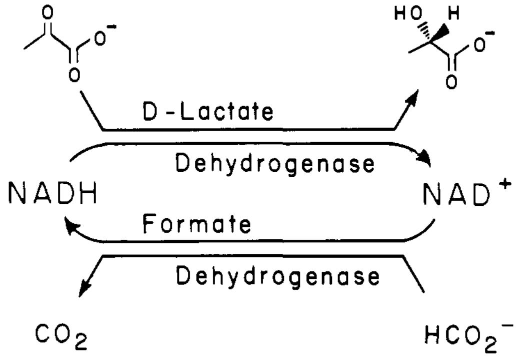
Scheme I. Synthesis of D-Lactate from Pyruvate, Using Formate and Formate Dehydrogenase to Regenerate NADH



formate and formate dehydrogenase to regenerate NADH: we believe this regeneration system is superior to others presently available for many applications in synthetic enzymology. Details of the operation of the system are illustrated by the enantioselective synthesis of D-lactate from pyruvate (Scheme I).

A 3-L three-necked round-bottomed flask was equipped with a pH electrode connected to a pH controller, an argon line, and a magnetic stirring bar. The flask was charged with 1 L of degassed distilled water. Sodium formate (99.9%, 34 g, 500 mmol), sodium pyruvate (99+%, 55.0 g, 500 mmol), dithiothreitol (DTT, 10 mmol), and EDTA (10 mmol) were added. The solution was adjusted to pH 7.6. Formate dehydrogenase (FDH, EC 1.2.1.2, Boehringer-Mannheim, from *Candida boidinii*)[4] and D-lactate dehydrogenase (D-LDH, EC 1.1.1.28, Sigma) were coimmobilized in PAN gel:[5] 240 mL of swollen gel contained 52 units[6] of FDH (47% yield on immobiliztion) and 310 units of D-LDH (51% yield). The gel particles were suspended in the reaction mixture, and NAD (0.39 mmol) was added.[7] The stirred reaction mixture was maintained at ambient temperature between pH 7.4 and 7.8 by addition of 2 N HCl, using an automatic pH controller. Argon was bubbled gently through the mixture. Reaction was complete in 15 days.[8] The gel was allowed to settle, and the supernatant was decanted under positive argon pressure by using a stainless-steel cannula. The gel was washed, and the washings were combined with the original reaction solution. Zinc lactate (47.9 g, 395 mmol of lactate, 79% based on pyruvate) was isolated in 95% purity by using a modification of the procedure of Brin;[9] it contained a 92% enantiomeric excess of D-lactate.

The activities of FDH and D-LDH in the recovered gel after two consecutive runs (30 days) were respectively 86% and 89% of the original immobilized activities. After each run, the residual activity of nicotinamide cofactors (NAD plus NADH) was approximately 55%.[10] The turnover number for NAD in the experiment described was 1020; in other experiments, it reached 1500.

The formate–formate dehydrogenase system for NADH regeneration has advantages and disadvantages. The advantages are the following: formate is inexpensive and a strong reducing agent;[11] CO_2 and formate are innocuous toward most enzymes; CO_2 can be removed from the reaction as it is formed, and does not complicate the workup of the reaction; the enzyme is commercially available, readily immobilized, and stable (if protected against autoxidation). The disadvantages are the following: the commercial enzyme is presently expensive (~$62/100 U)[12] and is unable to accept NADP as substrate.[4,13]

Acknowledgment. We thank our colleagues D. Walt and V. Rios-Mercadillo for gifts of NAD and C.-H. Wong for advice concerning the isolation of zinc lactate.

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(3) The most common schemes for NADH regeneration are based on alcohol dehydrogenases. These use relatively high concentrations of organic reactants and products in solution, and generate aldehydes or ketones which are often deactivating toward enzymes. Other enzymatic methods involve expensive reactants and/or weak reducing agents. Most chemical and electrochemical methods show only modest selectivity for generation of NADH: Baricas, W. H.; Chambers, R. P.; Cohem, W. *Anal. Lett.* **1976**, *9*, 257–276. Mosbach, L.; Larsson, P. O.; Lowe, C. *Methods Enzymol.* **1976**, *44*, 859–887. Wang, S. S.; King, C.-K. *Adv. Biochem. Eng.* **1979**, *12*, 119–146.

(4) Schütte, H.; Flossdorf, J.; Sahm, H.; Kula, M.-R. *Eur. J. Biochem.* **1976**, *62*, 151–160. Michaelis constants for NAD and formate are 0.09 mM and 13 mM, respectively. Activities were assayed according to Makave, A. B.; McMartin, K. E.; Palese, M.; Tephly, T. R. *Biochem. Med.* **1975**, *13*, 117–126.

(5) Pollak, A.; Blumenfeld, M.; Wax, M.; Baughn, R. L.; Whitesides, G. M. *J. Am. Chem. Soc.*, in press.

(6) I U = 1 μmol product produced per min.

(7) NAD was synthesized in this laboratory from AMP, and used in crude (~30% purity) form; Walt, D.; Rios-Mercadillo, V., unpublished data. Indistinguishable results were obtained with commercial NAD (Sigma).

(8) The reduction of NAD to NADH was the rate-limiting step in the catalytic cycle. When the reaction was carried out at 40 °C (again at 500-mmol scale), conversion of pyruvate to lactate was complete in 7 days. Both enzymes retained ~100% of their activity over the course of this experiment. The aggregate activity of the nicotinamide cofactors (NAD + NADH) at the conclusion of the reaction was 34% of that at its start.

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(10) Pig heart L-lactate dehydrogenase catalyzes the conversion of NAD to an inhibitory complex of pyruvate and NAD: Wilton, D. C. *Biochem. J.* **1979**, *177*, 951–7. The same reaction may occur with the yeast D-LDH used here.

(11) The equilibrium constant for the reaction $HCO_2^- + NAD^+ \rightleftharpoons CO_2 + NADH$ is $\log K = 5.79$ (based on $\Delta G = -7.95$; "Biochemist's Hand Book"; Long, C., Ed.; Spon.: London, 1961; p 90).

(12) The effective use of the formate dehydrogenase system for regeneration of a NAD modified to improve retention in an ultrafiltration membrane reactor is described by Wichmann, R.; Wandry, C.; Bückmann, A. F.; Kula, M.-R. Abstracts, VIth International Fermentation Symposium, July 1980 London, Ontario; National Research Council, Ottawa, Canada; Abstr. F-12.1.24 (P), p 125. This group has also described an exceptionally useful new isolation procedure for formate dehydrogenase: Kula, M.-R.; Bückmann, A. F.; Hustedt, H.; Kroner, K. H.; Morr, M. *Ibid.*; Abstr. F-13.25 (P), p 139.

(13) After storage for 3 months under nitrogen at 4 °C, the coimmobilized FDH and D-LDH retained >95% of their activity.

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Unexpected Features in the Chemistry of Six- and Seven-Coordinate Alkyl Isocyanide Complexes of Chromium

Sir:

There exists within those *homoleptic* isocyanide complexes of the group 6 elements which are isoelectronic with their carbonyl congeners $M(CO)_6$ an intriguing dichotomy. While aryl isocyanides (ArNC) form the neutral six-coordinate monomers $M(CNAr)_6$,[1] which in the case of M = Cr may be oxidized both chemically and electrochemically to the mono- or dications M-

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(1) See, for example: Mann, K. R.; Cimolino, M.; Geoffroy, G. L; Hammond, G. S.; Orio, A. A.; Albertin, G.; Gray, H. B. *Inorg. Chim. Acta* **1976**, *16*, 97.

$(CNAr)_6^{n+}$,[2,3] the alkyl isocyanides (RNC) are, with the exception of $Cr(CNR)_6$,[4] known to favor the stabilization of the seven-coordinate 18-electron cations $M(CNR)_7^{2+}$, and then only for M = Mo and W.[5-8] The ability of ArNC to stabilize the lower oxidation states has been supported on experimental and theoretical grounds in terms of their greater π-acceptor ability compared to RNC.[1,3,9-11] Nonetheless, it seemed to us that this difference was not necessarily sufficient to preclude the formation of the elusive $M(CNAr)_7^{2+}$ and/or $M(CNR)_6^{n+}$ (n = 0, 1, or 2) species, the isolation of which would afford an opportunity to compare directly the properties of analogous pairs of isoelectronic homoleptic alkyl and aryl isocyanide complexes of these elements. Furthermore, in view of the current interest in the photochemistry of these complexes,[12,13] the reductive coupling of isocyanide ligands when bound to such metal centers [especially Mo(II)][14] and other of their properties,[9] an understanding of the relative stabilities of $M(CNAr)_7^{2+}$, $M(CNR)_7^{2+}$, $M(CNAr)_6$, and $M(CNR)_6$ is a matter of considerable importance. We have for the first time succeeded in preparing the alkyl derivatives $[Cr(CNR)_6](PF_6)_2$ (R = C_6H_{11} or CMe_3), thereby permitting a direct comparison with the previously characterized[2,3] aryl isocyanide analogues $[Cr(CNAr)_6](PF_6)_2$. The derivatives $[Cr(CNR)_7](PF_6)_2$ have also been prepared with remarkable ease, thereby providing an exceedingly rare example of a *homoleptic* seven-coordinate complex of a first-row transition element and the first involving alkyl or aryl isocyanide ligands.[15] Preliminary details of this work are reported herein.

The paramagnetic cyclohexyl and *tert*-butyl isocyanide complexes $[Cr(CNR)_6](PF_6)_2$[16] are prepared in high yield (50–75%) upon treating the deep blue Cr(II) solution which is generated upon passage of an ethanolic solution of $CrCl_3 \cdot 6H_2O$ through a Jones reductor with an excess of the appropriate alkyl isocyanide and KPF_6. Addition of *neat* alkyl isocyanide RNC to $[Cr(CNPh)_6](PF_6)_2$[2,3] or to $[Cr(CNR)_6](PF_6)_2$ produces the change to the seven-coordinate alkyl isocyanide complexes $[Cr(CNR)_7](PF_6)_2$ in almost quantitative yield.[17] In contrast to this novel and remarkably simple increase in coordination number from six to seven[15] (i.e., a 16-electron to 18-electron configuration change) without a concomitant variation in the metal oxidation state or the cation charge, the analogous reaction of neat phenyl isocyanide with $[Cr(CNPh)_6](PF_6)_2$ is followed by *reduction* to the Cr(I) complex $[Cr(CNPh)_6]PF_6$. Our isolation of $[Cr(CNR)_7](PF_6)_2$ provides, therefore, the first homologous series of homoleptic seven-coordinate complexes of any transition group (Cr, Mo,[5,6] and W[5,7,8]).

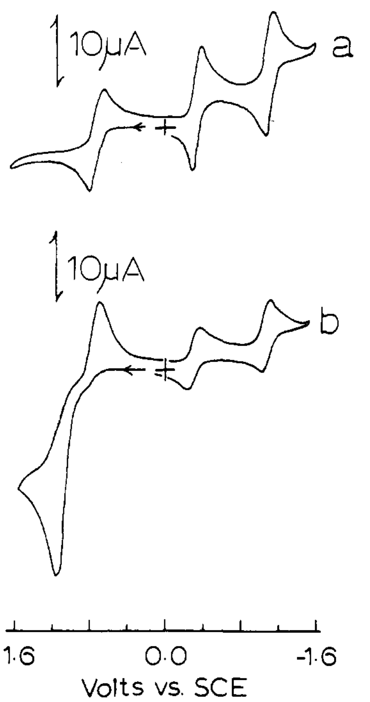

Figure 1. Cyclic voltammograms in 0.2 M tetra-*n*-butylammonium hexafluorophosphate–dichloromethane of (a) $[Cr(CNC_6H_{11})_6](PF_6)_2$ and (b) $[Cr(CNC_6H_{11})_7](PF_6)_2$. Both were recorded at 200 mV/s.

Cyclic voltammetric measurements on dichloromethane solutions of $[Cr(CNR)_6](PF_6)_2$ (R = C_6H_{11} or CMe_3) affords us a direct comparison with the comparable properties of the related aryl isocyanide complexes of chromium(II).[2,3] With 0.2 M Bu_4NPF_6 as supporting electrolyte, solutions of $[Cr(CNC_6H_{11})_6](PF_6)_2$ exhibit a quasi-reversible one-electron oxidation ($E_{1/2}$ = +0.75 V vs. SCE) and two one-electron reductions ($E_{1/2}$ = −0.31 V and −1.08 V vs. SCE).[18] Related behavior is noted for $[Cr(CNCMe_3)_6](PF_6)_2$. The cyclic voltammogram of $[Cr(CNC_6H_{11})_6](PF_6)_2$ is shown in Figure 1a. We note that in the case of $[Cr(CNCMe_3)_6](PF_6)_2$, the couple at the more negative potential is characterized by a large peak separation ($E_{p,a} - E_{p,c}$ = 320 mV) and an $i_{p,a}/i_{p,c}$ ratio (<1) which point to electrochemical irreversibility.[19] The voltammetric half-wave potentials for $[Cr(CNR)_6](PF_6)_2$ are to be contrasted with those of +1.00, +0.25, and −0.35 V for the phenyl isocyanide derivative $[Cr(CNPh)_6](PF_6)_2$.[2] This gives, for the first time, a direct measure of the difference in the thermodynamic stability of pairs of alkyl and aryl isocyanide complexes of the group 6 elements. The oxidation $Cr^{2+} \rightarrow Cr^{3+}$ is seen to be more favored with the alkyl isocyanides, whereas the reductions $Cr^{2+} \rightarrow Cr^{1+}$ and $Cr^{+1} \rightarrow Cr^0$, which occur at much more negative potentials than with the aryl isocyanide complexes, are clearly less favored. This explains why the reactions of complexes such as $Cr(C_2H_5OH)_n^{2+}$, $M_2(O_2CCH_3)_4$ (M = Cr or Mo),[1,6] and $W_2(mhp)_4$ (mhp is the anion of 2-hydroxy-6-methylpyridine)[7] with aryl isocyanides afford the

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(15) Drew, M. G. B. *Prog. Inorg. Chem.*, 1977, *23*, 67.

(16) The room-temperature magnetic moment of $[Cr(CNCMe_3)_6](PF_6)_2$ is 3.1 μ_B, very similar to the values report for the aryl isocyanide complexes $[Cr(CNAr)_6](PF_6)_2$.[2]

(17) Satisfactory elemental microanalyses were obtained for all complexes. Representative data for the *tert*-butyl isocyanide complexes are as follows. Anal. Calcd for $C_{30}H_{54}CrF_{12}N_6P_2$: C, 42.9; H, 6.5; N, 10.0. Found: C, 43.1; H, 6.75; N, 10.3. Calcd for $C_{35}H_{63}CrF_{12}N_7P_2$: C, 45.5; H, 6.9; N, 10.6. Found: C, 45.6; H, 7.0; N, 10.8. The infrared spectra (Nujol mulls) of $[Cr(CNR)_6](PF_6)_2$ exhibit the $\nu(C{\equiv}N)$ mode at ~2180 cm^{-1}, which is ~20 cm^{-1} higher than that reported[2] for the aryl isocyanide analogues $[Cr(CNAr)_6](PF_6)_2$. $\nu(C{\equiv}N)$ for the seven-coordinate cations $[Cr(CNR)_7](PF_6)_2$ is centered at ~2160 cm^{-1}.

(18) $Cr(CNR)_6^{3+}$ which is formed by the electrochemical oxidation of $Cr(CNR)_6^{2+}$ is isoelectronic with the V(II) complex $[V(CNCMe_3)_6](PF_6)_2$ recently prepared by Professor S. J. Lippard and co-workers (Silverman, L. D.; Dewan, J. C.; Giandomenico, C. M.; Lippard, S. J. *Inorg. Chem.*, accepted for publication).

(19) The dichloromethane solutions of the two alkyl isocyanide complexes have limited stability, those of the *tert*-butyl isocyanide complex showing signs of decomposition within 2 min of their preparation (as measured by the diminuition of peak currents in the CV). Although these solutions do not appear to exhibit any noticeable light sensitivity, photochemical studies on these complexes and their seven-coordinate analogues are planned.

stable zerovalent complexes $M(CNAr)_6$, while the alkyl isocyanides favor retention of these metals in the divalent state, either as $M(CNR)_6^{2+}$ or $M(CNR)_7^{2+}$.

Dichloromethane solutions of $[Cr(CNR)_7](PF_6)_2$ show an irreversible oxidation close to +1.15 V ($E_{p,a}$ = +1.12 V for R = C_6H_{11} and +1.16 V for R = CMe_3).[20] This oxidation to $Cr(CNR)_7^{3+}$ is followed by the loss of an isocyanide ligand and the formation of $Cr(CNR)_6^{3+}$, as identified through the appearance of the three couples (Figure 1b) which characterize these six-coordinate cations. Note that the rate of ligand loss is quite slow (as measured by peak currents), since considerable amounts of the seven-coordinate cation remain following completion of the single CV scan.[21] The decomposition of the $Cr(CNR)_7^{3+}$ ions following their electrochemical generation (possibly by a simple EC mechanism)[22] contrasts with the much greater stability of the analogous molybdenum and tungsten species. Solutions containing the $Mo(CNR)_7^{3+}$ and $W(CNR)_7^{3+}$ cations may be generated electrolytically[7] and decompose at much slower rates.

An alternative ligand loss mechanism is the spontaneous conversion of solutions of the unoxidized $Cr(CNR)_7^{2+}$ cations to $Cr(CNR)_6^{2+}$. This change can be monitored by cyclic voltammetry (on dichloromethane solutions of the complexes using switching potentials of +0.90 and −1.6 V) and, in the case of the formation of $[Cr(CNC_6H_{11})_6](PF_6)_2$ from $[Cr(CNC_6H_{11})_7](PF_6)_2$, was also followed by ^1H NMR spectroscopy. The cyclohexyl resonances at $\delta \sim 1.50$ and ~ 4.35 in the the diamagnetic seven-coordinate complex (data recorded in acetone-d_6 at room temperature relative to Me_4Si) collapse and new, broad resonances centered at δ 1.4, 3.25, and 5.4 emerge as the paramagnetic complex $[Cr(CNC_6H_{11})_6](PF_6)_2$ is formed.[23]

The XPS Cr $2p_{3/2}$ binding energies of the six- and seven-coordinate complexes are very similar (576.6 ± 0.2 eV),[24] being significantly higher than those we have measured for the phenyl isocyanide species $Cr(CNPh)_6^+$ and $Cr(CNPh)_6$ (575.3 and 574.5 eV, respectively). Accordingly, this smooth increase of E(Cr 2p) with increase in oxidation state implies that neither Cr to π^*(CNR) nor Cr to π^*(CNAr) back-bonding is particularly dominant in influencing the charge at the metal center. If it were then with PhNC a significantly better π-acceptor ligand than RNC, Cr to π^*(CNPh) back-bonding in $Cr(CNPh)_6$ and $Cr(CNPh)_6^+$ might well be expected to increase the Cr 2p binding energies to a point where they approach those of $Cr(CNR)_6^{2+}$. This we do not observe.

Preliminary studies point to a rich substitution chemistry for these new alkyl isocyanide complexes of Cr(II). Among the complexes already isolated are $[Cr(CNCMe_3)_5P(OMe)_3](PF_6)_2$ and $[Cr(CNR)_{5+x}(dppe)](PF_6)_2$, where x = 1 or 2, R = CMe_3 or C_6H_{11}, and dppe = 1,2-bis(diphenylphosphino)ethane. Further work is in progress and will be reported in detail at a later date.

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[20] A reduction wave at $E_{p,c}$ = +0.65 V which is associated with the seven-coordinate cation overlaps that arising from the reduction $Cr(CNR)_6^{3+} + e \rightarrow Cr(CNR)_6^{2+}$ (see Figure 1b).

[21] From the CV shown in Figure 1b, it is apparent that while $Cr(CNC_6H_{11})_6^{3+}$ is formed by ligand loss following the oxidation of $Cr(CNC_6H_{11})_7^{2+}$, the peak curents associated with the cathodic sweep are less than that which characterizes the oxidation $Cr(CNC_6H_{11})_7^{2+} \rightarrow Cr(CNC_6H_{11})_7^{3+} + e$. Accordingly, there must be partial decomposition of $Cr(CNC_6H_{11})_7^{3+}$ and/or $Cr(CNC_6H_{11})_6^{3+}$ to some electrochemically inactive species by a second unidentified mechanism.

[22] E means an electrochemical reaction, either an oxidation or a reduction, while C means a chemical reaction. Thus an EC reaction is an electrode process followed by a chemical reaction.

[23] Detailed temperature-range ^1H NMR spectroscopic measurements of the $[Cr(CNR)_7](PF_6)_2 \rightleftarrows [Cr(CNR)_6](PF_6)_2 + CNR$ equilibria are currently under way.

[24] X-ray photoelectron spectra (XPS) were measured on a Hewlett–Packard 5950A instrument as described in detail elsewhere.[25] Spectra were recorded at 250 K with the use of a cold probe and the Cr 2p binding energies are internally referenced to an aliphatic C 1s binding energy of 285.0 eV for the isocyanide ligands.

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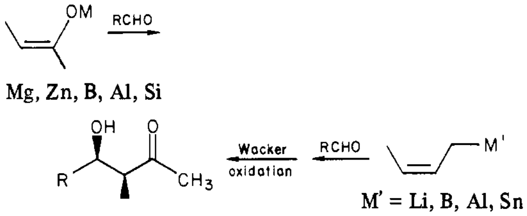
Erythro-Selective Addition of Crotyltrialkyltins to Aldehydes Regardless of the Geometry of the Crotyl Unit. Stereoselection Independent of the Stereochemistry of Precursors

Sir:

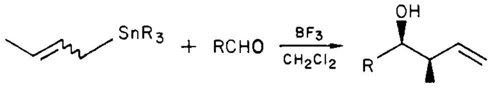
One of the most challenging problems for the synthetic organic chemist today is control of stereochemistry in conformationally nonrigid open-chain compounds. Especially, attention is focused on erythro-selective synthesis of β-hydroxycarbonyl compounds which may be applicable to the synthesis of macrolide antibiotics.[1] The hitherto known solution to this problem is to use the addition reaction of (i) (Z)-metal enolates[2] or (ii) (Z)-2-alkenylmetal derivatives[3] to aldehydes (eq 1). However, an important problem that arises from these approaches is the stereochemical control (Z configuration) of the starting materials, which still remains difficult despite numerous efforts in this kind of chemistry.[2,3] We report an entirely new approach to the stereoselection via the Lewis acid mediated addition[4] of crotyltrialkyltins to aldehydes, where it does not matter if the stereochemistry of the crotyl unit is either cis or trans (eq 2).



M = Li, Mg, Zn, B, Al, Si

M' = Li, B, Al, Sn

(1)



(2)

1 erythro selectivity >90%

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