Electrochemical methylation of a chelate anionic Ni^I complex with methylcobaloxime. Partial modeling of the action mechanism of the active center of acetyl-CoA synthase

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Electrochemically generated anions of Co and Ni chelate complexes can be alkylated with Bu^nBr, Bu^nI, and $(dmgH)_2CoMe$ (dmgH is the dimethylglyoximate anion). Unlike the anionic Co complexes, the anionic Ni complex cannot be alkylated with Bu^nBr; however, it reacts with stronger alkylating agents (Bu^nI and $(dmgH)_2CoMe$). It is assumed that the electrochemical alkylation of the Ni complex with $(dmgH)_2CoMe$ can serve as a model for alkylation occurring in biological synthesis of acetyl coenzyme A. Reactions of some Co chelate anions with Bu^nI can proceed *via* the reduction of the latter.

Key words: cobalt, nickel, chelate complexes, alkylation, methylcobaloxime, bioinorganic enzymology.

Previously,[1] we have reported the results of a study of the alkylation reaction of $[(Chel)_2M^I]^-$ chelate complex anions containing different chelating ligands and transition metal atoms (M = Co; Rh, Ir, Ni, Pd).

$$[(Chel)_2M^I]^- + RBr \longrightarrow (Chel)_2M^{III}{-}R + Br^-.$$

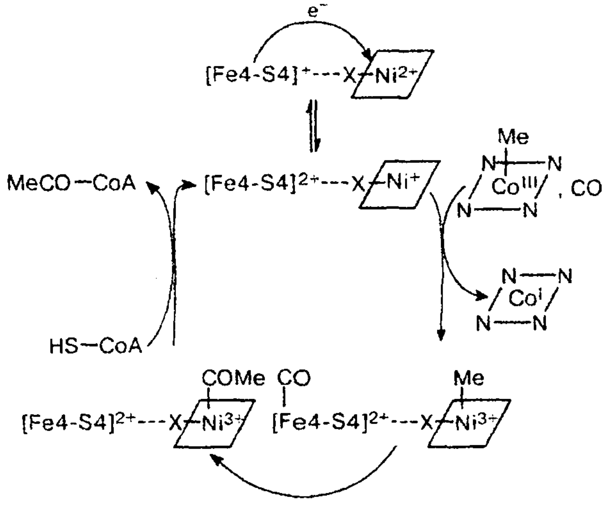
These anions were generated by electrochemical reduction of neutral complexes of di- or trivalent metals.

$$(Chel)_2M^{II} \underset{}{\overset{+e^-}{\rightleftharpoons}} [(Chel)_2M^I]^-.$$

n-Butyl bromide was chosen as the standard alkylating agent. However, it turned out that not all of the complexes studied react with this compound and that the possibility for the alkylation reaction to proceed depends on both the metal and ligand nature. For instance, the anion generated from the dimethylglyoximate nickel(II) complex reacts with *n*-butyl bromide, whereas that generated from nickel complex **1c** (the formula is given below) cannot be alkylated. The next step was to search for other reagents appropriate for alkylation of those anionic complexes that do not react with *n*-butyl bromide. In this work, Bu^nI and the methylcobalt dimethylglyoximate complex, $(dmgH)_2CoMe(py)$ (methylcobaloxime), were chosen as such agents. The choice of the latter compound is due to the fact that the alkylation of chelate nickel complexes proceeds in nature with participation of methylcobaloxime (MeCbl), which is structurally similar to $(dmgH)_2CoMe$.

Carbon monoxide dehydrogenase (CODH) was found in certain methanogenic, acetogenic, and sulfate-reducing bacteria. These bacteria can grow autotrophically due to carrying out two catalytic reactions: (1) CO → CO_2 and (2) synthesis of MeCO—CoA [2–4] (acetyl-CoA synthase). In these organisms the active center of the enzyme contains cubane iron-sulfur clusters (Fe4-S4)[2] as well as a chelate nickel complex linked to the Fe4-S4 cluster by a cysteine bridge. Four sulfur atoms or two sulfur and two nitrogen atoms are donors in the chelate nickel complex. The catalytic cycle carried out in the active center of CODH/MeCO—CoA synthase is shown in Scheme 1.

Scheme 1



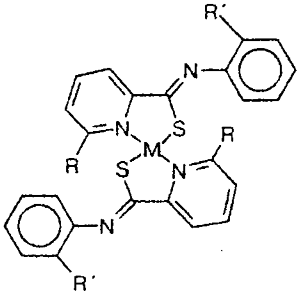
Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 1, pp. 55—58, January, 2000.

The first stage of the process is the electron transfer from the [Fe4-S4]$^+$ cluster to the Ni^{II} atom accompanied by change in the average oxidation state of the Fe and Ni atoms (from 2.25 to 2.50 and from 2.0 to 1.0, respectively). Then, the complex that formed binds CO and Me (likely by the [Fe4-S4]$^{2+}$ cluster and Ni atom, respectively). CO migration and insertion into the Ni—Me bond occur, and the acetyl group is transferred to the S atom of HS—CoA to form MeCO—CoA. It is likely that MeCbl is a methylating agent in this cycle.[2]

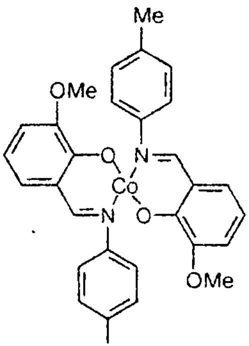
We assumed that similar reactions of chelate complexes of both Ni^{II} and other transition metals not bonded to the Fe4-S4 cluster can be carried out electrochemically using a cathode instead of this cluster.

Experimental

Reactive anions were electrochemically generated from (Chel)$_2$M complexes (**1a—c**, **2**) whose structures are given below.



1a—c



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a: M = Co, R = R′ = Me
b: M = Co, R = Me, R′ = OMe
c: M = Ni, R = Me, R′ = OMe

Complexes **1a—c** [5] and **2** [6] were synthesized according to the known procedures. The dimethylglyoximate Co^{II} complex and its Co-Me derivative (**3**) were obtained using the procedures reported in Refs. 7 and 8, respectively.

N,N-Dimethylformamide was purified by boiling and successive distillation *in vacuo* over anhydrous potassium carbonate, P_2O_5, and $CuSO_4$. Electrochemical studies of the complexes were carried out at a glassy-carbon electrode in DMF with Bu_4NBF_4 (0.05 mol L^{-1}) as supporting electrolyte; the potentials were measured *vs.* an AgCl electrode. Cyclic voltammetry (CVA) and rotating-disk electrode (RDE) techniques with a PI-50-1.1 potentiostat were used. All measurements were performed in Ar atmosphere.

Results and Discussion

The data on electrochemical oxidation and reduction of complexes **1a—c**, **2**, and **3** obtained by CVA at a glassy-carbon electrode in DMF with Bu_4NBF_4 (0.05 mol L^{-1}) as supporting electrolyte are listed in Table 1. Compounds **1a—c** and **2** are reduced in two stages. The first stage is quasi-reversible (Fig. 1, peaks *A* and *B*). The second stage is irreversible for complexes **1a—c** and quasi-reversible for compound **2**. According to recently published data,[1] the first reversible stage corresponds to the formation of a "supernucleophilic" anion in which the negative charge is mostly localized on the metal atom:

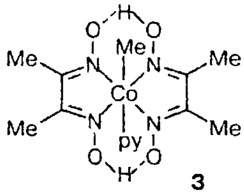

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Table 1. Potentials (E/V) of electrochemical reduction and oxidation of complexes **1—3** at a glassy-carbon electrode

Complex	Oxidation		Reduction		
	$E_{p,a}$	$E_{p,c}$	$-E^1_{p,c}$	$-E^1_{p,a}$	$-E^2_{p,c}$
1a	1.33	—	1.41	1.26	1.78
1b	0.82	—	1.27	0.94	1.93
1c	1.26	—	1.32	1.21	1.97
2	1.05	0.91	1.62	1.56	1.98
3	0.99	0.89	1.74	—	—

Note. Conditions of electrolysis: with MeCN as solvent, with 0.05 mol L^{-1} Bu_4NBF_4 as supporting electrolyte, *vs.* Ag/AgCl/KCl(sat.). The anodic and cathodic peaks are denoted by the "p,a" and "p,c" indices, respectively.

$$(Chel)_2M \xrightleftharpoons{e^-} [(Chel)_2M]^-.$$

1a—c, 2

The character of the polarization curves of the reduction of compounds **1a** and **1b** is changed as a five-

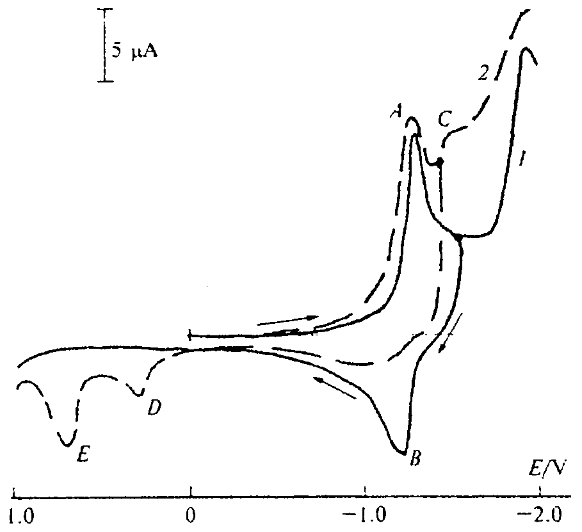


Fig. 1. Cyclic voltammograms of complex **1c** (1 · 10^{-3} mol L^{-1}) in DMF (with 0.05 mol L^{-1} Bu_4NBF_4 as supporting electrolyte): *1*, without Bu^{n}I; *2*, with Bu^{n}I (5 · 10^{-3} mol L^{-1}). For *A—E*, see text.

fold excess of Bu^nBr is added to the solution containing 10^{-3} mol L^{-1} of $(Chel)_2M$. A new peak appears in the potential region from −1.52 to −1.56 V; it can be assigned to the reduction of the alkylcobalt complex[1] formed as a result of the alkylation of $\mathbf{1a}^-$ and $\mathbf{1b}^-$ anions:

$$\underset{\mathbf{1a}^-,\ \mathbf{1b}^-}{[(Chel)_2Co]^-} + Bu^nBr \longrightarrow (Chel)_2CoBu^n + Br^-.$$

However, no changes on the polarization curve of nickel complex **1c** were observed after addition of Bu^nBr, which means that no alkylation reaction proceeds. This is likely associated with a lower nucleophilicity of the $\mathbf{1c}^-$ anion compared to those of the $\mathbf{1a}^-$ and $\mathbf{1b}^-$ anions or with instability of the butylnickel complex formed in the alkylation. To verify this assumption, we carried out the reaction of anion $\mathbf{1c}^-$ with a stronger electrophile (Bu^nI). In this case a new cathodic peak that appears on the polarization curve at a potential of −1.52 V (see Fig. 1, peak *C*) can be assigned to the reduction of the alkylnickel complex. In addition, the oxidation peaks of iodide ion are observed on the anodic branch of the curve at 0.35 and 0.70 V (see Fig. 1, peaks *E* and *D*, respectively). Thus, the following reactions proceed during the electrochemical activation of complex **1c**:

$$\underset{\mathbf{1c}}{(Chel)_2Ni^{II}} \xrightleftharpoons{e^-} [(Chel)_2\dot{N}i^{I}]^-,$$

$$[(Chel)_2\dot{N}i^{I}]^- + Bu^nI \longrightarrow (Chel)_2\dot{N}i^{III}Bu^n + I^-.$$

Formally, this reaction can be considered a redox reaction. In fact, in the Bu^nI molecule the C atom bound to the iodine atom has a formal oxidation state of −1. Assuming that in the $(Chel)_2Ni^{III}Bu^n$ molecule the Ni—C bond is polarized and the electron density is shifted from the Ni to the C atom, the formal oxidation state of the carbon atom bound to the nickel atom is −3, which corresponds to the reduction of the C atom and the oxidation of the nickel atom (its oxidation state changes from +1 to +3). The essential difference between the $\mathbf{1a}^-$, $\mathbf{1b}^-$ complex anions and the $\mathbf{1c}^-$ nickel complex anion is that the latter is a radical anion, whereas all electrons in the $\mathbf{1a}^-$ and $\mathbf{1b}^-$ anions (if they are in the low-spin state[1]) are paired. Then, Bu^nI can be considered a butyl radical carrier rather than a cation carrier and the reaction scheme is as follows:

$$[(Chel)_2\dot{N}i^{I}]^- + Bu^nI \longrightarrow [(Chel)_2Ni^{III}Bu^n]^- + I^{\cdot},$$

$$[(Chel)_2Ni^{III}]^- + I^{\cdot} \longrightarrow (Chel)_2Ni^{III}Bu^n + I^-.$$

However, the reaction product is the butylnickel(III) complex, anyway.

We also succeeded in performing the alkylation of electrochemically generated **1a—c** complex anions with the dimethylglyoximate methylcobalt complex **3**. For instance, the voltammogram of electrochemical generation of the $\mathbf{1b}^-$ complex anion in the presence of complex **3** contains a new peak at −1.54 V, which corresponds to the formation of the product of methylation of complex **1b**, and a pair of reversible peaks ($E_{p,c}$ = −1.03 V and $E_{p,a}$ = −0.96 V) corresponding to the dimethylglyoximate cobalt(II) complex:

$$\underset{\mathbf{1b}}{(Chel)_2Co^{II}} \xrightleftharpoons{e^-} [(Chel)_2Co^{I}]^-,$$

$$[(Chel)_2Co^{I}]^- + \underset{\mathbf{3}}{(dmgH)_2CoMe} \longrightarrow$$

$$\longrightarrow (Chel)_2CoMe + [(dmgH)_2Co^{I}]^-,$$

$$[(dmgH)_2Co^{I}]^- \xrightleftharpoons[+e^-]{-e^-} (dmgH)_2Co^{II}.$$

The polarization curve of the reaction of dimethylglyoximate complex **3** with the electrochemically generated $\mathbf{1c}^-$ anion also contains a new cathodic peak at −1.53 V (Fig. 2, peak *C*) that can be assigned to the product of alkylation of the $\mathbf{1c}^-$ anion and a pair of reversible peaks *E* and *D* ($E_{p,c}$ = −1.08 V and $E_{p,a}$ = −0.98 V) that can be assigned to the $(dmgH)_2Co^{II}(py)_2$ complex.

We believe that this reaction proceeds analogously to the methylation of nickel(II) chelates in the biological synthesis of acetyl coenzyme A (Scheme 2). Complex **1c** is reduced at the electrode at a potential of −1.32 V to the $\mathbf{1c}^-$ anion, which further reacts with compound **3**. Scheme 2 displays a half of the catalytic cycle shown in Scheme 1.

Previously,[1] we have found that the reduced form of complex **2** does not react with Bu^nBr analogously to

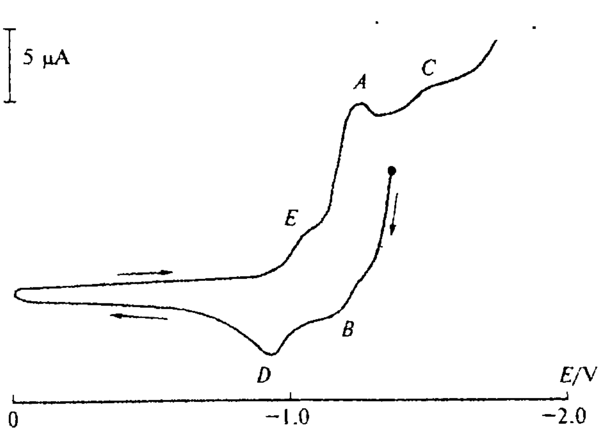
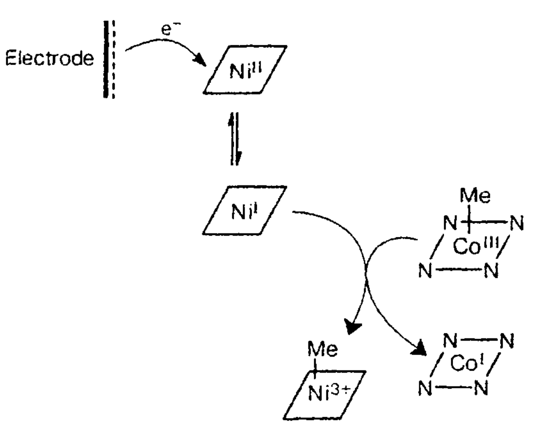


Fig. 2. CVA curve for the reduction of complex **1c** ($1 \cdot 10^{-3}$ mol L^{-1}) in DMF (with 0.05 mol L^{-1} Bu_4NBF_4 as supporting electrolyte) after 2 min of electrolysis at *E* = −1.20 V in the presence of complex **3** ($1 \cdot 10^{-3}$ mol L^{-1}). For *A*—*E*, see text.

Scheme 2



complex **1c**. No new cathodic peaks indicating the formation of $(\mathrm{Chel})_2\mathrm{CoBu^n}$ are observed on the CVA curve upon addition of five-fold excess of $\mathrm{Bu^nI}$ or $\mathrm{Bu^nBr}$ in the course of reduction of complex **2**. However, the pattern of the CVA curves is changed: (1) reversibility of the reduction of complex **2** is decreased; (2) the cathodic peak of the reduction of complex **2** increases; and (3) iodide ion appears in the solution. No peaks of $(\mathrm{Chel})_2\mathrm{CoMe}$ reduction are also observed on the CVA curve under the action of $(\mathrm{dmgH})_2\mathrm{CoMe}$; in this case reversibility of the reduction of complex **2** is decreased, the cathodic peak increases, and a pair of reversible peaks corresponding to the $[(\mathrm{dmgH})_2\mathrm{Co}]^-$ anion appears. These results are best explained assuming that anion $\mathbf{2}^-$ is a mediator of the outer-sphere reduction of $\mathrm{Bu^nI}$ and $(\mathrm{dmgH})_2\mathrm{CoMe}$:

$$\underset{\mathbf{2}}{(\mathrm{Chel})_2\mathrm{Co^{II}}} \xrightleftharpoons{e^-} [(\mathrm{Chel})_2\mathrm{Co^{I}}]^-,$$

$$[(\mathrm{Chel})_2\mathrm{Co^{I}}]^- + \mathrm{Bu^nI} \longrightarrow (\mathrm{Chel})_2\mathrm{Co^{II}} + \mathrm{Bu^{n\cdot}} + \mathrm{I^-},$$

$$[(\mathrm{Chel})_2\mathrm{Co^{I}}]^- + \underset{\mathbf{3}}{(\mathrm{dmgH})_2\mathrm{CoMe}} \longrightarrow$$

$$\longrightarrow (\mathrm{Chel})_2\mathrm{Co^{II}} + \mathrm{Me^{\cdot}} + [(\mathrm{dmgH})_2\mathrm{Co^{I}}]^-.$$

In fact, compound **2** has the most negative reduction potential among the other complexes studied (see Table 1), which enhances the thermodynamic driving force of the electron transfer to $\mathrm{Bu^nI}$ ($E_{\mathrm{p,c}} = -2.10$ V) and $(\mathrm{dmgH})_2\mathrm{CoMe}$ ($E_{\mathrm{p,c}} = -1.72$ V)**9**.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 97-03-32920a).

References

1. K. P. Butin, R. D. Rakhimov, and I. G. Il'ina, *Izv. Akad. Nauk, Ser. Khim.*, 1999, 71 [*Russ. Chem. Bull.*, 1999, **48**, 71 (Engl. Transl.)].
2. S. W. Ragsdale and M. Kumar, *Chem. Rev.*, 1996, **96**, 2515.
3. D. E. Fenton, in *Biocoordination Chemistry*, Oxford Univ. Press, Oxford, 1995.
4. M. S. Rum, C. G. Riordan, G. P. A. Yap, L. Liable-Sands, A. L. Rheingold, A. Marehaj, and J. R. Norton, *J. Am. Chem. Soc.*, 1997, **119**, 1648.
5. I. G. Mochalina, Ph.D. (Chem.) Thesis, M. V. Lomonosov Moscow State University, Moscow, 1964 (in Russian).
6. A. P. Terent'ev, G. P. Talyzenkova, and G. V. Panova, *Zh. Obshch. Khim.*, 1966, **36**, 1530 [*J. Gen. Chem. USSR*, 1966, **30** (Engl. Transl.)].
7. D. Dodd and M. D. Johnson, *J. Organomet. Chem.*, 1973, **52**, 1.
8. G. N. Schrauzer and R. J. Windgassen, *J. Am. Chem. Soc.*, 1966, **88**, 3738.
9. *Organic Electrochemistry*, Eds. M. M. Baizer and H. Lund, Marcel Dekker, Inc., New York—Basel, 1983.

Received April 21, 1999