In,out-ISOMERISM OF PHOSPHORUS BRIDGEHEAD CAGE COMPOUNDS. A REVIEW

Ingmar BAUER[1,*] and Wolf D. HABICHER[2,*]

Institute of Organic Chemistry, Technical University of Dresden, Mommsenstr. 13, 01062 Dresden, Germany; e-mail: [1] ingmar.bauer@chemie.tu-dresden.de, [2] wolf.habicher@chemie.tu-dresden.de

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Dedicated to Professor Ivan Stibor on the occasion of his 60th birthday in recognition of his outstanding contributions to the area of supramolecular chemistry.

The chemistry and stereochemical peculiarities, especially the phenomenon of *in,out*-isomerism of bi- and polycyclic compounds with one or more phosphorus bridgehead atoms, are reviewed in the present paper. The appearance of *in,out*-isomers depends on the ring size of the bi- and polycycles. In general graphic *in,out*-isomerism becomes only possible in medium sized ring systems and in particular in macrocyclic compounds. However even bicyclic systems containing small rings can be *trans*-configured if the third chain is long and flexible enough hence giving rise to pseudo-*in,out*-isomerism. *In*-phosphorus atoms exhibit a low reactivity in comparison to their *out*-counterparts. Nevertheless some few examples of reactions at *in*-positioned phosphorus atoms have been presented. This will potentially open the way to a specific modification of the cavity of such macrobi- and polycyclic compounds. A review with 53 references.

Keywords: Cage compounds; Cryptands; *In,out*-isomerism; Phosphorus macrocycles; Phosphatranes; Phosphonium salts; Phosphanes; Phosphane oxide; Phosphates.

1. INTRODUCTION

The phenomenon of *in*,*out*-isomerism appearing in medium and large bicyclic ring systems is not only an interesting structural feature but might become important for the specific modification of macrobicyclic compounds with regard to their potential application in supramolecular chemistry such as metal cation complexation, molecular recognition of neutral substrates but also as ligands for regio- and stereoselective metal catalyzed reactions in organic synthesis. Despite of their interesting properties, the number of *in*,*out*-isomers with phosphorus bridgehead atoms is still limited but has continuously grown during the last two or three decades.

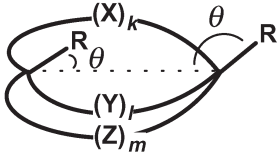
The present paper reviews the chemistry of phosphorus bridgehead bi- and polycyclic compounds with respect to possible *in*,*out*-isomerism at these positions. A certain number of bicyclic phosphorus compounds has been reported where the authors did not draw attention to this phenomenon because only one isomer (mostly the *out*-isomer) was exclusively formed. Such compounds which in our opinion might potentially show *in*,*out*-isomerism have been included in the present paper.

The subject of *in*,*out*-isomerism in general has been reviewed some years ago by Alder et al.[1] in terms of nomenclature, stability of the isomers, mechanism of interconversion, accessibility and reactivity of inside functionalities. This article also covered some few examples of structures with phosphorus bridgehead atoms.

In,*out*-descriptors describe a conformational situation at bridgehead atoms rather than a configurational. In a general bicyclo[*k.l.m*.]alkane up to four different stereoisomers (*R*,*R*), (*R*,*S*), (*S*,*R*) and (*S*,*S*) are possible. The extended form of the *R*/*S* nomenclature exactly describes the configuration of bicyclic systems even if two or even all three bridges of the bicycle are the same. In this case the *r*/*s* system has to be applied[2]. The (*R*,*R*)- and (*S*,*S*)-isomers may preferably exist in *in*,*out*- or *out*,*in*-conformations, while the (*R*,*S*) and the (*S*,*R*)-isomers will mainly adapt the *in*,*in*- or *out*,*out*-geometry[1]. Exceptions arise in very small bicyclic systems, where exocyclic substituents necessarily have to be *out*-positioned in any configurational case according to the *in*/*out* definition discussed below (Scheme 1). Very large and flexible macrobicyclic systems, however, may adapt many different conformations which depend less on the configuration of the cyclic skeleton (see the possibility of *intertwined* systems[1]).

Regardless of the limiting factors for the use of the *in*/*out* descriptors in many cases they give a graphic image of the geometrical situation of bridgehead substituents with respect to the cyclic system. This works especially

well for bicyclic systems with two bridgehead atoms and bridges of similar length. The "*in*-ness" or "*out*-ness" of a bridgehead substituent can be characterized by the angle θ between the substituent, the bridgehead atom to which it is attached and the other bridgehead atom (Scheme 1)[1,3]. An ideal *out*-substituent would have an angle θ of 180°, whereas the ideal *in*-position would be characterized by θ = 0°. Any conformational situation in between is possible and also angles of 90° can be observed which would not clearly refer to an *in*- or *out*-situation.



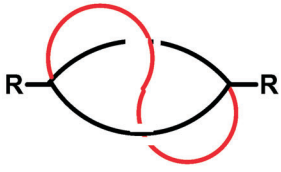
in-R: $0° \leq \theta \leq 90°$
out-R: $90° \leq \theta \leq 180°$

SCHEME 1

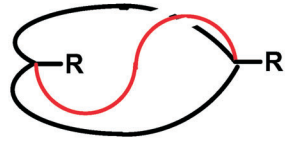
However, this system gives only graphic results in cases where *k*, *l* and *m* are not extremely different. If for example two of the chains are very short such as in bicyclo[*k*.1.1] and bicyclo[*k*.1.0] compounds or the bridgeheads are involved in a very rigid or planar ring system, the bridgehead groups would formally always adapt an *out*-position according to θ. This is true even if they are *trans*-configured which should clearly refer to an *out,in*-case as stated above.

In mono- and polybridgehead systems the application of the *in,out*-nomenclature using angle θ is also limited. In the first case, the reference point for θ on the opposite side of the molecule, which would be the second bridgehead atom in Scheme 1, is not clear. In the second case, if there is an asymmetric polycyclic compound, it is not obvious which second bridgehead atom should be used as a reference.

In very large and flexible ring systems many different conformations with small differences in energy are possible. So for example a number of different conformers which all had to be described as *out,out* are conceivable. This could be even true for an *R*(*r*),*R*(*r*)- or *S*(*s*),*S*(*s*)-configured compound if one of the bridges is threaded through the ring formed by the other two bridges (*intertwined* isomers, Scheme 2). In such cases homeo-



intertwined out,out-isomer



intertwined in,out-isomer

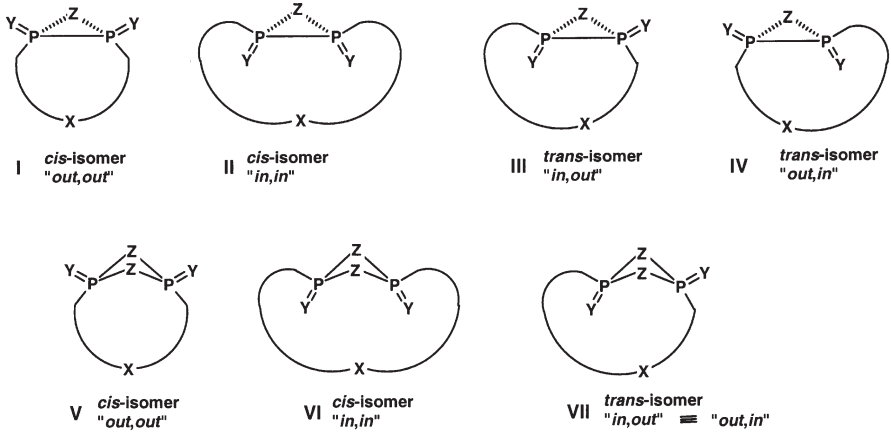
SCHEME 2

morphic isomerization from *out*,*out* to *in*,*in* and *in*,*out* to *out*,*in*, respectively, might be possible[1,3].

There is no clear estimation about the minimal limiting ring size for *in*,*out*-isomerism. In the case of bridges of equal length, the bicyclo[3.3.3] system seems to be at the borderline from where on *in*-geometry can be observed. An *in*-position can be stabilized in some of these cases by partial transannular bonding between the bridgehead atoms (see examples in Scheme 8). However, if this transannular interaction has to be regarded as a full bond, it would not correspond to an *in*,*out*-geometry at bridgehead atoms but represent a tricyclo[*k.l.m*.0] system (see phosphonium salts in Scheme 7).

2. DIPHOSPHABICYCLO[*k.l.m*] COMPOUNDS CONTAINING SMALL RINGS

Cage compounds with shorter chains than three can also potentially form *cis*- and *trans*-isomers or show some kind of *in*,*out*-isomerism if at least one bridge is much longer and flexible. Even bicyclic systems as small as bicyclo[*k*.1.0] and bicyclo[*k*.1.1] systems could be *cis*- or *trans*-configured if *k* is large enough (Scheme 3).



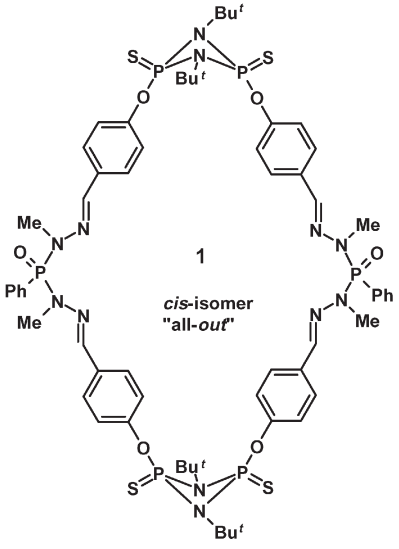
SCHEME 3

The *cis*-configured compounds (**I**, **II**, **V**, **VI**) might even adapt a conformation which is reminiscent of an *in*,*in*-geometry (**II** and **VI**), a situation that has not been observed until now. However, according to the definition by means of angle θ (Scheme 1) the bridgehead groups of all those isomers in Scheme 3 (**I**–**VII**) have to be indicated as *out* ($\theta \geq 90°$). This contradicts the statement above that a *trans*-configuration should correspond to an *in*,*out*-situation at the bridgeheads. Therefore those compounds do not

show graphic *in,out*-isomerism with exocyclic groups pointing into or out of a molecular cavity. They are rather reminiscent of simple macrocycles with incorporated small ring fragments. Such situation might be described as pseudo-*in,out*-isomerism. This type of structures will therefore only be exemplarily covered in the present paper.

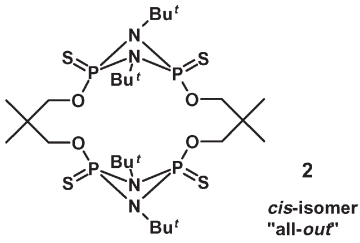
No examples for bicyclo[*k*.1.0] diphosphorus "bridgehead" compounds with a sufficient length of *k* to allow *trans*-configuration at the bridgeheads have been reported so far. The same is true for [*k*.2.0], [*k*.2.1] and [*k*.2.2] systems.

Bicyclo[*k*.1.1] phosphorus bridgehead compounds have been realized for example in the form of macrocyclic systems containing diphosphetidine moieties as reported by Majoral et al.[4–7] The authors obtained in all cases *cis*-configured "all-*out*"-structures such as compound **1** as they started from *cis*-configured aldehyde substituted diphosphetidines and bridged them in a stereospecific reaction with phosphonodihydrazides .

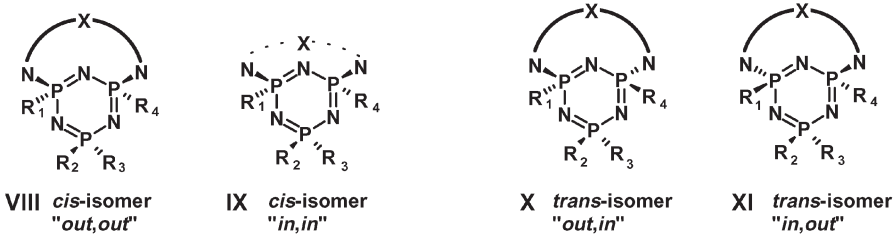


Other examples for *cis*-configured cyclodiphosphazanes incorporated into a macrocyclic skeleton such as **2** have been reported by Swamy[8]. *cis*-Configuration of **2** has been shown by X-ray analysis.

Bridged cyclophosphazenes represent bicyclo[*k*.3.1] systems with two of the bridges and the phosphorus bridgehead atoms included in a planar ring system (Scheme 4). For this reason their exocyclic residues at the bridge-

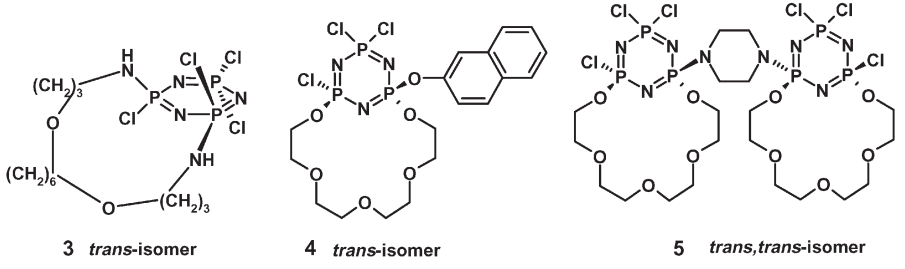


head atoms cannot adapt an *in*-position as defined by angle θ (Scheme 1) showing the same type of pseudo-*in*,*out*-isomerism as described above. The hypothetical structure **IX** exhibiting an "*in*,*in*"-conformation of the *cis*-isomer seems to have no energetic preferences which would allow its formation.



SCHEME 4

trans-Configured *ansa*-cyclophosphazenes (**X**, **XI**, Scheme 4), however, have already been described for example by Labarre[9,10] (**3**, Scheme 5) and Shaw et al.[11,12] (**4**, **5**, Scheme 5).



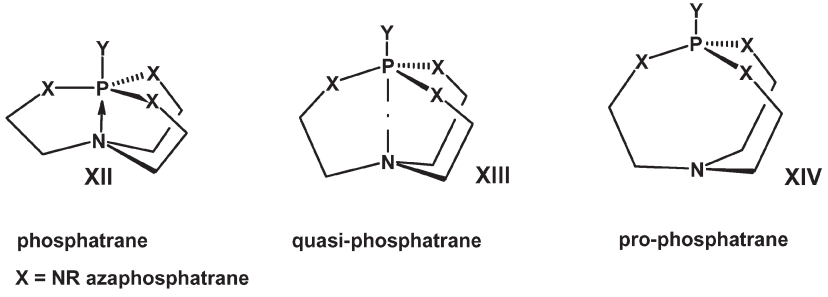
SCHEME 5

Even though it has been proved by few examples that it is possible to obtain both *cis*- and *trans*-configured bicyclic structures with such small bridging units, it is obvious that a clear *in*,*out*-isomerism can only be obtained in bi- or polycyclic systems with larger chains.

3. PHOSPHABICYCLO[*k.l.m*] AND -TRICYCLO[*k.l.m.n*] COMPOUNDS CONTAINING MEDIUM SIZE RINGS (*k, l, m, n* = 3, 4)

3.1. Phosphatranes

Examples from the border area concerning suitable ring size for *in,out*-isomerism are bicyclo[3.3.3] systems. Among the [3.3.3] compounds with phosphorus bridgehead atoms, the so-called pro-phosphatranes occupy the largest space. The chemistry of (aza)phosphatranes **XII**, quasi-(aza)phosphatranes **XIII** and pro-(aza)phosphatranes **XIV** (Scheme 6) has been extensively investigated and reviewed by Verkade et al.[13–15] These structures consist of a [3.3.3] (pro-(aza)phosphatranes, **XIV**) and a [3.3.3.0] ((aza)phosphatranes, **XII**) bi- and tricyclic system, respectively, with a phosphorus and a nitrogen bridgehead atom. Quasi-(aza)phosphatranes **XIII** occupy a position between both of them. They are characterized by a weak transannular N–P interaction being expressed by a measurable shortening of the P–N distance over the sum of the van der Waals radii.



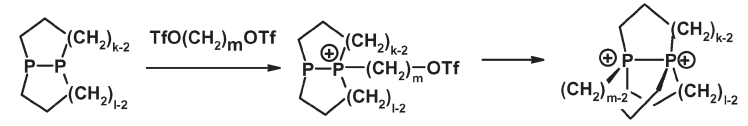
SCHEME 6

Pro-(aza)phosphatranes exhibit *out*-geometry at the phosphorus bridgehead atom whereas the nitrogen end is flattened owing to van der Waals interactions among the methylene protons adjacent to the axial nitrogen. (Aza)phosphatranes in an ideal case have, due to the transannular interaction, a trigonal bipyramidal configuration at the phosphorus atom which does not correspond to an *in,out*-situation and an inwards pointing nitrogen atom. Quasi-(aza)phosphatranes show a stretched transannular bond in all variations. Due to this interaction they show an *out*-geometry at the phosphorus bridgehead concerning the exocyclic rest. The geometry for the nitrogen bridgehead is in many cases nearly planar. As no *in*-geometry has ever been observed at the phosphorus bridgehead in these rather small bicyclic [3.3.3] structures, they will not be discussed in detail in this paper.

Pro-(aza)phosphatranes of type **XIV** are strong nonionic bases and have found application as selective catalysts and promoters for many reactions in organic chemistry (see lit.[15,16] and papers cited therein).

3.2. Diphosphabicyclo[3.3.3], [4.3.3], [4.4.3] and [4.4.4] Systems

Alder et al. reported on a series of bridgehead diphosphanes and phosphonium compounds in the bicyclo[3.3.3]undecane up to the bicyclo[4.4.4]-tetradecane series[17]. In most cases they synthesized such structures via propellane diphosphonium dications such as 1,6-diphosphoniatricyclo-[4.4.4.0^{1,6}]tetradecane bis(trifluoromethanesulfonate) **12**$(TfO)_2$, 1,6-diphosphoniatricyclo[4.4.3.0^{1,6}]tridecane bis(trifluoromethanesulfonate) **11**$(TfO)_2$ and 1,6-diphosphoniatricyclo[4.3.3.0^{1,6}]dodecane bis(trifluoromethanesulfonate) **10**$(TfO)_2$. These compounds were obtained by reaction of diphosphabicyclo[*k*.*l*.0]alkanes **6**–**8** [18] with bis(trifluoromethanesulfonyloxy)alkanes (Scheme 7).



6 k = l = 3
7 k = 4, l = 3
8 k = l = 4

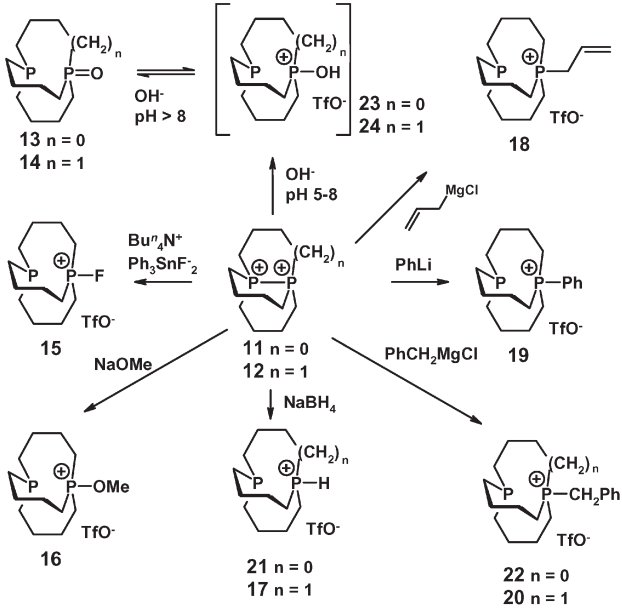
9 k = l = m = 3
10 k = 4, l = m = 3
11 k = l = 4, m = 3
12 k = l = m = 4

SCHEME 7

1,5-Diphosphoniatricyclo[3.3.3.0^{1,4}]undecane bis(trifluoromethanesulfonate) **9**$(TfO)_2$ is a very unstable compound and hydrolyzes rapidly in water whereas compounds **10**–**12** are stable in acidic aqueous solution.

The species **11** and **12** can react with a number of nucleophiles to give products with *in*,*out*-geometry and a partly retaining P–P interaction (Scheme 8)[17,19]. These derivatives are the smallest phosphorus bridgehead compounds described with real *in*-geometry at one bridgehead atom. **11** and **12** form hydroxide adducts (**23**, **24**) which are further deprotonated by an excess of hydroxide to the monoxides of diphosphanes **13** and **14**, respectively. The obtained structures have two resonance forms namely an *in*,*out*-phosphane-phosphane oxide structure and a phosphonium-phosphorane structure (see also Scheme 11). The contribution of the latter was indicated by a significant P–P coupling in ^{31}P NMR. **12** reacts with fluoride, methoxide and hydride to give the corresponding adducts **15**, **16** and **17**, respectively. Alkyl or phenyl groups can be attached to **12** by reactions with the corresponding Grignard and organolithium reagents, respectively,

to give compounds **18**–**20**. P–P coupling was taken as a measure for transannular P–P bonding as no such P–P interaction was observed for proved *out,out*-structures of this type. It ranged from 46 to 249 Hz in those adducts indicating significant P–P bonding combined with an *in*-positioned phosphane atom. The attached functionalities at the phosphonium bridgehead necessarily have to be in an *out*-position. In the case of an ideal trigonal bipyramidal structure at this phosphorus centre it would not fit into the *in,out*-terminology. The [4.4.3] hydride and benzyl adducts **21** and **22** show significantly larger J_{PP} values and hence stronger transannular bonding than the corresponding [4.4.4] structures **17** and **20**.



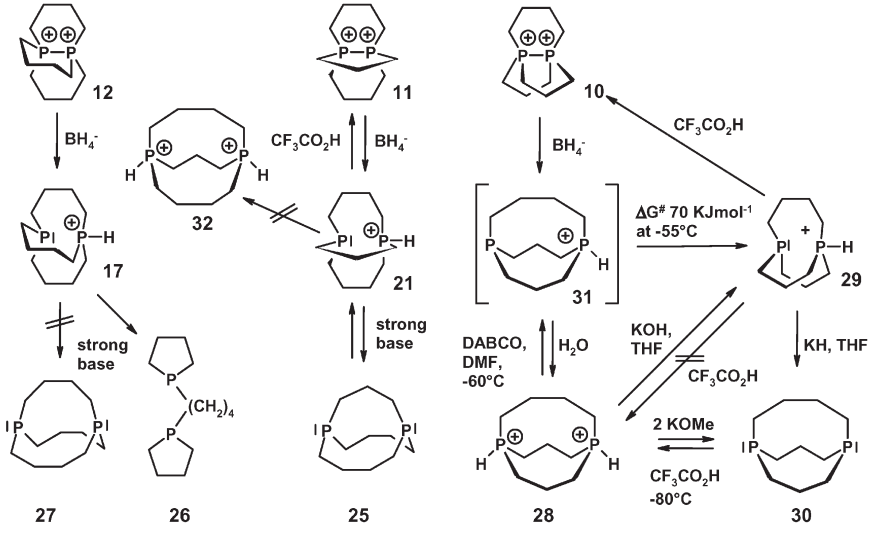
SCHEME 8

The X-ray structures of compounds **20**, **22** and **23** were reported confirming their *in,out*-geometry[20]. Surprisingly, no correlation between P–P distances and $^1J_{PP}$ values was found. This was explained by the stronger influence of other factors on P–P coupling such as the strain in the ring and the apicophilicity of the groups attached to the P(V) atom compared to the relatively weak P–P bonding. Apicophilic groups like hydride favor the phosphorus bearing the exocyclic substituent to adapt a trigonal bipyramidal configuration thus flattening the C–P–C angles, which allows closer interaction with the other P atom.

Of special interest is the reaction of **12** and **11** with BH_4^- to give the monohydride adducts **17** and **21** (Scheme 9). These compounds have

in,*out*-geometry with significant P–P bonding as was indicated by their J_{PP} values.

The hydride adduct of **11**, **21**, can be deprotonated with a strong base to give *out*,*out*-diphosphane **25** thus leading to an inversion of the configuration at the non-protonated phosphorus atom losing now its interaction with the opposite counterpart. This reaction is reversible. Reprotonation gives **21** back thus again inverting the configuration at the non-involved phosphorus centre to an *in*-geometry gaining a P–P interaction. In contrast deprotonation of **17** leads to an unexpected rearrangement to give compound **26** instead of diphosphane **27** via deproponation at an α-CH_2 group.



SCHEME 9

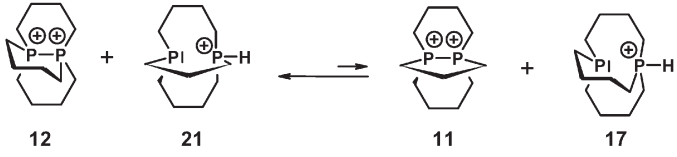
Treatment of **10**$(TfO)_2$ with less than one equivalent of KBH_4 in wet CH_3CN leads to the formation of *out*,*out*-diprotonated product **28** [21]. Both phosphorus atoms have inverted reflecting the higher stability of *out*,*out*-structures in such [4.3.3] systems. Reaction of **28** with one equivalent of base gives the *in*,*out*-monoprotonated salt **29**(TfO) which also shows a strong P–P coupling. Further deprotonation of **29** affords the *out*,*out*-diphosphane **30** which can also be obtained in one step from **28** with two equivalents of KOMe. Compounds **21** and **29** have remarkably low acidities. Their deprotonation by strong bases is combined with an inversion at the non-protonated phosphorus atom to give **25** and **30**, respectively.

Addition of an excess of trifluoroacetic acid to *out*,*out*-diphosphane **30** leads back to *out*,*out*-diphosphonium salt **28**. *Out*,*out*-intermediate **31** was

only monitored by ^{31}P NMR in the reaction of **28** with DABCO which finally leads to **29**. If the assumption is right that **31** is passed through, the inversion barrier for the phosphorus atom was established to be 70 kJ/mol at –55 °C, which is less than half of the typical value for trialkyl phosphanes. Adding other nucleophiles such as F^- (from tetrabutylammonium difluoro(triphenyl)silicate) or hydroxide to **10** led to the corresponding *in,out*-species without any evidence for the initial formation of *out,out*-products.

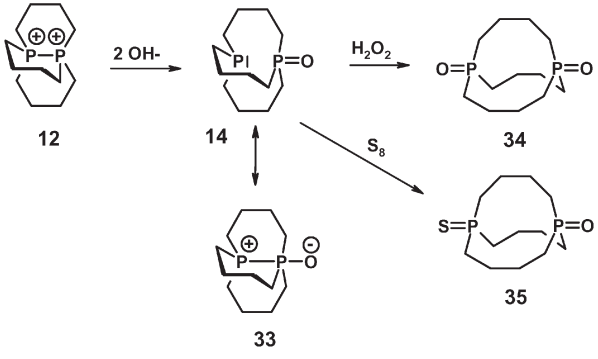
The unusual effect in the reaction of **10** with hydride is the inversion of the configuration at the leaving group namely the second phosphorus atom which has not been observed before[21].

The attempt to protonate **21** and **29** a second time with trifluoroacetic acid, presumably to obtain *out,out*-diprotonated species **32** and **28**, led to the parent propellane dications **11** and **10**, respectively, accompanied by the formation of hydrogen gas. In these cases, the P–H is acting as hydride source showing an unusual umpolung behavior. The attempt to transfer the hydride to benzaldehyde failed. However, hydride transfer between different ring systems was observed (Scheme 10)[20].



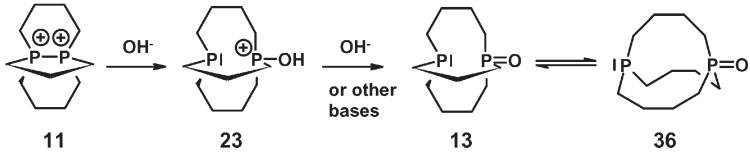
SCHEME 10

Treatment of the dications **12**, **11** and **10** with hydroxide leads to different results. Addition of two equivalents of hydroxide to [4.4.4.0] dication **12** affords the neutral *in,out*-monoxide **14** which is in resonance with the corresponding phosphonium-phosphorane structure **33** (Scheme 11)[20].



SCHEME 11

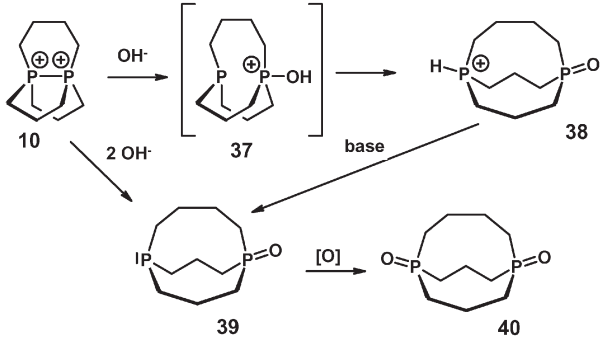
In contrast reaction of [4.4.3.0] dication **11** with one equivalent of OH^- furnished the stable *in*,*out*-adduct **23**$(TfO)_2$ for which the structure could be established by X-ray analysis (Scheme 12)[20].



SCHEME 12

Further treatment of **23** with OH^- or other bases gives the *in*,*out*-monophosphane oxide **13**. This species is in equilibrium with the corresponding *out*,*out*-compound **36**. The ratio between the two isomers depended on the amount of water present in the solution. Higher amounts of water favored the *in*,*out*-isomer **13** over the *out*,*out*-isomer **36**. This implies a much reduced barrier to inversion at the P(III) centre which was estimated[20] between 60 and 90 kJ/mol.

Addition of hydroxide to [4.3.3.0] dication **10** initially leads to *in*,*out*-**37**, however, after one hour the *out*,*out*-species **38** is formed (Scheme 13)[20].

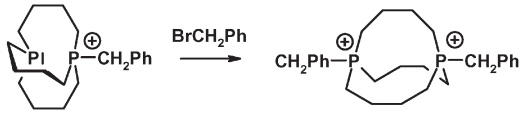


SCHEME 13

The preference for the *out*,*out*-geometry in this [4.3.3] system is also reflected in the direct preparation of *out*,*out*-monoxide **39** by reaction of [4.3.3] dication **10** with two equivalents of hydroxide. This compound can be further oxidized to the corresponding *out*,*out*-dioxide **40** [20].

Reactions from *in*,*out*-compounds to *out*,*out*-products can also proceed by slow inversion at the phosphorus atom and trapping of the P(III) centre in a temporary *out*-position with an electrophile.

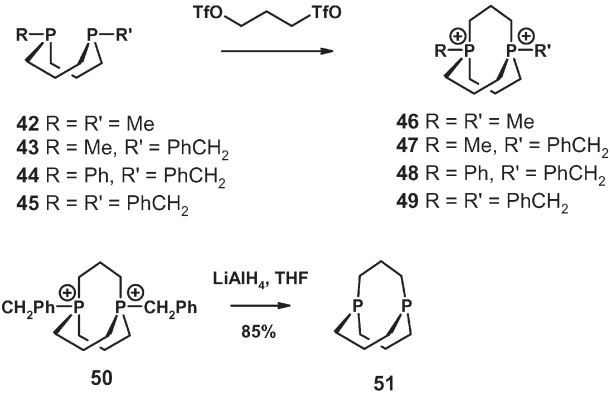
This is true for the formation of *out*,*out*-dibenzyl cation **41** from *in*,*out*-monobenzyl adduct **20** (Scheme 14)[17].



SCHEME 14

The authors also found that *in,out*-[4.4.4] monoxide **14** can be converted to *out,out*-dioxide **34** and *out,out*-oxide sulfide **35** via the same process (Scheme 11). They estimated the inversion barrier in **14** to be ≤110 kJ/mol at 80 °C [20]. Even lower was the barrier for the inversion of *out,out*-**31** to *in,out*-**29** (Scheme 9) with only 70 kJ/mol [17]. These values are considerably lower than for normal trialkylphosphane probably due to a flattening at the phosphorus atom in such bridgehead compounds.

The [3.3.3]diphosphane **51** (Scheme 15) could not be synthesized via alkylation of diphosphabicyclo[3.3.0]octane with the corresponding ditriflate and further hydride addition to the 1,5-diphosphoniatricyclo-[3.3.3.0^{1,4}]undecane bis(trifluoromethanesulfonate) **9**$(TfO)_2$ as described accordingly in Scheme 9 for the [4.4.4], [4.4.3] and [4.3.3] systems. This was due to the instability of compound **9**$(TfO)_2$ [17].



42 R = R' = Me
43 R = Me, R' = $PhCH_2$
44 R = Ph, R' = $PhCH_2$
45 R = R' = $PhCH_2$

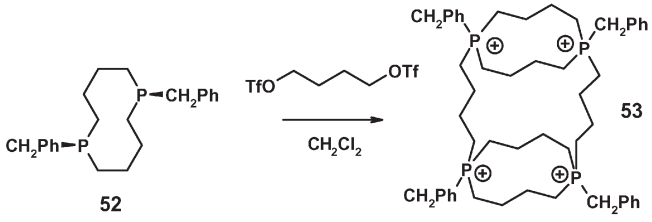
46 R = R' = Me
47 R = Me, R' = $PhCH_2$
48 R = Ph, R' = $PhCH_2$
49 R = R' = $PhCH_2$

SCHEME 15

Therefore a direct ring-closure route to 1,5-diphosphabicyclo[3.3.3]undecane was introduced. A number of diphosphacyclooctanes with different exocyclic rests were treated with $CH_2(CH_2TfO)_2$ to obtain the corresponding *out,out*-diphosphonium salts (Scheme 15)[17]. Of special interest is compound **49** with two benzyl residues which could be removed by reduction with $LiAlH_4$ to afford the [3.3.3]diphosphane **51** which adapts the *out,out*-

conformation as was proved by X-ray analysis[17]. This compound was already reported earlier by Norman et al.[22] by AIBN initiated reaction of allylphosphane. However, this structure was later corrected to be 1,5-diphosphabicyclo[3.3.0]octane.

This route, however, did not work for larger rings. In the reaction of the ten-membered ring diphosphane, *cis*-1,6-dibenzyl-1,6-diphosphacyclodecane (**52**), with $CH_2(CH_2TfO)_2$ the expected 1,6-dibenzyl-1,6-diphosphoniabicyclo[4.4.4]undecane ditriflate is not obtained. The major product was the cylindrical macrotricyclic product **53** (Scheme 16)[17]. This compound could give rise to interesting macrotricyclic phosphanes with a potentially complicated *in*,*out*-pattern.



SCHEME 16

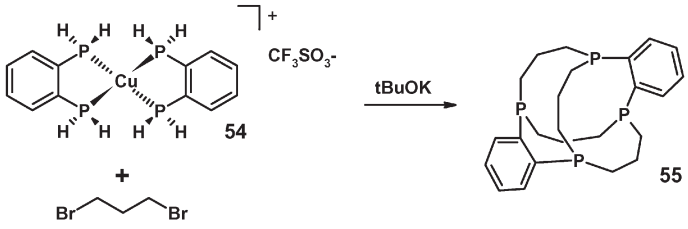
The basicities of the bicyclic phosphane compounds were found to be in the order: [3.3.3] system **51** (for the protonated ion pK_a ≈ 17.9) < [4.3.3] compound **30** (pK_a ≈ 22.5) < [4.4.3] bicycle **25** (pK_a ≈ 27.8)[23]. That means **51** is comparable with the most basic simple phosphane (*t*-Bu)$_3$P (pK_a ≈ 17.0). The latter matches the value for Schwesinger's P$_1$-*t*-Bu but is still significantly weaker than Verkade's pro-(aza)phosphatranes (**XIV**, Scheme 6). The strong basicity of **30** and **25** being associated with an *in*,*out*-protonated ion might be attributed to several factors such as strain relief on protonation, altered hybridization on P(H) and transannular P–P interaction.

Until now no synthetic application has been reported for such bridgehead diphosphane bases in contrast to the variety of application for Verkade's (aza)phosphatranes[15,16].

3.3. A Medium Size Tricyclic Phosphorus Compound

The tetrahedral cage **55** was synthesized in a reaction of complex **54** with 1,3-dibromopropane (Scheme 17)[24].

The appearance of four bridgehead atoms increases the number of theoretical possible *in*,*out*-isomers in this symmetric case with the same exocyclic substituent (lone pair) at each phosphorus bridgehead atom up to



SCHEME 17

six. However, products with more than one *in*-position seem to be very unlikely in this relatively small system and even this one might be considerably strained. The authors did not report on structural details. It can be presumed that the all-*out*-product was obtained[24].

4. MACROBI- AND POLYCYCLIC SYSTEMS WITH PHOSPHORUS BRIDGEHEAD ATOMS

Phosphorus containing cryptands are attractive molecules with potential applications in supramolecular and synthetic organic chemistry. Even though compared to their aza analogues much less work has been done on them, their chemistry has already been reviewed by Majoral and Caminade[25] and concerning their application as ionophores by Talanova[26].

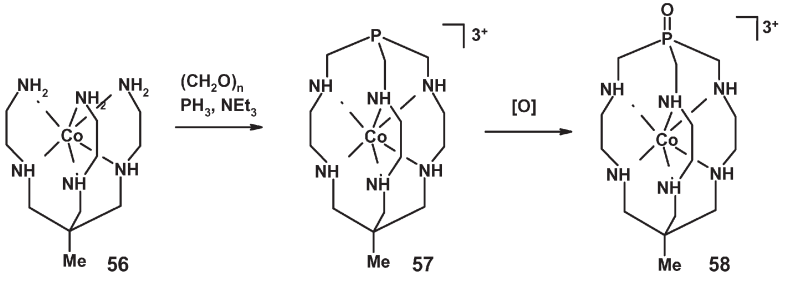
The emphasis of this section of the present paper is put on macrobicyclic compounds with phosphorus bridgehead atoms. Their total number is still not very high. The review by Majoral and Caminade[25] from the year 1994 counts about ten references on phosphorus cryptands which are also included in the present paper. During the last ten years this number has increased but not tremendously.

Phosphorus macrobicycles with configurationally stable tetrahedral phosphorus bridgehead atoms are predestinated to show *in,out*-isomerism with respect to their exocyclic rests. The larger and the more flexible the bicyclic structures are, the smaller are the energy differences for *in*- and *out*-isomers. Therefore the probability to obtain *in*-configured bicyclic compounds with larger groups in the *in*-position increases with increasing length and flexibility of the bridges.

4.1. Monophosphabicyclo[6.6.6] and [8.8.8] Systems

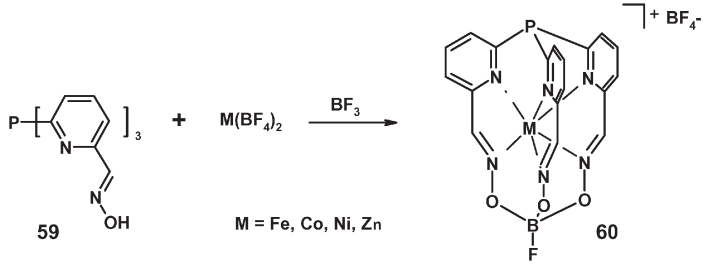
Using a template effect the cobalt complex of the amino podand **56** was cyclized in a Mannich type reaction with paraformaldehyde, phosphane and triethylamine to give the macrobicyclic phosphane complex **57**

(Scheme 18). Oxidation of the complex during work up afforded the phosphane oxide cryptate **58** [27]. The structure was proved by X-ray crystallography. It shows both the P=O residue and the exocyclic methyl group in an *out*-position. Otherwise it would have to displace the complexed metal ion inside the cavity. Hence the template also determines the *in*,*out*-selectivity of the reaction.



SCHEME 18

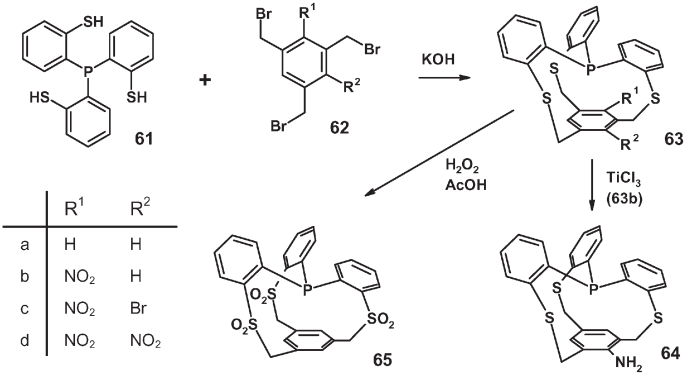
The first phosphorus cryptand reported dates back to 1970 [28]. In a template reaction tris(pyridyl)phosphane **59** was reacted with boron trifuoride in the presence of a metal tetrafluoroborate leading to a number of cryptates **60** (Scheme 19). The X-ray structure of the nickel complex has been presented showing both the phosphorus and the boron in an *out*-position[29].



SCHEME 19

4.2. Monophosphabicyclo[10.10.8], [11.11.9] and [12.12.10] Systems

Various phosphabicycles with only one bridgehead atom have been reported by Pascal et al. Their phosphacylophanes **63**–**65** with *ortho*-phenylene bridges all adapt an *in*-geometry as was shown by the X-ray structures of compounds **63a** [30,31], **63d** [32] and **64** [32] (Scheme 20). These phosphorus bridgehead bicyclic compounds are prepared by a *tripod–tripod coupling* method[33] starting from the phosphanetrithiol **61** and tribromomesitylene **62** under addition of KOH using high dilution conditions.

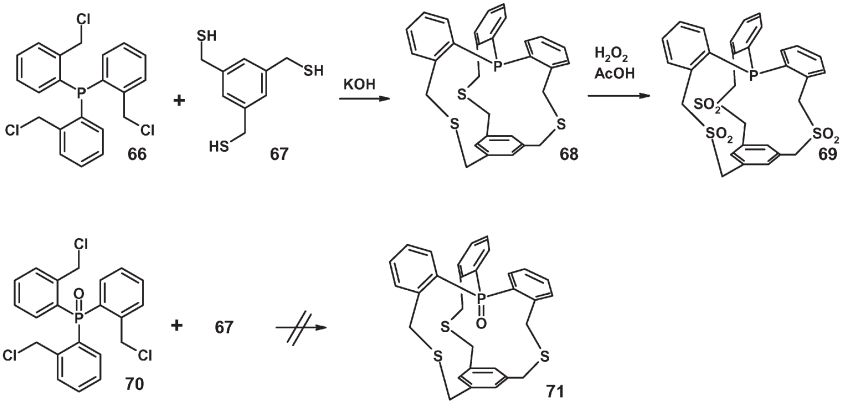


	R^1	R^2
a	H	H
b	NO_2	H
c	NO_2	Br
d	NO_2	NO_2

SCHEME 20

The phosphorus in **63a** is extraordinarily unreactive due to the poor availability of the *in*-lone pair. Even the treatment with hydrogen peroxide in refluxing acetic acid did not lead to the oxidation of the phosphorus but only of the sulfide moieties to give the corresponding trisulfone **65**. The phosphorus in aminophosphacyclophane **64**, which was obtained upon treatment of nitro compound **63b** with $TiCl_3$, was also proved to be inert against treatment with HBr.

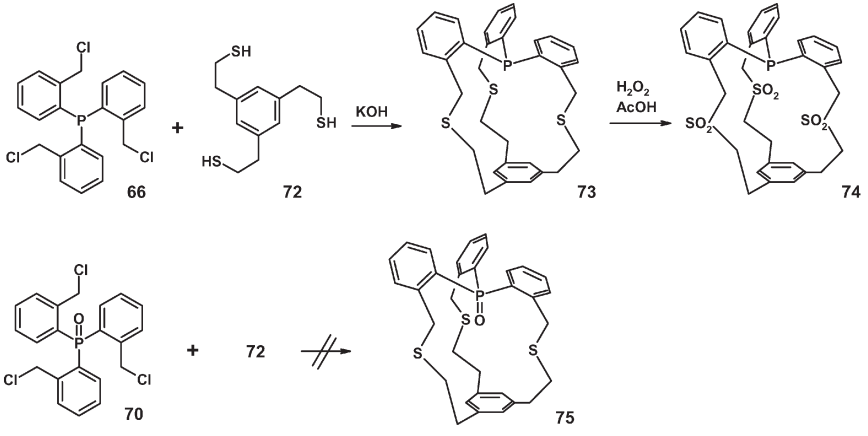
The reaction of tris[2-(chloromethyl)phenyl]phosphane (**66**) with 1,3,5-tris(sulfanylmethyl)benzene **67** gave the *in*-phosphane **68** in 59% yield. This compound was chosen to enlarge the cavity in order to provide more space for the accommodation of a larger *in*-function such as an phosphoryl oxygen. However, the oxidation of **68** with hydrogen peroxide in acetic acid afforded again only the corresponding sulfone **69** and left the phosphorus untouched (Scheme 21)[34].



SCHEME 21

AM1 calculations comparing the formation of *in*-products over *out*-isomers showed that phosphane oxide **71** has the strongest preference for an *in*-configuration of all cyclophanes investigated by Pascal et al.[35] The direct cyclization of tris[2-(chloromethyl)phenyl]phosphane oxide (**70**) with **67** to form *in*-phosphacyclophane **71** was unsuccessful (Scheme 21) as well as the reaction of **70** with various tripodal nucleophiles to get related *in*-phanes. Instead the authors were able to obtain a corresponding *in*-fluorosilaphane which are together with Vögtle's[36,37] *in*-methyl group the largest *in*-substituents reported.

Elongation of the spacer for another CH_2 group gave the same result. Even though the *in*-phosphane **73** was formed in 51% yield, subsequent oxidation resulted only in the oxidation of the sulfur atoms to the corresponding sulfone **74** whereas the phosphorus was inert (Scheme 22)[35]. Compound **73** was also characterized by X-ray analysis and revealed that the distances between the phosphorus atom and the basal aromatic ring is 5.402 Å, which is more than enough to accommodate an oxygen atom in between.

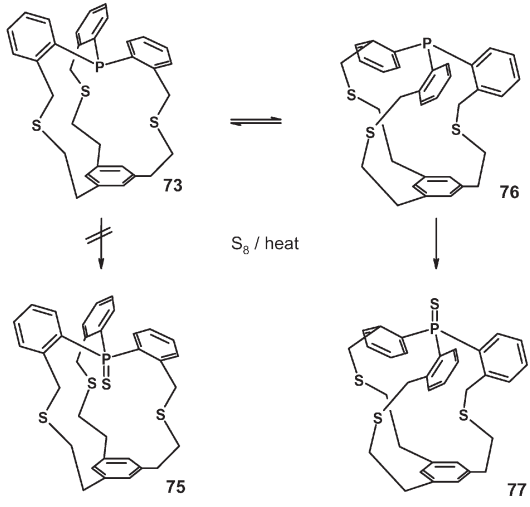


SCHEME 22

The direct synthesis of **75** from phosphane oxide **70** with the tripodal reagent **72** was also unsuccessful. The same was true for a synthetic way in which nucleophilic and electrophilic groups were reversed. So the authors stopped trying to place the phosphoryl oxygen in an *in*-position in this specific type of cyclophane at this point.

Heating of *in*-phosphane **73** to 200 °C for several days in order to surmount the inversion barrier of the phosphorus atom and to produce an *out*-isomer of **76** failed[38].

The activation Gibbs energy ($\Delta G^{\#}_{inv}$) for this inversion is expected to be about 113 kJ/mol for triarylphosphanes as extrapolated from data for trialkylphosphanes (ca. 151 kJ/mol)[39], dialkylarylphosphanes (ca. 138 kJ/mol)[39] and alkyldiarylphosphanes (ca. 126 kJ/mol)[39]. So the temperature applied should be high enough to cause such an inversion. Most likely the *out*-isomer is not stable enough and the equilibrium lies strongly on the side of the *in*-isomer. Treatment of the *in*-isomer **73** with sulfur in CS_2 at 185 °C in a sealed tube afforded the corresponding *out*-phosphane sulfide **77** demonstrating that the *in*-phosphane inverts and can be trapped in the *out*-position with sulfur. No *in*-phosphane sulfide could be obtained (Scheme 23).



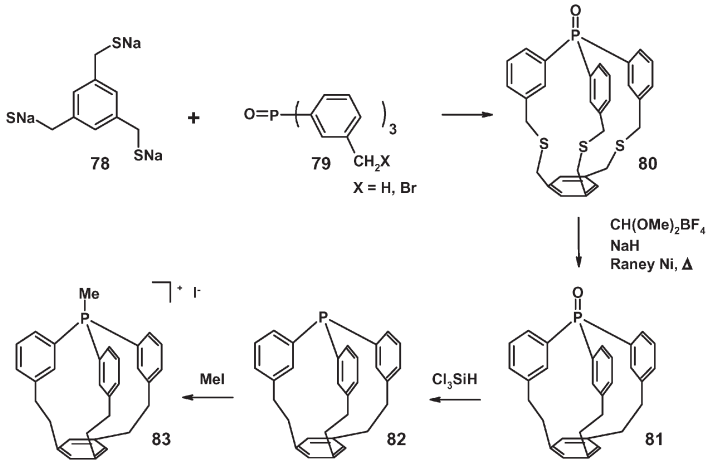
SCHEME 23

$\Delta G^{\#}_{inv}$ for the inversion of **73** to **76** was estimated to be 146 kJ/mol. This process corresponds to the reaction of *in,out*-monobenzyl cation **20** with benzyl bromide to give *out,out*-dibenzyl cation **41** (Scheme 14) or to the oxidation of *in,out*-monophosphane oxide **14** to *out,out*-dioxide **34** and *out,out*-oxide sulfide **35**, respectively, reported by Alder (Scheme 11)[20].

Attempts to synthesize the *out*-phosphane **76** by mild desulfurization of *out*-phosphane sulfide **77** with hexachlorodisilane at room temperature furnished the *in*-phosphane **73** quantitatively. This demonstrates that the difference in energy between **73** and **76** must be substantially greater than 42 kJ/mol to lower the activation energy for the reverse reaction significantly below 105 kJ/mol so that this process proceeds at room temperature

already. It was estimated by the authors to be 67 kJ/mol by a combination of experimental and computational methods.

Phosphabicycles with one bridgehead atom but with *meta*-phenylene bridges have been reported by Sharpless et al. (Scheme 24)[40]. In this case *out*-geometry was obtained at the phosphorus bridgehead exclusively.



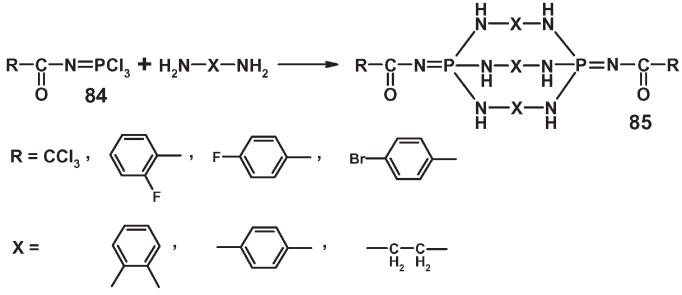
SCHEME 24

Sodium trithiolate **78** was reacted with *meta*-substituted phosphane oxide **79** in the sense of a *tripod–tripod coupling* reaction[33] to furnish the bicyclic phosphane oxide **80** in 17% yield. Reaction with $^{+}CH(OMe)_2BF_4^{-}$ provided a trisulfonium salt which by treatment with sodium hydride in THF underwent a Stevens rearrangement to give the corresponding tris(sulfide) which was subsequently desulfurized with Raney nickel. Reduction of the obtained *out*-phosphane oxide **81** with Cl_3SiH afforded the *out*-cage compound **82** which underwent fast racemization in terms of the helical chirality of the *meta*-phenylene units[40]. *Out*-phosphacyclophane **82** reacts straightforwardly with methyl iodide to form the *out*-phosphonium salt **83**. The ease of this reaction suggests the *out*-position of the lone pair at the phosphorus atom in **82**. Moreover, a complex can be easily formed from *out*-phosphacyclophane **82** with $PdCl_2(PhCN)$ which would not be possible in the case of an *in*-position of the lone pair[40].

It is worth noting that the description of conformers by the *in* and *out* system and a graduation of the "*in*-ness" and *out*-ness" of exocyclic substituents using angle θ (Scheme 1) is tricky in this case as there is no reference point in the form of the second tetrahedral bridgehead atom.

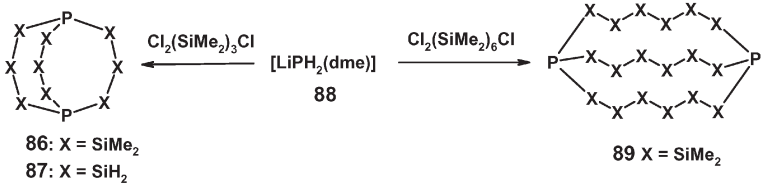
4.3. Diphosphabicyclo[6.6.6] and [8.8.8] Systems Together with Smaller Analogues

Reaction of the trichloro derivative **84** with a number of diamines gave phosphorus cryptands **85** in 68–73% yield (Scheme 25)[41]. Due to the relatively small ring size and the voluminous exocyclic substituent these cryptands have to adapt an *out,out*-arrangement.



SCHEME 25

The diphosphanonasilabicyclo[3.3.3]undecanes **86** and **87** and the diphosphaoctadecasilabicyclo[6.6.6]eicosane **89** reported by Gleiter et al. presumably adapt *out,out*-geometries according to the simple NMR spectra obtained for the isolated product (Scheme 26)[42].

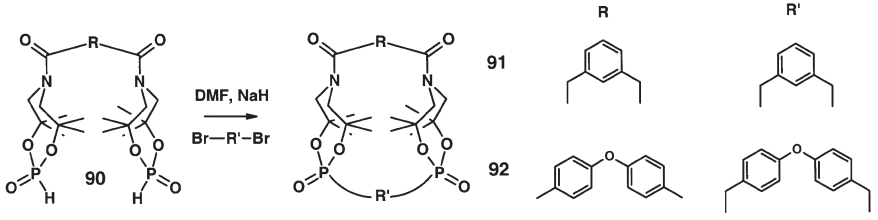


SCHEME 26

In particular the ^{31}P NMR spectrum shows one singlet each for the two compounds. This suggests that the phosphorus atoms must have the same geometry at both bridgehead positions. Compounds **86** and **87** relate to Alder's [3.3.3]diphosphane **51** which also exhibited an *out,out*-geometry. The larger [6.6.6] product **89** presumably has the chance to adapt an *in,out*- or even *in,in*-geometry alternatively. The former can be ruled out on the basis of the simple NMR spectrum obtained which does not reflect the lower symmetry of the diastereomeric *in,out*-isomer.

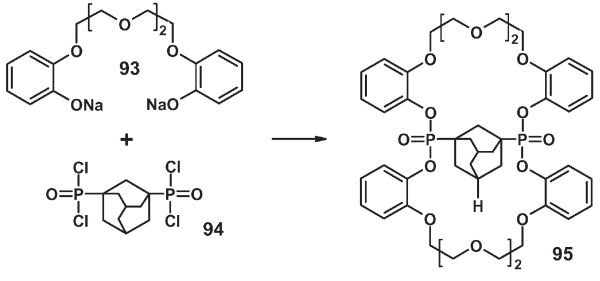
4.4. Higher Macrobicyclic Compounds

Macrobicycles **91** and **92** have been obtained by reaction of phosphonate podands with a dibromide by a Michaelis–Becker reaction (Scheme 27)[43]. The formation of Ca^{2+} and Mg^{2+} complexes with **91** and **92** has been investigated. Liquid–liquid extraction studies showed efficient extracting properties and good selectivities of Ca^{2+} over Mg^{2+}. The authors did not report on the geometry at the phosphorus bridgehead atoms. Most likely they adapt an *out*,*out*-geometry.



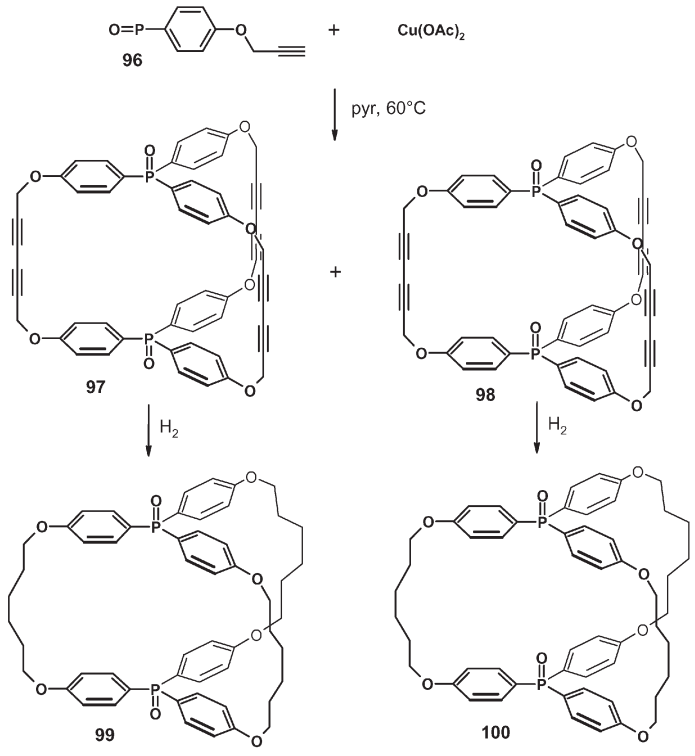
SCHEME 27

Cryptand **95** is obtained in 31% yield together with a dimacrocyclic compound in the reaction of a diphenoxy sodium salt **93** with adamantane-1,3-bis(phosphonoyl dichloride) **94** (Scheme 28)[44,45]. Even though this cryptand contains one very rigid adamantyl bridge, the flexibility and length of the two crown ether moieties seem to enable formation of *in*-isomers in this system which were, however, not reported by the authors.



SCHEME 28

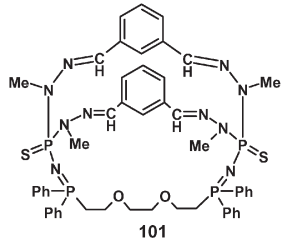
Large macrobicyclic phosphorus compounds have become available by copper(II) induced *tripod–tripod coupling*[33] of propargylphosphane oxide **96** (Scheme 29)[46,47]. The *out*,*out*-product **97** was obtained in 14% yield whereas the *in*,*out*-isomer **98** could be isolated in 7% yield.



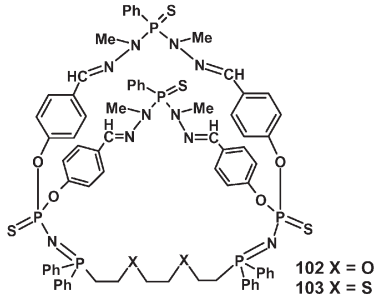
SCHEME 29

Hydrogenation of the triple bonds affords the corresponding isomeric alkylene bridged cryptands **99** and **100**, respectively. All four cage compounds were investigated in terms of their complexing abilities towards neutral guests. The *in,out*-alkylene cryptand **100** complexes initially via its *out*-P=O group while *in,out*-alkadiyne cryptand **98** preferably forms complexes via its *in*-P=O group. The reason can be due to changes in the host cavity. However the X-ray structure gives similar P–P distances for compounds **98** and **100**, 5.68 and 6.15 Å, respectively. That also means that no P–P interaction can be observed in such large macrocyclic compounds.

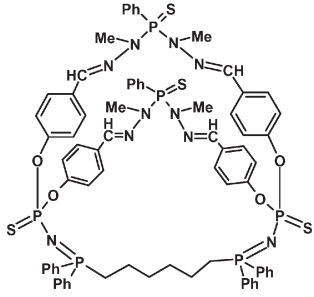
Majoral et al. reported on the reaction of bis(phosphanes) with macrocyclic phosphoryl azides under mild conditions (THF, room temperature) to afford five phosphorus containing cryptands (**101**–**105**) in remarkable high yield (78–86%) without high dilution (Scheme 30)[7,48]. These cryptands proved to be very stable against hydrolysis. No hydrolytic decomposition was observed after treatment with an 2:1 THF/water solution for 24 h.



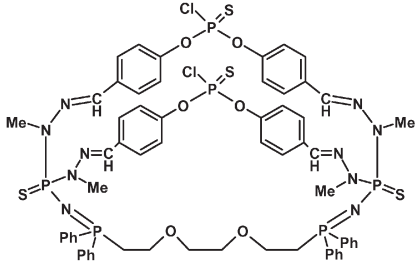
101



102 X = O
103 X = S



104

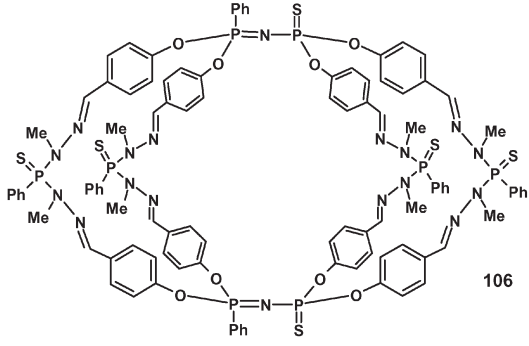


105

SCHEME 30

However, only *out*,*out*-isomers were obtained as can be concluded from the ^{31}P NMR spectra reported. They gave only one singlet and two doublets for each compound. In the case of an *in*,*out*-isomer the number of signals would be doubled. The *in*,*in*-isomer would also give only the mentioned set of signals but the probability of its formation in this not extremely large macrobicycles seems to be low.

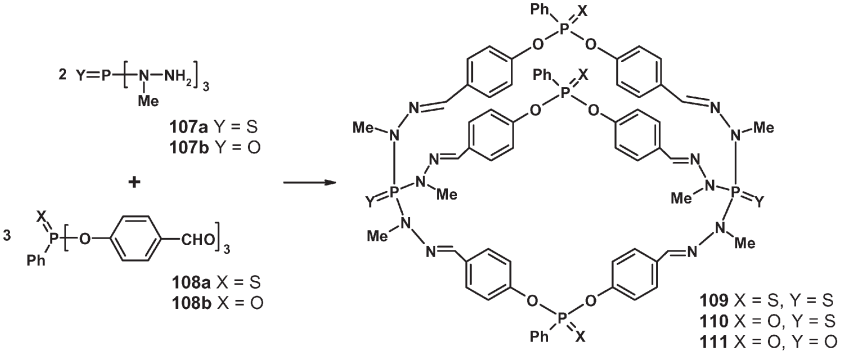
Additionally the authors were able to isolate the phosphorus spherand **106** by condensation of a macrocyclic diazide and a macrocyclic diphosphane. The ^{13}P NMR of this compound only shows one singlet and two doublets indicating the presence of the all-*out*-isomer **106** [7].



106

That means a single isomer has been isolated out of a variety of different isomers in terms of *cis,trans*-isomerism on the phosphorus atoms of the macrocyclic arms as well as of the *in,out*-isomerism on the four bridgehead positions. Theoretically up to nine *in,out*-isomers are possible in this case. A neighboring *in,in*-constellation, however, seems almost impossible to realize.

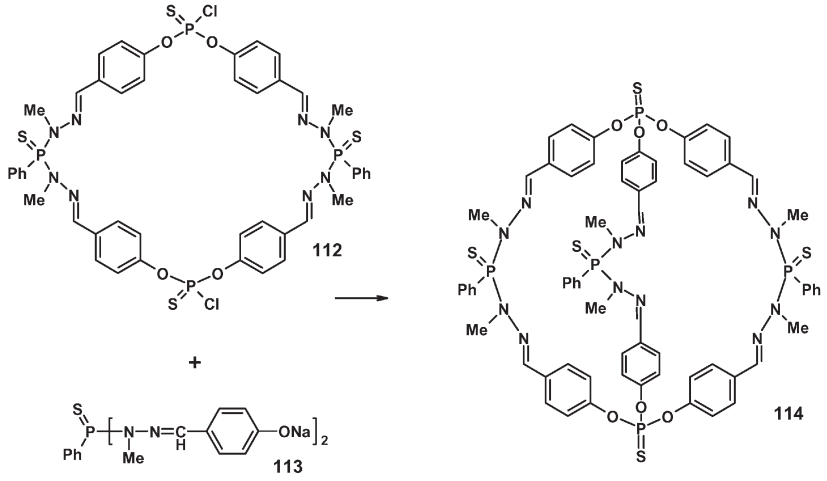
Moreover the same authors developed a method of the synthesis of symmetrical phosphorus cryptands. The reaction of a phosphorohydrazides **107** with phosphorus dialdehydes **108** in THF at room temperature in the presence of molecular sieve gave three different phosphorus cryptands **109**–**111** in a remarkable 50–60% yield (Scheme 31). Each derivative showed a set of ^{31}P signals consisting of two singlets thus indicating that presumably only one isomer was obtained. This reaction is a remarkable example of a *tripod-capping* reaction[33] assembling five components in one step to give a macrobicyclic product[7,49].



SCHEME 31

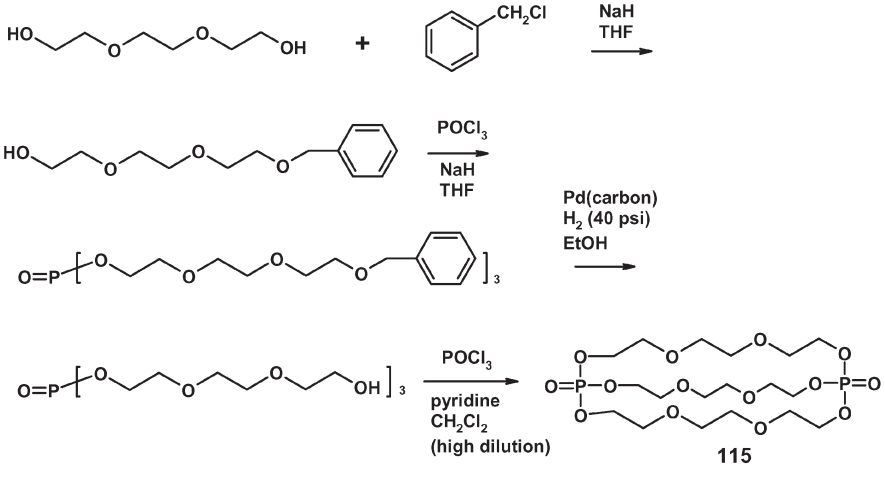
Another way to afford similar structures followed a stepwise procedure. Initially in a [2+2] macrocyclocondensation a simple macrocycle **112** was constructed bearing reactive groups at two phosphorus atoms. It could be bridged with the alcoholate **113** to give the symmetric macrobicycle **114** in 90% yield (Scheme 32)[7,49].

In this case also only one isomer was observed which is most likely the *out,out*-isomer **114**. *Out,out*- and *in,in*-isomers correspond to a *cis*-configuration of the starting macrocycle **112** in terms of the reactive positions, whereas *trans*-macrocycles can lead to the corresponding *in,out*-isomer only. This shows the diastereomeric relationship between the two pairs of conformers *in,in*/*out,out* and *in,out*/*out,in*[1].



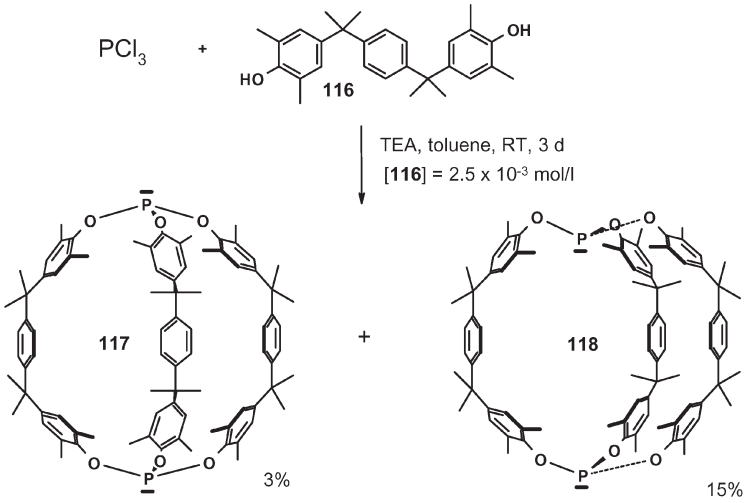
SCHEME 32

The synthesis of diphosphate cryptand **115** was reported via the reaction sequence shown in Scheme 33. The molecule is very flexible and *in*- and *out*-isomers might play a role in this system. However, the authors did not find any hints for *in*-positioned phosphoryl oxygen, which was in agreement with their MM2 calculations showing considerable strain in these conformations. The cryptand forms stable complexes with both K^+ and Rb^+. The p*K* values for phosphocryptand **115** are 1000-fold greater than those of comparably sized nitrogen bridgehead cryptands[50].



SCHEME 33

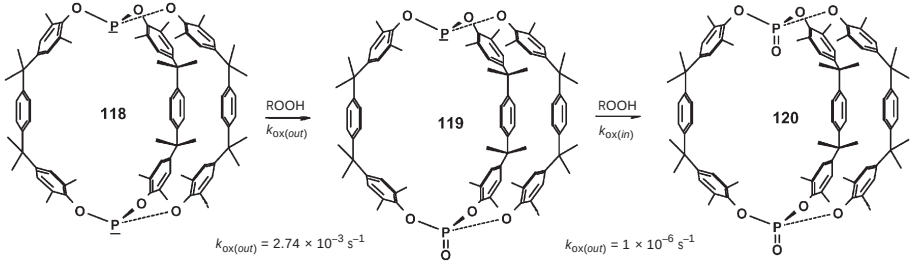
The *double-capping*[33] reaction of PCl_3 with trinuclear bisphenol **116** in toluene in the presence of triethylamine under moderate dilution conditions (2.5×10^{-3} mol/l) was reported by Bauer and Habicher[51]. This one-pot procedure afforded cryptands **117** and **118** in 3 and 15% yield, respectively, after chromatographic isolation (Scheme 34).



SCHEME 34

It is interesting to note that the ^{31}P NMR shifts for the *in*- and *out*-phosphorus in **118** are extremely different (δ 147.2 (*in*), 128.0 (*out*)). The chemical shift of the *in*-phosphorus belongs to the highest ^{31}P NMR shifts observed for phosphites whereas the shift for the *out*-phosphorus lies in the normal region for this type of compounds.

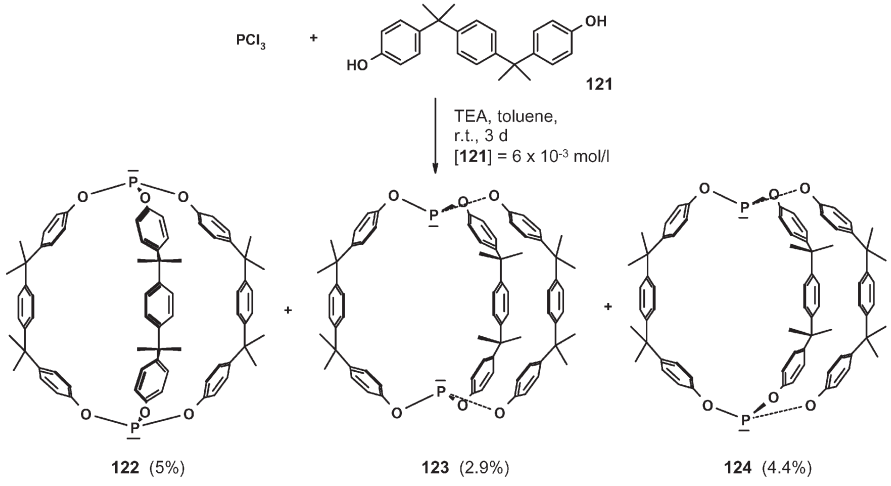
In,out-compound **118** was oxidized directly in the NMR tube with an excess of cumene hydroperoxide at room temperature (Scheme 35)[51]. It could be proved that the *in*-phosphorus in **118** is much less reactive (about 3000 times) than the *out*-phosphorus. The *out*-phosphorus was completely



SCHEME 35

oxidized within 25 min to give the ^{31}P NMR phosphate peak of compound **119**. In contrast, only half of the *in*-phosphorus is converted into the completely oxidized phosphate **120** after ten days. The isomer **117** is oxidized with the same rate as the *out*-phosphorus in **118** to give the corresponding *out*,*out*-cryptand.

The reaction of the non-hindered bisphenol **121** with PCl_3 in the presence of TEA in toluene at 25 °C under moderate dilution conditions affords all three possible homeomorphous isomers (*out*,*out*; *in*,*out*; *in*,*in*) in 2:2:1 (**122**, **124**, **123**) ratio with a crude total yield of 15% (Scheme 36)[52].

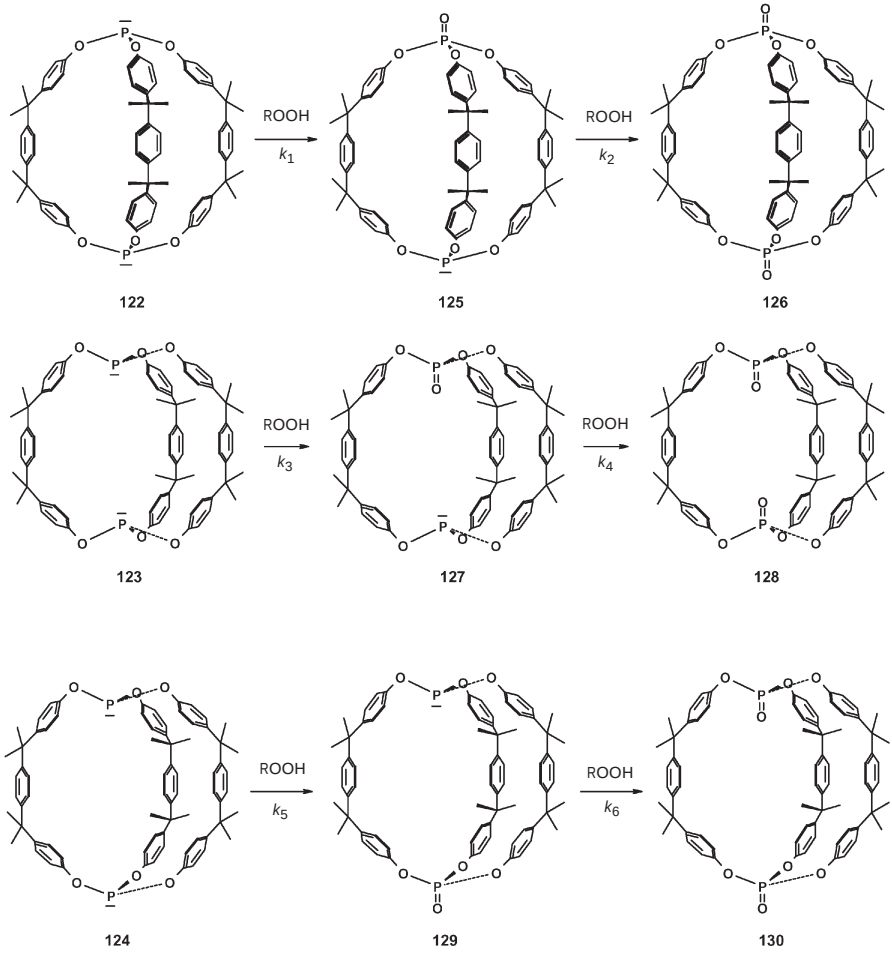


SCHEME 36

The three isomers **122**, **123** and **124** could be isolated by column chromatography and suitable crystals for X-ray analysis could be grown for *out*,*out*-isomer **122** and *in*,*in*-isomer **123**. The X-ray structures obtained clearly confirm the *out*,*out*- and the *in*,*out*-geometry at the phosphorus bridgeheads. Both isomers enclose solvent molecules such as methylene chloride and toluene in their cavity. The distance between the phosphorus bridgehead atoms in **122** reaches with 10.5 Å already into the nanometer range. The crystal structure of the *in*,*in*-isomer **123** showed two independent conformers of the molecule. The P–P distances in the two conformers of *in*,*in*-isomer **123** are with 8.5 and 8.3 Å almost the same but as expected markedly shorter than in *out*,*out*-isomer **122** (10.5 Å).

The chemical shifts of the *in*- and *out*-P atoms in ^{31}P NMR (**122**: δ 121.6 (*out*); **123**: δ 142.7 (*in*); **124**: δ 143.1 (*in*), 121.6 (*out*)) are rather different despite of their equal chemical environment as already observed for **117** and **118**, respectively.

Addition of an excess of cumene hydroperoxide to the solution of a mixture of **122**, **123** and **124** in $CDCl_3$ directly in the NMR tube leads to a rapid decrease in the *out*-phosphite peaks in favor of the corresponding *out*-phosphate peaks[52]. The *in*-P atoms are again much more slowly oxidized (Scheme 37). However the difference is less pronounced than for compound **118**.



SCHEME 37

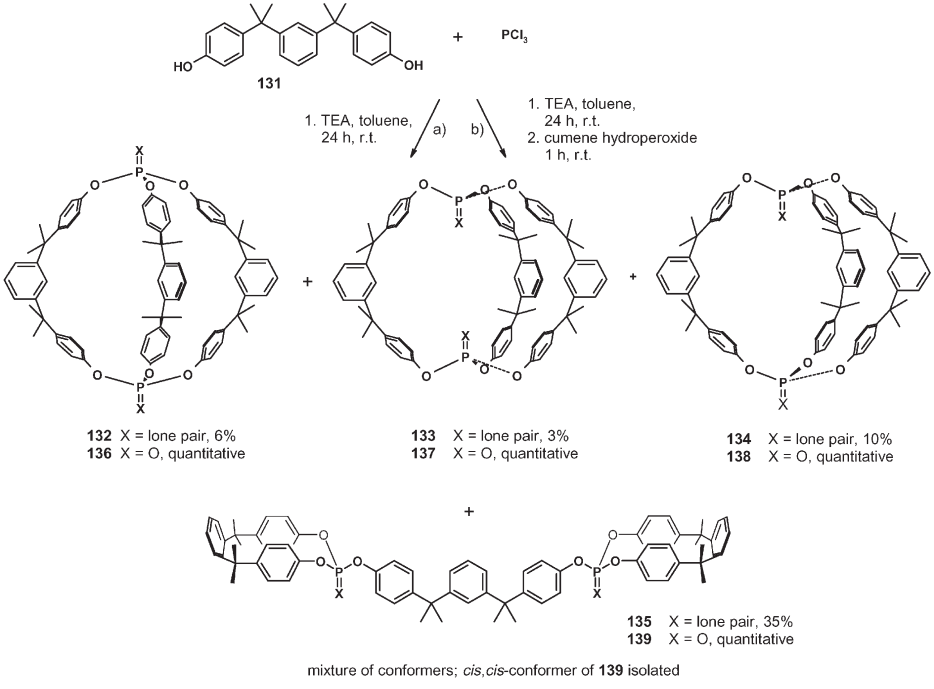
In,in-isomer **123** is most slowly oxidized. After the oxidation of the first P atom (k_3) giving intermediate **127**, further oxidation (k_4) is even slower due to the hindrance of the bulkier phosphate group pointing inwards (Scheme 37, Table I).

The reaction of **124** with cumene hydroperoxide leads to a fast oxidation of the *out*-phosphorus to give intermediate **129**, followed by a much slower oxidation of the *in*-position to afford *in*,*out*-phosphate **130** (Scheme 37, Table I, $k_5 >> k_6$). The difference of the rate constants is about one order of magnitude.

TABLE I
Rate constants (k_{ox}, s^{-1}) of the oxidation of cryptands **122**, **123** and **124**

	k_1 (*out*)	k_2 (*out*)	k_3 (*in*)	k_4 (*in*)	k_5 (*out*)	k_6 (*in*)
k_{ox}, s^{-1} (298 K)	13.7×10^{-3}	7.5×10^{-3}	15×10^{-4}	3×10^{-4}	9.0×10^{-3}	8×10^{-4}

Bauer and Habicher also reported on a *double-capping* synthesis of phosphorus macrobicycles starting from the trinuclear 1,3-phenylene bisphenol **131** and PCl_3 (Scheme 38, path a)[53].



SCHEME 38

The product mixture contains the three homeomorphic phosphorus cryptands **132**–**134** with crude yields of about 6 (**132**), 3 (**133**) and 10% (**134**), respectively, and compound **135** as the main product with a crude

yield of about 35% according to ^{31}P NMR. The yields of the macrobicycles **132**–**134** turned out to be in the same range as those for macrobicycles **122**–**124** from the reaction of the corresponding 1,4-phenylene diphenol **121** with PCl_3.

The homeomorphic macrobicycles **132** and **133** and compound **135** could be isolated by column chromatography on silica gel and were characterized by NMR spectroscopy, MALDI-TOF MS, and **132** and **133** also by X-ray analysis.

In,in-isomer **133** crystallizes in two different conformers as was also observed for the corresponding 1,4-phenylene-*in,in*-cryptand **123**. Both homeomorphic isomers **132** and **133** are very crumpled molecules and contain almost no space in their cavity due to the close distance of the opposite parts of the molecules. For this reason, no solvent molecules are complexed inside the cavity but only outside the macrobicycles.

The P–P distance varies from 4.47 to 5.33 Å for the two different *in,in*-conformers (**133**), whereas *out,out*-isomer **132** has a P–P distance of 4.94 Å which is surprisingly not longer than those of the *in,in*-isomers. This is caused by a distinct distortion from an ideal *out*-geometry as expressed by the "*out*-ness" of the bridgehead atom by means of angle θ. The values for θ in *out,out*-isomer **132** are 92.1 and 103.3° at the two bridgehead positions. That means that the lone pairs are almost perpendicularly positioned to the P–P-axis.

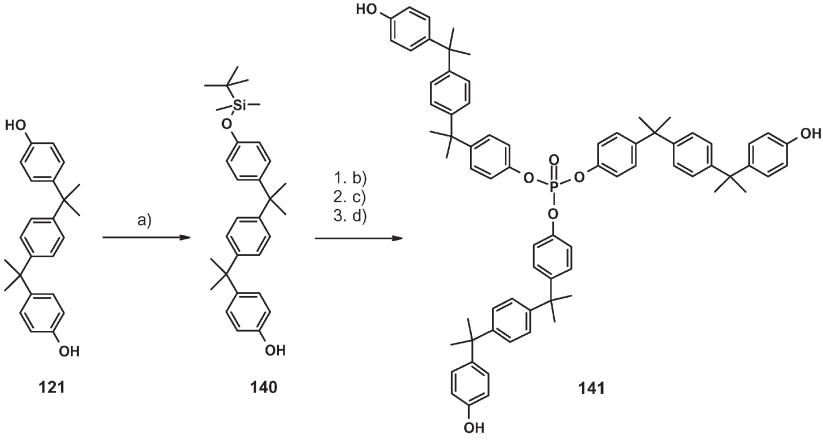
In the case of the *in,in*-isomer **133** an averaged $\bar{\theta}$ = 52.6° over all four bridgehead positions of the two conformers was observed showing also a pronounced deviation from an ideal *in*-position which would have θ = 0°. In comparison to the 1,4-phenylene macrobicycles **122**–**124**, cage compounds **132**–**134** are hydrolytically less stable. So they were found to be completely hydrolyzed in $CDCl_3$, standard NMR solvent, after several days.

In order to improve the hydrolytic behavior for structural investigation the *double-capping* reaction of **131** and PCl_3 was carried out with subsequent immediate oxidation of the mixture with an excess of cumene hydroperoxide. After 1 h the oxidation was complete. The corresponding homeomorphic macrobicyclic phosphates **136** and **137** could be separated as well as compound **139** as the main product (Scheme 38, path b)[53]. The oxidation reaction of all phosphorus moieties including the *in*-phosphorus atom positions of the reaction mixture with cumene hydroperoxide proceeded relatively fast. This result is rather surprising as no such fast oxidation for *in*-positions was obtained earlier with macrobicycles **123** and **124**. The reason for this rapid oxidation of normally less available *in*-positions is the distinct distortion from the ideal *in*-geometry. Even though these values are

true only for the solid state they might give a hint that also in solution the most preferred conformations might have lone pairs at the phosphorus bridgeheads that point more or less out of the cavity which increases their reactivity towards oxidizing agents.

In the ^{31}P NMR spectrum, the homeomorphic phosphite macrobicyles **132**–**134** show the characteristic pattern as was similarly observed for compounds **122**–**124**. All *in*-phosphorus atoms give downfield shifted signals compared to the normal values at around 128 ppm. *In*,*in*-phosphite **133** gives a ^{31}P NMR peak at 133.0 ppm, the *in*-P atom in the *in*,*out*-phosphite **134** at 131.2 ppm. *Out*-P atoms are upfield shifted to 123.3 ppm in *out*,*out*-phosphite **132** and 124.6 ppm in *in*,*out*-phosphite **134**. ^{1}H and ^{13}C NMR measurements for both *out*,*out*-phosphite **132** and *in*,*in*-phosphite **133** reflect the C_{3v} symmetry of these molecules in solution.

As an alternative to the one-step synthesis (*tripod-capping* method) of such cryptands, we also developed a stepwise route[52]. Initially the bisphenol **121** was monoprotected with TBDMSCl using a 1:1 ratio of the educts to give compound **140** (Scheme 39).



a) TBDMSCl, imidazole, CH_2Cl_2, r.t., 24 h; b) PCl_3, TEA, toluene, r.t., 15 h; c) cumene hydroperoxide, toluene, r.t., 2 h; d) TBAF, AcOH, r.t., 24 h

SCHEME 39

In the second step, **140** is treated with PCl_3. In contrast to the TMS protecting group, which is readily split by treatment with PCl_3 to form phosphorous esters, the TBDMS protecting group is inert to PCl_3. The phosphite formed from the reaction of PCl_3 with the unprotected OH group is immediately oxidized with cumene hydroperoxide to afford the corresponding TBDMS protected phosphate. This compound can be deprotected using TBAF in acetic acid to give tripodal phosphate **141**.

PCl3, TEA, toluene,
r.t., 2 d
8%
146
141
PCl3, TEA, toluene,
r.t., 2 d
12%
142
143
144
145

SCHEME 40

Phosphate **141** can be cyclized with PCl_3 to form P-bridged cage compounds (Scheme 40). All four possible *in*,*out*-isomers (**142**–**145**) could be detected in the crude product by ^{31}P NMR spectroscopy. Compounds **142** and **143** are the main components. **144** and **145** could be observed as traces only. After chromatography, a mixture of **142** and **143** was isolated.

Interestingly, a second fraction could be obtained which gives a single MALDI-TOF mass peak at *m/z* 2226. It was tentatively assigned to an isomeric mixture of the cylindrical macrotricycle **146**. The analogous pyramidal product having the same molecular weight cannot be formed due to the pre-set structure of educt **141**.

5. CONCLUSION

A not too large number of phosphorus bridgehead bi- and polycycles has been continuously reported during the last three decades. Due to a lack of suitable ring size only few of them show the interesting feature of *in*,*out*-isomerism. In many cases where *in*,*out*-isomerism seems possible, the attention of the authors has not been drawn to this aspect mostly because only one isomer was obtained. It appears promising to extend the work in this field in the future as many auspicious applications might arise from it especially concerning *in*-phosphorus cage compounds. If the exocyclic groups at the phosphorus are simply lone pairs, such cage compounds might exhibit excellent properties for metal complexation. This leads further to the design of ligands for metal catalyzed reactions and the tuning of their selectivities. No such macrobicyclic ligands have been reported so far. Moreover, additional functional groups can be attached to phosphorus bridgehead atoms. This gives rise to new applications in supramolecular chemistry. The cavity of macrobicyclic host compounds can be adapted for molecular recognition of a variety of different, in particular neutral, substrates. For these reasons, the authors expect and would like to stimulate growing attention to the chemistry of phosphorus bridgehead cage compounds.

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