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Report

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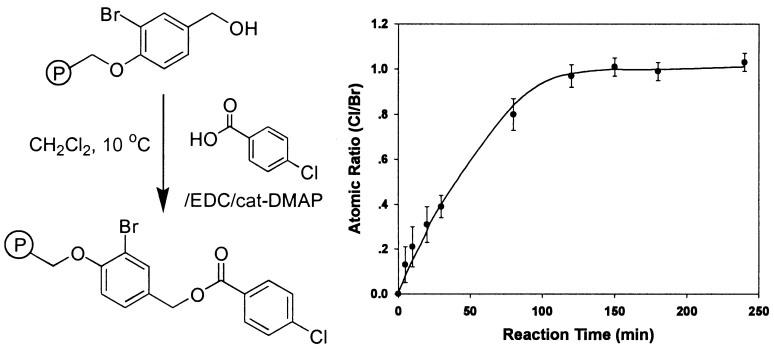

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Reports

X-ray Photoelectron Spectroscopy Analysis of Solid-Phase Reactions Using 3-Brominated Wang Resin

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There is even more interest in the development of the solid-phase synthetic approaches to small molecules, particularly those which embrace heteroatom-containing molecules, for the purpose of medicinal and agricultural chemistry.[1] Many heteroatom-containing molecules exhibit a broad range of biological activities for antiviral, antibacterial, antifungal, and antihypertensive drugs, as well as others.[2]

The major impediment in the solid-phase synthesis is the lack of analytical techniques for identifying the products and particularly for monitoring the progress of the reactions. As part of our continuing interest in the development of new solid-phase synthetic methods,[3] we were looking for a new analytical method for monitoring the reaction and for identifying the product still bound to the polymer. Although there are a few techniques known for direct monitoring of samples still bound to resins, namely IR,[4] NMR,[5] and mass spectroscopy,[6] we still need a new analytical method.[7]

X-ray photoelectron spectroscopy (XPS) has been widely used to acquire qualitative as well as detailed quantitative information about the composition and structure of organic and polymeric materials.[8] As an analytical tool for organic and polymeric materials, XPS is known to have several advantages: It is a semiquantitative technique with a high surface sensitivity and is capable of identifying all elements except H and He. Also, XPS provides information about chemical states of elements.[8]

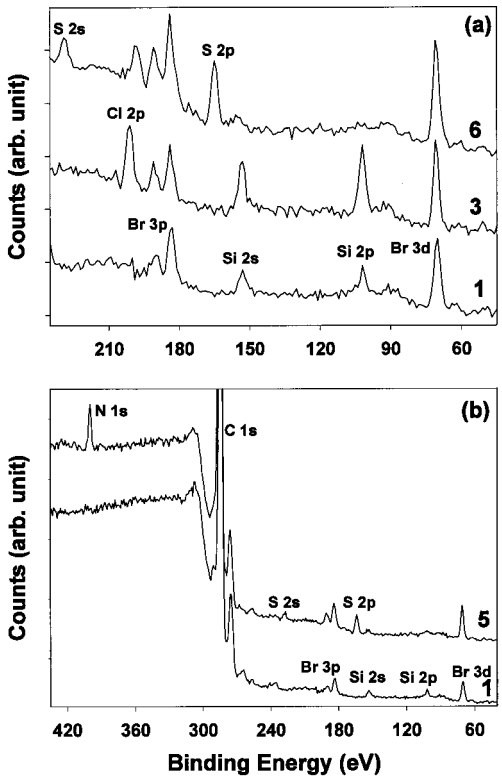

Figure 1. X-ray photoelectron survey spectra for resins **1**, **3**, **5**, and **6**. The elements in the polymer-bound compounds can be readily identified by determining the binding energies of the photoelectron peaks.

Since the most popular solid supports, such as the Wang and Merrifield resins, are mainly comprised of carbon and oxygen atoms and the concentration of the reacting site is very low (1−2 mmol per gram of resin), a simple XPS analysis of these polymers will only provide a limited piece of information.[9] However, we envisioned that if we insert a suitable heteroatom as an internal standard (a marker) in the polymer, then we might be able to monitor around the

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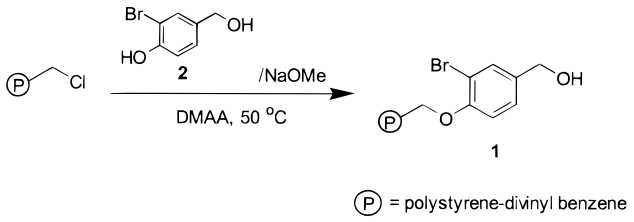
Scheme 1



reaction site by measuring the ratio between the marker atom and the heteroatoms being introduced in the reacting part.

In this paper we will describe a general strategy and the scope of a new analytical method using XPS in connection with solid-phase organic synthesis (SPOS) of heteroatom-containing organic molecules and solid-phase peptide synthesis (SPPS). As we discussed, we needed to incorporate a suitable heteroatom as a marker in the polymer. One has an option to incorporate a marker either in the polymer backbone or in the linker. However, it might be more practical and desirable to incorporate a marker somewhere in the linker part because of its easy introduction to the polymer. First, we chose bromine as a marker atom since the bromine atom has high sensitivity and is readily distinguishable from other elements in the XPS analysis. We selected the benzyl alcohol type of linker because of its relative stability toward organic and peptide reaction conditions and the 3-position of the phenyl ring for substitution to minimize any potential steric hindrance. Taking these factors into account, we chose the 3-brominated Wang type of linker for our purpose (Scheme 1).[10]

To prepare the sample for XPS analysis, the resin-bound compounds were mounted on the sample stub by double-sided adhesive tape.[11] The identification of elements present in the resin-bound compounds can be carried out in a straightforward manner by determining the binding energies of the various photoelectron core peaks.[8] Figure 1 shows the corresponding XP spectra of **1** and three polymer-bound compounds prepared by the solid-phase reactions.[12] The polymer **1** was identified by the presence of a single Br 3d peak at about 70 eV and Br 3p doublet peaks at 184 and 190 eV. The spectrum of **3** shows a single Cl 2p peak at 201 eV, indicating that **3** is formed from **1**. The S 2s and 2p peaks located at 228 and 164 eV are the evidence for the formation of **6**. The polymer **5** obtained from **1** by solid-phase peptide synthesis shows a N 1s peak at 402 eV and two S 2s and 2p peaks.

The rationale for the quantitative analysis by XPS is in the fact that the ionization cross-section of a core level is practically independent of the valence state of the respective element, so that the intensity is directly proportional to the number of atoms in the analyzed volume, regardless of its chemical state.[8] In the XPS analysis, the relative concentrations of various elements on a solid surface can be determined much more accurately than the absolute concentrations. Methods have been developed for quantifying the relative concentrations utilizing peak areas and the sensitivity factors.

It is well known that polymers are reasonably stable under XPS conditions, although a prolonged exposure (more than several hours) to X-ray beams of typical flux densities often indicates the damage by X-ray. However, in our preliminary experiment we found that the polymer-bound compounds were damaged much more rapidly by X-ray irradiation than was the polymer backbone. To determine the extent of damage during the analysis, we measured the decrease of the relative intensities of carbon and heteroatom peaks as a function of X-ray exposure. The intensities of the heteroatom peaks decrease to half within 40 min, showing that the X-ray-induced damage is significant in the XPS analysis of the polymer-bound compounds. To minimize the quantification error from the X-ray-induced damage, we reduced data acquisition time (within a few minutes) and used an extrapolation method. We measured the relative intensities of the heteroatom peaks as a function of X-ray exposure and extrapolated them to time zero. The extrapolated values to time zero can be considered as the relative concentrations for undamaged samples. The relative intensities of the heteroatom peaks of **3**, **4**, and **6** are almost constant within an error limit even though their absolute intensities decrease rapidly upon irradiation of X-rays.

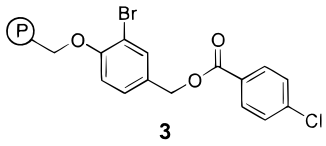
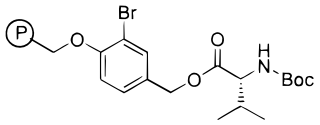
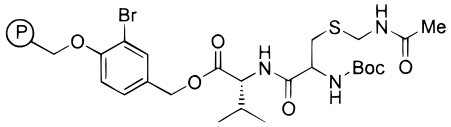
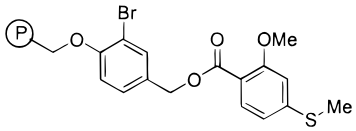
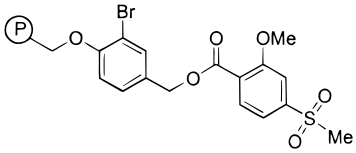
It is surprising to find that the ratios between the heteroatoms from the XP peak intensities indicate correct stoichiometry; Cl/Br = ~1/1 for **3**, N/Br = ~1/1 for **4**, and S/Br = ~0.9/1 for **6** (Figure 2). In the case of **5** in which the atomic ratios of N, S, and Br change rapidly upon X-ray exposure, we used the extrapolation method to compensate for the error caused by the X-ray damage to show an ~3:1:1 ratio for N:S:Br (Figure 2f). These results demonstrate that the quantitative analysis of XPS together with the extrapolation method can be a powerful technique for analyzing the polymer-bound samples (Table 1).

It is generally difficult to monitor solid-phase reactions during the course of a reaction. However, we expected that our technique would be capable of accomplishing this task.[13] To this end, we analyzed the polymer samples during the esterification reaction of 4-chlorobenzoic acid on 3-bromo-Wang resin **1** (Scheme 2) by XPS. Using the XP spectra of polymer **1** and the preformed polymer **3** (Figure 1a), we determined the progress of the reaction by measuring the Cl/Br ratio as a function of the reaction time (Figure 3). The reaction was quenched after specific amounts of reaction time by isolating the sample with filtration. It shows the general trend of an isotherm curve for solid surface reaction and the atomic ratio of 1, indicating the completion of the full formation of **3**, which takes about 2 h under the conditions.

This experiment clearly demonstrates that this technique is indeed a very convenient way to find a proper reaction time for solid-phase reactions since the quantitative ratio of the atoms can be easily measured and calculated from their spectra.[8] This example clearly shows the superiority of this method over the IR method for a quantitative analysis.[14] The value of this method is more appreciated in a peptide synthesis in which there are a number of similar amide groups. Using our method the progress of the peptide construction can be simply monitored by the increase of the N/Br ratio even if the incoming amino acid does not contain any other heteroatom such as S in cysteine or cystine.

By taking advantage of XPS, which is capable of

Table 1. Relative Quantitative Ratios Taken from Resins **3**, **4**, **5**, **6**, and **7** by XPS

Compounds	Theoretical ratio	XPS ratio(%)
 **3**	Br : Cl 1 : 1	Br : Cl 50 : 50
 **4**	Br : N 1 : 1	Br : N 51 : 49
 **5**	Br : N : S 1 : 3 : 1	Br : N : S 21 : 56 : 23
 **6**	Br : S 1 : 1	Br : S 54 : 46
 **7**	Br : S 1 : 1	Br : S 55 : 45

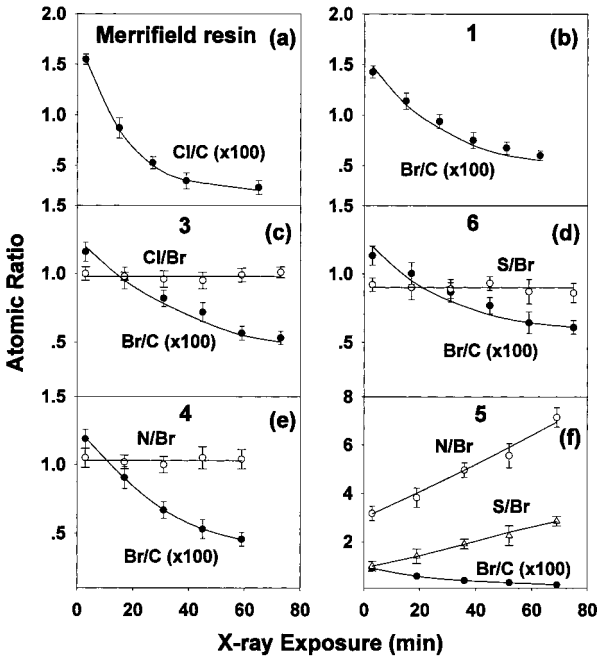


Figure 2. The relative intensities between the carbon and the heteroatom peaks as a function of X-ray exposure for the polymer and the polymer-bound compounds. The relative intensities of the heteroatom peaks **3**, **4**, and **6** are almost constant within an error limit.

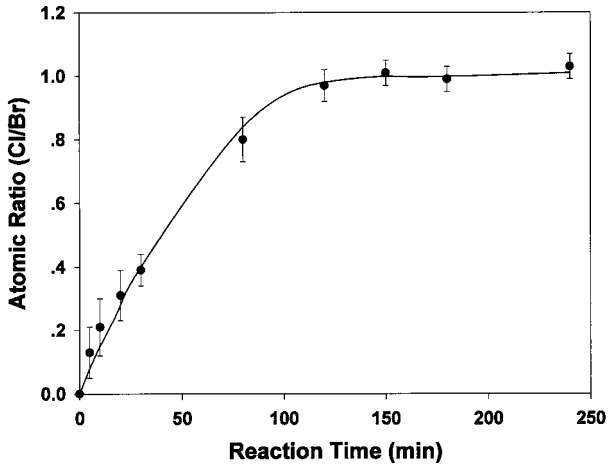
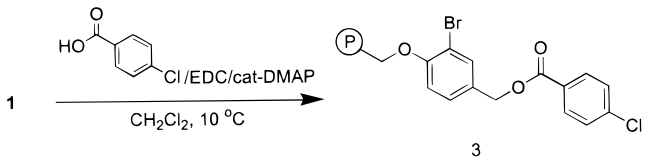


Figure 3. Reaction progress of Scheme 2. The XP spectra were taken from resin **3** at 0, 5, 10, 20, 30, 50, and 120 min after the initiation of esterification. The full formation of **3** was indicated by the stoichiometric atomic ratio of 1.

Scheme 2



resolving the small changes in electron binding energies corresponding to changes in the chemical states of the atoms, it might be possible to study the functional groups of different chemical states in polymer-bound compounds. The high-resolution XP spectra of the S 2p peaks of **6** and **7** display a change in binding energies from 163.8 to 168.4 eV, which are consistent with binding energies of thiolate and sulfonate, respectively (Figure 4). This analysis apparently indicates

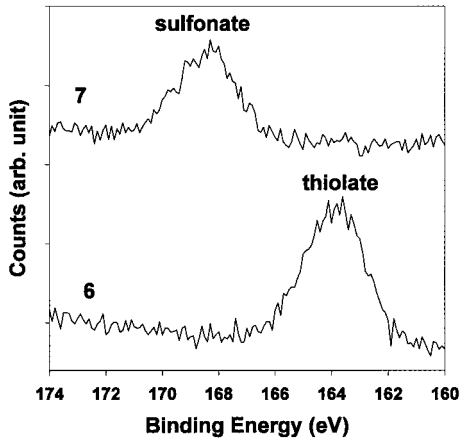


Figure 4. The high-resolution XP spectra of the S 2p peak of resins **6** and **7** display a binding energy change from 163.8 to 168.4 eV.

that the sulfur atom in **7** is indeed in a sulfonate form. The result demonstrates that XPS can also be a powerful technique for the analysis of the oxidation state of functional groups in the polymer-bound compounds.

In conclusion, we have demonstrated that XPS analysis, by incorporating a suitable heteroatom(s) in the linker part, can be a new powerful method for the identification of products and chemical states and for the progress of the reaction in a solid-phase synthesis. Studies for the improvement of this technique and the application in a real combinatorial synthesis are in progress.

Acknowledgment. This research was supported by the Ministry of Science and Technology of Korea.

Supporting Information Available. Experimental procedure for the synthesis of **1**−**7**, spectral and analytical data of **2** for the preparation of **1**, and IR and XPS data for **1** and **3**−**7**. This information is available free of charge via the Internet at http://pubs.acs.org.

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(9) Since XPS is a semiquantitative analysis technique, with an accuracy no better than a few percent,[8] it is difficult to determine accurately the small changes of the carbon and oxygen intensities using XPS without an internal standard.

(10) Torii, S.; Tanaka, H.; Siroi, T.; Akada, M. *J. Org. Chem.* **1979**, *44*, 3305.

(11) We discussed, in detail, the general method for XPS in the Supporting Information.

(12) X-ray photoelectron spectroscopy measurements were carried out in a UHV chamber, which has been described previously.[15] XP spectra were recorded on a VG Scientific ESCALAB MK II spectrometer using Mg Kα (source run at 15 kV and 10 mA). The binding energy scale was calibrated to 284.6 eV for the main C 1s peak. Each sample was analyzed at a 90° angle relative to the electron analyzer. Peak areas were calculated using Shirley background subtraction and were corrected by the elemental sensitivity factors.[8]

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(14) We also determined the progress of the same reaction (Scheme 2) by the IR method. However, we found that it was difficult to use for a quantitative purpose.

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