The Structure of Polymer-Supported Triphenylphosphine Ditriflate: A Potentially Useful Reagent in Organic Synthesis

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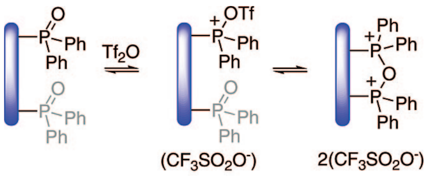

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The structure of a polymer-supported version of the Hendrickson "POP" reagent, prepared by the reaction of polymer-supported triphenylphosphine oxide **1** with triflic anhydride, is established as an equilibrium mixture of polymer-supported triphenylphosphine ditriflate **3** (δ 79.4 ppm) and polymer-supported phosphonium anhydride **4** (δ 73.3 ppm). The ^{31}P NMR chemical shift reported previously for **3** is shown to be incorrect.

The Hendrickson "POP" reagent[1,2] (triphenylphosphonium anhydride trifluoromethanesulfonate, or bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate **6**) brings about dehydrations and coupling reactions (such as ester and amide formation), in a similar manner to the Mitsunobu reaction[3–6] through what appears to be the same intermediate (an alkoxyphosphonium salt). In previous work,[7,8] it was shown that a polymer-supported version of this reagent could be readily prepared by reaction of the corresponding polymer-supported phosphine oxide with triflic anhydride (Tf$_2$O). This reagent has the advantage over the Hendrickson reagent that, unlike triphenylphosphine oxide (Ph$_3$PO), it is easily removed from the reaction product by simple filtration of the polymer beads. Moreover, it can be recycled and reused without loss of efficiency. The reagent is particularly useful in medicinal chemistry for the direct synthesis of sulfonamides from sulfonic acids and amines,[9] and since 2007, the precursor to the reagent, polymer-supported Ph$_3$PO, has been commercially available. We believe that this reagent has considerable potential in organic synthesis as a very powerful but mild dehydrating/activating agent. For example, it should prove useful as an alternative to the Hendrickson reagent for the synthesis of heterocycles such as oxazolines, thiazolines, and imidazolines.[10]

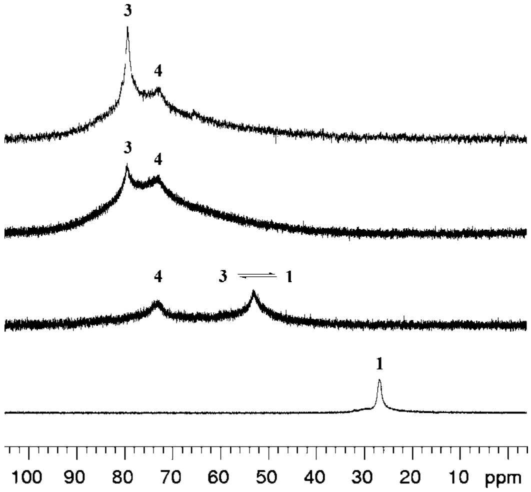

FIGURE 1. ^{31}P NMR stack spectra (162 MHz) of the addition of Tf$_2$O (0−4 equiv) to swollen, polymer-supported Ph$_3$PO beads, **1**, in CD$_2$Cl$_2$ at 25 °C (bottom to top): (a) 0, (b) 0.5, (c) 1.0, and (d) 4.0 equiv.

On the basis of ^{31}P NMR and other data, the structure of this polymer-supported reagent was assigned as **3** (where the majority of phosphoryl groups on the polymer bead were in the form of the ditriflate). However, characterization of **3** proved difficult due to its extreme sensitivity to moisture. Here, we provide evidence that the actual dehydrating reagent consists of a mixture of polymer-supported triphenylphosphine ditriflate **3** and polymer-supported triphenylphosphonium anhydride trifluoromethanesulfonate **4**.

Addition of freshly distilled Tf$_2$O (0.5 equiv) to an NMR tube of swollen, dried, polymer-supported Ph$_3$PO **1** in CD$_2$Cl$_2$ under nitrogen resulted in two peaks in the gel-phase ^{31}P NMR spectrum at δ 52.9 and 73.3 ppm, respectively (Figure 1b). When **1** was treated with 1.0 equiv of Tf$_2$O, the peak at δ 52.9 ppm was not observed. The original peak at δ 73.3 was still present, but in addition, a new peak appeared at δ 79.4 ppm

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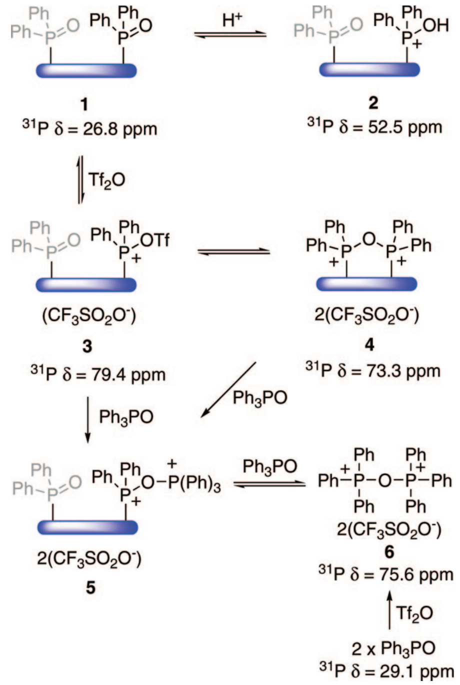
SCHEME 1. Formation of Polymer-Supported Reagent $3 \rightleftarrows 4$



(Figure 1c). The spectrum was unchanged after standing for 24 h. The relative intensity of the peak at δ 79.4 ppm increased as the Tf_2O was increased from 1 to 4 equiv (Figure 1d).

In the 0.5 equiv experiment, there is partial formation of the ditriflate **3**. Some of the phosphonium ditriflate [$Ph_2P(OTf)_2$] groups undergo further reaction with neighboring diphenylphosphoryl (Ph_2PO) groups on the polymer backbone to give anhydride (P−O−P) **4** (δ 73.3 ppm). However, such anhydride formation is presumably not possible for all $Ph_2P(OTf)_2$ groups on **3**, as not all would have a neighboring Ph_2PO group, and some would be more hindered or less accessible. This would mean that there should be three phosphorus species present, $Ph_2P(OTf)_2$ and Ph_2PO as shown in **3** and P−O−P as shown in **4**. We suggest that all three of these species are in equilibrium (Scheme 1). In the case of Ph_2PO (δ 26.8 ppm) and $Ph_2P(OTf)_2$ (δ 79.4 ppm), the equilibrium (represented by $\mathbf{1} \rightleftarrows \mathbf{3}$) must be fast (on the ^{31}P NMR time scale) to give a time-averaged peak at δ 52.9 ppm (very close to the calculated value of δ 53.1), whereas the equilibrium between **3** and **4** must be slow (on the ^{31}P NMR time scale) so that a separate signal is seen for the P−O−P species **4**. As expected, the gel-phase ^{31}P NMR signal for **4** (δ 73.3 ppm) is close to that of the solution-phase Hendrickson reagent **6** (δ 75.6 ppm).[11] The fact that the equilibrium between **1** and **3** is fast whereas that between **3** and **4** is slow (on the ^{31}P NMR time scale) is not surprising as the former involves a solution phase reagent (Tf_2O) interacting with Ph_2PO groups on the polymer, while the latter involves a gel-phase reaction where the relative movement of the phosphoryl groups is restricted by the (insoluble) cross-linked polymer network.

In the 1.0 equiv experiment (Figure 1c), there is sufficient Tf_2O to react with all of the Ph_2PO groups in **1**, so that only the ditriflate (**3**) and anhydride (P−O−P) species **4** are observed. With excess Tf_2O (4 equiv), the equilibrium shifts in favor of the ditriflate **3**.

It should be noted that there may be a contribution to the δ 52.9 ppm peak from the protonated polymer-supported Ph_3PO **2**, as a result of hydrolysis of some of the Tf_2O by adventitious moisture. Thus, treatment of **1** (δ 26.8 ppm) with 0.5, 1.0, and 2.0 equiv of triflic acid gave signals at δ 42.8 ppm (0.5 equiv), δ 52.5 ppm (1.0 equiv), and δ 56.0 ppm (2.0 equiv), respectively. Given the precautions taken in these experiments (Figure 1), and their reproducibility, this contribution should be minor. However, adventitious moisture may explain the previously reported ^{31}P NMR shift for **3** of δ 53.3 ppm.[4] Treatment of the polymer-supported reagent ($\mathbf{3} \rightleftarrows \mathbf{4}$, generated as before) with water (2 drops) resulted in immediate replacement of the peaks at δ 73.3 and 79.4 ppm by a peak at δ 38.2 ppm. This is consistent with hydrolysis to give a mixture of the starting material **1** (δ 26.8 ppm) in rapid equilibrium with the protonated phosphine oxide **2** (δ 52.5 ppm).

To provide further support for these assignments and equilibria, Ph_3PO (0.5 equiv relative to **1**) was added to the polymer-supported reagent ($\mathbf{3} \rightleftarrows \mathbf{4}$, generated as before). ^{31}P NMR signals were generated at δ 79.4, 75.6, and 52.9 ppm (relative amounts ca. 9:12:1). When 1.0 equiv of Ph_3PO was used, only the peaks at δ 75.6 and 52.9 ppm (ca. 5:2) remained. With excess Ph_3PO (4 equiv), a single peak at δ 40.7 ppm was observed.

A small amount of Ph_3PO (0.5 equiv) would be expected to react preferentially with the anhydride **4** to give the mixed anhydride **5** [reaction with $Ph_2P(OTf)_2$ groups in **3** would be slower as these groups were the ones that failed to form anhydride linkages previously, as a result of being more hindered or less accessible, therefore the ^{31}P NMR signal for **3** (δ 79.4 ppm) would remain]. The mixed anhydride **5** can undergo further reaction with Ph_3PO to give the Hendrickson reagent **6** (together with starting material **1**), or alternatively, a rapid (null) exchange reaction to give back **5**. This latter process would result in a time-averaged ^{31}P NMR signal of approximately δ 53 ppm arising from the Ph_3PO (δ 29.1 ppm),[12] polymer-supported Ph_3PO **1** (δ 26.8 ppm), and the "outer" phosphorus atom in **5** (ca. δ 75.6 ppm). Conversely, the "inner" phosphorus atom in **5** (the one attached directly to the polymer backbone) would not be subject to time-averaging and would therefore give a ^{31}P NMR signal of approximately δ 75 ppm (any conversion $\mathbf{5} \rightarrow \mathbf{4}$ would be expected to be slow on the ^{31}P NMR time scale by analogy with the equilibrium between **3** and **4**, while reaction between the two polymer beads **1** and **5** would be expected to be extremely slow). With excess Ph_3PO (4 equiv), there would be negligible **5** present and the ^{31}P NMR signal would be dominated by the exchange between **6** and Ph_3PO (i.e., the peak at δ 40.7 ppm).

It should also be noted that formation of the "POP" bond in **4** could be between separate polymer beads, or between phosphoryl groups on the same polymer bead. As the polymer loading is quite high (~3 mmol P/g of polymer, corresponding to almost 80% of the phenyl groups of the polystyrene backbone bearing a diphenylphosphoryl moiety), it might be expected that formation of a POP bond between adjacent phosphoryl groups on the same polymer bead, possibly to give a [3.3]paracyclophane-like structure **7**, would be most likely. The structure **7** would be expected to be more strained than [3.3]paracyclophane[13] itself due to the additional substituents on the ring and

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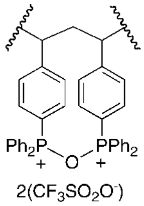
the fact that the POP linkage prefers to be linear.[14] However, examples of cyclic P−O−P compounds (such as **8** and **9**) where the P−O−P linkages cannot be linear are known.[15] As the concentration of phosphoryl groups within the swollen polymer bead is quite high, much larger rings containing P−O−P linkages could also be formed between phosphoryl groups in close proximity. Conversely, the likelihood of P−O−P formation between polymer beads seems much less likely given that these are insoluble polymer particles of the order of 0.05 mm in diameter. On a molecular scale, the polymer beads are huge and therefore their surface area is quite small.



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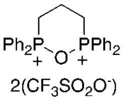

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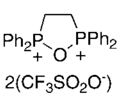

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Finally, it is interesting to note that the only product formed when Ph_3PO is treated with excess Tf_2O is the Hendrickson reagent **6**. Triphenylphosphine ditriflate is not observed. Such a species becomes possible, however, with polymer-supported Ph_3PO, where some of the phosphoryl groups are relatively inaccessible to attack by a second phosphoryl group, or where the formation of a POP species involves considerable ring strain.

In conclusion, these experiments provide evidence that the structure of the polymer-supported version of the Hendrickson "POP" reagent is an equilibrium mixture of polymer-supported triphenylphosphine ditriflate **3** (δ 79.4 ppm) and polymer-supported phosphonium anhydride **4** (δ 73.3 ppm). Or, more precisely, the polymer beads contain a mixture of $Ph_2P(OTf)_2$ and P−O−P groups. The ditriflate becomes the dominant structure only in the presence of excess Tf_2O. The fact that the structure consists of an equilibrium mixture of two distinct species does not appear to interfere with its use as a potent dehydrating agent.[7–9]

Experimental Section

Polymer-supported Ph_3PO, **1**, was prepared as described previously,[8] and dried under vacuum at 125 °C for 2 days, using a Kugelrohr oven.

^{31}P NMR spectra were determined at 162 MHz. In a typical procedure, the polymer beads were dried under high vacuum for 48 h prior to use. In a 5 mm NMR tube, dry polymer-supported Ph_3PO (75 mg, 0.23 mmol, 3 mmol/g) was allowed to swell in CD_2Cl_2 (750 μL) for 0.5 h to generate a gel-phase sample. Tf_2O (39 μL, 0.23 mmol) was added and the slurry mixed for 0.5 h. The ^{31}P NMR spectrum was then recorded at 25 °C.

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