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The use of 18-crown-6 as an ionizable phase label for the expedited synthesis of small molecules

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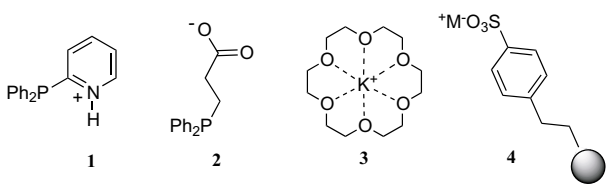
Abstract—A silica-supported propylbenzenesulfonic acid ion-exchange column was treated with a methanol solution of potassium carbonate to give the corresponding potassium sulfonate salt. This column was shown to effectively sequester 18-crown-6 and its derivatives presumably due to chelation of the macrocyclic ether with the ionically bound potassium cation. This phenomenon was also observed to a lesser extent with ammonium ion but not with other cations such as lithium and cesium. This crown ether technique was then used to facilitate the purification of an amidation reaction.

When a substrate, reagent, or catalyst is attached to an insoluble polymer, these entities can be separated from a reaction solution by a simple filtration step. This facilitated purification, especially when compared to traditional chromatographic techniques, renders the parallel synthesis of small molecules a task that can be easily automated. Indeed, solid-phase techniques have been widely used in numerous drug discovery efforts to synthesize large compound libraries for biological screening.[1] However, the property of insolubility of the support resin is also the chief drawback of the solid-phase method since any organic transformation involving substrates attached to the polymer support must be performed under heterogeneous conditions. Many important synthetic reactions cannot be easily adapted for use in a heterogeneous regime and this often presents an insurmountable barrier to the solid-phase synthesis of complex, non-peptide, small molecules. In recent years, several alternatives have been developed to overcome the heterogeneous limitation of the solid-phase approach most notably soluble-polymer matrices[2] and fluorous supports.[3]

If a substrate or reagent contains a functional group that is easily ionized (*ionizable label*)[4] then it can often be removed from the reaction mixture during an aqueous work-up or through the use of an appropriate ion-exchange resin. For example several phosphine reagents have been prepared so that upon acidic treatment they are converted to water-soluble species such as **1**[5] and **2**.[6] However, the use of Brønsted acid–base chemistry to ionize compounds for subsequent purification cannot be a general approach since many types of synthesis reactions are themselves mediated by acids or bases.

The chelation of metal cations by crown ethers presents an alternative ionization strategy that does not involve proton transfer chemistry.[7] We envisioned that crown–cation complexes such as 18-crown-6/K^+ (**3**) could be successfully removed from a reaction mixture through interaction with an ion-exchange resin. In order to examine this possibility, a series of experiments were conducted with 18-crown-6 and several metal salts of silica-supported ethylbenzenesulfonic acid **4**. 18-Crown-6 was chosen for the initial experiments since the cation binding properties of this macrocyclic ether have been well studied.[8]



1 **2** **3** **4**

A silica-supported ethylbenzenesulfonic acid (SCX) ion-exchange column[9] (2 g) was treated with a 10% solution of acetic acid in methanol (10 mL). To this column was added 18-crown-6 (50 mg in 1 mL of MeOH). The column was then rinsed with methanol (2×5 mL). The rinse methanol was collected and distilled off to give nearly quantitative recovery of the starting 18-crown-6. A second SCX column (2 g) was treated with a satu-

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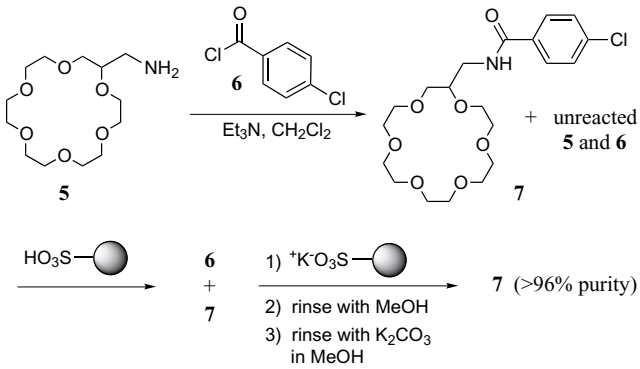
rated methanolic solution of potassium carbonate. To this column was added 18-crown-6 (150 mg in 1 mL of MeOH). The column was rinsed with methanol (2×5 mL) and some 18-crown-6 was recovered (22 mg). Additional rinses gave a slow bleeding off of the crown ether (2–5 mg per 5 mL of methanol rinses). When the amount of 18-crown-6 added to the SCX column (50 mg) was decreased no trace of the crown ether was found in the rinse solvent even after copious rinsing (>50 mL). The column containing the 18-crown-6 (50 mg) was then treated with a saturated solution of K_2CO_3 in methanol (5 mL). *Most of the starting crown ether (83%) was recovered in the rinsing solution* (to accurately determine the weight of the recovered crown ether, the solution was passed through a small plug of silica gel to remove the potassium carbonate salt). A second rinsing with the potassium carbonate solution (5 mL) gave near-quantitative recovery of crown ether (96%).

An SCX column was next treated with a saturated lithium carbonate methanol solution to give the corresponding lithium sulfonate salt. As before, 18-crown-6 (50 mg in 1 mL of MeOH) was loaded onto the column followed by rinsing with methanol. Nearly all of the 18-crown-6 (98%) was recovered in the first methanol rinse (5 mL). The experiment was also repeated with cesium carbonate giving nearly identical results as the lithium carbonate case. The cation specificity of the 18-crown-6 phase label is in keeping with the known cation binding properties of this crown ether in the solution phase.[8] The cation specificity of the 18-crown-6 phase label suggests that the SCX column sequesters the crown ether as the metal chelated complex.

Although the ammonium ion is chelated nearly 100 times more weakly than potassium by 18-crown-6,[8] we proceeded to investigate its use in this ion-exchange method since a crown ether ammonium complex can be freed of this salt under vacuum. Thus, an SCX column (2 g) was treated with a saturated methanol solution of ammonium formate. The column was then loaded with 18-crown-6 (50 mg, same as in the experiments described above). Nearly 92% of the crown ether was recovered from the column after 2 methanol rinses (10 mL). Additional methanol rinses (50 mL) did not lead to any additional recovery. The SCX column was then treated with saturated ammonium formate in methanol (2×5 mL) leading to the recovery of nearly all the remaining crown ether (3 mg, 6%). Additional experiments indicate that a much larger SCX column (10 g) can sequester up to 25 mg of 18-crown-6. We are currently investigating the use of other macrocyclic ethers that might improve the sequestration ability of ammonium/sulfonate ion-exchange column.

Next, the potential of the 18-crown-6/K^+ system was evaluated for use in reaction purification. As an initial experiment, aminomethyl-18-crown-6 (**5**) (100 mg, 0.34 mmol) was reacted with 4-chlorobenzoylchloride (**6**) (179 mg, 1.0 mmol) and triethylamine (138 mg, 1.36 mmol) in methylene chloride (3 mL) (Scheme 1). In order to give a mixture of products, *the reaction was*



Scheme 1. Use of 18-crown-6 in the purification of an amidation reaction.

only allowed to proceed to approximately 50% conversion to the amide product **7** (based on TLC analysis). The reaction mixture was transferred to an SCX column (10 g) conditioned with 5% AcOH/MeOH. The column was rinsed with methanol (2×10 mL). The methanol rinses were concentrated and found to contain the amide product **7** and the unreacted acid chloride **6** (TLC and NMR analysis).

The crude mixture of **6** and **7** was then dissolved in methanol (2 mL) and loaded onto an SCX column that was previously treated with saturated potassium carbonate in methanol. After the column was loaded, it was rinsed with methanol (3×10 mL). The rinses were found to contain only acid chloride **6** (as determined by NMR). The column was then rinsed with saturated K_2CO_3 in methanol (2×10 mL) to give amide **7** in >96% purity and in 47% yield.[10]

These experiments clearly indicate that small organic molecules containing the 18-crown-6 moiety can be sequestered by the potassium salt of a sulfonate ion-exchange resin. The application of this technique to the parallel synthesis of compound libraries is currently underway. In addition, our findings on crown ether sequestration using a volatile ammonium ion salt will be communicated in due course.

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9. These columns are commercially available in a range of sizes from Varian.
10. Compound **7** gave satisfactory ^{1}H NMR and MS data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (t, $J=4.8$ Hz, 1H), 7.82 (d, $J=8.4$ Hz, 2H), 7.50 (d, $J=8.4$ Hz, 2H), 3.69–3.57 (m, 3H), 3.54–3.24 (m, 22H). MS (ESI) m/z 432 $(M+H)^+$. The purity of **7** (>98%) was estimated from the integrated peak areas of an HPLC chromatograph of the crude with the UV detector monitoring at $\lambda=215$ nm. Analytical HPLC setup: C_{18} Vydac® column; solvent system = acetonitrile (0.1% TFA) and water (0.1% TFA); flowrate = 1 mL/min flow-rate; eluent gradient = 10% to 60% MeCN/H_2O over 45 min. The retention time of **7** is 20.3 min.