Report

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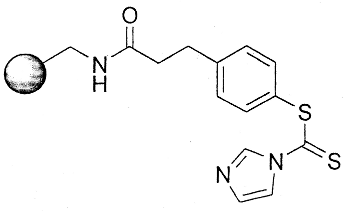

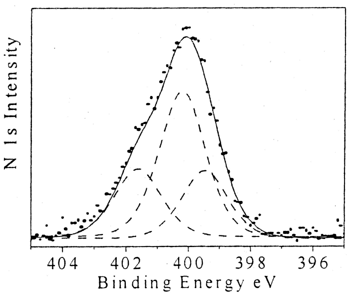

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Application of X-ray Photoelectron Spectroscopy in Determining the Structure of Solid-Phase Bound Substrates

David. M. Whitehead,[†] Toby Jackson,[†]
Stephen C. McKeown,[‡] Karen Wilson,*[,†] and
Anne Routledge*[,†]

Department of Chemistry, University of York, Heslington, York, YO10 5DD, U.K., and Medicines Research Centre, GlaxoSmithKline Research and Development, Gunnels Wood Road, Stevenage, SG1 2NY, U.K.

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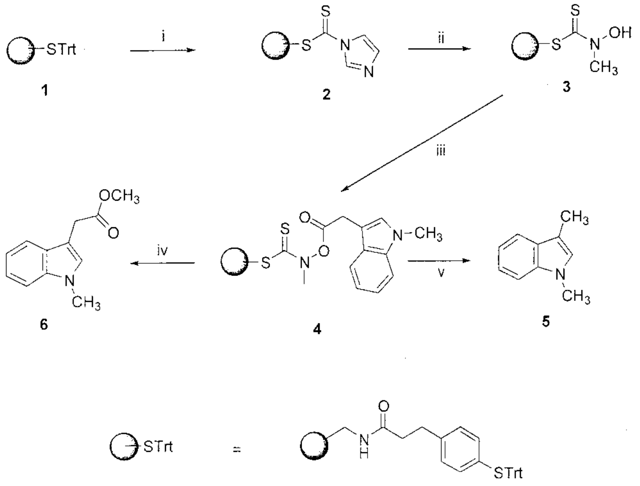
The synthesis of compounds on solid supports has grown rapidly in the past 10 years, but one of the hurdles to the routine adoption of solid-supported chemistry is the limited number of analytical methods available to characterize resin-bound compounds. There have been methods developed for on-bead reaction monitoring of solid-phase reactions; both magic angle spinning (MAS) NMR[1] and FTIR[2] are useful techniques, but much solid-phase chemistry still relies on releasing the product from the solid support for validation. As a result, there still remains the need for complementary techniques that could quantify and/or identify functional groups prepared during solid-phase synthesis.

In the recent literature, scanning confocal Raman spectroscopy was used to study the distribution of reactive sites within standard polystyrene resin beads.[3] The results showed that the reactive sites were essentially homogeneously distributed within the bead, agreeing with other studies performed in this area including autoradiography[4] and scanning secondary ion mass spectrometry.[5] Because the reactive sites within a bead can be considered to have a homogeneous distribution, analysis of the functionality at the bead surface should reflect the functionality within the entire bead. Photoelectron spectroscopy (XPS)[6] is a powerful and accessible method for analyzing the surface elemental composition of materials but has not, to date, been used to explore a synthetic sequence in solid-supported chemistry. This analytical method may not allow the determination of the exact structure of complex molecules bound to a solid support but could represent a powerful complement to NMR and IR for routine nondestructive analysis. Herein, we report our investigation of the use of XPS as a method for the analysis of solid-supported reactions.

As part of our ongoing research into traceless photolabile linkers,[7] we constructed a Barton thiohydroxamic acid on commercially available 3-((4-tritylmercapto)phenyl)propionylpolystyrene[8] **1** (Scheme 1). The commercial resin was deprotected and reacted with 1,1-thiocarbonyldiimidazole to yield resin-bound thiocarbonylimidazole **2**. Subsequent displacement of imidazole with *N*-methylhydroxylamine gave the resin-bound thiohydroxamic acid linker **3**. *N*-Methylindole-3-acetic acid was immobilized onto the resin-bound linker via DIC/HOBt mediated coupling, resulting in thiohydroxamic ester **4**. FTIR analysis of **4** showed a carbonyl stretch at 1804 cm^{-1} indicative of a thiohydroxamic ester, and a negative malachite green test[9] was observed. Resin **4** was cleaved with sodium methoxide to give methyl-*N*-methylindole 3-acetate **5** in 19% yield[10] based on the loading of resin **1**; photolysis of **4** furnished 1,3-dimethylindole **6** in 17% yield.[11] FTIR analysis of the photolyzed resin showed loss of the stretch at 1804 cm^{-1}, indicating complete consumption of the thiohydroxamic ester moiety. We were perturbed by these low yields, and neither gel-phase FTIR or gel-phase ^{13}C NMR could provide a suitable explanation. As a result, we decided to explore the application of XPS to monitor the solid-phase synthesis of thiohydroxamic acid linker **3**.

Scheme 1. Synthesis and Loading of Thiohydroxamic Acid Linker[a]



[a] (i) TFA/CH$_2$Cl$_2$/triethylsilane (9:10:1), ambient temp, 1 h, 1,1-thiocarbonyldiimidazole (3 equiv), CH$_2$Cl$_2$, ambient temp, 18 h; (ii) *N*-methylhydroxylamine hydrochloride (3 equiv), triethylamine (6 equiv), CH$_2$Cl$_2$, ambient temp, 18 h; (iii) *N*-methylindole-3-acetic acid (2 equiv), DIC (2 equiv), HOBt (2 equiv), DMAP (0.2 equiv), DMF, ambient temp, 18 h; (iv) THF/MeOH (4:1), excess NaOMe, ambient temp, 0.5 h; (v) THF/Bu$_3$SnH (40:1), 350 nm, 0.5 h.

The surface of resins **1**−**3** were analyzed using a Kratos Axis HSi X-ray photoelectron spectrometer equipped with a Mg Kα X-ray source, a five-channel hemispherical analyzer, and a charge neutralizer for analysis of insulating samples. Resins were dried thoroughly under vacuum to mitigate solvent contamination and were then loaded on a horizontal 20-position sample bar mounted on an automated manipulator enabling high-throughput analysis. Spectra were recorded using an X-ray power of 225 W and an analyzer pass energy of 160 or 20 eV for survey or high-resolution scans, respectively. Binding energies were referenced to the C−H transition in the C 1s spectra, which was assigned a binding energy of 285 eV. Deconvolution of the N 1s spectra

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* For main correspondence, contact A.R.: e-mail, ar30@york.ac.uk. For correspondence regarding XPS, contact K.W.: e-mail, kw13@york.ac.uk.

[†] University of York.

[‡] GlaxoSmithKline Research and Development.

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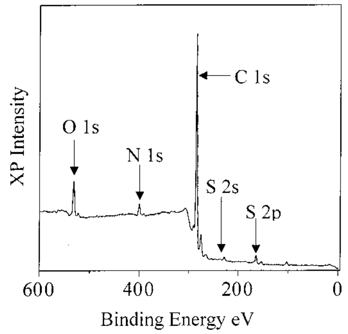


Figure 1. XPS wide scan of resin **1**.

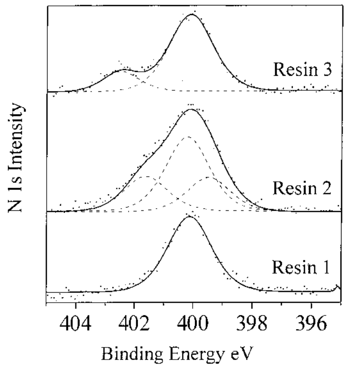
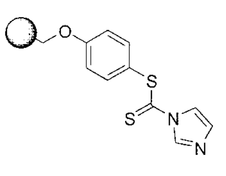


Figure 2. Curve-fitted N 1s envelopes for resins **1**−**3**.

was performed using a common symmetrical line shape, which consisted of a mixed Gaussian/Lorentzian function.

Figure 1 shows the survey spectrum of resin **1**, dominated by a peak at 285 eV assigned to carbon atoms *C*−C and *C*−H within the polystyrene backbone. Peaks corresponding to nitrogen, sulfur, and oxygen are also detected. Elemental compositions were determined by integration of peak areas observed in high-resolution scans followed by correction using the following relative sensitivity factors (RSF): C 1s, 0.318; N 1s, 0.505; O 1s, 0.736; S 2p, 0.723. Further details about the elemental composition can be attained through deconvolution of the high-resolution scans. The power of XPS in following the surface reaction and identifying different functional groups is demonstrated in Figure 2, which shows the curve-fitted N 1s envelopes for resins **1**−**3**. The parent resin **1** can be fitted to a component at 400 eV assigned the amide environment (100%). On deprotection of the sulfur and reaction with 1,1-thiocarbonyldiimidazole two states evolve at 401.7 and 399.6 eV, assigned to the imidazole ring N2 and N1, respectively, consistent with previous XPS studies of imidazole rings with nonequivalent N environments[12] and analysis of reference compound **9**. The nitrogenous signal is now resolved into amide (76%) and imidazole (24%). Finally, on reaction to form the resin-bound hydroxylamine **3**, complete loss of the 401.7 and 399.6 eV states is evident accompanied by the evolution of a new state at 402.6 eV, which is assigned to the hydroxylamine nitrogen. The nitrogenous signal is thus resolved into amide (82%) and hydroxylamine (18%). The low yield of imidazole functionality could be accounted for by conversion of resin **1** to resin **2** resulting in cross-linking to either disulfide **7** or trithiocarbonate **8** (Scheme 2) or hydrolysis of the resin-bound thioimidazole **2**. This suggests that the chemical transformations from thioimidazole **2** to the thiohydroxamic ester **4** are relatively efficient and the low yields obtained on the cleavage from thiohydroxamic ester **4** are a reflection of the inefficient formation of thioimidazole **2** from the parent resin **1**.



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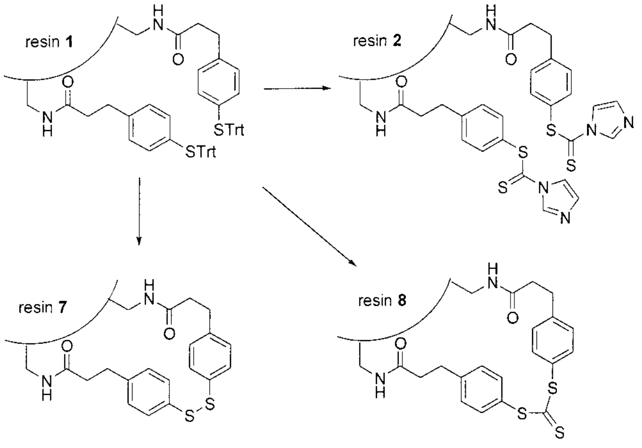
Scheme 2. Possible On-Bead Dimer Formation



In summary, we have demonstrated that photoelectron spectroscopy (XPS) can be used to determine the structure of solid-phase bound substrates; we envisage it as a complementary technique for quantifying and/or identifying functional groups manipulated during solid-phase synthetic protocol. The extension of this analytical tool using a monochromatic X-ray source is in progress.

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(10) Procedure for the cleavage of methyl-*N*-methylindole 3-acetate **5** from resin **4**. Resin **4** (0.05 g) was swollen in THF/MeOH (4:1), and excess NaOMe was added. The mixture was agitated for 18 h, the resin was removed by filtration, and the solution was made up to 10 mL. Indole was added (as an internal standard), and an aliquot of the solution was removed and analyzed by HPLC (diode array detection). The yield is based on the loading of resin **1**.

(11) Procedure for the photolytic release of 1,3-dimethylindole **6** from resin **4**. Resin **4** (0.05 g) was swollen in THF/Bu_3SnH (40:1), and the solution was degassed with nitrogen for 10 min. The solution was photolyzed at 350 nm using a Rayonet photochemical reactor for 30 min. The resin was removed by filtration, and the solution was made up to 10 mL. Indole was added, and an aliquot of the solution was removed and analyzed by HPLC (diode array detection). The yield is based on the loading of resin **1**.

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