C_6-methyl group in TC, consistent with the aromatization of ring C. Similar spectra for peak A and AHTC were also

AHTC

2.39 (s, 3 H), 2.59 (s, 6 H), 3.15 (m, 1 H), 3.59 (m, 1 H), 3.63 (b, 1 H), 3.73 (d, 1 H)

peak A

2.40 (s, 3 H), 2.59 (s, 6 H), 3.12 (m, 1 H), 3.62 (b, 2 H), 3.7 (d, 1 H)

observed in MeOH-d_4. Typical yields of AHTC by HPLC recovered from the photolysis mixture ranged from 40% to 45%.

In previous studies of TC photochemistry, three different photoproducts have been reported,[4-6] although in no case has the identification been unequivocal. Thus, (a) Hlavka and Bitha[4] found that irradiation of TC in MeOH leads to dimethylamine formation and concluded that they had photoreductively deaminated TC at the 4 position, (b) Davies et al.[5] isolated a red product formed on irradiation of an air-saturated solution of TC at pH 9 and concluded on the basis of its chemical properties that it was a quinone formed on oxidation of photodeaminated TC at the 4 position, and (c) Sanniez and Pilpel[6] photolyzed TC in an oil–water mixture and identified AHTC as one of the principal products formed on the basis of TLC and UV spectroscopy, although little detail was provided. Given this rather complex background we thought it important to determine the TC photoproduct formed under the conditions of our photoaffinity labeling experiments. Our results present the first well-documented proof for the formation of AHTC on photolysis of TC under mildly reducing conditions (presence of β-mercaptoethanol). This photodehydration is undoubtedly driven by the aromatization of ring C. Such reactions are otherwise rather rare, although it is worth noting that ethylene glycol has been shown to photodehydrate to acetaldehyde in a reaction that, like the one described in this paper, requires the presence of SH compounds.[7]

Elsewhere we have shown that the identities of products produced on TC photolysis are strongly influenced by redox conditions (O_2 vs. N_2 atmosphere, presence or absence of β-mercaptoethanol).[2] We are currently seeking to determine whether the products formed in the absence of β-mercaptoethanol correspond to those put forward by earlier workers, as described above. If the singlet oxygen that is produced on photolysis of oxygen-containing solutions of TC[8] is a reactant in the formation of these products, then it is possible that β-mercaptoethanol exerts its marked effect on product formation by preventing the accumulation of singlet oxygen in solution. Such an explanation would also provide a rationale for the difference in the results obtained by Davies et al.[5] and by Sanniez and Pilpel[6] since in the latter study photolysis proceeds in the oil phase, away from the oxygen dissolved in the aqueous phase.

The formation of AHTC on TC photolysis is quite consistent with the photoaffinity labeling studies alluded to above, since AHTC is only a poor inhibitor of ribosomal function[9] and would not be expected to show strong site-specific binding. In addition, formation of AHTC, which has known cutaneous phototoxicity,[3] could account for TC-induced cutaneous phototoxicity.

Experimental Section

HPLC analysis was performed on a Waters Associates chromatograph consisting of 6000A and M-45 pumps, a 660 programmer, and a U6K Universal injector. The detection system was a Waters extended wavelength module (214 nm) and a Model 440 absorbance detector connected in series. UV–vis spectra were recorded on a Beckman D-8 spectrophotometer. NMR spectra were obtained on either an IBM-200 FT-NMR or a Bruker 250-MHz FT NMR. Photolysis experiments were carried out in 100-mL round-bottomed Pyrex flasks with either Rayonet RPR 3500-Å lamps or with a UV Products, Inc., PCQ 008L lamp assembly having a maximal output between 3400 and 3800 Å.

Tetracycline was obtained from Lederle Laboratories and was ≳98% pure. It was used without further purification. AHTC was prepared by acid-catalyzed dehydration of TC.[10] Deuterated solvents were obtained from Aldrich Chemical Company; both the methanol and pyridine used in the study had 99.9 atom % D. All other chemicals were of the highest grade of purity available.

Acknowledgment. This work was supported by NSF grants to B.S.C. (PCM81-04360 and PCM84-10152). Support for T.H. from the A.O. and G.N. Wellman Foundation is also gratefully acknowledged.

Registry No. AHTC, 1665-56-1; TC, 60-54-8.

(4) Hlavka, J. J.; Bitha, P. *Tetrahedron Lett.* **1966**, 3843.
(5) Davies, A. K.; McKellar, J. F.; Phillips, G. O.; Reid, A. G. *J. Chem. Soc., Perkin Trans. 2* **1979**, 369.
(6) Sanniez, W. H. K.; Pilpel, N. *J. Pharm. Sci.* **1980**, *69*, 5.
(7) Rudakova, I. P.; Ershova, T. E.; Belikov, A. B.; Yurkevich, A. M. *J. Chem. Soc., Chem. Commun.* **1978**, 592.
(8) Wiebe, J. A.; Moore, D. E. *J. Pharm. Sci.* **1977**, *66*, 186.
(9) Summ, H. D.; Christ, O. *Arzneim-Forsch.* **1967**, *17*, 1186.
(10) Green, A.; Wilkinson, R. G.; Booth, J. H. *J. Am. Chem. Soc.* **1960**, *82*, 3946.

Nitrogen-15 and Phosphorus-31 NMR Spectroscopy of *N*-Aryl-*P*,*P*,*P*-triphenylphospha-λ⁵-azenes. Applicability to pπ–dπ Bonding

Martin Pomerantz,*[1a] Barbara T. Ziemnicka,[1a,b] Zohar M. Merchant,[1a] Whe-Narn Chou,[1a] Wesley B. Perkins,[1a] and Shmuel Bittner[1c]

Department of Chemistry, The University of Texas at Arlington, Arlington, Texas 76019-0065, and Department of Chemistry, Ben-Gurion University of the Negev, Beer Sheva 84105, Israel

Received September 18, 1984

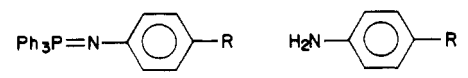
The concept of pπ–dπ overlap has long been employed to explain observations involving molecules containing a third-row element such as phosphorus bound to a second-row element such as nitrogen or oxygen containing nonbonding electrons.[2] One such system is the phospha-λ⁵-azene, shown below as a resonance hybrid of structures A and B.

$$\underset{\text{A}}{R_3\overset{+}{P}\overset{-}{N}R'} \longleftrightarrow \underset{\text{B}}{R_3P{=}NR'}$$

The numerous reports which claim that the ^{31}P NMR chemical shifts of phospha-λ⁵-azenes, particularly of the type 1, are sensitive to the contribution of the pπ–dπ resonance form to the hybrid,[3-5] and a very recent com-

(1) (a) The University of Texas at Arlington. (b) On leave from the Institute of Physics, Technical University of Lodz, Poland. (c) Ben-Gurion University of the Negev.
(2) Kwart, H.; King, K. G. "d-Orbitals in the Chemistry of Silicon, Phosphorus and Sulfur"; Springer-Verlag: Berlin, 1977. Allcock, H. R. "Phosphorus–Nitrogen Compounds"; Academic Press: New York, 1972; Chapter 3.

0022-3263/85/1950-1757$01.50/0



1 2

a, R=NO_2 c, R=H e, R=OCH_3
b, R=Cl d, R=CH_3 f, R=$N(CH_3)_2$

munication concerning ^{15}N and ^{31}P NMR studies of phosphorimidates,[6] prompt us to report our results on *N*-aryl-*P*,*P*,*P*-triphenylphospha-λ^5-azenes **1a–f**. We demonstrate that ^{15}N and ^{31}P chemical shifts exhibit similar behavior as the aryl substituent is changed and show that this is not directly related to the extent of $p\pi$–$d\pi$ bonding as suggested in the literature. Further, the one-bond PN coupling constant ($^1J_{PN}$) behaves differently as a function of substituent and seems to be influenced by resonance interaction (electron donation) with the substituent in the *N*-aryl ring.

Table I shows the ^{31}P chemical shifts, extrapolated to infinite dilution, the natural-abundance ^{15}N chemical shifts, and the one-bond PN coupling constants for a series of *N*-aryltriphenylphospha-λ^5-azenes (**1a–f**). A plot of δ_{31P} vs. the Hammett σ_P^- constants[9,17] gives an excellent straight line whose slope is 2.91 and whose correlation coefficient (r) is 0.989. This type of behavior has been observed previously.[3-5] In two studies, however, concentrations considerably greater than that used here were employed and chemical shifts were not extrapolated to infinite dilution,[3,5] thus introducing large errors, as pointed out below. Also, the different concentrations used in these studies gave rise to very different values for δ_{31P}.[3,5]

A third report states that ^{31}P chemical shifts were obtained by extrapolating to zero concentration but the values were not given. A plot of σ^- vs. δ_{31P} gave a straight line whose slope was 3.19 (r was stated to be between 0.97 and 0.99).[4] This value for the slope is in good agreement with that obtained here, 2.91 (r = 0.989).

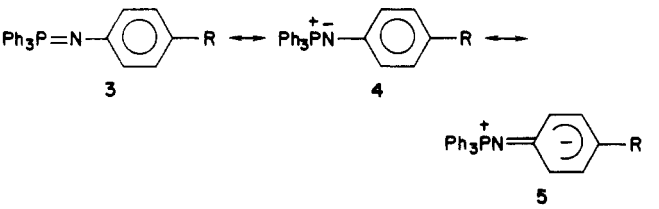
It is important to point out that in the case of the *N*-aryltriphenylphosphaazenes 1 not extrapolating to infinite dilution results in serious errors when comparing ^{31}P chemical shifts. In four of the six cases examined (**1b–e**) a plot of δ_{31P} vs. concentration gave a line of negative slope, while in the other two cases (**1a** and **f**; with the most electron-donating and most electron-withdrawing groups) the slope was positive and, in addition, the slopes varied numerically over a factor of about 10. Since our concentrations (30, 100, 200, and 300 mg/3 mL) varied over a 10-fold range, down to a value of about 0.025–0.03 M, we consider our extrapolated chemical shifts to be quite reliable. Further, in five of six cases the extrapolated value of δ_{31P} was within 0.02 ppm of the value obtained at the lowest concentration (10 mg/mL). In the case of **1f** [R = $N(CH_3)_2$] the extrapolated value (δ 2.61) was within 0.04 ppm of the lowest concentration value (δ 2.65) but the slope of the plot of concentration vs. δ_{31P} was the largest.

Table I. NMR Parameters of Phospha-λ^5-azenes 1a–f and δ_{15N} for Corresponding Anilines 2a–f

no.	R	δ_{31P}[a]	δ_{15N}[b]	$^1J_{PN}$[c], Hz	δ_{15N} (for *p*-X anilines)
1a	*p*-NO_2[d]	7.79	100.10	32.2	**2a**, 76.2[e]
1b	*p*-Cl	4.59	77.59	32.7	**2b**, 56.8[e]
1c	H	3.73	77.66	32.9	**2c**, 56.5[e]
1d	*p*-CH_3	3.35	74.79	32.9	**2d**, 53.9[e]
1e	*p*-OCH_3	3.13	71.77	34.2	**2e**, 50.7[e]
1f	*p*-$N(CH_3)_2$	2.61	70.07	34.7	**2f**, 51.1[f]

[a] ppm downfield from external 85% H_3PO_4; extrapolated to infinite dilution. [b] ppm downfield from liquid NH_3. [c] ±0.2 Hz. [d] δ_{15N} for the NO_2 group is 369.74. [e] From ref 8 (Me_2SO solvent) and converted to the liquid NH_3 scale using $\delta_{aniline}$ = 56.5 (ref 7). [f] This work (Me_2SO solvent); δ_{15N} for the $N(CH_3)_2$ group is 37.5. δ_{15N} ($CDCl_3$ solvent) for NH_2 and NMe_2 respectively is 48.8 and 37.6.

It has been argued that since δ_{31P} varies directly with σ^-, resonance form **3** increases in its contribution relative to **4** and **5** as the R group becomes more electron donating.[3-5] Actually, forms **4** and **5** alone will explain the data. That



3 4

5

δ_{31P} is not necessarily related to resonance form **3** is shown by the following. A plot of δ_{15N} (for **1a–f**) vs. δ_{31P} was linear (correlation coefficient r = 0.986; slope = 5.74), and a plot of δ_{15N} vs. σ_P^-,[9] as in the case of δ_{31P} vs. σ_P^-, also gave a straight line whose slope was 16.70 (r = 0.974). Further, and more significantly, a plot of δ_{15N} for **1a–f** vs. δ_{15N} for anilines with the same substituents (**2a–f**, Table I)[8] gave a nearly perfect straight line (r = 0.998) with a slope (1.149) close to unity. These results show that the ^{15}N chemical shifts of the phospha-λ^5-azenes are apparently sensitive to the same effects as those of the anilines, and this would seem to rule out changes in the contribution of resonance form **3** as the major cause of the changes in δ_{15N}, since an analogous form cannot be drawn for the anilines. Thus δ_{15N} is sensitive to forms **4** and **5** and not to form **3**. Likewise, the phosphorus chemical shifts must also be a reflection of the contributions of forms **4** and **5**, but not of form **3**, to the resonance hybrid, which is in direct contrast to the literature suggestions that ^{31}P chemical shifts reflect the extent of $p\pi$–$d\pi$ bonding in these systems.[3-5]

It should be noted that δ_{31P} is a complicated combination of a number of factors, only one of which involves d-orbital occupancy on phosphorus, and as such δ_{31P} is not expected to necessarily be directly related to $p\pi$–$d\pi$ bonding.[10] Nitrogen chemical shifts are also comparably complex.[11]

Plots of $^1J_{PN}$ vs. the resonance parameters σ_R and σ_R^+[12] gave reasonably straight lines (slope = −2.48, r = 0.965 and slope = −1.29, r = 0.960, respectively). When other parameters (such as σ or σ^-) were used, the fit was quite poor. It is thus clear that the PN coupling constant is sensitive to a very different property (or properties) of the substituent, R, than the ^{15}N and ^{31}P chemical shifts and that

(3) Bödeker, J.; Köckritz, P.; Köppel, H.; Radeglia, R. *J. Prakt. Chem.* **1980**, *322*, 735.
(4) Murphy, P. C.; Tebby, J. C. In "Phosphorus Chemistry–Proceedings of the 1981 International Conference"; American Chemical Society: Washington, D.C., 1981; ACS Symp. Series No. 171, p 573.
(5) Briggs, E. M.; Brown, G. W.; Cairns, P. M.; Jiricny, J.; Meidine, M. F. *Org. Magn. Reson.* **1980**, *13*, 306. (These authors do not plot δ_{31P} vs. σ but present a qualitative argument.)
(6) Martin, G. J.; Sanchez, M.; Marre, M.-R. *Tetrahedron Lett.* **1983**, *24*, 4989.
(7) Levy, G. C.; Lichter, R. L. "Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy"; Wiley: New York, 1979; Chapter 3.
(8) Axenrod, T.; Pregosin, P. S.; Wieder, M. J.; Becker, E. D.; Bradley, R. B.; Milne, G. W. A. *J. Am. Chem. Soc.* **1971**, *93*, 6536.
(9) Exner, O. In "Correlation Analysis in Chemistry. Recent Advances"; Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York, 1978; Chapter 10.
(10) Gorenstein, D. G. In "Phosphorus-31 NMR, Principles and Applications"; Gorenstein, D. G., Ed.; Academic Press: Orlando, FL, 1984; pp 23–27.
(11) Levy, G. C.; Lichter, R. L., ref 7, Chapter 1.
(12) Ehrenson, S.; Brownlee, R. T. C.; Taft, R. W. *Prog. Phys. Org. Chem.* **1973**, *10*, 1.

this property is the ability of the substituent to interact by resonance (overlap) and, in particular, by electron donation. The most reasonable acceptor of this electron back-donation would seem to be a $p\pi$–$d\pi$ bond as in resonance form **3**, but a number of other explanations are possible and these are being actively explored.

Experimental Section

Phospha-λ^5-azenes 1a–e were made by the Staudinger reaction using the appropriate azide and triphenylphosphine[13–15] and **1f** was made by the method of Horner.[15,16] The properties matched those reported. The NMR spectra were obtained on a Nicolet NT-200 wide bore spectrometer with a 4.7 T superconducting solenoid. ^{31}P spectra were taken at 80.99 MHz using an external 85% H_3PO_4 standard. The spectra were taken in $CDCl_3$ (12-mm tubes) at concentrations of 300 mg/3 mL, 200 mg/3 mL, 100 mg/3 mL, and 30 mg/3 mL and extrapolated to infinite dilution. Two level broad band proton decoupling was employed with a pulse angle of approximately 90° and a post acquisition delay of 1 s. Natural-abundance ^{15}N spectra were obtained at 20.28 MHz using gated broad band proton decoupling (decoupler on during acquisiton), a pulse angle of about 23°, and a post acquisition delay of 6 s. Samples were about 1.3–1.8 M in $CDCl_3$ and 20-mm tubes were employed. ^{15}N chemical shifts were measured using an external $K^{15}NO_3$ solution in H_2O which had been standardized against neat CH_3NO_2. The shifts relative to liquid NH_3 were calculated by using $\delta(NH_3) = \delta(CH_3NO_2) + 380.23$.[7]

Acknowledgment. We thank the Robert A. Welch Foundation (Grant No. Y-684), The University of Texas at Arlington–Organized Research Fund, and the National Science Foundation (Grant Nos. CDP-80075014 and PRM-8108132) for support of this work. We also thank Mr. Michael Morgan for help with several NMR spectra and Professors K. L. Brown and D. S. Marynick for helpful discussions.

Registry No. **1a**, 14562-02-8; **1b**, 31641-65-3; **1c**, 2325-27-1; **1d**, 2327-67-5; **1e**, 14796-89-5; **1f**, 77116-68-8; **2a**, 100-01-6; **2b**, 106-47-8; **2c**, 62-53-3; **2d**, 106-49-0; **2e**, 104-94-9; **2f**, 99-98-9.

(13) Staudinger, H.; Hauser, E. *Helv. Chim. Acta* **1921**, *4*, 861.
(14) Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37*, 437.
(15) Wiegräbe, W.; Bock, H. *Chem. Ber.* **1968**, *101*, 1414.
(16) Horner, L.; Oedinger, H. *Justus Liebigs Ann. Chem.* **1959**, *627*, 142.
(17) Actually σ_P^- for R = NO_2 and, since σ^- is the same as σ for the other substituents which cannot accept an electron pair by resonance, σ_P for the other substituents was used.

Coupling Reactions of α-Halo Esters with Allyl- and Acetonyltin Reagents. An Improved Synthesis of α-Acetonyl-γ-butyrolactone

James H. Simpson and J. K. Stille*

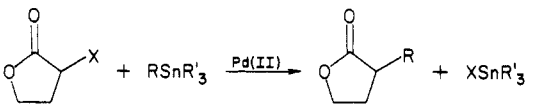
Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received September 20, 1984

The palladium-catalyzed coupling reactions of organic electrophiles with organotin reagents provide a convenient, high yield pathway for carbon–carbon bond formation. The coupling reactions of acyl chlorides,[1] allyl chlorides and bromides,[2] and vinyl triflates[3] as the electrophilic partner take place with a wide variety of tin reagents under conditions that are mild enough that diverse functionality is acceptable in both coupling partners. Generally, in the reactions where an sp^3 carbon undergoes oxidative addition, β-hydrogens on an sp^3 carbon cannot be present in the electrophile but can be present in the organotin partner. This is because the product of oxidative addition with the electrophile is able to undergo β-hydride elimination.[4] Apparently the diorganopalladium(II) complex can have a β-hydrogen because the transmetalation step which follows oxidative addition of the electrophile to a palladium(0) complex is slow, while the 1,1-reductive elimination which follows the transmetalation is fast.[5] Surprisingly, however, α-bromo-γ-butyrolactone which possesses β-hydrogens was observed to cross-couple in good yield.

Coupling reactions of organotin reagents with α-halo esters have been reported using free radical conditions. However, high temperatures were required and only moderate yields were reported.[6] Milder reaction conditions and a greater variety of coupling partners might be expected when palladium catalysts are used, however. Consequently, it appeared to be worthwhile to attempt the coupling reaction of α-halo esters with various organotin reagents in the presence of a palladium catalyst.

The coupling reactions of α-bromo- and α-iodo-γ-butyrolactone with allyltin reagents and tributylacetonyltin were carried out under different conditions to give high yields of coupled products (Table I). Only moderate yields could be obtained with α-bromoacetate esters, even at higher reaction temperatures. Much shorter reaction



times were required when dibutyldiallyltin was used rather than tributylallyltin. The reaction with acetonyltin required higher temperatures than that with allyltin. Other organotin reagents such as tributylphenyltin, tributylvinyltin, tributyl(2-phenylethyl)tin, and tributylcyanomethyltin gave poor yields of coupled products (<10%) under all conditions studied.

The coupling reaction with α-iodo-γ-butyrolactone appeared to proceed primarily through a radical mechanism since both galvinoxyl and 1,4-cyclohexadiene completely stopped the 30 °C reaction with tributylallyltin while the 50 °C reaction with tributylacetonyltin was slightly supressed. In both cases, in the absence of the palladium catalyst, the reaction still proceeded to some extent. Similar results are also observed for the coupling of α-iodo-γ-butyrolactone with tributylacetonyltin. The coupling was slightly supressed in the presence of galvinoxyl but also took place in the absence of the palladium catalyst. The coupling of α-bromo-γ-butyrolactone with the acetonyltin reagent did not take place in the absence of the palladium catalyst, and it was not stopped by galvi-

(1) (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992. (b) Milstein, D.; Stille, J. K. *J. Org. Chem.* **1979**, *44*, 1613. (c) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 669. (d) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *103*, 6129. (e) Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634. (f) Soderquist, J. A.; Leong, W. W.-H. *Tetrahedron Lett.* **1983**, *24*, 2361.
(2) (a) Godschalx, J. P; Stille, J. K. *Tetrahedron Lett.* **1980**, *21*, 2599. (b) Sheffy, F. K.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 7173. (c) Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833.
(3) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630.
(4) Yamamoto, A.; Morifuji, K.; Ikeda, S.; Saito, T.; Uchida, Y.; Misono, A. *J. Am. Chem. Soc.* **1968**, *90*, 1878.
(5) Moravskiy, A.; Stille, J. K. *J. Am. Chem. Soc.* **1981**, *103*, 4182.
(6) (a) Grianon, J.; Servens, C.; Pereyre, M. *J. Organomet. Chem.* **1975**, *96*, 225. (b) Migita, T.; Nagai, K.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2480.

0022-3263/85/1950-1759$01.50/0