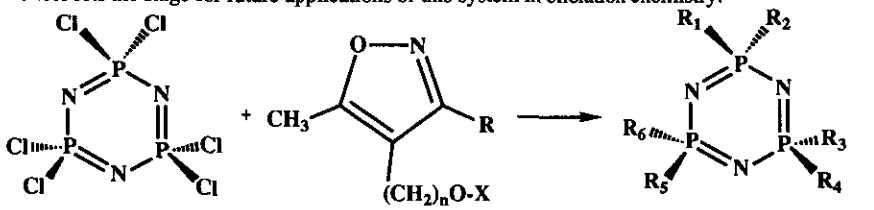
SYNTHESIS OF ISOXAZOLYLPHOSPHAZENE

Mark S. Munsey and Nicholas R. Natale*
Department of Chemistry, University of Idaho
Moscow ID 83843, U.S.A.

Abstract - The reaction of phosphonitrilic dichloride cyclic trimer (**1**) with 4-hydroxymethyl-3,5-disubstituted isoxazoles leads to incomplete substitution, and forcing conditions gave rise to fragmentation to the corresponding 4-chloromethylisoxazole derivatives. Two carbon homologation of the C-4 isoxazole moiety, followed by reaction with (**1**) produced the hexakis-substitution product (**9**). Preliminary studies indicate that (**9**) functions as a ligand in complexes with Co(II), Cr(III) and Mn(III).

The removal of metal ions from dilute solutions is a central task in hazardous waste clean-up. The selective chelation of metal ions is essential for this task to be accomplished efficiently. Bureau of Mines sponsored research is being conducted at the University of Idaho to prepare membrane materials capable of removing metal ions from dilute aqueous solutions and hazardous gases from waste streams. The ideal separation reagent would be capable of high selectivity in the discrimination among chemically similar species in a readily reversible process. Our interest focuses on generating and understanding separating agents designed with specific chemical and physical interactions at the molecular level. The phosphazenes have many useful properties which have found widespread application.[1] One especially useful property of alkoxy phosphazenes is their temperature stability. In the course of our investigations into the chemistry of isoxazoles,[2] it occurred to us that association with the phosphazenes might allow the useful properties of the isoxazole as a ligand for several metals[3] to be expanded. We have encountered surprising difficulty in the preparation of isoxazolylphosphazenes, and herein describe both those difficulties and our ultimate success, which we feel sets the stage for future applications of this system in chelation chemistry.



1

2 R=CH_3, n=1, X=H

7 R=Ph, n=1,X=H

8 R=CH_3 , n=3, X=H

3 R_1=R_2=R_3=R_4= (**2**), R_5=R_6=Cl

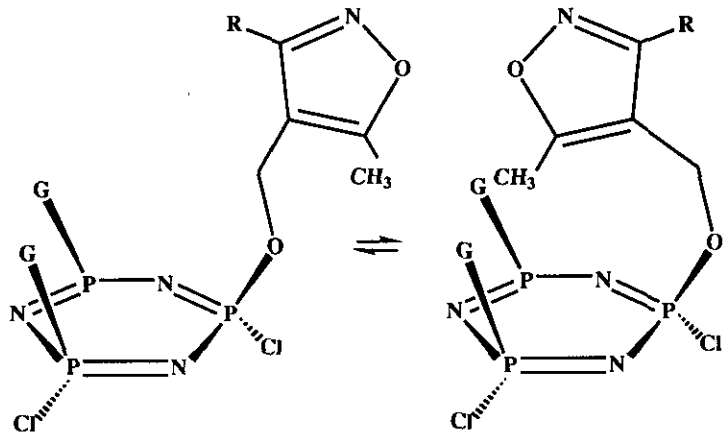
4 R_1=R_2=R_3=R_4=R_5=(**2**), R_6=Cl

5 R_1=R_2=R_3=R_4=(**2**), R_5=R_6= OCH_2CF_3

9 R_1=R_2=R_3=R_4= R_5=R_6= (**8**)

In our initial studies, we studied the reaction of hexachlorocyclotriphosphazene (**1**) with 4-hydroxymethyl-3,5-dimethyl-isoxazole (**2**), using reaction conditions analogous to the numerous studies by Allcock: that is, excess alcohol (**2**). We

consistently obtained a highly moisture and temperature unstable material which exhibited an A_2X pattern in the ^{31}P nmr, indicative of incomplete substitution. Examination of the reaction products by Fast Atom Bombardment Mass Spectrometry indicated an ion corresponding to tetraisoxazolyl substitution (m/z 639). It seemed to us more likely that this ion would arise from loss of two chlorine atoms (i.e., from the tetraisoxazolylphosphazene (**3**), than by loss of one chlorine atom and cleavage of a stable oxygen phosphorus bond (i.e., from the pentaisoxazolylphosphazene(**4**)). Although *in situ* reaction with sodium trifluoroethoxide provided evidence for the tetraisoxazolylditrifluoroethoxyphosphazene (**5**), frustratingly, under the reaction conditions the major product from the trapping studies was 4-chloromethyl-3,5-dimethylisoxazole (**6**), which must arise by nucleophilic attack of chloride on (**3**).[4] Similarly, reaction of (**1**) with 4-hydroxymethyl-5-methyl-3-phenylisoxazole (**7**) produced a moisture and temperature unstable material, which was characterized by its A_2X ^{31}P nmr, in this case mass spectrometry indicated the presence of four chlorines, and evidenced the presence of two isoxazoles. We had not anticipated that the 3,5-disubstituted isoxazoles would behave any differently than the numerous alkoxides which readily substitute the phosphazenes, hence, we were drawn to the conclusion that the isoxazolyl moiety must occupy quite a large sweep volume, due to free rotation about the O-CH_2 bond,[5] as illustrated in the Scheme shown below . We reasoned that extension of the carbon chain between the isoxazole



and alcohol functional groups would both eliminate the steric clash between adjacent isoxazoles and slow down re-attack by chloride at the heterobenzylic position. Reaction of homologated alcohol (**8**)[6] with (**1**) in fact produced a stable product (**9**), with a clean singlet in the ^{31}P nmr, and ^{1}H and ^{13}C spectra consistent with the *hexakis- substituted* product. Preliminary complexation studies were carried out with $CoCl_2$, $Cr(NO_3)_3$ and $MnCl_2$. Qualitatively, cobalt readily formed a complex at room temperature, while chromium and manganese complexes were formed only after reflux for two hours. The close correspondence of the uv absorption for the complexes of (**9**) with those reported previously for 3,5-dimethylisoxazole[7] appears to indicate that the complexation occurs via the isoxazole nitrogen lone pair.

Studies on the use of isoxazolylphosphazenes as ligands, as well as other applications, will be reported in due course.

EXPERIMENTAL SECTION

Reactions conducted under inert atmosphere were done so after several cycles of evacuation and nitrogen purging. Tetrahydrofuran was distilled from sodium and benzophenone. Hexachlorocyclotriphosphazene was obtained from the Shinnisso Kako Co., and used without further purification; alternatively , material obtained from the Aldrich Chemical

Co. must be purified before use by recrystallization from pentane followed by sublimation. Radial chromatography was performed on a Harrison Associates Chromatotron. Preparative hplc was performed on a Rainin Rabbit System, using silica gel unless otherwise noted. All chromatography solvents were distilled. Commercial reagents were purified by recrystallization or distillation before use. Nmr spectra were obtained on an IBM AF300 (300 MHz for ^{1}H) or a JEOL FX90Q (90 MHz for ^{1}H). Ir spectra were obtained on a Digilab FTS-80 or Qualimatic spectrophotometers. Mass spectra were obtained on a VG Micromass 70/70 HS Mass spectrometer, gcms analysis was performed using a fused silica capillary column. Combustion analyses were performed by Desert Analytics , Tucson. AZ.

Hexakis-[3-(3,5-dimethyl-4-isoxazolyl)propyloxy]cyclotriphophazene (9). To a solution of 3,5-dimethyl-4-(3-hydroxypropyl)isoxazole (**8**) (291 mg, 1.8 mmol), in freshly distilled THF (15 ml) was added sodium hydride (56 mg, 2.3 mmol). The resulting mixture was stirred until hydrogen evolution ceased (ca. 20 min) and phosphonitrilic dichloride cyclic trimer (**1**) (107 mg, 0.3 mmol) and a catalytic amount of tetrabutylammonium bromide (7 mg, 0.02 mmol) were added. The reaction mixture was warmed to reflux for 13.5 h, cooled to room temperature, and quenched with a minimum of 2N HCl/ THF solution. Filtration and concentration in vacuo produced an oil which was purified by column chromatography on silica gel, using gradient elution (hexane / ethyl acetate, 4:1, 300 ml, followed by ethyl acetate, 300 ml). Concentration of the ethyl acetate fraction produced (**9**) as a viscous, colorless oil (202 mg, 62%). ^{31}P Nmr ($CDCl_3$, 121.5 MHz): 17.7 (s). ^{1}H Nmr ($CDCl_3$, 300 MHz): 3.76 (m, 2H); 2.37 (t, 2 H, J=7 Hz); 2.26 (s, 3H); 2.16 (s, 3H); 1.75 (pentet, 2H, J=7 Hz). ^{13} C Nmr ($CDCl_3$, 75.47 MHz): 164.9, 159.3, 112.0, 64.3, 29.8, 18.0, 10.8, 10.1. Ir - 2956, 2929, 2892, 1636, 1452, 1425, 1229, 1198, 1072, 1016, 964. Mass spectrum (Fast Atom Bombardment): m/z 1059 (5.9 % rel. Intensity), 950(0.5), 923(3.4), 813 (0.2), 785(1.7), 767(0.4), 649(1.1), 632(0.3), 511(1.0), 493(0.3), 375(1.5), 357(1.2), 293(2.2), 240(4.3), 223(5.1), 140(42.1), 109(26.3). Anal. Calcd for $C_{48}H_{72}N_9O_{12}P_3$, C, 54.38; H, 6.84; N, 11.89. Found: C, 54.55; H, 6.84; N, 11.71.

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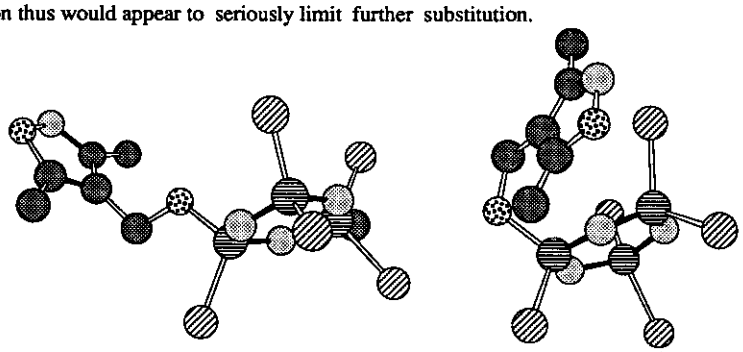
5. Molecular modeling was carried out for the proposed conformers and geometry optimized structures are shown below for (i) and (ii). If one postulates a trigonal bipyramidal intermediate for substitution on phosphorus, analogous to the classical tetrahedral intermediate for substitution on acid chlorides, then approach vector analysis would predict a significant steric inhibition to approach in (ii) from the *syn*- direction with respect to the isoxazole. The extended conformer (i) should be easily accesible until the point of tetrasubstitution, whereupon the isoxazole on the geminally substituted phosphorus could be expected to have a higher conformational population of proximal conformer (ii). Tetrasubstitution thus would appear to seriously limit further substitution.



(i) (ii)

Calculations were performed on a MacIntosh IIcx computer using Chem3D^{Plus} Version 2.01 (1989, Cambridge Scientific Computing, Inc.). Atom numbering schemes and Cartesian coordinates for (i) and (ii) are available from the authors upon request.

6. The homologation sequence was accomplished from 3,5-dimethylisoxazole-4-carboxaldehyde[2o] by (i) Wittig reaction with $Ph_3PCH_2CO_2C_2H_5(Br)$ and NaH in THF, (ii) conjugate reduction with $LiAlH_4$ /CuI in THF -HMPA (iii) ester reduction with either DiBAL-H or $LiAlH_4$. The full experimental details of this homologation sequence will be described elsewhere.

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