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# INVESTIGATING HIGHLY CROSSLINKED MACROPOROUS RESINS FOR SOLID-PHASE SYNTHESIS

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**Abstract**: The washing efficiencies of a chromophore and the reaction rates of a classical esterification reaction are improved with macroporous resins (MRs) relative to a classical Merrifield resin. Furthermore, Wacker-oxidation of a MR bound alkene yielded the expected methylketone product whereas an alkene bound to a low-crosslinked Merrifield resin gave no product, a function of the relative permeability of each of these resins to the aqueous solvent conditions employed. 

Incompatibilities between traditional solution chemistry and solid-phase synthesis (SPS) often arise because polymer supports exhibit different degrees of swelling dependent upon the choice of reaction solvent and temperature. In a "poor" solvent system, the polymer matrix may collapse upon itself and hence block internal reactive sites leading to low yields. However, it is well known that resins with high levels of internal crosslinking contain rigid porous structures that neither collapse nor significantly swell in different solvents.1 These so-called macroporous resins (MRs) have been used for many years as ion-exchange resins, polymeric adsorbents, and for preparative reverse phase chromatography purification of biomolecules.2 When properly swollen, the Merrifield-type resins allow greater access to their internal reaction sites as compared to macroporous supports, however, the internal sites of MRs remain accessible across the broad spectrum of solvent polarities.[1–6]

The MRs are receiving considerable interest as supports in organic synthesis as reagents and catalysts.[3–6] A recent report describes the utilization of a MR during a combinatorial library construction involving the acylsulfonamide "safety-catch". It was suggested that there is greater site accessibility under anionic reaction conditions in MRs than with standard low crosslinked resins.[7,8] Herein we report our findings on the use of commercially available macroporous resins in solid-phase synthesis and offer some comparison with low crosslinked homologues.

Five MRs manufactured by Rohm & Haas and sold through Supelco were selected for the study and functionalized, using standard methodology, as outlined in Scheme 1.[9–11] Loading capacities were calculated by either UV analysis of Fmoc release, following treatment with a solution of 20% piperidine/DMF to a weighed amount of resin,[12,13] or by the increase in the dry weight of the resin after attachment of the Fmoc group. It

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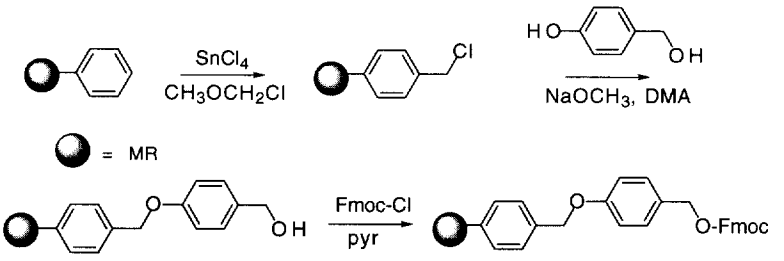
should be noted that only one standard set of reaction conditions were employed for the chloromethylation of all the resins studied. A trend between surface area and loading capacity was observed, which is intuitively satisfying as resins with a greater internal surface area should be expected to provide more sites for functionalization (Table 1). At this stage, the AmberchromR CG resins were dropped from further study because of their poor loading capacities and small particle size which made handling and transfer of these resins complicated.




**Scheme 1**. Functionalization of macroporous supports.

**Table 1**. Loading capacities and physical properties of the macroporous resins under study.

| Resin | Loading Capacity ($mmolg^{-1}$) by UV[a] | by dry weight[b] | Surface areac ($m2g^{-1}$) | Pore size diameter (nm) | Particle size (Å) |
|---|---|---|---|---|---|
| XAD 16 | 0.81 | 0.88 | 800 | 100 | 250–850 |
| XAD 2010 | 0.54 | 0.64 | 660 | 280 | 250–850 |
| XAD 1180 | 0.48 | 0.54 | 600 | 300 | 250–850 |
| CG 300cd | 0.35 | 0.33 | 700 | 300 | 80–160 |
| CG 1000sd | 0.35 | 0.36 | 250 | 1000 | 20–50 |

[a]Calculation based upon quantification of released Fmoc ($\varepsilon 290 = 4950\ mol^{-1}Lcm^{-1}$).[12]
[b]Estimation based upon increased weight after coupling of Fmoc group.
[c]Values reported by commercial source (Supelco).

The remaining MRs, AmberliteR XAD resins, were compared in subsequent studies to a commercially available Merrifield resin (2% crosslinked, chloromethylated polystyrene, Aldrich Chem. Co., with a loading capacity of *ca.* 1 $mmolg^{-1}$). A feature critical to the success of SPS is the ability to isolate the solid-phase support by filtration and rinse away unwanted reaction components after each synthetic step. To test the efficiency of solvent washes to remove unbound contaminants, unfunctionalized resins (approximately 50 mg) were pretreated with a solution of 2-hydroxybiphenyl (5 mM) in 1 mL of $CH_2Cl_2$ for 30 min at room temperature. The resins were then filtered and washed successively with 1 mL of solvent. The amount of chromophore recovered in the rinsate was measured by UV spectroscopy (Table 2, $CH_2Cl_2$ is the rinsing solvent). It is interesting to note that MR XAD 1180, with the largest pore size, has the highest washing efficiency (see Table 1). The slightly improved efficiency in washing the MRs over the Merrifield resin is assumed to be a consequence of the rigid pores speeding the migration of material from the internal polymer

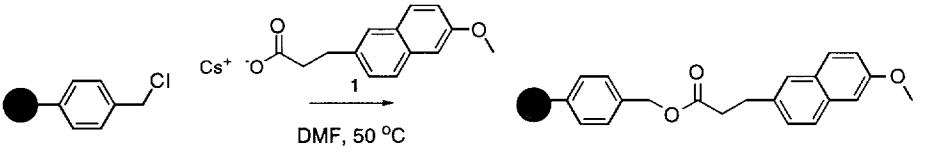
matrix into bulk solvent. This increased efficiency of MR washing was observed also when dioxane or 3:1 dioxane:water were employed as rinsing solvents. However, a single wash with methanol led to nearly quantitative recovery of 2-hydroxybiphenyl for all resins, including the Merrifield resin. Methanol being a poor solvent for the Merrifield resin caused it to collapse, and at least in this case, the chromophore was efficiently expelled from the polymer matrix.

**Table 2**. Resin rinsing efficiency.

| Resin | Recovery of 2-hydroxybiphenyl[a] (μmol) | | | | Recovery (%) |
|---|---|---|---|---|---|
| | Filtrate | Wash 1 | Wash 2 | Wash 3 | |
| XAD 16 | 3.98 | 0.58 | 0.09 | 0.02 | 93 |
| XAD 2010 | 3.76 | 0.72 | 0.14 | 0.02 | 93 |
| XAD 1180 | 4.21 | 0.56 | 0.10 | 0.02 | 98 |
| Merrifield resin | 3.41 | 0.82 | 0.17 | 0.03 | 89 |

[a]5 μmol initially applied to the resin, elution solvent $CH_2Cl_2$.

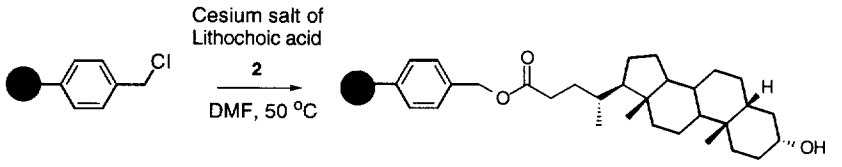
The accessibility of polymer-bound chloromethyl groups in a standard nucleophilic esterification reaction was investigated with 2-(6-methoxy-2-naphthyl)propionic acid, cesium salt **1** and lithochoic acid, cesium salt **2** (Schemes 2 and 3).[14] Reaction rates were slower with the carboxylic acid **2** compared to **1** perhaps due to a composite of both steric considerations and its lower solubility in DMF (Tables 3 and 4). In both cases, overall loading is highest, as expected, for the Merrifield resin. Inspection of the loading of **2** after 48 h relative to amount of material bound after 4 h and 20 h (Table 4) gives some indication of the relative rates of reaction. Although the Merrifield resin has the highest loading capacity, this support has a lower percentage of filled sites after 4 h when compared to the macroporous resins XAD 2010 and XAD 1180. The XAD 16 MR exhibited the slowest overall reaction rate, perhaps as a consequence of its smaller pore size relative to the other MRs (see Table 1).




**Scheme 2**. Esterification of **1** with chloromethylated resins.

**Table 3**. Reaction of chloromethylated resins with **1**

| Resin | Loading (mmolg$^{-1}$) | |
|---|---|---|
| | t = 1.5 h | t = 20 h |
| XAD 16 | 0.21 | 0.63 |
| XAD 2010 | 0.38 | 0.60 |
| XAD 1180 | 0.23 | 0.61 |
| Merrifield Resin | 0.88 | 1.44 |



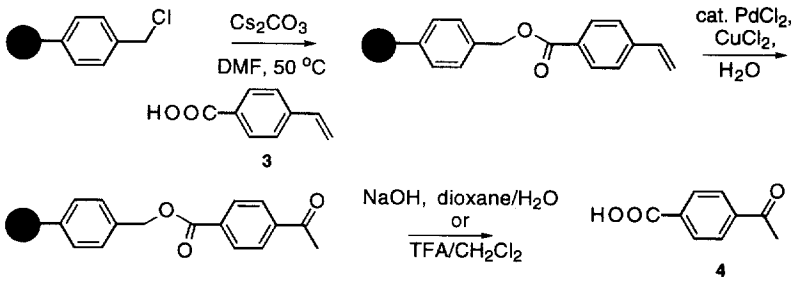

**Scheme 3**. Esterification with **2** and chloromethylated resins.

**Table 4**. Reaction of chloromethylated resins with **2**.

| Resin | Loading ($mmolg^{-1}$) | | | Loading relative to t = 48 h (%) | |
|---|---|---|---|---|---|
| | 4 h | 20 h | 48 h | 4 h | 20 h |
| XAD 16 | 0.09 | 0.46 | 0.62 | 14 | 74 |
| XAD 2010 | 0.16 | 0.54 | 0.61 | 26 | 88 |
| XAD 1180 | 0.14 | 0.47 | 0.55 | 25 | 85 |
| Merrifield | 0.23 | 0.71 | 1.14 | 20 | 62 |

The $S_N2$ esterification reactions outlined in Schemes 2 and 3 were both performed in warm DMF, a solvent system that satisfactorily swells Merrifield resin. However other polar, protic solvents such as alcohols or water are incompatible with low crosslinked resins. To emphasize the benefit of MRs in SPS, the palladium-catalyzed oxidation of alkenes to ketones (Wacker-type oxidation), a reaction traditionally conducted in water, was undertaken on resin bound alkenes.[15,16] Sherrington has reported that macroporous resins that complex palladium (0) are effective catalysts for Wacker oxidations,[4–6] but no solid-phase homologue, where the alkene is bound to the resin is yet known. This modification makes the Wacker-oxidation much more useful in a SPS format because the resin-bound ketone product can be subjected to further transformations.

Therefore, to discover if this mild transformation could be effected on solid-phase supports, the MRs and Merrifield resin were subjected to the conditions outlined in Scheme 4. The first indication of success is linked to a coloration of some of the resins (see Table 5), caused by the precipitation of the black Pd(0) species.[4–6] Cleavage of both unreacted 4-vinylbenzoic acid **3** and the product, 4-acetylbenzoic acid **4** from the MRs occurs readily using a solution of dioxane: 0.5 N NaOH (1:2). However, this aqueous treatment failed to liberate any material from the Merrifield resin and instead, TFA:$CH_2Cl_2$ (95:5) was employed.[17,18] The observation of no discoloration of the Merrifield resin and absence of any product formation are consistent with the conjecture that the collapsed state of the polymer matrix in aqueous systems prevents access of Pd (II) to the bound alkenes. On the other hand, the same reaction conditions led to significant product formation on all the MRs. The yields were improved by modifying reaction conditions, sometimes at the expense of increased discoloration. Overnight treatment of the MRs with 1 N HCl removed most of the Pd(0), but not all. Thus, it was found best to minimize color formation by employing a more effective co-oxidation system involving an oxygen atmosphere and/or adjusting the co-oxidant (CuCl2) levels.




**Scheme 4**. Reaction sequence for Wacker oxidation of polymer-supported olefins.

**Table 5.** Wacker oxidation on solid-phase supports.

| Resin | Reaction[a] | Cleavage | Appearance of resin | Yield[b] (%) |
|---|---|---|---|---|
| XAD 16 | A | NaOH(aq)/dioxane | Grey | 7 |
| XAD 2010 | A | NaOH(aq)/dioxane | Grey | 11 |
| XAD 1180 | A | NaOH(aq)/dioxane | Grey | 5 |
| Merrifield | A | TFA/$CH_2Cl_2$[c] | unchanged | 0 |
| R&H[d] | A | NaOH(aq)/dioxane | Grey | 8 |
| R&H | B | NaOH(aq)/dioxane | Light grey | 10 |
| R&H | C | NaOH(aq)/dioxane | Light grey | 34 |
| R&H | D | NaOH(aq)/dioxane | Black | 42 |

[a]A = 10% $PdCl_2$, 30% $CuCl_2$, air, overnight. B = 10% $PdCl_2$, 30% $CuCl_2$, O2 (2 atm), overnight. C = 10% $PdCl_2$, 30% $CuCl_2$, O2 (1 atm), 50 °C, overnight. D = 1 equiv $PdCl_2$, 3 equiv $CuCl_2$, air, overnight.
[b]Determined by HPLC.
[c]No cleavage occurred with NaOH(aq)/dioxane.
[d]Resin provided by Rohm & Haas exhibiting physical properties (900 Å pore size) similar to the resin described in ref 4.

Undoubtedly, additional work is required to optimize the Wacker oxidations on MRs, both in terms of overall yield and rinsing of the resin, but the preliminary results are very encouraging. While there is a report of palladium-catalyzed oxidation of olefins in the presence of PEG, yields decrease with increasing chain length of PEG[19] and our lab has been unsuccessful in its attempts to perform Wacker oxidations on alkenes bound to water-soluble, PEG-based supports.[20] Thus, this use of MRs is the primary example of Wacker-type oxidations of polymer-supported alkenes highlighting the utility of these supports in SPS for reactions that are traditionally incompatible with the more classical low crosslinked polymer supports.

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$$\text{Fmoc concentration} = \frac{(A290 - A450) - (A290 - A450)\text{control}}{4950}$$

Finally, loading capacity (mmol/g) was obtained from the number of millimoles released Fmoc (concentration multiplied by 1.00 mL) divided by the amount of weighed resin.
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