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A Congested *in,in*-Diphosphine

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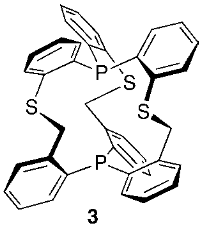
ABSTRACT



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The synthesis and characterization of the bis(triarylphosphine) 3 are described. Slow protonation of an inwardly directed phosphine is possible, but the phosphines do not react with larger reagents. X-ray structures of the parent compound, its HCl salt, and the corresponding trisulfone are reported. Compound 3 was resolved by chiral chromatography, but the barrier to racemization is only 20.7 kcal/mol.

The *in,out*-isomerism of bridged bicyclic compounds has been extensively studied for compounds containing amines, ammonium ions, and methine groups at bridgehead positions.[1] Much less common are the analogous bridgehead phosphorus compounds, and a recent review of this specific topic[2] provided no examples of an *in,in*-bisphosphine,[3,4] although *out,out*-bisphosphines (e.g., **1**, Scheme 1) and bisphosphonium ions are well-known, and the protonation of medium-ring *out,out*-bisphosphines can give remarkable *out*-protonated *in,out*-isomers (e.g., **2**).[2,5] We recognized that our own studies of *in*-phosphaphanes[6] had left us with the starting materials for a simple synthesis of the *in,in*-diphosphine **3** and that this compound would likely possess only high-energy *out,out*- and *in,out*-isomers, thus permitting the study of the spectra and reactivity of face-to-face, interacting phosphines. We now report the synthesis and full characterization of compound **3**, its hydrochloride salt, and the corresponding trisulfone, all of which exist as *in,in*-isomers.

Base-promoted condensation of tris[2-(chloromethyl)-phenyl]phosphine[7] (**4**) and tris(2-mercaptophenyl)phosphine[8] (**5**) at high dilution provided cyclophane **3** in 10% yield. Given that B3PW91/6-31G(d) calculations[9] place *in,in*-**3** more than 18 kcal/mol lower in energy than either *in,out*-isomer, and fully 30 kcal/mol lower than the *out,out*-isomer, the *in,in*-isomer was the expected product. Immediate evidence for interacting phosphorus atoms was provided by its ^{31}P NMR spectrum, which shows a pair of doublets with J_{PP} = 175 Hz, comparable to the J_{PP} = 178 Hz for compound **2**, where the P–P contact distance is only 2.58 Å.[5b] Eventually, single crystals of compound **3** were obtained from $CHCl_3$–MeOH, and its X-ray structure was determined. The structure contains two

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(1) Review: Alder, R. W.; East, S. P. *Chem. Rev.* **1996**, *96*, 2097–2111.

(2) Review: Bauer, I.; Habicher, W. D. *Collect. Czech. Chem. Commun.* **2004**, *69*, 1195–1230.

(3) However, there exists two examples of very large, macrobicyclic *in,in*-diphosphites, but the phosphorus atoms in these molecules are far apart.

(4) (a) Bauer, I.; Rademacher, O.; Gruner, M.; Habicher, W. D. *Chem.—Eur. J.* **2000**, *6*, 3043–3051. (b) Bauer, I.; Fröhlich, R.; Ziganshina, A.; Prosvirkin, A.; Gruner, M.; Kazakova E., Kh.; Habicher, W. D. *Chem.—Eur. J.* **2002**, *8*, 5622–5629.

(5) (a) Alder, R. W.; Ellis, D. D.; Gleiter, R.; Harris, C. J.; Lange, H.; Orpen, A. G.; Read, D.; Taylor, P. N. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1657–1668. (b) Alder, R. W.; Butts, C. P.; Orpen, A. G.; Read, D.; Oliva, J. M. *J. Chem. Soc., Perkin Trans. 2* **2001**, 282–287. (c) Alder, R. W.; Butts, C. P.; Orpen, A. G.; Read, D. *ibid.* **2001**, 288–295.

(6) (a) Pascal, R. A., Jr.; West, A. P., Jr.; Van Engen, D. *J. Am. Chem. Soc.* **1990**, *112*, 6406–6407. (b) L'Esperance, R. P.; West, A. P., Jr.; Van Engen, D.; Pascal, R. A., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 2672–2676. (c) West, A. P., Jr.; Smyth, N.; Kraml, C. M.; Ho, D. M.; Pascal, R. A., Jr. *J. Org. Chem.* **1993**, *58*, 3502–3506. (d) Dell, S.; Ho, D. M.; Pascal, R. A., Jr. *J. Org. Chem.* **1999**, *64*, 5626–5633. (e) Chen, Y. T.; Baldridge, K. K.; Ho, D. M.; Pascal, R. A., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 12082–12087.

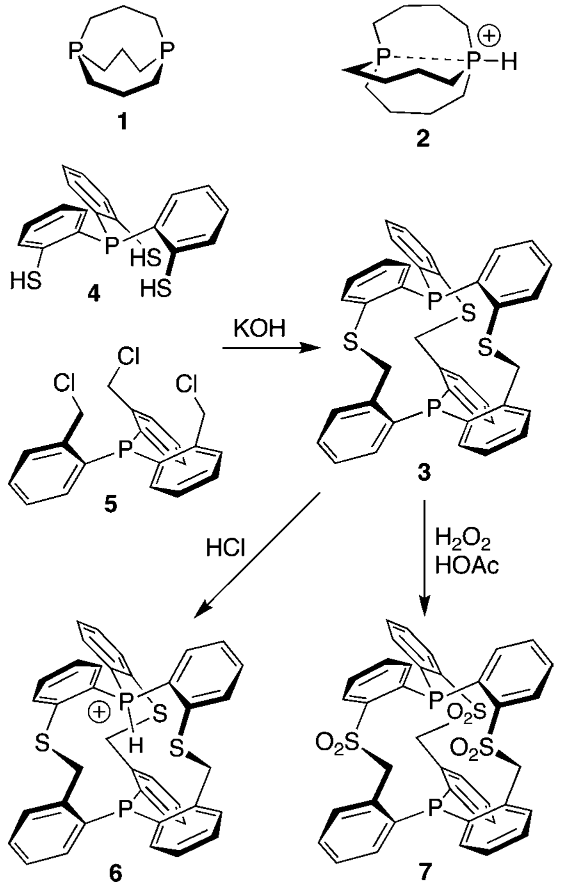
(7) Letsinger, R. L.; Nazy, J. R.; Hussey, A. S. *J. Org. Chem.* **1958**, *23*, 1806–1807.

(8) Block, E.; Ofori-Okai, G.; Zubieta, J. *J. Am. Chem. Soc.* **1989**, *111*, 2327–2329.

(9) DFT calculations were performed by using GAUSSIAN 09, revision A.02; its built-in default thresholds for wave function and gradient convergence were employed. All potential minima and transition states were characterized by analytical frequency calculations, and all relative energies quoted include zero-point energy corrections.

10.1021/ol400728m

Scheme 1



independent molecules, each with crystallographic C_3 symmetry; the molecular structure of one of these is illustrated in Figure 1. As expected, the cyclophane adopts an *in,in*-conformation, with P–P contact distances of 3.72 and 3.51 Å in the two independent molecules, both somewhat shorter than the calculated distance of 3.79 Å at the B3PW91/6-31G(d) level.[10]

Compound **3** is a chiral molecule with twin molecular propellers, but its configurational stability was uncertain. High temperature ^{1}H NMR spectra showed no coalescence or even broadening of its diastereotopic methylene resonances at δ 4.06 and δ 5.16; therefore, a chromatographic resolution was pursued. Clear separations of the enantiomers were achieved by using supercritical fluid chromatography (SFC) on a Chiralpak IA column with both $EtOH/CO_2$ and *i*$PrOH/CO_2$ as mobile phases. However, both chromatograms show a "bridge" between the peaks (see the Supporting Information), indicating that significant racemization occurs during the separation. The method of Trapp[11] was employed to extract the rate constants for racemization from these "dynamic chromatograms", ultimately yielding barriers to racemization ($\Delta G^{\ddagger}_{\mathrm{rac}}$) of 20.7 and 20.6 kcal/mol, respectively, for the two separations at 22 °C. This corresponds to a half-life of *ca.* 7 min at this temperature, too short for any simple isolation of the resolved enantiomers.

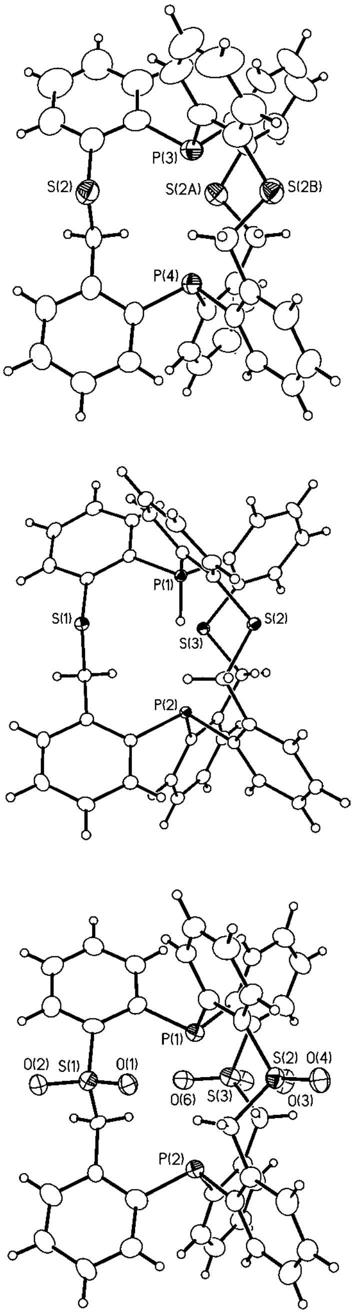


Figure 1. Molecular structures (top-to-bottom) of diphosphine **3** (top), the monohydrochloride **6**, and the trisulfone **7** (50% thermal ellipsoids have been employed).

The possibility that **3** might exhibit some internal reactivity was most interesting to us. Is the internal cavity accessible to reagents, or would phosphine inversion (a high-energy process) be required for reactivity? When HCl gas was bubbled into chloroform solutions of compound **3**, protonation occurred as a first-order process with

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[10] DFT methods commonly overestimate the contact distances in strained cyclophanes: Pascal, R. A., Jr. *J. Phys. Chem. A* **2001**, *105*, 9040–9048.

[11] Trapp, O. *Chirality* **2006**, *18*, 489–497.

a half-life of 26 min, as monitored by ^{1}H NMR. The new proton resonance (δ 14.08) was a doublet of doublets with J_{PH}'s of 584 and 13 Hz, clearly indicating an asymmetric protonation of the diphosphine, and the coupling of the phosphorus atoms (J_{PP}) increased to 304 Hz, nearly double the value in **3**. Single crystals of the hydrochloride **6** were obtained from $CHCl_3-MeOH$, and the X-ray structure confirmed the asymmetric protonation of the *in,in*-diphosphine (Figure 1). The proton is bound to the more basic, sulfur-substituted triaryl phosphine (d_{P-H} = 1.29 Å) with the second phosphine at a reasonable hydrogen-bonded distance (2.59 Å).[12,13] It seems that protonation is slow because the *in*-phosphine lone pair only rarely tips away from the center of the molecule to permit a reaction with an acid, raising the question: can larger electrophiles react at phosphorus?

When compound **3** was heated in a refluxing solution of acetic acid and 30% H_2O_2, the hexaoxide **7** was obtained; mass spectrometric analysis of the reaction mixture showed no evidence of a seventh oxygen atom (on a phosphorus). The X-ray structure of this relatively insoluble material (recrystallized from hot DMSO) confirmed that only the trisulfone had been obtained (Figure 1). The interior of the molecule seems to be completely shielded from further reaction, even under these harsh conditions, by the surrounding sulfone groups.

We have previously observed the formation of an *out*-phosphine sulfide from an *in*-phosphine containing cyclophane upon prolonged heating with sulfur in benzene in a sealed tube at 145 °C.[6e] However, a similar treatment of compound **3** gave no addition of sulfur, either *in* or *out*. The transition states for inversion of *in,in*-**3** to give each of the *in,out*-isomers was located at the B3PW91/6-31G(d) level, and the $\Delta G^{\ddagger}{}_{\text{inv}}$'s for these processes were calculated to be 26.2 and 28.8 kcal/mol; thus the formation of *out*-atom adducts would be very slow at best, and the existence of the *in,out*-isomers, which have barriers of only 8–10 kcal/mol to return to the *in,in* ground state, would be fleeting.

Other *in*-functionalization experiments included heating with S_2Cl_2, BF_3, and silver and gold salts (to form linear metal diphosphine complexes) in various solvents at various temperatures, but all were unsuccessful. It must be admitted that, with the possible exception of a BF_3 complex, these larger atoms would be a tight fit for the interior cavity of the diphosphine.

In conclusion, the six benzo groups of the diphosphine **3**, by means of bond angle and torsion angle restrictions, enforce a strong preference for an *in,in*-geometry, despite a presumably unfavorable interaction of the inwardly directed phosphine lone pairs. The resulting cage is sufficiently rigid to prevent all but the smallest reagents, a proton, from gaining access to the interior cavity.

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Supporting Information Available. Experimental procedures and NMR spectra for compounds **3**, **6**, and **7**; chromatograms showing the resolution of compound **3**; crystallographic information files (CIF) for the structure determinations of **3**, **6**, and **7** as well as the atomic coordinates and energies of the calculated structures of the conformational isomers of **3** and the calculated transition states for its *in*/*out* isomerization. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] The proton's position was refined in the X-ray structure, but the P–H bond distance is likely to be underestimated because, having no core electrons, the peak of the hydrogen electron density is displaced slightly toward the phosphorus.[13] The actual P–H distance is probably about 1.4 Å.

[13] Churchill, M. R. *Inorg. Chem.* **1973**, *12*, 1213–1214.

The authors declare no competing financial interest.