A Square-Planar Nickel(III) Complex of an Innocent Ligand System

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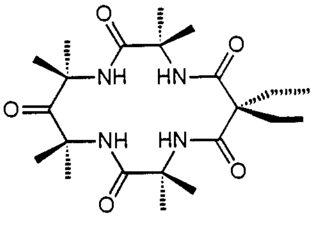
Recently, high valent nickel chemistry[2] has attracted increased attention as it has become clear that the III oxidation state is biologically significant.[3] High valent nickel species may also be intermediates in newly discovered catalytic oxidations[4] and in the nickel-mediated sequence-specific oxidative cleavage of DNA by designed metalloproteins.[5] Here, we report the synthesis, first structural characterization, and spectroscopic properties of a four-coordinate nickel(III) complex of an innocent ligand system, $[Et_4N][Ni(\eta^4\text{-}\mathbf{1})]$. EPR spectroscopy has been of special significance to the study of enzymatic systems containing nickel(III).[3] While the currently accepted EPR signature for square-planar Ni(III) is an axial spectrum with $g_\parallel > g_\perp$,[3,6] we present evidence indicating that $[Ni(\eta^4\text{-}\mathbf{1})]^-$ is a distorted square planar Ni(III) complex with $g_\perp > g_\parallel$. Low-potential Ni(III) is found in nickel hydrogenases,[7] and it is interesting to note that the innocent abiological ligand complement employed here can also produce highly stabilized nickel(III); the Ni(III)/Ni(II) couple of $Ni(\eta^4\text{-}\mathbf{1})]^-$ occurs at −0.58 V vs Fc^+/Fc (CH_2Cl_2, 0.1 M $[Bu_4N][ClO_4]$ supporting electrolyte, 0.13 V vs NHE).[7c]



$H_4\mathbf{1}$

The complex was synthesized as follows: $H_4[\mathbf{1}]$[8] (0.100 g, 0.23 mmol) was dissolved in dry deoxygenated THF (20 mL) under N_2 at room temperature, and $Li[(Me_3Si)_2N]$ in THF (1.0 mL, 1.0 M) was added. Dry $(Ph_3P)_2NiBr_2$ (0.180 g, 0.24 mmol) was added under N_2. After stirring (5 min), THF removal, and CH_2Cl_2 washing, the pale orange nickel(II) product was dissolved in absolute ethanol (50 mL) and oxidized with benzoyl peroxide (50 mg) (stirring for 30 min). $[Et_4N][F]$ (40 mg) was added, the ethanol was removed, and the excess peroxide was washed from the residue with benzene. The deep purple $[Et_4N][Ni(\eta^4\text{-}\mathbf{1})]$ was dissolved in CH_2Cl_2 (15 mL), and LiF, LiBr, and excess $[Et_4N][F]$ were removed by filtration. Large purple crystals suitable for X-ray analysis (Figure 1)[9] were obtained by diffusion of pentane into a 1,2-dichloroethane solution (30% yield starting from ligand).[10]

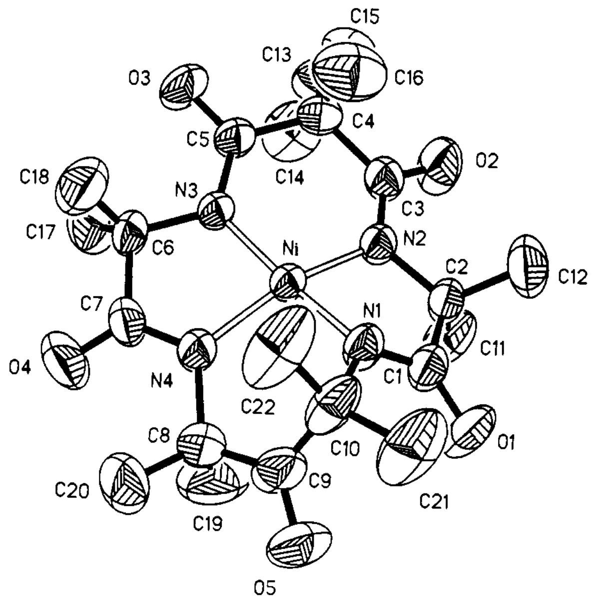


Figure 1. Molecular structure of $[Et_4N][Ni(\eta^4\text{-}\mathbf{1})]$; ORTEP drawing with all non-hydrogen atoms drawn to encompass 50% of electron density. Important bond distances (Å) and angles (deg): Ni–N1, 1.849 (3); Ni–N2, 1.825 (4); Ni–N3, 1.848 (3); Ni–N4, 1.849 (4); N1–Ni–N2, 84.4 (1); N1–Ni–N3, 170.1 (2); N1–Ni–N4, 94.9 (2); N2–Ni–N3, 97.2 (1); N2–Ni–N4, 158.6 (2); N3–Ni–N4, 87.1 (1).

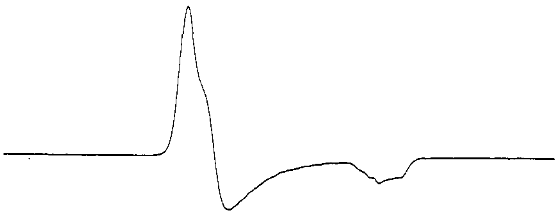


Figure 2. EPR spectra of $[Ni(\eta^4\text{-}\mathbf{1})]^-$ at 5 K, 1500 G sweep width, 3100 G midrange, 9.46 GHz, in toluene/CH_2Cl_2 (g_1 2.366; g_2, 2.303; g_3, 1.994).

The structure of $[Ni(\eta^4\text{-}\mathbf{1})]^-$ (Figure 1) is distorted square planar, since the amide nitrogen donor atoms alternate 0.25 Å above and below their mean plane and the Ni atom sits 0.09 Å above this mean plane. The average $Ni(III)-N_{sp^2}$ distance in $[Ni(\eta^4\text{-}\mathbf{1})]^-$ (1.84 Å) is considerably shorter (ca. 0.1 Å) than other Ni(III)–N distances.[11] The complex, $[Et_4N][Ni(\eta^4\text{-}\mathbf{1})]$, contains

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[2] (a) Haines, R. I.; McAuley, A. *Coord. Chem. Rev.* **1981**, *39*, 77–119. (b) Nag, K.; Chakravorty, A. *Coord. Chem. Rev.* **1980**, *33*, 87–147. (c) Lappin, G.; McAuley, A. *Adv. Inorg. Chem.* **1988**, *32*, 241–296. (d) Sacconi, L.; Mani, F.; Bencini, A. Nickel. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Guillard, R. D., McCleverty, J. A., Eds.; Pergamon Press: New York, 1987.

[3] (a) Cammack, R. *Adv. Inorg. Chem.* **1988**, *32*, 297–333. (b) *Bioinorganic Chemistry of Nickel*; Lancaster, J. R., Jr., Ed.; VCH: New York, 1988.

[4] See: Yoon, H.; Wagler, T. R.; O'Connor, K. J.; Burrows, C. J. *J. Am. Chem. Soc.* **1990**, *112*, 4568–4570 and references therein.

[5] Mack, D. P.; Dervan, P. B. *J. Am. Chem. Soc.* **1990**, *112*, 4604–4606.

[6] See, for example: (a) Lovecchio, F. V.; Gore, E. S.; Busch, D. H. *J. Am. Chem. Soc.* **1974**, *96*, 3109–3118. (b) Jacobs, S. A.; Margerum, D. W. *Inorg. Chem.* **1984**, *23*, 1195–1201. (c) Fox, S.; Wang, Y.; Silver, A.; Millar, M. *J. Am. Chem. Soc.* **1990**, *112*, 3218–3220.

[7] See, for example: (a) Cammack, R.; Fernandez, V. M.; Schneider, K. In *Bioinorganic Chemistry of Nickel*; Lancaster, J. R., Jr., Ed.; VCH: New York, 1988; Chapter 8. (b) Krüger, H.-J.; Holm, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 2955–2963. (c) Cf. Figure 9 of the following: Krüger, H.-J.; Peng, G.; Holm, R. H. *Inorg. Chem.* **1991**, *30*, 734–742 and references therein.

[8] The synthesis of $H_4[\mathbf{1}]$ is described in the supplementary material section of this report. For other papers concerning the use of $H_4[\mathbf{1}]$ and related ligands, see: (a) Collins, T. J.; Uffelman, E. S. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1509–1511. (b) Collins, T. J.; Powell, R. D.; Slebodnick, C.; Uffelman, E. S. *J. Am. Chem. Soc.* **1990**, *112*, 899–901. (c) Collins, T. J.; Kostka, K. L.; Münck, E.; Uffelman, E. S. *J. Am. Chem. Soc.* **1990**, *112*, 5637–5639. (d) Collins, T. J.; Slebodnick, C.; Uffelman, E. S. *Inorg. Chem.* **1990**, *29*, 3432–3436.

[9] Crystal data: The structure was solved by Crystalytics Company. Single crystals of $[Et_4N][Ni(\eta^4\text{-}\mathbf{1})]$ at 20 ± 1 °C are monoclinic, space group $P2_1/c\text{-}C_{2h}^5$ (No. 14) with $a = 16.173$ (2) Å, $b = 14.538$ (4) Å, $c = 15.977$ (4) Å, $\beta = 112.81$ (1)°, $V = 3462$ (1) Å^3, and $Z = 4$ ($d_{calcd} = 1.196$ g cm^{-3}; μ_a(Cu K$\bar{\alpha}$) = 1.11 mm^{-1}). A total of 5154 independent reflections having 2θ(Cu K$\bar{\alpha}$) < 120.0° (the equivalent of 0.65 limiting Cu K$\bar{\alpha}$ spheres) were collected by using θ–2θ scans and Nickel-filtered Cu K$\bar{\alpha}$ radiation. The structural parameters have been refined to a convergence of R_1 (unweighted, based on F) = 0.053 for 2849 independent reflections having $2\theta_{CuK\bar{\alpha}} < 120.0°$ and $I > 3\sigma(I)$. The four ethyl groups of the cation appear to be statistically disordered in the lattice with two alternate resolvable orientations.

[10] Anal. Calcd for $[Et_4N][Ni(\eta^4\text{-}\mathbf{1})]$, $C_{30}H_{54}N_5O_5Ni$: C, 57.79; H, 8.73; N, 11.23. Found: C, 57.92; H, 9.00; N, 11.18.

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a significantly nonplanar amido-N ligand (amide O1C1N1: $\tau = 17.3°$, $\chi_N = 28.6°$, $\chi_C = 2.9°$).[12]

The purple complex $[Ni(\eta^4\text{-}\mathbf{1})]^-$ has a low affinity for axial ligands in solution at 20 °C. Neat MeCN, pyridine, acetone, 2,5-Me_2THF, THF, CH_2Cl_2, water, and EtOH all give purple solutions.[13] In contrast, addition of cyanide results in an immediate color change from purple to yellow;[14] mole ratio plots indicate a 1:1 adduct ($K_{20°C} = 3.2\ (9) \times 10^3\ mol^{-1}$). At 77 K, frozen solutions of $[Ni(\eta^4\text{-}\mathbf{1})]^-$ in water, MeCN, 2,5-Me_2THF, THF, CH_2Cl_2, or acetone remain purple, as do CH_2Cl_2 solutions containing Cl^-, Br^-, Ph_3P, or Et_3N. In contrast, when purple solutions of $[Ni(\eta^4\text{-}\mathbf{1})]^-$ in 2,5-Me_2THF containing any one of the potential ligands ethanol, pyridine, 2,6-lutidine, or Me_3P are cooled to 77 K, pale green (EtOH, pyridine) or yellow (other ligands) glasses are obtained. These observations coupled with the solid-state information suggest that the nickel(III) anion is purple when it is four-coordinate and pale green or yellow when it is higher coordinate.

EPR studies of this system further support this color/coordination number relationship. The 4 K EPR spectrum of $[Bu_4N][Ni(\eta^4\text{-}\mathbf{1})]$ with excess CN^- is rhombic in a yellow frozen solution of CH_2Cl_2[15a] or a yellow EtOH glass.[15b] Use of $^{13}CN^-$ confirms that only one CN^- binds at 4 K.[15c] The 5 K spectrum of $[Ni(\eta^4\text{-}\mathbf{1})]^-$ in a yellow 2,5-Me_2THF/pyridine (2:1) glass is also rhombic and confirms that one pyridine is coordinated.[15d] While Margerum et al. have found that water coordinates weakly to nickel(III) complexes of tetradentate ligands containing two amido-N donors,[16] in glasses of 2,5-Me_2THF/CH_2Cl_2 or toluene/CH_2Cl_2 at 5 K, $[Ni(\eta^4\text{-}\mathbf{1})]^-$ remains purple, suggesting that axial coordination is not occurring.[17] The EPR spectra of these glasses have $g_\perp > g_\parallel$ (e.g., Figure 2). The structuring in $g_\perp$ may indicate slight rhombicity or the presence of frozen-out conformers which might contribute to the structuring in $g_\parallel$. Superhyperfine interactions are also a possible source of some of the structuring in $g_\parallel$. Saturation of the 2,5-Me_2THF/CH_2Cl_2 (1:1) or toluene/CH_2Cl_2 (2:1) aprotic solvent mixtures with $H_2{}^{16}O$ or $H_2{}^{17}O$ (45% enrichment) leads to EPR spectra that are virtually identical with those found in the glasses produced from the dried solvents. This evidence suggests that impurity water or solvent molecules are not axially bound to $[Ni(\eta^4\text{-}\mathbf{1})]^-$ in noncoordinating solvent glasses that are purple, i.e., that the EPR spectra of these purple glasses are predominantly of four-coordinate species.[18]

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Supplementary Material Available: Tables of data collection information, atom coordinates, Gaussian amplitudes, and bond lengths and angles, a listing of references to structural studies of four-coordinate nickel(III/II) complexes with noninnocent ligands where an integer oxidation state assignment is impractical, details of ligand synthesis, and EPR spectra (38 pages); listing of structure factor amplitudes (14 pages). Ordering information is given on any current masthead page.

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(11) (a) Ito, T.; Sugimoto, M.; Toriumi, K.; Ito, H. *Chem. Lett.* **1981**, 1477-1478. (b) Zeigerson, E.; Bar, I.; Bernstein, J.; Kirschenbaum, L. J.; Meyerstein, D. *Inorg. Chem.* **1982**, *21*, 73-80. (c) van der Merwe, M. J.; Boeyens, J. C. A.; Hancock, R. D. *Inorg. Chem.* **1983**, *22*, 3489-3490. (d) Grove, D. M.; van Koten, G.; Zoet, R. *J. Am. Chem. Soc.* **1983**, *105*, 1379-1380. (e) Meek, D. W.; Alyea, E. C.; Stalick, J. K.; Ibers, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 4920-4921. For a discussion of four-coordinate Ni complexes in which integer oxidation state assignments for the metal are impractical because of noninnocent ligands, see pp 121-136 of the following: McCleverty, J. A. *Prog. Inorg. Chem.* **1968**, *10*, 49-221. See also the references in the supplementary material.

(12) See: Collins, T. J.; Coots, R. J.; Furutani, T. T.; Keech, J. T.; Peake, G. T.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1986**, *108*, 5333-5339 and references therein.

(13) Electronic spectra of $[Ni(\eta^4\text{-}\mathbf{1})]^-$ (values in parentheses are molar absorptivities in $M^{-1}\ cm^{-1}$): CH_2Cl_2, 380 nm (5.48×10^3), 532 nm (3.62×10^3), 650 nm (2.33×10^3), 808 nm (4.18×10^3); CH_3CN/CH_2Cl_2 (9:1), 380 nm (5.45×10^3), 530 nm (3.59×10^3), 650 nm (2.26×10^3), 806 nm (3.98×10^3); pyridine, 380 nm (4.76×10^3), 534 nm (3.10×10^3), 647 nm (1.90×10^3), 817 nm (3.30×10^3); EtOH, 376 nm (4.79×10^3), 525 nm (3.00×10^3), ≈660 nm (shoulder) (2×10^3), 794 nm (3.78×10^3); H_2O, 372 nm (2.7×10^3), 519 nm (1.7×10^3), 767 nm (2.4×10^3).

(14) The electronic spectrum of $[Ni(\eta^4\text{-}\mathbf{1})]^-$ with excess CN^- in CH_2Cl_2 is a featureless curve, tailing into the visible region from just above the UV cutoff of the solvent, and there is essentially zero absorbance above 450 nm.

(15) EPR spectra of $[Ni(\eta^4\text{-}\mathbf{1})]^-$ (4-6 K, 9.46 GHz): (a) excess $[Bu_4N][CN]$ in CH_2Cl_2 (g_1, 2.234; g_2, 2.159; g_3, 2.019); (b) excess KCN in EtOH (g_1, 2.223; g_2, 2.144; g_3, 2.010); (c) excess $K^{13}CN$ in EtOH (g values same as in b; a_1, 89 G; a_2, 83 G; a_3, 100 G); (d) in 2,5-Me_2THF/pyridine (2:1) (g_1, 2.380; g_2, 2.269; g_3, 1.994; superhyperfine on g_3 only, a_3, 25 G).

(16) Margerum, D. W.; Anliker, S. L. In *Bioinorganic Chemistry of Nickel*; Lancaster, J. R., Jr., Ed.; VCH: New York, 1988; Chapter 2.

(17) All solvents, except 2,5-Me_2THF, Aldrich Sureseal (anhydrous); EPR tubes vacuum dried, charged and sealed under an inert atmosphere.

(18) It is of interest to note that the EPR spectrum of $[Ni(\eta^4\text{-}\mathbf{1})]^-$ at 4 K in 2,5-Me_2THF/2,6-lutidine (ca. 2:1) can be interpreted as resulting from a mixture of $[Ni(\eta^4\text{-}\mathbf{1})]^-$ and the five-coordinate complex of the sterically hindered 2,6-lutidine ligand (g_1 and g_2 obscured by g_1 and g_2 of $[Ni(\eta^4\text{-}\mathbf{1})]^-$; g_3, 1.997; superhyperfine on g_3 only, a_3, 25 G). The spectrum of $[Ni(\eta^4\text{-}\mathbf{1})]^-$ in an absolute ethanol glass at 6 K is markedly different from Figure 2, although several features may be interpreted as arising from residual amounts of four-coordinate $[Ni(\eta^4\text{-}\mathbf{1})]^-$ (see supplementary material).

Varacin: A Novel Benzopentathiepin from *Lissoclinum vareau* That Is Cytotoxic toward a Human Colon Tumor

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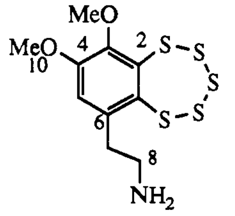
Ascidians of the genus *Lissoclinum* have been an exceptional source of interesting and often biologically active natural products. *Lissoclinum patella* has yielded cytotoxic cyclic peptides,[4] cytotoxic and antiviral polypropionate-derived macrocycles,[5] and a polyketide lactone.[6] *Lissoclinum vareau*, a lavender-colored encrusting species collected in the Fiji Islands, is the source of the recently reported bright red heteroaromatic pigments varamine A and varamine B.[7] We now report the benzopentathiepin varacin (**1**), a novel *L. vareau* metabolite that exhibits potent antifungal activity against *Candida albicans* (14-mm zone of inhibition of 2 μg of varacin/disk) and cytotoxicity toward the human colon cancer HCT 116 with an IC_{90} of 0.05 μg/mL, 100 times the activity of 5-fluorouracil (5-FU) in this assay. Varacin also exhibited a 1.5 differential toxicity toward the CHO cell line EM9 (chlorodeoxyuridine sensitive) versus BR1 (BCNU resistant), providing preliminary evidence that varacin damages DNA.



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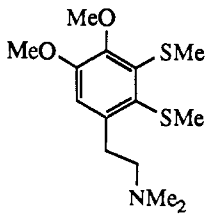

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