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Microwave-assisted PEGylation of Merrifield resins

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Abstract—Modification of insoluble polymers through covalent attachment of short chain soluble polymers can produce hybrids that combine some of the advantages of both types of polymers such as physical stability and solvent-like characteristics. A convenient microwave-assisted PEGylation method of Merrifield resin (MR) was developed using focused microwave irradiation under atmospheric pressure conditions. The effect of molecular weight of PEG, % cross-link and chloride load of MR on the yield of the hybrid polymer was investigated and compared with yields obtained under conventional heating. The data indicated that the yield decreased with increasing the molecular weight of PEG and increasing chloride load of MR and that the highest yield (92.6%) was obtained with PEG molecular weight of 200 and MR (2% cross-link) with 1.25 mequiv./g of chloride. Thermal degradation observed of the grafted PEG increased with increasing heating time under conventional heating conditions.

The use of cross-linked polystyrene based resins such as Merrifield (MR) as solid support in combinatorial synthesis, is becoming increasingly important due to their stability, high compatibility and good swelling characteristic with a wide range of non-polar solvents.[1,2] But, these resins fail to perform when polar solvents are needed due to hindered accessibility to the reactive sites.[3] Modification of solid surfaces of MR with polar and soluble polymers such as poly(ethylene glycol) (PEG) derivatives can serve several functions depending on the use of the resulting hybrid polymer. Such hybrid polymers can combine some of the advantages of both types of polymers such as the physical stability of insoluble polymers and solvent-like character of liquid polymers that allow different substrates to approach the reactive sites more efficiently and hence increase the reaction rates. They can be used in sample preparations, organic synthesis, sensor technology and as chromatographic support material.

The most widely used solid-phase synthesis support is PEG attached to 1–2% cross-linked polystyrene. Advantages of using PEGylated support will be enhanced reactivity in both protic and non-polar organic solvents and increased yield and purity of the products. The surface viscosity of the polymers are also lowered allowing greater penetration of reagents in the interface pores, this in turn can increase the diffusion rate of reagents and increase the rate of solid phase reactions. PEGylated polystyrenes were first introduced by Itsuno et al.[4] PEG was capped first at both ends with styrene moieties by reaction of *p*-chloromethyl styrene using NaH in DMF. The final cross-linked polystyrene resin was prepared by suspension polymerization of the above product with styrene at 85°C. No other procedures are reported in the literature.

As part of our ongoing investigation on microwave-assisted processes (MAP™),[5,6] we report here a convenient and fast PEGylation procedure starting with commercially available Merrifield resins (Fig. 1). In a typical experiment 1.22 g±0.05 of the Merrifield's resin was suspended in excess poly(ethylene glycol) with a catalytic amount (1.5–3.5 mmol) of solid NaOH. The mixture was then irradiated using the following pulsed

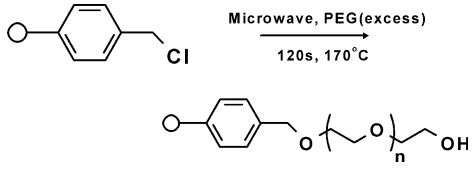

Figure 1. Microwave-assisted synthesis of PEGylated Merrifield resin.

Keywords: microwave; synthesis; Merrifield resin; poly(ethylene glycol).

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sequence: 40 s ON 15 min OFF, 40 s ON 15 min OFF, 15 s ON, for a total of 120 s of irradiation (170°C) at 300 W (unless otherwise specified) focused microwave power under atmospheric pressure conditions, using the Synthewave™ 402 (Prolabo, France). The use of focused irradiation increases the efficiency and reproducibility of the synthesis.

Excess PEG acts as solvent and at the same time prevents cross-linking of MR. The product was purified by washing with 30 mL of water, 20 mL of 10% HCl, 2×20 mL of water and 4×20 mL of methanol in succession and dried. The efficiency of the reaction was determined by measuring the chloride ion released in the wash using the Mohr method. The actual amount of PEG grafted unto the MR was estimated by three methods, one based on the number of moles of chloride ion released, the other based on the measured weight of the product (see Table 2) and the third based on the estimation of the free hydoxyl groups by UV quantitation (λ_{max} 258 nm) of Fmoc chromophore after reaction with Fmoc glycine.

To determine the optimum conditions for the synthesis, the effect of molecular weight of PEG as well as the percent cross-link and the chloride load of MR on the yield of the hybrid polymer was investigated. The data given in Table 1 show that PEGs with higher molecular weights and MRs with higher number of reactive sites resulted in lower yields of the hybrid polymers. This can be explained by steric hindrance effect. Due to the bulkier structure of the higher-molecular-weight PEG, it becomes more difficult to approach the reactive sites on the MR. The most efficient synthesis at 300 W microwave power (76.5% PEGylation sites) was achieved by the use of PEG (mol wt. 200) and Merrifield resin having 2% cross-link with average of 1.25 mmol Cl^-/g (see Table 1). This resin was used for further studies such as investigation of the effect of microwave power and conventional heating on the yield of the reaction. Table 2 summarizes the result of these experiments.

The data in Table 2 indicate that not all predicted PEG (based on the chloride ion released) was incorporated into the MR (for example, 0.173 g instead of 0.235 g),

Table 1. Effect of PEG and MR on the % yield and % PEGylated sites during microwave-assisted PEGylation of Merrifield resin

Experiment[a]	Cl^- released (mmol)	Yield (%)[b]	SD	PEGylated sites (%)[c]	SD[d]
PEG_{200}–MR2% (1.25)	1.17	91.9	0.9	76.5	5.5
PEG_{200}–MR2% (1.25)[e]	1.28	92.6	0.9	83.1	5.5
PEG_{200}–MR1% (1.75)	1.60	85.3	0.5	75.4	2.1
PEG_{200}–MR 2% (2.25)	1.61	80.3	0.2	59.5	0.6
PEG_{400}–MR1% (1.75)	1.57	78.1	2.2	73.1	5.3
PEG_{400}–MR1% (3.25)	1.54	54.5	0.6	41.2	0.7
PEG_{600}–MR2% (2.25)	1.54	57.9	0.3	56.0	0.5
PEG_{1000}–MR1% (1.75)	1.29	49.0	1.8	62.3	2.9
PEG_{1000}–MR1% (3.25)	1.43	34.0	0.5	35.8	0.6

[a] PEG_{MW}–MR% cross-link (mequiv. of chloride/g of resin).
[b] % yield = actual wt×100/theoretical wt.
[c] % PEGylation is based on chloride ion released relative to reported chloride ion content.
[d] Standard deviation, based on three replicate experiments.
[e] Performed under reduced microwave power (from 300 to 210 W).

Table 2. Comparison of the weight of grafted PEG in grams between conventional[a] and microwave-assisted synthesis

Experiment[b]	$PEG_{theoretical}$[c]	$PEG_{based\ on\ chloride\ ion}$[d]	$PEG_{based\ on\ wt\ of\ product}$[e]	PEGylation (%)[f]	Decomposition (%)[g]
PEG_{200}–MR2% (120 s)	0.307	0.235 ± 0.017	0.173 ± 0.005	56.3 (91.9)[i]	26.4
PEG_{200}–MR2% (120 s)[h]	0.307	0.255 ± 0.005	0.189 ± 0.011	60.0 (92.6)	25.0
PEG_{200}–MR2% (10 m)[a]	0.307	0.182	0.145	47.0 (90.5)	20.3
PEG_{200}–MR 2% (25 m)[a]	0.306	0.192	0.142	46.4 (90.2)	26.0
PEG_{200}–MR2% (35 m)[a]	0.306	0.21	0.124	40.5 (88.7)	41.7

[a] Reactions were performed in a Reacti-Therm block heated at 170°C using 20 mL open vials. Each sample required 30 min to reach 170°C as measured by a fiber optic probe, the reported times in minutes, indicate heating times after reaching 170°C.
[b] PEG_{MW}–MR% cross-link (reaction time).
[c] Based on the mequiv. of chloride of the starting Merrifield resin (1.22 g, 1.25 mequiv./g).
[d] Based on the mequiv. of chloride ion released after the reaction.
[e] Calculated from the weight difference between the starting resin and the product after correction for the weight loss of chloride.
[f] % PEGylation = $PEG_{based\ on\ wt\ of\ product}/PEG_{theoretical}$×100.
[g] % decomposition = $(PEG_{based\ on\ chloride\ ion} - PEG_{based\ on\ wt\ of\ product})/PEG_{based\ on\ chloride\ ion}$×100.
[h] Performed under reduced microwave power (from 300 to 210 W).
[i] % yield (as defined in Table 1).

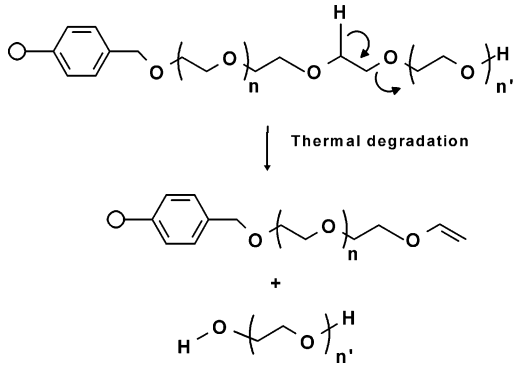

Figure 2. Thermal degradation of PEGylated Merrifield resin based on pyrolysis–GC/MS analysis.

this might be due to thermal cleavage of PEG after being grafted onto the MR backbone during synthesis (see Fig. 2). Pyrolysis–GC/MS analysis[7] of PEGylated MR have indicated the propensity of PEG moiety to undergo carbon–oxygen bond cleavage to produce terminal ethenyloxy group instead of the intact ethanol group, by loss of smaller PEG fragments (Fig. 2).

Preliminary studies with lower microwave power (210 W) have indicated the possibility of controlled synthesis to minimize the observed degradation. Elemental analysis[8] of this sample indicated the following composition of C 84.7%, O 8.8% and Cl 0.1%. When the synthesis was also carried out by conventional heating, at the same temperature, to assess the differences, if any, between the two procedures, the results also indciated occurrence of similar thermal degradations, which was a function of heating time.

The results listed in Table 2 also show that the highest yield obtained by microwave (92.6%) was not achieved by conventional heating, even after 35 min of heating. In fact, the yield decreased with longer heating times due to decomposition of the grafted PEG as shown in Fig. 2. Although the amount of grafted PEG estimated based on the chloride ion released increased with increasing heating time, however, the actual amount of grafted PEG decreased over time, further supporting the above conclusion.

This conclusion was also corroborated by the determination of free hydroxyl groups remaining in the product by UV quantitation (λ_{max} 258 nm) of Fmoc chromophore[9] after esterification with Fmoc glycine followed by basic cleavage. The number of moles of hydroxyl groups estimated by this method was within 5% of number of moles of grafted PEG calculated based on the final weight of the product ($PEG_{based\ on\ wt\ of\ product}$) in Table 2.

Ability to control this side reaction can improve the homogeneity of the product. Table 2 further indicates the possibility of modulating the microwave power to reduce degradative side reactions occurring during synthesis. Currently, efforts are underway to investigate the effect of temperature, time of exposure and microwave power on the % decomposition of PEGylated Merrifield resins. Finally, the synthesis of the hybrid polymer was reproducible on a larger scale (sixfold) under the same reaction conditions.

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