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COBALOXIME TEMPLATE REACTIONS

I. THE FORMATION OF *N*-NITROSAMINES

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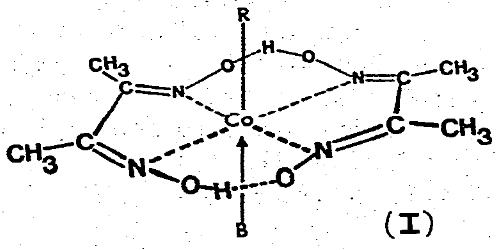
Summary

The synthesis of a potent carcinogen, *N*-nitroso-*N*-methylaniline, employing a bis(dimethylglyoximato)cobaltate template is described. Carbon bonded *N*-methyleneaniline adducts of cobaloxime with pyridine, NO_2^- or CN^- in the basal (sixth) coordination position of the cobalt atom were prepared and isolated. These cobaloxime methyleneaniline adducts were found to readily undergo nitrosation when treated with nitrous acid. The resulting *N*-nitrosamine adducts were characterized by IR, NMR and mass spectroscopy. Interesting *trans* effects of the basal substituents are noted. Final template reaction products were identified by thermal degradation and chemical cleavage with Cr^{2+}.

Introduction

Cobaloximes, bis(dimethylglyoximato)cobaltate species, are octahedral cobalt complexes, I, which have been cited as being simple models for the naturally occurring, highly complex, vitamin B_{12} molecule [1]. The reactions of reduced cobaloximes with alkyl halides [1, 2] or other substrates [3] which are amenable to nucleophilic attack are quite rapid, usually quantitative, and the cobalt—carbon bonds formed in these reactions are in general quite stable [1, 4].

In this paper we describe several methyleneaniline-cobaloxime adducts that have been prepared in our laboratory. Evidence that nitrosation reactions occur on the secondary amine site of the cobaloxime adducts to yield potentially potent carcinogens, *N*-nitrosamines [5], is presented.



(I)

Experimental

All chemicals used in this study were purchased from commercial sources and were of the highest purity available. They were used without further purification. Infrared spectra were taken on a Perkin—Elmer Infracord Spectrometer. Mass spectroscopy data were collected on a Varian Mat 311 mass spectrometer operating at 25°C and 10^{-6} mm. Carbon-13 NMR spectra were recorded on a Varian Associates XL-100/15 spectrometer operating at 23.5 kilogauss.

All reactions reported in this study were virtually quantitative and the compounds in the solid state are air stable and can be isolated as described below.

Complete exclusion of oxygen is vital for reactions involving the Co^I species.

Caution: The nitrosamine adducts should be handled with gloves so that skin contact is avoided. Experiments involving these compounds should be performed in highly efficient hoods to avoid possible contact with reaction products.

Sodium nitrobis(dimethylglyoximato)-C-methyleneanilinatocobaltate, compound A

Schrauzer's method [6] was used to obtain the diaquocobaloxime(II) species, which was subsequently reduced by hydrogen gas to produce the reactive cobaloxime(I) species. The experimental conditions for the reaction between the (Co^I) species and aniline and formaldehyde have only been "discussed" elsewhere [3], but are presented in detail here.

Dry methanol (400 ml) was placed in a 1l, three-necked, round-bottom flask. Dry nitrogen gas (deoxygenated) was bubbled through the solution and 24.9 g (0.1 mol) of cobaltous acetate and 23.2 g (0.2 mol) of dimethylglyoxime was added and stirred under nitrogen for 1 h. At this time the nitrogen was replaced by a stream of hydrogen. and with rapid stirring. 9.3 ml (0.1 mol) of aniline and 9.4 ml (0.125 mol) of 40% formaldehyde were injected into the system. After the cobaloxime completely dissolved (1 h) the hydrogen was removed and 6.9 ml (0.1 mol) of $NaNO_2$ was added. An equal volume of water was added to the solution and the product was stirred for an additional hour. After standing for 12 h the product was filtered, recrystallized from methanol, then washed with acetone ether and dried in vacuo. (Anal.: Found: C, 38.92; H, 5.09; N, 17.17. $Na(C_{15}H_{22}N_6O_6Co)\cdot 2\ CH_3OH$ calcd.: C, 38.70; H, 5.24; N, 16.93%.)

An alternative method of preparing this compound will follow the preparation of Compound E later in this section (vide infra).

Sodium nitrobis(dimethylglyoximato)-C-methylene-N-nitrosoanilinatocobaltate, compound B

Compound A, 21.5 g (0.05 mol), was dissolved in a minimum amount of methanol. To this solution was added 3.45 g (0.05 mol) $NaNO_2$ followed by 15 ml of glacial acetic acid. The reaction mixture was stirred for 1 h. The solution was then reduced to half of its original volume and diethyl ether was slowly added to precipitate the product. The product was filtered, washed with ether and dried in vacuo. This compound may be recrystallized from acetone to yield dark brown crystals. (Anal.: Found: C, 40.81; H, 5.37; N, 16.01. $Na(C_{15}H_{21}N_7O_7Co)\cdot 2\ C_3H_6O$ calcd.: C, 41.37; H, 5.41; N, 16.09%.)

Potassium cyanobis(dimethylglyoximato)-C-methyleneanilinatocobaltate, compound C

The method of preparation of Compound A was duplicated exactly except that 6.7 g of KCN (0.1 mol) was substituted for the $NaNO_2$ used in its preparation. The product was filtered, washed with acetone and ether and dried in vacuo. (Anal.: Found: C, 36.05; H, 5.73; N, 16.23. $K(C_{16}H_{22}N_6O_4Co)\cdot 4\ H_2O$ calcd.: C, 36.09; H, 5.63; N, 15.78%.)

Potassium cyanobis(dimethylglyoximato)-C-methylene-N-nitrosoanilinatocobaltate, compound D

Compound B, 23.4 g (0.05 mol) was dissolved in a minimum amount of methanol and 3.35 g (0.05 mol) of KCN was added. An equal volume of water was added and the solution was stirred for 1 h and then left for 12 h. The product was collected, recrystallized from acetone, washed with ether and dried in vacuo. (Anal.: Found: C, 43.87; H, 5.12; N, 16.47. $K(C_{16}H_{21}N_7O_5Co)\cdot 2\ C_3H_6O$ calcd.: C, 43.63; H, 5.45; N, 16.19%.)

Bis(dimethylglyoximato)-C-methyleneanilinatopyridinatocobalt(III), compound E

Dry methanol (400 ml) was placed into a 1 l three-necked round bottom flask and dry nitrogen gas (deoxygenated) was passed through the solution. Cobaltous acetate, 24.9 g (0.1 mol), dimethylglyoxime, 23.2 g (0.2 mol) and pyridine, 8.1 ml (0.1 mol), were added and the mixture stirred under nitrogen for 1 h. The nitrogen was then replaced by a stream of hydrogen gas and aniline 9.3 ml (0.1 mol) and a 40% formaldehyde solution, 9.4 ml (0.125 mol) were added. After 1 h the solution was doubled in volume by the addition of water and allowed to stand for 12 h. The crystalline product was collected, washed with ether and dried in vacuo. (Anal.: Found: C, 46.76; H, 5.95; N, 16.65. $(C_{20}H_{27}N_6O_4Co)\cdot 2.5\ H_2O$ calcd.: C, 46.79; H, 6.03; N, 16.18%.)

Compound A

This complex was also obtained from the reaction of stoichiometric quantities of Compound E and $NaNO_2$ dissolved in a minimum amount of methanol containing 5% acetic acid. An equal volume of water was added and the solution was allowed to stand for 12 h. The product was collected, recrystallized and analyzed. The results of the analysis were virtually identical to those given earlier for Compound A.

Cr^{2+} Cleavage reactions

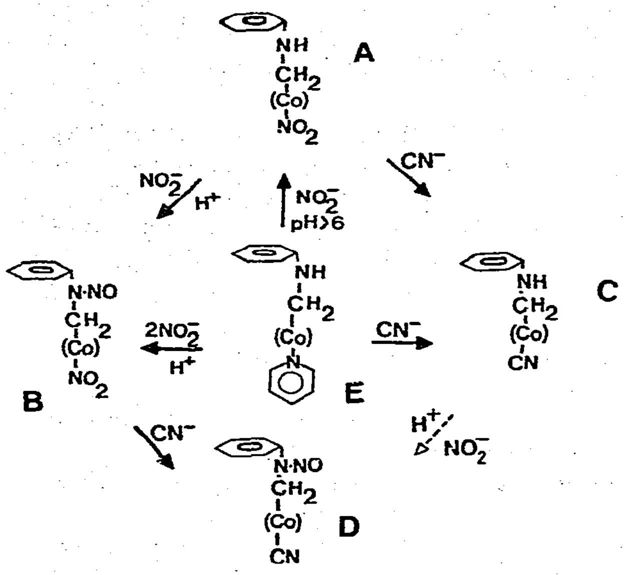
The cobalt—carbon bond in Compound A was cleaved as follows: A solution (100 ml) of methanol containing 4 g (9.1×10^{-3} mol) of Compound A was stirred under nitrogen for 0.5 h. To this solution was added 100 ml of 0.1 *M* aqueous Cr^{2+} solution and the reaction mixture was stirred for 24 h. The resulting solution was filtered and allowed to stand in the air for an additional 24 h, then extracted with five 20 ml portions of benzene. The combined benzene fractions were filtered, the benzene removed by evaporation and the residue identified as *N*-methylaniline by mass spectroscopy.

Compound B, when treated in an analogous manner, yielded a product that was similarly identified as *N*-nitroso-*N*-methylaniline.

Results and discussion

Scheme 1 illustrates the interconversion reactions that are described in detail in the Experimental Section (charge types have been omitted for purposes of clarity).

SCHEME 1



Elemental analysis shows that Complex E has a composition corresponding to that indicated in Scheme 1. The infrared data, given in Table 1 for this compound, show all of the characteristic absorbance bands observed for planar metal complexes employing dimethylglyoxime ligands such as $Ni^{II}(dmgH)_2$ [7], Cu^{II} $(dmgH)_2$ [8], $Co^{III}(dmgH)_2(NH_3)_2$ [8] as well as the other complexes studied in this work. Mass spectral data also confirmed the presence of the pyridine adduct. Upon addition of one equivalent of NO_2^- to an acidic solution of Complex E, the crystalline A complex was formed. An infrared investigation of this complex resulted in no absorbances arising from pyridine molecules, but rather an emergence of rather strong absorbances at 1398, 1300 and 800 cm^{-1}. These new bands correlate well with other cobalt-bonded NO_2 absorbances and are diagnostic of the presence of this group [9]. No additional absorbances in the 1120 to 1140 cm^{-1} region were present. However, treatment of Compound A with an additional mole of nitrite in acid media yielded a complex with an infrared absorbance band at 1120 cm^{-1}, labeled Complex B in Scheme 1 (see Table 1). This absorbance is attributed to the presence of an N-bonded N=O group [10]. It was also found that compound B could be formed directly when compound E was treated with two equivalents of nitrous acid. All attempts to nitrosate the nitrogen in the carbon bonded methyleneaniline adduct of Complex E (pyridine in the basal position), resulted in the complete displacement of the basal pyridine by NO_2^- before any *N*-nitrosated product (*N*-nitrosamine) could be detected.

To confirm the structural assignment of Complex A, a mass spectrum of the compound was obtained. Major *m/e* peaks characteristic of *N*-methylaniline were

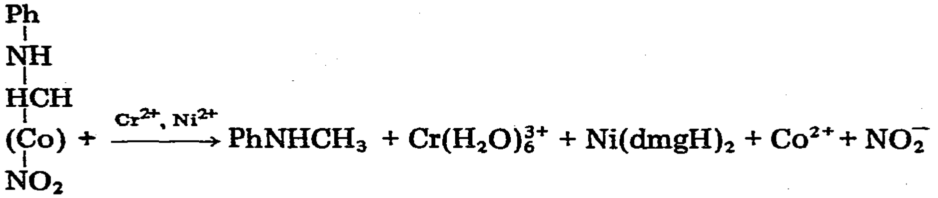
TABLE 1

CHARACTERISTIC FREQUENCIES OF THE IR SPECTRA[a] (cm^{-1}) OF COMPOUNDS A THROUGH E.

Complex	(dmg) (C=N)	(NO_2)	(CN)	(N—NO)
A	1508	1398 1300 800		
B	1520	1400 1300 824		1120
C	1530(br)		2100	
D	1530		2100	1140
E	1550			
$Ni^{II}(dmgH)_2$[b]	1560			
$Cu^{II}(dmgH)_2$[c]	1580			
$Co(dmgH)_2(NH_3)(NO_2)$[c]	1570	1450 1312 810		
$Co^{III}(dmgH)_2NO_2\cdot H_2O$[d]		1453 1321 819		

[a] 1% solid mixture in KBr. [b] Ref. 9. [c] Ref. 10. [d] Ref. 11.

observed, and no peaks representative of *N*-nitroso-*N*-methylaniline were present. As a further test, Compound A was treated with excess Cr^{2+} in a mildly acidic aqueous/methanol solution to yield the reaction:



$$\begin{array}{l}\mathrm{Ph}\\ \mid\\ \mathrm{NH}\\ \mid\\ \mathrm{HCH}\\ \mid\\ \mathrm{(Co)} + \xrightarrow{\mathrm{Cr^{2+},\ Ni^{2+}}} \mathrm{PhNHCH_3} + \mathrm{Cr(H_2O)_6^{3+}} + \mathrm{Ni(dmgH)_2} + \mathrm{Co^{2+}} + \mathrm{NO_2^-}\\ \mid\\ \mathrm{NO_2}\end{array}$$

The freed dimethylglyoxime was converted to the bis(dimethylglyoximato)-nickelate(II) complex, by the addition of a stoichiometric amount of Ni^{2+}, and removed by filtration. Benzene extraction of this solution then gave a product which was identified by mass spectroscopy as *N*-methylaniline. These results show that the NO_2 group was not bonded to the organic ligands, and must therefore be bonded to the cobalt.

Having firmly identified Complex A, its nitrosation product (Complex B) was then analyzed by mass spectroscopy. The characteristic *m/e* peak for *N*-nitroso-*N*-methylaniline was observed for this complex as well as for the product of the Cr^{2+}·cleavage reaction with Compound B. This suggested that the structure of of Compound B is indeed that indicated in Scheme 1. To confirm the idea that the point of attachment of the N=O group is indeed on the nitrogen atom of the methyleneaniline adduct, and not elsewhere on the molecule, a ^{13}C FT NMR spectrum of product B was obtained. The proton decoupled ^{13}C spectrum of Compound B indicated that the N=O substituent was not attached to the phenyl ring of the adduct because only four carbon resonances were observed instead of a possible five as would be the case if it possessed N=O substitution anywhere on the ring (except the *para* position). Further, three of these four ring carbon resonances exhibit nuclear Overhauser enhancements (NOE), a phenomenon commonly observed in proton decoupled ^{13}C spectra of carbon atoms directly bound to protons. If *para* substitution had occurred, only two of the carbon resonances would exhibit NOE and the other two would not. Also, from a chemical point of view, one would not expect N=O substitution to occur on the phenyl ring since the reaction conditions were such that the electrophilic requirements for such reactions were not met [11].

The addition of cyanide ion to a methanolic solution of Compound A resulted in the formation of Compound C whose IR spectrum showed no trace of the cobalt-bonded NO_2 group (1398, 1300 and 800 cm^{-1} as in A) but instead exhibited a strong absorbance at 2100 cm^{-1} indicative of cobalt bonded CN^-. Elemental analysis confirmed the composition of the compound as being that given in Scheme 1. Cyanide addition to Compound B (Scheme 1) also supported the idea that NO_2 replacement does occur upon the addition of CN^-, since the IR spectrum of the product of this reaction (Compound D) showed no evidence of the cobalt bonded NO_2 group but did exhibit a Co—CN stretching frequency at 2100 cm^{-1}. The N—N=O absorbance frequency for Compound B was only shifted slightly as a result of the CN^-—NO_2^- exchange in the basal position of the molecule (see Table 1).

Attempts to nitrosate the nitrogen of the *N*-methyleneaniline adduct of Complex C were virtually unsuccessful. Only trace quantities of Complex D could be produced from the acidic nitrosation after two weeks of reaction. This result seems to indicate that the substituent in the basal position of the complex has a direct influence on the reactivity of the nitrogen atom of the methyleneaniline adduct toward nitrosation. Similar so-called *trans* effects have been observed for other cobaloxime complexes [12, 13]. The exact nature and extent of such effects will be the text of future studies in this laboratory.

Acknowledgments

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