The Bromination and Mercuration of bis-Dimethylglyoxymato-(alkyl)pyridinecobalt(III), Alkyl Cobaloxime[1]

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(Received October 2, 1975)

The bromination and mercuration of *cis*-2-methoxycyclohexyl(pyridine)cobaloxime (I) gave *trans*-1-bromo-2-methoxycyclohexane (V) and *trans*-2-methoxycyclohexylmercury(II) chloride (VII), along with other by-products derived from the cyclohexene formed by β-elimination. β-Elimination is an exclusive degradation path with *trans*-2-hydroxycyclohexyl(pyridine)cobaloxime(II). The reaction of *cis* and *trans*-4-*t*-butylcyclohexyl(pyridine)cobaloximes (III and IV) gave *trans* and *cis*-1-bromo-4-*t*-butylcyclohexanes (X and XI), and *trans* and *cis*-4-*t*-butylcyclohexylmercury(II) chloride, with an exculsive or preferential inversion at the reaction center. These results show that the S_E2 reaction of alkyl cobaloxime takes a stereochemical course of inversion.

The electrophilic rupture of the alkyl group from cobalamine, the coenzyme B_{12} derivative,[2] is considered to be a simple metabolic pathway to produce methane, acetic acid, and methyl mercurial. Especially, methyl cobalamine has been recognized to be responsible for the transformation of mercury(II) ion into dimethylmercury in the sludge of river and sea, which causes a serious pollution problem.[3] Schrauzer[4] demonstrated that bis-dimethylglyoxymato(alkyl)pyridinecobalt(III) (the conventional name, alkyl cobaloxime, will be used hereafter) constituted a superior model system for the alkyl derivative of the B_{12} coenzyme. Much attention has been paid to the stereochemistry of the electrophilic displacement of alkyl σ-metal complexes, and the steric courses of both retention and inversion have been reported.[1,5-12] Kinetic studies have established the nature of these electrophilic reactions of alkyl cobaloximes to be a bimolecular substitution, a S_E2 reaction.[13,14] We reported in preliminary form about the steric consequence of the bromination and mercuration of alkyl cobaloxime;[1] in this paper we wish to report the details of our study.

Experimental

Preparation of cis-*2-Methoxycyclohexyl(pyridine)cobaloxime (I) and* trans-*2-Hydroxycyclohexyl(pyridine)cobaloxime (II).* Cobaloxime I was synthesized by the reaction of *trans*-1-bromo-2-methoxycyclohexane (5.0 g) with the cobaloxime anion prepared *in situ* from $CoCl_2 \cdot 6H_2O$ (5.95 g), dimethylglyoxime (5.80 g), sodium hydroxide (2.0 g), pyridine (2.0 g), and sodium tetrahydroborate (200 mg)under nitrogen in methanol (90 ml) at 0 °C for 1 h and at room temperature for 12 h. The reaction mixture was condensed to *ca.* 30 ml under reduced pressure, and the residue was extracted with chloroform (30 ml×3) after the addition of water (30 ml). The condensation of the extract after drying over sodium sulfate gave a residue containing cobaloxime I. The separation of I from the residue was achieved by column-chromatography on Florisil (30 g), eluting with benzene (unreacted 1-bromo-2-methoxycyclohexane) and chloroform (cobaloxime I). The repeated chromatography of the latter fraction on Florisil gave 3.85 g (32%) of the pure I.

The cobaloxime, II, was synthesized from cyclohexene oxide by a similar method, but using hydrogen as the reducing agent, in a 24% yield. Spectroscopic data showed the I and II cobaloximes to be identical with the compounds described by Jensen *et al.*[15]

I, NMR ($CDCl_3$): 8.7—7.1 (5H, pyridine), 3.30 (broad singlet, $W_{1/2}$=9 Hz, 1H), 3.15 (singlet, 3H), 2.10 (singlet, 12H), and 2.1—0.9 ppm (δ) (multiplet, 9H).

II, NMR ($CDCl_3$): 8.7—7.1 (5H, pyridine), 3.05—2.70 (sextet, $W_{1/2}$=19 Hz, 1H), 2.07 (singlet, 6H), 2.13 (singlet, 6H), and 2.1—0.8 ppm (δ) (multiplet, 9H).

Preparation of cis-*4t-Butylcyclohexyl(pyridine)cobaloxime (III) and* trans-*4-t-Butylcyclohexyl(pyridine)cobaloxime (IV).* Cobaloxime III was synthesized in essentially the same way as cobaloxime I, using *trans*-4-*t*-butylcyclohexyl tosylate. The reaction period was prolonged to 21 h, and the crude product was chromatographed on Florisil to give the unreacted tosylate in a benzene eluate and the cobaloxime III in a chloroform eluate. The yield was poor (7.7%), but it was fruitless to continue the reaction further because of the deterioration of the cobaloxime anion. The reaction of *cis*-4-*t*-butylcyclohexyl tosylate with the cobaloxime anion in the same manner for 13 h gave the cobaloxime IV in a higher yield (40.7%).

III, mp 110—120 °C (dec.). Found: C, 54.47; H, 7.40; N, 13.59%. Calcd for $C_{23}H_{38}N_5O_4Co$: C, 54.43; H, 7.55; N, 13.80%. IR(KBr): 2690, 1600, 1550, 1448, 1365, 1232, 1090, and 520 cm^{-1}. NMR ($CDCl_3$): 8.5—7.0 (5H, pyridine), 2.10 (singlet, 12H), 1.9—0.8 (10H), and 0.77 ppm (δ) (singlet, 9H).

IV, mp 150—160 °C (dec.). Found: C, 54.34; H, 7.48; N, 13.92%. Calcd for $C_{23}H_{38}N_5O_4Co$: C, 54.43; H, 7.55; N, 13.80%. IR (KBr): 2940, 1595, 1550, 1445, 1360, 1230, 1082, and 515 cm^{-1}. NMR ($CDCl_3$): 8.4—7.0 (5H, pyridine), 2.10 (singlet, 12H), 1.9—0.8 (10H), and 0.76 ppm (δ) (singlet, 9H).

Bromination of the Cobaloximes (I and II). To a solution of the I cobaloxime (120 mg) in dichloromethane (50 ml) we added, drop by drop, a solution of bromine (42 mg, 1.0 equivalent) in benzene (3 ml) under cooling to −70 °C. After stirring for 3 h under argon, the reaction mixture was passed through a column of Florisil (20 g) to remove the inorganic complex formed. The subsequent evaporation of the eluate gave a mixture (11 mg) of *trans*-1-bromo-2-methoxycyclohexane (V), *trans*-1,2-dibromocyclohexane (VI), and cyclohexanone, whose GLC analysis (OV-17 on Chromosorb W, N_2) showed signal intensities of *ca.* 2:1:2 respectively. The treatment of the II cobaloxime (500 mg) under the same reaction conditions, but at the reaction temperature of 0 °C, gave the VI dibromide (169 mg, 65%).

Bromination of the Cobaloximes (III and IV). The III cobaloxime (25 mg) in dichloromethane (1 ml) was cooled in an ice-water bath to −5 °C and then treated with 22 mg of bromine (2.6 equivalents) in dichloromethane. The reaction mixture was subsequently stirred for 6 h under nitrogen.

After the careful evaporation of the solvent, the product was chromatographed on Florisil (1 g), using hexane as the eluent. The careful evaporation of the eluate yielded *ca.* 10 mg of a product (*ca.* 92%). GLC analysis (Carbowax 20 M on Chromosorb W, N_2) showed the product to be a 1: 3 mixture of *cis* and *trans*-1-bromo-4-*t*-butylcyclohexanes, XI and X, which were identical with authentic samples. The same treatment of the IV cobaloxime gave exclusively the XI bromide in a *ca.* 90% yield.

Mercuration of the Cobaloximes (I and II). To a solution of the I cobaloxime (360 mg) in ethanol (30 ml) containing acetic acid (0.02 mol/l), we added solid mercuric acetate (360 mg, 1.48 equivalents), after which the reaction mixture was refluxed for 2.5 h under nitrogen. Excess sodium chloride was added to the cooled mixture, which was then further stirred for 2.5 h at room temperature. The filtrate of the mixture was condensed and extracted with chloroform after the addition of water to the condensate. The passing of the extract through Florisil gave products in benzene eluate, while the I cobaloxime (73 mg) was recovered in the chloroform eluate. The chromatography of the products on silica gel eluted with dichloromethane gave a mixture of *trans*-2-methoxycyclohexylmercury(II) chloride (VII) and *trans*-2-ethoxycyclohexylmercury(II) chloride (VIII) (77 mg, 36% based on the I cobaloxime consumed). The ratio of VII to VIII was determined by the transformation of these mercurials into *trans*-1-bromo-2-methoxycyclohexane (V) and *trans*-1-bromo-2-ethoxycyclohexane (IX) by bromine in pyridine at −20 °C. The V and IX bromides, obtained in 40 mg after chromatography on alumina eluted by hexane, were found by analysis to exist in the ratio of 3: 2.

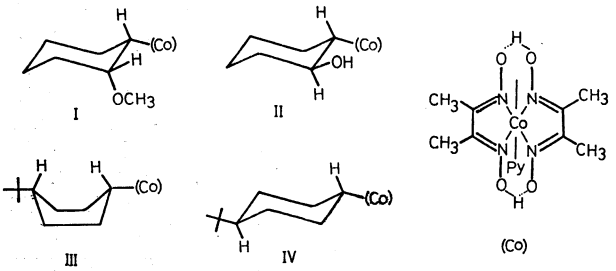
The treatment of the II cobaloxime (467 mg) with mercuric acetate in methanol under essentially the same reaction conditions, but at the reaction temperature of 20 °C, gave *trans*-2-methoxycyclohexylmercury(II) chloride (VIII) in a 70% yield; this substance was identified with an authentic sample obtained by the methoxymercuration of cyclohexene.

Mercuration of the Cobaloximes (III and IV). To a solution of cobaloxime III (204 mg) in methanol (20 ml) we added powdered mercuric nitrate hydrate (274 mg), after which the solution was stirred for 120 h under nitrogen at room temperature. The reaction mixture was further stirred for 2.5 h after the addition of excess sodium chloride. The product was extracted with chloroform after the evaporation of methanol under reduced pressure and the addition of water to the condensed mixture. The extract was chromatographed on Florisil (6 g) to give the product as a benzene eluate and the recovered cobaloxime as a chloroform–methanol (9: 1) eluate. The chromatography of the product on silica gel (2 g) gave *trans*-4-*t*-butylcyclohexylmercury(II) chloride, XII (3 mg, 2.0%), in a benzene eluate; this substance was identified with an anthentic sample synthesized from *trans*-4-*t*-butylcyclohexylmagnesium(II) bromide[16] and, further, by the transformation of XII into *trans*-1-bromo-4-t-butylcyclohexane (X) in the same way as was used for the transformation of mercurial VII and VIII into the V and IX bromides.

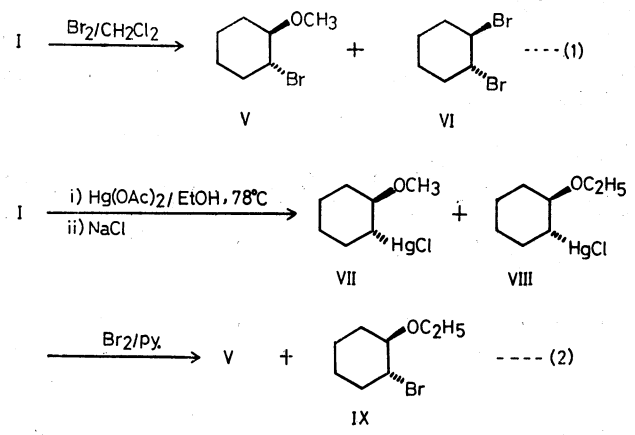
The mercuration of the IV cobaloxime (127 mg) was carried out in the same manner, but for 5 h at 50 °C. The chromatography of the products on Florisil (5 g) gave the products as the benzene eluate and the recovered IV cobaloxime (66 mg) as the chloroform eluate. Repeated chromatography of the products on silica gel (6 g) gave a mixture of *cis* and *trans*-4-*t*-butylcyclohexylmercury(II) chloride. The structure and ratio of the isomers were determined, by the transformation of the mercurials into bromides as has been described above, to be *cis*(XI): *trans*(X)=3: 2.

Results and Discussion

cis-2-Methoxycyclohexyl(pyridine)cobaloxime (I) was synthesized by the substitution of *trans*-1-bromo-2-methoxycyclohexane with the cobaloxime anion, $(Co)^-$, prepared *in situ* by the sodium tetrahydroborate reduction of the complex from dimethylglyoxime, cobalt(II) chloride, and pyridine. The steric course of this reaction has been proved to proceed with an inversion at the reaction center, and the *trans* arrangement of the methoxy group and the cobaloxime moiety was confirmed by the NMR spectrum of I. The signal due to the hydrogen attached to the carbon bearing methoxy group is at 3.30 ppm (δ), with a half-band width of 9 Hz, which shows a lack of diaxial coupling and the axial conformation of the methoxy group. This feature unequivocally limits the stereochemistry of the I cobaloxime to *cis*, since the large steric requirement of the ligand enforces the cobaloxime group to take an equatorial conformation.[15] *trans*-2-Hydroxycyclohexyl(pyridine)cobaloxime (II), prepared from cyclohexene oxide and the cobaloxime anion, $(Co)^-$, has an NMR signal at 3.05—2.70 ppm as a diffused sextet with a half-band width of 19 Hz (J=10, 10, and 5 Hz), indicating the presence of two diaxial coupling and one axial-equatorial coupling. *Cis* and *trans*-4-*t*-butylcyclohexyl(pyridine)cobaloxime (III and IV) were prepared by the S_N2 displacement of *trans* and *cis*-4-*t*-butylcyclohexyl tosylate respectively. The reaction of the *trans* tosylate to give the *cis*-cobaloxime (III) was sluggish, and the yield was poor, 7.7%, even after a prolonged reaction period. This behavior can be accounted for by the steric hindrance on the approach of the cobaloxime anion from the axial direction when the S_N2 mechanism operates.[17] The large substituents at the 1,4-position of the cyclohexane ring suggest that the conformation of III is a boat form. The spectroscopic data do not discriminate the stereochemistry of III and IV, but the S_N2 nature of the reaction suggests the stereochemistry of the cobaloximes to be *cis* and *trans* respectively.[15] This reasoning was proved by the bromination of III and IV giving different products, as will be described below.

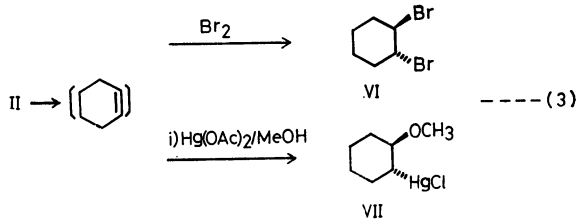


The bromination of *cis*-2-methoxycyclohexyl(pyridine)cobaloxime (I) in dichloromethane gave a complex mixture at an ambient temperature, but the reaction at a lower temperature (−70 °C) yielded *trans*-1-bromo-2-methoxycyclohexane (V) in a poor yield, besides *trans*-1,2-dibromocyclohexane (VI) and cyclohexanone (Eq. 1). The formation of V, in spite of the low yield, clearly shows that the reaction proceeds



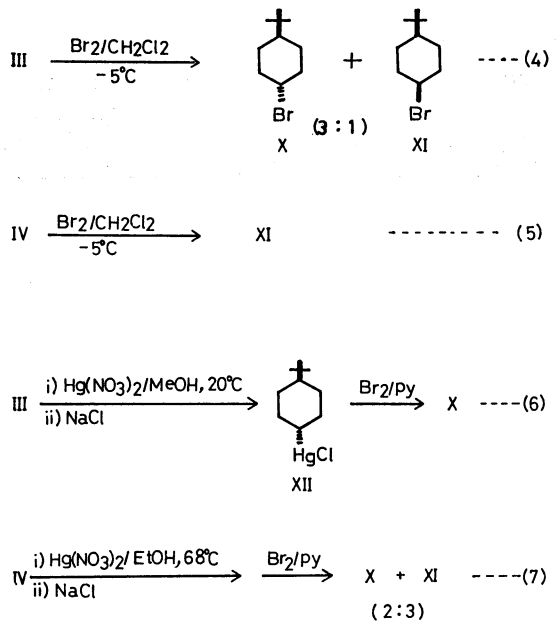
with an inversion of the configuration, though the formation of VI indicates the side reaction *via* cyclohexene as an intermediate. The mercuration of I with mercuric acetate was attempted under the conditions in which Schrauzer *et al.*, determined the kinetic property of the reaction to be second order.[13] In our preliminary report, we errornously recorded the formation of *trans*-2-methoxycyclohexylmercury(II) chloride (VII) when *cis*-2-hydroxycyclohexyl(pyridine)cobaloxime was treated with mercuric acetate in methanol; we attributed this result to a mercury-assisted corbonium ion. A detailed analysis of the NMR spectrum, however, clarified that the cobaloxime in some synthetic lots contained varying amounts of II due to the intervention by cyclohexene oxide when *cis*-2-hydroxycyclohexyl-(pyridine)cobaloxime was prepared under the basic conditions. The mercuration of the I cobaloxime was sluggish at an ambient temperature, but gave a mixture of *trans*-2-methoxycyclohexylmercury(II) chloride (VII) and *trans*-2-ethoxycyclohexylmercury(II) chloride (VIII) when the ethanol solution of I and mercuric acetate was refluxed. The bromination of the resulting mixture in pyridine gave a mixture of *trans*-1-bromo-2-methoxyhexane (V) and *trans*-1-bromo-2-ethoxyclohexane (IX) in the ratio of 3: 2—the yield of the mixture from I was 36% (Eq. 2). The bromination of organo-mercurial in pyridine has been determined to proceed with a retention of the configuration;[18] hence, the mercuration of *cis*-2-methoxycyclohexyl(pyridine)-cobaloxime (I) clearly proceeds with inversion. The formation of the by-product, 1-bromo-2-ethoxycyclohexane, must be accounted for by the intermediate formation of cyclohexene upon mercuration as in the case of bromination.

The bromination and mercuration of *trans*-2-hydroxycyclohexyl(pyridine)cobaloxime (II), under the same reaction conditions as were used for the reaction of the I cobaloxime, gave *trans*-1,2-dibromocyclohexane (VI)



(65%) and *trans*-2-methoxycyclohexylmercury(II) chloride (VII) (70%) (Eq. 3). This implies that the *trans* arrangement of the hydroxy and cobaloxime groups in II brings about a facile β-elimination to give cyclohexene, and that the bromination or mercuration of the resulting cyclohexene takes place efficiently.

The bromination of *cis*-4-*t*-butylcyclohexyl(pyridine)cobaloxime (III) in dichloromethane at -5 °C gave a mixture of *trans*-1-bromo-4-*t*-butylcyclohexane (X) and its *cis* isomer, XI, in the ratio of 3: 1 and in a 92% yield (Eq. 4). The same treatment of *trans*-cobaloxime IV gave exclusively the XI *cis* isomer in a 90% yield (Eq. 5). The incompleteness of the stereospecificity in the bromination of III may arise from the intrusion of the radical process, since the back-side attack of III, in boat-like conformation, by bromine is hardly allowed. The mercuration of III and IV with mercuric acetate is sluggish, so the reaction was attempted by using the more reactive mercuric nitrate in methanol (Eqs. 6 and 7). The product from the reaction of III was identified with authentic *trans*-4-*t*-butylcyclohexylmercury(II) chloride (XII) prepared from the corresponding Grignard reagent.[16] The mercuration itself was a rather smooth process and the complete disappearance of III and IV was observed by the thin-layer chromatography of the reaction mixture. The addition of sodium chloride to convert the resulting organo-mercurial into the more stable organo-mercuric chloride, or the condensation of the reaction solution for isolation reverted the reaction and regenerated the III and IV cobaloximes.[19] This behavior was also suggested by observing the NMR spectrum of the reaction solution of IV. The signal at 2.17 ppm (δ) in methanol due to the four methyl groups of the dimethylglyoxymato-ligand of IV was displaced to 2.22 ppm by the addition of the mercuric ion. The addition of powdered sodium chloride to this solution regenerated the original signal. Several efforts to isolate the resulting mercurial in a practical yield from III and IV were unsuccessful in this situation. The stereochemistry of



the mercurials thus obtained in poor yields was determined by the transformation of these mercurials into bromides by the action of bromine in pyridine. GLC analyses of the resulting bromides revealed that the bromide from III was exclusively *trans*-1-bromo-4-*t*-butylcyclohexane (X), while the bromide from IV was a 3:2 mixture of *cis* and *trans*-1-bromo-4-*t*-butylcyclohexanes. The latter result may be due to the incomplete stereospecificity upon the bromination of the *cis*-4-*t*-butylcyclohexylmercury(II) chloride derived from IV, since the *cis* mercurial can be expected to have a mercuric chloride group in the axial conformation;[20] the bromination with retention may not be favored.

In general, the S_E2 reaction is known to proceed with retention at the reaction center.[21] Reactions with inversion, however, have been reported in several instances, such as the brominations of tri-norbornyl borane in the presence of sodium methoxide,[22] alkyl tin,[23] and the alkyl iron complex.[5] Jensen *et al.*,[24] and Johnson *et al.*,[25] showed in preliminary reports, independently from ours, that the bromination of cobaloxime took a reaction path with an inversion at the reaction center; our results described in the preliminary report[1] and in the present paper are in good accordance with the results by those authors.

The bromination and mercuration of the II cobaloxime were found not to be suitable for the test of stereospecificity because of the reaction path of β-elimination. The equilibrium between 4-*t*-butylcyclohexyl(pyridine)cobaloxime and the mercuric ion, as proved by TLC and NMR analyses, may confuse the stereochemical course of the mercuration, but the reverse reaction must take the same stereochemical course as that of mercuration since the transition state is common to both the reactions in the equilibrium (Eq. 8).

$$Hg^{2+} + \rangle R\text{-}(Co) \rightleftharpoons [Hg\cdots C\cdots(Co)]^{2+} \rightleftharpoons Hg\text{-}R + (Co)^{+} \quad \cdots (8)$$

transition state

The discussions in this paper define the stereochemical nature of the bromination and mercuration as involving inversion, despite some incomplete stereospecificity in the systems with difficult geometries to take a penta valent transition state for the S_E2 reaction.

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