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(25) Conditions ($PhCH_2N^+(CH_3)_3{}^-OMe/CH_2Cl_2$) favoring the *Z,E*-enolate geometry afforded mainly two tetracyclic compounds (ca. 1:1) with the correct gibberellin C-4, C-5 relative stereochemistry. Conditions (LiOMe, $LiClO_4$, ether) favoring the *Z,Z*-enolate geometry gave two tetracyclic compounds (ca. 1:1) with the opposite C-4, C-5 relative stereochemistry.
(26) Jackman, L. M.; Lange, B. C., *Tetrahedron*, 1977, *33*, 2737–2769, and references cited therein.
(27) NOTE ADDED IN PROOF. The total synthesis of gibberellic acid has been reported since submission of this article: Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Keck, G. E.; Gopalan, B.; Larsen, S. D.; Siret, P.; Gras, J-L. *J. Am. Chem. Soc.*, **1979**, *100*, 8035.

Lewis N. Mander,* Stephen G. Pyne
Research School of Chemistry
Australian National University, Canberra 2600, Australia
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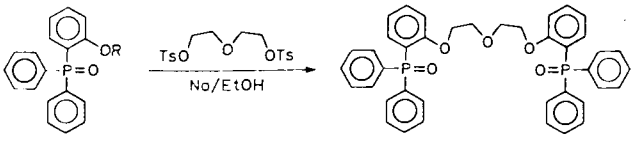
Isolation and X-ray Study of a Host–Guest Complex of an Amino Acid Ester Salt and a Simple Acyclic Ligand Derived from Triphenylphosphine Oxide

Sir:

The design of organic compounds which mimic biologically important phenomena such as molecular complexation is a fascinating challenge.[1] Considerable progress has been made in this area following the introduction of crown ethers[2] and cryptands[3] and a number of complexes of these macrocyclic receptors with ionic and neutral substrates has now been reported.[4] Recently it has been shown that acyclic polydentate ligands can form stable complexes as well.[5]

We describe here the synthesis of a simple acyclic ligand which has the ability to complex ammonium compounds. The complex of an amino acid ester salt and this ligand was isolated and its structure determined by X-ray techniques.

The ligand **2** was prepared as follows. (*o*-Methoxyphenyl)-diphenylphosphine oxide **1a,** mp 175–176 °C, was made in 78% yield from addition of *o*-methoxyphenylmagnesium bromide to diphenylchlorophosphine. Subsequent oxidation of the resulting (*o*-methoxy)diphenylphosphine, mp 126–127 °C, with 30% hydrogen peroxide in acetone[6] and demethylation with hydrogen iodide[7] gave (*o*-hydroxyphenyl)diphenylphosphine oxide **1b,** mp 258–259 °C, in 92% yield. Reaction of 2 equiv of the anion of **1b**[8] with diethylene glycol ditosylate in ethanol at reflux for 3 h afforded the ligand **2** in 94% yield, mp 158–160 °C, after recrystallization from dichloromethane–hexane.[9,10]



1a R = CH_3
1b R = H

2

The affinity of **2** for transition metal ions[11] was demonstrated in a serendipitous manner when in one run we purified **2** by column chromatography. The presence of traces of paramagnetic ions leached from silica gel with **2** in dichloromethane gave rise to broadening of the ^1H NMR spectrum. In addition, **2** formed complexes with ammonium compounds. Cyclohexylamine, isopropylamine, *tert*-butylamine, phenethylamine, and DL-phenylglycine ethyl ester were extracted as ammonium salts from a 0.2 N aqueous perchloric acid solution into chloroform with the aid of **2** at room temperature. After addition of a twofold excess of guest, the 1:1 complexes were found to be present in the organic layer as indicated by ^1H NMR. The selectivity of **2** was remarkable. Methylamine, ethylamine, *n*-propylamine, and *n*-butylamine **1a** were inactive in these extraction experiments. The crucial role of the diethylene glycol moiety was illustrated by preparing a ligand from **1b** and 1,5-dibromopentane (replacement of the central oxygen atom by a methylene function). This ligand obtained in 75% yield, mp 153–154 °C, was totally unable to extract ammonium salts under the conditions described above.

Using the trifluoromethanesulfonate counterion, we successfully isolated the complex of an amino acid ester salt and ligand **2**. When DL-phenylglycine ethyl ester trifluoromethanesulfonate[13] (5 mmol in 3 mL of water) was extracted with **2** (1 mmol in 1.5 mL of deuteriochloroform), the 1:1 adduct was found to be present in the organic layer as indicated by ^1H NMR. Slow addition of diethyl ether caused the complex to crystallize as white needles, mp 159–160 °C. The

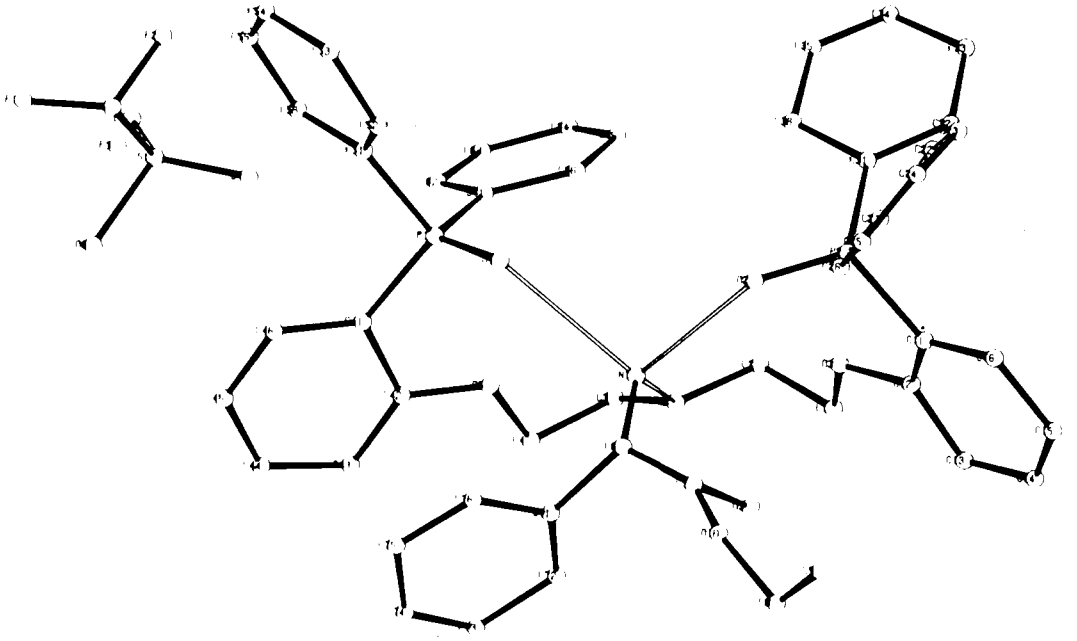


Figure 1. ORTEP drawing of the host–guest complex of **2** with DL-phenylglycine ethyl ester trifluoromethanesulfonate.

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structure was determined by X-ray techniques. Crystal data: space group $P\bar{1}$; a = 10.626 (7), b = 14.553 (6), c = 17.335 (8) Å; α = 109.57, β = 97.19, γ = 95.85 (5)°; V = 2476.0 Å^{-3}; Z = 2; $F(000)$ = 1032; μ (Mo Kα) = 2.0 cm^{-1}. The crystal structure was solved by direct methods (MULTAN 77) and refined by block-diagonal least-squares techniques (coordinates and anisotropic thermal parameters for the nonhydrogen atoms) to a current R factor of 0.10.[14,15]

The ligand is folded around the ammonium group, the N-O distances to the two phosphine oxide groups and the central oxygen atom of the diethylene glycol unit being the shortest. Triphenylphosphine oxide is known to have very high formation constants in hydrogen-bond formation.[16] The trifluoromethanesulfonate anion is remote from the complexed ammonium ion. As observed in the complex of the PF_6 salt of DL-phenylglycine methyl ester and a chiral macrocyclic polyether,[4b] the phenyl group and the ester function of the amino acid ester in **3** were parallel to aromatic groups of the ligand. Thus the hypothesis[4b] of charge transfer and/or hydrophobic interactions contributing to the stability of the complex seems to be valid.

Isolation of the adduct **3** is the first example of a characterized complex of an amino acid ester salt and an acyclic ligand. The ease of preparation of **2** should allow access to new ligands containing chiral carbon or phosphorus centers which may be used to effect enantioselective molecular complexation.

Supplementary Material Available: Atomic coordinates of the bonded atoms and bond distances and angles of the osculate atoms of the asymmetric unit (17 pages). Ordering information is given on any current masthead page.

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(8) Generated by reaction of **1b** with 1 equiv of sodium ethoxide in ethanol.
(9) Initially obtained as the clathrate with CH_2Cl_2, mp 123–124 °C. The solvent molecule is lost after heating at 130 °C in vacuo for 3 h.
(10) Correct elemental analyses and spectral data were obtained for all compounds.
(11) Quantitative results of solvent extraction experiments with **2** and transition metal ions will be reported elsewhere.
(12) Extraction of NH_4^+ in this manner resulted in a protonated species derived from **2** (NMR). Attempts at isolation as the ClO_4^- or trifluoromethanesulfonate salt gave an amorphous solid which could not be satisfactorily characterized by elemental analysis, but did not contain nitrogen.
(13) Prepared from DL-phenylglycine ethyl ester hydrochloride and silver trifluoromethanesulfonate in 88% yield, mp 155–156 °C.
(14) Key structural parameters follow. Distances: N-O(1), 2.69 (2); N-O(2), 2.65 (2); N-O(4), 2.82 (2); N-O(5), 3.24 (3); N-O(3), 3.25 (2); N-C(6), 1.39 (2) Å. Angles: O(1)-N-O(2), 97; O(1)-N-O(4), 109; O(2)-N-O(4), 115; O(1)-N-C(6), 112; O(2)-N-C(6), 104; O(4)-N-C(6), 118°.
(15) Owing to the high thermal motion of the molecule, it is not possible to locate the hydrogen atoms unambiguously. A low temperature X-ray study is underway and will be reported in a full paper.
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(17) We tentatively account for the selectivity with regard to complexation of isopropylamine in terms of hydrophobic interactions of the isopropyl group with phenyl groups of the ligand.

Albert H. Alberts,* Klaas Timmer, Jan G. Noltes*
Institute for Organic Chemistry TNO, Croesestraat 29 3522 AD Utrecht, The Netherlands

Antony L. Spek
Laboratorium voor Structuurchemie, Rijksuniversiteit Padualaan 8, 3584 CH Utrecht, The Netherlands

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Resonance Raman Evidence for Charge-Transfer Interactions of Phenols with the Flavin Mononucleotide of Old Yellow Enzyme

Sir:

During the reaction of various flavoenzymes with substrates, nonsemiquinone-type intermediates often appear and show a broad absorption band at longer wavelengths. These reaction intermediates are usually assigned to charge-transfer complexes of oxidized or reduced enzymes with substrate or product, but the details are not clear. In the case of Old Yellow Enzyme (NADPH oxidoreductase, EC 9.6.99.1) (OYE) which has a flavin mononucleotide (FMN) per monomer, many phenolic compounds are bound tightly to OYE when the flavin is in the oxidized state, giving rise to a long wavelength absorption in the same manner as the reaction intermediates,[1] and a systematic correlation exists between λ_{max} of the complexes and σ_{para} of Hammet constant of the para substituents of phenol.[2] Existence of such correlation suggests that the phenol is the charge-transfer donor and oxidized flavin of the enzyme is the acceptor. Although phenols are inhibitors of the enzymatic reaction, physicochemical investigation of the complexes is substantially necessary to determine chemical properties of the coenzymes and also to elucidate the catalytic mechanism of the enzymatic reaction.

It was recently demonstrated that the resonance CARS[3,4] and spontaneous resonance Raman scattering of flavoproteins[5] selectively revealed the vibrational frequencies of in-plane modes of isoalloxazine without interference by vibrations of the apoenzyme. The Raman lines were assigned empirically based on the data of isotopic frequency shift for the ^{13}C- and ^{15}N-labeled riboflavin.[6] Since resonance Raman spectroscopy offers, in principle, the vibrational frequencies of chromophoric group, excitation of Raman scattering of the OYE-Phenol complex at the long wavelength band might provide Raman lines associated with its chromophore, i.e., internal modes of both flavin and phenol besides the flavin-phenol stretching mode, if the band were caused by a charge-transfer transition. Thus it was expected that the resonance Raman spectroscopy could reveal details of the flavin-ligand interactions, although observation of their spectra was generally very difficult because of strong fluorescence. In the present study we successfully applied the technique to the OYE-pentafluorophenol complex by exciting Raman scattering in the long wavelength band of the complex, observing the Raman lines characteristic of the charge-transfer complex.

OYE from beer yeast (M_r = 4.9 × 10^4) and its apoprotein were purified according to Abramovitz and Massey.[2,7] Enzyme concentration was determined spectrophotometrically using ϵ_M = 1.06 × 10^4 M^{-1} cm^{-1} at 462 nm[7] and the concentration of apoprotein was determined by fluorometric titration of FMN. Excess apoprotein was added to the enzyme solution to remove fluorescence. Pentafluorophenol (F_5Ph) was purchased from Wako Pure Chemicals. Raman scattering was excited by an Ar-Kr mixed-gas laser (Spectra Physics, Model 162) and recorded with a JEOL-400D Raman spectrometer equipped with a cooled HTV-R649 photomultiplier. For Raman experiments, ~300 μL of sample solution was put in a longitudinal type cell placed in a thermostated cell holder and was kept at 20 ± 2 °C during the measurements. The laser power at sample point was ~35 mW. Before and after the Raman experiments an identical value of specific activity of OYE was obtained and the absorption spectrum was unaltered.

Figure 1 shows the Raman spectra of OYE, F_5Ph, and their complex excited at 568.2 nm. The concentration of OYE or F_5Ph was the same as in their mixed solution and all of the samples commonly contained 3.3% (w/w) of $(NH_4)_2SO_4$.

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