

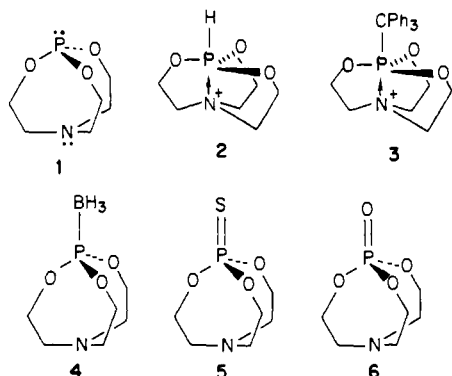
New Hypervalent Phosphorus Compounds: Neutral and Cationic 10-P-5 Species from $\text{O}=\text{P}(\text{OCH}_2\text{CH}_2)_3\text{N}$ and Lewis Acids

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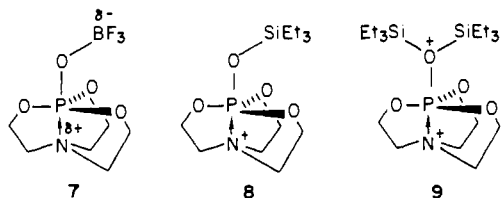
Abstract: BF_3 binds with the phosphoryl oxygen of the title phosphatrane **6** to form a neutral 10-P-5 adduct, Et_3Si^+ binds once or twice to the phosphoryl oxygen of **6** to yield a monovalent or a divalent 10-P-5 cation, respectively, which can be isolated, and H_3PO_4 forms an isolable 1:1 adduct with **6** in which the phosphoryl oxygen of **6** is protonated. Evidence is presented for the trigonal-bipyramidal stereochemistry of phosphorus in these hypervalent compounds, and their stability is attributed in part to enhanced electronegativity effects on the apical atoms arising from the electron-withdrawal properties of the attacking Lewis acid.

In an earlier publication¹ we reported that the 8-P-3 phosphatrane **1** reacts with H^+ or Ph_3C^+ to form the novel hypervalent 10-P-5 species **2** and **3**, respectively. The structure shown for cation **2** was verified by X-ray means.² Similar structural analysis



of the borane adduct **4** and thiophosphate **5** showed that neutral Lewis acids such as BH_3 and S do not induce transannulation of the nitrogen to form the corresponding 10-P-5 species. This is also true of the phosphoryl oxygen in **6** which displays ^1H NMR, ^{31}P NMR, and IR spectra typical of organophosphates.^{1,3}

Here we report the surprising results that **6** can be transformed into the neutral 10-P-5 adduct **7** upon reaction with BF_3 , that **6** sequentially adds two Et_3Si^+ ions to give the 10-P-5 cations **8** and **9**, respectively, and that **6** forms a protonated insoluble 1:1 adduct with H_3PO_4 .



Results

When a molar equivalent of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ is added to **6** in CD_3CN (Scheme I) there is observed a strong upfield shift of the ^{31}P NMR peak, downfield shifts of the OCH_2 and NCH_2 protons, the appearance of $^3J(\text{PNCH})$ coupling (3.1 Hz), and the disappearance of the $\text{P}=\text{O}$ stretching frequency. Further addition of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ resulted in no significant changes in the spectra. Addition of BF_3 to the parent phosphite **1** did not lead to a characterizable product.

Addition of a molar equivalent of $\text{Et}_3\text{SiClO}_4$ to **6** in CD_3CN (Scheme II) gives a new ^{31}P NMR peak at -18.7 ppm well upfield of that for **6**, ^1H resonances which are shifted downfield, and the appearance of $^3J(\text{PNCH})$ coupling, all of which have typical values for 10-P-5 phosphatrane species.¹ Further addition of $\text{Et}_3\text{SiClO}_4$ (Scheme II) gives rise to a single new peak in the ^{31}P NMR spectrum at -25.6 ppm. In addition to further downfield ^1H NMR shifts for **9** compared to **8**, the $^3J(\text{POCH})$ and $^3J(\text{PNCH})$ couplings increase from **8** to **9**. When solutions of **9** are evaporated, a white solid is obtained which when redissolved in CD_3CN shows the presence of a mixture of **8** and **9** in the ^{31}P NMR spectrum. Thus **9** appears to dissociate under these conditions to **8** and volatile $\text{Et}_3\text{SiClO}_4$. Efforts to obtain crystals of **8** or **9** have thus far been unsuccessful.

Addition of 1 equiv of anhydrous H_3PO_4 to **6** in MeCN (Scheme III) quantitatively precipitates a compound tentatively assigned the geometry depicted in the resonance structure shown for **10**. Other than $\text{Me}_2\text{SO}-d_6$ in which **10** dissociates to **1** and H_3PO_4 as shown by ^{31}P and ^1H NMR spectroscopy, **10** is highly insoluble in all other organic solvents tried and efforts to grow crystals have met with no success.

Reaction of **6** with $\text{Co}(\text{ClO}_4)_2$ and $\text{Zn}(\text{ClO}_4)_2$ (Scheme IV) under conditions where $\text{OP}(\text{OMe})_3$ as a ligand leads to $\text{CoL}_5(\text{ClO}_4)_2$ and $\text{ZnL}_5(\text{ClO}_4)_2$, respectively,⁴ gave spectral results consistent with retention of the bicyclic ligand structure of **6** in the case of $[\text{Zn}(\text{I})_n](\text{ClO}_4)_2$. Because of the paramagnetism of the $[\text{Co}(\text{6})_n](\text{ClO}_4)_2$ complex, UV-visible ($\lambda_{\text{max}} = 575, 595, 620, 643$ in MeNO_2) and IR spectra ($\nu(\text{P}=\text{O})$ 1260 cm^{-1} in MeNO_2) were compared with those of the $[\text{Co}[\text{OP}(\text{OEt})_3]_3](\text{ClO}_4)_2$ complex. The IR spectrum of $[\text{Co}(\text{6})_n](\text{ClO}_4)_2$ is in accord with retention of a bicyclic ligand structure while the UV-visible spectrum is inconclusive. Although the value of n for the Zn(II) and Co(II) complexes was not determined, it is likely that it is the same as in the analogous $\text{OP}(\text{OMe})_3$ complexes of zinc and cobalt ($n = 5$) since the ligand cone angles are very similar.

Reactions of **1** with *cis*- $\text{Cl}_2\text{Pt}(\text{NCPh})_2$, AgBF_4 , $\text{Ni}(\text{ClO}_4)_2$, and $\text{Co}(\text{BF}_4)_2$ under conditions which yield well-behaved complexes with a variety of $\text{P}(\text{OR})_3$ ligands^{5,6} gave only intractable materials.

Discussion

Synthesis and Structures. In the preparation of **7**, **6** (Scheme I) successfully competes for the BF_3 with the Et_2O in the $\text{BF}_3 \cdot \text{Et}_2\text{O}$ starting material. Attempts to isolate the BF_3 adduct failed, however, suggesting that this reaction is an equilibrium one. The changes in the NMR¹ and IR spectra of **6** are consistent with the formation of the neutral 10-P-5 species **7**.

(1) Milbrath, D. S.; Verkade, J. G. *J. Am. Chem. Soc.* 1977, 99, 6607.

(2) Clardy, J. C.; Milbrath, D. S.; Springer, J. P.; Verkade, J. G. *J. Am. Chem. Soc.* 1976, 98, 623.

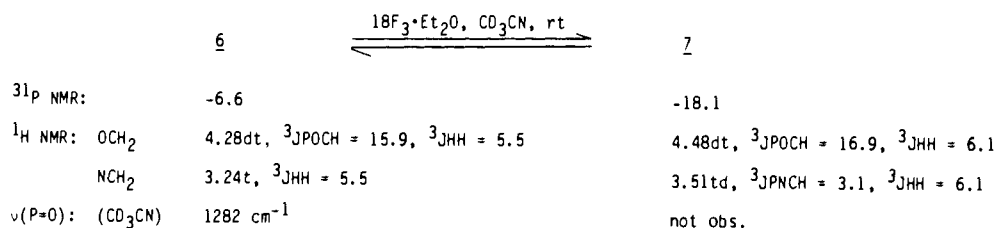
(3) This is also apparently the case in compounds wherein the phosphoryl oxygen is replaced by Se or $(\text{OC})_3\text{W}$ (see ref 1).

(4) Karayanis, N. M.; Bradshaw, E. S.; Pytlewski, L. L.; Labes, M. M. *J. Inorg. Nucl. Chem.* 1970, 32, 1079.

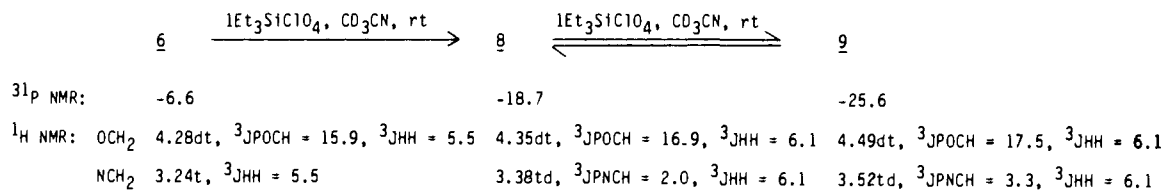
(5) Verkade, J. G. *Coord. Chem. Rev.* 1972, 9, 1.

(6) Verkade, J. G.; Coskran, K. J. In "Organic Phosphorus Compounds"; Kosolapoff, G. M., Maier, L., Eds.; John Wiley and Sons, Inc.: New York, 1972; Vol. 2, pp 1-187.

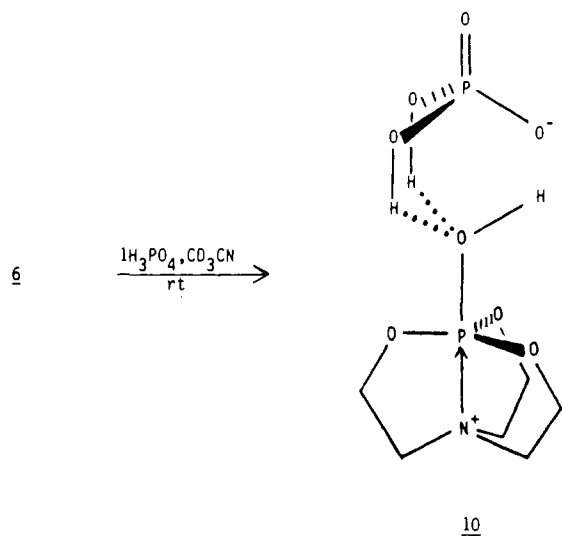
Scheme I



Scheme II



Scheme III

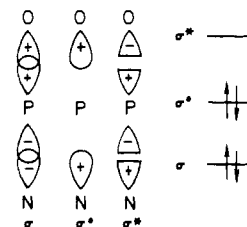


As might be expected on the basis of increased positive charge from **8** to **9**, there is an accompanying downfield movement of the 1H NMR peaks and increases in the $^3J(POCH)$ and $^3J(PNCH)$ couplings (Scheme II). The upfield ^{31}P chemical shift from **8** to **9**, whose configurations are isoelectronic and isostructural with one another, is in accord with similar trends in $\delta^{31}P$ with charge in several series of d⁶ octahedral coordination complexes of the type $M[P(OR)_3]_n^+$, for example, where n ranges from zero to 3+.⁷

Evidence for formulating **10** as a monoprotonated phosphatranes stems from its solid-state ^{31}P NMR spectrum⁸ which contains a peak at 0 ppm corresponding to the H_3PO_4 moiety and another absorption at -11 ppm, which is closer to the solution value for **8** (-18.1 ppm) than to that for the disilylated species **9** in solution (-25.6 ppm). The reluctance of **10** to dissolve intact may be related to the suggested structure shown, which would be expected to possess an extraordinarily large dipole moment (ca. 10 D).⁹

Bonding. It has been well established that chelation effects play a crucial role in the stabilization of a variety of hypervalent

nonmetals.^{10,11} In phosphatranes this was demonstrated by the failure of a combination of $P(OEt)_3$ and $(HOCH_2CH_2)_3NHC1$ to form $[HP(OEt)_3N(CH_2CH_2OH)_3]Cl$ wherein chelation is absent.¹ Electronegativity effects are also important, particularly in stabilizing trigonal-bipyramidal (TBP) structures wherein the more electronegative phosphorus substituents occupy the apices of the threefold TBP axis.¹² Chelation effects and accompanying molecular constraint apparently predominate over this apicophilicity rule in **2**, **3**, **7**, **8**, **9**, and **10**. To the extent that the positive charge in **2**, **3**, and **7-10** is localized on the apical atoms of the threefold axis in each of these species, the electronegativities of these atoms are enhanced. Unlike the three pairs of electrons which all reside in 4-center delocalized bonding MO's in the equatorial plane of TBP 10-E-5 species, the two electron pairs in the two axial linkages can be viewed as occupying a bonding and a nonbonding MO in a 3-center system as shown below for **7-10**. Here the negative charge which accumulates on the apical



oxygen and nitrogen atoms in the nonbonding MO is stabilized by electron pair donation from oxygen to BF_3 in **7**, to one or two Et_3Si^+ ions in **8** and **9**, respectively, and to a proton in **10**.

The relatively nonapicophilic hydrogen and carbon moieties in **1** and **2**, respectively, are apparently able to stabilize the 3-center 4-electron system along the axis of the TBP structure. This is not the case with the stable borane adduct **4**¹ or the analogous BF_3 adduct whose attempted synthesis here resulted only in polymer formation and decomposition. In contrast, **6** in the presence of BF_3 sacrifices a normally very stable $P=O$ linkage to form **7**. Interesting in this regard is the prediction we made earlier on the basis of CNDO/2 calculations that **6** should adopt a TBP configuration.¹³ Apparently the observed tetrahedral configuration of **6** is sufficiently close in energy to TBP that a neutral BF_3 molecule is capable of facilitating the structural transformation from **6** to **7**.

It seems odd at first that both **1** and **6** fail to become TBP in the presence of positively charged metal ions. Compound **1** in the presence of *cis*- $Cl_2Pt(NCPh)_2$, $AgBF_4$, $Ni(ClO_4)_2$, or $Co(BF_4)_2$ generates only intractable materials, some of which are insoluble in organic solvents. It is likely that the rate of ligand oligomer

(7) Yarbrough, L.; Verkade, J. G., to be published.

(8) We thank Dr. J. S. Frye of the Colorado State University Regional NMR Center for this result.

(9) The dipole moment of 7.1 D for $OP(OCH_2)_3CMe$ (Brown, T. L.; Verkade, J. G.; Piper, T. S. *J. Phys. Chem.* **1961**, *65*, 2051) can be taken to approximate the $OP(OCH_2)_3$ moiety of **10**. Similarly, 0.63 D for NMe_3 and 3.02 for $O=P(OMe)_3$ (McClellan, A. L. "Tables of Experimental Moments"; W. H. Freeman and Co., San Francisco, 1963) are reasonable values for the $N(CH_2)_3$ and $O=P(OH)_3$ moieties, respectively. Since all three moieties are unidirectional in **10**, their moments can be summed, giving an approximate dipole moment of 10.7 D for **10**. This moment could well be augmented by development of the charges indicated in **10**.

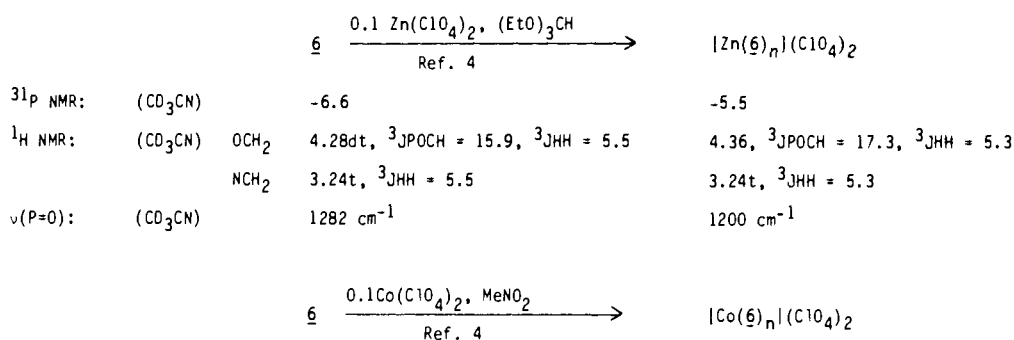
(10) Martin, J. C. *Science* **1983**, *221*, 509.

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(12) Musher, J. *Angew. Chem., Int. Ed Engl.* **1969**, *8*, 54.

(13) van Aken, D.; Castelyns, A. M. C. F.; Verkade, J. G.; Buck, H. M. *J. R. Neth. Chem. Soc.* **1979**, *98*, 12.

Scheme IV



assembly¹ (in uncoordinated and/or metal-coordinated form) exceeds that of formation of nonlabile complexes wherein all the ligands remained monomeric. Any lability of desired complexes which may have formed would also be expected to lead to oligomers. On the other hand, **1** and **2** are apparently quite inert to dissociation.¹ Bicyclic **6** is also dissociatively inert, but its coordination to Zn^{2+} or Co^{2+} did not result in TBP ligand formation. While the presence of the metallic positive charges in the complexes might be expected to induce this transformation, its absence could be ascribed to the greater ligand–ligand repulsion that the sterically larger 10-P-5 ligands in such complexes would experience, although presumably dissociation of one or more ligands could occur to accommodate the more sterically demanding form of the ligand. The fact that such a configurational change at phosphorus is not favored in complexes of **6**, however, is consistent with the conclusion drawn from numerous studies of phosphoryl oxygen-bound complexes, namely, that the primary role of the metal ion is merely to orient the ligands by a predominantly polarizing interaction with the phosphoryl group rather than by significant electron delocalization from ligand into metal orbitals.¹⁴

The positively charged Et_3Si^+ ion which requires only one Lewis base moiety can both sterically and electronically accommodate the TBP structure of **8**. A similar observation was made earlier for analogous carbenium derivatives of **5** and **6**, the former of which (where $\text{R} = \text{Et}$) was confirmed to have a TBP structure by X-ray means.¹⁵ More remarkable, however, is the formation of **9** as a solid (albeit as a presently inseparable mixture with monosilylated **8**). A rationale for the stabilization of the unique dication **9** is that the two positive charges are largely localized on the apical atoms, thus lowering the electronic energy of the doubly occupied σ -nonbonding orbital.

Although the extraordinarily high dipole moment of **10** (ca. 10 D^9) could be largely responsible for its insolubility, it is interesting that a stoichiometric compound such as **10** forms at all in view of the expected lability of a proton bound to a poorly basic phosphoryl oxygen. Even given the unusual basicity of this oxygen in **10**, however, this compound might have been expected to be a 1:1 electrolyte, if **6** was mono- or diprotonated. In addition to the electronic and chelation arguments given above for the stability of the TBP structure of 10-P-5 species such as **10**, three additional influences acting in concert are probably important in stabilizing the “double-cage” structure of this molecule. First, there are three hydrogen-bonded resonance structures implied by the configuration shown for **10**. Second, the hydrogen bonding of two of the phosphoric acid protons to the “phosphoryl” oxygen in **10** is stabilized by the two chelating arms of the H_2PO_4^- moiety in each of the three resonance forms, thus forming an average structure which is a stable and relatively strainless bicyclo[2.2.2]octane composed of six-membered rings involved in hydrogen bonding as well as protonation. Third, the molecular dipoles of the bicyclo[2.2.2]octane and the tricyclo[3.3.3.0]undecane components

of **10**⁹ are lined up in a stable “head-to-tail” fashion.

These studies suggest that other nonmetallic compounds which are not hypervalent can, under appropriate conditions, be induced to expand their octets with a variety of Lewis acids. Furthermore, many 10-E-5 systems which are not TBP may approach this geometry in the presence of Lewis acids. Additional studies of this type are underway.

Experimental Section

OP(OCH₂CH₂)₃N (6). This compound was synthesized by a modification of the preparation given earlier.¹ Into 750 mL of dry refluxing $\text{C}_6\text{H}_5\text{Me}$ was simultaneously added with a syringe drive over a period of 24 h and under nitrogen a solution of 7.5 g (50 mmol) of $\text{N}(\text{CH}_2\text{CH}_2\text{OH})_3$ in 20 mL of CHCl_3 with enough $\text{C}_6\text{H}_5\text{Me}$ to make 50 mL and a 50 mL $\text{C}_6\text{H}_5\text{Me}$ solution of 9.0 g (55 mmol) of $\text{P}(\text{NMe}_2)_3$. After the reaction mixture was cooled to 45–50 °C, 14.2 g (200 mmol) of KO_2 and 0.2 g (0.75 mmol) of 18-crown-6 ether were added and the mixture heated to 90–100 °C for 1 h after gas evolution ceased. After being cooled and filtered, the solution was evaporated under vacuum, the resulting yellow oil was taken up in CH_2Cl_2 and hexane added to the cloud point. When the mixture was left to stand at room temperature for 1 to 2 days, crystals of **6** formed on the sides of the vessel along with a yellow oil at the bottom. On further standing (2–4 days) crystals formed in the oil which were collected on a clay plate. The crude product was recrystallized from $\text{CH}_2\text{Cl}_2/n\text{-C}_6\text{H}_{12}$ or $\text{CH}_2\text{Cl}_2/\text{CHCl}_3$ at –78 °C (yield, 7%).

F₃BOP(OCH₂CH₂)₃N (7). To 0.1 g (0.5 mmol) of **6** dissolved in 3 mL of CD_3CN was added under nitrogen and at room temperature an equimolar amount of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.07 g). Addition of another equivalent of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ resulted in no detectable spectral changes (see Results), and attempted isolation led to oily decomposition products.

[Et₃SiOP(OCH₂CH₂)₃N]ClO₄ (8) and [(Et₃Si)₂OP(OCH₂CH₂)₃N]ClO₄ (9). To a solution of 0.1 g (0.5 mmol) of **6** dissolved in 3 mL of CD_3CN was added under nitrogen and at room temperature 0.1 g (0.5 mmol) of $\text{Et}_3\text{SiClO}_4$.¹⁶ After obtaining spectral data (see Results) an additional molar equivalent of $\text{Et}_3\text{SiClO}_4$ was added. Upon removal of the solvent under vacuum, a white solid consisting of **8** and **9** was recovered.

OP(OH)₂OP(OCH₂CH₂)₃N (10). To 0.1 g (0.5 mmol) of **6** dissolved in 2 mL of CD_3CN was added under nitrogen and at room temperature 0.05 g (0.05 mmol) of anhydrous H_3PO_4 dissolved in 1 mL of CD_3CN . A white solid precipitated immediately and ^{31}P NMR examination of the supernatant revealed the absence of detectable amounts of phosphorus-containing compounds. After being filtered and dried under vacuum, the solid was subjected to a variety of organic solvents. It was soluble only in $(\text{CD}_3)_2\text{SO}$ wherein only ^{31}P resonances for dissociated **6** and H_3PO_4 could be observed.

[Co(6)_n](ClO₄)₂. After dehydrating 0.03 g (0.08 mmol) of $\text{Co}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ with 5 mL of $(\text{EtO})_3\text{CH}$ for 1 h, the solution was evaporated to give a pink crystalline solid which was dissolved in 3 mL of MeNO_2 . To the latter solution was added 0.1 g (2 mmole) of **6** which caused the pink solution to turn blue. Evaporation of the solvent under vacuum left a deep blue solid which was spectroscopically examined (see Results).

[Zn(6)_n](ClO₄)₂. This complex was made in a manner analogous to the cobalt(II) complex except that **6** was added directly to the room temperature $(\text{EtO})_3\text{CH}$ solution of the dehydrated $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$. After the mixture was stirred for 1 h, the solvent was removed under vacuum, leaving a pale yellow solid.

Attempted Synthesis of *cis*-Cl₂Pt(1)₂, [Ag(1)₄], [Ni(1)₅](ClO₄)₂, [Co(1)₃](ClO₄), and [Co(1)₆](ClO₄)₃. To a stirred reaction solution of **1** (see

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preparation of **6**) at room temperature was added the metal substrates. Thus 1.77 g (3.75 mmol) of *cis*-Cl₂Pt(NCPh)¹⁷ was added neat, 0.324 g (1.66 mmol) of AgBF₄ was added as a solution in 5 mL of Me₂CO, 0.548 g (1.50 mmol) of Ni(ClO₄)₂·6H₂O was added after being dissolved in 20 mL of MeC(OMe)₂Me and stirred for 2 h, and 0.549 g (1.5 mmol) of Co(ClO₄)₂·6H₂O was added after being dissolved in 15 mL of Me₂CO and 15 mL of MeC(OMe)₂Me and stirred for 2 h. After the reaction solutions of **1** to which the metal compounds had been added were stirred for 1 h, the precipitates (colorless for the first two metals and yellow for the latter two) were filtered and the filtrates evaporated to dryness. All

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attempts to recrystallize the precipitates and the filtrate residues using a variety of solvents produced either insoluble materials or solutions which displayed complicated ¹H and ³¹P NMR spectra.

Acknowledgment. J.G.V. thanks NSF for support of this research in the form of a grant.

Registry No. **6**, 10022-55-6; **7**(P-5 entry), 98777-08-3; **7**(P-3 entry), 98777-09-4; **8**(P-5 entry), 98760-10-2; **8**(P-3 entry), 98760-13-5; **9**(P-5 entry), 98760-11-3; **9**(P-3 entry), 98760-14-6; **10**, 98760-12-4; [Co(6)₃](ClO₄)₂, 98799-14-5; [Zn(6)₃](ClO₄)₂, 98799-16-7; P(NMe₂)₃, 1608-26-0; N(CH₂CH₂OH)₃, 102-71-6.

The Use of Polymer-Bound Oximes for the Synthesis of Large Peptides Usable in Segment Condensation: Synthesis of a 44 Amino Acid Amphiphilic Peptide Model of Apolipoprotein A-1

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Contribution from the Departments of Chemistry and Biochemistry, The University of Chicago, Chicago, Illinois 60637, and the Laboratory of Bioorganic Chemistry and Biochemistry, The Rockefeller University, New York, New York 10021. Received March 25, 1985

Abstract: A 44-peptide was synthesized by using the polymer-bound oxime method and subsequent segment condensation. The peptide was designed to model the surface properties of apolipoprotein A-1, and it has the following sequence: H-(Pro-Lys-Leu-Glu-Glu-Leu-Lys-Glu-Lys-Leu-Lys-Glu-Leu-Leu-Glu-Lys-Leu-Lys-Glu-Lys-Leu-Ala)₂-OH. The peptide readily forms α -helical secondary structure in 50% trifluoroethanol, at the air-water interface, and by self-association in water. The peptide's amphiphilic properties equal those of the apolipoprotein A-1 itself, whereas the 22-peptide corresponding to one-half of the 44-peptide was significantly less amphiphilic. Thus, the optimal structural unit responsible for the surface properties of apolipoprotein A-1 consists of at least two amphiphilic 22-peptides linked by helix breakers. The synthesis of the 44-peptide demonstrates the advantages of the oxime method for the synthesis of long peptide chains.

The most widely used method for the synthesis of polypeptides is the stepwise addition of carboxyl activated amino acids to a growing chain covalently linked to a solid-phase support.^{1,2} In our previous papers³⁻⁵ we reported the usefulness of *p*-nitrobenzophenone oxime bound to polystyrene-1% divinylbenzene copolymer as a solid support in peptide synthesis. The polymer was used for the stepwise synthesis of oligopeptides from the carboxyl termini, and the subsequent cleavage of the peptides from the polymer support gave peptide segments with appropriate protecting groups which were suitable for the further elongation of peptide chains.

In the synthesis of long peptide chains it is strategically important to be able to introduce at some locations activated peptides instead of individual amino acids. This is often necessary for regions of the peptide which present difficulties of synthesis or which contain chemical functions which are not conducive to normal stepwise synthesis.

The advantage of the use of the oxime method is the facile cleavage of the peptides from the solid support under mild conditions, which leave intact most common protecting groups such as *tert*-butyl or benzyl groups. We demonstrated this by cleavage of protected peptides from the oxime resin with amino acid esters in the presence of acetic acid as a catalyst to give peptide esters⁴ or with 1-hydroxypiperidine to give 1-piperidyl esters.⁵ Protected peptide 1-piperidyl esters are subsequently converted to the corresponding free carboxylic acids by reduction with zinc in acetic acid. No significant racemization accompanied these procedures. The protected oligopeptide segments thus obtained then can be purified and assembled for the synthesis of larger peptides either

on the solid support or in solution.

In order to demonstrate the feasibility of segment condensations of peptides activated by the oxime method, we chose to synthesize a 44 amino acid peptide, **2** (tetracontapeptide or 44-peptide⁶), designed to model the amphiphilic secondary structure of apolipoprotein A-1. We had already synthesized a 22-peptide segment, **1**, of this model peptide by the oxime method in our laboratory. The synthesis of a 44-peptide containing two repeating 22-peptide segments presented in this paper not only demonstrates the usefulness of the chemical method but it has also provided us with a peptide with which the consequences of the covalent attachment of two secondary amphiphilic domains could be investigated.

Results

The amino acid sequence⁷ designed for the target 44-peptide, **2**, is shown in Figure 1. This peptide is composed of two identical

(1) Merrifield, R. B. *J. Am. Chem. Soc.* 1963, 85, 2149-2154.

(2) Barany, G.; Merrifield, R. B. "The Peptides, Analysis, Synthesis, Biology"; Gross, E., Meienhofer, J., Eds., Academic Press: New York, 1980; Vol. 2, pp 1-284.

(3) DeGrado, W. F.; Kaiser, E. T. *J. Org. Chem.* 1980, 45, 1295-1300.

(4) DeGrado, W. F.; Kaiser, E. T. *J. Org. Chem.* 1982, 47, 3258-3261.

(5) Nakagawa, S. H.; Kaiser, E. T. *J. Org. Chem.* 1983, 48, 678-685.

(6) The peptide-size nomenclature follows the proposal by Bodanszky (Bodanszky, M. "Peptide, Proceedings of the Fifth American Peptide Symposium"; Goodman, M., Meienhofer, J., Eds.; Wiley: New York, 1977; pp 1-13).

(7) All amino acids are of L-configuration. Standard abbreviations for amino acids, peptides, and protecting groups follow the recommendations of the IUPAC-IUB Commission on biochemical nomenclature. Abbreviations used in the text are the following: apo A-1, apolipoprotein A-1; DCC, *N,N'*-dicyclohexylcarbodiimide; DIEA, *N,N'*-diisopropylethylamine; DMF, *N,N'*-dimethylformamide; HOBt, 1-hydroxybenzotriazole; HOPip, 1-hydroxypiperidine; NMM, *N*-methylmorpholine; TFA, trifluoroacetic acid; CD, circular dichroism; HPLC, high-performance liquid chromatography; TLC, thin-layer chromatography.

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