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POLYMER-SUPPORTED BASES. XI. ESTERIFICATION AND ALKYLATION IN THE PRESENCE OF POLYMER-SUPPORTED BICYCLIC AMIDINE OR GUANIDINE MOIETIES

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ABSTRACT

Polymer-supported 1,5,7-triazabicyclo[4.4.0]deca-5-ene (TBD) was prepared by the reaction of chloromethylated polystyrene resins, cross-linked with 2 mol% of divinylbenzene, with TBD. The reaction of benzoic acid with bromobutane was carried out in toluene or acetonitrile in the presence of polymer-supported TBD or polymer-supported 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The rate of esterification was dependent on the ring substitution of the supported bases and the solvent. The reduced ring substitution resulted in the increased swellability of the polymeric beads containing benzoate or bromide ions for toluene and thereby in the increased reaction rate. The rate with the high ring-substituted bases increased in acetonitrile, because of the high swellability of the immobilized salts and the high nucleophilicity of benzoate anion in the solvent. The supported bases were also effective for alkylation of an active methylene compound with bromoalkane.

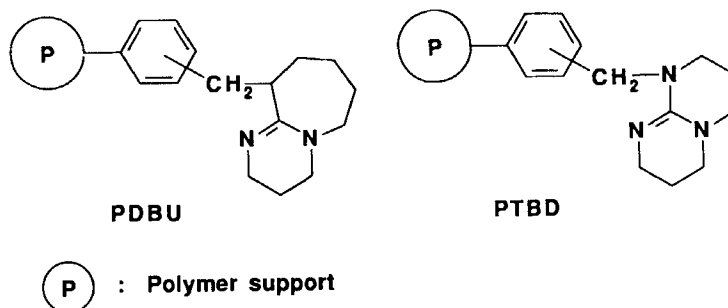
INTRODUCTION

Bicyclic amidines or guanidines, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,5,7-triazabicyclo[4.4.0]deca-5-ene (TBD), are useful reagents in synthetic organic chemistry [1, 2]. DBU results in efficient dehydrohalogenation of

organic halides [3], esterification of carboxylic acids with alkyl halides [4], and formation of carboxylic acids [5], carbonates [6], or carbamates [7] from carbon dioxide and active methylene compounds, alcohols, or amines, respectively. The amidine is also effective for alkylation and acylation of active methylene compounds [8] and is a catalyst for acylation of alcohols with acylimidazoles [9, 10]. TBD, more basic than DBU [2], was used successfully for tautomerizing pyrrocorphins and decarboxylation of arylalkyl carboxylic acids [11, 12].

Polystyrene-supported DBU, prepared from DBU and haloalkylated polystyrenes, was also an effective reagent for dehydrobromination, esterification, and lactone synthesis: the recovered base could be reused without decrease in reactivity [13, 14].

This paper reports on the preparation of polystyrene-supported TBD (PTBD) and on its reactivity for esterification of a carboxylic acid or alkylation of an active methylene compound with an alkyl bromide, compared with polymer-supported DBU (PDBU).



EXPERIMENTAL

Materials

DBU (Sanyo Chem. Ind.) was refluxed and distilled over CaH_2 under reduced pressure. Tetrahydrofuran (THF) was refluxed and distilled over sodium wire in the presence of benzophenone. Microporous chloromethylated polystyrene resins were prepared by suspension copolymerization of a commercial mixture (6:4) of *m*- and *p*-chloromethylstyrene with styrene and 2 mol% of divinylbenzene (DVB) [15]. Polymer-supported DBU (PDBU) was prepared according to the previously described procedure [13]. Other reagents and solvents were obtained commercially and used as received.

Measurements

IR spectra were taken using a Shimadzu FTIR-4000 spectrophotometer. ^1H NMR spectra were recorded on a 270-MHz instrument (JEOL EX-270) using CDCl_3 as solvent and tetramethylsilane as internal standard. Esterification and alkylation were followed by GLC on a Shimadzu 4C-PT thermal conductivity instrument with a 2-m glass column of 20 wt% SF-96 on Chromosorb W at 170 and 165°C, respectively.

Preparation of Polystyrene-Supported TBD (PTBD)

A 500-mL, four-necked flask with a mechanical stirrer, a reflux condenser, and a nitrogen inlet tube was charged with 250 mL of anhydrous THF and 9.1 g (65 mmol) of TBD (Fluka). The stirred solution was cooled to -78°C , and 40 mL (65 mmol) of *n*-butyllithium in hexane was added dropwise over a period of 1 h under nitrogen. After the addition was complete, the solution was stirred for additional 2 h, and 25.0 g of chloromethylated polystyrene resin (Cl content: 1.75 mmol/g; crosslinked with 2 mol% DVB) in limited amounts was added to the solution by use of an Erlenmeyer flask for addition of solids. The mixture was allowed to slowly warm to room temperature and stirred for 48 h. After 20 mL of methanol was added to the reaction mixture, the polymer beads were isolated by using a fritted glass funnel, washed thoroughly with THF/methanol (1:1), methanol, methanol/water (1:1), acetone, THF, and dichloromethane, and dried at 60°C *in vacuo*. Yield of PTBD: 28.9 g.

The degree of functionalization was determined by acid-base titration. A 100-mL Erlenmeyer flask with a stopper was charged with 100 mg of PTBD, 20 mL of 0.1 M methanolic HCl, and 20 mL of 1,4-dioxane. After the mixture was stirred magnetically for 3 h at room temperature, the supernatant solution (5 mL), diluted with 20 mL of water, was titrated with 0.01 N aqueous NaOH using cresol red as indicator. The TBD content was calculated from the HCl concentrations of the original and resulting solutions: degree of functionalization of PTBD, 1.12 mmol/g.

PTBD with 2.06 or 2.40 mmol/g of TBD content was prepared, in a similar manner, from polystyrene resins with 40 or 60 mol% of chloromethylstyrene units, respectively.

Preparation of 7-Benzyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (BTBD)

A 100 mL, four-necked flask was charged with 7.0 g (50 mmol) of TBD, 13.8 g of K_2CO_3 (100 mmol), and 50 mL of chlorobenzene. The mixture was stirred at 100°C , and 6.3 g of benzyl chloride was added dropwise under nitrogen. After the addition was complete, the mixture was stirred at the same temperature for 3 h. The reaction mixture was filtered and the resulting filtrate was distilled under reduced pressure to afford benzylated TBD: bp, $118\text{--}122^{\circ}\text{C}/0.4$ mmHg; yield, 49%.

IR spectrum (neat), 1610 (C=N), 700 cm^{-1} (phenyl).

NMR spectrum (δ), CDCl_3 , 1.71–2.01 multiplet (4H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.93–3.47 multiplet (8H, NCH_2), 4.59 singlet (2H, benzylic CH_2), 7.26 singlet (5H, phenyl).

Swelling of Polymer-Supported DBU or TBD and the Salts

The polymer-supported salts were prepared from the supported bases and aqueous HBr or benzoic acid, respectively, in a mixture of methanol/dioxane (1:1). The resulting salts, separated by filtration, were washed with methanol, methanol/acetone (1:1), acetone, and dichloromethane, and dried at 60°C *in vacuo*. The amount of imbibed solvents in PTBD, PDBU, or the corresponding salts was determined by the previously described method [15].

Esterification of Benzoic Acid with 1-Bromobutane

A 30-mL, three-necked flask was charged with 1.0 molar equivalent of the polymer-supported base (based on benzoic acid), benzoic acid (5 mmol), solvent (15 mL), and 2-methylnaphthalene (0.1 g, internal standard for GLC). The mixture was stirred mechanically at 70°C for 0.5 h, 1-bromobutane (7.5 mmol) was added at zero time, and samples of the reaction mixture were analyzed by GLC.

Alkylation of Ethyl Cyanoacetate with 1-Bromobutane

A 30-mL, three-necked flask was charged with the polymer-supported base (DBU or TBD unit, 5 mmol), ethyl cyanoacetate (5 mmol), 2-methylnaphthalene (0.1 g, internal standard for GLC), and solvent (10 mL). The mixture was stirred mechanically at 30°C for 0.5 h, a solution of 1-bromobutane (5 mmol) in the solvent (5 mL) was added by use of a syringe at zero time, and samples of the reaction mixture were analyzed by GLC.

Adsorption of Ethyl Cyanoacetate

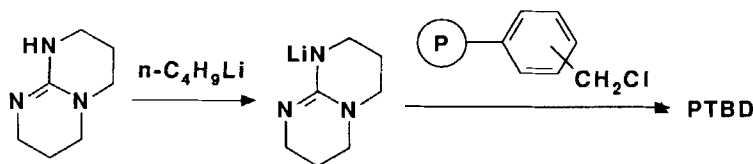
A 30-mL Erlenmeyer flask with a stopper was charged with the polymer-supported base (DBU or TBD unit, 5 mmol), ethyl cyanoacetate (5 mmol), *p*-cymene (0.1 g, internal standard for GLC), and solvent (15 mL). The mixture was stirred mechanically at 30°C for 1 h, and the amount of remaining ethyl cyanoacetate in the supernatant solution was determined by GLC.

RESULTS AND DISCUSSION

Polystyrene-supported TBD (PTBD) as well as polystyrene-supported DBU (PDBU) [13] was prepared according to Scheme 1. The IR spectra of PTBD show an absorption band at 1600 cm^{-1} due to the C=N linkage. The analysis of TBD contents by acid-base titration indicates an extent of reaction of chloromethyl groups in the polymer supports of 70–85%. This route via lithiation afforded PTBD with 1.12–2.40 mmol/g of TBD content (14–43% ring substitution) and PDBU with 1.22–2.75 mmol/g of DBU content (16–54% ring substitution).

Esterification of benzoic acid with 1-bromobutane proceeded smoothly in toluene or acetonitrile in the presence of PTBD (Figs. 1 and 2) or PDBU (Figs. 3 and 4). The rate of esterification depended on the percentage of ring substitution (% RS) of the polymer-supported bases and on the solvent used.

The rate increased with an increase in the RS of PTBD or PDBU. The low



SCHEME 1.

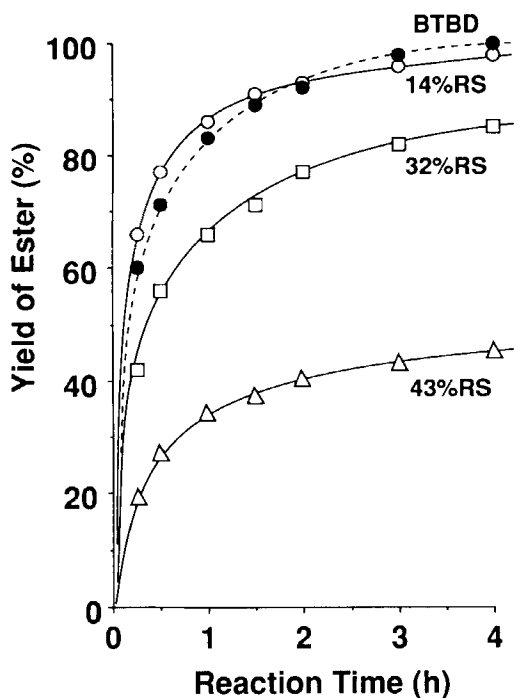


FIG. 1. Esterification of benzoic acid with 1-bromobutane in the presence of PTBD with 14–43% ring substitution (RS) or BTBD in toluene.

ring-substituted PTBD or PDBU exhibited high reactivity similar to that of the corresponding soluble model compounds, 7-benzylated TBD (BTBD) or DBU, respectively.

In the presence of DBU, benzoic acid reacts with the base to form a salt that consists of benzoate anion and protonated DBU. The resulting benzoate anion with high nucleophilicity in aprotic solvents causes S_N2 reaction with bromobutane to afford an ester [4].

After benzoic acid was treated with the supported base in toluene or acetonitrile at 70°C for 0.5 h, the supernatant solution contained almost no acid. This result indicates that the acid reacts with the base residue to form benzoate anion and protonated base residue in the polymer beads. The benzoate anion reacts with bromobutane, which enters from the liquid phase into the beads, to produce butyl benzoate and the HBr salt of the supported base such as PTBD·HBr or PDBU·HBr (Scheme 2).

In the case of polymer-supported esterification, the density of the salt in the polymer reagent, determined by ring substitution (RS), is an important factor to control the rate of reaction, because the swellability of the polymer beads containing ionic species in organic solvents is strongly dependent on the density, i.e., the RS.

Table 1 shows the swellability of the supported bases and their salts in toluene or acetonitrile. PTBD and PDBU without ionic species swelled well in toluene, although the swellability decreased with increasing RS; the supported bases in acetonitrile had rather less swellability, which was not largely dependent on the RS.

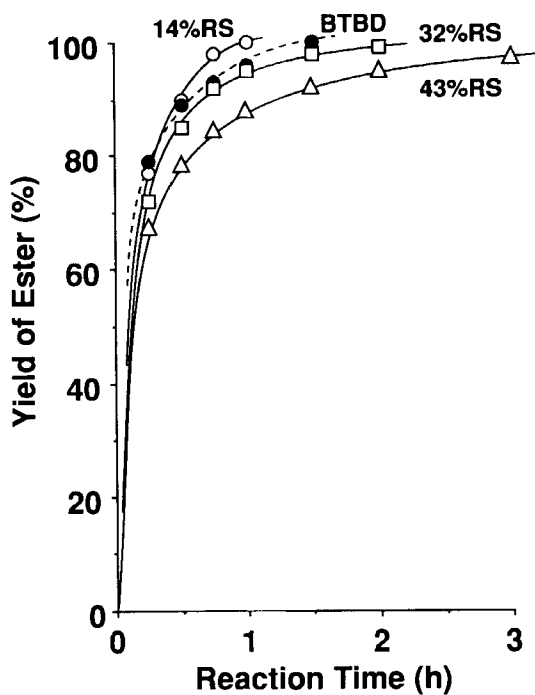


FIG. 2. Esterification of benzoic acid with 1-bromobutane in the presence of PTBD or BTBD in acetonitrile.

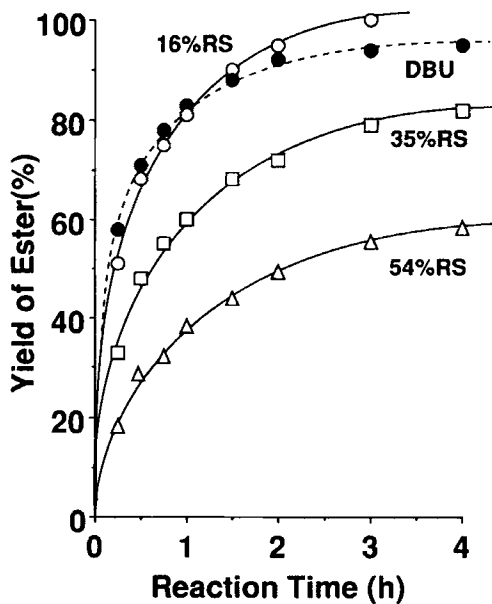


FIG. 3. Esterification of benzoic acid with 1-bromobutane in the presence of PDBU with 16–54%RS or DBU in toluene.

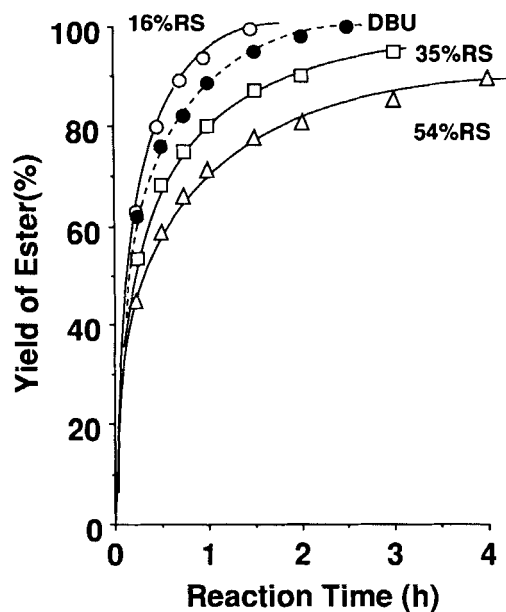
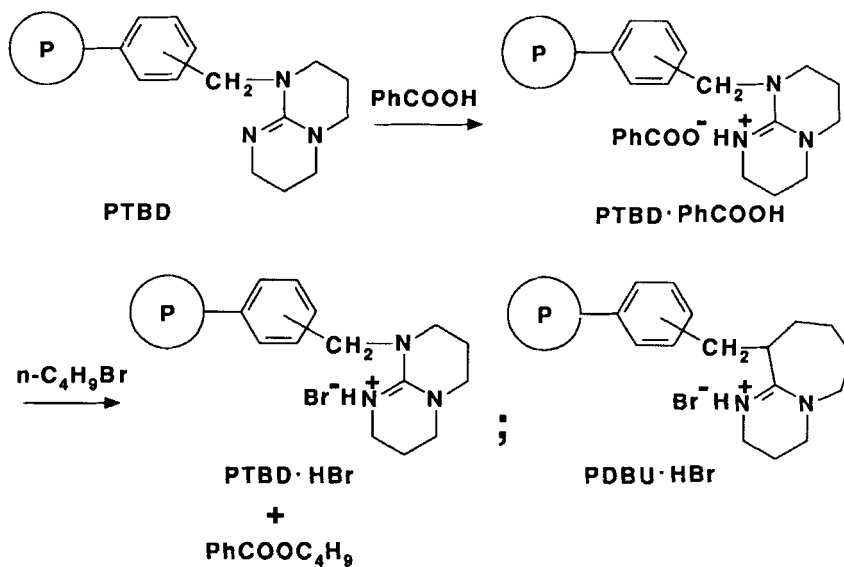


FIG. 4. Esterification of benzoic acid with 1-bromobutane in the presence of PDBU or DBU in acetonitrile.



SCHEME 2.

TABLE 1. Amount of Imbided Solvent into Polymer-supported TBD or DBU and the Salts at Room Temperature

Resin	Ring substitution (%)	Imbided solvent (mL/g) ^a	
		C ₆ H ₅ CH ₃	CH ₃ CN
PTBD	14	1.59	0.28
	32	1.31	0.33
	43	0.97	0.33
PTBD·PhCOOH ^b	14	0.54	0.54
	32	0.14	0.52
	43	0.07	0.47
PTBD·HBr ^c	14	0.45	0.60
	32	0.07	0.57
	43	0.06	0.42
PDBU	17	1.69	0.27
	35	1.30	0.29
	54	0.90	0.25
PDBU·PhCOOH ^b	17	0.61	0.49
	35	0.19	0.50
	54	0.09	0.34
PDBU·HBr ^c	17	0.53	0.54
	35	0.12	0.52
	54	0.06	0.37

^aDetermined on the basis of weight of dry resin.

^bPolymer-supported TBD or DBU salt with benzoic acid.

^cPolymer-supported TBD or DBU salt with hydrogen bromide.

The immobilized salts with benzoic acid, PTBD·PhCOOH and PDBU·PhCOOH, containing benzoate anion and the protonated base residues were difficult to swell in toluene, compared to the original immobilized bases: the salts with more than 32% RS exhibited very low swellability. The salts with hydrogen bromide, PTBD·HBr and PDBU·HBr, exhibited a slightly lower swellability for toluene than the salts with benzoate anion.

In conclusion, the high rates with low ring-substituted PTBD or PDBU in toluene, as shown in Figs. 1 and 3, are attributed to the high swellability of their salts with benzoate or bromide ions, compared with the salts derived from the high ring-substituted bases.

The rates in acetonitrile were higher than those in toluene. The swellability of the immobilized salts in acetonitrile was moderate and not largely dependent on the RS (Table 1). The nucleophilic reactivity of benzoate anion must be higher in aprotic dipolar acetonitrile ($\epsilon = 35.94$) than in toluene ($\epsilon = 2.38$) [16]. In practice, the rate with BTBD was higher in acetonitrile than in toluene (Figs. 3 and 4). The increased rates with the high ring-substituted (32–54%) bases in acetonitrile are due to high intrinsic reactivity of the active species and the increased swellability of the salts containing benzoate or bromide ions.

In the case of esterification with soluble DBU, the HBr salt of the base did not dissolve completely in toluene and formed a separated liquid phase in which a part of the salt of benzoic acid might dissolve. This resulted in a rate that reduced steeply in the latter half of the reaction and was a little lower than that with low ring-substituted PDBU. The HBr salt of BTBD, however, was easy to dissolve in toluene compared with that of DBU, and the rate with BTBD did not decrease largely at high conversion (Fig. 3). The HBr salts of BTBD and DBU were soluble in acetonitrile. The rate with low ring-substituted PTBD or PDBU in acetonitrile was a little larger than that with BTBD or DBU, respectively. This may be explained by an increase in the bromobutane concentration in the beads: the less polar bromide must prefer the low ring-substituted beads, which mainly consist of styrene units and are less polar than acetonitrile. Such a rate increase, induced by enhanced reactant concentrations in polymeric beads, has been reported for other polymer-supported reactions [17, 18].

The rate with low ring-substituted PTBD in toluene was a little larger than that with corresponding PDBU in the former half of the esterification, but the opposite behavior appeared in the latter half (Figs. 1 and 3). The reactivity of benzoate anion formed in the presence of TBD residue must be larger than that of the anion formed in the presence of DBU residue, because the former base has higher basicity than the latter [2]. The fast esterification with PTBD proceeds mainly near the surface layer of the beads in the former half of the reaction, and the formed HBr salt causes shrinkage of the surface layer, resulting in the reduced rate in the latter half. However, the rates with PTBD in acetonitrile were larger than those with PDBU, because the HBr salts formed do not cause the shrinkage of the beads in the solvent (see Table 1).

The esterification with high ring-substituted PDBU was facilitated when the ratio of DBU unit to the acid increased from 1.0 to 2.0 (Fig. 5). This result also emphasizes the importance of density of the salt in the supported reagent for the polymer-supported reaction. The reduced salt density, induced by the presence of excess DBU unit, results in increased swellability of the supported salt containing benzoate and bromide ions, and thereby in the increased rate.

DBU has been reported to cause efficient alkylation of active methylene compounds [8]. Table 2 shows the result of the reaction of ethyl cyanoacetate (ECA) with bromobutane in toluene in the presence of PDBU or PTBD. Ethyl cyanoacetate (pK_a 9) is a weaker acid than benzoic acid (pK_a 4.2) [19]. Therefore, a part of the active methylene compound forms ionic species such as PTBD·ECA in the presence of the supported bases (Scheme 3): benzoic acid forms such a salt quantitatively, as described earlier.

The cyanoacetate carbanion formed reacts with bromobutane to yield a butylated ester: the monobutylated compound can be further butylated to afford a dibutylated ester. In this reaction system, the rate of alkylation depends on the amount of the reactive carbanion and the swellability of the polymer-supported bases.

The reaction rate in the presence of PTBD with 14% RS was larger than that in the presence of PDBU with 17% RS: the former rate was comparable to that with soluble-base BTBD. 7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), which is a soluble base similar to the base residue of PTBD and BTBD, is reported to have about 13-fold (12.85) basicity compared with DBU, the model compound for PDBU [2]. Assuming PTBD and PDBU, which adsorbed ECA, contain only the ionized

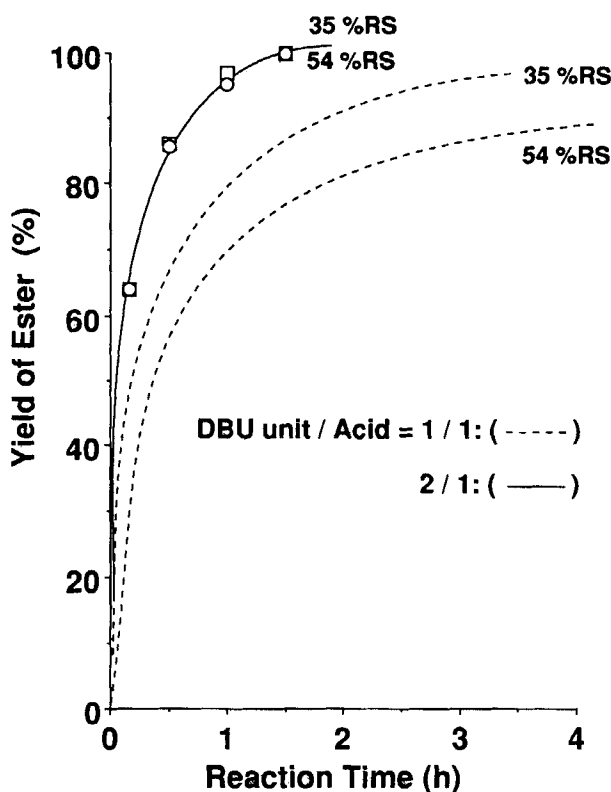


FIG. 5. Esterification of benzoic acid with 1-bromobutane in the presence of excess PBDU with 35 or 54%RS in acetonitrile: DBU unit/benzoic acid = 2/1.

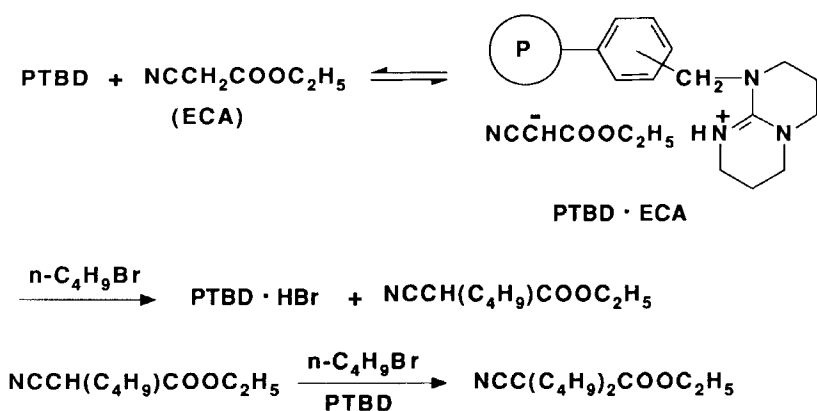
carbon acid (Scheme 3), we can estimate approximate equilibrium constants (K) for the acid-base reaction from the data of adsorption, shown in Table 2: the K values for PTBD with 14% RS and PDBU with 17% RS were 9.25 and 0.90 L/mol, respectively. The ratio of these K values ($9.25/0.90 = 10.3$) is similar to the relative basicity (12.85) of MTBD and DBU. This result suggests that the low ring-substituted PTBD and PDBU behave like the corresponding soluble bases in acetonitrile. A difference in rate, therefore, must be due to the high basicity of TBD residue compared with DBU residue. However, the rate with PTBD was suppressed with increasing reaction time. This result suggests that the fast alkylation proceeds mainly near the surface layer in the polymeric beads and the HBr salt of TBD residue, formed near the surface layer, causes shrinkage of the beads. A similar reaction behavior has been observed for esterification of benzoic acid in the presence of PTBD, as described before, and dehydrobromination of bromoalkane in the presence of PDBU [13].

The rate decreased with increasing RS of PTBD. The adsorption of the ester into the beads also decreased as the RS increased. High ring-substituted PTBD has low swellability for toluene (Table 1), and the salt containing the ester carbanion as well as the salt containing benzoate anion must be difficult to swell in toluene. The reduced rate with high ring-substituted PTBD is attributed to the decreased amount

TABLE 2. Alkylation of Ethyl Cyanoacetate with 1-Bromobutane

Base	Ring substitution (%)	Adsorbed ester (%) ^a	Reaction time:	Yield of alkylated ester (%)								
				2 h			5 h			24 h		
				Mono ^b	Di ^c	Total	Mono ^b	Di ^c	Total	Mono ^b	Di ^c	Total
PDBU	17	19.5		6.4	0	6.4	15.2	0.1	15.3	43.6	0.9	44.5
BTBD	—	—		26.2	0.4	26.2	42.6	1.1	43.7	64.8	3.5	68.3
PTBD	14	57		39.2	0.9	39.2	50.5	2.1	52.6	56.3	3.3	59.6
	32	46		32.3	0.4	32.3	42.2	0.6	42.8	44.5	0.9	45.4
	43	39		11.6	0.1	11.6	16.0	0.1	16.1	20.6	0.2	20.8

^aDetermined on the basis of feed ethyl cyanoacetate; see text.^bMono = monobutylated ester.^cDi = dibutylated ester.



SCHEME 3.

of the carbanion species in the beads and the low swellability of the beads containing the base residue and the salts.

CONCLUSION

In conclusion, polymer-supported bases containing TBD or DBU residues were effective for esterification of benzoic acid and alkylation of ethyl cyanoacetate with bromobutane. The rates with the low ring-substituted (14–17%) polymer bases were comparable to those with soluble bases BTBD or DBU.

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