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An *in*-Triphenylaminophane

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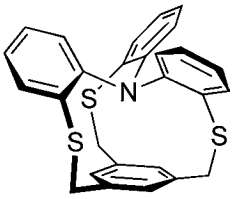
ABSTRACT



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The synthesis and characterization of the triphenylamine-capped cyclophane 3 are described. It proved to be a conformationally rigid molecular propeller, with an inwardly pyramidalized, unreactive amine.

For 25 years, we have pursued the synthesis of sterically congested, mostly C_3-symmetric *in*-cyclophanes (**1**, Figure 1) bearing functional groups (X−Y = C−H, C−Me, Si−H, Si−F, and P−lp) projected toward aromatic rings.[1,2] Prominent among these compounds are the *in*-phosphaphanes **2a**−**d**, which possess unusual structure, spectra, and reactivity: the shortest reported phosphorus−arene nonbonded contact distances,[1,3−5] strong spin−spin coupling between the phosphorus atoms and the carbons of the basal aromatic rings,[3−5] strong circular dichroism of the resolved enantiomers,[5] and exceptional resistance to protonation or oxygenation of the *in*-phosphine.[3,4] Only the *in*-isomers of these phosphines have been observed, but the *out*-isomer of a related cyclophane was trapped by sulfuration of the phosphorus.[6]

The analogous aminophane **3** would provide interesting points for comparison. For example, triarylphosphines are pyramidalized and have high barriers to inversion,[6,7] but free triphenylamine has an essentially planar, sp^2-hybridized nitrogen atom,[8] and even pyramidal amines have low barriers to inversion. One may ask, will compound **3** exhibit an inwardly pyramidalized nitrogen atom? Will **3** be conformationally flexible or relatively rigid? Will it be reactive?

Cyclophane **3** has long been elusive. The synthesis of the phosphaphanes was facilitated by Block's one-step synthesis of tris(2-mercaptophenyl)phosphines,[9] but this method is not applicable to amines. Earlier attempts to prepare the key precursor of **3**, tris(2-mercaptophenyl)amine (**9**, Scheme 1), from the readily available[10] tris(2-chlorophenyl)amine (**5**) invariably failed. In this paper we report at last a four-step synthesis of the triphenylaminophane **3** and its crystallographic and spectroscopic characterization.

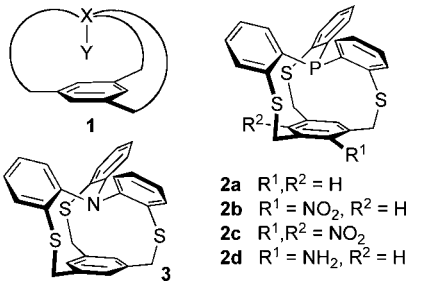

Figure 1. *in*-Cyclophanes.

Nucleophilic substitution of the chlorine atoms of **5** with sodium isopropylthiolate to give thioether **8** appears to fail

(1) Review: Pascal, R. A., Jr. *Eur. J. Org. Chem.* **2004**, 3763–3771.
(2) Selected examples: (a) Pascal, R. A., Jr.; Grossman, R. B.; Van Engen, D. *J. Am. Chem. Soc.* **1987**, *109*, 6878–6880. (b) Pascal, R. A., Jr.; Winans, C. G.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 3007–3010. (c) Dell, S.; Ho, D. M.; Pascal, R. A., Jr. *J. Org. Chem.* **1999**, *64*, 5626–5633. (d) Song, Q.; Ho, D. M.; Pascal, R. A., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 11246–11247. (e) Qin, Q.; Mague, J. T.; Pascal, R. A., Jr. *Org. Lett.* **2010**, *12*, 928–930.
(3) Pascal, R. A., Jr.; West, A. P., Jr.; Van Engen, D. *J. Am. Chem. Soc.* **1990**, *112*, 6406–6407.
(4) L'Esperance, R. P.; West, A. P., Jr.; Van Engen, D.; Pascal, R. A., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 2672–2676.
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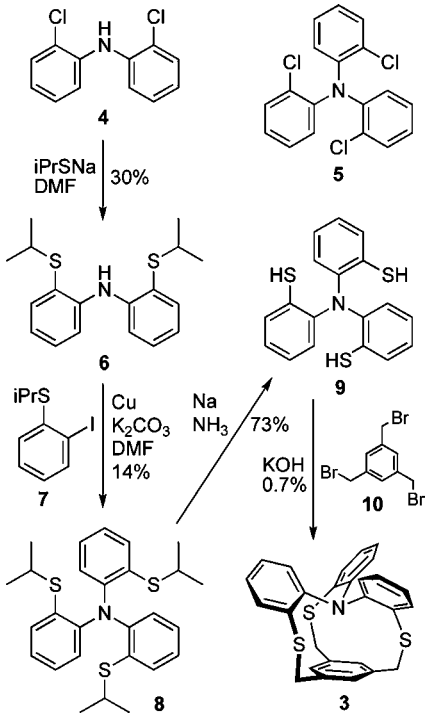
due to steric impediments. However, the Ullmann synthesis of amines is relatively insensitive to crowding; thus we decided to prepare **8** from precursors already containing the bulky isopropyl thioethers. Treatment of bis(2-chlorophenyl)amine (**4**), available as an abundant byproduct of the synthesis of **5**,[10] with sodium isopropylthiolate gave thioether **6** in fair yield after purification (28%). A similar monosubstitution of *o*-diiodobenzene gave the thioether **7**. Ullmann reaction of **6** and **7** in refluxing NMP produced only *N*-arylphenothiazines (data not shown), but when the reaction was carried out under the milder condition of refluxing DMF, the crowded thioether **8** was obtained in a low but tolerable 14% yield.[11] The crowding in **8** is evident in its ^{1}H NMR spectrum, which shows broadened methyl resonances due to the slow interconversion of diastereomeric conformations of the molecule. Finally, reductive cleavage of the thioethers by sodium in ammonia gave the key trithiol **9** in good yield (73%).

Scheme 1. Synthesis of Cyclophane **3**



Condensation of **9** with 1,3,5-tris(bromomethyl)benzene[13] (**10**) gave cyclophane **3** in an abysmal 0.7% yield, but the product was easily isolated by chromatography. This very low yield stands in contrast to the much higher, but still modest, yields (typically 15−20%) for the syntheses of phosphaphanes **2**.[3−5]

The ^{1}H NMR spectrum of **3** is similar in most respects to that of the phosphaphane **2a**. However, **2a** displays two distinct resonances for its diastereotopic methylene protons,[3] due to the lack of enantiomerization of the molecular propeller at room temperature, but the methylene protons of **3** exhibit a single sharp resonance at δ 3.78 in $CDCl_3$, suggesting that **3** is conformationally much more mobile than **2a**. This at first seemed reasonable, given that easy inversion at nitrogen provides a conformational degree of freedom not available to the phosphaphanes. However, no low-energy pathway for enantiomerization was found in our computational studies (see below), pointing to a possible accidental isochrony of the diastereotopic methylene resonances in **3**. Indeed, when the spectrum was recorded in benzene-d_6, two sharp doublets were observed at δ 3.55 and δ 3.67, clearly indicating that enantiomerization of **3** is slow (at least on the NMR time scale). Other spectroscopic data provide little to distinguish the properties of compounds **3** and **2a**. For example, given the difference in the UV spectra of triphenylamine (λ_{max} = 303 nm in $CHCl_3$) and triphenylphosphine (260 nm), the UV spectra of **3** and **2a** are surprisingly similar: in $CHCl_3$, aminophane **3** has strong absorption bands at 292 and 336 nm, while phosphaphane **2a** displays absorptions at 292 and 341 nm,[4] with comparable extinction coefficients.

An X-ray structural analysis of compound **3** was thus of prime importance. Single crystals of **3** were obtained by addition of methanol to an NMR sample in $CDCl_3$, and the crystals yielded a high-quality determination without complications. The structures of the two crystallographically independent molecules of **3** are illustrated in Figure 2; both have approximate C_3 symmetry, as expected. The shallow inward pyramidalization of the apical nitrogen atoms is immediately apparent, but to a degree that is much less pronounced than in the phosphaphanes **2**. Thus, the average pyramidality[14] of the triarylamines in the two molecules of **3** is 0.248 Å, but the average pyramidality of the phosphaphanes is 0.741 Å. As noted previously, triphenylamine's nitrogen is not pyramidalized; however, a search of the Cambridge Structural Database[15] found that triarylamines with three *ortho*-substituted benzene rings[16] are pyramidalized to nearly the same degree (average pyramidality, 0.235 Å) as compound **3**. With such a flattened amine in **3**, it is not surprising that the distance of the apical nitrogen from the center of the basal aromatic ring (d_{N-Ar}), 3.419 and 3.398 Å in the two independent molecules, is nearly 0.5 Å greater than the phosphorus−

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(11) We are not unaware of modern methods for the synthesis of arylamines, but, for example, when $Pd(OAc)_2$/DPEphos/NaO*t*Bu/-toluene[12] was used for the coupling, no triarylamine was formed.

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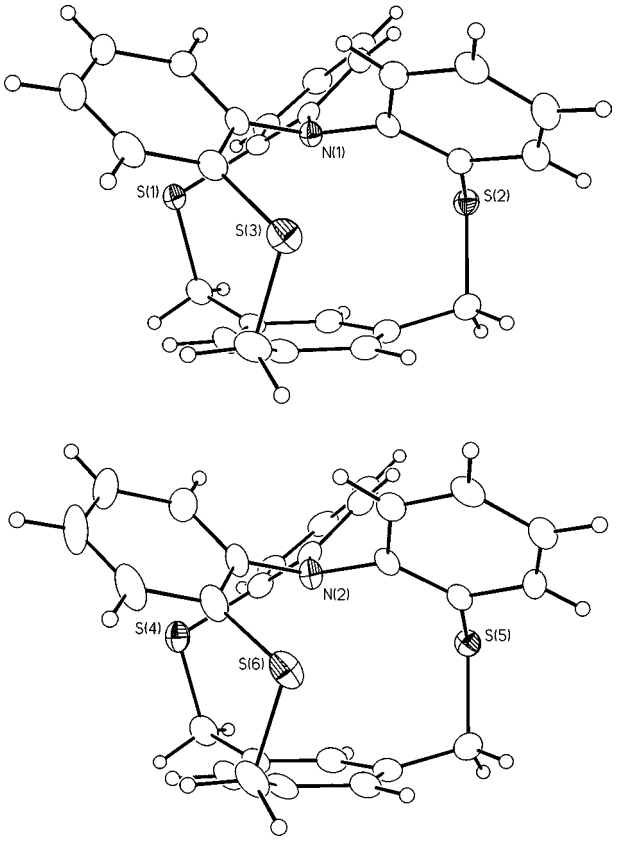

Figure 2. Molecular structures of the two crystallographically independent molecules of cyclophane **3** (50% thermal ellipsoids have been employed).

arene contacts of 2.90−2.98 Å observed in the various phosphaphanes **2**.[3−5]

DFT-computed structures of **3** accurately mimic its overall crystal conformation and the shallow pyramidalization of the nitrogen. These calculations do overestimate, to varying degrees, the nitrogen−arene contact distance, with B3PW91/6-311G(d,p) calculations (d_{N-Ar} = 3.437 Å) giving the best agreement with experiment among many methods.[17] An important aspect of these calculations was the finding of only two potential minima for compound **3**, one with the observed C_3 symmetry, and a higher energy conformation [+11.0 kcal/mol at the B3LYP/6-31G(d) level] with C_1 symmetry. All attempts to locate an *out*-isomer, whether with C_3 or C_1 symmetry, were unsuccessful. This represents a significant difference from the *in*-phosphaphanes, which possess high-energy *out*-isomers.[6]

There exists insufficient compound **3** at present to attempt a resolution into pure enantiomers, but DFT calculations suggest that the barrier to racemization is very high. A C_s-symmetric transition state structure was located at the B3LYP/6-31G(d) level for the direct interconversion of the two enantiomeric C_3 ground state conformations; however, the calculated free energy of this transition state gives $\Delta G^{\ddagger}_{rac}$ = 85 kcal/mol! A more reasonable pathway for enantiomerization is a two-step sequence, C_3 to C_1 to enantiomeric C_3 conformations, for which the calculated transition state free energies are "merely" 44 and 63 kcal/mol (see the Supporting Information). We do not exclude the possibility of lower energy pathways, but compound **3** is almost certainly resolvable.

Finally, there is the question of protonation of compound **3**. Triphenylamine itself is far less basic than triphenylphosphine (for the protonated species, the pK_a's are *ca.* −5 and 2.7, respectively). Furthermore, at the B3LYP/6-31G(d) level, the *out*-protonated amine is calculated to be a full 26 kcal/mol higher in energy than the sterically inaccessible *in*-protonated species, due chiefly to severe angle strain in the *out*-isomer. In the event, dry HCl gas was bubbled into a solution of **3** in $CDCl_3$ for 30 s, and the sample was left to stand for 2 h. ^{1}H NMR analysis at this time showed no change in the cyclophane resonances, and after 24 h, the spectra showed evidence of extensive decomposition and still no evidence of a protonated cyclophane.

In conclusion, the substitution of nitrogen for phosphorus in a triaryl-element-capped cyclophane results in reduced inward pyramidalization of the apical nitrogen, but the compound remains a rigid, unreactive, molecular propeller.

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Supporting Information Available. Experimental procedures and NMR spectra for compounds **6**−**9** and **3**; DFT-calculated pathways for the enantiomerization of **3**; a crystallographic information file (CIF) for the structure determination of **3**; and an ASCII text file containing the atomic coordinates and energies of the calculated structures of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(17) Other methods gave the following distances: B3LYP/6-31G(d), 3.515 Å; B3LYP/6-311G(d,p), 3.502 Å; B3LYP/cc-pVDZ, 3.503 Å; B3LYP/cc-pVTZ, 3.516 Å; B3PW91/6-31G(d), 3.459 Å; B3PW91/cc-pVDZ, 3.438 Å; B3PW91/cc-PVTZ, 3.460 Å.