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Review

Bispidine-Based Macrocycles: Achievements and Perspectives

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Abstract: This review presents all currently known macroheterocyclic compounds that include a bispidine (3,7-diazabicyclo[3.3.1]nonane) fragment in their structure. A classification of bispidine-containing macroheterocycles, which is based on the ring size and the nature of bispidinic nitrogen atoms, is suggested. Synthetic approaches to the studied compounds are classified and considered. The features of the crystal structures and solution behavior of bispidine macroheterocycles are analyzed. Prospects for the development of these organic receptors are proposed.

Keywords: supramolecular chemistry; 3,7-diazabicyclo[3.3.1]nonane; bispidine; macroheterocycles; crown ethers; Mannich reaction; macrolactamization reaction; alkylation reaction; ring-closing metathesis; selective complexing agents

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1. Introduction

Starting as the chemistry of selective ionophores [1] and biologically active compounds [2], the chemistry of macro(hetero)cycles continues its rapid development as one of the most important sections of supramolecular chemistry [3–9]. Indeed, for macroheterocycles, there are more and more new applications as receptors, selective sensors, supramolecular catalysts [10,11], parts of supramolecular machines, and various models for studying conformational transitions [12,13]. Medicinal chemistry of macrocycles has emerged in recent years as a separate independent direction [14,15].

The purpose of this review is to give the reader a complete picture of all currently existing bispidine-based macroheterocycles (bispidine is a short name for 3,7-diazabicyclo[3.3.1]nonane). This class of compounds emerged recently, and the chemistry and applications of such macrocycles are in their infancy. At the same time, dozens of publications in this area have indicated that bispidine-based macroheterocycles deserve a review paper.

The first question that arises when one starts reviewing a new area is: what is best and most suitable for readers' classification principle. Bispidine-based macroheterocycles can be classified according to the following features: (a) the number of bispidines per macrocycle (known macrocycles contain from one to five bispidine units in the macrocycle); (b) the nature of the nitrogen atoms in the bispidine fragment (amide, amine, or combinations thereof; we mean the nitrogens that are involved in macrocycle formation). In turn, crown ethers, macrocyclic lactams, and diaminoalkanes can be distinguished from other fragments that are part of the same bispidine-based macroheterocycle. Synthetic approaches to obtaining the molecules under study can also be classified using the nature of the reaction applied, for example: ring closure metathesis, Mannich reaction, macrolactamization, alkylation, and acylation.

In the following sections, the presentation of the material will be based on the ***type*** of macrocycle and the ***method*** of synthetic assembly of each type, with the analysis of their structure and published properties. Conventionally, in this review, the macrocycles will be denoted as follows: A-$N_x{}^BO_yFe_z$, where A is the number of atoms that form the macrocycle; N is nitrogen atom; O is oxygen atom; Fe is iron atom; x, y and z are the

number of nitrogen, oxygen and iron atoms, respectively, in the macrocycle; and B is the type of nitrogen atom—amide (B = CO) or amine (B = H) (Figure 1). Some cases that do not follow this classification will be noted separately.

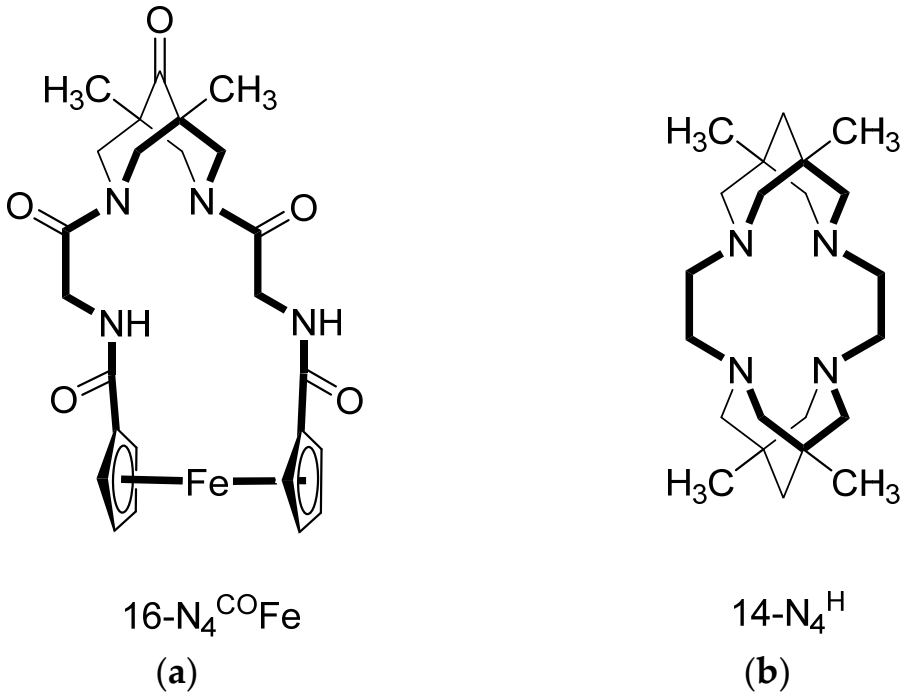
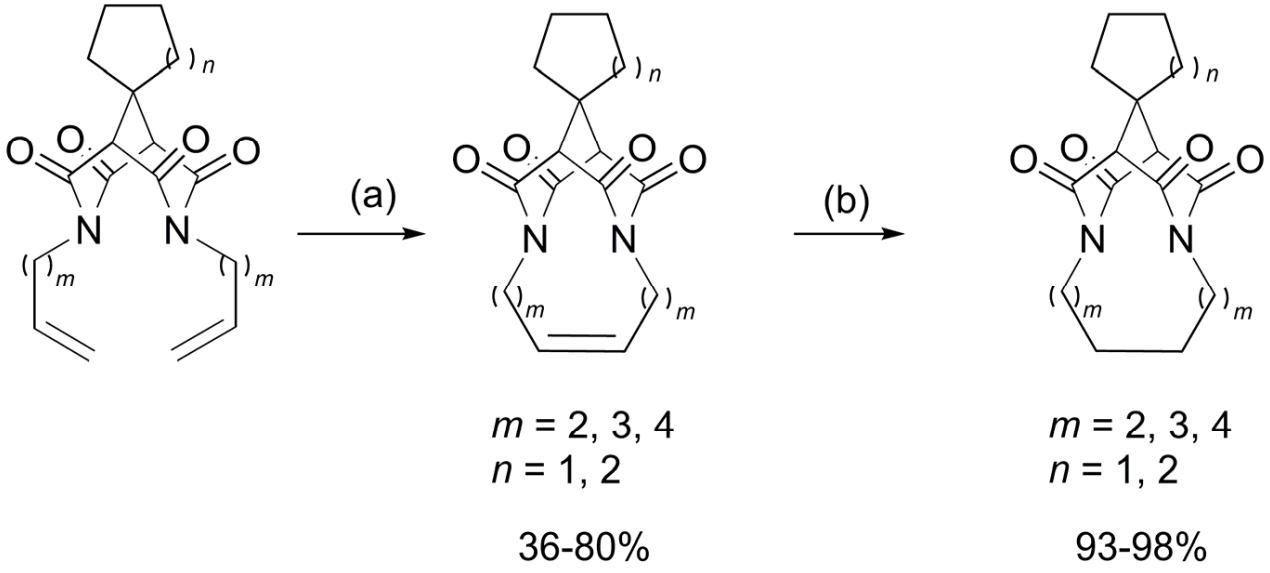


Figure 1. Examples of the proposed designation of (**a**) amide and (**b**) amine bispidine macrocycles. Cycles are indicated by bold lines; ferrocene is counted as three atoms of the macrocycle.

2. Macrocycles with One Bispidine Fragment

2.1. Full-Amide Macrocycles

Diazamacrocycles containing no other heteroatoms, except for those that are part of the bispidine skeleton, were obtained by the metathesis reaction from the corresponding alkenes [16] (Scheme 1).



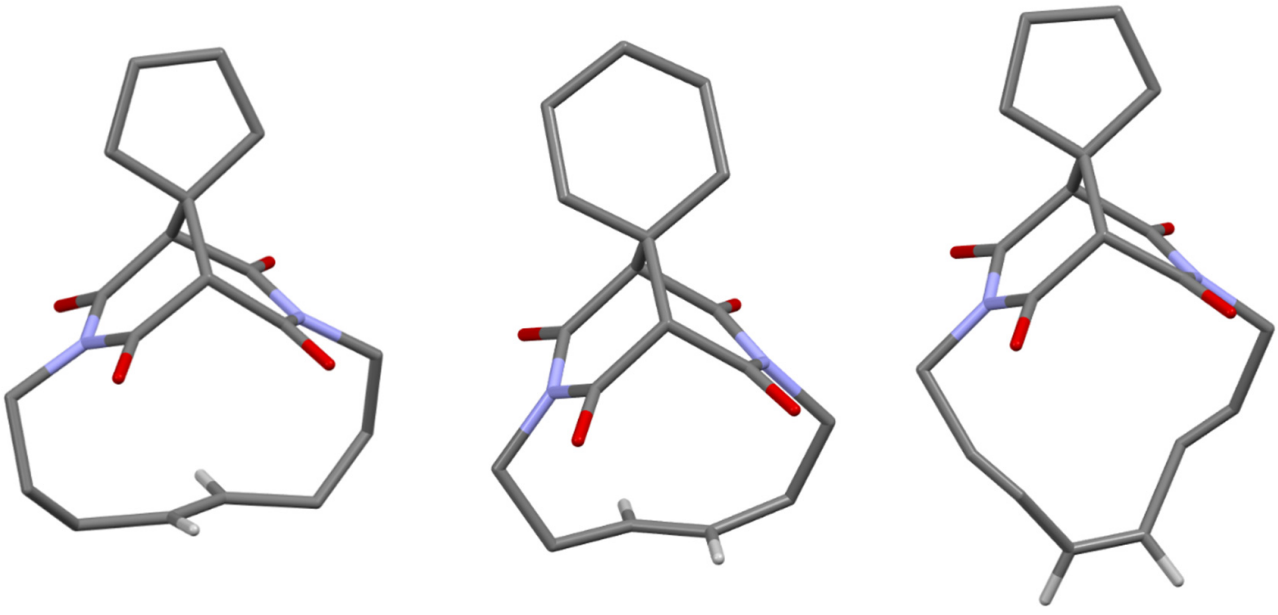
Scheme 1. 11-N_2^{CO}, 13-N_2^{CO}, 15-N_2^{CO}-macrocycles. (a) Grubbs' 1st or 2nd generation catalyst, CH_2Cl_2, reflux, 15 h. (b) 10% Pd/C, H_2, 60 psi, EtOH, dioxane [16].

In the case of $m = 1$, no metathesis occurs. If $m = 2$ or 3, a product with one particular configuration is selectively formed, for example, *E* in the case of $m = 2$. In the case of $m = 3$, depending on the generation of the catalyst, either *E* (Grubbs' cat. 1st generation) or *Z* (Grubbs' cat. 2nd generations) is formed. Metathesis for long chains with $m = 4$ is non-selective with a predominance of the *Z*-isomer (Table 1).

Table 1. Grubbs' catalyst selectivity in metathesis reaction. Conditions: CH_2Cl_2, reflux, 15 h [16].

m (for *n* = 1)	Catalyst's Generation	Double Bond Configuration	Yield
2	**1**	***E***	**53%**
3	**1**	***Z***	**60%**
4	**1**	***Z*:*E* = 2.6:1**	**51%**
2	**2**	***E***	**80%**
3	**2**	***E***	**79%**
4	**2**	***Z*:*E* = 1.5:1**	**36%**

Figure 2 shows, as an example, the molecular structures of the products of the metathesis cycle closure for the cases $n = 1$ and $m = 3$ (Figure 2a,b) and $n = 2$ and $m = 3$ (Figure 2c).

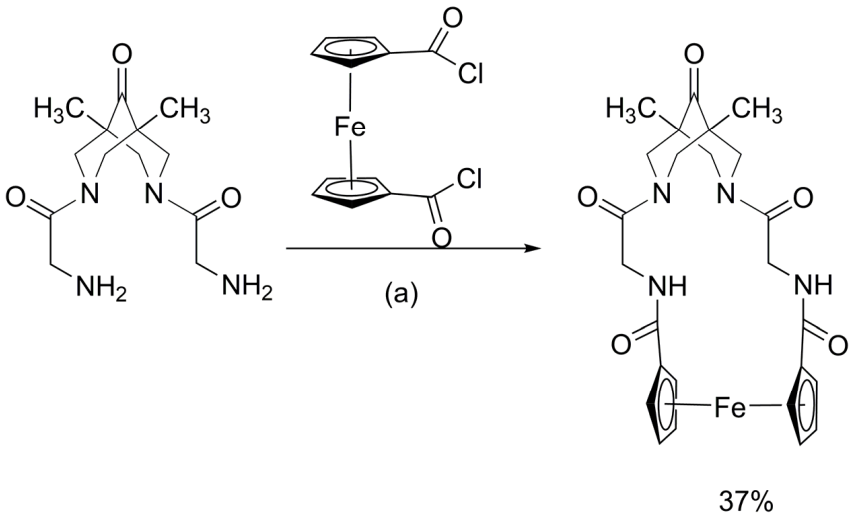


(**a**) (**b**) (**c**)

Figure 2. Molecular structure of (**a**) 13-N_2^{CO}-macrocycle and (**b**) 11-N_2^{CO}-macrocycle with *trans* double bonds and (**c**) 13-N_2^{CO}-macrocycle with *cis* double bond according to X-ray diffraction study [16].

The resulting bis-imides were reduced to the corresponding diamines (see below).

The incorporation of the functional unit with a known property (for example, redox active, catalytically active, photoactive) in the macrocycle would allow for the production of the functional hybrid, which could ideally combine the properties of bispidine and that additional unit. An example of such a macrocycle containing ferrocene as a redox active group is the tetra amide compound obtained by acylation of the corresponding amino acid derivative of bispidine with ferrocenedicarboxylic acid chloride [17] (Scheme 2). The macrolactamization reaction proceeds virtually as *one-pot* as two successive acylations, which explains the low yield.



Scheme 2. 16-$N_4{}^{CO}Fe_1$-macrocycle. (a) Et_3N, DCM [17].

It can be seen from the X-ray diffraction data (Figure 3a) that the bispidine framework is somewhat distorted, since the distance between opposite ferrocene carbon atoms is greater (3.300 Å) than the distance between nitrogen atoms (2.832 Å). The macrocycle is stabilized by internal p-p, p-p interactions and intramolecular hydrogen bonds within the amide unity. In solution, according to NMR data, the *anti*-conformation of amide fragments is preserved. To change the *anti*-configuration to the *syn* at the bis-amide fragment, bispidine must undergo a chair-boat conformational transition, which is energetically unfavorable for a small cycle [18].

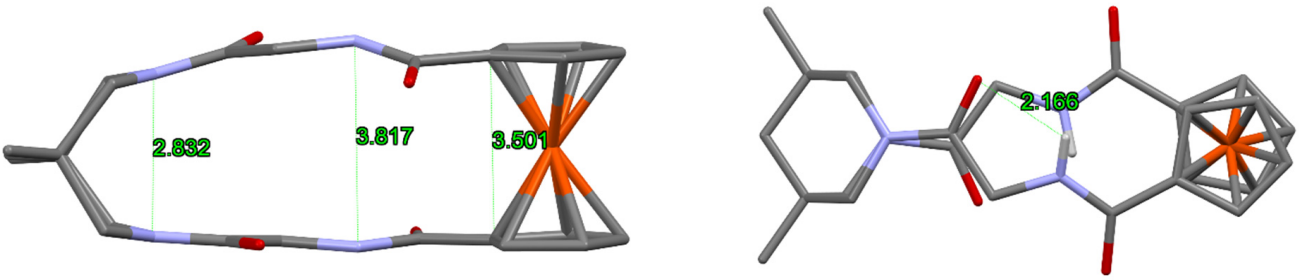


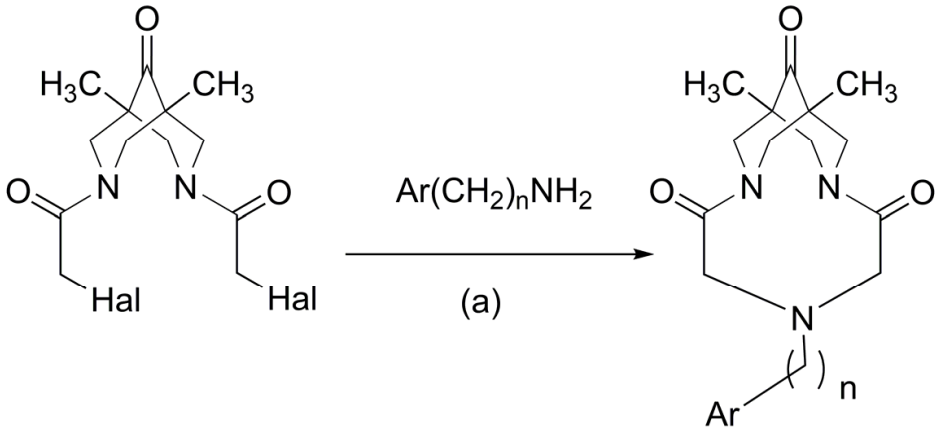
Figure 3. Molecular structure of 16-$N_4{}^{CO}Fe_1$-macrocycle according to X-ray diffraction study [17]: (**a**) side view and (**b**) top view.

The same authors reported [19] the chiral analogues of the 16-$N_4{}^{CO}Fe_1$-macrocycles, using as the starting material both (S) and (R) enantiomers of alanine instead of the glycine used in [17].

It should be noted that for full-amide cycles, their properties as complexing agents or supramolecular receptors are not reported. Apparently, this is because the lone electron pair of nitrogen is involved in conjugation with the amide bond and cannot act as an electron density donor to the acceptor molecule. In general, the mutual orientation of two amide carbonyl groups at the bispidine backbone is *anti*, which is not preorganized for any type of sufficient coordination [18]. At the same time, for bispidine macrocycles with a sufficiently large size/conformationally mobile ring, a transition from *anti*- to *syn*-conformation is possible, which would allow for the formation of complexes with metals due to interaction with lone pairs of carbonyl oxygen atoms. In any case, from the point of view of the selective intermolecular interactions, the most promising examples of bispidine are those containing an *amine* rather than *amide* functionality.

2.2. Mixed Amide-Amine Macrocycles

A more common type of bispidine-based macrocycle is mixed amide-amine macrocycles. Usually, such compounds are synthesized via the nucleophilic substitution of halogen atoms in substituted haloacetylbispidine [18,20–22] (Scheme 3).



Scheme 3. 10-$N^{H}N_2{}^{CO}$-macrocycle. (a) [18]—DIPEA, CH_3CN, Δ, n = 1; [20]—$NaHCO_3$, iPrOH, Δ, n = 1; [21,22]—K_2CO_3, CH_3CN, Δ, n = 2.

The yields in such reactions are usually high. Due to the presence of amide nitrogen atoms in the framework itself, bispidine makes the structure more rigid due to a rather high barrier to rotation around the amide bond (see discussion above). Thus, it was shown that the amide fragments in bispidine-containing dopamine residue are in the *syn*-conformation both in the crystal and in solution [18] (Figure 4).

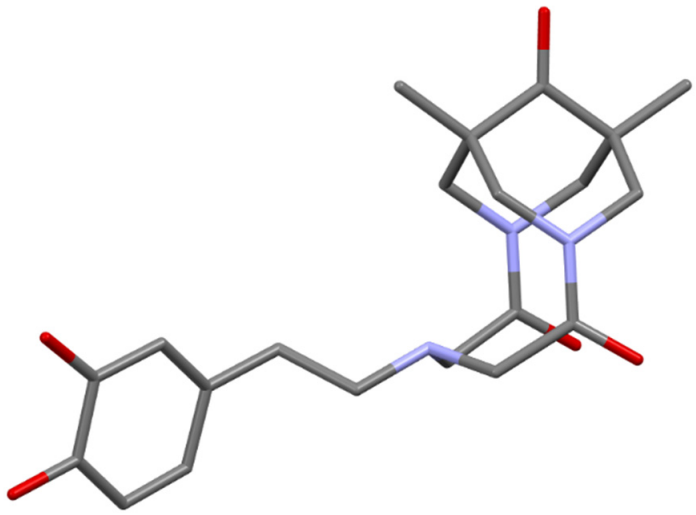
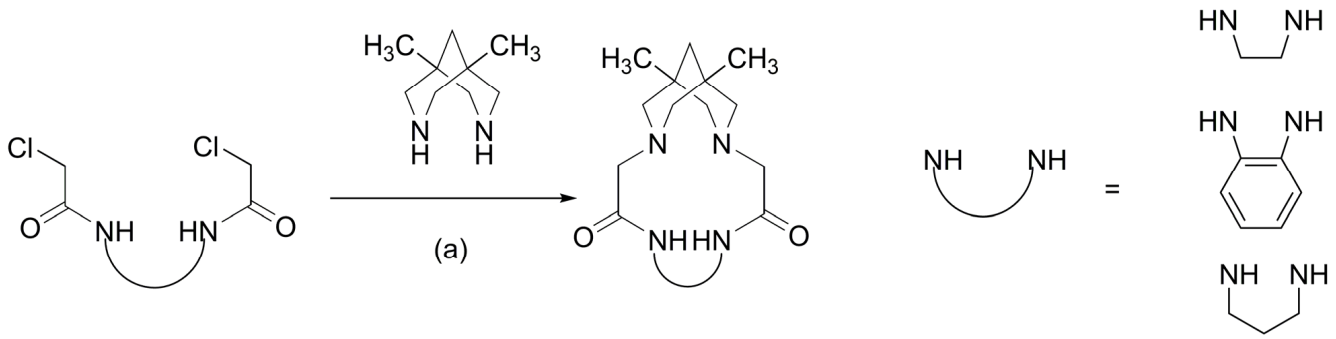


Figure 4. Molecular structure of 10-$N^{H}N_2{}^{CO}$-macrocycle according to X-ray diffraction study [18].

Such ten-membered diazamacrocycles are proposed as allosteric modulators of ionotropic glutamate receptors [20–22]. At the same time, we are not going to discuss these compounds in detail, since the ring size is actually not sufficient to call them real *macrocycles*; they would be better described as *medium-sized cycles*.

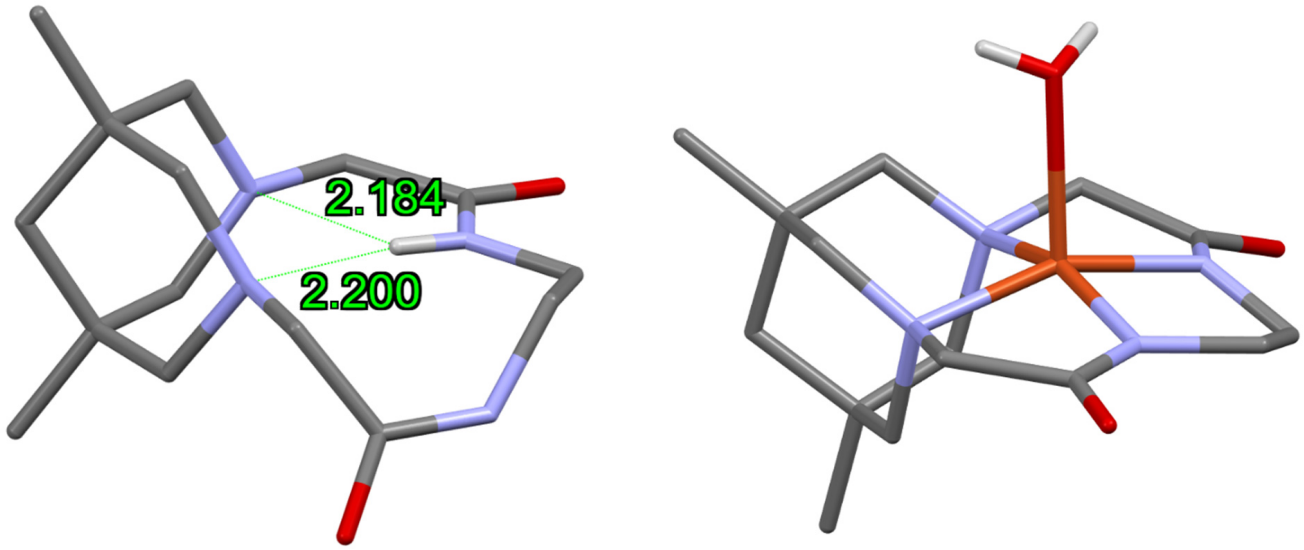
Mixed amido-amine macrocycles can also be obtained by alkylation of bispidine [23] (Scheme 4). In this case, the bispidine nitrogen atoms are explored as nucleophilic centers; the final macrocycle is characterized by a large conformational mobility and the possibility for these N atoms to act as electron density donors to metal ions or small organic molecules, such as solvent molecules (Figure 4).



34-74%

Scheme 4. 13-$N_2{}^{H}N_2{}^{CO}$ and 14-$N_2{}^{H}N_2{}^{CO}$-macrocycles. (a) K_2CO_3, CH_3CN [23].

Copper complexes 13-$N_2{}^{H}N_2{}^{CO}$ and 14-$N_2{}^{H}N_2{}^{CO}$-macrocycles were obtained in the reaction with copper acetate in 56% yields, while the amide group of the linker between N-atoms of the bispidine was deprotonated during the reaction. Although the structure of the initial macrocycles is not preorganized for complex formation, due to the existence of intramolecular hydrogen bonds, the copper coordination polyhedron in the complexes is a regular tetrahedral pyramid (see Figure 5). The rigid structure of the dianion ligands in the complexes made it possible to increase the stability of the resulting complexes with respect to superoxide dismutase. Their lipophilicity and biodistribution were also studied, which made it possible to propose them as a positron emission label based on ^{64}Cu [23].

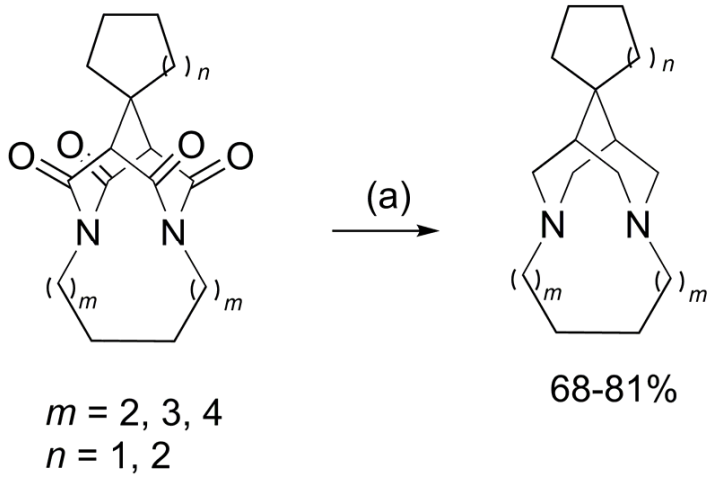


(**a**) (**b**)

Figure 5. Molecular structure of (**a**) 13-$N_2{}^{H}N_2{}^{CO}$–macrocycle according to X-ray diffraction study and (**b**) of its Cu complex [23].

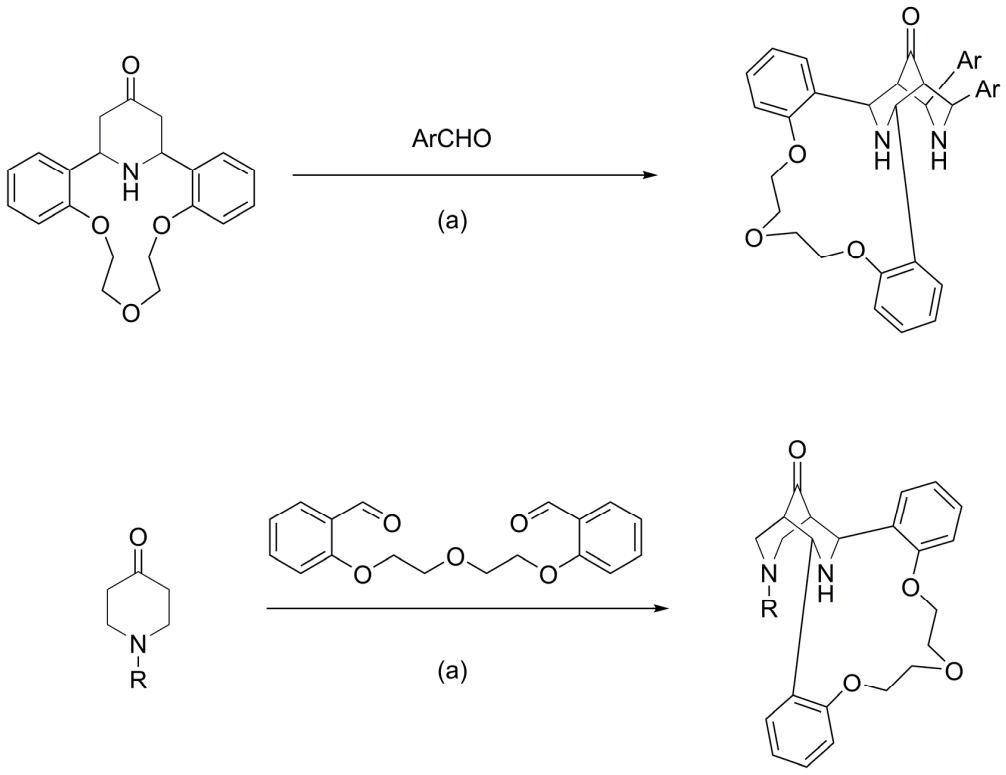
2.3. Full-Amine Macrocycles

Macrocycles with only amine nitrogen atoms are of greater interest due to the possibility of forming stable coordination compounds. Thus, macrocycles containing no other heteroatoms except nitrogen were obtained by reduction of the corresponding amides [16] (Scheme 5). However, the obtained amines turned out to be unstable, which did not allow one to study their properties as complexing agents.



Scheme 5. 11-N_2^H, 13-N_2^H, 15-N_2^H-macrocycles. (a) Red-Al, toluene [16].

Based on bispidines, analogues of azacrown ethers were obtained, in which neither N-atom of the bispidine is involved in the formation of the macrocycle (Scheme 6, first reaction). If an appropriate crown derivative of piperidine-4-one is available, the Mannich reaction is used to obtain an asymmetric macrocycle [24,25]. Otherwise, when the appropriate laurate-type bis-aldehyde is available, the alternative Mannich construction of the bispidin core is possible (Scheme 6, second reaction).



Scheme 6. 14-N^HO_3-macrocycle. (a) NH_4OAc, AcOH, EtOH (Ar = 2-Py, 4-F-C_6H_4, 3,4-$(MeO)_2$-C_6H_3) [24,25], (R = Ac, n-Pr) [26–28].

The crown ether fragment in the obtained compounds is in the equatorial position of the piperidone ring, which is in the boat conformation, so that potentially only one atom of bispidine can participate in complexation (Figure 6) [26]. At the same time, it is worth mentioning the bifurcated hydrogen bond between the N-H group of bispidine and two oxygen atoms of the crown moiety.

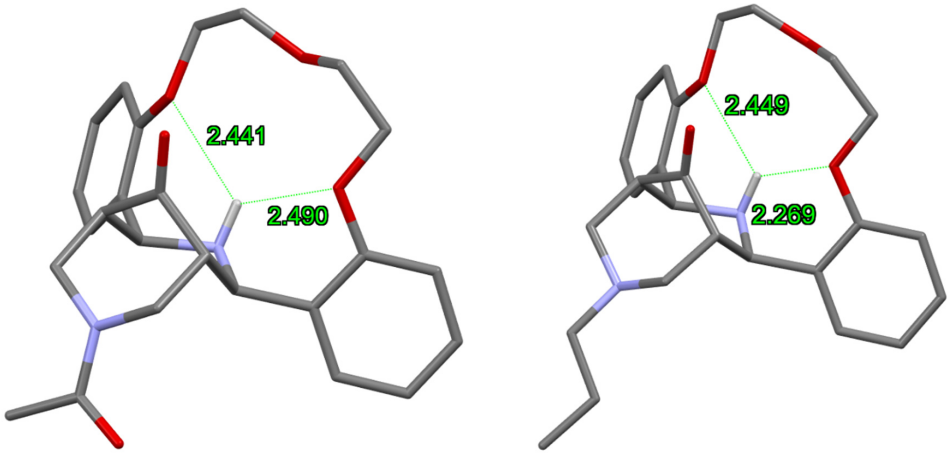
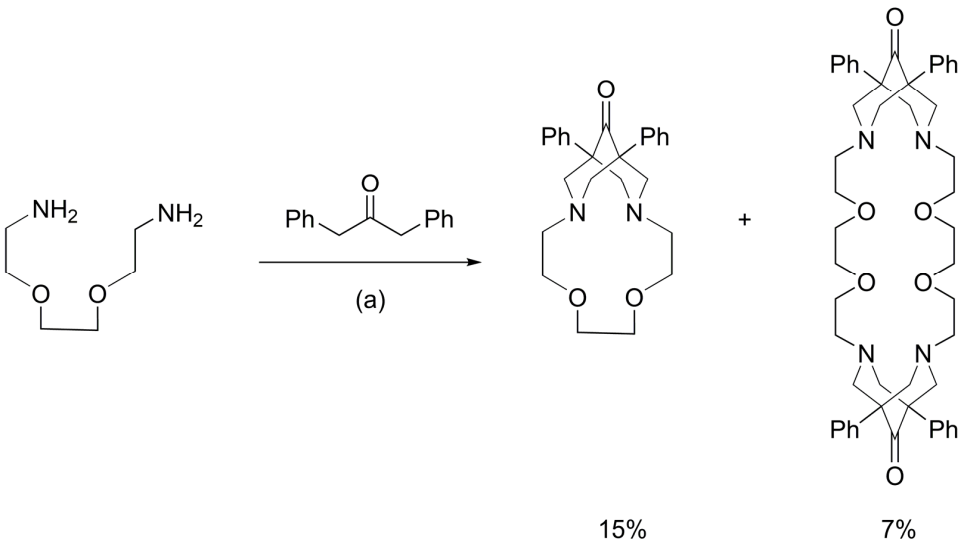


Figure 6. Molecular structures of 14-N^HO_3-macrocycles according to X-ray diffraction study [26].

Macrocycles of type 14-N^HO_3 with 2-pyridinic groups at the positions 2 and 4 of the bispidine (Scheme 6, Ar = 2-Py) are able to form complexes with transition and non-transition metals (Co^{2+} [25,29]; Cu^{2+} and Zn^{2+} [30]; Hg^{2+} [31]; Ni^{2+} [32]); however, the coordination involves only pyridine and bispidine N atoms and does not explore the azacrown fragment. Furthermore, it is worth mentioning here that in all molecules, the bifurcated hydrogen bond between the N-H group of bispidine and two oxygen atoms of the crown moiety is sustained.

It should be noted here that although the 14-aza-4-crowns described in [24–32] do not formally contain molecules that use N atoms of the bispidine to construct the macrocycle, they are added to this review for the purpose of completeness.

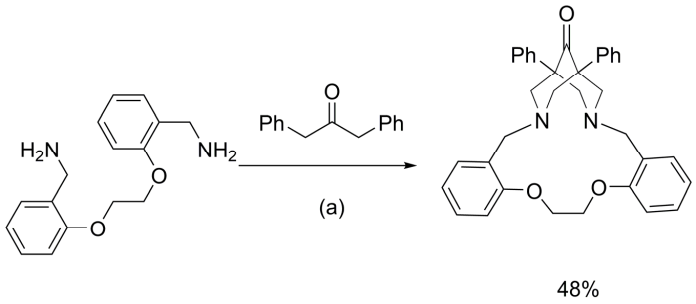
To obtain symmetrical N,N′-disubstituted macrocycles, the double Mannich reaction is used; however, the yield in such a reaction is quite low [33] (Scheme 7), which is obviously due to the formation of several products. In both products, 13-$N_2{}^HO_2$- and 26-$N_4{}^HO_4$-macrocycles, the bispidine core is in a "chair-boat" conformation.



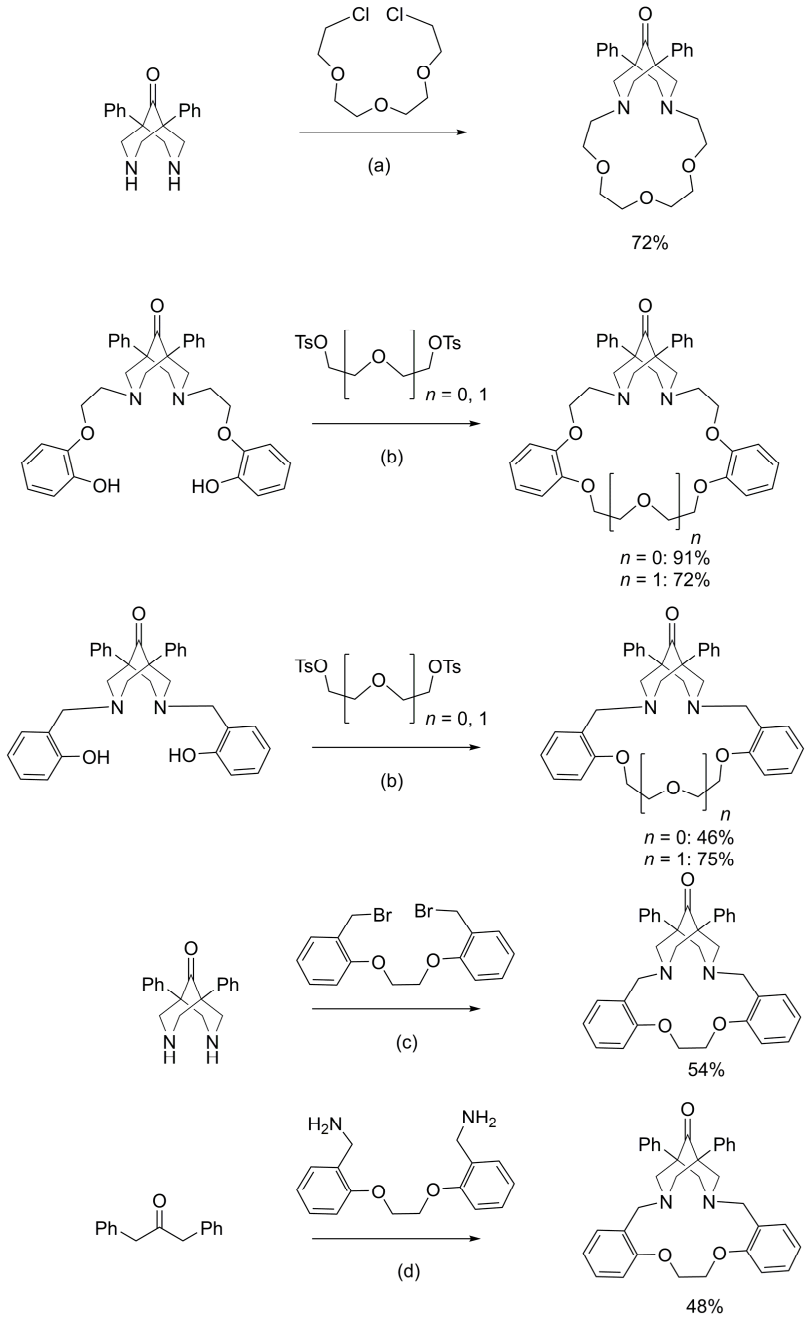
Scheme 7. 13-$N_2{}^HO_2$- and 26-$N_4{}^HO_4$-macrocycles. (a) $(CH_2O)_n$, AcOH, MeOH [33].

Slightly larger rings are formed in the double Mannich reaction with better yields (Scheme 8) [34].

However, a more convenient method is the Pedersen reaction, which gives yields from 46 to 91% in the synthesis of 15-17-$N_2{}^HO_3$ [34–36]. Scheme 9 shows the synthesis of various macrocycles using this approach.



Scheme 8. 15-$N_2{}^HO_2$-macrocycle. (a) $(CH_2O)_n$, AcOH, EtOH [34].



Scheme 9. 16-$N_2{}^HO_3$-macrocycle: (a) Na_2CO_3, NaI, CH_3CN, reflux. 19-$N_2{}^HO_4$-, 22-$N_2{}^HO_5$-, 15-$N_2{}^HO_2$- and 18-$N_2{}^HO_3$-macrocycles: (b) KOH, THF, H_2O. 15-$N_2{}^HO_2$-macrocycle: (c) KOH, DMSO, H_2O and (d) $(CH_2O)_n$, AcOH, EtOH [34].

Due to the large size of the macrocycle and to the presence of two phenyl groups at the postiions 1 and 5, bispidine presents in the "chair-boat" conformation. The macrocycle itself is strongly distorted, so that one of the oxygen atoms is directed outward from the cavity of the macrocycle (Figure 7).

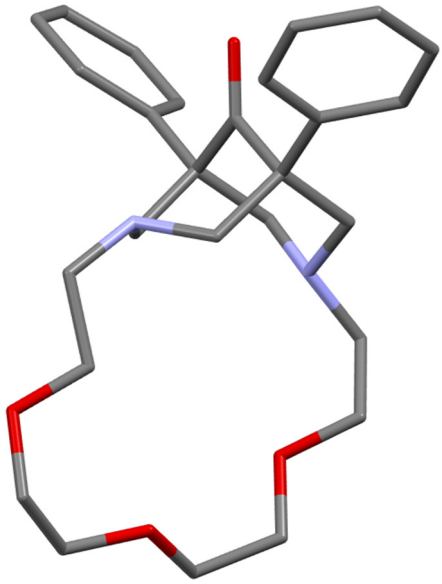


Figure 7. Molecular structure of 16-$N_2{}^{H}O_3$-macrocycle according to X-ray diffraction study [35].

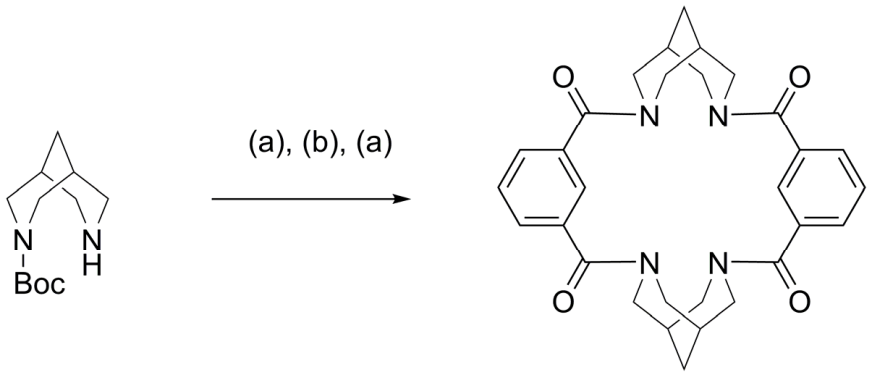
It should be noted here that although the aza-crowns shown in Schemes 7–9 represent potential host-type molecules, no data on their intermolecular interactions with appropriate guest molecules are reported.

3. Macrocycles with Two or More Bispidine Fragments

3.1. Full-Amide Macrocycles

Macrocycles containing several bispidine fragments seem to be more promising compared to mono-bispidine macrocycles due to the higher preorganization of bispidines compared to other, more flexible amines. At the same time, the macrocycle size increases: the range of cycle sizes with one bispidine is 10–17, and with two or more bispidines, the size ranges from 14 to 50.

A 20-membered macrocycle containing isophthalic fragments is obtained by stepwise acylation of mono-protected bispidine [37]. This is followed by the step of removing the protective group and repeated double acylation with bis-acyl chloride—a process that is called "macrolactamization reaction" (Scheme 10).



Scheme 10. 20-$N_4{}^{CO}$-macrocycle. (a) Isophthaloyl dichloride, Et_3N, 0–20 °C, 12 h, DCM. (b) TFA, DCM, 4 h [37].

The spatial form of the tetraamide is a calixarene-like cone with co-directed hydrophilic carbonyl groups (Figure 8). Compounds of this type are positioned as promising molecular receptors, since they can form crystalline hydrates; however, no other data are reported.

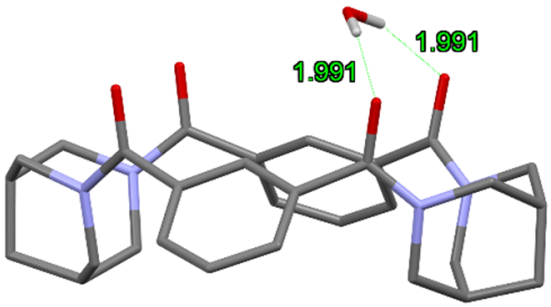
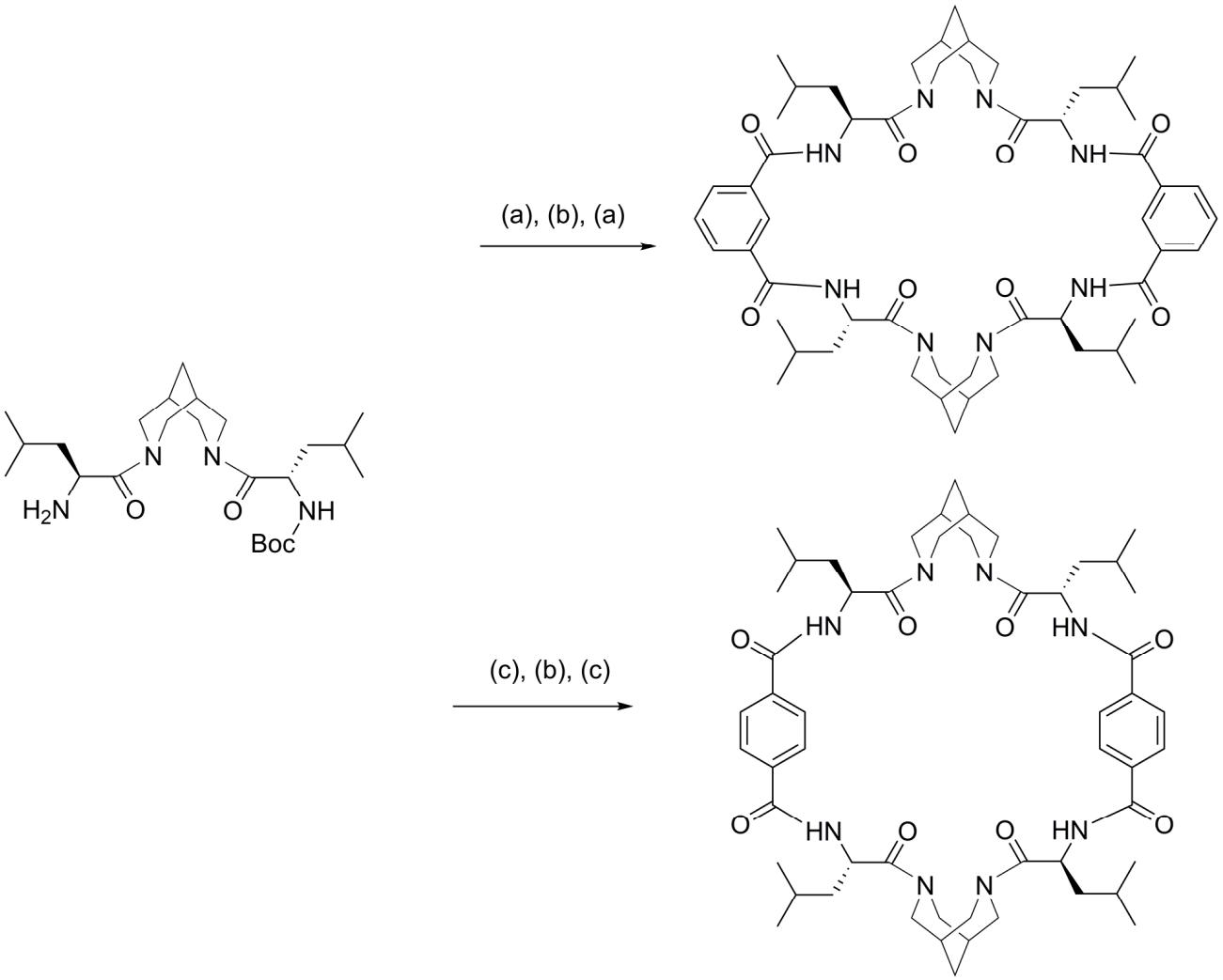


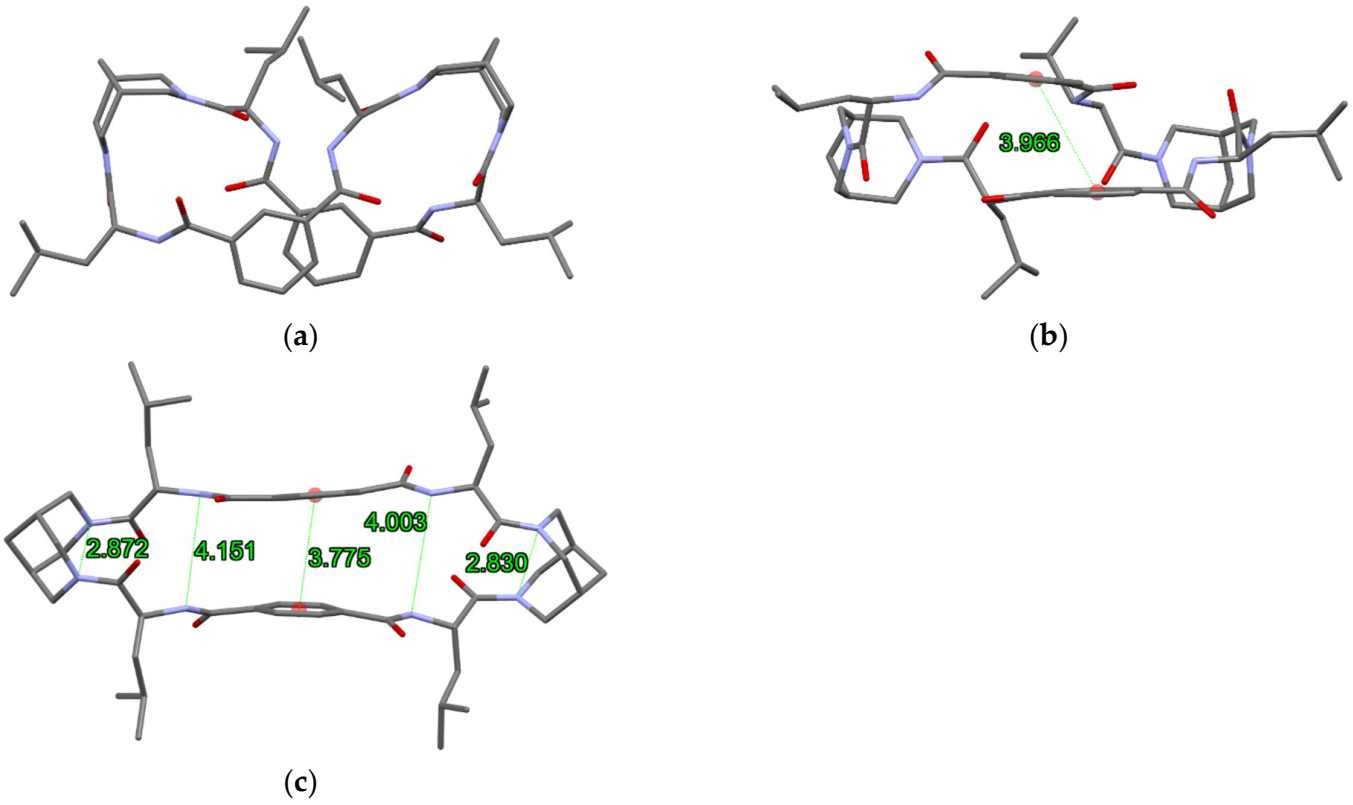
Figure 8. Molecular structure of 20-N_4^{CO}-macrocycle hydrate according to X-ray diffraction study [37].

If bispidine itself is not used but its amino acid derivatives are and the reaction is also carried out in stages, larger macrocycles are obtained in a similar way to those mentioned above (Scheme 11) [38].



Scheme 11. 32-N_8^{CO}- and 34-N_8^{CO}-macrocycles. (a) Isophthaloyl dichloride, Et_3N, 0–20 °C, 12 h, DCM. (b) TFA, DCM, 4 h. (c) Terephthaloyl dichloride, Et_3N, 0–20 °C, 12 h, DCM [38].

At the same time, in the case of isophthaloyl bridges, the macrocycle turns out to be twisted into a spiral form (Figure 9a,b), and in the case of terephthaloyl bridges, a cavity is formed from almost crossing bridge fragments (Figure 9c). The presence of this cavity makes it structurally similar to the 16-$N_4{}^{CO}Fe_1$-macrocycle described above [17] (Figure 3); the only difference is that in the latter, the role of the second bispidine is played by ferrocene.



(**a**) (**b**) (**c**)

Figure 9. Molecular structures of 32-$N_8{}^{CO}$-macrocycle ((**a**) top view and (**b**) side view) and of (**c**) 34-$N_8{}^{CO}$-macrocycle according to X-ray diffraction study [38].

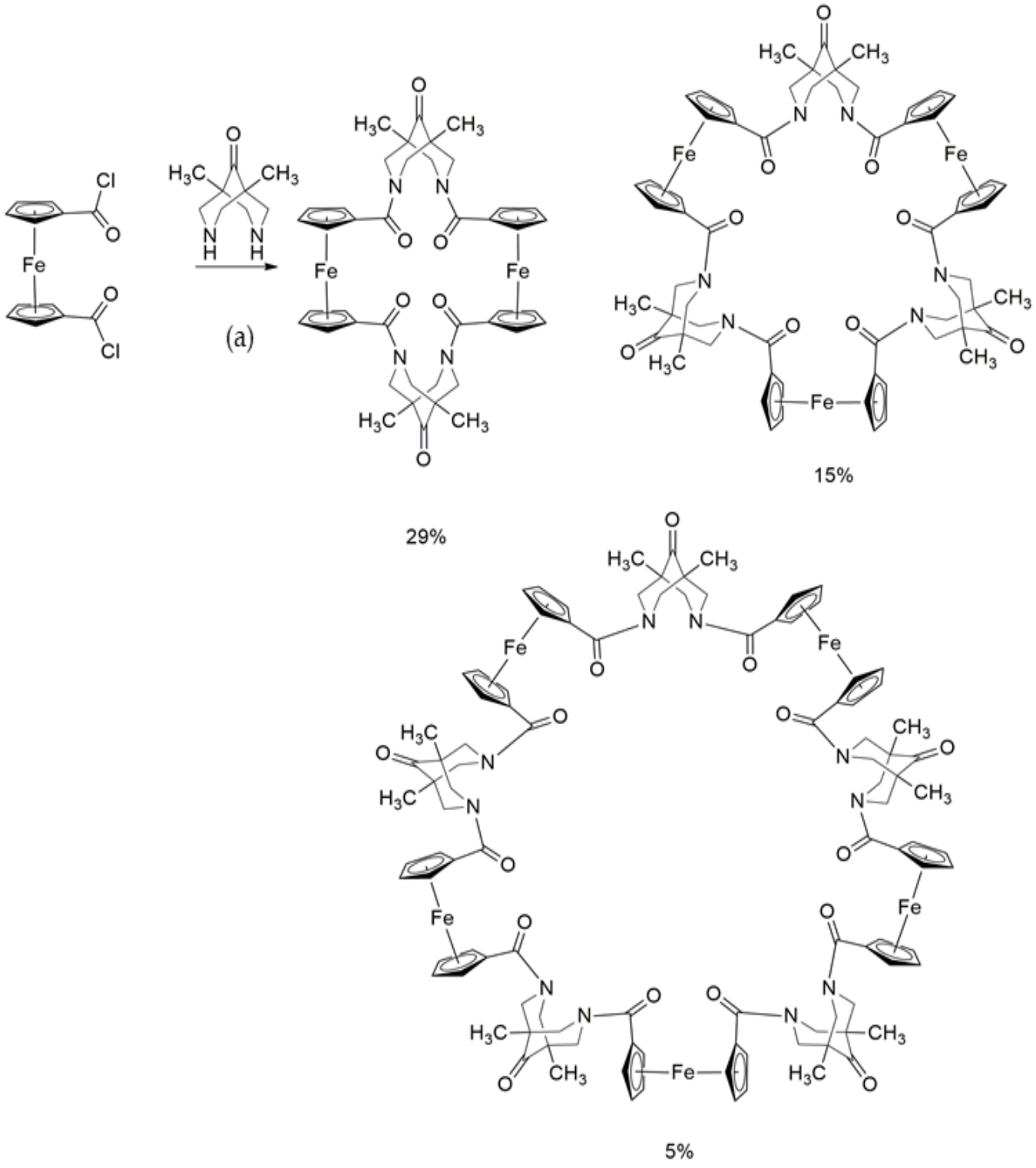
Other examples of macrocycles with several bispidine fragments are presented by poly(bispidine-ferrocenes) [17]. Thus, a series of compounds containing two, three, and five bispidine and ferrocene fragments was obtained in the acylation reaction using a large dilution of the reagents (Scheme 12).

The structure of the 20-$N_4{}^{CO}Fe_2$-macrocycle in the solid state was studied using X-ray diffraction analysis (Figure 10). All carbonyl groups are in mutual *anti*-conformation, while the cycle is rather rigid, which is confirmed by VT NMR data. The molecule presents in a twisted conformation that possesses a formal C_2 symmetry axis passing through the carbonyl groups at positions 9 of the bispidines. The cavity in the center of the macrocycle is not sufficient to accept any guest molecule.

When obtaining mixed amide-amine macrocycles, instead of two acylation reactions, the sequence "acylation-alkylation" is also used. This concept is illustrated by macrocycles with short bridges between the nitrogen atoms of two bispidine building blocks (Scheme 13).

These amides, according to X-ray diffraction analysis (Figure 11), are rather rigid molecules with a stepped arrangement of bispidine fragments. In this case, the carbonyl groups are in the *syn*-position relative to each other and are directed outside the cavity.

The alkylation-acylation sequence is also used to obtain macrocycles with larger linkers (Scheme 14) [37].



Scheme 12. 20-$N_4^{CO}Fe_2$-, 30-$N_6^{CO}Fe_3$- and 50-$N_{10}^{CO}Fe_5$-macrocycles. (a) Et_3N, toluene, 20 °C [17].

The structures of the obtained macrocycles (Figure 12) are, in general, similar to the structure of the 20-N_4^{CO}-macrocycle (Figure 8). The only difference is observed in the angles between the planes of the benzene rings, which change from 112.68° for the 21-$N_2^{H}N_2^{CO}$-macrocycle to 128.36° for the 22-$N_2^{H}N_2^{CO}$-macrocycle.

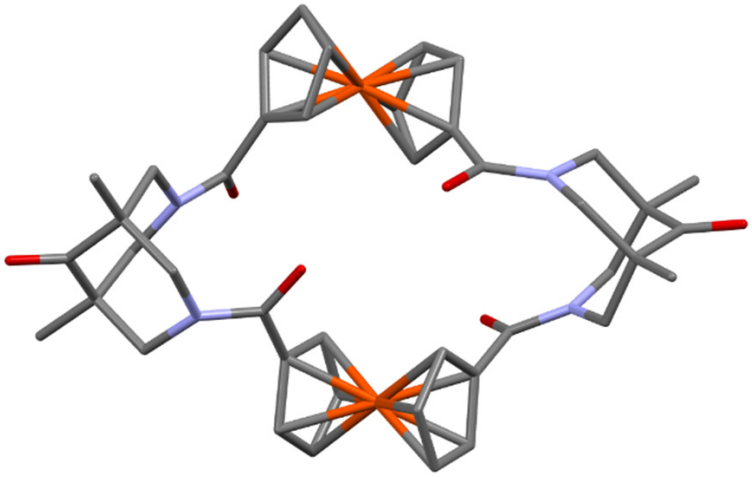
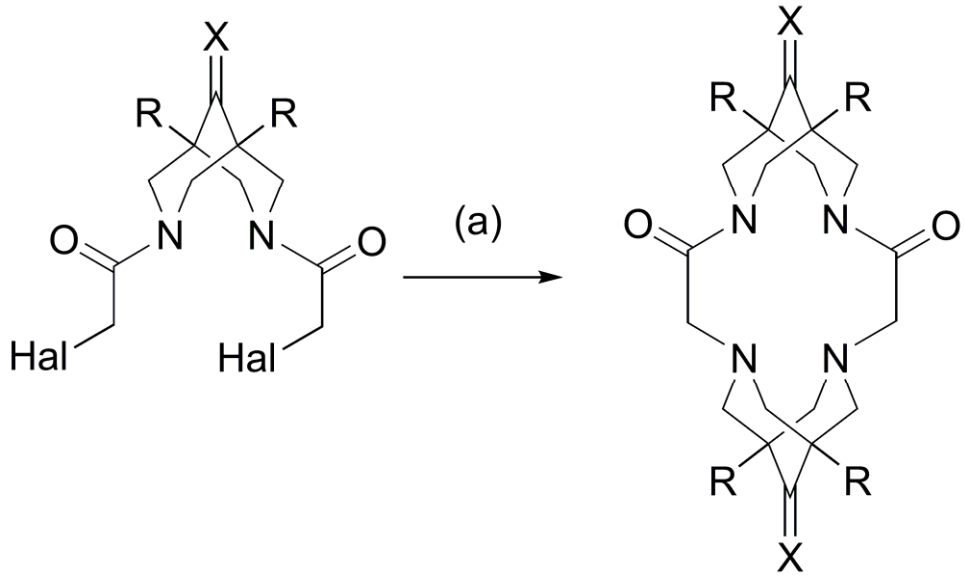


Figure 10. Molecular structures of 20-$N_4^{CO}Fe_2$-macrocycle according to X-ray diffraction study [17].



Scheme 13. 14-$N_2^{H}N_2^{CO}$-macrocycles. (a) R = Ph, X = CH_2, Hal = Cl, Na_2CO_3, CH_3CN [39], or R = CH_3, X = CH_2, Hal = Br, $NaHCO_3$, THF, H_2O [40], or R = H, X = $C(OEt)_2$, Hal = Br, NaOH, THF [41].

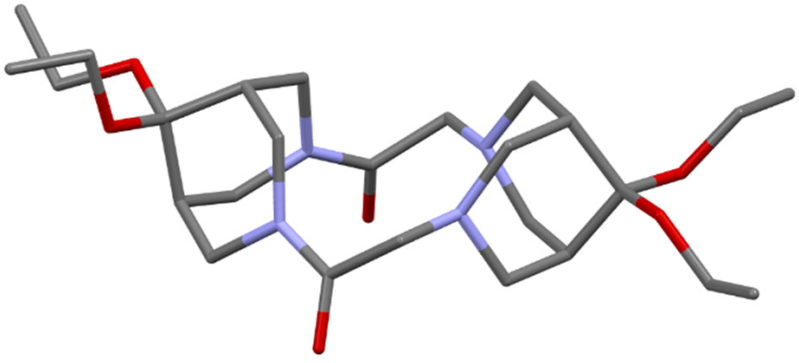
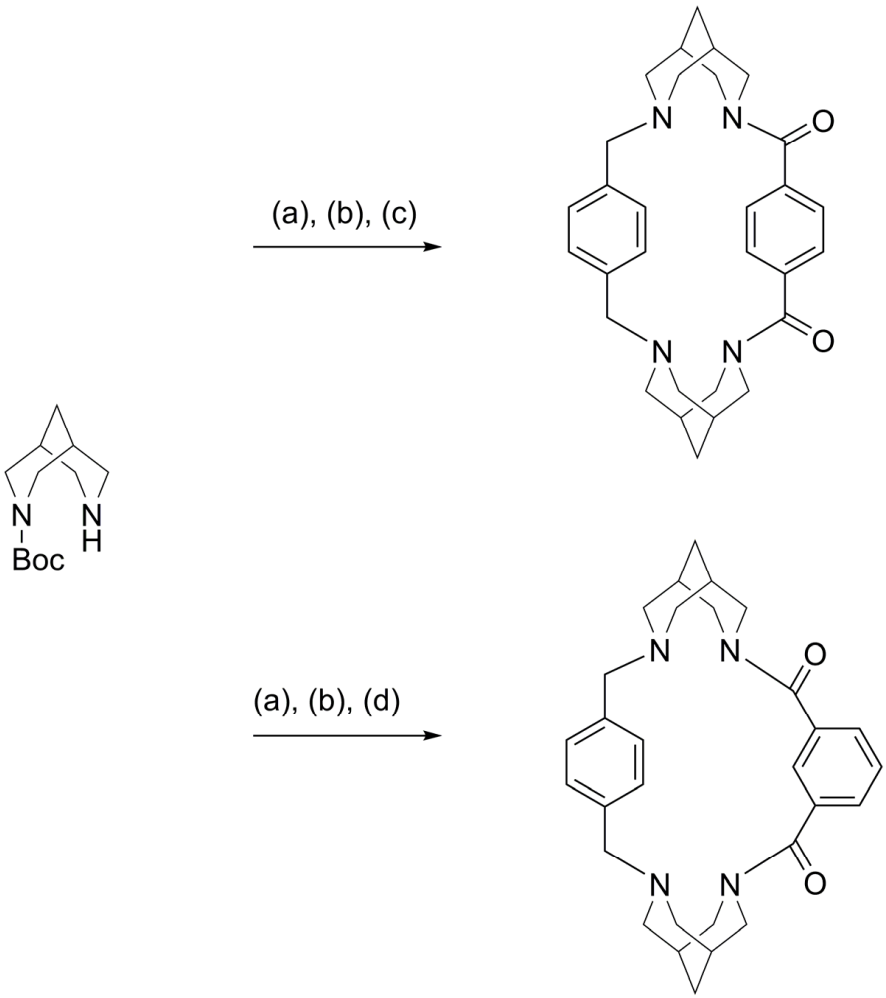


Figure 11. Molecular structure of 14-$N_2^{H}N_2^{CO}$-macrocycle according to X-ray diffraction study [41].



Scheme 14. 22-$N_2{}^{H}N_2{}^{CO}$- and 21-$N_2{}^{H}N_2{}^{CO}$-macrocycles. (a) p-dibromoxylene, Et_3N, 0–20 °C, 12 h, DCM. (b) TFA, DCM, 4 h. (c) Terephthaloyl dichloride, Et_3N, 0–20 °C, 12 h, DCM. (d) Isophthaloyl dichloride, Et_3N, 0–20 °C, 12 h, DCM [37].

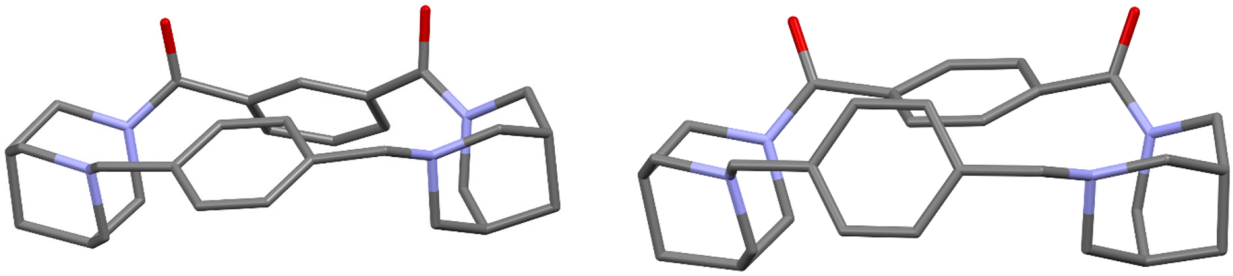
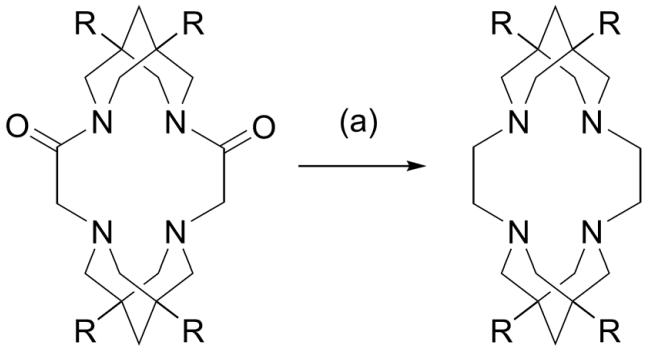


Figure 12. Molecular structures of 21-$N_2{}^{H}N_2{}^{CO}$- and 22-$N_2{}^{H}N_2{}^{CO}$-macrocycles according to X-ray diffraction study [37].

The principle difference between the amine-amide-type macrocycles shown in Figures 11 and 12 is that in the former, two amide functions belong to one bispidine, while in the latter, each bispidine fragment possesses both amide- and amine-type nitrogen atoms.

3.2. Full-Amine Macrocycles

Amine-type macrocycles are obtained by reduction of the corresponding amides [39–45] (Scheme 15).



Scheme 15. 14-$N_4{}^H$-macrocycle. (a) DIBAH (R = Ph or CH_3).

The authors of [39,42] showed that the resulting tetraamines have a very high basicity, higher than that of 1,8-bis(dimethylamino)naphthalene ("proton sponge"). The dication (14-$N_4{}^H$-macrocycle) $2H^+$ donated only one proton during titration, behaving like a monoacid. The resulting compound also proved to be a complexing agent with respect to the Li^+ ion, and the binding constant with the latter was equal to 2.2×10^6 M.

Bis-bispidine macrocycles of this type possessing carbonyl, diethylketal, ethoxycarbonyl [43], and hydroxymethylmethylene groups [44] at the C(9) position could also be obtained (Figure 13).

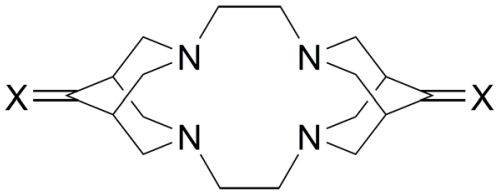


Figure 13. General view of the bis-bispdine macrocycles (type 14-$N_4{}^H$) possessing various functional groups at the C(9) position (X = O, H_2, $CHCO_2Et$ [43], $CH(CH_2OH)$ [44]; X = $(OEt)_2$ [41,45]).

The crystal structure of the 14-$N_4{}^H$-macrocycle with diethyxoketal groups at the C(9) position reveals a channeled organic crystal, in which weak directional interactions, such as long-range CH···O hydrogen bonds and N-C···O-C dipole–dipole interactions, are indicated [45].

An X-ray diffraction study of one of the amines showed that it has a zigzag (also called "stepped") structure similar to the amide 14-$N_2{}^HN_2{}^{CO}$-macrocycle [23], whose cavity is already capable of coordinating the divalent copper ion [40] (Figure 14).

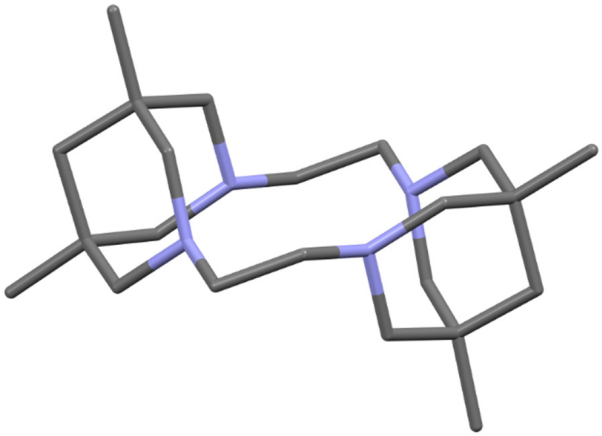
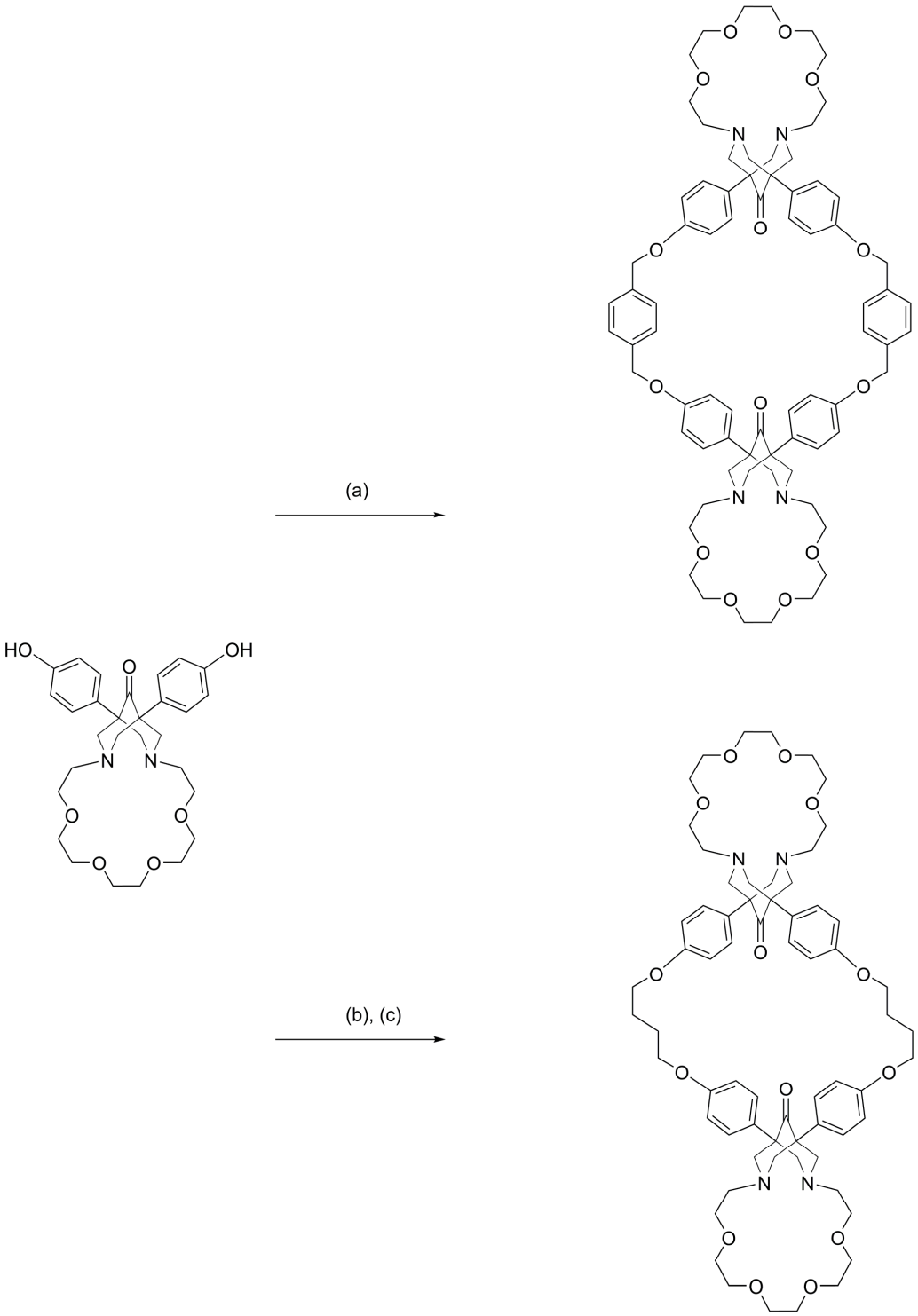


Figure 14. Molecular structure of 14-$N_4{}^H$-macrocycle according to X-ray diffraction study [40].

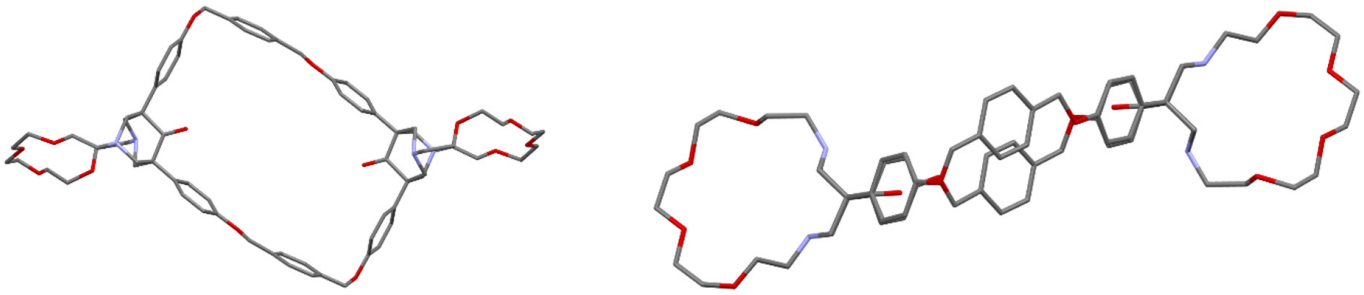
The quantum chemical calculations of the N_4-tetraminomacrocycle reveals a C_{2h} molecular structure with stepped ethylene bridges, as is found in the X-ray study [46]. The calculations are confirmed by NMR and photoelectron spectral analyses.

In the synthesis of macrocycles with two bispidines that each contain a crown ether fragment, the Pedersen reaction can also be used [36]. In this case, hybrid macrocycles with several functional fragments in one molecule are obtained (Scheme 16).



Scheme 16. 19-$N_2{}^HO_4$-38-O_4-19-$N_2{}^HO_4$- and 19-$N_2{}^HO_4$-34-O_4-19-$N_2{}^HO_4$-macrocycles. (a) p-xylylene dibromide, Cs_2CO_3, CH_3CN, reflux, 14%. (b) 1,4-dichlorobutane, NaH, DMF, 20 °C, 99%. (c) Cs_2CO_3, DMF, 80 °C, 18%.

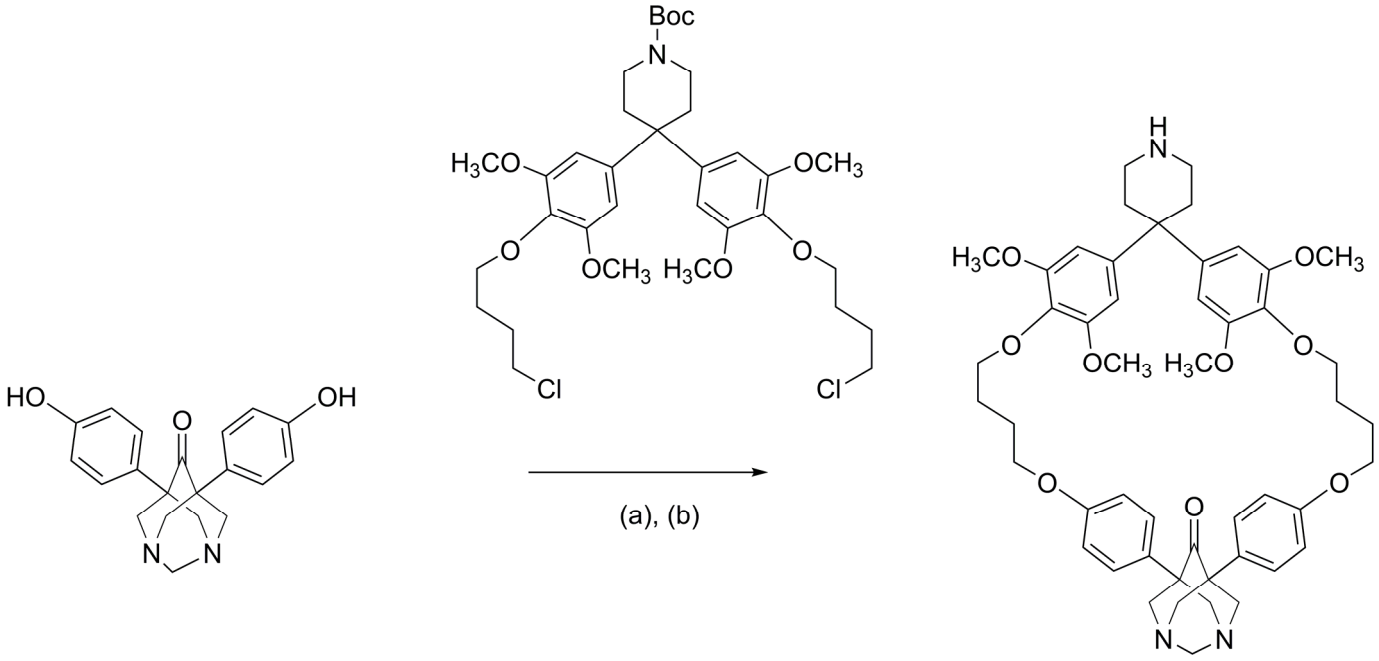
According to X-ray diffraction analysis, these compounds have a large cavity that can potentially bind "guest" molecules (Figure 15).



(**a**) (**b**)

Figure 15. Molecular structure of 19-$N_2{}^HO_4$-38-O_4-19-$N_2{}^HO_4$-macrocycle: (**a**) top view and (**b**) side view.

However, a detailed study of the receptor properties of this macrocycle (Scheme 16, Figure 15) showed that binding between the 19-$N_2{}^HO_4$-38-O_4-19-$N_2{}^HO_4$-macrocycle and hydrocortisone, cholic acid, and adamantane-1-acetic acid was not observed. Then, the authors of [47] obtained a hybrid 32-O_4-macrocycle (Scheme 17), which turned out to be able to form complexes with some hydrophobic compounds, for example, 6-hydrozynaphthalene-2-carbonitrile, although with a low stability constant of about 200 M. It should be noted that in such a compound, bispidine nitrogen atoms do not participate in any way in the coordination of the guest molecule.



Scheme 17. 32-O_4-macrocycle. (a) Cs_2CO_3, DMF, 50–55 °C, 6 d, 13%. (b) TFA, DCM, 20 °C, 52%.

4. Concluding Remarks

In writing this review, we try to paint the whole picture of all known macrocycles containing one or more bispidine units in their structures. As a result, we could state that there is a limited amount of structural types, which are collected in Table 2.

Table 2. The known types of bispidine-containing macrocycles (for notation, see Figure 1).

Cycle Size	Full Amine	Full Amide	Amino-Amide
10			10-$N^{H}N_2{}^{CO}$
11	11-$N_2{}^{H}$	11-$N_2{}^{CO}$	
13	13-$N_2{}^{H}$ 13-$N_2{}^{H}O_2$	13-$N_2{}^{CO}$	13-$N_2{}^{H}N_2{}^{CO}$
14	14-$N_4{}^{H}$ 14-$N^{H}O_3$ *		14-$N_2{}^{H}N_2{}^{CO}$
15	15-$N_2{}^{H}$ 15-$N_2{}^{H}O_2$	15-$N_2{}^{CO}$	
16	16-$N_2{}^{H}O_3$	16-$N_4{}^{CO}Fe_1$	
18	18-$N_2{}^{H}O_3$		
19	19-$N_2{}^{H}O_4$ 19-$N_2{}^{H}O_4$-38-O_4-19-$N_2{}^{H}O_4$ 19-$N_2{}^{H}O_4$-34-O_4-19-$N_2{}^{H}O_4$		
20		20-$N_4{}^{CO}$ 20-$N_4{}^{CO}Fe_2$	
21			21-$N_2{}^{H}N_2{}^{CO}$
22	22-$N_2{}^{H}O_5$		22-$N_2{}^{H}N_2{}^{CO}$
26	26-$N_4{}^{H}O_4$		
30		30-$N_6{}^{CO}Fe_3$	
32		32-$N_8{}^{CO}$	
34		34-$N_8{}^{CO}$	
50		50-$N_{10}{}^{CO}Fe_5$	

*—the second N-atom of the bispidine is not involved in the macrocycle formation.

The supramolecular and coordination chemistry of bispidine macrocycles is still at the beginning of its journey. Indeed, the key properties of bispidine-based macroheterocycles have not been studied in many respects. For example, the high stability of the complexes of 14-N_4-tetraazamacrocycles with Cu^{2+} ion coud be mentioned; and also, the high basicity of the same macrocycle is worth mentioning. At the same time, no data on the successful application of bispidinic macroheterocycles as selective host molecules or catalysts are reported.

Nevertheless, based on the data collected and analyzed in this review and based on the logic of the development of the supramolecular chemistry of macroheterocycles, we can predict a fast and imminent development in the following directions: (i) the creation of selective host molecules for various types of guest molecules, including metal cations and neutral organic molecules; (ii) the application of chiral macrocycles as selective sensors for chiral analytes; (iii) the use of bispidine macrocycles in the field of supramolecular catalysis; and (iv) the application of such molecules in medicinal chemistry.

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