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Convenient Selective Monoacylation of 1,*n*-Diols Catalyzed by Ion-Exchange Resins

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Several 1,*n*-diols, ranging from 1,2-ethanediol to 1,16-hexadecanediol, were selectively monoacylated by transesterification in ester/octane solvent mixtures catalyzed by strongly acidic ion-exchange resins. This method of selective esterification is quite simple and practical. The selectivity for monoester formation and initial rates of monoester formation depended on the ester/octane ratio of the solvents. The reasons for the selectivity are as follows: (1) The sulfonic acid-type ion-exchange resins usually contain 50–80% water, and a strongly acidic aqueous layer is formed on the surface of the resins. (2) A partition equilibrium between the aqueous layer and the aprotic ester/octane layer is setup, and diols have higher partition coefficients than the product monoesters. (3) Acylation of the alcohols occurs in the aqueous layer and/or at the interface between the aqueous and the nonaqueous liquid layer. (4) The formed monoesters move away from the aqueous layer into the aprotic layer.

Introduction

Methods for selective protection of multiple identical functional groups in a similar chemical environment are important in organic synthesis. In some cases, the monoacylation of 1,*n*-diols can be achieved by careful control of the reaction conditions,[1] by continuous extraction,[2] by the use of alumina,[3] phase-transfer catalysts,[4] inorganic polymer supports,[5] or distannoxane,[6] or via cyclic compounds.[7]

We have reported that symmetric diols are selectively monoprotected by monoacylation[8] in an ester/alkane solvent mixture or monotetrahydropyranyl ether formation[9] in a dihydropyran/alkane solvent in reactions catalyzed by metallic sulfates supported on silica gel. In these reactions, it is believed that the selective monoprotection results from two factors. One is the selective adsorption of the diols in preference to the corresponding monoesters or the corresponding monoethers on the surface of the catalysts. The other is the formation of diol layers of an appropriate thickness on the surface of the catalysts. The formation of the diol layers is attributable to the limited solubility of the diols in the solvents. The formation of diol layer suggests that selective reactions such as the monoacylation of diols may occur when the solubility in the solvent successively increases from the least in a starting material through the largest in a final product and when the solvating power of the solvent is suitable, even if a solid catalyst is not adsorptive. Although silica gel-supported metallic sulfates can be prepared easily, the use of readily available reagents as catalysts makes experiments simpler. Here we would like to report the selective monoacylation of 1,*n*-diols catalyzed by strongly acidic ion-exchange resins, which is quite simple to perform.

$$\mathrm{HO(CH_2)_{\mathit{n}}OH} \xrightarrow[\mathrm{RCO_2R'-alkane}]{\text{ion-exchange resin}} \mathrm{RCO_2(CH_2)_{\mathit{n}}OH} + [\mathrm{RCO_2(CH_2)_{\mathit{n}}OCOR}]$$

Results and Discussion

Conditions for Monoacylation of 1,*n*-Diols. For the examination of the catalytic activity of the various ion-exchange resins and the selectivity of the monoacylation, 1,6-hexanediol and an ion-exchange resin were heated at 100 °C with stirring in a mixture of ethyl propionate and octane (1:4) (Table 1). Initial rates for the monoacylation of the diol were readily obtained since no induction periods were observed (see Figures 1 and 3). There seems to be no clear relation between initial rates and the particle size of the resins. Carboxylic acid-type resins were inactive. The yields of 6-(propionyloxy)-1-hexanol at the points where the yields of 1,6-bis(propionyloxy)hexane were 2% and 5% depended little on the particle size, the degree of cross-linking, or the brand name of the resin. These monoester yields indicate that the reaction is selective for monoester formation. Amberlist had slightly higher activity and selectivity when powdered. The selectivity of Nafion was low. In the reactions catalyzed by methanesulfonic acid, which were carried out as control

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[1] (a) Wilkinson, S. G. In *Comprehensive Organic Chemistry*; Stoddart, J. F., Ed.; Pergamon Press; New York, 1979; Vol. 1, p 681. (b) Furhop, J.; Penzlin, G. *Organic Synthesis*; Verlag Chemie: Weinheim, 1983; p 143.

[2] Babler, J. H.; Coghlan, M. J. *Tetrahedron Lett.* **1979,** *22,* 1971.

[3] (a) Ogawa, H.; Chihara, T.; Taya, K. *J. Am. Chem. Soc.* **1985,** *107,* 1365. (b) Ogawa, H.; Ichimura, Y.; Chihara, T.; Teratani, S.; Taya, K. *Bull. Chem. Soc. Jpn.* **1986,** *59,* 2481. (c) Ogawa, H.; Chihara, T.; Teratani, S.; Taya, K. *J. Chem. Soc., Chem. Commun.* **1986,** 1337.

[4] Zerda, J. D. L.; Barak, G.; Sasson, Y. *Tetrahedron Lett.* **1989,** *29,* 1533.

[5] Leznoff, C. C. *Acc. Chem. Res.* **1989,** *11,* 327.

[6] Otera, J.; Dan-Oh, N.; Nozaki, H. *J. Chem. Soc., Chem. Commun.* **1991,** 1742.

[7] Murahashi, S.; Oda, Y.; Naota, T. *Chem. Lett.* **1992,** 2237 and references cited therein.

[8] (a) Nishiguchi, T.; Kawamine, K.; Ohstuka, T. *J. Org. Chem.* **1992,** *57,* 312. (b) Nishiguchi, T.; Taya, H. *J. Am. Chem. Soc.* **1989,** *111,* 9102.

[9] (a) Nishiguchi, T.; Kawamine, K.; Ohstuka, T. *J. Chem. Soc., Perkin Trans.* **1992,** 153. (b) Nishiguchi, T.; Kawamine, K. *J. Chem. Soc., Chem. Commun.* **1990,** 1776.

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Table 1. Catalytic Activity and Selectivity of Ion-Exchange Resins[a]

resin and acid	initial rate × 10^3 (M min^{-1})	yield of monoester (%)[b]	
		1	2
Dowex 50W × 2 (50–100 mesh)[c]	2.4	57	76
Dowex 50W × 2 (200–400 mesh)[c]	2.5	55	76
Dowex 50W × 2 (200–400 mesh)[c,d]	2.5	55	78
Dowex 50W × 4 (200–400 mesh)[e]	1.8	62	79
Dowex 50W × 4 (200–400 mesh)[d,e]	1.9	65	82
Dowex 50W × 8 (50–100 mesh)[f]	1.7	60	77
Dowex 50W × 8 (200–400 mesh)[f]	2.2	67	81
Dowex 50W × 8 (200–400 mesh)[d,f]	2.5	68	79
Amberlyst 15	1.2	52	66
Amberlyst 15[d]	1.1	55	64
Amberlite IR-118 (H)	1.0	55	72
Nafion NR-50	1.7	37	56
methanesulfonic acid[g]	1.2	23	37
methanesulfonic acid[g,h]	1.2	21	35

[a] 1,6-Hexanediol (1 mmol) and a resin (0.03 g) were heated at 100 °C in $EtCO_2Et$/octane (1:4, 3 mL). [b] Yield of the monoester at 2% yield (1) and at 5% yield (2) of the diester. [c] 2% cross-linking. [d] The resin was ground to a powder with a mortar and pestle. [e] 4% cross-linking. [f] 8% cross-linking. [g] The amount of the catalyst was 0.01 mmol. [h] Reaction in $EtCO_2Et$/octane (1:1).

experiments, the selectivity was much lower than that in the reactions catalyzed by solid catalysts. Dowex 50W × 2 (50–100 mesh) was used in all the transesterifications described hereafter because it dispersed most easily in the solutions.

Table 2 shows that all of the 1,*n*-diols that were examined, ranging from 1,2-ethanediol to 1,16-hexadecanediol except for 1,4-butanediol, gave the corresponding monopropionyl esters in acceptable yields and selectivities. This result confirms the general applicability and practical utility of this method. In the reaction of 1,4-butanediol, the yield of the corresponding monoester was low because tetrahydrofuran was formed by competitive intramolecular dehydration of the diol. Each diol had a particular ester/octane solvent ratio that gave the highest selectivity. When the acyl group of the solvent was changed from propionyl to acetyl, butyryl, isobutyryl, or valeryl, 1,6-hexanediol gave the corresponding monoester with considerable yield and selectivity (entries 4–9). The larger the acyl group, the slower the acylation. The selectivity of the monoester formation depended little on the amount of the catalyst (entries 18–22). This result contrasts with the results obtained for the acylations catalyzed by silica gel-supported metallic sulfates, where smaller amounts of catalyst gave higher selectivity. When the amount of the catalyst was too large, the timing of termination of the reaction became more difficult because of the high reaction rate. The contrast suggests that the mechanisms of selectivity differ in the reactions with the two kinds of catalysts.

When the ratio of octane in the solvent system was gradually increased in the reaction of 1,6-hexanediol, the yield of the monoester at which the yield of the corresponding diester was 5% reached a maximum value and then declined (Figure 2). The maximum yield was realized when the proportion of octane was 75–80%. The initial rate of monoester formation also showed a maximum when the octane proportion was 80–85% and a pattern similar to the change of the monoester yield. This result differs from those obtained in the reactions catalyzed both by silica gel-supported sulfates and dried ion-exchange resin, as will be described later.

The initial rate of monoester formation is proportional to the concentration of 1,6-hexanediol, up to a point (Figure 5). Beyond the critical concentration, the rate deviates from linearity, probably because of the limited solubility of the diol as described later. The selectivity of the monoester formation was independent of the concentration of the diol over a wide range of concentrations. Unless otherwise noted, the transesterifications described hereafter were carried out by heating 1,6-hexanediol (1 mmol) and the resin (0.1 g) at 100 °C in ethyl propionate/octane (1:4, 6 mL).

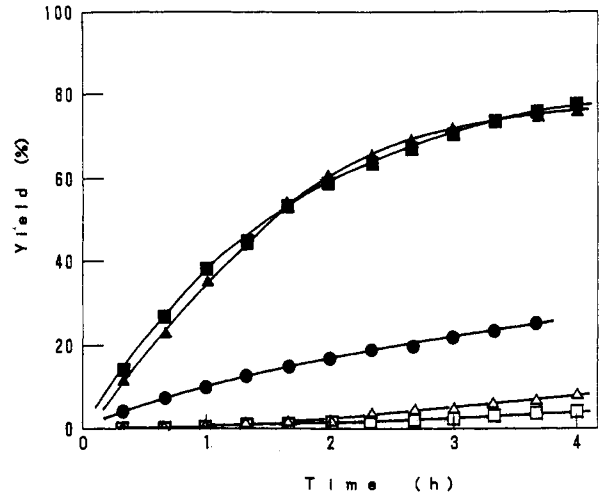

Figure 1. Yields vs reaction time. 1,6-Hexanediol or 6-(propionyloxy)-1-hexanol and Dowex 50W × 2 (50–100 mesh) (0.06 g) were heated at 100 °C in $EtCO_2Et$/octane (1:4, 6 mL): monoester (▲) and diester (△) from the diol (2 mmol); monoester (■) and diester (□) from the diol (1 mmol); and the diester (●) from the monoester (2 mmol).

Rationalization of the Selectivity. Figure 1 shows examples of the dependence of the product yield upon the reaction period. The yield of the diester did not increase rapidly, even when the increase of the yield of the monoester became slow. This result shows that the monoester reacts much more slowly than the diol, even after most of the diol has been consumed, and suggests that there is no competition between the diol and the corresponding monoester for the surface of the catalyst. These results contrast sharply with those obtained in the reactions catalyzed by silica gel-supported sulfates, in which monoprotected substrates react much more rapidly in the absence of diols than in their presence.[8,9] The difference suggests that in the reactions of ion-exchange resins there is no saturation in the affinity of the diols for the catalyst and that the selectivity is due to factors other than the catalyst saturation by which the selectivity in the reactions catalyzed by silica gel-supported sulfates is realized. This suggestion is also supported by the above-mentioned relation between the amount of the catalyst and the selectivity. In fact, the acylation rate of 6-(propionyloxy)-1-hexanol in the absence of any diol is about $^1/_4$–$^1/_3$ as fast as that of 1,6-hexanediol (Figure 1). This rate relationship holds true both in cases where the initial number of both substrates was equal and where the number of hydroxyl groups in the two substrates was equal. This outcome shows that the selectivity of the monoester formation results from the fact that the reactivity of the diol is apparently much higher than that of the monoester. That the yield of the diester does not increase rapidly even after most of the diol has been consumed enhances

Table 2. Selective Monoacylation of $HO(CH_2)_nOH$ with $R^1CO_2R^2$ Catalyzed by Ion-Exchange Resin[a]

		ester							
entry	*n*	R^1	R^2	%	catalyst (g)	time (min)	yield of monoester (%)	yield of diester (%)	recovered diol (%)
1[b,c]	2	Et	Et	60	0.03	240	81	5	
2[c,d]	3	Et	Et	60	0.1	140	92	5	
3[b]	4	Et	Et	40	0.03	100	62	2	12
4	6	Me	Et	20	0.04	240	75	5	18
5	6	Et	Et	20	0.06	240	81	5	12
6	6	Et	Et	20	0.1	140	84	6	5
7	6	Pr	Me	20	0.1	140	76	5	5
8	6	Pr^i	Me	20	0.1	260	73	3	7
9	6	Bu	Me	25	0.1	240	71	6	5
10[b]	8	Et	Et	20	0.03	200	80	7	10
11	10	Et	Et	8	0.1	200	75	8	15
12	10	Et	Et	10	0.1	160	78	9	11
13	12	Et	Et	10	0.1	140	74	6	13
14	12	Et	Et	10	0.1	180	80	9	8
15[e]	12	Et	Et	10	0.1	450	85	6	9
16	16	Et	Et	5	0.1	240	64	7	22
17	16	Et	Et	8	0.1	220	72	12	15
18	6	Et	Et	20	0.05	130	63	2	28
19	6	Et	Et	20	0.06	115	61	2	27
20	6	Et	Et	20	0.1	64	60	2	26
21	6	Et	Et	20	0.2	29	59	2	18
22	6	Et	Et	20	0.24	18	58	2	13

[a] Diol (1.0 mmol) and Dowex 50W × 2 (50–100 mesh) (0.1 g) were heated at 100 °C in an ester–octane mixture (6 mL). [b] The amount of solvent was 3 mL. [c] Recovery of the diol was not measured. [d] Reaction temperature was 90 °C. [e] Reaction temperature was 70 °C.

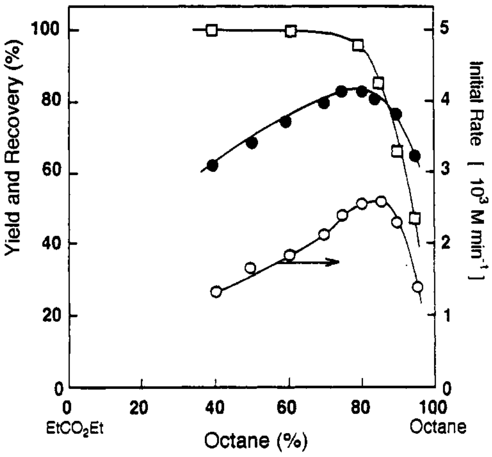

Figure 2. Yield, initial rate, and recovery vs solvent composition. 1,6-Hexanediol (1 mmol) and Dowex 50W × 2 (50–100 mesh) (0.1 g) were heated at 100 °C in $EtCO_2Et$/octane (6 mL): yield of the monoester at 5% yield of diester (●) and initial rate of monoester formation (○). Recovery of the diol from supernatants of the mixtures without catalysts is also shown (□).

the utility of this reaction because the timing of the termination of the successive esterification is not so important.

We presume that the selectivity arises from the factors enumerated below. (1) Because the sulfonic acid-type ion-exchange resins usually contain 50–80% water,[10] a strongly acidic water layer is formed on the surface of the resins. (2) A partition equilibrium between the aqueous layer and the aprotic ester/octane layer is setup, and the diols have higher partition coefficients than the product monoesters. The relative ratio of the diols to the monoesters depends on the composition of the solvent. (3) Acylation of the alcohols occurs in the aqueous layer and/or at the interface between the aqueous and the nonaqueous liquid layer. (4) The product monoesters move away from the aqueous layer into the aprotic layer, which does not contain protons, through a process resembling continuous extraction and remain there without reacting further.

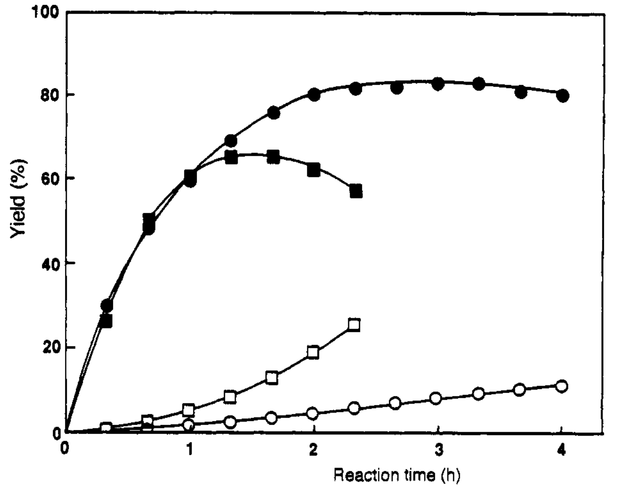

Figure 3. Yields vs reaction time. 1,6-Hexanediol (1 mmol) and Dowex 50W × 2 (50–100 mesh) were heated at 100 °C in $EtCO_2Et$/octane (1:4, 6 mL): monoester (●) and diester (○) with wet resin (0.1 g); monoester (■) and diester (□) with dried resin (0.04 g).

In order to prove these assumptions, we performed the reactions with catalysts that had been dried over P_2O_5. Figure 3 shows the time dependence of the product yields in the reactions catalyzed by the wet and the dried resin. The amounts of both catalysts were chosen so that similar initial rates were obtained. The plots in the figure show that the selectivity of the reaction with the dried catalyst decreased as the reaction proceeded. It is assumed that the diol layer formed initially by the limited solubility of the diol disappeared and that the selectivity decreased considerably as the diol was consumed. This result shows that a certain amount of water in the resin is essential for the high selectivity.

When the percentage of octane in the solvent was increased in the dried resin-catalyzed reaction, the yield of the monoester at 5% yield of the diester increased gradually and then decreased rather sharply (Figure 4).

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(10) Suppliers' catalogs.

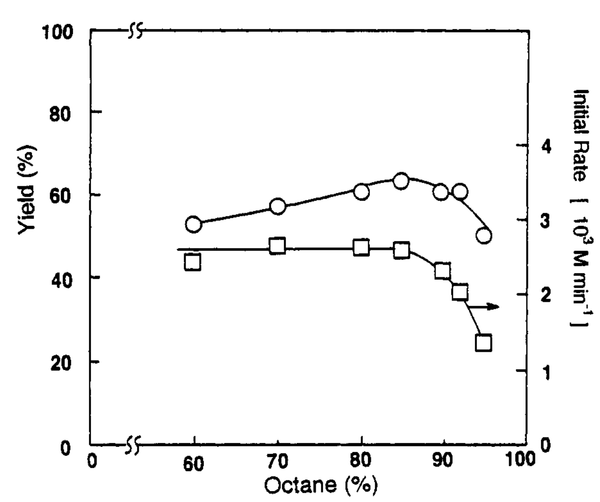

Figure 4. Yield and initial rate vs solvent composition. 1,6-Hexanediol (1 mmol) and dried Dowex 50W × 2 (50–100 mesh) (0.04 g) were heated at 100 °C in $EtCO_2Et$/octane (6 mL): yield of monoester at 5% yield of the diester (○) and initial rate of monoester formation (□).

The initial rate of monoester formation remained constant at octane percentages lower than 85% and then decreased. The initial rate pattern differs from that obtained in the corresponding reaction with the wet resin (see Figure 2) and is similar to that obtained in the reactions catalyzed by silica gel-supported sulfates.[8]

As will be described later, it is presumed that the higher the percentage of octane in the solvent system the larger the amount of the diol in the aqueous layer on the resin. Therefore, both the rate of monoester formation and the selectivity should increase as the percentage of octane in the solvent increases. However, both the rate and the selectivity decreased when the percentage of octane exceeded about 80%. In order to determine the reason, we stirred 1,6-hexanediol at 100 °C for a short while in ethyl propionate/octane mixtures in the absence of catalysts. The percentages of the diol detected again in the supernatant solutions, that is, the recovery of the diol, depended on the composition of the solvent (see Figure 2 and also the Experimental Section). When the ratio of octane reached 80%, the recovery of the diol began to decrease sharply. This result suggests that at octane percentages higher than 80%, a proportion of the diol separated without dissolving completely. It is inferred that, in the presence of the resin, some of the diol dissolves in the aqueous layer of the catalyst and that the separated diol covers the surface of the aqueous layer as a film. When the diol layer becomes too thick, it prevents ethyl propionate from reaching the aqueous layer, and the rate of acylation of the diol is lowered.

In a model experiment to estimate roughly the distribution of the diols and the corresponding monoesters between the aqueous layer on the solid surface of the resin and the surrounding organic layer, 1,6-hexanediol and 6-(propionyloxy)-1-hexanol were distributed between water and ethyl propionate/octane layers. Figure 6 shows that the diol resides in the water layer much more than in the organic layer. Moreover, a significant amount of the monoester dissolved in the water layer when the percentage of octane in the organic layer was high. It is inferred that a similar phenomenon occurred with the aqueous layer of the ion-exchange resin and the surrounding organic layer and that this phenomenon explains at least partly the result that the selectivity and the reaction rate first increased and then decreased as the ratio of octane in the solvent system was increased.

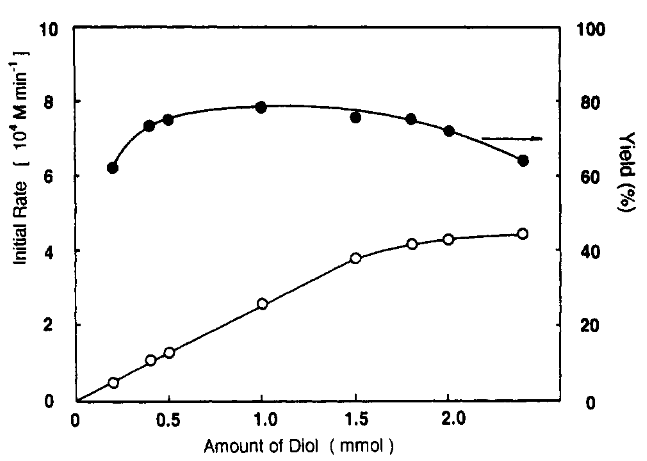

Figure 5. Initial rate and yield vs diol concentration. 1,6-hexanediol and Dowex 50W × 2 (50–100 mesh) (0.1 g) were heated at 100 °C in $EtCO_2Et$/octane (1:4, 6 mL): initial rate of monoester formation (○) and yield of the monoester at 5% yield of the diester (●).

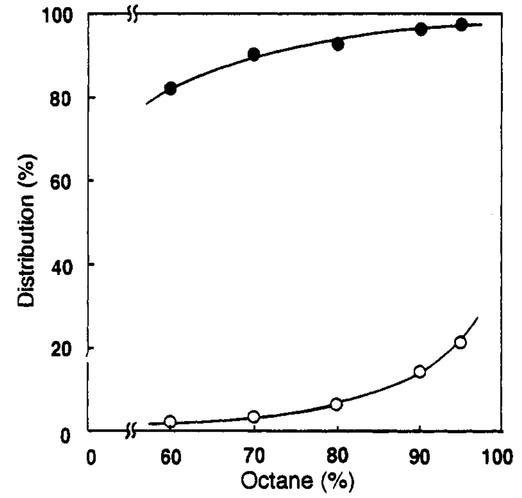

Figure 6. Distribution of diol and monoester in the aqueous layer in a partition equilibrium between water and ethyl propionate/octane (see Experimental Section).

The dissolution of the diol in the water layer of the resin is also inferred from the fact that the amount of the diol in the reaction solution decreased when the amount of the catalyst was increased (Table 2, entries 18–22).

In the monoprotection of diols catalyzed by the silica gel-supported sulfates, the selectivity was very low when the reaction temperature was lower than the melting point of the diol because solid diols do not form a liquid film. However, in the resin-catalyzed reaction, the selectivity of the reaction of 1,12-dodecanediol whose melting point is 82 °C was not lowered at a reaction of 70 °C (Table 2, entries 13–15). This fact, too, supports the assumption that the selectivity results from the fact that the diols are more soluble than the corresponding monoesters in the aqueous layer of the sulfonic acid-type ion-exchange resins. Similar selectivities are anticipated for reactions catalyzed by water-containing ion-exchange resins when the water solubility decreases successively from starting materials to final products.

Experimental Section

Reagents and solvents were 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 SE-52.

Analytical-Scale Monoacylation of 1,*n*-Diols. The acylation of 1,6-hexanediol is typical. A stirred mixture of 1,6-hexanediol (0.118 g, 1 mmol), Dowex 50W × 2 (50–100 mesh) (0.1 g), pentadecane (GLC internal standard, 20 μL), and 1:4 (vol/vol) ethyl propionate/octane (6 mL) was warmed at 100 ± 1 °C. Samples of the supernatant liquid were then removed periodically and analyzed by GLC. The retention times of the monoester and the diester were identical to those of authentic samples prepared by the conventional method described in the previous paper.[8]

The yield of monoester at a particular yield of diester was derived from a plot of product yield vs time, such as those shown in Figures 1 and 3.

Preparative-Scale Selective Monoacylation of 1,*n*-Diols. The acylation of 1,6-hexanediol is typical. 1,6-Hexanediol (0.59 g, 5.0 mmol) and Dowex 50W × 2 (50–100 mesh) (0.50 g) were stirred at 100 ± 1 °C for 4.5 h in a mixture of ethyl propionate (6 mL) and octane (24 mL). The catalyst was removed by filtration, and the solution was evaporated. The residue was chromatographed with hexane/EtOAc (4:1) to give the monoester (0.78 g, 83%) and the diester (0.07 g, 5%) in addition to recovered diol (0.06 g, 10%).

Drying of Ion-Exchange Resin. Dowex 50W × 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 transesterification.

Determination of the Amount of Diol in the Supernate. A mixture of 1,6-hexanediol (0.118 g, 1 mmol), pentadecane (GLC internal standard, 20 μL), and ethyl propionate/octane (6 mL) was heated with stirring for 10 min at 100 ± 1 °C. Then the mixture was left unstirred for 10 min at 100 [illegible] 1 °C. A sample of the supernatant was then analyzed by GLC. It is noteworthy that the amounts of the diol and the solvent and the reaction temperature were the same as those in the reactions shown in Figure 2.

Distribution of Diol and Monoester in Aqueous Layer. 1,6-Hexandiol (0.059 g), 6-(propionyloxy)-1-hexanol (0.087 g), water (0.6 mL), and ethyl propionate/octane (6 mL) were stirred for 10 min at rt. The mixture was then allowed to stand, and 0.5 μL of the water layer was injected into the GLC.