Influence of the redox state of the ligand on the dealkylation of substituted methylcobaloximes in the presence of heavy metal ions

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The synthesis of cobaloxime and methylcobaloxime containing sterically hindered 2,6-di-*tert*-butylphenol fragments in the ligand is described. Spectral studies of the demethylation of methylbis(dimethylglyoximato)cobalt (**1a**), methylbis(diphenylglyoximato)cobalt (**1b**), methylbis[methyl-(3,5-di-*tert*-butyl-4-hydroxyphenyl)glyoximato]cobalt (**1c**) pyridinates were carried out in the presence of Cd^{2+}, Hg^{2+}, Sn^{4+}, Pb^{2+}, and Pb^{4+} ions. The free radical forms of the complexes containing a phenoxy radical in the ligand are formed during oxidation. The ESR spectra are given. The unpaired electron in the periphery of the methylcobaloxime ligand **1c** interacts with the Co—CH_3 fragment through the conjugated systems, enhancing the donating properties of the equatorial ligand of the complex, which leads to the rapid cleavage of the Co—C bond. Therefore the demethylation of methylcobaloxime in the presence of heavy metal ions occurs in a significantly shorter time.

Key words: cobaloxime, methylcobaloxime, heavy metals, sterically hindered phenol, free radical ligand, demethylation.

Recently many data have emerged that attest to the presence of alkyl derivatives of heavy metals in the environment.[1] These extremely toxic organometallic compounds are not only of anthropogenic origin but can also be formed as a result of biological or chemical processes.[2]

Methylcobalamin, a derivative of vitamin B_{12}, is a chemical alkylating agent able to transport methyl groups to metal ions.[3]

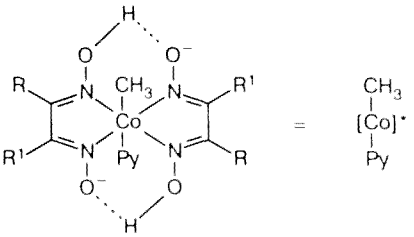
$$CH_3CoB_{12} + M^{n+} \xrightarrow{H_2O} (H_2O)CoB_{12}^{+} + CH_3M^{(n-1)}$$

The attention of researchers has mainly concentrated up to the present on the study of the dependence of the characteristics of the Co—C bond in methylcobalamin and its analogs, in particular, methylcobaloximes,[4] on the degree of oxidation and spin state of the central metal ion.[1]

This work deals with the study of the influence of the redox state of a ligand on the reactivity of methylcobaloximes in the reactions of dealkylation in the presence of metal ions, using a model containing easily oxidizable sterically hindered phenol fragments in the ligand.

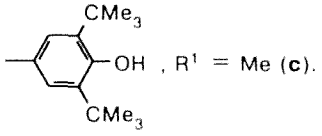
Results and Discussion

Methylcobaloximes (**1a—1c**) were used to solve the problem in this work.



1a—c

R = R¹ = Me (**a**); R = R¹ = Ph (**b**);



, R¹ = Me (**c**).

* [ ] is a conventional symbol for two ligands, which are substituted glyoxymate anions.

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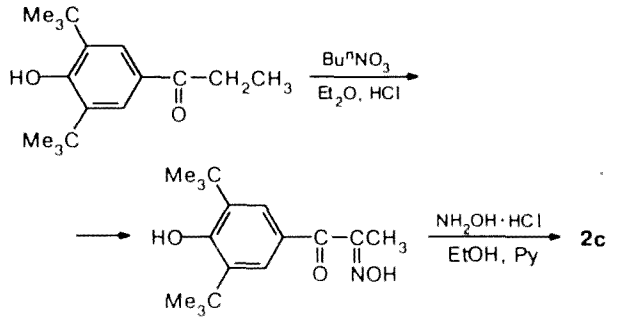
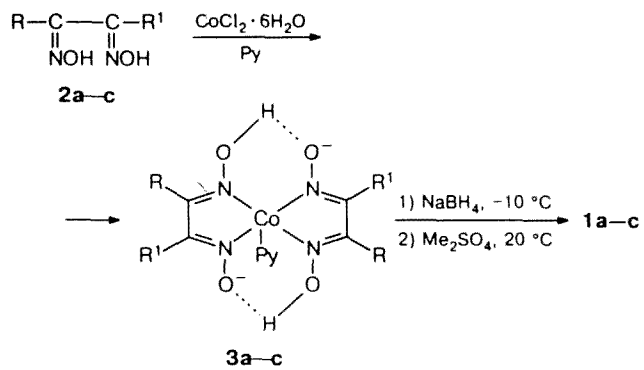
Dimethylglyoxime (**2a**), 1,2-dioximinodiphenylethane (**2b**) obtained according to an earlier described procedure,[5] and 1,2-dioximino-1-(3′,5′-di-*tert*-butyl-4′-hydroxyphenyl)propane (**2c**) synthesized from 1-(3′,5′-di-*tert*-butyl-4′-hydroxyphenyl)propanone-1 by the reaction given below were the organic ligands in the synthesis of complexes **1a—1c**:



A modified variant of the general method for the synthesis of methylcobaloximes,[6] developed for phenol-containing complex **1c** and used for the synthesis of compounds **1a—1c**, has been proposed in this work.

The reaction was carried out in two stages with the separation of cobaloxime pyridinates **3a—3c**:



The best conditions for the preparation of complex **3c** involve carrying out the reaction in an argon flow in the dark, using equimolar amounts of alkali because of the inclination of 2,6-di-*tert*-butylphenols to be oxidized with the formation of quinoid-type products in basic media.[7]

A significant requirement of methylation is that the process should be carried out under homogeneous conditions. In this connection, intermediate cobaloximes **3a—3c** were dissolved in a great amount of methanol and then treated with $NaBH_4$ and Me_2SO_4 in a flow of argon. A successive change in the oxidation state of the central metal ion thereby takes place: $Co^{II} \rightarrow Co^{I} \rightarrow Co^{III}$, accompanied by a change in the color of the reaction mixture that allows spectrophotometric monitoring of the course of the reaction.

Compounds **3a—3c** were isolated in the form of brown powders slightly soluble in organic solvents. This is explained by the fact that these systems exist as dimers with the *trans*-position of the axial bases, which dissociate in the solutions.[8] Methyl derivatives **1a—1c** are bright orange crystalline substances easily soluble in polar solvents. These compounds were characterized by the data of elemental analysis, by IR and ^1H NMR spectroscopy, and by their electronic absorption spectra.

The IR spectra of complexes **1c** and **3c** have characteristic absorption bands corresponding to stretching vibrations of the C=C and C=N multiple bonds in the 1540—1570 cm^{-1} range. The vibrations of the hydrogen bond O···H···O, which confirms the existence of the macrocyclic ligand, lie in the 1730—1760 and 3200—3400 cm^{-1} ranges, manifesting themselves as broadened bands. Phenol-containing complexes as well as the starting ligand **2c** retain the band of the stretching vibrations of the O—H bond in the 3630—3650 cm^{-1} range typical for non-associated hindered hydroxyl groups. This fact allows us to state that no oxidation of the phenol group of the ligand occurs during complex formation. The 428, 459, 536 cm^{-1} bands corresponding to the symmetric and asymmetric stretching vibrations of the Co—N bonds of the equatorial ligand, which are observed for similar systems in the 420—540 cm^{-1} range, were also identified for compound **1c**.[6]

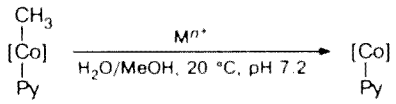
The ^1H NMR spectra confirm unambiguously that alkylation of the central metal ion takes place. The signals of the protons of the methyl group connected to Co lie in the strong field in the 0—1 ppm range.[9] The introduction of a strong base (Py) into the *trans*-axial position results in a considerable shift of the signal. For compounds **1a—1c** these values are found in the 0.74 ($CDCl_3$), 1.1 [$(CD_3)_2SO$], and 1.04 (Py) ppm ranges, respectively. The signals of *tert*-butyl groups (1.4 ppm), aromatic protons (7—8 ppm), and methyl groups of the ligand (2—2.5 ppm) are observed in the ^1H NMR spectrum of compound **1c**; a weak broadened signal of the O···H···O proton lies in the 18.6 ppm range (CD_3COCD_3).

The most informative method for identifying methylcobaloximes with a Co—CH_3 bond is electronic absorption spectroscopy. An allowed α-band[9] of low energy transition in the 400—500 nm range corresponds to charge transfer in the coordination site containing the Co—CH_3 fragment and is considered to be proof of the presence of a covalent axial metal—carbon bond. For methylcobaloxime pyridinate in aqueous ethanol this band was registered at 438 nm.[10] The λ_{max} values for the α-bands in the spectra of compounds **1a—1c** are given in Table 1.

Table 1. The λ_{max} values of the α-band in the electronic absorption spectra of compounds **1a—c** (nm)

Compound	Solvent		
	DMF	DMF/H_2O	CH_3OH/H_2O
1a	440	440	438
1b	450	449	448
1c	454	452	452

Dealkylation of methylcobaloximes **1a—1c** in the presence of heavy metals was performed in the presence of Cd^{2+}, Hg^{2+}, Sn^{4+}, Pb^{2+}, Pb^{4+} in order to determine the reactivity of phenol-containing complex **1c** in its main diamagnetic state.



The process was monitored spectrophotometrically by the change in the intensity of the α-band. The reactions were carried out under conditions corresponding to natural conditions (20 °C, pH 7.2, MOPS buffer, aerobic conditions). Water containing minor amounts of methanol (50 : 1, 50 : 2) was used as the solvent, which allowed the complexes to be soluble at their concentrations of 10^{-4}—10^{-5} mol L^{-1}. The use of aqueous solutions and neutral media also allowed us to prevent the oxidation of the phenol fragment, which could make the interpretation of the spectral data more complicated. In all cases reference experiments were carried out under the indicated conditions without the addition of metal salts. Without metal salts, the change in the intensity of the α-band due to the spontaneous decomposition of the compounds was observed after 10—15 days, whereas when metal salts were added the reactions took from a few minutes to 20 h (Table 2). A typical view of the spectral changes corresponding to the dealkylation process is shown for phenol-containing complex **1c** in Fig. 1.

Table 2 summarizes the dealkylation time for methylcobaloximes **1a—1c** under identical conditions in the presence of metal ions with oxidation states +2 and +4. $Cd(OCOMe)_2$, $HgCl_2$, $Hg(OCOC_6H_4OH\text{-}o)_2$, Me_2SnCl_2, $Pb(OCOMe)_2$, and $(NH_4)_2PbCl_6$ were used as substrates. It can be seen from Table 2 that methylcobaloxime **1c** with a phenol substituent holds an intermediate position in the series of complex activity in the dealkylation reaction. This fact seems to be due to the inclusion of aromatic substituents into the conjugation system of the equatorial ligand, which leads to an increase in its donor character and enhances the tendency of the Co—C bond to undergo cleavage.[9] In this case, the only effect of the introduction of a sterically

Table 2. Duration of dealkylation of methylcobaloximes **1a—1c** in the presence of metal salts (τ/min)

Compound	M^{IV}			M^{II}		
	Pb	Sn	Hg[a]	Cd	Pb	Hg[b]
1b	2	6	12	14	17	25
1c	13	25	120	180	210	240
1a	40	210	1080	1200	1920	2400

Note. H_2O/MeOH, 25 : 1, 20 °C, pH 7.2, the concentrations of compounds **1a—1c** are $4 \cdot 10^{-4}$ mol L^{-1}.
[a] Mercury chloride. [b] Mercury salicylate.

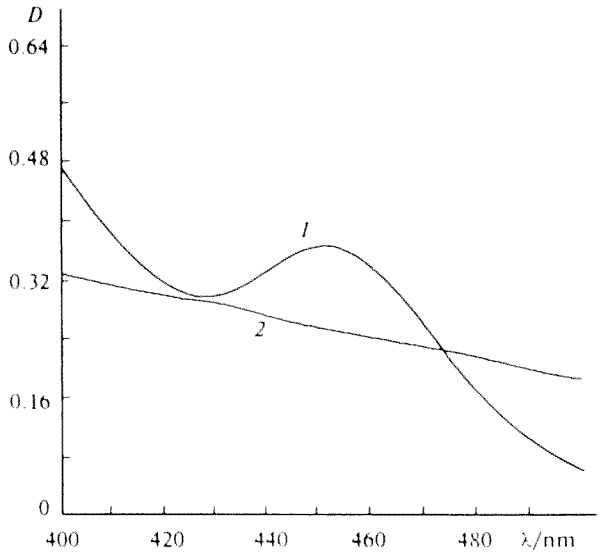


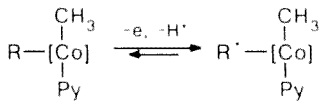
Fig. 1. A spectral picture of the dealkylation of methylcobaloxime **1c** in the presence of $HgCl_2$ in H_2O/MeOH (25 : 1), 20 °C, pH 7.2: *1* refers to the beginning of the reaction, and *2* refers to the end of the reaction.

hindered phenol fragment into the ligand of the complex is its influence as an aryl substituent in the series of ligands: bis(dimethylglyoxymate) (**1a**), bis(methylarylglyoxymate) (**1c**), and bis(diphenylglyoxymate) (**1b**).

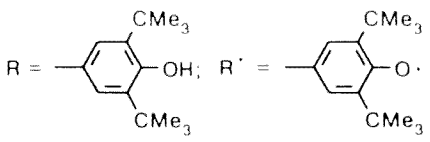
Dealkylation of methylcobaloximes **1a—1c** was thoroughly studied with $HgCl_2$ as the substrate. The reasonably linear character of the time dependence of the log of the methylcobaloxime concentrations (Fig. 2) is consistent with the earlier known data[1] that in an excess mercury salt the reaction is first order with respect to methylcobaloxime.

Thus, it is shown that in the absence of oxidants the presence of a phenol substituent on the periphery of the ligand does not cause significant changes in the behavior of methylcobaloxime during dealkylation in the presence of metal ions.

However, if an oxidant is present in the medium, oxidation of the phenol fragment in compound **1c** can proceed to give a free radical form of a complex of trivalent cobalt with saturated coordinate bonds.



1c



In this case one can expect that the unpaired electron of the ligand has an effect on the properties of the Co—C bond.

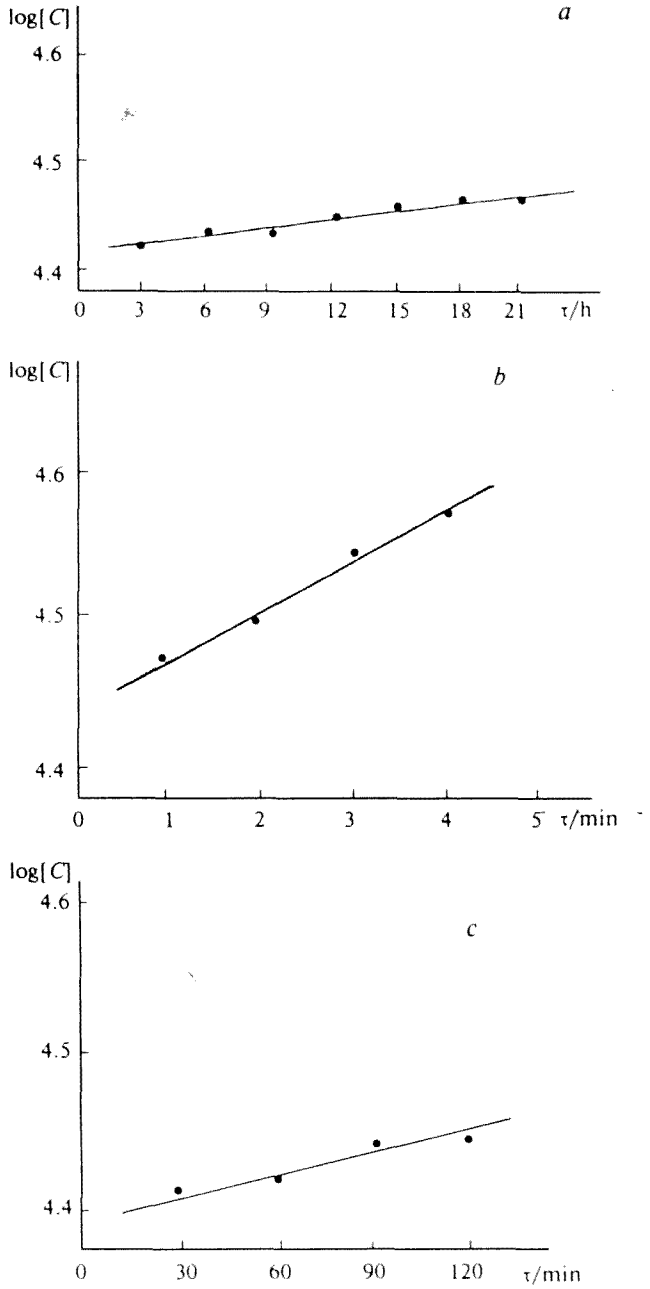
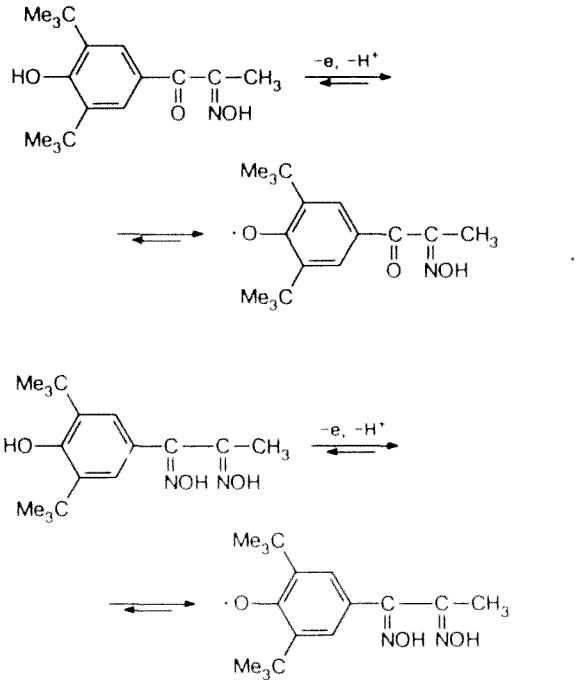


Fig. 2. Logarithmic time-dependence of the concentration of methylcobaloximes **1a** (*a*), **1b** (*b*), and **1c** (*c*) in the presence of $HgCl_2$ (H_2O/MeOH, pH 7.2, 20 °C). The initial concentrations of the complexes were $3.6 \cdot 10^{-5}$ mol L^{-1}, the initial concentration of $HgCl_2$ was $1.8 \cdot 10^{-4}$ mol L^{-1}.

The ESR method was used to study the interaction of the free radical of the ligand periphery with the coordination site of the complex. Phenoxy radicals were generated from the fragments of 2,6-di-*tert*-butylphenol by heterophase oxidation of the compounds with PbO_2. The spectral data of the radicals of methylated complex **1c** and its non-methylated analog **3c** were analyzed by comparing them with the spectra of the monooxime and dioxime of the corresponding α-ketone, their organic precursors.



The ESR spectra of organic radicals of the ligands are presented in Fig. 3. In the first case (Fig. 3, *a*) the hyperfine structure of the spectrum consists of six lines caused by the interaction of the unpaired electron with the two *meta*-protons of the phenoxy ring (a_{2H} = 2 G) and the nucleus of the nitrogen atom (a_N = 0.75 G); the *g*-factor is 2.0054. The spectrum of the dioxime radical (Fig. 3, *b*) contains eight lines, suggesting interaction with the *meta*-protons (a_{2H} = 2 G), the nucleus of the nitrogen atom, and the proton of a hydroxyl group ($a_N = a_H$ = 3.75 G); the *g*-factor is 2.0054.

Oxidation of non-methylated cobaloxime **3c** results in the formation of the corresponding paramagnetic

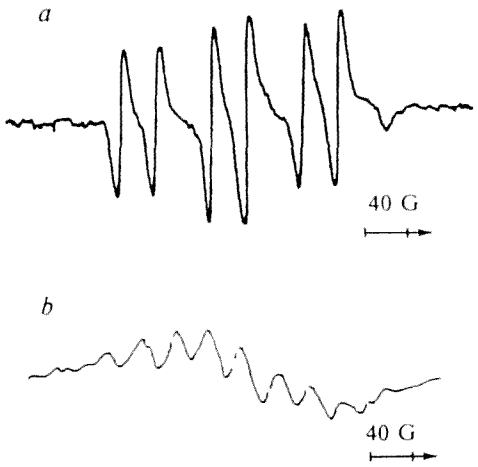


Fig. 3. The ESR spectra of the radicals of monooxime (*a*) and dioxime (*b*) 1-(3′,5′-di-*tert*-butyl-4′-hydroxyphenyl)propanediones-1,2 (toluene, 20 °C, PbO_2).

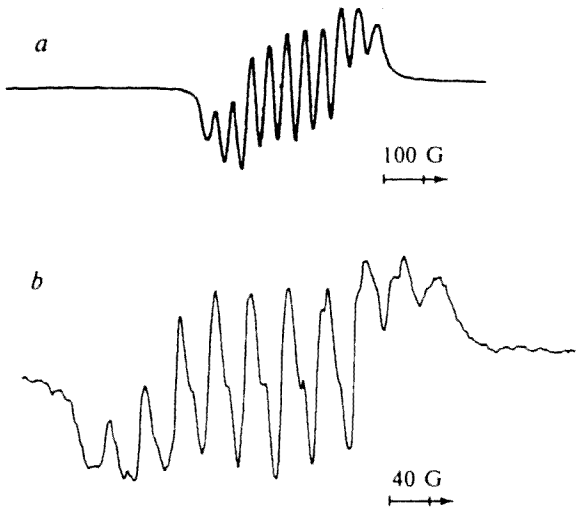
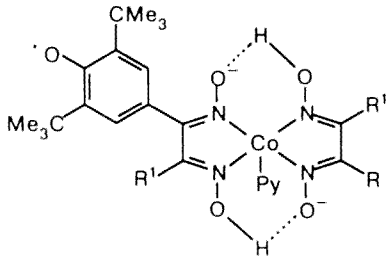
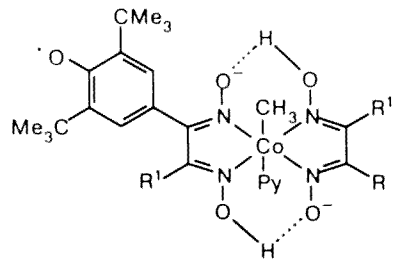


Fig. 4. The ESR spectra of the radicals of cobaloxime **3c** (*a*) and methylcobaloxime **1c** (*b*) (toluene, 20 °C, PbO_2).

product with an unpaired electron in the organic part of the molecule, which is evidenced by the value of the g-factor (2.005). The spectrum consists of ten lines representing the interaction of the unpaired electron with ^{14}N and ^{59}Co nuclei having equal hyperfine interaction constants ($a_N = a_{Co} = 4.25$ G). The interaction with the *meta*-protons cannot be seen since the values of a_{2H} lie within the line widths (Fig. 4, *a*).



Oxidation of methylcobaloxime **1c** also results in the formation of a free radical product with a g-factor of 2.005, but the spectral picture is a more complex multiplet (Fig. 4, *b*). Despite the general coincidence of the spectral parameters with the analogous values for the radical of compound **3c**, each line of the spectrum has additional splitting, caused by the interaction of the unpaired electron with the methyl group at the Co atom.



The free radical forms of complexes **1c** and **3c** are relatively stable in solutions at room temperature and do not undergo spontaneous decomposition to liberate the radicals of the ligand or the products of their transformations into the solution.

Oxidation of methylcobaloxime **1c** was also performed with the superoxide ion $O_2^{-\cdot}$ in DMF. In addition to ESR, which confirmed formation of the radical, electronic absorption spectra were recorded and examined. To generate the paramagnetic product in a spectrophotometric cell, KO_2 was added to a solution of compound **1c** in DMF in the presence of 18-crown-6 ether. A bathochromic shift of the α-band to 466 nm was observed in the spectrum, which corresponds to the idea[9] that the electronic density at the cobalt atom increases and coincides with the analysis of ESR data. The action of this oxidant on methylcobaloximes **1a** and **1b**, which do not contain a phenol fragment, does not result in a shift of the bands in the electronic absorption spectra.

In contrast to the spontaneous decomposition of methylcobaloxime **1c**, which occurs over a period of 10—15 days, the free radical form is demethylated almost completely in 5—6 h, which suggests easy cleavage of the Co—C bond in the presence of the unpaired electron in the ligand. This fact was confirmed by ESR while studying dealkylation in the presence of metal salts. An oxidized form of complex **1c** containing a phenoxy fragment as a substituent and with an ESR spectrum characteristic of a methyl derivative (Fig. 4, *b*), was generated in the first stage. When a metal salt was added to the solution, the spectral picture changed instantaneously. The additional splitting corresponding to the presence of the methyl group at the Co atom disappeared and the spectrum observed corresponded entirely to the spectrum of the oxidized form of nonmethylated cobaloxime (Fig. 4, *a*), which can be transformed into the initial diamagnetic compound **3c** by reduction. The latter can, in turn, be reduced to a Co^I complex and alkylated to give compound **1c**, which was confirmed using spectrophotometry. This fact allows us to conclude that in the presence of heavy metal ions demethylation of the paramagnetic complex occurs almost instantaneously.

Thus, a comparison of the times required for the dealkylation of methylcobaloximes **1a—1c** (Table 2) with the time of the demethylation reaction for the paramagnetic form of complex **1c**, which amounts to a few seconds, indicates that the presence of an unpaired electron in the methylcobaloxime ligand significantly enhances its reactivity.

Therefore, the ligands in methylcobaloximes are capable of participating in the redox process. An unpaired electron, which appears on the periphery of the ligand, thereby interacts with the metal through the system of conjugated bonds, enhancing the donor properties of the equatorial ligand and facilitating cleavage of the Co—C bond.

Table 3. The data of elemental analysis and the yields of compounds **1a—1c** and **3a—3c**

Compound	Yield (%)	Found / Calculated (%)			Molecular formula
		C	H	N	
1a	65	43.54 43.86	5.62 5.74	17.94 18.28	$C_{14}H_{22}N_5O_4Co$
1b	62	64.56 64.66	4.78 4.75	10.95 11.09	$C_{34}H_{30}N_5O_4Co$
1c	64	62.82 62.91	7.63 7.60	9.20 9.17	$C_{40}H_{58}N_5O_6Co$
3a	55	41.85 42.39	4.98 5.16	19.04 19.02	$C_{13}H_{19}N_5O_4Co$
3b	38	63.82 64.29	4.07 4.38	11.35 11.36	$C_{33}H_{27}N_5O_4Co$
3c	44	62.50 62.57	7.02 7.35	9.49 9.36	$C_{39}H_{55}N_5O_6Co$

Note. Compounds **1—3** decompose between 200 and 300 °C.

Experimental

The IR spectra were recorded on UR-20 and Brucker IR Fourier spectrophotometers (Nujol and KBr). The ^1H NMR spectra were recorded on a Tesla spectrometer (80 MHz) in $CDCl_3$, Py, $(CD_3)_2CO$, and $(CD_3)_2SO$ (with or without HMDS as the internal standard). The electronic absorption spectra were obtained with a Varian Cari-219 spectrophotometer in $CHCl_3$, MeOH, H_2O, and DMF. The ESR spectra were recorded on a Varian E-12A instrument.

1,2-Dioximinodiphenylethane (2b) was obtained from benzyl according to the procedure given in Ref. 5 in a 78 % yield, m.p. 240 °C (from pentane) (*cf.* Ref. 5: m.p. 240 °C).

1-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)-2-oximinopropanone-1. *n*-Butyl nitrite (0.04 mol) was added in small portions to a suspension of 1-(3′,5′-di-*tert*-butyl-4′-hydroxyphenyl)propanone-1[11] (0.025 mol) in 80 mL of ether, while a flow of HCl was passed constantly through the suspension. After all of the *n*-butyl nitrite had been added, HCl was bubbled for an additional 30 minutes, and then the reaction mixture was allowed to stand for 12 h. The solution in ether was extracted with a 10% NaOH solution, and the extract was poured into a mixture of conc. HCl and ice. The white precipitate obtained was washed with water. Yield 65 %, m.p. 190 °C (from toluene). Found: C, 70.57; H, 8.50; N, 4.66. $C_{17}H_{25}NO_3$. Calculated: C, 70.10; H, 8.59; N, 4.81. M^+ 291. IR (KBr, ν/cm^{-1}): 3543 (OH); 3304 (NOH); 1649 (C=O); 1572, 1597 (C=N). ^1H NMR (δ, $CDCl_3$): 1.38 (s, 18 H, 6 Me); 2.12 (s, 3 H, Me); 5.2 (s, 1 H, OH); 7.6 (s, 2 H, arom.). UV (λ_{max}/nm, $CHCl_3$): 237.7; 301.3.

1,2-Dioximino-1-(3′,5′-di-*tert*-butyl-4′-hydroxyphenyl)propane (2c). The monooxime (0.005 mol) obtained in the preceding reaction was dissolved in a mixture of pyridine (20 mL) and anhydrous ethanol (20 mL). Hydroxylamine hydrochloride (0.006 mol) was added to the solution obtained and was refluxed for 4.5 h. The reaction mixture was concentrated to a small volume, and a white crystalline precipitate was filtered off and washed with toluene. Yield 75 % (from toluene), m.p. 223—225 °C. Found: C, 66.78; H, 8.37; N, 9.27. $C_{17}H_{26}N_2O_3$. Calculated: C, 66.66; H, 8.50; N, 9.15. M^+ 306. IR (KBr, ν/cm^{-1}): 3639 (OH); 3223 (NOH); 1643 (C=N). ^1H NMR (δ, $CDCl_3$): 1.33 (s, 18 H, 6 Me); 2.20 (s, 3 H, Me); 5.6 (s, 1 H, OH); 7.4 (s, 2 H, arom.); 10.26 (br.s., 2 H, NOH). UV (λ_{max}/nm, MeOH): 223.6; 281.4.

General procedure for preparation of cobaloximes 3a—3c. A mixture of compounds **2a—2c** (0.015 mol) and $CoCl_2 \cdot 6H_2O$ (0.0075 mol) in 20 mL of MeOH was stirred in an argon flow, and then NaOH (0.015 mol) in water and pyridine (0.0075 mol) were added. The sediment that precipitated was filtered off and washed with water and ethanol. Yields and data of elemental analysis are given in Table 3.

General procedure for preparation of methylcobaloximes 1a—1c. Cobaloximes **3a—3c** (0.0037 mol) were dissolved in MeOH, cooled to −10 °C, and an argon flow was passed through the solution. Then a 50 % aqueous solution of NaOH (0.0037 mol) and $NaBH_4$ (0.001 mol) was added in small portions. The reaction mixture turned green. Then dimethyl sulfate (0.004 mol) was added dropwise. The temperature was raised to 20 °C, and the reaction mixture was stirred for 1.5 h in a reaction vessel shielded from the light, with an argon flow passing through it. Then the mixture was poured into water with a small amount of pyridine, and a bright orange precipitate was filtered off and washed with water. Yields and data of elemental analysis are given in Table 3.

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