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An effective strategy of P,N-containing macrocycle design

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ABSTRACT

An effective strategy of P,N-containing macrocycle design is described, which is based on covalent self-assembly processes in the course of Mannich-type condensations in three-component systems: primary phosphine (or secondary diphosphine)–formaldehyde–diamine with spatially divided functional groups (or primary amine). This approach allowed the authors to obtain various types of macrocyclic phosphines, namely cage cyclophanes with a 1,5-diaza-3,7-diphosphacyclooctane fragment in the basic framework, cyclophanes with linear P,N-containing spacers, P,N-containing corands and the first P,N-containing cryptand with four phosphine centers.

1. Introduction

Macrocycles are promising building blocks for the creation of nanosized molecular devices and nanomaterials on the "bottom-up" principle. Their unique properties are based on the relative rigidity of their spatial characteristics in comparison with acyclic compounds of similar size and on the presence of an empty intramolecular space, the so-called intramolecular cavity. The fragments of organic and organoelement guest molecules or even whole molecules are able to penetrate into these cavities and to be binded inside. The macrocyclic structure provides the effective binding of the guests (so-called macrocyclic effect) due to multiple host–guest interactions. It should be mentioned that these binding and orientational interactions may vary from very weak (for example, hydrophobic, Van-der-Waals, π–π, H–π interactions) to relatively strong ones (hydrogen and coordination bonds) [1]. The penetration of the guest molecules inside the macrocyclic cavities may result in their isolation from the environment (molecular containers and reactors), may change their characteristics (molecular sensors, solubilisers and molecular transport) or may even cause the appearance of the unique properties (molecular devices and machines) [1].

The availability of the macrocyclic compounds is one of the key points for their use in the field of supramolecular chemistry and nanomaterials. If some types of macrocycles with a unique shape, distinct architecture, and set of functional groups become easily available from natural or synthetic sources, they stimulate the chemists to the wide and effective search for novel molecular materials and devices.

At present three main strategies of the macrocyclic synthesis may be separated:

1. the macrocyclization under high-dilution conditions;
2. the template synthesis of macrocycles;
3. the covalent self-assembly of macrocycles.

The first two approaches have been used for a long time and have a number of well-known advantages and disadvantages. The high-dilution macrocyclization, as a rule, requires fast irreversible reactions, and the participation of more than two molecules is undesirable. Another

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disadvantage is a large amount of a solvent and/or the use of special dosing devices for the slow simultaneous addition of both reagents. It increases the reaction time and complicates the technique. In addition, the regio- and stereoselectivity of the irreversible macrocyclization reactions are usually low [1].

The template macrocyclization requires that one of the reagents contains the donor center (or centers) which is able to form the coordination compound of the desirable structure. Another problem is the final demetallation step for the release of the obtained macrocyclic ligand because the metal complexes are usually very stable due to the macrocyclic effect [1].

The last approach, namely the covalent self-assembly of macrocycles, has been formed recently. The self-assembly conception came from supramolecular chemistry. J.-M. Lehn used the biochemical conceptions of templating, self-assembly and self-organization for the explanation of the drawing forces of the supramolecular structures formation [1e]. Later in the 1990s, the self-assembly phenomenon was successfully used for the directed design of the macrocyclic systems formed by the coordination bonds [2]. It has been shown that the main necessary conditions for the self-assembly of metallamacrocycles are the reversibility of all steps of the reaction, the mutual spatial correspondence of the building block sizes and their geometry for the formation of the definite type of the macrocycle with higher thermodynamic stability or lower solubility in comparison with other possible products for the desirable equilibrium shift. The distinctive feature of the self-assembly processes is their ability for the self-correction, then the "incorrect" intermediate or product is able to decompose into initial compounds due to the reversibility of the reaction. These compounds react further to give the more thermodynamically stable "correct" combination. The self-correction is the reason of the high selectivity of the self-assembly processes [2c]. So similar principles are expected to be applicable to macrocyclization processes via the reversible formation of covalent bonds.

Thus a series of the self-assembly processes [2b] of organic and organoelement macrocyles synthesis via covalent bonds formation was found during the last two decades. Most of them are based on several types of reversible reactions:

1. esterification of organic acids (and reesterification of esters) [3] or organoelement compounds (boronic [4], iodine [5] and organophosphorus acids [6]);
2. the amidation of organic [7] and organophosphorus [8] acid derivatives;
3. the olefine metathesis in the presence of catalysts [9];
4. the formation of imines (Shiff bases) and hydrazones [10] including organophosphorus ones [11];
5. the formation of Mannich bases [12];
6. the formation of organic disulfides or diselenides under reversible oxidation conditions [13].

In addition, the formation of calixarenes and, especially, of calixresorcines [14] may be probably considered as covalent self-assembly processes. There is also a number of reactions whose high yields and selectivity have been explained by the templating effects of some particles which were weakly bound by the substrates and (or) final macrocycles. It is very probable that the templating plays only an auxiliary role in such cases. It may accelerate the covalent self-assembly process or shift its equilibrium position to the macrocyclic product by the increase of the thermodynamic preference of the last one [10f,13c] or by its removal from the reaction sphere.

The indication of self-assembly phenomenon is the high yield of macrocycles and the regio- and stereoselectivity of their formation in the course of the reversible reaction (often at elevated temperature) between two or more initial molecules (at least one of them must possess spatially divided functional groups) under conditions of relatively high concentration and without any templating reagents.

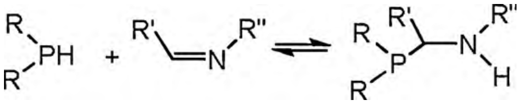
This synthetic strategy has been applied for the synthesis of P,N-containing macrocycles by our research group in A.E. Arbuzov Institute of Organic and Physical Chemistry (Kazan) for the last 10 years and appeared to be very effective [15].

1.1. P,N-Containing cyclophanes with large hydrophobic molecular cavities

The Mannich-type condensation of primary and secondary phosphines as proton-donating reagents (Scheme 1) has been chosen as the basic reaction for the use of covalent self-assembly approach to the synthesis of P,N-containing macrocycles. These condensations are an effective tool for the targeted synthesis of aminomethylphosphine ligands including chiral, water-soluble and polymer or dendrimer-supported ones. At the same time, the direct experiments, interconversions of different types of aminomethylphosphines or stereoisomers of cyclic aminomethylphosphines showed the reversibility of these reactions, the equilibrium being especially fast in the presence of donors of protons [16].

The condensation of bis(hydroxymethyl)phenylphosphine and bis(4-aminophenyl)methane as the bifunctional reagent with spatially divided amine groups in hot DMF (110 °C) at the phosphine concentration of 0.1–0.2 M indeed led to a cage P,N-containing macrocycle **1** in a very good yield (Scheme 2) [17].

The formation of **1** was the first example of the covalent self-assembly of the macrocycle in the reactions of this type. But if some types of macrocycles can form spontaneously from the relatively large number of smaller molecules, their analogues seem to be also available on the basis of the starting reagents with the changed periphery, but with the same (or similar) main framework. The suggested reaction appeared to be applicable to a wide series of primary phosphines including sterically hindered



Scheme 1. The reversible addition of phosphines to imines.