Table I. The Rates of Transport from the Source Phase to the Receiving Phase of Various *N*-(3,5-Dinitrobenzoyl)amino Acid Derivatives

analyte	rate,[a] (*S*)-enantmr	rate,[a] (*R*)-enantmr	ratio of rates	ee (%)
alanine butyl ester	3.8	0.78	4.9	66
valine butyl ester	6.1	1.9	3.3	53
(α-methyl)valine butyl ester	4.4	1.7	2.6	44
leucine methyl ester	5.0	0.71	7.2	76
leucine butyl ester	6.4	1.6	3.9	59
leucine octyl ester	21	12	1.7	26
leucine butyl amide	2.1	0.28	7.6	77
leucine butyl ester (33% *S*-enriched)	10.6	1.5	6.9	75

[a] Rates are in units of μgrams min^{-1} and are relatively constant during the first 25–40% of the run.

of transport change with time as concentrations in the source and receiver phases change. Those rates cited in Table I are for the initial linear portions of the rate curves.

Using the aforementioned analyte, a run in which both kettles were maintained at 18 °C was stopped arbitrarily after 1700 min. The source and receiver phases were evaporated to dryness to afford, respectively, 30.9 mg of 52.4% enantiomeric excess, ee, (*R*)-enriched and 17.4 mg of 57.3% ee (*S*)-enriched analyte after chromatographic removal (silica, methylene chloride) of small amounts of leached transport agent. By lowering the temperature of the source kettle to 0 °C, the rate of the achiral transport process is slowed, while the rate and enantioselectivity of the facilitated process is increased owing to an increase in the association constant of the (S–S) complex; the analyte enters the dodecane solution in a 14:1 (*S*):(*R*) ratio. By raising the temperature of the receiver kettle to 50 °C, the rate of scrubbing increases as diffusion rates increase, and the complex is more extensively dissociated. The net result is that the analyte initially enters the receiving phase in a 9:1 (*S*):(*R*) ratio. By using successive "stages", further enantiomeric enrichment can be obtained. By using 50 mg of 11.5% (*S*)-enriched *N*-(3,5-dinitrobenzoyl)leucine *n*-butyl ester as feed stock, a source phase temperature of 0 °C, and a receiver phase temperature of 60 °C, a 14.2:1 *S*:*R* ratio (87% ee) of analyte enantiomers was observed in the 18 mg of material transported during the first 335 min.

The rate of transport of analyte into the dodecane phase is essentially proportional to the concentration of the transport agent. High transport agent concentrations also increase the enantiomeric purity of the entering material as a larger fraction of the material is transported by the chiral agent. It is evident that the more lipophilic the analyte, the faster the rate of transport and the lower the enantiomeric purity of the initially transported material. A major reason for this is that the rate of the achiral transport process increases with increased tendency of the analyte to partition into dodecane. Increasing the proportion of methanol in the source phase decreases this tendency, slows transport, and significantly increases the enantiomeric purity of the transported material.

The enantioselectivity noted for these complexing agent–analyte combinations in simple liquid–liquid partitioning experiments using dodecane and 4:1 methanol–water somewhat exceeds the separation factors noted for chromatographic separation of these analyte enantiomers on the corresponding chiral stationary phase.[7] This doubtless reflects the effect of the underlying silica and the neighboring strands of bonded phase. However, the differences are not great, and it is doubtful that membrane devices will perform enantiomer separations which cannot be effected chromatographically on the corresponding chiral phase.

Acknowledgment. This work has been supported by grants from the National Science Foundation and from Eli Lilly and Company.

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(7) The enantiomer distribution coefficients noted for the analytes in Table 1 range between 7 and 32 at room temperature. These values assure facile separations of the enantiomers in this series using the various liquid–liquid countercurrent partitioning devices currently available.

Are d^0 ML$_6$ Complexes Always Octahedral? The X-ray Structure of Trigonal-Prismatic [Li(tmed)]$_2$[ZrMe$_6$]

Paige M. Morse and Gregory S. Girolami*

School of Chemical Sciences
University of Illinois at Urbana—Champaign
505 S. Mathews, Urbana, Illinois 61801

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Transition-metal six-coordination is dominated by octahedral geometries. Occasionally, complexes that have ligands of significantly disparate sizes or complexes with electronically "noninnocent" chelating ligands exhibit nonoctahedral structures. Examples of such nontraditional complexes are $FeH_2(PR_3)_4$,[1] which has been described as a bicapped tetrahedron, and $Mo(S_2C_6H_4)_3$,[2] which is trigonal-prismatic. *In no case* has a transition-metal complex with six identical unidentate ligands been shown to adopt a nonoctahedral structure.[3] We wish to report the first such example of what may prove to be an entire class of nonoctahedral ML$_6$ species.

Alkylation of the zirconium phosphine complex $ZrCl_4$(dippe), dippe = 1,2-bis(diisopropylphosphino)ethane, with 2 equiv of dimethylmagnesium in diethyl ether followed by crystallization from pentane yields colorless crystals of the thermally unstable compound, $ZrMe_4$(dippe).[4] The analogous hafnium complex

$$MCl_4(dippe) + 2MgMe_2 \rightarrow MMe_4(dippe) + 2MgCl_2$$

1, M = Zr
2, M = Hf

$HfMe_4$(dippe) may be prepared similarly.[5] Surprisingly, the ^{1}H NMR spectra of the complexes in toluene-d_8 show a *single* resonance for the metal-bound methyl groups that is split into a triplet by coupling to two phosphorus nuclei. The $^{13}C\{^1H\}$ NMR spectra confirm the presence of only a single M–Me environment. The equivalence of the methyl groups is inconsistent with a cis octahedral structure unless there is an unusually low exchange barrier; however, the ^{1}H and ^{13}C NMR spectra of both compounds are temperature independent and show no broadening even at −80 °C that would suggest the onset of decoalescence. An alternative possibility is that these d^0 complexes are *trigonal-prismatic*. This suggestion would explain the presence of only one methyl environment if the bidentate phosphine ligand bridges between the two triangular faces.

The addition of 6 equivalents of methyllithium to zirconium tetrachloride in diethyl ether followed by filtration and addition of *N,N,N′,N′*-tetramethylethylenediamine (tmed) yields colorless crystals of the hexamethyl zirconate salt, [Li(tmed)]$_2$[ZrMe$_6$].[6]

$$MCl_4 + 6LiMe + 2tmed \rightarrow [Li(tmed)]_2[MMe_6] + 4LiCl$$

3, M = Zr
4, M = Hf

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(3) We refer specifically to significant changes in the interligand *angles*. There are several solid-state materials such as MoS_2 in which the metal atoms exhibit trigonal-prismatic geometries: Wells, A. F. *Structural Inorganic Chemistry*, 5th ed.; Oxford University Press: Oxford, 1984; p 757.

(4) ^{1}H NMR (C_7D_8 −60 °C) δ 1.05 (t, J_{PH} = 3.0 Hz, Zr-*Me*).

(5) ^{1}H NMR (C_7D_8, −60 °C) δ 0.65 (t, J_{PH} = 3.0 Hz, Hf-*Me*); ^{13}C NMR (C_7D_8, −60 °C) δ 49.0 (q, J_{CH} = 110 Hz, Hf-*Me*). Anal. Calcd for $C_{18}H_{44}P_2Hf$: C, 43.2; H, 8.79. Found: C, 42.7; H, 8.75.

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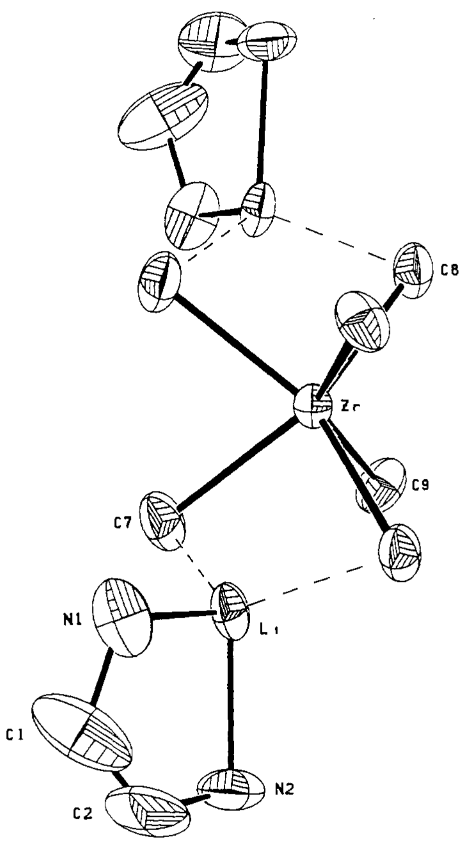

Figure 1. Molecular structure of $[Li(tmed)]_2[ZrMe_6]$. The methyl groups of the tmed ligands have been omitted for clarity. Important bond distances (Å) and angles (deg) are as follows: Zr–C7 = 2.43 (1), Zr–C8 = 2.37 (1), Zr–C9 = 2.35 (1), Li⋯C7 = 2.17 (2), Li⋯C8′ = 2.16 (2), C7–Zr–C8′ = 89.0 (4), C7–Zr–C9 = 82.4 (4), C8′–Zr–C9 = 84.7 (4), C7–Zr–C7′ = 78.2 (4), C8–Zr–C9 = 77.5 (4), C7–Zr–C8 = 141.5 (3), C7–Zr–C9′ = 128.2 (3), C8–Zr–C8′ = 121.0 (3), C9–Zr–C9′ = 143.5 (4).

The hafnium analogue may be prepared similarly.[7] Their ^{1}H and ^{13}C NMR spectra show a single resonance for the metal-bound methyl groups at all temperatures between −80 °C and 25 °C; this observation is consistent with either an octahedral or trigonal-prismatic geometry.

The X-ray crystal structure of $[Li(tmed)]_2[ZrMe_6]$ shows that *the methyl groups describe a trigonal prism* around the zirconium center (Figure 1).[8] The torsion angles C–Cn–Cn′–C′ (Cn = centroid of a trigonal face) of 0°, 16°, and 16° are far from the 60° twist angle in a regular octahedron. The values are scattered around the angle of 0° for an ideal trigonal prism because the triangular faces are not exactly equilateral.

Although the two $[Li(tmed)^+]$ cations are interacting with the anion, we do not believe these interactions dictate the trigonal-prismatic geometry of this compound. The $[Li(tmed)^+]$ units bridge between two methyl groups that lie along a trigonal edge of the prism; it has been suggested previously that capping the trigonal face or bridging a square edge would enhance the preference for a trigonal prism but such is *not* the case here. Furthermore, the C–Zr–C angles between the methyl groups bridged by the $[Li(tmed)^+]$ cations are 89.0°, a value which is similar to the lithium-bridged C–M–C angles of 93° in octahedral complexes such as $[Li(tmed)]_3[ErMe_6]$.[9] Thus it does not appear the the local geometries of the $Zr(\mu\text{-}Me)_2Li(tmed)$ units dictate the structure, since virtually identical Li⋯CH_3 interactions are observed in octahedral complexes. Another possibility is that crystal-packing forces subtly favor the observed geometry over an octahedron, but it is difficult to assess this factor.[10] We note, however, that the analogous d^3 complex $[Li(tmed)]_2[MnMe_6]$ manages to adopt the expected octahedral structure despite having exactly the same stoichiometry and similar Li⋯CH_3 interactions.[11] We conclude that the trigonal-prismatic structure is probably *intrinsic* to the $[ZrMe_6^{2-}]$ anion.

The trigonal-prismatic structure of the $[ZrMe_6^{2-}]$ anion is not explicable in terms of ligand field theory and contradicts the octahedral prediction of a simple electrostatic points-on-a-sphere model. Several theoretical treatments of d^0 ML_6 complexes have attempted to account for the trigonal-prismatic structures of the tris(dithiolate) complexes, and other studies have predicted nonoctahedral ground states for molecules such as $[TiH_6^{2-}]$.[12] The nonoctahedral structure of $[ZrMe_6^{2-}]$ can be accounted for similarly by a second-order Jahn–Teller effect: for a d^0 molecule of O_h symmetry, the HOMO (of T_{1u} symmetry, formed from metal p-orbitals and ligand σ-orbitals) and the LUMO (the nonbonding T_{2g} d-orbitals) cannot mix by symmetry. Upon lowering the symmetry to D_{3h}, the HOMO and LUMO transform as $E' + A_2''$ and $E' + A_1'$, respectively. Thus, the E' ($d_{x^2-y^2}$, d_{xy}) set of orbitals that constitute the LUMO can mix with the occupied metal–ligand σ-bonding orbitals. The net effect of this mixing is to lower the energy of the HOMO.[12] Accordingly, *d^0 ML_6 complexes evidently have an intrinsic electronic preference for nonoctahedral geometries*, in the absence of steric or π-bonding effects. The latter two factors, in fact, would then be responsible for the octahedral structures of other six-coordinate d^0 species such as $[ZrCl_6^{2-}]$[13] and $[Zr(NMe_2)_6^{2-}]$.[14]

The current results suggest that other sterically uncrowded d^0 ML_6 species that lack metal–ligand π-bonding such as $[NbMe_6^-]$, $[TaMe_6^-]$, and WMe_6 should also be trigonal-prismatic, and the unusual XPS spectra of the latter molecule[15] may be more readily interpretable if such is the case.[16] We are continuing work in this area.

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(6) ^{1}H NMR (C_7D_8, 20 °C) δ 0.24 (s, Zr-*Me*); ^{13}C NMR (C_7H_8, 20 °C): δ 32.0 (q, J_{CH} = 107 Hz, Zr-*Me*). Anal. Calcd for $C_{18}H_{50}N_4Li_2Zr$: C, 50.6; H, 11.7; N, 13.1; Li, 3.24. Found: C, 49.7; H, 11.5; N, 13.2; Li, 3.24. See, also: Berthold, H. J.; Groh, G. *Z. Anorg. Allg. Chem.* **1970**, *372*, 292–295.

(7) ^{1}H NMR (C_7D_8, 20 °C) δ 0.15 (s, Hf-*Me*); ^{13}C NMR (C_7D_8, 20 °C) δ 31.1 (q, J_{CH} = 109 Hz, Hf-*Me*). Anal. Calcd for $C_{18}H_{50}N_4Li_2Hf$: C, 42.0; H, 9.72; N, 10.9; Li, 2.72. Found: C, 42.5; H, 9.70; N, 12.0; Li, 2.49.

(8) Crystal data for $C_{18}H_{50}N_4Li_2Zr$ (T = 198 K): space group *Aba*2, a = 15.782 (2) Å, b = 14.210 (1) Å, c = 12.196 (2) Å, V = 2735 (1) Å^3, Z = 4, R_F = 0.049, R_{wF} = 0.065 for 113 variables and 1142 unique data for which $I > 2.58\sigma(I)$. All non-hydrogen atoms were refined anisotropically; hydrogen atoms were not included in the refinement. The zirconium center resides on a 2-fold crystallographic axis.

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(1988–1990) and a Henry and Camille Dreyfus Teacher–Scholar Award (1988–1993).

Supplementary Material Available: Tables of atomic coordinates, thermal parameters, and bond distances and angles for **3** (2 pages); table of final observed and calculated structure factors for **3** (6 pages). Ordering information is given on any current masthead page.

A Practical Synthesis of the Chinese "Nootropic" Agent Huperzine A: A Possible Lead in the Treatment of Alzheimer's Disease

Yan Xia and Alan P. Kozikowski*

Departments of Chemistry and Behavioral Neuroscience
Chevron Science Center
University of Pittsburgh
Pittsburgh, Pennsylvania 15260

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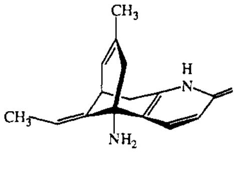
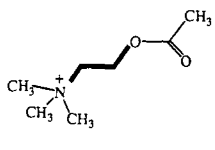
In this article we report the first total synthesis of the alkaloid huperzine A.[1] This tricyclic system represents one of nature's own contributions of a nootropic agent to mankind.[2] In studies carried out in China, huperzine A was found to improve memory and learning in animal models.[3] Of substantial interest was the finding that huperzine A could, in fact, improve memory in aged individuals suffering from various forms of memory impairment.[4] Pharmacologically, huperzine A functions as a potent inhibitor of the degradative enzyme, acetylcholinesterase, with a PI_{50} on acetylcholinesterase from erythrocyte membrane of 7.2.[5] In molecular graphics comparisons, the heteroatoms of acetylcholine in its completely extended {180°, 180°} conformation overlay well with those of huperzine A. This extended conformation is believed to be the one which is operative during hydrolysis by acetylcholinesterase.[6] Huperzine A is, in fact, more active than other well-documented acetylcholinesterase inhibitors such as physostigmine and neostigmine. Furthermore, the memory facilitating effects of huperzine A in higher order primates have been confirmed in studies carried out in the U.S. and Switzerland.



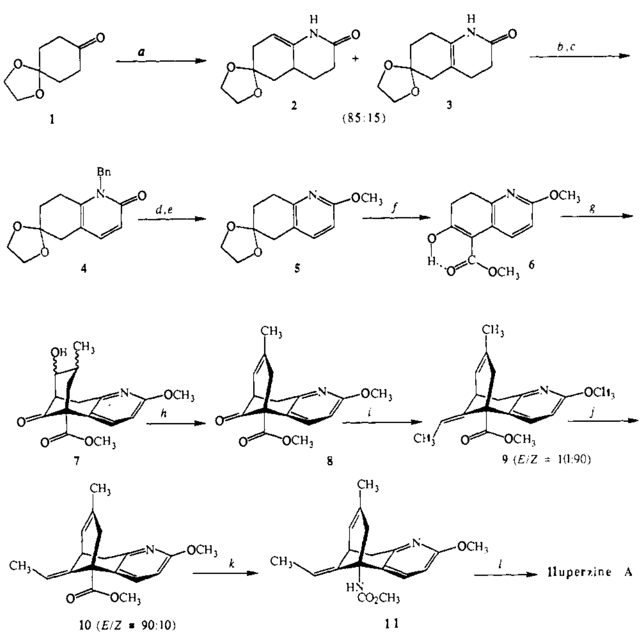
Huperzine A



Acetylcholine

In our program aimed at improving upon nature's original contribution of a nootropic agent, we have designed a short and practical route to this molecule. This route described below is sufficiently flexible to allow for the production of a variety of structural analogues.[7]

Scheme I.[a] Synthesis of Huperzine A



[a] (a) Pyrrolidine, PhH, p-TsOH (catalyst), reflux; acrylamide, dioxane, reflux; H_2O, dioxane, reflux (70% overall); (b) KH, BnCl, THF, room temperature (100%); (c) LDA, PhSeCl, THF, −78 °C; $NaIO_4$; Et_3N, MeOH, reflux (80%); (d) H_2, $Pd(OH)_2/C$, HOAc, room temperature (80%); (e) Ag_2CO_3, MeI, $CHCl_3$, room temperature (92%); (f) 5% HCl, acetone, reflux (85%); KH, $(MeO)_2CO$, reflux (87%); (g) methacrolein, tetramethylguanidine, CH_2Cl_2, room temperature (93%); (h) MsCl, Et_3N, DMAP, CH_2Cl_2 (96%); NaOAc, HOAc, 110 °C, 24 h (50%); (i) $Ph_3P{=}CHCH_3$, THF, 0 °C to room temperature (73%); (j) PhSH, AIBN, 170 °C, 24 h (100%); (k) 20% NaOH, THF, MeOH, reflux, 2 days (78% based on E ester); $SOCl_2$, toluene, 80 °C, 2 h; NaN_3, 80 °C; MeOH, reflux (80% overall); (l) TMSI, $CHCl_3$, reflux (92%).

The synthesis (Scheme I) begins by annealing a pyridone ring to the monoethylene ketal of 1,4-cyclohexanedione. This is done by reacting the pyrrolidine enamine of **1** with acrylamide in dioxane followed by refluxing with aqueous dioxane.[8] A mixture of the double bond regioisomers **2** and **3** (**2**/**3** = 85/15) is isolated in 70% yield. The ring nitrogen is next protected by *N*-benzylation and dehydrogenation to the pyridone system **4** brought about by α-selenenylation followed by oxidative elimination and base-catalyzed isomerization.[9] While a variety of logical transformations were subsequently examined using this N-protected pyridone, these all proved problematic as a consequence presumably of the instability of the pyridone ring. On several occasions aromatization of the cyclohexane ring was found to take place. Far better results were achieved on protecting the pyridone ring system on oxygen rather than nitrogen and carrying the fully aromatic methoxypyridine derivative on in the synthesis. Accordingly, pyridone **4** was debenzylated using palladium hydroxide in acetic acid and O-methylation brought about with silver carbonate and methyl iodide. Next, the ketal group of **5** was removed by aqueous acid hydrolysis, and the free ketone was then carbomethoxylated at its doubly activated site by heating with potassium hydride and dimethyl carbonate.[10]

While several methods were studied to introduce the unsaturated carbon bridge, we were most pleased to find that methacrolein could be added across the β-keto ester **6** in a single pot reaction

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