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Development of a New Ultraporous Polymer as Support in Organic Synthesis

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Abstract—This paper describes the preparation and post-functionalisation of a new polymeric support based on emulsion-derived foams and called polyHIPEs. The remaining pendant vinylic bonds are easily functionalised by a free radical mechanism. The large pores and channels of this material allow an easy access of the reagent in solution toward the grafted species. PolyHIPE-supported thiol, in the presence of an excess of triethylsilane, showed a good activity and selectivity toward reductive cyclisation of 6-bromohex-1-ene and 1-allyloxy-2-bromobenzene. © 2002 Elsevier Science Ltd. All rights reserved.

The development of polymer-supported chemistry is one of the main features of modern organic synthesis. The supports generally used in these applications are based on lightly cross-linked styrene/divinylbenzene (DVB) beads called gel resins. These resins have no permanent porosity, and therefore are usable only in solvents allowing the polymer to swell such as toluene or THF.[1] An impressive amount of work using these resins as supported catalysts,[2] supported reagents[3] and for solid-phase organic synthesis[4] have been reported. The use of macroporous beads with a permanent porosity can be an alternative but is not completely satisfactory because of the poor permeability of these materials[5] that reduces their usefulness for organic synthesis.

An alternative approach consists in the use of porous polymer foams having a low resistance to flow which makes them usable in low-pressure, continuous flow methods. These materials are well-known and have been produced by a wide variety of techniques ranging from leaching soluble fillers through gas-blowing to phase separation, although the structure of these materials is often irregular and difficult to control.[6] A novel method for producing porous materials with a more regular structure has been developed based on high internal phase emulsion (HIPE). These foams are called emulsion-derived foams and were initially developed by Unilever[7] and called polyHIPE®. The characteristics and syntheses of such polyHIPE materials have already been reviewed.[8]

The system is composed of two phases: an organic phase (called the continuous phase) containing the monomers and a suitable amount of emulsifier and an aqueous phase (called the dispersed phase) containing the radical initiator.

By introducing droplets of aqueous phase in the organic mixture, under constant agitation, a dilute reverse (water-in-oil) emulsion is produced. If the amount of water is increased a highly concentrated emulsion is obtained. The structure is now analogous to soap bubbles, with thin films surrounding and separating the drops. During the polymerisation step, holes are formed in the thin films separating the droplets and an open structure is formed. The water is removed to produce a foam of the corresponding structure.[9]

The free radical polymerisation of commercial divinylbenzene led to a crosslinked macroporous monolith.[10] The overall interconnected open-cellular macrostructure of the material can be clearly seen by scanning electron microscopy (Fig. 1).

It is worthwhile to note the relatively large cells (up to 10–20 μm in diameter) and the large number of about 1-μm 'windows' between adjacent cells. The large

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pore volume results directly from the large internal volume of water incorporated in the HIPEs (more than 95%). The large average cell size corresponds roughly to the size of the water droplets in the HIPEs.

The general range of measurement/properties of the emulsion-derived foam prepared may be summarised as follows:

1. macroscopic density as low as 0.05 g/cm^3,
2. internal void volume about 95%, that is 95% pore volume/5% polymer,
3. fully interconnected uniform structure, with cells being connected to all their neighbours, allowing liquids circulation through the porous structure and,
4. the large channels and the fully interconnection allow flow rate under low pressure.

Free radical copolymerisation of divinylbenzene gave crosslinked resins that have been shown to often still bear many unreacted pendant vinyl groups.[11] These remaining pendant vinyl bonds as well as the crosslinking level could be quantified by FTIR. The value obtained for the produced support was about 3.0 mmol/g of pendant vinyl bonds.

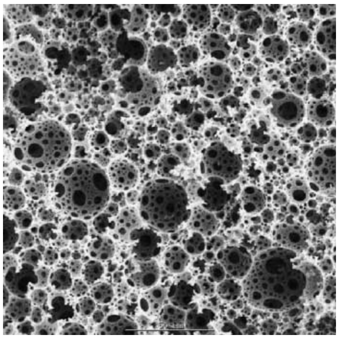
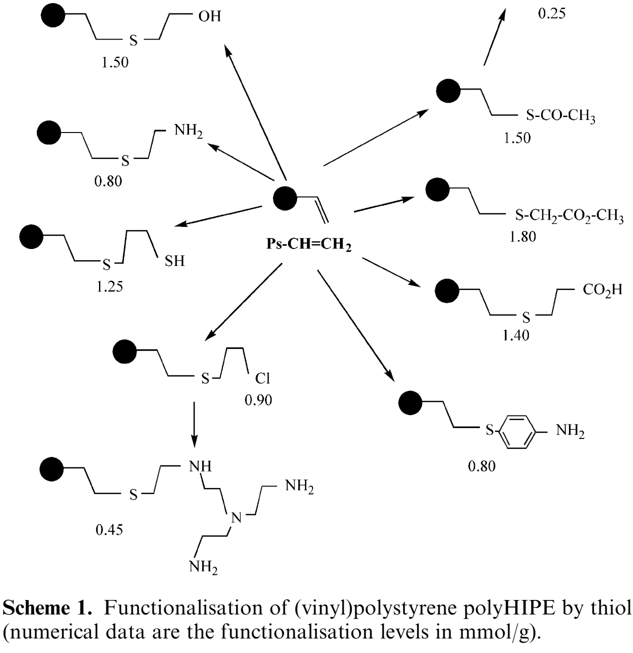


Figure 1. Scanning electron micrograph of (vinyl)polystyrene polyHIPE.



Scheme 1. Functionalisation of (vinyl)polystyrene polyHIPE by thiols (numerical data are the functionalisation levels in mmol/g).

The functionalisation of these residual pendant vinyl group by its extremity would be a convenient way to incorporate a dimethylene spacer for more stable attachments of the grafted species through a non-benzylic position. Thiols adding to olefins under an anti-Markovnikov way by a free radical mechanism,[12] this approach was used to diversely functionalise our polyHIPEs. Several functionalities were introduced onto the resin such as amine, alcohol, ester, thiols, alkyl chlorides, acid and thioacetic acid (Scheme 1).

Yields of functionalisation of the modified resins were in the range 10–60% depending on the thiol and the method employed. The grafted function contain was between 0.25 and 1.9 mmol/g of polymer.[13,14]

Different applications of these functional materials can be designed like their use as scavenger—in particular for supported amine and acids—and as supported catalysts. An example of such a last application could be found in the reduction and cyclisation of alkyl halides by triethylsilane.

Free radical reactions such as dehalogenation of alkyl, vinyl, or aryl halides often followed by intra- or intermolecular C–C coupling are in increasing use in organic synthesis[15] since a large variety of functional groups is tolerated avoiding laborious protection and deprotection sequences. These reactions are generally performed at the laboratory stage with tributyltin hydride. However, the toxicity of this reactant is now well established[16] and this drawback strongly limits the development of its use in the synthesis of pharmaceutical derivatives. A less toxic alternative consists in the combination of triethylsilane, the reducing agent, with small amounts of a thiol, as proposed by Roberts et al.[17] Reduction proceeds by a radical chain mechanism and the thiol acts as a polarity reversal catalyst which mediates hydrogen-atom transfer from the Si–H group of the silane to the alkyl radical (Scheme 2). However this methodology is limited by the stench of thiols.

The post-functionalisation of a polyHIPE-supported unsaturation led to mercaptan functionalities after free radical addition of thioacetic acid and deprotection.[18]

The reduction of 1-bromoadamantane **1** by ***PH*-SH** regenerated in situ by triethylsilane, was performed as a test reaction for our system.[19]

$$\begin{aligned}
&\mathrm{R\text{-}S^{\bullet} + Et_3SiH} \longrightarrow \mathrm{R\text{-}SH + Et_3Si^{\bullet}}\\
&\mathrm{Et_3Si^{\bullet} + R'\text{-}X} \longrightarrow \mathrm{Et_3SiX + R'^{\bullet}}\\
&\mathrm{R'^{\bullet} + R\text{-}SH} \longrightarrow \mathrm{R'\text{-}H + R\text{-}S^{\bullet}}
\end{aligned}$$

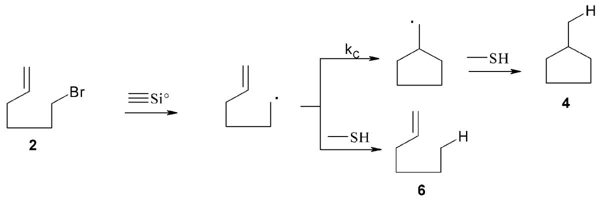
Scheme 2. Radical chain mechanism involving the reducing agent Et$_3$SiH and a polarity reversal catalyst thiol.

Table 1. Conversion and reaction conditions of radical reduction of **1** (***PH*-SH/1** = 0.05; T = 70 °C; 1 h)

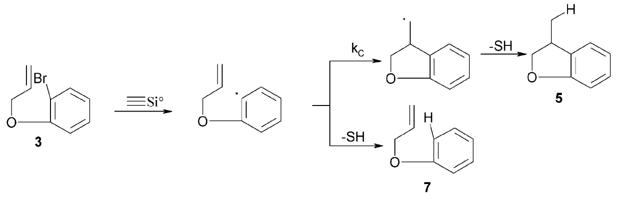
Entry	Catalyst	Reducing agent (equiv)	Yield adamantane (%)
1	None	Et_3SiH (2)	0
2	$C_{12}H_{25}SH$	Et_3SiH (2)	100
3	***PH*-SH**	Et_3SiH (2)	70

Table 2. Conversion and reaction conditions of radical reduction of **2** by ***PH*-SH**/Et_3SiH (***PH*-SH/2** = 0.05; T = 70 °C; 6 h)

Et_3SiH/**2**	2	10	20	40	100
4 Yield (%)	0	5	55	90	100
6 Yield (%)	0	0	0	0	0
Unreacted **2** (%)	100	95	45	10	0



Scheme 3. Radical reduction mechanism of 6-bromohex-1-ene **2**.



Scheme 4. Radical reduction mechanism of -1-allyloxy 2-bromobenzene **3**.

Table 1 summarises the relative and overall yield of formed products resulting from the reduction of **1**, using various reducing agents and supported catalysts.

The observation of a relatively high conversion in one hour proved the efficient regeneration of the hydrogen transfer agent, the thiol, in the reaction of the intermediate thiyl radical, with the reducing agent employed, triethylsilane. The first hour conversion using the polyHIPE-supported reagent is lower than its solution phase counterpart (entries 2 and 3). This could be due to slower elementary reactions rates when one of the reactive species is attached to the polyHIPE; this is certainly caused by the diffusion of only the small molecules and radicals towards the backbone of the supported reagents.

Once the efficiency of the supported hydrogen transfer was proven, it appeared of interest to study the reduction of unsaturated bromides. Then, the reduction of 6-bromohex 1-ene **2** and of 1-allyloxy 2-bromobenzene **3** was investigated using the polyHIPE. These free radical reactions would produce two major compounds: the products of reductive cyclisation (**4** from **2**, **5** from **3**) and the ones arising from the direct reductions (respectively, **6** and **7**) (Schemes 3 and 4).

The treatments of **2** and **3** by triethysilane in the presence of ***PH*-SH**, under the same conditions as the reduction of **1**, did not lead to any of the expected hydrocarbons **4** or **6** from **2** (about 100% of **2** recovered unchanged), meanwhile the cyclic ether **5** was formed with a yield of 10% from **3** (90% unchanged) after 6 h. As pointed out by Roberts,[17] the possible addition of the thiyl radical to the double bonds present in the medium could be responsible of such an inefficient reduction. The increase of the concentration of the silane would allow to direct the reaction of the thiyl radical towards the regeneration of the thiol by hydrogen abstraction to the silane and, then, to allow the free radical chain reduction of the unsaturated bromide to occur. The results summarised in Table 2 indicate that the reductive cyclisation of **2** could be carried out to completion in 6 h with a one hundred fold excess of silane relatively to the bromide with ***PH*-SH**.

The possible use of a catalytic system, even with primary alkyl bromide, involving an organic reducer totally soluble in the organic medium (triethylsilane) and this selectivity are good arguments to select the thiol/triethylsilane system instead of the tin one.[20] Nevertheless, it is important to underline the necessary use of a high ratio silane/thiol to perform the reduction of bromide compounds possessing terminal vinyl group. This could be a drawback when the required reaction product has a boiling point close to triethylsilane. In this case, the commercial availability of numerous silanes would allow to circumvent this problem.

The reductive cyclisation of **3** with the thiol-silane system (***PH*-SH**/Et_3SiH/ **3** = 0.05/75/1) is quantitative in 6 h at 70 °C. These results confirmed the interest of the thiol supported reagent over the tin one.

In conclusion, this paper reports an example of application in organic synthesis of the new kind of polymer support, called polyHIPE, we are currently developing in our group. These polyHIPEs are highly porous materials easy to synthesise and functionalise which could become an alternative to conventional resins in Supported Organic Chemistry.

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10. In a typical experiment, a volume V_{org} of organic phase constituted of commercial grade solution of DVB (80:20 DVB/EVB) as the monomer and sorbitan monooleate (Span®80) as emulsifying agent (20% w/w of the organic phase) was placed in a reactor. The mixture was stirred with a rod fitted with a D-shaped paddle, connected to an overhead stirrer motor, at approximately 300 rpm. A V_{aq} volume of aqueous phase was prepared separately by dissolving the initiator, potassium persulfate $K_2S_2O_8$, and sodium chloride NaCl (1.5% w/w of the aqueous phase) in distilled water. This solution was added dropwise, under constant mechanical stirring, to the organic solution in order to obtain a thick white homogeneous emulsion without apparent free water. Once all the aqueous phase had been added, stirring was continued for a further 15 min to produce an emulsion as uniform as possible. The high internal phase emulsion obtained was then placed in a polyethylene bottle. The polymerisation occurred by immersing the plastic bottle in a water bath, heated to 60 °C for 10 h. The container was then cut away to collect the resulting polymeric monolith. This one was extracted with acetone in a Soxhlet apparatus for 48 h, then was dried under vacuum at 60 °C for 48 h. The resulting monolith was cut in cubes (approx. 5 mm per side). The polyHIPE ***PH*-VB** thus synthesised was characterised by the volumic fraction of pore precursor (water) $\phi = V_{aq}/(V_{aq} + V_{org})$.

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18. Small cubes of ***PH*-VB** (500 mg, 1.50 mmol C=C) were impregnated with toluene by freezing/unfreezing method and suspended in 40 mL of toluene. Five equivalents of thioacetic acid (570 mg, 7.50 mmol), AIBN (0.015 mmol) were then added. The suspension was heated at 70 °C for 48 h. The polymer was filtered off, extracted with acetone overnight on a Soxhlet apparatus and dried under vaccum at 60 °C, overnight. FT-IR (KBr): 1690 cm^{-1} (C=O). S, 1.50 $mmol.g^{-1}$ (Elemental Analysis). The resulting ***PH*-TAc** (500 mg, 0.75 mmol SAc) was then treated with 10 equiv of *n*-butylamine (550 mg, 7.5 mmol) and $NaBH_4$ (4 mg) in DMF (20 mL) to produce ***PH*-SH**.

19. One equivalent of 1-bromoadamantane **1** (322 mg, 1.50 mmol) was reduced by 0.02 equiv of thiol (***PH*-SH** or dodecanethiol), (100 mg, 0.03 mmol) in the presence of 2 equivalents of Et_3SiH (348 mg, 3.0 mmol) and dilauroyl peroxide (0.05 equiv). The conversion was followed by gas chromatography.

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