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Nickel Complexes of Carboxylate-Containing Polydentate Ligands as Models for the Active Site of Urease

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Two new carboxylate-containing polydentate ligands have been synthesized, the symmetric ligand 2,6-bis[*N*-(*N*-(carboxylmethyl)-*N*-((1-methylimidazol)methyl)amine)methyl]-4-methylphenolate (BCIMP) and the corresponding asymmetric ligand 2-(*N*-isopropyl-*N*-((1-aminomethyl)-4-methylphenol (ICIMP). The ligands have been used to prepare model complexes for the active site of the dinuclear nickel enzyme urease, viz. $[Ni_2(BCIMP)Ac_2]^-$ (**6**), $[Ni_2(BCIMP)(Ph_2Ac)_2]^-$ (**7**), $[Ni_2(ICIMP)(Ph_2Ac)_2]$ (**14**), $[Ni_4(ICIMP)_2(Ph_2Ac)_2][ClO_4]_2$ (**15**), $[Ni_4(ICIMP)_2(Ph_2Ac)_2(DMF)_2][ClO_4]_2$ (**16**), and $[Ni_4(ICIMP)_2(Ph_2Ac)_2(urea)(H_2O)][ClO_4]_2$ (**17**), where the latter complex contains urea coordinated in a unidentate fashion through the carbonyl oxygen. The $N_2O–N_2O_2$ donor set of ICIMP provides a good framework for the preparation of urease models, but in some cases tetranuclear nickel complexes are formed due to coordination of the carboxylate moiety of one dinickel-ICIMP unit to one or both of the nickels of a second Ni_2 unit. Reactivity and kinetics studies of **7** and **15** show that these model complexes catalyze hydrolysis of 2-hydroxypropyl *p*-nitrophenyl phosphate (HPNP) at basic pH. In this assay, complexes based on the asymmetric ligand ICIMP exhibit a significantly faster rate of hydrolysis than the corresponding BCIMP complexes. Magnetic measurements indicate that there are weak antiferromagnetic interactions between the nickel ions in complex **16**.

Introduction

Urease is an enzyme that catalyzes the hydrolysis of urea to carbamate and an ammonium ion;[1−6] subsequent spontaneous decompositon of carbamate leads to the formation of a second ammonium ion and carbon dioxide. The enzyme has also been determined to catalyze the hydrolysis of small amides to their corresponding carboxylic acids.[7] Urease is present in various bacteria, fungi, and plants and has been found to be important in the virulence of *Helicobacter pylori* and *Proteus mirabilis*.[8] Several crystal structures of the wild-type enzyme have been published.[9−15] They portray a metalloprotein with three dinuclear nickel sites in the active

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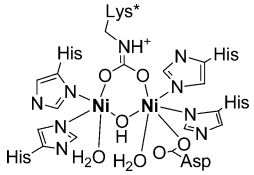

Figure 1. Schematic depiction of the structure of the active site of *Bacillus pasteurii* urease.[11]

protein, one in each of three major subunits. The two nickel ions in each site are separated by about 3.5 Å and weakly antiferromagnetically coupled.[16] Each nickel ion is in the native structure coordinated by two histidine residues and one water molecule, while a carbamylated lysine residue and one hydroxyl group bridge the two ions (Figure 1). One aspartate residue is coordinated through one carboxylate oxygen to one of the nickel atoms, normally referred to as Ni(2), while Ni(1) has an open coordination site. A number of crystal structures of *Klebsiella aerogenes* and *Bacillus paseurii* urease with bound inhibitors have also been published.[15,17−21]

Several suggestions for the enzymatic mechanism of urease have been made.[7,11,22,23] A common feature in the published mechanistic proposals is that the reaction is initiated by the coordination of the urea oxygen to the coordinatively unsaturated nickel ion, Ni(1). The source of the attacking hydroxide has been debated.[6,24] Both the deprotonated terminal water molecule on Ni(2) and the bridging hydroxide have been suggested. The inhibition of urease by the fluoride anion has been proposed to be due to the replacement of the bridging hydroxide/water by fluoride, implicating the bridging hydroxide as the active nucleophile.[24] A process involving a cyanate intermediate has also been mentioned.[23,25]

To study the proposed mechanisms, we have attempted the preparation of structural and functional mimics of the urease active site.[26] For this reason, we have prepared phenolate-based ligands that include imidazole and carboxylate donor functionalities. Here, we wish to report the syntheses of the symmetric ligand 2,6-bis[*N*-(*N*-(carboxylmethyl)-*N*-((1-methylimidazol)methyl)amine)methyl]-4-methylphenolate (BCIMP) and the corresponding asymmetric ligand 2-(*N*-isopropyl-*N*-((1-methylimidazolyl)methyl)aminomethyl)-6-(*N*-carboxylmethyl-*N*-((1-methylimidazolyl)methyl)aminomethyl)-4-methylphenol (ICIMP). The preparations of di- and tetranuclear nickel complexes, some of which have shown the ability to coordinate urea, are also described. The hydrolytic activity of the complexes has been tested in the hydrolysis of the organophosphoester 2-hydroxypropyl *p*-nitrophenyl phosphate (HPNP). A comparative kinetic study of the complexes has been undertaken to study the function of an open coordination site on one of the nickel ions. Part of this work has been described in an earlier communication.[26]

Results and Discussion

The use of dinucleating ligands with central bridging phenolate moieties is widespread in the modeling of active sites in metalloenzymes.[27−31] The efficacy of such ligands in the formation of dinuclear complexes and their capability of stabilizing dinuclear frameworks during reaction cycles is well established.[32−35] We therefore decided to prepare such ligands that may adequately mimic the ligand environment of the dinuclear nickel site in urease (cf. Figure 1), even though the bridging phenolate might prevent reactivity that faithfully reproduces that of urease. Ligands of this type that employ pyridyl or imidazolyl substituents as mimics of histidine have been prepared.[36−39] However, to our knowledge, there are no known examples of such ligands with terminal carboxylate donor moieties that may simulate aspartate and/or glutamate residues. For this reason, we prepared the ligand BCIMP.

Synthesis of Na_3BCIMP (5). The synthetic route to the trisodium salt of 2,6-bis[*N*-(*N*-(carboxylmethyl)-*N*-((1-methylimidazolyl)methyl)amine)methyl]-4-methylphenolate (Na_3-BCIMP, **5**) is outlined in Scheme 1. The amine sidearms (**3**) are prepared by the reductive amination of glycine ethyl ester by 1-methylimidazole-2-carbaldehyde, which is readily available in a one-step synthesis from commercial reactants. These sidearms are subsequently connected via an S_N2 reaction to 2,6-bis(chloromethyl)-4-methylphenol (**1**), which in turn was prepared by chlorination of the corresponding alcohol. The final product is deprotected by reaction with NaOH to yield the ligand in its phenolate form (**5**).

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Scheme 1. Outline of the Synthesis of BCIMP

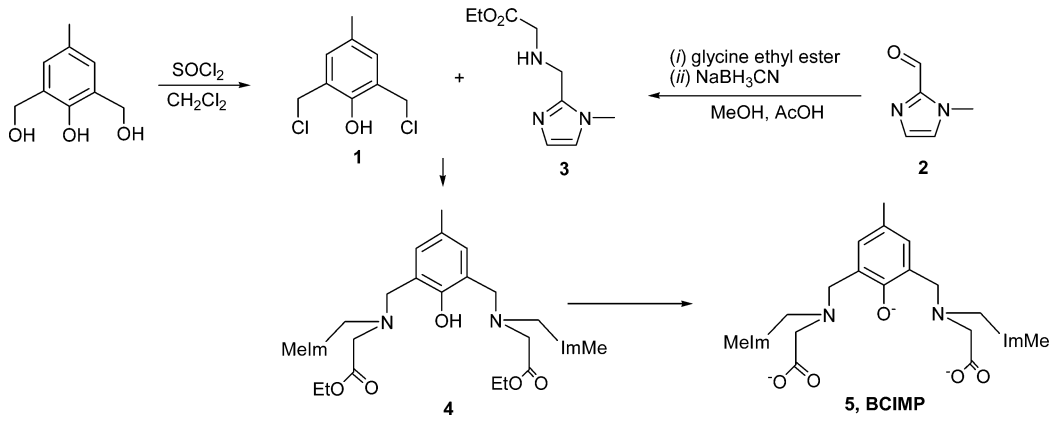

Table 1. Crystal Data for Compound **6**

empirical formula	$C_{28}H_{38.5}Br_{0.5}N_6Na_{1.5}Ni_2O_{10.75}$
fw	823.01
temp (K)	120(2)
λ (Å)	0.710 73
cryst syst	monoclinic
space group	$P2_1$
a (Å)	12.0778(2)
b (Å)	22.9808(6)
c (Å)	13.1273(3)
β (deg)	97.835(2)
V (Å^3)	3609.57(14)
Z	4
ρ_{calc} (Mg/m^3)	1.514
μ(Mo Kα) (mm^{-1})	1.676
R1[a] ($I \geq 2\sigma$(I))	0.0478
wR2[b] ($I \geq 2\sigma$(I))	0.1144

[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR2 = [\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2}$.

Preparation of $Na_{1.5}[Ni_2(BCIMP)Ac_2]Br_{0.5}$ (6) and Crystal and Molecular Structure of $Na_{1.5}[Ni_2(BCIMP)Ac_2]Br_{0.5}\cdot MeOH\cdot 3/4H_2O$. The symmetric ligand BCIMP readily forms complexes with nickel. Reaction of Na_3BCIMP with $Ni(ClO_4)_2\cdot 6H_2O$ and sodium acetate in methanol solution gave the anionic complex $[Ni_2(BCIMP)Ac_2]^-$ in good yield. The rapid color change from the light green of the nickel perchlorate to the turquoise complex indicates that compound **6** is generated instantaneously upon addition of the nickel solution to the ligand. Addition of sodium bromide was found to be useful for crystallization, and it was possible to grow single crystals of the complex by slow evaporation of the reaction solution. The crystal structure was determined to confirm the dinuclear nature of the complex; crystallographic data are summarized in Table 1. The crystal structure contains two crystallographically unique $[Ni_2(BCIMP)Ac_2]^-$ anions ($Z = 4$); one has one sodium ion associated with the dinickel unit while the other has two sodium ions in close proximity. In addition to the sodium ions, two bromide ions, four methanol molecules, and three water molecules are found in the unit cell.

The molecular structure of one of the $[Ni_2(BCIMP)Ac_2]^-$ anions in **6** is shown in Figure 3, and relevant bond distances and bond angles are listed in Table 2; the bond distances and bond angles for the second Ni_2 anion are very similar. The molecule possesses pseudo-C_2 symmetry with the C_2 axis passing through O(1) and the phenyl moiety. Each nickel ion is coordinated by the bridging phenolate, one imidazole nitrogen atom, one amine nitrogen atom, one ligand carboxylate oxygen atom, and two carboxylate oxygens from bridging acetates. The nickel ions possess overall octahedral coordination geometries with distortions that are imposed by the ligand(s). Thus, the N(1)−Ni(1)−N(5)/N(3)−Ni(2)−N(6) and O(6)−Ni(1)−N(5)/O(8)−Ni(2)−N(6) angles are 82.1° (average) and 79.0° (average) because of the relatively

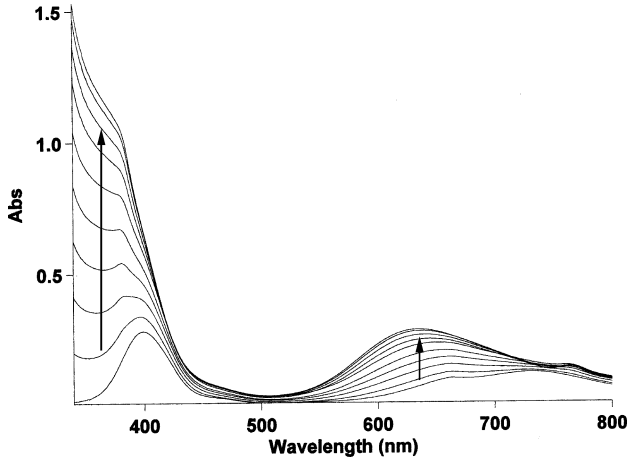

Figure 2. Results from a titration of BCIMP and diphenylacetate with a nickel perchlorate solution (0.05 M).

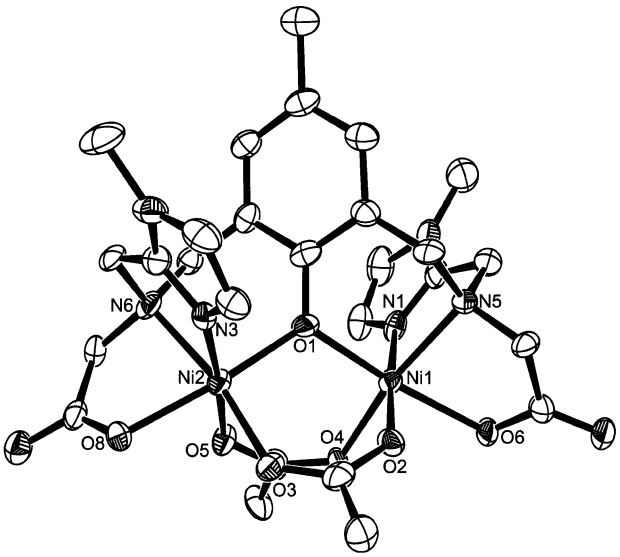

Figure 3. ORTEP diagram of the molecular structure of one crystallographically unique dimer of $[Ni_2(BCIMP)Ac_2]^-$ (**6**).

Table 2. Relevant Bond Distances (Å) and Bond Angles (deg) for Compound **6**

	Distances		
Ni1---Ni2	3.396(2)	Ni1−O1	1.992(4)
Ni3---Ni4	3.415(2)	Ni2−N3	2.043(5)
Ni1−N1	2.056(5)	Ni2−N6	2.124(5)
Ni1−N5	2.122(5)	Ni2−O8	2.103(4)
Ni1−O6	2.080(4)	Ni2−O3	2.045(4)
Ni1−O2	2.085(4)	Ni2−O5	2.098(4)
Ni1−O4	2.039(4)	Ni2−O1	1.994(4)
	Angles		
Ni1−O1−Ni2	116.88(18)	N1−Ni1−O6	94.40(17)
Ni2−O10−Ni4	116.51(0)	N3−Ni2−N6	82.07(19)
N1−Ni1−N5	82.08(19)	N3−Ni2−O8	92.96(17)

short bites of the ligand sidearms. This also gives rise to somewhat longer Ni−N(amine) distances, 2.13 Å (average) than what have been observed in related complexes.[40,41] The nickel−nickel distances in the two crystallographically unique molecules are 3.396(2) Å [Ni(1)−Ni(2)] and 3.415(2) Å [Ni(3)−Ni(4)], which is relatively short when compared to other model complexes for the urease active site,[42−45] e.g. a number of pyrazolyl-bridged dinickel complexes prepared by Meyer and co-workers,[42,43] where the Ni−Ni distances vary from approximately 3.5 to 4.6 Å depending on the nature of a second bridging ligand (hydroxide, acetate, urea, cyanate) and pyrazine. The relatively short distance found in **6** may be attributed to the presence of three bridging moieties (two carboxylates and one phenolate). On the other hand, the Ni−Ni distance in $[Ni_2(BCIMP)Ac_2]^-$ is significantly longer than triply bridged dinickel complexes developed by Barrios and Lippard,[23,46] in which the bridges consist of a pyrazine (phthalazine) moiety and bridging water or hydroxide ligands. The observed Ni−Ni distance in **6** is also in good agreement with the internuclear distances found in the crystal structures of urease (approximately 3.5 Å). The Ni(1)−O(1) and Ni(2)−O(1) distances are 1.99 Å (average) and the Ni(1)−O(1)−Ni(2) angle is 116.8(2)°, which is in good agreement with corresponding distances and angles found in related phenolate-bridged dinickel complexes.[38,47,48]

Preparation of $[Ni_2(BCIMP)(Ph_2Ac)_2]^-$ (7). While $[Ni_2(BCIMP)Ac_2]^-$ might be an adequate structural model for urease, it is not expected to be a good catalyst for hydrolysis reactions since the coordination spheres of both nickel ions are filled. It was thought that the use of a carboxylate with bulky substituents might facilitate the formation of a dinuclear complex with one BCIMP ligand and only one bridging carboxylate during catalysis, and we therefore investigated the use of diphenyl acetate as a bridging ligand. Nickel perchlorate was reacted with BCIMP and diphenyl acetic acid in methanol solution in the presence of sodium methoxide. Compound **7** was isolated from this reaction and identified as $[Ni_2(BCIMP)(Ph_2Ac)_2]^-$ on the basis of mass spectrometry, but a significant peak envelope corresponding to $[Ni_2(BCIMP)(Ph_2Ac)]$ was also detected (cf. Experimental Section). Further support for the dinuclear nature of the complex was obtained from a titration of BCIMP and diphenyl acetate with nickel perchlorate that was monitored by UV/vis spectrophotometry (Figure 2). Aliquots of the dinucleating BCIMP ligand and diphenyl acetate (0.05 and 0.1 equiv of each, respectively) were added to a solution of $NiClO_4 \cdot 6H_2O$, and the UV/vis spectrum was collected immediately after each addition. The orderly, stepwise conversion of the reactants ($\lambda = 400$ nm) to the product ($\lambda = 639$ nm) indicates a relatively fast and ordered reaction.

Reactivity Study of 7. Functional studies of **7** were made to assess its capacity to act as catalyst for substrate hydrolysis. Rather than studying the hydrolysis of urea, we used transesterfication of 2-hydroxypropyl *p*-nitrophenyl phosphate (HPNP) to assess the catalytic capacity of the compound. This hydrolytic reaction is often used because it is easy to monitor and quantify, and the availability of previous data for the reaction is useful for comparisons to related published catalysts.[34,49] Our primary objective was to assess whether our dinickel complex may act as a Lewis acid toward water. However, a study of HPNP hydrolysis/transesterification is admittedly flawed as a benchmark for urea hydrolysis since the substrates are not closely related and the possibility of direct deprotonation of the alcohol moiety in HPNP exists.[50] In a regular assay, a water/MeCN solution (1:1) containing buffer, catalyst, HPNP, and sodium perchlorate was prepared and the evolution of *p*-nitrophenolate at 400 nm was studied. The result was then converted to nitrophenolate concentration and recalculated to total *p*-nitrophenol/*p*-nitrophenolate concentration by using the pK_a for the acid/base pair. The experiment was reproduced at five different pH between pH 7 and 9 (the pH optimum of urease is 8). The result from the series can be seen in Figure 4. The activity of the uncatalyzed reaction is shown for comparison. The overall trend is that the reaction is faster at higher pH for both the catalyzed and the uncatalyzed reaction, which may be expected since hydroxyl groups are more potent nucleophiles than water.[46] The reactivity of the catalyst is relatively low but still considerably higher (approximately one order of magnitude) than for the uncatalyzed reaction at the corresponding pH.

Synthesis of H_2ICIMP (13). Although the BCIMP complex did show catalytic activity toward the hydrolysis of HPNP, the catalytic efficiency was low. To induce coordinative unsaturation, an asymmetric dinucleating ligand that contains all donor moieties of BCIMP but one was

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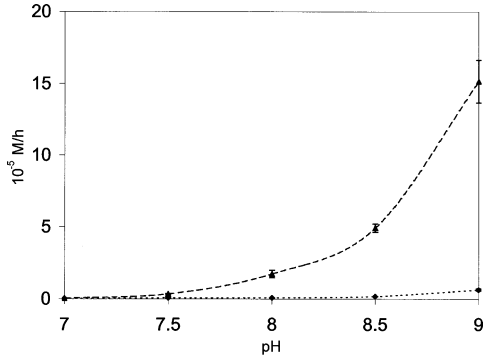

Figure 4. Dependence on the initial rates of hydrolysis of HPNP at different pH values for catalyzed ($[Ni_2(BCIMP)(Ph_2Ac)_2]^-$ (**7**)) and uncatalyzed reactions.

designed and synthesized. The synthetic route to the resultant ligand, 2-(*N*-isopropyl-*N*-((1-methylimidazol)methyl)aminomethyl)-6-(*N*-(carboxylmethyl)-*N*-((1-methylimidazol)methyl)aminomethyl)-4-methylphenol (H_2ICIMP, **13**), is outlined in Scheme 2. In similarity to the BCIMP synthesis, each sidearm can be synthesized by reductive amination. The carboxylate sidearm is identical with that developed for BCIMP, while the glycine derivative is replaced by isopropylamine in the synthesis of the second sidearm (**8**). The asymmetry is generated in the selective oxidation of 2,6-bis(hydroxymethyl)-4-methylphenol.[51] The generated aldehyde (**9**) is untouched by the chlorination in the following step. After the substitution, the aldehyde (**10**) is reduced back to the alcohol (**11**), which in turn can be chlorinated, substituted, and deprotected yielding the product. Direct synthesis of the asymmetric ligand, i.e., reaction of 2,6-bis(chloromethyl)-4-methylphenol (**1**) with the two amine sidearms of the ligand (**3** and **8**) and subsequent separation of the three different possible isomers, has also been attempted; however, it did not prove possible to separate the products.

$Na[Ni_2(ICIMP)(Ph_2Ac)_2]ClO_4$ (14). When the asymmetric ligand and nickel perchlorate are reacted in association with diphenyl acetate in excess (4 equiv), a complex precipitates. The mass spectrum and elementary analysis indicate a molecular formula of $Na[Ni_2(ICIMP)(Ph_2Ac)_2]ClO_4$. The compound is not soluble in methanol, except if a polar coordinating ligand such as triphenylphosphine oxide is added.

Preparation of $[Ni_4(ICIMP)_2(Ph_2Ac)_2][ClO_4]_2$ (15) and $[Ni_4(ICIMP)_2(Ph_2Ac)_2(DMF)_2][ClO_4]_2\cdot 2.5DMF$ (16) and Crystal and Molecular Structure of 16. Reaction of ICIMP with 2 equiv of both diphenylacetate and nickel perchlorate in ethanol results in the formation of a compound with spectroscopic properties (UV and IR) that differ from those of **14**. The mass spectrum indicates the presence of a tetranuclear compound with a molecular formula corresponding to $[Ni_4(ICIMP)_2(Ph_2Ac)_2(ClO_4)]^+$, and the suggested formula of this compound is $[Ni_4(ICIMP)_2(Ph_2Ac)_2][ClO_4]_2$ (**15**). Compound **15** is even less soluble than **14** but dissolves well in DMF. If a DMF solution is left in an atmosphere of *tert*-butyl methyl ether, blue crystals of $[Ni_4(ICIMP)_2(Ph_2Ac)_2(DMF)_2][ClO_4]_2\cdot 2.5DMF$ (**16**) are formed.

The crystal structure of **16** was determined to establish the nuclearity of the complex and the coordination mode of the ICIMP ligand.[26] The molecular structure of **16** is shown in Figure 5a. The structure consists of a dimer of dimers in which the two nickel ions in each dimer are ligated by one ICIMP ligand and one bridging phenylacetate molecule. The nominally vacant coordination sites of each Ni_2 moiety are filled by one DMF molecule and the ligand (ICIMP) carboxylate from the neighboring Ni_2 unit. The latter two carboxylates coordinate in two different modes—in one Ni_2 unit, the carboxylate from the neighboring ICIMP ligand coodinates in a didentate mode, bridging the two nickels, while, in the second nickel dimer, the corresponding carboxylate coordinates in a chelating mode to one nickel (cf. Figure 5a). The two coordination modes thus impart an asymmetry in the dimer of dimers. The crystal structure also includes two perchlorate ions and two and a half DMF molecules per tetramer. A predominant feature in the crystal packing is the π-stacking of the phenylacetate ligands from neighboring tetramers.

Crystal and Molecular Structure of $[Ni_4(ICIMP)_2(Ph_2Ac)_2(urea)(H_2O)][ClO_4]_2\cdot 0.5EtOH\cdot H_2O$ (17). Treatment of the supernatant from the synthesis of **15** with urea resulted in the formation of blue crystals of $[Ni_4(ICIMP)_2(Ph_2Ac)_2(urea)(H_2O)][ClO_4]_2\cdot 0.5EtOH\cdot H_2O$ (**17**) after relatively long incubation. The crystal structure of **17** was determined to compare the molecular structure to that of **16** and establish the coordination mode of the bound urea. The molecular structure of **17** (Figure 5b) is virtually identical with that of **16**, with one urea molecule and one water replacing the coordinated DMF molecules of **16**.[26] The urea molecule is coordinated to the dimer which has the bridging neighboring carboxylate while the water is bound to the "chelated" Ni_2 unit. The coordination of the urea molecule leads to changes in bond distances and angles of the ligand with respect to free, i.e., noncoordinated, urea. The interatomic distance between the urea oxygen and carbon is elongated from 1.255(9) Å in a regular urea molecule[52] to 1.352(13) Å in **17**. The same tendency is seen in the nitrogen to carbon distances, which are found to be 1.33(1) Å in free urea and 1.426(12) and 1.421(15) Å in the nickel complex. The weakening of the electron density in the oxygen carbon bond can also be seen in the divergence of the four nonhydrogen atoms from the plane defined by the torsion angle N1−C−O−N2. This angle is normally small (1.1(5)°), but in **17** it is 7.41(18)°.

The structure of each Ni_2 unit in **16** and **17** may be compared to that of the $[Ni_2(BCIMP)Ac_2]^-$ ions found in the **6** (vide supra); some molecular distances and angles in the three crystal structures are compared in Table 3. As in **6**, the nickel ions in **16** and **17** are hexacoordinate with

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(52) Based on 10 entries in the Cambridge Structural Database that contain "free" urea, i.e., where there are no apparent interactions between the urea molecules and any other molecules in the unit cells.

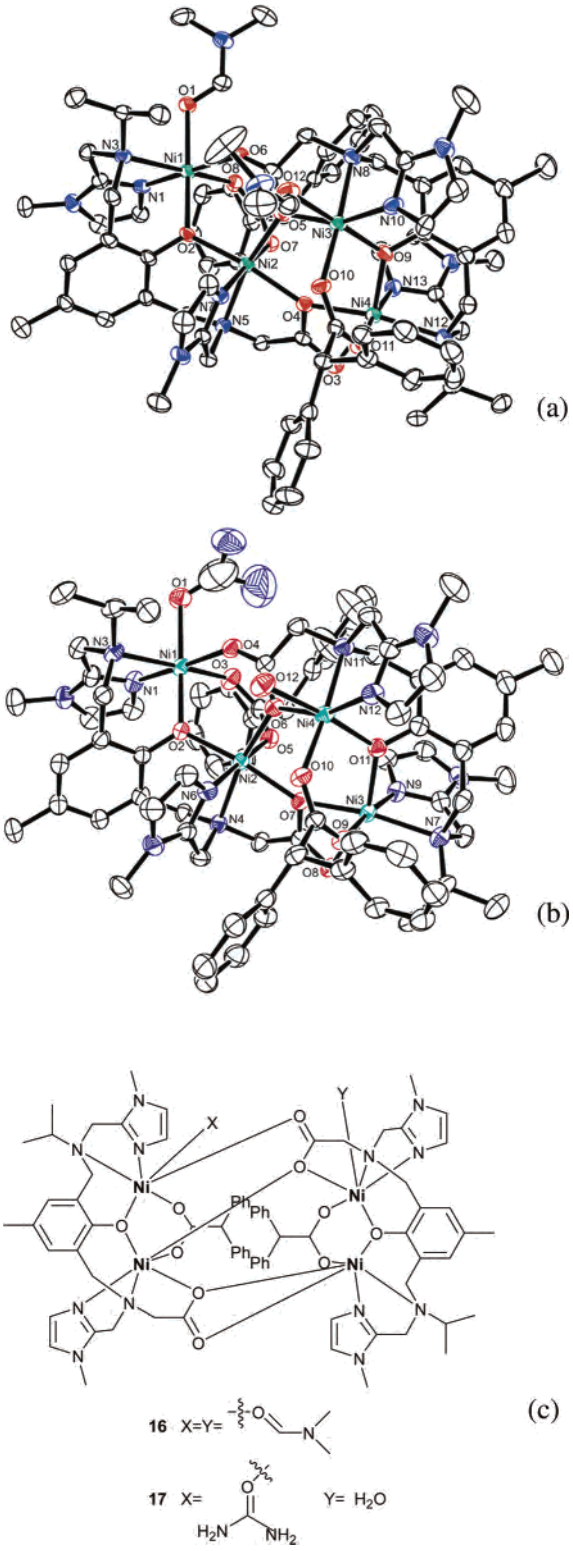

Figure 5. ORTEP diagrams of the molecular structures of (a) compound **16** and (b) compound **17** and schematic presentation of (c) the two complexes.[26]

deviations from perfect octahedral geometry that may be attributed to the coordinating ligands. Again, the relatively narrow bites of the ligand arms impart angles that are more acute than 90°. Thus, the average N(amine)−Ni−N(imidazole) angle in **16** and **17** is 81.5° (cf. Table 3) and the O−Ni−O angles imparted by the chelating carboxylates are 60.82(12)° (**16**) and 58.99(10)° (**17**). The Ni−O(DMF) (**16**), Ni−O(urea), and Ni−O(water) (**17**) distances do not vary significantly from the Ni−O(carboxylate) distances found in **6**, **16**, and **17**, suggesting that the BCIMP and ICIMP ligands mainly impose geometrical rather than distance constraints upon formation of the di-/tetranuclear complexes. The Ni−O(phenolate)−Ni angles in **16** and **17** are all slightly more obtuse (>120°) than that observed for **6**, possibly because the tridentate coordination of ICIMP to one nickel permits a less constrained fit of this ligand to the dinickel unit than BCIMP, which acts as a tetradentate donor to both nickels. The intermetal distances in the Ni_2 units are very similar in the ICIMP complexes **16** and **17**, regardless of whether the nickel ions are bridged by one carboxylate ("chelated" Ni_2 units) or two ("bridged" Ni_2 units), and they are consistent with the distance of about 3.5 Å that is found in the native enzyme. The distance for the Ni_2 complex based on the symmetric ligand (BCIMP) (**6**) is shorter by approximately 0.1 Å. A potential problem with carboxylate sidearms is that they easily attract additional coordination, which in this case generates dimers of dimers. Even if this as such is an unwanted side effect, it has shown to be a useful property as the urea molecule in compound **17** only binds to the nickel ion resembling Ni(1) in the asymmetric dimer of dimers. This suggests that the first step in the hydrolysis of urea by urease is coordination of the urea carbonyl oxygen to Ni(1).

Magnetic Studies. The magnetic susceptibility of $[Ni_2(ICIMP)_2(PhAc)_2(DMF)_2](ClO_4)_2$ (**16**) has been investigated in the temperature range 5−300 K at four fields between 0.5 and 5 T. Figure 6 illustrates the temperature dependence of the molar magnetic susceptibility (χ_M) at 0.5 T. A smooth increase of χ_M is observed as T decreases. The data have been simulated using a full matrix diagonalization program taking into account both J and D parameters. The tetranickel pattern does not possess any symmetry. Nevertheless, to avoid an overparametrization of the system, the following model was used which includes only three different J values. Interactions within the μ-phenoxo μ-carboxylato bridging patterns between Ni(1)− Ni(2) and Ni(3)− Ni(4) are noted J_1 and J_3, respectively. In addition, those between Ni(2)− Ni(3), Ni(1)− Ni(3), and Ni(2)− Ni(4) which are mediated by a carboxylate bridge were taken to be equal to J_2. Since there is no direct bridge between Ni(1) and Ni(4), the corresponding exchange was set to 0. In addition, it was assumed that the four Ni atoms had the same zero-field parameter $D_1 = D_2 = D_3 = D_4 = D$. A very good simulation of the data represented in Figure 6 was obtained with the following set of parameters: $J_1 = -2.65$ (4) cm^{-1}; $J_2 = J_4 = J_5 = -11$ (1) cm^{-1}; $J_3 = -15$ (4) cm^{-1}; $g = 2.25(3)$; $D = -1.2(5)$ cm^{-1}.

The g value is in very good agreement with the literature. The moderate values of the exchange interactions noted here are in the range of those observed for various dinuclear and tetranuclear nickel complexes. Magneto−structural correlations have been obtained for a few series of dinuclear Ni

Scheme 2. Outline of the Synthesis of the Asymmetric Ligand ICIMP

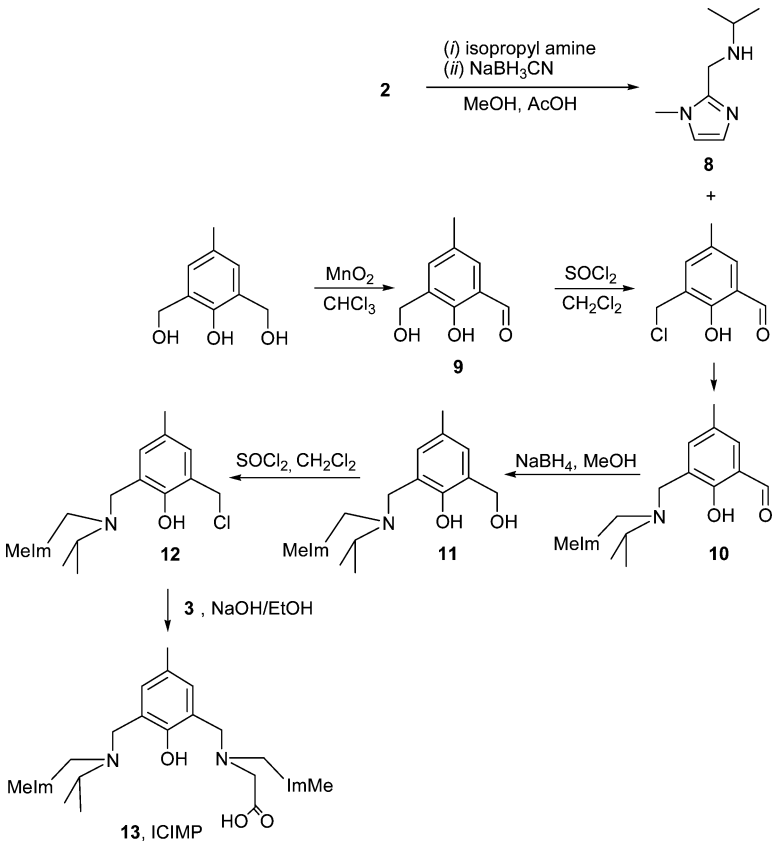

Table 3. Average Bond Distances (Å) and Bond Angles (deg) for Compounds **6**, **16**, and **17**

	6	**16**	**17**
Ni---Ni	3.406	3.492	3.480
Ni−N(amine)	2.125	2.179	2.182
Ni−N(imidazole)	2.046	2.042	2.033
Ni−O(term. carbox)	2.089	2.133	2.113
Ni−O(bridg. phenoxide)	2.001	2.011	2.003
Ni−O−Ni	116.70	120.46	120.66
N(amine)−Ni−N(imidazole)	82.15	81.61	81.47

units in bis(μ-phenoxo) complexes[53] and in μ-alkoxo tetranuclear nickel compounds.[54] In all cases, a strengthening of the exchange interaction paralleled an increase of the Ni−O−Ni angle, as expected. A limited number of (μ-phenoxo)-(μ-carboxylato)dinickel complexes has been reported in the literature, which precludes establishing a correlation. Nevertheless, the same trend is certainly operative although it must be taken into account that the extent of nonplanarity of the phenol and the Ni_2O_2 core is likely to play a significant role. In this respect, the value of J_3 appears rather in line with the high value of the Ni−O−Ni angle (121.81(0)°) but the value of J_1 appears greatly reduced comparatively, despite a slightly decreased angle (119.12(0)°). This probably reflects additional distortions of the μ-phenoxo μ-carboxylato bridging pattern. Further studies, including low-temperature magnetization experiments and EPR measurements, are needed to fully characterize the magnetic behavior of the complex leading to a possible differentiation of D and/or J values of the four metal centers.

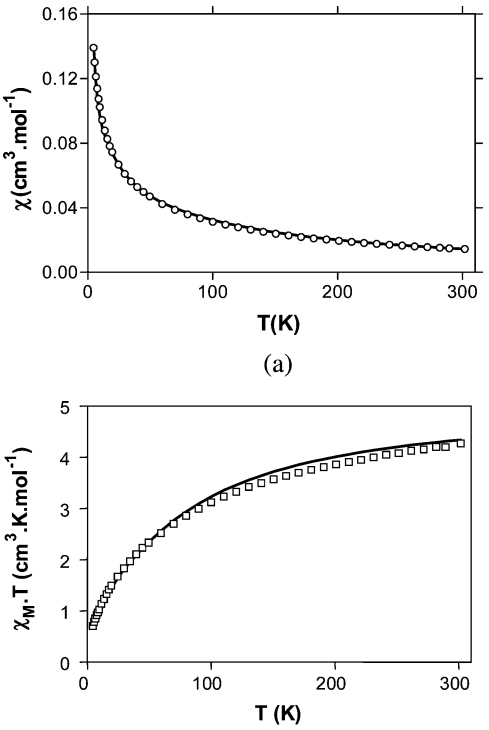

Figure 6. (a) Temperature dependence of the molar susceptibility and (b) the product of the molar susceptibility at 0.5 T.

DFT Calculations. To assess the relative stability of the two Ni_2 units in **16**, the crystallographic data for the two

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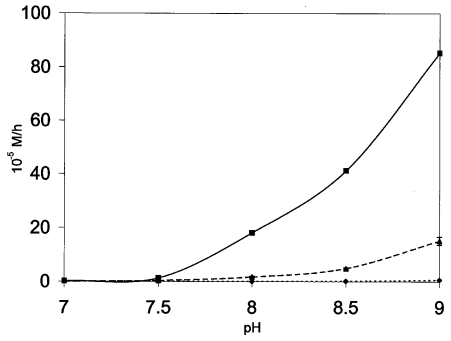

Figure 7. Dependence on the initial rates of hydrolysis of HPNP at different pH values for catalyzed (compound **15**, ■) and uncatalyzed (●) reactions. The reactivity of compound **7** (▲) is shown for comparison.

Table 4. Initial Rates of Hydrolysis of HPNP by Published Catalysts[34] in Comparison to Complexes **7** and **15** in MeCN/Buffer (0.01 M CHES, pH 8.5) and [HPNP] = 0.82 mM

catal	init rate (10^{-5} M/h)	rate ratio vs uncatal
7	0.49	27
15	4.1	230
$[ZnFe(BPMOP)]^{4+}$	2.1	112
$[ZnFe(BPMP)]^{4+}$	1.0	54
$[Fe_2(BPMOP)]^{4+}$	3.0	11
$[Fe_2(BPMOP)]^{4+}$	0.059	3
uncatal (this work)	0.0178	1
uncatal (published)	0.0192	1

dimers from the structure were separated. The contribution from the neighboring ligand was accounted for by replacing it by acetate. The single-point energy was then determined through a DFT calculation. This yielded a result that the Ni(1)−Ni(2) pair, which is bridged by the neighboring carboxylate and possesses a structure more resemblant of the urease active site, is more stable by about 30 kJ/mol. This indicates that the Ni(1)−Ni(2) pair is more likely a better model for urease than the chelated Ni(3)−Ni(4) dimer.

Reactivity Study of 15. The capacity of compound **15** to act as a catalyst was studied in the hydrolysis of HPNP. Mass spectrometry of the reaction mixture indicates that the catalyst decomposes/dissociates completely into the corresponding dimeric units when it comes in contact with water and substrate—the largest observed mass peak at 1013 amu corresponds to $Na[Ni_2(ICIMP)(Ph_2Ac)_2]$. The mass spectrum of the decomposed catalyst is also very similar to that of compound **14**, the dimeric compound based on ICIMP, and the kinetic rates for the two complexes are similar (only 10% difference at pH 8.5). Overall the catalyst based on the asymmetric ligand, complex **15**, is the most effective by about 1 order of magnitude (Figure 7). This underscores the importance of an open coordination site on the catalyst. It is noteworthy that the present model complex is hydrolytically active even though it is unlikely that any bridging oxygen donor (hydroxide) is available to partake in the catalytic reaction. The rates can be compared to other published dinuclear models investigated by similar methods.[34] For comparison, the rates have been recalculated to an assumed dinuclear catalyst concentration of 0.25 mM in Table 4.

Conclusions

We have successfully completed the synthesis of two new dinucleating ligands, BCIMP and ICIMP, that are based on a central (bridging) phenolate moiety, and carboxylate sidearms have for the first time been introduced in this type of ligand. The polydentate ligands easily form dinuclear complexes. While we have observed the formation of mononuclear derivatives of the asymmetric ligand ICIMP,[55] no mononuclear products could be found in reactions of the two ligands with nickel.

The urea molecule in $[Ni_4(ICIMP)_2(Ph_2Ac)_2(urea)(H_2O)][ClO_4]_2$ (**17**) binds in a terminal fashion to one nickel ion in the asymmetric dimer of dimers. The nickel in this model complex corresponds to the nickel ion (Ni(1); cf. Figure 1) that is implicated as the initial binding site of urea in urease. There has been considerable debate regarding how urea is activated in urease. Both the bridging mode (Ni(1)−O−C−N−Ni(2)) and the terminal Ni(1)−O mode have been discussed. Bridging coordination of urea to two nickel ions (in its deprotonated form) has indeed been found in a number of model complexes,[56] and in one case, it has been shown that (deprotonated) urea may bridge three Ni ions.[43,57,58] However, to our knowledge, bridging coordination of urea in its "protonated" form, as originally suggested by Ciurli and co-workers,[6,11,59] remains to be demonstrated in a model complex. Although the coordination environments found in model complexes are not identical with that of the urease enzyme, the results obtained from model chemistry suggest that the first step in the hydrolysis of urea by urease is coordination of the urea carbonyl oxygen to Ni(1). This is in agreement with recent computational modeling of the urease mechanism.[60,61]

The model complexes described here have been demonstrated to exhibit hydrolytic activity, viz. hydrolysis/transesterification of HPNP. The retardation of hydrolytic activity in $[Ni_2(BCIMP)(Ph_2Ac)_2]^-$ (**7**) relative to that of $[Ni_4(ICIMP)_2(Ph_2Ac)_2][ClO_4]_2$ (**15**) emphasizes the importance of a vacant coordination site at one nickel ion; a vacant or solvated coordination site is believed to be available in aqueous solutions of **15**, where the tetranuclear complex appears to dissociate into dinickel units. This has been shown by the selective coordination of urea (compound **17**) and the inhibition of the hydrolytic activity in compound **7**, in which the free coordination site has been blocked. It has also been shown that the complexes exhibit hydrolytic activity (with respect to HPNP) even though a bridging hydroxy group is absent, i.e., replaced by a phenolate group.

Experimental Section

Materials. Glycine ethyl ester hydrochloride, 2,6-bis(hydroxylmethyl)-4-methylphenol, and 1-methylimidazole were obtained from Sigma-Aldrich and used as received. Preparation of 2-(chlorometh-

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yl)-6-carbaldehyde-4-methylphenol from 2-(hydroxymethyl)-6-carbaldehyde-4-methylphenol (**9**; vide infra) was done according to a previously published method.[51] Ether and THF were dried using Na/benzophenone and distilled under nitrogen. Methanol was dried over CaH_2 and distilled. Dimethyl formamide (DMF) was dried over molecular sieves.

Physical Measurements. The electronic spectra and kinetic measurements were recorded on a Varian 300 Bio UV/vis spectrophotometer. Infrared spectra were collected on solid KBr disks on Nicolet 20SXR and Biorad FTS 6000 FT-IR spectrometers; residual water (from solvents) could be detected in some samples. NMR data were recorded on a Varian Unity 300 MHz spectrometer. Fast atom bombardment (FAB+) and high-resolution mass spectra were measured on a JEOL SX-102 instrument, while a LCQ Finnigan-Thermoquest was used for electron spray ionization (ESI) mass spectrum. The magnetic measurements were made on a Quantum Design MPMS 5 SQUID magnetometer.

Synthesis of BCIMP. 2,6-Bis(chloromethyl)-4-methylphenol (1). This procedure has been adapted and modified from a previously published synthetic method.[62] A dry round-bottomed flask was charged with 2,6-bis(hydroxymethyl)-4-methylphenol (16.8 g, 0.10 mol) and ether (300 mL). Thionyl chloride (24.0 g, 0.20 mol) was added dropwise to the stirring mixture. The stirring was continued for 1.5 h, and the solvent was evaporated. The product was recrystallized from 1:1 ether/*n*-hexane yielding 7.75 g (37.7%) of **2**. ^{1}H NMR ($CDCl_3$) [δ (ppm)]: 2.27 (s, 3H), 4.65 (s, 4H), 5.52 (bs, 1H), 7.08 (bs, 2H).

1-Methylimidazole-2-carbaldehyde (2). This procedure has been adapted and modified from a previously published synthetic method.[63] A dry round-bottomed flask was charged with 1-methylimidazole (28.7 g, 0.350 mol) and 350 mL of THF. The solution was cooled to −40 °C, and 165 mL of a 2.3 M hexane solution of butyllithium (0.385 mol) was added dropwise for a period of 1 h. This gave an orange solution, which was stirred for 1 h at −40 °C. Next, DMF (28 g, 0.388 mol) was added dropwise and a white solid precipitated. Water (300 mL) was added to quench the reaction, and the THF phase was removed and saved. The water phase was washed with chloroform, and the organic phases were combined, dried over $MgSO_4$, filtered, and evaporated to give 40.6 g of crude product. The product was purified by distillation (2.5 Torr, 76−80 °C) to yield 12.5 g (32.3%) of **2**. ^{1}H NMR (DMSO-d_6) [δ (ppm)]: 3.95 (s, 3H), 7.26 (s, 1H), 7.59 (s, 1H), 9.70 (s, 1H) (cf. ref 63).

***N*-(Ethoxycarbonylmethyl)-*N*-((1-methylimidazol)methyl)-amine (3).** (19.5 g, 0.14 mol) was dissolved in methanol (150 mL) and acetic acid (4.2 g, 0.07 mol) in a round-bottomed flask. To the stirred solution was added molten **2** (7.7 g, 0.07 mol) dropwise. The solution became darker and was stirred for about 10 min. Neat sodium cyanoborohydride (4.4 g, 0.07 mol) was slowly added, which gave rise to a gas and heat evolution. A white precipitate resulted, and the suspension was stirred overnight. Concentrated HCl was used to attain a pH of 2, and gas evolution was seen. The pH was then made basic using NaOH(aq). The methanolic solvent was removed, and the white residue was redissolved in water. Extraction from the water phase was made with dichloromethane. The organic phases were combined, dried over $MgSO_4$, filtered, and evaporated to give 11 g of crude product. Kugelrohr distillation yielded 6.67 g (48.9%) of **3**. ^{1}H NMR ($CDCl_3$) [δ (ppm)]: 1.22 (t, 3H), 2.47 (bs, 1H), 3.38 (s, 2H), 3.65 (s, 3H), 3.85 (s, 2H), 4.13 (q, 2H), 6.79 (s, 1H), 6.87 (s, 1H). HRMS: 198.1243 (calcd exact mass MH^+ 198.1240).

2,6-Bis[*N*-(*N*-(ethoxycarbonylmethyl)-*N*-((1-methylimidazol)-methyl)amine) methyl]-4-methylphenol (4). A round-bottomed flask was charged with **3** under nitrogen (4.34 g, 0.22 mol), methanol (70 mL), and triethylamine (3.1 mL) and cooled to −25 °C in an acetone/dry ice bath. A methanol solution (45 mL) of **1** (2.26 g, 0.11 mol) was added using an addition funnel. The resulting mixture was stirred for 30 min before returning to room temperature. Next, the reaction mixture was heated on an oil bath to reflux. After 30 min, the oil bath was removed and the solution was stirred overnight. The solvent was then evaporated, and the residue was redissolved in chloroform. An equivalent volume of water was added, and the mixture was extracted with chloroform three times. The organic phases were combined, dried over $MgSO_4$, filtered, and evaporated to give a brownish oil. The crude product was purified by flash chromatography using 5:4:1 dichloromethane/heptane/triethylamine yielding 4.4 g (76.0%) of **4**. ^{1}H NMR ($CDCl_3$) [δ (ppm)]: 1.23 (t, 6H), 2.20 (s, 3H), 3.33 (s, 4H), 3.57 (s, 6H), 3.74 (s, 4H), 3.80 (s, 4H), 4.12 (q, 4H), 6.79 (s, 2H), 6.89 (s, 4H), 9.63 (bs, 1H). HRMS 527.2986 (calcd exact mass MH^+ 527.2982).

2,6-Bis[*N*-(*N*-(carboxylmethyl)-*N*-((1-methylimidazol)methyl)-amine)methyl]-4-methylphenolate, Trisodium Salt (Na_3BCIMP) (5). A round-bottomed flask was charged with NaOH (6.0 g, 0.15 mol) and ethanol (125 mL). Separately, **4** (3.95 g; 7.5 mmol) was dissolved in ethanol (60 mL) and added dropwise through an addition funnel. A fine white precipitate rapidly formed, yielding a milky suspension. After the mixture was stirred overnight, the precipitate was filtered off, washed with ethanol, and dried under high vacuum, giving 2.7 g (67%) of **5**. ^{1}H NMR (CD_3OD) [δ (ppm)]: 2.17 (s, 3H), 3.01 (s, 4H), 3.47 (s, 6H), 3.57 (s, 4H), 3.59 (s, 4H), 6.57 (s, 2H), 6.84 (s, 2H), 6.86 (s, 2H). FAB-MS [*m*/*z* (rel intensity, %)]: 559 (Na_4BCIMP, 10), 537 (Na_3HBCIMP, 25), 515 (Na_2H_2BCIMP, 20). HRMS: 559.1649 (calcd exact mass NaM^+ 559.1634), 537.1820 (calcd exact mass MH^+ 537.1814). IR (KBr disk): 3381 (m, br), 3127 (m), 3104 (m), 2974 (m), 2911 (m), 2864 (m), 2809 (m), 2712 (w), 1605 (s, br), 1527 (w), 1472 (s, br), 1411 (s, br), 1335 (s), 1253 (m), 1110 (m), 1011 (m), 919 (m), 862 (s), 811 (w), 799 (w), 785 (w), 759 (m), 735 (m), 695 (w), 680 (w), 653 (w), 624 (w), 611 (w), 580 (w), 557 cm^{-1} (w). UV/vis (MeCN/H_2O): 286 nm.

Synthesis of Complexes. $[Ni_2(BCIMP)Ac_2]^-$ (6). Compound **5** (67 mg, 0.125 mmol) was dissolved in methanol (2 mL) in a small vial. Separately, nickel(II) perchlorate hexahydrate (91 mg, 0.25 mmol) was dissolved in a small volume of methanol and slowly added to the ligand solution yielding a turquoise solution. Sodium acetate (21 mg, 0.25 mmol) and sodium bromide (13 mg, 0.125 mmol) were also dissolved in methanol and added. The complex was precipitated with diethyl ether, filtered off, and dried to yield 102 mg (98%) of product (**13**). FAB-MS [*m*/*z* (rel intensity, %)]: 665 (Na[Ni_2BCIMP(Ac)], 100). HRMS: 665.0784 (calcd exact mass Na[Ni_2BCIMP(Ac)] 665.0780). IR (KBr disk): 3420 (s, br), 3128 (w), 3000 (w), 2927 (m), 2856 (w), 2025 (w), 1583 (s, br), 1510 (m), 1478 (m), 1416 (m, br), 1347 (w), 1319 (m), 1281 (m), 1095 (s, br), 1020 (w), 955 (w), 924 (w), 881 (w), 809 (w), 739 (w), 666 (m), 626 (m), 500 cm^{-1} (w). UV/vis (MeCN): 634 (br), 307 (m), 254 nm (sh). The above-mentioned solution was also left separately to evaporate to yield small turquoise crystals of $Na_{1.5}$-[Ni_2(BCIMP)Ac_2]$Br_{0.5}$·MeOH·0.75H_2O suitable for X-ray crystallography.

$[Ni_2(BCIMP)(Ph_2Ac)_2]^-$ (7). **5** (67 mg, 0.125 mmol) was dissolved in methanol (1.5 mL) in a small vial. Separately, nickel(II) perchlorate hexahydrate (91 mg, 0.25 mmol) was dissolved in

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a small volume of methanol and slowly added to the ligand solution yielding a turquoise solution. Diphenylacetic acid (53 mg, 0.25 mmol) and sodium methoxide (14 mg, 0.25 mmol) were also dissolved in methanol and added. The complex was precipitated with diethyl ether, filtered out, and dried to yield 94 mg (94%) of product (**14**). FAB-MS [*m*/*z* (rel intensity, %)]: 1051 (Na_2-[Ni_2(BCIMP)(Ph_2Ac)$_2$], 8), 817 (Na[Ni_2(BCIMP)(Ph_2Ac)], 80). HRMS: 1051.2060 (calcd exact mass $Na_2M(Ph_2Ac)$ 1051.2063), 817.1407 (calcd exact mass NaM 817.1406). IR (KBr disk): 3410 (s, br), 3060 (w), 3027 (w), 2925 (w), 2855 (w), 2363 (m), 2337 (w), 1594 (s, br), 1509 (m), 1477 (m), 1452 (w), 1387 (s), 1319 (m), 1285 (m), 1100 (s, br), 954 (w), 924 (w), 882 (w), 809 (w), 798 (w), 749 (m), 705 (m), 680 (w), 624 (m), 591 (w), 499 cm^{-1} (w). UV/vis (MeCN): 639 (br), 305 (m), 254 nm (sh).

Synthesis of ICIMP. *N*-Isopropyl-*N*-((1-methylimidazol)-methyl)amine (8). Isopropylamine (12.0 g, 0.20 mol), acetic acid (6 g, 0.1 mol), and methanol (150 mL) were put in a round-bottomed flask and cooled to 7 °C under a nitrogen atmosphere. Compound **2** (10.5 g, 0.095 mol) was dissolved in the reaction mixture and the resulting mixture stirred, whereafter sodium cyanoborohydride (6.3 g, 0.10 mol) was added. The cooling bath was removed, and the mixture was stirred overnight. Concentrated HCl was used to attain a pH of 2. After the gas evolution had stopped, the pH was made basic using a methanolic solution of NaOH. The solution was filtered, and the solvent was removed from the filtrate yielding a white residue, which was extracted with dichloromethane three times. The combined dichloromethane fractions were evaporated and kugelrohr distillation yielded 10.6 g (73.6%) of **8**. ^{1}H NMR ($CDCl_3$) [δ (ppm)]: 1.07 (d, 6H), 2.83 (m, 1H), 3.63 (s, 3H), 3.80 (s, 2H), 6.78 (s, 1H), 6.89 (s, 1H). HRMS: 154.1353 (calcd exact mass MH^+ 154.1344).

2-(Hydroxymethyl)-6-carbaldehyde-4-methylphenol (9). This procedure has been adapted and modified from a previously published synthetic method.[64] A large round-bottomed flask was charged with 2,6-bis(hydroxymethyl)-4-methylphenol (25.0 g, 0.15 mol), manganese dioxide (80.0 g, 0.92 mol), and chloroform (4 L). After 48 h, the reaction mixture was filtered and evaporated to give 24 g of crude product. Eluation with ethyl acetate through a short silica column gave 14.4 g (58.3%) of **9**. ^{1}H NMR ($CDCl_3$) [δ (ppm)]: 2.33 (s, 3H), 4.72 (s, 2H), 7.28 (s, 1H), 7.39 (s, 1H), 9.85 (s, 1H), 11.16 (s, 1H).

2-(*N*-isopropyl-*N*-((1-methylimidazol)methyl)aminomethyl)-6-carbaldehyde-4-methylphenol (10). Compound **8** (5.66 g, 0.037 mol) and triethylamine (11.2 g, 0.11 mol) were dissolved in THF (150 mL). A THF solution (20 mL) of 2-(chloromethyl)-6-carbaldehyde-4-methylphenol[51] (6.83 g, 0.037 mol) was added, and a white precipitate was observed. After the reaction mixture was stirred overnight, it was filtered and the filtrate was evaporated. Flash chromotography (1:2 ethyl acetate/dichloromethane) and recrystallization was used to yield 9.0 g (81%) of **10**. ^{1}H NMR ($CDCl_3$) [δ (ppm)]: 1.12 (d, 6H), 2.24 (s, 3H), 3.09 (m, 1H), 3.57 (s, 3H), 3.68 (s, 2H), 3.74 (s, 2H), 6.78 (s, 1H), 6.92 (s, 1H), 7.08 (s, 1H), 7.35 (s, 1H), 10.23 (s, 1H). HRMS: 302.1867 (calcd exact mass MH^+ 302.1868).

2-(*N*-isopropyl-*N*-((1-methylimidazol)methyl)aminomethyl)-6-hydroxymethyl-4-methylphenol (11). Compound **10** (9.0 g, 0.030 mol) was dissolved in methanol (100 mL) and treated with sodium borohydride (5.4 g, 0.14 mol). Bleaching of the mixture along with gas and heat evolution was observed. The mixture was stirred for 15 min at room temperature and then refluxed for 30 min. It was acidified to pH 2 using HCl and filtered, and the filtrate was evaporated. The residue was redissolved in saturated $NaHCO_3$-(aq) and extracted with dichlorometane. The organic phase was evaporated and the product washed with hexane and dried to yield 9.0 g (99%) of **11**. ^{1}H NMR ($CDCl_3$) [δ (ppm)]: 1.13 (d, 6H), 2.21 (s, 3H), 3.18 (m, 1H), 3.58 (s, 3H), 3.68 (s, 2H), 3.76 (s, 2H), 4.63 (s, 2H), 6.74 (s, 1H), 6.81 (s, 1H), 6.91 (s, 1H), 6.95 (s, 1H). HRMS: 304.2016 (calcd exact mass MH^+ 304.2025).

2-(*N*-isopropyl-*N*-((1-methylimidazol)methyl)aminomethyl)-6-(*N*-(ethoxycarbonylmethyl)-*N*-((1-methylimidazol)methyl)aminomethyl)-4-methylphenol (12). Compound 11 (9.0 g, 0.030 mol) was dissolved in 20 mL of $SOCl_2$, and the mixture was stirred for 1 h. The remaining solvent was removed under reduced pressure, and the residue was washed with hexane and dichloromethane and then dried under reduced pressure. The crude product (13.6 g) was dissolved in methanol (50 mL) and added dropwise to a solution containing 3 (5.89 g, 0.030 mol), triethylamine (20 mL), and methanol (150 mL). After complete addition, the mixture was refluxed for 1 h and the solvent was removed by evaporation. The residue was washed with phosphate buffer (pH 7, 0.1 M) and extracted with dichloromethane several times. The organic phases were combined, dried, and evaporated. The remaining solid was dissolved in THF, and the solution was filtered and evaporated again. The product was further purified by flash chromotography (4:4:1 hexane/dichloromethane/triethylamine) to yield 7.18 g (50%) of 12 as a light yellow oil. ^{1}H NMR ($CDCl_3$) [δ (ppm)]: 1.09 (d, 6H), 1.22 (t, 3H), 2.19 (s, 3H), 3.04 (m, 1H), 3.31 (s, 2H), 3.54 (s, 2H), 3.59 (s, 2H), 3.66 (s, 3H), 3.70 (s,2H), 3.80 (s, 2H), 4.11 (d, 2H), 6.78 (m, 3H), 6.88 (m, 3H). HRMS: 483.3091 (calcd exact mass MH^+ 483.3084).

2-(*N*-isopropyl-*N*-((1-methylimidazol)methyl)aminomethyl)-6-(*N*-(carboxylmethyl)-*N*-((1-methylimidazol)methyl)aminomethyl)-4-methylphenol (H_2ICIMP) (13). Compound 12 (6.5 g, 0.013 mol) was dissolved in ethanol (50 mL) and NaOH (2.5 g, 0.063 mol). The mixture was refluxed for 12 h and then evaporated to dryness. The remaining solid was dissolved in water and acidified with concentrated HCl until pH 7.5 was achieved. The mixture was treated with active coal, filtered, and evaporated to dryness. The residue was extracted with chloroform, filtered, dried, filtered again, and evaporated to give 5.8 g (98%) of 13, a glassy solid. ^{1}H NMR ($CDCl_3$) [δ (ppm)]: 1.14 (d, 6H, *i*-Pr), 2.19 (s, 3H, phenol−Me), 3.07 (m, 1H, *i*-Pr), 3.33 (s, 2H, CH_2CO_2), 3.41 (s, 3H, CH_3Im*i*Pr), 3.63 (s, 3H, CH_3Im-CO_2), 3.74 (bs, 4H, CH_2Ph), 3.82 (s, 2H, ImCH_2*i*Pr), 3.84 (s, 2H, ImCH_2CO_2), 6.80 (s, 1H, ImH-*i*Pr), 6.81 (s, 1H, ImHCO_2), 6.84 (d, 1H, ImHCO_2), 6.89 (s, 1H, ImH*i*Pr), 6.93 (s, 1H, Ph), 6.99 (s, 1H, Ph). IR (KBr disk): 3136 (m), 3109 (m), 2965 (s), 2934 (m), 2869 (m), 2828 (m), 1955 (m, br), 1711 (w), 1613 (s), 1533 (m), 1500 (w), 1481 (s), 1388 (m), 1366 (m), 1321 (w), 1283 (m), 1221 (m), 1047 (m), 862 (m), 751 cm^{-1} (s). UV/vis (MeCN): 288 nm.

Na[Ni_2(ICIMP)(Ph_2Ac)$_2$]ClO_4 (14). Nickel(II) perchlorate hexahydrate (110 mg, 0.30 mmol) was dissolved in dry ethanol (5 mL) in a round-bottomed flask. Separately, H_2ICIMP (68 mg, 0.15 mmol), diphenylacetic acid (255 mg, 1.20 mmol), and sodium methoxide (49 mg, 1.50 mmol) were added to another flask and dissolved in dry ethanol (5 mL) by heating. The ligand mixture was then added to the nickel complex to yield a green solution. The solution was stirred overnight, and a greenish precipitate was formed, which was filtered off, washed in ethanol, and dried. This yielded 80 mg (53%) of **14**. FAB-MS [*m*/*z* (rel intensity, %)]: 1013 (Na[Ni_2(ICIMP)(Ph_2Ac)$_2$], 70), 779 (Ni_2(ICIMP)(Ph_2Ac), 100). IR (KBr disk): 3404 (s, br), 3061 (w), 3027 (m), 2929 (w), 1599 (s, br), 1512 (m), 1494 (w), 1481 (m), 1451 (m), 1388 (s, br), 1316

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(m), 1285 (m), 1156 (w), 1093 (s, br), 1032 (w), 964 (w), 923 (w), 876 (w), 813 (m), 745 (s), 702 (s), 648 (m), 623 (m), 503 cm^{-1} (w). UV/vis (MeCN): 676 (br), 376 (sh), 304 (m), 247 nm (sh).

$[Ni_4(ICIMP)_2(Ph_2Ac)_2][ClO_4]_2$ (15). Nickel(II) perchlorate hexahydrate (219 mg, 0.60 mmol) was dissolved in dry ethanol (5 mL) in a round-bottomed flask. Separately, H_2ICIMP (136 mg, 0.30 mmol), diphenylacetic acid (127 mg, 0.60 mmol), and sodium methoxide (65 mg, 1.20 mmol) were added to another flask and dissolved in dry ethanol (5 mL) by heating. The ligand mixture was then added to the nickel complex to yield a green solution. The solution was stirred overnight, and a blue-greenish precipitate was formed, which was filtered off, washed in ethanol, and dried. This yielded 120 mg (45%) of **15**. FAB-MS [*m*/*z* (rel intensity, %)]: 1661 ($Ni_4(ICIMP)_2(Ph_2Ac)_2ClO_4$, 30), 779 ($Ni_2(ICIMP)(Ph_2Ac)$, 100). ES-MS [*m*/*z* (rel intensity, %)]: 1662.1 ($Ni_4(ICIMP)_2(Ph_2Ac)_2ClO_4$, 40), 779.3 ($Ni_2(ICIMP)(Ph_2Ac)$, 100). IR (KBr disk): 3443 (s, br), 3123 (w), 2971 (w), 2933 (m), 1609 (s), 1517 (m), 1479 (m), 1450 (w), 1395 (s), 1315 (m), 1285 (m), 1100 (s), 927 (w), 871 (m), 806 (m), 740 (m), 723 (m), 706 (m), 682 (w), 650 (w), 624 (m), 600 (w), 501 cm^{-1} (w). UV/vis (MeCN): 641 (br), 368 (sh), 302 nm (m).

X-ray-quality crystals of $[Ni_4(ICIMP)_2(Ph_2Ac)_2(DMF)_2][ClO_4]_2 \cdot 2.5DMF$ (16) were grown by slow diffusion of *tert*-butyl methyl ether into a DMF solution of **15**. FAB-MS [*m*/*z* (rel intensity, %)]: 1662 ($Ni_4(ICIMP)_2(Ph_2Ac)_2ClO_4$, 40), 779 ($Ni_2(ICIMP)(Ph_2Ac)$, 100). Anal. Calcd for $C_{89.5}H_{117.5}Cl_2N_{16.5}Ni_4O_{22.5}$: C, 51.43; H, 5.67; N, 11.06. Found: C, 51.13; H, 5.22; N, 10.22. IR (KBr disk): 3448 (s, br), 3125 (m), 3062 (w), 3027 (m), 2967 (s), 2935 (s), 1659 (s), 1635 (s), 1606 (s), 1517 (w), 1480 (m), 1391 (s), 1313 (m), 1285 (m), 1273 (w), 1257 (w), 1156 (w), 1098 (s), 1022 (w), 953 (m), 934 (w), 870 (m), 806 (w), 755 (m), 681 (m), 624 (m), 599 (w), 559 (w), 501 (w), 458 (w). UV/vis (MeCN) 640 (br), 376, 302 cm^{-1} (m).

$[Ni_4(ICIMP)_2(Ph_2Ac)_2(urea)(H_2O)][ClO_4]_2 \cdot 0.5EtOH \cdot H_2O$ (17). Synthesis of **17** was performed according to the procedure for compound **15** above. After precipitation and filtration of the product, the mother liquor was treated with urea (11 mg, 0.18 mol) dissolved in 2 mL of methanol and set aside to crystallize in a closed vial. After 3 weeks, blue X-ray grade crystals of **17** appeared (6 mg, 4.3%). FAB-MS [*m*/*z* (rel intensity, %)]: 1662 ($Ni_4(ICIMP)_2(Ph_2Ac)_2ClO_4$, 30), 779 ($Ni_2(ICIMP)(Ph_2Ac)$, 100). Anal. Calcd for $C_{78}H_{97}Cl_2N_{14}Ni_4O_{21.5}$: C, 49.82; H, 5.20; N, 10.43. Found: C, 49.36; H, 5.22; N, 9.46.

X-ray Structure Determinations. The X-ray diffraction data were collected with a Nonius Kappa CCD diffractometer using Mo Kα radiation ($\lambda = 0.710\,73$ Å). Single crystals of **6**, **16**, and **17** were mounted in inert oil under the cold gas stream of the diffractometer. Slight disorder appeared in all structures. In **6** the bromide anion was found in two alternative positions with population ratio of 0.666:0.333, and in **16** the oxygen atoms of one of the counteranions, ClO_4^- (O(20), O(21), and O(22)), were disordered in two positions with an occupation parameter ratio of ca. 0.6:0.4. In **17** the oxygen atoms around the Cl atoms in both ClO_4^- units were disordered. The detailed crystallographic parameters of **6** are displayed in Table 1. The parameters for structures **16** and **17** have been published previously.[26]

Magnetic Measurements. The magnetic susceptibility of the compound was measured over the temperature range 5−300 K at four fields 0.5, 1, 2.5, and 5 T. The sample (5.86 mg) was contained in a kel F bucket which had been independently calibrated at the same fields and temperatures. The data were corrected from diamagnetism using Pascal's constants.[65] The data obtained under the four fields have been fitted simultaneously by the classical MINUIT program for the fitting part and an exact full matrix diagonalization taking into account both *J* and *D* parameters, for the magnetic susceptibility calculation part.[66]

Kinetic Measurements. The kinetic studies were performed in 3 mL UV cells in 1:1 H_2O/MeCN solution. The solution was buffered using HEPES or CHES buffers (0.01 M total concentrated). The ionic strength was maintained at 0.1 by addition of sodium perchlorate (0.1 M). Dissolved complexes were added to a total concentration of 0.25 mM of dinuclear complex, and 2-hydroxypropyl *p*-nitrophenyl phosphate (HPNP, 0.82 mM) was used as substrate. All the ingredients were mixed in a thermostatic cell (25 °C), and the visual spectrum was recorded at 400 nm, where the extinction coefficient for the hydrolysis product *p*-nitrophenolate is 18 500 M^{-1} cm^{-1}. The data were plotted, and the linear slope was used to deduce the initial rates. The total amount of *p*-nitrophenol/phenolate was determined by using the pK_a (7.15).[34] Mass spectrometry was used at pH 7 to determine the identity of the catalyst during catalytic conditions. The result was peaks at *m*/*e* 1013 and 779 indicating that the active catalyst is dinuclear (cf. compound **15**). The mass peaks attributable to the corresponding Ni_4 complex are present up to the addition of water and substrate but then rapidly disappears (faster than the reaction mixture can be subjected to MS sampling).

DFT Calculations. The density functional calculations were performed with the Amsterdam Density Functional (ADF) program version 2003.01[67−71] using a triple-ζ STO basis set. The implementation of the local density approximation (LDA) uses the standard Slater exchange term[72] and the correlation term due to Vosko, Wilk, and Nusair.[73] Total energies were calculated using Becke's 1988[74] and Perdew's 1986[75] gradient corrected functionals for exchange and correlation, respectively. The experimental X-ray structure was divided into two dimers, replacing the neighboring ligand contributions with acetate residues at the same positions. The energies were determined using single point calculations.

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Supporting Information Available: X-ray crystallographic data in CIF and PDF formats. This material is available free of charge via the Internet at http://pubs.acs.org.

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