Selective Monotetrahydropyranylation of Symmetrical Diols Catalyzed by Ion-Exchange Resins

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Primary and secondary symmetrical diols with 2−10 carbon atoms gave selectively monotetrahydropyranyl ethers in the reaction catalyzed by wet sulfonic acid-type ion-exchange resins in 3,4-dihydro-2*H*-pyran (DHP)/toluene or DHP/hexane. The yields of the monoethers were higher than 80% while those of the corresponding diethers were lower than 5%. In these reactions the rate of the formation of the diethers did not increase much even after most of the diols had been consumed. In the reaction of 1,10-decanediol in DHP/hexane, the yields of the monoether were increased by the addition of DMF or DMSO. Each diol was found to have a particular DHP/hydrocarbon ratio that gave the highest selectivity for the monoether. Generally, the larger the number of carbon atoms of the diols, the smaller the ratio of DHP in the solvents to give high selectivity for the monoether. This method of the selective etherification is quite simple and practical.

Introduction

Methods for the selective protection of one of two identical functional groups, which exist in symmetrical sites in a molecule, are important in organic synthesis. Selective monoacylation of symmetrical diols has been well studied.[1] Since the protection of hydroxyl groups by etherificaion is quite common in organic syntheses,[2] it would be valuable to develop the methods to obtain monohydroxy ethers selectively from symmetric diols. In some cases, the monoetherification of symmetrical diols can be achieved by Williamson reaction,[1g,3] by the use of alumina and diazomethane,[1e] or via cyclic compounds.[4] We have already reported the selective formation of monotetrahydro-2*H*-pynanyl (THP) ethers from 1,*n*-diols in 3,4-dihydro-2*H*-pyran (DHP)/hexane catalyzed by metallic sulfates supported on silica gel.[5] In that reaction,

it is inferred that the selective monoprotection results from two factors: the selective adsorption of the diols on the surface of the catalysts in preference to the corresponding monoethers and the formation of the diol layers of appropriate thickness on the surface of the catalysts. The formation of the diol layers is attributed to the limited solubility of the diols in the solvents. The latter factor realizing the selectivity suggests that selective reactions such as monoetherification of symmetrical diols may occur, even if a solid catalyst is not adsorptive, when the following conditions are fulfilled: (1) the solubility in solvents increases in numerical order from the smallest in starting materials (diols) to the largest in final products (diethers) and (2) the dissolving power of solvents is appropriate.

Although maximum yields of the monoethers are high,[5] the selective monoetherification in DHP/hexane catalyzed by metallic sulfates supported on silica gel has one serious problem: the diethers form very rapidly after the majority of the diols has been consumed. Therefore, close attention must be paid to when to terminate the reaction. Here, we report the selective formation of monoethers from symmetrical diols in DHP/hydrocarbon catalyzed by strongly acidic ion-exchange resins, in which the disadvantage mentioned above is greatly improved.

It is already known that alcohols are tetrahydropyranylated by DHP in the presence of acidic ion-exchange resins such as Amberlite IR-120,[6] Amberlist H-15,[7] Rellex 425,[8] or Nafion-H.[9] As for the selective reactions using ion-exchange resins, the formation of monoesters from symmetrical diols[1a] and dicarboxylic acids[10] has been

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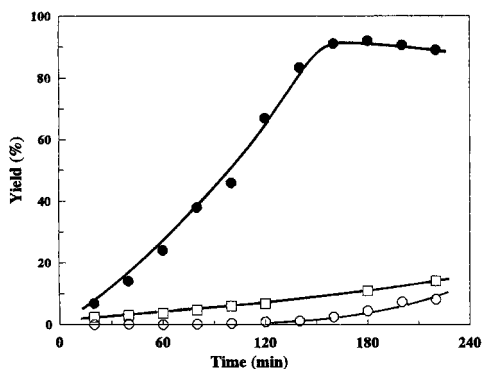
Figure 1. Yields vs reaction time. 1,6-Hexanediol or 6-(tetrahydropyranyloxy)-1-hexanol (1 mmol) and Dowex 50W × 2 (50−100 mesh) (0.2 g) were stirred at 30 °C in DHP/toluene (5:95, 6 mL): monoether (●) and diether (○) from the diol; diether (□) from the monoether.

reported. In these reactions it was inferred that the water contained in the ion-exchange resins was crucial for the selectivity. A part of the results of the etherification of 1,n-diols in DHP/hydrocarbon catalyzed by Dowex 50 has been published as a preliminary report.[11] This method of selective etherification is quite simple and practical.

Results and Discussion

Selective Monoetherification of Symmetrical Diols. The selective monotetrahydropyranyration in this study was carried out by stirring a diol and an ion-exchange resin in DHP/toluene or DHP/hexane under observation by GLC. Most reactions were carried out at 30 °C in pursuit of good reproducibility, although they proceeded at room temperature.

Figure 1 shows an example of the dependence of the product yields on the reaction period in the etherification of 1,6-hexanediol (1 mmol) in DHP/toluene (5:95, 6 mL). The yield of the diether was 3% when that of the monoether reached 95%. The yield of the diether did not increase rapidly even after the yield of the monoether reached its maximum. This result shows that the reaction rate of the monoether is far lower than that of the diol and that the rate of the formation of the diether does not increase very much even after most of the diol has been consumed. This result differs from the result obtained in the reactions catalyzed by silica gel-supported sulfates, in which the monoethers reacted much more rapidly in the absence of diols than in their presence.[5] The result described above enhances the value of the reaction catalyzed by ion-exchange resins because the timing to terminate the successive etherification is not so important in this reaction as in the reaction catalyzed by the supported sulfates.

Table 1 shows that symmetrical primary and secondary diols with 2−10 carbon atoms gave the corresponding monotetrahydropyranyl ethers in higher yields than 85%. Benzenedimethanols are among the diols (Table 1, entries 17 and 18). In the reaction of 1,2-cyclohexanediols,

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the cis-diol showed higher reactivity and lower selectivity than the trans-diol (Table 1, entries 10 and 11). It is well-known that axial hydroxyl groups on a cyclohexane ring are more reactive than equatorial ones. We postulate that this fact explains our result, since both the diol and the monoether in cis-form seem to undergo the etherification on the axial hydroxyl group while those in trans-form seem to be etherified on the equatorial one.

In the reaction of 1,10-decanediol in DHP/toluene, yields of the monoether were low. They increased by the change of solvents from DHP/toluene to DHP/hexane and with the addition of DMF or DMSO (0.1 mL) (Table 1, entries 21 and 22). In the reaction of 1,12-dodecanediol, the yields of the monoether were considerably lower than those in the reactions of the diols with not more than 10 carbon atoms (Table 1, entry 23). When 67% of the monoether and 8% of the diether were formed (Table 1, entry 23), 21% of the unreacted diol was detected in the organic layer and no other byproducts from the diol were found.

2-Hydroxytetrahydropyran was formed in all reactions involving DHP and wet strongly acidic ion-exchange resins as byproducts. Under the conditions shown in Figure 1, the molarity of the byproduct was about twice as much as that of the diether formed while 1,6-hexanediol remained. The cyclic hydroxy ether was formed when Dowex 50W was stirred in DHP/toluene or DHP/hexane. This result shows that it was formed by the reaction between DHP and the water in the resin.
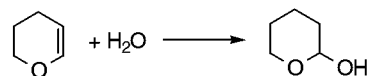
To examine the catalytic activity and the selectivity of the various ion-exchange resins, 1,6-hexanediol and an ion-exchange resin were stirred at 30 °C in a mixture of DHP and toluene (59:5) (Table 2). The yields of the monoether were higher than 90% when the yields of the diether were 2% and 5% in the reactions catalyzed by some sulfonic acid-type ion-exchange resins. Wet type resins, such as Dowex 50W, Amberlite 118, and Amberlite 120, showed higher selectivity than resins for non-aqueous solutions, such as Nafion NR50 and Amberlyst 15. Dowex 50W × 2 (50−100 mesh) lost 75% of its weight by being dried over P_2O_5 (see Experimental Section). The dried resin showed lower selectivity than the original resin. The selectivity was low in the reaction catalyzed by camphorsulfonic acid, which was carried out as a control experiment. The carboxylic acid-type resin (Amberlite IRC-50) was inactive. Dowex 50W × 2 (50−100 mesh) was used in all etherifications described hereafter because it dispersed most easily in the solutions.

Rationalization of the Selectivity. Figure 1 also shows the yield of 1,6-bis(tetrahydropyranyloxy)hexane in the reaction of 6-(tetrahydropyranyloxy)-1-hexanol (starting material). Conditions of this reaction were the same as those of the etherification of 1,6-hexanediol. The yields of the diether in the reaction of monoether as starting material were much lower than the yields of monoether in the reaction of diol as starting material. This outcome shows that the diol reacted much more rapidly than the monoether to realize the selective formation of the monoether from the diol.

We presume that the selectivity for monoethers arises from the following assumed factors: (1) a strongly acidic

Table 1. Selective Monotetrahydropyranylation of Symmetrical Diol with DHP Catalyzed by an Ion-Exchange Resin[a]

entry	diol	DHP/%	time/min	yield (%)[b]	
				monoether	diether
1	1,2-ethanediol	10	100	95	2
2	1,3-propanediol	80	30	78	3
3	1,3-propanediol[c]	40	220	92	4
4	cis−2-butene-1,4-diol[d]	10	140	88	5
5	1,6-hexanediol	5	210	95	3
6	1,6-hexanediol[e]	60	40	85	5
7	2,5-hexanediol	20	140	93	4
8	3-methyl-1,5-pentanediol	20	100	94	3
9	2-ethyl-2-methyl-1,3-propanediol	10	120	95	2
10	cis−1,2-cyclohexanediol	20	120	93	6
11	trans−1,2-cyclohexanediol	20	360	96	4
12	1,3-cyclohexanediol	20	140	95	2
13	1,4-cyclohexanediol	20	220	94	4
14	1,4-cyclohexanediol	40	90	95	3
15	1,8-octanediol	3	270	95	2
16	1,4-cyclohexanedimethanol	5	200	96	2
17	1,2-benzenedimethanol	5	220	94	5
18	1,4-benzenedimethanol	5	200	85	13
19	1,10-decanediol[f]	3	160	64	15
20	1,10-decanediol[e,f]	3	240	74	9
21	1,10-decanediol[e,f,g]	3	355	87	8
22	1,10-decanediol[e,f,h]	3	290	83	9
23	1,12-dodecanediol[e,f,g]	3	165	67	8

[a] Diol (1.0 mmol) and Dowex 50W × 2 (50−100 mesh) (0.1 g) were heated at 30 °C in a DHP/toluene (6 mL). [b] GLC yields obtained by the use of internal standards (see Experimental Section). [c] Amount of the catalyst was 0.04 g. [d] This diol was used instead of 1,4-butanediol because in GLC analysis the retention time of 1,4-butanediol and 2-hydroxytetrahydropyrane was nearly the same. [e] The solvent was the DHP/hexane mixture. [f] Reaction temperature was 40 °C. [g] DMSO (0.1 mL) was added. [h] DMF (0.1 mL) was added.

Table 2. Selectivity and Catalytic Activity of Ion-Exchange Resins[a]

resin and acid	yield of monoether (%)[b]		initial rate (×10³) (M/min)
	(1)	(2)	
Dowe × 50W × 2 (50−100 mesh)	91	96	0.81
Dowe × 50W × 2 (50−100 mesh)[c]	60	65	0.83
Dowe × 50W × 2 (200−400 mesh)	79	92	1.3
Dowe × 50W × 4 (200−400 mesh)	72	82	1.4
Dowe × 50W × 8 (50−100 mesh)	92	94	0.65
Dowe × 50W × 8 (200−400 mesh)	86	92	1.4
Amberlyst 15[d]	6	9	1.2
Amberlyst 15 (wet)	50	71	0.96
Amberlyst × N-1010[d]	57	64	0.72
Amberlite IR-118 (H)	89	91	0.46
Amberlite IR-120 (plus)	86	96	0.39
Nafion NR50[d]	3	7	0.43
(+)-10-camphorsulfonic acid[e]	17	23	1.2

[a] 1,6-Hexanediol (1 mmol) and a resin (0.1 g) were stirred at 30 °C in DHP/toluene (5:95, 6 mL). [b] Yield of the monoether at 2% yield of (1) and at 5% yield of (2) of the diether. [c] Dried catalyst (0.02 g) was used. [d] For nonaqueous applications. [e] The amount of the catalyst was 0.01 mmol.

water layer is formed on the surface of the porous resins, because the sulfonic acid-type ion-exchange resins usually contain 50−80% water;[12] (2) the ratios of the diols in the water layer are much higher than those of the monoethers; (3) the diols react in preference to the monoethers in the aqueous layer, which also contains DHP; (4) the formed monoethers migrate from the aqueous layer into the surrounding aprotic organic layer, which does not contain catalytic proton.

When the dried catalyst described before was used, the selectivity, the initial rate, and the maximum yield of the monoether were low (Table 2). When increasing amounts of water were added to the reaction system using the dried catalyst, both the selectivity and the initial rate rose, exhibited maximum values, and then declined gradually (Figure 2). It was also found that the amount of the water contained in the original purchased Dowex 50W was suitable for the high selectivity and reactivity.

(12) Suppliers' catalogs.

These results support, at least in part, the presumed mechanism noted above.

The resin (Dowex 50W) once used in the etherification was recovered by filtration and used again. Although the selectivity and the activity of the recovered catalyst were a little lower than those of the fresh resin, they recovered intensity by the addition of the same weight of water as that of the resin. This result suggests that the water in the catalyst was lost considerably during the reaction. The relation between the amount of the catalyst and the selectivity also supports this suggestion. In the reaction of 1,6-hexanediol (1 mmol) in DHP/toluene (20:80, 6 mL), the selectivity was hardly influenced by the amount of the catalyst when the amount of resin used was in the range of 0.02−0.4 g. When the amount of the catalyst was smaller than in this range, the selectivity decreased, probably because of the loss of the water in the catalyst during the reaction. When too large an amount of the catalyst was used, the reaction proceeded so fast that the

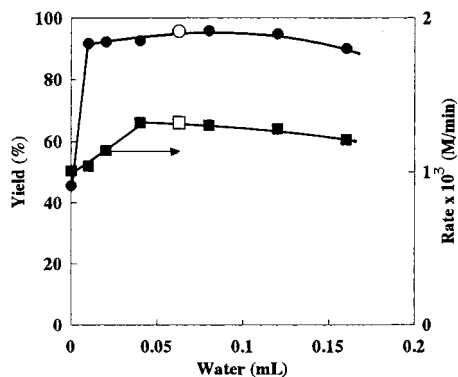**Figure 2.** Yield and rate vs amount of water. 1,6-Hexanediol (1 mmol) and dried Dowex 50W × 2 (50−100 mesh) (0.02 g) and water were stirred at 30 °C in DHP/toluene (10:90, 6 mL): yield of the monoester at 4% yield of the diester (●) and initial rate of the formation of the monoether (■). The yield (○) and the rate (□) in the reaction catalyzed by the original wet resin (0.08 g) are also shown.
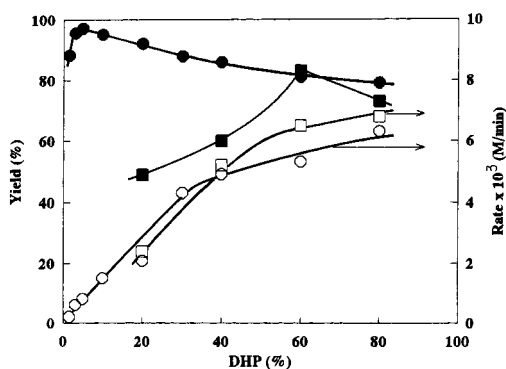

Figure 3. Yield and initial rate vs solvent composition. 1,6-Hexanediol (1 mmol) and Dowex 50W × 2 (50−100 mesh) (0.1 g) were stirred at 30 °C in DHP/toluene or DHP/hexane (6 mL): yield of the monoether at 3% yield of diether (●) and initial rate of the formation of the monoether (○) in DHP/toluene. The yield (■) and the rate (□) in DHP/hexane.

time to terminate the reaction was critical to achieve good selectivity.

Figure 3 shows the relationship between the composition of solvents and the yields of the monoether at the yield of 3% of the diether in the reaction of 1,6-hexanediol. In both DHP/toluene and DHP/hexane systems, the selectivity depended on the solvent composition and showed gentle peaks. The percentages of DHP at which the peaks appeared were 5 and 60% in DHP/toluene and in DHP/hexane, respectively. This result may be explained by the fact that the solvents dissolve the diol and the monoether in the following decreasing order: DHP > toluene > hexane. It was also found that the yields of the monoether at the 3% yield of the diether in the reaction of 1,6-hexanediol in DHP/toluene were higher than those in DHP/hexane. The rates of the formation of the monoether in the reaction in DHP/toluene and those in DHP/hexane of the same DHP percentages were not so different (Figure 3). The smaller the ratio of DHP in the solvent, the lower the rate of the etherification and consequently the larger the quantity of catalyst needed. This is the reason the amount of catalyst noted in Table 1 is different in each reaction.

Each diol had the particular ratio of DHP/hydrocarbon that gave the highest selectivity. Generally, the larger

the number of carbon atoms of a diol, the smaller the DHP/hydrocarbon ratio to realize the highest selectivity. However, the selectivity in this system did not depend on the DHP/hydrocarbon ratio so greatly as that in the reaction catalyzed by metallic sulfates supported on silica gel.[5] This dull response of the selectivity to reaction conditions is also an advantage of this reaction system.

In the reaction of 1,6-hexanediol, the selectivity was higher in DHP/toluene than in DHP/hexane, as described before. However, it was higher in DHP/hexane than in DHP/toluene in the reaction of 1,10-decanediol. Moreover, the lower the ratio of DHP in DHP/hexane, the higher the selectivity, though when the percentage of DHP in the solvent was 1%, the reaction rate was extremely slow and the yield of the monoether did not exceed 80%. These results may be explained by the presumption that 1,10-decanediol has lower solubility in the water layer of the catalyst and higher solubility in the organic solvent than 1,6-hexanediol.

As shown in Table 1, the addition of DMF and DMSO raised the selective in the reaction of 1,10-decanediol. The increase of the selectivity may be explained by the presumption that these strongly polar additives were distributed mainly in the water layer of the catalyst and that the solubility of the water layer for the diol is enhanced more than that for the monoether. The effect of the additives was not observed in the reaction of 1,8-octanediol, which is more soluble in the water than 1,10-decanediol.

When we increased the concentration of 1,6-hexanediol from 0.1 M while keeping the other conditions the same as those shown in Figure 1, the selectivity was independent of the concentration of the diol up to 0.45 M. The selectivity then decreased as the concentration increased. The initial rate of monoether formation was constant in the range of the concentration examined (0.1−0.6 M). This result suggests that the concentration of the diol in the water layer of the catalyst was almost constant even if the amount of the diol added was varied and that the water layer was nearly saturated with the diol. The reason the rate of the formation of the diether began to increase when the concentration of the diol reached 0.45 M is not clear yet.

Experimental Section

Reagents and solvents were purchased and used without purification. GLC analyses were performed on an instrument with an autoinjector. The column was a 30 m × 0.25 mm i.d. fused silica capillary column coated with NB-5.

Analytical-Scale Monoetherification of Symmetrical Diols. The etherification of 1,6-hexanediol is typical. A mixture of 1,6-hexanediol (0.118 g, 1 mmol), Dowex 50W × 2 (50−100 mesh) (0.1 g), 1-octadecane (GLC internal standard, 20 μL), and 5:95 (v/v) DHP/toluene (6 mL) was stirred at 30 ± 1 °C. Samples of the supernatant liquid were then removed periodically and analyzed by GLC. The retention times of the monoether and the diether were identical to those of authentic samples prepared by the conventional method described in the previous paper.[5] The yields of monoethers at a particular yield of diethers were derived from plots of product yield vs time, such as those shown in Figure 1.

Preparative-Scale Selective Monoetherification of Symmetrical Diols. The etherification of 1,6-hexanediol is typical. 1,6-Hexanediol (0.59 g, 5.0 mmol) and Dowex 50W × 2 (50−100 mesh) (1 g) were stirred at 30 + 1 °C in a mixture of DHP (1.5 mL) and toluene (30 mL), and the mixture was monitored by GLC. After 2.5 h, the catalyst was removed by filtration and the solution was evaporated. The residue was

chromatographed with hexane/EtOAc (4:1) on silica gel column to give the monoether (0.89 g, 89%) and the diether (0.03 g, 2%).

Drying of Ion-Exchange Resin. Dowex 50W $\times$ 2 (50–100 mesh) (1 g) was kept over P_2O_5 (30 g) in a desiccator. The weight of the resin decreased to 26% in 1 day and 25% in 7 days. The resin dried for 7 days was used in the etherification.

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