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The β-Heteroatom Effect on Carbenes

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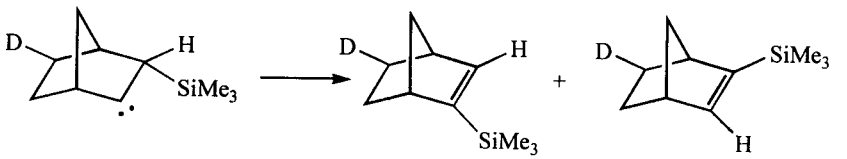
Abstract: The β-thiophosphinoyl carbene $PhCCH_2P(S)Ph_2$ (**5**) has been prepared by irradiation of the corresponding diazo compound. The relative rates for insertion into the OH bond of methanol and for addition to the double bond of 2-methyl-2-butene indicate enhanced nucleophilic properties of the carbene, comparable to those of $PhCCH_2CH_3$. The unusual effect of increased nucleophilicity by an electron-withdrawing substituent probably results from hyperconjugative electron donation by the C-P bond, as recently documented for the same group in a carbocation. © 1997 Elsevier Science Ltd.

The effects of heteroatoms that are directly bonded (α) to a carbene center (HCX and YCX) have comprised a central part of the history of the subject.[1] Such atoms and groups can interact electronically with the carbene center directly. A β heteroatom that is separated from the carbene center by a saturated carbon atom can interact only indirectly by a mechanism such as hyperconjugation. Such effects have been examined sparingly. There is an analogy with electronic effects on carbocations, in which the α effect as in $CH_3O\text{-}CH_2^+$ involves direct conjugation but the β effect as in $Me_3SiCH_2\text{-}CH_2^+$ must invoke hyperconjugation.[2] β Heteroatoms that are integral parts of functional groups such as the oxygens in ketones or esters are considered to contribute to the α effect of the functionality and are not considered in this context, e.g., $HCCO_2Et$.

Creary and Wang carried out one of the few studies on the β effect of heteroatoms on carbenes, using the trimethylsilyl group as the β functionality.[3] The bicyclic carbene **1** primarily underwent 1,2-trimethylsilyl and 1,2-hydride shift to produce **2** and **3**. The unsubstituted norbornyl carbene gave nortricyclane exclusively by 1,3 insertion. Thus the β-trimethylsilyl group has a higher migratory aptitude than normal hydrogens but in addition enhances the migratory aptitude of the geminal hydrogen. Shimizu and Gordon[4] examined the effect of β-silyl groups on the carbene singlet-triplet splitting. Replacing a methyl group (as in $HCCH_3$) with CH_2SiH_3 ($HCCH_2SiH_3$) stabilizes



1 2 3

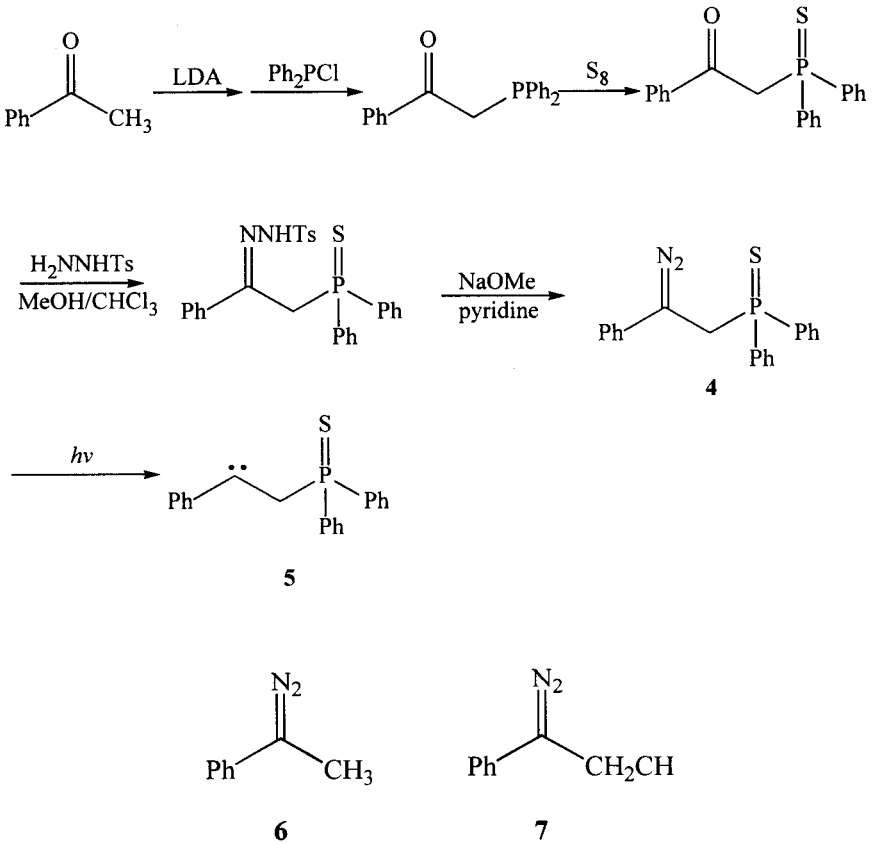
the singlet state by 4.4-5.4 kcal mol^{-1}, depending on the level of theory, sufficient to invert the singlet-triplet order and favor the singlet state. Substitution of CH_2SiH_3 also increases the π orbital population by about 0.1 electron. This β effect is almost as large as the α effects of Cl or F but is much smaller than the α effects of OH or NH_2.

Experimental studies of the β effect of silicon on carbenes have been hampered by synthetic difficulties. Efforts by us and others to examine simple systems such as $PhCCH_2SiMe_3$ have been thwarted by inability to convert the ketone $Ph(CO)CH_2SiMe_3$ to the corresponding tosylhydrazone without loss of trimethylsilyl. Consequently, we have sought an alternative β group in which to examine these effects. Recently we discovered that thiophosphinoyl (phosphine sulfides), as in $Ph_2P(=S)$-, is a very strong β-effect group for stabilizing carbocations.[5] We found that the trans to cis ratio for solvolysis of β-diphenylthiophosphinoyl mesylates in six-membered rings was $3.2x10^6$ at 25°C in 97% trifluoroethanol (trans can hyperconjugate, whereas cis cannot). At the MP2 level, we found that $H_2P(S)$-CH_2-$\overset{+}{C}HCH_3$ was 10.5 kcal mol^{-1} more stable when the P-C bond was parallel to the empty orbital than when perpendicular. These observations suggested that a β-thiophosphinoyl group on a carbene may exhibit interesting properties and moreover may be more amenable to synthesis than β-silyl groups. We report herein the preparation and characterization of the first carbene carrying a β-thiophosphinoyl group.

RESULTS AND DISCUSSION

The β-thiophosphinoyl carbene was prepared by the sequence described in Scheme I. Conversion of acetophenone to its anion with lithium diisopropylamide (LDA, iPr_2NLi) and reaction of the anion with chlorodiphenylphosphine gave diphenyl(benzoylmethyl)phosphine. Immediate sulfuration produced the analogous phosphine sulfide, which was converted to the tosylhydrazone by action of tosylhydrazine. Reaction of the hydrazone with methoxide yielded the diazo compound (**4**) as a deep red liquid. As models to assess the effect of the thiophosphinoyl group, two other diazo substrates (**6** and **7**) were prepared, in which the β groups respectively are hydrogen and methyl.

Scheme I



The method of Doering and Henderson[6] was used to examine carbene reactivity. Simple alkenes such as 2-methyl-2-butene are efficient trapping agents for many electrophilic carbenes, but are not always reactive toward nucleophilic carbenes.[7] On the other hand, methanol is known to be very reactive with both electrophilic and nucleophilic carbenes.[8] The rate ratio for insertion (k_{ins}) into the OH bond of methanol to addition (k_{add}) to the double bond therefore provides a measure of the philicity of the carbene. According to the method of Doering and Henderson,[6] the rate ratio of rates may be obtained from the ratio of molar concentrations of products (P_{ins} and P_{add}), adjusted for the initial molar concentrations (I_{ins} and I_{add}), as in eq 1. For example, Tomioka and co-workers

$$\frac{k_{ins}}{k_{add}} = \frac{P_{ins}}{P_{add}} \frac{I_{add}}{I_{ins}} \tag{1}$$

recently applied this method to aryl carbenes carrying α-hydroxy, phosphonato, carboxy, carbomethoxy, or carboxylato groups.[9] For the carboxylate carbene $ArC(CO_2^-)$ they found k_{ins}/k_{add} to be >100, whereas for carboxy ($ArCCO_2H$) and carbomethoxy ($ArCCO_2Me$) (Ar = *p*-nitrophenyl) the ratio was 0.3-0.5. The carboxylate anion, they reasoned, participates as a neighboring group with the carbene and reduces its electrophilicity and hence its reactivity with the alkene.

The three diazo compounds, **4**, **6**, and **7**, were subjected to irradiation without sensitizer to produce their respective carbenes (**5**, $PhCCH_3$, and $PhCCH_2CH_3$) in a binary mixture of methanol (for k_{ins}) and 2-methyl-2-butene (for k_{add}) in various ratios. Scheme II indicates the expected reactions that took place, and Table 1 contains the measured product ratios. The thiophosphinoyl diazo compound was not soluble in the 1/10 solution.

Scheme II

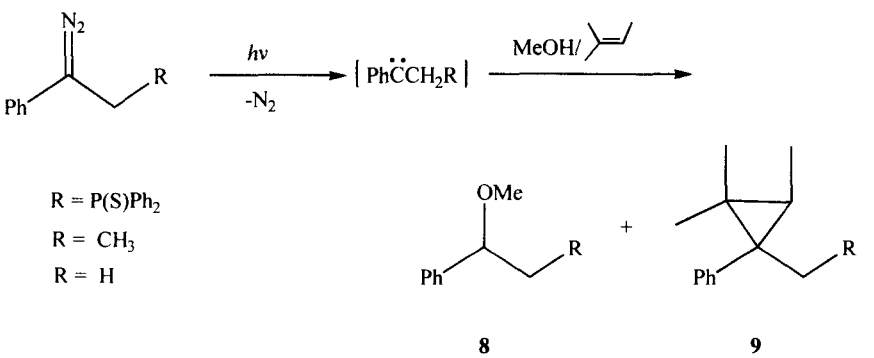


Table 1. Insertion/Addition Selectivities (k_{ins}/k_{add}) for $PhCCH_2R$

CH_3OH / 2-methyl-2-butene	**8/9**		
	R = $PSPh_2$	R = CH_3	R = H
1/1	>100	>100	33/1
1/3.5	>100	>100	8/1
1/10	insoluble	25/1	3/1

According to these results, the three carbenes $PhCCH_2R$ follow the nucleophilicity order for the group R of $PSPh_2$ ~ CH_3 > H. Without data at 1/10, we cannot distinguish between $PSPh_2$ and CH_3. The high preference for insertion over addition clearly indicates that the $CH_2P(S)Ph_2$ group

is in the same category as CH_2CH_3 and CO_2^-, in distinction to CO_2H and CO_2Me. As a general rule, electron-withdrawing groups such as CO_2R enhance the electrophilicity of a carbene and electron-donating groups such as OCH_3 enhance the nucleophilicity.[10] Electrophilic carbenes tend to have low-lying LUMOs. Adjacent electron donors raise the carbene LUMO and lower its HOMO, enhancing nucleophilic characteristics. The β-thiophosphinoyl group is electron withdrawing by any measure (for example, $\sigma_m = 0.29$, $\sigma_I = 0.15$)[11] and normally would be expected to enhance electrophilicity. The results in Table 1, however, indicate that its effect in the β position is to enhance nucleophilicity. Hyperconjugation through electron donation from the β C-P bond can simulate the more familiar effects of α donors and compensate for inductive withdrawal.

These results parallel those for β-thiophosphinoyl-substituted carbocations, for which β C-P hyperconjugation was proved calculationally and supported experimentally.[5] The reactivity of thiophosphinoyl, in which the effects of hyperconjugation outweigh those of induction, parallel the α reactivity of alkoxy or amino, in which the effects of simple conjugation outweigh those of induction. In this fashion a β electron-withdrawing group can provide electron donation and enhance carbene nucleophilicity in **5**. The results with the carbene $PhCCH_2P(S)Ph_2$ must be regarded as preliminary. A referee has pointed out the possibility that there may be steric retardation of the reaction of the carbene with 2-methyl-2-butene. Further experiments are planned on the reactions of the carbene with alkenes in the absence of alcohol in order to refine its placement on the electrophile/nucleophile continuum.

EXPERIMENTAL SECTION

Diphenyl(benzoylmethyl)phosphine Sulfide. To a solution of LDA (0.023 mol), prepared from 4 g of iPr_2NH and 9.2 mL of 2.5 M BuLi in 30 mL of THF, 2.4 g (0.02 mol) of acetophenone in 10 mL of THF was added under N_2 at -78°C. After about 30 min, 3.6 mL (0.02 mol) of chlorodiphenylphosphine was added, and the solution was allowed to warm to room temperature. Then 4 mL of H_2O was added to quench the reaction. Immediately after quenching, 1.6 g (0.05 mol) of sulfur powder was added. The deep red solution was stirred at room temperature for 2 h. Saturated aqueous NH_4Cl solution (10 mL) and brine (10 mL) then were added, and the layers were separated. The aqueous layer was extracted with THF (2 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). After removal of the solvent under rotary evaporation, a red oil was obtained. Chromatography (silica gel, 1/3 acetone/petroleum ether) gave 3.2 g (48%) of a yellow solid: ^1H NMR ($CDCl_3$) δ 4.3 (d, J = 15 Hz, 2H), 7.45 (m, 9H), 7.85 (m, 6H); ^{13}C

NMR ($CDCl_3$) δ 44.6, 45.3, 128.4, 128.4, 128.6, 129.3, 131.4, 131.6, 131.7, 131.7, 133.5, 192.5; ^{31}P NMR ($CDCl_3$) δ 55.20.

Synthesis of Diphenyl(benzoylmethyl)phosphine Sulfide p-Toluenesulfonylhydrazone. To a round-bottomed flask charged with 0.55 g (0.003 mol) of *p*-toluenesulfonylhydrazine and 10 mL of MeOH, was slowly added a solution of 1 g (0.003 mol) of the corresponding ketone in 10 mL of $CHCl_3$. The mixture was stirred at room temperature until the product fully crystallized. The crystals were filtered and recrystallized from MeOH/$CHCl_3$ to give 1.0 g (68%) of colorless crystals: ^1H NMR ($CDCl_3$) δ 2.55 (s, 3H), 4.20 (d, 2H), 6.98 (m, 4H), 7.10 (m, 1H), 7.30 (m, 4H), 7.40 (m, 4H), 7.55 (m, 4H), 8.0 (d, 2H); ^{13}C NMR ($CDCl_3$) δ 21.7, 35.3, 36.0, 126.5, 127.8, 128.4, 128.5. 128.6, 129.3, 131.0, 131.1, 132.1, 135.5, 136.3, 143.8, 149.8, 149.9; ^{31}P NMR ($CDCl_3$) δ 53.13. *Anal.* Calcd for $C_{27}H_{25}N_2O_2PS_2$: C, 64.27; H, 4.99; N, 5.55. Found: C, 64.21; H, 5.00; N, 5.57.

Synthesis of 1-Propiophenone p-Toluenesulfonylhydrazone.[12] In a 100 mL, round-bottomed flask, 13.42 g (0.1 mol) of propiophenone was added to a heated solution containing 18.63 g (0.1 mol) of *p*-toluenesulfonylhydrazine in 23.4 mL of acetic acid. The mixture was heated to the boiling point or until product crystallization began, and then was cooled to room temperature. The crystalline product was filtered and washed with cold acetic acid (2 x 50 mL), cold aqueous acetic acid (50 mL), and cold H_2O (3 x 50 mL). Recrystallization from acetic acid gave 26 g (86%) of cubic crystals: ^1H NMR ($CDCl_3$) δ 1.10 (t, 3H), 2.41 (s, 3H), 2.57 (q, 2H), 7.35 (m, 5H), 7.64 (dd, 2H), 7.90 (d, 2H).

Synthesis of Acetophenone p-Toluenesulfonylhydrazone.[12] The procedure was the same as that for the propiophenone hydrazone. The reaction yielded 14.4 g (50%) of a white powder: ^1H NMR ($CDCl_3$) δ 2.15 (s, 3H), 2.42 (s, 3H), 7.35 (m, 5H), 7.65 (dd, 2H), 7.91 (d, 2H).

1-Phenyldiazopropane (7).[12] In a dry flask, 1.50 g (5 mmol) of 1-propiophenone *p*-toluenesulfonylhydrazone and 270 mg (5 mmol) of NaOMe were mixed in 15 mL of fresh pyridine. The mixture was protected under N_2 and heated with stirring for 1 h in a water bath held at 60-65°C. The initial precipitate dissolved and a granular precipitate began to form, while the supernatant solution turned wine red. At the end of the heating period, the mixture was poured into ice-water (75 mL) and extracted with pentane (2 x 30 mL). The combined pentane extracts were washed with cold H_2O (4 x 45 mL) and once with saturated aqueous NaCl. The organic solution then was dried (Na_2SO_4) at 5°C, filtered, and evaporated to dryness under vacuum at room temperature to give 0.31 g (43%) of a red oil: ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H), 2.53 (q, 2H), 6.94 (d, 2H), 7.03 (t, 1H), 7.33 (t, 2H).

1-Phenyl-2-(diphenylthiophosphinoyl)diazoethane (4). The procedure was almost the same as

that for 1-phenyldiazopropane, except the oil bath was heated to 95-100°C and the reaction time was 10 min. The reaction yielded 0.21 g (20%) of a wine red liquid: ^{31}P NMR ($CDCl_3$) δ 57.7.

1-Phenyldiazoethane (6).[12] The procedure was almost the same as that for 1-phenyldiazopropane, except the temperature of the water bath was 75-80°C and the reaction time was 40 min. The reaction yielded 0.43 g (39%) of a wine red liquid: ^1H NMR ($CDCl_3$) δ 2.16 (s, 3H), 6.92 (d, 2H), 7.04 (t, 1H), 7.33 (t, 2H).

Kinetic Method. In a typical run, a solution of the diazo compound (ca. 100 mg) was placed in a Pyrex tube along with reaction partners (methanol and 2-methyl-2-butene). The solution was degassed by three freeze-thaw cycles. Then the solution was irradiated with a high-pressure, 400 W Hg lamp at room temperature until all the diazo compound was destroyed (the color of the mixture changed from wine red to slightly yellow).

Product Studies. The irradiation mixtures were analyzed by GCMS. Some individual components (**8** (R = CH_3, H) and **9** (R = CH_3, H)) were isolated by preparative gas chromatography (2.8% Apiezon L, 1/4 in. x 20 ft). **8** (R = CH_3) was identified by ^1H NMR δ 0.9 (t, 3H), 1.7 (m, 1H), 1.8 (m, 1H), 3.2 (s, 3H), 4.0 (t, 1H), 7.3 (m, 5H); ^{13}C NMR δ 10.2, 30.9, 59.6, 85.5, 127.4, 128.3, 131.0, 142.2; MS peak at 150 (M^+). **8** (R = H) was identified by ^1H NMR δ 1.4 (d, 3H), 3.2 (s, 3H), 4.3 (q, 1H), 7.3 (m, 5H); ^{13}C NMR δ 23.9, 56.4, 79.6, 126.2, 127.4, 128.4, 143.6; and MS peak at 136 (M^+). **9** (R = CH_3, H) were identified by MS (M^+ = 188, 174). **9** (R = $P(S)Ph_2$) was identified by GCMS (M^+ = 352).

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REFERENCES AND NOTES

1. Kirmse, W. *Carbene Chemistry*; Academic Press: New York, 1964, Chapters 8 and 9.
2. For a review of the β effect of silicon on carbocations, see Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677-2689.
3. Creary, X.; Wang, Y.-X. *Tetrahedron Lett.* **1989**, *30*, 2493-2496.
4. Shimizu, H.; Gordon, M. S. *Organometallics* **1994**, *13*, 186-189.
5. Lambert, J. B.; Zhao, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3156-3167.
6. Doering, W. von E.; Henderson, W. A., Jr. *J. Am. Chem. Soc.* **1958**, *80*, 5274-5277.

7. Quast, H.; Huning, S. *Chem. Ber.* **1966**, *99*, 2017-2038. Richter, R.; Ulrich, H. *J. Org. Chem.* **1971**, *36*, 2005-2008. Brown, J. M.; Place, B. D. *Chem. Commun.* **1971**, 533-534. Hartzler, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 4379-4387.
8. Kirmse, W.; Loosen, K.; Sluma, H. D. *J. Am. Chem. Soc.* **1981**, *103*, 5935-5937. Kirmse, W. *Adv. Carbene Chem.* **1994**, *1*, 1-57 and references therein.
9. Tomioka, H.; Hirai, K.; Tabayashi, K.; Murata, S.; Izawa, Y.; Inagaki, S.; Okajima, T. *J. Am. Chem. Soc.* **1990**, *112*, 7692-7702. Tomioka, H.; Nunome, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 1243-1244. Tomioka, H.; Hirai, K. *J. Chem. Soc., Chem. Commun.* **1990**, 1611-1613.
10. Moss, R. A. *Acc. Chem. Res.* **1980**, *13*, 58.
11. Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; John Wiley & Sons: New York, 1979.
12. Farnum, D. G. *J. Org. Chem.* **1963**, *28*, 870-872.

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