Research Article

Magnetic Resonance in Chemistry

Received: 6 November 2008 Revised: 12 January 2009 Accepted: 15 January 2009 Published online in Wiley Interscience: 5 March 2009

(www.interscience.com) DOI 10.1002/mrc.2412

^{31}P Solid state NMR study of structure and chemical stability of dichlorotriphenylphosphorane

Nina C. Gonnella,* Carl Busacca, Scot Campbell, Magnus Eriksson, Nelu Grinberg, Teresa Bartholomeyzik, Shengli Ma and Daniel L. Norwood

Solid state ^{31}P NMR spectroscopy was used to examine, monitor and quantify the compound integrity of the chemical reagent dichlorotriphenylphosphorane. Comparison was also made with solution ^{31}P NMR spectra which showed that this highly reactive species could be observed in dry benzene prior to conversion to the hydrolyzed product. This is the first reported solid state NMR study of the stability and reactivity of dichlorotriphenylphosphorane and the first account of its observation and comparison in the solution state. In the solid state, the ionic and covalent forms for dichlorotriphenylphosphorane were observed along with hydrolyzed products, however, the degree of hydrolysis was dependent upon the rotor packing conditions. Calculation of the relative percent composition of dichlorotriphenylphosphorane with hydrolyzed product was made for samples prepared in air *versus* under nitrogen atmosphere. This information was critical in adjusting the amount of reagent used in chemical development syntheses and scale up laboratories. All hydrolyzed products were identified, based upon chemical comparisons with spectra of pure materials.

Keywords: NMR; ^{31}P; solid state; dichlorotriphenylphosphorane; triphenylphosphine oxide; hydrolysis; quantitative comparison

Introduction

Dichlorotriphenylphosphorane (DCTP) is an efficient reagent for alkyl halide synthesis in organic chemistry.[1] This reagent is very sensitive to moisture, hence requires careful storage and handling in a dry atmosphere. Upon exposure to air, DCTP rapidly converts to phosphine oxide rendering the molecule inactive as a chlorinating agent. This rapid hydrolysis has made examination of the integrity of the phosphorane elusive since exposure to moisture in the air or solvent will immediately convert the reagent to hydrolyzed product. Most analytical methods do not provide sufficient protection from atmospheric moisture to render them viable for monitoring the compound's chemical state. This becomes particularly important in batch process synthesis where product yields are critical in compound production; hence development of a method to assess the purity of the reactant is necessary.

For the past decade, solid state NMR (ssNMR) has emerged as an important technology in pharmaceutical research and development.[2] With the advent of cross polarization and magic angle spinning (MAS),[3,4] spectra that provide the quality required for structural identification and quantitation of inorganic, organic and biological compounds are now possible. Unlike solution NMR, this technology does not require use of a solvent that will introduce moisture. Hence, materials may be examined directly and monitored over time without external interference.

Because ssNMR spectroscopy provides a powerful means of chemical identification, we elected to use ^{31}P ssNMR to examine, monitor and quantify the compound integrity of dichlorotriphenylphosphorane. These studies allowed the identification of hydrolyzed product and enabled calculation of the percent composition of DCTP when samples were prepared in air *versus* under nitrogen atmosphere. This is the first reported study in which ^{31}P ssNMR was used to determine the reactivity of this compound and unambiguously identify the resultant hydrolyzed products. This information was critical in adjusting the amount of reagent used in chemical development syntheses and scale up laboratories.

Experimental

All chemicals were purchased from either Sigma-Aldrich or Digital Speciality Chemicals. Triphenyl phosphine oxide (TPPO) and two different batches of dichlorotriphenylphosphorane (Batch 1 and Batch 2) were purchased and stored in a dessicator.

Solution ^{31}P NMR: ^{31}P NMR spectra were acquired using a Bruker Avance III 500 MHz NMR spectrometer (Bruker-Biospin) operating at 202.46 MHz for ^{31}P with a Hewlett Packard computer and a Linux operating system. Spectra were acquired at 298 °K with a sweep width of 80 000 – 100 000 Hz, relaxation delay of 1.0 s, 90° pulse width of 25 µs, acquisition time of 0.4 s and 65.5 K data points. Waltz-16 proton decoupling was used and the total number of transients was 16.

Samples were dissolved in either deuterated dimethylsulfoxide or deuterated benzene as saturated solutions and placed in a 5-mm NMR tube.

Solid state ^{31}P NMR: Solid state ^{31}P NMR spectra were acquired using a Bruker Avance III 400 MHz wide bore NMR spectrometer

* *Correspondence to: Nina C. Gonnella, Boehringer Ingelheim Pharmaceuticals Inc., 900 Ridgebury Road, Ridgefield, CT 06877, USA.*
E-mail: nina.gonnella@boehringer-ingelheim.com

Boehringer Ingelheim Pharmaceuticals Inc., 900 Ridgebury Road, Ridgefield, CT 06877, USA

(Bruker-Biospin) operating at 162.1 MHz for ^{31}P. A Bruker H/X CP/MAS probe equipped with a 4-mm rotor was used to acquire all spectra.

Samples were packed into 4-mm Zirconia rotors and sealed with Kel-F caps. Preparation occurred either under atmospheric conditions or under dry nitrogen. Spectra were acquired using variable amplitude cross polarization,[4–7] magic angle spinning (MAS)[8,9] and high power proton decoupling with two phase pulse modulation (TPPM).[10–13] Contact time of 3 ms was used to acquire all spectra. The MAS frequency was 15 kHz and the proton decoupling field was approximately 49 kHz. Recycle delays, based upon saturation of ^{31}P signal intensity, were sufficiently long to allow full relaxation of ^{31}P signal. Phosphorous chemical shifts are quoted with respect to phosphoric acid.

Results and Discussion

The ^{31}P NMR chemical shifts of dichlorotriphenylphosphorane, and its hydrolyzed products obtained from both ssNMR and solution NMR are given in Table 1. The ssNMR data show that dichlorotriphenylphosphorane exists in the pseudo-trigonal bipyramidal form as evidenced by the peak at −43.44 ppm and in the ionic quasi-phosphonium salt appearing at 63.62 ppm.[14,15] Multiple peaks for the dichlorotriphenylphosphorane at −43.44 ppm and 63.62 ppm are due to ^{31}P, ^{35,37}Cl dipolar coupling in ^{31}P MAS spectra.[16,17] Measured ^{31}P–^{35}Cl isotropic (*J*) scalar couplings for the peaks at −43.44 and 63.62 ppm were approximately 230 and 317 Hz with quadrupole-perturbed dipolar and anisotropic scalar distortions of approximately +14 Hz and −179 Hz, respectively.[18]

Because of the phosphorane's susceptibility to hydrolysis on exposure to moisture, this compound required handling in a dry atmosphere. When NMR rotors were packed under a dry nitrogen atmosphere, the monohydrate phosphine oxide, at 27.04 ppm, was present in the phosphorane spectrum as the only hydrolyzed product. The identity of the monohydrate was confirmed via a preparation, according to a known procedure.[19] The ^{31}P NMR data, comparing the dichlorotriphenylphosphorane spectrum with the hydrolyzed monohydrate spectrum are shown in Fig. 1. The hydrolyzed product was also evident from the loss of dipolar coupling of chlorine with phosphorous that is characteristic of a ^{31}P–^{35}Cl bond.

Table 1. Phosphorous-31 NMR chemical shifts for dichlorotriphenylphosphorane and hydrolyzed products

Compound	ss NMR δ^{31}P/(ppm)[a]	solution NMR δ^{31}P/(ppm)
$Ph_3PCl^+Cl^-$	63.62	69.8[b]
Ph_3PCl_2	−43.44	−29.8[b]
Ph_3PO	28.65	38.96[c]
		(38.87–40.81)[b]
$Ph_3PO \cdot H_2O$	27.04	(38.87–40.81)[b]
$Ph_3PO \cdot HCl$	42.97	40.81[b]
		44.40[d]

[a] Referenced from 85% H_3PO_4.
[b] Dichlorotriphenylphosphorane and hydrolyzed products (Batch 1) acquired in benzene-d_6.
[c] Triphenylphosphine oxide (purchased material) spectrum acquired in DMSO-d_6.
[d] Hydrolyzed product of dichlorotriphenylphosphorane (Batch 1) after standing in benzene-d_6 for 1 h.

Upon standing at atmospheric conditions for 16 h, dichlorotriphenylphosphorane was hydrolyzed to a product where the phosphorous chemical shift is at 42.97 ppm. Since the chemical shift of commercially obtained triphenylphosphine oxide appeared at 28.65 ppm, the downfield shift of about 15 ppm suggested a significant change in this hydrolyzed product. While multiple polymorphs of TPPO are known to exist, their preparation and characterization have not been reported.[20] However, because of the significant downfield shift from triphenyl phosphine oxide, it was proposed that the unknown peak may be due to the hydrochloride salt of TPPO as opposed to an alternate polymorph form. To confirm this hypothesis, the hydrochloride salt of TPPO was prepared according to an internally developed procedure. Initial attempts to prepare the hydrochloride salt of TPPO, based upon a known procedure,[21] were unsuccessful. It was found, however, that the desired product could be reproducibly prepared from a 'slurry-to-slurry' conversion in which TPPO was added to anhydrous 2M ethereal HCl under argon. The resultant slurry was allowed to age overnight at ambient temperature to yield the desired product as a solid after filtration under an inert atmosphere. The ^{31}P NMR spectrum showed the unknown peak to be the hydrochloride salt of TPPO with the monohydrate as a minor component (Fig. 2).

Solid state ^{31}P NMR data were collected for DCTP obtained from two different commercial batches (Batch 1 and Batch 2). The rotors were packed in dry nitrogen atmosphere and ^{31}P ssNMR spectra were collected. The phosphorous ssNMR data showed a higher composition of DCTP for the material from Batch 2, having only 3% conversion to the hydrolyzed form. The material from Batch 1, however, showed about 8% conversion to the hydrolyzed form. The percent of reagent and hydrolyzed impurity was determined from the relative integrated intensities of the phosphorous peaks. These data were in agreement with its use as a synthetic reagent where complete conversion to product was consistently found for material showing lower levels of hydrolysis product (internal communication).

When the rotors were packed in the laboratory atmosphere, the exposure to air for a short duration of several minutes increased the amount of hydrolyzed product to about 30%. This hydrolyzed product consisted of the monohydrate at 27.04 ppm[19] and hydrochloride salt at 42.97 ppm. Spectra of DCTP prepared under dry nitrogen atmosphere and under laboratory atmospheric conditions are shown in Fig. 1 (b–d).

A comparison of solution NMR with solid state NMR was also carried out. The ^{31}P NMR solution spectrum of the dichlorotriphenylphosphorane was difficult to acquire because of the almost instant conversion to the hydrolyzed form upon dissolution in solvent. This was found to be the case in DMSO where the chemical shift of the phosphorane showed complete conversion to the hydrolyzed form with the ^{31}P chemical shift at 39.96 ppm which is identical with the ^{31}P solution NMR chemical shift of the purchased TPPO. In benzene, however, it was possible to trap the covalent form long enough to get a spectrum of the dichlorotriphenyphosphorane (Fig. 3). The spectrum showed that the covalent dichlorotriphenylphosphorane phosphorous atom resonates at −29.6 ppm and ionic dichloride at 69.8 ppm. Peaks consistent with the hydrolyzed forms appear between 38.8 and 40.8 ppm. Upon standing in solution, complete conversion to the TPPO was observed. All solution NMR chemical shifts appeared downfield relative to that in the solid state.

Unlike solution NMR, the solid state phosphorous NMR spectra show that dichlorotriphenylphosphorane does not rapidly convert

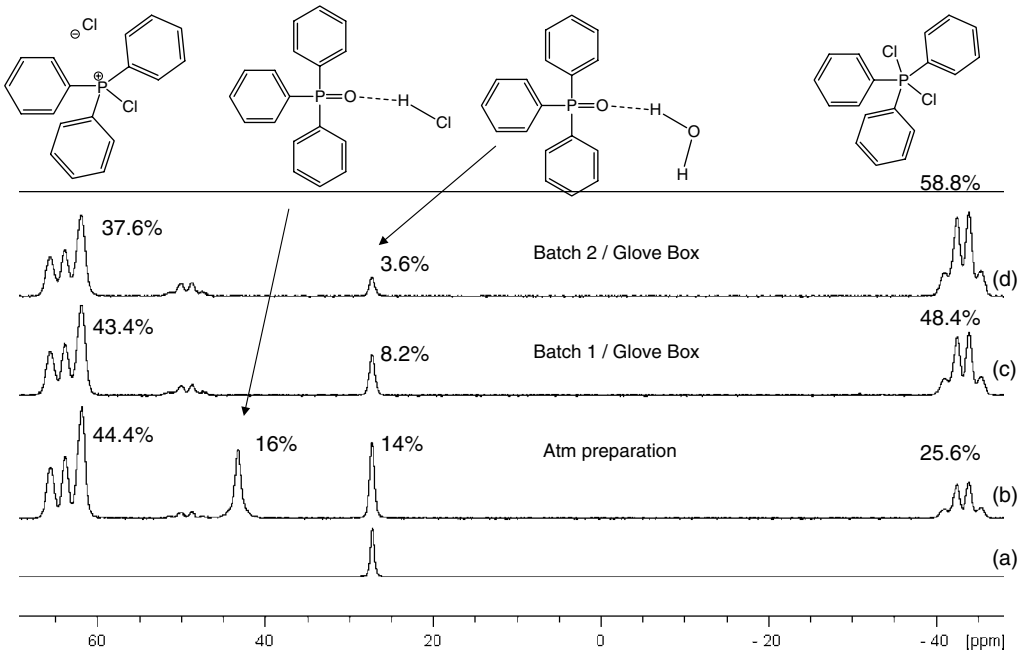

Figure 1. ^{31}P CP/MAS NMR spectra (B_0 = 9.4 T, ν_{rot} = 15 000 Hz). (a) Triphenyl phosphine oxide monohydrate prepared according to reported procedure.[19] (b) Dichlorotriphenylphosphorane (Batch 1) prepared in laboratory atmosphere shows the presence of 30% TPPO hydrolyzed products; existing as 14% monohydrate and 16% hydrochloride salt. (c) Dichlorotriphenylphosphorane (Batch 1) prepared under dry nitrogen atmosphere shows the presence of 8.2% TPPO monohydrate. (d) Dichlorotriphenylphosphorane (Batch 2) prepared under dry nitrogen atmosphere shows the presence of 3.6% TPPO monohydrate.

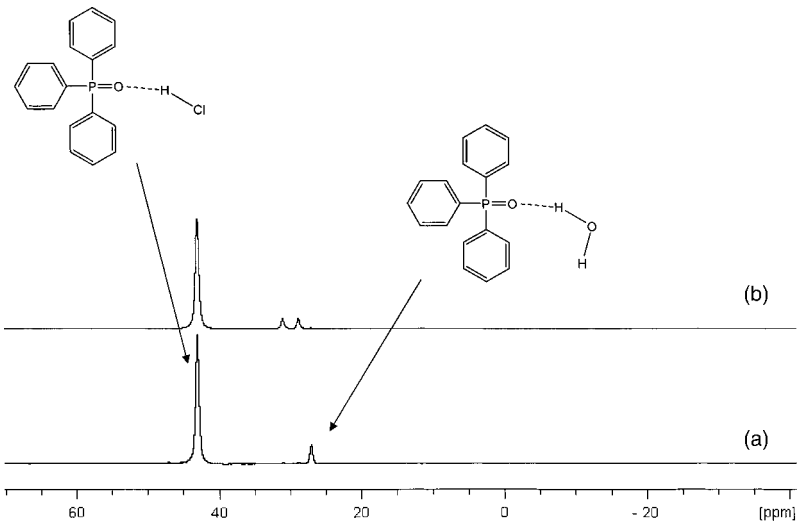

Figure 2. (a)^{31}P CP/MAS NMR spectrum of triphenyl phosphine oxide hydrochloride (B_0 = 9.4 T, ν_{rot} = 15 000 Hz) shows the trace amounts of the TPPO monohydrate present. (b) ^{31}P CP/MAS NMR spectrum of dichlorotriphenylphosphorane (B_0 = 9.4 T, ν_{rot} = 15 000 Hz) after exposure to atmosphere for 16 h. The spectrum shows nearly complete conversion to the hydrochloride salt with trace amounts of triphenylphosphine oxide.

to hydrolyzed product when packed in a rotor, since spectra of the compound remained virtually unchanged for weeks. Clearly the packed rotor protects the compound from exposure to moisture in the atmosphere and prevents the formation of hydrolysis products. Hence insights into the appropriate handling of this material could be readily ascertained from the solid state NMR spectra.

The data do, however, show that the samples with the lowest concentration of hydrolyzed product have the highest amount of covalent DCTP reagent. As the conversion to hydrolyzed product increases, the ionic form of the material becomes more prevalent (Fig. 1 (b–d)). This suggests that the mechanism for conversion of the covalent form of DCTP to the hydrolyzed form consists of transition through an intermediate ionic state. The data also show that the conversion to hydrolyzed products is initiated with the formation of the monohydrate followed by final formation of the hydrochloride salt.

Conclusion

^{31}P Solid state NMR spectroscopy proved to be a valuable technology for monitoring the physical characteristics and

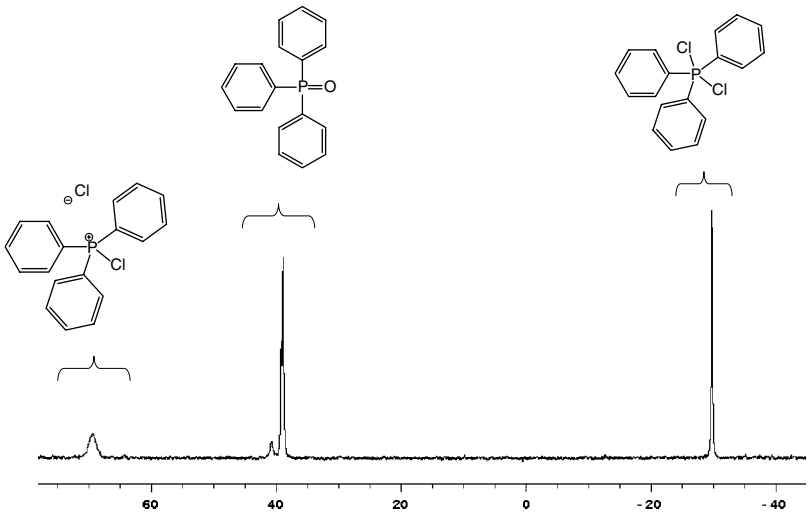

Figure 3. ^{31}P NMR spectrum (202.46 MHz) of dichlorotriphenylphosphorane in dry benzene-d_6. Upon standing in solution, the compound rapidly converts to a broad peak at 44.4 ppm.

chemical integrity of highly reactive reagents. These results enabled chemists to accurately estimate the relative excess of reagent to allow reactions to go to completion. This becomes particularly important in large production scale up reactions where associated costs of materials and time become significant.

Our data also provided insight into the structural forms of dichlorotriphenylphosphorane, indicating that both the ionic and covalent forms of the molecule coexist and suggesting that the ionic form represents an intermediate in the transition to hydrolyzed product.

References

[1] G. A. Wiley, R. L. Hershkowitz, B. M. Rein, B. C. Chung, *J. Am. Chem. Soc.* **1964**, *86*, 964.
[2] D. D. Laws, H.-M. L. Bitter, A. Jerschow, *Angew. Chem. Int. Ed.* **2002**, *41*, 3096.
[3] I. J. Lowe, *Phys. Rev. Lett.* **1959**, *2*, 285.
[4] A. Pines, M. G. Gibby, J. S. Waugh, *J. Chem. Phys.* **1973**, *59*, 569.
[5] S. R. Hartmann, E. L. Hahn, *Phys. Rev.* **1962**, *128*, 2042.
[6] A. Pines, M. G. Gibby, J. S. Waugh, *J. Chem. Phys.* **1972**, *56*, 1776.
[7] O. B. Peersen, X. Wu, S. O. Smith, *J. Magn. Reson., Ser. A* **1994**, *106*, 127.
[8] E. R. Andrew, *Prog. Nucl. Magn. Reson. Spectrosc.* **1971**, *8*, 1.
[9] E. R. Andrew, A. Bradbury, R. G. Eades, *Nature* **1959**, *183*, 1802.
[10] J. Schaefer, E. O. Stejskal, *J. Am. Chem. Soc.* **1976**, *98*, 1031.
[11] J. Schaefer, E. O. Stejskal, R. Buchdahl, *Macromolecules* **1975**, *8*, 291.
[12] E. O. Stejskal, J. Schaefer, J. S. Waugh, *J. Magn. Reson.* **1977**, *28*, 105.
[13] A. E. Bennett, C. M. Rienstra, M. Auger, K. V. Lakshmi, R. G. Griffin, *J. Chem. Phys.* **1995**, *103*, 6951.
[14] B. Dillon, T. A. Straw, *J. Chem. Soc., Chem. Commun.* **1991**, 234.
[15] M. A. H. A. Al-Juboor, P. N. Gates, A. S. Muir, *J. Chem. Soc., Chem. Commun.* **1991**, 1270.
[16] A. Rabis, A. R. Grimmer, B. Thomas, E. Brender, S. Beck, M. Meisel, *Solid State Nucl. Magn. Reson.* **2005**, *28*, 57.
[17] B. Thomas, S. Paasch, S. Steuernagel, K. Eichele, *Solid State Nucl. Magn. Reson.* **2001**, *20*, 108.
[18] A. Olivieri, *J. Am. Chem. Soc.* **1992**, *114*, 5758.
[19] P. W. Baures, J. V. Silverton, *Acta Crystallogr.* **1990**, *C46*, 715.
[20] P. W. Baures, *Acta Crystallogr.* **1991**, *C47*, 2715.
[21] H. J. Haupt, F. Huber, C. Krueger, H. Preut, D. Thierbac, *Z. Anorg. Allg. Chem.* **1977**, *436*, 229.