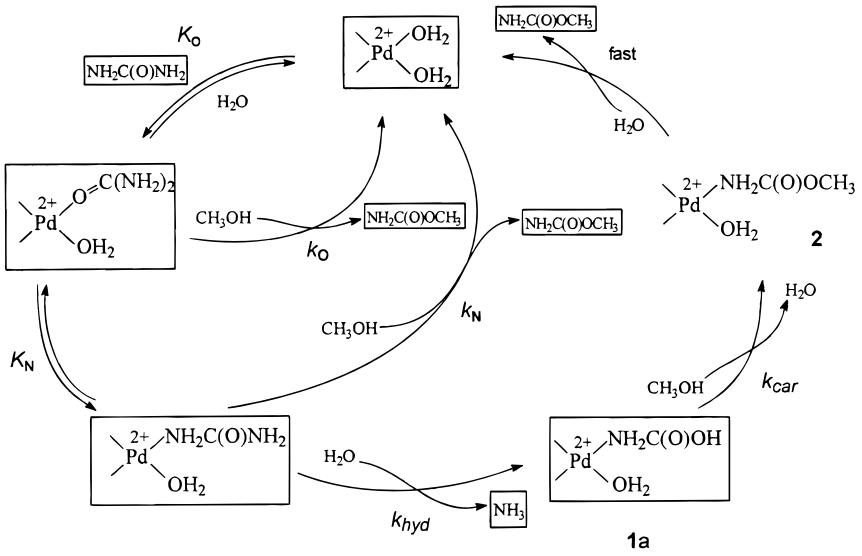
Catalytic Turnover and the Overall Mechanism. The ammonia produced in the alcoholysis of urea inhibits this reaction by converting the catalytically active aqua complexes into the inactive ammine complexes. Since ammonia poisons the palladium(II) catalyst and inhibits methanolysis of urea, sequestration of ammonia is expected to promote methanolysis. Indeed, Table 9 shows that, when ammonia is coordinated to the Ag(I) cation, methanolysis occurs with turnover—1 equiv of *cis*-$[Pd(en)(H_2O)_2]^{2+}$ effects complete methanolysis of 8 equiv of urea. In control experiments without *cis*-$[Pd(en)(H_2O)_2]^{2+}$,

Table 9. Effects of Solvent[a] and the Catalyst Concentration on the Initial Rates of Urea[b] Disappearance, Methyl Carbamate Appearance, and Carbon Dioxide Appearance[c]

conc of *cis*-$[Pd(en)(H_2O)_2]^{2+}$, M	initial rates in acetone-d_6, M min^{-1}			initial rates in methanol-d_4, M min^{-1}	
	$-\nu_0^{NH_2C(O)NH_2}$	$\nu_0^{NH_2C(O)OCH_3}$	$\nu_0^{CO_2}$	$-\nu_0^{NH_2C(O)NH_2}$	$\nu_0^{NH_2C(O)OCH_3}$
0.150	5.52×10^{-3}	2.55×10^{-3}	2.93×10^{-3}	2.57×10^{-3}	2.60×10^{-3}
0.075	3.75×10^{-3}	1.50×10^{-3}	2.24×10^{-3}	1.05×10^{-3}	1.00×10^{-3}
0.038	3.15×10^{-3}	0.68×10^{-3}	2.47×10^{-3}	0.87×10^{-3}	0.80×10^{-3}

[a] Either acetone-d_6 that is made 4.55 M in methanol-d_4 or neat methanol-d_4. [b] Initial concentration was 0.30 M. [c] The concentration of $AgClO_4$ is 0.10 M, and the temperature is 333 K.

Scheme 5. Catalytic Mechanism for Methanolysis of Urea via Direct (Reactions k_O and k_N) and Indirect (Consecutive Reactions k_{hyd} and k_{car}) Pathways



methanolysis of urea was undetectable in the presence of silver(I) ions. To our knowledge, this is the first report of catalytic methanolysis of urea in the presence of a metal complex.

Catalytic methanolysis of urea in a 4.5 M solution of methanol-d_4 in acetone-d_6 is relatively fast. Urea is hydrolyzed by the adventitious water into carbon dioxide and ammonia and methanolyzed into methyl carbamate and ammonia. Measurements of initial rates showed that at concentrations of *cis*-$[Pd(en)(H_2O)_2]^{2+}$ lower than 0.075 M, hydrolysis is favored over methanolysis, as shown in Table 9. The rates for the catalytic methanolysis in neat methanol-d_4 are comparable to the corresponding rates in acetone-d_6 solution, but the reaction in methanol-d_4 is selective. Hydrolysis is not observed, and urea is completely converted into methyl carbamate.

The overall mechanism for methanolysis of urea catalyzed by *cis*-$[Pd(en)(H_2O)_2]^{2+}$ is shown in Scheme 5. All the species in boxes have been experimentally observed and characterized by NMR spectroscopy, often of multiple nuclei. Their reactivity, however, precluded their isolation and structural analysis. All the equilibrium constants, initial rates, and rate constants shown have been determined. The final product, free methyl carbamate, is obtained by three pathways: indirectly via N-bound carbamic acid **1a** and directly from the O-bound and N-bound urea ligands. The indirect pathway contributes approximately 20% of methyl carbamate, the direct pathways 80%.

Decomposition of Urea by Different Mechanisms. The mechanism involving elimination via palladium(II)-bound isocyanate is inconsistent with two kinds of evidence: Neither free nor bound NCO^- ion was observed in our experiments, and *cis*-$[Pd(en)(H_2O)_2]^{2+}$ does not promote the conversion of NCO^- to CO_2 and ammonia to a detectable extent. Decomposition of urea by different metal complexes seems to occur by different mechanisms. In the presence of $[Pt(dien)(acetone)]^{2+}$, the reaction is elimination and is noncatalytic.[10] In the presence of *cis*-$[Pd(en)(H_2O)_2]^{2+}$, the reaction is hydrolysis and is catalytic.

Effects of the Steric Bulk of an Aliphatic Alcohol. Alcohols other than methanol also react with urea in the presence of *cis*-$[Pd(en)(H_2O)_2]^{2+}$ complex. As Table 4 shows, the rate constant for the carbamate ester formation decreases as the bulkiness of the attacking alcohol increases in the following order: methanol and then primary, secondary, and tertiary alcohols. For the same type of alcohol, however, the rate constant does not markedly depend on the molecular size, as represented by the molecular mass.

Effects of the Alcohol Nucleophilicity. Table 5 shows that reactivity of primary alcohols decreases as their nucleophilicity (represented by the pK_a value) decreases[37] while their steric bulk remains almost unchanged. The low reactivity of *tert*-butyl alcohol (Table 4) despite its high nucleophilicity ($pK_a > 19$)[37] is evidence for the dominant effect of the steric bulk on the reactivity.

Alcoholysis with Diols. The presence of high concentrations of various diols does not affect urea binding to *cis*-$[Pd(en)(H_2O)_2]^{2+}$, as shown in Table 2. Clearly, diols are weaker ligands than urea and do not detectably coordinate to the *cis*-$[Pd(en)(H_2O)_2]^{2+}$ complex.[38] We conclude that the intramolecular reaction between coordinated urea and coordinated monodentate diol within the coordination sphere of palladium(II)

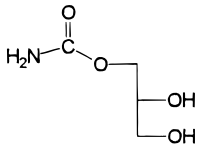
(37) (a) Wilkinson, S. G. In *Comprehensive Organic Chemistry*; Stoddart, J. F., Ed.; Pergamon Press: New York, 1979; p 579. (b) Whiting, D. A. In *Comprehensive Organic Chemistry*; Stoddart, J. F., Ed.; Pergamon Press: New York, 1979; p 707.

is not feasible and that the alcoholysis takes place by external attack, as shown in Scheme 3.

At low concentrations of ethylene glycol, the initial rate for the ester formation increases with the glycol concentration, as shown in Table S1 in the Supporting Information. Alcoholysis of urea in neat ethylene glycol as the solvent is slower than methanolysis in neat methanol-d_4.[39]

As a general finding, symmetrical primary diols (Table 6) are only slightly more reactive than primary alcohols of similar steric bulk (Table 4), possibly because of two opposing factors. The doubling of the concentration of the hydroxyl groups may enhance the reactivity, but lowering of the nucleophilicity of one hydroxyl group by the inductive effect of the other may inhibit the reactivity. The latter factor is most pronounced in ethylene glycol, whose pK_a (13.3) is appreciably lower than that of ethanol (15.9)[37] and whose k_{obs} value is less than twice that for ethanol. The k_{obs} values for the longer diols, in which the inductive effect is negligible, are approximately twice the values for the similar monoalcohols. The rigid and bulky *cis*-1,2-cyclohexanediol does not react with urea to an appreciable extent. The results in Table 6 confirm that primary alcohols are more reactive than secondary alcohols.

Unsymmetrical diols react at rates similar to those for analogous primary monoalcohols. The primary ester is always formed. Urea alcoholysis with glycerol yields esters of both primary (**3**) and secondary (**4**) alcohols. The overall rate for



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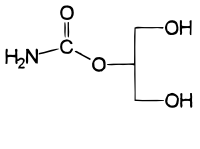

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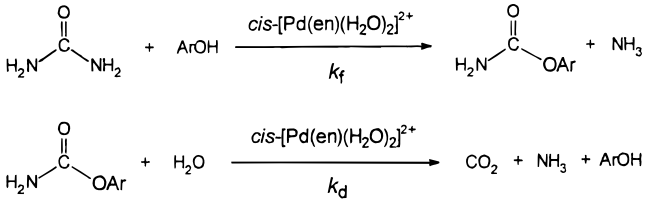
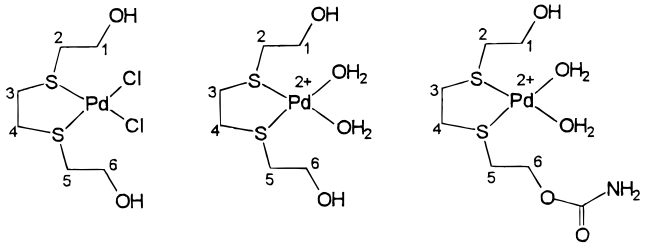
their formation is relatively low, presumably because glycerol (pK_a = 14.4) is less nucleophilic than aliphatic alcohols.[37]

Alcoholysis with Amino Alcohols. Amino alcohols $H_2N-(CH_2)_n-OH$ for which $n = 2$ and 4 act as amines and displace one or both aqua ligands in *cis*-$[Pd(en)(H_2O)_2]^{2+}$ to form *cis*-$[Pd(en)(H_2O)(NH_2(CH_2)_nOH)]^{2+}$ (**5**) and *cis*-$[Pd(en)(NH_2(CH_2)_n-OH)_2]^{2+}$ (**6**), depending on the initial concentration of the amino alcohol. Complexes of both kinds were detected by ^{1}H NMR spectroscopy. Complexes **6** are unreactive in the hydrolysis and alcoholysis of urea because urea cannot displace amino alcohol from palladium(II), as judged from ^{13}C NMR spectra. Urea, however, can displace the aqua ligand in the complexes **5**. The equilibrium constants for this displacement, given in Table 7, are comparable to the values in Table 2. That amino alcohols (Table 7) are somewhat more reactive than diols (Table 6) may be the consequence of internal attack by the former, as shown in Scheme 3. The low affinity of urea for palladium(II) in the presence of the amino alcohol for which $n = 3$ is evident in Table 7. This may be a consequence of bidentate coordination of this amino alcohol upon displacement of both aqua ligands in *cis*-$[Pd(en)(H_2O)_2]^{2+}$.

Intramolecular Alcoholysis by *cis*-$[Pd(C_6H_{14}O_2S_2)(H_2O)_2]^{2+}$ Complex. To investigate more possibilities for intramolecular alcoholysis we synthesized the palladium(II) complexes **7** and **8**. Because they do not racemize at 293 K, each of these

Scheme 6. Formation and Hydrolysis of Aryl Carbamates





7 8 9

complexes exists in two enantiomeric and one meso forms, which are distinguishable by ^{13}C NMR spectroscopy. In each form the following carbon atoms have the same chemical shifts: 1 and 6, 2 and 5, and 3 and 4. The ^{13}C NMR spectra of **7** at two temperatures are shown in Figure S6 in the Supporting Information. There are five resonances at 293 K, at 60.5, 41.0, 40.6, 39.3, and 39.0 ppm, but only three at 313 K, at 60.5, 40.8, and 39.15 ppm. The estimated coalescence temperature for complex **7** (<313 K) is lower than that of *cis*-$[PtCl_2(2,5$-dithiohexane)], measured by ^{1}H NMR spectroscopy.[40,41] The coalescence can be attributed to the increased rate of intramolecular inversion at the sulfur atoms.[42,43] Because ^{13}C NMR spectra of complexes **7** and **8** are very similar, we conclude that hydroxyl groups do not coordinate to palladium(II) upon aquation and remain available for alcoholysis of urea.

Urea binds to complex **8** in acetone-d_6 solution relatively strongly, with the equilibrium constant $K_O = 33\ M^{-1}$. As compound **9** is formed, the carbonyl ^{13}C NMR resonance appears at 156.2 ppm. The observed rate constant of $(5.6 \pm 0.5) \times 10^{-2}\ min^{-1}$ is at least 100 times greater than the rate constants for reactions of various aliphatic alcohols. Evidently, an alcohol group and urea in the coordination sphere of palladium(II) undergo fast, intramolecular alcoholysis.

Alcoholysis of Urea by Aryl Alcohols. Despite their low nucleophilicity,[37] phenol derivatives react with urea and form carbamates. Aryl carbamates in the presence of the palladium(II) complex are hydrolyzed to carbamic acid and parent alcohols, as shown in Scheme 6. Carbamic acid further decomposes into carbon dioxide and ammonia by the mechanism studied previously.[35] The appearance and disappearance of the ester was followed by ^{13}C NMR spectroscopy, and the results are shown in Table 8. Because alcoholysis is fast, the rate constants k_f, determined by ^{13}C NMR spectroscopy, are less precise than the other rate constants for alcoholysis in this study. Although these aromatic alcohols are much less nucleophilic

(38) (a) Nelson, S. M. In *International Review of Science, Inorganic Chemistry*; Sharp, D. W., Ed.; University Park Press: Baltimore, MD, 1974; p 173. (b) Klonis, H. B.; King, E. L. *Inorg. Chem.* **1972**, *11*, 2933.

(39) *Handbook of Chemistry and Physics*; Lide, R. D., Ed.; CRC Press: New York, 1996−1997; pp 6−208.

(40) Müller, A.; Diemann, E. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon Press: New York, 1987; p 555.

(41) Abel, E. W.; Bush, R. P.; Hopton, F. J.; Jenkins, C. R. *Chem. Commun.* **1966**, 58.

(42) Haake, P.; Turley, P. C. *J. Am. Chem. Soc.* **1967**, *89*, 4611, 4617.

(43) Eekhof, J. H.; Hogeveen, H.; Kellogg, R. M.; Klei, E. *J. Organomet. Chem.* **1978**, *161*, 183.

than aliphatic alcohols (Tables 4−7), they react with urea approximately 10^4 times more rapidly. This marked difference in reactivity can be attributed to the greater acidity of the aromatic alcohols in the reactions in which the nucleophiles are actually the phenoxide and alkoxide anions. The rate constants k_d, which are more reliable, show that the nitro group enhances decomposition, as expected when the leaving group is activated.

The decomposition reaction of phenyl carbamate was studied in some detail. In the absence of catalysts, in wet acetone-d_6 that was 0.10 M in $HClO_4$, and at 318 K, phenyl carbamate is stable and does not detectably hydrolyze even after 1 week. However, upon addition of 0.30 M of *cis*-$[Pd(en)(H_2O)_2]^{2+}$, this ester hydrolyzes with an estimated rate constant of 4×10^{-3} min^{-1}. Carbamic acid was not detected because of its spontaneous decomposition into ammonia and carbon dioxide. The final products (phenol and carbon dioxide) were monitored by ^{13}C NMR spectroscopy. Evidently, the *cis*-$[Pd(en)(H_2O)_2]^{2+}$ complex catalyzes not only the formation of carbamate esters but also decomposition of aryl carbamates, as shown in Scheme 6.

Conclusions

The simple palladium(II) aqua complex *cis*-$[Pd(en)(H_2O)_2]^{2+}$ catalyzes alcoholysis of urea to carbamate esters and ammonia. The rate enhancement over the uncatalyzed reaction is as high as 10^5-fold. Carbamate esters of aliphatic alcohols are stable toward further hydrolysis.

Cleavage of the amide bond in urea by alcoholysis rather than hydrolysis is interesting for two reasons. First, study of this cleavage may shed light on the action of the nickel enzyme urease.[15] Because palladium and nickel are congeners in the periodic table, their divalent cations have similar electronic structures. Although nickel(II) and palladium(II) behave differently in ligand-substitution reactions and although simple metal complexes are very different from the enzyme, these kinetic studies may contribute to the understanding of the enzymatic mechanism. Second, a prospect of cleaving amide bonds in proteins by alcoholysis has emerged. Alcoholysis of proteins in nonaqueous solutions would be particularly advantageous for hydrophobic or membrane-bound proteins, because their insolubility in water precludes the use of hydrolysis.

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Supporting Information Available: A table of initial rates with ethylene glycol and six figures showing dependence of $v_0^{CO_2}$ on CH_3OH concentration; dependence of $v_0^{NH_2C(O)OCH_3}$ on concentration of added acid; dependences of k_{hyd}, k_N, and $v_0^{NH_2C(OH)OCH_3}$ on the concentration of added H_2O; and ^{13}C NMR spectra of **7** are available (7 pages). Ordering information is given on any current masthead page.

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