Russian Chemical Reviews **76** (4) 327 – 338 (2007) © 2007 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RC2007v076n04ABEH003667

Synthesis of arylenephosphamacrocycles using tri- and pentavalent phosphorus compounds

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Abstract. Key results of research into the reactions of cyclophosphorylation of dibasic phenols and related compounds with tri- and pentavalent phosphorus compounds are analysed. Structural features and chemical modification of macrocyclic systems obtained are considered. The bibliography includes 63 references.

I. Introduction

Research into macrocyclic phosphorus-containing systems began after the discovery of plasmids that are giant DNA molecules containing cyclic structures.[1] Probably, this fact and considerable advances in the synthesis and investigations of crown ethers and other macroheterocycles gave an impetus to intensive studies dealing with the design and chemical properties of cyclic systems containing tri- and pentavalent phosphorus acid residues.[2–5] It should be noted that the attention of researchers was focussed on the products of cyclophosphorylation of dibasic phenols. The results obtained in this field allow one to relate the reactivities of the cyclic compounds to their sizes, mutual position of phosphorus-containing groups and other factors. Now one can expect the design of original supramolecular assemblies based on novel phosphorus-containing macrocycles, observation of molecular recognition effects,[6,7] discovery of novel catalytic systems, *etc*.

At present, cyclic compounds of different nature are available. Their molecules comprise two to six phosphorus-containing fragments and the same number of arylene substituents. In this review we will dwell on the studies devoted to the synthesis and investigations of the properties of such systems that mainly include the phosphite and phosphonite moieties.

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Received 25 September 2006
Uspekhi Khimii **76** (4) 362 – 374 (2007); translated by A M Raevskiy

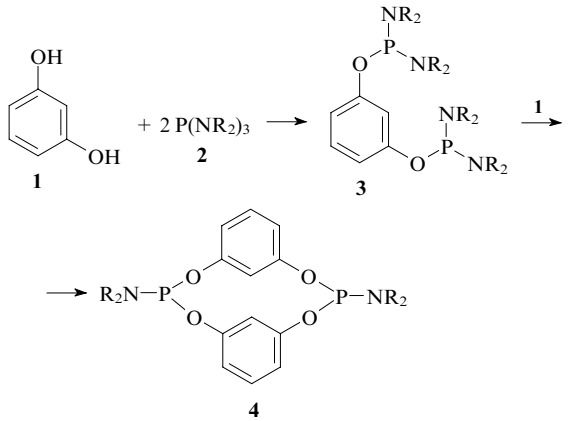
II. Syntheses using trivalent phosphorus compounds

1. Syntheses of diphosphamacrocycles

This problem attracted the attention of scientists from several research centres. They studied the reactions of dibasic phenols with equivalent and inequivalent amounts of phosphorylating agents (direct cyclophosphorylation and molecular assembly techniques, respectively).

a. Cyclophosphorylation of dihydroxybenzenes and 4,4′-dihydroxybiphenyl

The first phosphacyclophanes comprising two resorcinol (**1**) residues linked by two phosphoramidite bridges were synthesised in 1997 by the reactions of **1** with hexaalkylphosphorous triamides **2** taken in a 1 : 2 molar ratio.[8–10] Then, 1,3-bis(phosphordiamidite)benzene **3** formed in the first stage was introduced into the reaction with an equimolar amount of **1**:

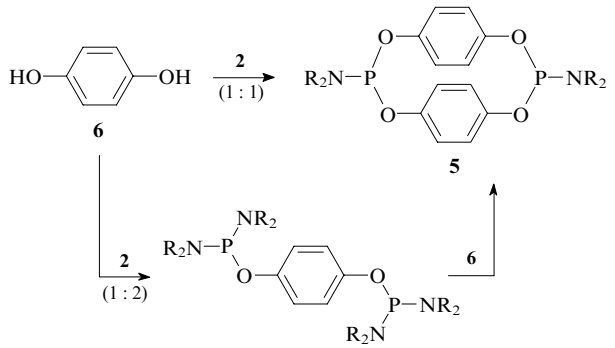


R = Me, Et.

In addition to this process (we will call it 'molecular assembly'), a direct reaction between equimolar amounts of resorcinol and phosphorous triamide is also possible. This reaction, which can be called 'direct cyclophosphorylation' or 'direct synthesis', is more convenient and often gives better results. Both reactions proceed in acetonitrile or 1,4-dioxane at room temperature.

Cyclic bis(phosphoramidites) **4** are oily substances characterised by good solubility in conventional organic solvents and high oxidisability.

Cyclic phosphoramidites **5** based on hydroquinone **6** were also synthesised by the molecular assembly and direct phosphorylation techniques (from this point on, figures in parentheses above or below the arrow denote the reactant ratio).[11]



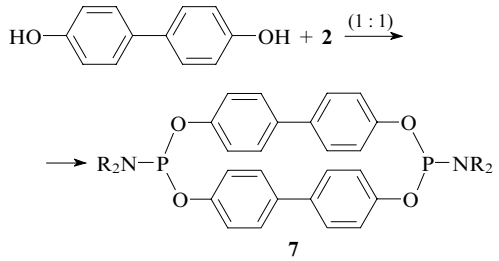
R = Me, Et.

The direct phosphorylation method resulted in higher yields of compounds **5** compared to the molecular assembly technique.

The structures and individuality of the reaction products as well as cyclic phosphoramidites and their derivatives (see below) were proved by physicochemical methods (^{1}H and ^{31}P NMR spectroscopy, IR spectroscopy and mass spectrometry) and confirmed by the results of elemental analysis. Cyclic phosphoramidites **5** synthesised in different ways exhibited identical physicochemical characteristics. These are solid, low-melting and poorly soluble substances that are unstable upon storage even in inert atmosphere. Probably, the labile behaviour of these compounds is due to strain in the macrocycle caused by the proximate arrangement of two aromatic rings. This assumption was confirmed by the results of calculations of the most stable conformations, according to which the molecules of cyclic bis(phosphoramidites) **5** have an eclipsed cyclophane structure.[12]

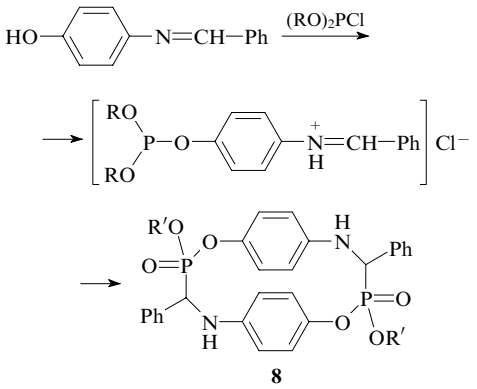
Compounds **5** readily add oxygen and sulfur to give corresponding cyclic bis(phosphoramidates) and bis(phosphoramidothioates).

Similar heterophanes (hereafter, phosphacyclophanes) **7** are formed in the reactions of 4,4′-dihydroxybiphenyl with phosphorous triamides **2**.[11]



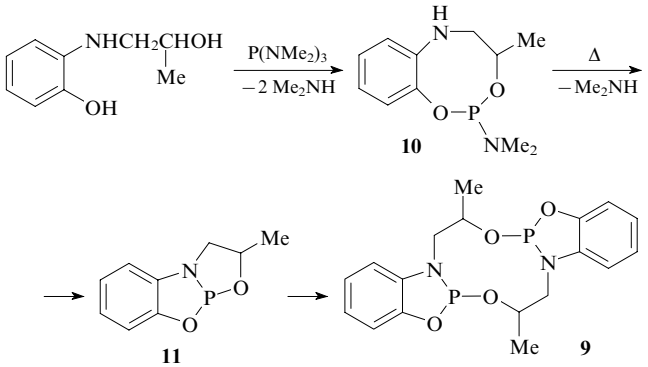
Compounds **5** and **7** were introduced into the oxidation reactions and into complexation with $Mo(CO)_6$ and $Rh(CO)_2(acac)$ (acac stands for acetylacetonate). The oxidation and complexation with $Rh(CO)_2(acac)$ occurred in dichloromethane at room temperature. Complexes with $Mo(CO)_6$ formed only on heating in dioxane (95 °C) in the presence of excess carbonyl. All derivatives were isolated and studied by physicochemical methods (^{1}H and ^{31}P NMR spectroscopy and IR spectroscopy).

Nitrogen-containing phosphacyclophanes **8** were obtained from (*N*-benzylidene)-*p*-aminophenol and dialkylphosphorochloridites $(RO)_2PCl$.[13] The reactions proceeded in chloroform at room temperature and completed in 5 days.



R = R′ = Et; $(RO)_2$ = OCH_2CH_2O, R′ = CH_2CH_2Cl.

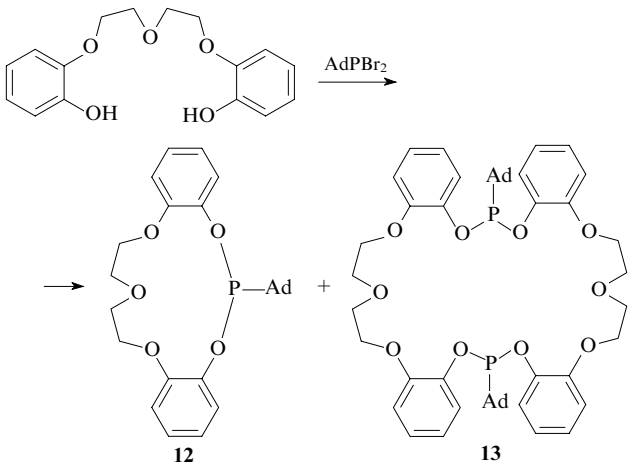
Phosphacyclophane **9** was synthesised by phosphorylation of *N*-(β-hydroxypropyl)-*o*-aminophenol with hexamethylphosphorous triamide.[14] Monitoring by ^{31}P NMR spectroscopy revealed the formation of cyclic compound **10** with one phosphorus-containing fragment. When heated, compound **10** transformed into heterobicycle **11** which in turn experienced spontaneous dimerisation into phosphoramidite **9**. The structure of compound **9** was proved by X-ray analysis.



At 20 °C, the transformation **11** → **9** takes a very long time to complete (about a year).

b. Cyclophosphorylation of organylenebisphenols

Among the first examples of this type of chemical transformation is the reaction of 1,7-bis(2-hydroxyphenyl)-1,4,7-trioxaheptane with 1-adamantyldibromophosphine ($AdPBr_2$).[15]

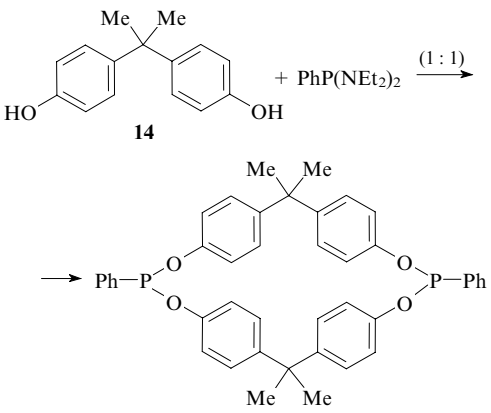


Ad is 1-adamantyl.

This cyclophosphorylation results in the fourteen-membered adamantylphosphonous acid diester **12** (yield 10%) and

diphosphorus cyclic compound **13** (yield 11%–44%). The structures of the products were confirmed by NMR spectroscopy and by measuring the molecular mass (ebullioscopy). Substance **13** appeared to be a stable and convenient reactant, which can be oxidised, alkylated, *etc*.

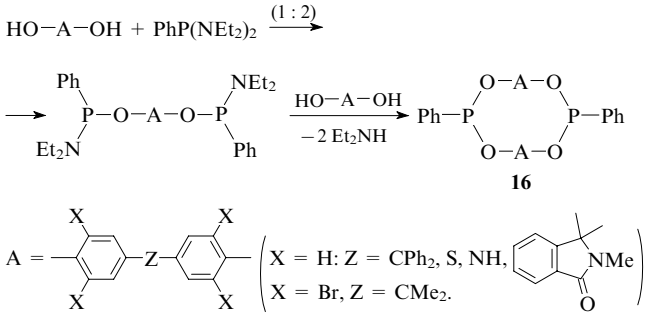
The cyclophosphorylation of an available commercial product, namely, 2,2-bis(*p*-hydroxyphenyl)propane (DIAN) (**14**) with phenylphosphonous acid tetraethyldiamide was studied in the 1990s.[16]



14 **15**

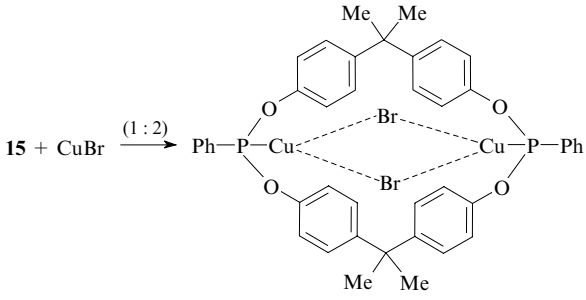
The reaction was carried out in toluene under (relatively) severe conditions (115–120 °C). The structure of cyclophenylphosphonite **15** was studied by X-ray analysis.[17] The phosphorus atoms and the quaternary carbon atoms approximately occupy the corners of a square. The angle between the DIAN aromatic rings is 35° so the whole system has a cavity. The diphosphonite macrocycle **15** was found to be a stable compound.

This allowed one to extend the range of dinuclear bisphenols used in cyclocondensation and synthesise new macrocycles **16** containing not only isopropylidene, but also sulfide, imide and other bridges.[18]



16

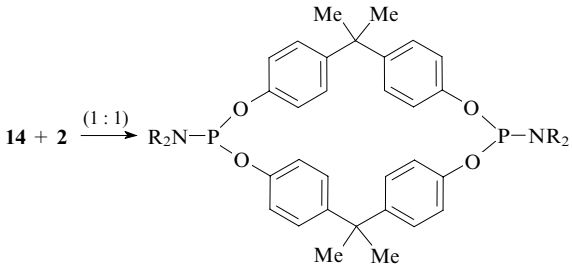
Cyclic bis(phenylphosphonites) **16** were introduced into the complexation, oxidation and sulfurisation reactions, easily resulting in cyclophosphonates and their thio analogues. An X-ray diffraction study revealed considerable changes in the cavity volume and configuration for cyclic bis(phosphonates) compared to the starting cyclic bis(phenylphosphonites).[18] Some cyclic bis(phenylphosphonites), *e.g.*, compounds **15** and **16**, can form complexes with CuBr.[19,20] The assumption of metal coordination to two phosphorus atoms was confirmed by ^{31}P NMR data.



17

Complexes **17** exhibit high catalytic activity in the reactions accompanied by transfer of hydrogen atoms in homogeneous media.

Phosphorylation of bisphenol **14** with equimolar amount of phosphorous triamides **2** under mild conditions results in reactive cyclic phosphoramidites **18**.[21]



18

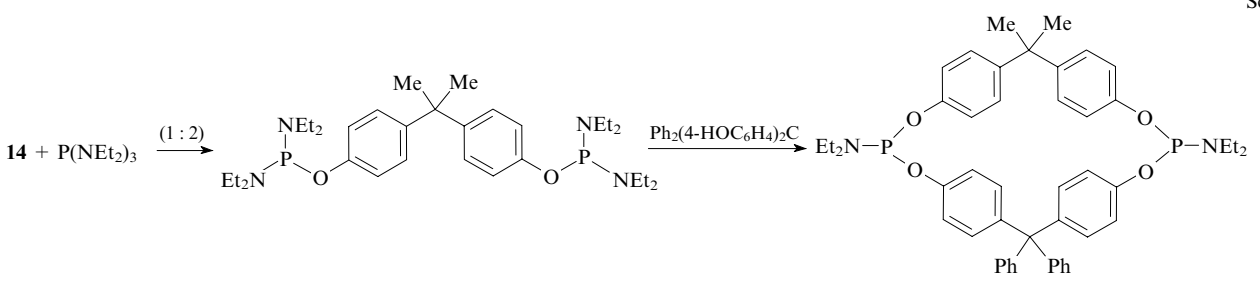
R = Me, Et.

This approach can be extended to molecular assembly of unsymmetrical bis(phosphoramidite) macrocycles (Scheme 1).

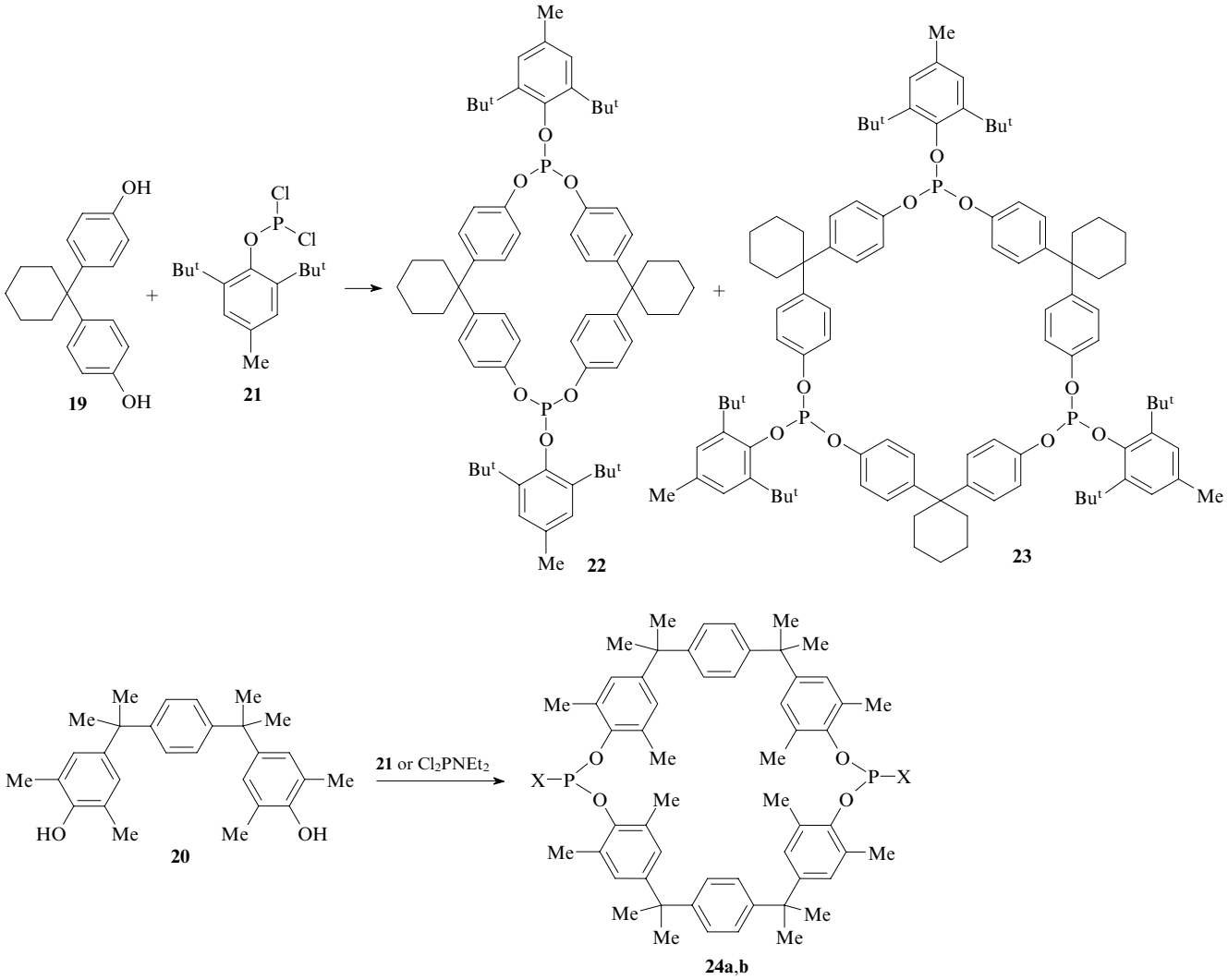
Using bisphenols **19** and **20** as matrices and 2,6-di-*tert*-butyl-4-methylphenylphosphonous dichloride (**21**) and diethylamidophosphonous dichloride as phosphorylating reagents, in the last decade Habicher and Bauer [22–25] synthesised a series of even more complex macrocycles **22**–**24**. The syntheses were carried out at room temperature in toluene in the presence of triethylamine upon high dilution (Scheme 2).

Habicher and Bauer also established that many unsymmetrical macrocycles undergo spontaneous symmetrisation. For instance, the interaction of bisphenol **14** with bis(phosphorodiamidite) based on bisphenol **20** results in cyclic phos-

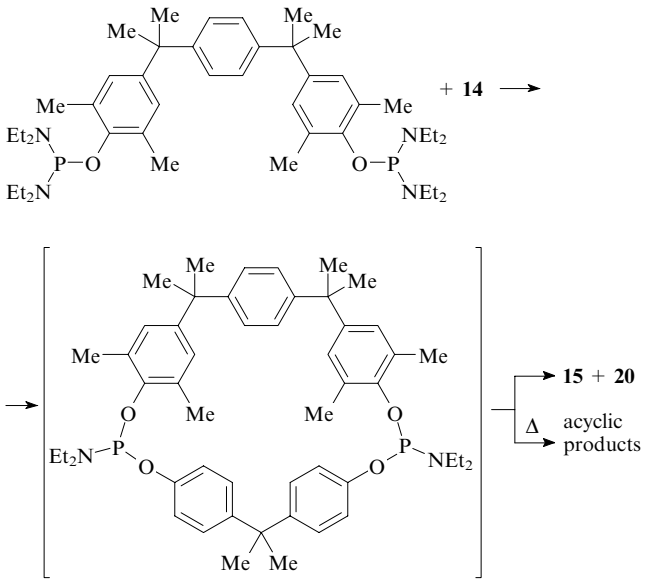
Scheme 1



Scheme 2

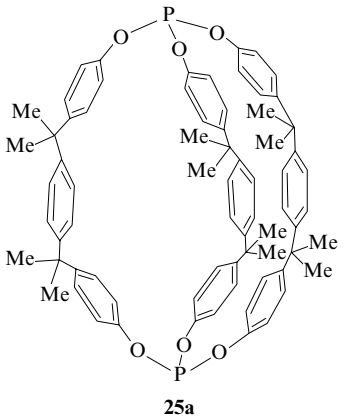


phoramidite **15** and free bisphenol **20**. When carried out on heating, this reaction affords acyclic oligomeric products.

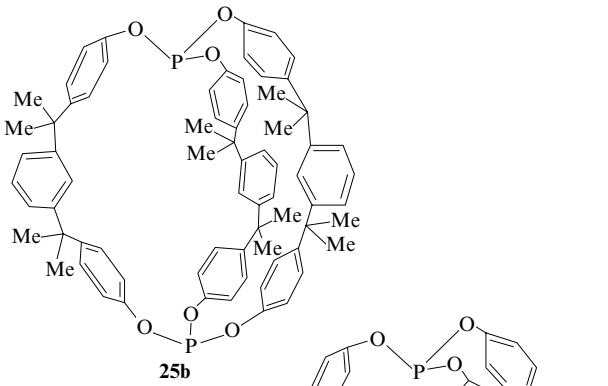


The above series of reactions is completed by the synthesis of phosphorus-containing cryptands **25a–c** by the reaction of bisphenol **20** with phosphorus trichloride.[26]

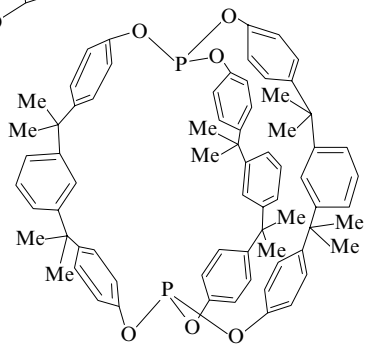
Analysis of the structures of cryptands **25** revealed the 'in–out' isomerism. All three stereoisomers were chromatographically separated. The structures of isomers **25a–c** were proved by NMR spectroscopy and X-ray diffraction analysis. In addition, all three cryptands were introduced into the



25a



25b

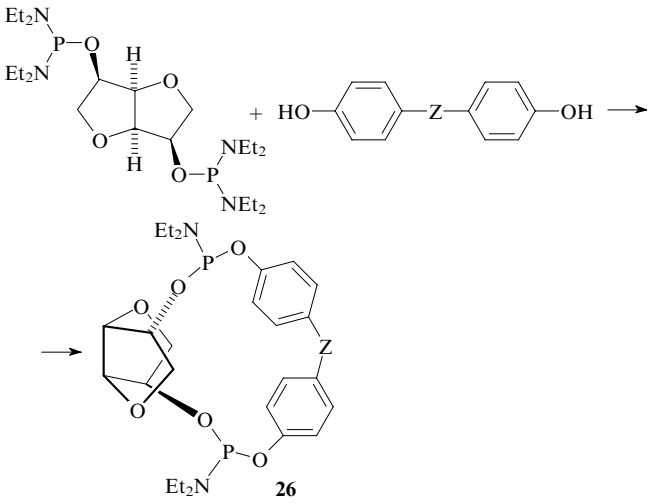


25c

reactions characteristic of simple phosphites.[27] The synthesis and investigations of the chemical features of cyclic phosphites and phosphorus-containing cryptands have been well documented in a review.[28]

At present, cyclophosphorylation reactions are carried out using phosphorochloridites and phosphoramidites, the latter often being more convenient because they react with phenols at room temperature in various solvents and do not require removal of amines released. Additionally, the amide groups show different reactivities, namely, the first amide group is replaced rapidly while the third amide group remains almost unsubstituted. At the same time the use of reaction mixtures based on phosphorochloridites requires introduction of acceptors in order to bind hydrogen chloride evolved, all chlorine atoms being almost equally reactive. Probably, the next stage of research and development in this field of synthetic chemistry will require optimisation of reaction conditions, *e.g.*, the search for appropriate catalysts.

Progress in the synthesis of complex macrocyclic diphosphorus systems using phosphorous triamides **2** led to the preparation of multinuclear chiral structures **26** based on the



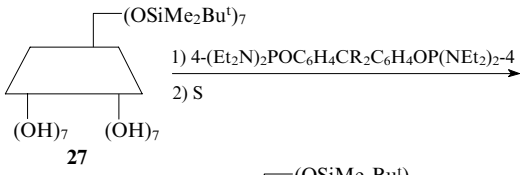
26

Z = O, S, CMe_2, CPh_2.

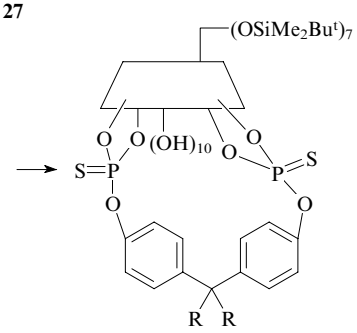
available bisphosphorylated 1,4;3,6-dianhydro-D-mannitol derivative.[29–31] The reaction was carried out in benzene with distillation of diethylamine (75 °C) in inert atmosphere.

Products **26** were converted *in situ* into corresponding bis(thiophosphates), which were isolated from the reaction medium in 60% – 88% yields by column chromatography.

Structures with large cavities were also synthesised starting from silylated β-cyclodextrin derivative **27** and various dinuclear phosphorylated bisphenols.[32] The reactions in benzene at 75 °C completed in 6 h and resulted in the so-called 'capped' cyclodextrins **28** isolated in 62% – 75% yields by column chromatography. 'Capping' of the cyclodextrin molecule enhances its ability to form inclusion complexes with various 'guest' molecules.



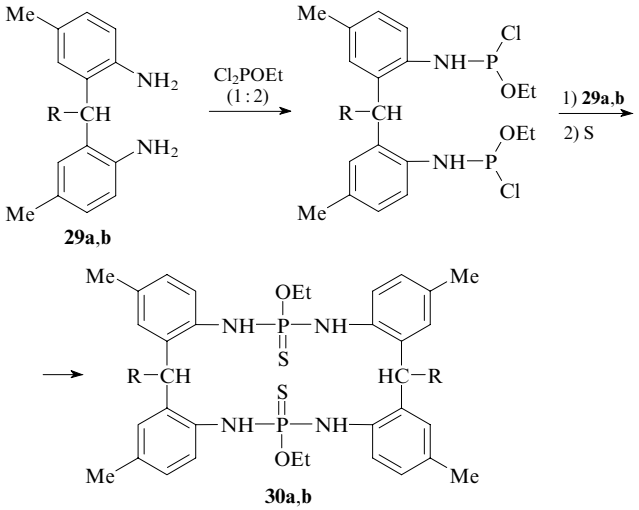
27



28

R = Me, Ph.

In addition to bisphenols, aromatic diamines were also employed to design related macrocyclic systems. For instance, bis(2-amino-5-methylphenyl)methane (**29a**) and its phenyl analogue **29b** served as building blocks for the synthesis of 16-membered nitrogen-containing macrocycles **30a**,**b**.[33] The reaction was carried out using the molecular assembly technique in dioxane in the presence of triethylamine at 5 °C with ethyl phosphorodichloridite as phosphorylating agent.



30a,**b**

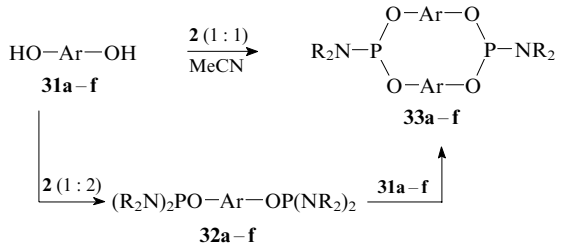
R = H (**a**), Ph (**b**).

The best results were obtained in the phosphorylation of primary amines with alkyl phosphorodichloridites. ^{31}P and ^{1}H NMR studies showed that the macrocycles synthesised exist as mixtures of two conformers.

c. Cyclophosphorylation of dihydroxynaphthalenes and dihydroxyanthracenes

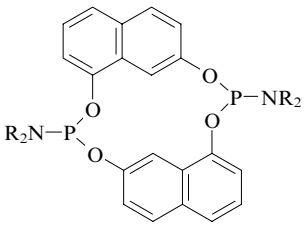
The cyclophosphorylation of dihydroxynaphthalenes is a promising method for the synthesis of previously unknown phosphacyclophanes. At present, it has been shown that both symmetrical (1,5-; 2,6-; 2,7-) and unsymmetrical (1,3-; 1,6- and 1,7-) dihydroxynaphthalenes **31** efficiently react with phosphorous triamides **2** following the single-step or two-step (involving intermediate amido esters **32**) schemes.[17, 34–39]

All reactions were carried out in acetonitrile at room temperature and completed in 3 to 40 h depending on the substituent in the phosphorylating agent. The cyclic products **33a–f** were obtained in 70%–80% yields.

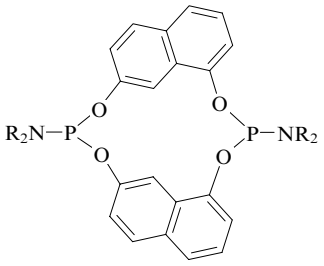


R = Me, Et, Pr^i; R–R = $(CH_2)_5$; Ar = *i,j*-naphthylene; $i = 1$: $j = 7$ (**a**), 6 (**b**), 3 (**c**), 5 (**d**); $i = 2$: $j = 7$ (**e**), 6 (**f**).

Cyclophosphorylation of 1,7-dihydroxynaphthalene (**31a**) results in two structural isomers with differently arranged naphthylenedioxy groups, namely, a series arrangement in compound **33a** (1,7,1,7) and a pairwise arrangement in compound **33a** (1,1,7,7). The former isomer was isolated and studied by NMR spectroscopy and X-ray diffraction analysis.[36, 37] Its ^{31}P NMR spectrum exhibits a singlet. The second isomer was characterised by ^{1}H NMR spectroscopy in the form of thio derivative. The ^{31}P NMR spectrum of **33a** (1,1,7,7) exhibits two singlets.

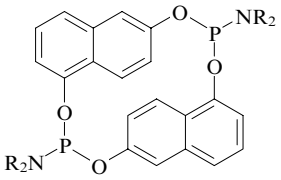


33a (1,7,1,7)

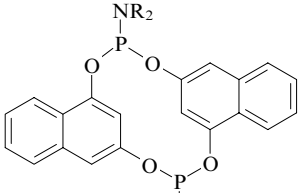


33a (1,1,7,7)

Products of cyclophosphorylation of 1,6- or 1,3-dihydroxynaphthalene exist as single structural isomers [compounds **33b** (1,6,1,6) or **33c** (1,3,1,3), respectively] with a series arrangement of naphthylenedioxy groups in the ring.[38, 39]

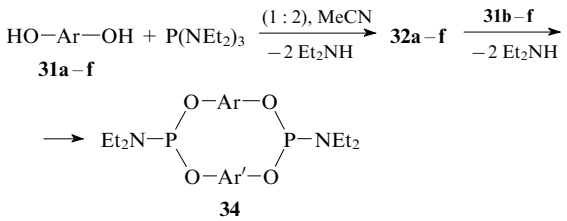


33b (1,6,1,6)



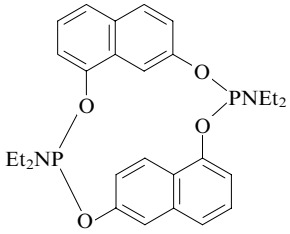
33c (1,3,1,3)

The molecular assembly technique was also used for the synthesis of phosphacyclophanes **34** the molecules of which comprise different arylene moieties. A number of 'non-uniform' naphthophosphacyclophanes containing two different naphthylenedioxy units were obtained.[40]

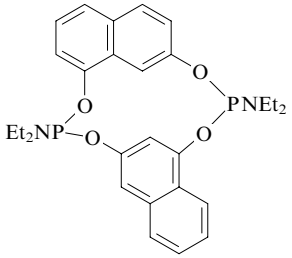


Ar = *i,j*-naphthylene, Ar′ = *i′,j′*-naphthylene; $\{i,j\} \neq \{i',j'\}$.

Similarly to the case of 'uniform' naphthophosphacyclophanes based on 1,6- and 1,3-dihydroxynaphthalenes, cyclophosphorylation of unsymmetrical 1,7-, 1,6- and 1,3-dihydroxynaphthalenes only resulted in structural isomers with a series arrangement of the naphthylenedioxy groups in the ring.



34 (1,6,1,7)

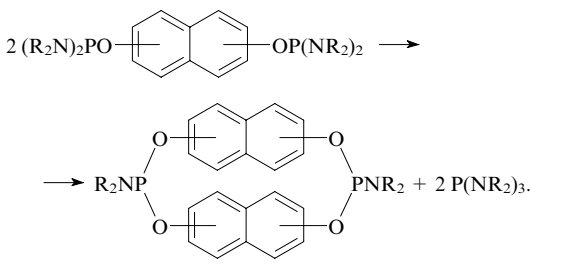


34 (1,3,1,7)

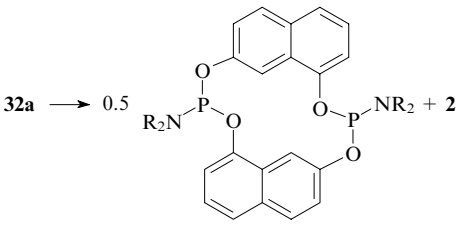
The reaction is regioselective; therefore, the products were isolated in a pure state. The naphthophosphacyclophanes **33** and **34** were oxidised and sulfurised. The reactions in dichloromethane at room temperature took a short time (20 h) to complete. Thiophosphoramidates were isolated by column chromatography (yields ~55%) and cyclophosphoramidates were isolated by reprecipitation (yields ~90%). The structures and individual character of all macrocycles **33**, **34** and their thio and oxo derivatives were confirmed by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy and by MALDI mass spectrometry. MM2 calculations of the steric energies of the 'uniform' and 'non-uniform' naphthophosphacyclophanes made it possible to predict the stabilities of corresponding phosphites, thiophosphates and phosphates.

Cyclic phosphoramidites **33** and **34** readily form complexes with Mo(0) and Rh(I). The complexation of 'uniform' naphthophosphacyclophanes occurs more easily than that of 'non-uniform' compounds.

Recently, the syntheses of naphthalene-based phosphacyclophanes using dismutation of bis(phosphoramidites) were reported.[41, 42] The process can be described as follows:



The rate of this reaction depends on position of substitution in naphthylenedioxy groups and on the nature of the substituent at the phosphorus atom. In particular, the reaction of unsymmetrical 1,7-dihydroxynaphthalene results in one structural isomer with a series arrangement of naphthylenedioxy groups in the ring.[37]

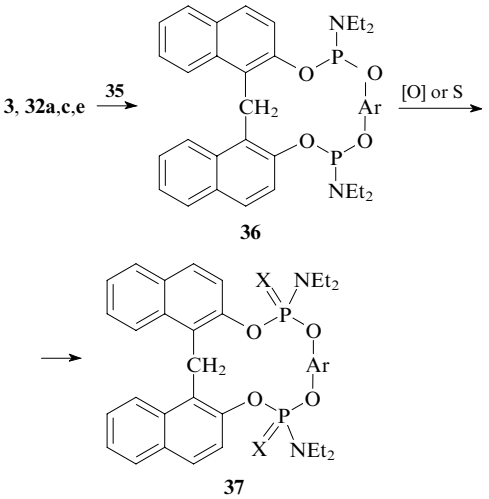


As mentioned above, the direct synthesis and molecular assembly techniques afford a mixture of two structural isomers, one with a series (1,7,1,7) and the other with a pairwise (1,1,7,7) arrangement of naphthylenedioxy groups in the ring. Therefore, the dismutation is a regioselective reaction.

The dismutation of bis(phosphoramidites) based on dibasic phenols and naphthols has been studied in considerable detail.[41,42] The process is governed by many factors including the nature of the aromatic fragment, the substituent at the phosphorus atom, the solvent and especially the existence of conjugation in the starting reactant molecule. The derivatives of condensed aromatic systems undergo dismutation faster than their mononuclear analogues. Dismutation of the amide derivatives with aliphatic substituents at nitrogen also proceeds more readily than that of their heterocyclic analogues. The reaction in dichloromethane proceeds at the highest rate irrespective of the aromatic component and substituents at phosphorus. Non-polar solvents (benzene, diethyl ether) do not favour dismutation. Temperature does not affect the duration of the dismutation reaction. In the presence of a catalyst (amine hydrochloride) the process time is shortened by a factor of 1.5–2.

In addition, MM2 calculations of the steric energies were carried out for all the compounds synthesised. Generally, the steric energies of phosphorous diamido esters **32** are higher than those of phosphorous amido diesters **33**, **34**.

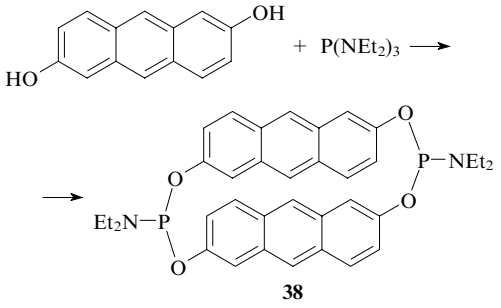
Cyclic phosphoramidites **36** were synthesised from bisphosphorylated aromatic diols **3**, **32a**,**c**,**e** and 2,2′-dihydroxy-1,1′-dinaphthylmethane (**35**) by the molecular assembly technique at room temperature in dioxane.[43]



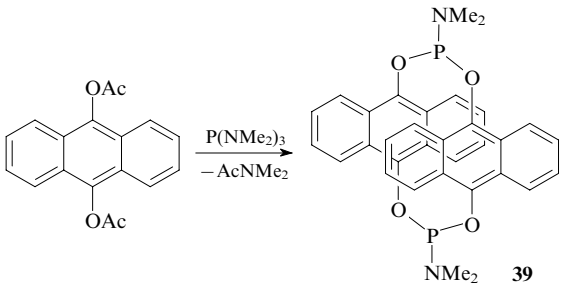
Ar = 1,3-phenylene, 1,7-, 1,3- or 2,7-naphthylene; X = S, O.

The oxidation occurred in dioxane or dichloromethane at room temperature and completed in 24 h. The structures of the resulting macrocycles **37** were confirmed by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy and by MALDI mass spectrometry.

Phosphacyclophanes were also synthesised from dihydroxyanthracenes. For instance, the reaction of 2,6-dihydroxyanthracene with hexaethylphosphorous triamide results in a symmetrical ring system **38**.[44] This compound is similar in chemical properties to the naphthalene analogues studied earlier.



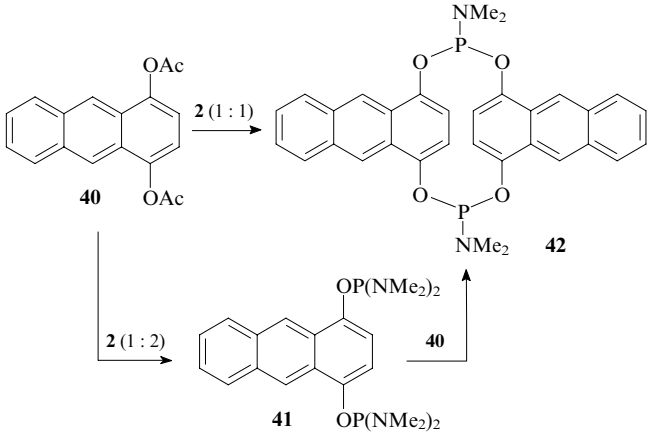
A cage product **39** comprised of two anthracene residues linked by two phosphoramidite bridges at positions 9,10 was prepared from 9,10-diacetoxyanthracene, which was used instead of very unstable 9,10-dihydroxyanthracene, and hexamethylphosphorous triamide.[45,46]



The reaction proceeded at 20 °C and completed after 96 h. Phosphacyclophane **39** was isolated in a 42% yield using two methods, at equimolar reactant ratio and by dismutation.

Product **39** appeared to be unstable in solution and decomposed with release of anthraquinone. This is consistent with the results of MM2 calculations.

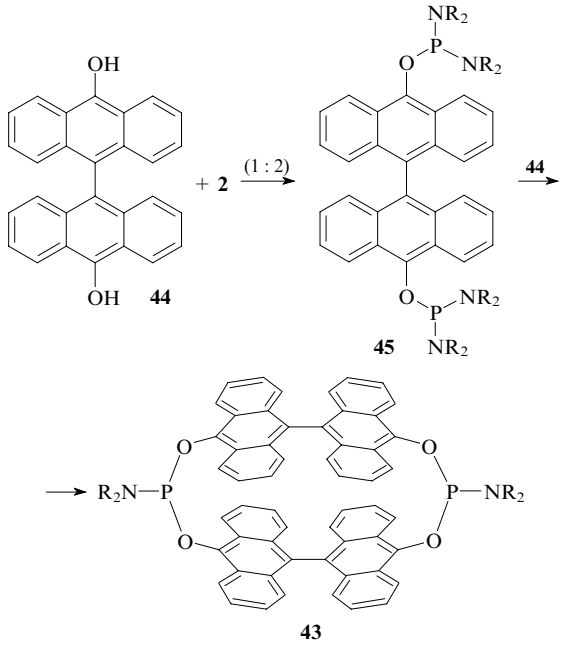
A dimer based on 1,4-dihydroxyanthracene was also synthesised from its diacetate derivative **40** using the molecular assembly technique involving bis(phosphoramidite) **41** and the direct synthesis.[46,47]



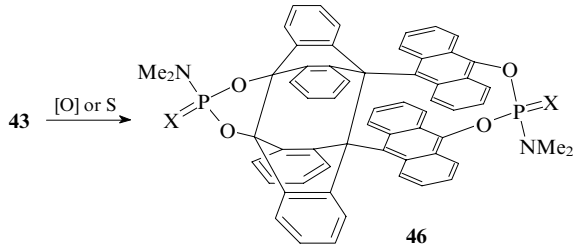
The reaction was carried out at room temperature. Phosphacyclophane **42** was isolated in 37% (molecular assembly technique) and 58% (direct synthesis) yields. A MALDI mass spectrometric study showed that the cyclic product contains two anthracene moieties and two phosphorus-containing groups. Compound **42** is much more stable than compound **39**, because the aromatic fragments in the former can be more distant from each other.

Macrocycle **43** is based on dianthrone **44**, a bisphenol containing two mutually perpendicular 9-anthrone residues

linked by a C–C bond at positions 10.[48] It was phosphorylated with phosphorous amides **2** in pyridine only on heating in the temperature range of 50–120 °C depending on the substituent in the phosphorylating agent. Cyclic systems **43** were only synthesised by the molecular assembly technique using corresponding bisphosphorylated derivatives **45**.

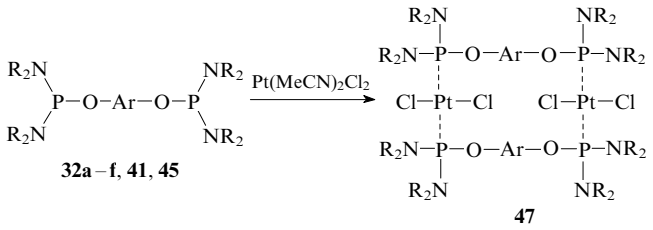


The direct synthesis affords a mixture of cyclic systems containing two to four dianthrone residues. It was established that oxidation of cyclic compound **43** (R = Me) results in a 'cross-linked' structure **46** containing a five-membered ring with two quaternary carbon atoms. It was assumed that in this case one deals with isomerisation, which obeys the pattern of intramolecular Diels–Alder reaction and is similar to intramolecular cycloaddition of some compounds with two anthracene residues.



X = S, O.

Metallaphane complexes **47** containing bridging Pt(II) atoms are based on dihydroxynaphthalene derivatives **32a–f** and bisphosphorylated dihydroxyanthracenes **41** and **45**. The synthesis was carried out in dichloromethane or pyridine at room temperature with diacetonitriledichloroplatinum(II) as the starting complex.[35, 49–51]

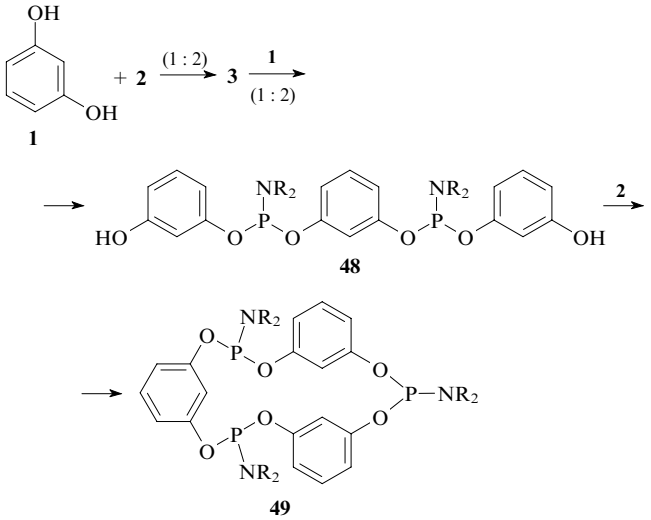


Complexes **47** are powder-like compounds which decompose upon melting. They were isolated in 60%–80% yields. The structures and compositions of the complexes were confirmed by ^{1}H and ^{31}P NMR spectroscopy and by cryoscopy. The spin–spin coupling constants $^{1}J_{PPt}$ equal to 3441 and 3347 Hz indicate that the complexes are *trans*-isomers.

2. Synthesis of triphosphamacrocycles

Recently, macrocyclic compounds larger than molecule **4** containing regularly arranged phosphoramidite groups and resorcinol fragments have been synthesised. The resulting compounds resemble Pedersen's crown ethers.[6] Therefore, they or corresponding pentavalent phosphorus derivatives can found practical applications in supramolecular chemistry.

The simplest representatives of these macrocyclic compounds were synthesised following the scheme:



R = Me, Et.

The reactions of resorcinol and phosphorous amides **2** were carried out at 1:2 molar ratio of the reactants at room temperature. Then, phosphorodiamidite **3** was introduced into the reaction with resorcinol. Linear reaction product **48** undergoes cyclisation in the reaction with phosphoramide **2**.[52–54]

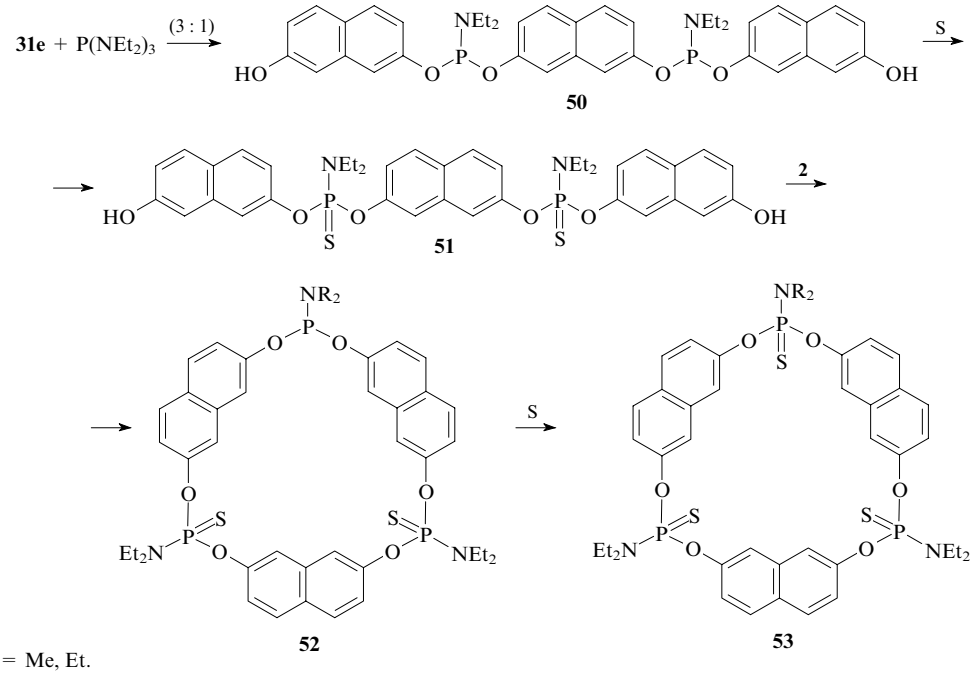
Sulfurisation of macrocyclic tris(phosphoramidite) **49** results in a crystalline *cis*,*cis*,*trans*-product (one P atom is above and the other two P atoms are below the macrocycle plane); its structure was established by X-ray diffraction analysis.[53] Later on, dismutation of macrocyclic pentakis(phosphoramidite) (see Section II.3) afforded the *cis*,*cis*,*cis*-isomer of heterocycle **49** (all P atoms are on one side of the macrocycle), which significantly differs from the *cis*,*cis*,*trans*-isomer in properties.[54, 55]

Mention should be made of the possibility of bis(phosphoramidite) **4** formation in the first stage of this reaction. Unfortunately, other procedures for the synthesis of cyclic phosphoramidites are also non-selective. For instance, the reactions of resorcinol with phosphorous triamides **2** in acetonitrile result in cyclic bis(phosphoramidite) **4** and cyclic tris(phosphoramidites) **49** as the major products.[8, 9]



Cyclic tris(naphthylenephosphoramidites) have also been synthesised (Scheme 3).[51, 56] One route to these compounds begins with the synthesis of linear bis(phosphoramidite) **50** containing three naphthylene fragments, two of which bear hydroxyl groups, at a 1:3 ratio of the starting reactants (this is

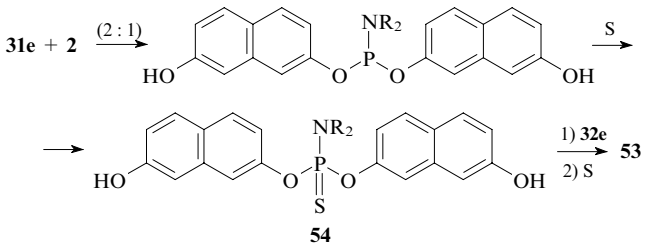
Scheme 3



R = Me, Et.

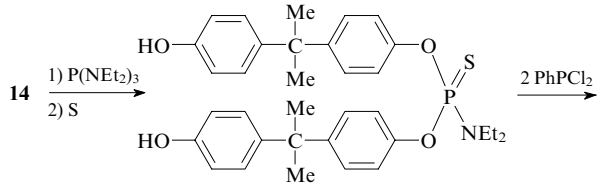
a necessary condition). Otherwise, the reaction results in cyclic bis(phosphoramidite) **33e**. Bisphenol **50** was sulfurised and product **51** was isolated by column chromatography. Phosphocyclisation of **51** with phosphorous triamides **2** resulted in compound **52** which was again sulfurised. Tris(thiophosphate) **53** was isolated by column chromatography in ~60% yield.

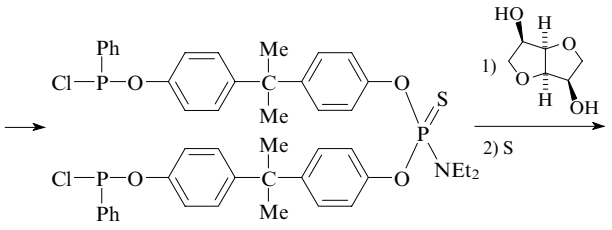
The second method involves the synthesis of stable acyclic *O,O*-bis(7-hydroxy-2-naphthyl) *N,N*-dialkyl thiophosphoramidates **54**. Cyclisation of **54** with bisphosphorylated 2,7-dihydroxynaphthalene **32e** followed by sulfurisation affords the desired cyclic tris(thiophosphate) **53**.

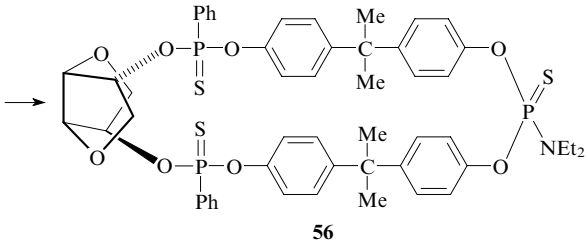


Cyclic thiophosphates **53** synthesised using both methods exhibited fully identical physicochemical characteristics.[51, 56] These tris(thiophosphates) can be used as, *e.g.*, ligands for binding 'soft' metals or as starting compounds in syntheses of cyclic tris(phosphites).

Bisphenol **14**, $P(NEt_2)_3$ and phenylphosphonous dichloride were used for the synthesis of a phosphorylating agent **55**, which was then employed in the phosphorylation of 1,4;3,6-dianhydro-D-mannitol[31] in order to obtain a chiral large-cavity system **56**.







The reaction was carried out in benzene, the second and third stages being conducted in the presence of triethylamine. Macrocycle **56** was isolated in 40% yield and characterised by ^{31}P and ^{1}H NMR spectroscopy.

3. Synthesis of higher phosphorus-containing macrocycles

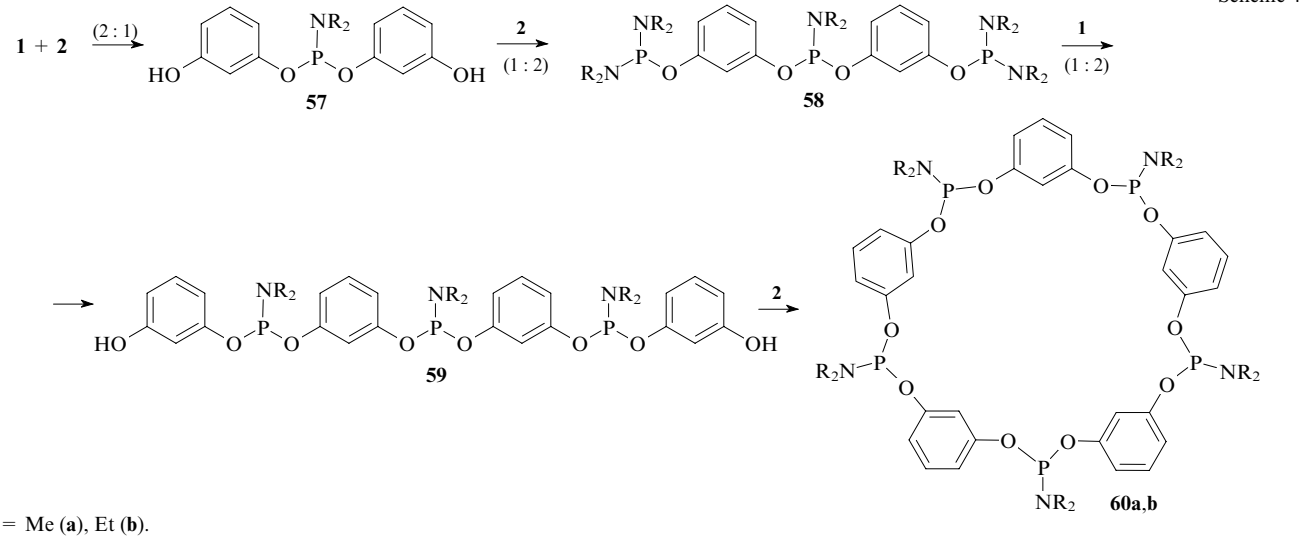
Higher macrocyclic systems were designed using the molecular assembly technique starting from resorcinol and phosphorous triamides **2** (see above). The oligomer chain terminated with hydroxyl groups at both ends was extended in a sequential manner. Then, the diols thus obtained were cyclophosphorylated with phosphorous triamides **2**. One-pot synthesis under control of the composition of intermediates **57** – **59** resulted in cyclic pentakis(phosphoramidites) **60** (Scheme 4).[53, 54]

The reaction was carried out in acetonitrile or benzene at room temperature. Cyclic compound **60a** is unstable and undergoes a rearrangement resulting in cyclic bis- and tris-(phosphoramidites) when stored in benzene solution.

60a ⟶ **4** + **49**

In contrast to this, cyclic pentakis(phosphoramidite) **60b** does not undergo rearrangement.[54, 55]

Scheme 4

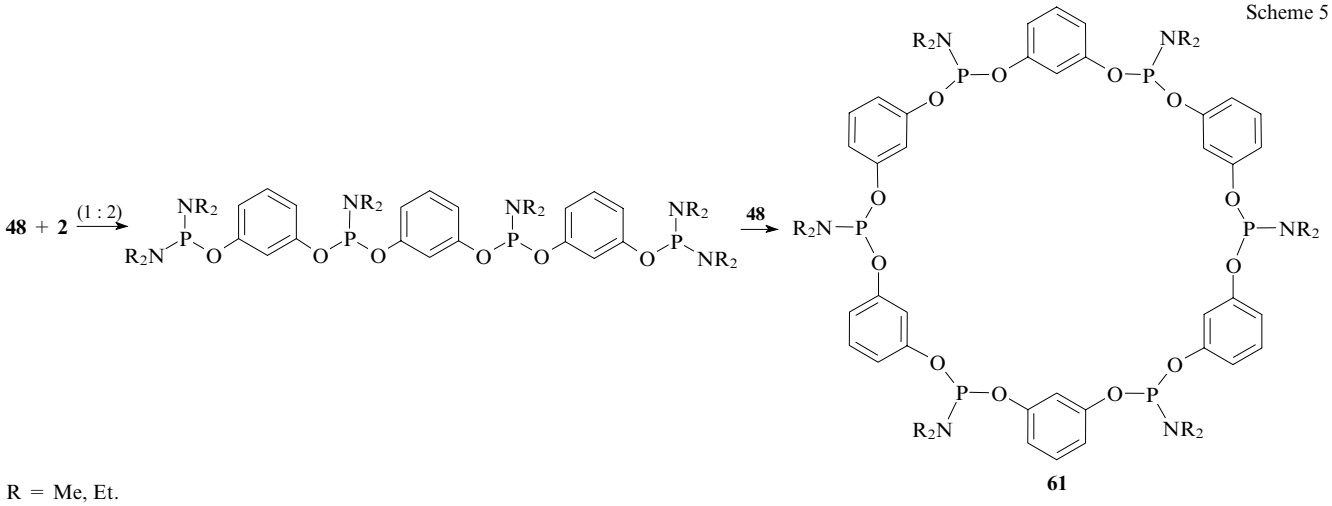


R = Me (**a**), Et (**b**).

Regarding even more complex macrocycles, it is appropriate to synthesise them from two fragments of a target system with similar compositions. An example is provided by the synthesis of cyclic hexakis(phosphoramidites) **61** (Scheme 5).

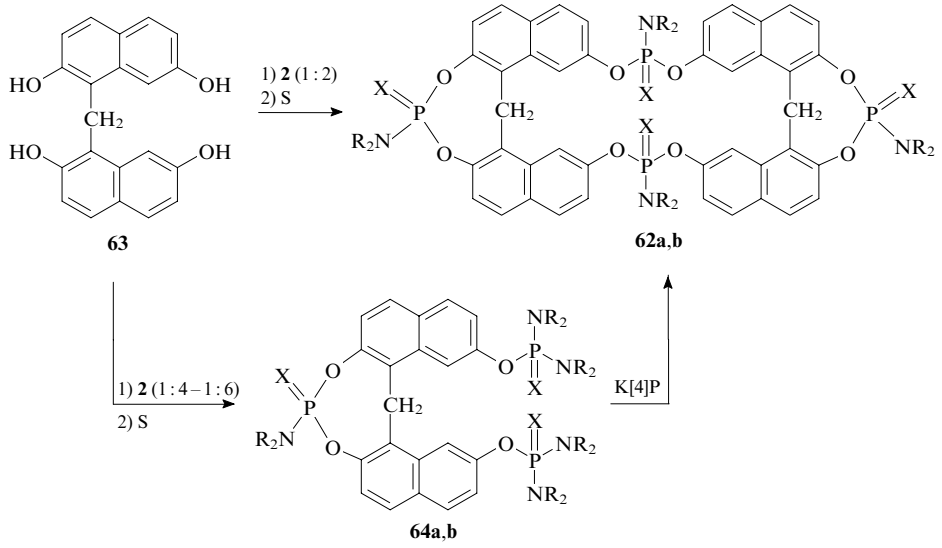
Cyclic oligomeric phosphoramidites considered above were introduced into the sulfurisation and oxidation reactions. Some of them were introduced into the complexation reactions with $Rh(CO)_2(acac)$. The results of cryoscopic determination

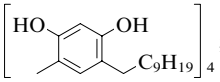
Scheme 5



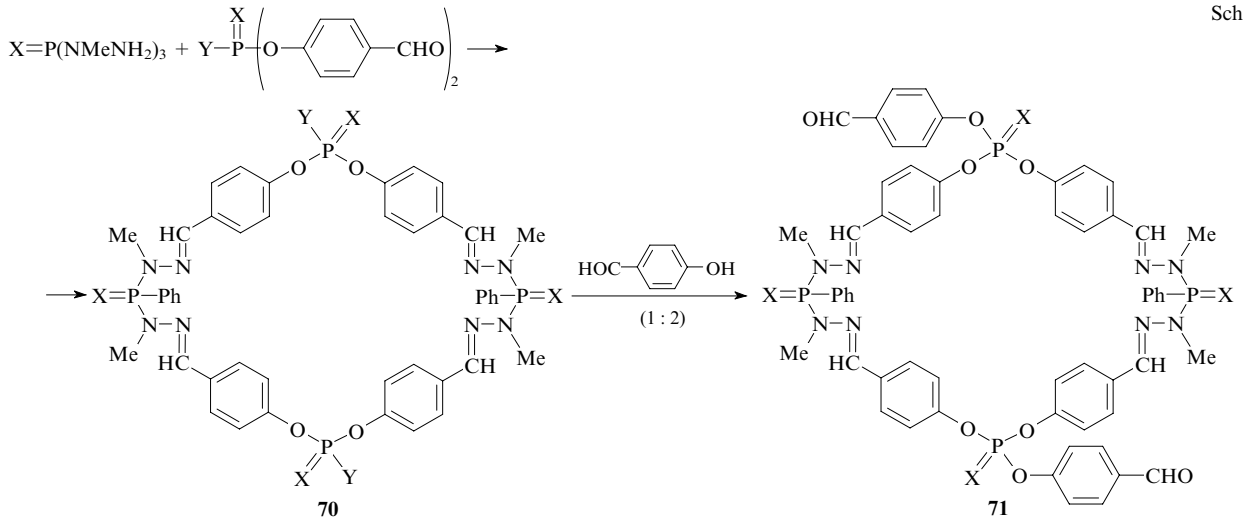
R = Me, Et.

Scheme 6



K[4]P =  ; R = Me, Et; X = UEP (**a**), S (**b**).

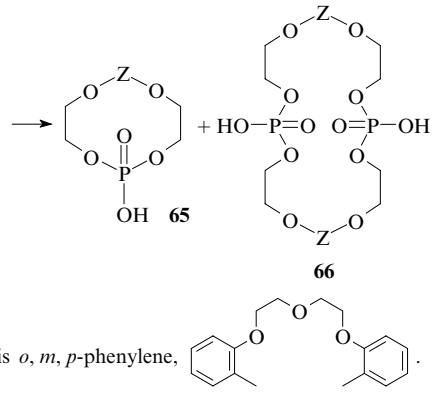
Scheme 7



X = O, S; Y = Cl, N_3.

of the molecular masses and the NMR spectra confirm the structures of these compounds.

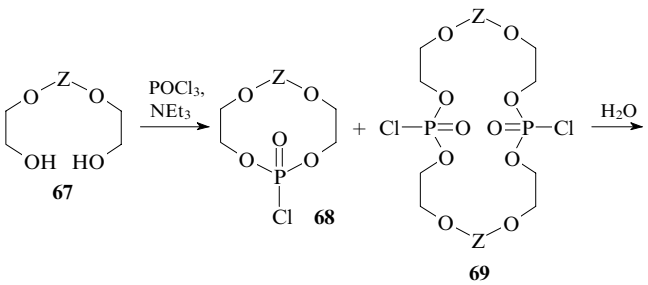
Macrocycles **62** were synthesised based on 2,2′,7,7′-tetrahydroxy-1,1′-dinaphthylmethane **63**. Macrocycles **62** contain four phosphorus atoms, two of them form phosphocine fragments. Phosphorous triamides **2** served as phosphorylating agents. Macrocycles **62** can be synthesised using two procedures, by direct phosphorylation at 1 : 2 reactant ratio and in a stepwise reaction using the action of calix[4]resorcinarene (K[4]P) with bulky hydrophobic substituents in the lower rim on the phosphate derivative **64** in the second stage.[57] All reactions were carried out in dioxane under argon at room temperature (Scheme 6). The yields of the target products **62** were 55% – 63%.



Z is *o*, *m*, *p*-phenylene, .

III. Syntheses using pentavalent phosphorus compounds

Compared to trivalent phosphorus compounds, pentavalent phosphorus derivatives are usually poor phosphorylating agents. Nevertheless, in some cases it is more appropriate to synthesise complex phosphorus-containing macrocyclic systems using phosphochloridates, phosphoramidates and other pentavalent phosphorus derivatives. This is confirmed by the stereochemical features of the pentavalent phosphorus derivatives and by their stabilities against oxidation and disproportionation and, therefore, by the stability upon storage. Recently, novel polyfunctional crown ethers representing macrocyclic phosphates and phosphonates have been synthesised. For instance, arylenephosphate **65** and bis(arylenediphosphate) **66** were synthesised in two stages by the reactions of various arylenediols **67** with phosphorus oxochloride in the presence of triethylamine followed by hydrolysis of intermediate phosphochloridates **68**, **69** (compounds **69** were not isolated).[58]



Pentavalent phosphorus derivatives were also employed to design polyfunctional phosphate-phosphonate macrocyclic systems **70** and **71** reported by Caminade *et al.*[59–61] Of particular interest are those systems that can be readily modified due to the presence of aldehyde groups (*e.g.*, compound **71**), which favour chain extension and formation of bulky cryptands, crown ethers and dendrimers (Scheme 7).[62, 63]

IV. Conclusion

Summing up, an original field of chemistry of phosphorus-containing macroheterocycles has emerged in the last decade. Progress in this research avenue is due to the availability of reactants and efficiency of synthetic methods. The strategies of synthesis have been well developed, the molecular assembly technique being used more often. In turn, the alternative route, the direct synthesis of bismacrocyclic systems, is sometimes more preferable because it ensures higher yields of end products. Carrying out reactions at high temperatures and under solvent-free conditions can result in macrocycles containing more than two phosphorus-containing groups. Usually, the best results are obtained in phosphorylation and cyclophosphorylation with amides, which results in a smaller content of side products. Research on the synthesis of novel phosphorus-containing heterocycles revealed a number of interesting chemical facts including the 'in – out' structural isomerism of cage structures and dismutation of unsymmetrical aromatic mono- and bisphosphorus systems.

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