Mechanistic study of the reaction of vitamin B_{12s} with 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane

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The reaction of vitamin B_{12s} with 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane results in the formation of *trans*-4,4′-dichlorostilbene in a two-step process. In the first step, there is a nucleophilic attack by the cobalt(I) at C-1 resulting in the displacement of chloride ion and formation of an alkyl cobalamin with a chlorine atom on the α-carbon. The second step is a cobalt chloride α-elimination which proceeds through a carbenoid type intermediate that readily rearranges to the product.

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La vitamine B_{12s} réagit avec le dichloro-1,1 bis(*p*-chlorophényl)-2,2 éthane et conduit en deux étapes à la formation du dichloro-4,4′ stilbène *trans*. La première étape est une attaque nucléophile du cobalt(I) au niveau du carbone en position 1 qui provoque le déplacement de l'ion chlorure et conduit à la formation d'une cobalamine alkylée avec un atome de chlore sur la carbone en position α. La seconde étape consiste en une élimination α de cobalt et de chlore qui se fait via un intermédiaire du type carbénoïde qui se transpose facilement pour donner le produit final.

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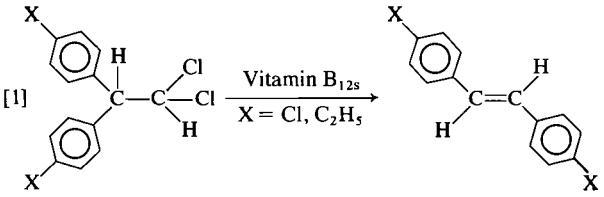
Introduction

The reactions of vitamin B_{12} with a wide variety of inorganic and organic compounds, in aqueous and micellar environments, have been reported (1–6). It was recently demonstrated (7), that the reaction of vitamin B_{12s} with 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane (DDD) results in the formation of *trans*-4,4′-dichlorostilbene (DCS). A similar reaction using 1,1-dichloro-2,2-bis(*p*-ethylphenyl)ethane resulted in the production of *trans*-4,4′-diethylstilbene (eq. [1]) (7). The above



described reactions appear to be mechanistically interesting since, for the product to be formed, two chlorine atoms must be eliminated and a phenyl migration should occur.

It is our purpose to report some studies on the interactions of vitamin B_{12s} with several possible intermediates, the results of which clarify the mechanism of this dechlorination reaction.

Experimental

All melting points are uncorrected. Infrared spectra were determined with a Perkin-Elmer 720 spectrophotometer. Nuclear magnetic resonance spectra were run in $CDCl_3$ on a Varian HA-100 spectrometer using tetramethylsilane as internal reference. Ultraviolet spectra were obtained in methanol by means of a Varian 634 spectrophotometer.

Vitamin B_{12a}, aquocobalamin, was purchased from Merck Chemical Co., 1,1-dichloro-2,2-bis(*p*-ethylphenyl)ethane from Chemical Service, and 1,1-dichloro-2,2-bis(*p*-chlorophenyl)-ethane (DDD) from Aldrich Chemical Co. The purity of the three reagents mentioned above was found to be satisfactory by thin-layer chromatographic analysis.

The intermediate 1-chloro-2,2-bis(*p*-chlorophenyl)ethane (DDMS) was prepared by a slight modification of a previously described procedure (8) and crystallized several times from ethanol, mp 51–51.5°C (lit. (8) mp 51–51.5°C). The observed nmr spectra (A_2B_2 aromatic protons, multiplet centered at 7.19 ppm, doublet at 3.95 ppm, and triplet at 4.25 ppm, integration 8:2:1) was identical with that reported elsewhere (9).

A sample of 2-chloro-1,2-diphenylethanol was prepared by the treatment of benzoin with thionyl chloride, in order to form desyl chloride, followed by sodium borohydride reduction (10). The compound presented fine structure in the 250–260 nm region, with a molar absorptivity of about 500, and when treated with zinc dust in acetic acid and crystallized afforded diamond-shaped irridescent plates of *trans*-stilbene as already described (10).

The compound 1-chloro-1,2-bis(*p*-chlorophenyl)ethane (DDMF) was prepared by treatment of a 10.0 g dry sample of 2,2-bis(*p*-chlorophenyl) acetic acid with lithium aluminum hydride in diethyl ether forming 2,2-bis(*p*-chlorophenyl)ethanol (yield 90%). Reaction of the alcohol (6.0 g) with thionyl chloride (1.7 mL) resulted in the formation of DDMF and DCS. The reaction mixture was purified by column chromatography using a 60 cm × 25 mm silica gel column and hexane (Ecibra) as the eluent. The uv spectra showed fine structure with maxima at 276.5, 268, and 261 nm; nmr showed an aromatic proton multiplet centered at 7.13 ppm, a doublet at 3.27 ppm, and a triplet at 4.90 ppm, integration 8:2:1. Besides, chemical treatment of a sample with alcoholic KOH resulted in quantitative transformation of DMF to DCS, as would be expected. All the other compounds were the best available reagent grade.

In a typical reaction, a solution of aquocobalamin (400 mg in 25 mL of water) was purged with purified nitrogen in a closed vessel through rubber septa for 2 h. A capillary tube punched just through the rubber septum provided the vent. Subsequent to deoxygenation, 200 mg of $NaBH_4$ was added, and the mixture

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allowed to react for 10 min. A solution of polyhalogenated hydrocarbon (30 times molar excess, dissolved in 250 mL of methanol, also purged for 2 h with purified nitrogen), was added and allowed to react. The reactions were monitored by thin-layer chromatography (using silica gel GF_{254}, type 60, Merck, and petroleum ether, fraction 30–60, Ecibra, as developing solvent). The colored solution was then extracted with several portions of chloroform to remove the organic fraction. The chloroform extract was rotary evaporated to dryness, and dried *in vacuo* in a Abderhaldem type apparatus over P_2O_5. The different products were separated by column chromatography using silica gel and then used for subsequent analysis. In all the reactions more than 90% of the organic compounds were recovered. In the reaction of vitamin B_{12s} with DDMS a vitamin B_{12} complex was formed. The alkyl cobalamin was purified by column chromatography using silica gel (Merck) and methanol as eluent. All the procedures for the isolation of the vitamin B_{12}–DDMS′ complex were done in the absence of light in order to prevent its photolysis.

Results and Discussion

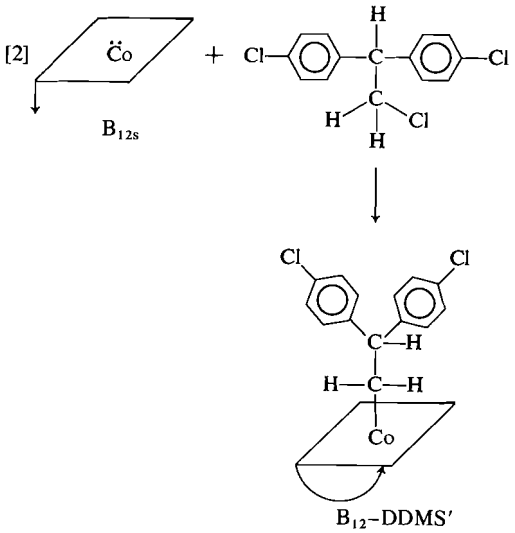
Vitamin B_{12s}, generated by the $NaBH_4$ reduction of aquocobalamin, appears to be the reactive species in the dechlorination of DDD. Indeed vitamin B_{12r}, generated by photolysis of methylcobalamin in a nitrogen atmosphere, does not react with DDD to produce DCS. Furthermore, if the Co(I) nucleophile is generated by an independent method, like treatment of the vitamin B_{12}–DDMS′ complex with base in a nitrogen atmosphere, DCS is also formed upon reaction with DDD. The first step of the reaction must be a nucleophilic attack of the cobalt(I) on DDD resulting in the formation of a vitamin B_{12}–DDD′ complex, a reaction which involves formation of a cobalt–carbon sigma (σ) bond and which is expected for a cobalt(I) supernucleophile such as vitamin B_{12s} (1, 2, 11).

Since DDD is present in large excess as compared with vitamin B_{12s} and the reaction goes to completion, it is obvious that the vitamin B_{12}–DDD′ complex must be unstable and regenerates the cobalt(I) nucleophile or vitamin B_{12r}, the latter of which is reduced by sodium borohydride to the vitamin B_{12s} form.

The main question to be answered in order to clarify the reaction pathway is whether the reaction proceeds via any isolable intermediate which subsequently reacts with vitamin B_{12s} to form DCS or, if the vitamin B_{12}–DDD′ complex directly decomposes to generate DCS.

There are three possible reactive intermediates to be formed upon decomposition of the vitamin B_{12}–DDD′ complex. Namely, 1,1-bis(*p*-chlorophenyl)-2-chloroethane (DDMS), 1,2-bis(*p*-chlorophenyl)chloroethane (DDMF), and 1,2-bis(*p*-chlorophenyl)-2-chloroethanol (DDMFOH). Thus in order to test the different reaction pathways, the compounds DDMS, DDMF, and an analog of DDMFOH were synthesized and their reactions with vitamin B_{12s} were investigated under conditions identical to those for which the reaction of DDD was studied.

DDMS reacts with vitamin B_{12s} in stoichiometric 1:1 proportion and all the excess of DDMS added can be recovered as unreacted material. Since DCS was not detected in the reaction mixture, and DDMS reacts in stoichiometric rather than catalytic proportions, it cannot be the reactive intermediate. Equation [2] describes the reaction occurring under our experimental conditions. Vitamin B_{12s} displaces chloride ion (detected by $AgNO_3$ titration) through a nucleophilic substitution process, forming a product which displays all the characteristics of a typical alkyl cobalamin. Treatment of the vitamin B_{12}–DDMS′ complex with hydroxide ion, using hexadecyldimethyl-2-hydroxyethyl ammonium bromide as catalyst, results in the formation of 1,1-bis(*p*-chlorophenyl)ethylene and vitamin B_{12a} as products, a result which is consistent with the proposed structure for the alkylcobalamin. Figure 1 shows a spectrum of the purified reaction product. As can be seen, the γ-band at 350 nm which is typical of vitamin B_{12a} is absent, and no sharp absorption band is observed in the 320–370 nm region. Indeed, the observed spectrum (Fig. 1, dotted line) is very similar to that reported for methyl cobalamin (2). Upon addition of 0.1 *M* hydrochloric acid, the alkylcobalamin turns yellow, reflecting the shift in the protonation equilibria of the benzimidazol in the fifth coordination position upon alkylation of the cobalt (Fig. 1, dashed line). Using the change in the absorption spectrum upon protonation, the pK_a for the base-on – base-



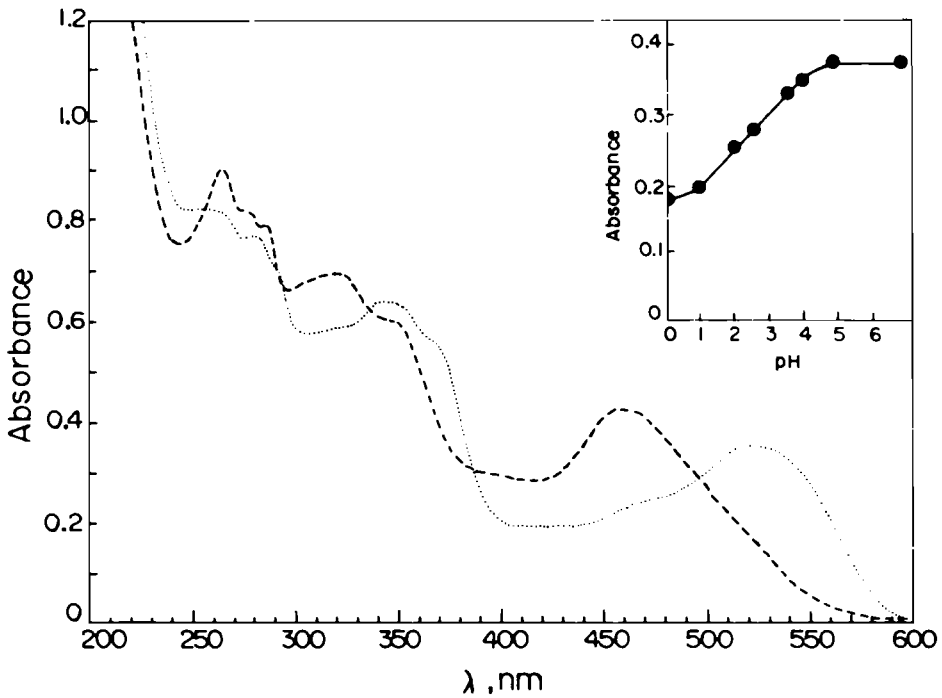
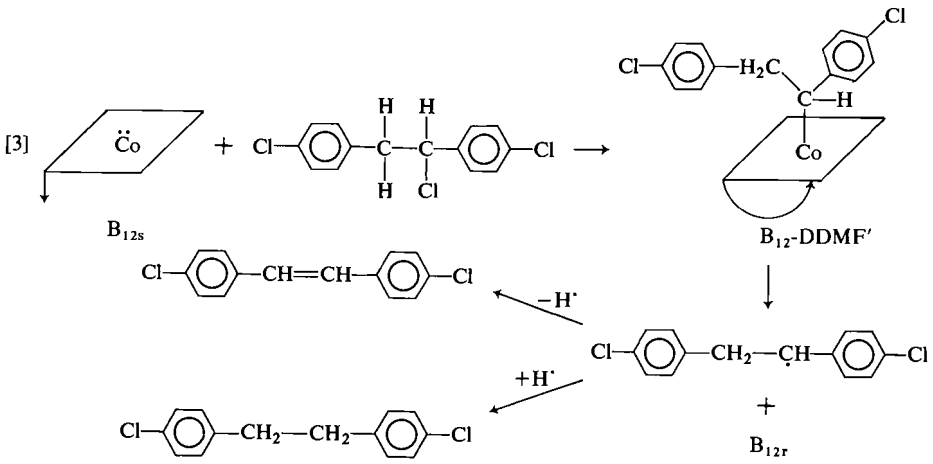


FIG. 1. Absorption spectrum of the vitamin B_{12}–DDMS′ complex at pH 7.0 (...) and pH 1.0 (---). The insert shows the absorbance at 462 nm as a function of pH.

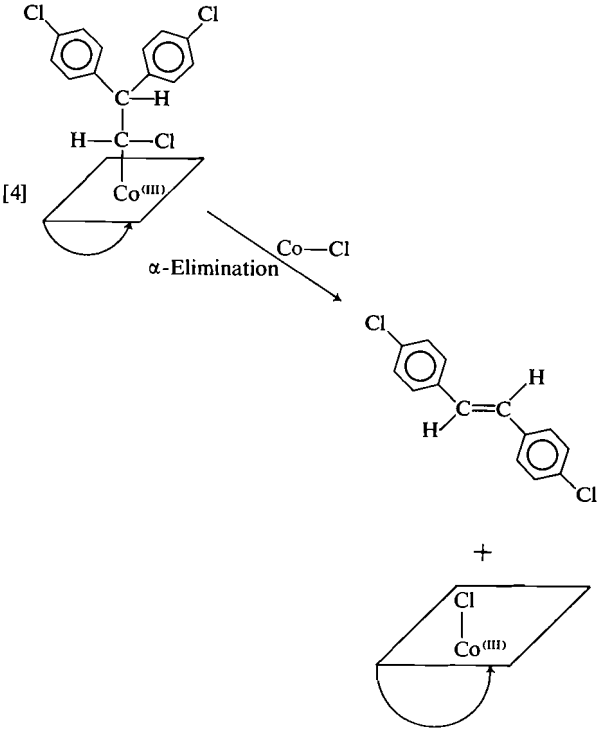
off equilibria was determined spectrophotometrically to be 2.5 (insert of Fig. 1). The obtained value is in close agreement with that normally reported for alkyl cobalamins (2).

Since DDMS was excluded as the reaction intermediate, the pathways involving phenyl migration and leading to the formation of DDMF and DDMFOH were analyzed. Under our experimental conditions 2-chloro-1,2-diphenylethanol, a chemical analog of DDMFOH without the chloro substituents in *para* position, did not react with vitamin B_{12s} to produce *trans*-stilbene and was therefore excluded as a possible reaction intermediate. Considering that the effect of the phenyl group should be somewhat between those of the *p*-ethylphenyl and *p*-chlorophenyl substituents, the choice of 2-chloro-1,2-diphenylethanol as an analog of DDMFOH seems reasonable since both DDD and 1,1-dichloro-2,2-bis(*p*-ethylphenyl)ethane react with vitamin B_{12s} to form the corresponding *trans*-stilbene. The interaction of DDMF with the cobalt(I) nucleophile was then investigated; eq. [3] describes our experimental results. Two organic products were detected in the analysis of the reaction mixture, namely DCS and 1,2-bis(*p*-chlorophenyl)ethane. Since the participation of vitamin B_{12s}, in the presence of $NaBH_4$, is catalytic, the vitamin B_{12}–DDMF′ complex formed upon nucleophilic attack of the cobalt(I) on DDMF must be unstable. The instability of the vitamin B_{12}–DDMF′ complex is not unexpected, since many examples are available showing the lack of stability of a cobalt–carbon bond involving a secondary carbon atom (2, 8). Thus, the reaction of isopropyl iodide with vitamin B_{12s} resulted in the production of vitamin B_{12r} via homolytic bond rupture of the initially formed alkyl cobalamin (11). Our results are entirely consistent with this type of mechanism, since homolytic cobalt–carbon bond cleavage of the vitamin B_{12}–DDMF complex would generate a free radical, which upon uptake or loss of a hydrogen atom will result in the formation of DCS and 1,2-bis(*p*-chlorophenyl)ethane respectively. Considering that in the reaction of vitamin B_{12s} with DDD only DCS was detected as reaction product, and that 1,2-bis(*p*-chlorophenyl)ethane could not be detected even in trace amounts, our evidence indicates that DDMF is not a reaction intermediate.

Thus, the reaction most likely proceeds directly from the vitamin B_{12}–DDD′ adduct to DCS without the participation of any isolable reaction intermediate; eq. [4] describes such a possibility. The vitamin B_{12}–DDD′ complex reacts via a cobalt chloride α-elimination to yield DCS and a vitamin B_{12} – chloride complex, in which the cobalt atom is formally in the Co(III) oxidation state. Hydrolysis of this complex will result in liberation of vitamin



B_{12a} and free chloride ion. The reaction described in eq. [4] is not unprecedented by any means, indeed it is analogous to the Simmons–Smith procedure (12), and to the reaction of organic *gem*-



dihalides with copper (13) among others (14), since the α-elimination will generate a carbene or carbenoid type intermediate which will readily rearrange to the products. Attempts to trap a free carbene using cyclohexene were unsuccessful, a result which was somewhat expected since DCS itself may act as a carbene trapping agent. Besides, alkylcarbenes generally undergo rearrangement so rapidly that additions to double bonds and insertion reactions, which are normally expected for carbene itself, are seldom found with alkyl carbenes. Our results seem to be more consistent with a carbenoid type intermediate rather than a totally free carbene. Accordingly, the rearrangement should occur concurrently with the α-elimination.

We are currently working on the development of a procedure for the synthesis of cyclopropane derivatives based on a modification of the above described reaction, using simple cobalt complexes.

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