Decomposition of Alkyl-Substituted Urea Molecules at a Hydroxide-Bridged Dinickel Center

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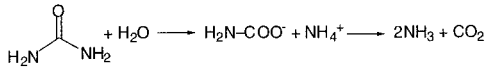
Received August 15, 2000

The interactions between *N*-methylurea, *N*,*N*′-dimethylurea, *N*,*N*-dimethylurea, tetramethylurea, and thiourea and the hydroxide-bridged dinickel complex $[Ni_2(\mu\text{-}OH)(\mu\text{-}H_2O)(bdptz)(H_2O)_2](OTs)_3$ were investigated. Structural characterization of $[Ni_2(\mu\text{-}OH)(\mu\text{-}H_2O)(bdptz)(Me\text{-}urea)(CH_3CN)](ClO_4)_3$ (**1**) and $[Ni_2(\mu\text{-}OH)(\mu\text{-}H_2O)(bdptz)(thiourea)(CH_3CN)](ClO_4)_3$ (**2**) provided insight into the interactions of the substrates with the dinickel center. In **1**, the methylurea molecule coordinates to the dinickel complex through its carbonyl oxygen atom. Complex **2** has a similar geometry, with the thiourea molecule bound to a nickel ion through its sulfur atom. When the urea substrates are heated in the presence of the hydroxide-bridged dinickel complex, *N*-methylurea and *N*,*N*-dimethylurea react to form methylammonium cyanate and dimethylammonium cyanate, respectively. After long reaction times, thiourea reacts similarly, producing ammonium thiocyanate. The other substrates are unreactive. These results indicate that the dinickel complex promotes the elimination of alkylamines from urea substrates to form cyanate but cannot effect the direct hydrolysis of such substrates.

Introduction

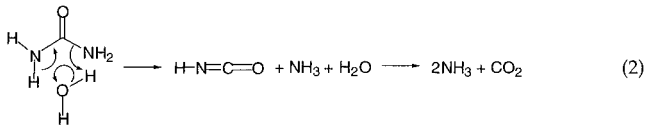
Urease is a nickel-dependent enzyme[1] that catalyzes the transformation of urea ultimately into two molecules of ammonia and one molecule of carbon dioxide.[2] The crystal structures of urease isolated from several different microorganisms have provided a detailed picture of the dinuclear nickel active site, which is nearly identical in all of the characterized enzymes.[3−7] The dinickel center is bridged by a carbamylated lysine residue and a water molecule or hydroxide ion. Each nickel ion is further ligated by two histidine residues and a water molecule, and one nickel ion also coordinates to an aspartate residue. The result is an asymmetric active site with one nickel ion in a pseudo-octahedral coordination environment and the other having a square pyramidal geometry. A schematic representation of the active site of urease isolated from *Klebsiella aerogenes* is provided in Figure 1.[3]

At the dinickel active site of urease the hydrolysis of urea to ammonia and carbon dioxide[2] is generally accepted to occur as shown in eq 1. This transformation is remarkable because the



(1)

uncatalyzed hydrolysis of urea has never been observed.[8] In aqueous solution urea has a half-life of 3.6 years and the eventual decomposition is not hydrolytic but involves an elimination reaction to form ammonium cyanate, as shown in eq 2.[8] The stability of urea has been attributed to its resonance



(2)

energy, which is estimated to be 30−40 kcal/mol.[9] It has been proposed that the hydrolysis occurs by nucleophilic attack of a coordinated water molecule at the carbonyl carbon atom of a bound urea molecule, producing ammonium carbamate, which spontaneously decomposes to form ammonia and carbon dioxide (eq 1).[4,6,10,11] An alternative pathway for the hydrolysis of urea involves elimination of ammonia to form cyanate, which can be further hydrolyzed to ammonia and carbon dioxide under the appropriate conditions.[12,13]

To mimic the active site chemistry of urease, a number of investigators have prepared synthetic model

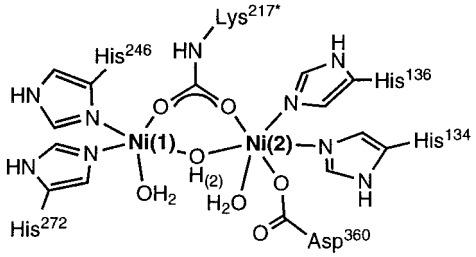


Figure 1. Representation of the active site of urease from *Klebsiella aerogenes.*[3]

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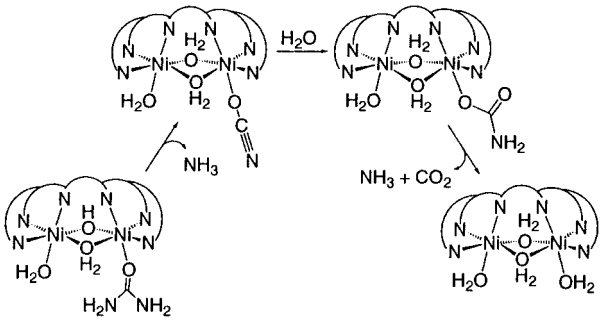
10.1021/ic000933w CCC: $20.00
Published on Web 02/07/2001

Scheme 1



complexes. These dinickel compounds reproduce some of the key features of the enzyme active site and can provide insight into the chemical steps that may occur during the catalytic reaction cycle. For example, several dinickel urea complexes serve as models for the interaction of the substrate with the enzyme active site.[14−16] On the basis of this work, it seems likely that urea coordinates to nickel in urease through its carbonyl oxygen atom.

Despite the preponderance of dinickel complexes that can serve as structural models for urease,[17−20] none can effect the direct hydrolysis of urea (eq 1). Some complexes promote the ethanolysis of urea,[8,15,21] presumably by attack of an external solvent molecule on bound urea. On the other hand, several dinickel compounds promote the elimination of ammonia from a coordinated urea to form a cyanate complex.[13,22,23] Work in our laboratory revealed that a phthalazine-bridged dinickel complex with a bridging hydroxide ion and coordinated urea molecules eliminated ammonia upon heating to form cyanate, which could then be hydrolyzed in the presence of water.[13] This reaction, representing the first example of urea hydrolysis by a dinickel complex, is shown in Scheme 1. It is remarkable that this dinickel−urea complex undergoes elimination rather than hydrolysis in the initial step, even though it has a bound hydroxide ion that could serve as a nucleophile for direct attack on the coordinated substrate. We therefore wondered whether such an elimination occurs only for urea or whether this result represented one manifestation of a more general mechanism. To pursue this possibility, we carried out an investigation of the reactions between the dinickel complex $[Ni_2(OH)(H_2O)_3(bdptz)](OTs)_3$ and a series of alkyl-substituted urea molecules. Some of the substrates were able to undergo an elimination to form cyanate, but others could not. As described in this report, direct hydrolysis of coordinated urea does not occur to a measurable extent in this system.

Experimental Section

General Considerations. Urea, *N*-methylurea, *N*,*N*-dimethylurea, *N*,*N*′-dimethylurea, tetramethylurea, sodium cyanate, and nickel perchlorate were obtained from commercial sources and used without further purification. Thiourea was obtained from the Aldrich Chemical Co. and recrystallized twice from water prior to use. The ligand 1,4-bis(2,2′-dipyridylmethyl)phthalazine (bdptz) and the dinickel complex $[Ni_2(OH)(H_2O)_3(bdptz)](OTs)_3$ were synthesized as previously described.[24] Vibrational spectra were measured on a Biorad FTS-135 FTIR instrument, and UV−vis spectra were obtained by using a Hewlett-Packard 8453-A diode array spectrophotometer. *Warning: The procedures below involve the use of perchlorate as a counterion. Perchlorate salts are known to detonate explosively and without warning. Although no problems were experienced in this work, special care should be taken when handling these substances.*

$[Ni_2(\mu\text{-}OH)(\mu\text{-}H_2O)(bdptz)(N\text{-methylurea})(CH_3CN)](ClO_4)_3$ (1). A 69 mg, 188 μmol, portion of nickel perchlorate was dissolved in acetonitrile with stirring. A 41 mg, 88 μmol, portion of bdptz was added to the nickel solution, resulting in a purple solution. One equivalent of a 1.0 M NaOH solution was added to the reaction mixture in a dropwise manner. Finally, 5 equiv of methylurea was added as a solid and allowed to dissolve. A 77% yield of the purple-brown crystalline product was formed upon diethyl ether vapor diffusion into the acetonitrile solution. FTIR (KBr, cm^{-1}): 3436 (br), 3063 (w), 2990 (w), 2944 (w), 2893 (w), 1655 (s), 1605 (s), 1570 (s), 1509 (w), 1474 (m), 1446 (m), 1370 (m), 1340 (w), 1098 (vs, br), 772 (m), 624 (m), 581 (m). UV−vis [CH_3CN] λ, nm (ϵ): 575 (12), 770 (sh, 11), 965 (38). Anal. Calcd for **1**·$3H_2O$·CH_3CN ($Ni_2Cl_3C_{36}H_{43}N_{10}O_{18}$): C, 38.35; H, 3.84; N, 12.42. Found: C, 38.27; H, 3.61; N, 12.33.

$[Ni_2(\mu\text{-}OH)(\mu\text{-}H_2O)(bdptz)(thiourea)(CH_3CN)](ClO_4)_3$ (2). To a gently heated acetonitrile solution containing 86 mg, 234 μmol, of nickel perchlorate was added 52 mg, 111 μmol, of bdptz with stirring, followed by 1 equiv of a 1.0 M NaOH solution. Addition of 18 mg, 236 μmol, of thiourea resulted in an olive-green solution. X-ray quality crystals of **2** were obtained by slow diffusion of diethyl ether into the reaction solution. A 93% yield (75 mg) was obtained. FTIR (KBr, cm^{-1}): 3349 (w), 3283 (w), 3192 (w), 3104 (w), 1610 (s), 1473 (m), 1446 (m), 1398 (m), 1362 (m), 1088 (vs), 771 (s), 729 (w), 622 (w). UV−vis [CH_3CN] λ, nm (ϵ): 546 (34), 810 (sh, 28), 925 (38). Anal. Calcd for **2**·H_2O ($Ni_2Cl_3SC_{33}H_{34}N_9O_{15}$): C, 37.66; H, 3.26; N, 11.98. Found: C, 37.78; H, 3.25; N, 12.29.

Reactivity Assays. Ammonia was detected by using a colorimetric assay as reported previously.[24,25] The formation of dimethylamine was determined qualitatively with a sensitive spot test for secondary amines.[26] A drop of the test solution was mixed with a drop of a reagent solution containing 1% sodium nitroprusside and 10% acetaldehyde, and the mixture was made basic with a 2% solution of potassium carbonate. A deep-violet-blue color developed in the presence of dimethylamine. FTIR spectroscopy was used to determine the presence of cyanate, methylisocyanate, and carbamate.

Kinetics of Substrate Decomposition. Kinetics of cyanate complex formation were followed by FTIR spectroscopy. In a typical experiment, the substrate was mixed with the dinickel complex in varying ratios in acetonitrile solution. The mixtures were heated to 60 °C in an incubator with 200 rpm shaking for 40 h. After the samples had cooled to ambient temperature, aliquots were taken and evaporated onto NaCl plates. The FTIR spectra of the samples were obtained and integrated, and the intensity of the cyanate peak at 2185 cm^{-1} was normalized to the intensity of a ligand vibration at 817 cm^{-1} in the nickel complex. The ratio of the cyanate peak to the ligand peak was proportional to the ratio of cyanate to dinickel complex in the sample, as determined by calibrating the relative intensities, allowing facile determination of the amount of cyanate formed in the reactions. The data were fit to the

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Table 1. Summary of X-ray Crystallographic Data

	1·2CH_3CN·H_2O	**2**·3CH_3CN
formula	$C_{36}H_{39}N_{10}O_{16}Ni_2Cl_3$	$C_{41}H_{43}N_{13}O_{14}Ni_2Cl_3S$
fw	1091.54	1197.71
space group	$P2/c$	$P2_1/c$
a, Å	12.950(5)	10.636(7)
b, Å	10.225(5)	21.599(14)
c, Å	36.049(5)	22.699(18)
β, deg	93.085(5)	90.73(2)
V, Å^3	4767(3)	5214(6)
Z	4	4
ρ_{calcd}, g/cm^3	1.521	1.526
temp, °C	−85	−85
μ(Mo Kα), mm^{-1}	1.034	0.991
2θ limits, deg	3−57	3−57
total no. data	28 894	32 443
no. unique data	10 969	12 000
obsd data[a]	7364	7396
no. parameters	758	688
R^b	0.0838	0.0589
$wR2^c$	0.2369	0.1586
max, min peaks, e/Å^3	1.483, −0.628	0.970, −0.699

[a] Observation criterion: $I > 2\sigma(I)$. [b] $R = \sum||F_o| - |F_c||/\sum|F_o|$. [c] $wR^2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{1/2}$.

"improved" steady-state rate equation[27] with a preequilibrium assumption.[28]

Collection and Reduction of X-ray Data. Procedures for the collection and reduction of X-ray data have been reported previously.[29] In brief, the crystals were mounted on the tips of glass fibers with Paratone-N (Exxon) and cooled rapidly in the −85 °C cold stream of a Bruker (formerly Siemens) CCD X-ray diffractometer controlled by a Pentium-based PC running the SMART[30] software package. The structures were solved by using the direct methods programs XS and SIR, part of the SHELXTL[31] and TEXSAN[32] program packages, respectively, and refinements were carried out using XL. All nonhydrogen atoms were refined by a series of least-squares cycles. Hydrogen atoms were assigned to idealized positions and given a thermal parameter 1.2 times that of the atom to which they are attached. Empirical absorption corrections were calculated and applied for each structure using the program SADABS,[33] and PLATON[34] was used to search for higher symmetry. Selected crystallographic information for each compound is given in Table 1, and a more complete listing can be found in Tables S1−S10 in the Supporting Information.

Results

In all urea complexes of nickel reported thus far, the urea molecule coordinates to nickel preferentially through the carbonyl oxygen atom.[13−16,35] Compound **1** follows this trend, with the methylurea molecule coordinating to the dinickel center through its carbonyl oxygen atom, as shown in Figure 2. The synthesis of **1** is relatively straightforward, and X-ray quality purple-brown crystals were obtained by recrystallizing the product from aqueous acetonitrile upon diethyl ether vapor diffusion. Selected interatomic distances and angles are listed in Table 2. The two nickel atoms are bridged by the phthalazine moiety of the bdptz ligand, a hydroxide ion, and a water molecule. Each metal ion is further ligated by two pyridine donor arms. The water and hydroxide ligands are readily distinguished on the basis of the average Ni−O distances, which are 2.206 and 2.030 Å, respectively. The remaining terminal coordination sites are occupied by a methylurea and an acetonitrile molecule. These two terminally coordinated ligands are disordered over the two positions, each at 50% occupancy. The methylurea molecule coordinates to a nickel ion through its carbonyl oxygen atom, and the NH_2 moiety donates a hydrogen bond to the bridging hydroxide ion (Figure 2). The interatomic methylurea distances do not deviate significantly from the distances found in methylurea alone[36] or in

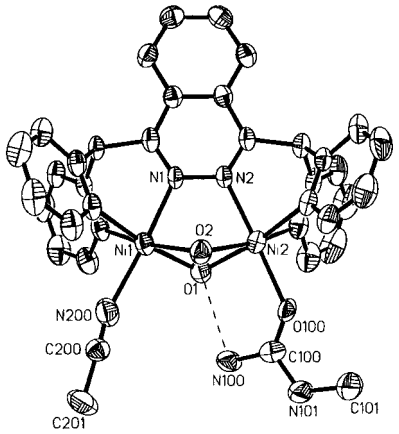

Figure 2. ORTEP diagram of the cation of **1**, showing 50% probability ellipsoids. The hydrogen atoms and the disorder in the terminal coordination positions have been omitted for clarity.

Table 2. Selected Interatomic Distances (Å) and Angles (deg) for **1** and **2**[a]

	1		**2**
Ni(1)···Ni(2)	3.069(4)	Ni(1)···Ni(2)	3.116(3)
N(100)···O(1)	2.603(4)	N(11)···O(2)	2.718(4)
Ni(1)−N(1)	2.050(4)	Ni(1)−N(1)	2.039(3)
Ni(1)−N(3)	2.076(4)	Ni(1)−N(3)	2.074(3)
Ni(1)−N(4)	2.050(4)	Ni(1)−N(4)	2.087(4)
Ni(1)−O(1)	2.031(4)	Ni(1)−N(1A)	2.060(4)
Ni(1)−O(2)	2.208(4)	Ni(1)−O(2)	2.013(3)
Ni(1)−O(20A)	2.00(4)	Ni(1)−O(3)	2.222(3)
Ni(1)−N(200)	2.12(6)		
Ni(2)−N(2)	2.046(4)	Ni(2)−N(2)	2.058(3)
Ni(2)−N(5)	2.081(4)	Ni(2)−N(5)	2.111(3)
Ni(2)−N(6)	2.056(5)	Ni(2)−N(6)	2.071(3)
Ni(2)−O(1)	2.029(4)	Ni(2)−S(1)	2.388(2)
Ni(2)−O(2)	2.205(4)	Ni(2)−O(2)	2.035(3)
Ni(2)−O(100)	2.03(4)	Ni(2)−O(3)	2.250(3)
Ni(2)−N(10A)	2.05(5)		
O(100)−C(100)	1.27(4)	S(1)−C(1A)	1.685(5)
C(100)−N(100)	1.34(2)	C(1A)−N(10)	1.323(6)
C(100)−N(101)	1.34(2)	C(1A)−N(11)	1.334(6)
N(101)−C(101)	1.45(2)		
Ni(1)−O(1)−Ni(2)	98.18(15)	Ni(1)−O(2)−Ni(2)	100.70(15)
Ni(1)−O(2)−Ni(2)	88.08(13)	Ni(1)−O(3)−Ni(2)	88.36(13)

[a] Numbers in parentheses are estimated standard deviation of the last significant figure. Atoms are labeled as indicated in Figures 2 and 3.

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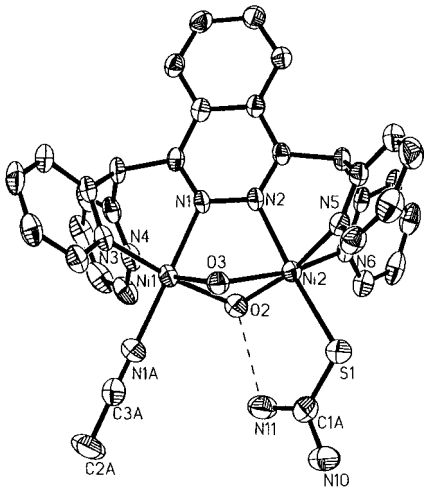

Figure 3. ORTEP diagram of the cation of **2**, showing 50% probability ellipsoids. Hydrogen atoms have been omitted for clarity.

$[Co(Me\text{-}urea)_6](SO_4)$,[37] a cobalt(II) complex with six methylurea ligands coordinated to the cobalt ion via the carbonyl oxygen atoms. The methylurea C−O bond lengths are 1.248(10) Å in each case, with C−N distances ranging from 1.330(5) to 1.348(5) Å, and the N−CH_3 distance is 1.443(10) Å.

The electronic spectrum of an acetonitrile solution of **1** displays two intense bands centered at 220 and 260 nm attributed to the bdptz ligand and three broad, weak transitions in the visible region at 575, 770, and 965 nm, characteristic of nickel(II) in a pseudo-octahedral environment. This result is consistent with **1** having a structure in solution similar to that in the solid state, with a methylurea or solvent molecule coordinated to the dinickel center. The solid-state FTIR spectrum of **1** has a carbonyl stretching frequency of the coordinated methylurea at 1651 cm^{-1}. The FTIR spectrum of an ethanolic solution of **1** displays a broad peak at 1660 cm^{-1}, shifted slightly from the free methylurea carbonyl stretching frequency of 1672 cm^{-1}.

Thiourea also coordinates to nickel, through the sulfur atom, as seen in the crystal structure of **2** (Figure 3). In this dinickel complex, the bdptz ligand coordinates in the same fashion as in **1**, with the phthalazine moiety bridging the two metal ions and the ligand arms providing two pyridine donors to each metal. The two nickel ions are further bridged by a hydroxide ion and a water molecule, at average distances of 2.024(3) and 2.236(3) Å, respectively. An acetonitrile and a sulfur-bound thiourea molecule occupy the two remaining terminal coordination sites. Selected interatomic distances and angles for **2** are listed in Table 2.

The internal geometry of the thiourea molecule is similar to that found in the free ligand. The sulfur−carbon bond length of 1.685(5) Å is somewhat shorter than that of uncoordinated thiourea, 1.721(4) Å.[38] A range of C−S distances from 1.697(13) to 1.752(12) Å occurs in other structurally characterized nickel−thiourea complexes.[39,40] The carbon−nitrogen bond lengths do not vary much for free thiourea, other nickel−thiourea complexes, and **2**, falling between 1.320 and 1.335 Å in most cases. Another notable feature of the X-ray structure of **2** is the 2.718(4) Å hydrogen-bonding interaction between one of the thiourea NH_2 groups and the hydroxide ion that bridges the two nickel ions. This interaction has been observed in all bdptz-ligated dinickel complexes of urea and urea analogues characterized thus far.[13]

The electronic spectrum of **2** is similar to that of **1**, with intense, broad bands at 220 and 265 nm attributable to the bdptz ligand and three weak d−d transitions in the visible region characteristic of divalent nickel in a pseudo-octahedral ligand environment. The vibrational spectrum of **2** is consistent with coordinated thiourea. The carbon−sulfur stretching frequency has shifted from the value of 1630 cm^{-1} in uncoordinated thiourea to 1610 cm^{-1} in **2**, indicative of coordination through the sulfur atom.[41]

Initial investigations were made to determine the products of the reactions between the substituted urea substrates and the dinickel complex $[Ni_2(\mu\text{-}OH)(\mu\text{-}H_2O)(bdptz)(H_2O)_2](OTs)_3$ (**3**). The substrates investigated were *N*-methylurea, *N*,*N*′-dimethylurea, *N*,*N*-dimethylurea, tetramethylurea, and thiourea. In a typical experiment, an acetonitrile solution 10 mM in each reagent was heated to 70 °C in a closed vial for 40 h with stirring. After the reaction mixtures were allowed to cool to room temperature, the solutions were tested for ammonia, alkylamine, and cyanate content. No ammonia could be detected in any of the reaction mixtures. The *N*-methylurea and *N*,*N*-dimethylurea reactions each produced measurable amounts of alkylamine and cyanate ion, but no such products were observed with *N*,*N*′-dimethylurea, tetramethylurea, or thiourea. None of these products formed when either the substrate or **3** was heated alone in acetonitrile under the same conditions, indicating that interaction of the substrate with the dinickel complex is required to promote the elimination of alkylamine and concomitant formation of a cyanate complex.

A detailed kinetic investigation of the methylurea elimination reaction was then undertaken. In each experiment, the concentration of substrate was varied and the concentration of **3** was held constant, or vice versa. The reaction vials were swirled at 200 rpm in a 60 °C incubator for 40 h, allowed to cool to room temperature, and then analyzed using FTIR spectroscopy. Samples were prepared as thin films on NaCl plates, and the intensity of the cyanate band at 2185 cm^{-1} was measured and normalized to the 877 cm^{-1} peak of **3**. The ratio of cyanate to dinickel complex concentration was calibrated against standards of known composition and used to determine the amount of cyanate produced in the reactions. Figure 4 shows plots of the initial rate of cyanate formation vs the initial concentrations of both methylurea and **3**. The reactions show saturation behavior consistent with a preequilibrium involving coordination of methylurea to the dinickel complex. A binding constant of 26 $\pm$ 5 M^{-1} was obtained for this interaction by fitting the data to the "improved" steady-state equation[27] with a preequilibrium assumption.[28] The rate constant for the elimination of methylamine from the complex to form cyanate was calculated to be $(1.2 \pm 0.2) \times 10^{-3}$ h^{-1}. The reaction between *N*,*N*-dimethylurea and **3** was quantitated by an analogous procedure, and the data are presented in Figure 5. A substrate binding constant of 100 $\pm$ 30 M^{-1} was obtained, and the elimination rate constant was $(3.3 \pm 0.6) \times 10^{-3}$ h^{-1}.

N,*N*′-Dimethylurea and tetramethylurea are incapable of undergoing an elimination reaction to form cyanate, and the only decomposition pathway available to these substrates is hydrolysis. No hydrolysis products were observed in these

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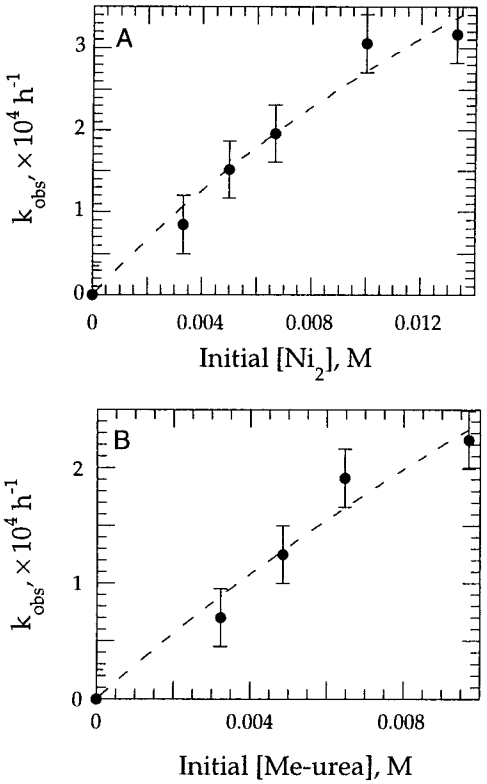


Figure 4. Plots showing the initial rate of cyanate formation vs (A) the initial concentration of **3** and (B) the initial concentration of methylurea. The dashed line shows a fit of the data to the improved steady-state rate equation with a preequilibrium assumption. A binding constant of methylurea to **3** of 26 ± 5 M^{-1} was obtained from the fit, along with an elimination rate constant of $(1.2 \pm 0.2) \times 10^{-3}$ h^{-1}.

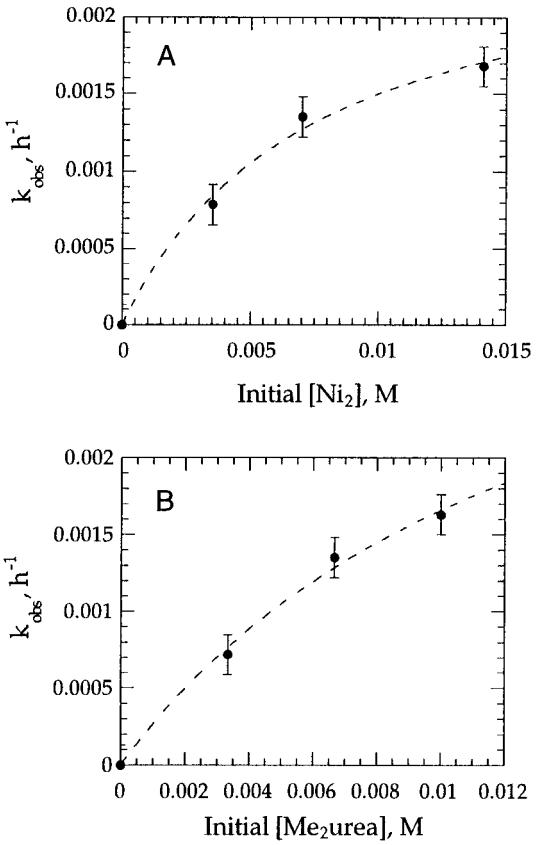
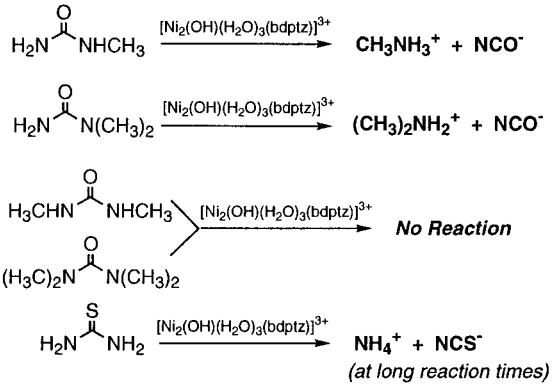


Figure 5. Plots showing the initial rate of cyanate formation vs (A) the initial concentration of **3** and (B) the initial concentration of *N*,*N*-dimethylurea. A binding constant of dimethylurea to **3** of 100 ± 30 M^{-1} was obtained from the fit, along with an elimination rate constant of $(3.3 \pm 0.6) \times 10^{-3}$ h^{-1}.

reactions, however. When gently heated, **2** did not produce detectable amounts of ammonia. This result is consistent with the knowledge that the facile spontaneous or metal-promoted decomposition of thiourea at moderate temperatures is much slower than that of urea.[42] After 7 days of heating at 70 °C, the IR spectrum of **2** displayed a peak at 2230 cm^{-1}, indicating the presence of sulfur-bound thiocyanate.[43] The results of these substituted urea reactivity studies are summarized in Scheme 2.

Scheme 2



Discussion

The recent discovery of the nickel-promoted elimination of ammonia from urea followed by hydrolysis of the resulting cyanate ion[13] led to this investigation of the interaction of substituted urea substrates with the dinuclear nickel center in [Ni_2(μ-OH)(μ-H_2O)(bdptz)(H_2O)$_2$](OTs)$_3$. The chemistry was studied with crystallographic, spectroscopic, and kinetic techniques. To our knowledge, complex **1** is the first example of a structurally characterized dinickel−methylurea complex. The methylurea molecule coordinates to the dinickel center through its carbonyl oxygen atom, a widely encountered mode generally accepted to be the manner in which urea binds nickel in urease. The C−O bond length does not change appreciably upon coordination, indicating very little polarization of this bond. It has frequently been proposed that coordination of urea to the dinickel center in urease polarizes the carbonyl moiety, activating it for nucleophilic attack. It seems likely that extensive interactions of the urea molecule with other residues in the active site play a more important role in directing the activity of the substrate.[3,4,6,10] The thiourea complex **2** has a similar geometry but does not react under the relatively mild conditions employed.[42] An important feature in both complexes **1** and **2** is the hydrogen-bonding interaction between the urea N−H moiety and the hydroxide ion that bridges the two nickel ions. This interaction may affect the reactivity of these complexes.

The reactivity of the hydroxide-bridged dinickel center in [Ni_2(μ-OH)(μ-H_2O)(bdptz)(H_2O)$_2$](OTs)$_3$ (**3**) with a series of substituted urea molecules was investigated. When methylurea is combined with **3**, there are a number of possible outcomes. The two may not react at all or simply form a dinickel−methylurea complex similar to **1**. By analogy to the decomposition of urea at a dinickel center reported previously,[13] an amine may be eliminated and a cyanate complex produced. In the case

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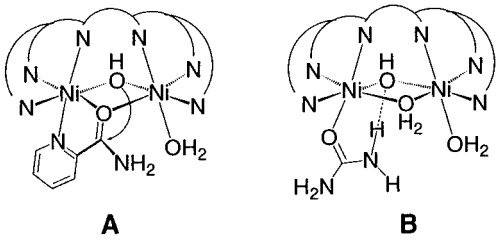
Scheme 3



of methylurea, two possible elimination products are possible, ammonia and methylisocyanate or methylamine and cyanate. A third possibility is direct hydrolysis of methylurea by the coordinated hydroxide ion or an external nucleophile. The hydrolysis of methylurea could produce either ammonium methylcarbamate or methylammonium carbamate as an intermediate, but the ultimate products in either case would be equimolar amounts of methylamine, ammonia, and carbon dioxide.

All of the substituted urea substrates investigated here show analogous reactivity when combined with **3**. Substrates having alkyl substitutents on only one of the urea nitrogen atoms all undergo alkylamine elimination to form a dinickel−cyanate complex. Such an elimination reaction pathway is shut down for *N*,*N*′-alkylated substrates, and no reaction is observed. It is interesting to consider why no substrate hydrolysis occurs, since complex **3** is capable of hydrolyzing picolinamide through intramolecular attack of the bridging hydroxide ion on the coordinated amide substrate.[24] A similar intramolecular attack of hydroxide ion on a coordinated urea substrate can be envisioned but is not observed. One possibility may be the differing geometries of the complexes, as depicted in Scheme 3. In the reactions of both picolinamide and ureas with **3**, saturation kinetics are observed, indicating that coordination of the substrate to the dinickel complex must occur prior to any reaction. In the case of picolinamide (Scheme 3A), both the pyridyl nitrogen atom and the carbonyl oxygen atom bind to the dinickel center, positioning the carbonyl carbon atom for hydrolytic attack and the amide N−H group away from the coordinated hydroxide ion. In contrast, the urea molecules have no appending ligand to help position the substrate for hydrolytic attack (Scheme 3B). Instead, the N−H groups form a hydrogen bond with the coordinated hydroxide. The hydroxide ion, instead of functioning as a nucleophile as in the picolinamide hydrolysis reaction, may serve as a general base, facilitating the deprotonation of urea and the elimination of ammonia.

Another reason for the lack of urea hydrolysis may be the inherent stability of ureas compared to amide substrates. The hydroxide ion of **3**, while potent enough to effect picolinamide hydrolysis, may not be sufficiently nucleophilic to hydrolyze urea. Most likely it is a combination of these and other properties of these dinickel−urea complexes that promote elimination at the expense of hydrolysis. Tuning the nucleophilicity of the coordinated hydroxide ion by increasing the donor strength of the spectator ligands may provide a system in which urea hydrolysis can be achieved.

The preference for elimination over hydrolysis observed in this as well as other model systems may have implications for the mechanism of urease. As we recently reported, the hydrolysis of urea can be effected via this pathway,[13] and it is conceivable that the enzymatic hydrolysis of urea may actually follow this path. Although the specificity of urease for urea was once considered absolute, substrates other than urea can indeed be processed by the enzyme.[44] Alternative substrates include *N*-methylurea, *N*-hydroxyurea, and semicarbazide as well as small amides such as formamide and acetamide.[45] The interaction between urease and *N*,*N*′-dialkylureas has not been reported, and thiourea is both an inhibitor[44] of the enzyme and a substrate,[46] although the products of this reaction have not been well-characterized. The fact that urease can hydrolyze substrates that can undergo an elimination reaction rather than direct hydrolysis in the initial step, whereas the urease-catalyzed hydrolysis of substrates not capable of elimination has not been reported, may lend support to this alternative mechanism of urea hydrolysis.

Conclusions

The mechanism of action of the metalloenzyme urease has been a subject of discussion for many years.[47−50] Although considerable progress has been made toward providing a thorough understanding of this enzyme, many questions still remain about the precise geometry by which urea binds to the dinickel center, the interactions between the substrate and the active site residues, and the nature of the hydrolytic attack.[51] Carbamate has been implicated as the first intermediate to be *released* from the active site of urease,[52] but there is no evidence that it is the first intermediate *formed* in the reaction. There is increasing evidence that the interaction of urea with dinickel model compounds often results in the elimination of ammonia to form a cyanate complex.[13,22,23,53] Recent studies demonstrating the feasibility of cyanate hydrolysis lend support to the possibility that the urease-catalyzed hydrolysis of urea may proceed via initial elimination of ammonia.[13,53]

The present study was undertaken to investigate the limits of this elimination reaction and the possibility of promoting hydrolysis in this system by shutting down the elimination pathway. Substituted urea substrates either react with the dinickel center to eliminate an alkylamine and form a cyanate complex or do not react at all. Substrate hydrolysis was not promoted by the dinickel center to any detectable extent. The propensity of model complexes to effect the elimination of ammonia from urea rather than direct hydrolysis does not rule out hydrolysis as a viable enzymatic mechanism, but if such is the case, more advanced dinuclear nickel complexes are needed because thus far elimination is preferred over hydrolysis.

Acknowledgment. This work was supported by grants from the National Science Foundation and the National Institutes of Health. A.M.B. thanks the NIH for a predoctoral fellowship. We thank Dr. Bernhard Spingler for helpful discussions about the crystallographic data.

Supporting Information Available: X-ray crystallographic files (Tables S1−S10), in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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