Methyl phenylacetate enolate generated with the P4-*t*Bu Schwesinger base: 'naked' or not?

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Abstract—NMR studies revealed that methyl phenylacetate enolate generated with the P4-*t*Bu phosphazene base was 'naked' or tightly associated with P4-*t*BuH$^+$ cation depending on very small variations in solvent composition. Both forms reacted more rapidly than the corresponding lithium enolate in a model alkylation experiment using dimethyl sulfate. © 2001 Elsevier Science Ltd. All rights reserved.

Schwesinger phosphazene bases[1] are useful reagents in organic synthesis and have been used in miscellaneous applications both in solution[2] and on a solid phase.[3]

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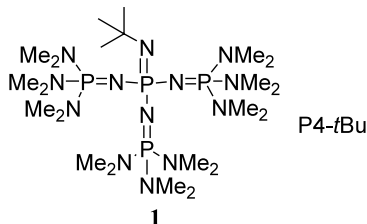
In particular, the P4-*t*Bu base **1**, is an extremely strong [pK_{BH^+} (THF) 28.0)], neutral and metal-free base, which, following abstraction of a proton, has its positive charge delocalized over a volume of ca. 500 Å^3. The P4-*t*Bu base has been found to generate anionic species of extraordinary reactivity, allowing conversions that have otherwise not been possible, particularly in the field of enolate chemistry. The high reactivity of P4-*t*Bu enolates has often been attributed to the formation of 'naked' anions, even if this point has never been precisely addressed. To shed light on this important aspect of enolate chemistry, we have studied the behavior of P4-*t*Bu methyl phenylacetate enolate **3** in solution by ^{1}H and ^{13}C NMR (Scheme 1), and evaluated the impact of structural changes upon its reactivity in a model alkylation experiment.

Methyl phenylacetate **2** was chosen for this study since it was expected to be a good 'sensor' of enolate structure according to litterature data. Indeed, Corset et al. have extensively studied Na, Li and K enolates of methyl and *t*Bu phenylacetates by IR and ^{13}C NMR.[4] The extent of association of the enolate with the cation and its state of aggregation can be estimated by the ^{13}C-4 negative shift relative to the starting ester, which is influenced by the charge delocalization of the enolate into the phenyl ring.[5] The K methyl phenylacetate enolate in THF or DMSO, and the Li methyl phenylacetate enolate in DMSO or THF/HMPA are free ions or solvent-separated ion pairs. Consequently, the corresponding ^{13}C-4 negative shift of about −15 ppm (^{13}C-4 at about 112 ppm) was found to be maximal. Alternately, Li methyl phenylacetate enolate in THF was found to exist as solvated tight ion pairs (^{13}C-4 at 117.0 ppm) or dimers (^{13}C-4 at 118.5 ppm). The strong O$^-$Li$^+$ interaction within the ion pairs results in a reduction of charge delocalization, which is more pronounced in the aggregated species.[6]
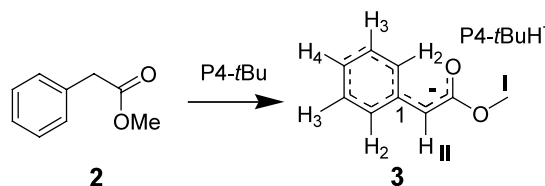
Scheme 1.

The aromatic regions of ^{1}H and ^{1}H–^{13}C HSQC NMR spectra of enolate **3** in THF/hexane: 9/1 (by vol) are shown in Fig. 1a. The signals at 5.89 ppm (^{13}C 111 ppm) and 6.57 ppm (^{13}C 127.3 ppm) corresponded to H-4 (C-4) and H-3 (C-3), respectively. H-2 protons appeared as a very large signal centred at about 7.20 ppm. H-II was found at 3.83 ppm (^{13}C-II 67.4 ppm) and only one isomer was observed.[7] The high $\Delta\delta$ ^{13}C-4 shift indicates that enolate **3** was present as a 'naked' enolate using these experimental conditions. Lowering the temperature down to 223K permitted the acquisition of a ^{1}H spectrum at a slow exchange regime (Fig. 1b, intermediate exchange was observed at 260 K). In this spectrum, H-2 protons were found at 8.12 and 6.21 ppm, and the H-3 protons were split into two triplets situated at 6.51 and 6.64 ppm. This behaviour is probably the consequence of the charge delocalization of the enolate into the aromatic ring which confers to C-II-C-1 some double bond character.

Spectra of enolate **3** in THF/hexane: 8.4/1.6 (by vol) were found to be similar to the previous one at 300 or 223K ('naked' enolate). The linewidth was found to be slightly larger but the intermediate exchange was also observed at 260K. Surprisingly, increasing further the hexane concentration (THF/hexane: 7.8/2.2 by vol) led to completely different ^{1}H and ^{13}C spectra (Fig. 1c). Signals corresponding to the 'naked' enolate were not observed. All the aromatic protons were shifted to lower fields. In particular, H-4 was found at 7.08 ppm and was correlated in the ^{1}H–^{13}C HSQC spectrum to C-4 situated at 122.5 ppm. H-2 protons were clearly detected at 7.49 ppm as a doublet, indicative of a free rotation around the C-II-C-1 bond.[8] The fact that the ^{13}C-4 chemical shift is larger than that found in tight ion pairs or dimers of Li methyl phenylacetate enolate in THF is particularly noteworthy. These data suggest a tight interaction of P4-tBu^{+} cation with the enolate, which results in a diminished delocalization of the negative charge into the phenyl ring.

The fact that the 'naked' to 'tight ion pair' transition occurs following a slight modification of hexane concentration (16–22% by vol) shows that the interpretation of P4-tBu enolate reactivity must be tackled with great care, especially when there is no available data allowing an easy determination of enolate structure as in the case of methyl phenylacetate. We have examined the influence of P4-tBu enolate structure upon its reactivity in a model alkylation experiment. The enolate was generated as 'naked' or 'tight ion pair' species and reacted at −50°C with dimethyl sulfate. The yield of alkylation was estimated following quenching with acetic acid and RP-HPLC analysis (Fig. 2). The enolate was found to be slighly more reactive in the 'naked' than in the 'tight ion pair' form, but in both cases, alkylation of enolate **3** was very rapid since conversion was complete following 1 min of reaction. Interestingly, the 'tight ion pair' form reacted significantly more rapidly than the Li enolate, which as indicated before, adopts a tight ion pair or dimer structure in THF.[9]

In conclusion, the data presented in this letter shows that P4-tBu enolates are not necessarily 'naked', and that the 'naked' to 'tight ion pair' transition may occur following a slight modification of solvent composition. For methyl phenylacetate, the structure of the P4-tBu enolate has a minor impact upon its reactivity. However, in other cases, the situation may be different. So, it seems important, when working with P4-tBu base, to check the influence of hexane concentration (the P4-tBu base is sold 1M in hexane) on the kinetics and stereochemistry of the reaction.
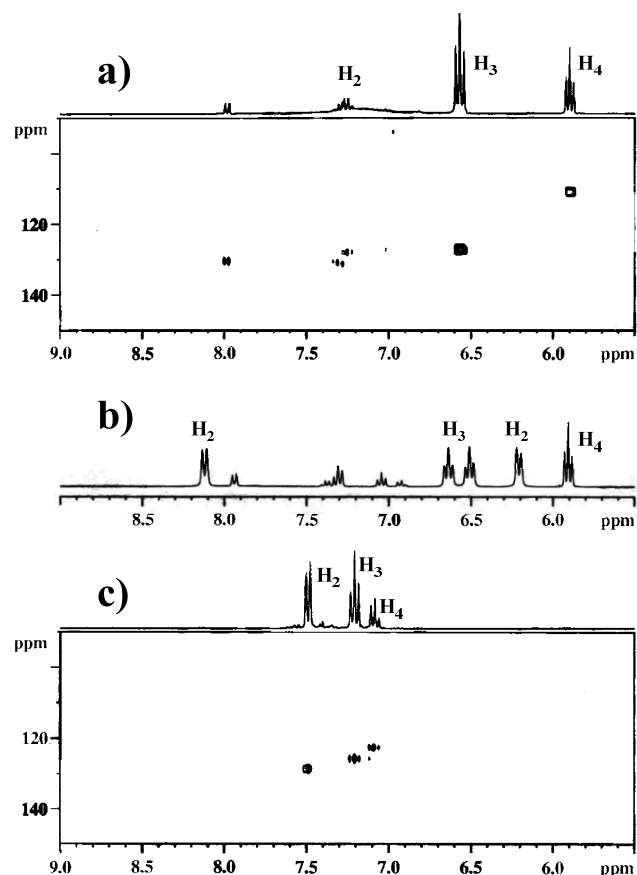

Figure 1. ^{1}H and ^{1}H–^{13}C HSQC spectra (300 MHz) of enolate **3**. (a) THF-d_8/hexane: 9/1 by vol at 300 K; (b) THF-d_8/hexane: 9/1 by vol at 223 K; (c) THF-d_8/hexane: 7.8/2.2 by vol at 300 K.
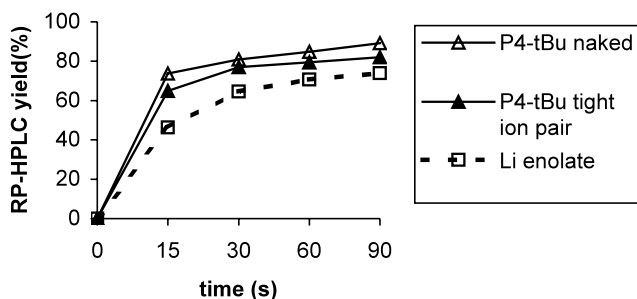

Figure 2. Alkylation of P4-tBu or Li methyl phenylacetate enolate with dimethyl sulfate.

Acknowledgements

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6. The degree of aggregation of aryl amides or aryl ketone enolates has been found to influence the ^{13}C chemical shifts, with the less aggregated species exhibiting higher C-4 upfield shifts, see: (a) Jackman, L. M.; Scarmoutzos, L. M. *J. Am. Chem. Soc.* **1987**, *109*, 5348; (b) Jackman, L. M.; Smith, B. D. *J. Am. Chem. Soc.* **1988**, *110*, 3829.

7. This isomer is probably the Z-enolate. According to Ref. 4, free ions or cryptand-separated ion pairs of K or Li phenylacetate enolate display essentially the Z geometry.

8. Only one signal was observed for H-II (3.74 ppm, correlated in the ^{1}H–^{13}C HSQC spectrum with C-II situated at 65.7 ppm), but methyl protons displayed two singlets at 3.40 and 3.47 ppm (^{13}C 45.8 and 47.4 ppm, respectively). Li methyl phenylacetate enolates in THF (tight ion pairs or dimers) were found essentially in the E configuration. Two conformers around the C-OMe bond were observed by IR spectroscopy.

9. Li methyl phenylacetate enolate was generated at −50°C (0.07 M) in THF using lithium diisopropylamide. Li methyl phenylacetate enolate has been shown to adopt a tight ion pair or dimer structure in THF in a broad concentration range (0.25–0.025 M), see Ref. 4.