Synthesis, Characterization, and Coordination Chemistry of a New Geometrically Hindered Trifunctional Ligand, 4,5-Bis(diphenylphosphino)-*sym*-octahydroacridine *N,P,P′*-Trioxide

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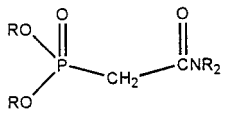
Received February 14, 2000

The ligand 4,5-bis(diphenylphosphino)-*sym*-octahydroacridine *N,P,P′*-trioxide (**10**) was obtained from a multistep synthesis and characterized by spectroscopic methods, and two crystal forms were examined by single-crystal X-ray diffraction techniques. The coordination behavior of the trifunctional ligand toward $La(NO_3)_3$ and $Nd(NO_3)_3$ was examined, and the molecular structures of the complexes $La(\mathbf{10})(NO_3)_3 \cdot MeOH$ and $Nd(\mathbf{10})(NO_3)_3 \cdot MeOH$ were determined by single-crystal X-ray diffraction methods. The molecules form chains along the *z* axis in which the ligand bonds in a bidentate mode to one $La(NO_3)_3$ or $Nd(NO_3)_3$ by using the N−O and one of the P═O donor centers. The second P═O donor group in the ligand bridge bonds to a second $La(\mathbf{10})(NO_3)_3$ or $Nd(\mathbf{10})(NO_3)_3$ unit. The coordination behavior of **10** contrasts with that of the related but structurally more flexible trifunctional ligand 2,6-bis[(diphenylphosphino)methyl]pyridine *N,P,P′*-trioxide, which acts as a tridentate ligand toward f-element ions.

Introduction

Ligand design is a dynamic research area that is, in part, motivated by practical issues in a wide range of technologies.[1] Our own interests in ligand design are largely stimulated by needs for multifunctional ligands that are selective chelators for f-element species present in highly acidic nuclear materials solutions. The rational development of useful chelating ligands for f-element ions is a daunting task because the ligands must be stable in concentrated mineral acids and they must select a single metal ion or class of metal ions over protons despite a typical 10^6-10^8 concentration excess of H^+ over metal. Despite these requirements, some successes have appeared. For example, selected monofunctional phosphonates, phosphine oxides, and organoamides function as liquid−liquid extraction agents at low acid concentrations, although they are not especially effective at high acid concentrations.[2] Siddall[3] suggested that bifunctional ligands that combine these donor groups, such as in **1** and **2**,



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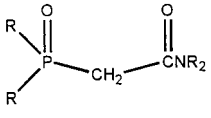

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might serve as better ligands and improved extractants for lanthanide (Ln) and actinide (An) trivalent ions because they should adopt bidentate chelate structures in solution. Indeed, **1** (CMP) and **2** (CMPO) are better extractants of trivalent ions in acidic aqueous solutions than the monofunctional component ligands, although this behavior may not result from the formation of bidentate chelate structures in extractant solutions.[2−6] Unexpectedly, **1** and **2** show increasing distribution ratios ($K_D = [M]_{org}/[M]_{aq}$) with increasing acid strength even at proton concentrations above 4 M. The discovery of this technologically favorable behavior stimulated searches for new ligand families that might also display improved extraction characteristics at high acid concentrations.[7,8] In this regard, we have reported the design, synthesis, and extraction behavior of bifunctional and trifunctional ligands **3**−**9**, which contain one or more phosphonate or phosphine oxide groups and pyridine *N*-oxide donor groups.[9−18] Ligands **3**−**6** generally bind to metal centers in a bidentate manner; **7** and **8** serve as tridentate ligands, and **9**

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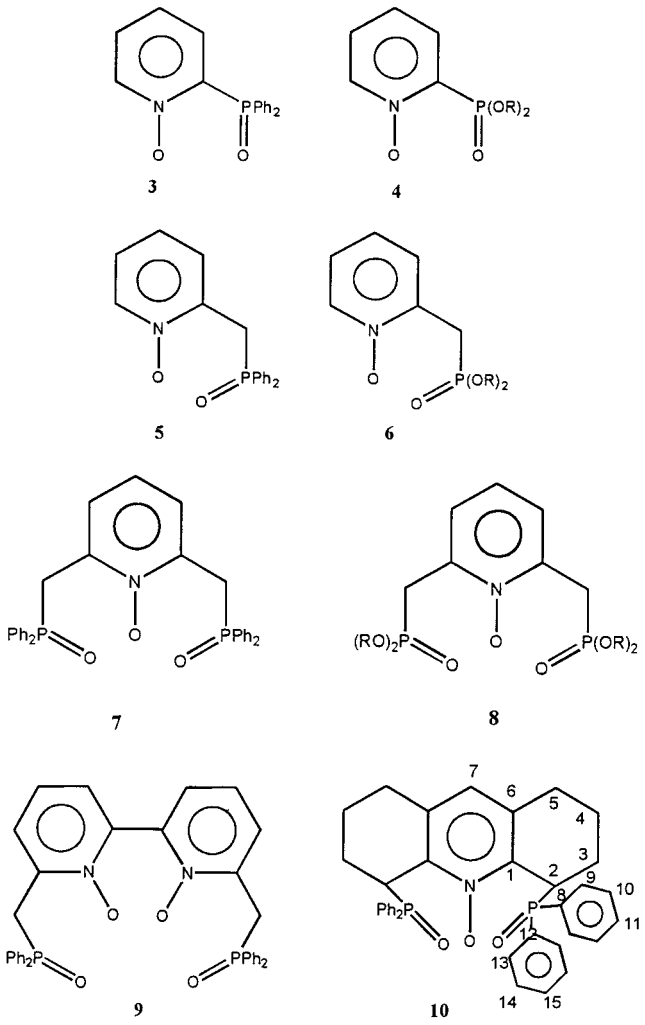
10.1021/ic000153n CCC: $19.00
Published on Web 09/13/2000



acts as a tetradentate ligand. The chelate rings formed by **5**−**9** are seven-membered, and their complexes are more stable than the six-membered chelate complexes of **1**−**4**.[11−18] In fact, **7** is a superior extractant toward Ln(III) and An(III) ions.[16−18] From a ligand design perspective, this is an unexpected result because in most cases five-membered chelate rings are more stable than six-membered rings, which are much more stable than seven-membered rings.[1] We are interested in examining other structural features of **7** and **8**, and we are particularly interested in the possibility of constraining the rotational flexibility of the donor centers in the trifunctional ligand **7**. Consequently, compound **10** was selected as a target for study of the effect of donor group steric constraints on coordination chemistry and extraction characteristics. We report here the multistep synthesis of **10** and its subsequent coordination behavior toward $Nd(NO_3)_3$ and $La(NO_3)_3$.

Experimental Section

General Information. The organic reagents employed in the syntheses were purchased from Aldrich Chemical Co. and used without purification unless noted otherwise. The inorganic reagents were purchased from Fisher Scientific. The $La(NO_3)_3 \cdot 6H_2O$ and $Nd(NO_3)_3 \cdot 6H_2O$ were obtained from Ventron. Infrared spectra were recorded on a Mattson 2020 FTIR spectrometer. Mass spectra were obtained from the Midwest Center for Mass Spectrometry, University of Nebraska. NMR spectra were measured on Bruker FX-250 and JEOL GSX-400 spectrometers. The NMR standards were Me_4Si (^1H,^{13}C) and 85% H_3PO_4 (^{31}P), and downfield shifts from the standards were assigned as $+\delta$. Elemental analyses were obtained from Galbraith Laboratories.

Preparation of 4,5-Bis(diphenylphosphino)-*sym*-octahydroacridine *N,P,P′*-Trioxide (10). (a) 2-Dimethylaminomethylcyclohexanone (11). A mixture of cyclohexanone (89.2 g, 0.909 mol), dimethylamine hydrochloride (39.6 g, 0.486 mol), and formaldehyde (36.9 g of 37% solution in water) was refluxed (oil bath at 130 °C, 30 min) and then cooled to room temperature. Sodium chloride (17 g) was added, and the mixture was stirred at 23 °C (20 min). The mixture was transferred to a separatory funnel, and the organic phase and aqueous phase were separated. The aqueous phase was extracted with Et_2O (4 × 40 mL) to further remove unreacted cyclohexanone. The aqueous phase was adjusted to pH = 13.5 by addition of 38 g of KOH in 90 mL of water. The Mannich base (**11**) was separated as a yellow oil from the upper layer, which exhibited a strong amine odor. The aqueous phase was extracted with Et_2O (3 × 80 mL), and the yellow oil and the ether extracts were combined and then dried with anhydrous sodium sulfate. After removal of the ether at 23 °C under reduced pressure, the remaining oil was distilled under vacuum (42−43 °C/100 mTorr): yield 64.0 g (90.6%).

(b) 2,2′-Dicyclohexanoylmethane (12). Compound **11** (78.0 g, 0.502 mol) and cyclohexanone (148.0 g, 1.51 mol) were mixed and refluxed (oil bath at 205 °C, 1.5 h), and the resulting mixture was distilled under vacuum. The fraction collected at 90−100 °C/100 mTorr was a colorless oil (83 g). Hexane (100 mL) was added to the oil, and the mixture was cooled to −30 °C overnight. A white solid was collected and washed with cold hexane (3 × 50 mL). The colorless solid product, 2,2′-dicyclohexanonylmethane (**12**), was obtained: yield 58.5 g (56.2%).

(c) *sym*-Octahydroacridine (13). Hydroxylamine hydrochloride (30.5 g, 0.439 mol) was added with stirring to a boiling solution of **12** (56.5 g, 0.271 mol) in EtOH (400 mL). The mixture was refluxed (20 min), then the ethanol was removed under reduced pressure, and 100 mL of water was added to dissolve the residue. A solution of NaOH (20 g in 100 mL of water) was added at 0 °C to bring the pH of the solution to 13.5. The solid that appeared was collected and washed with water. The remaining solid was dried over $CaCl_2$ under vacuum, leaving *sym*-octahydroacridine (1,2,3,4,5,6,7,8-octahydroacridine) (**13**) as a white solid: yield 46.8 g (92.2%).

(d) *sym*-Octahydroacridine *N*-Oxide (14). A mixture of **13** (46.0 g, 0.246 mol) and 3-chloroperoxybenzoic acid (71 g, 77% max) in $CHCl_3$ (400 mL) was stirred (17 h) at 23 °C. The resulting reaction mixture was extracted with $NaHCO_3$ (130 g) and Na_2CO_3 (15 g) in water (1400 mL). The aqueous phase (pH = 8.5) was washed with CH_2Cl_2 (2 × 300 mL), and the chloroform and dichloromethane solutions were combined and dried with anhydrous sodium sulfate. After removal of the solvent at 23 °C under reduced pressure, the product *sym*-octahydroacridine *N*-oxide (**14**) was obtained as a light yellow solid: yield 48.0 g (96.3%).

(e) 4-Acetoxy-*sym*-octahydroacridine (15). Compound **14** (32.0 g, 0.157 mol) in acetic anhydride (180 mL) was added to boiling acetic anhydride (120 mL) with stirring. The mixture was refluxed (1 h) with an oil bath (145−150 °C). The acetic anhydride was removed by vacuum evaporation, and the residue was dissolved in CH_2Cl_2 (100 mL) and then extracted with $NaHCO_3$ (15 g) and Na_2CO_3 (25 g) in water (250 mL). The aqueous phase (pH = 8.5) was washed with CH_2Cl_2 (3 × 60 mL), and the CH_2Cl_2 solutions were combined and dried over anhydrous sodium sulfate. The solvent was evaporated at 23 °C under reduced pressure, leaving a brown sticky oil, 4-acetoxy-*sym*-octahydroacridine (**15**): yield 35.2 g (91.1%).

(f) 4-Acetoxy-*sym*-octahydroacridine *N*-Oxide (16). A mixture of **15** (34.9 g, 0.141 mol) and 3-chloroperoxybenzoic acid (50 g, 77% max) in $CHCl_3$ (300 mL) was stirred (19 h) at 23 °C. The reaction mixture was extracted with $NaHCO_3$ (30 g) and Na_2CO_3 (35 g) in water (400 mL), and the aqueous phase (pH = 8.5) was washed with CH_2-

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Cl_2 (2 × 150 mL). The $CHCl_3$ and CH_2Cl_2 solutions were combined and dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure at 23 °C, leaving 4-acetoxy-*sym*-octahydroacridine *N*-oxide (**16**) as an orange solid: yield 36.0 g (96.8%).

(g) 4,5-Diacetoxy-*sym*-octahydroacridine (17). A sample of **16** (36 g, 0.14 mol) in acetic anhydride (150 mL) was added to boiling acetic anhydride (100 mL) with stirring. The mixture was refluxed (oil bath at 145−150 °C) for 1.5 h. The acetic anhydride was evaporated under vacuum, leaving a residue that was dissolved in CH_2Cl_2 (100 mL). The solution was extracted with $NaHCO_3$ (20 g) and Na_2CO_3 (30 g) in water (250 mL), and the aqueous phase (pH = 8.5) was washed with CH_2Cl_2 (2 × 100 mL). The combined CH_2Cl_2 solution was dried with anhydrous sodium sulfate and then evaporated at 23 °C under reduced pressure. An orange solid, 4,5-diacetoxy-*sym*-octahydroacridine (**17**), was obtained: yield 40.0 g (95.7%).

(h) 4,5-Dihydroxy-*sym*-octahydroacridine (18). A sample of **17** (40 g, 0.13 mol) was dissolved in 1:3 hydrochloric acid (240 mL), and the mixture was refluxed (2 h). The resulting mixture was made alkaline (pH = 8.5) with 70 g of Na_2CO_3 in water (400 mL). The mixture was extracted with CH_2Cl_2 (4 × 200 mL). The combined CH_2Cl_2 solutions were dried with anhydrous sodium sulfate, and the solvent was evaporated at 23 °C under reduced pressure, leaving an orange solid, 4,5-dihydroxy-*sym*-octahydroacridine (**18**): yield 27.0 g (93.3%).

(i) 4,5-Dichloro-*sym*-octahydroacridine (19). Thionyl chloride (60 mL) in $CHCl_3$ (60 mL) was added to **18** (27 g, 0.12 mmol) in $CHCl_3$ (100 mL). The mixture was stirred at 23 °C (10 min) and then refluxed with an oil bath at 80 °C (1 h). The excess thionyl chloride and volatile byproducts were vacuum evaporated, and the residue was dissolved in CH_2Cl_2 (400 mL). The solution was extracted with Na_2CO_3 (30 g) in water (500 mL), and the aqueous phase (pH = 8.5) was washed with CH_2Cl_2 (2 × 400 mL). The CH_2Cl_2 extract was dried with anhydrous Na_2SO_4 and vacuum evaporated at 23 °C, leaving an orange solid, 4,5-dichloro-*sym*-octahydroacridine (**19**): yield 28.0 g (88.7%).

(j) 4,5-Bis(diphenylphosphino)-*sym*-octahydroacridine *P,P′*-Dioxide (20). Ethyl phenylphosphinate (15 g, 0.088 mol) in dry benzene (30 mL) was added dropwise to PhMgBr (60 mL, 3 M solution in Et_2O, 0.18 mol) over 30 min, during which time the temperature of the solution rose. After addition, tetrahydrofuran (THF) (50 mL) was added, and the mixture was heated with an oil bath at 66 °C (1 h). A sample of **19** (11.2 g, 0.0411 mol) in THF (60 mL) was added, and the mixture was refluxed with an oil bath at 70 °C (4 h). The resulting mixture was allowed to stand at 23 °C overnight. A clear orange upper layer separated in the flask and was decanted. A sticky oil remained, which was combined with NH_4Cl in water (200 mL) and $CHCl_3$ (100 mL). The mixture was transferred to a separatory funnel, and the organic phase and aqueous phase (pH = 7−8) were separated. The aqueous phase was washed with CH_2Cl_2 (2 × 100 mL), and the combined organic phase was dried with anhydrous Na_2SO_4. The solvent was vacuum evaporated, and the residue was redissolved in $CHCl_3$ (150 mL). The resulting solution was refluxed with an oil bath at 75 °C (5 h) in order to drive the meso isomer to the threo isomer. The solution was cooled, and the volume was reduced to ∼70 mL. Acetone (200 mL) was added and then slowly removed by evaporation. A solid formed, which was collected by filtration and washed with cold ethyl acetate, leaving a light orange solid, **20**: yield 17.0 g (65.7%); mp 210−212 °C. Mass spectrum (FAB) *m*/*e* (fragment, relative intensity): 588.1 ($M + 1^+$, 100%), 587.1 (M^+, 10%), 386.1 ($M - Ph_2P(O)^+$, 15%). Infrared spectrum (KBr, cm^{-1}): 3437 (m), 3051 (m), 2931 (m), 2866 (m), 1593 (w), 1560 (w), 1483 (w), 1437 (s), 1280 (w), 1188 (s, ν_{PO}), 1143 (sh), 1112 (s), 1072 (w), 920 (w), 750 (m), 700 (s), 640 (w), 559 (m), 530 (s), 511 (m). NMR spectra (23 °C, $CDCl_3$): $^{31}P\{^1H\}$ δ 36.6; ^1H δ 1.52−1.96 (multiplet, 4H, H_5), 2.14−2.29 (multiplet, 4H, H_4), 2.56−2.66 (multiplet, 4H, H_3), 3.29−3.38 (multiplet, 2H, H_2), 7.01 (1H, H_7), 7.22−7.81 (multiplet, 20H, phenyl); $^{13}C\{^1H\}$ δ 20.25 (C_5), 23.48 (C_4), 27.66 (C_3), 41.45 (doublet, J = 65.2 Hz, C_2), 127.29 (doublet, J = 12.0 Hz), 128.37 (doublet, J = 11.7 Hz) (C_{10}, C_{14}), 130.68, 131.33 (C_{11}, C_{15}), 131.52 (doublet, J = 8.9 Hz), 132.00 (doublet, J = 9.2 Hz) (C_9, C_{13}), 132.32 (doublet, J = 4.5 Hz, C_6), 132.99 (doublet, J = 94.3 Hz), 133.12 (doublet, J = 89.3 Hz) (C_8, C_{12}), 137.18 (C_7), 147.97 (doublet, J = 10.0 Hz, C_1). Solubility: soluble in $CHCl_3$, benzene, toluene, and xylene; insoluble in hexane and heptane.

(k) 4,5-Bis(diphenylphosphino)-*sym*-octahydroacridine *N,P,P′*-Trioxide (10). A sample of **20** (6.8 g, 11.6 mmol) in glacial acetic acid (35 mL) was combined with 30% H_2O_2 (2.0 mL, 17.6 mmol) and stirred under nitrogen at 63 °C (16 h). The acetic acid was vacuum evaporated at 23 °C, and water (10 mL) was added to the residue. The mixture was vacuum evaporated at 23 °C, and the residue was dissolved in CH_2Cl_2 (30 mL). This solution was extracted with saturated aqueous $NaHCO_3/Na_2CO_3$ solution (50 mL), and the water phase (pH = 8.5) was separated and washed with CH_2Cl_2 (2 × 30 mL). The CH_2Cl_2 solution was washed with saturated aqueous $NaHCO_3$ solution (20 mL), and the remaining CH_2Cl_2 solution was dried over Na_2SO_4. The CH_2Cl_2 solution was then vacuum evaporated, and the residue was combined with ethyl acetate (20 mL) and held at 0 °C overnight. The cold solution was filtered, and the solid product was washed with fresh ethyl acetate (2 × 10 mL), leaving a white solid, **10**: yield 6.2 g (88.7%); mp 221−222 °C. Single crystals used in the X-ray diffraction study were obtained from $CHCl_3$/EtOAc mixtures. Mass spectrum (FAB) *m*/*e* (fragment, relative intensity): 604.3 ($M + 1^+$, 100%), 603.3 (M^+, 10%), 588.3 ($M + 1 - O^+$, 15%), 386.2 ($M - O - Ph_2P(O)^+$, 15%). Infrared spectrum (KBr, cm^{-1}): 3437 (m), 3051 (m), 2941 (m), 2872 (w), 1587 (w), 1485 (m), 1435 (s), 1309 (s), 1284 (s, ν_{NO}), 1176 (s, ν_{PO}), 1109 (s), 1035 (w), 752 (s), 700 (s), 580 (w), 530 (s), 509 (m). NMR spectra (23 °C, $CDCl_3$): $^{31}P\{^1H\}$ δ 36.2; ^1H δ 1.41−1.74 (multiplet, 4H) (H_5), 2.23−2.82 (multiplet, 8H) (H_3, H_4), 3.77 (doublet of doublets, J_1 = 14.2 Hz, J_2 = 5.6 Hz, 2H) (H_2), 6.70 (1H) (H_7), 7.08−8.27 (multiplet, 20H, phenyl); $^{13}C\{^1H\}$ δ 20.06 (C_5), 22.91 (C_4), 27.21 (C_3), 36.92 (doublet, J = 65.5 Hz) (C_2), 125.51 (C_7), 126.39 (doublet, J = 12.5 Hz), 128.16 (doublet, J = 12.0 Hz), (C_{10}, C_{14}) 130.19 and 131.62 (C_{11}, C_{15}), 130.75 (doublet, J = 10.0 Hz), 132.51 (doublet, J = 9.2 Hz) (C_9 and C_{13}), 132.69 (doublet, J = 95.8 Hz) and 133.45 (doublet, J = 101.7 Hz) (C_8 and C_{12}), 133.33 (doublet of doublets, J_1 = 4.1 Hz, J_2 = 4.1 Hz) (C_6), 141.75 (doublet, J = 10.8 Hz) (C_1). Solubility: soluble in $CHCl_3$, benzene, and toluene; insoluble in hexane and heptane. Anal. Calcd for $C_{37}H_{35}NO_3P_2$: C, 73.62; H, 5.84; N, 2.32. Found: C, 72.12; H, 6.14; N, 2.25.

Preparation of Complexes 21 and 22. A sample of **10** (0.12 g, 0.20 mmol) in MeOH (20 mL) was combined with $La(NO_3)_3 \cdot 6H_2O$ (0.3 g, 0.1 mmol) or $Nd(NO_3)_3 \cdot 6H_2O$ (0.4 g, 0.1 mmol). The mixture was stirred (1 h, 23 °C). For the La(III) complex, the reaction mixture was treated with ethyl acetate (20 mL); the resulting mixture was filtered, and the filtrate was allowed to slowly evaporate at 23 °C. After several days, single crystals were obtained. For the Nd(III) complex, ethyl acetate was not used, and single crystals were obtained by slow evaporation of the methanol solution. Infrared spectra (KBr, cm^{-1}): **21**, 1224 (m, ν_{NO}), 1146 (m) and 1096 (m) (ν_{PO}); **22**, 1232 (m, ν_{NO}), 1146 (m) and 1096 (m) (ν_{PO}).

X-ray Diffraction Studies. Single crystals were mounted in glass capillaries, and X-ray diffraction data were collected by variable speed ω scans on a Siemens R3m/V diffractometer using a graphite monochromator and Mo Kα (λ = 0.710 73 Å) radiation. Lattice and data collection parameters (XSCANS)[19] are summarized in Table 1. All structure solution calculations were performed with SHELXL97,[20] and the structures were solved by using direct methods. Full matrix least-squares refinements using neutral atom scattering factors and anomalous dispersion terms included anisotropic thermal parameters for all non-hydrogen atoms. The quantity minimized was $\sum w(|F_o| - |F_c|)^2$. Data were corrected for absorption using XPREP.[21] Some individual details for each structure determination are provided. The data crystal for **10′** was a small thin colorless plate (0.276 × 0.207 × 0.092 mm), and octants h, k, $\pm l$ and $-h$, $-k$, $\pm l$ were collected. The data crystal for **10″** was a colorless prism (0.552 × 0.529 × 0.299 mm), and octants h, k, $\pm l$ and $-h$, $-k$, $\pm l$ were collected. A CH_3OH solvent molecule

(19) Data collection, cell refinement, and data reduction utilize the program XSCANS: *XSCANS*, version 2.10; Siemens Corp.: Madison, WI, 1994.

(20) Structure solutions, structure refinements, and final data packets for publication are prepared using SHELXL 97. Sheldrick, G. M. *Programs for the Refinement of Crystal Structures*; University of Gottingen: Germany, 1997.

(21) Absorption corrections are made with XPREP: *XPREP*, version 5.03; Siemens Corp.: Madison, WI, 1994.

Table 1. Crystallographic Data

	10′	**10″**	**21**	**22**
empirical formula	$C_{39}H_{37}Cl_6NO_3P_2$	$C_{34}H_{43}NO_5P_2$	$C_{38}H_{39}N_4NdO_{13}P_2$	$C_{38}H_{39}LaN_4O_{13}P_2$
formula weight	842.34	667.68	965.91	960.58
space group	$P2_1/c$	$C2/c$	$P2_12_12_1$	$P2_12_12_1$
a, Å	21.183(3)	24.351(4)	13.131(2)	13.146(1)
b, Å	11.645(4)	11.543(2)	17.579(8)	17.691(2)
c, Å	16.791(6)	17.211(5)	17.853(7)	17.962(3)
α, deg	90	90	90	90
β, deg	104.86(2)	133.48(1)	90	90
γ, deg	90	90	90	90
volume, Å^3	4003(2)	3510.3(13)	4121(3)	4177.3(9)
Z	4	4	4	4
density, g/cm^3	1.398	1.263	1.557	1.527
T, K	293	293	293	293
μ, mm^{-1}	0.547	0.168	1.406	1.167
R1[a]	0.0475	0.0425	0.0386	0.0432
wR2[b]	0.1059	0.1211	0.0750	0.0805

[a] $R1 = \sum ||F_o| - |F_c|| / \sum |F_o|$. [b] $wR2 = [\sum (F_o^2 - F_c^2)^2 / \sum [w(F_o^2)^2]]^{1/2}$.

in the lattice is positionally disordered, as evidenced by large anisotropic *U*'s on O(3) and C(20). The H atoms on C(20) were not located in difference maps and were placed in idealized positions using the riding model. The fixed isotropic *U*'s were set to 1.25*U* (equiv) of the parent atom. The other hydrogen atoms were located in difference maps and had individually variable isotropic *U*'s. The data crystal for **21** was a colorless needle (0.253 × 0.069 × 0.046 mm), and data for $-h$, $\pm k$, $\pm l$ were collected. The solution was consistent with racemic twinning, and the refinement incorporated the TWIN instruction. The components are the model with *hkl* and $-h$, $-k$, $-l$ with each component having $k_n = 50\%$. All non-hydrogen atoms were refined anisotropically except O(13), C(38), N(1)*, N(4)*, C(1)*, C(2)*, C(8)*, and C(13)*. The data crystal for **22** was a colorless needle (0.420 × 0.161 × 0.115 mm), and data for $\pm h$, $\pm k$, $\pm l$ were collected. It is isostructural with **21**, and the refinement also incorporated the TWIN instruction.

Results and Discussion

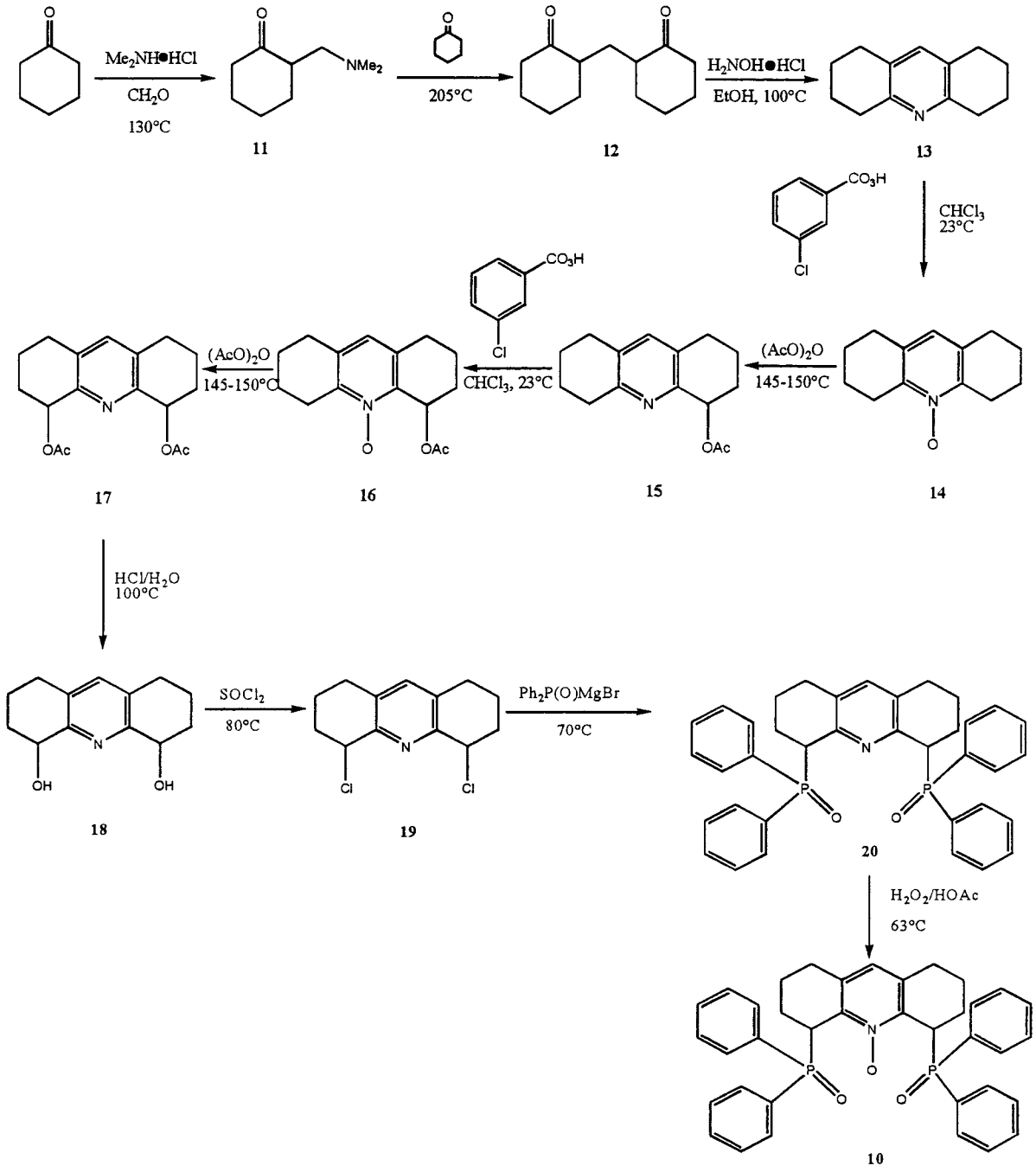
As mentioned in the Introduction, phosphine oxides and pyridine *N*-oxides are known to be good donor groups toward hard metal ions including lanthanides and actinides. When these groups are organized into flexible organic backbones that permit ligand chelation with a metal acceptor, extra complex stability is expected.[1] Furthermore, where data exist for classical acyclic chelating ligands such as polyamines, polyketones, and polycarboxylates, complexes with five-membered chelate rings are usually more stable than complexes with six-membered rings, and these in turn are more stable than complexes with seven-membered rings.[1] Ligands containing *N*-oxide and phosphoryl donor groups capable of forming five-membered chelate rings have not yet been prepared, but **3** and **4** act as chelating ligands forming six-membered rings and **5** and **6** produce seven-membered rings. Direct measurements of thermodynamic heats of formation have not yet been completed; however, liquid−liquid extraction and NMR data suggest that **5** and **6** form significantly more stable complexes with Ln(III) ions than do **3** and **4**.[16−18] It is also well recognized with classical chelators that tridentate and tetradentate ligands produce more stable complexes than bidentate complexes,[1] and indeed **7**, **8**, and **9** form especially stable complexes with Ln(III) ions.[16−18]

Molecular modeling of the coordination complexes formed by **3, 5**, and **7** suggests that a portion of the stability of the complexes formed by **5** and **7** may result from the flexibility allowed by the CH_2 group in the spacer arm between the pyridine *N*-oxide ring and the phosphoryl groups. In particular, in **7** the flexibility allows for the three donor oxygen atoms to dock on the eight- or nine-vertex coordination polyhedra adopted by Ln(III) ions with minimal strain in the ligand backbone. Given these observations, we have been interested in preparing ligands that might have structural features that would be expected to either enhance or detract from the chelation ability of **5** or **7**. In this regard, the previously unknown trifunctional ligand **10** became a target for study. In this ligand, the CH_2 spacer groups between the pyridine *N*-oxide ring and the phosphine oxides should be considerably more hindered with respect to chelate ring formation than those in **7**. This, in turn, should weaken or even prevent tridentate chelation.

The target ligand **10** was obtained as a colorless crystalline solid from the multistep synthesis outlined in Scheme 1. The syntheses of **11**−**19** have been partially described in the literature;[22−26] however, many details are absent in these papers. As a result, full descriptions for each step are provided and some particular points are mentioned here. The Mannich reaction (step 1) was previously reported by Frank and Pierle[22] to form **11** in 56% yield after reflux for 5 min. This provides a relatively bad start for a multistep process, and further study revealed that **11** is obtained in >90% yield when the reaction mixture is allowed to reflux for 30 min. The addition reaction that forms **12** was reported by Potts and co-workers[23] to produce a liquid product in 63% yield. This is basically correct; however, careful recrystallization of the oil from cold hexane produces a colorless solid with little loss of product. Furthermore, the absence of impurities present in the oil provides for a cleaner reaction in step 3. Compound **12** is obtained as a 50:50 mixture of meso and threo isomers. The subsequent cyclization that produces *sym*-octahydroacridine (**13**) was briefly reported by Stobbe[24] without mention of the yield. In the present study, **13** is formed in 92% yield as a white microcrystalline solid. Prior to acetylation of **13**, it is necessary to form the *N*-oxide, which is accomplished in 96% yield with 3-chloroperoxybenzoic acid. This offers an improvement over a brief literature report[25] employing H_2O_2/CH_3COOH mixtures that gave **14** in 76% yield. The subsequent acetylation, performed as described by Klimov[26] (no reported yield), provides **15** in 91% yield as a brown sticky oil. N-Oxidation (step 6) is accomplished with 3-chloroperoxybenzoic acid, and **16** is obtained as an orange solid in 97% yield. The Klimov description[26] results in hydrolysis of the acetyl group, and the 5-hydroxy derivative is obtained in 88% yield.

(22) Frank, R. L.; Pierle, R. C. *J. Am. Chem. Soc.* **1951**, *73*, 724.
(23) Gill, N. S.; James, K. B.; Lions, F.; Potts, K. T. *J. Am. Chem. Soc.* **1952**, *74*, 4923.
(24) Stobbe, H. *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 3978.
(25) Tilichenko, M. N.; Klimov, G. A. *Zh. Org. Khim.* **1965**, *1*, 947.
(26) Klimov, G. A.; Tilichenko, M. N.; Karaulov, E. S. *Chem. Heterocycl. Compd.* **1969**, *5*, 226. *Khim. Geterotsikl. Soedin.* **1969**, *2*, 297.

Scheme 1



The second acetylation (step 7) is efficient, with **17** being formed as an orange solid in quantitative yield. Subsequent hydrolysis with aqueous HCl gives the orange solid 4,5-dihydroxy-*sym*-octahydroacridine (**18**) in 93% yield. The chlorination of **18** is also briefly described by Klimov and co-workers.[26] They stirred **18** and thionyl chloride together for 7 h at 23 °C and then refluxed the mixture for 1 h. The resulting orange solid (**19**) was obtained in 55% yield. In the present study, **18** was combined with excess $SOCl_2$ in $CHCl_3$, stirred at 23 °C for 10 min, and then refluxed (80 °C) for 1 h. Compound **19** is isolated in this procedure in 89% yield as a mixture of meso and threo isomers. Overall, the scheme developed here provides a more efficient, higher yield route to **19**, which is the key intermediate to the desired final product.

Treatment of **19** with 2 equiv of $Ph_2P(O)MgBr$ at 70 °C results in smooth replacement of the chloride groups with $Ph_2P(O)$ groups. As expected, workup reveals that both meso and threo isomers of **20** are formed in a 1:1 ratio, but the mixture can be driven fully to the threo isomer by refluxing a $CHCl_3$ solution of the mixture for 5 h. Subsequent treatment of **20** with H_2O_2/CH_3COOH at 63 °C for 16 h produces **10** as a white solid, which is recrystallized and isolated in 89% yield. The overall yield for the 11-step process is approximately 18%, and further optimization is possible.

Each of the intermediate species **11**−**19**, previously reported in the literature, has been further characterized by ^1H and $^{13}C\{^1H\}$ NMR spectroscopy, and these data appear in the Supporting Information.[27] The new compounds **20** and **10** have been characterized by elemental analysis,[28] mass spectrometry, infrared spectroscopy, and ^1H, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR spectroscopy. Both molecules show an intense ($M + H^+$) ion and a less intense (M^+) ion in their FAB mass spectra. This

Table 2. Selected Bond Distances (Å)

	10′	**10″**	**21**	**22**
M−O(P)			Nd−O(2) 2.324(13)	La−O(2) 2.405(7)
			Nd−O(3) 2.330(8)	La−O(3) 2.382(4)
M−O(N)			Nd−O(1) 2.424(10)	La−O(1) 2.490(5)
$M-O(nitrate)_{av}$			Nd−O 2.547(13)	La−O 2.603(7)
P═O	P(1)−O(2) 1.488(4)	P−O(2) 1.492(2)	P(1)−O(2) 1.562(14)	P(1)−O(2) 1.487(7)
	P(2)−O(3) 1.487(4)		P(2)−O(3) 1.515(8)	P(2)−O(3) 1.508(5)
N−O	N−O(1) 1.302(6)	N−O(1) 1.309(3)	N(1)−O(1) 1.323(13)	N(1)−O(1) 1.341(7)

behavior has also been observed for **3**−**9** and their pyridine precursors.[9,10,13,14] The infrared spectra display bands that can be tentatively assigned to the ν_{NO} and ν_{PO} stretching frequencies: **10**, ν_{NO} = 1284 cm^{-1} and ν_{PO} = 1176 cm^{-1}; **20**, ν_{PO} = 1188 cm^{-1}. The values for the fully oxidized *N*,*P*,*P*′-trioxide **10** compare favorably with the frequencies reported: **3**,[9] ν_{NO} = 1273 and 1284 cm^{-1} and ν_{PO} = 1186 cm^{-1}; **5**,[13,14] ν_{NO} = 1229 cm^{-1} and ν_{PO} = 1186 cm^{-1}; **7**,[13,14] ν_{NO} = 1233 cm^{-1} and ν_{PO} = 1195 cm^{-1}. The ^{31}P{^{1}H} NMR spectrum of **20** displays a single resonance at δ 36.6,[9] and this value is slightly downfield of the resonances observed for **21** ([$Ph_2P(O)CH_2$]C_5H_4N), δ 30.2, and **22** (2,6-[$Ph_2P(O)CH_2$]$_2C_5H_3N$), δ 34.[13,14] The ^{31}P-{^{1}H} NMR spectrum of **10** displays a single resonance centered at δ 36.2. This shift is very close to that shown by **20**, but mixtures of the two compounds obtained from incomplete oxidations show the two resonances fully resolved at 161.85 MHz (^{31}P obs). The ^{31}P resonance in **10** appears in the same region reported for those of **5**, δ 31.7, and **7**, δ 31.3,[13,14] in which the $Ph_2P(O)$ groups are bonded to aliphatic methylene carbon atoms. All of these resonances are significantly downfield of the ^{31}P resonance in **3**, δ 19.1, in which the $Ph_2P(O)$ group is bonded to the 2-position of the pyridine ring. The low field shift for **10** is then consistent with the $Ph_2P(O)$ groups bonded to the aliphatic tetrahedral 4,5-carbon atoms in the octahydroacridine ring system. The ^{13}C{^{1}H} NMR spectra for **10** and **20** are consistent with the proposed structures, and they have been fully assigned.

The molecular structure of the free ligand is of interest, and two crystallographic modifications are obtained depending upon the recrystallization solvent: **10′** from $CHCl_3$ and **10″** from MeOH. The structures were determined by single-crystal X-ray diffraction techniques, and views of the two molecular structures are shown in Figures 1 and 2. Both modifications adopt the threo form, and **10′** contains no molecular symmetry element. The pyridine *N*-oxide fragment in the fused ring structure is planar and symmetrical within 3σ of the bond length estimated standard deviations. The N−O bond length, 1.302(6) Å (Table 2), is identical to the N−O distance in **7**, 1.315(6) Å,[14] and the average N−C and C−C distances are 1.370(3) and 1.374(7) Å, respectively. The two cyclohexyl ring fragments have twisted chair arrangements, with one $Ph_2P(O)$ group below the fused ring best-plane and the second $Ph_2P(O)$ group above the best-plane. The P═O bond vectors are both rotated away from the N−O bond vector due to nonbonded repulsions. A similar effect is seen in the structure of **7**.[14] The average P═O bond length,

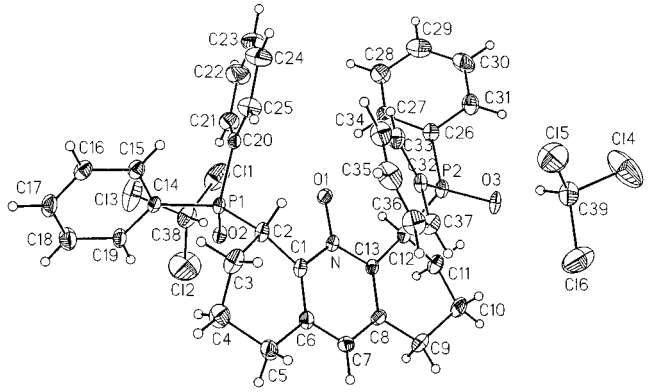


Figure 1. Molecular structure and atom labeling scheme for [Ph_2P-(O)C(H)$(CH_2)_3]_2C_5HNO\cdot CHCl_3$ (**10′**).

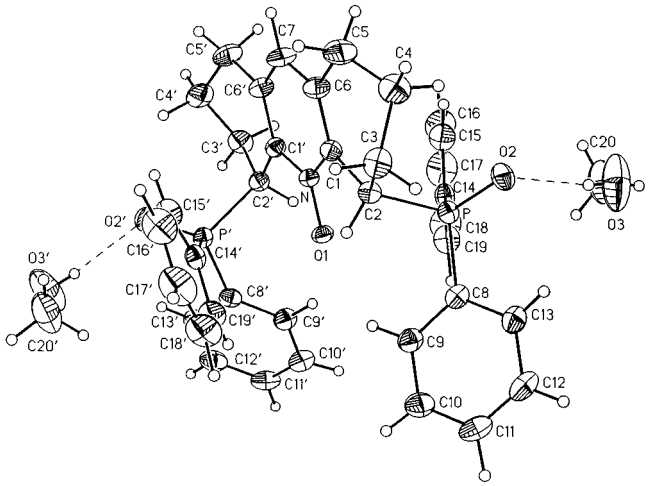


Figure 2. Molecular structure and atom labeling scheme for [Ph_2P-(O)C(H)$(CH_2)_3]_2C_5HNO\cdot CH_3OH$ (**10″**).

1.488(4) Å, is identical to the average value in **7**, 1.480(3) Å, and the average P−C(H) distance involving the phosphine oxide group and cyclohexyl ring in **10′** is 1.855(1) Å. The latter is slightly longer than the average P−C(H)$_2$ distance in the methylene arms in **7**, 1.813(4) Å. This lengthening provides evidence for greater steric constraints in **10′** relative to **7**.

The crystal structure of **10″** has one-half molecule of ligand and a molecule of MeOH in the asymmetric unit. The molecule **10″** has a 2-fold axis that passes through O(1), N, and C(7). The N−O, N−C, C−C(pyr), P═O, and P−C(H) distances are 1.309(3), 1.367(2), 1.384(3), 1.492(2), and 1.858(2) Å, respectively. Each is comparable with the bond lengths in **10′**. The primary differences in the structures of **10′** and **10″** appear in the hydrogen-bonded interactions between the ligand and solvent. In **10′**, there are short hydrogen-bonding interactions between P−O(2) and H(3C)−O(3) in the methanol (O(2)···O(3) separation, 2.818 Å). In **10″**, there are several short H-bonding contacts, N−O(1)···H(27)−C(27), P(1)−O(2)···H(38)−C(38), P(2)−O(3)···H(39)−C(39), and C(38)−Cl(2)···H(18)−C(18),

(27) The ^{13}C{^{1}H} NMR spectrum for **12** displays 14 resonances arising from 7 inequivalent carbon atoms in each of the meso and threo isomers. The ^{13}C{^{1}H} spectra for **15** and **16** contain 15 resonances resulting from 15 inequivalent carbon atoms. The ^{13}C{^{1}H} NMR spectra for **18** and **19** would be expected to display 14 resonances for a mixture of meso and threo isomers, and all 14 resonances are resolved. Compound **17** should display a total of 18 resonances (meso and threo, 9 each); however, only 15 are resolved.

(28) CHN analyses for **10** and **20** are consistently low in carbon and hydrogen. This trend has been observed with other phosphonopyridine oxide ligands, and it results from incomplete combustion.

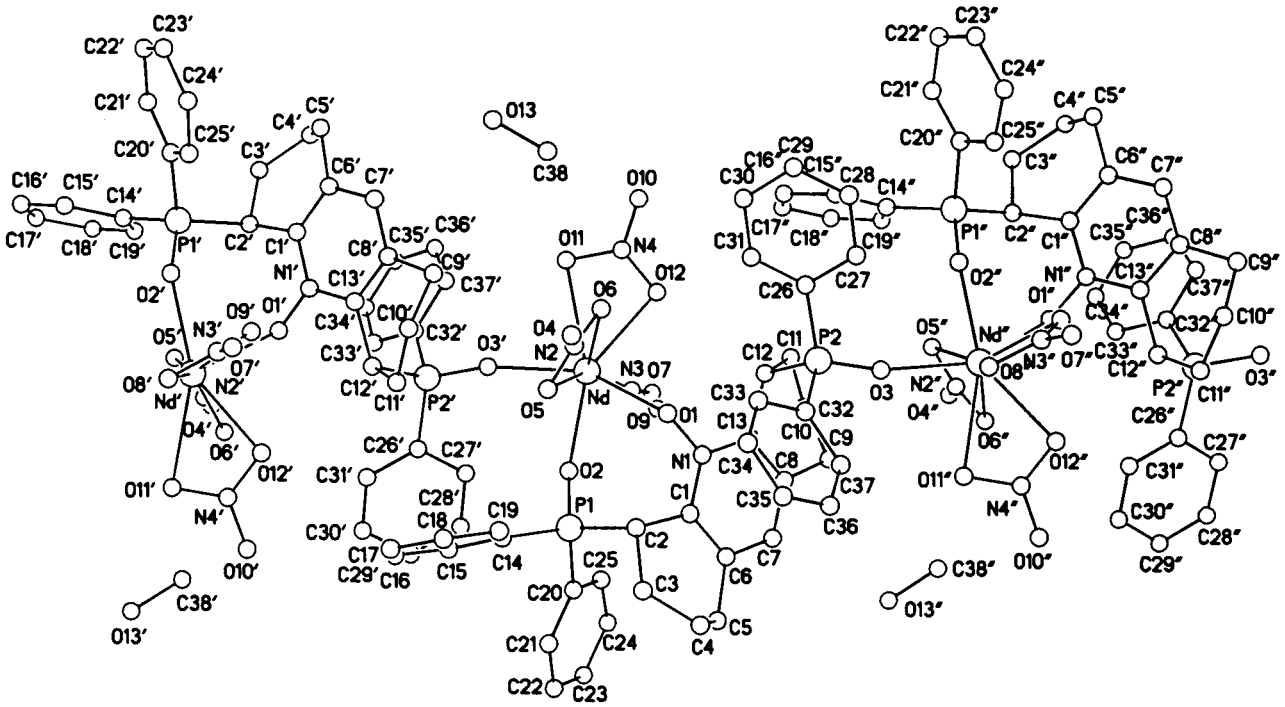


Figure 3. Molecular structure and atom labeling scheme for Nd(**10**)$(NO_3)_3$·MeOH showing chain formation along *z* axis.

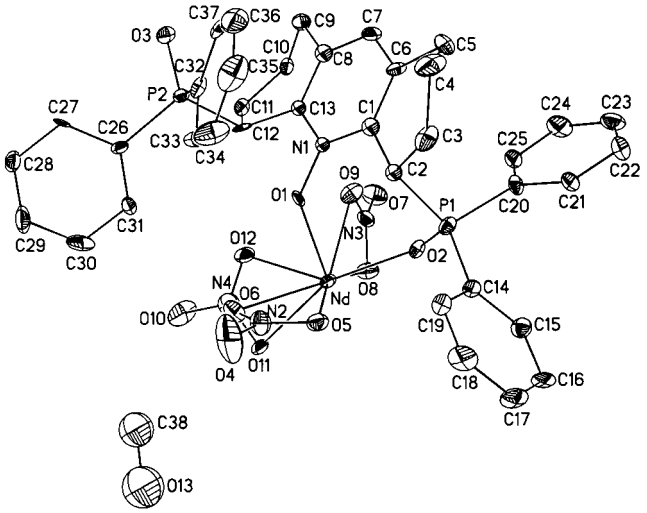


Figure 4. Molecular structure and atom labeling scheme for a single molecular unit of Nd(**10**)$(NO_3)_3$·MeOH.

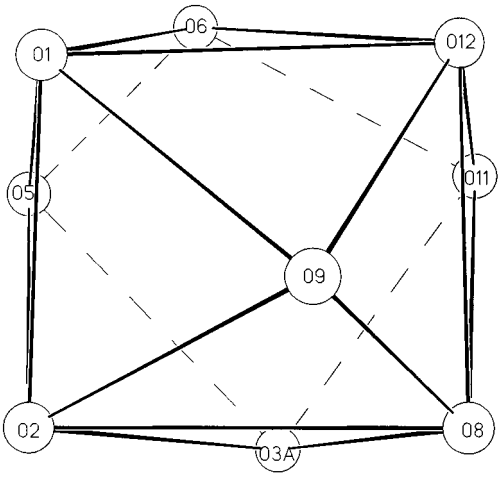


Figure 5. Inner sphere coordination polyhedron for Nd(**10**)$(NO_3)_3$·MeOH.

with nonbonded heavy atom separations of 3.147, 3.113, 3.007, and 3.543 Å, respectively.

The coordination complexes of **10** were formed by combination of the threo ligand and $La(NO_3)_3$·$6H_2O$ and $Nd(NO_3)_3$·$6H_2O$ in a 2:1 ratio in MeOH. Recrystallizations were accomplished from mixed MeOH/ethyl acetate (La) or from MeOH by slow evaporation of the solvent. The La(III) complex is colorless, and the Nd(III) complex is blue. Single-crystal X-ray diffraction analyses confirm that the complexes have a 1:1 ligand/metal stoichiometry with overall compositions M(**10**)-$(NO_3)_3$·MeOH, where M = Nd (**21**) or La (**22**). The complexes crystallize in the chiral orthorhombic space group $P2_12_12_1$, and the solutions of the structures are consistent with racemic twinning. The molecules form chains along the *z* axis, with **10** acting as a bidentate ligand toward one $M(NO_3)_3$ unit using one phosphoryl group and the *N*-oxide group. The second phosphoryl group bonds in a monodentate fashion to a second $M(NO_3)_3$. A view of the molecular chain for the Nd(III) complex **21** is shown in Figure 3 and a view of the structure around one $Nd(NO_3)_3$ is shown in Figure 4. The Nd(III) coordination number is 9, and a view of the monocapped square antiprism coordination polyhedron is shown in Figure 5. The Nd−O (ligand) bond lengths are as follows: Nd−O(1)N, 2.424(10) Å; Nd−O(2)P, 2.324(13) Å; Nd−O(3), 2.330(8) Å. These distances can be compared with the bond lengths in $[Nd\{[(Ph)(Bz)P(O)CH_2]_2C_5H_3NO\}(NO_3)](NO_3)_2$ (**23**),[29] which contains a trifunctional, tridentate ligand similar to **7** except that one phenyl group on each phosphoryl is replaced by a benzyl group. In **23**, the average Nd−O(P) distance is 2.384(3) Å and the Nd−O(N) distance is 2.382(3) Å. The Nd complex of the tetradentate ligand **9**, $[Nd(\mathbf{9})_2^{3+}](NO_3^-)_3$, displays average Nd−O(P) and Nd−O(N) distances of 2.400(6) and 2.471(6) Å. The three nitrate anions in Nd(**10**)$(NO_3)_3$·MeOH are coordinated to the central Nd(III) ion in an asymmetric bidentate fashion. The individual Nd−O (nitrate) distances are as follows: (nitrate 1), 2.566(12) and

(29) Gan, X.-M.; Duesler, E. N.; Paine, R. T. Manuscript in preparation.

2.566(12) Å; (nitrate 2), 2.509(11) and 2.520(10) Å; (nitrate 3), 2.496(11) and 2.626(14) Å; average Nd−O (nitrate), 2.547 Å. The average is identical to the average value in **23**, 2.542(3) Å. The MeOH molecules in the lattice appear to be hydrogen bonded to a neighboring metal bonded nitrate anion, O(13)−H···O(4)−N(2), with the heavy atom separation O(13)···O(4) of 2.93(3) Å. Finally, the La−O bond lengths in the La(**10**)-$(NO_3)_3$·MeOH complex **22** are longer, in all cases, than the Nd−O bond lengths, as would be expected for the larger central cation: La(III), 1.20 Å; Nd(III), 1.09 Å.[30] The infrared spectra for **21** and **22** are consistent with the structural results. The ν_{NO} bonds are shifted down frequency (**21**, $\Delta\nu_{NO} = 52$ cm^{-1}; **22**, $\Delta\nu_{NO} = 60$ cm^{-1}) from the free ligand, and the ν_{PO} band of the ligand is split into two absorptions, $\Delta\nu_{PO} = 30$ and 80 cm^{-1}.

Conclusion

A multistep synthesis for the trifunctional bis(phosphino)-octahydroacridine *P*,*P*′-dioxide (**20**) has been developed. The molecule contains chiral carbon atoms, C2 and C2′, that produce a 50:50 meso/threo isomer mixture. The mixture can be thermally driven to the pure threo form. Subsequent N-oxidation of **20** provides the target trifunctional bis(phosphine)octahydroacridine *N*,*P*,*P*′-trioxide (**10**), also in the threo form. In contrast to **7**, which can readily reorient its $-CH_2P(O)Ph_2$ coordination arms, **10** cannot reorganize about the ring-constrained C2 and C2′ atoms to produce the meso isomer that would more closely resemble the chelating conformation of **7**.[31] Instead, the favored threo isomer acts as a bidentate N−O/P═O chelating ligand to one $M(NO_3)_3$ fragment and as a monodentate P═O bridging ligand to a second $M(NO_3)_3$ fragment. It is expected that this change in chelation will modify the liquid−liquid extraction performance of **10** relative to **7** and its derivatives.

Acknowledgment. Financial support for this study came from the U.S. Department of Energy, Office of Basic Energy Sciences, Grant No. DE-FG03-94ER14446.

Supporting Information Available: Proton and $^{13}C\{^1H\}$ NMR data for compounds **11**−**19** and four X-ray crystallographic files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

IC000153N

(30) Values quoted are for coordination number (CN) = 9. Shannon, R. D.; Prewitt, C. T. *Acta Crystallogr*. **1969**, *B25*, 925.

(31) The rotation about the exo $Ph_2P(O)$−C(ring) bonds in **10** is also severely restricted by steric interactions. This has been shown by molecular mechanics calculations[32] of single-point energies at 10° increments of bond rotation about the P(1)−C(2) bond. The steric collisions occur between the phenyl groups and the N−O bond.

(32) The single-point energy calculations were accomplished using Gaussian 98, revision A.7, with the basis set equal to STO-3G: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Colli, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.