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FOREWORD

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PREFACE

During the first week of June 1981 some 400 chemists actively engaged in research on phosphorus chemistry gathered at Duke University, Durham, North Carolina for the continuation of a series of International Conferences on Phosphorus Chemistry. These chemists came from 29 different nations. During the two decades that these International Conferences have been held, the meetings have taken place in Europe, thus making the Durham Conference the first of its kind in the United States. The growth of the activity in phosphorus-based research in this country, and throughout the world, has been remarkable in recent years. No diminution in this activity is in sight, for new discoveries are constantly being made that open up fresh channels of research. Phosphorus chemistry as a field can only be partially categorized by the traditional lines of organic and inorganic compounds. In modern phosphorus chemistry increasing attention is also being paid to biological involvement of phosphorus compounds. In designing the 1981 Conference, papers describing research in all of these aspects of phosphorus chemistry were included, marking the first time this has been done in any of the international conferences. The Durham meeting therefore attracted a broad variety of participants and papers, from both academic and industrial research laboratories; the opportunities for interaction among persons of diverse backgrounds were abundant.

The program was unique in another sense: with the exception of the opening lecture by Professor Rolf Appel, the oral presentations were of equal length (25 minutes) and all chemists, regardless of age and stature, had an equal opportunity for gaining a place on the oral program. Investigators with research results that were insufficient to fill the allotted time period were encouraged to make use of the poster medium. A further stipulation was that only new research results should be presented; review papers or extensive literature discussions were discouraged.

This volume contains the manuscripts provided by 128 of the participants in the oral part of the program. (A few papers on the original program were not delivered). To publish a volume at a reasonable price with such a large number of papers required a severe restriction in the length of the manuscripts; authors were asked to present their results in "Communication to the Editor" style in a maximum of four pages of text. The authors have complied faithfully with this request, and the Editors

xv
thank them all for the care with which they prepared their papers. The Editors also are grateful to the foreign authors for their excellent efforts in preparing their manuscripts in English. With a collection of papers of such diversity in topic and geographic origin, the style is more varied than is normal for such a symposium volume, but these variations do not interfere with the quality of the chemical discussions, and the Editors chose not to enforce strict adherence to detailed uniformity.

The 127 posters on the program presented another fascinating array of research results. It is unfortunate that space limitations do not permit the inclusion of the abstracts of these presentations in this volume. However, the titles and addresses of the authors are provided on pages 623–630 for the convenience of those who may wish to contact the authors for copies of their abstracts.

A feature of the Conference program was the inclusion of sessions recognizing the signal accomplishments of two pioneers in phosphorus chemistry, Nobel Laureate Professor Georg Wittig and Professor Frank H. Westheimer. Papers in these special sessions were solicited by Professor Hans-Jurgen Bestmann and Professor Steven Benkovic, respectively. The work of Professor Wittig in the use of phosphorus compounds in organic synthesis, which among other contributions was responsible for his receiving the Nobel Prize in Chemistry in 1979, was recognized by the session "New Organic Synthetic Methods Based on Reagents Containing Phosphorus." The noteworthy accomplishments of Professor Westheimer on the mechanistic aspects of phosphate ester chemistry stimulated the session "Biochemistry of Phosphorus Compounds."

This Conference was enthusiastically supported by the American scientific community; the chemical industry, the U.S. National Science Foundation, and the Petroleum Research Fund, all made contributions that ensured an adequate financial base, and many chemists worked diligently on the numerous tasks that are associated with such an undertaking. The Editors express their deep appreciation to all.

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June 29, 1981.
Phosphorus–Carbon Compounds with $p_\pi-p_\pi$ Bonds

Opening Lecture

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In this lecture some new routes to phosphorus-carbon compounds with P-C multiple bonds, found in connection with our investigations on reactions of tertiary phosphanes with chlorinated carbon compounds, such as tetrachloromethane, hexachloroethane, phosgene, and isocyanide dichlorides are reported. Furthermore some stereochemical problems concerning this type of compound will be discussed.

Action of tetrachloromethane on trimethylsilyl-substituted methyl-diphenylphosphanes causes quantitative chloroform elimination with formation of trimethylsilylated (TMS) methylenechlorodiphenylphosphoranes. Heating the bistrimethylsilyl substituted

$$\text{Ph}_2\text{P-CH(Tms}_3\text{)}_2 + \text{CCl}_4 \xrightarrow{-\text{HCCl}_3} \text{ClPh}_2\text{P=C(Tms}_3\text{)}_2$$

Tms = SiMe$_3$ -Me$_3$SiCl 120°C

$$\text{PhP = CPh(Tms}_3\text{)} + [\text{Ph}_2\text{P=CTms}_3\text{}]$$

compound causes spontaneous gas evolution of TmsCl at 120°C. The product is identified by elemental analysis, molecular mass determination, and the characteristic $^{31}$P nmr shift. It is a greenish-yellow liquid which can be distilled in vacuo without decomposition. The general applicability of this synthesis, based upon migration of an organyl substituent from phosphorus to the ylid-carbon is restricted so far to P-aryl substituted compounds.

Another route to a number of theoretically interesting compounds of two-coordinate phosphorus is the reaction of P-trimethylsilyl-substituted phosphanes with phosgene. The reaction proceeds via several isolable intermediates. The first is the phosphino-substituted methylene-phosphane, which is generated by silyl-group migration from phosphorus to oxygen. Treatment with further phosgene then causes further elimination of CO and chlorotrimethylsilane, yielding a compound with a P-P bond which
no longer shows the characteristic $^{31}$P nmr shift of two-coordinate phosphorus. An x-ray structure determination which was carried out by Dr. Halstenberg and Professor Hutten at Konstanz, showed that it is the first 2,3,5,6-tetraphosphabicyclo[2.2.0]hexane, which contains an asymmetric and distorted bicyclohexane skeleton with two sets of equivalent phosphorus atoms in different environments. Thus far the bicyclohexane skeleton can only be obtained in the reaction of COCl₂ with phenyl-bis(trimethylsilyl)phosphane. Initially t-butyl-bis(trimethylsilyl)phosphane indeed reacts analogously to give the phosphino-substituted methylenephosphane, which can be isolated as a pure substance and which can be converted to the P-H phosphine by methanol. What happens in the second step with further phosgene, however, depends very much upon the rate of addition. If the addition occurs very slowly at -80°, the five-membered ring system with a C-C double bond is formed, while rapid mixing of solutions of both components in the molar ratio 1:1 affords a five-membered ring containing four phosphorus atoms bridged by a CO moiety.

The reaction of phenyl(bistrimethylsilyl) phosphine with phenylisocyanide dichloride, the aza-analogue of phosgene yields tetraphosphahexadiene according to elemental analysis, cryoscopic molecular mass determination, and $^{31}$P nmr studied. To understand the interesting structural problem of this compound, we must look in detail at the $^{31}$P nmr spectrum. At ambient temperature the substructure of an AA'XX' 4-spin system is observed. The downfield signals at 258 ppm are assigned to the two-coordinate phosphorus and the upfield multiplet at -12.3 ppm arises from the trivalent phosphane moiety. Between both groups there is a
diffuse absorption at 115.7 ppm which sharpens on heating to 60°C while the other signals broaden. The significance of the broad signal can be elucidated by cooling to −70°C. In addition to the two sharp multiplets already mentioned, a second 4-spin AA'XX' system appears, the left half indicating two-coordinate phosphorus and the right, at −3.2 ppm., the diphosphane P atoms. Renewed heating to ambient temperature results in coalescence of the two inner multiplets at 115 ppm. Thus the process is reversible. On further cooling to about −80°C, however, the outer multiplets labelled 5a totally disappear. The reason for this is precipitation due to insufficient solubility. Low temperature filtration of the crystals and redissolving them at 30° again gives the complete $^{31}$P nmr spectrum as before. Firstly, according to elemental analysis and molecular mass determination, the compound is homogeneous, that is to say, the broad absorption is
caused by an isomer. Furthermore the splitting into a second AA'XX' system at -70° indicates a diastereomeric tetraphosphahexadiene, since both the characteristic multiplets of diphosphate- and methyleneephosphane-phosphorus can be identified. An explanation, which elucidates the reversible temperature-dependent coalescence of the inner signals and also rationalizes why only one stereoisomer displays this phenomenon is now given.

Attempts to explain the coalescence by migration of the silyl group between the nitrogen and phosphorus atom or by a rotation around the C-N or P=C double-bond are not supported by the experimental data. We came to the conclusion that a pericyclic reaction occurs, which is analogous to the Cope rearrangement for hexadiene-1,5. In a [3.3]-sigmatropic reaction of the tetraphosphahexadiene, the bond between the two phosphorus atoms breaks with simultaneous formation of the P=C double bond and a new P-P bond. The original nmr signals of the P atoms with the coordination number 2 and 3 must collapse in the middle because the rearrangement is a symmetrical one and because it occurs on the nmr time scale. The fact that only one diastereomer shows coalescence can be explained as follows. As is well known, symmetrical, differently substituted diphosphanes which are comparable to our type in substitution have two centers of chirality. Their synthesis usually yields a 1:1 proportion of the meso form and racemic mixture, which can be characterized by their different 31P nmr shifts. In our case the outer set of multiplets must be assigned to one diastereomer and the inner set to the other. From the observation that the spectrum of the crystals filtered at low temperature shows two signal groups again at room temperature, we must conclude that the configurational equilibrium between the meso form and racemic mixture is promptly achieved.

The fast exchange in the 31P nmr spectrum of one isomer at room temperature, which is not observed for isomer 5a, leads to the conclusion that only one form fulfills the stereochemical demands of the Cope-rearrangement. This is the racemic mixture as shown. If this is correct, the crystals filtered at low temperature, which show no coalescence, should be the meso form. The x-ray analysis of these crystals verifies this assertion since the substituents at the P-P bond are indeed trans to one another.

Of course, we must be careful when transferring conceptions from carbon compounds to other elements. Nevertheless there are interactions between electrons of the 2p and electrons of the 3p level which is considerably higher. Therefore we looked for further proof of this hypothesis. The following experiment seemed to be a linking one between the fields of carbon and phosphorus chemistry. We treated succinic acid dichloride with bis-(trimethylsilyl)silylphenyl phosphane. According to our hypothesis a primary halosilane condensation followed by a silyl migration and formation of the P=C double bond, and finally a [3.3]-sigmatropic rearrangement to the diphosphane should occur. In the 31P nmr spectrum. We observe a halosilane condensation to
the corresponding diphosphide of the succinic acid, which is stable only below -10°C. The following step is a double 1,3-silylmigraiton resulting in a 1,6-diphosphahexadiene-1,5 which spontaneously passes over by a [3.3]-sigmatropic rearrangement to the substituted 1,2-diphenyl-1,2-divinylphosphane.

The observation that the C-C bond is cleaved in favor of a P-P bond and the formation of 2 olefinic double-bonds surprised us and we decided to obtain further verification of the structure of the divinyl diphosphane by a classical decomposition reaction. Indeed, mild methanolation yields instead of the C₄ unit of the succinic acid 2, C₂ units in the form of methylacetate. Moreover, both of the other fragments, the 1,2-diphenylphosphane and the silylmethylether, could be unambiguously identified.

After the elucidation of the reaction of phenylisocyanide dichloride with phenyl(trimethylsilyl)phosphane, several other differently substituted isocyanide dichlorides react extremely slowly, so that high temperatures are necessary which prevent the
isolation of interesting intermediates and yield only cyclophosphanes. In the reaction of the ring-substituted phenylisocyanide dichlorides absolute agreement with the results of phenylisocyanide dichloride was only observed with the p- and m--monochlorophenyl compounds. The isolable phosphinomethylene phosphanes are formed first, which react with additional isocyanide dichloride with elimination of trimethylchlorosilane and isocyanide to give the tetraphosphahexadiene. The $^3$P nmr spectra are also very similar. At ambient temperature, a broad absorption is observed in the middle of the two-fold 4-signal spectrum of the AA'XX' type, which splits on cooling to -80° into two signal groups of the same type. The results of the reaction of the o- and o,m-di-halogen substituted phenylisocyanide dichlorides with PhPTms$_2$ are discussed in detail in the paper by Dr. Knoll in this Conference, with special attention given to the question of E and Z isomerism.

The story of the reaction of isocyanide dichlorides with bis(trimethylsilyl)phenylphosphate, however, does not end here. Like the reaction of t-butyl-bis(trimethylsilyl)phosphate with phosgene, the conversions with isocyanide dichlorides depend very much upon the reaction conditions. If the reaction is carried out at ambient temperature in a molar ratio of 1:1 in such a way that the isocyanide dichloride is rapidly dropped into the phosphane solution, the hitherto unknown, 2,4-bis(phenylimino)-1,3-diphenyl-1,3-diphosphatanes are obtained besides the phosphinomethylene phosphanes. Several findings, suggest that their

\[
\text{PhPTms}_2 + \text{Cl}_2\text{C}=\text{NR} \rightarrow (\text{PhP}=\text{C}=\text{NR}) + \text{PhP} \begin{array}{c} \text{C} \\ \text{PPh} \end{array} \]

formation occurs by way of the not yet isolated monophosphacarbodiimide, which readily dimerizes to give the diphosphetane. The $^3$P nmr spectra of the diphosphetanes exhibit three signals between 84.3 and 74 ppm. All signals are rather broad, although the substances proved to be homogeneous by sharp melting points, crystal structure and mass spectra. The observation of several signals is caused by stereo isomers which are in a dynamic equilibrium at room temperature. This can be confirmed by high and
low temperature $^{31}\text{P}$ nmr spectroscopy. If crystals of the dichlorosubstituted compound are dissolved at $-80^\circ$ in deuterated methylene chloride, only one sharp signal is observed. On heating to $30^\circ$ the broadened 3-line spectrum appears which at $115^\circ$ shows coalescence to give one broad signal. On cooling to $-100^\circ$ the spectrum shows three relatively sharp signals. The different stereoisomers can easily be explained by the possible cis or trans arrangements of the P-phenyl groups or the imino substituents at the C atom relative to the plane of the four-membered ring. The approximate planarity of the 4-membered ring has been proved by an x-ray structure analysis for the 2,4-bis(2,5-dichlorophenyl)imino-1,3-diphenyl-1,3-diphosphetane.

Up to now the unexpected stability of methyldenephosphanes was always thought to be due to the shielding of the P=C bond by bulky substituents at phosphorus or carbon. This assumption is
only partly right. Several halogen (Cl,Br,I) methyldenediphosphanes could be obtained by deprotonation of α-CH acidic primary dihalogenophosphanes with tertiary amines. The P-chloro-

\[
\begin{align*}
T_{\text{ms}} & \rightarrow \text{PhC=}{P}\text{-OR} \\
\text{PhCHP}_{\text{x}}_{2} \text{Base} & \rightarrow \text{PhC=}{P}\chi_X \\
T_{\text{ms}} & \rightarrow \text{PhC=}{P}\text{-SR} \\
T_{\text{ms}} & \rightarrow \text{PhC=}{P}\text{-PR}_{2}
\end{align*}
\]

methylenephosphane is an easily accessible key compound for the synthesis of new methylenephosphanes. In addition to compounds with known basic structures, the P-alkoxy and P-alkylthio and P-phosphino methylenephosphanes could be prepared for the first time. Our particular interest in this compound was focused on the trimethylchlorosilane elimination, because this reaction should provide a route to phenylmethinephosphane (phosphophenylacetylene). Heating a sample to 700°C in the vacuum provided by a Hg-diffusion pump, indeed spontaneously causes this reaction. Having optimized this elimination process by means of a mass spectrometer directly connected to the pyrolysis apparatus, we readily succeeded in synthesizing the methinephosphane on a preparative scale and characterized it further. The PC triple bond in the phospha-alkyne has been confirmed by its characteristic \(^{13}C\) and \(^{31}P\) nmr data as well as by stepwise HCl addition. The phospha-alkene is obtained first, which is transformed to benzylchlorophosphane by a second mole of HCl. By \(^{31}P\) nmr spectroscopic studies we could show that benzylchlorophosphane can be dehydrochlorinated by tertiary amines in reversal of its formation reaction. In addition to the E isomer, the Z isomer is also formed. Yet HCl addition to the phospha-alkyne does not produce any trans-compound. This can be explained in terms of a stereospecific cis-addition to the triple bond.

The direct vacuum pyrolysis of benzylidichlorophosphane also yields some phospha-alkyne in addition to a large amount of unidentified side products. In addition to the phenylphospho-acetylene which has a half-life of 7 minutes at 0°C, we could prepare the considerably more stable trimethylsilyl derivative which has a half-life at room temperature of 50 minutes. The t-butyl derivative is entirely stable, as Becker reported recently.

To sum up, we can state that today a surprisingly great number of stable compounds with PC double bonds is known. At the moment we have several methods for the formation of this double bond. In addition to the dehydrohalogenation of halogenophosphines, the thermal elimination of trimethylchlorosilane and the elimination of hexamethyldisiloxane can be utilized. Prior to elimination, the silyl group can migrate from phosphorus to the oxygen, nitrogen, or sulfur of an α-carbonyl or hetero carbonyl function subsequent to initial TmsCl addition to or condensation with silylphosphanes. Most importantly, there is no longer any reason for the preparative chemist to balk at $2p_\pi-3p_\pi$ interactions. Very clearly the $^{13}C$ nmr spectra support this view, since they beyond any doubt show that the carbon in the methylidene-phosphanes is sp$^2$-hybridized and sp-hybridized in the phospha-alkynes. The existence of E and Z isomers at the PC double bond can also be demonstrated. Moreover, the fluctuating structure of the tetraphosphahexadiene is absolutely analogous to purely olefinic compounds.

Whether the hopes will be fulfilled that these studies of the last five years have turned the first pages of a new chapter of phosphorus-carbon chemistry still remains to be seen. Whether, for instance, it will be possible to construct conjugated PC systems suitable for Diels-Alder reactions, is not yet certain. Exploration of the coordination chemistry of these new species may also prove fruitful.

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Selective Bond Formation of Organophosphorus Acids with Functional Groups of Biological Importance

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A knowledge of the interaction of nucleophiles with the phosphorylating agent, (modified in its reactivity by the use of different leaving-groups) is a precondition for the selective bonding of biologically important groups (e.g. OH, NH₂, SH) to organophosphorus acids in a controlled manner. The following variations were investigated:

\[
\begin{align*}
R'P-X + RYH + B & \rightarrow R'-P-YR + BHX \\
\end{align*}
\]

Phosphinic acid derivatives, phosphonic acid derivatives, phosphoric acid derivatives

\(X = \text{Cl}, \text{F}, \text{CN}, \text{N}_3, \text{OC}_6\text{H}_4\text{NO}_2(p)\); for \(RYH: Y = \text{O}, \text{NR}, \text{S}\)

The relative reactivities were determined by means of competition with different nucleophiles \(RYH\) and \(RY'H\).

Examples:
\(X = \text{Cl} (a); X = \text{F} (b); X = \text{N}_3 (c); X = \text{CN} (d); X = \text{OC}_6\text{H}_4\text{NO}_2(p) (e)\)
\(RYH = \text{n-BuNH}_2; RY'H = \text{n-BuOH}\)

(a) \(\text{P} - \text{YR} = \text{Amide} (94 \%); \text{P} - \text{Y'R} = \text{Ester} (2 \%)\)
(b) \(\text{P} - \text{YR} = \text{Amide} (0 \%); \text{P} - \text{Y'R} = \text{Ester} (87 \%))

(c) $\text{P} - YR = \text{Amide} (~80\%); \text{P} - Y'R = \text{Ester} (~20\%)$
(d) $\text{P} - YR = \text{Amide} (0\%); \text{P} - Y'R = \text{Ester} (~90\%)$
(e) $\text{P} - YR = \text{Amide} (0\%); \text{P} - Y'R = \text{Ester} (~90\%)$

$X = \text{Cl} \ (a); \ X = \text{N}_3 \ (b); \ X = \text{CN} \ (c)$

$\text{RYH} = \text{n-BuNH}_2; \ \text{RY'H} = \text{n-BuSH}$

(a) $\text{P} - YR = \text{Amide} (~90\%); \ \text{S-ester} \ (\text{trace})$
(b) $\text{P} - YR = \text{Amide} (~80\%); \ \text{S-ester} (~20\%)$
(c) $\text{P} - YR = \text{Amide} \ (\text{trace}); \ \text{S-ester} (~90\%)$

With $X = \text{F}$ and $\text{OC}_6\text{H}_4\text{NO}_2$: no reaction

Three products are possible when the two competing nucleophiles are situated in the same molecule (e.g. ethanolamine, cysteamine, serine and cysteine).

\[
\begin{align*}
\text{P} - X + \text{HOCH}_2\text{-CH}_2\text{-NH}_2 & \rightarrow \text{P} - \text{NH}-\text{CH}_2\text{-CH}_2\text{-OH} \\
\text{P} - X + \text{HOCH}_2\text{-CH}_2\text{-NH}_2 & \rightarrow \text{P} - \text{O}-\text{CH}_2\text{-CH}_2\text{-NH}_2 \\
\text{P} - X + \text{HOCH}_2\text{-CH}_2\text{-NH}_2 & \rightarrow \text{P} - \text{NH}-\text{CH}_2\text{-CH}_2\text{-O (P)}
\end{align*}
\]

\[\text{P} = (\text{C}_6\text{H}_5)_2\text{P}(0)\]

Several selectivity studies were also carried out for serine (important in the active site of many enzymes) and for cysteamine and cysteine (also in view of their biological importance).

Selectivity in the reaction of serine-$N$-butylamide with $\text{Ph}_2\text{P}(0)X \ (X = \text{Cl or F})$:

\[\begin{align*}
\text{HOCH}_2\text{-CH}-\text{C}-\text{NHBu} & \rightarrow \text{HOCH}_2\text{-CH}-\text{C}-\text{NHBu} \\
\text{HOCH}_2\text{-CH}-\text{C}-\text{NHBu} & \rightarrow \text{HOCH}_2\text{-CH}-\text{C}-\text{NHBu}
\end{align*}\]
Selectivity in the reaction of cysteamine with diphenylphosphinic acid cyanide:

\[ \text{HS-CH}_2\text{-CH}_2\text{-NH}_2 + \text{Ph}_2\text{P(O)CN} \rightarrow \text{Ph}_2\text{P(O)-S-CH}_2\text{-CH}_2\text{-NH}_2 \]

\[ \text{HS-CH}_2\text{-CH-NH}_2 + \text{Ph}_2\text{P(O)CN} \rightarrow \text{Ph}_2\text{P(O)-S-CH}_2\text{-CH-NH}_2 \]

Diphenylphosphoric acid derivatives \((\text{C}_6\text{H}_5\text{O})_2\text{P(O)X} \ (X = \text{Cl, F, N}_3, \text{CN, OC}_6\text{H}_4\text{NO}_2(p))\) are as selective as the corresponding phosphinic acid derivatives \((\text{C}_6\text{H}_5)_2\text{P(O)X}\).

Corresponding competition reactions \((\text{BuNH}_2, \text{BuOH, BuSH})\) were also carried out with the diphenylthiophosphinic acid derivatives \(\text{Ph}_2\text{P(S)X} \ (X = \text{Cl, F, CN})\).

Organophosphorus compounds bearing a fluorescent group were specifically introduced into the active sites of the serine-enzymes \(\alpha\)-Chymotrypsin, Trypsin and Butyrylcholin-esterase using the agents 2, 3 and 4. This was shown using electrophoresis.

\[
\begin{align*}
1 & \quad R = \text{SO}_2\text{Cl} \\
2 & \quad \text{PhP(O)F} \\
3 & \quad \text{PhP(O)-OC}_6\text{H}_4\text{NO}_2(p) \\
4 & \quad R = \text{EtOP(O)F}
\end{align*}
\]

(dansylchloride)

1, 2, 3 and 4 are effective inhibitors of serine enzymes (\(\alpha\)-Chymotrypsin, Trypsin, Butyrylcholin-esterase and Acetylcholin-esterase (only 4)).

RECEIVED July 13, 1981.
Chemical Synthesis and Biological Properties of the 5'-Terminus of Eukaryotic Messenger Ribonucleic Acids (mRNA)

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In contrast to prokaryotic mRNAs, mRNAs from various eukaryotic cells and viruses have been found to contain a terminal 7-methylguanosine (m^7G) residue linked from its 5'-position through a triphosphate bridge which was presented commonly as shown in the following Scheme 1.

![Scheme 1](image_url)

R = H or CH₃

\((m^7G_5^p)p(X)pypypZ\ldots\)

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We first describe the synthesis of unsymmetrical α,γ-dinucleoside triphosphates involving 7-methylguanosine. For the construction of the terminal cap structure, there might be two possible reaction modes where an activatable protecting group (X) was introduced into a nucleotide by direct displacement with phosphate hydroxyl group (Method A) and by pyrophosphorylation between Xp and pN (Method B).

**Method A:**

```
   pN  \( \xrightarrow{X} \) XpN \( \xrightarrow{pN'} \) N^5'pppN'
   ppN \( \xrightarrow{X} \) XppN \( \xrightarrow{pN'} \) N^5'pppN'
```

**Method B:**

```
   pN  \( \xrightarrow{Xp} \) XppN \( \xrightarrow{pN'} \) N^5'pppN'
```

As the former type of reaction, we have developed the triphosphate bond formation by means of phosphinothioyl bromide as shown in the following scheme.

```
  HOPO   \( \xrightarrow{Bu_2P(S)Br} \) pyridine \( \rightarrow \) BpppB'
      O   \( \xrightarrow{Bu_2P-O-P-O} \) B
             \( \xrightarrow{ppB'} \) BpppB'
```

The latter requires a phosphorylating species possessing an activatable protecting group for the preparation of the starting material (XppN). Now, we found a convenient method for the synthesis of this type of pyrophosphorylating reagent by the reaction of methyl phosphoro dichloridate with thiophenol in pyridine. A promising capping reagent, \( P^1-S\)-phenyl \( P^2-7\)-methylguanosine-5'-pyrophosphorphothioate, was synthesized as described below.

```
  MeOPCl + pyridine  \( \xrightarrow{PhSH} \) PhS-Cl  \( \xrightarrow{pm^7G} \) PhSppm^7G
```

The phenylthio group could serve as the temporary protecting group which was easily activated by treatment with silver acetate, silver nitrate or iodine. By the above methods, we synthesized several kinds of unsymmetrical α,γ-dinucleoside triphosphates involving methylated or nonmethylated cap structures. The above-mentioned methods have been also applied to the synthesis of cap structure containing oligoribonucleotides. Furuiich and Miura discovered the terminal structure of cytoplasmic polyhedrosis virus (CPV) mRNA which was represented as \( m^7G^5pppAmGpU... \). In order to confirm the structure by chemical synthesis and investigate the function and the mechanism of its formation in vitro \( m^7G^5pppAm, m^7G^5pppAmG, \) and \( m^7G^5pppAmGpU \) were synthesized by utilizing the present capping reactions and the phosphotriester approach. However, we have felt during the investigation that 7-methylguanylic acid and its derivatives used for the construction...
of the cap structure should be appropriately protected because of their extreme instability and poor solubility. In most of mosaic virus mRNAs, there exists the common terminal structure of \( m^7G^5pppGpU \ldots \) In order to elucidate its biological meaning, we tried the synthesis of this part by using monomethoxytrityl and dimethoxytrityl groups as the highly lipophilic protecting groups of \( N^2 \)-amino functions of guanosine and \( 7 \)-methylguanosine. Consequently, \( m^7G^5pppGpU \) was obtained in good yield and some related compounds of \( m^7G^5pppGpUpU \) and \( m^7G^5ppGpU \) were also synthesized in a simililar manner.

We have tested some of biological properties of the cap structure by employing unusual man-made cap analogues which were synthesized by the above methods.

Here, we shall describe the methylation reactions at the \( 7 \)-position of guanosine residue of the cap structure.

First, the methylation of guanosine moiety of the cap structure with \( S \)-adenosylmethionine (SAM) was examined. When only GTP was added as a substrate to the in vitro RNA synthesizing system of CPV in the presence of SAM, GTP was not methylated. However, GTP and ATP were added to the same system, \( m^7G^5pppA \) and \( m^7G^5pppApG \) were formed. On the basis of the above facts, chemically synthesized \( G^5pppA \) was added as a substrate in place of GTP and ATP, \( m^7G^5pppA \) was obtained expectedly. In this case no methylation took place of \( 2' \)-OH of adenosine moiety. In the same system \( G^5pppG \) was not methylated. Therefore, the cap structure of CPV was formed as follows:

\[
\begin{align*}
GTP + ATP & \rightarrow G^5pppA \\
G^5pppA + SAM & \rightarrow m^7G^5pppA \\
m^7G^5pppA + GTP & \rightarrow m^7G^5pppApG
\end{align*}
\]

On the other hand, mRNAs from reovirus were represented as \( m^7G^5pppGmpU \ldots \). In the in vitro RNA synthesizing system of reovirus, \( G^5pppG \) was methylated selectively at the \( 7 \)-position of one of two guanosine residues, but any methylation is not caused for \( G^5pppA \). This shows that the methylation enzymes either in CPV or in reovirus recognized strictly the structure of the confronting nucleoside residues.

Next, we examined the structural requirement for the confronting phosphate bridge in the methylation. The CPV system as described previously was employed.

It was found that \( G^5pppA \) and \( G^5pppA \) were methylated imperfectly about 50\% relative to \( G^5pppA \) in the presence of SAM and no methylation was observed in the case of \( G^5ApA \).

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Triphenylphosphane-diethylazodicarboxylate: A Useful System for Directed Structural Variation of Carbohydrates

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Nucleophilic substitution reactions at alcoholic substrates with HX initiated by activation of the hydroxy-group by means of TPP/DEAD first developed by Mitsunobu (1) are being increasingly utilized (1,2). This principle has been seldom applied until now in the field of carbohydrates. In order to diminish hydrophilicity, the mono- and bis-t-butylidimethylsilyl ether derivatives of a series of carbohydrates were prepared, which represent very useful substrates with two or even three free OH groups for realizing a series of interesting transformations by means of TPP/DEAD or TPP/DEAD/HX.

The methyl-β-glucopyranoside 1a can be transformed in this way exclusively to the 3-desoxy-3-X-allose derivatives 2a-2d (X = N3, I, p-NO2-C6H4COO) (figure 1), whereas the corresponding methyl-α-D-glucopyranoside 1b gives exclusively the analogous 4-desoxy-4-X-galactose derivatives 3a-3d. This useful substitution reaction especially by means of TPP/DEAD/HN3 can be applied also to the methyl-2-acetamido-6-

(t-butyldimethylsilyl)-2-desoxy-α-D-glucopyranoside 4 and methyl-2-acetamido-3,6-bis-O(t-butyldimethylsilyl)-2-desoxy-α-D-glucopyranoside 5. The former is

\[ \begin{array}{c}
1a \quad 2a: X = N_3 \\
1b \quad 2b: X = NO_2-C_6H_4COO \\
2c: X = Br \\
2d: X = J
\end{array} \]
transformed to the methyl-2-acetamido-3-azido-6-O-(t-butyldimethylsilyl)-2,3-didesoxy-α-D-allopyranoside 6 whereas the latter goes over to the corresponding galactose derivative 7. When 1a, 1b and 4 are treated with TPP/DEAD alone the preparatively useful 3,4-anhydro-galactose derivatives 8 (methyl-3,4-anhydro-2,6-bis-O-(t-butyldimethylsilyl)-α-D-galactopyranosid), 9 (methyl-3,4-anhydro-2,6-bis-O-(t-butyldimethylsilyl)-α-D-galactopyranosid) and 10 (methyl-acetamido-3,4-anhydro-6-O-(t-butyldimethylsilyl)-2-desoxy-α-D-galactopyranoside) arise. Under similar conditions methyl-6-O-(t-butyldimethylsilyl)-α-D-glucopyranoside 11 yields the methyl-2,3-anhydro-6-O-(t-butyldimethylsilyl)-α-allopyranosid 12 which can be subjected additionally an substitution process at C4 by means of TPP/DEAD/HN3 resp. p-1,02-06:4:1,002 without any opening of the oxirane function by HX. Methyl-2,3-anhydro-4-azido-6-O-(t-butyldimethylsilyl)-4-desoxy-α-D-gulopyranoside 13a and methyl-2,3-anhydro-6-O-(t-butyldimethylsilyl)-4-O-(p-nitrobenzoyl)-α-D-gulopyranoside 13b are formed.

The transformations of 2,6-O-bissilyl-methyl-α-D-mannopyranoside are represented in figure 2. The predominating product is the methyl-3,4-anhydro-talo-pyranoside 15 even when TPP/DEAD/HN3 is used. Obviously the substitution process leading to the alto-sugar 16 is greatly hindered by the well known 1,3-diaxial interaction. All the epoxy sugars 8, 9, 10 and 15 serve as very useful starting points for further interesting structural modifications by opening the epoxide ring with HX (2, 3).

Figure 2.

The behaviour of the D-1,4-gluconolactone derivative 17 towards TPP/DEAD/HX is summarized in figure 3. The exclusive activation of the C1 group at C5 using one equivalent TPP/DEAD followed by a substitution by HX opens an interesting approach to the L-1,4-idono-lactone derivative 18 whereas the activation of the second C1 group at C3 yields by an elimination process...
the unsaturated sugar lactone 19. By applying such procedures to the analogous 2,6-bis-O-(t-butyldimethylsilyl)-ether derivative of D-1,4-galactonolactone 20 the corresponding L-altronolactone derivatives 21a \((X = H_2)\) and 21b \((X = p-\text{NO}_2-C_6\text{H}_4\text{OCO})\) on the one and 2,6-bis-O-(t-butyldimethylsilyl)-5-C-p-nitrobenzoyl-L-erythro-hex-2-en-1,4-lactone 22 on the other hand are resulting. A similar pattern can be observed in the case of the 2,6-bis-O-(t-butyldimethylsilyl)-ether derivative of L-mannonolactone 23. By omission of \(\text{HX}\) the olefin sugar lactone 24 (2,6-bis-C-(t-butyldimethylsilyl)-3-desoxy-L-erythro-hex-2-en-1,4-lactone) is formed without any involvement of the C5-\(\text{OH}\). In contrast the D-1,4-gulonolactone derivative 25 is transformed into the 3,6-anhydro-D-gulonolactone 26 (figure 4).

![Figure 3.](image)

![Figure 4.](image)

The 4,9-bis-O- and 4,8,9-tris-O-t-butyldimethylsilyl ether derivatives 27 and 28 of the biologically important neuraminic acid represent useful starting points for the synthesis of the new structurally varied nonulosonic acid derivatives 29 (figure 5) 30 and 31 (figure 6). Opening of the oxirane ring of 29 with \(\text{HNO}_3\) leads to the 8-desoxy-8-azido-neuraminic acid derivative 30 which corresponds completely 28. By the reaction of the tris-silyl ether derivative 28 with \(\text{TPP/DEAD/MN}_3\) an interesting result was observed
The primary activated OH group of C7 is attacked obviously as a result of ideal stereochemical conditions by the acetamido group of O5. As a consequence of this neighbouring group participation an inversion of the configuration of C7 leading to the D-glycero-L-altro-5-(5'-methyl-1-N-tetrazolo)-nonulosonic acid derivative 31 occurred.

**Figure 5.**

**Figure 6.**

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Synthetic Application of Element Organic Substituted Phosphorus Ylides

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The trimethylsilylated ylides 1 (1), easily generated from trimethylchlorosilane and ylides, react with aldehydes 2 to form vinylsilanes 3 (2,3). The vinylphosphonium silanolates 4 are also formed. Compounds 3 are versatile reagents for further reactions (4). The ylide 1 (with R' = H) reacts with aldehydes 2 to give the dienes 9. The oxidation of 1 with the adduct 6, from triphenylphosphite and ozone, gives access to a general synthesis of acylsilanes (trimethylsilylketones) 8 (2). The silylated ylides 1 react to form phosphonium salts 7 with halogen compounds. The salts 7 can be desilylated by fluoride ions. The disubstituted ylides 10 formed can be converted in situ nascendi with aldehydes 11 into the tris-substituted olefin 12 (2,3). In the case of R'=I, vinyl...
iodides $12$, $R^3=I$, are obtained (2). Using deuterated halogen compounds $R^3X$ (and $R^1=H$) partially selectively deuterated pheromones can be obtained by this method (5). Recent results show, that (tert. butyl-dimethylsilyl)-methylene phosphorane $1$ ($R^1=H$, and tert. butyl-dimethylsilyl instead of Me$_3$Si) gives a Wittig reaction which affords a vinyl silane with terminal double bond in high yields (2).

The hexaphenylcarbodiphosphorane $13$ (6) can be understood as an elementorganically substituted ylide with a particular character. It reacts with $S_8$ to form $CS_2$, $14$, which immediately reacts further with one more molecule of $13$ via a betaine intermediate as described previously (7) to make thiketenyldiene triphenylphosphorane $15$ (8).

\[
\begin{align*}
\text{Ph}_3\text{P}-\text{C}=\text{PPh}_3 & \quad \xrightarrow{S_8} \quad \text{CS}_2 \\
13 & \quad 14 \\
\text{H}_3\text{COOC}-\text{C}=\text{C}-\text{COOCH}_3 & \quad \xrightarrow{13} \quad \text{Ph}_3\text{P}-\text{C}=\text{C}=\text{S} \\
16 & \quad 15
\end{align*}
\]
Compound 13 reacts with 2 moles of acetylene dicarboxylic ester 16 via a twofold cycloaddition and a subsequent electrocyclic ring opening reaction (9) to form the allene bisylid 18 (8). The radialene 20 is formed (8) from 13 and fluorenylidene ketene 17. Compound 13 probably reacts first with 17 to give the phosphacumulene ylide 19 (10), from which a pentatetraen is formed with 17. This then reacts with 19 to give a cycloaddition yielding 20 (9).

Phosphorus ylides 21 combine with BH3 22 to yield adducts 23 (11), which rearrange thermally to give the monoalkyl borane-triphenylphosphane adducts 24. On further heating these disproportionate to trialkyloboranes 29 and the adduct from BH3 and triphenylphosphane 30 (12).

We were able to direct the rearrangement 23–24 so that no disproportion into 29 and 30 occurred (13). The adducts 24 are stable and can now be used for hydroboration reactions whereby a suitable method for the elimination of triphenylphosphate from complex 24 must be used. This can be achieved with benzyl-iodide 25. On addition of the iodo compound 25 and an olefin 26 to a solution of 24 in tetrahydrofuran, the benzyl-triphenylphosphonium iodide precipitates and the free R-BH2 adds to the olefin 26 forming the tri-
alkylborane 27 (13). The latter can be converted into tertiary alcohols 31 by subsequent treatment with CO and H₂O₂ (14).

The reaction of 24 and HCl yields alkylchloroborane triphenylphosphine complexes 28, which can be converted with olefins in the presence of benzylidiodide 25 (15). The dialkylchloroboranes 32 thus formed can be transformed into ketones 33 with sodium methylate and then the DCME-technique of H.C. Brown (16).

These last results combine the Wittig ylide chemistry with Brown's hydroboration reaction. We hope that a preparatively interesting ylide-borane chemistry will arise from this new "alloy".

I thank my coworkers, named in the references, for their enthusiastic engagement in the solution of our common problems.

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Mono-, Di-, and Multi-Ylides in Organometallic Chemistry

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The ylid function in an organophosphorus compound is described in the various theoretical models as a reactive molecular site with a combination of donor and acceptor capacity – or as a set of adjacent nucleophilic and electrophilic centers at carbon and phosphorus, respectively. The situation is not unlike the characteristics of the carbonyl group, one of the most important reactive functions in classical organic chemistry. Following the pioneering work by G. Wittig (1) and his collaborators, the synthetic potential of phosphorus ylids – and the reaction with carbonyl compounds in particular – has been widely exploited and the literature witnesses an ever increasing range of new preparative uses (2).

In most of these reactions the P-C bond of the ylid is cleaved and formally a carbene moiety is exchanged with a corresponding part of the substrate. In contrast, the majority of the reactions of ylids with acceptor sites centered at metals or metalloids occur with conservation of the P-C bond and lead to organometallic/organometalloidal products containing M-C-P bridges (3,4,5). Depending on the nature of M, these carbon bridges between phosphorus and heteroatoms may show CH acidity and may be deprotonated when exposed to strong bases or to an excess of ylid, which acts as a transyldiating agent.

Bonding in the resulting products again depends strongly on the nature of M, and cases with the character of metallated ylids R3P=CH-M⁻ are also known (3) as are their phosphoniumcarbene metal counterparts R3P⁺P=CH=M⁺²⁻ (6,7,8).

A second feature, also uncommon in reactions of ylids with organic substrates, is the additional ylidation of the substituents at phosphorus (3,4,5). This alternative provides for an enormous variety of bridged and chelated metal complexes, amply described in a large number of papers in recent years.