A Study of the Catalytic Deuteration of 1,4-Butynediol

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The stereoselective semihydrogenation of alkynes is an important and useful reaction in organic chemistry.[1] Recently, the stereoselective hydrogenation of 1,4-butynediol to 1,4-butenediol using an interlamellar montmorillonite–diphenylphosphinepalladium(II) complex has been reported.[2] The reaction proceeds with high selectivity (97%), and no reduction of the alkene was observed with the absorption of 1 equiv of hydrogen.

We have been interested in catalytic reduction to stereospecifically introduce deuterium into butynediol[3] and related dialkyl maleates and fumarates.[4] Partial hydrogenation of 1,4-butynediol with a variety of partially poisoned catalysts has been reported.[5] Our previous work has involved the use of Lindlar catalyst, which we found to catalyze the uptake of deuterium very slowly. Large-scale reduction of 1,4-butynediol required weeks for completion, and the isolated yield of the olefin was reduced from overreduction if the reaction was not carefully monitored and from competing condensation or polymerization reactions.

We report the results of our studies relating to the reduction of 1,4-butynediol using Lindlar catalyst, 5% palladium on charcoal, and montmorillonite–diphenylphosphinepalladium(II) complex. This study was prompted by (1) a need for a convenient large-scale production of both cis-2,3-dideuteriobutenediol (200–500 g) and 2,2,3,3-tetradeuteriobutanediol[6] and (2) an interest in understanding why the use of 5% palladium on charcoal or Lindlar catalyst produces both low chemical and isotopic yields of the 1,4-butanediol-d_4 when the reduction is allowed to go to completion. We have previously reported the reduction of 1,4-butynediol to cis-2,3-dideuterio-2-butene-1,4-diol, an important precursor in the synthesis of chiral 2,3-dideuteriosuccinic acid.[3] We were particularly concerned about the possible implications that low deuterium incorporation in the two internal methylene groups of the saturated diol could have on the isotopic abundances in the vinyl positions of the corresponding butenediol precursor. The use of capillary gas chromatographic columns separated each of the reduced diols and significantly enhanced our ability to follow the course of the reductions.

The initial reduction of 1,4-butynediol with each of the catalysts mentioned previously proceeds smoothly, and the major product detected early in the reduction was cis-2,3-dideuterio-1,4-butenediol. The relative rates of reduction at 1 atm of pressure of deuterium gas at room temperature were as follows: montmorillonite–diphenylphosphinepalladium(II) complex > 5% palladium/carbon >> Lindlar catalyst. cis-2,3-Dideuterio-1,4-butenediol was isolated from these reductions in high yield provided the reaction was carefully monitored and terminated following the absorption of 1 equiv of reducing gas. The stereochemistry about the double bond was characterized by conversion of the cis diol to dl-2,3-dibromo-2,3-dideuteriobutane-1,4-diol,[7] isolated after purification in 52% yield. ^{1}H NMR analysis indicated high deuterium abundances at the vinyl positions, and ^{13}C NMR indicated the absence of detectable splittings due to deuterium at the methylene positions.

When the reduction was allowed to continue and all the butynediol was consumed, overreduction of the 1,4-butenediol was observed with all three catalysts. In addition to the formation of 1,4-butanediol, the reaction was complicated by competitive formation of a new peak with a much shorter gas chromatographic retention time. This new peak was formed by all three catalytic systems investigated and required the presence of hydrogen or deuterium gas. At low deuterium or hydrogen pressures (~1 atm or less), this product was produced in yields up to ~70% (Table I). cis-1,4-Butenediol allowed to stir in the presence of the catalyst under the reaction conditions in the absence of H_2 or D_2 was not affected. However, if hydrogen or deuterium gas was introduced, the new peak appeared along with the presence of the saturated 1,4-diol. This new material was found to be isomeric with cis-2-butene-1,4-diol by GCMS and was identified as 2-hydroxytetrahydrofuran by spectroscopic and chemical characterization. Formation of this material competes with reduction to 1,4-butanediol and is responsible for the low chemical and isotopic yield previously obtained in the recovered butane-1,4-diol. Under our reaction conditions, 2-hydroxytetrahydrofuran exists in equilibrium with 4-hydroxybutanal,[8] which complicated the initial spectral analysis. Our failure to detect this ether earlier was due in part to limitations of our analytical system and its volatility under the conditions used to vacuum distill 1,4-butanediol.

2-Hydroxytetrahydrofuran was identified by its spectral properties and by conversion to the known 2,4-dinitrophenylhydrazone derivative. The ^{13}C NMR chemical shifts of the small amount of 4-hydroxybutanal in equilibrium with the cyclic form were consistent with those previously reported for 4-hydroxybutanal prepared from 1,4-butanediol by bis(η^5-cyclopentadienyl)zirconium dihydride catalyzed Oppenauer oxidation.[9]

Table I summarizes the results obtained in this study. Reductions with the clay–Pd catalyst are fastest in THF,

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Table I. Catalyzed Reductions of 1,4-Butyne- and 1,4-Butenediol[a]

starting catalyst diol	catalyst	reactn time (h)	mol H$_2$/D$_2$ absorbed	% 1,4-diols, GC analysis			
				butyne	butene	butane	HTHF[e]
butyne	clay	2.0	~1	10	87	0	3
		2.5	>1	0	28	37	35
		3.2	>1	0	0	55	45
butyne[b]	clay	5.0	<1	13	84	2	1
		6.5	~1	0	97	2	1
		7.2	>1	0	75	15	10
butyne	Pd/C	5.0	<1	84	15	1	0
		8.0	~1	63	35	1	1
		24.0	>1	0	20	36	44
butene	clay	0.8	<1		12	60	28
		1.2	~1		0	68	32
butene[c]	clay	2.0	<1		17	41	41
		3.5	~1		4	47	49
butene[d]	clay	23.0	<1		22	21	57
		30.0	~1		0	77	22
butene[d]	Lindlar	72.0	<1		52	32	15
		144.0	~1		19	55	27

[a] All reductions at 25 °C, 1 atm or less, in THF unless noted otherwise. [b] Ethyl acetate. [c] 50 °C. [d] No solvent. [e] 2-Hydroxytetrahydrofuran.
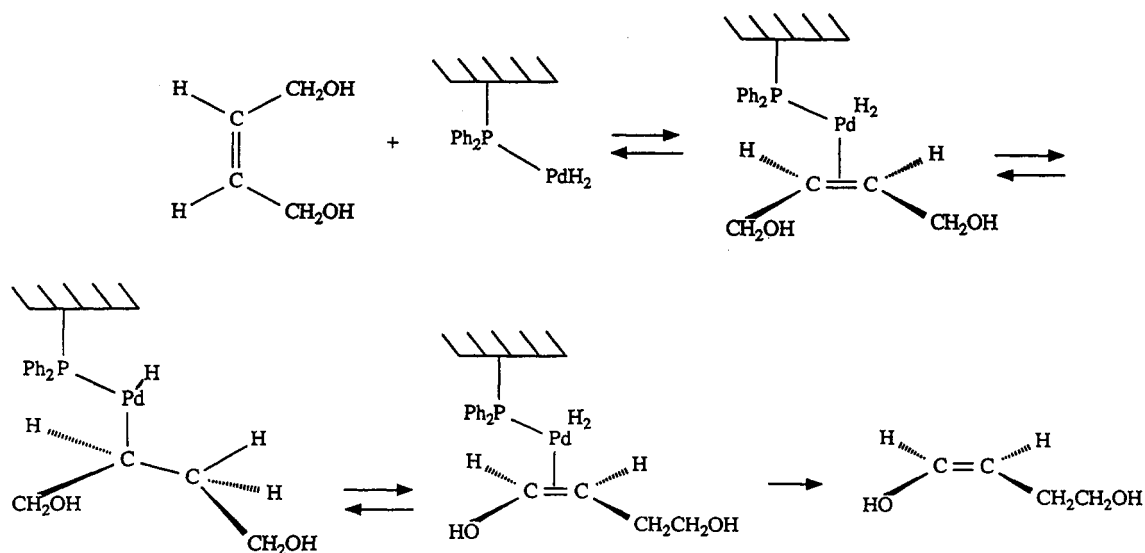

Figure 1. Possible mechanism for formation of 4-hydroxybutanal.

and this has been explained in terms of the swelling properties of montmorillonite in this solvent.[2c] Temperature seems to have some effect on the amount of isomerization of 1,4-butenediol to 2-hydroxytetrahydrofuran in THF (row 4 and 5), but clearly the results obtained without solvent produce the most isomerization (row 6). The effects of temperature at these solvent-free conditions were not investigated. Temperature effects on the reduction of acetylenic alcohols have previously been reported.[10]

Although 2-hydroxytetrahydrofuran can be produced on a commercial scale from Rh–carbonyl-catalyzed hydroformylation of allyl alcohol,[11] formation of this material in overall 72% yield by isomerization of *cis*-butene-1,4-diol represents an attractive one-step laboratory preparation of this material from inexpensive, readily available starting materials. Other recent reports of the synthesis of 4-hydroxybutanal include the zirconium-catalyzed oxidation of butanediol mentioned previously[9] and from the reaction of ethylene oxide with dihydro-1,3-oxazines.[8]

The isomerization of *cis*-2-butene-1,4-diol to 4-hydroxybutanal can be explained by the generally accepted mechanism for reduction of olefins as illustrated in Figure 1. Formation of an olefin–palladium π complex followed by collapse of this complex to an alkyl–palladium σ complex with formation of a new carbon–hydrogen bond are likely to be the first steps in the reaction. Reduction of the metal–carbon bond leads to alkane. Many of these steps, however, are known to be reversible and dependent on experimental conditions. The alkyl–palladium σ complex can also revert back to an olefin–palladium π complex. Depending on which hydrogen is removed, reversibility at this point can lead to the original olefin or, as in the case of 1,4-butenediol, to the enol form of 4-hydroxybutanal. In the case of 1-butene-1,4-diol, ketonization of the enol and cyclization appears to make this step irreversible.

The method of preparation of the montmorillonite catalyst suggests that the palladium is highly dispersed in the clay. The similarity in product distribution of all the catalysts examined in this study, as indicated in Table I, suggests that their mode of action is very similar. The catalysts differ mainly in the relative rates of each step in the reduction. The montmorillonite–Pd catalyst appears to be the most active and the most reversible in this re-

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Table II. Isotopic Distribution of Deuterium in Succinic Anhydride as Obtained from Reduction of Diethyl Maleate and Fumarate with Deuterium Gas

		catalyst		
		5% Pd/C		montmoril-lonite-diphenyl-phosphine-palladium complex
	m/e		%	%
diethyl fumarate[a]	100	d_0	1	d_0 1
	101	d_1	10	d_1 18
	102	d_2	100	d_2 100
	103	d_3	1	d_3 1
diethyl maleate[a]	100	d_0	4	d_0 5
	101	d_1	16	d_1 25
	102	d_2	100	d_2 100
	103	d_3	8	d_3 3
	104	d_4	1	d_4 1

[a] Reductions at 25 °C, 1 atm or less, no solvent; deuterium content analyzed by conversion to succinic anhydride.[4]

spect. To test if this behavior of the montmorillonite–Pd catalyst is a characteristic of the catalyst, we have also examined the reduction of diethyl fumarate and diethyl maleate with deuterium gas and have compared the results to those previously observed with Pd/C.[4] The amount of deuterium incorporated, as summarized in Table II, suggests that the clay catalyst may not be as useful as Pd/C in olefin reductions with deuterium. It is interesting in this regard that less d_3 species is produced from reduction of diethyl maleate by use of the palladium–clay complex than with Pd/C. This again may reflect differences in the relative rates of the various steps involved in the reductions.[4] The palladium–clay catalyst appears to be well-suited for deuteration of 1,4-butynediol and is superior to both Pd/C and the Lindlar catalyst for this purpose, provided the progress of the reduction is carefully monitored.

Experimental Section

Bis(benzylcyano)palladium Dichloride.[12] Palladium dichloride (5.0 g) was heated with PhCH$_2$CN (50 mL) at 80 °C for 40 min, and the hot mixture was filtered. The filtrate was diluted with ether, resulting in the separation of yellow crystals of bis(benzylcyano)palladium dichloride, mp 93 °C (lit.[12] mp 93 °C).

Chloromontmorillonite.[2,13] A mixture of thionyl chloride (50 mL), dry benzene (50 mL), and vacuum-dried montmorillonite (5 g, Volclay Accu-Gel, American Colloid Co.) were refluxed for 24 h. The initial brown color of the mixture changed to deep black-green after 24 h of reflux. The excess thionyl chloride and benzene were evaporated, and the residue was washed with benzene and then dried in vacuum.

Montmorillonite–Diphenylphosphinepalladium(II) Complex. Freshly distilled chlorodiphenylphosphine (17.2 g, 0.078 mol) was added dropwise under argon to lithium metal (1.5 g, 0.22 mol) slurried in dry tetrahydrofuran (20 mL of THF).[14] The mixture was stirred and cooled as necessary during the initial

exothermic period. After being stirred overnight, the deep red solution was separated from salts and unreacted lithium by syringe and added to a suspension of chloromontmorillonite (3.5 g) in dry THF (20 mL). The mixture was refluxed for 24 h. The clay was filtered and washed with THF/H$_2$O (8/2, v/v). The color of the clay after vacuum drying was gray.

Montmorillonite–diphenylphosphine complex (2.9 g) was stirred with PdCl$_2$(PhCH$_2$CN)$_2$ (0.55 g) in dry benzene (20 mL) at room temperature under Ar for 6 h. Filtration of the mixture afforded the PdCl$_2$-anchored montmorillonite catalyst as a brown solid (3.05 g). In the presence of hydrogen or deuterium, the clay catalyst immediately turned black. This material was generally recovered and reused in other reductions without a noticeable decrease in activity.

Hydrogenation and Deuteration Studies. All reductions were carried out in a classical hydrogenation apparatus at pressures ~1 atm. Commercial samples of 5% Pd/C (Pfaltz and Bauer) and Lindlar (Fluka A G) catalysts were used. The hydrogenation flask was equipped with a Teflon stopcock and septum to allow for periodic removal of sample. A substrate to catalyst ratio of 10 was used in all reductions. When fresh clay catalyst was used, the catalyst was activated by treating with H$_2$ or D$_2$. The gases and vapor above the solution were pumped away to remove as much of the hydrogen chloride or deuterium chloride as possible. All reactions were monitored on a HP Model 5890 gas chromatograph with a 30 m × 0.32 mm DP5 capillary column, which resolved all starting materials and products described previously. The comparisons of reaction times in Table I are qualitative since the pressure of the reducing gas was not controlled; the composition of the compounds reported in column 6 of this table are gas chromatographic results and represent 90+% of the total composition of the reaction mixtures.

Reduction of Diethyl Maleate and Diethyl Fumarate. Diethyl maleate and diethyl fumarate were reduced in the absence of solvent and converted to the corresponding succinic anhydride as previously reported.[4]

4-Hydroxybutanal–2-Hydroxytetrahydrofuran. The best yield of 2-hydroxytetrahydrofuran (72%) was obtained by use of the following: the montmorillonite–palladium complex at a catalyst to substrate ratio of 0.1; room temperature; 1 atm of pressure or less of hydrogen; no solvent; and a 30-h reaction period. Separation of 2-hydroxytetrahydrofuran from butanediol was achieved by vacuum distillation (^{13}C NMR (2-hydroxytetrahydrofuran, CDCl$_3$) 97.8, 66.7, 32.7, 23.1 ppm). Weak resonances were also observed for 4-hydroxybutanal (^{13}C NMR 25.7, 31.8, 61.6 ppm (lit.[9])). The carbonyl resonance at 199.6 ppm was not observed under these conditions; 2,4-dinitrophenylhydrazone of 4-hydroxybutanal, mp 116–117 °C (lit.[8,15] mp 116–118 °C). Both fresh and recovered catalyst, as well as Pd/C and Lindlar catalysts, gave similar results, suggesting that the isomerization is not catalyzed by traces of hydrogen chloride. Self-condensation of 2-hydroxytetrahydrofuran is probably responsible for some of the nonvolatile tars formed during prolonged reaction times, particularly when using the Lindlar catalyst.

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