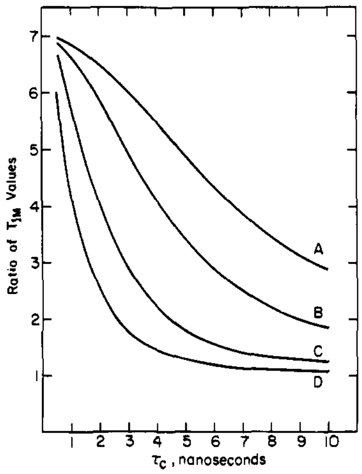

Figure 1. Determination of the correlation time (τ_c) for the dipolar interaction of enzyme-Mn^{2+} from the ratio of T_{1M} for $^6Li^+$ and $^7Li^+$ at various magnetic field strengths; (A) 14 kG, (B) 23 kG, (C) 47 kG, (D) 85 kG.

for both ions. It is assumed that τ_c is the same for both ions. Shown in Figure 1 is a theoretical plot of the ratio of T_{1M} values for $^6Li^+$ and $^7Li^+$ at various magnetic field strengths vs. a range of correlation times commonly found in enzyme–Mn^{2+} complexes. Examination of the figure shows that this method is very sensitive for the determination of τ_c values of $<10^{-8}$ s since in this range the T_{1M} values for $^6Li^+$ and $^7Li^+$ are quite different. Similar plots can also be constructed for the two isotopes of NH_4^+ (^{15}N and ^{14}N) and Rb^+ (^{87}Rb and ^{85}Rb).

We have measured the T_{1p} values for both $^6Li^+$ and $^7Li^+$ in the pyruvate kinase–Mn^{2+}–phospho(enol)pyruvate–Li^+ complex at a magnetic field strength of 47 kG (29.45 MHz for ^6Li, 77.77 MHz for ^7Li) by using a multinuclear Brüker WP-200 NMR spectrometer.[5] The T_{1p} values were calculated by using eq 2,

$$f(1/T_{1p}) = 1/T_{1(\mathrm{Mn})} - 1/T_{1(\mathrm{Mg})} \qquad (2)$$

where $T_{1(\mathrm{Mn})}$ and $T_{1(\mathrm{Mg})}$ are observed spin-lattice relaxation times[6] in the presence of either Mn^{2+} or Mg^{2+} bound to the enzyme, and f is the mole fraction of enzyme-bound Li^+. The observed $1/T_{1p}$ values at 30 °C for the enzyme complexes with $^7Li^+$ and $^6Li^+$ are $(3.2 \pm 0.3) \times 10^3$ and $(1.3 \pm 0.1) \times 10^3$ s^{-1}, respectively.[7] The ratio of these T_{1p} values is 2.4; thus, a τ_c of $(3.7 \pm 0.6) \times 10^{-9}$ s is calculated from Figure 1 (assuming fast chemical exchange).[8] The distance between enzyme-bound Mn^{2+} and Li^+ is 5.7 ± 0.2 Å, using eq 1 and the values obtained for T_{1M} and τ_c. This is in agreement with the results of Hutton et al.[3a]

This distance of 5.7 Å is longer than the previously determined distance of 4.9 Å between Mn^{2+} and $^{205}Tl^+$ with pyruvate kinase.[9] Since Li^+ activates the enzyme only 3% as well as Tl^+,[10] this suggests that a substantial difference in the orientation between the divalent and monovalent cations at the active site of pyruvate kinase could be responsible for the large difference in maximal activities. Different enzyme conformations stabilized by Tl^+ and Li^+ are indicated by the dissimilar Mn^{2+}–Li^+ and Mn^{2+}–Tl^+ distances. We are now in the process of extending these studies to several other monovalent cations that activate pyruvate kinase.

The new method that we report in this communication for the accurate measurement of τ_c should be applicable to quite a number of enzymes that are activated by monovalent cations. Also, since the measurements are made at one magnetic field strength,[11] the field dependence of the correlation time is no longer a potential source of error.

Acknowledgment. This research was supported in part by grants from the National Science Foundation (for instrumentation and research, PCM-7807845). J.J.V. is an Established Investigator of the American Heart Association. F.M.R. is a National Research Service Awardee (AM-05966).

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(5) Spin-lattice relaxation measurements were performed on 1.25-mL samples in 10-mm NMR tubes containing 50 mM tris(hydroxymethyl)-aminomethane, pH 7.5, 20% D_2O, 100 mM ^7LiCl or ^6LiCl (obtained from Oak Ridge National Laboratory), 1.0 mM phospho(enol)pyruvate, 40 μM (in sites) pyruvate kinase (obtained from Sigma Chemical Co.), and either 200 μM $MnCl_2$ or 2.5 mM $MgCl_2$. When $MgCl_2$ was used, 1.0 mM EDTA was also added to remove any bound paramagnetic impurities that may have been introduced with the enzyme.

(6) The spin-lattice relaxation times were determined with a 180°–τ–90° pulse sequence. The relaxation times for $^6Li^+$ were 93 and 2.0 s in the enzyme complexes with Mg^{2+} and Mn^{2+}, respectively. For $^7Li^+$, the relaxation times were 10.8 and 0.79 s for these same enzyme complexes. The mole fraction of enzyme-bound Li^+ was calculated by using a dissociation constant of 11 mM.[3a]

(7) The experimental $1/T_{1p}$ values have not been corrected for the relative amounts of the two interconvertible forms of the enzyme–Mn^{2+}–Li^+–PEP complex[3b] because of the large uncertainty in the actual size of the correction. If the maximum possible correction is made, the $1/T_{1p}$ values for Li^+ increase by only 19%, and the distance decreases by 0.2 Å.

(8) The large T_{1p}/T_{2p} ratios found in Ash et al.[3b] indicate that the fast exchange conditions prevail in this system.

(9) Reuben, J.; Kayne, F. J. *J. Biol. Chem.* **1971**, *246*, 622.

(10) Kayne, F. J. *Enzymes, 3rd Ed.* **1970–1976**, *8*, 353–382.

(11) Multinuclear spectrometers are becoming common place in several laboratories, and, thus, this approach should be widely applicable.

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Theoretical Models for Transition-State Structure and Catalysis in Carbonyl Addition

Sir:

The formation of methanediol from water and formaldehyde (eq 1) is suggested by ab initio self-consistent field molecular orbital calculations at the 4-31G level[1] to be a quite difficult

$$H_2O + CH_2O \rightarrow CH_2(OH)_2 \qquad (1)$$

process, passing through a transition state[2,3] for simultaneous proton transfer and carbon–oxygen bond formation. A significant feature of the transition-state structure (Figure 1) is the presence of an essentially planar four-membered ring formed between the O–H bond of the attacking water molecule and the C–O bond of formaldehyde. Furthermore, the water is oriented in such a fashion as to enable one of its lone pairs to align approximately along the newly forming O–C bond. A rather large activation energy of 44.1 kcal mol^{-1} exists for water–formaldehyde addition, and the reaction is exothermic by 16.8 kcal mol^{-1}.

If proton transfer is disallowed by imposing a C_s symmetry constraint on the approach of water to formaldehyde, carbon–oxygen bond formation would yield a zwitterionic adduct. However, as shown by curve (d) of Figure 2, the interaction of water with formaldehyde as a function of carbon–oxygen distance[4] is wholly repulsive along this path. This zwitterionic structure and its rotamers, which were also examined, are therefore unbound states, and reaction through the transition state of Figure 1 is an example of *enforced concertedness*[5] of proton transfer and heavy-atom bond formation. Because the zwitterionic intermediate does not exist, generation of methanediol by C–O bond formation and proton transfer in two discrete steps cannot occur. Thus, the

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(1) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724–728.

(2) The calculated structure satisfies the requirements for a transition state, as discussed in a number of works. See, for example: Maggiora, G. M.; Christoffersen, R. E. "Transition States in Biochemical Processes"; Gandour, R. D., Schowen, R. L., Eds.; Plenum Press: New York, 1978; Chapter 3.

(3) The calculations were carried out with a modified version of HONDO/G on the NRCC's VAX 11/780 computer, using a gradient-search procedure.

(4) The carbon–oxygen distance is a chemically reasonable coordinate with which to follow reaction progress, although it is not a true "reaction coordinate"; see, for example: Miller, W. H.; Handy, N. C.; Adams, J. E. *J. Chem. Phys.* **1980**, *72*, 99–112. The subject will be discussed in greater detail in a forthcoming paper.[6]

(5) Jencks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425; *Ibid.* **1980**, *13*, 161.

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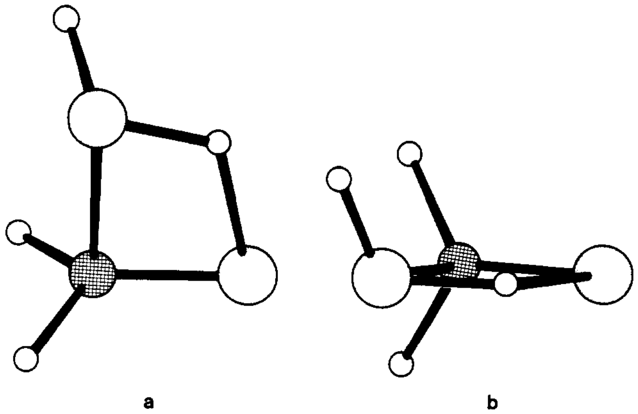
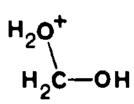


Figure 1. (a) "Side" view of the water–formaldehyde transition state. (b) "Top" view.

two processes must occur concertedly, i.e., in a single transition state.

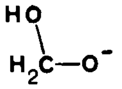
Examination of the transition-state vibrational mode corresponding to the imaginary frequency ($\nu = i1996.6$ cm^{-1}) indicates that the dominant motion (viewed as in Figure 1a) is an approximately clockwise rotation of the water molecule about its oxygen atom in the plane of the four-membered ring, coupled to a transfer of the ring proton. The motions of all the atoms in the formaldehyde molecule are very small in this "decomposition mode."

The resistance to adduct formation may be removed by either prior protonation of formaldehyde (so that adduct **1** forms) or prior deprotonation of water (so that reaction leads to adduct **2**).



$H_2O^+{-}CH_2{-}OH$

1



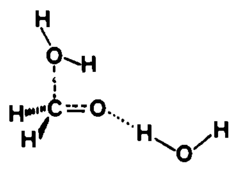
$HO{-}CH_2{-}O^-$

2

Then **1** and **2** are generated from their respective reactants with no barrier to reaction.[6] This greater ease of adduct formation corresponds to specific acid catalysis (formation of **1**) and specific base catalysis (formation of **2**) of the process of carbonyl addition.

Of course, these results are models for gas-phase chemistry and cannot be used to infer solution chemistry, because the solvent may differentially stabilize various intermediates or transition states. As a first step toward examining the effect of solvent, a second water molecule was introduced into the model. Because such a water molecule is both acidic and basic, this also allowed the simulation of general-acid–base catalysis.

Simulation of general-acid catalysis by a water molecule as in **3** leads to a reduction in the energy requirement[7] at O···C distances beyond 1.5 Å [curve (a), Figure 2] but to no alteration in the fundamental chemistry. General-base catalysis as depicted in **4** [curve (b) of Figure 2] yields a similar result. The action of the water molecules in these two cases may be considered *passive catalysis*, facilitation without profound changes in chemistry.



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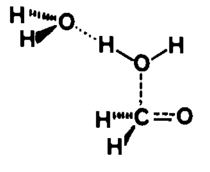

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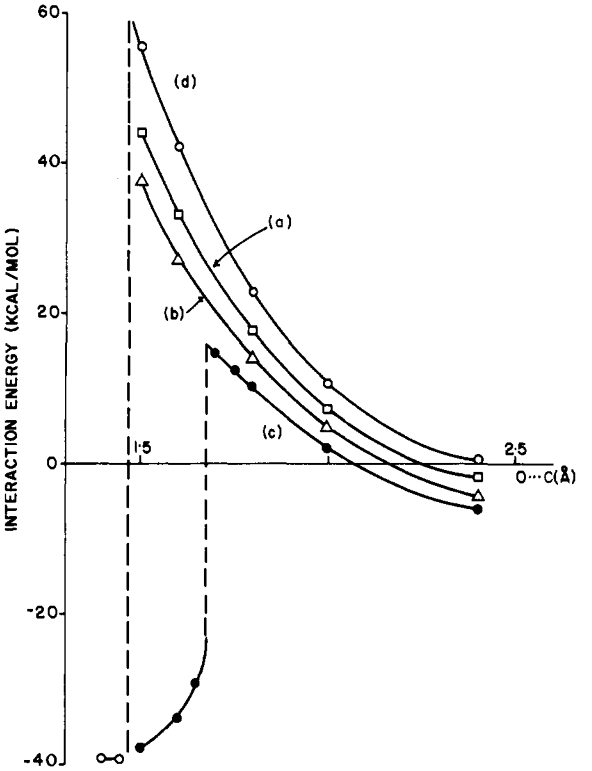
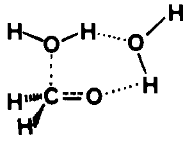


Figure 2. STO-3G interaction energy[7] vs. intermolecular oxygen–carbon distance for (a) general-acid-catalyzed, (b) general-base-catalyzed, and (c) bifunctional general-acid–base-catalyzed carbonyl additions $2H_2O$ + H_2CO via **3**, **4**, and **5**, respectively, and (d) uncatalyzed carbonyl addition H_2O + H_2CO. Curve (d) corresponds to structures, optimized in C_s symmetry, in which both the water moiety and the carbonyl bond lie in the mirror plane bisecting the HCH angle. Curves (a), (b), and (c) correspond to structures as in (d) but to which a second water molecule is appropriately hydrogen bonded in ways preserving the mirror symmetry. The choice of the carbon–oxygen distance as a "distinguished coordinate" (Rothman, M. J; Lohr, L. L. *Chem. Phys. Lett.* **1980**, *70*, 405–409) gives discontinuous energy changes for curves (c) and (d) because the constrained energy minimization scheme does not lead curve (d) through the exact transition-state structure (which must be found otherwise[2,3]) nor curve (c) through the exact transition-state structure for its reaction. The potential-energy surface near the actual transition-state structure (Figure 1) is not discontinuous, but smooth and rather gently curved (as indicated by the magnitude of the imaginary frequency; see text).

When the acidic and basic potentialities of the catalyst are combined as in **5** [curve (c) of Figure 2], the catalysis remains passive at C···O distances of 1.75 Å and greater. In fact, the stabilization produced in **5** is approximately the sum of the effects obtained in **3** and **4**. Near a C···O distance of 1.7 Å, however, *active catalysis* is seen: proton transfer and nucleophilic bond formation occur simultaneously, yielding methanediol without incurring the energetically unfavorable charge separation required by proton transfer to or from the catalyst in **3** or **4**. Introduction of a single ancillary water molecule has a profound influence upon the reactivity of the system. This finding provides a theoretical example of the type of dramatic solvation effect which has been observed previously in ICR studies of gas-phase carbonyl substitution reactions.[8]



5

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[6] Williams, I. H.; Maggiora, G. M.; Schowen, R. L. *J. Am. Chem. Soc.* **1980**, in press.

[7] Calculations at the STO-3G level (Hehre, W. J.; Stewart, R. F.; Pople, J. A. *J. Chem. Phys.* **1969**, *51*, 2657–2664) were carried with GAUSSIAN 70 (Hehre, W. J.; Lathan, W. A.; Ditchfield, R.; Newton, M. D.; Pople, J. A. *QCPE* **1973**, *11*, 236) as modified by D. Spangler to run on the Honeywell 66/60 computer.

[8] Fukuda, E. K.; McIver, R. T. *J. Am. Chem. Soc.* **1979**, *101*, 2498–2499.

Acknowledgment. This work is supported in part by grants from the National Institute of General Medical Sciences (R01-GM-20198) and by the National Resource for Computation in Chemistry under grants from the National Science Foundation (CHE-7721305) and the Division of Basic Energy Sciences of the U.S. Department of Energy (W-7405-NG-48).

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Clusterification of Reactive Species Generated through Chemical Reduction of Metallocenes: Synthesis and Stereochemical Characterization of a New Hexameric Series of Metal–Cyclopentadienyl Clusters, $[Ni_6(\eta^5\text{-}C_5H_5)_6]^n$ (n = 0, +1)

Sir:

In the course of efforts to systematize our knowledge of different modes of metal-cluster formation and the interrelationships among coordination geometries, electronic structures, and reactivity patterns of polynuclear metal clusters, we have uncovered a synthetic route to several new series of metal–cyclopentadienyl oligomers, formulated generally as $M_x(C_5H_5)_yH_z$. The reaction scheme involves reduction of the metallocenes $M(\eta^5\text{-}C_5H_5)_2$ (M = Fe, Co, Ni) to highly reactive species whose clusterification to a complex mixture of products is accompanied by formation of the cyclopentadienide anion. Reported herein is a preliminary account of the reductive chemistry of nickelocene which has resulted in the isolation and physicochemical characterization of two nickel cyclopentadienyl hexamers, $Ni_6(\eta^5\text{-}C_5H_5)_6$ (**1**) and its one-electron oxidized species $[Ni_6(\eta^5\text{-}C_5H_5)_6]^+[PF_6]^-$ (**2**), which are unprecedented (to our knowledge) as polynuclear metal–cyclopentadienyl clusters possessing no other ligands.

Previously reported cyclopentadienyl–metal clusters formed from cyclopentadienyl complexes under reducing conditions have invariably been hydride-containing species.[1-3] These include $Co_4(\eta^5\text{-}C_5H_5)_4(\mu_3\text{-}H)_4$[1] and $Ni_4(\eta^5\text{-}C_5H_5)_4(\mu_3\text{-}H)_3$,[2] which are formed by the reductions of $Co_2(\eta^5\text{-}C_5H_5)_2(\mu\text{-}NO)_2$ and $Ni(\eta^5\text{-}C_5H_5)NO$, respectively, with $LiAlH_4/AlCl_3$, and $Rh_3(\eta^5\text{-}C_5H_5)_3(\mu_3\text{-}C_5H_5)(\mu_3\text{-}H)$,[3] which was prepared by the reduction of $RhCl_3$ with $(C_5H_5)MgBr$. Prior chemical reductions of $Ni(\eta^5\text{-}C_5H_5)_2$ with either Na(Hg)/ROH[4] or K/liquid NH_3[5] have yielded only such materials as $Ni(\eta^5\text{-}C_5H_5)(\eta^3\text{-}C_5H_7)$ and nickel metal, respectively. Geiger and co-workers[6] have carried out an extensive electrochemical investigation of several metallocenes. Two of their observations relevant to our work are the following: (1) the nickelocene monoanion (which decomposes to unidentified products) generated in a cyclic voltammetric experiment has a room-temperature half-life of ca. 1 s; and (2) the exhaustive electrolytic "reduction of nickelocene is mechanistically very complex",[6b] with resulting solutions exhibiting several polarographic waves indicative of a mixture of electroactive species.

Our reductions of $Ni(\eta^5\text{-}C_5H_5)_2$ and its ring-alkylated derivatives[7] were accomplished (in yields exceeding 80%, based upon recovery of this starting material) by treatment of a THF solution of vacuum-sublimed nickelocene with an equimolar amount of sodium naphthalenide in THF.[8] After removal of solvent from the resulting reddish brown solution, extractions of the residue with various organic solvents produced solutions which were chromatographed on alumina. This procedure produced 5–7 intensely colored air-sensitive bands,[9,10] depending upon the rate of addition of the reducing agent and the temperature of the reaction. To date, analyses of mass spectral, ^1H NMR, IR, and electrochemical measurements on these fractions and their oxidized species along with X-ray diffraction examinations have shown the existence of five different kinds of cyclopentadienyl–nickel clusters, viz., $Ni_2(C_5H_5)_2(\mu\text{-}C_5H_6)$,[11] $Ni_3(C_5H_5)_4$, $Ni_4(C_5H_5)_4H_x$ (x = 1,[10] 3[2]), $Ni_5(C_5H_5)_5H_3$, and $Ni_6(C_5H_5)_6$.

The first such fraction to be adequately characterized was the hexameric $Ni_6(\eta^5\text{-}C_5H_5)_6$ species (**1**). Deep red-brown solutions of **1** in CH_2Cl_2 and THF yielded (after removal of solvent) a black amorphous solid which is insoluble in hexane, only slightly soluble in benzene or acetone, and moderately soluble in dichloromethane or THF. Although amorphous powders or solutions of **1** are air sensitive, the compound in the crystalline state is reasonably air stable. A solid-state (KBr) infrared spectrum displayed absorption bands characteristic of π-bonded C_5H_5 rings. The initial formulation of **1** as a hexamer was made from a mass spectrum (70-eV ion source; inlet temperature 200 °C), which showed a well-defined parent molecular ion envelope for $Ni_6C_{30}H_{30}$ (m/e 738 for ^{58}Ni). Cyclic voltammograms[12] of **1** in CH_2Cl_2/0.1 M TBAH indicated four one-electron couples at $E_{1/2}$ values (vs. SCE) of $[Ni_6]^-$ −0.97 V $[Ni_6]^0$ −0.26 V $[Ni_6]^+$ +0.19 V $[Ni_6]^{2+}$ +1.00 V $[Ni_6]^{3+}$, where $[Ni_6]$ is an abbreviation for **1**.

Chemical oxidation of **1** with a 1:1 molecular ratio of $AgPF_6$ in diethyl ether produced (in 93% yield) the brown-colored $[Ni_6(\eta^5\text{-}C_5H_5)_6]^+[PF_6]^-$ (**2**), which is relatively soluble in acetone. Further oxidation of **2** with $AgPF_6$ in acetone solution yielded an insoluble black precipitate (presumably the $[PF_6]^-$ salt of the dication) which is slightly soluble in dimethyl sulfoxide. In contrast to **1**, solutions of **2** (e.g., in acetone) are not noticeably attacked by air after minutes of exposure. Magnetic susceptibility measurements of **2** by the Faraday method (μ_{eff} = 3.94–3.97 μ_B from 100 to 300 K) indicate the presence of three unpaired electrons;[13,14] this expected paramagnetic character was corroborated from a solid-state room-temperature EPR spectrum.

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(1) (a) Müller, J.; Dorner, H. *Angew, Chem., Int. Ed. Engl.* **1973**, *12*, 843. (b) Huttner, G.; Lorenz, H. *Chem. Ber.* **1975**, *108*, 973–983.

(2) (a) Müller, J.; Dorner, H.; Huttner, G.; Lorenz, H. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 1005–1006. (b) Huttner, G.; Lorenz, H. *Chem. Ber.* **1974**, *107*, 996–1008. (c) Koetzle, T. F.; Müller, J.; Tipton, D. L.; Hart, D. W.; Bau, R. *J. Am. Chem. Soc.* **1979**, *101*, 5631–5637.

(3) (a) Fischer, E. O.; Wawersik, H. *Chem. Ber.*, **1968**, *101*, 150–155. (b) Fischer, E. O.; Mills, O. S.; Paulus, E. F.; Wawersik, H. *Chem. Commun.* **1967**, 643–644. (c) Mills, O. S.; Paulus, E. F. *J. Organomet. Chem.* **1968**, *11*, 587–594.

(4) Dubeck, M.; Filbey, A. H. *J. Am. Chem. Soc.* **1961**, *83*, 1257–1258.

(5) Watt, G. W.; Baye, L. J. *J. Inorg. Nucl. Chem.* **1964**, *26*, 2099–2102.

(6) (a) Geiger, W. E., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 2632–4. (b) Holloway, J. D. L.; Bowden, W. L.; Geiger, W. E., Jr. *Ibid.* **1977**, *99*, 7089–90. (c) Holloway, J. D. L.; Geiger, W. E., Jr. *Ibid.* **1979**, *101*, 2038–44.

(7) Analogous reductions of 1,1′-dimethyl- and 1,1′-dibenzyl-substituted nickelocenes gave less air-sensitive fractions from chromatography. However, attempted crystallizations of these materials have to date been unsuccessful.

(8) Preliminary experiments show that Na(Hg) in polar *aprotic* solvents also reduces nickelocene to a mixture of deep brown oligomers.

(9) Final yields of pure individual products ranged from 1–10% because of severe problems with insolubility and band tailing. Fractions often had to be rechromatographed in order to secure adequate purity for characterization. Moderate success has recently been achieved in our laboratories through the utilization of gel permeation chromatography.[10]

(10) Murphy, M. A.; Paquette, M. S.; Dahl, L. F., unpublished results.

(11) Fischer, E. O.; Meyer, P.; Kreiter, C. G.; Müller, J. *Chem. Ber.* **1972**, *105*, 3014–26.

(12) Cyclic voltammetric measurements were performed under ambient conditions on **1** in CH_2Cl_2 solutions (0.10 M TBAH as supporting electrolyte) with a gold disk working electrode at a scan rate of 500 mV/s. Analogous cyclic voltammetric measurements on **2** in CH_3CN solutions (0.10 M TBAH) exhibited five one-electron couples at $E_{1/2}$ values (vs. SCE) of $[Ni_6]^{2-}$ −1.74 V $[Ni_6]^-$ −1.01 V $[Ni_6]^0$ −0.42 V $[Ni_6]^+$ +0.26 V $[Ni_6]^{2+}$ +0.80 V $[Ni_6]^{3+}$ at a scan rate of 500 mV/s. Evidence for chemical reversibility of the waves is given by their approximate conformity to the criterion $|i(\text{peak, anodic scan})| = |i(\text{peak, cathodic scan})|$.

(13) $Ni_4(\eta^5\text{-}C_5H_5)_4(\mu_3\text{-}H)_3$ also contains three unpaired electrons (μ_{eff} = 4.10 μ_B at 295 K)[2a] which were shown from a molecular orbital investigation by Hoffmann et al.[14] to occupy a low-lying triply degenerate t_1 orbital.

(14) Hoffmann, R.; Schilling, B. E. R.; Bau, R.; Kaesz, H. D.; Mingos, D. M. P. *J. Am. Chem. Soc.* **1978**, *100*, 6088–93.

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