

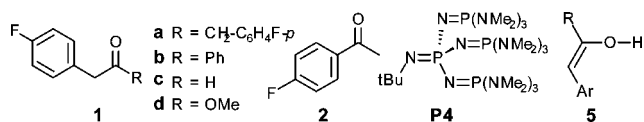
## Stabilization of Ketone and Aldehyde Enols by Formation of Hydrogen Bonds to Phosphazene Enolates and Their Aldol Products

Kristopher J. Kolonko and Hans J. Reich\*

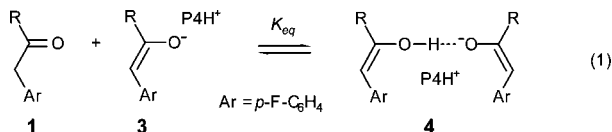
Department of Chemistry, University of Wisconsin, 1101 University Avenue, Madison, Wisconsin 53706

Received June 4, 2008; E-mail: reich@chem.wisc.edu

The strong nonmetallic phosphazene or “Schwesinger” bases<sup>1</sup> have found a variety of uses, from enolate and peptide alkylations<sup>2a</sup> to catalytic aldol reactions,<sup>2b</sup> desilylations<sup>2c</sup> and even aromatic<sup>2d</sup> and alkynyl<sup>2e</sup> deprotonations. The anionic species produced by deprotonation with Schwesinger bases have been termed “naked” due to the noncoordinating phosphazene counterion. The few reported studies of the solution structure of these species have focused on ester enolates whose behavior is complicated by decomposition reactions.<sup>3</sup> Here we report NMR solution studies of phosphazene enolates formed by deprotonation of *p,p'*-difluorodibenzyl ketone (**1a**), 1-phenyl-2-*p*-fluorophenylethanone (**1b**), *p*-fluorophenylacetaldehyde (**1c**), methyl *p*-fluorophenylacetate (**1d**) and *p*-fluoroacetophenone (**2**) with <sup>t</sup>Bu-P4 (**P4**, p*K*<sub>BH+</sub> (MeCN) = 42.6<sup>1</sup>).



A full equivalent of **P4** base quantitatively deprotonated **1a** to generate a single species. The much larger <sup>13</sup>C chemical shift difference of the vinyl carbons compared to the lithium enolate dimer<sup>4,5</sup> suggest the formation of a “naked” P4H<sup>+</sup> enolate **3a**.



Addition of smaller increments of **P4**, however, unexpectedly formed a different intermediate enolate species (Figure 1). At 0.25 equiv of **P4** at  $-125\text{ }^{\circ}\text{C}$  no **3a** was present, and half of the ketone **1a** was converted to this new species, which becomes the major component ( $\geq 95\%$ ) at 0.5 equiv of base. Further addition of **P4** converted the intermediate to **3a**. The vinyl carbon <sup>13</sup>C shifts of the new species were similar to those of the dimeric lithium enolate,<sup>4,5</sup> as were the two signals in the <sup>19</sup>F NMR spectrum. On the basis of this data, as well as the observation of a downfield singlet at  $\delta$  18.4 in the <sup>1</sup>H NMR spectra, which is characteristic of low-barrier hydrogen bonds (LBHB),<sup>6</sup> we have identified it as the enol-enolate H-bonded dimer **4a**.<sup>7,8</sup> The H/D isotope shift was +0.35 (D upfield), consistent with a strong unsymmetrical LBHB.<sup>6</sup> Evidently the strength of this hydrogen bond is sufficient to overcome the unfavorable keto–enol equilibrium.

All three components in these equilibria (eq 1) are in slow exchange on the NMR time scale below  $-15\text{ }^{\circ}\text{C}$ . With 0.5 equiv of **P4** at  $-35\text{ }^{\circ}\text{C}$  **1a**, **3a**, and **4a** are present in a 1:2.4:7 ratio, giving an association *K*<sub>eq</sub><sup>a</sup> of 650 M<sup>-1</sup>. Free energies of activation for the exchange of **3a** and **4a** at several ratios of **3a** to **4a** were measured by <sup>19</sup>F DNMR at  $-25\text{ }^{\circ}\text{C}$ , and were found to be independent of the concentration of **3a**. Thus, this is a unimolecular dissociation

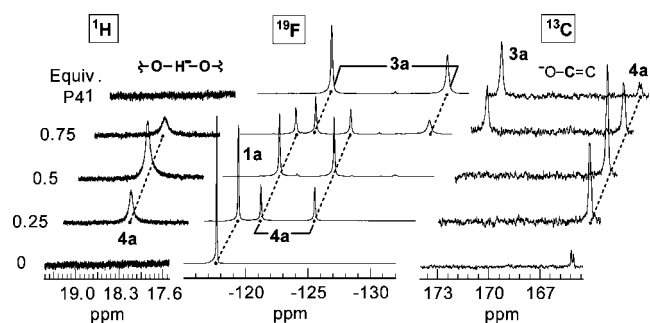


Figure 1. Titration of ketone **1a** with **P4** at  $-125\text{ }^{\circ}\text{C}$  in 3:2 THF/ether.

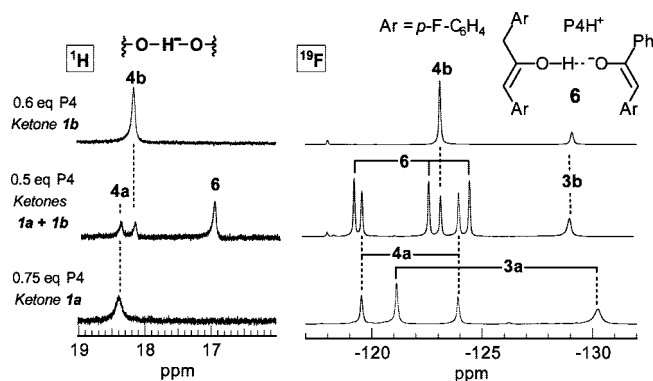


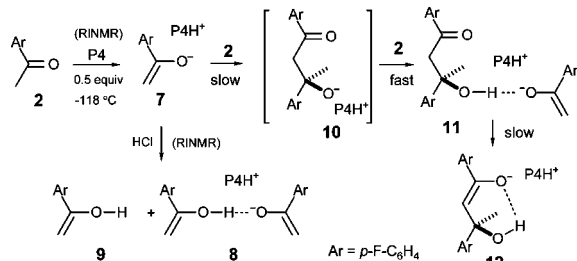
Figure 2. Mixing experiment with **P4** and ketones **1a** and **1b** at  $-125\text{ }^{\circ}\text{C}$  in 3:2 THF/ether.

of **4a** to its components, and the barrier of 11.4 kcal/mol represents an upper limit on the strength of the hydrogen bond.

Injection of ethereal HCl or HBF<sub>4</sub> into a solution of **3a** using RINMR<sup>9</sup> gave solutions of the enol **5a**, which were stable for hours at  $-118\text{ }^{\circ}\text{C}$ , allowing full spectroscopic characterization.<sup>4</sup> If less than 1 equiv of acid was added, mixtures of **1a**, **4a**, and **5a** were formed. The enol, like the enolate, was in slow dynamic exchange with the H-bonded dimer **4a** below  $-120\text{ }^{\circ}\text{C}$ .

We investigated other enolizable carbonyl compounds to see if H-bonded dimers were commonly formed during deprotonations with **P4** base. Ketone **1b** also gave a preponderance of the H-bonded dimer **4b** at substoichiometric amounts of **P4**, although the equilibrium was less favorable than for **1a** (*K*<sub>eq</sub><sup>b</sup> = 13 M<sup>-1</sup> at  $-37\text{ }^{\circ}\text{C}$ ).

Further evidence for the dimeric nature of the H-bonded structures was obtained by titrating **P4** into a 1:1 mixture of ketones **1a** and **1b**. This produced the two homo H-dimers **4a** and **4b** at  $<0.5$  equiv of **P4**, as well as a new mixed H-dimer **6** (Figure 2). It is surprising that **6** forms in larger than statistical amounts, even though the upfield <sup>1</sup>H shift of the H-bonded proton (from  $\delta$  18.4 for **4a** to 16.9 for **6**) suggests a weaker H-bond interaction.<sup>10</sup> Increasing the amount of **P4** to 0.75 equiv produced a solution of



**Figure 3.** Self-aldol reaction of **2** at  $-125\text{ }^{\circ}\text{C}$  in 3:2 THF/ether. In the first step, **2** was injected into a solution of **P4**.

the H-dimer **4a** and the enolate **3b**, with **P4** preferentially deprotonating the more acidic ketone **1b**. At a full equivalent of base, the solution consisted of the enolates **3a** and **3b**.

Like **1a**, the aldehyde **1c** is converted quantitatively to the enolate **3c** with 1 equiv of **P4**. At lower equivalents the H-bonded dimer **4c** (mixture of *E/Z* isomers) is the major species formed (60% at 0.5 equiv of **P4**), but there are several minor components that have not been identified (possible aldol products). Because of their high propensity for aldol reactions, aldehyde metal enolates have been rarely studied spectroscopically.<sup>11</sup>

The interaction of ester **1d** with **P4** has been previously studied.<sup>3</sup> We find that **P4** stoichiometrically forms the enolate **3d** at  $-120\text{ }^{\circ}\text{C}$ , with no indication of any H-bonded dimer **4d** or Claisen products. Apparently the energetic cost of enolization of **1d** to **5d** outweighs the stabilizing effect of H-bond formation. Even the RINMR injection of HCl into the enolate at  $-135\text{ }^{\circ}\text{C}$  failed to form either **4d** or the ester enol **5d**, only **1d** was detected.

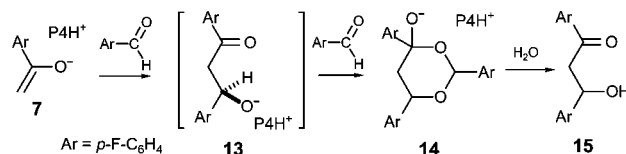
The effect of **P4** on *p*-fluoroacetophenone (**2**) was more complex. Unlike the behavior of **1a**, the addition of 0.5 equiv of **P4** to solutions of **2** at  $-78\text{ }^{\circ}\text{C}$  did not produce the H-dimer **8**, but instead the ketone self-aldol condensation product **12**. RINMR experiments using  $^{19}\text{F}$  and  $^1\text{H}$  NMR spectroscopy in which **2** was injected into a solution of **P4** at  $-118\text{ }^{\circ}\text{C}$  initially produced the enolate **7** ( $t_{1/2}$ , ca. 1 min), followed by a self-aldol process with a  $t_{1/2} = 30$  min (Figure 3). During the first 10 min a small amount of H-bonded dimer **8** (3.5% compared to **7**) was detected.<sup>12</sup> The first-formed product was a new species which we have identified as a 1:1 aldolate enolate hydrogen bonded complex **11** ( $\delta_{\text{OH}}$  12.4).<sup>13</sup> The rate of formation of **11** was first order in **2** and **7** and showed a deuterium isotope effect of 1.0 when  $\alpha$ -trideuterated **2** was used. Intermediate **11** was then converted over several hours to the final stable product of this sequence, the hydrogen-bonded aldolate enolate **12** ( $\delta_{\text{OH}}$  11.7). This conversion showed a H/D kinetic isotope effect of 2.4.

From these and other observations we conclude that the H-dimer **8** is in an unfavorable equilibrium with the enolate **7** and ketone **2**. Formation of the aldolate **10** is the rate determining step, but none was detected since it rapidly deprotonates another ketone producing the observed **11**. Finally, **11** is converted by proton transfer and loss of ketone in an irreversible step to **12**.

In comparison, the reaction of **7** with *p*-fluorobenzaldehyde was too fast to measure at  $-127\text{ }^{\circ}\text{C}$  by RINMR ( $k_{\text{obs}} \geq 2\text{ s}^{-1}$ ).<sup>14</sup> Based on temperature extrapolation of the rate of reaction of **2** with **7**, the aldehyde is at least 50000 times as reactive as the ketone. Interestingly, the first-formed aldolate **13** was again not detected. The products were acetal 1:2 adducts (**14**),<sup>15</sup> in which the aldolate is stabilized by addition to a second equivalent of aldehyde.

We have identified and characterized several phosphazanium enolates generated with **P4**. Some of these enolates (**3a**, **3b**, and **3c**) form unique kinetically stable hydrogen-bonded dimeric

structures (**4**) when excess carbonyl compound is present, and these are thermodynamically more stable than the isomeric aldolates. This “self-enolization” clearly has relevance to the role that LBHBs play in enzyme catalyzed enolizations.<sup>16</sup> Carbonyl compounds with less favorable keto–enol equilibria do not form such dimers (**1d**), or form them only transiently (**2**). In the latter case we were able to follow the self-aldol condensation and elucidate its mechanism.



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**Supporting Information Available:** Experimental details and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- Transient solutions of **8** ( $t_{1/2} = \text{ca. } 5\text{ s}$ ), and **9** ( $t_{1/2} = \text{ca. } 30\text{ min}$ ) could be formed by injection of HCl-etherate into solutions of **7** in 3:2 THF/ether at  $-118\text{ }^{\circ}\text{C}$ . More stable solution of **8** ( $t_{1/2} = \text{ca. } 15\text{ min}$ ), and **9** ( $t_{1/2} > 2\text{ h}$ ) were formed in Me<sub>2</sub>O at  $-138\text{ }^{\circ}\text{C}$ , which allowed characterization by  $^{19}\text{F}$ ,  $^1\text{H}$ , and  $^{13}\text{C}$  NMR spectroscopy.
- Compound **11** could be fully characterized by  $^{13}\text{C}$ ,  $^1\text{H}$ ,  $^{31}\text{P}$ , and  $^{19}\text{F}$  NMR spectroscopy. Saturation transfer measurements showed the enolate portion of **11** to be in exchange with the enolate **7** in solution.
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