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Aromatic and heteroaromatic azacrown compounds: advantages and disadvantages of rigid macrocyclic ligands

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Current approaches to the synthesis of aromatic and heteroaromatic azamacrocycles and their derivatives are summarized and systematized. The relationship between the structure of azacrown compounds and their complexation behaviour towards metal cations is analyzed. The diversity of practical applications of azamacrocyclic derivatives in medicine, biology and analytical and organic chemistry, as well as for the design of molecular devices is demonstrated.
The bibliography includes 307 references.

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1. Introduction

Since J.Pedersen's discovery of the first crown ethers,[1] a multitude of diverse macrocycles containing various heteroatoms and aliphatic or aromatic moieties in the molecules have been synthesized. The ability to bind alkaline earth, heavy and transition metals not only in organic solvents, but also in water accounts for the keen attention of contemporary researchers to azacrown compounds. These compounds are successfully used in various fields of science and technology: in catalytic processes of organic synthesis, as highly selective receptors for cations and anions in analytical chemistry, for the development of contrast agents for magnetic resonance imaging and radiopharmaceuticals in medicine. In addition, azacrown compounds are used as reagents in biochemical assays and as important constituent blocks in molecular devices for various purposes.

A variety of aspects of the chemistry of crown compounds were fully and comprehensively covered in the book of Professor M.Hiraoka [2] published in 1982. The monograph of J.S.Bradshaw [3] (1993) is devoted to the complexing properties and applications of azacrown macrocycles. More recent studies describe phenylaza- and benzoazacrown compounds with a nitrogen atom conjugated with the benzene ring,[4] azamacrocycles connected by linkers,[5] phenanthroline-containing macrocycles,[6] halogenated benzocrown ethers [7] and macrocyclic Schiff bases.[8] Particular attention is drawn by studies of the properties and elucidation of possible applications of crown compounds.[9–12]

This review summarizes the data published over the last 15 years on the methods of synthesis of azacrown compounds containing benzene, pyridine or another aromatic ring and their derivatives with chelating groups. Currently, it has been shown that the introduction of aryl and hetaryl groups into azacrown molecules endows the macrocyclic system with rigidity, thus providing preorganization of the cavity towards complex formation. In the case of azacrown compounds, this is an important issue, because they chelate, first of all, heavy metal and lanthanide cations, the complexation of which may be slow. Owing to the absence of time and energy consumption for unfolding of the macrocyclic cavity, the complex formation is faster and more efficient. In addition, an aryl moiety can act as the site for the introduction of reactive groups, which can serve for incorporation of the macrocycle into a functional molecule or into an organic biological polymer. This opens up broad prospects for the practical application of these materials.

It is known that crown compounds can strongly and selectively bind cations, anions and organic and inorganic neutral molecules.[13–16] The stability of such complexes depends on many factors, the key of them being the size of the macrocyclic cavity; the number the nature, and the relative arrangement of heteroatoms; the rigidity of the macrocyclic core; the nature of the solvent; the nature of the counter-ion; and so on. Since these regularities must be understood for the design of ligands with specified characteristics, the second part of this review gives analysis of the complexing properties of macrocyclic ligands depending on their structural features.

The final Section of this review considers practical applications of azacrown compounds and their complexes and the challenges and prospects of application of macrocycles of this type.

The following acronyms and designations are used in the review:

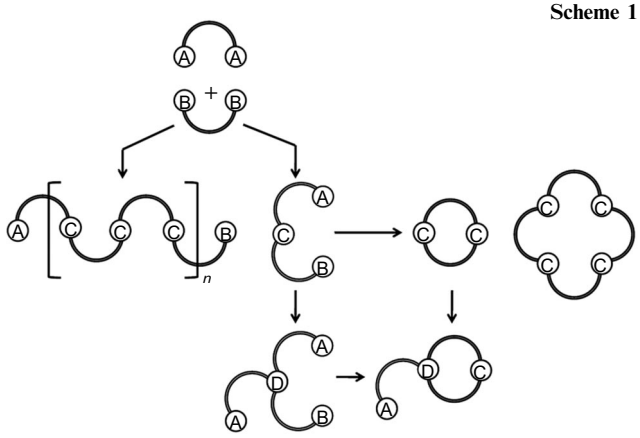
Boc — *tert*-butoxycarbonyl,
Cbz — benzyloxycarbonyl,
Cy — cyclohexyl,
Dep — diethoxyphosphoryl,
DTPA — diethylenetriaminepentaacetic acid,
EDTA — ethylenediaminetetraacetic acid,
HIV — human immunodeficiency virus,
MRI — magnetic resonance imaging,
Ms — methanesulfonyl (mesyl),
Ns — *p*-nitrobenzenesulfonyl (nosyl),
*o*NBS — *o*-nitrobenzenesulfonyl,
PET — positron emission tomography,
PG — protecting group,
Py — pyridyl,
SPECT — single-photon emission computed tomography,
Th — thienyl,
Ts — *p*-toluenesulfonyl (tosyl).

2. Synthesis of azacrown compounds

The key step of the synthesis of azacrown compounds is macrocyclization, which represents, most often, the reaction of two acyclic molecules accompanied by the formation of two new bonds between their terminal groups. It should be borne in mind that competitive reactions can result in mixtures of linear, branched and cyclic oligomers (Scheme 1).

Unfortunately, under conditions characteristic of macrocyclization, linear polymerization predominates, because the formation of a macrocyclic product requires that the long and flexible intermediate molecule adopts an appro-

Scheme 1



A, B are reacting groups; C is the group formed upon the reaction of A and B; D is the group formed upon the reaction of A and C

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Translation: Z.P.Svitanko

priate pseudocyclic conformation. Therefore, the synthesis may give a complex mixture of products containing only trace amount of the target macrocyclic compound. Therefore, in the synthesis of macrocyclic ligands, primary attention is devoted to overcoming this problem. As a result, several synthetic strategies for conducting macrocyclization in satisfactory yields have been developed. These methods, which minimize the probability of side reactions, are based on the restriction of the frequency of intermolecular collisions (high dilution [17] and high pressure [18] methods) or on the provision of the appropriate conformation of reactants (template synthesis and preorganization induced by external factors [19, 20]). In recent years, several research groups have implemented a new approach to this synthetic problem, which includes the static and dynamic combinatorial chemistry methods.[21–23]

The high dilution method implies conducting the reaction at low concentrations of the reactants to decrease the probability of intermolecular collisions between the species formed upon the reaction of one pair of terminal groups of the two acyclic molecules. This suppression of chain propagation induced by the intermolecular reaction favours the ring closure, which is an intramolecular reaction.

The template synthesis of macrocycles implies the use of metal cations as templating agents. In the literature, this process is regarded as a sort of catalytic reaction in which the metal cation stabilizes the cyclic intermediate. The formation of the template complex accounts for the thermodynamic effect favourable for the reaction. In addition, the formation rate of the cyclic product sharply increases because of preorganization of reactants in the template complex, *i.e.*, the template effect is also a kinetic factor accelerating the reaction. The alkali, alkaline earth and transition metal cations and also lanthanide cations can behave as templating agents. The highest yields of macrocyclization are observed when the cation size corresponds to the size of the cavity of the crown compound.[24]

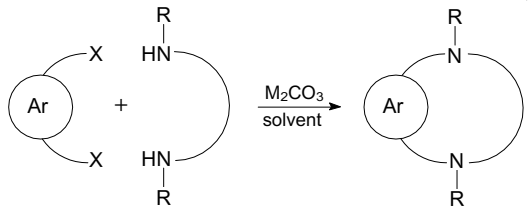
The synthetic routes to azacrown compounds reported in the literature differ by reactants, reaction conditions, the chosen solvent and the purity and yield of the products. Usually, crown compounds are prepared *via* reactions that give ethers, secondary or tertiary amines and amides.

2.1. Reactions of halides with amines

2.1.1. Reactions of terminal dihalides with α,ω-diamines

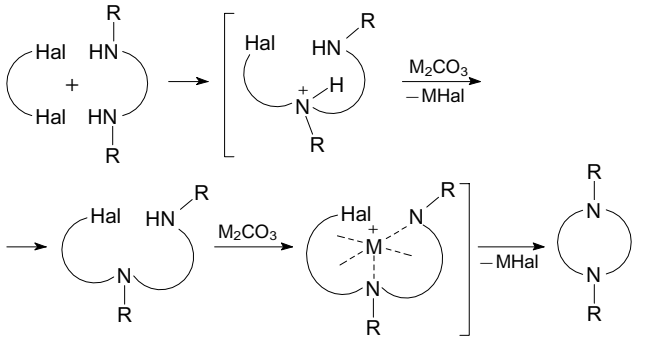
The macrocyclization between terminal dihalides, ditosylates, dimesylates and α,ω-diamines is a direct route towards azacrown compounds (Scheme 2). The reaction is carried out at room temperature or under reflux with vigorous stirring of the reaction mixture for 6–75 h. The predominance of intramolecular cyclization can be attained by both the template effect of metal ions and high dilution.[24, 25]

Scheme 2



R = H, Me; M = Na, K; X = Cl, Br, I, OTs, OMs; Ar = 1,2-phenylene, pyridine-2,6-diyl; solvent: DMF, MeCN, xylene, THF, EtOH, Bu^{t}OH (Ts is tosyl, Ms is mesyl)

Scheme 3



R = H, Me; M = Na, K

A putative reaction mechanism is shown in Scheme 3. The acyclic intermediate forms a complex with an alkali metal cation. Owing to its favourable orientation, the terminal groups approach each other and efficiently react to give a macrocycle. On the other hand, the coordination of the terminal amino group to the metal cation may prevent the interaction with the halide and, hence, the ring closure. Therefore, the product yield depends on a combination of these factors and the nature of the solvent.[26]

This method was used to prepare compounds **1**–**28**. The yields of macrocycles varied from 22% to 86%. It can be seen that the lowest yields were observed for azacrown compounds **5** and **20** (28% and 22%, respectively). The decrease in the yield in the former case is the possibility of side reactions, that is, alkylation of secondary amino groups of the initial triethylenetetramine. The target macrocyclization product **5** has four secondary amino groups, which can also be alkylated with the initial halide. In the latter case, the 12-membered macrocycle **20** being formed is small, which may give rise to the conformational strain, hampering the intramolecular ring closure in the second step and, hence, the product formation. This is indirectly indicated by the fact that a similar azacrown compound **21** of a larger size is formed in a markedly higher yield (53%).[28]

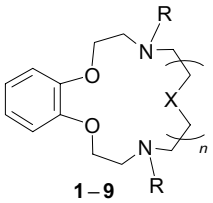
A study of the effect of alkali metal carbonates on the product yield and the reaction time demonstrated that the presence of a base increases the efficiency of the synthesis, that is, the reaction time decreases (from 280 to 75 h) and the yield of the macrocyclization product increases.[28] In addition, it was ascertained that the synthesis of some azacrown compounds does not require high dilution; the solvents of choice are acetonitrile or a THF–water mixture (1 : 1).[26]

2.1.2. Palladium-catalyzed amination

The synthesis of macrocycles from aromatic dihalides (chlorides or bromides) is accomplished *via* Pd-catalyzed amination.[34–37] The reaction proceeds on prolonged reflux in dioxane in the presence of sodium *tert*-butoxide as a base and usually gives moderate yields of products. This approach was used to prepare a number of benzo- (**29**–**43**) and pyridino-azacrown compounds (**44**–**53**).

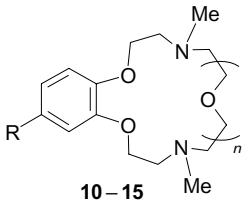
The Pd-catalyzed amination makes it possible to vary the macrocycle size and the number of nitrogen and oxygen atoms it contains.[36] The yield of the target product decreases with decreasing length of the polyamide chain and when di- or trioxamines are used.[38]

Structures 1 – 28



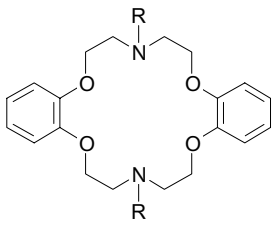
1 – 9

1: R = Me, X = O, *n* = 1 (79%);[27]
2: R = H, X = O, *n* = 1 (76%);[27]
3: R = Me, X = O, *n* = 2 (80%);[28]
4: R = H, X = O, *n* = 2 (77%);[28]
5: R = H, X = NH, *n* = 2 (28%);[28]
6: R = H, X = $CH_2N(Me)CH_2$, *n* = 1 (73%);[28]
7: R = n-$C_{12}H_{25}$, X = O, *n* = 2 (74%);[29]
8: R = Bn, X = O, *n* = 2 (76%);[29]
9: R = $Ph(CH_2)_2$, X = O, *n* = 2 (54%) [30]



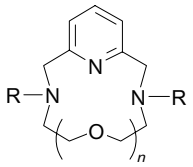
10 – 15

10: R = CHO, *n* = 1 (83%);[31]
11: R = CHO, *n* = 2 (86%);[31]
12: R = Br, *n* = 1 (64%);[31]
13: R = Br, *n* = 2 (50%);[31]
14: R = NO_2, *n* = 1 (78%);[32]
15: R = NO_2, *n* = 2 (74%) [32]



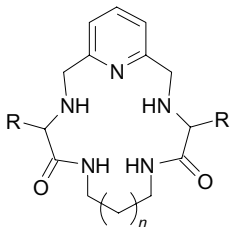
16 – 19

16: R = n-C_6H_{13} (75%);[29]
17: R = n-C_8H_{17} (73%);[29]
18: R = Bn (72%);[29]
19: R = $Ph(CH_2)_2$ (45%) [30]



20 – 22

20: R = Me, *n* = 1 (22%);[28]
21: R = Me, *n* = 2 (53%);[28]
22: R = $C_6H_4(OCH_2CH_2)_2$-1,2, *n* = 2 (41%) [28]



23 – 28

23: R = Pr^i, *n* = 2 (62%);[33]
24: R = Pr^i, *n* = 3 (50%);[33]
25: R = Pr^i, *n* = 4 (63%);[33]
26: R = Bn, *n* = 2 (62%);[33]
27: R = Bn, *n* = 3 (56%);[33]
28: R = Bn, *n* = 4 (65%) [33]

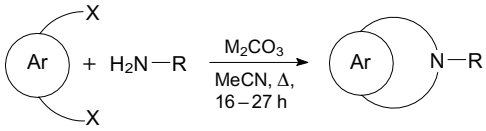
2.1.3. Cyclization of dihalides with primary amines

The cyclization of dihalides (ditosylates) with primary amines was proposed for the synthesis of macrocycles containing one nitrogen atom.[39 – 42] The reaction was carried out on refluxing in acetonitrile in the presence of sodium or potassium carbonate (Scheme 4).

This macrocyclization method is suitable for the preparation of a broad range of derivatives (compounds **54 – 71**) containing an oxaethylene moiety, azide and propargyl groups, and tosyl, *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz) and benzyl (Bn) protections.[39 – 43]

Despite the fact that the reaction is conducted at relatively low reactant concentrations (6×10^{-2} mol L^{-1}), azacrown compounds are formed in high yields, which was attributed to the template effect of the cation, hampering the intermolecular reaction giving by-products.[41]

Scheme 4

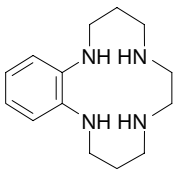


Ar = 1,2-phenylene, 1,1′-binaphthyl-1,2′-diyl; X = Cl, I, OTs; M = Na, K; R = Alk

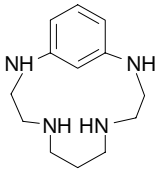
2.1.4. Intramolecular cyclization

One more synthetic route to azacrown compounds with one nitrogen atom in the macrocycle is intramolecular cyclization (Scheme 5). The reaction conditions depend on the relative arrangement of the amino group and the halogen atom. In the case where the amino group is located at the

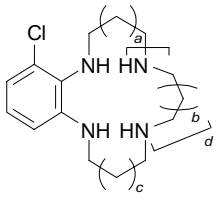
Structures 29 – 53



29 (12%) [38]

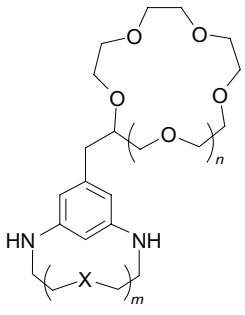


30 (39%) [38]



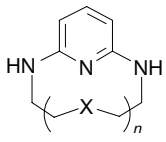
31 – 35

31: *a* = 1, *b* = 0, *c* = 1, *d* = 1 (47%);[38]
32: *a* = 0, *b* = 0, *c* = 0, *d* = 1 (27%);[38]
33: *a* = 0, *b* = 1, *c* = 0, *d* = 1 (17%);[38]
34: *a* = 0, *b* = 0, *c* = 0, *d* = 2 (12%);[38]
35: *a* = 0, *b* = 0, *c* = 0, *d* = 3 (10%) [38]



36 – 43

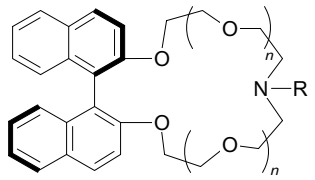
36: X = NH, *n* = 1, *m* = 1 (29%);[36]
37: X = NH, *n* = 1, *m* = 2 (28%);[36]
38: X = O, *n* = 1, *m* = 2 (41%);[36]
39: X = O, *n* = 1, *m* = 3 (53%);[36]
40: X = NH, *n* = 2, *m* = 1 (27%);[36]
41: X = NH, *n* = 2, *m* = 2 (20%);[36]
42: X = O, *n* = 2, *m* = 2 (14%);[36]
43: X = O, *n* = 2, *m* = 3 (32%) [36]



36 – 43

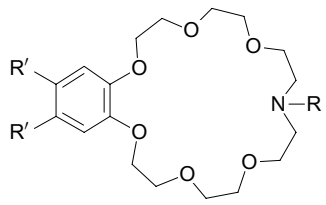
44: X = NH, *n* = 1 (11%);[37]
45: X = CH_2NHCH_2, *n* = 1 (14%);[37]
46: X = NH, *n* = 2 (13%);[37]
47: X = $NH(CH_2)_3NH$, *n* = 1 (21%);[37]
48: X = $CH_2NH(CH_2)_2NHCH_2$, *n* = 1 (24%);[37]
49: X = $CH_2NH(CH_2)_3NHCH_2$, *n* = 1 (32%);[37]
50: X = NH, *n* = 3 (11%);[37]
51: X = NH, *n* = 4 (13%);[37]
52: X = O, *n* = 2 (9%);[37]
53: X = $CH_2[O(CH_2)_2]_2OCH_2$, *n* = 1 (7%) [37]

Structures 54 – 71



54 – 61

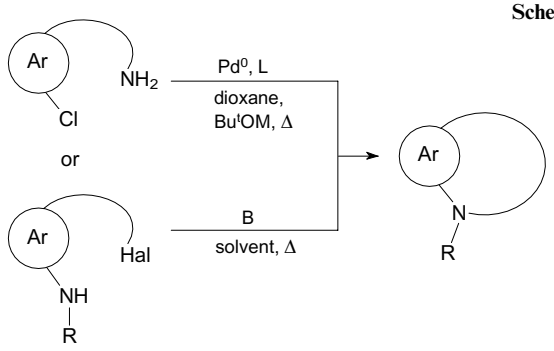
54: R = $(CH_2)_3Me$, *n* = 1 (49%);[42]
55: R = $(CH_2)_3OH$, *n* = 1 (42%);[42]
56: R = $(CH_2)_3OMe$, *n* = 1 (77%);[42]
57: R = Ts, *n* = 1 (59%);[43]
58: R = $(CH_2)_2C_6H_4OMe$-2, *n* = 1 (33%);[42]
59: R = $(CH_2)_2C_6H_4OMe$-3, *n* = 1 (19%);[42]
60: R = $(CH_2)_2C_6H_4OMe$-4, *n* = 1 (29%);[42]
61: R = $(CH_2)_2C_6H_3(OMe)_2$-3,4, *n* = 1 (13%)[42]



62 – 71

62: R = $(CH_2)_2NHBoc$, R′ = H (58%);[40]
63: R = $(CH_2)_2NHBoc$, R′ = CO_2Me (79%);[39]
64: R = $(CH_2)_2NHCbz$, R′ = CO_2Me (68%);[41]
65: R = $(CH_2)_3NHBoc$, R′ = CO_2Me (72%);[41]
66: R = $(CH_2)_4NHBoc$, R′ = CO_2Me (63%);[41]
67: R = Bn, R′ = CO_2Me (86%);[41]
68: R = $CH_2C_6H_4CH_2NHBoc$-4, R′ = CO_2Me (76%);[41]
69: R = $CH_2C{\equiv}CH$, R′ = CO_2Me (71%);[41]
70: R = $(CH_2)_2N_3$, R′ = CO_2Me (69%);[41]
71: R = $(CH_2)_2O(CH_2)_2OMe$, R′ = CO_2Me (78%)[41]

Scheme 5

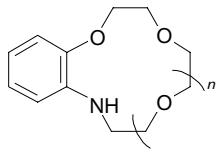


R = Me, H; Hal = Cl, I; B = M_2CO_3, NaOH, NaH;
M = Li, Na, K, Rb, Cs; solvent: MeCN, THF, dioxane;
Ar = 1,2-phenylene

end of the oxaethylene chain, the intramolecular amination proceeds in the presence of a Pd catalyst.[44] If the amino group is bound to an aromatic ring, the macrocycle is closed *via* the alkylation reaction.[45 – 48]

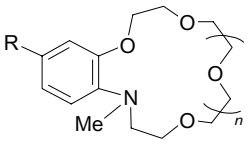
The best conditions for the catalytic reaction include the use of Pd^0 generated *in situ*, sterically hindered N-heterocyclic carbene [*N*,*N*′-bis(2,6-diisopropylphenyl)dihydroimidazol-2-ylidene, SIPr] as the ligand, ButOM (M = Li, Na, K) as the base and dioxane as the solvent. It is noteworthy that high dilution is not necessary to avoid the formation of by-products.[44] This method was used to prepare compounds **72 – 74**.

Structures 72 – 80



72 – 74

72: *n* = 1 (77%);[44]
73: *n* = 2 (45%);[44]
74: *n* = 3 (35%)[44]



75 – 80

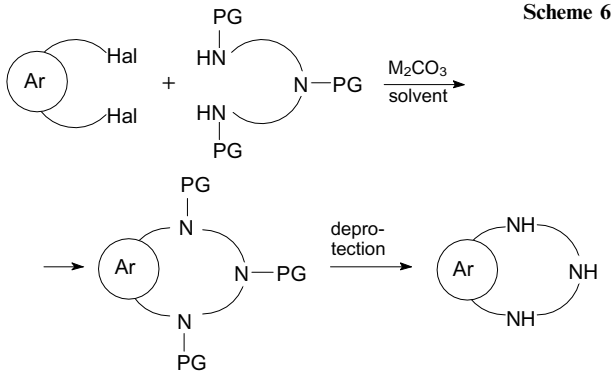
75: R = CHO, *n* = 0 (68%);[47]
76: R = CHO, *n* = 1 (63%);[47]
77: R = CHO, *n* = 2 (57%);[47]
78: R = NO_2, *n* = 0 (36%);[48]
79: R = NO_2, *n* = 1 (80%);[48]
80: R = NO_2, *n* = 2 (71%)[48]

The intramolecular cyclization of the second type can also take place without a base; however, the addition of a base and increasing the strength of the base results in faster reaction and higher yields of products. It is important to note that this method allows the synthesis of formyl (**75 – 77**) and nitro derivatives (**78 – 80**) of benzocrown compounds.

2.2. Reactions involving protected amines

The synthesis of polyazacrown compounds requires the use of polyamines as the starting reactants; the presence of several reaction centres in polyamines results in the formation of numerous by-products. This can be avoided by using protecting groups (PG) (Scheme 6). The protecting groups used for the synthesis of azacrown compounds include tosyl,[49 – 54] 2-nitrobenzenesulfonyl (*o*-NBS),[55, 56] nosyl (Ns),[57, 58] butanedione,[59, 60] mesyl, diethoxyphosphoryl (Dep) and other groups. Tosyl protection is the most popular for the synthesis of macrocycles.

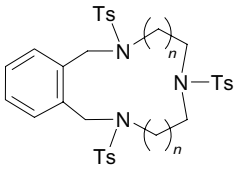
Scheme 6



Hal = Cl, Br, I; M = Li, Na, K, Cs; PG = Ts, *o*-NBS, Ns, Ms, Dep;
Ar = 1,2-phenylene, pyridine-2,6-diyl, 2,2′-bipyridine-4,4′-diyl,
1,10-phenanthroline-2,9-diyl

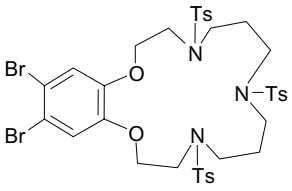
The introduction of protecting groups into polyamine molecules solves simultaneously several problems. First, bulky protecting groups fix the conformation of polyamine molecules. This is necessary to eliminate the unfavourable decrease in the entropy associated with the decrease in the number of rotational and vibrational degrees of freedom. Second, secondary amino groups lose their reactivity, which prevents some side reactions. Third, the introduction of the

Structures 81 – 116

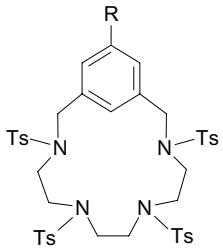


81, **82**

81: n = 1 (85%);[61]
82: n = 2 (87%)[61]

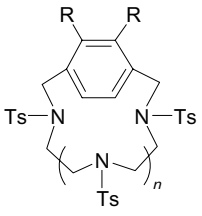


83 (68%)[62]



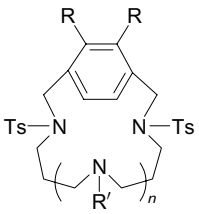
84, **85**

84: R = H (65%);[63]
85: R = NO_2 (67%)[63]



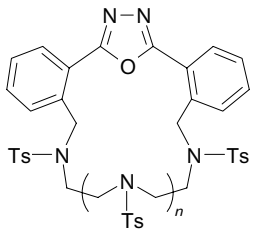
86 – 89

86: R = H, n = 1 (96%),[64] (44%);[65]
87: R = H, n = 2 (96%),[66] (77%);[65]
88: R = H, n = 3 (72%),[64] (86%);[65]
89: R = Me, n = 2 (71%)[65]



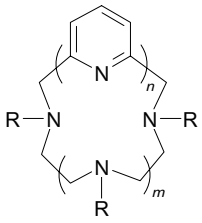
90 – 94

90: R = H, R′ = Ts, n = 1 (71%);[65]
91: R = H, R′ = Ts, n = 2 (96%);[65]
92: R = Me, R′ = Ts, n = 1 (81%);[65]
93: R = Me, R′ = Ts, n = 2 (76%);[65]
94: R = Me, R′ = Me, n = 1 (50%)[65]



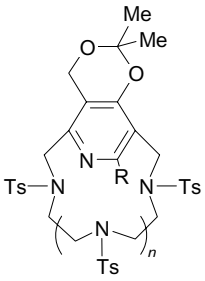
95 – 97

95: n = 1 (72%);[66]
96: n = 2 (54%);[66]
97: n = 3 (54%)[66]



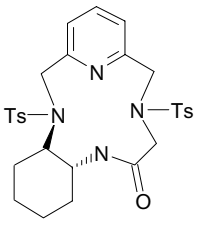
98 – 103

98: R = Ts, n = 1, m = 1 (79%);[67]
99: R = Ts, n = 2, m = 2 (76%);[68]
100: R = Ms, n = 2, m = 2 (16%);[69]
101: R = *o*-NBS, n = 1, m = 1 (76%);[56]
102: R = Dep, n = 1, m = 1 (70%);[70]
103: R = Dep, n = 1, m = 2 (63%)[70]

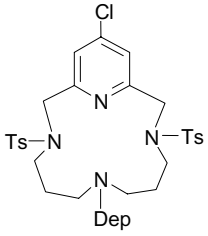


104 – 109

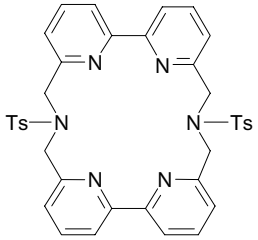
104: R = Me, n = 1 (94%);[64]
105: R = H, n = 1 (95%);[64]
106: R = Me, n = 2 (70%);[64]
107: R = H, n = 2 (98%);[64]
108: R = Me, n = 3 (47%);[64]
109: R = H, n = 3 (68%)[64]



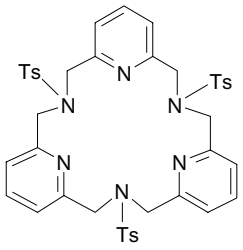
110 (59%)[71]



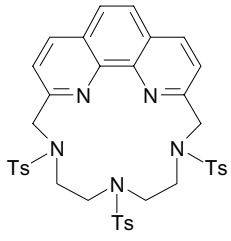
111 (29%)[72]



112 (19%)[72]

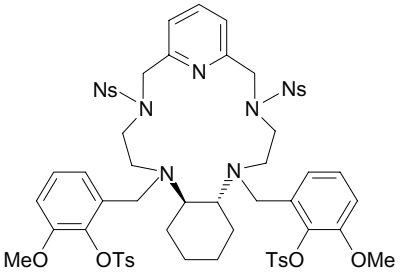


113 (59%)[73]



114, **115**

114: n = 1 (32%);[74]
115: n = 2 (31)[74]



116 (93%)[57]

tosyl protection converts terminal amino groups into amide groups, and hence the hydrogen atom in them becomes more reactive towards substitution reactions.[24] All these factors facilitate macrocyclization. Quite a number of products (compounds **81 – 116**) have been prepared using protected amines.

According to the original Richman – Atkins procedure,[75] polyazamacrocycles are obtained by cyclization of the disodium salt of N-tosylated polyamine with a compound containing tosyl leaving groups in DMF. Studies of the efficiency of macrocyclization as a function of the reaction conditions (the base and the solvent used) demonstrates that the employment of acetonitrile instead of DMF considerably increases the yield of the target product.[64]

Investigation of the effect of the cation nature on the product yield indicates that the template effect is negligible in this case. The nature of the cation has a more pronounced effect on the reaction rate than on the product yield. Since a caesium salt is the most basic, the anion is formed very easily and the reaction is fast. The basicity of a lithium salt is so low that the reaction does not occur. Similarly, the activity of a sodium salt is low. Thus, potassium carbonate is used most widely because of efficiency and relatively low cost.

After the synthesis, the tosyl group can be removed by hydrolysis in an acid medium or by reduction. Most often, this is done by hydrolysis with a mixture of hydrobromic and acetic acids conducted by refluxing the reaction mixture for 18 – 72 h. The product yields are 35% to 97%.[65, 67, 68, 74]

Purification of azacrown compounds by column chromatography leads to some decrease in the yields (35% – 53%). The product can be isolated as an HBr salt using recrystallization, which does not reduce the yield (85% – 97%). In other cases, deprotection is carried out by treatment with concentrated sulfuric acid; the reaction is carried out at 110 °C for 28 – 48 h.[69, 76 – 78] The yields of the products are 33% – 90%. The removal of the tosyl group by reduction is performed using sodium in n-butanol[79] or sodium amalgam and sodium hydrogen phosphate in methanol.[65, 80]

2.3. Reactions of carboxylic acid derivatives with amines

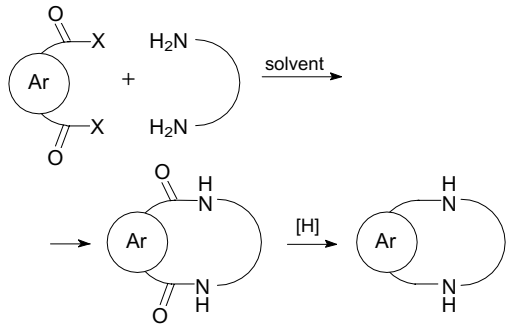
Macrocyclization to give azacrown compounds also takes place when dicarboxylic acid derivatives (esters or chlorides) are allowed to react with α,ω-diamines (Scheme 7). The reaction with acid chlorides is conducted at high dilution with vigorous stirring in acetone, ethyl acetate or dichloromethane for several minutes. Esters react with amines at room temperature or on refluxing in an alcohol without high dilution. Both methods do not require template agents and give products in high yields.[23, 81, 82] Since the reaction proceeds in two steps *via* the product of substitution at one ester group, macrocycles resulting from [2 + 2]-cycloaddition and oligomers can be formed as by-products.[83 – 86] The amide groups of the obtained azacrown compounds can be reduced with $LiAlH_4$ or borane complexes ($BH_3 \cdot THF$, $BH_3 \cdot SMe_2$) in 54% – 98% yields.[87 – 89] However, the presence of bulky substituents and metal-coordinating substituents complicates the amide reduction.[57]

It is of interest that methanol proved to be the most appropriate solvent for this reaction. A possible reason is the ability of the methanol molecule to form intermolecular hydrogen bonds with the intermediate 'amino-amido-ester', which increases the probability of ring closure over the formation of oligomerization products.[83] This method allows the synthesis of a broad range of azacrown compounds (**117** – **167**) containing various aromatic moieties by varying the size of the macrocycle.

It was found that unlike primary diamines, secondary diamines give only traces of macrocyclic diamides, because the amide proton is a significant factor for preorganization of the reaction intermediate towards the subsequent closure of the macrocycle. When amines have a rigid configuration, the macrocycle is not formed due to the arising steric hindrance.[63, 83]

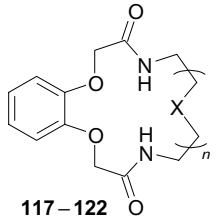
The addition of salts (NaCl, KCl, CsCl, $MgSO_4$, $CaCl_2$) does not affect significantly the course of the reaction, and in some cases (NH_4Cl, $CuSO_4$), it leads to decreasing yield of the product. However, in the presence of a base (MeONa), the reaction rate increases, and the reaction is completed in 72 h instead of 7 days.[84]

Scheme 7



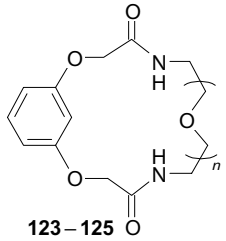
X = Cl, OMe, OEt; solvent: DMF, MeCN, MeOH, EtOH;
Ar = 1,2-phenylene, pyridine-2,6-diyl, 1,10-phenanthroline-2,9-diyl, 1,1′-binaphthyl-2,2′-diyl; [H] = $LiAlH_4$, $BH_3 \cdot THF$, $BH_3 \cdot Me_2S$

Structures 117 – 136



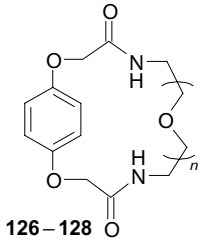
117 – **122**

117: X = O, *n* = 1 (77%);[23]
118: X = O, *n* = 2 (75%);[23]
119: X = O, *n* = 3 (29%);[23]
120: X = NH, *n* = 1 (45%),[90] (80%);[91]
121: X = NH, *n* = 2 (84%);[92]
122: X = CH_2NHCH_2, *n* = 1 (35%)[93]



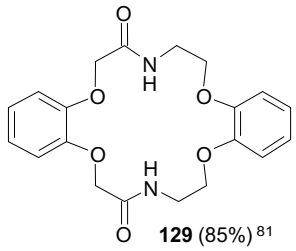
123 – **125**

123: *n* = 1 (25%);[23]
124: *n* = 2 (22%);[23]
125: *n* = 3 (30%)[23]

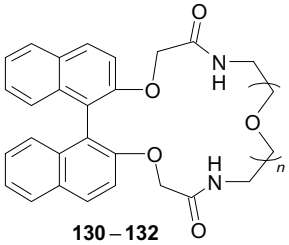


126 – **128**

126: *n* = 1 (1%);[23]
127: *n* = 2 (20%);[23]
128: *n* = 3 (18%)[23]

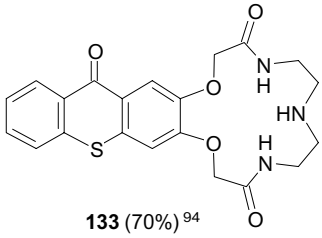


129 (85%)[81]

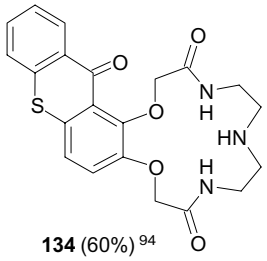


130 – **132**

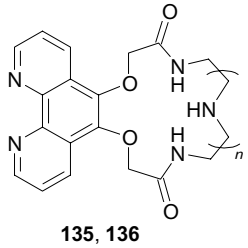
130: *n* = 1 (60%);[84]
131: *n* = 2 (67%);[84]
132: *n* = 3 (52%)[84]



133 (70%)[94]



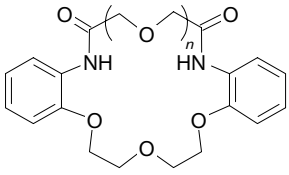
134 (60%)[94]



135, **136**

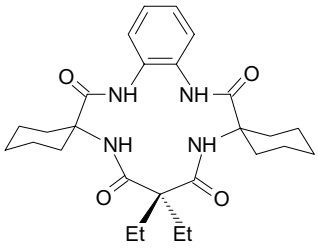
135: *n* = 1 (57%);[95]
136: *n* = 2 (52%)[95]

Structures 137 – 167

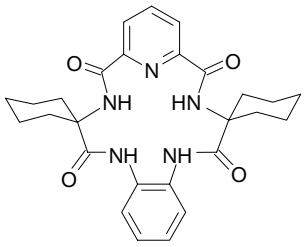


137, **138**

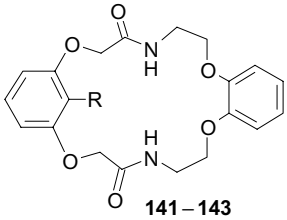
137: n = 0 (61%);[87]
138: n = 1 (88%) [87]



139 (25%) [96]

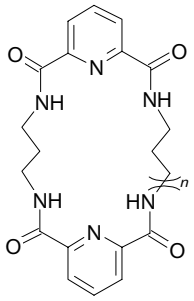


140 (55%) [96]



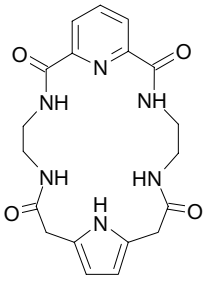
141 – 143

141: R = $OCH_2C_6H_4NO_2$-4 (44%);[97]
142: R = $OCH_2C_6H_4Br$-4 (31%);[97]
143: R = $O(CH_2)_2Ph$ (29%) [97]

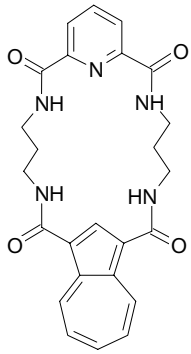


144, **145**

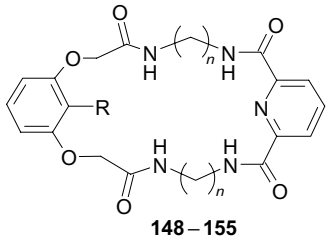
144: n = 1 (21%);[98]
145: n = 2 (17%) [98]



146 (15%) [99]

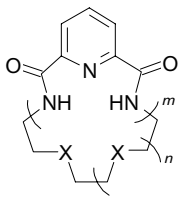


147 (41%) [100]



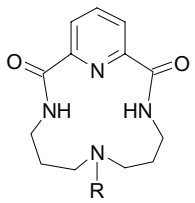
148 – 155

148: R = $NHC(O)C_6H_4NO_2$-4, n = 2 (61%);[101]
149: R = $NHC(O)C_6H_4NO_2$-4, n = 3 (56%):[101]
151: R = $C(O)NHC_6H_4NO_2$-4, n = 3 (31%);[101]
152: R = $C(S)NHC_6H_4NO_2$-4, n = 3 (89%);[101]
153: R = $NHC(S)C_6H_4NO_2$-4, n = 1 (32%);[20]
154: R = $NHC(S)C_6H_4NO_2$-4, n = 2 (78%);[20]
155: R = $NHC(S)C_6H_4NO_2$-4, n = 3 (74%);[20]
157: R = $NHCO_2Bu^t$, n = 4 (61%) [19]



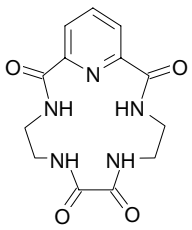
158 – 163

158: X = O, n = 0, m = 1 (70%);[102]
159: X = O, n = 1, m = 1 (84%),[83] (77%);[103]
160: X = NH, n = 1, m = 1 (52%),[102] (74%);[103]
161: X = NH, n = 2, m = 1 (62%);[103]
162: X = O, n = 1, m = 2 (4%);[83]
163: X = NH, n = 1, m = 2 (32%) [104, 105]

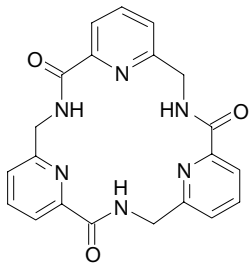


164 – 165

164: R = H (3%);[105]
165: R = Me (30%) [106]



166 (12%) [107]

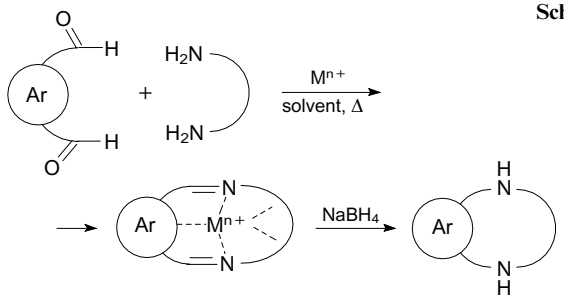


167 (17%) [108]

2.4. Reaction between aldehydes and amines

Reactions of dialdehydes and polyamines giving Schiff bases are often used to prepare azacrown compounds.[8] To avoid the side oligomerization, the reaction is carried out in the presence of template agents, particularly, alkaline earth or transition metal salts or lanthanide salts. The imine that forms is reduced to amine with $NaBH_4$; simultaneously the complex with the template is destroyed (Scheme 8).[109, 110]

Scheme 8

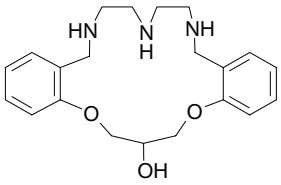


M = Mg, Ca, Ba, Mn, Co, Ni, Cu, Zn, Cd, Pb, Ln; Ar = 1,2-phenylene, pyridine-2,6-diyl, 2,2′-bipyridine-4,4′-diyl, 1,10-phenanthroline-2,9-diyl, naphthalene-1,2-diyl, 1,1′-binaphthyl-2,2′-diyl;
solvent: MeOH, EtOH, $C_2H_4Cl_2$, DMF

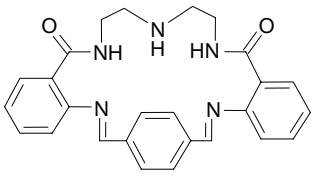
A benefit of these reactions is relatively high yield of the target product and the possibility to obtain structurally diverse azacrown compounds (**168** – **201**), including unsymmetrical and chiral ones.[21, 111 – 125]

It is noteworthy that metal cations that act as template agents have a considerable effect on the macrocyclization *via* Schiff bases. In the presence of cations of moderate size (Mn^{2+}, Fe^{2+}, Co^{2+}, Mg^{2+}), the [1 + 1]-cyclization product is formed, while in the presence of large cations (Ca^{2+}, Sr^{2+}, Ba^{2+}, Pb^{2+}), the [2 + 2]-cyclization product is obtained. Furthermore, it is possible to prepare [3 + 3]- and [4 + 4]-cyclization products using Ln^{3+} cations.[9] However, there are examples in which template cations virtually do not affect macrocyclization.[111, 112, 119, 126] Templates are used in the case of high probability that the reaction will give a mixture of products of [1 + 1]-, [2 + 2]-, [3 + 3]-cycliza-

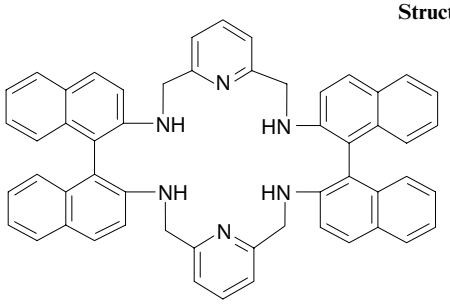
Structures 168 – 201



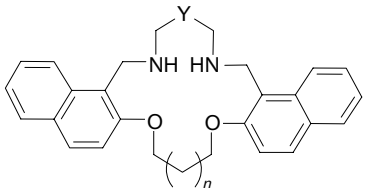
168 (82%) [111]



169 (65%) [112]

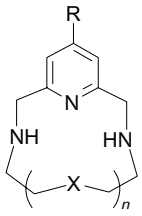


170 (87%) [113]



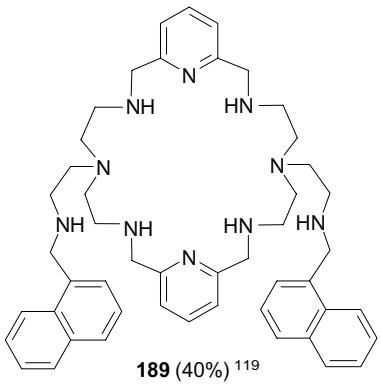
171 – 177

171: Y = CH_2, *n* = 1 (53%);[110]
172: Y = CH_2, *n* = 3 (41%);[110]
173: Y = $(CH_2)_2$, *n* = 2 (68%);[109]
174: Y = $(CH_2)_3$, *n* = 2 (71%);[109]
175: Y = $(CH_2)_4$, *n* = 3 (77%);[109]
176: Y = $(CH_2)_3O(CH_2)_4O(CH_2)_3$, *n* = 2 (70%),[109]
177: Y = $(CH_2)_3O(CH_2)_4O(CH_2)_3$, *n* = 3 (67%);[109]

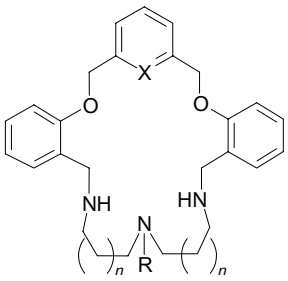


178 – 188

178: X = O, R = OMe, *n* = 2 (86%);[21]
179: X = O, R = OMe, *n* = 3 (79%);[21]
180: X = O, R = OMe, *n* = 4 (70%);[21]
181: X = O, R = H, *n* = 2 (74%);[114]
182: X = O, R = H, *n* = 3 (95%);[21]
183: X = O, R = Br, *n* = 3 (100%);[115]
184: X = O, R = I, *n* = 3 (100%);[115]
185: X = O, R = Me, *n* = 3 (82%);[115]
186: X = NH, R = H, *n* = 2 (49%);[116]
187: X = NH, R = H, *n* = 3 (59%);[117]
188: X = $NH(CH_2)_3NH$, R = H, *n* = 1 (46%);[118]

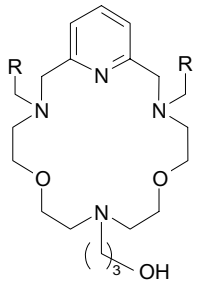


189 (40%) [119]



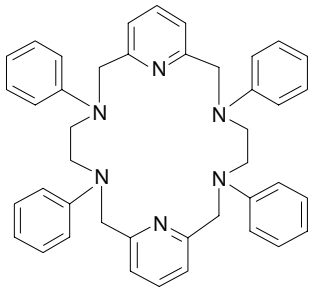
190 – 192

190: X = CH, R = $(CH_2)_2NH_2$, *n* = 0 (70%);[120]
191: X = N, R = $(CH_2)_2NH_2$, *n* = 0 (64%);[121]
192: X = N, R = Me, *n* = 1 (58%) [121]

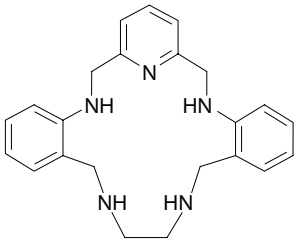


193 – 195

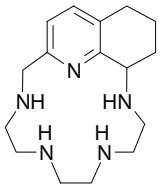
193: R is palmityl (41%);[122]
194: R is cholesteryl (46%);[122]
195: R = Bn (65%) [120]



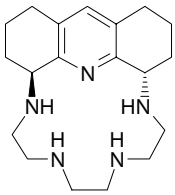
196 (45%) [113]



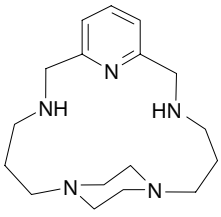
197 (50%) [123]



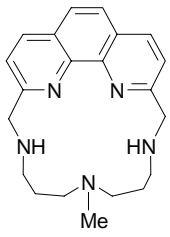
198 (73%) [116]



199 (74%) [116]



200 (20%) [124]



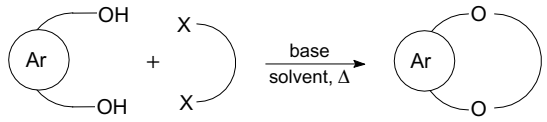
201 (41%) [125]

tion, *etc*. This approach furnishes the target macrocycle as a complex in 61% – 93% yield.[113,116] The complex is destroyed by treatment with an excess of a competing ligand (for example, propylenediamine) and thus a pure macrocyclic Schiff base is produced in 37% – 47% yield. However, most often, the intermediate complex is reduced *in situ* with sodium borohydride; in this case, the complex is destroyed owing to precipitation of insoluble metal salts or hydroxides and the yield of the macrocyclic amine amounts to 61% – 94%.[117 – 121,123 – 125] If the reacting groups of the reactants are initially preorganized for closure of the macrocycle in only one fashion, there is no need to use a template. This is most often the case for the syntheses of unsymmetrical azacrown compounds. The product yields are in the 70% – 85% range and do not depend on the chain length of acyclic reactants.[109 – 112]

2.5. Reaction between alcohols and halides

The Williamson reaction between dihalides (or ditosylates) and diols is used to synthesize crown compounds containing oxygen atoms, along with nitrogen atoms, in the ring (Scheme 9).[127 – 131] The bimolecular nucleophilic substitution of alkoxide anions for Cl, Br and OTs groups gives rise to ether bonds. The reaction is conducted in the

Scheme 9



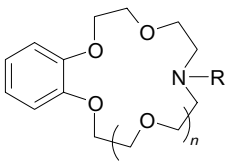
Ar = 1,2-phenylene, pyridine-2,5-diyl, 4,4′-biphenylene, 2,2′-bipyridine-4,4′-diyl; X = Cl, Br, OTs; base: NaH, NaOH, KOH, K_2CO_3; solvent: THF, dioxane, toluene, MeOH, MeCN, DMF

presence of a base on refluxing the reaction mixture for 5 min to 50 h. High dilution is not used in this case. The yields of crown ethers in this reaction vary over a broad range (from 8% to 84%) and depend on the structure of the starting compounds and on the ability of the diol to form an alkoxide in the presence of bases used in the reaction. It is noted that KOH, NaOH, NaH or K_2CO_3 added to the reaction mixture serve, in some cases, not only as bases, but also as template agents, which probably increases the yield. This macrocyclization reaction is utilized for the synthesis of benzo-[127,128,131–136] and pyridino-,[129–131,137,138] chiral[129,135,136,139] and unsymmetrical[131,140] azacrown compounds **202** – **232**.

2.6. Reactions of alcohols with carbonates

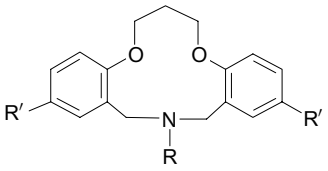
There are known macrocyclization methods based on reactions of aromatic diols with dialkyl carbonates, which are classified as green reagents (Scheme 10).[141] This is, first of all, due to the fact that these compounds are nontoxic and

Structures 202 – 232



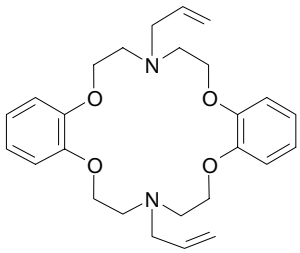
202 – **205**

202: R = H, *n* = 1 (16%);[132]
203: R = H, *n* = 2 (26%);[132]
204: R = n-C_8H_{17}, *n* = 1 (9%);[133]
205: R = Bn, *n* = 1 (32%) [133]

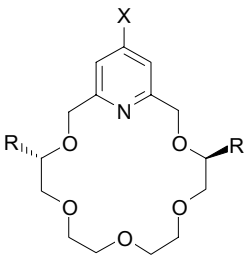


206 – **208**

206: R = Me, R′ = Me (75%);[127]
207: R = Me, R′ = Et (75%);[127]
208: R = Pr^n, R′ = Me (75%) [127]

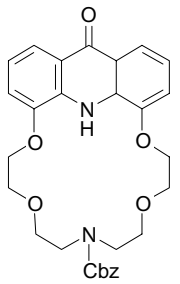


209 (42%) [128]

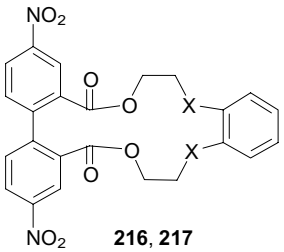


210 – **214**

210: X = Cl, R = Bu^i (13%);[129]
211: X = Br, R = Me (8%);[129]
212: X = Br, R = Bu^i (12%);[129]
213: X = OMe, R = Me (18%);[129]
214: X = Cl, R = Me (9%) [129]

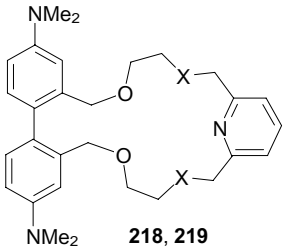


215 (47%) [140]



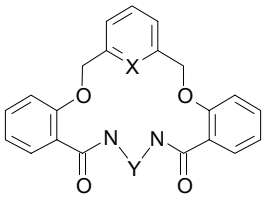
216, **217**

216: X = O (37%);[134]
217: X = NMe (18%) [134]

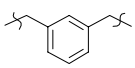
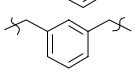


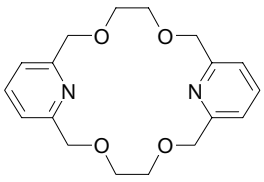
218, **219**

218: X = O (20%);[130]
217: X = NMe (33%) [130]

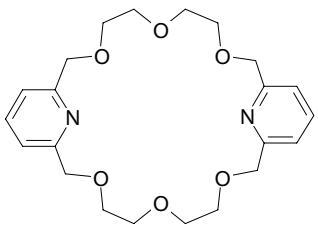


220 – **223**

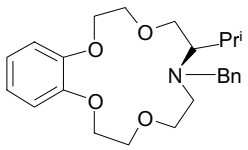
220: X = CH, Y = $(CH_2)_2$ (50%);[131]
221: X = CH, Y = $(CH_2)_3$ (40%);[131]
222: X = CH, Y =  (56%);[131]
223: X = N, Y =  (76%) [131]



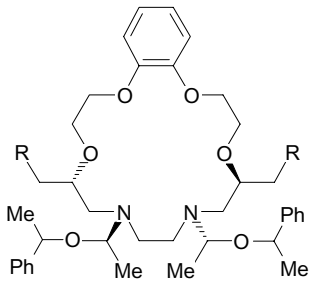
224 (11%) [137]



225 (20%) [138]

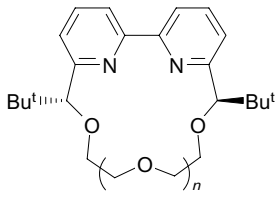


226 (46%) [136]



227, **228**

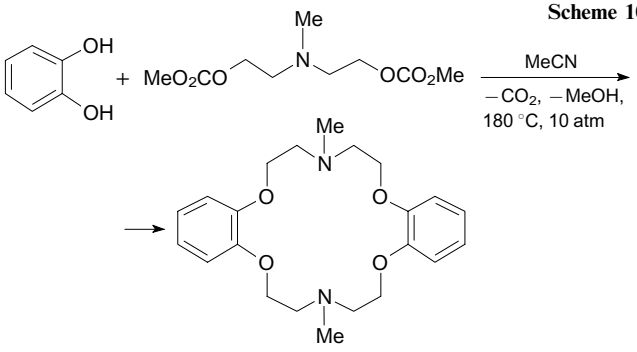
227: R = H (22%);[135]
228: R = OCH(Ph)Me (20%) [135]



229 – **232**

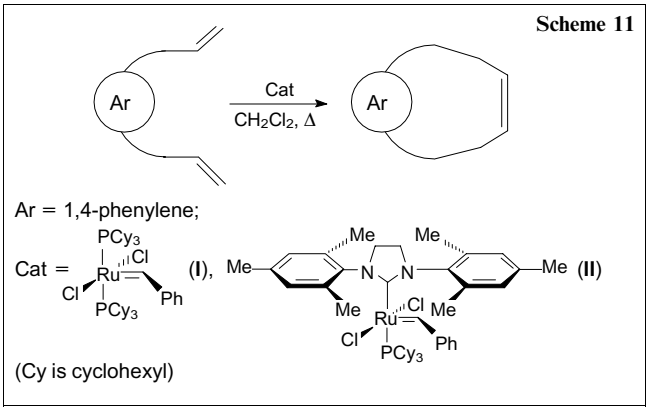
229: *n* = 2 (35%);[139]
230: *n* = 3 (40%);[139]
231: *n* = 4 (19%);[139]
232: *n* = 5 (17%) [139]

Scheme 10



233 (18%) [144]

Scheme 11



have no irritating or mutagenic action. Another advantage of dialkyl carbonates is the fact that they contain environmentally benign CO_2 as a building unit. Furthermore, this method does not require the addition of a base or a template.

Macrocycles **233** – **239** prepared in this way were previously difficult to obtain due to a large number of steps of the synthesis.[141]

2.7. Metathesis of α,ω-dienes

Metathesis of α,ω-dienes is an efficient atom-economical method for the synthesis of azacrown compounds. The reaction proceeds in the presence of first- and second-generation Grubbs catalysts on refluxing in dichloromethane for 2 – 24 h (Scheme 11).[142 – 144] The yields of the products are usually high, up to quantitative.

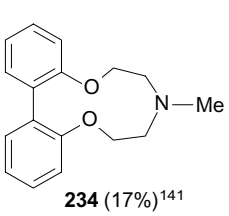
The metathesis of α,ω-dienes is highly stereoselective, results in the formation of a *cis*-double bond and makes it possible to synthesize a broad range of 8- to 40-membered azacrown compounds **240** – **251** with various additional functional groups.[144]

2.8. Multicomponent reactions

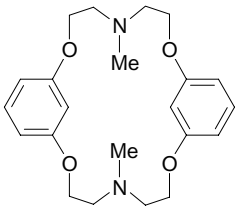
Currently, multicomponent domino reactions are attracting great attention of researchers. They are used, in particular, for the synthesis of macroheterocyclic compounds.[145] One example of their use is the synthesis of dibenzo(pyridino)-crown compounds **252** – **261** based on the condensation of diketones, aromatic aldehydes and ammonium acetate in acetic acid (Scheme 12).[146, 147] The yield of the product does not depend on the nature of substituents in the starting aldehyde and amounts to 37% – 46%. This new efficient one-step method affords macrocycles in a good yield owing to the template effect of ammonium ions.[145]

Another multicomponent condensation of dialdehydes, ketones and ammonium acetate in acetic acid – ethanol mixture was employed to prepare dibenzocrown compounds **262** – **265** (Scheme 13).[148] This reaction proceeds at a lower temperature than that in the previous method, but it takes longer time. The yields vary over a wider range (22% – 75%), with the lowest yield being obtained for the ketone containing an ester group as the substituent, which is apparently associated with side reactions involving this group.[148]

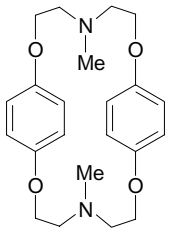
Structures 234 – 251



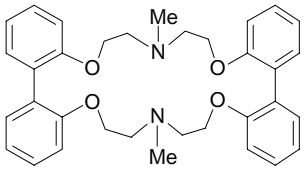
234 (17%)[141]



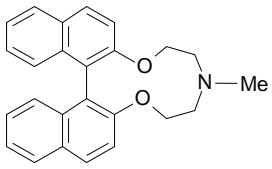
235 (12%) [141]



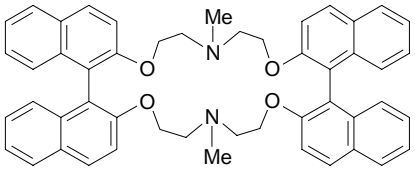
236 (12%) [141]



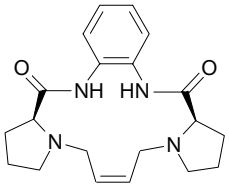
237 (23%) [141]



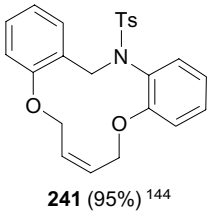
238 (19%) [141]



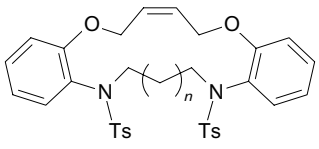
239 (22%) [141]



240 (92%) [143]

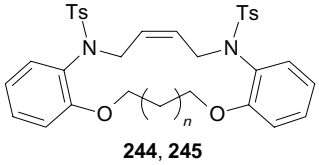


241 (95%) [144]



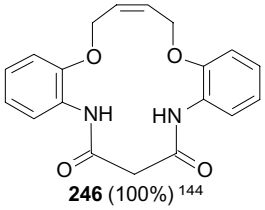
242, **243**

242: n = 1 (76%);[144]
243: n = 2 (100%) [144]

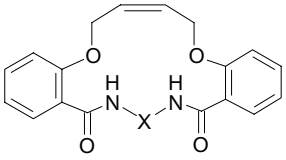


244, **245**

244: n = 1 (100%);[144]
245: n = 2 (100%) [144]



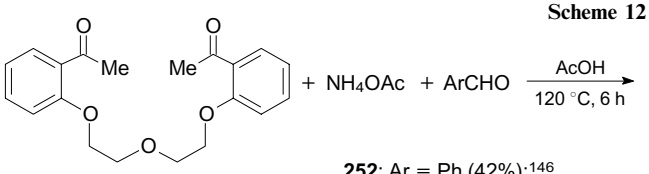
246 (100%) [144]

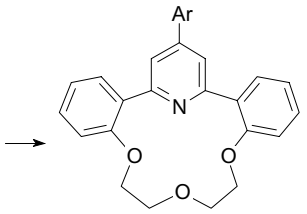


247 – **251**

247: X = $(CH_2)_2$ (100%);[144]
248: X = $(CH_2)_3$ (60%);[144]
249: X = 1,2-C_6H_4 (100%);[144]
250: X = 1,3-C_6H_4 (60%);[144]
251: X = 1,4-C_6H_4 (70%) [144]

Scheme 12

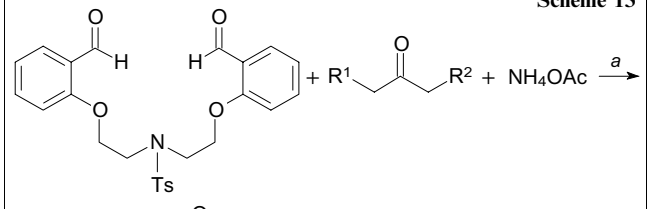


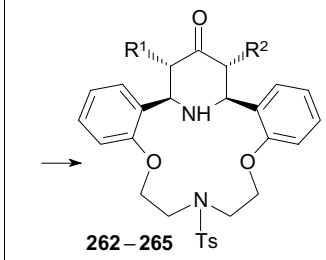


252 – 261

252: Ar = Ph (42%);[146]
253: Ar = C_6H_4OMe-4 (40%);[146]
254: Ar = C_6H_4OH-2 (37%);[146]
255: Ar = C_6H_4OH-4 (40%);[146]
256: Ar = C_6H_4Cl-4 (42%);[146]
257: Ar = C_6H_4Cl-2 (43%);[146]
258: Ar = C_6H_4Br-4 (45%);[146]
259: Ar = $C_6H_4NO_2$-4 (40%);[146]
260: Ar = 2-thienyl (46%);[147]
261: Ar = 2-pyrrolyl (44%) [147]

Scheme 13





262 – 265

262: $R^1 = R^2$ = Ph (53%);
263: R^1 = H, $R^2 = CO_2Et$ (22%);
264: R^1 = H, R^2 = Me (52%);
265: R^1 = H, R^2 = Ph (75%)

(*a*) AcOH, EtOH, 40 – 50 °C, 24 h

3. Synthesis of azacrown derivatives with chelating groups

The introduction of additional coordinating groups into the macrocyclic molecules furnishes ligands that exhibit both macrocyclic and chelation effects towards metal cations. It is known that these compounds form more stable complexes than their non-chelating analogues. This is caused, first of all, by the favourable spatial arrangement of the complexing groups, which can be selected in accordance with the nature and stereochemical requirements of the ion.

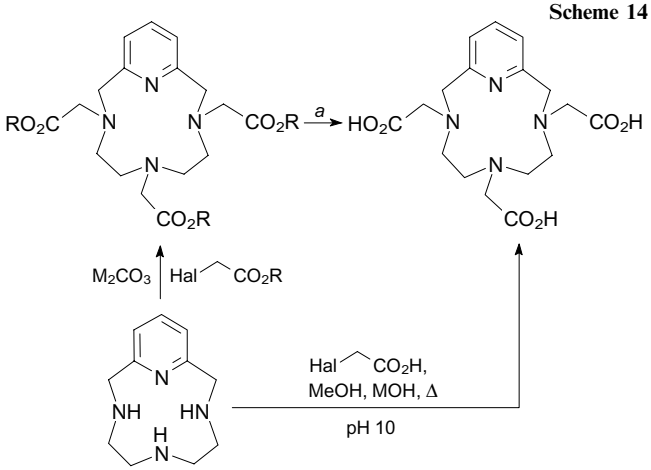
Depending on the characteristics required of the ligand, a macrocycle can be decorated with ester,[67, 149] phosphonate,[150 – 155] amide,[156, 157] amine,[158 – 162] carbamate,[77] nitrile,[163 – 166] alcohol,[167 – 169] phenol,[57, 170] quinoline [171, 172] and other groups. Of most interest are carboxy, pyridyl and picolinate derivatives of azacrown compounds, as they bound a broad range of metal cations in aqueous solutions.

3.1. Synthesis of azacrown compounds containing carboxyl groups

The reported methods for the synthesis of azacrown compounds containing carboxyl groups can be conventionally divided into two types: (1) *N*-alkylation of azacrown compounds with haloacetic acid or its esters; (2) macrocyclization involving *tert*-butyl esters or anhydrides of polyaminocarboxylic acids.

When esters are used as reactants, the reactions are carried out in the presence of sodium, potassium or caesium carbonates in DMF or acetonitrile.[67, 173, 174] In the second step, the ester group is hydrolyzed, with base catalysis being used in the case of ethyl ester and acid catalysis being used for the *tert*-butyl ester (Scheme 14). Alternatively, the *tert*-butyl ester can be hydrolyzed without the addition of an acid by refluxing in water.[92, 175]

Scheme 14



(*a*) H_2O, H^+/OH^-; M = Na, K, Cs; Hal = Cl, Br; R = Et, Bu^t

The reaction of azacrown compounds with chloro- or bromoacetic acids is conducted by refluxing in methanol under highly alkaline conditions (pH 10) (see Scheme 14).[176, 177] Compounds **266 – 276** were prepared by a similar route.

According to the second method for the preparation of carboxyl-containing azacrown compounds, dibromides and polyamines with *tert*-butyl acetate groups are used as reactants (Scheme 15).[179 – 182] The reaction is carried out under reflux in acetonitrile in the presence of sodium carbonate as a base and a template agent. The *tert*-butyl ester groups are hydrolyzed in an acid medium in 85% – 100% yield.

Azacrown compounds **277 – 286** with chelating ester groups were prepared by this method.[183 – 185]

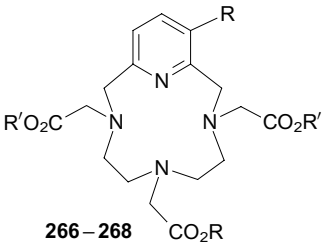
One more method for the synthesis of azamacrocycles containing carboxyl groups is based on the reaction of diamines with ethylenediaminetetraacetic (EDTA) and diethylenetriaminepentaacetic (DTPA) acid anhyrides (Scheme 16).[186, 187] Depending on the structure of the starting amine, both [1 + 1]- and [2 + 2]-cycloaddition products can be formed.

Acylation is performed in an anhydrous medium under inert atmosphere using dry DMF as the solvent. The yield of the target product is usually low. The method is applicable for the preparation of benzo- and pyridino-crown compounds **287 – 294**.

3.2. Synthesis of azacrown compounds containing pyridyl groups

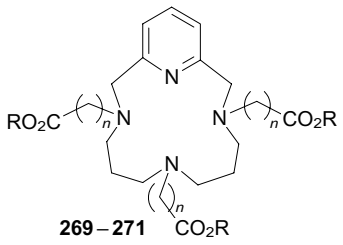
Azacrown compounds **295**, **296** containing pyridyl side groups are prepared in two ways. Most often, the pyridylmethyl group is introduced into the macrocycle *via* *N*-alkylation using 2-chloromethylpyridine as the alkylating agent. The reaction is carried out in the presence of a base (Cs_2CO_3, K_2CO_3, Na_2CO_3, NEt_3) by refluxing in acetoni-

Structures 266 – 276



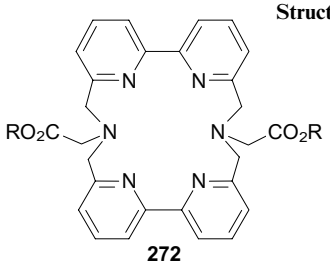
266 – 268

266: R = H, R′ = Et (50%);[66]
267: R = H, R′ = H (49%);[176]
268: R = O(CH$_2$)$_3$SH:
R′ = Bu^t (92%), H (93%) [173]



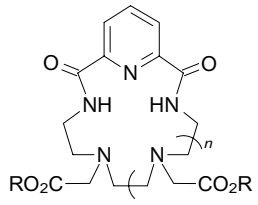
269 – 271

269: R = Bu^t (81%), H (76%), *n* = 1;[174]
270: R = Bu^t (90%), H (75%), *n* = 2;[174]
271: R = H, *n* = 1 (55%) [177]



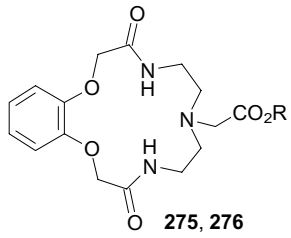
272

R = Bu^t (71%), H (89%) [178]



273 – 274

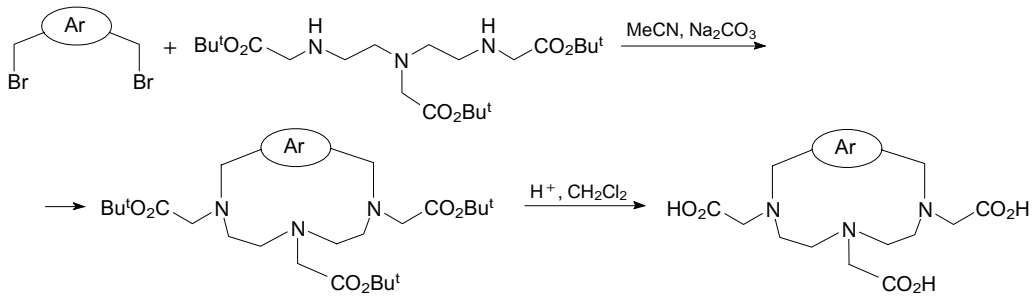
273: R = Bu^t (100%),
H (91%), *n* = 1;[175]
274: R = Bu^t (98%),
H (75%), n = 2 (see [175])



275, **276**

275: R = Bu^t (100%),
H (100%), *n* = 1;[92]
276: R = Bu^t (100%),
H (100%), *n* = 2 (see [92])

Scheme 15



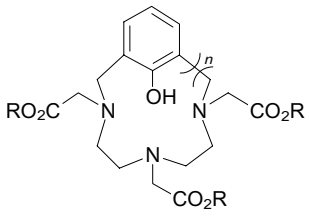
[H$^+$] = CF_3CO_2H, HCO_2H, HCl; Ar = 2,2′-bipyridine-4,4′-diyl, pyridine-2,6-diyl

trile [165, 190] or ethanol [191] under inert atmosphere or in the dichloromethane – aqueous NaHCO$_3$ or NaOH [192, 193] two-phase system at room temperature (Scheme 17).

This procedure was used to prepare azacrown compounds **297 – 303**.

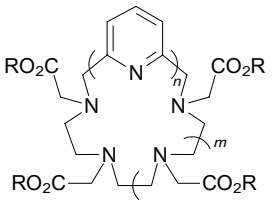
The second approach to the synthesis of azacrown compounds with pyridyl side groups is based on macrocyclization using pyridyl-substituted polyamines as the starting compounds. A variety of macrocyclization techniques are applicable: using dihalides and amines

Structures 277 – 286



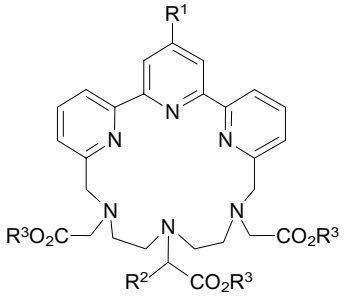
277, **278**

277: R = Bu^t (31%),
H (92%), *n* = 1;[180]
278: R = Bu^t (55%),
H (85%), *n* = 2 (see [180])



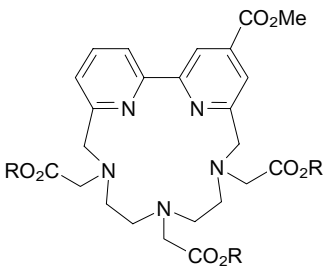
279 – 281

279: R = Bu^t (87%), H (100%),
n = 1, *m* = 0;[182]
280: R = Bu^t (54%), H (100%),
n = 1, *m* = 1;[181]
281: R = Bu^t (58%), H (100%),
n = 2, *m* = 1 (see [181])



281 – 285

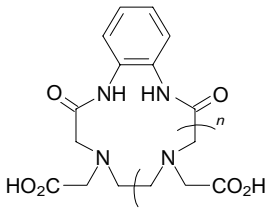
282: R^1 = H, R^2 = H,
R^3 = Bu^t (56%), H (77%);[184]
283: R^1 = CO_2Et, R^2 = H,
R^3 = Bu^t (34%), H (87%);[184]
284: R^1 = $CH_2OCH_2CO_2Me$, R^2 = H,
R^3 = Bu^t (43%), H (95%);[184]
285: R^1 = H, R^2 = $(CH_2)_4NH_2$,
R^3 = Bu^t (50%), R = H (96%) [185]



286

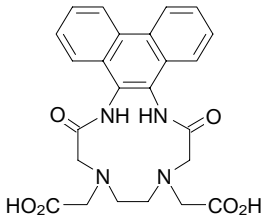
R = Bu^t (51%),
H (97%) [183]

Structures 287 – 294

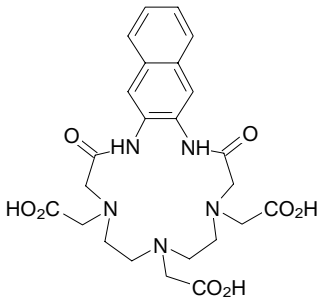


287, **288**

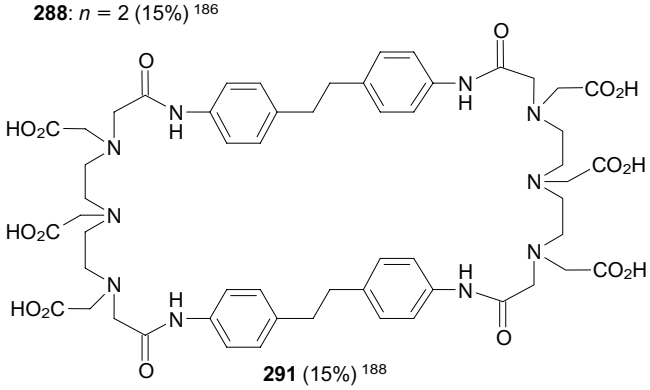
287: n = 1 (60%);[186]
288: n = 2 (15%) [186]



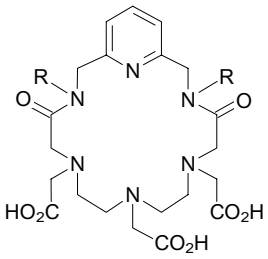
289 (20%) [186]



290 (14%) [187]



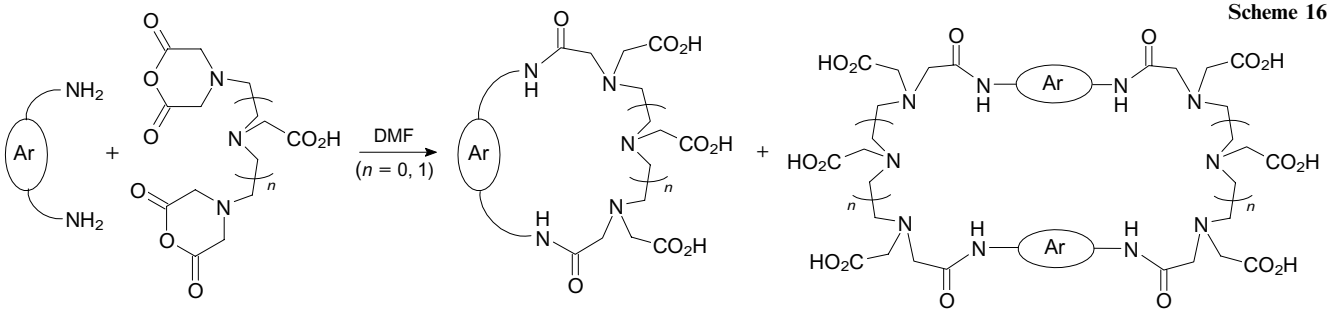
291 (15%) [188]



292 – **294**

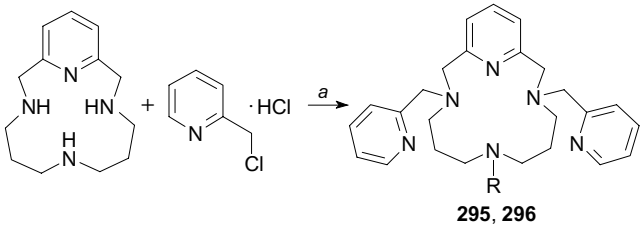
292: R = Bu^n (39%);[189]
293: R = n-$C_{10}H_{21}$ (25%);[189]
294: R = n-$C_{12}H_{25}$ (25%) [189]

Scheme 16



Ar = 1,2-phenylene, naphthalene-2,3-diyl

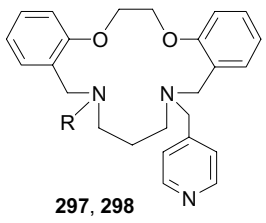
Scheme 17



295, **296**

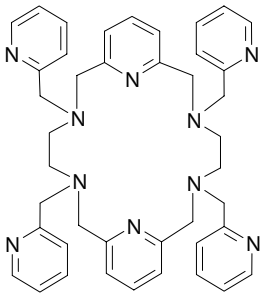
(*a*) M_2CO_3, MeCN, Δ or NaOH, H_2O, CH_2Cl_2 (M = Na, K, Cs);
R = H (**295**, 75%),[192] CH_2Py-2 (**296**, 55%) [192]

Structures 297 – 303

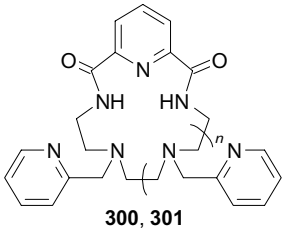


297, **298**

297: R = H;[193]
298: R = Bn (see [193])

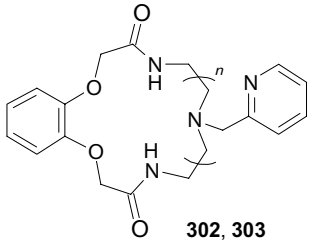


299 (67%) [165]



300, **301**

300: n = 1 (75%);[175]
301: n = 2 (54%) [175]



302, **303**

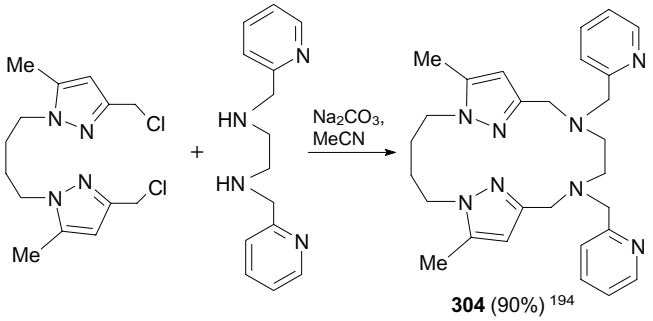
302: n = 1 (75%);[92]
303: n = 2 (89%) [92]

(Scheme 18),[194] protected amines (Scheme 19) [57] or aldehydes and amines (Scheme 20).[195] This one-step approach to the synthesis of pyridyl azacrown derivatives can serve for the preparation of target products **304** – **309** in high yields (77% – 90%). The challenge is to prepare the starting polyamine.

3.3. Synthesis of azacrown compounds containing picolinate groups

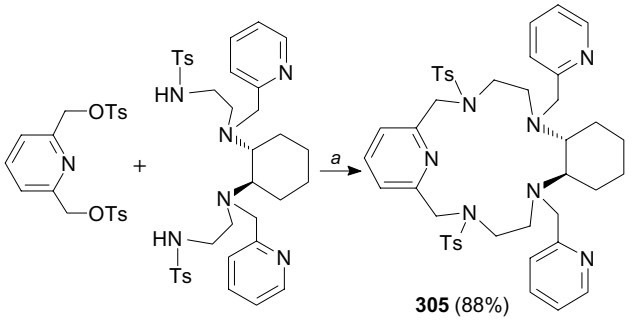
Picolinate groups are introduced into macrocycles by alkylating the macrocycle with methyl 6-(chloromethyl)picoli-

Scheme 18



304 (90%) [194]

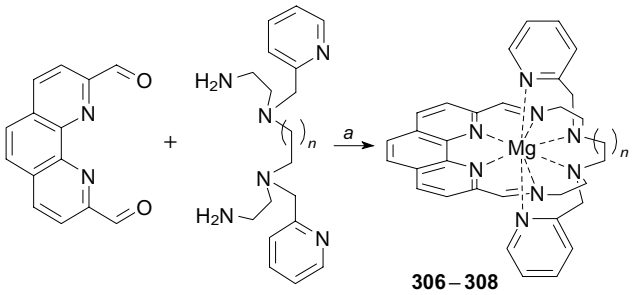
Scheme 19



305 (88%)

(*a*) Cs_2CO_3, DMF

Scheme 20

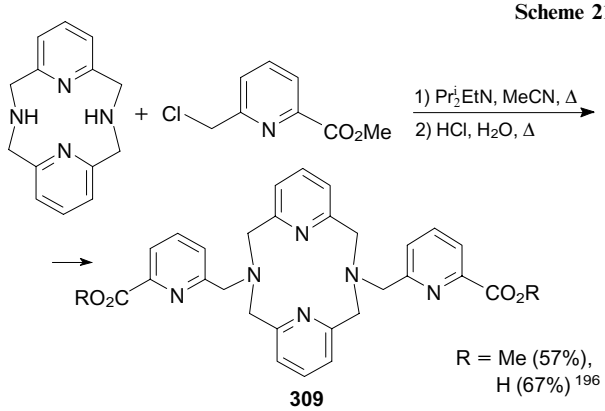


306 – **308**

(*a*) MeOH, Mn^{2+}

306: *n* = 1 (83%); **307**: *n* = 2 (81%), **308**: *n* = 3 (77%)

Scheme 21

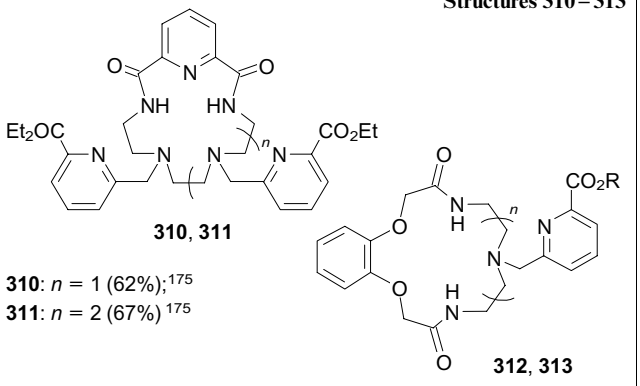


309

R = Me (57%), H (67%) [196]

nate followed by hydrolysis in an acid [196, 197] or alkaline [92, 175] medium (Scheme 21).

Structures 310 – 313



310, **311**

310: *n* = 1 (62%);[175]
311: *n* = 2 (67%) [175]

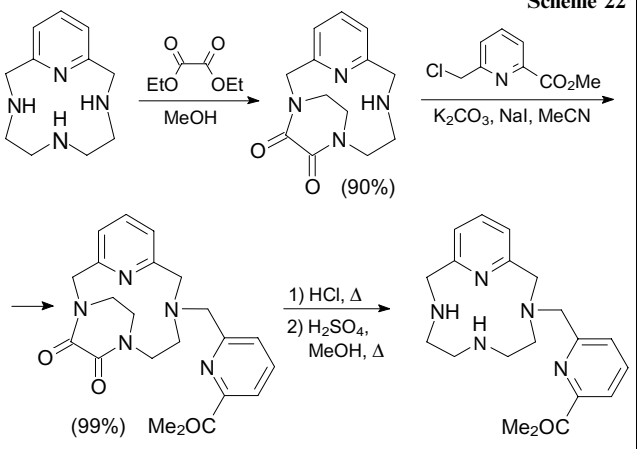
312, **313**

312: R = Me (86%), Na (100%); *n* = 1;[92]
313: R = Me (81%), Na (100%); *n* = 2 (see [92])

Compounds **310** – **313** were prepared in a similar way using potassium carbonate as the base. Hydrolysis of the methyl esters in the presence of NaOH affords the target picolinate derivatives in a quantitative yield.

A monoalkylation process was developed for azacrown compounds containing three amino groups accessible for the reaction (Scheme 22).[197] In this method, two amino groups are initially protected *via* acylation with diethyl oxalate. The alkylation of crown ether with methyl 6-(chloromethyl)picolinate proceeds in an almost quantitative yield and, after that, the protection is removed by refluxing in hydrochloric acid to give compound **314**.

Scheme 22



314 (63%) [197]

It is noteworthy that alkylation reactions performed to introduce chelating groups into pyridine-containing crown compounds were never accompanied by pyridine quaternization. Most likely, this is attributable to steric hindrance, because pyridine incorporated in the macrocycle is less accessible to attack by an alkylating agent than the amino groups.

4. Complexation of azacrown compounds with metal ions and factors affecting the complexing ability

The most important properties of the complexes formed by crown compounds with metal cations, such as stability in aqueous solutions, the rate of establishment of equilibrium,

solubility and so on, depend on a large number of diverse factors, the key factors being the nature of the cation, the structure of the ligand and the composition of the complex. The most important characteristics of the central ion include the oxidation state the size, the electron shell structure and coordination characteristics, while the main features of the ligand are the flexibility, the charge, the nature and number of donor sites, and the modes of their connection in the molecule. The exceptionally wide range of variation of each of the above parameters in complexes of various metals and ligands complicates the consideration of the general features inherent in chelators as a whole. However, the accumulated experimental data make it possible to reveal some local trends and features characteristic of particular groups of ligands.[198]

The present review focuses attention on the influence of structural factors, such as the macrocycle rigidity and size and the presence and nature of chelating groups, on the complexing ability of azacrown compounds.

Azacrown compounds can bind a broad range of metal cations such as alkali, alkaline earth and transition metal ions and lanthanide ions.[199–202] They are also known to coordinate anions: Hal^-, AcO^-, $PhCOO^-$, $H_2PO_4^-$, HSO_4^-, CN^-, $PhCOO^-$, $4\text{-}O_2NC_6H_4O^-$.[16,98,99,101] However, the complexation trends have been studied in most detail for heavy metal cations. Therefore, in this Section, primary attention is paid to the complexation of particularly these cations. Comparison is carried out fot the stability constants of complexes formed by various azacrown compounds with Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+}, Fe^{3+}, Ga^{3+}, In^{3+}, Y^{3+}, La^{3+}, Nd^{3+}, Gd^{3+}, Dy^{3+} and Lu^{3+} cations, determined by potentiometric titration in aqueous solutions. The structures of these complexes determined by X-ray diffraction are considered.

4.1. Structural rigidity of macrocycles

It was shown that aliphatic azamacrocycles possess good complexing properties; they form highly stable and inert complexes (*i.e.*, complexes that decompose slowly under the action of external factors or competing ligands) even in very acidic media. Nevertheless, the practical application of the complexes is restricted by low formation rate. The search for ligands capable of fast formation of complexes with high stability constants and high selectivity for particular metal ions stimulated studies on the synthesis and complexing behaviour of macrocycles containing structurally rigid moieties.[203]

The entropy factor makes a considerable contribution to the stability of complexes in solutions. It is known that polyatomic ligand molecules exist in solutions as a mixture of several conformers in dynamic equilibrium. Being bound in the complex, they lose some of their degrees of freedom, as the complex formation results in the fixing of some particular conformer and, hence, the entropy decreases. The entropy of the system as a whole increases because of the release of water molecules from the hydration shell of the metal cation. Since structurally rigid ligands occurring in the complex in the same configuration as they exist in the free state initially possess a lower entropy, they form more stable complexes owing to the more pronounced increase in the entropy of the system upon complexation, which is thermodynamically more favourable.[198]

In addition, macrocycles may dictate the particular geometry of the metal ion complex, whereas open-chain chelators are more easily adjusted to the coordination characteristics of the metal centre.[11] For this reason, an increase in the ligand rigidity also results in increasing selectivity of binding of a definite cation.[49]

4.1.1. Introduction of the benzene ring

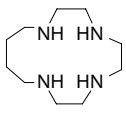
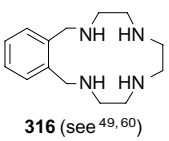
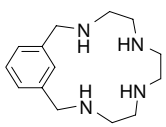
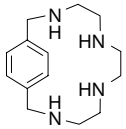
The benzene ring is often introduced into a macrocycle as a structurally rigid moiety. The role of the benzene ring and the type of substitution (*ortho*, *meta* or *para*) are important factors of the coordination chemistry of azacrown compounds, especially with small-size polyamines.[204]

While comparing two macrocyclic ligands of the same size and equal numbers of nitrogen atoms, one being aliphatic polyamine **315** and the other containing a benzene ring (**316**), one can see (Table 1) that complexes of ligand **316** with the Cu^{2+}, Zn^{2+} and Cd^{2+} ions are more stable than the complexes of ligand **315**. Furthermore, the effect of introduction of a rigid moiety is less pronounced for the Cd^{2+} cation, while for Ni^{2+} and Pb^{2+} ions, the stability, conversely, decreases. This is due to the fact that Cu^{2+} and Zn^{2+} ions place large geometric and electronic requirements on the ligand.[49]

The results of potentiometric titration of the Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+} and Pb^{2+} complexes with ligand **316** attest to the highest stability of the Cu^{2+} complex over the complexes of other cations, which is typical of amine ligands.[49]

The position of the benzene ring in the macrocycle considerably affects not only the stability, but also the type of the complexes formed.[204] To gain insight into the

Table 1. Stability constants (log *K*) of complexes formed by ligands **315** – **318** (T = 25.0 °C, I = 0.10 mol L^{-1}).

Composition of the complex	log *K*			
	 **315** (see [49,60])	 **316** (see [49,60])	 **317** (see [60])	 **318** (see [60,205])
$\mathbf{L}\cdot Ni^{2+}$	15.47	14.64	See [b]	See [b]
$\mathbf{L}\cdot Cu^{2+}$	15.47 [a]	19.58 [a]	13.52	10.41
$\mathbf{L}\cdot Zn^{2+}$	12.90 [a]	13.77 [b]	6.27	4.55
$\mathbf{L}\cdot Cd^{2+}$	11.30	11.42	See [b]	See [b]
$\mathbf{L}\cdot Pb^{2+}$	11.59	11.33	See [b]	See [b]

[a] I = 0.15 mol L^{-1}; [b] no data available.

influence of the type of substitution in the benzene spacer, complexing properties of macrocycles with *o*-, *m*- and *p*-phenylene moieties towards Zn^{2+} and Cu^{2+} cations were analyzed (see Table 1), and considerable differences in the coordination chemistry of these compounds were revealed.[60, 205] The stability of complexes decreases in the order *ortho*- > *meta*- > *para*-substitution in the ligand, with the complexes of *meta*- and *para*-substituted ligands being markedly less stable than complexes containing aliphatic polyamine **315**.

These data can be interpreted taking account of the structural characteristics of the ligands. First, unlike the *meta*- and *para*-substituted compounds, the *ortho*-derivative has an appropriate size for the coordination of a single metal ion by all of the donor nitrogen atoms. The molecular modelling of free macrocycles **316**–**318** demonstrated that the distance between the benzylic nitrogen atoms is 3.57, 5.34 and 6.95 Å, respectively (Fig. 1).[60]

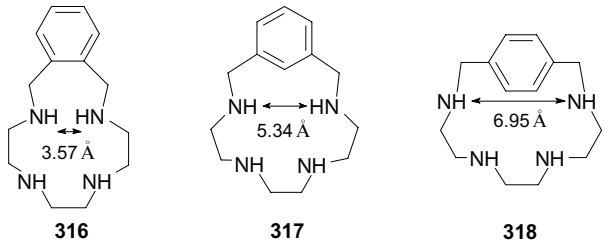


Figure 1. Structures **316**–**318** calculated by molecular mechanics.[60]

Comparison of the stability constants of ligands **316** and **317** suggests that in the latter case, the complex formation involves only three nitrogen atoms.[60] The rigidity of the aromatic moiety prevents the simultaneous coordination of both benzylic nitrogen atoms of **317** to the same metal ion, on the one hand, and promotes the formation of binuclear complexes, on the other hand.[204] The latter is confirmed by the crystal structure of binuclear Cu^{2+} complex **318** (Fig. 2) in which the tetramine chain behaves as two independent ethylenediamine groups, each being involved in the coordination to the Cu^{2+} ion.[205]

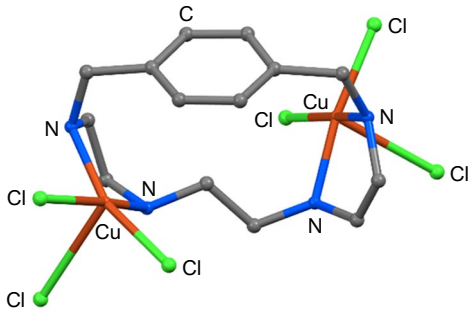


Figure 2. Molecular structure of complex **318**·$(Cu^{2+})_2$ (Ref. 205).

These results give a strong idea of how different coordination modes can be implemented in the benzene-containing macrocyclic ligands depending on the type of substitution in the aromatic ring. Whereas *ortho*-derivative **316** forms only mononuclear complexes, *meta*- and *para*-derivatives **317** and **318** can be converted to coordinatively unsaturated binuclear complexes.[60, 205]

4.1.2. Introduction of a heterocycle

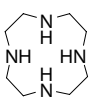
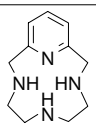
Another popular rigid moiety used as a part of azamacrocycles is pyridine, which, unlike the benzene ring, has an additional binding site for metal cations, namely, the heteroaromatic nitrogen atom. 2,2′-Bipyridine- and 1,10-phenanthroline-based spacers, with two nitrogen atoms present in the heterocycle, are also used; their lone pairs of electrons can be involved together in the cation binding.[68, 206] In addition, these moieties increase the general rigidity of the macrocyclic system and thus generate a high degree of preorganization towards metal coordination. In addition, heteroaromatic moieties are rather hydrophobic and can create a hydrophobic environment of a metal. All these factors can affect the complexing properties of the ligands.[207]

A study of a series of pyridine-containing macrocycles revealed a very important feature: they form complexes more rapidly than the corresponding aliphatic macrocycles, but these complexes often have lower stability constants (Tables 2–4).[176, 177] This may be due to the fact that it is more difficult for a rigid ligand to adjust to a metal cation.[203] In addition, the overall basicity and the stepwise protonation constants of pyridine-containing macrocycles are lower than those of aliphatic analogues due to the electron-withdrawing effect of the pyridine ring.[11]

In view of the foregoing, it is clear why ligand **320** forms less stable complexes with all of the studied metal cations except for Ni^{2+} (see Table 2).[203] A similar trend holds for the complexes of 15-membered macrocycle **186** with Mn^{2+} and Ni^{2+} cations (see Table 3).[114, 118] The increase in the Mn^{2+} coordination number from six (for **321**) to seven (for **186**) should be noted.[114]

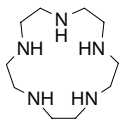
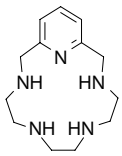
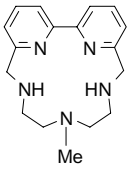
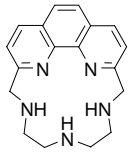
The stability constant of the Cu^{2+} complex with macrocycle **322** is markedly lower than that with ligand **321**. Complex **321**·Cu^{2+} is little prone to protonation, which is in line with the fact that the metal has a saturated coordination sphere, as it is wrapped into the flexible ligand **321**. The decrease in the stability of the complex formed by macrocycle **322** compared to that formed by **321** cannot be attributed to different binding abilities of aliphatic secondary amino and heteroaromatic groups, since stabilities of the Cu^{2+} complexes with 2,2′-bipyridine and *N*,*N*′-dimethylethylenediamine are similar (log*K* = 9.0 and 9.54, respectively). In the crystal structure of complex **322**·Cu^{2+}

Table 2. Stability constants (log *K*) of complexes formed by ligands **319** and **320** (T = 25.0 °C, I = 0.10 mol L^{-1}).

Composition of the complex	log *K*	
	 **319** (see [49])	 **320** (see [176])
L·Ni^{2+}	16.4	17.05
L·Cu^{2+}	23.29	20.14
L·Zn^{2+}	16.2 [a]	14.40
L·Cd^{2+}	14.3 [a]	12.67
L·Pb^{2+}	15.9 [a]	15.42

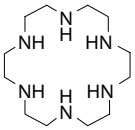
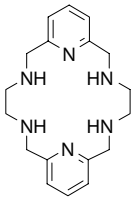
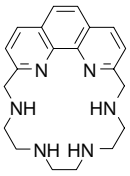
[a] I = 0.20 mol L^{-1}.

Table 3. Stability constants (log *K*) of complexes formed by ligands **186**, **321** – **323** (T = 25.0 °C, I = 0.10 mol L^{-1}).

Composition of the complex	log *K*			
	 **321** (see [118])	 **186** (see [114, 118])	 **322** (see [207, 208])	 **323** (see [74, 162, 209])
$L \cdot Mn^{2+}$	See [a]	10.89	See [d]	See [d]
$L \cdot Ni^{2+}$	18.1 [b]	21.71	See [d]	See [d]
$L \cdot Cu^{2+}$	28.3 [c]	23.31	19.8	See [d]
$L \cdot Zn^{2+}$	19.1 [c]	17.76	17.5 [b]	16.30
$L \cdot Cd^{2+}$	19.2 [c]	16.85	See [d]	17.20
$L \cdot Pb^{2+}$	17.3 [c]	15.44	See [d]	18.70

[a] No complex formation; [b] T = 35.0 °C; [c] I = 0.20 mol L^{-1}; [d] no data available.

Table 4. Stability constants (log *K*) of complexes formed by ligands **324** – **326** (T = 25.0 °C, I = 0.10 mol L^{-1}).

Composition of the complex	log *K*		
	 **324** (see [211])	 **325** (see [117, 211])	 **326** (see [68, 74])
$L \cdot Mn^{2+}$	10.50 [a]	11.79	See [d]
$L \cdot Co^{2+}$	18.9 [b]	See [c]	See [d]
$L \cdot Ni^{2+}$	19.6 [b]	22.75	See [d]
$L \cdot Cu^{2+}$	24.40 [a]	24.72	17.53
$L \cdot Zn^{2+}$	17.8 [b]	20.61	See [d]
$L \cdot Cd^{2+}$	17.9 [b]	17.78	See [d]
$L \cdot Pb^{2+}$	14.13 [b]	13.79	15.62

[a] I = 0.15 mol L^{-1}; [b] I = 0.20 mol L^{-1}; [c] no complex formation; [d] no data available.

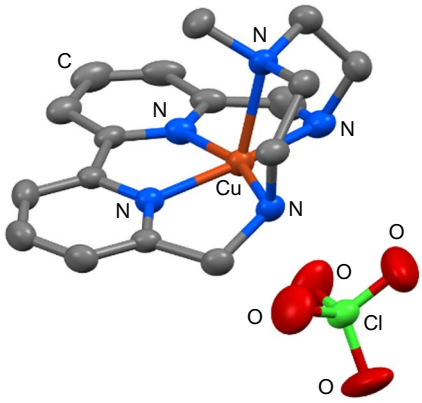


Figure 3. Molecular structure of complex **322** · Cu^{2+} (Ref. 20).

(Fig. 3), there is a space around the metal atom filled by weakly bound oxygen of the perchlorate anion, rather than by donor atoms. In aqueous solutions, this oxygen is most likely replaced by a water molecule. In addition, the metal is coordinated by five nitrogen atoms and has a highly distorted square planar environment, with the bonds to two amino groups being longer. This feature is specific to transition metal complexes with phenanthroline- and bipyridine-containing polyazamacrocycles. Most likely, because of the rigidity of these large heteroaromatic moieties, together with the presence of short ethylene bridges between the amino groups, the nitrogen atoms cannot be arranged in the optimal way around the metal ion.[208]

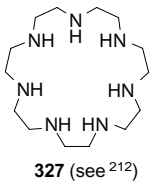
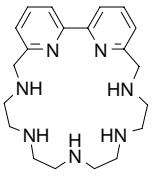
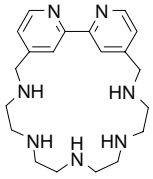
The stability constants of the complexes of phenanthroline-containing ligand **323** with Zn^{2+} and Cd^{2+} cations are lower than those of analogous complexes of ligand **322**; however, in the case of Pb^{2+} ion, the stability of the complex increases. The decrease in the constants can be attributed to the lack of saturation of the metal coordination sphere caused by weak binding to benzylic nitrogen atoms,[209] as was shown in relation to complex **323** · Zn^{2+} by X-ray diffraction.[210] On the other hand, 1,10-phenanthroline and *N*,*N*′-dimethylethylenediamine form Zn^{2+} and Cd^{2+} complexes with similar stability constants (log *K* = 6.55 and 5.47 for Zn^{2+} complexes; log *K* = 4.9 and 5.2 for Cd^{2+} complexes, respectively). This means that the rigid structure of ligand **323** precludes full-scale coordination of the Zn^{2+} or Cd^{2+} ion to all nitrogen atoms, which decreases the stability of the complexes.[162]

The stability constants of the Pb^{2+} complexes with phenanthroline-containing ligands **323** and **326** are higher (see Tables 3, 4) compared with those for complexes with the corresponding aliphatic macrocycles **321** and **324**. Apparently, this difference is due to the fact that heteroaromatic nitrogen atoms have higher coordination ability towards large and soft metal cations such as Pb^{2+} (Ref. 74).

The complex formation constants for ligand **325** containing two pyridine rings with Mn^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} cations are also higher than those for the aliphatic analogue **324** (see Table 4). It can be seen that Co^{2+} complexes with **325** are unstable, whereas those with aliphatic macrocycle **324** are relatively stable.[211]

The Cu^{2+} complex with phenanthroline-containing macrocycle **326** is less stable than a similar complex with **324**. It was shown [74] that it is highly prone to protonation even in slightly acidic solutions, which is a consequence of

Table 5. Stability constants (log K) of complexes formed by ligands **327**–**329** (T = 25.0 °C, I = 0.10 mol L^{-1}).

Composition of the complex	log K		
	 **327** (see [212])	 **328** (see [206, 207])	 **329** (see [206])
L·Ni^{2+}	16.56 [a]	15.54	5.71
L·Cu^{2+}	19.48 [a]	18.72	13.91
L·(Cu^{2+})$_2$	30.49 [a]	9.43	7.83

[a] I = 0.15 mol L^{-1}.

weak interaction of the donor heteroatoms of macrocycle **326** with the metal.[68]

It is of interest to compare the stability of mononuclear Cu^{2+} complexes with ligands **327** and **328** (Table 5). The stability constant of the complex with heteroaromatic compound **328** is only slightly lower than that of the complex with aliphatic ligand **327**. This difference corresponds to a lower binding ability of bipyridine in comparison with ethylenediamine (log$K$ = 9.00 and 10.09 for 2,2′-bipyridine and *N*,*N*′-dimethylethylenediamine, respectively) and to higher flexibility of macrocycle **327**, which allows more favourable arrangement of the donor atoms around the metal cation.[206]

The stability constants of complex **328**·Ni^{2+} are somewhat lower than those for the corresponding complex with ligand **327** (see Table 5). Unlike for copper complexes, this cannot be attributed to the replacement of the ethylenediamine moiety in **327** by the bipyridine moiety in **328**, since bipyridine and ethylenediamine show similar complexing properties towards the Ni^{2+} cation (log$K$ = 7.04 and 7.11 for 2,2′-bipyridine and *N*,*N*′-dimethylethylenediamine, respectively). Lower stability of complex **328**·Ni^{2+} is apparently associated with the fact that increasing rigidity may decrease the ability of the ligand to be adjusted to the coordination characteristics of Ni^{2+}, which are more strict than those of Cu^{2+}.

In the mononuclear complexes of macrocycle **328**, the metal is coordinated by the bipyridine moiety, as evidenced by the red shift in the absorption spectrum and by crystal structure data for complexes **328**·Cu^{2+} and **328**·Ni^{2+} (Fig. 4). High protonation constants of the complexes indicate that some amino groups are weakly bound to the metal.

In ligand **328**, the heteroaromatic nitrogen atoms are located inside the macrocyclic cavity convenient for accommodation of a metal ion. Unlike ligand **328**, ligand **329** has separated binding sites, both inside the macrocyclic cavity (ethylenediamine moieties) and outside the cavity (bipyridine moiety). This structural feature increases the diversity of the coordination behaviour of this ligand in aqueous solutions. A study of the complex formation of **329** demonstrated that both these sites can bind the metal. The Cu^{2+} cation is coordinated by the polyamine chain inside the cavity. The complex is protonated at the most basic aliphatic amino groups, which results in migration of the metal out of the cavity. It is noteworthy that in all Ni^{2+} complexes of ligand **329**, the metal atom is coordinated by

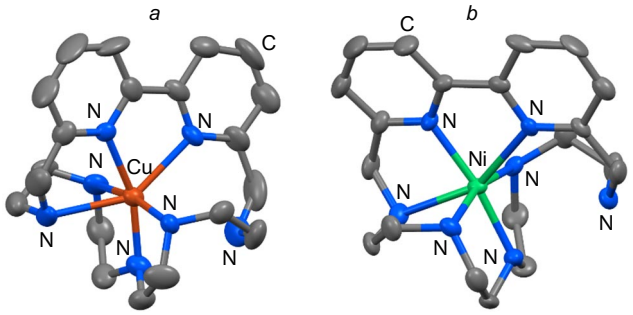


Figure 4. Molecular structures of complexes **328**·Cu^{2+} (*a*) and **328**·Ni^{2+} (*b*).[206]

bipyridine nitrogens outside the cavity. Therefore, the stability constant of complex **329**·Ni^{2+} is only slightly lower than that in the case of the 2,2′-bipyridine ligand (see Table 5). Thus, the appropriate binding site is determined by not only protonation of the complex, but also by characteristics of the metal.[206]

4.2. Size of the macrocycle

An interesting trend in the complexation is observed when the macrocycle size is changed *via* elongation of the aliphatic chain between donor nitrogen atoms. It is known that complexation of the ligand and the cation gives a chelate ring the size of which affects the stability of the final complex. Molecular modelling revealed the most stable conformations of the five- and six-membered rings (Fig. 5). It is obvious that the distance between two donors ('bite size') is larger for the five-membered chelate ring in comparison with the six-membered ring, and the angle formed by the bonds to the metal ion is smaller for a longer metal–donor distance. The cyclohexane model for the six-membered ring predicts a larger angle, but a shorter distance between the donor groups and between the metal ion and the donor groups. Therefore, complexes formed by small metal ions such as Cu^{2+}, Ni^{2+} and Zn^{2+} should be more stable when form a six-membered chelate ring, whereas for large metal ions, a five-membered ring is preferred.[213]

However, it should be borne in mind that the replacement of the ethylene chain between the amino groups by a propylene chain results, among other changes, in increasing size of the macrocyclic cavity, which may have an adverse

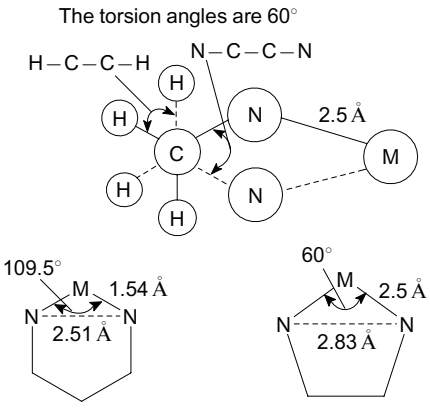


Figure 5. Least strained structures of five- and six-membered chelate rings calculated by molecular mechanics.[213]

effect on the strength of binding of small-size cations due to the arising conformational strain in the ring. Therefore, experimental data on the stability of complexes of various sizes reflect the balance of these two factors.

Tables 6 – 11 summarize the results of potentiometric titration of macrocycles of different size with heavy metal cations. Ligands **316** and **330** differ by one CH_2 group in the macrocycle; this does not affect significantly the complexation with the Zn^{2+} cation, while the stability of the Cu^{2+} complex decreases by two orders of magnitude (see Table 6).

meta-Substituted derivatives with different macrocycle sizes were obtained by introducing CH_2 groups between the donor nitrogen atoms (**331**) and by addition of one more $(CH_2)_2NH$ group (**332** and **333**) (Table 7). The stability constants of Cu^{2+} complexes with compounds **317** and **331** proved to be virtually equal. It is of interest that macrocycle **331** does not form binuclear complexes, unlike other *meta*-substituted derivatives. As the number of donor atoms increases (compounds **332** and **333**), more stable Cu^{2+} complexes are formed.[214]

A comparison of the stability of the Cu^{2+} complexes with the *para*-derivatives of benzocrown ethers **318**, **344** – **337** (Table 8) indicates that increasing length of the aliphatic chain between the nitrogen atoms of tetraazamacrocycles **318** and **334** leads to increasing stability constants. In the case of pentaazamacrocycles **335** and **336**, an opposite situation is observed. The addition of amino groups increases the strength of complexes; however, the stability of the complex with ligand **337** is comparable with that for compound **335**.

The stability constants of complexes with ligands **331** and **334** are virtually equal, which indicates that the numbers of donor atoms involved in the metal coordination are equal. This is confirmed by the results of potentiometric titration: complex **334**$\cdot Cu^{2+}$ has a high protonation constant ($\log K = 8.19$), which is similar to the first protonation constant of the free ligand. Thus, the first coordination sphere of the metal can contain not more than three nitrogen atoms of the macrocycle. One more coordination site of the cation is, most likely, occupied by a water molecule or an anion.[214]

Ligand **334**, which differs from compound **318** only by the presence of two additional carbon atoms in the chain, does not form binuclear complexes, because higher flexibility of the polyamine chain makes the ligand able to adjust to the cation and, as a consequence, leads to strong coordination of the metal in the mononuclear complex, which prevents the formation of a binuclear complex.[205]

Table 6. Stability constants ($\log K$) of complexes formed by ligands **316**, **330** (T = 25.0 °C, I = 0.15 mol L^{-1}).

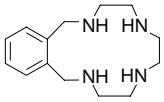
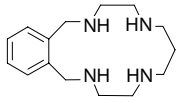
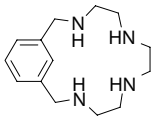
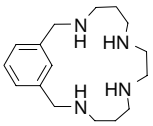
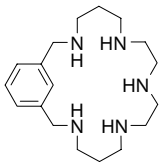
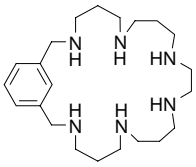
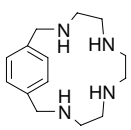
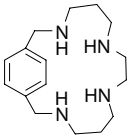
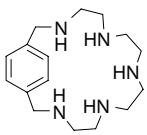
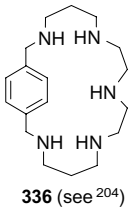
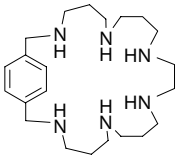
Composition of the complex	$\log K$	
	 **316** (see [60])	 **330** (see [60])
$L \cdot Cu^{2+}$	19.58	17.73
$L \cdot Zn^{2+}$	13.45	13.77

Table 7. Stability constants ($\log K$) of complexes formed by ligands **317**, **331** – **333** (T = 25.0 °C, I = 0.15 mol L^{-1}).

Composition of the complex	$\log K$			
	 **317** (see [60])	 **331** (see [214])	 **332** (see [204])	 **333** (see [214])
$L \cdot Cu^{2+}$	13.52	13.22	19.05	17.74
$L \cdot (Cu^{2+})_2$	10.67 [a]	See [b]	9.05 [c]	24.29

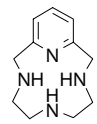
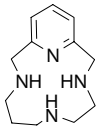
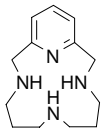
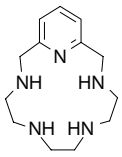
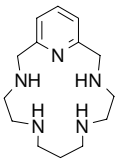
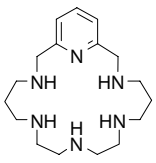
[a] The composition of the complex is $L \cdot (Cu^{2+})_2(OH^-)$; [b] no complex formation; [c] the composition of the complex is $L \cdot (Cu^{2+})_2(OH^-)_2$.

Table 8. Stability constants ($\log K$) of complexes formed by ligands **318**, **334** – **337** (T = 25.0 °C, I = 0.15 mol L^{-1}).

Composition of the complex	$\log K$				
	 **318** (see [205])	 **334** (see [205])	 **335** (see [205])	 **336** (see [204])	 **337** (see [214])
$L \cdot Cu^{2+}$	10.41	13.02	17.73	15.70	17.19
$L \cdot (Cu^{2+})_2$	3.44 [a]	See [b]	24.29	22.00	23.84

[a] The composition of the complex is $L \cdot (Cu^{2+})_2(OH^-)_2$; [b] no complex formation.

Table 9. Stability constants (log *K*) of complexes formed by ligands **186**, **320**, **338**–**341** (T = 25.0 °C, I = 0.10 mol L^{-1}).

Composition of the complex	log *K*					
	 **320** (see [176, 203])	 **338** (see [203])	 **339** (see [203])	 **186** (see [114, 118])	 **340** (see [118])	 **341** (see [215])
L·Mn^{2+}	8.81	7.29	5.48	10.89	See [b]	See [b]
L·Fe^{2+}	12.55	10.76	9.34	See [b]	See [b]	See [b]
L·Ni^{2+}	17.05	16.81	16.27	21.71	16.81	See [b]
L·Cu^{2+}	20.14	18.62	19.76	23.31	20.76	20.44 [a]
L·Zn^{2+}	14.40	14.27	12.82	17.76	15.30	See [b]
L·Cd^{2+}	12.67	11.64	9.76	16.85	15.53	See [b]
L·Pb^{2+}	15.42	12.28	9.72	15.44	12.93	See [b]

[a] I = 0.15 mol L^{-1}; [b] no data available.

It is of interest that the stability constants of Cu^{2+} complexes with large macrocycles **333** and **337** are comparable with each other and correspond to this value for the complex with their acyclic analogue, 4,8,11,15-tetraazaoctadecane-1,18-diamine, for both mono- and binuclear complexes.[214]

For a series of pyridine-containing ligands **186**, **320**, **338**–**341** (Table 9), the stability constants of metal complexes obey the Irving–Williams series: $Mn^{2+} < Fe^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+} \gg Zn^{2+}$. It can be noted that the increase in the macrocycle size by replacement of the ethylene bridge between amino groups by a propylene bridge leads to decreasing constants in all cases, except for Cu^{2+} complexes, which have different stability, and the Cu^{2+} complex with macrocycle **339** has a higher stability constant than that with compound **338**.

Crown compound **340** forms 1.3–4.9 orders of magnitude less stable complexes than macrocycle **186**, with the lowest stability being observed for Ni^{2+} and Cu^{2+} complexes. The differences in the cavity size between ligands **186** and **340** account for the fact that compound **340** forms more stable complexes with Cd^{2+} than with Zn^{2+}, while for azacrown ether **186** the relationship is opposite.[118]

The stability constant of complex **355**·Cu^{2+} is lower than that of the complex formed by its aliphatic analogue **310** (see Tables 4 and 9). This is caused by the fact that not all nitrogen atoms of the ligand are involved in the metal coordination. The protonation constant of complex **341**·Cu^{2+} is comparable with the constant for the third protonation step of the free ligand. Study of the crystal structure of complex **341**·Cu^{2+} (Fig. 6) attests to a highly distorted octahedral coordination of the metal centre by nitrogen atoms.[215]

With the goal to understand how the increase in the cavity size affects the stability and the conformation of complexes of hexaazamacrocycles containing two pyridine moieties, 18- , 20- and 22-membered macrocycles **325**, **342** and **343** were studied [211] (Table 10). The results of molecular mechanics calculations demonstrated that these macrocycles are sufficiently flexible and suitable for encapsulation of metal ions of various sizes. In all cases, mononuclear complexes were formed. An attempt was made to prepare binuclear complexes, but they were not detected in aqueous solutions.

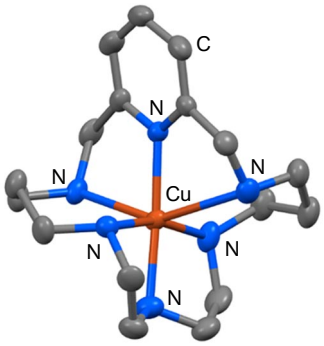
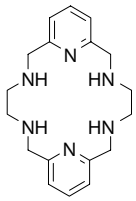
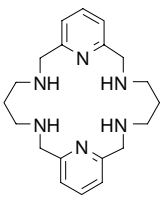
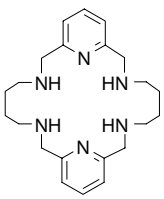


Figure 6. Molecular structure of complex **341**·Cu^{2+} (Ref. 215).

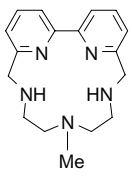
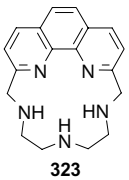
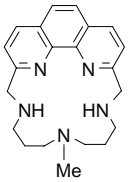
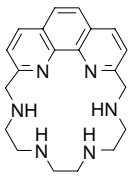
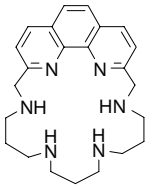
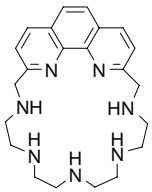
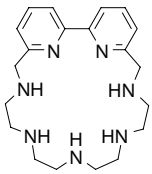
The stability constants of complexes of all metals decrease with increasing size of the macrocyclic cavity in the series of ligands **325** > **342** > **343**. The stability of complexes formed by each ligand with different metals corresponds to the Irving–Williams series:

Table 10. Stability constants (log *K*) of complexes formed by ligands **325**, **342**, **343** (T = 25.0 °C, I = 0.10 mol L^{-1}).[211]

Composition of the complex	log *K*		
	 **325**	 **342**	 **343**
L·Mn^{2+}	11.79	8.22	See [a]
L·Ni^{2+}	22.75	20.31	9.40
L·Cu^{2+}	24.72	21.13	12.83
L·Zn^{2+}	20.61	15.40	6.92
L·Cd^{2+}	17.78	14.01	7.86
L·Pb^{2+}	13.79	9.42	6.61

[a] No complex formation.

Table 11. Stability constants (log *K*) of complexes formed by ligands **201**, **322**, **323**, **326**, **328**, **344**, **345** (T = 25.0 °C, I = 0.10 mol L^{-1}).

Composition of the complex	log *K*						
	 **322** (see [207,208])	 **323** (see [74,162,209,210])	 **201** (see [125])	 **326** (see [74])	 **344** (see [209,216])	 **345** (see [74])	 **328** (see [206,207])
L·Cu^{2+}	19.8	See [a]	13.17	See [a]	13.90	See [a]	18.72
L·Zn^{2+}	17.5	16.30	9.05	See [a]	9.83	See [a]	12.11
L·Cd^{2+}	See [a]	17.20	9.82	See [a]	10.21	See [a]	15.69
L·Pb^{2+}	See [a]	18.70	8.65	15.62	8.6	13.09	12.96

[a] No data available.

$Mn^{2+} < Ni^{2+} < Cu^{2+} \gg Zn^{2+}$. For other metals, the relationship is as follows: $Zn^{2+} > Cd^{2+} \gg Pb^{2+}$. High stability constants mean that all of the donor atoms of the ligands are involved in complexation.[211]

The stability constants of the complexes formed by phenanthroline- and bipyridone-containing macrocycles of various sizes are summarized in Table 11. The expansion of the macrocyclic cavity by replacing the ethylene bridge between amino groups by a propylene chain (ligand **201**) leads to a considerable decrease in the stability of all complexes, which is likely to be due to the formation of six-membered chelate rings. The increase in the macrocycle size upon the introduction of additional CH_2CH_2NH moieties (ligands **323**, **326** and **345**) results in a sharp decrease in the stability of complexes formed by the Pb^{2+} cations. This result is fairly surprising considering the fact that the number of donor nitrogen atoms capable of coordination has increased.[74]

An explanation of the decrease in the stability of complexes in the series **323**·Pb^{2+} > **326**·Pb^{2+} > **345**·Pb^{2+} can be gained from analysis of the protonation of these complexes, because this provides characterization of the strength of the N–Pb bond. It was shown that complex **323**·Pb^{2+} has a very low tendency for protonation (log K = 1.9). The first protonation constants of complexes **326**·Pb^{2+} and **345**·Pb^{2+} are much higher. In particular, the latter complex can bind up to two protons in aqueous solution with relatively high constants (log K = 6.17 and 5.85). These findings suggest that five donor atoms in ligand **323** are arranged optimally for the coordination of Pb^{2+}, providing strong Pb–N interaction, whereas in complexes **326**·Pb^{2+} and **345**·Pb^{2+}, some donor nitrogen atoms are weakly, or not at all, bound to the metal atom. Examining the crystal structures of complexes **323**·Pb^{2+} and **345**·Pb^{2+} (Fig. 7) reveals two major differences between the coordination behaviours of the ligands forming them.[74]

In the complex with ligand **323**, the metal atom is coordinated by all five nitrogen atoms and the average Pb–N bond length is 2.60 Å. In the complex with macrocycle **345**, the average Pb–N distance between the donor nitrogen atoms and the metal is somewhat greater (2.73 Å). In particular, the Pb–N(2), Pb–N(3) and Pb–N(4) bond lengths are markedly longer than 2.85 Å, which attests to a weak interaction of these nitrogen atoms with the metal atom. Despite the fact that the complex of macrocycle **323** has a twisted conformation, no evidence for the conformational strain is present. Probably, strong interaction with the metal atom is ensured without considerable conformational changes in the cyclic structure. Meanwhile, in complex **345**·Pb^{2+}, the ligand wraps around the metal ion to allow all donor atoms to participate in the coordination. This process gives rise to conformational strain in the macrocyclic structure, as indicated by the angles in the aliphatic chain. The combination of these factors accounts for lower stability of complex **345**·Pb^{2+} compared with analogue **323**·Pb^{2+} (Ref. 74).

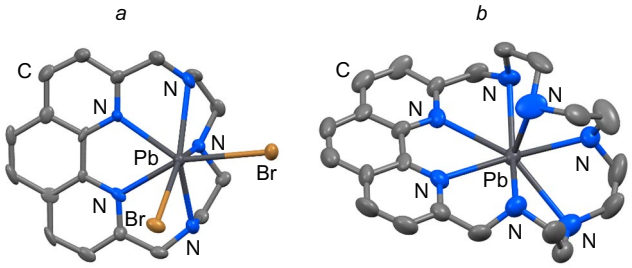


Figure 7. Molecular structures of complexes **323**·Pb^{2+} (*a*) and **345**·Pb^{2+} (*b*).[74]

Complex **323**·Zn^{2+} is not protonated in aqueous solution. On the other hand, the crystal structure of this complex (Fig. 8) indicates that the coordination sphere of the metal is not saturated by the ligand donor groups and that both benzylic nitrogen atoms interact very weakly with the metal (the Zn–N distance is 2.4–2.5 Å).[210] The absence of protonated species is apparently attributable to

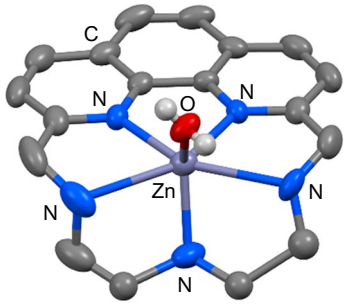


Figure 8. Molecular structure of complex **323**·Zn^{2+} (Ref. 210).

the small size of the macrocyclic cavity, which precludes the simultaneous accommodation of the metal cation and the proton proximate to each other.[209]

Bipyridine-containing ligand **322** can form only mononuclear complexes with the Zn^{2+} cation, while macrocycle **328** shows a marked tendency to add a second metal atom ($\log K = 4.61$), owing to a larger size of the macrocyclic cavity and the greater number of donor nitrogen atoms capable of coordination.[207] Complex **322**·Zn^{2+} is considerably more stable than other complexes with polyamine ligands, which suggests the metal coordination of all donor atoms; this is supported by a crystallographic study of complex **322**·Zn^{2+} (Fig. 9).

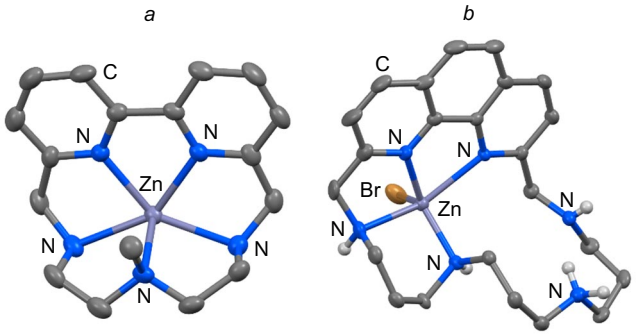


Figure 9. Molecular structures of complexes **322**·Zn^{2+} (*a*)[207] and **344**·Zn^{2+} (*b*).[209]

Complex **344**·Zn^{2+} is highly prone to protonation in aqueous solutions, giving even triply protonated species. This is confirmed by crystallographic studies of complex **344**·Zn^{2+} (see Fig. 9) in which the metal is coordinated to only four nitrogen atoms (two phenanthroline and two amine ones), two of which weakly bind the metal. As a result, the ligand does not saturate the coordination sphere of the metal, leaving vacant binding sites, which accounts for low stability of the complex.[209]

4.3. Chelating groups and their nature

The flexibility of the macrocycle can be decreased not only by increasing the rigidity of the carbon skeleton, but also by introducing substituents into the amino group. Substituents containing donor heteroatoms can also participate in the complex formation. The chelate effect generated by additional coordinating groups depends on the nature and structure of these groups. The most frequently used groups are carboxyl, pyridyl and picolinate ones. Their presence affects not only the strength of complexes, but also the selectivity for definite cations.

4.3.1. Carboxyl groups

The benefits of carboxyl groups include the ability to bind the metal cation *via* not only donor-acceptor interactions, but also Coulomb forces. Furthermore, the carboxyl group is a very efficient ligand, as it has a small size and its donor atoms can be located relatively close to the metal ion (Fig. 10).[217]

The complexing ability of the ligand is strongly affected by the distance between the carboxyl group and the nitrogen atom. It is known that acetate groups form more stable chelate structures than propionate groups; hence, moving a carboxyl group away from nitrogen results in decreasing strength of complexes with most cations.[218]

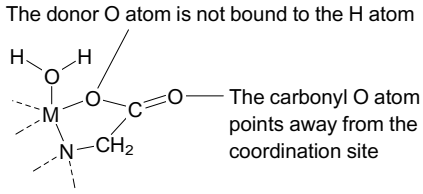


Figure 10. Fragment of the complex of aminoacetate with a metal cation.[217]

Table 12 shows the stability constants of complexes of pyridine-containing crown compounds with additionally introduced carboxyl groups.

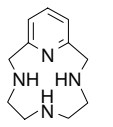
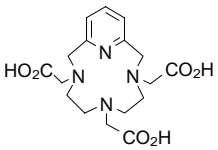
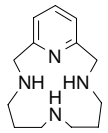
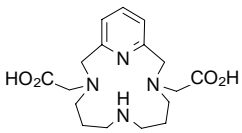
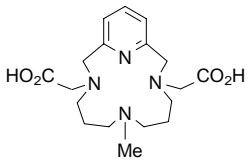
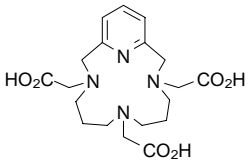
A comparison of the stabilities of complexes with ligands **267** and **320** demonstrates that the stability constants are higher in the former case, which implies that at least one carboxyl group is involved in coordination. However, the stability constant for the Ni^{2+} complex increases insignificantly, while that for the Cu^{2+} complex decreases. Analysis of the stability constants of the complexes of azacrown ether **267** leads to some interesting conclusions. Ligand **267** does not show selectivity for first transition row metal ions, as indicated by similar stability constants of all complexes. For macrocycle **267**, the stability constants are lower for the complexes of Cu^{2+} and Ni^{2+} than for the complexes of Co^{2+} and Zn^{2+}; in other words, cation binding does not comply with the Irving–Williams series. Complexes of alkaline earth metal ions follow the expected trend: the stability constants of the complexes decrease with increasing ionic radius of the metal. The complexes of trivalent metal ions show the trend usually typical of polyaminocarboxylate complexes, which predicts the highest stability for the Fe^{3+} complex. Nevertheless, the stability constant of this complex is lower than the expected value when compared with those of Ga^{3+} and In^{3+} complexes.[176]

Most often, *N*-carboxymethyl derivatives of 14-membered macrocycles are more selective for divalent transition metal ions than their 12- and 13-membered analogues.[177] However, there are some exceptions For example, complexes of ligands **346**, **347** and **271** with all studied metals, except for Ni^{2+} and Cu^{2+}, have lower stability constants than the complex of macrocycle **267** (see Table 12). The thermodynamic stability of complexes with alkaline earth metal ions always decreases with increasing size of the cavity, and the stability constants of alkaline earth metal complexes with ligands **346**, **347** and **271**, containing propyl chains, are very low.

The stability constants of complexes based on bis- and tris(*N*-carboxymethyl)-substituted ligands **346** and **271** with most metal cations, except for Ca^{2+} and Mn^{2+}, are very similar (see Table 12). This was to be expected in view of the fact that the two mentioned ligands differ only in the number of carboxyl groups (2 *vs.* 3), and ligand **346** has a sufficient number of donor atoms to satisfy the coordination requirements of most of studied metal ions. The Ca^{2+} and Mn^{2+} ions have coordination numbers above six and, hence, they can form thermodynamically more stable complexes with ligand **271**.[177]

Analysis of the stability constants of complexes formed by *N*-carboxymethyl-substituted macrocycles **346**, **347** and **271** with various types of metals (see Table 12) demonstrates the selectivity of these ligands for Cu^{2+} and Ni^{2+} ions and low affinity for first row transition metals. The

Table 12. Stability constants (log *K*) of complexes formed by ligands **267**, **271**, **320**, **339**, **346**, **347** (T = 25.0 °C, I = 0.10 mol L^{-1}).

Composition of the complex	log *K*					
	 **320** (see [176, 203])	 **267** (see [177, 219])	 **339** (see [177, 203])	 **346** (see [177])	 **347** (see [150, 177])	 **271** (see [150, 177])
L·Mg^{2+}	See [a]	11.82	See [a]	See [a]	5.30	2.89
L·Ca^{2+}	See [a]	12.38	See [a]	3.32	3.74	5.85
L·Mn^{2+}	8.81	18.59	5.48	9.99	See [a]	11.81
L·Fe^{2+}	12.55	See [b]	9.34	See [b]	See [b]	See [b]
L·Co^{2+}	15.69	18.92	See [a]	15.58	14.41	15.07
L·Ni^{2+}	17.05	17.31	16.27	18.53	16.59	19.38
L·Cu^{2+}	20.14	17.49	19.76	21.75	21.61	21.84
L·Zn^{2+}	14.40	18.22	12.82	15.26	14.1	15.01
L·Cd^{2+}	12.67	19.53	9.76	See [b]	See [b]	See [b]
L·Pb^{2+}	15.42	17.48	9.72	11.99	10.89	12.83
L·Ga^{3+}	See [a]	19.37	See [a]	See [a]	18.02	20.10
L·Fe^{3+}	See [a]	21.77	See [a]	20.49	20.64	19.21
L·In^{3+}	See [a]	21.42	See [a]	See [a]	18.94	21.16

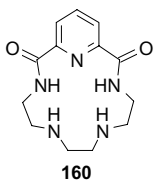
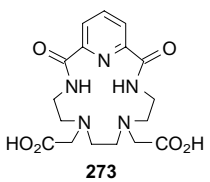
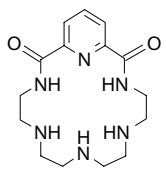
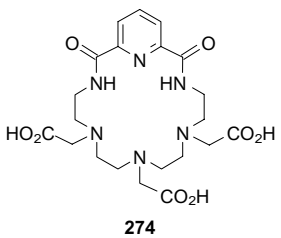
[a] No complex formation; [b] no data available.

complexes with larger ions such as Ca^{2+} and Pb^{2+} have low constants. The obtained results suggest that the coordination behaviour of ligands **346**, **347** and **271** depends on the metal nature and ion size and on the conformation adopted by the macrocycle. On the basis of quantum chemical calculations, it was concluded that macrocycle **346** is sufficiently flexible and has a sufficient number of donor atoms to adjust to the metal centre in various coordination geometries. Meanwhile, its tris(*N*-carboxymethyl) analogue **271** does not use all donor atoms for coordinating double-charged metal ions.[177]

Among amide macrocycles, ligand **274** forms the most stable complexes (Table 13). From a comparison of the complexation constants for macrocycles **273** and **274**, it is evident that an increase in the number of carboxyl groups increases the stability of complexes by 4.5 – 5.5 orders of magnitude, although this is less pronounced for Zn^{2+} ions. It is noteworthy that the increase in the stability constants of complexes caused by the interaction of the chelating carboxyl groups with the metal cations is accompanied by decreasing selectivity of the ligand. Indeed, whereas crown compounds **160** and **161** show selectivity for the Cu^{2+} ion, in the case of ligand **273**, the stability constants of Cu^{2+} and Zn^{2+} complexes are approximately equal, and in the case of ligand **274**, the stability constants of Cu^{2+}, Ni^{2+} and Pb^{2+} complexes differ insignificantly.[175]

Analysis of the crystal structure of complex **274**·Pb^{2+} demonstrated that macrocyclic ligand binds the cation through all three carboxyl groups (Fig. 11). The coordination environment of the metal ion is completed by three amino groups and a water molecule. The Pb^{2+} cation is completely encapsulated inside the macrocyclic cavity. Nevertheless, the macrocyclic effect of this ligand is not

Table 13. Stability constants (log *K*) of complexes formed by ligands **160**, **161**, **273** and **274** (T = 25.0 °C, I = 0.10 mol L^{-1}).[175]

Composition of the complex	log *K*			
	 **160**	 **273**	 **161**	 **274**
L·Ni^{2+}	5.5	9.5	6.0	14.3
L·Cu^{2+}	8.8	11.24	10.8	15.77
L·Zn^{2+}	3.9	11.5	4.1	12.6
L·Cd^{2+}	3.6	7.3	4.2	11.71
L·Pb^{2+}	See [a]	8.7	4.9	14.12

[a] No complex formation.

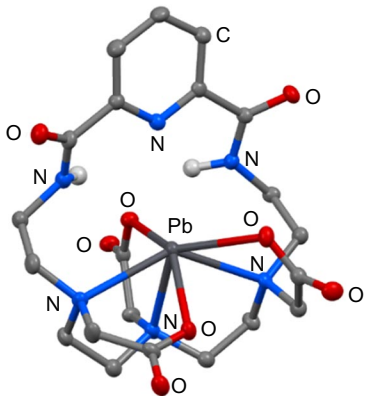


Figure 11. Molecular structure of complex **274**·Pb^{2+} (Ref. 175).

fully manifested, because no coordination bonds with the Pb^{2+} ion are present on the pyridine side.[175]

4.3.2. Pyridyl groups

Pyridyl substituents are also of considerable interest as chelating groups. The heterocyclic nitrogen atoms they contain, which are softer in terms of the Pearson's theory of hard and soft acids and bases, efficiently coordinate soft heavy metal cations and can be selective. The introduction of pyridine rings with their pronounced ability to bind transition metals (especially Co^{2+} and Ni^{2+}) and some heavy metals (U^{3+}, V^{3+}, Pb^{2+}, *etc.*) to give stable complexes gave rise to new chelators selective for heavy metals.[218] Examples of such chelators and stability constants of their complexes are summarized in Table 14.

The introduction of two pyridyl groups into macrocycle **339** (compound **295**) results in higher stability of the complexes with all of the studied cations. The stability constants of complexes formed by tripyridyl-substituted ligand **296** are most often lower than expected in comparison with those for the complexes with dipyridyl-substituted ligand **295** and unsubstituted macrocycle **339**. Presumably, the third pyridyl group in macrocycle **296** not only does not participate in the metal ion coordination, but also considerably enhances the steric restrictions of the ligand on complexation, which leads to decreasing stability constants. This is confirmed by analysis of the crystal structure of complex **296**·Cu^{2+} in which the cation is encapsulated in the macrocycle in a highly distorted square pyramidal geometry, being coordinated by only one out of the three pyridyl groups (Fig. 12).[192]

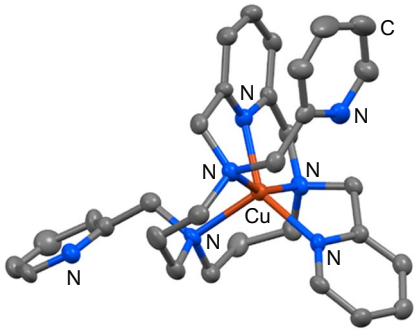


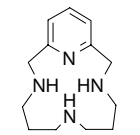
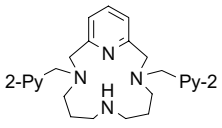
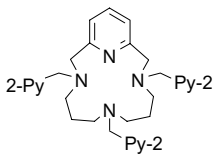
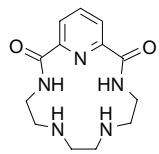
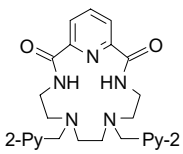
Figure 12. Molecular structure of complex **296**·Cu^{2+} (Ref. 192).

Despite the generally lower complexation constants for macrocycle **296** compared with ligands **295** and **339**, one can see that ligand **296** has a high selectivity for Cd^{2+} ions. Probably, only in the Cd^{2+} complex, all donor atoms of ligand **296** are involved in cation binding, at least, to a higher extent than in the complexes of other metal ions.[192]

It is noteworthy that the presence of pyridyl substituents in compound **300** does not have a significant effect on the complexation with a Cu^{2+} cation in comparison with unsubstituted analogue **160**, while in the case of Zn^{2+} and Cd^{2+} cations, the stability constants of the complexes decrease and only hydroxo complexes are formed. Meanwhile, the stability of the Pb^{2+} complex substantially increases. This may be due to the higher affinity of the soft Pb^{2+} cation to the pyridine nitrogens.

According to X-ray diffraction data for complex **300**·Pb^{2+}, both pyridyl groups are involved in complex formation (Fig. 13 *a*). In addition, the coordination sphere of the lead cation contains two amino groups and two perchlorate oxygen atoms.

Table 14. Stability constants (log *K*) of 1 : 1 complexes ($L : M^{n+}$) formed by ligands **160** , **295**, **296**, **300** and **339** (T = 25.0 °C, I = 0.10 mol L^{-1}).

Composition of the complex	log *K*				
	 **339** (see [177, 203])	 **295** (see [177, 192])	 **296** (see [192])	 **160** (see [103])	 **300** (see [175])
L·Co^{2+}	See [a]	13.5	See [a]	See [b]	See [b]
L·Ni^{2+}	16.27	16.94	15.61	5.5	6.5
L·Cu^{2+}	19.76	20.13	19.42	8.8	8.9
L·Zn^{2+}	12.82	14.65	11.92	3.9	See [a]
L·Cd^{2+}	9.76	14.85	16.55	3.6	See [a]
L·Pb^{2+}	9.72	10.69	9.62	See [a]	5.35
L·Fe^{3+}	See [a]	15.87	15.70	See [b]	See [b]
L·In^{3+}	See [a]	14.01	14.10	See [b]	See [b]

[a] No complex formation; [b] no data available.

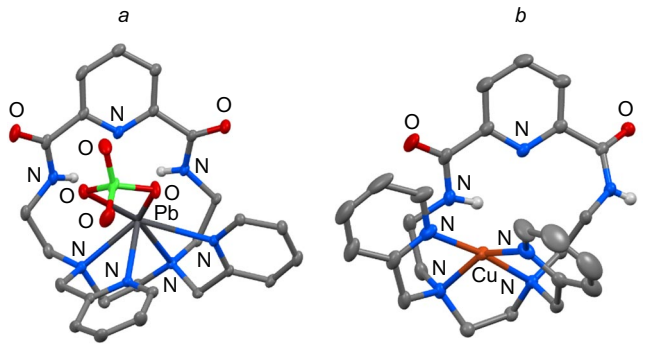


Figure 13. Molecular structures of complexes **300**·Pb^{2+} (*a*) and **300**·Cu^{2+} (*b*).[175]

When crown compound **300** is coordinated to the smaller Cu^{2+} cation, the complex adopts a different geometry, although the metal atom is bound in the same way to two pyridine nitrogens and two amino group nitrogens. The proximity of the Cu^{2+} cation to the amide group on one side of the square plane formed by four nitrogen atoms and to the perchlorate anion on the other side of this plane suggests an octahedral geometry for the Cu^{2+} complex with two weaker bonds. As a result, the stability constant of complex **300**·Cu^{2+} can decrease.

4.3.3. Picolinate groups

It is known that picolinate groups, which are bidentate ligands, possess unusual coordination properties towards various metal ions, especially if these groups are components of a macrocyclic structure.[191] Picolinate groups contain both hard donor oxygen atoms and a soft nitrogen atoms of the heterocycle, which can simultaneously participate in the coordination of the metal cation. It was proved that macrocycles containing picolinate groups strongly bind various metal ions such as Zn^{2+}, Cd^{2+}, Pb^{2+}, Sr^{2+} and Ln^{3+} (Refs 220 and 221).

Benzocrown compound **312** with one picolinate group forms complexes with all of the considered cations (Table 15). The stability constants of the resulting complexes are approximately equal, except for the Cu^{2+} complex, which may be due to identical coordination of metal cations involving three heteroatoms: the nitrogen atoms of the aminopicoline group and the oxygen atom of the carboxyl group. Upon the introduction of the second picolinate group into the macrocycle (compound **313**), the stability of the complexes increases by 8 – 10 orders of magnitude. Study of the complexation of ligands **276**, **303** and **313** with heavy metal cations demonstrated that all complexes of picolinate derivative **313** are more stable than those based on analogous macrocycles containing carboxyl (compound **276**) and pyridyl (compound **303**) chelating groups.

According to X-ray diffraction data, benzocrown compounds **303** and **313** coordinate the Cu^{2+} cation outside the macrocyclic cavity *via* two chelating picolinate groups and amino groups of the macrocycle (Fig. 14 *a*,*b*). Complex **303**·Cu^{2+} has a distorted square pyramidal structure in which the copper cation is coordinated by two nitrogen atoms of the macrocycle, two pyridine nitrogen atoms and a water molecule. The Cu^{2+} ion complexed with derivative **313** has an octahedral environment in which all eight bonds (two of which are ionic) are provided by the ligand. Consequently, complex **313**·Cu^{2+} is five orders of magnitude more stable than **303**·Cu^{2+}, according to the results of potentiometric titration.[92]

Studying the effect of the position of the picolinate substituent in the macrocycle revealed differences between the complex formation by two isomers **348** and **349** (Table 16). For example, complex **348**·Y^{3+} proved to be more labile than complex **349**·Y^{3+}, which may be caused by weaker coordination of the carboxyl groups located at the opposite nitrogen atoms of the macrocycle.[197]

The complexing properties of the picolinate derivative of pyridino-crown compound **309** were studied using lanthanide ions (see Table 16). The data of NMR spectroscopy (in D_2O) and quantum chemical calculations lead to the conclusion about an octadentate binding of the cation *via* four nitrogen atoms of macrocycle **309** and the nitrogen and oxygen atoms of the picolinate groups. The relatively low stability constants of lanthanide complexes **309** are apparently attributable to the mismatch between the cavity and metal ion sizes.[196]

5. Applications of azacrown compounds

The discovery of a previously unknown phenomenon or a new compound is reasonably followed by the search for their possible practical applications. In turn, wide scope of applicability stimulates further research along this line.

Table 15. Stability constants (log *K*) of complexes formed by ligands **276**, **303**, **312** and **313** (T = 25.0 °C, I = 0.10 mol L^{-1}).[92]

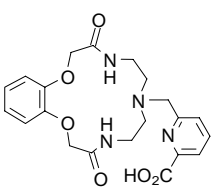
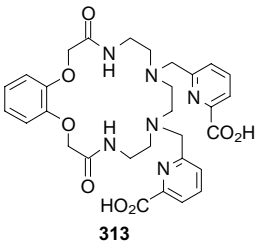
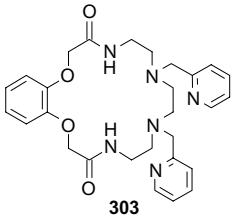
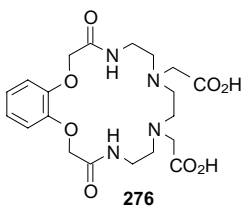
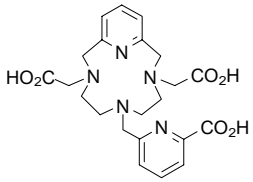
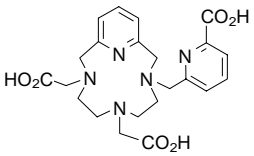
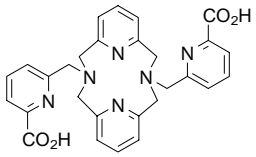
Composition of the complex	log *K*			
	 **312**	 **313**	 **303**	 **276**
L·Ni^{2+}	4.81	14.4	8.20	11.7
L·Cu^{2+}	5.78	15.7	10.37	13.31
L·Zn^{2+}	4.3	14.16	7.1	9.42
L·Cd^{2+}	4.2	12.53	6.76	7.9
L·Pb^{2+}	4.64	13.9	6.3	9.75

Table 16. Stability constants (log K) of complexes formed by ligands **309**, **348**, **349** (T = 25.0 °C, I = 0.1 mol L^{-1}).

Composition of the complex	log K		
	 **348** (see [197])	 **349** (see [197])	 **309** (see [196])
L·Y^{3+}	19.89 [a]	22.44 [a]	See [b]
L·La^{3+}	See [b]	See [b]	12.48
L·Nd^{3+}	See [b]	See [b]	13.32
L·Gd^{3+}	See [b]	See [b]	13.62
L·Dy^{3+}	See [b]	See [b]	14.18
L·Lu^{3+}	See [b]	See [b]	13.86

[a] I = 0.15 mol L^{-1}; [b] no data available.

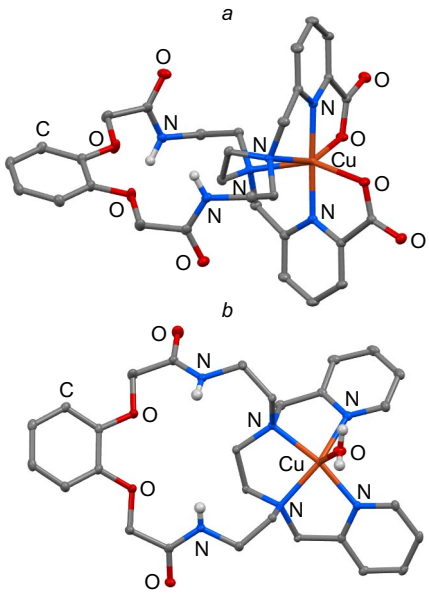


Figure 14. Molecular structures of complexes **313**·Cu^{2+} (*a*) and **303**·Cu^{2+} (*b*).[92]

Crown ethers are among the most important classes of macrocyclic compounds. The introduction of a nitrogen atom into the crown ether molecules gives rise to a series of specific properties of the resulting macrocycle.[2,3] The applications of azacrown compounds include analytical and organic chemistry, ecology, biochemistry and medicine and also the fabrication technology of molecular devices.

5.1. Molecular recognition

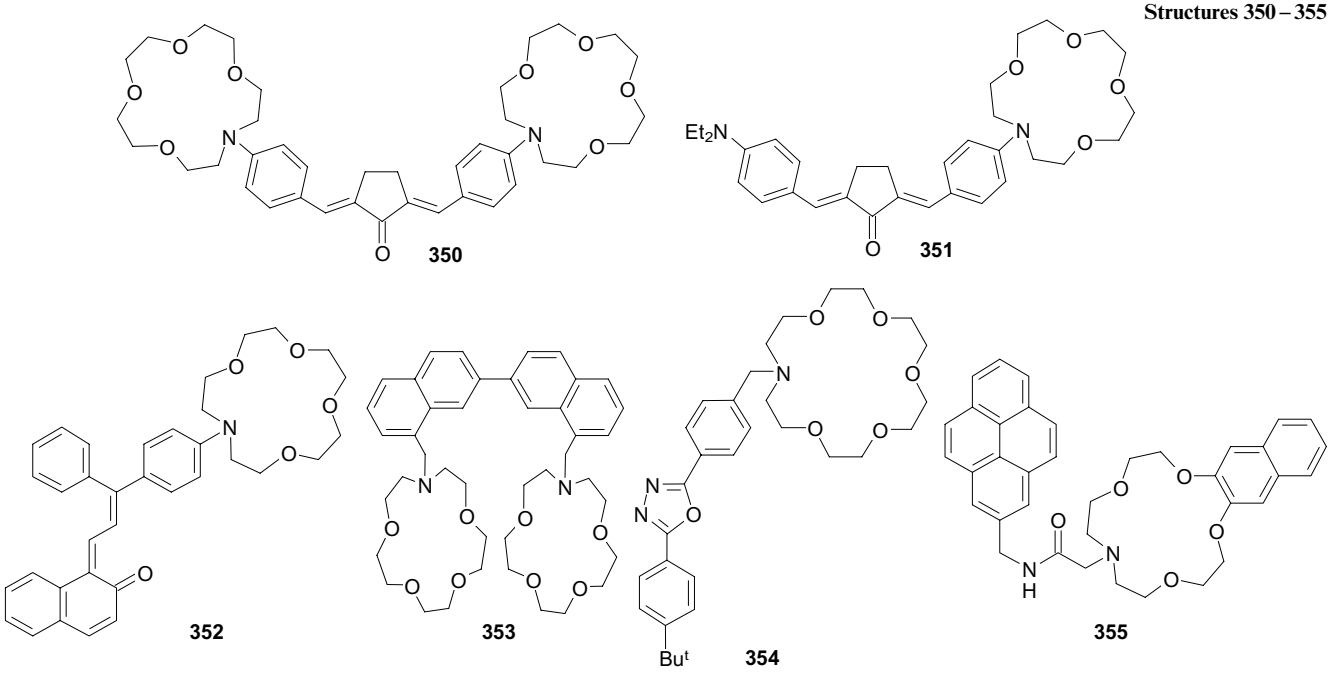
The applications of crown ethers are based on their most important and unique feature: the ability to selectively capture strictly definite ions in conformity with the size of the macrocyclic cavity.[222,223] Using this feature of crown compounds, sensitive methods for analysis and selective extraction of substances have already been developed and are being developed now. Crown compounds acquired importance as an efficient class of receptors for cations,[8,171,199,224] anions[99,105] and neutral molecules.[19,20,90] Combining a crown ether receptor molecule with a molecule possessing signalling function resulted in the development of chemosensors. Depending on the properties of the signalling molecule, a chemosensor can be fluorescent,[225] or electrochemical,[226] or combine both mechanisms.[108,130,227] Chemosensors are used to detect trace amounts of definite ions in water, soil, food products, biological objects, cosmetic products and medications and represent a convenient tool for both qualitative and quantitative analysis.[228]

The development of selective fluorescent sensors for alkali and alkaline earth metal ions to be used in biology is in progress because of the necessity to study processes associated with variation of concentrations of these ions in biological objects. In particular, phenylazacrown derivatives **350** and **351** showed promising results owing to their amphiphilic properties and large numbers of binding sites on the cell membrane. This probe was successfully used for the monitoring of the temperature-dependent phase transitions in the lipid bilayer of human red cell membranes.[229,230]

An efficient optode membrane developed on the basis of amide benzoazacrown compound **120** demonstrated high selectivity for the Co^{2+} ion. The use of the proposed fluorescence optode permits successful determination of Co^{2+} content in vitamin B_{12} products, cobalt alloys and tap water samples.[82]

Pyridino-dibenzocrown compound **190** containing a hydroxyquinoline fluorophore showed promising results to be used as a sensor for Cu^{2+}, Zn^{2+}, Cd^{2+}, Al^{3+} and Cr^{3+} cations.[120] Quite a few phenanthroline-containing macrocyclic sensors for the Cu^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+} and Hg^{2+} ions were prepared.[210,216,231,232] Binaphthyl- and biphenylazacrown derivatives **57**, **217** and **218** showed high sensitivity to Hg^{2+}, Pb^{2+} and Cu^{2+} ions.[43,134,233] Other examples include a chromene-containing sensor **352** for Ca^{2+} cations,[234] sensor **353** for Ba^{2+} cations forming an intramolecular sandwich complex,[235,236] sensor **354** for Ce^{3+} and Eu^{3+} cations in the presence of other rare earth metals,[237] highly sensitive sensor for K^+ cations suitable for highly sensitive determination of K^+ in the presence of Na^+,[238] naphthalimide-based fluorescent sensor for Ag^+ (Ref. 239) and a variety of chemosensors for Cu^{2+} (for example, **355**).[240,241]

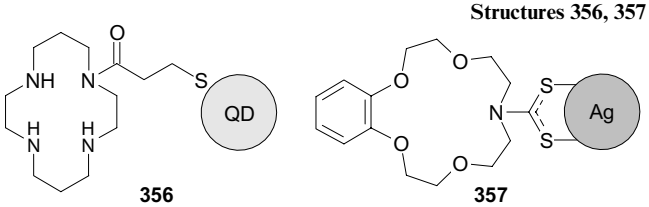
Structures 350 – 355



350 **351** **352** **353** **354** **355**

Recently a new family of fluorescent nanosensors **356** consisting of azacrown compounds covalently bound to the surface of quantum dots (QD) was developed. They showed very high sensitivity and selectivity for Zn^{2+} ions at physiological pH. It is assumed that the mechanism of their action is based on photoinduced hole transfer.[242] One more type of nanosensors is based on colourimetric detection of various ions by means of crown ether derivatives adsorbed on the surface of gold, silver and iron oxide nanoparticles (for example, compound **357**). Using these sensors, it is possible to detect the presence of Ca^{2+}, Mg^{2+}, Ba^{2+} and Pb^{2+} ions even by a naked eye.[243]

Structures 356, 357



356 **357**

Crown compounds containing hydrophobic moieties are able to dissolve metal ions in organic solvents or in membrane media, which allows them to be used as models of carrier molecules to study the transport phenomena of reactive ions [192] and as extractants of toxic metals, which is highly important for environmental protection.[74] There are benzo-, pyridine- and phenanthroline-containing macrocycles able to selectively bind Cd^{2+} (Ref. 192), Pb^{2+} (Refs 74, 244) and Hg^{2+} ions [245] and thus remove them from the environment.

The macrocyclic ligands immobilized on a solid substrate and capable of selective separation and preconcentration of elements are used for solid-phase extraction. The capability for the recognition of these materials persists at very low cation concentrations, which allows removal of single toxic elements or a group of elements, rare nonferrous metals and radionuclides from solutions.[140, 156, 200, 244]

The recognition of anions is a vigorously developing area of supramolecular chemistry, which is practically utilized to design molecular devices such as sensors, responsive materials, extraction systems and simple and transmembrane transporters.[99] In most cases, protonated [16, 246] and amide [98, 105] azamacrocycles serve as receptors. The complex formation is due to electrostatic and hydrogen bonds. The shape and size of the macrocyclic cavity also affect the binding and selectivity.[15, 247]

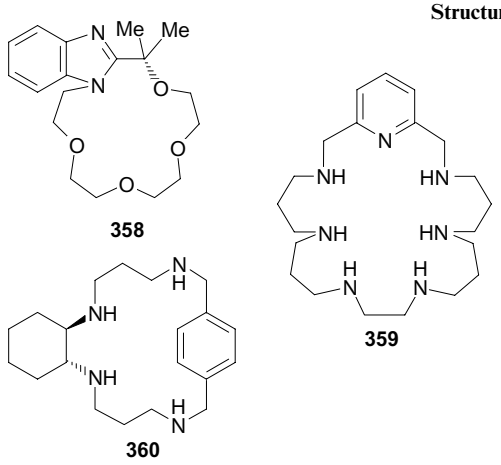
A new fluorescent sensor for determining pyrophosphate ions in the presence of other phosphate anions has been developed on the basis of a zinc complex of pyridino-azacrown compound **320** with a naphthalene fluorophore.[248] Benzoazacrown compound **317**, which selectively recognized phosphatidylinositol-4,5-bis(phosphate) among other phosphorylated inositols, was reported.[63] Both sensors efficiently operate both in aqueous solution and in blood serum at physiological pH.

A new class of receptors **148** – **157** with a rigid macrocyclic structure have been prepared *via* coupling of amide bonds and (hetero)aromatic rings; some of them proved to be selective for the Cl^- ion over $H_2PO_4^-$ and AcO^- ions.[101, 249, 250] Tetraamide pyridine-crown compounds **144** – **145** also proved to be selective for Cl^- (over Br^-, CN^-, $PhCOO^-$, AcO^-, $H_2PO_4^-$, $4\text{-}NOC_6H_4O^-$ and HSO_4^-).[98] Another pyridine-containing receptor exhibited higher selectivity for AcO^- over Cl^- or F^- (Ref. 251). Flouorophores for determining $PhCOO^-$, $H_2PO_4^-$, F^-, Cl^-, Br^- and I^- anions were obtained.[99, 252] A sensor based on a cellulose-immobilized pyridino-azacrown compound proved to distinguish between F^-, AcO^-, CN^- and $H_2PO_4^-$ ions in an aqueous medium.[253]

The search for synthetic chiral receptors for analysis of the stereochemical purity of biologically significant molecules, such as amino acids, sugars, pharmaceutical products and so on, is permanently carried out all over the world. Their action is based on the difference between the interaction energies of the receptor with the analytes. The structural features required to detect enantiomers include the size of the macrocyclic cavity, symmetry, additional

binding sites, conformational rigidity and accessibility of a π-rich unit near the stereogenic centre.[254] Chiral azacrown compounds proved to be suitable receptors for the molecular recognition of enantiomers. They are used to estimate the optical purity and enantiomeric excess in the products of organic reactions, as selectors for chromatographic separation and for the preparation of fluorescent and electrochemical sensors for amines and ammonium salts (derivative **57** and compound **358**),[43, 254 – 256] carboxylic acids (compound **170**),[14, 113] amino acids (compound **226** and **359**)[136, 257, 258] and anions (compound **360**).[51] For example, fluorescent sensors for uridine[259] and thymidine[260] ribonucleotides were prepared.

Structures 358 – 360



The possibility of direct absorption of CO_2 from the atmosphere using binuclear complexes of azacrown compounds with Cu^{2+} (Ref. 261) and Ni^{2+} (Ref. 262) cations was demonstrated. Since continuous release of CO_2 is the main cause of the global greenhouse effect, CO_2 scavenging and isolation techniques are necessary for decreasing its concentration in the atmosphere and providing its storage and transportation. In addition, reversible systems that make it possible to subsequently release CO_2 for the use in industrial processes are of interest.[262]

Currently, research is concentrated on the synthesis of chemosensors soluble in water and operating in the near-infrared region with the goal of increasing the sensitivity of *in vivo* analysis.[263] Photoswitchable smart receptors for various ions are being developed.[264] Despite the progress achieved in this area, there are still unsolved problems and challenges. The available series of ligands for detecting some important metal ions are still very limited. For example, a fluorescent sensor with high selectivity and sensitivity for Na^+ ions has not yet been developed. Sensors for Ni^{2+} and Co^{2+} ions, especially those operating in the near-infrared region, are very rare, despite the important role of these metals in biochemistry and biomedicine.[265] The subsequent goals of molecular recognition chemistry include the design of 'living' complex functional systems *via* spontaneous self-assembly of receptor molecules and materials.[266]

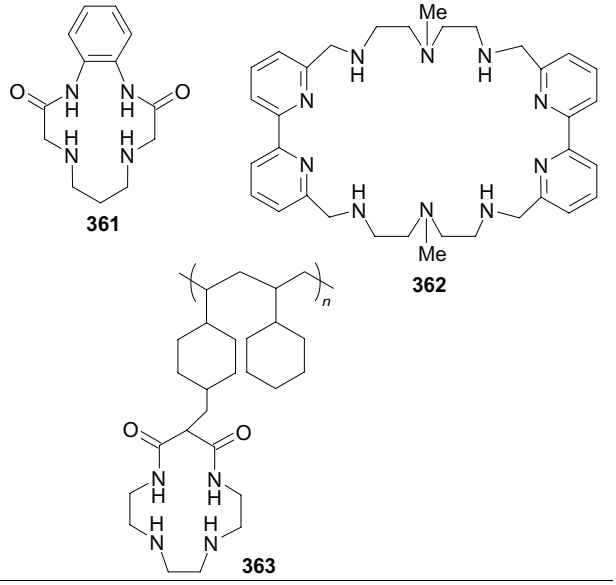
5.2. Catalysts

The catalytic activity of macrocyclic complexes made a large contribution to green chemistry. Many synthetic macrocyclic complexes of transition metals act as catalysts owing to their high thermal stability and unusual structural and electrochemical properties. Some natural macrocyclic complexes such as vitamin B_{12} also catalyze many transformations. Oxygen-containing crown ethers are widely used as phase transfer catalysts, while their aza analogues are more often utilized in homogenous catalysis.

A catalyst for regioselective opening of the epoxide ring was designed using benzoazacrown compound **133**. The authors noted[94] the ease of catalyst regeneration, tolerance of the reaction conditions to various sensitive functional groups and the ease of application. A catalyst for asymmetric epoxidation of chalcones was developed on the basis of an azacrown compound containing BINOL (1,1′-bi-2-naphthol) moieties; the catalyst ensures high yields of the target epoxide and good enantioselectivity.[267] The palladium complex of amide azacrown compound **361** was used as the catalyst for the Suzuki and Heck cross-coupling, although the outcome was moderate.[268] Zinc complexes of azacrown compounds **328** and **362**, containing a bipyridine moiety, showed good results as catalysts for phosphate hydrolysis.[207] The copper complex of polystyrene-grafted tetraazacrown compound **363** was used to catalyze polymerization, which resulted in a high degree of monomer conversion.[269] Chiral pyridine-containing azacrown compounds proved to be promising catalysts for enantioselective allylation of *para*-nitrobenzaldehyde (derivative **110**)[58] and Michael addition of 2-nitropropane to chalcones.[270]

An efficient, environmentally pure nanocatalyst was developed on the basis of amide benzocrown compound **120** immobilized on the surface of magnetic nanoparticles $Fe_3O_4@SiO_2$ for the green synthesis of 1,2,3-triazoles, 5-phenyl-1*H*-tetrazoles and 1-phenyltetrazoles. The benefits of this catalyst include thermal stability, the of preparation, short reaction time, high yields and simple separation and isolation of the product. In addition, this nanocatalyst can be easily magnetically recovered and reused in subsequent reactions.[271]

Structures 361 – 363



5.3. Biological activity

The biological activity of crown compounds is due to their influence on the ionic and substrate permeability of biological membranes and on enzyme systems.[9] Crown compounds exhibit psychotropic, cardiotropic,[272] cytotoxic,[273]

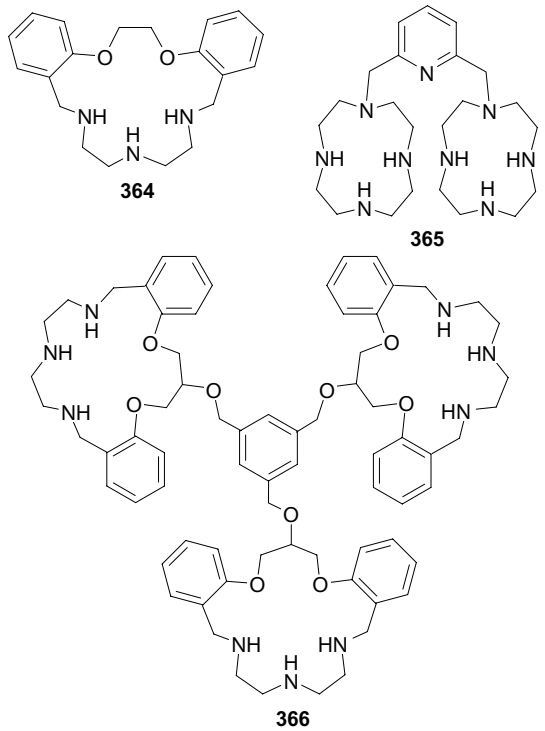
antibacterial,[274] antiparasitic[77, 158, 159, 275] and antiviral[5] activities.

Methods for the treatment of various diseases based on the regulation of the contents of vital metals in the body are known to be widely used. The use of crown compounds, in this case, is a tool for affecting the vital activity associated with the transport of metal ions through biological membranes. For example, diseases characterized by increased body levels of Cu^{2+} ions (Wilson disease, some types of cancer) and Ni^{2+} ions (pulmonary and renal fibrosis, cardiovascular diseases) are treated by chemotherapy. Macrocyclic compounds, which bring about minimum side effects due to selectivity, are employed as chelating agents.[11]

Azamacrocycles and their complexes exhibit activity against the human immunodeficiency virus (HIV), owing to their ability to bind to the chemokine receptor CXCR4, which acts as the key receptor in the HIV infection, numerous types of cancer and other pathologies such as rheumatoid arthritis and asthma.[5] Currently, there exist several drugs based on azacrown compounds that have passed clinical trials.[276] A CXCR4 inhibitor based on the Mn^{2+} complex of pyridine-containing azacrown compound **186** was recently developed;[116] the product showed good prospects for the use against HIV infection.[277]

Mono- and binuclear complexes of azacrown compounds with Mn^{2+}, Cu^{2+}, Zn^{2+} and Co^{3+} ions attract particular attention, because they can mimic active sites of metalloenzymes. For example, phosphodiesterase analogues not only cleave the phosphodiester bonds of RNA, but can also recognize structures of bases such as uracil and thymine.[278] Zinc complexes of crown compounds (for example, **264**), analogues of alkaline phosphatase, carbonic anhydrase, carboxypeptidase, dehydrogenase peptide, lactamase and alcohol dehydrogenases, were prepared.[279] Benzene-containing macrocycles show higher activity as a model of hydrolase enzymes in comparison with analogues.[280, 281]

Structures 364 – 366



364 **365** **366**

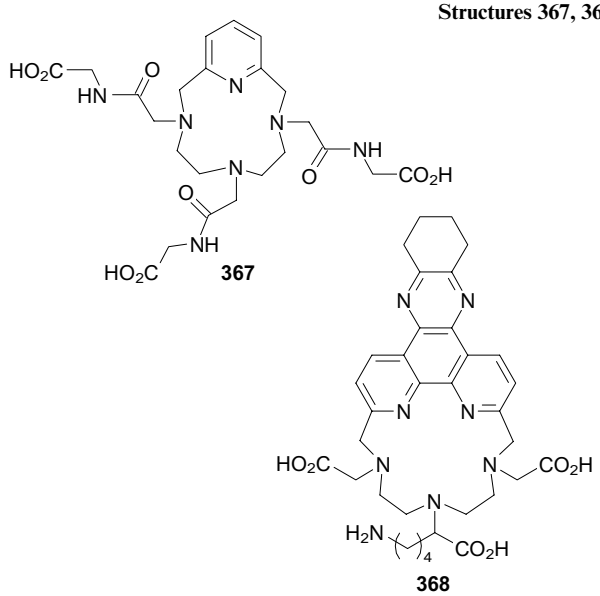
Copper(II) complexes mimic the action of phosphatases, nucleases and peptidases. The detoxification after the action of some pesticides and chemical weapons was considered as possible application of these compounds.[282]

DNA-cleaving agents are being developed, since the ability to efficiently and selectively manipulate genes by means of synthetic systems is of considerable interest as a mechanism for studying the interaction of natural hydrolases with DNA. Macrocyclic Schiff bases were among the first examples of synthetic nucleases;[283] later, Cu^{2+}, Zn^{2+} and lanthanide complexes of azacrown compounds able to cleave DNA were developed (for example, compounds **365** and **366**).[214, 284 – 286] These agents can be designed in such a way as to block the gene-specific transcription; this enables their use as antibiotics and for chemotherapy. Furthermore, synthetic hydrolases are useful as specific restriction enzymes for molecular biology.[283]

The activity of Mn^{2+} complexes of pyridino-crown compounds **186**, **198** and **199** proved to be similar to the action of superoxide dismutase;[96, 287, 288] therefore, these complexes showed high potential in the treatment of diseases associated with excessive amount of superoxide, for example, ischemic reperfusion injury, inflammatory and vascular diseases; also, they exhibited antitumour, antiarthritis and analgesic activities.[54, 57, 289, 290]

Owing to good water solubility, high sensitivity and long lifetime, lanthanide complexes of azacrown compounds **280 – 282**, **367** and **368** are used as fluorescent probes and labels in biology, biochemistry and clinical diagnosis, in particular, for fluorometry, optical microscopy, hybridization, enzymatic or receptor assays, for cell sorting and detection of biologically active ions.[157, 179, 184, 185]

Structures 367, 368



367 **368**

5.4. Radiopharmaceuticals and contrast agents

Owing to the ability of azacrown compounds and their derivatives to form highly stable complexes with radionuclide ions, they are actively used as components of diagnostic and therapeutic anticancer agents — radiopharmaceuticals. The use of macrocycles as chelators for radiopharmaceuticals and the development of bifunctional chelators gained wide popularity in the 1980s – 1990s.[11] The radionuclide ion should be strongly bound to a ligand,

which is often modified by adding a vector biomolecule for the drug delivery to the desired target.[291, 292] The diagnosis is based on tumour imaging by means of single-photon emission computed tomography (SPECT), which employs γ-emitters,[293] or positron emission tomography (PET), which employs β^+-emitters.[294, 295] Therapeutic radionuclides emit α, β and Auger electrons.[202, 296, 297] For safe use in medical practice, it is necessary to take into account the coordination behaviour, including affinity for donor atoms (N, O, S), coordination number and geometry for each particular radionuclide; however many key conditions can be applied universally.[298] Many clinically used radiopharmaceuticals contain the azacrown compound DOTA (1,4,7,10-tetraazacyclodecane-1,4,7,10-tetraacetate), which is the 'gold standard' for ^{111}In, ^{177}Lu, $^{86/90}$Y, ^{225}Ac and $^{44/47}$Sc isotopes; however, the drawbacks caused by slow complexation stimulate the search for new chelators. The complex formation can be accelerated by increasing the rigidity of the macrocycle *via* introduction of benzene [299] or pyridine [102, 300] rings.

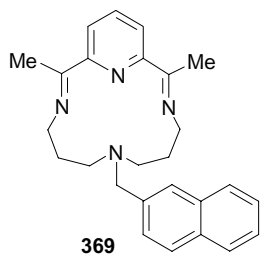
The necessity of improving the quality of magnetic resonance imaging (MRI) as a diagnostic method in medicine resulted in the synthesis of contrast agents, which accelerate relaxation of water protons near the compound. The effect is manifested as enhanced contrast between the injured and healthy tissues or metabolic changes.[11] Currently, drugs based on Mn^{2+} and Gd^{3+} complexes of azacrown compounds have been developed; the interest in the use of other lanthanides is increasing.[53, 114, 157, 196] There exist hybrid materials combining the action of MRI contrast agents and PET or SPECT contrast agents.[301, 302] The key challenge in this field is to develop systems providing enhanced relaxation, sensitivity and the possibility of specific targeting.[173, 183, 303]

5.5. Molecular devices

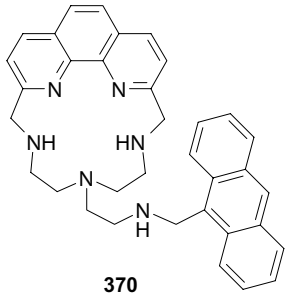
In molecular devices, single molecules serve as active components functioning as wires, switches, diodes, transistors, light absorbing and light emitting centres, *etc*. Azacrown compounds as components of more complex systems, in which electron or energy transfer can take place, are of interest for the use in various devices such as molecular switches operating under the action of light, pH changes, the presence of definite cations or redox processes.[304, 305]

Some complexes of azacrown compounds exhibit different fluorescence properties when exist as two forms, which can be used to control switching. An example is the Ni^{2+} complex with the naphthyl-substituted pyridino-azacrown compound **369**, which exhibits fluorescence. The reduction of the metal cation to Ni^+ considerably decreases the radiation intensity.[306] The properties of the Zn^{2+} complex with the anthracene-substituted azacrown compound **370** can be controlled by varying the pH of the medium or by light radiation; a change in the visible light radiation is observed.[307]

Structures 369, 370



369



370

6. Conclusion

Azamacrocycles containing arene substituents incorporated in the core are being actively studied. They are fairly interesting compounds possessing high practical value, because they can be used to bind both inorganic or organic ions and neutral molecules. The aromatic ring incorporated in the molecule enables the molecular recognition and biological activity. Their metal complexes possess reactivity that can be considered as mimicking the action of enzymes. In addition, the aromatic part of the macrocycle can be used as a platform, which expands the scope of applicability of azacrown compounds by enabling creation of more complex and efficient systems.

Quite a few azacrown compounds that contain aromatic and heteroaromatic moieties differing in the macrocycle size and flexibility have now been synthesized. Azamacrocycles containing rigid arene rings in the molecule are synthesized using approaches developed for other types of azacrown compounds. For example, there are eight key methods for the preparation of azacrown compounds using various combinations of initial linear molecules: amines, alcohols, halides, aldehydes, esters, acid chlorides, carbonates and alkenes. However, as in the case of any other crown compound, the synthesis of new macrocyclic ligands requires the selection of individual conditions for the isolation and purification.

Derivatives with carboxyl, pyridyl and picolinate chelating groups can be prepared in good yields by two conceptual approaches: modification of the ready macrocycle and introduction of chelating groups into starting compounds to be subjected to macrocyclization.

Studying the properties of azacrown compounds indicates that the complexing behaviour is influenced by a set of factors, including both the structural characteristics of the ligand and the nature of the metal cation. Increase in the macrocycle rigidity increases the rate of complexation, but does not always lead to higher stability of the resulting complex. The expansion of the macrocycle by replacement of ethylene chains by propylene ones decreases, most often, the stability of the complex, while the insertion of additional heteroatoms has a beneficial effect on the complexing behaviour of azacrown compounds up to a certain extent. However, the excess number of these atoms may reduce the stability constants of mononuclear complexes, resulting in the formation of binuclear complexes.

Chelating groups introduced into the side chain of the macrocycle expand the coordination space of the ligand and thus influence its complexing ability. The additional coordinating groups inside and outside the macrocyclic cavity enhance the chelating effect of the ligand, which increases the stability of metal complexes. The introduction of chelating carboxyl groups always increases the strength of metal cation binding. Owing to the large size and weak donor properties, pyridyl groups lead to lower stability constants of the formed metal complexes, but provide higher selectivity for soft cations. The number of chelating groups and their arrangement in the macrocycle are also important.

A promising trend for the further development of the chemistry of azacrown compounds containing aromatic groups is the use of an aromatic moiety as a convenient

platform for functionalization and subsequent introduction of a macrocycle into complex functional systems. The number of such studies is still moderate, since azamacrocycles have low stability in chemical transformations. The success in this synthesis will open up great prospects for the application of azacrown compounds in chemical sensorics, development of biomimetic systems, preparation of biologically active compounds, molecular devices and machines.

All Figures were either changed or composed by the authors using published data. In particular, crystal structures of the complexes were drawn using cif files, which were processed by the Mercury program. The references to relevant publications are indicated in the Figure captions.

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