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Microenvironmental Effect in Polymer-Supported Reagents. 1. Influence of Copolymer Architecture on the Mitsunobu Reaction

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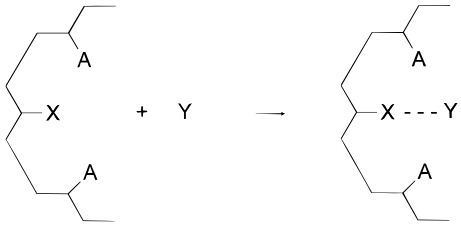
ABSTRACT: The microenvironment surrounding the active sites in polymer-supported reagents can be tailored for maximized kinetics and yields in organic reactions. Results with the Mitsunobu reaction are presented. Cross-linked copolymers of poly(vinylbenzyl chloride) are substituted with diphenylphosphine ligands at 18, 40, 67, and 100% substitution and used under Mitsunobu conditions to probe benzyl benzoate formation. It is found that the choice of groups surrounding a ligand can be as important as the choice of ligand. Decreasing the percent substitution while increasing the number of unsubstituted phenyl rings directly bonded to the polymer backbone increases the percent alcohol conversion at a 0.1 h contact time (41.7, 68.4, 83.7, and 94.5% conversion for polymers at 100, 67, 40, and 18% substitution). Polymers at 18 and 40% substitution give an equilibrium solution that is purer (97.6 and 97.0% ester) than that with a comparable soluble reagent (85.3% ester). The rapid conversion and high yield obtained as the percent substitution decreases is not due to a dilution effect: replacing the phenyl rings in the polymer at 18% substitution with carbomethoxy groups yields a polymeric reagent which allows for only 1.3% alcohol conversion at 0.1 h and a maximum product yield of 29.8%. Replacing the ester groups with the more strongly hydrogen-bonding carboxylic acid groups results in no conversion of alcohol. Thus, increasing reactant conversion with decreasing degree of substitution on a polystyrene support is a microenvironmental effect of the less polar aromtic rings superimposed on the inherent electronic effect of the CH_2-PPh_2 ligand. It is proposed that decreasing the polarity of the microenvironment surrounding the active sites increases the reactivity of the benzoate/phosphonium ion pair and lowers the energy of the S_N2 transition state (due to the accompanying charge dispersal, as described by the Hughes−Ingold theory), resulting in an increase in the rate of product formation.

Introduction

The importance of polymer-supported reagents as applied to organic chemistry is now well established.[1] Advantages include ease of product purification, adaptability to continuous processing, and obviating toxicity concerns with volatile reagents. Studies to date have emphasized immobilizing structural units analogous to the soluble reagents on different polymer supports: immobilized peroxy acids oxidize alkenes to give epoxides,[2] Wittig reagents form alkenes,[3] carbodiimides oxidize alcohols to aldehydes,[4] tin hydrides reduce aldehydes and ketones to alcohols,[5] and lipase esterifies ibuprofen.[6]

Results from a limited number of studies indicate that groups surrounding the active site can influence product formation. It was observed that the reaction of cumene with poly(*N*-bromomaleimide) differed considerably depending upon whether the homopolymer or poly(*N*-bromomaleimide-*co*-styrene) was used: the polarity of the polymer when succinimide moieties were adjacent to each other was determined to favor dehydrobromination of the expected product.[7] In another example, the efficacy of (dialkylamino)pyridine ligands covalently bound to a polystyrene support as an acylation catalyst was found to be greater when the degree of functionalization was less than 50% due to a more hydrophobic environment around each ligand.[8] This *microenvironmental effect* may be defined as the influence of groups ***A*** on the strength of the X−Y interaction at the active site (eq 1) and could arise from changes in polarity affecting the charge stabilization, hydrophilicity, lipophilicity, or any such mechanism which does not involve



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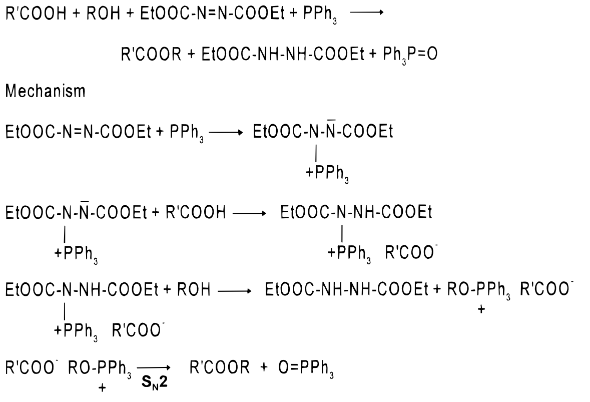
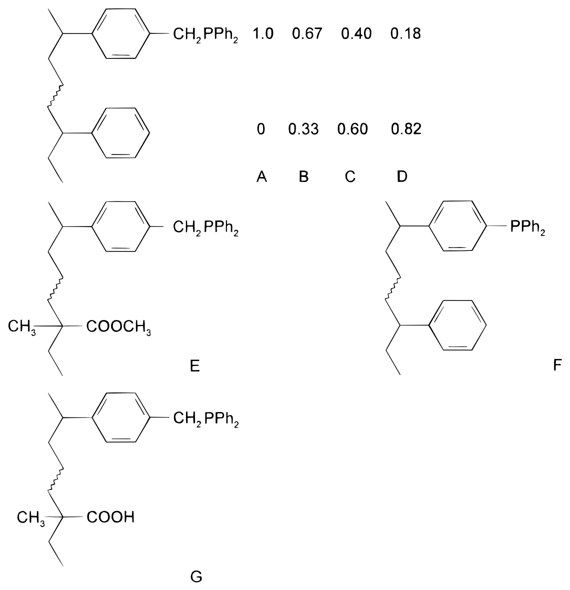
Scheme 1



Scheme 2



group ***A*** in product formation at the active site.[9] The microenvironmental effect can shift the ionic recognition properties of polymer-supported reagents:[10] the binding constant of Cu(II) and Co(II) to a series of poly(*N*-vinylimidazole-*co*-ethyl acrylate) copolymers is dependent on the ratio of the two comonomers. The microenvironment also affects the binding constants of soluble molecules interacting with polymer-supported reagents.[11]

The present report details how the microenvironmental effect can be used to maximize reaction rates and product yields, using the Mitsunobu reaction[12] as our initial example. The Mitsunobu reaction allows for the synthesis of different esters,[13] phosphinates,[14] lactones,[15] and natural products.[16] The reaction is useful in preparing optically active compounds since it proceeds under mild conditions with inversion of configurations at the carbon bearing the hydroxyl group.[17] The mechanism is illustrated in Scheme 1.

A difficulty in using the Mitsunobu reaction is product isolation from the hydrazine and phosphine oxide. Attempts have been made to immobilize the azodicarboxylate[18] and the triphenylphosphine[19] onto polystyrene in order to simplify recovery of the ester. It has been noted that the hydrazine is the easier of the two byproducts to separate.[19] Immobilized phosphines are the focus of this study because of previous research which indicates that ionic and molecular recognition by phosphorus ligands are both strongly influenced by the microenvironment surrounding those ligands. It is thus reasonable to expect that the microenvironment around covalently bound phosphorus ligands can be used as a variable to affect product formation rates and yields.

The microenvironmental effect on reactant conversion and product yield for the esterification of benzoic acid with benzyl alcohol was studied using a series of polymer-supported phosphines (Scheme 2). Benzyldiphenylphosphines were synthesized from copolymers of vinylbenzyl chloride (VBC) and styrene (St) with decreasing levels of substitution (mole ratio VBC/[VBC + St] of 1.0 (***A***), 0.67 (***B***), 0.40 (***C***), and 0.18 (***D***)). The microenvironment around the CH_2PPh_2 ligands was further modified in polymer ***E*** by replacing styrene with the more polar methyl methacrylate at the same level as polymer ***D***. The results were contrasted with polymer ***F***, an immobilized triphenylphosphine at a ratio identical to polymer ***C***. A mechanistic hypothesis for the microenvironmental effect was tested with polymer ***G***, synthesized similarly to polymer ***E*** except for methyl methacrylate being replaced by methacrylic acid.

Experimental Section

Copolymer Synthesis. Copolymers were synthesized as gel (i.e., microporous) beads by suspension polymerization[20] and cross-linked with 2% divinylbenzene (DVB) based on total monomer weight. All chemicals were from Aldrich Chemical Company unless otherwise noted.

In a typical preparation, the aqueous phase consisted of 1.93 g of gelatin (Knox Gelatin Co.), 23.68 g of poly(diallyldimethylammonium chloride) (Calgon Corp.), 1.26 g of boric acid, and 634 g of water adjusted to pH 10 with 50% NaOH. The monomer phase consisted of 286.7 g of styrene, 10.3 g of technical grade (55.4 wt %) DVB, and 3.0 g of benzoyl peroxide. The VBC beads were prepared in an identical manner except for the monomer weights: (***A***) 114.70 g of VBC; (***B***) 85.85 g of VBC, 28.62 g of St; (***C***) 57.23 g of VBC, 57.23 g of St; (***D***) 28.63 g of VBC, 85.85 g of St; each also had 4.33 g of DVB and 1.20 g of benzoyl peroxide. Elemental analyses for the copolymer beads showed chlorine capacities of 6.32, 4.74, 3.16, and 1.58 mmol/g and corresponding mole ratios of chloride-substituted to total sites of 1.0, 0.67, 0.40, and 0.18 for copolymers ***A***, ***B***, ***C***, and ***D***, respectively. The VBC/methyl methacrylate (MMA) copolymer beads (***E***) were prepared with 29.48 g of VBC, 84.99 g of MMA, 4.33 g of DVB, and 1.20 g of benzoyl peroxide. The beads had a chlorine capacity of 1.57 mmol/g and a mole ratio of chloromethylene-substituted to total sites of 0.18.

Polymerizations were carried out at 80 °C for 18 h. The copolymer beads were isolated by filtration and washed (with 30 min stir times at 25 °C unless otherwise noted) to remove surface impurities:[21] 1 N NaOH at 70 °C for polystyrene and 25 °C for VBC-containing beads; 1 N HCl at 70 °C; 2 N NaOH:dioxane (1:2 (v/v)) at 70 °C for polystyrene and 25 °C for VBC-containing beads; 2 N HCl:dioxane (1:2 (v/v)) at 70 °C; H_2O at 70 °C; DMF at 70 °C; 2 N HCl in methanol; H_2O; methanol; methanol:CH_2Cl_2 (1:3 (v/v)); and methanol:CH_2Cl_2 (1:10 (v/v)). The beads were dried at 60 °C under vacuum for 24 h. All reactions were carried out with copolymer beads sieved to a diameter of 0.25−0.42 mm.

VBC was copolymerized with methacrylic acid (MAA) under bulk conditions by combining 8.22 g of VBC, 20.40 g of MAA, 1.08 g of DVB, and 0.30 g of BPO in a 4-ounce screw-cap jar and placing in an oil bath heated at 80 °C for 18 h. The polymer was removed from the jar, ground to 0.25−0.42 mm diameter particles, and extracted in a Soxhlet apparatus with toluene for 17 h. The wash sequence was as noted above. The dry copolymer had an acid capacity of 8.20 mmol/g (theoretical acid capacity calculated from the monomer weights is 7.90 mmol/g) to give a mole ratio of CH_2Cl to total sites of 0.18.

Bromination of Polystyrene Beads.[21] Polystyrene beads (0.25−0.42 mm diameter) were brominated by first swelling 24.85 g in 250 mL of CCl_4 at room temperature for 1 h, then adding 4.10 g of $FeCl_3$, and stirring in the absence of light while a solution of 6.5 mL of Br_2 in 25 mL of CCl_4 was added slowly. Stirring was continued for 24 h at room temperature.

The beads were recovered by filtration, washed with acetone, 2:1 (v/v) dioxane:water, and methyl ethyl ketone, and then dried at 65 °C under vacuum for 18 h. Bromine elemental analysis showed a capacity of 3.60 mmol/g.

Polymer-Supported Phosphine Reagents. A solution of 52.5 g of chlorodiphenylphosphine in 235 mL of tetrahydrofuran (THF) was added slowly through an addition funnel to a stirred mixture of 5.1 g of lithium metal in 100 mL of THF under argon. Stirring was continued for 24 h. The resulting lithium diphenylphosphide was contacted with polymer beads swollen in 200 mL of THF for 1 h at room temperature (20 g of copolymer ***A***, 25 g of copolymer ***B***, 30 g of copolymer ***C***, 60 g of copolymer ***D***, 35 g of copolymer ***E***, and 30 g of copolymer ***F*** (i.e., brominated polystyrene beads)). Reaction continued at room temperature for 24 h under argon, except for reaction with copolymer ***E***, which was refluxed. The beads were recovered by filtration and washed with THF, diethyl ether, 2:1 (v/v) THF:water, water, THF, toluene, and methanol, each with 30 min stir times, followed by drying under vacuum at 60 °C for 44 h. The polymer-supported phosphine reagents thus synthesized, summarized in Scheme 2 as ***A***−***F***, have phosphorus capacities of 3.18, 2.68, 2.28, 1.17, 1.14, and 2.10 mmol/g, respectively. Theoretical phosphorus capacities for full functionalization of copolymers ***A***−***F*** are 3.23, 2.76, 2.13, 1.27, 1.26, and 2.19 mmol/g, respectively.

Polymer-supported phosphine reagent ***G*** was prepared by contacting 10 g of copolymer particles in 80 mL of THF with lithium diphenylphosphide (prepared as above with 16 g of chlorodiphenylphosphine in 70 mL of THF and 1.5 g of Li in 30 mL of THF) for 24 h at room temperature. The particles were recovered by filtration and added to fresh lithium diphenylphosphide solution for 24 h at reflux. The functionalized polymer had a phosphorus capacity of 0.82 mmol/g (theoretical capacity of 1.42 mmol/g), acid capacity of 6.46 mmol/g, and chlorine capacity from unreacted CH_2Cl groups of 0.96 mmol/g. The mass balance calculates to exactly 1 g/g of copolymer, indicating no unexpected side reactions. The mole ratio of phosphine to total (i.e., phosphine and acid) sites is 0.11, which is less than the target 0.18 but still sufficiently high to determine reagent reactivity.

Swelling ratios were determined by adding 1 mL of dry polymer to a 10 mL graduated cylinder and then adding solvent. The graduated cylinder was capped and periodically shaken. The final volume of the beads was taken after 6 days. The swelling ratio was calculated as the ratio of final to initial volumes.

General Procedure for the Esterification Reaction. To a 100 mL three-necked round-bottom flask, 7.5 mmol of benzoic acid, 15 mmol of phosphine reagent, 65 mL of anhydrous THF, and 7.5 mmol of dry benzyl alcohol in 10 mL of THF, were added, in that order, under an argon atmosphere. The flask was placed in a water bath held at 25 °C, and 2 mL (12.7 mmol) of diethyl azodicarboxylate was added. Microliter samples were analyzed, at intervals noted in the next section, by gas chromatography (Hewlett-Packard 5890; 0.53 mm × 15 m poly(dimethylsiloxane) capillary column) with THF used as the internal standard. The detector response factors for benzyl alcohol and benzyl benzoate were determined in order to quantify the amounts present during the course of the reaction. Percent conversion was calculated from the decrease in the benzyl alcohol peak and percent yield from the increase in the benzyl benzoate peak. A stir rate of 252 rpm was used in all runs due to the absence of mass transfer effects at that rate. Particle size studies with polymer ***A*** (0.25−0.42 and 0.075−0.15 mm diameter) show the absence of diffusion effects on the results, given identical reactant conversion data.

Results

Figure 1 illustrates the decrease in $PhCH_2OH$ concentration as a function of time in the presence of PPh_3 and each of the polymeric reagents ***A***−***F***. Table 1 gives the initial data points in terms of percent conversion as well as the equilibrium values. Addition of the soluble reagent, PPh_3, to the reactant solution leads to a very rapid approach to equilibrium (<0.1 h) with 100% benzyl alcohol conversion and 85.3% yield of ester. In contrast to this, the fully functionalized polymeric reagent ***A*** gives a significantly lower rate of ester formation, with 41.7% alcohol conversion in 0.1 h and 96.6% conversion requiring 8.5 h; the percent yield of ester is somewhat lower than with the soluble reagent.

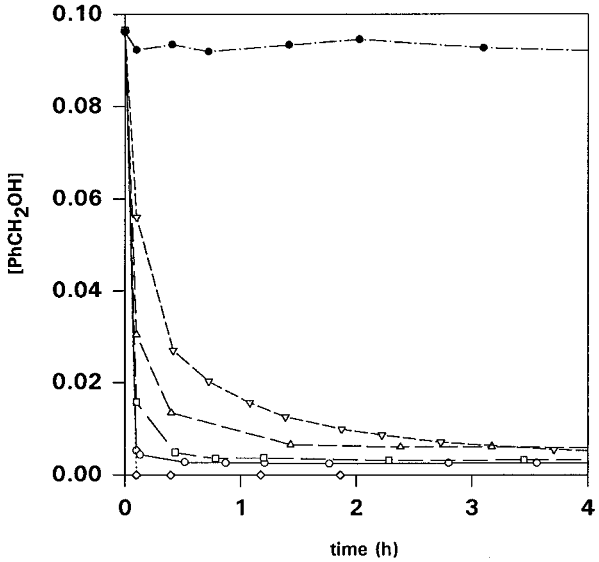


Figure 1. Concentration of benzyl alcohol as a function of time for the Mitsunobu reaction in the presence of triphenylphosphine (◇) and polymer-supported phosphines (polymer ***A***, ▽; polymer ***B***, △; polymer ***C***, □; polymer ***D***, ○; polymer ***E***, ●; polymer ***F***, ◇).

Table 1. Percent Conversion of Benzyl Alcohol and Percent Yield of Ester in the Mitsunobu Reaction of Benzyl Alcohol and Benzoic Acid at 25 °C

	percent conversion of benzyl alcohol						
time (h)	PPh_3	***A***[a]	***B***[b]	***C***[c]	***D***[d]	***E***[e]	***F***[f]
0	0	0	0	0	0	0	0
0.10	100	41.7	68.4	83.7	94.5	1.3	100
0.40		71.9	86.1	95.0	97.2	2.7	
equil[g]	100	96.6	94.2	97.0	97.6	56.3	100
% yield[h]	85.3	79.8	77.8	96.0	95.1	29.8	84.6

[a] Fully functionalized phosphine CH_2PPh_2 polymer. [b] Phosphine/backbone phenyl mole ratio 0.67/0.33. [c] Phosphine/backbone phenyl mole ratio 0.40/0.60. [d] Phosphine/backbone phenyl mole ratio 0.18/0.82. [e] Phosphine/methyl methacrylate mole ratio 0.18/0.82. [f] Phosphine PPh_2 polymer. [g] Time to equilibrium for each is <0.1, 8.5, 6.0, 2.3, 0.5, 80, and <0.1 h. [h] Percent yield of ester at equilibrium.

Results with fully functionalized ***A*** quantify the electronic effect of the polymeric ligand: its polar character is the only influence on the chemical reaction since each ligand is surrounded by other ligands of exactly the same structure. The microenvironmental effect is superimposed on the electronic effect by varying the area surrounding the ligand with groups that cannot interact with the active site but can influence the polarity surrounding that site. The results given in Table 1 show that the choice of groups surrounding a given ligand can be as important as the choice of ligand. Increasing the number of unsubstituted aromatic rings to give polymers ***B***, ***C***, and ***D*** results in a dramatic increase in the rate of benzyl alcohol conversion to the extent that polymer ***D*** gives kinetic results that are comparable to those with the soluble PPh_3. Additionally, polymers ***C*** and ***D*** give a final solution that is purer than that with PPh_3 since the reactant conversion and product yield match almost exactly.

The rapid conversion and high yield obtained with polymer ***D*** are not due to a simple dilution of the active sites within the polymer matrix but, rather, to a microenvironmental effect of the surrounding moieties. This is indicated from results with polymer ***E***, which was synthesized with the same phosphine ligand capacity as polymer ***D*** but with the more polar methacrylate groups substituted in place of the phenyl rings. This increase in polarity is shown by the fact that polymer ***E*** has a swelling ratio in acetonitrile (dielectric constant 37.5) of 1.7 and in toluene (dielectric constant 2.379) of 1.1, whereas polymer ***D*** has swelling ratios of 1.3 and 2.6, respectively. Table 1 shows that the substitution of ester groups for phenyl rings has a detrimental effect on the conversion and yield: conversion is slowed to the extent that even at a reaction time of 80 h, only 56.3% of the benzyl alcohol reacts and only about half of that goes to the desired product, given that the yield of ester is only 29.8%. Replacing the ester groups with the more strongly hydrogen-bonding carboxylic acid groups in polymer ***G*** results in no product formation and no alcohol conversion whatsoever even after 93 h. The mechanistic implications are discussed in the next section.

The trend in increasing conversion with polymers ***A***−***D*** is a microenvironmental effect superimposed on the inherent electronic effect of the CH_2PPh_2 ligand. A strong electronic effect is indicated with triphenylphosphine itself and polymer ***F***, which is structurally identical to polymer ***C*** except for the absence of the methylene spacer between the aromatic ring and the diphenylphosphine moiety (both have the same number of unsubstituted phenyl rings within the matrix). Polymer ***F*** behaves in a manner identical to the soluble phosphine; polymer ***C*** is somewhat slower in reaching equilibrium (being outperformed by polymer ***D***) but is more selective than polymer ***F*** given that its yield of ester is higher than that for polymer ***F*** (96.0 vs 84.6%, respectively).

Discussion

Yield and conversion data with soluble reagents in a given solvent establish the baseline electronic effect against which the behavior of polymer-supported reagents can be understood. A comprehensive mechanistic study of the Mitsunobu reaction has shown that S_N2 displacement on the phosphonium cation by the carboxylate anion is the rate-determining step with acids of pK_a similar to acetic acid.[22] Adduct formation between the triphenylphosphine and DEAD occurs almost instantaneously. The rate of product formation is increased by decreasing solvation of the carboxylate anion, which increases its nucleophilicity. It is also known that reaction rates can be increased by variables which stabilize the transition state. In a representative example, the addition of a small amount of dimethyl sulfoxide to a toluene solution of 1,5-naphthylene diisocyanate and polycaprolactone increased the rate of polymerization by stabilizing the activated complex and thus lowering the energy of activation.[23] This is, of course, consistent with the Hughes−Ingold theory of solvent effects on reaction rates: "...a more polar solvent will accelerate or retard reaction according as the transition state is more or less polar than the initial state.".[24] It is proposed that the microenvironmental effect operates by the same principles (*vide infra*).

The fully functionalized poly(benzyldiphenylphosphine) ***A*** is not a direct analogue of triphenylphosphine, but it is the polymer of choice because it can be synthesized as a well-characterized reagent from poly(vinylbenzyl chloride) copolymer beads. It does, however, form product much more slowly than the soluble triphenylphosphine. It is important to note that accessibility of the reactants into the polymer matrix is not a variable: all resins reported swell as least twofold in the THF solvent; additionally, polymer ***F***, with exactly the same cross-link level as ***A***, gives the same results as the soluble reagent, indicating also that accessibility of DEAD into the polymer is not a limiting factor. The results are consistent with an electronic effect wherein the S_N2 attack by the benzoate anion on the phosphonium cation in the rate-determining step is slower in ***A*** than in ***F***. This would be true if the phosphonium ion were less electrophilic in the former, and this is probably the case because the benzyl moiety is more electron-donating than the phenyl group: from a tabulation of Hammett σ constants,[25] it is seen that σ_m/σ_p values for benzyl are $-0.08/-0.09$, while the same values for phenyl are $0.06/-0.01$, respectively.

The results in Figure 1 indicate that whereas the electronic effect of the ligand at the active site is an important influence on the rate and extent of product formation, it is not the sole influence: keeping the ligand type constant but decreasing its level of substitution within the polymer matrix (polymers ***A***−***D***) results in a significant increase in both reactant conversion and product yield. Polymer ***D*** with only 18 mol % CH_2PPh_2, is superior to the soluble reagent given that alcohol conversion is almost as rapid and ester formation is greater due to an apparently cleaner reaction. A possible explanation would be that diluting the active sites within the matrix decreases steric hindrance to the reaction, thus increasing the rate of conversion. Polymer ***E***, with the same degree of substitution as polymer ***D*** but with the phenyl rings replaced by ester groups, was used to test this rationale. The ester groups would not be expected to be directly involved in the Mitsunobu reaction but, by being more polar than the phenyl rings, could influence the microenvironment surrounding the active sites. The results show a much slower rate of conversion with polymer ***E*** than polymer ***D*** (much slower, in fact, than polymer ***A***), indicating that the observed trend with polymers ***A***−***D*** is not simply a dilution effect but, rather, due to the ability of surrounding groups to influence the chemistry at an active site. This is confirmed with the behavior of polymer ***G***, which leads to no reactant conversion.

Given the mechanism of the Mitsunobu reaction, it is proposed that decreasing the degree of CH_2PPh_2 substitution while concomitantly increasing the number of unsubstituted phenyl rings results in a decrease of polarity in the microenvironment surrounding the active sites in the order ***A*** > ***B*** > ***C*** > ***D***. This, in turn, increases the reactivity of the benzoate/phosphonium ion pair and favors the subsequent S_N2 attack due to the attendant charge dispersal in the transition state (as suggested by the Hughes−Ingold theory), resulting in an increase in the rate of product formation, with ***D*** > ***C*** > ***B*** > ***A***. This hypothesis is supported by results with polymer ***G***. If the microenvironment affects reactant conversion, then the presence of COOH groups should stabilize the benzoate anion through hydrogen bonding and decrease the kinetics more than polymer ***E***. This is observed, in agreement with results from the mechanistic study with soluble reagents.[22] Polymer **D**, with no hydrogen-bonding interactions stabilizing the benzoate/phosphonium ion pair and with the most nonpolar microenvironment to favor the S_N2 transition state, is the preferred polymer-supported reagent for the Mitsunobu reaction. The microenvironmental effect, thus superimposed on the electronic effect, results in the synthesis of an efficient polymer-supported reagent for a targeted reaction.

Conclusions

Polymer-supported reagents can be optimized for a given reaction by tailoring the microenvironment surrounding the active sites to the reaction mechanism. The present study indicates that if the mechanism passes through ionic intermediates, as it does in the Mitsunobu reaction, a nonpolar microenvironment can be used to enhance the reactivity of the intermediates and the rate of product formation. Optimized polymer-supported reagents illustrating this feature are being applied to the Prins reaction and the aldol condensation, and will be reported in future publications.

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