Observation of a Betaine Lithium Salt Adduct During the Course of a Wittig Reaction

Robert A. Neumann and Stefan Berger*

Institut für Analytische Chemie,
Linnéstraße 3, D-04103 Leipzig
Fax: (internat.) +49(0)341/9711833 or 9736115
e-mail: stberger@rz.uni-leipzig.de

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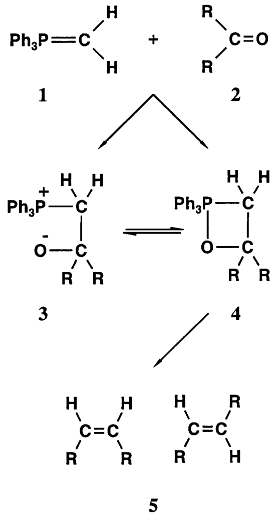
A stable betaine lithium salt adduct is observed during the course of a Wittig reaction. The stabilization of this adduct has been achieved by complexation with lithium ions and by using the chelating effect of pyridyl ligands. Dynamic NMR spectra are observed when the corresponding oxaphosphetanes complex with sodium or lithium ions.

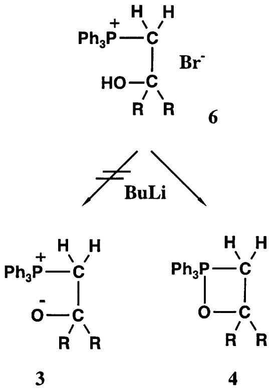
The Wittig reaction between ylides (**1**) and aldehydes or ketones (**2**) to form olefins (**5**) is one of the fundamental transformations in organic chemistry[1] and is constantly used in natural product synthesis as well as industrial synthesis[2] (see Scheme 1).

Scheme 1



The mechanism of the reaction, however, is still being debated.[3][4] Whereas in his first publication[5] G. Wittig proposed oxaphosphetanes (**4**) as intermediates, the subsequent literature[6] postulated betaines (**3**) even after in 1973 Vedejs[7] was able to demonstrate unequivocally by ^{31}P NMR the occurence of only oxaphosphetanes. Indeed, since then, no direct spectroscopic proof for the possibility of the existence of betaines has been published to our knowledge. Early postulations, mainly put forward by Schlosser and others, lacked convincing spectroscopic evidence.[8] With the Rapid Injection NMR (RI) technique we have not been able to observe these species,[9] even not in the case, when the synthesis of a betaine was attempted from a β-hydroxy phosphonium salt (**6**).[10] Deprotonation of **6** with butyllithium under RI conditions[9] did not reveal ^{31}P NMR signals in the expected betaine chemical shift region of $\delta_P = +10$ to $+30$ (see Scheme 2) but instead showed a signal consistent with an oxaphosphetane.

Scheme 2



In a recent communication it was shown by Ustynyuk[11], that thiobetaines can be formed during the reaction of ylides with thioketones. Subramanyam[12] reported the failure of a Wittig reaction when triphenylmethylenephosphorane (**1**) and 2,2′-dipyridyl ketone were allowed to react after generation of the ylide using butyllithium as base. Substituting lithium by potassium, however, resulted in the normal olefin formation. This behaviour was explained by the proposal of the formation of betaine (**3a**) complexed by a lithium ion; however, no spectroscopic evidence has been given. The chelating effect of the pyridyl nitrogen atoms should stabilize the betaine form according to the author. We have reported[9] earlier on the complexation of oxaphosphetanes by lithium ions and were thus prepared to investigate the reaction of Subramanyam in detail. Here we wish to report the first direct spectroscopic evidence of the formation of a betaine lithium salt adduct during the course of a Wittig reaction.

1434–193X/98/0606–1085 $ 17.50+.50/0

Scheme 3

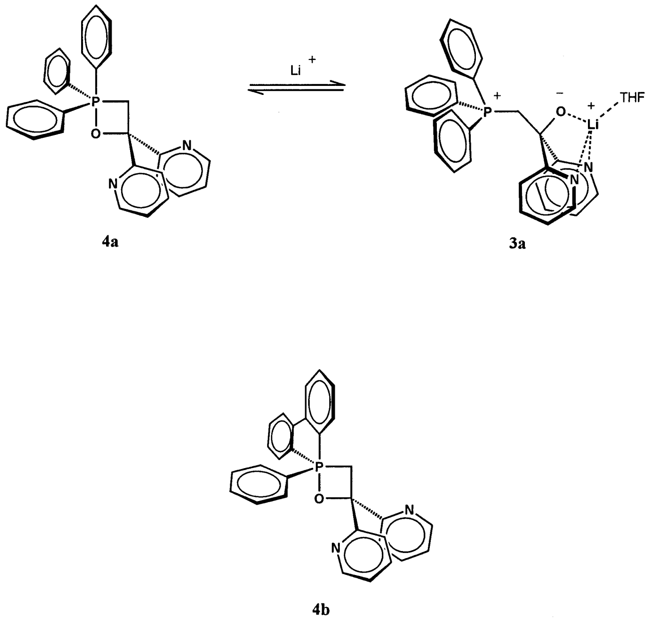
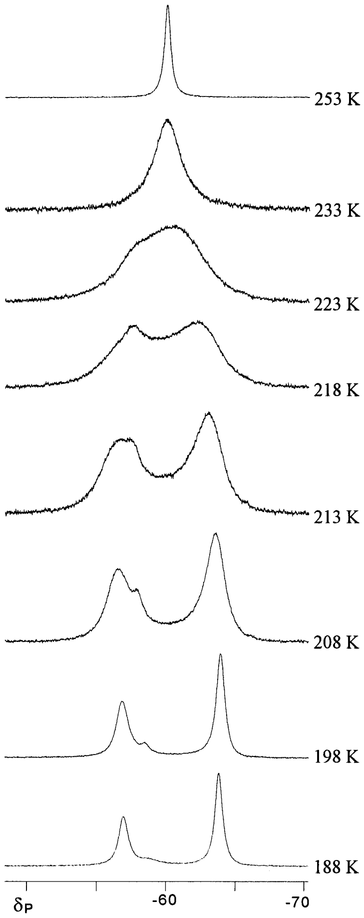


Figure 1. Temperature-dependent ^{31}P NMR spectra of **4a** in the presence of NaI in THF



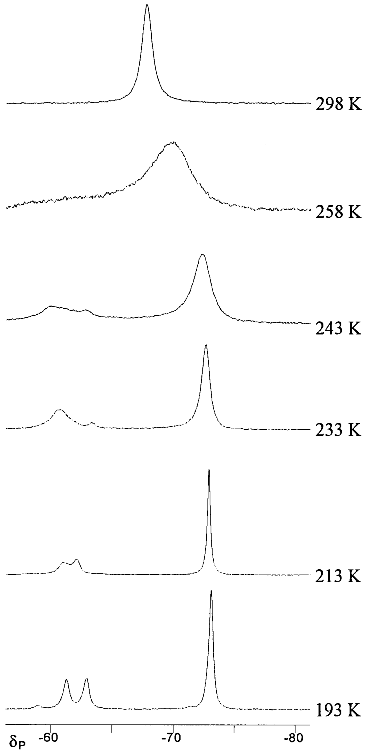
Using sodium hexamethyldisilazide as base[13] to generate the ylide **1**, followed by treatment with 2,2′-dipyridyl ketone results in the formation of the corresponding oxaphosphetane **4a**. The ^{31}P NMR spectrum reveals only a singlet at $\delta_P = -63.2$. On addition of lithium bromide, the signal of **4a** disappears and a weak signal at $\delta_P = +23.7$ emerges from the spectrum. The recording of this signal, however, is hindered by precipitation of solid material. We ascribe the resonance signal to betaine **3a**, because by addition of 12-crown-4 to scavenge the lithium ion one can observe the reformation of oxaphosphetane **4a**. The high insolubility of **3a** prevented so far the growing of crystals suitable for an X-ray determination and the recording of ^{13}C NMR spectra; however we could purify the material to the extent that a solid state CP/MAS ^{31}P NMR spectrum[14] could be recorded under high power proton decoupling at a spinning speed of 4000 Hz; it reveals only one signal at $\delta_P = +16.8$. If one tries to redissolve this material in DMSO or acetonitrile, the Wittig reaction sets in as shown by an olefinic signal in the proton NMR spectrum.

Replacing two phenyl groups in **1** by the 2,2′-biphenyl ligand should stabilize the oxaphosphetane making ring opening and olefin formation less likely.[15] Indeed, we were able to prepare this rather stable oxaphosphetane **4b** and we find for this oxaphosphetane dynamic NMR spectra as reported earlier[9] for other oxaphosphetanes. Both lithium and sodium ions are complexed, and free and complexed form are in dynamic equilibrium. In this case, ring opening to a betaine is probably prevented due to the chelating bite angle of the biphenyl ligand preferring fivefold coordination at the phosphorus atom.

A typical dynamic NMR spectrum in the presence of sodium ions is shown for **4a** in Figure 1, where we ascribe the two signals at the low temperature limit to the complexed and free form of the oxaphosphetane. Addition of lithium ions to **4a** leads immediately to the precipitation of betaine **3a**, as described above. In addition to the two main signals which coalesce at about 223 K below 210 K a third weak signal is observed which is probably due to double complexation. Neglecting this signal, the dynamic NMR spectra were analyzed by line shape analysis and the thermodynamic parameters have been determined. We find an activation energy $\Delta G^{\neq}(298)$ of 43 kJ/mol with an activation enthalpy $\Delta H^{\neq}$ of 25 kJ/mol and an activation entropy $\Delta S^{\neq}$ of -60 J/mol. The large negative entropy value clearly indicates an intermolecular exchange process which corroborates our interpretation. On cooling of a solution of **4b** in the presence of lithium ions (Figure 2) quite similar spectra to those shown in Figure 1 are registered. At very low temperatures the spectra are even more complex and give at least four signals which are interchanging with each other. Subsequent addition of sodium or lithium ions changes the relative intensity of these signals.

Though the stereochemical consequences of carrying out the Wittig reaction under "lithium salt free" and "lithium salt containing" conditions are very well known[13], they are not really understood at present. Our dynamic NMR spectra show physical evidence of the interaction of metal salts with oxaphosphetanes. Although this happens in a temperature regime where the oxaphosphetanes are stable and the

Figure 2. Temperature-dependent ^{31}P NMR spectra of **4b** in the presence of LiBr in THF



second part of the Wittig reaction has not yet set in, it could well be, that this complexation is responsible for the stereochemical outcome.

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Experimental Section

1. Dynamic NMR Measurements: Low temperature ^{31}P NMR: Bruker AM-400 NMR spectrometer in THF using a 10-m multinuclear probe head under standard measurement condition and proton decoupling.

2. Synthesis: For the preparation of the oxaphosphetane **4a** 0.81 g (2.0 mM) of triphenylmethylphosphonium iodide were suspended in 10 ml dry THF. To this suspension 1 equiv. NaHMDS in 2 ml THF (Aldrich) were added at −15°C and stirred for 30 min. The reaction mixture was cooled to −60°C and transferred to an NMR tube under exclusion of moisture and air. Finally 1 equiv. of 2,2′-dipyridyl ketone dissolved in THF was added to the NMR tube at −60°C and directly measured.

For the preparation of the oxaphosphetane **4b** 1-phenyldibenzophosphol was prepared according to reference[16]. 4.54 g (17 mM) of this material were methylated in 30 ml of dry toluene using 5.3 ml (5 equiv.) methyl iodide for 16 h at 120°C. The precipitated white phosphonium salt was washed with diethyl ether (5.06 g, 74%). 0.506 (1.26 mM) of 1,1′-biphenylmethylphenylphosphonium iodide were suspended in 10 ml dry THF. To this suspension 1 equiv. NaHMDS in 2 ml THF (Aldrich) were added at −10°C and stirred for 30 min. The THF was evaporated and the residue suspended in dry petroleum ether. Undissolved solid material was filtered off and the petroleum ether was evaporated. The residue was redissolved in THF, cooled to −60°C and transferred to an NMR tube under exclusion of moisture and air. Finally 1 equiv. of 2,2′-dipyridyl ketone dissolved in THF was added to the NMR tube at −60°C and directly measured.

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