Pergamon

Tetrahedron Letters, Vol. 36, No. 27, pp. 4757-4760, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00885-3

Modification of Substrate Reactivity Using Soluble Polymeric Supports

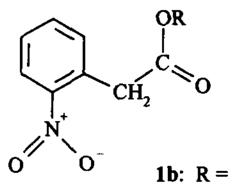
David E. Bergbreiter,* Tamar Kimmel and John W. Caraway

Department of Chemistry, Texas A&M University, College Station, Texas 77843

Abstract: The effects of polymer size and solvent on the reactivity of a soluble polymer-bound substrate in heterogeneous hydrogenation reactions has been examined using PEG polymer ligands. Hydrogenation of a substrate was completely suppressed by virtue of the polymer's size and/or immiscibility with some catalysts. Changing solvents significantly perturbed reactivity of such soluble polymer-bound substrates even using Pt/C.

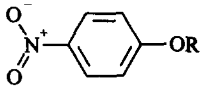
Poly(ethylene oxide) polymers and oligomers are widely used materials that serve as supports for soluble or insoluble polymeric catalysts and reagents and as solubilizing groups for bioactive molecules.[1-3] These supports and similar insoluble polymeric supports are of increased interest recently because of the importance of repetitive synthetic steps in synthesis and because of the popularity of combinatorial synthesis.[4] However, while PEG-bound substrates in solution or attached to a support are commonly used, the limits of the common assumption that the reactivity of terminally bound groups is not appreciably changed by the polymer has not been explored. While this assumption is generally true, cases where it is not true could both increase understanding of the limits of chemistry of PEG-supported substrates and lead to the use of PEG supports as macroscopic protecting groups. Because of our other interests in soluble polymeric catalysts and reagents,[5] we became interested in exploring these questions. Our initial results from a survey of several systems show that both solvent and a polymer's macroscopic size can usefully affect the reactivity of pendant groups attached to soluble polymers in hydrogenation reactions with heterogeneous catalysts.

The terminal groups of soluble polymers usually behave kinetically like their low molecular weight analogs in reactions with low molecular weight substrates. Indeed, this is the basis for many kinetic models for polymerization reactions.[6] However, in reactions with other macroscopic substrates, the character of the polymer can appreciably affect a terminal group's reactivity.[7,8] This is illustrated by the data in Table 1 for the reaction of polymer-bound nitroarenes like **1** or **2** with heterogeneous Pd or Pt catalysts. If a sterically



1a: R = H

1b: R = $-(CH_2CH_2O)_{45}OCH_3$



2a: R = $-CH_2(CH_2)_2CH_3$

2b: R = $-(CH_2CH_2O)_7OCH_3$

2c: R = $-(CH_2CH_2O)_{45}OCH_3$

2d: R = $-(CH_2CH_2O)_{113}OCH_3$

Table 1. Hydrogenation of nitroarenes containing PEG-ethers or esters or low molecular weight analogs using various heterogeneous catalysts.[a]

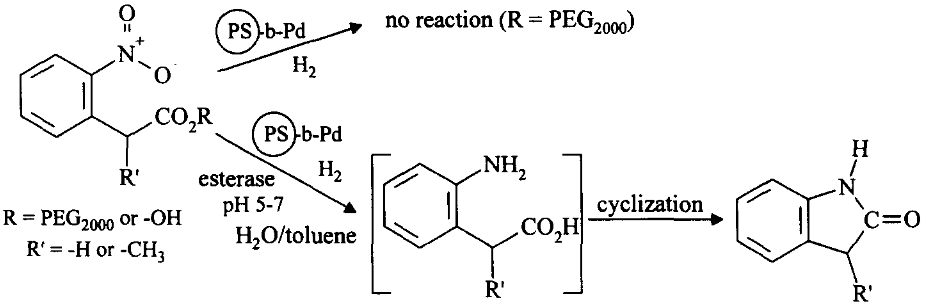
Substrate	Catalyst	Solvent	Hydrogenation Product (%, time in h)	Relative Velocity (moles-min^{-1}-mg atom catalyst^{-1})
1a	PS-b-Pd[b]	$H_2O/PhCH_3$	85 (15)	-[c]
1b	PS-b-Pd[b]	$H_2O/PhCH_3$	0 (19)	0
2a	Pd-graphite[d]	EtOH[e]	100 (-[c])	-[c]
2a	PtO_2	EtOH	100 (0.4)	-[c]
2b	Pd-graphite[c]	EtOH[e]	0 (12.7)	0
2b	Pd/C[f]	EtOH	0 (2.3)	0
2b	Pd black[g]	EtOH	74 (11.8)	1.4 x 10^{-6}
2b	PtO_2	EtOH	100 (0.5)	2.4 x 10^{-5}
2b	Pt/C[h]	EtOH	100 (2.6)	1.0 x 10^{-5}
2c	PtO_2	EtOH	100 (2.6)	6.3 x 10^{-6}
2c	Pt/C[h]	EtOH	100 (5)	7.2 x 10^{-6}
2d	Pt/C[h]	EtOH[i]	100 (40.4)	0.3 x 10^{-6}

[a] Hydrogenations were run at ca. 23 °C using ca. 20 mM substrate solution at 30 psi or less pressure. [b] The catalyst dispersion in DVB-crosslinked polystyrene (reference 9) contained ca. 0.5 % Pd. [c] This value was not measured. [d] This was a commercially available (Alfa) Pd-graphite intercalate containing 1 % Pd. [e] This experiment used 95% ethanol. [f] This was a 5% Pd/C catalyst (Aldrich). [g] This catalyst was a purified Pd black catalyst (D. Mackay, Inc.). [h] This was a 5% Pt catalyst (Aldrich). [i] Aqueous ethanol (75%) was used.

unencumbered catalyst like Pt/C is used, there is little effect on the reactivity of a substrate by the attached PEG group so long as a good solvent is used. However, if a sterically less accessible catalyst is used, significant effects are seen. Using an intercalated palladium-graphite catalyst, a *p*-nitrophenyl butyl ether is quantitatively hydrogenated. However, similar nitrophenyl ethers containing PEG groups of even modest size are not hydrogenated. Experiments using mixtures of butyl ethers of *p*-nitrophenol and unfunctionalized

PEG ethers gave hydrogenated nitroarene but similar experiments with PEG_{350} ethers of *p*-nitrophenol and either nitrobenzene or *p*-butoxynitrobenzene led to no hydrogenation. This shows that the PEG-substituted substrate poisoned the catalyst. These experiments are most simply explained by the idea that the macroscopic polymer-substituted nitroarene irreversibly absorbed into the intercalated catalyst. Similar effects were seen using a DVB-crosslinked polystyrene containing an internal dispersion of Pd(0) crystallites.[9] No hydrogenation occurred with this catalyst (PS-b-Pd) unless the PEG group was first removed. In this example, the soluble polymer essentially serves as a protecting group.

The premise that soluble polymers can serve a transient protecting group is illustrated by the use of **1** in a multistep catalytic process (eq 1). While the effect of the PEG-ester size on the lipase kinetics was not studied, we did observe that the PEG-ester served as a protecting group. No hydrogenation of the PEG-ester of the 2-nitrophenylpropanoic acid occurred before lipase hydrolysis. The overall reaction illustrates how a soluble polymer's size can be used to kinetically isolate a substrate for the first step in a sequential process.



(1)

Solvent effects also substantially affect the reactivity of a soluble polymer-bound substrate. Polymer-solvent interactions are known to vary substantially with the size of a polymer.[10] The relative rate data in Figure 1 dramatically show that solvation changes can substantially affect a soluble polymer-bound substrate's reactivity. This was particularly evident with the larger PEG_{5000}-supported substrates where water substantially increased hydrogenation activity. Water could alternatively have affected the catalyst or produced some catalyst dissolution. However, this alternative explanation of our results does not explain the effects of different relative rates with differnent-sized PEG supports. Furthermore, the hydrogenation ceased when agitation ceased, qualitatively supporting the idea that the reactions involved a heterogeneous catalyst. The absolute hydrogenation rates for the various sized polymer-bound nitroarenes were all within a factor of two but the relative rates as a function of the amount of alcohol varied significantly even though the various PEG-bound substrates were all visually in solution under the reaction conditions.

In summary, soluble polymer supports usefully affect a bound substrate's chemistry. They can serve as protecting groups in reaction with an appropriate macroscopic reagent or catalyst. In a multistep process a removable soluble polymer group can effect a kinetic isolation and can in effect produce the equivalent of a two flask environment within a one pot setup. Finally, the effects of solvent on a soluble polymer can significantly affect a terminal groups reactivity when soluble polymers of varying size are used.

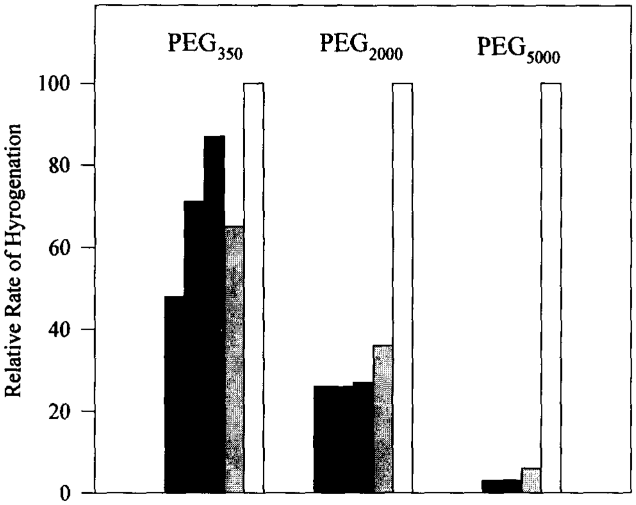


Figure 1. Bar graph showing the relative hydrogenation rate for PEG_{XX}-$C_6H_4NO_2$ with Pt/C in H_2O-EtOH solutions whose volume percentages of H_2O was varied(0% black; 25%, dark gray; 50%, gray; 75%, light gray; 100%, white).

Acknowledgments. Support from the National Science Foundation (Grant CHE-9308414), the Robert A. Welch Foundation and of J. Caraway (a Texas A&M Minority Merit Fellowship) is acknowledged.

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(*Received in USA* 4 *April* 1995; *revised* 17 *May* 1995; *accepted* 18 *May* 1995)