determining the configurations or conformations of α-glycols, and furthermore, it can probably be extended to α-amino alcohols and other similar compounds. Extension of this method to acyclic systems is under investigation.

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Hydridocobalamin and a New Synthesis of Organocobalt Derivatives of Vitamin B_{12}

Sir:

The Co(I) derivatives of vitamin B_{12} and of other corrins are now well known to exist as the powerful nucleophiles in alkaline medium.[1,2] However, their nature in acidic solution is still not understood. The view that vitamin B_{12s} is a cobalt hydride was first expressed by Müller and Müller,[3] and later by Smith, *et al.*,[4] Dolphin, *et al.*,[5] and Bernhauer, *et al.*[6] However, it was later recognized that all reactions of vitamin B_{12s} cited in support of its hydridic structure were in fact typical of those of the free Co(I) nucleophile.[7] It was subsequently shown that solutions of vitamin B_{12s} slowly decompose into vitamin B_{12r} and molecular hydrogen,[8] indicating that hydridocobalamin, if it exists, must be an unstable or metastable species. This was confirmed by studies in our laboratory, which showed that vitamin B_{12s} decomposition into vitamin B_{12r} and hydrogen in solutions below pH 9.9 could be significantly enhanced by the addition of a platinum catalyst.[1] Absence of definite spectral changes in solutions of vitamin B_{12s} in the pH range between 5 and 14 finally prompted Das, *et al.*,[9] to consider hydridocobalamin a species of altogether questionable existence.

The successful synthesis of the first hydridocobaloximes[10] prompted us to reconsider the possible synthesis or characterization of hydridocobalamin, particularly since the model studies led to the discovery of chemical reactions permitting the distinction of hydridocobalt species from the free Co(I) nucleophiles. Of particular importance in this context are reactions with activated olefins. Ethyl acrylate, for example, reacts with the Co(I) nucleophiles to form the β-carbethoxyethylcobaloxime. With the hydridocobaloximes in buffered neutral or acidic solutions, the α isomers are formed exclusively.[10,11] Vitamin B_{12s} reacts with ethyl acrylate in alkaline medium to yield β-carbethoxyethylcobalamin,[11] readily recognized by its tendency to undergo reversible Co–C bond cleavage in more strongly alkaline solution.[11,12] The formation of α-carbethoxyethylcobalamin has not yet been verified, however. Hydridocobaloximes also react with olefins to form alkylcobaloximes. Generating hydrido(pyridine)cobaloxime from cobaloxime(II) and H_2 *in situ* in polar solvents, we have previously observed the formation of isopropyl(pyridine)cobaloxime.[11] Accordingly, it appeared reasonable to explore the reduction of vitamin B_{12} in acidic media under conditions preventing catalytic destruction of hydridocobalamin. This was achieved by reducing vitamin B_{12a} (hydroxocobalamin) with zinc dust in anhydrous glacial acetic acid under strict exclusion of oxygen. Green solutions formed within a few minutes which turned pink immediately on exposure to air. Rapid decomposition into yellow-brown vitamin B_{12r} and hydrogen was also observed under anaerobic conditions, when a trace of a noble metal catalyst (*e.g.*, platinum oxide or a solution of palladous acetate in glacial acetic acid) was added. Separated from the excess of zinc, the dark green solutions of the reduced cobalamin turn yellow-brown within 15 min of standing at ambient temperature. In the presence of excess zinc the green solutions remain unchanged for several hours, permitting spectroscopic and chemical investigations. In the following we report evidence which demonstrates conclusively that vitamin B_{12} reduced under these conditions is present to a substantial degree in the form of the protonated Co(I) nucleophile, which we designate "hydridocobalamin."[13] The optical absorption spectrum of hydridocobalamin in anhydrous acetic acid is distinctly different from that of vitamin B_{12s} generated by reduction with zinc in aqueous NH_4Cl or with alkaline $NaBH_4$ in water–methanol (Figure 1). The latter two spectra are essentially identical, indicating that reduction of vitamin B_{12a} with zinc in aqueous NH_4Cl buffer produces the Co(I) nucleophile rather than detectable amounts of the hydridocobalamin. The most striking differences between vitamin B_{12s} in the form of the Co(I) nucleophile and the hydride are observed in the chemical reactivities, however. Thus, it has been known for years that vitamin B_{12s} does not react with normal, unactivated olefins. Hydridocobalamin in anhydrous acetic acid, but also in acetic acid–methanol, 1:1, reacts with ethylene rapidly to form ethylcobalamin. After dilution of the reaction solution, the absorption spectrum is identical with that of ethylcobalamin prepared from the nucleophile and ethyl iodide in alkaline solution (Figure 2). The reaction with propylene similarly affords isopropylcobalamin, which is readily distinguished from *n*-propylcobalamin on the basis of the absorption spectrum. In the latter the axial 5,6-dimethylbenzimidazole is attached to cobalt, in the former it is not, causing the spectrum to become similar to that of isopropylcobinamide. Reaction is also observed with cyclohexene, yielding cyclohexylcobalamin, whose ab-

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(13) The axial base 5,6-dimethylbenzimidazole is probably protonated in solutions of hydridocobalamin in glacial acetic acid. Accordingly, the absorption spectrum of hydridocobinamide is similar to that of hydridocobalamin in glacial acetic acid.

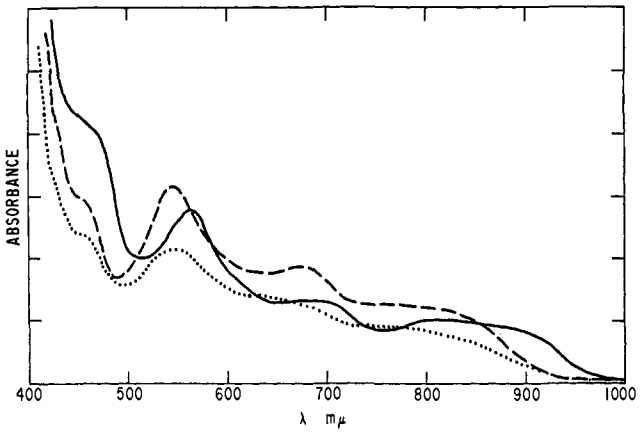

Figure 1. Optical absorption spectra of hydridocobalamin, ——— (in glacial acetic acid); - - - - -, vitamin B_{12s} in 10% aqueous NH_4Cl solution; and ·····, vitamin B_{12s} in 0.1 *M* NaOH in 10% CH_3OH in water. The absorption spectra of the cobinamide (I) nucleophile in aqueous NaOH or of hydridocobinamide in anhydrous acetic acid are similar to those of the corresponding cobalamin derivatives.

sorption spectrum is again identical with that of authentic cyclohexylcobalamin reported previously,[14] and with cyclohexylcobinamide.[15] All organocobalamins prepared by the new method proved equally as light sensitive as the samples prepared by the method involving the Co(I) nucleophile. Hydridocobalamin also reacts with ethyl acrylate, affording a product with an absorption spectrum typical of a secondary alkylcobalamin (Figure 2). The compound must be α-carbethoxyethylcobalamin, as it is insensitive to 0.3 *M* aqueous NaOH, under conditions where the β isomer undergoes rapid Co–C bond cleavage. For similar observations in the cobaloxime series, see ref 11 and 12. Hence, all the chemical evidence available is in accord with the presence of a species comparable in reactivity with hydridocobaloximes and substantially different from known reactions of the Co(I) nucleophile. Hydridocobaloximes as well as hydridocobalamine are best formulated as protic acids of Co(I) with a small covalent contribution. The limiting structure C probably contributes only slightly, but this may be responsible for the tendency of hydridocobalamin to decompose into vitamin B_{12r} and molecular hydrogen.

$$\underset{A}{H^+Co^I} \longleftrightarrow \underset{B}{H\text{–}Co} \longleftrightarrow \underset{C}{^-H\text{–}Co^{III}}$$

The ability of hydridocobalamin and hydridocobinamides to react with unactivated olefins in polar acidic media is of utmost importance with respect to the possible mechanism of catalytic action of corrinoid coenzymes, but is also of considerable utility for the synthesis of new organocorrins. Thus, numerous alkyl- or substituted-alkylcobalamins and -cobinamides have been synthesized which previously were unaccessible. For example, reaction of hydridocobalamin with norbornene yielded 1-norbornylcobalamin (Figure 2). Since most secondary alkylcobalamins prepared thus far exhibit absorption spectra resembling those of alkylcobinamides, this shows that bulky alkyl groups cause a conformational change of the corrin ligand

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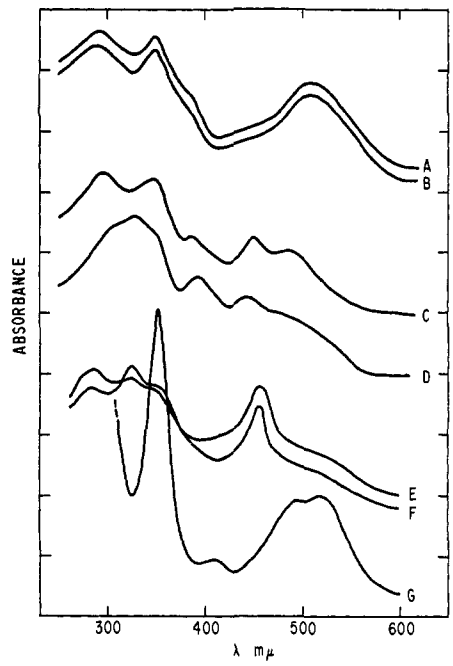
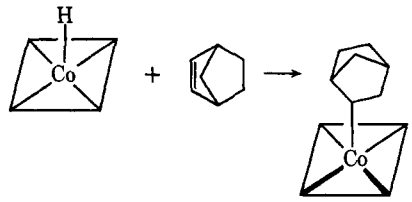


Figure 2. Optical absorption spectra of organocobalamins prepared from hydridocobalamin or by alternate methods where indicated: (A) ethylcobalamin (from ethylene); (B) ethylcobalamin from vitamin B_{12s} and C_2H_5I; (C) isopropylcobalamin (from propylene); (D) norbornylcobalamin (from norbornene); (E) reaction product from hydridocobalamin with ethyl acrylate in glacial acetic acid, after dilution, in water at pH 5.8; (F) same as E after treatment with 0.3 *M* NaOH and reacidification with dilute acetic acid to pH 5.8; (G) typical spectrum of complexes A–E after photolysis (5 min of irradiation with a 150-W Westinghouse projection flood lamp (tungsten filament) at a distance of 35 cm.

leading to the displacement of the coordinated 5,6-dimethylbenzimidazole.



(1)

Not all secondary alkylcobalamins proved isolable, however. Styrene reacts with hydridocobalamin even at 0 or −20° (in 1:1 methanol–glacial acetic acid with zinc dust as the reducing agent). However, only vitamin B_{12r} is detectable. This suggests that α-phenylethylcobalamin is too unstable to be isolated, a fact which is supported by the demonstrated thermolability of the corresponding cobaloxime derivative.[11] Attempts to synthesize tertiary alkylcobalamins and -cobinamides (*i.e.*, by reacting the hydrides with 2-methyl-2-butene) failed. Although reaction was observed, vitamin B_{12r} was the only product isolated. This indicates that tertiary alkylcobalamins and -cobinamides are inherently unstable due to a genuine steric limitation. Nevertheless, the demonstrated existence of a large number of secondary alkylcobalamins removes some of the possible objections against proposed biochemical mechanisms involving secondary substituted alkylcobalamins or -cobinamides as intermediates.

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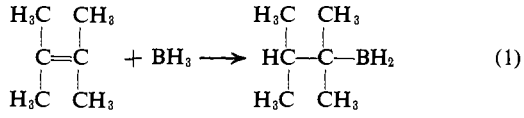
A Simple General Synthesis of Monoalkylboranes and Their Applicability for the Preparation of Mixed Organoboranes *via* Hydroboration

Sir:

B-Alkylcatecholoboranes (2-alkyl-1,3,2-benzodioxaboroles (**1**), readily available *via* the hydroboration of olefins with catecholborane,[1] undergo a smooth reduction with either lithium aluminum hydride (LAH) or aluminum hydride (AlH_3) to give the corresponding monoalkylboranes in nearly quantitative yield. This facile synthesis constitutes the first general preparative route to monoalkylboranes (1,2-dialkyldiboranes), and a simple new route to mixed trialkylboranes.

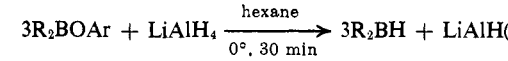
The hydroboration of 2,3-dimethyl-2-butene can be controlled to give the monoalkylborane, thexylborane (eq 1).[2] Otherwise, the synthesis of monoalkylboranes


(1)

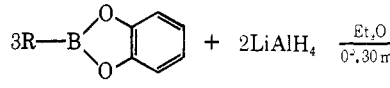
has been quite difficult. Thus, the redistribution of trialkylboranes with diborane gives the unsymmetrical 1,1-dialkyldiborane, rather than the desired 1,2-dialkyldiborane.[3] The reduction of alkylboron dihalides with metal hydrides results in the formation of a mixture of several organoboron products.[4] Recently, certain monoalkylborane addition compounds with trimethylamine have been synthesized *via* the reduction of the corresponding trialkylboroxine with LAH in the presence of the tertiary amine.[5] However, these addition compounds hydroborate olefins and dienes only at relatively high temperature.[6]

The parent monoalkylboranes, such as thexylborane, free of coordinating amine, possess highly interesting properties as reagents for selective reduction,[7] for the cyclic hydroboration of dienes,[8] the synthesis of cyclic and other ketones,[9] and the synthesis of olefins and dienes.[10] These potentialities offer major incentives for a convenient synthesis of monoalkylboranes.

Unfortunately, the methods which had proven successful (eq 2) in converting dialkylborinic acid esters to


(2)

dialkylboranes and their derivatives[11-13] proved unsatisfactory. Thus the treatment of dimethyl alkylboronates with LAH or AlH_3 gives the monoalkylborane in yields of only 40–45%. Utilization of the cyclic trimethylene esters[14] gives slightly improved yields, 60–68%. However, reduction of the *o*-phenylene esters of alkaneboronic acids (*B*-alkylcatecholboranes (**1**)) with either LAH (eq 3) or with AlH_3 (eq 4)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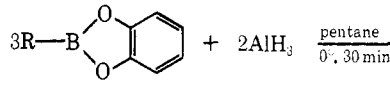
(4)

makes available highly satisfactory routes to the monoalkylboranes. In the lithium aluminum hydride reduction a moderate excess (33%) of the reducing agent, corresponding to conversion to the $Li_2(C_6H_4O_2)_3Al_2H_2$ stage, was necessary to achieve optimum yields. The addition of an olefin to the filtrate provides the corresponding mixed trialkylborane. The structure of these mixed boranes was confirmed by glpc analysis, whenever possible, using the previously identified samples,[13] and by their transformation *via* carbonylation[15] into the corresponding trialkylcarbinylboronates. A solution of 2-*n*-butyl-1,3,2-benzodioxaborole (1.76 g, 10 mmol) in ethyl ether (10 ml) was cooled with an ice bath and a clear solution of LAH in ethyl ether (3.35 ml of 2 *M*, 6.7 mmol) added over 2 min. The mixture was stirred for 1 hr at 0° and then diluted with pentane (20 ml). A white crystalline precipitate separated. The mixture was filtered through Celite under nitrogen. Evaporation of the filtrate provided *n*-butylborane as a clear liquid: ir (CCl_4) 2550, 1590, 1480 cm^{-1}. Addition of water evolved 19.2 mmol of hydrogen gas.

Alternatively, addition of amines provides corresponding amine–monoalkylborane. Thus, 17.6 g (100 mmol) of 2-*n*-butyl-1,3,2-benzodioxaborole in 100 ml of ethyl ether was treated with 67 mmol of LAH solution as above. After 1 hr at 0°, the mixture was diluted with pentane (100 ml) and filtered. Addition of trimethylamine (150 mmol) to the filtrate provided 10.3 g (80%) of trimethylamine–*n*-butylborane: bp 48° (0.5 mm); $n^{20}D$ 1.4320.

In the above synthesis (eq 3) the lithium aryloxyaluminohydride by-product retains reactive hydride. Consequently, it must be separated from the monoalkylborane if the latter is to be used to hydroborate olefins containing reducible functional groups. The aluminum hydride procedure (eq 4) circumvents the need for this separation. This synthetic potential is described in the following procedure. A solution of 2-*n*-butyl-1,3,2-

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