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Polymer-supported synthesis of mono-substituted porphyrins

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Abstract—Anchoring of substituted benzaldehydes to soluble and insoluble polymers allows for the synthesis of mono-substituted tetraarylporphyrins without the production of di-, tri-, and tetra-substituted porphyrin side products. The exclusion of the aforementioned side products during the synthesis of mono-substituted tetraarylporphyrin acids greatly reduced the complexity during purification of the product.

Porphyrins have received a great deal of attention as receptors for chiral recognition due to several unique features.[1] Their planar structures provide a well-defined binding pocket that is accentuated by substitutions on the ring. There are many sites that can be derivatized such as the *meso* and β-positions, the central metal, and the inner nitrogen atoms. They are highly chromophoric and ideal for detecting subtle changes in their close environment such as binding of chiral ligands. These intermolecular interactions can be easily followed by UV–vis, CD, fluorescence, NMR, and resonance Raman.[1] Our own interest in the use of porphyrins as host systems stems from their ability to report the chirality of bound guests in alkyl connected bis-metalloporphyrins based on exciton coupled circular dichroic spectroscopy.[2–7] The synthesis of these hosts depends heavily on procuring mono-substituted porphyrins efficiently. Herein, we describe the selective synthesis of mono-substituted porphyrins on insoluble and soluble polymers.

The synthesis of structurally complex porphyrins has seen tremendous progress in the last 30 years,[8–11] and as such the synthesis of mono-substituted porphyrins can be achieved by utilizing many of the methods that have been developed.[12] However, the most common and direct methodology to synthesize these mono-substituted porphyrins is to condense a mixture of pyrrole, benzaldehyde, and the appropriately substituted benzaldehyde in a 4:3:1 ratio. This leads to the synthesis of the desired mono-substituted porphyrin along with a mixture of tetraphenylporphyrin, and di-, tri-, and tetra-substituted compounds. Not only can the chromatographic separation of these compounds be tedious and time consuming, but also, depending on the substituted benzaldehyde utilized in the reaction, wasting of this compound by synthesizing undesired porphyrins can be synthetically limiting.

We have modified the synthesis of mono-substituted porphyrins by using insoluble and soluble polymers. The method of utilizing insoluble support for the synthesis of mono-substituted porphyrins was first developed by Leznoff and Svirskaya.[13] There are several advantages in synthesizing mono-substituted porphyrins on polymers. First, it is easy to separate the polymer-supported species from the small molecules present in the reaction medium by simple filtration, which in turn allows for the use of excess soluble starting material to gain higher yields. Second, the size of the polymer renders the resin-bound species inaccessible to each other and, therefore, cross reactions are avoided. This advantage excludes the formation of di-, tri-, and tetra-substituted porphyrins. Finally, the use of polymers in the synthesis of mono-substituted porphyrins eases the purification of the desired product.

In the strategy presented here, the substituted aromatic aldehyde that will eventually become the mono-substituted portion of the final porphyrin is anchored onto a polymeric backbone. This allows for the construction of the porphyrin on the polymeric support with pyrrole and an aldehyde in solution. In this manner, free mono-substituted aldehyde is not utilized and thus di-, tri-, and

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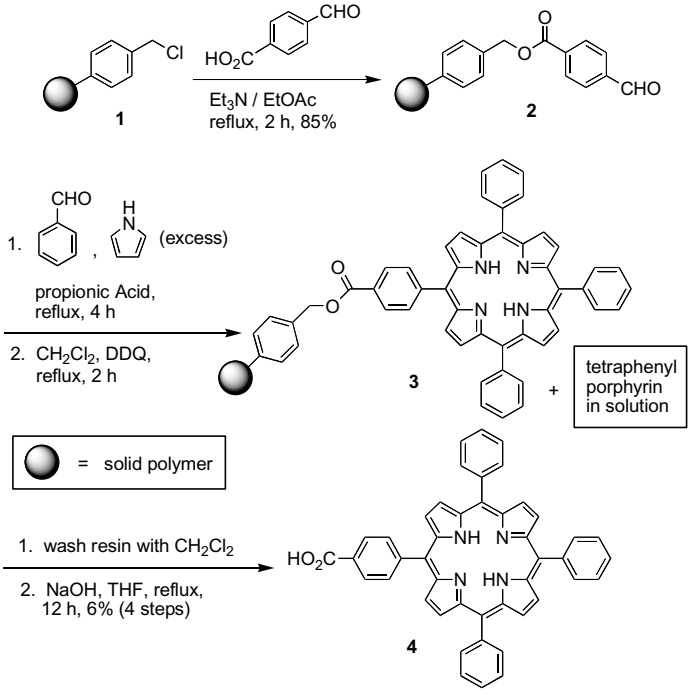
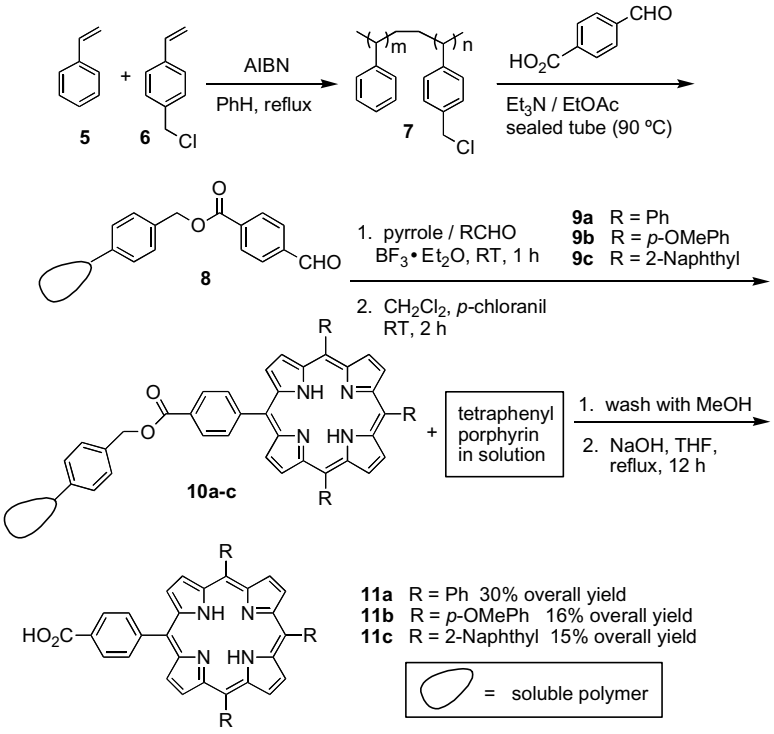
tetra-substituted porphyrins are not synthesized. As illustrated in Scheme 1, 4-carboxybenzaldehyde was attached to a 2% cross-linked divinylbenzene/polystyrene beads containing 1 mmol/equiv of benzyl chloride (**1**) by reported procedures.[14] The functionalized polymer support with the bound aldehyde **2** was used to synthesize the porphyrin. Addition of pyrrole and benzaldehyde to the polymer in refluxing propionic acid followed by DDQ oxidation yielded the mono-substituted product **3** on the resin and only tetraphenylporphyrin in the solution phase. Since benzaldehyde and pyrrole are inexpensive reagents, the sacrifice in making tetraphenylporphyrin in solution is well compensated by the fact that only the mono-substituted porphyrin is synthesized on the polymer. After washing the unbound reagents and products from the resin with CH_2Cl_2 (Soxhlet extraction), cleavage of the covalently attached porphyrin from the beads with NaOH led to the isolation of the desired compound **4** in good purity and 6% overall yield. The yield is comparable to solution phase synthesis of **4** in refluxing propionic acid, however, the crude isolate is not complicated with mixtures of multi-substituted porphyrins, and thus the purification proved to be straightforward from the polymer beads.

Limitations in the use of solid polymers in synthetic chemistry are pronounced by the difficulty in using NMR to characterize intermediates, and the heterogeneous nature of the chemistry that could result in low yields. However, soluble polymers can be used as an alternate matrix for organic synthesis. These polymers are non-cross-linked long chains, and exhibit both soluble and insoluble characteristics depending on the solvent used in the reaction.[15] Synthetic approaches that utilize soluble polymers couple the advantages of homogeneous solution chemistry (high reactivity, lack of diffusion phenomena, and ease of analysis) with those of solid phase methods (use of excess reagents and easy isolation and purification of products). Non-cross-linked polystyrene polymers are soluble in THF, CH_2Cl_2, $CHCl_3$, and ethyl acetate even at low temperatures, and are insoluble in water and methanol. Consequently, after the homogeneous reaction of supported intermediates, the polymer and its uniquely bound product can be easily separated from excess reactants and byproducts by treating with cold methanol, in which the soluble polymer precipitates as a solid polymer, and the soluble reagents and byproducts are filtered away. Because the polymer is soluble in $CHCl_3$, NMR analysis of all intermediates can be accomplished easily.

Non-cross-linked chloromethylate polystyrene (NCPS, **7**) was prepared as reported by Chen and Janda by the copolymerization of styrene (**5**) with 3 mol% of 4-(chloromethyl) styrene (**6**) in the presence of 0.06 mol% 2,2′-azobis(isobutyronitrile) (AIBN) in benzene at 70 °C for 40 h.[16] The MW_{avg} of 60,000 and a PDI of 2.14 were measured by GPC for the latter soluble polymer.[17] A variety of conditions were probed to attach 4-carboxybenzaldehyde to the soluble polymer **7**, and the best results were obtained by using triethylamine as the base and heating the reaction mixture in ethyl acetate to 90 °C in a sealed tube (Scheme 2).[18] Condensation of pyrrole with excess of either benzaldehyde (**9a**), *p*-methoxybenzaldehyde (**9b**), or 2-naphthylaldehyde (**9c**) with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 (similar to reported procedures for normal porphyrin synthesis in solution)[19] and subsequent oxidation with *p*-chloranil led to the formation of the corresponding soluble polymer bound porphyrins **10a**–**c**. Since the polymer is soluble in chloroform, the



Scheme 1. Synthesis of mono-substituted porphyrins on insoluble polystyrene/divinyl benzene cross-linked polymer.



Scheme 2. Synthesis of mono-substituted porphyrins on soluble polystyrene polymer.

synthesis could be followed easily by ^{1}H NMR. Figure 1 illustrates the ^{1}H NMR of **10a**. The peak broadening is as a result of the size of the soluble polymer, however, the porphyrin signals are clearly visible amongst the polymeric resonances.

The product in each case was isolated by basic hydrolysis of the ester functionality (2 N NaOH) to yield the porphyrin acids **11a**–**c** in yields comparable to solution phase synthesis. However, in comparison to non-polymer-supported solution phase synthesis, the purity of the crude product is substantially improved, and each product was easily purified by a simple silica chromatography step. The yields were calculated based on the amount of bound aldehyde **8** used in the reaction. The loading of the aryl aldehyde in **8** was calculated from NMR integrations of the latter moiety versus the polymer backbone signals. The mono-substituted porphyrin acids were purified by silica column chromatography, eluted with 3% methanol in CH_2Cl_2. Non-aromatic aldehydes such as *i*-butyl aldehyde, propanal, and acetaldehyde did not yield any product, presumably due to the polymerization of these reagents under the reaction conditions.

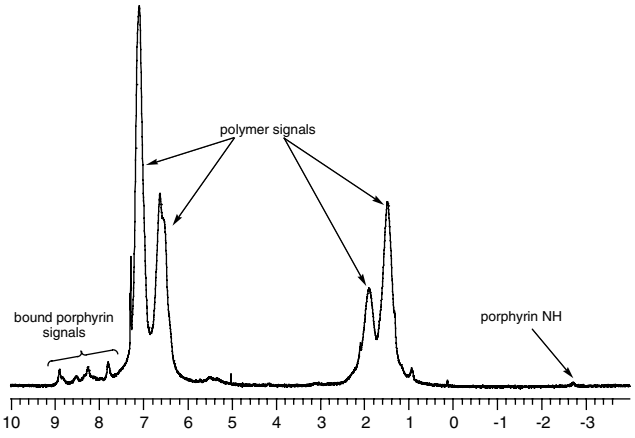


Figure 1. ^{1}H NMR of **10a**. The polymer signals are due to the aliphatic backbone and the aromatic side chains. The porphyrin signals can be clearly seen, although they are broadened due to the large molecular size of the soluble polymer.

In conclusion, synthesis of porphyrins on polymeric backbone can be used as a strategy to selectively synthesize mono-substituted porphyrins without the troublesome contamination from multiply-substituted products.

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18. Soluble polymer-supported aldehyde **8**: soluble polymer NCPS (2 g, 0.58 mmol), 4-carboxybenzaldehyde (0.9 g, 6 mmol) and Et_3N (1 mL) were added to EtOAc (20 mL). The reaction mixture was refluxed for 3 days. The reaction was then cooled down and the solvent was rotovaped. The oil like residue became a white powder as soon as cold methanol was added. The precipitate was filtered and redissolved with acetyl acetate. This cycle was repeated until all the 4-carboxybenzaldehyde was removed. Mono-substituted porphyrin **11a**: to a mixture of the soluble polymer-supported aldehyde **8** (1 g, 0.27 mmol) and benzaldehyde (1.58 g, 15 mmol) in freshly distilled CH_2Cl_2 (30 mL) was added pyrrole (1.32 g, 20 mmol). Nitrogen gas was purged into the solution with vigorous stirring, and after 15 min, catalytic amount of $BF_3{\cdot}OEt_2$ (0.1 mL) was added. After 10 min, the solution turned from colorless to amber. The reaction flask was shielded from light with aluminum foil, and the reaction was stirred at room temperature for another 1 h. Excess amount of *p*-chloranil (3 g) was added to the solution, and it was stirred for additional 2 h to generate the polymer-supported porphyrin. The solvent was then removed under reduced pressure and the residue was precipitated in cold methanol to aid in removing the tetraphenylporphyrin side product (not bound to polymer).
To the solution of polymer-supported porphyrin in THF (10 mL) was added 2 N NaOH aqueous solution (5 mL), and the solution was refluxed overnight. After it was cooled to room temperature, the pH of the mixture was adjusted to 4 with 6 N HCl solution. The THF was removed under reduced pressure, and the aqueous layer was extracted with MeOH–CH_2Cl_2 (1:100, 3×20 mL) until all the purple color was removed from the aqueous layer. The organic layers were combined and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (5 mL) and precipitated in cold methanol–THF (10:1). This cycle was repeated three times. The solvent of the combined organics was removed under reduced pressure, and the residue was purified by column chromatography (3% MeOH in CH_2Cl_2) to afford 53 mg (30%) of the pure porphyrin acid **2** as a purple solid.
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