Synthesis of Stereospecifically Deuterated Vinyl Methyl Ethers

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ABSTRACT: The reduction of methoxyacetylene with lithium aluminum deuteride has been found to be a highly stereospecific process which yields exclusively isomeric deuterated methyl vinyl ethers of high isotopic purity. By choice of suitable reagents, the method becomes a versatile synthesis for all of the mono-, di-, and trideuterated methyl vinyl ethers.

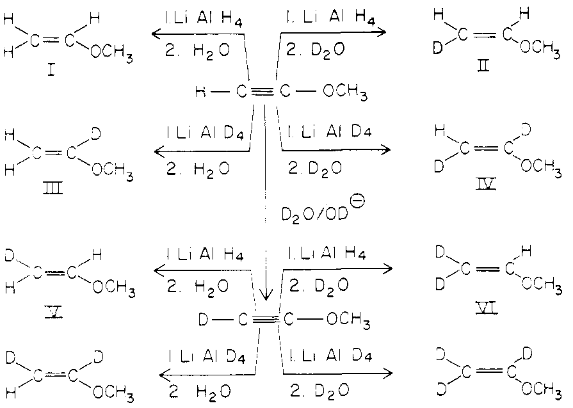
Although lithium aluminum hydride normally has no action at room temperature on an isolated triple bond, under more severe conditions (110–140°) lithium aluminum hydride has been reported to hydrogenate acetylenic hydrocarbons and lead to olefinic products upon hydrogenolysis.[1,2] More generally known is the facile reduction of a triple bond when a carboxyl function[3,4] or carbinol[5-8] is α to the triple bond; acetylenic carbinols containing an α-hydroxyl group are reduced with lithium aluminum hydride to α,β-unsaturated alcohols.[5-8] The same reagent also reduces acetylenic ethers but little is found in the literature describing the reaction.[9] This is unfortunate because the more commonly used diborane and hindered organoboranes[10,11] in our hands produced primarily methyl acetate (from the reaction of acetic acid on unconverted methoxyacetylene[12] present during protolysis) and only traces of methyl vinyl ether.

This paper presents the details of our studies on the reduction of methoxyacetylene and methoxyacetylene-d_1 with lithium aluminum hydride and lithium aluminum deuteride. The work described herein represents the first detailed study of this stereospecific reduction and nmr interpretation of labeled methyl vinyl ethers. We undertook the present investigation for the purpose of obtaining stereospecifically labeled methyl vinyl ethers as potential monomers for polymerization. It is well recognized that deuterated vinyl monomers are especially valuable tools which have aided interpretation of polymer propagation mechanisms[13-18] and polymer microstructure.[19-26]

Results and Discussion

Methoxyacetylene was allowed to react for 0.5 hr with a suspension of lithium aluminum hydride in diglyme at room temperature. Following decomposition of the reduction complex with water, the volatile component of the reaction was collected and found to consist almost entirely of methyl vinyl ether (I) in a yield of 34% (Scheme I). The nmr absorptions for

SCHEME I
STEREOSPECIFIC REDUCTION OF METHOXYACETYLENE AND METHOXYACETYLENE-d_1



I, methyl vinyl ether (ethynyl methyl ether)
II, methyl vinyl-β-*cis*-d_1 ether
III, methyl vinyl-α-d_1 ether
IV, methyl vinyl-α-*cis*-β-d_2 ether
V, methyl vinyl-β-*trans*-d_1 ether
VI, methyl vinyl-β-d_2 ether
VII, methyl vinyl-α-*trans*-β-d_2 ether
VIII, methyl vinyl-α,β-d_3 ether

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the vinyl protons of I gave the expected ABX pattern[27] (Figure 1). When deuterium oxide, rather than water, was used to destroy the reduction complex, we obtained compound II as the volatile part of the reaction product in a yield of 26%. The nmr spectrum of this compound is shown in Figure 1. The methoxyl singlet is situated at δ 3.55 in this and all other d_0, d_1, d_2, and d_3 methyl vinyl ethers. The doublet, centered at δ 4.00, is assigned to the β-*trans* proton, since the coupling constant (J = 6.6 Hz) indicates *cis* coupling with the α-proton. As expected, geminal (H^1–H^2) coupling was too small to observe.[13] The α-proton gives rise to a sextet at δ 6.54 consisting of six equivalent lines, the spacing of which (1.8 Hz) corresponds to *trans*-(H^1–H^2) coupling.[28, 29] The observed *trans*-(H^1–H^2) coupling constant (J = 1.8 Hz) agrees favorably with the predicted value which should be approximately one-seventh of the *trans*-(H^1–H^1) coupling constant (J = 14.4 Hz).[30] Thus, deuteration occurred exclusively at the β-carbon, *cis* to the methoxyl group. Mass spectral analysis of II showed the compound to be 92.7% d_1 species with the molecular ion at *m/e* 59.

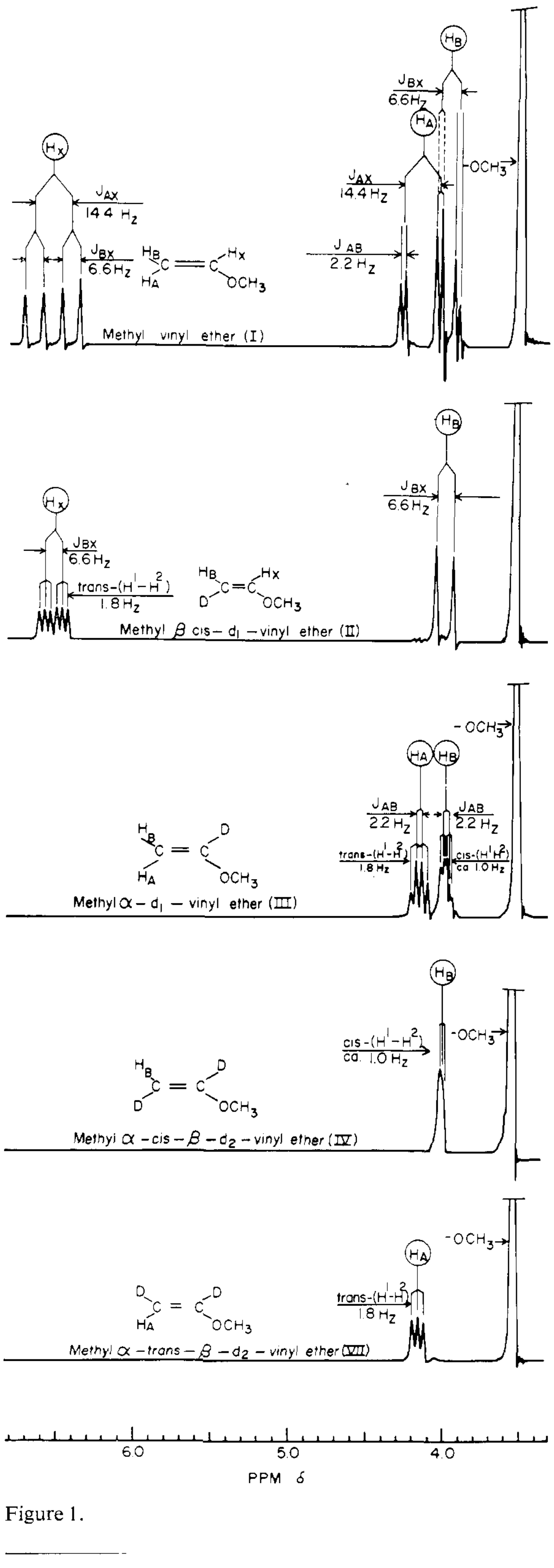

Figure 1.

Compound III was synthesized by the reduction of methoxyacetylene with lithium aluminum deuteride and subsequent decomposition of the reduction complex with water. The nmr spectrum of this compound (Figure 1) shows the absence of the α-proton. The β-*trans* proton at δ 4.00 is observed as a multiplet resulting from geminal coupling with the β-*cis* proton (J = 2.2 Hz) and weak *cis*-(H^1–H^2) coupling (J = ∼1.0 Hz). The *cis*-(H^1–H^2) coupling constant (J = ∼1.0 Hz) is almost the predicted value of one-seventh the J value for *cis*-(H^1–H^1) coupling (J = 6.6 Hz). The β-*cis* proton at δ 4.15 is observed as a quartet resulting from geminal coupling with the β-*trans* proton and strong *trans*-(H^1–H^2) coupling (J = 1.8 Hz).

Compound IV was obtained by the reduction of methoxyacetylene with lithium aluminum deuteride followed by decomposition of the reduction complex with deuterium oxide. The spectrum (Figure 1) reveals the absence of the α- as well as the β-*cis* protons. The β-*trans* proton at δ 4.00 is observed as a broadened singlet resulting from weak *cis*-(H^1–H^2) coupling (J = ∼1.0 Hz). Therefore, deuteration occurred *trans*.

Methyl vinyl-α-*trans*-β-d_2 ether (VII) was prepared in an analogous manner by the reduction of methoxyacetylene-d_1 with lithium aluminum deuteride. Following decomposition of the reduction complex with water, VII was obtained in a yield of 26%. The nmr spectrum (Figure 1) shows the β-*cis* proton as a 1:1:1 triplet at δ 4.15 resulting from strong *trans*-(H^1–H^2) coupling (J = 1.8 Hz). The deuterium nucleus, which possesses a spin of 1 and therefore has three equally probable orientations in a magnetic field, causes an adjacent proton to appear as a triplet.[31]

The other deuterated isomers (V, VI, and VIII) indicated in Scheme I were not synthesized during the course of this study. It is felt that the four deuterated monomers presented above were the most useful for the purpose of demonstrating the versatility and stereospecificity of this reduction technique.

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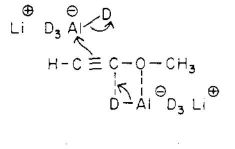
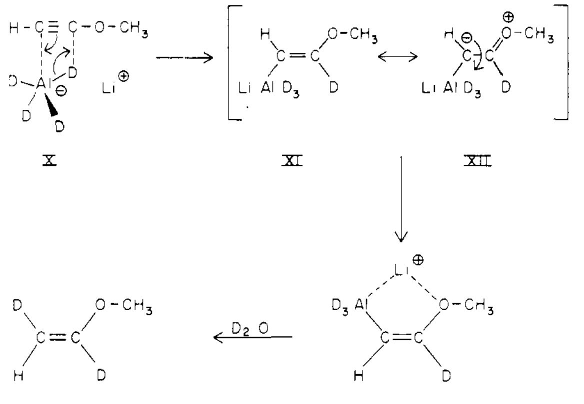
As portrayed in Scheme I, the structure of methyl vinyl-α-*cis*-β-d_2 ether (IV) and methyl vinyl-α-*trans*-β-d_2 ether (VII) indicate that lithium aluminum deuteride added *trans* to the triple bond of methoxyacetylene. Mechanistically, this is somewhat difficult to rationalize. It is known that methoxyacetylene undergoes nucleophilic attack preferentially at the α-carbon.[32] Thus, *trans* opening of the triple bond would likely involve formation of a C–Al bond *via* concerted attack by the β-carbon on a properly oriented electropositive aluminum center (IX) with release of a deuteride anion, a highly unfavorable process.



IX



X XI XII

XIII IV

It is probable that the actual mode of addition is initially *cis*, through a four-center transition state with the deuteride initiating nucleophilic attack at the α-carbon of methoxyacetylene (X). Subsequent rotational isomerism (XII) of the initially formed *cis*-vinylaluminum adduct (XI)[33] may be a highly favorable process. The relationship between solvent and the steric course of the reduction is not understood. As indicated by Slaugh,[2] *cis* addition of lithium aluminum hydride to acetylenic hydrocarbons occurs in nonpolar toluene; however, *trans* addition occurs in polar ether solvents. Other evidence for enhanced s character of the olefinic bond of vinyl ethers comes from the high shielding of the terminal ethylenic hydrogen nuclei as noted in the nmr spectra and is thought to result from delocalization effects involving resonance forms.[27] Such delocalization would lead to the electron density of the terminal ethylenic carbon atom approaching that expected of an alkane carbon atom.[34] Rotational isomerism about the C–C bond of the initially formed vinylaluminum adduct may be further enhanced by the likelihood of chelation involving a Li^+ bridge between the ether oxygen and the terminally bonded aluminum (XII).

Experimental Section

Physical Constants. The proton nmr spectra were obtained on a Varian Associates A-60A spectrometer using 2% tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in parts per million (ppm) downfield from TMS. The mass spectrum of II was determined with a Hitachi-Perkin-Elmer RMU-6H spectrometer at an ionization potential of 70 eV.

Materials. Bis(2-methoxy ethyl) ether (diglyme) was stirred over small pieces of calcium hydride for 12 hr and decanted into a distilling flask. Sufficient lithium aluminum hydride was added to ensure an excess of active hydride and the solvent was distilled under nitrogen at 75° (35 mm). To the distillate was added sodium potassium alloy and benzophenone. The flask was placed on a high vacuum manifold, and after degassing the contents, the characteristic purple color of the benzophenone dianion appeared. The diglyme was then distilled through the manifold from the storage flask as required.

Lithium aluminum deuteride and lithium aluminum hydride, from Alfa Inorganics, were used without further purification.

Methoxyacetylene was prepared by the reaction of chloroacetaldehyde dimethyl acetal with sodium amide in liquid ammonia. A procedure was used similar to that of Wasserman and coworkers,[35] except that commercially prepared sodium amide was added to avoid the use of sodium metal for *in situ* generation of sodium amide, and other minor changes were made for safety. The earlier methods can prove hazardous since specks of unreacted sodium are difficult to remove completely and are often present during the decomposition of the sodium methoxyacetylide salt with water.[12,35]

Anhydrous ammonia (1.2 l., dried through a soda lime tube) was stirred with a glass enclosed magnetic stirrer, while sodium amide was added (80 g in 20-g portions from individual wax-sealed bottles (Fisher Scientific)). The suspension was stirred for an additional 0.5 hr and 90 g (0.72 mol, 10% excess) of chloroacetaldehyde dimethyl acetal (previously distilled under nitrogen through a short Vigreux column at 46° (75 mm)) was added dropwise over a period of 1 hr. The ammonia was then allowed to evaporate over 24 hr while a slow stream of dry nitrogen passed through the system which was kept sealed from the air by a mercury trap. The flask containing the dry sodium methoxyacetylide was cooled for 1 hr in a chloroform–carbon tetrachloride–Dry Ice bath (−78°) while the flow of nitrogen was increased to prevent the entrance of air during cooling. Calcium chloride dihydrate (1.5 lb) was dissolved in water and diluted to a volume of 1 l. A saturated sodium chloride solution (100 ml) was added to depress the freezing temperature of the solution. The resulting salt solution was freed of air by boiling *in vacuo*, charged with nitrogen while cooling to −40°. The flow of nitrogen through the reaction vessel was increased while the cold salt solution was added as rapidly as possible. The funnel was replaced by a stopper and the flow of nitrogen was reduced. The mixture was allowed to warm to 0° and the flask was then swirled several times. The flask was fitted with a thermometer, a nitrogen bleed tube, simple distillation head, and a Dry Ice cooled receiver. The methoxyacetylene was distilled out under nitrogen while slowly heating the reaction in an oil bath. Distillation was continued until the inner temperature reached 55° and the oil bath temperature was 65°. Caution should be exercised during the distillation step to prevent the inner temperature from exceeding 65°. Methoxyacetylene is heat sensitive and can decompose

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explosively at elevated temperatures.[36] The distillate (~25 g) was warmed to 0° and 5 g of ice was added along with a few drops of phenophthalein. The basic lower layer was neutralized by the dropwise addition of a saturated solution of sodium dihydrogen phosphate. The lower aqueous layer was frozen out by cooling the flask in Dry Ice. The methoxyacetylene was decanted and dried over calcium sulfate at 0° for 2 hr and then distilled under nitrogen through a 12-in. Vigreux column and collected in a Dry Ice cooled receiver. The product (23.7 g, 67% yield) was subsequently dried over calcium hydride and distilled through the vacuum line manifold to calibrated break-seals.

Methoxyacetylene-d_1. Deuterium oxide (15 ml) was added under nitrogen to a Pyrex glass assembly which had been dried under high vacuum (10^{-5} Torr) for 8 hr. The deuterium oxide (99.8% D, Stohler Isotope Chemicals) was cooled to 0° and made basic by the addition, under nitrogen, of ~100 mg of lithium aluminum hydride. After 15 min, 8 ml of methoxyacetylene was added to the deuterium oxide *via* a break-seal and the two phases were stirred well magnetically. After 1 hr the methoxyacetylene-d_1 was distilled into a Dry Ice cooled receiver under a stream of dry, purified nitrogen. Nmr analysis of the distillate showed that the product was 92% isotopically pure after the first exchange, 97% after the second, and of ~99% isotopic purity after the third exchange. Methoxyacetylene-d_1 was dried over calcium sulfate and stored in vacuum sealed calibrated ampoules.

Reduction Apparatus. The preparation of deuterated vinyl methyl ethers was carried out in Pyrex glass assemblies which were dried under high vacuum (10^{-5} Torr) for a period of 8 hr with intermittent flaming. When necessary, the system was opened to atmospheric pressure under a flow of dry nitrogen. All reagents were added to the reaction flask from break-seals.

Deuterated Methyl Vinyl Ether Synthesis. Lithium aluminum hydride or deuteride (2.5 g, 66 or 60 mmol) and 60 ml of diglyme were added to the dry reaction assembly through a ball break-seal. The hydride suspension was well stirred while 8 ml (120 mmol) of methoxyacetylene or methoxyacetylene-d_1 was added dropwise by means of a Teflon stopcock. The reduction process was exothermic and required intermittent cooling to maintain the temperature between 35 and 40°. After the addition of methoxyacetylene or methoxyacetylene-d_1 was completed, the reaction mixture was stirred for an additional 0.5 hr at room temperature. Deuterium oxide (9 ml, 99.8% D) or water was added dropwise through a Teflon stopcock while the reaction temperature was maintained between 20 and 30°. The volatile reduction product (2.5–2.6 ml, ~26–27% yield) was distilled from the reaction vessel under a stream of nitrogen and collected in a Dry Ice cooled trap. The product was subsequently distilled through a high vacuum manifold to an ampoule containing calcium hydride. After degassing several times, the ampoule was melted off the vacuum line. The product was allowed to stand over calcium hydride for 12 hr. Traces of methoxyacetylene and other impurities were ultimately removed by allowing the product to stand over a freshly prepared sodium mirror for several days.

The nmr spectrum ($CDCl_3$) of methyl vinyl-*cis*-β-d_1 ether (II) showed the following absorptions: a singlet at δ 3.55 (3 H) for the methoxyl group, a doublet at 4.00 (1 H, J = 6.6 Hz) for the β-*trans* proton, and a sextet at 6.54 (1 H) consisting of six equivalent lines with spacing of 1.8 Hz for the α-proton: mass spectrum (70 eV) m/e (relative intensity) 59 (M^+, 24), 44 (24), 43 (12), 31 (11), 30 (8), 29 (22), 28 (11), 26 (5), 18 (100), 17 (30), 16 (24), 15 (14). The nmr spectrum ($CDCl_3$) of methyl vinyl-α-d_1 ether (III) showed the following absorptions: a singlet at δ 3.55 (3 H) for the methoxyl group, a multiplet at 4.00 (1 H) for the β-*trans* proton, and a quartet at 4.15 for the β-*cis* proton. The nmr ($CDCl_3$) of methyl vinyl-α-*cis*-β-d_2 ether (IV) showed the following signals: a singlet at δ 3.55 (3 H) for the methoxyl group and a 1:1:1 triplet at 4.00 (1 H) with spacing of ~1.0 Hz for the β-*trans* proton; methyl vinyl-α-*trans*-β-d_2 ether (VII) showed a singlet at δ 3.55 (3 H) for the methoxyl group and a 1:1:1 triplet at 4.15 (1 H) with spacing of 1.8 Hz for the β-*cis* proton.

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