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Tri(indolyl)phosphine Oxides: Attempted Formation of Lower Rim-Capped Cone Conformers of Calix[3]indoles

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ABSTRACT

*3-(p-Chlorophenyl)-4,6-dimethoxyindole (***1a***), 3-(p-bromophenyl)-4,6-dimethoxyindole (***1b***), 5-benzyloxyindole (***1c***), and indole (***1d***) yield the corresponding tri(indolyl)phosphine oxides (***2a–d***), on sequential treatment with n-butyllithium and phosphoryl chloride. The related phosphines, arsines, and stibines were not isolated. The stibine from indole (***1a***) is implicated as a reactive intermediate in the formation of the calix[3]indole (***5***), following its interaction with formaldehyde. © 1996 John Wiley & Sons, Inc.*

INTRODUCTION

Calix[3]indoles, comprising three indole rings connected to each other at positions 2 and 7 through methylene or substituted methine links, have been reported [1–4]. Under most preparative circumstances, flattened partial cone conformers (one indole ring up, one down, and one horizontal) have been produced, but cone conformers (all three indole rings up) of some carboxamido-substituted calix[3]indoles have been achieved as the result of special hydrogen bond stabilization effects. Molecular modeling studies suggest that the steric hindrance between the three indole NH protons is a significant factor in destabilizing the cone conformation. By removal of the three indole NH protons and their replacement with a single linker, this steric hindrance should be removed. Such a linker could be a group-V element that could hold the three indoles in an orientation similar to that which they adopt in the cone conformation. The synthetic approach to the desired capped calix[3]indoles would be to link three indoles to a group-V element to form a template that would need to remain intact while the lower rim-capped calix[3]indole formed. Removal of the linking element would then produce the cone conformer of the calix[3]indole, which might or might not isomerize to the flattened partial cone conformer.

Covalently linked group-V elements were chosen over metals because of the more predictable nature of their stereochemistry and substitution. The resulting compounds should also behave more like normal organic molecules rather than metal complexes. The element size could be increased from phosphorus through arsenic and antimony to bismuth. The differing oxidation states of phosphorus (+3 and +5) would allow the investigation of trigonal or tetrahedral geometries, respectively. Various heteroatom compounds have been prepared from pyrroles, benzimidazoles, and imidazoles. For instance, the tri(pyrrolyl)phosphine, phosphine oxide, thiophosphine oxide, and arsine have been synthesized by reacting the potassium salt of pyrrole with the appropriate trichloride [5–7]. A recent report refers to an improved preparation of

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Dedicated to Prof. Louis D. Quin on the occasion of his retirement from the Department of Chemistry of the University of Massachusetts at Amherst.

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tri(pyrrolyl)phosphines with the use of triethylamine in tetrahydrofuran [8]. This report also contains a footnote comment about the preparation of tri(indolyl)phosphine. Unlike the aminophosphines, both the tri(pyrrolyl)phosphine and tri(pyrrolyl)-phosphine oxide were stable to nucleophilic attack by water and alcohols but were cleaved by weak base [5–7]. The stability to water and alcohols was attributed to the steric bulk around the phosphorus center. While both the phosphine and phosphine oxide were thermally stable, the corresponding tri(pyrrolyl)arsine decomposed at room temperature and the stibine and bismine could not be isolated. The change in oxidation state and, thus, geometry in the conversion of the phosphine to the phosphine oxide had a significant effect on the properties of the molecule. The tetrahedral phosphine oxide displayed free rotation about the N–P bonds, while the trigonal phosphine showed restricted rotation. This was proposed to be caused by the closer proximity of the pyrroles in the trigonal geometry, which was established by X-ray crystallography. The tri(benzimidazolyl)phosphine oxide has been synthesized by reacting benzimidazole with phosphoryl chloride in tetrahydrofuran with no added base [9]. Interestingly, the tri(5,6-dimethylbenzimidazolyl)phosphine oxide could not be synthesized, and, instead, only formation of the disubstituted product occurred.

RESULTS AND DISCUSSION

Synthesis of Tri(indolyl)phosphine Oxides

Three equivalents of 3-(*p*-chlorophenyl)-4,6-dimethoxyindole (**1a**) were mixed with three equivalents of triethylamine in tetrahydrofuran, and then one equivalent of phosphoryl chloride was added. ^{1}H NMR spectroscopy showed that no reaction occurred, and only the starting indole was recovered. *n*-Butyllithium was then used to achieve lithium salt formation of indole (**1a**) in tetrahydrofuran at −78°C, and this was accompanied by an instant color change. Phosphoryl chloride was added to the resulting indolyllithium salt, and the mixture was allowed to warm to room temperature to yield tri(indolyl)phosphine oxide (**2a**) in 50% yield. As this appeared to be the first example of this class of compounds, the same reaction was performed on 3-(*p*-bromophenyl)-4,6-dimethoxyindole (**1b**), 5-benzyloxyindole (**1c**), and indole (**1d**) to form the corresponding tri(indolyl)phosphine oxides (**2b–d**), respectively, in approximately 50% yield. The two highly substituted indolylphosphine oxides (**2a**) and (**2b**) were stable crystalline solids, while the less-substituted indolylphosphine oxides (**2b**) and (**2c**) were oily solids that slowly decomposed on standing. The ^{1}H NMR spectrum of tri(indolyl)phosphine oxide (**2a**) is almost identical to the spectrum of the starting indole (**1a**). The differences are that the indole NH is not present and that H2 occurs as a doublet from the three-bond coupling to phosphorus of 2.9 Hz. The ^{13}C NMR spectrum shows carbon–phosphorus coupling in four resonances. C2 and C7*a* occur as doublets split by 24 Hz at δ 122.4 and 141.0, respectively, from a two-bond coupling to phosphorus, while C3 and C3*a* appear at δ 125.1 and 113.9, respectively, as doublets with a coupling constant of 36 Hz from the *trans*-oriented three-bond coupling to phosphorus.

Attempted Macrocycle Formation from Tri(indolyl)phosphine Oxide

The formation of methylene bridge capped calix[3]indoles was investigated in two ways. The first was to attempt tri-formylation, followed by reduction to the tri-alcohol and treatment with acid. Formylation of the phosphine oxide (**2a**) by use of phosphoryl chloride and dimethylformamide and subsequent basic workup with aqueous sodium hydroxide yielded 3-(*p*-chlorophenyl)-4,6-dimethoxyindole-7-carbaldehyde (**3**) [2] as the sole product. The N–P bonds were apparently being cleaved by the basic workup, and so milder bases, such as dilute sodium hydroxide, sodium bicarbonate, and water, were used to decompose the iminium chloride. The best results gave a mixture of starting material (**2a**), 7-carbaldehyde (**3**), and partially formylated mixtures of the tri(indolyl)phosphine oxide (**2a**). Conversely, three equivalents of the 7-carbaldehyde (**3**) were reacted with three equivalents of *n*-butyllithium, followed by one equivalent of phosphoryl chloride, but no reaction occurred, and only starting material (**3**) was recovered. The second approach was to react the phosphine oxide (**2a**) directly with an aldehyde under acidic catalysis. When the phosphine oxide (**2a**) was reacted with formaldehyde in acetic acid at room temperature or at reflux temperature, no reaction occurred. Starting material was again completely recovered when the phosphine oxide (**2a**) was treated with three equivalents of *p*-chlorobenzaldehyde and phosphoryl chloride in refluxing chloroform.

Tri(indolyl)phosphines

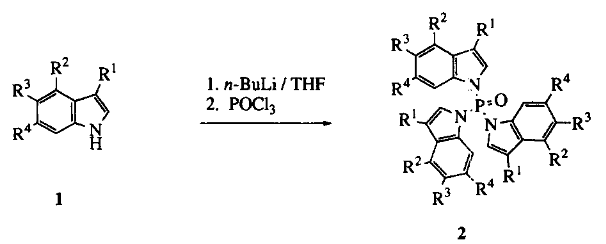
The tri(indolyl)phosphine (**4**) should not only be more reactive than the phosphine oxide (**2a**), because of the lack of the electron-withdrawing oxygen atom, but would also have a trigonal geometry that, according to CPK models, would be better for the capping of cone-shaped calix[3]indoles. The tri(indolyl)phosphine (**4**) was formed by first reacting indole (**1a**) with *n*-butyllithium, followed by one-third of an equivalent of phosphorus trichloride. Although it was detected as the only product by NMR spectroscopy, it was not isolated but treated directly with formaldehyde in acetic acid; however, again, no further reaction was observed.

*Tri(indolyl)*arsines

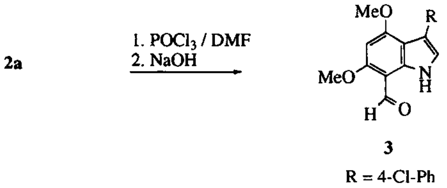
The larger group-V element, arsenic, was then employed, but, due to the reported thermal instability of the tri(pyrrolyl)arsine [8], no attempt was made to detect or isolate the tri(indolyl)arsine. Indole (**1a**) was reacted with *n*-butyllithium and then with one-third of an equivalent of arsenic trichloride in order to yield the tri(indolyl)arsine. The reaction mixture was treated with formaldehyde in acetic acid to give a complex mixture of products. None of these products appeared to be the desired calix[3]indole.

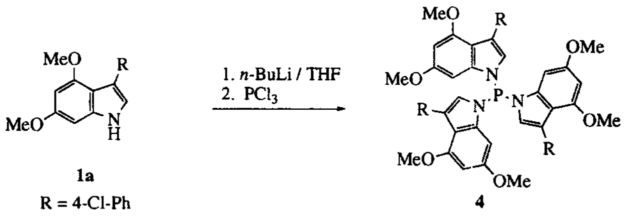
Tri(indolyl)stibines

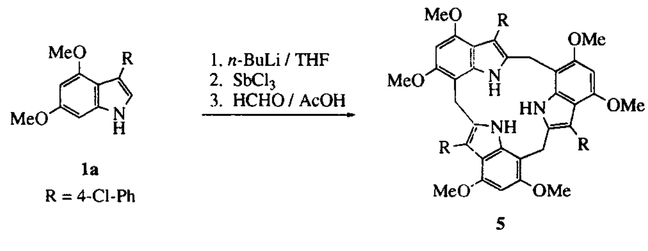
It became clear during initial experimentation with antimony that the tri(indolyl)stibine was not stable, if indeed it was being formed; thus, no isolation of this compound was attempted. Indole (**1a**) was reacted with *n*-butyllithium, followed by antimony trichloride, in order to form the presumed tri(indolyl)stibine, and the reaction mixture was treated with formaldehyde and acetic acid. The resulting compound was shown to be a methylene-bridged calix[3]indole (**5**) with no antimony present in the structure. This calix[3]indole had been synthesized previously by treatment of the corresponding 7-hydroxymethylindole with hydrochloric acid in tetrahydrofuran [3,4]. This result was unprecedented, as synthesis of calix[3]indoles with methylene bridges has not previously been achieved in a one-pot combination of indole and formaldehyde. When antimony trichloride was absent from the reaction, no calix[3]indole (**5**) was formed. If 3-aryl-4,6-dimethoxyindoles are reacted with formaldehyde and acetic acid, only polymer is obtained; this suggests that a template effect is occurring when antimony trichloride is present. The formation of the flattened partial cone conformer of the calix[3]indole (**5**) and not the cone conformer suggests that, if the antimony is required as a template, it must then fall out of the macrocycle, allowing inversion from the cone to the flattened partial cone conformer. The tri(indolyl)stibine was again formed from indole (**1a**), as described earlier, but was then reacted with *p*-chlorobenzaldehyde and phosphoryl chloride. It was thought that the larger aryl group might inhibit conversion of a template-formed cone conformer to the flattened partial cone conformation, but a complex mixture of products was obtained.



1,2	R¹	R²	R³	R⁴
a	4-Cl-Ph	OMe	H	OMe
b	4-Br-Ph	OMe	H	OMe
c	H	H	OCH_2Ph	H
d	H	H	H	H







EXPERIMENTAL

General Information

^1H and ^{13}C NMR spectra were recorded at 300 MHz on a Bruker AC300F spectrometer and at 500 MHz on a Bruker AM500 spectrometer, and ^{31}P NMR spectra were recorded at 121.49 MHz on a Bruker ACP spectrometer. Chemical shifts were measured on the δ scale internally referenced to the solvent peaks: $CDCl_3$ (7.30, 77.7) and d_6-DMSO (2.30, 39.0). EI mass spectral analyses were performed on a VG Quattro mass spectrometer at 70 eV ionization voltage and 200°C ion source temperature. High molecular weight compounds were run on matrix-assisted laser desorption mass spectrometers Finnigan MAT, lasermat, and lasermat 2000 using a matrix of either α-cyano-4-hydroxycinnamic acid or sinapinic acid. Microanalyses were carried out by Dr. Phung Pham of the microanalytical service. Infrared spectra were obtained on a Perkin-Elmer 298 IR spectrometer and a Mattson Sirius FTIR, using KBr discs, while ultraviolet spectra were carried out on Hitachi U-3200 and Carey 5 spectrophotometers.

Tri(3-(4′-chlorophenyl)-4,6-dimethoxyindol-1-yl)phosphine Oxide (2a)

The indole (1a) (2.02 g, 7.02 mmol) was dissolved in anhydrous tetrahydrofuran (50 mL), cooled to − 78°C with an acetone/Dry Ice bath, and stirred under a nitrogen atmosphere. *n*-Butyllithium (2.5 M hexane solution) (2.8 mL, 7.02 mmol) was then added, and the solution was allowed to warm to room temperature and to stir for 15 minutes. Phosphoryl chloride (0.18 mL, 1.93 mmol) was added, and the solution was stirred for 1.5 hours. Addition of water and extraction with dichloromethane gave the phosphine oxide (2a) (1.06 g, 50%) as colorless needles, mp 248–249°C (from dichloromethane/light petroleum). Found: C, 63.9; H, 4.6; N, 4.6. $C_{48}H_{39}Cl_3N_3O_7P$ requires C, 63.6; H, 4.3; N, 4.6%. IR ν_{max} 1615, 1290, 1210, 1160, 1130, 660 cm^{-1}. UV λ_{max} 227 (ε81,900), 244 (83,100), 275 nm (49,200). ^1H NMR ($CDCl_3$): δ 3.70, 3.76, 2s, OMe; 6.37, 6.82, 2d, *J* 1.9 Hz, H5, H7; 6.46, d, *J* 2.9 Hz, H2; 7.29, 7.36, 2d, *J* 8.6 Hz, aryl. ^{13}C NMR ($CDCl_3$): δ 55.8, 56.4, OMe; 90.4, C5, 96.2, C7; 113.9, d, *J* 36 Hz, C3a; 122.4, d, *J* 24 Hz, C2; 128.5, 131.4, aryl CH; 125.1, d, *J* 36 Hz, C3; 141.0, d, *J* 24 Hz, C7a; 132.8, 133.7, 155.4, 160.2, aryl C. ^{31}P NMR (CH_2Cl_2): δ −10.32, s, P = O. MS *m/z* 911 ($M^{37}Cl^{37}Cl^{37}Cl$, 2%), 909 ($M^{37}Cl^{37}Cl^{35}Cl$, 10%), 907 ($M^{37}Cl^{35}Cl^{35}Cl$, 20%), 905 ($M^{35}Cl^{35}Cl^{35}Cl$, 20%), 286 (100).

Tri(3-(4′-bromophenyl)-4,6-dimethoxyindol-1-yl)phosphine Oxide (2b)

This was synthesized according to the method of compound (2a) using 3-(4′-bromophenyl)-4,6-dimethoxyindole (1b) (0.37 g, 1.11 mmol), anhydrous tetrahydrofuran (15 mL), *n*-butyllithium (2.5 M hexane solution) (0.44 mL, 1.11 mmol), and phosphoryl chloride (31 μL, 0.34 mmol). The resulting crude solid was recrystallized from dichloromethane/light petroleum to yield the phosphine oxide (2b) (0.35 g, 50%) as colorless needles. ^1H NMR ($CDCl_3$): δ 3.70, 3.76, 2s, OMe; 6.37, 6.82, 2d, *J* 1.9 Hz, H5, H7; 6.46, d, *J* 2.9 Hz, H2; 7.29, 7.36, 2d, *J* 8.6 Hz, aryl. ^{13}C NMR ($CDCl_3$): δ 55.9, 56.4, OMe; 90.5, C5; 96.3, C7; 113.8, d, *J* 36 Hz, C3a; 122.4, d, *J* 24 Hz, C2; 125.2, d, *J* 36 Hz, C3; 131.4, 131.8, aryl CH; 141.1, d, *J* 24 Hz, C7a; 122.0, 133.4, 155.4, 160.2, aryl C. ^{31}P NMR (CH_2Cl_2): δ −10.34, s, P = O. MS *m/z* 1037 (M, <1%).

Tri(5-benzyloxyindol-1-yl)phosphine Oxide (2c)

This was synthesized according to the method of compound (2a) using 5-benzyloxyindole (1c) (2.8 g, 12.54 mmol), anhydrous tetrahydrofuran (40 mL), *n*-butyllithium (2.5 M hexane solution) (5.00 mL, 12.54 mmol), and phosphoryl chloride (0.32 mL, 3.43 mmol). The resulting crude solid was purified using gravity column chromatography with dichloromethane eluant to yield the phosphine oxide (2c) (1.32 g, 54%) as a white solid, mp 63–64°C. Found: C, 75.8; H, 5.3; N, 5.7. $C_{45}H_{36}N_3O_4P$ requires C, 75.7; H, 5.1; N, 5.9%. IR ν_{max} 1610, 1580, 1220, 1150, 1010, 795, 720, 695 cm^{-1}. UV λ_{max} 230 (ε19,700), 258 (13,800), 286 nm (5000). ^1H NMR ($CDCl_3$): δ 5.14, s, CH_2; 6.55, t, *J* 3.3 Hz, aryl; 6.63, t, *J* 3.4 Hz, aryl; 7.02, dd, *J* 9.0; 2.5 Hz, aryl; 7.20, br, aryl; 7.38–7.51, m, aryl; 7.71, d, *J* 9.0 Hz, aryl. ^{13}C NMR ($CDCl_3$): δ 71.2, CH_2; 105.6, 115.3, 115.6, 128.1, 128.6, 129.2, 156.3, aryl CH; 110.5, d, *J* 36 Hz, aryl CH; 128.1, 137.7, aryl C; 132.7, d, *J* 40 Hz, aryl C; 133.2, d, *J* 24 Hz, aryl C. ^{31}P NMR (CH_2Cl_2): δ − 10.87, s, P = O. MS *m/z* 714 (M + 1, 2%), 713 (M, 2%), 623 (2), 622 (5).

Tri(indol-1-yl)phosphine Oxide (2d)

This was synthesized according to the method of compound (2a) using indole (1d) (2.90 g, 24.76 mmol), anhydrous tetrahydrofuran (40 mL), *n*-butyllithium (2.5 M hexane solution) (9.87 mL, 24.76 mmol), and phosphoryl chloride (0.63 mL, 6.76 mmol). The resulting crude solid was purified using gravity column chromatography with chloroform/methanol (90:10) eluant to yield the phosphine oxide (2d) (1.34 g, 50%) as a white solid, mp 144°C. IR ν_{max} 1260, 1155, 1140, 1010, 750, 665 cm^{-1}. UV λ_{max} 253 nm (ε27,900). ^1H NMR ($CDCl_3$): δ 6.56, t, *J* 3.5 Hz, aryl; 6.72, t, *J* 3.5 Hz, aryl; 7.30–7.34, m, aryl; 7.68–7.70, m, aryl; 7.86–7.89, m, aryl. ^{13}C NMR ($CDCl_3$): δ 110.5, d, *J* 36 Hz, C3; 114.9, 122.1, 124.1, 125.4, aryl; 127.4, d, *J* 28 Hz, C2; 131.8, d, *J* 36 Hz, C3*a*; 138.5, d, *J* 24 Hz, C7*a*. ^{31}P NMR ($CDCl_3$): δ − 11.01, s, P = O. MS *m/z* 395 (M, 10%), 278 (10), 231 (10), 163 (25), 116 (100), 89 (80).

3-(4'-Chlorophenyl)calix[3]indole (**5**). The indole (**1a**) (1.01 g, 3.51 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL) and cooled to −78°C with an acetone/Dry Ice bath and stirred under a nitrogen atmosphere. *n*-Butyllithium (2.5 M hexane solution) (1.40 mL, 3.51 mmol) was then added, and the mixture was allowed to warm to room temperature and stirred for 15 minutes. The solution was cooled to −78°C again, antimony trichloride (0.26 g, 1.13 mmol) added, and the solution was allowed to warm to room temperature and was stirred at this temperature for 30 minutes. A deoxygenated solution of acetic acid and aqueous formaldehyde was added rapidly. The resulting precipitate was filtered off, washed with water, and dried under reduced pressure to yield calix[3]indole (**5**) (0.42 g, 40%) as a pink solid, mp >285°C. ^{1}H NMR ($CDCl_3$): δ 3.73, 3.73, 2s, OMe; 4.16, s, CH_2; 6.26, s, H5; 7.34, s, aryl; 7.85, br, NH. MS *m/z* 896 (M, 50%). The product was identical with an authentic sample [3,4].

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