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Design and Study of Phosphocavitands—A New Family of Cavity Systems

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ABSTRACT

The design of phosphorus-containing cavity architectures that are of interest for biomimetics and other interdisciplinary sciences is among the most high-priority lines of research in modern organophosphorus chemistry. This Account acquaints the readers with methods for the design of rigid phosphomacrocyclic systems based on resorcinarenes, which differ in the nature of the phosphorus functions on the upper rim of the molecular bowl and have fixed dimensions of the molecular cavity. The authors demonstrate the possibility of attaining stereoselectivity in the synthesis of phospho(III)cavitands and their various transformations.

I. Introduction

Study of macroheterocyclic compounds can be regarded, by full right, as a priority line of development of synthetic and structural organic chemistry in the past decades. The interest in these objects is due to chemist's endeavor to the design of analogues of biomolecules, for example, artificial enzymes, sensors, and other receptor systems. By varying the components of macrocyclic systems by introducing functional groups and heteroatoms into their ensembles, one can prepare cavity structures with different levels of preorganization and different lability, size, and properties of the molecular cavities.

The age of synthetic receptor systems was opened by Pedersen's,[1] Lenn's,[2] and Cram's[3] studies devoted to the design of macrocyclic architectures of various types. In the early 1980s, D. J. Cram and co-workers[4] prepared compounds that can be described as molecular bowls or cavities. The researchers called them cavitands after the Latin word *cavitas*. For the synthesis of cavitands, D. J. Cram used reactions of readily available symmetrical octaols, resorcinarenes, with bifunctional electrophiles, for example, dihaloalkanes or dihalosilanes.[5] The condensation of bifunctional compounds with the polyhydroxycalixarene system forms the upper rim of this structure.

A logical development of these studies has been the synthesis of phosphocavitands, that is, molecular bowls with phosphorus functions incorporated in their upper rim. Thus in the early 1990s, studies on the design of phosphocavitands and investigation of their structures and the most important chemical properties were started in several laboratories independently of each other.[6–8]

II. Synthesis of Phosphocavitands

Phosphorylating reagents used most widely in organophosphorus chemistry are phosphorus acid halides and amides. Representatives of these classes of compound were employed to form the upper phosphorus-containing rim in cavitand molecules (Scheme 1).

A. Cyclophosphorylation of Resorcinarenes with Phosphorus Acid Chlorides. R. J. Puddephatt and co-workers[6] performed cyclophosphorylation of resorcinarene **1** with phenylphosphonous dichloride in the presence of triethylamine (Scheme 2). This reaction gave a moderate yield of symmetrical diastereomer **2**, in which the phenyl groups at each phosphorus atom occur in equatorial positions relative to the molecular bowl formed. Note that in this case, it was necessary to purify the major product from the amine hydrochloride. This influenced the outcome of the synthesis. Subsequently, R. Schmutzler and co-workers[9] have described a similar reaction with dichloromethylphosphine and phosphorus trichloride but without a hydrogen chloride acceptor. The researchers reported the preparation of P–Me and P–Cl phosphitocavitands in high yields and also as individual diastereomers. X-ray diffraction showed that in the P–Cl phosphitocavitand, the exocyclic substituents in all phosphocin rings are axial. The experimental details of the synthesis of the P–Me phosphitocavitand have not been reported.

Cyclophosphorylation of resorcinarene **1** phosphorodichloridates was performed,[8,10–13] resulting in a mixture of stereoisomers with different orientation of oxo groups at phosphorus atoms (Scheme 3). In most cases, symmetric stereoisomers with all oxo groups oriented inside

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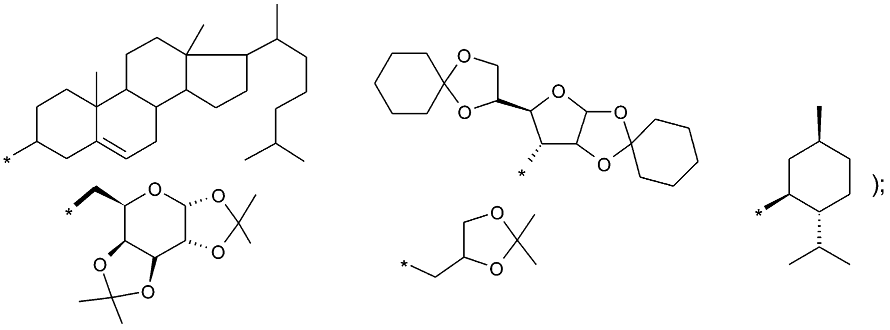
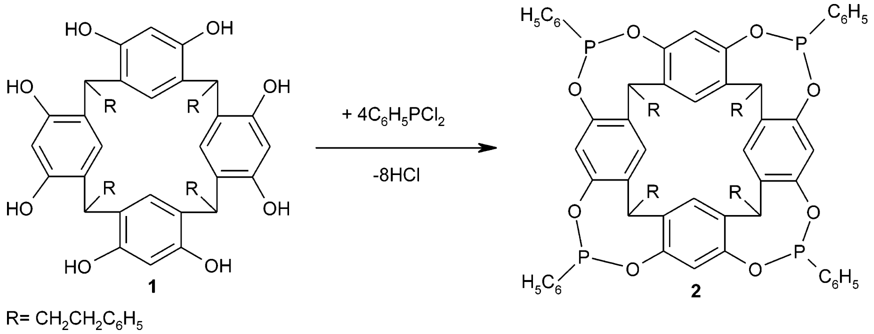
Scheme 1. Phosphorylating Reagents Used for the Synthesis of Phosphocavitands

a. PCl_3;
b. $RPCl_2$ (R= CH_3, C_6H_5);
c. $XP(O)Cl_2$ (X= C_2H_5, 4-methyl-phenyl, 2-methyl-phenyl, 2,6-diisopropyl-phenyl, 2,4,6-trimethyl-phenyl.);
d. $C_6H_5P(O)Cl_2$;
e. $P(NR`_2)_3$ (R`= CH_3, C_2H_5, piperidyl);
f. $R``OP(NR`_2)_2$ (R``= CH_3, C_2H_5, C_3H_7-i, $CH_2C_6H_5$,



g. $ArOP(NR`_2)_2$ (R`= CH_3, C_2H_5;
Ar= C_6H_5, $CH_3C_6H_5$, 2-i-propyl-phenyl, 2,6-di-tert-butyl-4-methyl-phenyl, 1-naphthyl, 2-naphthyl).

Scheme 2. Cyclophosphorylation of Resorcinarene with Dichlorophenylphosphine



(i,i,i,i) or outside (o,o,o,o) the cavity were absent or present in trace amounts; the i,i,i,o isomer was usually predominant.[8,10]

The use of dichlorophenylphosphine oxide[12,14,15] in this reaction changed the steric direction of the process and increased the yield of the symmetric i,i,i,i isomer to 53%.

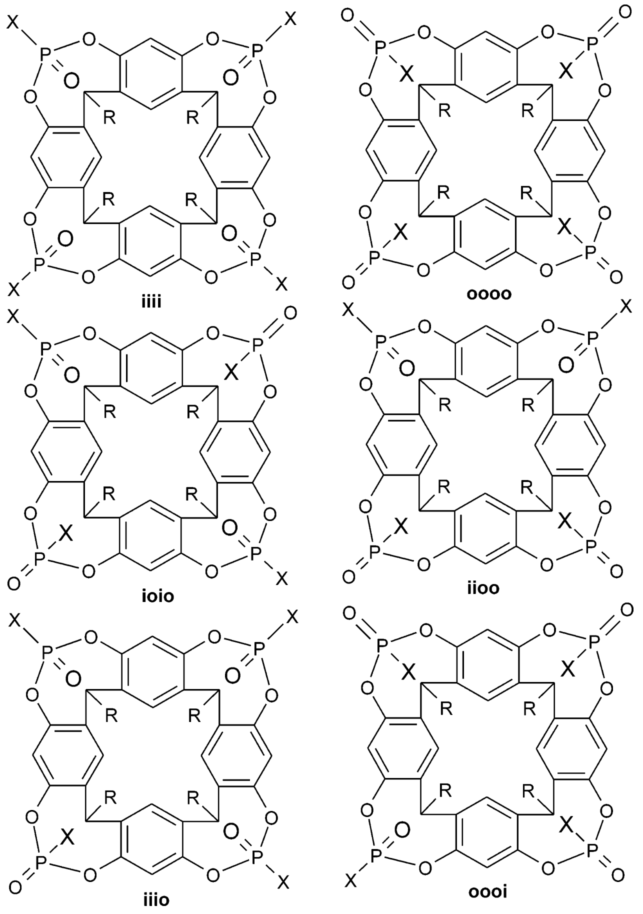
B. Cyclophosphorylation of Resorcinarenes with Phosphorus Amides. We have proposed and studied in detail the amide method of phosphorylation of resorcinarenes,[7,16−22] which made accessible many types of stereochemically pure phosphocavitands. Note that this method has later been used by other research groups, for example, see refs 23−26.

Phosphorus triamides and alkyl and aryl phosphorodiamidites have been used as cyclophosphorylation reagents (Scheme 4). In most cases, the reaction took place on mere mixing the reactants and keeping the reaction mixture at room temperature or on moderate heating. The evolved amine was easily removed from the reaction area. Phosphocavitands **3** and **4** crystallized either directly from the reaction mixtures or upon partial evaporation of the solvent.

The process direction depended on the nature and the bulk of substituents at the phosphorus atom in the phosphorylating reagent. With phosphorus triamides and resorcinarenes **1** containing various aliphatic substituents (R) in the methylene bridges, the reactions proceeded stereospecifically to give symmetrical amidophosphitocavitands **3** with equatorial orientation of the amino groups at all the phosphorus atoms, as confirmed by NMR and X-ray diffraction data.[16−19] The yields of individual stereoisomers were 72−96%. In the case where phosphorus diamides with small alkoxy substituents (R′ = Me, Et) at phosphorus atoms were used, the reactions gave mixtures of isomeric cavitands **4** with a different arrangement of alkoxy groups relative to the macrocycle cavity.[18] Meanwhile, cyclophosphorylation of resorcinarenes with isopropyl and benzyl phosphorodiamidites gave mainly symmetrical stereoisomers.[18−20] Thus, in these cases, the process can be classified as stereoselective.

Note that cyclophosphorylation of resorcinarenes **1** with phosphorodiamidites is suitable for preparing hybrid systems, namely, cavitand conjugates with biomolecules.[21] To this end, we studied the reactions of resorcinarenes **1** not only with phosphorodiamidites containing simple alkoxy groups, but also with phosphorus ester diamides prepared from monosaccharides, glycerides, menthol, and cholesterol (Scheme 1). This resulted in the synthesis of cavitand **4** in which the macrocycle bowl is surrounded by a belt of chiral fragments of biomolecules. On the basis of NMR spectra, these compounds were concluded to be mixtures of stereoisomers with different orientations of

Scheme 3. Possible Orientation of Substituents at the Phosphorus Atoms in Phospho(IV)Cavitands



bioalcohol fragments with respect to the central macrocycle axis. Only cholesterylphosphocavitand was isolated as a single symmetrical stereoisomer. The reaction of resorcinarenes with phosphorus ester diamides derived from glucose and menthol has also been considered by Kazakova and co-workers.[24−26] The reaction products were described as mixtures of resorcinarenes phosphorylated to different extents and containing both cyclic and acyclic phosphorus fragments.

C. Intramolecular Control of the Regioselectivity of the Cyclophosphorylation of Resorcinarenes with Aryl Phosphorodiamidites. The cyclophosphorylation of resorcinarenes **1** with aliphatic ester amides followed, in all cases, the classical pattern with cleavage of two P−N bonds and formation of phosphitocavitands[17−19,21] (Scheme 4). However, the use of phosphorus ester diamides with aromatic groups brings about an abnormal reaction route,[20,22] which is of fundamental importance. Conventionally, this process can be divided into two steps (Scheme 5). The first step is the same as that involved in the classical phosphorylation of alcohols and phenols with phosphorus amides. It involves cleavage of one P−N bond and ends in the formation of the intermediate **5**. Within the bounds of the traditional views on the reactivity of phosphorodiamidites,[27] the second step, phosphocyclization of intermediate **5**, should take place through cleavage of the last P−N bond to give phosphitocavitands **6**. However, in this case, the reaction follows an abnormal route; in particular, the second step involves cleavage of the P−O bond in the intermediate to give amidophosphitocavitands **3**. The phosphocyclization route does not depend on the size or the nature of the hydrocarbon groups (R) in the calixarene matrix, the type of aryl phosphorodiamidite used (Scheme 1), or the ratio of the reactants. The reaction may be hampered if the molecule of the phosphorylating reagent contains ortho substituents in the phenoxy group.

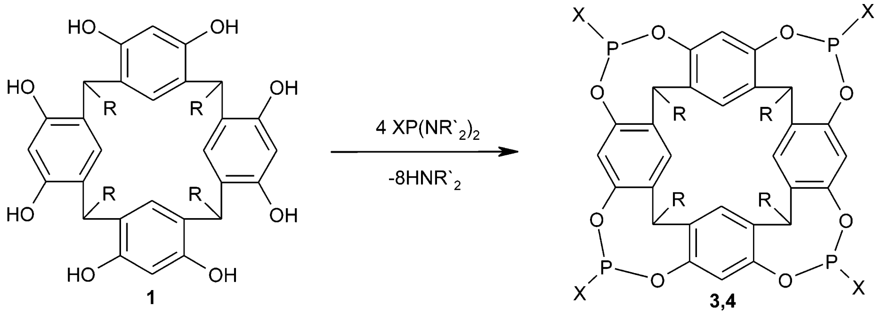
As shown by computer simulation,[20] in the phosphorylated intermediate **5**, the amino group is located at the system periphery and is far removed from the activating reaction center. This topological situation is probably due to the stacking interaction in the intermediate involving the aromatic nuclei located in the aryl phosphite moiety and the nearest benzene ring of the resorcinarene system. In this case, the phenoxy group comes close to the reaction center and is thus activated by the center, which enables intramolecular phosphocyclization through cleavage of the P−O bond, that is, transesterification.

III. Reactivity of P(III)-Phosphocavitands

P(III)-Phosphocavitands are derivatives of phosphorus and phosphonous acids, and therefore, they enter into many reactions typical of trivalent phosphorus derivatives. However, the rigid structure of the molecular cage can bring about specific reaction routes.

A. Nucleophilic Substitution. Chlorophosphitocavitands **7** exhibit a traditional activity in nucleophilic

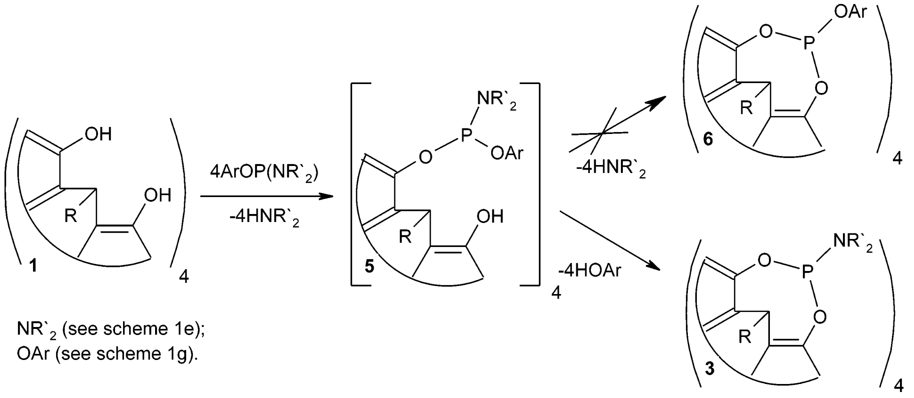
Scheme 4. Cyclophosphorylation of Resorcinarenes by Phosphorus Amides



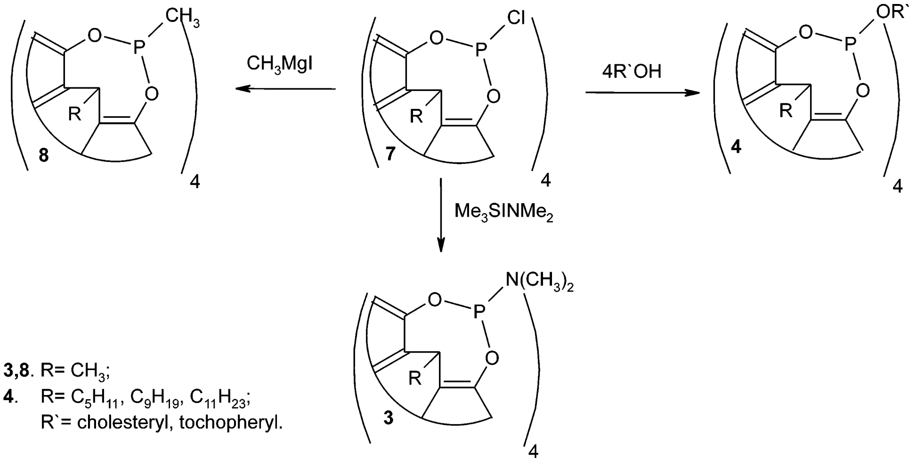
R= CH_3 - C_6H_{13}, C_9H_{19}, $C_{11}H_{23}$

3. X= NR`$_2$ (see scheme 1e);
4. X= OR`` (see scheme 1f).

Scheme 5. Regiochemical Outcome of the Cyclophosphorylation of Calix[4]resorcinarenes with Phosphorus Ester Diamides



Scheme 6. Nucleophilic Substitution at the Phosphorus Atoms in Tetrachlorophosphocavitands



substitution.[9,21,28] For example, they react with natural hydroxides (cholesterol, α-tocopherol) to give cavitand conjugates with biomolecules **4**[21] (Scheme 6) and react with MeMgI and Me_3SiNMe_2 to give P-Me-phosphonito- and amidophosphitocavitands **8** and **3**, respectively[9,28] (Scheme 6).

The products formed in these reactions are stereochemically individual compounds with an equatorial orientation of the exocyclic substituents at the phosphorus atoms. The stereochemical outcome of the syntheses is due to two factors, namely, the use of symmetrical stereoisomers of chlorophosphitocavitands **7** with an axial orientation of chlorine atoms as the substrates and the rigid cavitand structure.

Meanwhile, amidophosphitocavitands are passive in the well-known nucleophilic replacement of the amino group at phosphorus.[29,30] Indeed, alcoholysis and hydrolysis of these compounds occur under rigorous conditions and can be accompanied by opening of the phosphocin rings.

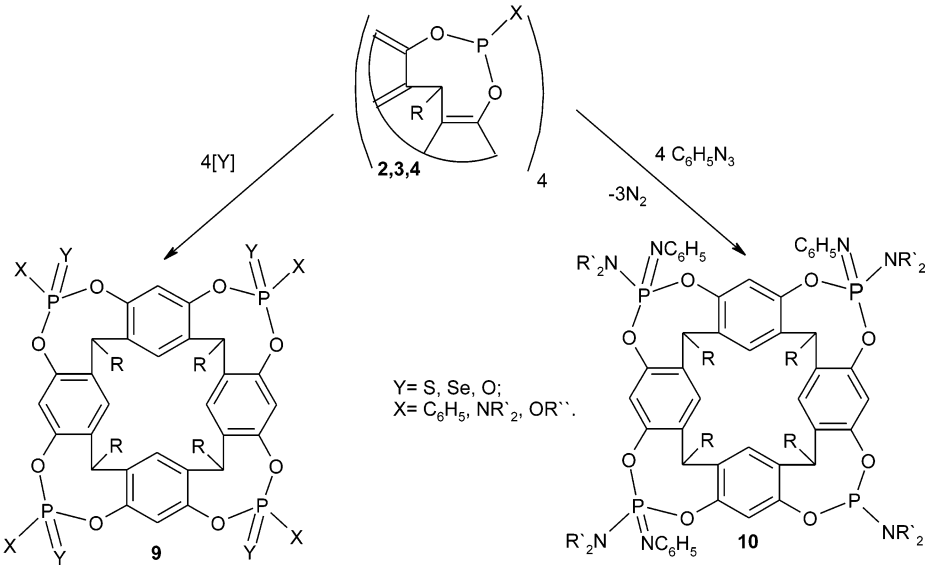
B. Oxidation Reactions. On moderate heating, phospho(III)cavitands easily add sulfur,[16,17,19−21,31−33] and at higher temperatures, they add selenium[19,31] (Scheme 7). The addition of sulfur and selenium to amidophosphitocavitands **3** was stereospecific.[16,17,19−21,31] Single stereoisomers of thio- and selenophosphates **9** in which all four atoms of the oxidant are axially attached to phosphorus, that is, directed toward the cavitand cavity, were isolated in high yields (72−96%). Correspondingly, the amino groups occupy the equatorial positions.

A high stereoselectivity was also observed in the sulfurization of phosphonitocavitand **2** (R = $(CH_2)_{10}$-CH_3).[32,33] The reaction gave symmetric thiophosphonatocavitand **9** (i,i,i,i stereoisomer, Scheme 3) with a yield of 52%.

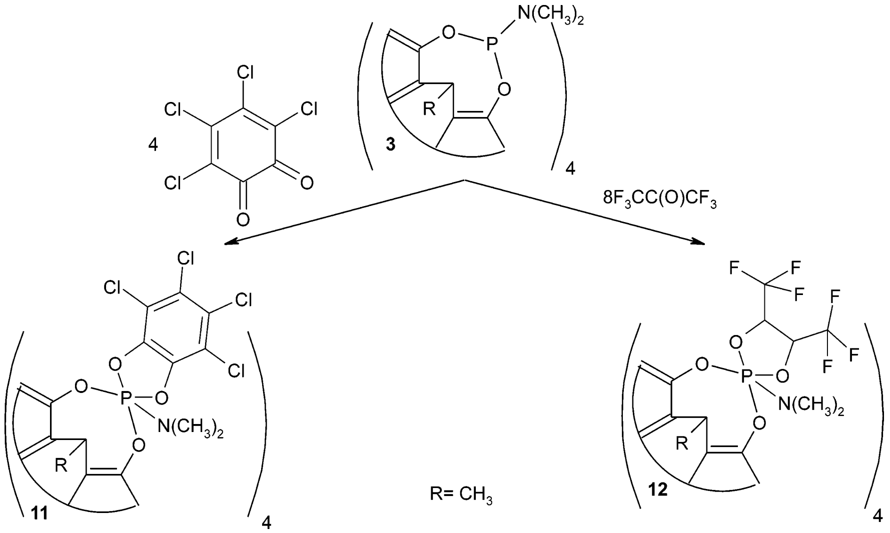
Phosphites showed a different type of behavior in these reactions. The sulfurization of cavitands the phosphite fragments of which contained small groups (X = OMe, OEt) resulted in a mixture of stereoisomers with different arrangements of substituents at phosphorus relative to the cavitand cavity.[31] However, the addition of sulfur and selenium to phosphites **4** with more bulky substituents at the phosphorus centers (X = OPr-i, OBz, OHol) afforded mainly symmetrical stereoisomers with an axial orientation of all atoms of the oxidant.[19−21,31] Thus, sulfurization of phosphitocavitands displayed an interesting dependence of reaction stereochemistry on the size of the alkoxy groups at the phosphorus atoms. A similar type of behavior of P(III)-phosphocavitands was observed in reactions with oxidants, namely, oxygen (UV activation), ozone, nitrogen oxide, iodosobenzene, and hydrogen peroxide ($H_2O_2(H_2N)_2CO$)[9,19,28] (Scheme 7). The best results were attained with the use of hydrogen peroxide adduct with urea as the oxidant.

It is worth noting that in each of the above-mentioned processes, the substituents newly attached to the phos-

Scheme 7. Oxidation of P(III)-Phosphocavitands



Scheme 8. Oxidative Addition of Hexafluoroacetone and Tetrachloro-*O*-benzoquinone to Phosphocavitand



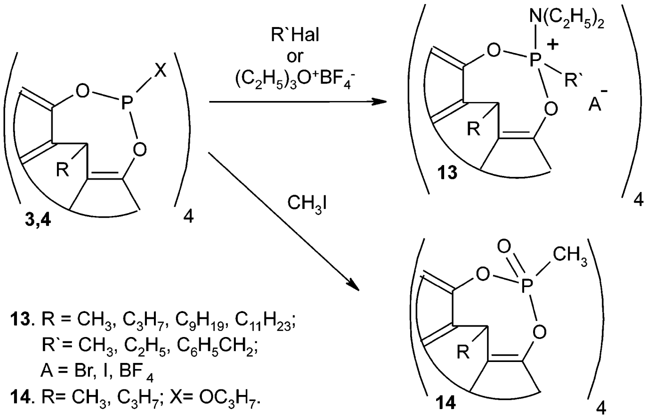
phorus atoms were monatomic and had relatively small sizes. Therefore, no steric restrictions hampering the accommodation of four oxidant atoms inside the cavitand cavity were involved. A different situation was observed for oxidative imination of amidophosphitocavitands using phenyl azide[34] (Scheme 7). In this case, modification of the phosphorus atoms was accompanied by insertion of multiatomic and rather bulky phenylimino groups into the cavity.

The reactions were carried out in chloroform or dioxane or without a solvent in the temperature range of 20−100 °C at different reactant ratios. The experiments showed that complete imination of amidophosphitocavitands does not take place under these conditions. The resulting macrocyclic systems **10** contain imino groups only at three phosphorus atoms, while the fourth phosphorus atom remains trivalent. The situation cannot be changed even by using a large excess of phenyl azide and long-term keeping of the reaction mixture at high temperature. Any attempts to intensify the process and to insert an imino group to the fourth phosphorus atom of the cavitand result in destruction of the macrocyclic system.

Note that in oxidative addition of hexafluoroacetone and tetrachloro-*O*-benzoquinone to an amidophosphinocavitand **3** considered by R. Schmutzler and co-workers,[9,28] bulky groups were introduced to each of the four phosphorus atoms of the macrocycle (Scheme 8). However, the presence of several signals in the ^{31}P NMR spectra of the resulting tetraphosphoranes **11** and **12** points to magnetic nonequivalence of phosphorus atoms in the molecules. This can be due to a distortion of the macrocycle cage caused by “pushing aside” of the bulky substituents at the phosphorus atoms.

C. Alkylation. Amidophosphitocavitand **3** is alkylated with alkyl halides[19,35] and triethyloxonium tetrafluoroborate[36] to give quasiphosphonium salts **13** (Scheme 9). The stereochemical outcome of the process depends on the nature of the alkylating reagent. Indeed, the reactions of amidophosphitocavitands **3** with methyl or ethyl iodide

Scheme 9. Alkylation of P(III)-Phosphocavitands



13. R = CH_3, C_3H_7, C_9H_{19}, $C_{11}H_{23}$;
R` = CH_3, C_2H_5, $C_6H_5CH_2$;
A = Br, I, BF_4
14. R= CH_3, C_3H_7; X= OC_3H_7.

and with triethyloxonium tetrafluoroborate occur stereoselectively, the isolated quasi-phosphonium salts **13** being single stereoisomers with an axial orientation of the alkyl groups at all the phosphorus atoms.[19,35,36] In the case of alkylation of one phosphocavitand with benzyl bromide,[35] the cavitand molecular bowl in the resulting product is distorted, similarly to that in tetraphosphoranes,[9] as the benzyl groups attached to phosphorus and located close in space push one another away.

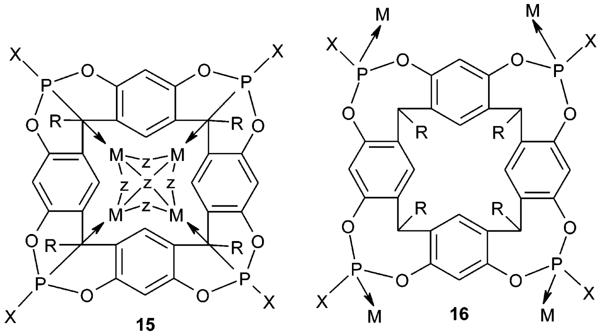
Thus, by alkylation of amidophosphitocavitands, we performed the first synthesis of lipid-like derivatives of macrocyclic systems of this type. The upper rim of these compounds contains charged phosphorus fragments, while the lower rim bears lipophilic hydrocarbon radicals.

The alkylation of phosphitocavitands **4**, which are full phosphorus esters, considered for the reaction with methyl iodide taken as an example, occurs in a different way[35] (Scheme 9). The reaction follows the standard Arbuzov rearrangement pattern and gives most often mixtures of phosphonate stereomers **14**, which are difficult to separate. Only once were we able to isolate the symmetrical isomer with the axial orientation of the methyl groups at all phosphorus atoms in a pure state.

D. Transition Metal Complexes. P(III)-Phosphocavitands containing four reactive phosphorus centers in the molecule are highly promising compounds for the formation of coordination systems of different configurations. The molecules of most of the tetradentate ligands mentioned above are constructed in such a way that exocyclic substituents at the phosphorus atoms are arranged strictly equatorially, while the lone electron pairs of phosphorus atoms are oriented axially. This structure of the starting macrocyclic systems is favorable for stereoselectivity of the processes that involve the lone pairs of phosphorus. Due to the rigidity of the cavitand molecular cage and the limited size of the cavity, both the course of the reaction and the composition and structure of the products may depend appreciably on the bulk and the nature of the groups attached to the phosphorus atoms.

(i) Tetranuclear Complexes of Phosphocavitands. The first coordination systems based on phosphocavitands and transition metals were synthesized by Canadian chemists.[6,37−39] Phenylphosphonitocavitand **2** was used as the ligand and simple silver, copper, gold, and platinum complexes were used as the complex forming agents. The researchers showed that all four phosphorus centers of the starting phosphonite are coordinated to the above metals (Scheme 10).

Scheme 10. Tetranuclear Complexes of Phosphocavitands with Transition Metals



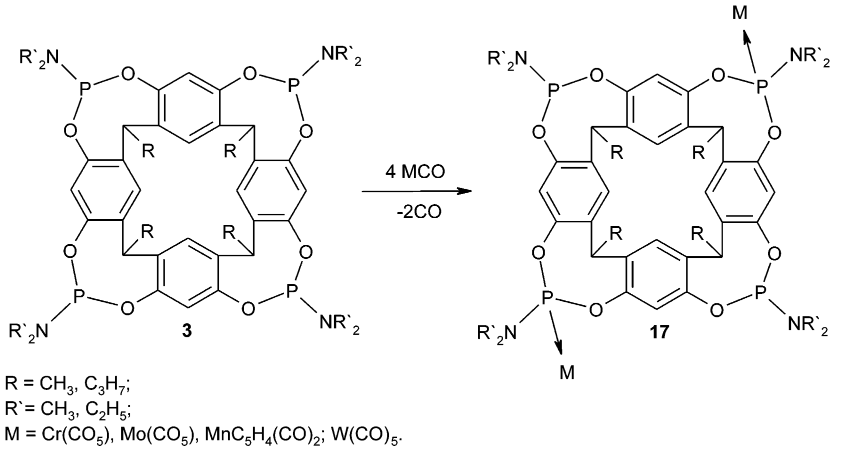
R= CH_3, C_3H_7, C_9H_{19}, $CH_2CH_2C_6H_5$;
X= C_6H_5, $N(CH_3)_2$, $N(C_2H_5)_2$;
M= Ag, Cu;
Z= Cl, Br.

R= CH_3, C_3H_7, $CH_2CH_2C_6H_5$;
X= OC_3H_7-i, C_6H_5, $N(CH_3)_2$, $N(C_2H_5)_2$;
M= AuCl, $PtCl_2S(CH_3)_2$, acacRhCO, $Mo(CO)_5$, $Cr(CO)_5$.

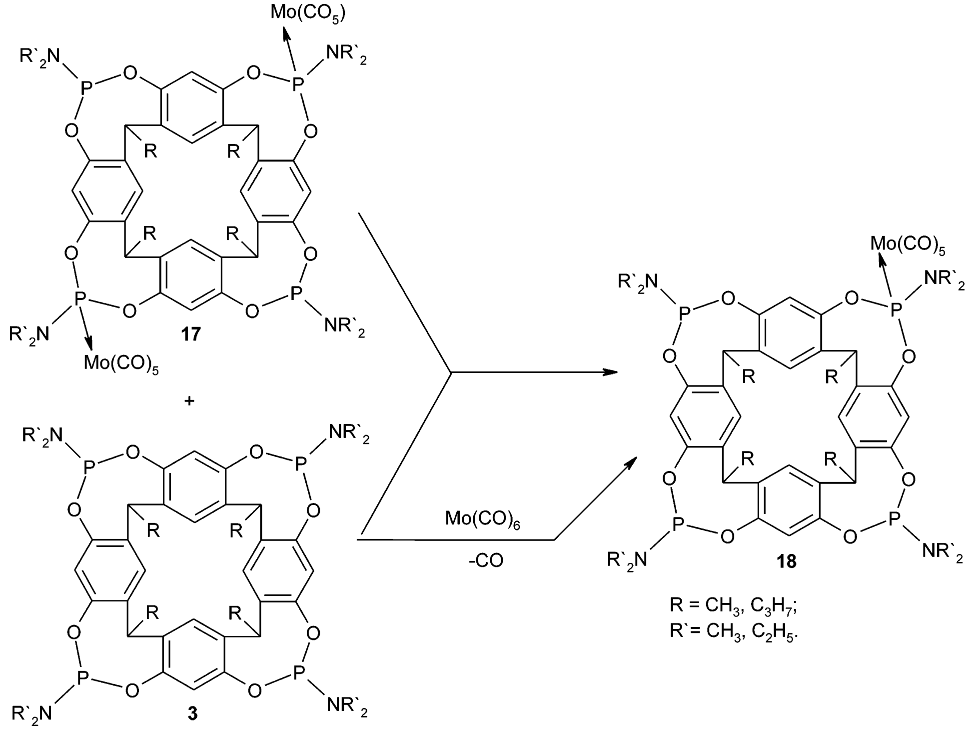
An X-ray diffraction study has shown that cavitand **2** is complexed with silver and copper halides to form anionic complexes **15** due to accepting of the halide anion in the macrocycle cavity (Scheme 10). Later, anionic complexes have been prepared on the basis of amidophosphitocavitands and copper chloride[40] or silver bromide.[41] Note that the ligand remains fully symmetrical in any of the above-mentioned metal complexes.

Our research group studied the regularities of formation of coordination systems from phosphite **4** or phosphorus amide **3** as tetradentate ligands and transition metal (Rh, Fe, Cr, Mo, Mn) carbonyl complexes. Considerable attention was given to the design of asymmetrical cavitands containing different structural fragments in the molecule. For example, the reaction of phosphito- and amidophosphitocavitands with $acacRh(CO)_2$[42] results in the formation of asymmetrical tetranuclear rhodium(I) complexes **16** (Scheme 10). This was proved by NMR spectroscopy and X-ray diffraction. The ^{31}P NMR spectra of the resulting complexes show the nonequivalence of the phosphorus nuclei even at 0 °C; at −60 °C, each spectrum exhibits three clear-cut doublets with similar chemical shifts and the $^1J_{PRh}$ spin−spin coupling constants. The ratio of the integrated intensities of the signals is 1:2:1. This spectral pattern points to a structural difference between the phosphocin rings. An X-ray diffraction study of the rhodium complex **16** (R = Me, X = O*i*-Pr)[42] showed that three phosphocin rings have a chair−boat conformation typical of symmetrical phosphocavitands[9,16−20,31,37−41] and the fourth one is in a boat conformation; the rhodium fragments are directed equatorially, while the isopropoxy groups have an axial orientation. Thus, the introduction of the bulky rhodium-containing fragments to four phosphorus atoms results in a distortion of the molecular cage of the cavitand and in the loss of symmetry for the whole system.

Scheme 11. Synthesis of Binuclear Complexes of Amidophosphitocavitands



Scheme 12. Synthesis of Mononuclear Molybdenum Complexes of Amidophosphinocavitands

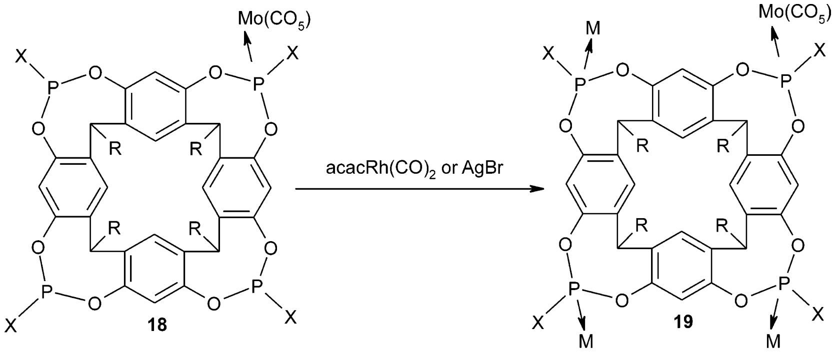


The reactions of phosphocavitands with group VI metal (Cr, Mo, W) carbonyls[43,44] and (cyclopentadienyl)tricarbonylmanganese[44] took place upon thermal ($Mo(CO)_6$, $Cr(CO)_6$, 95−105 °C) or photochemical ($W(CO)_6$, $C_5H_5Mn(CO)_3$, 20 °C) activation of metal hexacarbonyls. Despite the identical reaction conditions, the products of complexation of amidophosphito- and phosphitocavitands differed in the degree of modification. The reactions of phosphitocavitand **4** (R = Me, X = O*i*-Pr) with Cr or Mo hexacarbonyl gave tetranuclear complexes[43,44] (Scheme 10). A ^{31}P NMR study of the tetramolybdenum complex carried out at a reduced temperature showed that at 0 °C the phosphorus nuclei in the cavitand molecule become magnetically nonequivalent and at −60 °C the spectrum exhibits four singlets with similar chemical shifts and equal integrated intensities. These data indicate that, similarly to the tetrarhodium complexes of phosphocavitands,[42] the tetramolybdenum complexes of phosphitocavitands are conformationally labile systems.

(ii) Binuclear Complexes of Phosphocavitands. The reactions of amidophosphitocavitands **3** with metal (Cr, Mo, W, Mn) carbonyls, even in the presence of a 2-fold excess of the complex-forming agent and long-term heating or irradiation of the reaction mixture, afford binuclear complexes **17**[43,44] (Scheme 11). As shown by NMR and X-ray diffraction data,[44] the cavitand cage remains intact, while the phosphorus atoms arranged on a diagonal of the macrocycle molecular bowl are coordinated to the metal.

The binuclear metal complexes **17**, containing two uncoordinated trivalent phosphorus atoms in the molecule, are potential bidentate ligands. However, the two pentacarbonyl metal-containing fragments shield com-

Scheme 13. Synthesis of Tetranuclear Heterometallic Complexes Formed by Amidophosphitocavitands



R= CH_3, C_3H_7;
X= $N(C_2H_5)_2$;
M= AgBr, acacRhCO.

pletely the cavitand cavity and the trivalent phosphorus atoms,[44] which precludes further complexation.[41]

(iii) Mononuclear Complexes of Phosphocavitands. The reactions of binuclear complexes **17** with the amidophosphitocavitands **3** taken in equimolar ratios give rise to mononuclear complexes **18**[44] (Scheme 12). Apparently, in this case, the metal fragments are redistributed between the binuclear complex **17** and the nonfunctionalized phosphocavitand **3**. Mononuclear molybdenum complexes **18** have also been prepared by an alternative synthesis using equimolar amounts of amidophosphitocavitands **3** and $Mo(CO)_6$[44] (Scheme 12).

(iv) Tetranuclear Heterometallic Complexes of Phosphocavitands. The molecules of mononuclear complexes **18** contain only one phosphorus atom coordinated to Mo(0). The only pentacarbonylmolybdenum fragment shields the trivalent phosphorus atom to a much lesser extent than in the binuclear complexes **17**. Therefore, compounds **18** are tridentate ligands and can be involved in further complexation[41,45] (Scheme 13). (Acetylacetonato)dicarbonylrhodium(I)[45] and silver bromide[41] have been used as secondary complexing agents. The reactions proceeded under mild conditions giving rise to tetranuclear complexes **19**, in the molecules of which three phosphorus atoms are coordinated to rhodium or silver and one phosphorus atom to molybdenum.

IV. Conclusion and Outlook

To summarize this Account, we can state that resorcinarenes represent a convenient matrix for the design of phosphocavitands, rigid cavity systems with various functional groups at phosphorus atoms. It is significant that the regioselectivity and the stereochemical outcome of the considered reactions and the degree of modification of the phosphorus atoms in the cavitand are controlled by the macrocyclic system itself. By selecting appropriate reagents, it is possible to introduce various functional groups, in particular, metal fragments into the molecule and to arrange them on the matrix according to a definite pattern. There exist data indicating that phosphocavitands can be used as receptor systems for selective extraction of some compounds, for example, metal cations[14,32,38] and secondary and tertiary amines.[10,13,14,38,46,47] In addition, they hold promise in the design of original conjugates, polynuclear metal complex catalysts, and other products that are of interest for the development of new interdisciplinary lines of research.

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