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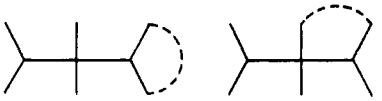
Synthesis and Characterization of the First ansa-Cyclotriphosphazene

Sir:

There have been several studies of the reactions between halocyclotriphosphazenes and difunctional reagents.[1-7] There are three possible routes for these reactions: (1) replacement of two geminal chlorine atoms to give a spiro compound, (2)

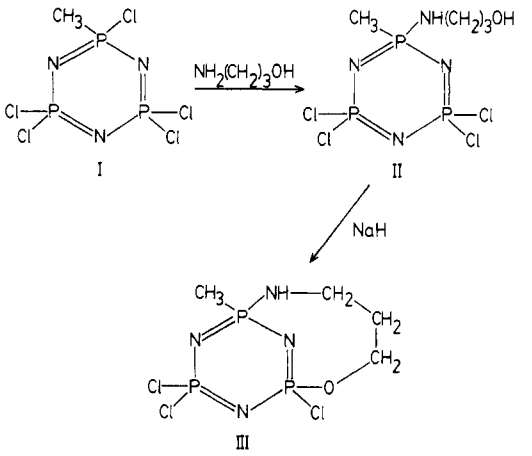


spiro ansa

replacement of two cis, non-gem chlorine atoms to give an ansa type derivative, or (3) intermolecular condensation reactions to yield cyclolinear or cyclomatrix polymers. The structures of the monomeric derivatives have long been a point of controversy;[3-5] however, recent crystallographic data have confirmed the spiro structure for these compounds.[1,2,7]

We report here the synthesis of the first ansa type of phosphazene to contain a simple organic bridging group.[8] The structure is shown in III (Scheme I). This compound was formed by a two-step reaction between methylpentachlorocyclotriphosphazene (I) and 3-amino-1-propanol, as shown in Scheme I. The synthetic route to III is as follows: treatment of methylpentachlorocyclotriphosphazene with 2 equiv of 3-amino-1-propanol in dry dichloromethane (freshly distilled from P_4O_{10}) led to the isolation of the gem-alkylamino compound (II) as a colorless oil in yields as high as 95%. Compound II was characterized from the following data.[9] Mass spectrum: found, m/z 364 ($^{35}Cl_4$); calculated, m/z 364 ($^{35}Cl_4$). ^{31}P NMR (ppm, proton decoupled, $CDCl_3$ solution): 25.0

Scheme I



(triplet, J_{PNP} = 19.5 Hz; this peak broadened significantly upon proton coupling and was subsequently assigned to the P(CH_3)(NHR) group), 19.8 (doublet, J_{PNP} = 19.5 Hz; this peak remained virtually unchanged upon proton coupling and was assigned to the $P(Cl)_2$ groups). ^1H NMR ($CDCl_3$ solution, after treatment with D_2O to remove NH and OH protons): $\delta(PCH_3)$ = 1.67 (3 H, doublet of triplets, J_{PCH} = 15.9 Hz, J_{PNPCH} = 2.1 Hz); $\delta(-NHCH_2CH_2CH_2OH)$ = 3.10 (2 H, unresolved multiplet); $\delta(-NHCH_2CH_2CH_2OH)$ 1.80 (2 H, unresolved multiplet); $\delta(-NHCH_2CH_2CH_2OH)$ = 3.75 (triplet, J_{HCCH} = 7.0 Hz). Infrared spectrum (cm^{-1}, liquid film): 3320 (m, br, $\nu_{NH,OH}$), 2940 (m), 2890 (m, ν_{CH}), 1230 (vs), 1180 (vs, ν_{PN}). Correct microanalytical data were also obtained.[10]

Formation of the ansa derivative (III) was accomplished by treatment of a highly dilute solution of compound II in dry tetrahydrofuran (freshly distilled from sodium–benzophenone ketyl) with an excess of sodium hydride, for 50 h at room temperature. After filtration of the mixture to remove sodium chloride and any unreacted sodium hydride, compound III was isolated in 40–60% yield as white crystals, mp 144–145 °C, from *n*-hexane. Compound III was characterized from the following data. Mass spectrum: found, m/z 328 ($^{35}Cl_3$); calculated, m/z 328 ($^{35}Cl_3$). ^{31}P NMR (ppm, proton decoupled, $CDCl_3$ solution): 31.2 (1 P, doublet of doublets, J_{PNP} = 9.8 Hz, J_{PNP} = 4.0 Hz; this peak broadened to an unresolved multiplet upon proton coupling), 29.3 (1 P, doublet of doublets,

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(10) Anal. Calcd for Compound II, $C_4H_{11}N_4OP_3Cl_4$: C, 13.11; H, 3.00; N, 15.30. Found: C, 13.20; H, 2.94; H, 15.18. Calcd for Compound III, $C_4H_{10}H_4OP_3Cl_3$: C, 14.57; H, 3.03; H, 17.00. Found: C, 14.76; H, 3.06; N, 16.87.

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J_{PNP} = 4.0 Hz, J_{PNP} = 48.8 Hz; this peak became a triplet of doublet of doublets upon proton coupling, J_{POCH} = 20 Hz), 24.5 (1 P, doublet of doublets, J_{PNP} = 9.3 Hz, J_{PNP} = 48.8 Hz; this peak remained virtually unchanged upon proton coupling). ^{1}H NMR ($CDCl_3$ solution): $\delta(PCH_3)$ = 1.71 (3 H, doublet of triplets, J_{PCH} = 16.9 Hz, J_{PNPCH} = 3.3 Hz), $\delta(-NHCH_2CH_2CH_2O-)$ = 3.04 (unresolved multiplet), $\delta(-NHCH_2CH_2CH_2O-)$ = 3.30 (resolved multiplet), $\delta(NHCH_2CH_2CH_2O-)$ = 1.85 (unresolved multiplet), $\delta(-NHCH_2CH_2CH_2O-)$ = 4.45 (unresolved multiplet). Infrared spectrum (cm^{-1}, KBr disk): 3310 (m, ν_{NH}), 2970 (m), 2940 (m), 2890 (w, ν_{CH}), 1190 (vs, ν_{PN}). Correct microanalytical data were also obtained.[10]

The assignment of an ansa structure to compound III comes from a careful inspection of the spectroscopic data for this compound, as well as a comparison of this data to that of known spiro derivatives.[1,2,7]

First, the PCH_3 resonance for compound III comes at δ 1.71. The region between δ 1.8-1.6 is where the methyl resonances for all geminally disubstituted compounds are found;[11] however, the resonance for a $P(Cl)CH_3$ group is found at δ 2.1.[9,11] From these facts alone it is clear that the nitrogen atom from the propanolamine residue is linked geminally to the methyl group. The proton NMR data for the propanolamine group is listed above, along with the assignments. The couplings for each peak are not informative. However, this is to be expected from a compound having an ansa type structure, where each and every proton is in a unique magnetic environment and thus would show an extremely complex set of resonances.

The ^{31}P NMR data can be interpreted in the following manner. The resonance at 31.2 ppm is assigned to the $P(CH_3)(NHR)$ group. This is the furthest downfield resonance, in the general area for an alkylated phosphorus,[11] although it is upfield shifted from a $P(Cl)(CH_3)$ resonance.[9,11] This resonance is the most severely broadened upon proton coupling, which indicates the close proximity of both the methyl and the $NHCH_2$- protons. The resonance at 29.3 ppm is assigned to the P(Cl)O group, whereas the peak at 24.5 ppm is assigned to the $P(Cl)_2$ group. The argument is as follows: although the two resonances lie close together, they can be assigned simply on the basis of the proton-coupled spectrum. The resonance assigned to the $P(Cl)_2$ group is virtually unchanged, whereas the P(Cl)O resonance is split into a triplet, indicating the proximity of two protons. These coupling patterns can occur only if compound III has the ansa structure. A spiro compound would show a quartet for the $P(Cl)(CH_3)$ resonance and a multiplet for the spiro phosphorus upon proton coupling; this is not the case.

The extension of this synthetic route to other ansa type phosphazene derivatives, together with their detailed structure determinations, is currently under investigation in our laboratory.

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Registry No. I, 71332-21-3; II, 89619-72-7; III, 89619-73-8; 3-amino-1-propanol, 156-87-6.

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Activation of Oxygen and Mediation of DNA Degradation by Manganese-Bleomycin

Sir:

The bleomycins are a group of glycopeptide antibiotics employed clinically for the treatment of squamous cell carcinomas and Hodgkin's disease.[1] These agents appear to mediate their therapeutic effects at the level of DNA strand scission,[2] a transformation that requires a source of oxygen[3] and a metal cation.[3,4] While the metal ion(s) responsible for the action of bleomycin in situ are unknown, both the ferrous[4] and cuprous[5] complexes of bleomycin mediate DNA degradation in the presence of dioxygen. Recently, it has been shown that in the presence of oxygen surrogates such as iodosobenzene the corresponding ferric and cupric complexes will also effect the conversion of supercoiled covalently closed circular (form I) DNA to form II (linear duplex) DNA.[5b,6] In addition to the copper and iron complexes of bleomycin, a Co(III)-bleomycin complex has been reported to form an active complex capable of cleaving ϕX174 cccDNA in the presence of light.[7]

Studies performed in this laboratory[5,6,8] have probed the mechanistic similarities between bleomycin and cytochrome P-450.[9] Bleomycin and the porphyrin moiety of cytochrome P-450 both coordinate metal ions, are activated anaerobically by iodosobenzene or aerobically by dioxygen, and mediate the stereospecific epoxidation of olefinic compounds.[10,11] Further, both species form ferrous complexes that bind CO with attendant spectral changes, and it has recently been shown that at least two metallobleomycins can be activated by NADPH-cytochrome P-450 reductase.[8b] In an effort to extend further the analogy between cytochrome P-450 and bleomycin, additional metal ions (e.g., Mn[11,12]) known to form redox-active porphyrin complexes were tested for their ability to bind to bleomycin and effect oxygen-dependent transformation of olefinic substrates and DNA strand scission. Herein we report that Mn-bleomycin can mediate these oxidative transformations.

Figure 1 illustrates the HPLC elution profile of products formed from *cis*-stilbene[13] in the presence of Mn(III)-bleo-

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