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The mechanism of the first step of the Mitsunobu reaction

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ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

Keywords:

electrocyclic

betaine

Michael addition

O,N-phosphorane

Mitsunobu

ABSTRACT

Previous DFT calculations employing phosphine (PH₃) and dimethyl azodicarboxylate showed that a cyclic *O,N*-phosphorane was energetically favored relative to betaine formation. In this study strong experimental support for the formation of the phosphorane is described. The question of whether betaine formation occurs via nucleophilic attack of the phosphine on the azodicarboxylate as has been previously assumed, or via a [4+2] cycloaddition (cheletropic) reaction to give the *O,N*-phosphorane, followed by ring-opening to give the betaine has not been resolved. An answer to this intriguing question is provided.

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1. Introduction

The Mitsunobu reaction is one of the most useful reactions in organic synthesis, particularly for the inversion of configuration of secondary alcohols.¹ The first step in the Mitsunobu reaction involves reaction of triphenylphosphine (Ph₃P) with diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) to form a betaine **1** as originally proposed by Morrison² and substantiated by Brunn and Huisgen over 40 years ago.³

Three possible mechanisms have been proposed for the first step of the Mitsunobu reaction: (1) Michael-type nucleophilic attack by the phosphine on the azodicarboxylate (Scheme 1),²⁻⁴

Scheme 1. Nucleophilic Mechanism

(2) a single electron transfer (SET) process (Scheme 2),⁵ and (3) an initial [4+2] cycloaddition (cheletropic) reaction⁶ followed by ring-opening (Scheme 3).

Scheme 2. SET Mechanism

Each of these mechanisms is consistent with the observed second-order reaction kinetics,⁷ and the irreversibility of the

reaction.^{4,8} All three mechanisms appear *a priori* to be equally likely.

Scheme 3. Cheletropic Mechanism

The second possible mechanism appeared the most likely for a while following the discovery that radicals are formed in the Mitsunobu reaction^{5,9} (see later). However, in work that is not widely known, the SET mechanism has been excluded by Ebersson and co-workers using cyclic voltammetry. The SET reaction between Ph₃P and DEAD was found to be far too endergonic to be a realistic step under any conditions,¹⁰ leaving mechanisms (1) and (3) as contenders. As far as we are aware, there has been no definitive proof to exclude an initial cheletropic reaction followed by ring-opening as being the mechanism of formation of the Morrison-Brunn-Huisgen betaine **1**.

Recently, Anders et al¹¹ have performed an extensive density functional [BP86/6-311++G(3df,3pd) level] investigation of the hypersurface of the Mitsunobu reaction and shown that the first step can lead to either a five-membered oxadiazaphosphole ring (*O,N*-phosphorane) **2** or the betaine **1**. Interestingly, the *O,N*-phosphorane (**2**, R = H, R' = Me) was 12 kcal/mol more stable

than the betaine **1** ($R = H$, $R' = Me$) in acetonitrile. This suggests that the betaine **1** could indeed be formed via an initial [4+2] cycloaddition (cheletropic) reaction followed by ring-opening (Scheme 3). There are precedents for trivalent phosphorus compounds participating in cheletropic reactions. Thus, triphenylphosphite¹² and various cyclic phosphites¹³ react with azodicarboxylates to afford *O,N*-phosphoranes while halogenophosphines undergo [4+2] cycloaddition with *cis*-1,3-dienes, α,β -unsaturated ketones and α -dicarbonyl compounds to form five-membered ring phosphorus heterocycles.¹⁴

Only betaine **1** ($R = Ph$, $R' = Et$, *i*-Pr or *t*-Bu) has been observed by ³¹P NMR under typical conditions and not the corresponding *O,N*-phosphorane **2**. Moreover, the chemical shift of **1** ($R = Ph$, $R' = Et$, *i*-Pr or *t*-Bu) varies little with solvent polarity (e.g. $\delta_P +43.9$ /benzene to $+45.4$ /DMF for $R' = i$ -Pr) indicating that any equilibrium between an *O,N*-phosphorane **2** and betaine **1** lies very much towards the betaine.⁴

Anders et al.¹¹ point out that three phenyl ligands on phosphorus (rather than three hydrogens used in the calculations) can be expected to stabilize the betaine **1** relative to the *O,N*-phosphorane **2**, so we thought it would be of interest to investigate the reaction of 9-phenyl-9-phosphafluorene (**3**) with an azodicarboxylate. Phosphine **3** is a close analogue of triphenylphosphine but it contains a five-membered ring that should facilitate formation of a phosphorane.¹⁵⁻¹⁷

Scheme 4. Phosphorane formation with 9-phenyl-9-phosphafluorene

2. Results and Discussion

Treatment of 9-phenyl-9-phosphafluorene (**3**, 0.33 mmol) in tetrahydrofuran (THF, 2 mL) at 0 °C with DIAD (0.33 mmol) under nitrogen gave a yellow-orange solution, the ³¹P NMR spectrum of which showed a major peak at $\delta -33.6$ ppm, consistent with the formation of the spirophosphorane **4** ($R' = i$ -Pr). There was also a minor peak at $\delta +30.1$ ppm corresponding to the oxide of **3** [Lit¹⁸ $\delta +29.1$ (CDCl₃)]. Evidence for a rapid equilibrium between the phosphorane **4** ($R' = i$ -Pr) and the betaine **5** ($R' = i$ -Pr) was obtained from the marked solvent effect on the ³¹P NMR chemical shift (Table 1).

Table 1. ³¹P NMR data for Phosphorane **4**

Solvent	δ_P (ppm)
Benzene	-34.1
THF	-33.6
CH ₂ Cl ₂	-24.5
CH ₃ CN	-21.9

The formation of an *O,N*-phosphorane **4** rather than a betaine **5** with 9-phenyl-9-phosphafluorene (Scheme 4) provides strong experimental support for the results of the DFT calculations of Anders et al.¹¹

In order to distinguish between Michael-type addition (Scheme 1) or a pericyclic reaction (Scheme 3), a competition experiment involving reaction of DIAD with a mixture of Ph₃P and **3** was undertaken. The relative reactivity of cyclic versus acyclic trivalent phosphorus compounds has been reviewed by Hudson and Brown.¹⁹ Hence, when phosphorus acts as a nucleophile, as in a Michael-type addition, a small deviation from the C–P–C angle of Ph₃P (~100°) to near that of the tetrahedral angle of ~109° would occur. However, the C–P–C angle of the phosphafluorene ring of **3** is only 89°, so that an increase in ring strain would be expected when **3** reacts as a nucleophile and it would be expected to be *less reactive* than Ph₃P. On the other hand, in a cheletropic mechanism, the cyclic compound, **3**, should display *enhanced reactivity* relative to Ph₃P as formation of a pentacoordinate phosphorane would result in a decrease in ring strain.¹⁹ It is well known that the presence of a five-membered ring stabilizes pentacoordinate phosphoranes.¹⁵⁻¹⁷

Treatment of a 1:1 mixture of **3** (0.33 mmol) and Ph₃P (0.33 mmol) with a limiting amount of DIAD (0.33 mmol) under conditions similar to those employed above, resulted in the formation of two peaks at $\delta_P +43.8$ and -33.6 ppm in a 2:1 ratio, respectively. The downfield signal corresponds to **1** ($R = Ph$, $R' = i$ -Pr) while the upfield peak at -33.6 ppm is due to the spirophosphorane **4** ($R' = i$ -Pr). As expected, signals corresponding to the unreacted phosphines, Ph₃P ($\delta_P -5.2$ ppm) and **3** ($\delta_P -9.3$ ppm), were present in the complementary ratio of 1:2, respectively. Betaine formation in this system was irreversible. Thus, addition of **3** to **1** ($R = Ph$, $R' = i$ -Pr) resulted in no change to the ³¹P NMR spectrum. Similarly, addition of Ph₃P to **4** did not afford **1** ($R = Ph$, $R' = i$ -Pr) after one month at 4 °C. The irreversibility of betaine formation is consistent with the results of Crich et al.⁸ and, coupled with the mixed phosphine experiment, shows that Ph₃P reacts faster with DIAD than does **3**. This result is consistent with Michael-type nucleophilic addition and inconsistent with a pericyclic reaction. In the case of the phosphine **3**, the first step of the reaction involves nucleophilic addition to the azodicarboxylate to give the betaine **5** which subsequently undergoes ring-closure to give the more stable *O,N*-phosphorane **4**. It is interesting to note in this regard that Anders et al.¹¹ did not succeed in cleanly locating transition structures for the attack of PH₃ on the azodicarboxylate in either the gas phase or solution.

Analogous results were obtained when a 1:1 mixture of Ph₃P and **3** was treated with methyl iodide instead of DIAD, i.e. the Ph₃P reacted faster than the cyclic analogue **3**. Two peaks were observed by ³¹P NMR spectroscopy ($\delta_P +23.2$ and $+26.7$ ppm, THF) in a 4:1 ratio corresponding to the methiodide salts of Ph₃P and **3**, respectively. This confirms the nucleophilic nature of both the alkylation reaction and the Michael-type addition to the azodicarboxylate.

In addition to the P–N betaine **1** formed initially in the Mitsunobu reaction employing Ph₃P and either DEAD or DIAD, a minor reaction pathway results in the formation very small amounts of the radical species **7** and **8**.^{5,9,10} These radicals are formed^{9,10} by oxidation of the P–O betaine **6** by excess DIAD or DEAD (or if the Ph₃P is added to the azodicarboxylate rather

than the other way around). The P–O betaine **6** could be formed directly by Michael-type addition to the carbonyl oxygen (Scheme 5) or by “normal” betaine formation (Scheme 1) followed by ring-closure to give the *O,N*-phosphorane **2** (R = Ph, R' = Et or *i*-Pr) and then ring-opening at the P–N bond rather than the P–O bond. Both radical species **7** and **8** are decomposed immediately by carboxylic acids and do not appear to be involved in normal Mitsunobu reactions.

Scheme 5. Formation of radicals in the Mitsunobu reaction

3. Conclusions

Evidence is provided that the first step in the Mitsunobu reaction, the reaction of a phosphine with DIAD or DEAD, can produce either an *O,N*-phosphorane or a betaine, depending on the phosphine employed. This represents the first experimental confirmation of previous DFT predictions. Evidence is also provided for a rapid equilibrium between the *O,N*-phosphorane and the corresponding betaine. Significantly, we now know that the first step in the Mitsunobu reaction proceeds via a Michael-type nucleophilic attack by the phosphine on the azodicarboxylate, and not via a concerted pericyclic reaction or a SET mechanism.

4. Experimental Section

Materials. Triphenylphosphine, diisopropyl azodicarboxylate, and methyl iodide were commercial samples and used without further purification. THF was dried and distilled prior to use. 9-Phenyl-9-phosphafluorene (**3**) was synthesized according to the procedure of Nesmeyanov et al.²¹

³¹P NMR competition experiments. Ph₃P (94.4 mg, 0.36 mmol) and 9-phenyl-9-phosphafluorene (93.6 mg, 0.36 mmol) were dissolved in dry THF (3 mL) under nitrogen in a 10 mm NMR tube. The solution was cooled to 0 °C and DIAD (18 µL, 0.09 mmol) then added dropwise over 1 min to the swirled, cooled solution. A cap was placed on the tube and sealed with Parafilm before recording the ³¹P NMR spectrum at 10 °C on a 300 MHz instrument within 5 min. The experiment was repeated using methyl iodide in place of DIAD. All spectra were acquired at an operating frequency of 121.47 MHz using a 45° flip angle, 3 s recycle delay, and a 0.33 s acquisition time with gated decoupling. Negative ³¹P chemical shifts are upfield of external phosphoric acid (85%).

Acknowledgement.

We thank Griffith University for financial support.

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