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Encapsulation of organic and inorganic anions: synthesis of macropolycyclic ligands and their anion-receptor properties

Ya Z Voloshin, A S Belov

Contents

I.	Introduction	161
II.	Encapsulation of halide ions by an octaazamacrobicycle, the ethylenediamine derivative	161
III.	Binding of anions to macrobicycles with larger cavities, derivatives of terminal diaminoalkanes and their analogues	162
IV.	Binding of anions to macrobicycles with aromatic substituents in ribbed fragments	163
V.	Encapsulation of anions by polyamide macrobicycles	167
VI.	Cyclophane-type macrobicyclic polyamines and their anion-receptor properties	169
VII.	Binding of anions to metallamacrobicycles	170
VIII.	Anion-receptor properties of calixarenes containing azacrown ether fragments	172
IX.	Macrobicyclic calixpyrroles and their anion-receptor properties	173
X.	Binding of anions to metallated cryptophanes	174

Abstract. Main types of macropolycyclic ligands capable of encapsulating anions of various nature are considered, as well as coordination-chemical properties of these ligands, structural features of complexes with encapsulated anions and the reasons and the ways of attaining selective complexation to particular anions. The bibliography includes 46 references.

I. Introduction

Encapsulation of cations, anions and neutral molecules by three-dimensional cavities of macropolycyclic ligands imparts peculiar and often unique physical and physicochemical properties to these species that are almost completely isolated from the influence of external factors.[1]

The majority of reviews[2–8] and monographs[1, 9–21] devoted to this subject deal with the problems of the synthesis, structures and physicochemical properties (including redox and photochemical properties), as well as with practical applications of complexes with encapsulated metal cations [cryptates, sepulchrates, sarcophaginates and tris(diiminate)-clathrochelates]. The number of publications devoted to the synthesis of macropolycyclic cage anion receptors and physicochemical studies of anion encapsulation by these ligands is substantially smaller; to date there have been no exhaustive reviews and monographs, except for the review[22] devoted to polyamine receptors for anions.

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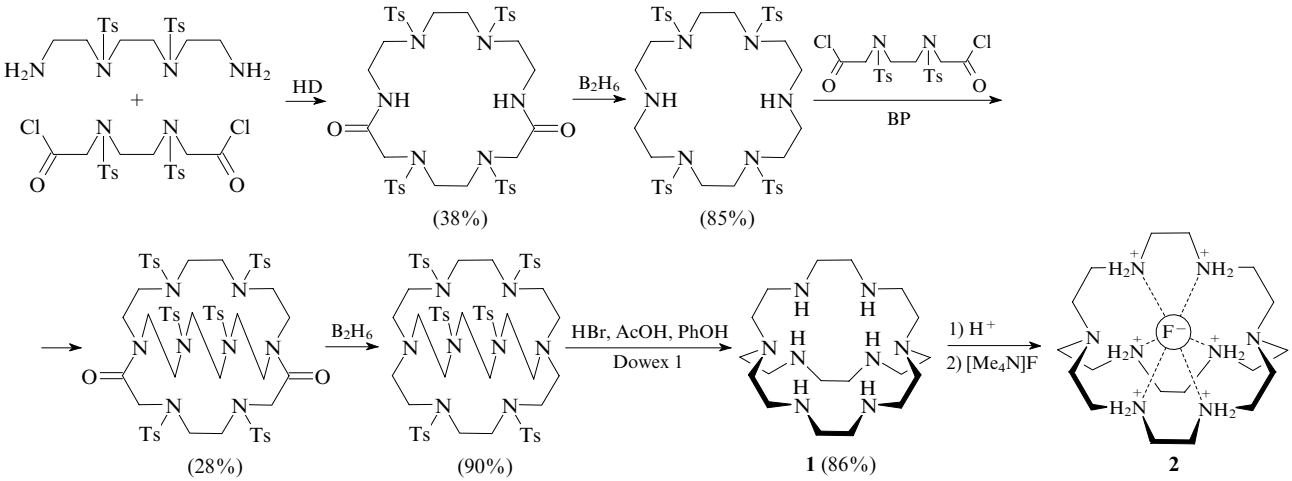
II. Encapsulation of halide ions by an octaazamacrobicycle, the ethylenediamine derivative

Octaazabicycle **1** was first synthesised by Lehn and co-workers[23] (Scheme 1). Binding of the fluoride ion by this ligand has been studied; the structure of hexaprotonated complex with this anion (**2**) was determined by X-ray diffraction: the F^- ion is coordinated to six protonated secondary nitrogen atoms of the ligand, the apical tertiary nitrogen atoms remain non-protonated.

Encapsulation of the fluoride ion by protonated octaazamacrobicycle **1** in solution has comprehensively been studied by NMR spectroscopy and potentiometry.[24] The degree of protonation increases with a decrease in pH (Fig. 1). Potentiometric titration revealed the hexaprotonated form $\mathbf{1}\cdot 6\,H^+$; this was the maximum degree of protonation achieved under the experimental conditions. The pentaprotonated form of ligand **1** could not be detected,[24] the content of this form did not exceed 5% with respect to the overall concentration of macrobicycle **1**. The interaction with fluoride ion was observed beginning from the triprotonated form $\mathbf{1}\cdot 3\,H^+$. It was shown[24] that binding of the fluoride ion increases the affinity of the macrobicyclic ligand to the H^+ ions. In addition, a synergistic effect of binding of protons and fluoride ions was observed: an increase in the degree of protonation of fluoride-containing complex results in an increase in its affinity to H^+ ions. For triprotonated ligand $\mathbf{1}\cdot 3\,H^+$, the affinity to the H^+ ions after binding of fluoride ions increases 32-fold, for the tetraprotonated form $\mathbf{1}\cdot 4\,H^+$, the affinity increases by more than six orders of magnitude. At the same time, the affinity of a more protonated form of this macrocycle to the fluoride anions is also substantially greater.

Macrobicycle **1** binds chloride ions substantially weaker than fluoride ions: the stability constant of the complex with encapsulated Cl^- ion was determined only with a 55-fold

Scheme 1



HD is high dilution conditions.

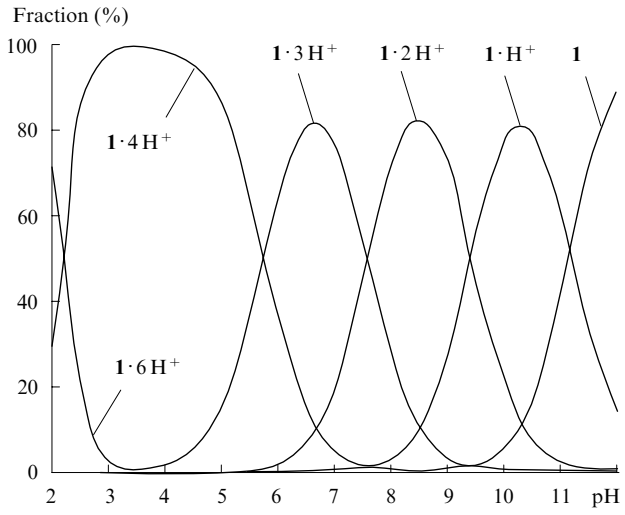


Figure 1. The distribution diagram of protonated forms of octaazamacrobicycle **1** *versus* pH.[24]

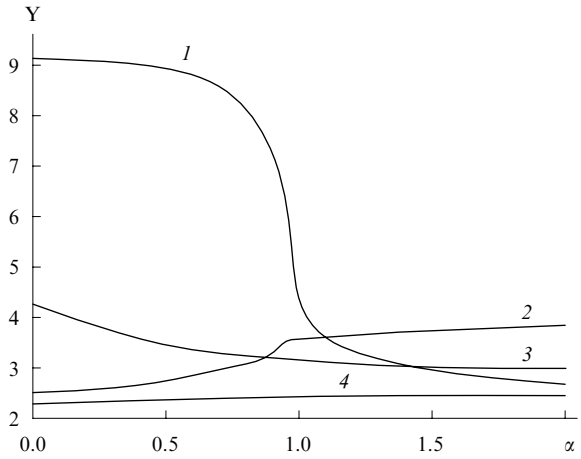


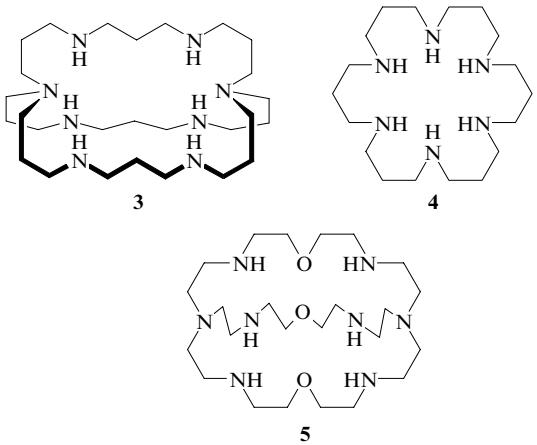
Figure 2. The curves of potentiometric titration of octaazamacrobicycle **1** by fluoride ion {(*1*) Y = p[F^-], (*2*) Y = pH} and chloride ion [(*3*) Y = p[Cl^-], (*4*) Y = pH];[24]
α is the number of equivalents of F^- or Cl^-.

excess of this ion; the selectivity coefficient F^-/Cl^- is equal to $10^{7.6}$. In the titration curve (Fig. 2) of ligand **1** by the fluoride ion, the formation of a 1 : 1 complex is distinctly observed at low pH values; in the case of Cl^- ion, no changes in the curve were observed. The interaction of macrobicyclic ligand **1** with nitrate ions was studied by ^{1}H NMR titration; it was found that this anion is bound even weaker than the chloride ions.

It is of note that efficient pH-controlled binding of the fluoride ion and high selectivity of binding of the latter as compared to that of the Cl^- anion open wide prospects for the application of the systems based on ligand **1** as sensors for fluoride ions.[24]

III. Binding of anions to macrobicycles with larger cavities, derivatives of terminal diaminoalkanes and their analogues

A comparative study of binding of anions to polyamine macrobicycle **3** with 1,3-diaminopropane ribbed fragments, its macrobicyclic analogue **4** and macrobicycle **5** was carried out[25] for hexaprotonated forms of ligands **3** and **5**, because hepta- and octaprotonated forms of ligand **5** have very low pK_a values.

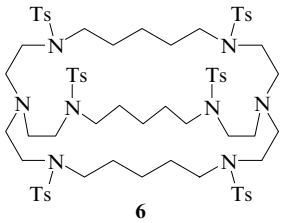


Protonated macrobicycle **3** forms complexes with Cl^-, Br^- and I^- anions, the most protonated form of this cage ligand giving the most stable compounds. The stability of these macrobicyclic complexes increases in the series $Cl^- < Br^- < I^-$. This order indicates that binding of halide

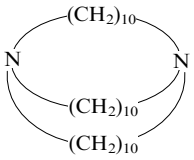
ions to ligand **3** is determined not only by electrostatic interactions, but also by fit of the substrate (halide ion) size to the size of the ligand cavity. For macrobicycle **5**, the inverse sequence (as compared with ligand **3**) is observed for changes in stability of complexes with halide ions ($Cl^- > Br^- > I^-$), which is associated with structural difference of these ligands: macrobicycle **3** has a bigger and more spherical cavity than its analogue **5** and forms more stable complexes with bulkier iodide ion. The preference of larger I^- anion with lower charge density can be associated with a more symmetrical distribution of charged groups in hexaprotonated ligand **3**. At the same time, the positive charge is localised to a greated extent in smaller hexaprotonated macrobicycle **5**, which allows it to be efficient encapsulating ligand for the Cl^- anion.

A comparative study of binding of oxalate and malonate dianions by macrobicyclic ligand **3** and its macrocyclic analogue **4** was reported.[25] For the same degrees of protonation, the hexaprotonated form of macrobicycle **3** binds the oxalate ion better than the corresponding form of macrocyclic ligand **4**, whereas the latter gives a more stable complex with the malonate ion. Larger selectivity of complexation with the oxalate/malonate ions is observed for hexa- and pentaprotonated forms of macrobicycle **3** as compared to the corresponding forms of macrocycle **4**. This is associated with the ability of the oxalate ion to fit the three-dimensional cavity of macrobicycle **3**, whereas the malonate ion cannot be completely encapsulated into the cavity. Thus, binding of organic dianions to ligands **3** and **4** demonstrates the so-called macrobicyclic effect of an increase in stability of complexes with encapsulated dianions and an increase in selectivity of complexation.

Lehn *et al.*[26] studied the possibility of using macrobicyclic complexes **6** and **7** with longer aliphatic chains in ribbed fragments for membrane anion transport.



6



7

N-Tosyl derivative **6** allowed an increase in the ligand hydrophobicity and reduction of the number of potential protonation sites to two apical nitrogen atoms. A bulky lipophilic counter-ion, dinonylnaphthalenesulfonate ($DNNS^-$), was always located outside the macrobicyclic cavity, but remained in the organic phase, *i.e.*, in the membrane. The scheme of the membrane anion transport is presented in Fig. 3. In an acidic medium, ligand protonation and extraction of an HX species into the membrane occur to give a complex with the encapsulated X^- anion. In neutral medium, ligand deprotonation and extrusion of HX from the membrane prevail, but further deprotonation is limited by both pH of the solution and the pK_a value of the carrier and low solubility of the $DNNS^-$ anion in water. A comparative study of membrane transport of Cl^-, Br^-, NO_3^- and ClO_4^- by macrobicyclic ligand **6** and trioctylamine has been carried out.[26] Even in the absence of the $DNNS^-$ anion, the selectivity of anion transport by macrobicycle **6** qualitatively differs from that by trioctylamine. In the pesence of the $DNNS^-$ anion, the selectivity of binding remains constant in the case of trioctylamine, while in the case of ligand **6**, the selectivity of binding of Br^-/NO_3^- is markedly larger. The system macrobicyclic

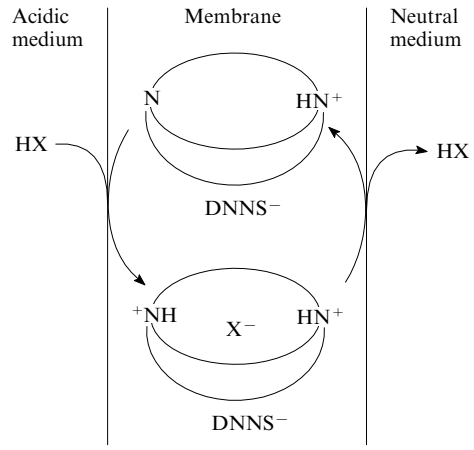
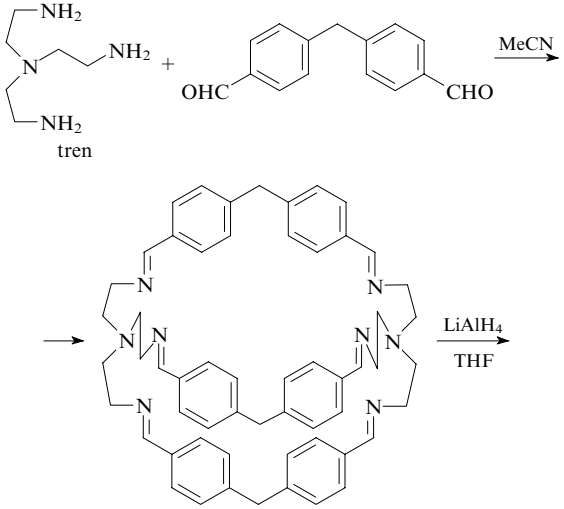


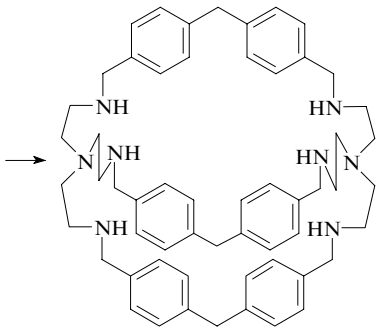
Figure 3. Membrane transport of the anion X^- (see the text).[26]

ligand **7** – $DNNS^-$ anion demonstrates the same selectivity. In the absence of a membrane carrier, no anion transport occurs. The selectivity of Br^-/ClO_4^- membrane transport is not high in all cases indicating the participation of outer-sphere complexes in membrane transport, which compete with compounds with encapsulated anions. It was found that in chloroform solution, the complex of macrobicyclic ligand **6** with encapsulated bromide ion is four orders of magnitude more stable than the outer-sphere complex of this ligand with the perchlorate anion. Anion transport does not depend on the Na^+ concentration, and no membrane transport of this cation occurs. Thus, the selectivity of membrane anion transport was revealed, which is inherent in these macrobicyclic amines as anion receptors.[26]

IV. Binding of anions to macrobicycles with aromatic substituents in ribbed fragments

Lehn *et al.*[27] obtained one of the first representatives of this type of ligands (compound **8**). In neutral medium, this ligand gives inclusion complexes with metal ions and after protonation it is able also to encapsulate anions. In particular, 1 : 1 complexes of ligand **8** with organic dianions (succinate, tartrate and terephthalate) were identified in aqueous solutions by NMR spectroscopy.



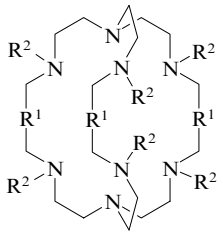


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For the terephthalate anion, the formation of a complex with another stoichiometry was also suggested.

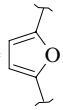
NMR titration was used to obtain the stability constant values for 1 : 1 complexes, which had close values for this anion series. The fit of substrate (organic dianion) sizes to cavity sizes determines efficiency of the interaction of each carboxy group of the substrate with protonated $N(CH_2CH_2NH_2^+-)_3$ fragments of the macrobicyclic ligand.

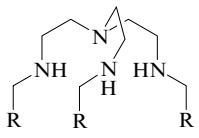
This type of ligands **9a**–**h** were prepared and studied [28] as extractants of ReO_4^- and TcO_4^- anions; their properties were compared to those of their tripodal analogues **10a**–**f**, **11a**,**b**.



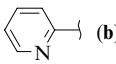
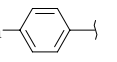
9a–**h**

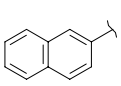
R^1 = : R^2 = H (**a**), Me (**b**); R^1 = : R^2 = H (**c**), Me (**d**);

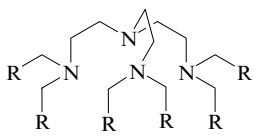
R^1 = : R^2 = H (**e**), Me (**f**); R^1 = : R^2 = H (**g**), Me (**h**).



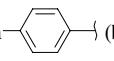
10a–**f**

R = Ph (**a**),  (**b**),  (**c**), Ph (**d**),

 (**e**),  (**f**).



11a,**b**

R = Ph (**a**), Ph (**b**).

Different protonated forms of a macrobicyclic ligand are in equilibrium depending on pH. NMR studies showed that the pentaprotonated form of ligand **9c** forms a complex with the perrhenate ion, the potentiometric titration indicates that binding of this anion also occurs in the case of smaller degree of protonation. Encapsulation of the ReO_4^- anions occurs to a larger extent than that of the perchlorate ion due to better fit of the former to the size and the shape of the cavity of the macrobicyclic ligand. Crystal and molecular structures of the complexes of the perrhenate ion with hexaprotonated forms of ligands **9c**,**g** were determined by X-ray diffraction analysis. In complex **9c**, the perrhenate ion is bound to the macrobicyclic ligand by both direct electrostatic interactions $NH_2^+ - O(An)$ (An is the anion) and by a system of hydrogen bonds with encapsulated water molecules. Studies of competitive complexation of the hexaprotonated form of ligand **9c** with the perchlorate and perrhenate ions showed [28] that in the system $\mathbf{9c} \cdot 6H^+ - ClO_4^- - ReO_4^-$ at the anion molar ratios from 1 : 1 to 1 : 6, only crystals with encapsulated perrhenate ions are formed in all cases, it was only the ratio between the outer-sphere counter-ions that varied. In the case of pyridine-containing ligand **9g**, the oxo anions are not included into the cavity of the macrocyclic ligand, and three perrhenate anions are held by its fragments. However, no experimental evidence for the formation of a compound of macrobicyclic ligand **9g** with the ReO_4^- anion in the ratio of 1 : 3 in aqueous solution was obtained; the NMR data corresponded to the 1 : 1 complex fairly well. The formation of 1 : 3 complexes can result in a loss of selectivity of binding of anions due to a more rigid conformation of the macrobicyclic ligand encapsulating the anion into its cavity.[28]

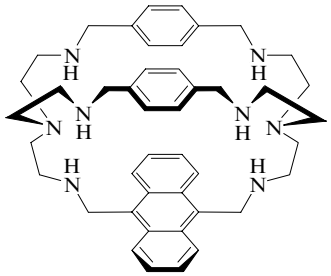
Extractive properties of macrobicyclic ligands **9a**–**h** and their open-chain analogues **10a**–**f**, **11a**,**b** with respect to the perrhenate ion and (or) pertechnenate ion were studied for systems $NaTcO_4(NaReO_4)$ – buffer – H_2O – ligand – $CHCl_3$. In all cases, the TcO_4^- anion was extracted somewhat better than the ReO_4^- anion, which was explained [28] by higher lipophilicity of the pertechnetate ion. The extractive ability of aminomacrocycles is rather limited under these conditions, however, it increases in the ligand series **9a** < **9g** < **9d** ≈ **9b** < **9f** < **9h**. In all cases, N-methylated derivatives demonstrated better extractive abilities than their NH-containing analogues. N-Methylated macrobicyclic pyridine derivative **9h** showed the maximum extractive ability. For acyclic derivatives of the tripodal amine 'tren' (**10a**–**f**, **11a**,**b**), a significant difference in extraction behaviour was observed: in some cases, their extractive ability was lower, but in some cases, it was higher as compared to that of macrobicyclic ligands. Ligands **10a**,**d** and **11a** demonstrated the extractive ability close to that of cage ligands. 2-Naphthyl-containing ligand **10f** extracted the pertechnetate ion better than all its analogues. At the same time, ligands **10c**,**e** and **11b** demonstrated low efficiency of the transport of these oxo anions to the organic phase.

For some macrobicyclic and tripodal ligands, the dependence of the degree of extraction of the ReO_4^- and TcO_4^- anions on pH has been studied. [28] In the case of ligands **9a**,**b** and **10b**, the greatest efficiency is achieved at pH 7–8 where the degree of ligand protonation is insignificant and the ligand is most hydrophobic. Thus, the phase transfer is more favourable for less charged complexes macrobicycle – anion despite the lower stability constant in aqueous solution. On the whole, pH value exerts lower effect on the extraction of the perrhenate ion by acyclic derivatives of tren than by its macrobicyclic analogues.

The lipophilicity of extractants determined from distribution coefficients between aqueous buffer solution with pH 7.4 and octan-1-ol increases in the series **9g** ≈ **9h** < **9a** < **9f** < **9b** < **9d** and **10c** < **10b** < **10a** < **10f** ≈ **11a** ≈ **11b**.

Despite the lowest lipophilicity, pyridine-containing ligands demonstrated good extractive ability. It is obvious that extractive properties of the ligands studied cannot be explained only by their lipophilicity.[28]

Macrobicycle **12**, the tren derivative with an anthracene fragment in one of spacers, was suggested as a fluorescent receptor.[29]



12

This ligand encapsulates two metal ions (in particular, two Cu^{2+} ions), and then, following a cascade mechanism, includes ambidentate anions, *e.g.*, N_3^- and NCO^-, as bridging ligands binding metal ions. However, this complex cannot be a fluorescent sensor because the Cu^{2+} ions quench fluorescence of any adjacent fluorophore. That is why complexes of ligand **12** with the zinc(II) ion devoid of this feature were used. After encapsulation of two Zn^{2+} ions, the macrobicyclic complex is able to bind efficiently linear ambidentate anions N_3^- and NCO^- bridging the zinc(II) ions. The dependence of the intensity of fluorescence of the parent macrobicyclic ligand **12** and its complexes on pH is presented in Fig. 4: ligand **12** fluoresces at pH < 6, after addition of two equivalents of Zn^{2+} ions, fluorescence is observed at pH 8–10 with the maximum intensity at pH ~ 8.5. Fabbrizzi *et al.*[29] believe that zinc(II) ions are included into the cavities of both tren fragments and coordinate to all amine nitrogen atoms thus preventing the electron transfer to the anthracene fragment. The maximum fluorescence corresponds to the maximum concentration of the complex $[Zn_2(\mathbf{12})]^{4+}$. Further pH increase results in intramolecular fluorescence quenching by coordinated OH^- anions. In the presence of azide ion, fluorescence is not increased at pH > 7 due to formation of the complex of $[Zn_2(\mathbf{12})(N_3)]^{3+}$ with the encapsulated azide ion. Potentiometric titration shows that this complex dominates in the pH range of 6.5–9.0. Fluorescence quenching can originate from the electron transfer from the electron-donating azide ion to the adjacent anthracene fragment.

A comparison of the data presented in Fig. 4 shows that the binuclear zinc(II) complex can be a fluorescent sensor for the azide ion: encapsulation of the azide ion results in substantial quenching of fluorescence of the anthracene substituent. According to the spectrophotometric titration data, 1 : 1 complex is formed at pH 8.5. In the case of other anions, (HCO_3^-, SO_4^{2-}, Cl^-, Br^- and NO_3^-), no fluorescence quenching occurs (Fig. 5); the titration curve by the azide ion is not changed even at a 10-fold excess of these ions. In the case of the NCO^- anion, no fluorescence quenching is observed; in the course of titration with the azide ion in the presence of this anion, quenching takes place, but much more slowly than in the absence of NCO^-. The higher the concentration of the NCO^- anion the more slow fluorescence quenching due to competition between encapsulation reactions of these two anions. The NCO^- anion yields the macrobicyclic complex easier than the azide ion, but it is unable to transfer the electron and to quench the fluorescence of the anthracene fragment. Relatively high stability constant values of macrobicyclic complexes result from fit of linear sizes of these anions to the distance between vacant axial donor positions of two Zn^{2+} cations. The linear triatomic NCS^- anion quenches fluorescence, but, as follows from a substantially less steep dependence plot, has much lower stability constant. Using the data on stability constants of the complexes, Fabbrizzi *et al.*[29] concluded that encapsulation of the thiocyanate anion, which is much larger in the linear size, causes an endothermic rearrangement of the cage ligand, thus weakening the binding of this anion as compared to that of the azide ion. Thus, binuclear macrocyclic zinc(II) complex is an efficient receptor for ambidentate anions, because it differentiates multiatomic and monoatomic anions and recognises multiatomic anions by their linear size.[29]

Complexes of similar octaamine cage ligand **13** with two encapsulated metal cations located in the proximity of tetra-

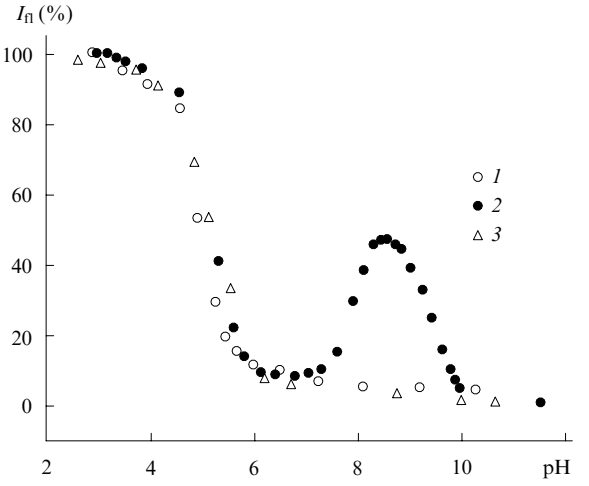


Figure 4. The pH-dependences of fluorescence intensity for aqueous solutions of ligand **12** in the presence of: excess of an acid (*1*); 2 equiv. of Zn^{2+} and excess of an acid (*2*); 2 equiv. of Zn^{2+}, 1 equiv. of N_3^- and excess of an acid (*3*).[29]

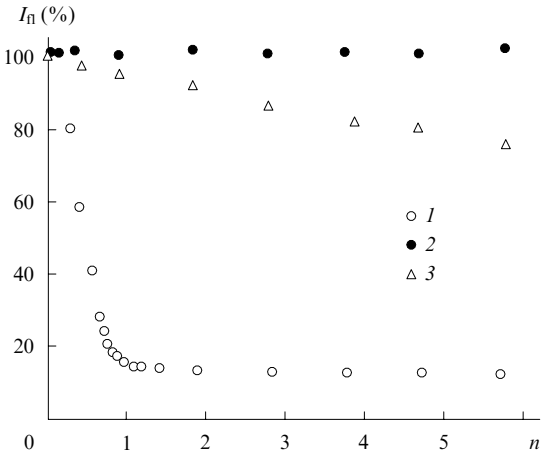
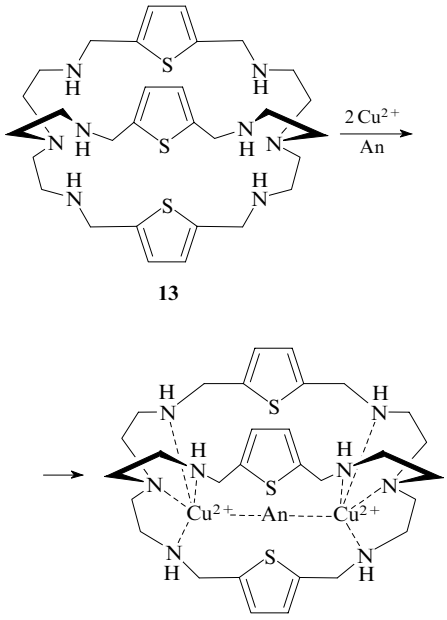


Figure 5. Spectrofluorimetric titration of macrobicyclic complex $[Zn_2(\mathbf{12})]^{4+}$ by azide ion at pH 8.5 (*1*); by nitrate ion (the similar results for HCO_3^-, SO_4^{2-}, Cl^-, Br^- and NCO^- anions) (*2*); by azide ion in solution containing 5 equiv. of NCO^- (*3*);[29]
n is the number added equivalents of anion.

amine apical fragments have been studied.[30] These complexes are receptors of anions having two donor atoms or two lone pairs on one atom. This anion can be a bridging ligand between two encapsulated metal cations, if the coordination sphere of these cations is not completely coordinatively saturated by four nitrogen atoms of the tripodal fragment.



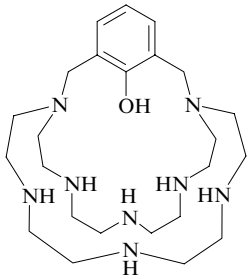
13

Cu^{2+} cation was selected [30] due to its tendency for trigonal pyramidal coordination; the interaction with the N_4 fragment leaves one coordination site vacant; this site is arranged on the apical tertiary amine–copper(II) axis. Binding of the Cu^{2+} ion to thiophene-containing ligand **13** in aqueous solution in the pH range 5–12 has been studied by potentiometric titration; the formation of binuclear complexes $[Cu_2(\mathbf{13})]^{4+}$, $[Cu_2(\mathbf{13})OH]^{3+}$ and $[Cu_2(\mathbf{13})(OH)_2]^{2+}$ was detected. A binuclear complex with a vacant cavity was identified at pH ~ 6 (the maximum content ~45% of the overall content of macrobicyclic complexes is observed at pH 5.9) along with an insignificant amount of mononuclear complexes $[Cu(\mathbf{13}\cdot H)]^{3+}$, $[Cu(\mathbf{13}\cdot 2H)]^{4+}$ and $[Cu(\mathbf{13}\cdot 3H)]^{5+}$. The content of a monohydroxy clathrochelate reaches the maximum at pH 6.9; at pH > 8, a dihydroxy complex prevails. Anion binding to a hydroxyl-containing clathrochelate has been studied [30] at pH 6.9. At this pH, no mononuclear complexes were detected, the content of a binuclear monohydroxy complex reached the maximum (~80%). In addition, according to the IR data, the coordinated OH^- ion forms no bridges between two copper(II) ions.

Binding of anions to binuclear macrobicycle **13** upon addition of the substoichiometric amount of the corresponding anion (N_3^-, NCO^-, NCS^-, Cl^-, Br^-, I^-, SO_4^{2-}, NO_3^-, HCO_3^- and AcO^-) has been studied [30] by spectrophotometric titration. For some of these anions, new absorption bands appeared, which corresponded to the charge transfer bands well known for the systems Cu^{2+}–anion. In particular, charge transfer bands appeared in the presence of the N_3^- and NCS^- anions. Upon addition of other anions, the absorption bands of the parent macrobicyclic complex $[Cu_2(\mathbf{13})OH]^{3+}$ were shifted and their intensities changed. The titration curves for anions N_3^-, NCS^- and NCO^- clearly demonstrate that their encapsulation is complete at a ratio macrobicyclic complex : anion = 1 : 1. The calculated stability constants for complexes with encapsulated anions decreased in the series $N_3^- > NCO^- > NCS^-$ differing for each subsequent anion by about two orders of magnitude. The dependence of the degree of binding of the azide ion on pH indicates that the most efficient binding occurs at pH 6.9. In the case of Cl^-, Br^-, I^-, SO_4^{2-}, NO_3^-, HCO_3^- and AcO^- anions, no changes in the UV–Vis spectra was observed even at the ratio complex : anion = 1 : 3; this suggests that the above anions either are not encapsulated by the binuclear macrobicyclic receptor or form complexes with very low stability constants (smaller than 100). Additional study of the dependence of degree of binding of halide ions on pH demonstrated the lack of binding.[30]

Crystal and molecular structures of the complex $[Cu_2(\mathbf{13})(N_3)](ClO_4)_3$ were established by X-ray diffraction. [30] The azide ion binds two Cu^{2+} cations to give virtually linear chain $Cu^{2+}\cdots NNN^-\cdots Cu^{2+}$ where all atoms are arranged on the C_3-pseudoaxis. The distance Cu···Cu appeared to be somewhat larger than that for similar ligand **9c** with *m*-xylylene bridges [31] and significantly larger than in furan-containing clathrochelate **9e** [31] due to a bigger size of the sulfur atom. Thus, this binuclear macrobicyclic copper(II) complex cannot change its geometry to the extent sufficient to bind efficiently monoatomic anions, but it efficiently and selectively encapsulates only bidentate anions with high affinity to the Cu^{2+} ions bound to the apical N_4 fragments.

Aminophenol-containing macrobicyclic ligand **14** (HL) has been synthesised;[32] the ability of this ligand and its binuclear derivative $[Zn_2L]^{3+}$ to bind anions has been studied. It was found that protonated ligand **14** efficiently recognises the chloride ions, and the complex of its deprotonated form with zinc recognises the phosphate ions.



14

The system ligand **14**–Cl^- in aqueous solution has been studied by potentiometry and in D_2O by ^{35}Cl NMR spectrocsopy. The results of potentiometric titration in the presence of chloride ion evidence for the formation of complex $(\mathbf{14}\cdot 6H^+)\cdot Cl^-$, but due to the lack of the data on the stability constant of protonated hexacation $\mathbf{14}\cdot 6H^+$, the exact value of the stability constant of chloride-containing complex was not obtained, its value was estimated to lie in the range of $10^{1.9}$–$10^{4.6}$. The ^{35}Cl NMR data confirmed the results of potentiometric titration. Since the ^{35}Cl nucleus has a quadrupole moment, the electric field gradient is very sensitive to the symmetry of charge distribution around this nucleus. In aqueous solution, the chloride ion has the spherical symmetry and manifests itself as a sharp signal in the ^{35}Cl NMR spectrum, whereas the coordinated anion is located in the non-symmetrical environment and is therefore characterised by a very broad signal. As is seen in Fig. 6, the chloride ion interacts not only with hexacation $\mathbf{14}\cdot 6H^+$, but also with less

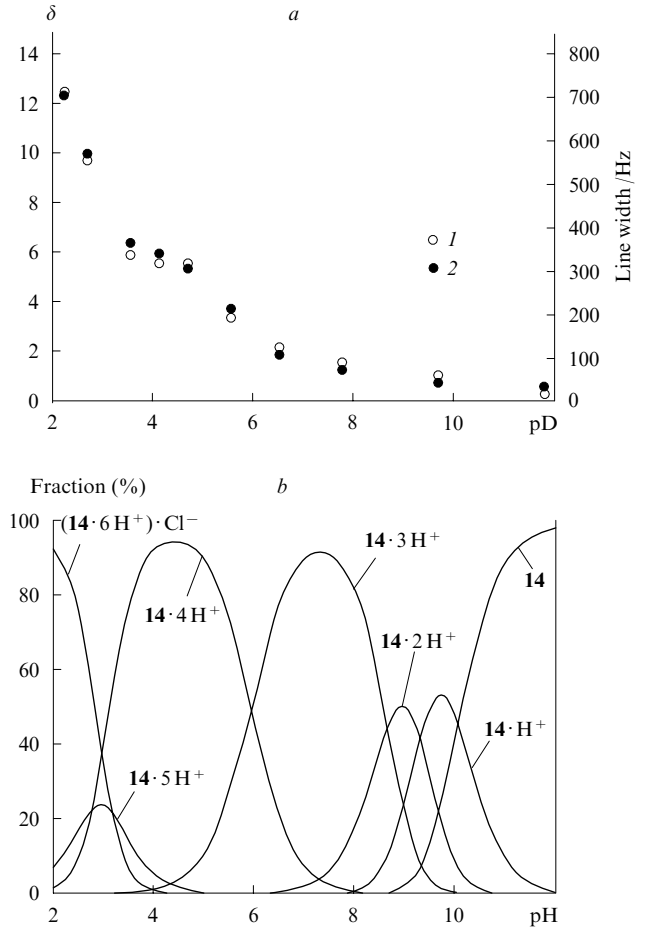


Figure 6. Characteristics of the system ligand **14**–Cl^- *versus* pH;[32]
(*a*) chemical shift of chloride ion (*1*) and line width (*2*) in the ^{35}Cl NMR spectrum in D_2O;
(*b*) distribution diagram for different forms of macrobicycle **14**.

protonated forms of ligand **14** (**14**·5 H^+ and **14**·4 H^+). The change in conformation of the macrobicycle and a decrease in positive charge on the cage lead to the extrusion of this anion out of the cavity of ligand **14** at pH 6.

The system $[Zn_2L]^{3+}$–PO_4^{3-} (HL is ligand **14**) in neutral aqueous buffer solution has been studied [32] by spectrophotometry. The method of competitive complexation with a less strongly binding 'guest', Pyrocatechol Violet (PCV), was used. In the presence of more strongly binding phosphate ions (at pH 7, HPO_4^{2-} and $H_2PO_4^-$ ions are the main species in solution), the following changes occur (Fig. 7): complex $[Zn_2L]^{3+}$·PCV dissociates, the intensity of the absorption band of free PCV increases with simultaneous decrease in the intensity of the absorption band of the adduct $[Zn_2L]^{3+}$·PCV, thus indicating the replacement of PCV in the complex by the phosphate ion. It was found that the equimolar amount of the phosphate ion (with respect to $[Zn_2L]^{3+}$) is sufficient for complete exchange of PCV.

At the same time, no interaction of this binuclear complex with other inorganic anions (Cl^-, Br^-, NO_3^- and SO_4^{2-}) and with other phosphate-containing compounds [4-nitrophenyl phosphate and bis(4-nitrophenyl) phosphate] was found.[32]

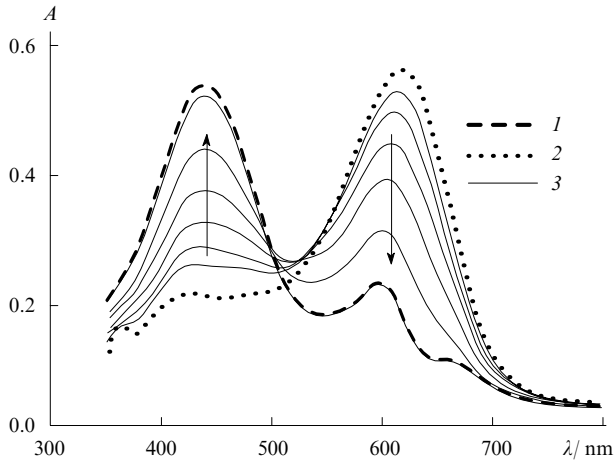
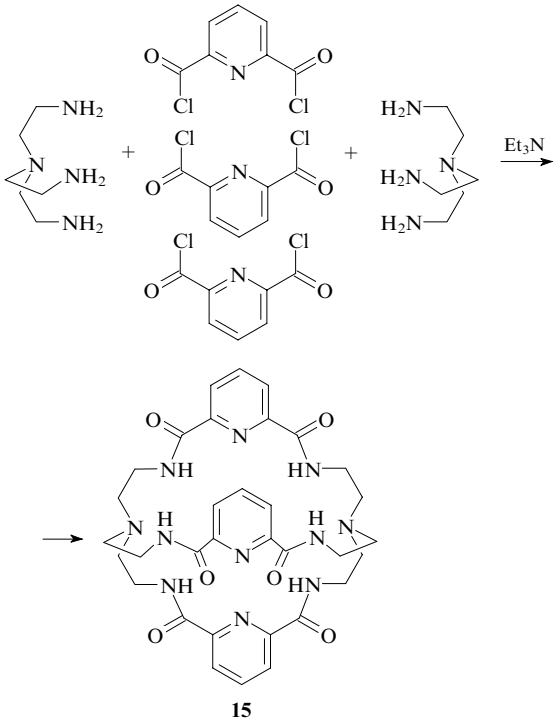


Figure 7. The UV–Vis spectra of free PCV (*1*) and complex $[Zn_2L]^{3+}$·PCV (HL is ligand **14**) (*2*) in aqueous solution and the system ligand **14**–Zn^{2+}–PCV in the presence of the phosphate ion (*3*).[32]
The arrows point to the changes in the spectra with increasing concentration of the phosphate ion.

V. Encapsulation of anions by polyamide macrobicycles

Macrobicyclic polyamide **15** was obtained [33] by condensation of tren with pyridine-2,6-dicarbonyl dichloride.

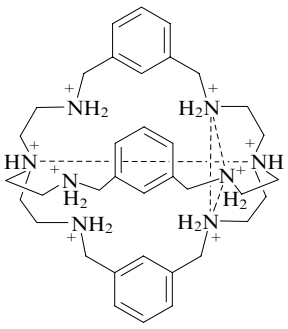


15

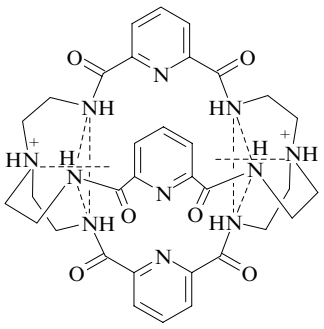
Binding of different singly charged anions (F^-, Cl^-, Br^-, HSO_4^-, $H_2PO_4^-$, AcO^- and NO_3^-) to this ligand has been studied by ^1H NMR titration in DMSO-d_6. The stability constants of complexes with encapsulated anions decrease in the series $F^- \gg Cl^- > AcO^- > H_2PO_4^- \gg NO_3^- > HSO_4^- > Br^-$; the NMR titration data suggest the formation of a compound with 1 : 1 stoichiometry. In the ^{19}F NMR

spectrum of fluoride-containing macrobicyclic complex, the signal characteristic of the F^- anion in the symmetrical environment of the protons of six equivalent amide fragments was observed. Hence, the cage structure of the complex with encapsulated fluoride ion established by X-ray diffraction is retained in solution. According to the X-ray data, in crystal the macrobicyclic complexes of ligand **15** with chloride and fluoride ions have different molecular geometries: the fluoride ion forms a complex with the C_3 pseudosymmetry, while the chloride ion deviates from the centre of the cavity of the macrobicyclic ligand.

A comparison between binding of the sulfate ion to polyamide ligand **15** and to polyamine macrobicycle **9c** of analogous structure was carried out.[34] Crystal and molecular structures were determined by X-ray diffraction for both complexes. Both ligands encapsulate one sulfate ion, but the coordination numbers and geometry of the coordination polyhedra differ substantially. In the complex with octaprotonated ligand **9c**, only five hydrogen atoms of the amino groups (**A**) are involved in binding of the sulfate ion, while the other amino groups form hydrogen bonds with the outher-sphere sulfate ions and solvent molecules. At the same time, the sulfate ion is bound to polyamide macrobicycle **15** through eight hydrogen atoms (**B**) to form a neutral complex (two apical nitrogen atoms are also protonated).



A



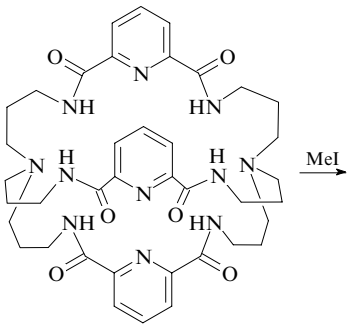
B

This difference in coordination mode of the sulfate ion is explained by the inward orientation of the amide hydrogen atoms with respect to the cavity of the macrobicyclic ligand, while in the case of the protonated polyamine ligand, the hydrogen atoms of amino groups can have inward and outward orientation. Nevertheless, in both complexes, the encapsulated sulfate ion is located in the centre of the cavity of the cage ligand.

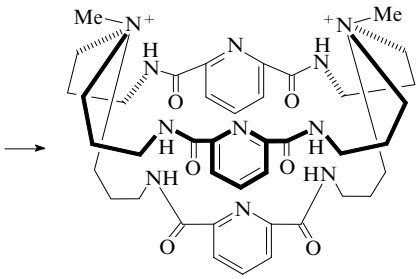
The stability constants for complexes of the SO_4^{2-} anion with different protonated forms of macrobicycle **9c** in aqueous solution were determined by potentiometry. Strong binding of this anion was observed for hexa- and heptaprotonated forms of the ligand as a result of the Coulomb interaction of the anion with the protonated ligand. Due to low solubility of this ligand in water, binding of the sulfate ion to ligand **15** was studied by the NMR spectroscopy. In both cases, the stability constants were approximately the same, however, the constants obtained by the NMR method depended on the solvent: in $CDCl_3$ and CD_3CN, the sulfate ion gave stable complexes, whereas in DMSO-d_6, binding appeared to be markedly weaker due to a significant contribution of solvation by this donor solvent.

Polyamide macrocyclic ligand **16** with an extended cavity was obtained [35] by substitution of tris(3-aminopropyl)amine for tren in the condensation reaction; the tertiary nitrogen atoms of this ligand could be quaternised. Ligand **16** forms complexes with anions; crystal and molecular structures of chloride- and sulfate-containing compounds of this macrocycle were established by X-ray diffraction. In these complexes, two of the diamide fragments of the ligand are co-oriented, while the third one is oriented in the opposite direction, *i.e.*, as viewed from the side of one of the tertiary nitrogen atoms, the complex has an inverted Y-shape. Due to a larger cavity size, ligand **16** can encapsulate two chloride ions bound by bridging water molecules.

Quaternised ligand **17** differs from macrobicycle **16** in conformation: three ribbed fragments are co-oriented and the macrobicyclic receptor is cup-shaped.



16

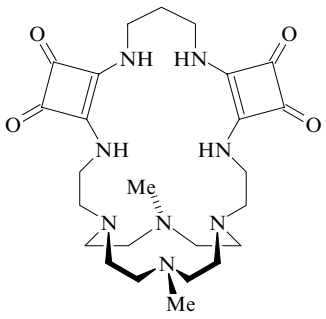


17

The crystal and molecular structures of complexes of ligand **17** with the chloride and oxalate anions were established by X-ray diffraction; for the chloride ion, a 1 : 2 complex was identified. The compounds obtained crystallise with solvent and water molecules, the latter are believed [35] to play an important role in stabilisation of complexes. These molecules form hydrogen bonds with both the coordinated anion and the amide hydrogen atoms of the ligand.

Binding of different anions to ligands **16** and **17** in solution has been studied by ^1H NMR titration.[35] In all cases, formation of 1 : 1 complexes was observed. It was found that, similar to polyamide ligand **15**, macrobicycle **16** shows extremely high selectivity with respect to the fluoride anion, whereas ligand **17** binds selectively the $H_2PO_4^-$ anion.

Ambrosi *et al.*[36] obtained ligand **18** having two donor sites, namely, a tetraazamacrocycle capable of coordinating metal ions and, depending on pH, being a donor or acceptor for hydrogen bonds and two squaramide groups in the ribbed fragments two opposite nitrogen atoms of 1,7-dimethyl-1,4,7,10-tetraazacyclododecane (DMTACD) to form the macrobicyclic structure.



18

Squaramide groups are donors of hydrogen bonds and are able to bind many simple anions, in particular, the chloride, phosphate, *etc*. The binding ability of complex $[Cu(\mathbf{18})]^{2+}$ with respect to halide ions for the systems ligand $\mathbf{18}-Cu^{2+}-X^-$ (X = F, Cl, Br and I) in a buffer solution (pH 6.1) at a molar ratio Cu^{2+} : ligand **18** = 1 : 1 was studied spectrophotometrically.[36] According to data from potentiometry, only complex $[Cu(\mathbf{18})]^{2+}$ exists in solution at this pH. After addition of the chloride ion to the system ligand $\mathbf{18}-Cu^{2+}$, the absorption band of the Cu^{2+}-containing chromophore in the range of 450–900 nm is shifted and simultaneously its intensity increases (Fig. 8), which suggests the coordination of the chloride ion to the metal site. The dependence of the absorbance at maximum on the number of moles of the chloride ion distinctly demonstrated the formation of the 1 : 1 : 1 complex Cu^{2+}–ligand **18**–encapsulated Cl^-.

Similar characteristic changes in UV–Vis spectra were observed also for F^- and Br^- anions. At the same time, in the presence of a 20-fold excess of the iodide ion the UV–Vis spectra are not changed, which suggests the lack of coordination of the I^- anion to the metal ion. The stability constants of complexes with encapsulated halide ions decrease in the series $F^- > Cl^- > Br^-$ and differ by two orders of magnitude on going from F^- to Br^-. Ambrosi *et al.*[36] found that only complex $[Cu(\mathbf{18})]^{2+}$ is involved in binding of these anions in contrast to other species that exist at other pH. Hydrogen bonding between the squaramide groups is believed to play the key role in the stabilisation of the complex with an encapsulated halide anion, which is confirmed by the X-ray data for cations $[Cu(\mathbf{18})F]^+$ and $[Cu(\mathbf{18})Cl]^+$ and by comparison with the behaviour of macrocyclic cation $[Cu(DMTACD)]^{2+}$: upon addition of halide ions to a solution of the latter under the same conditions, no changes in the UV–Vis spectrum are observed. According to the UV–Vis spectra of a $[Cu(\mathbf{18})]^{2+}$ solution, in the absorption range of squaramide chromophore (230–350 nm), the spectrum changes upon addition of anions F^- and Cl^-, whereas the addition of the bromide anion does not influence the spectrum. This is in accordance with the ability of these ions to form hydrogen bonds, this ability changing in the series $F^- > Cl^- > Br^-$.

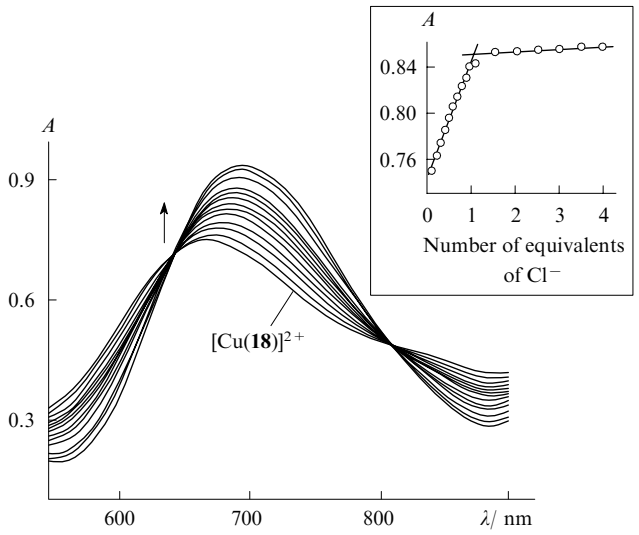
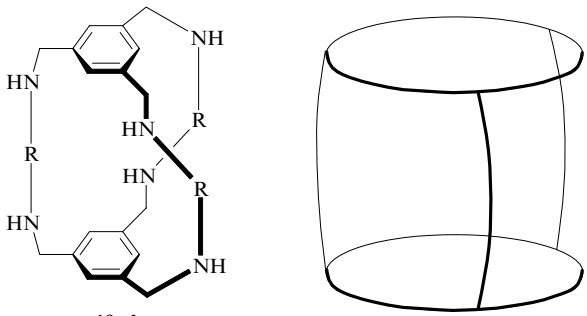


Figure 8. The UV–Vis spectra of complex $[Cu(\mathbf{18})]^{2+}$ in aqueous buffer solution (pH 6.1) in the presence of Cl^-. The arrow points to the change in the spectrum with increasing concentration of Cl^-.
The inset: the change in absorption of Cu^{2+}-containing chromophore of complex $[Cu(\mathbf{18})]^{2+}$ *vs*. the number of moles of chloride ion added.[36]

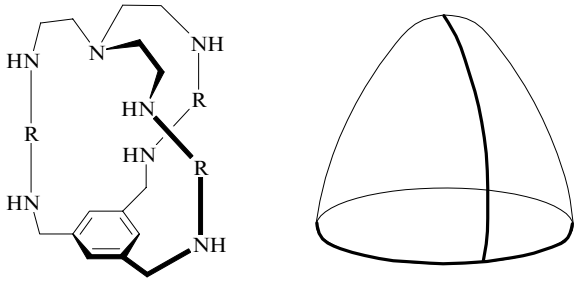
VI. Cyclophane-type macrobicyclic polyamines and their anion-receptor properties

Cylindrical and dome-shaped compounds **19a**,**b** and **20** were synthesised by Heyer and Lehn.[37] Protonation of six secondary amino groups yields macrobicyclic hexamine cationic ligands capable of binding anions. Complexation of macrobicycles **19**, **20** with anions has been studied by potentiometry and ^1H NMR spectroscopy.



19a,**b**

R = $(CH_2)_3$ (**a**), $(CH_2)_2O(CH_2)_2$ (**b**).



20

R = $(CH_2)_2O(CH_2)_2$.

Changes in chemical shifts in the NMR spectra evidence for the formation of complexes of macrobicyclic ligand $\mathbf{19a}\cdot 6H^+$ with anions NO_3^-, SO_4^{2-} and Cl^- (arranged in the order of decreasing spectral changes). The interaction of ligands $\mathbf{19b}\cdot 6H^+$ and $\mathbf{20}\cdot 6H^+$ with the same anions resulted only in little shifts in the NMR signals.

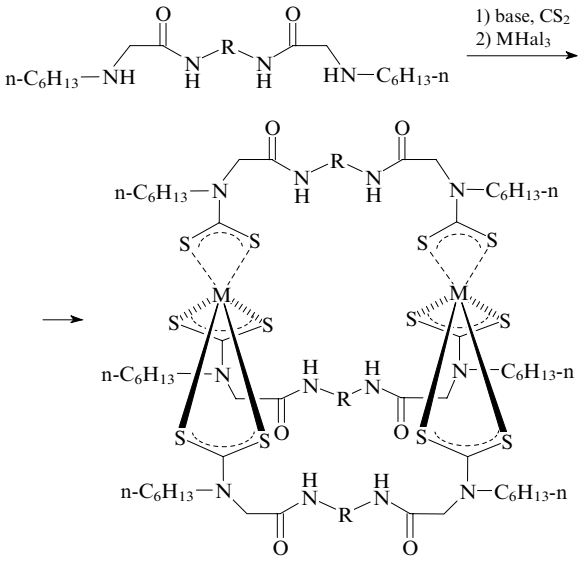
Heyer and Lehn[37] found by NMR titration that in the systems ligand $\mathbf{19a}\cdot 6H^+$ – (NO_3^-, Cl^-, $C_2O_4^{2-}$) anion, 1 : 1 complexes were formed. Macrobicyclic complex of ligand $\mathbf{19b}\cdot 6H^+$ with the dithionate anion $S_2O_6^{2-}$ was also isolated. It was found by potentiometry that hexaprotonated ligands $\mathbf{19a}\cdot 6H^+$, $\mathbf{19b}\cdot 6H^+$ and $\mathbf{20}\cdot 6H^+$ give stable complexes with

a number of anions; the stability constants of complexes with encapsulated anions are smaller for singly charged ions NO_3^-, Cl^- and N_3^- than for doubly charged anions SO_4^{2-}, $S_2O_6^{2-}$ and oxalate.[37]

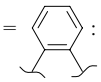
VII. Binding of anions to metallamacrobicycles

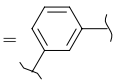
Pyrrole-containing dithiocarbamate metallamacrobicycles **21a–c** were obtained [38] by a sequence of reactions presented in Scheme 2. Nickel(II) and copper(II) complexes were synthesised from a tripodal triamine in a one-pot procedure, *viz*., by condensation with carbon disulfide under high dilution conditions in the presence of the corresponding metal salt. ^{1}H NMR studies of anion binding to nickel(II) macrobicyclic complexes **21a**,**b** was hampered due to complexity of the spectra and significant signal broadening. Complexation was detected [38] by spectrophotometry for a solution of macrobicyclic copper(II) complex **21c** upon addition of tetra-n-butylammonium chloride, benzoate and dihydrophosphate. Marked spectral changes were observed only for the benzoate anion; in the case of other anions, the changes in the UV–Vis spectra were insufficient for the correct determination of the stability constants. Binding of anions to macrobicyclic copper(II) complex **21c** has also been studied by electrochemistry using the shifts of the oxidation wave potentials for the redox pair Cu^{2+}/Cu^{3+} and the reduction wave for the pair Cu^{2+}/Cu^{+} in the presence of five equivalents of tetra-n-butylammonium chloride, benzoate and dihydrophosphate. In the presence of the chloride ion, the oxidation wave split by two, since the encapsulated halide ion changes the coordination sphere and electronic environment of the copper(II) ions. The same splitting of the oxidation wave was observed in the presence of benzoate and dihydrophosphate anions, however, this effect was not so pronounced. The appearance of an additional oxidation wave shifted to the cathodic region results from anion binding, because encapsulation of the anion stabilises the oxidised form [copper(III) complex]. Similar effects were observed for the pair Cu^{2+}/Cu^{+}: two reduction waves were found in the presence of anions. All three anions demonstrate this splitting, the difference consists only in intensities of redox waves.

Macrobicyclic dithiocarbamate-based systems are described:[39] in complexes **22a–d** the metalladithiocarbamate fragments occupy apical positions. Hexamide macrobicyclic iron(III) and cobalt(III) complexes were suggested as anion receptors; they were obtained by one-pot reaction of a secondary amine with carbon disulfide in the presence of a base and the corresponding transition metal salt.



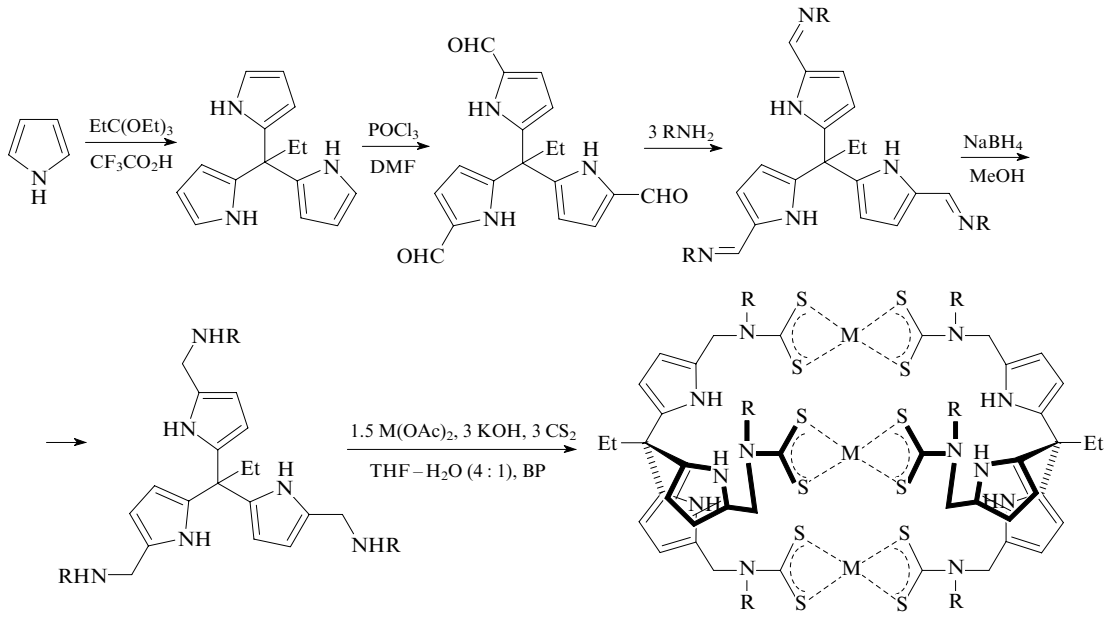
22a–d

R =  : M = Co^{III} (**a**), Fe^{III} (**b**);

R =  : M = Co^{III} (**c**), Fe^{III} (**d**).

Studies of anion receptor properties of macrobicyclic cobalt(III) complexes by ^{1}H NMR titration were hampered

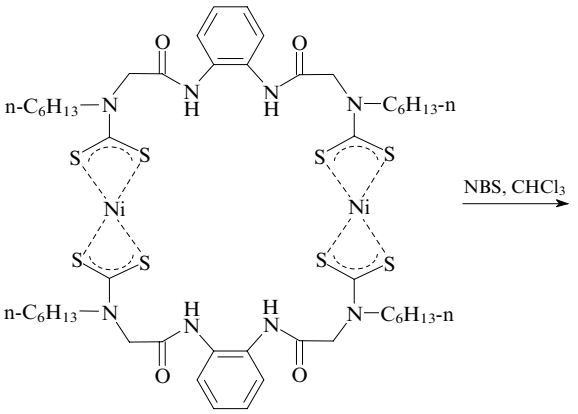
Scheme 2



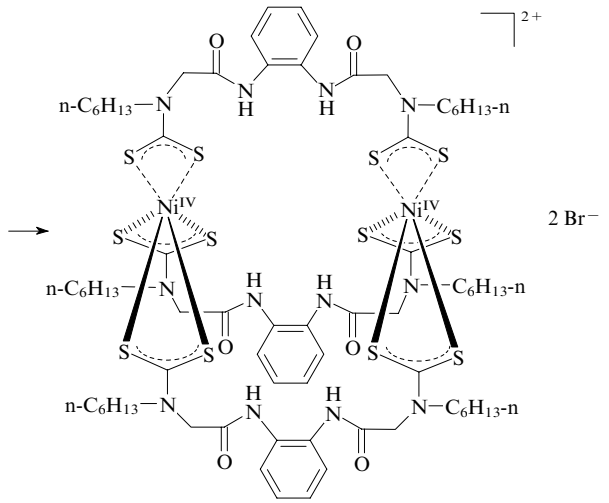
M = Ni: R = Bn (**a**), cyclo-C_6H_{11} (**b**); M = Cu, R = Bn (**c**).

21a–c

due to signal broadening. An electrochemical study showed that encapsulation of anions resulted in significalt shift of cathodic oxidation waves (maximum for $H_2PO_4^-$ anion); on the contrary, in the case of acyclic cobalt(III) tris(diethyldithiocarbamate), no shift of the redox waves was found indicating the lack of anion binding. An alternative method for the synthesis of binuclear compound **23** was suggested [39] using chemical oxidation of preformed binuclear macrocyclic nickel(II) complex **24**. Electrochemical studies of anion binding to macrobicyclic complex **23** showed that the greatest cathodic shift of the redox wave was observed for the chloride ion.



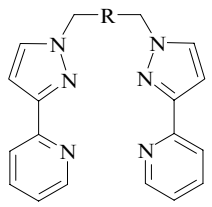
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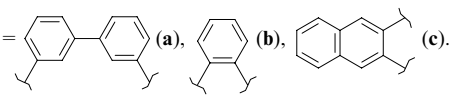
23

NBS is *N*-bromosuccinimide.

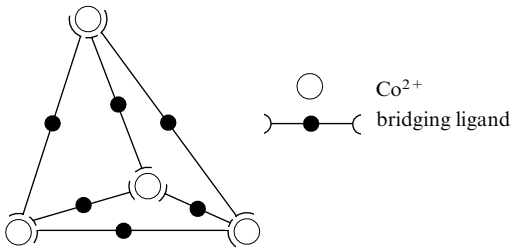
Tetranuclear cobalt(II) complexes $[Co_4L_6]X_8$ (L is compound **25a**; $X = BF_4^-$, ClO_4^-, PF_6^-, I^-) were synthesised [40] by the reaction of cobalt(II) acetate with ligand **25a** in the ratio of 2 : 3.



25a–c

R =  **(a)**, **(b)**, **(c)**.

Four cobalt(II) ions in these complexes form a distorted tetrahedral framework with six bidentate bridging ligands.



The reaction of ligands **25b**,**c** with Ni^{2+} ions yields simpler binuclear complexes. For ligand **25a** in which bidentate terminal ligands are more remote from one another due to a longer bridge the tetrahedral coordination is hampered, that is why tetranuclear complexes with a metal : ligand ratio of 4 : 6 are formed.

In tetranuclear complexes, the distances between the metal ions are larger than in binuclear complexes; as a result, the cavity size of the metallamacrobicyclic ligand allows binding of binuclear anions. Crystal and molecular structures of complex $[Co_4L_6](ClO_4)_8$ (L is ligand **25a**) were established by X-ray diffraction. The Co_4 polyhedron has a distorted geometry, since cobalt(II) cations have different coordination environment; in particular, the apical cobalt(II) ion differs from the other three Co^{2+} ions. Thus, the cage ligand in the complex has not a tetrahedral, but rather pseudo-C_3-symmetry. The encapsulated perchlorate anion is arranged not in the centre of the cavity, but is displaced to the apical Co^{2+} ion. The molecular structure of the complex with the encapsulated tetrafluoroborate ion is similar to that described above, however, the Co_4 polyhedron in this compound is more close to a regular tetrahedron. The BF_4^- anion also deviates from the centre of the cavity of the macrobicyclic ligand and is displaced to the apical cobalt(II) ion. The attempts [40] to find a template effect of anions in the formation of these complexes failed. The reaction of cobalt(II) acetate with ligand **25a** gave the product with a complicated and ill-resolved ^1H NMR spectrum. In the presence of tetrafluoroborate and perchlorate anions, no marked changes were observed, in contrast to the template effect proved earlier for cage complexes with macrobicyclic ligand **25b**, the cavity size of which fits the size of anions ClO_4^- and BF_4^-.

A complex of ligand **25a** with bulkier hexafluorophosphate anion was synthesised.[40] According to X-ray data, its molecular geometry is close to pseudotetrahedral with the pseudo-C_3-symmetry, as is the case for complexes with the perchlorate and tetrafluoroborate ions; the anion PF_6^- deviates from the centre of the cavity, it is displaced to the apical cobalt(II) ion. The cage complex with the encapsulated iodide ion has the similar structure and symmetry of the metallamacropolycyclic framework.

Dynamic behaviour of complexes with encapsulated anions BF_4^- and PF_6^- in solution at different temperatures has been studied by ^{19}F NMR spectroscopy. For the complex with BF_4^- at 233 K, two individual signals were observed, which broadened with increasing temperature and collapsed at 293 K. The ratio of their integral intensities at 233 K was approximately 10 : 1, while the calculated ratio is 7 : 1, which is explained by both the effect of paramagnetism of the cobalt(II) ion and by partial fragmentation of the cage ligand in solution [for tetranuclear zinc(II) complex with ligant **25c**,[41] this ratio is 7 : 1]. Similar results were obtained for hexafluorophosphate complex: at 233 K the integral intensity ratio was approx-

imately 10 : 1 and the signals appeared as doublets due to the interaction with the ^{31}P nucleus ($S = 1/2$). The activation energies of the anion exchange measured for these cage complexes have close values (50 kJ mol^{-1} for BF_4^- and 48 kJ mol^{-1} for PF_6^-). These values suggest that the exchange of these anions occurs by diffusion through the ribs of the cage ligand without clevage of bonds in the ligand (this would require larger energy). Low selectivity coefficient for these two anions means that in solution the size of the ribs of the metallamacropolycyclic ligand is sufficient for the diffusion of the hexafluorophosphate ion or any smaller anion.[40]

VIII. Anion-receptor properties of calixarenes containing azacrown ether fragments

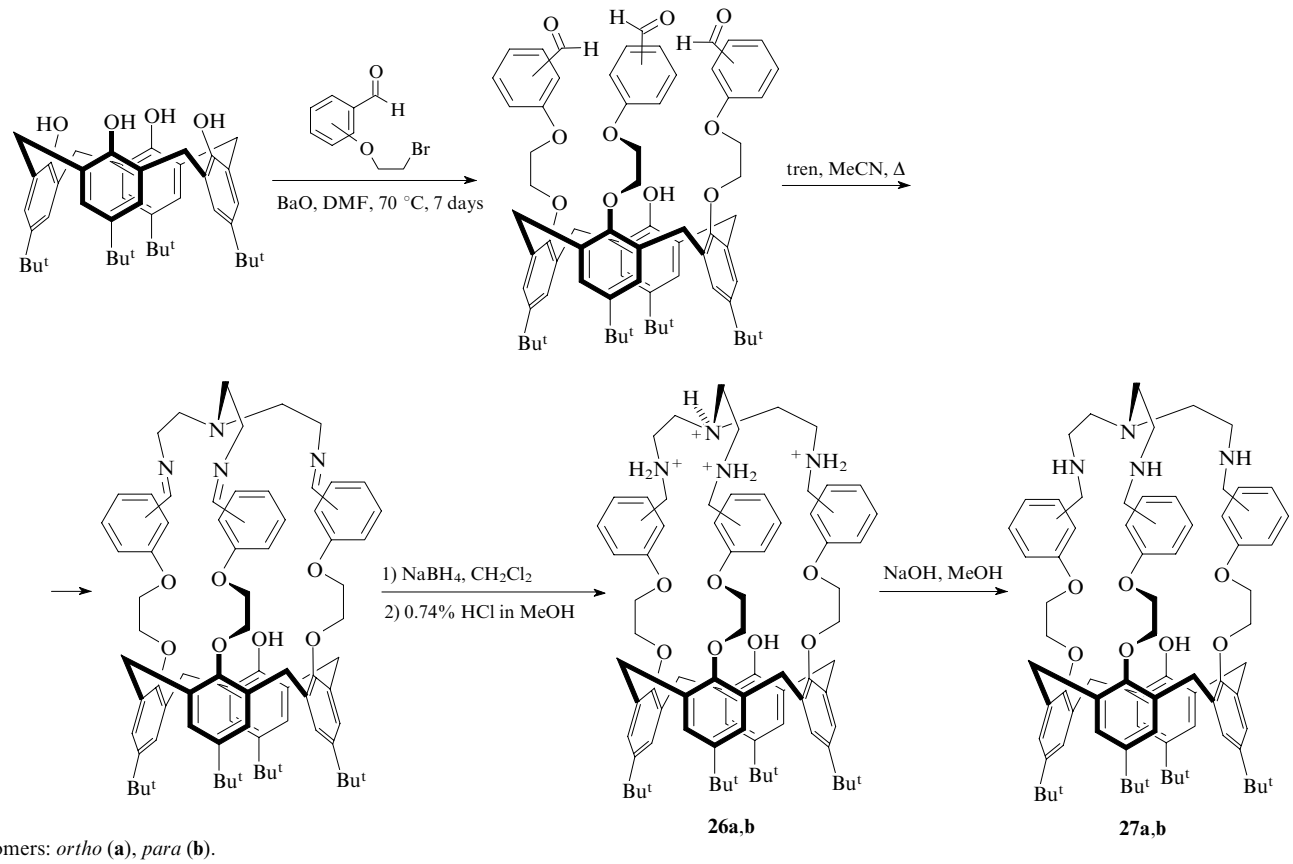
Hybrid ligands representing a combination of *p-tert*-butylcalix[4]arene, crown ether and tren were obtained[42] (Scheme 3). Three benzaldehyde substituents were attached to the calix[4]arene platform through ethylenedioxy bridges to form a crown ether-type cationic ionophore. Condensation of this trialdehyde with tren followed by reduction and protonation gave macrobicyclic receptors **26a**,**b**, which are biphilic ionophores capable of encapsulating both metal cations and anions. According to the X-ray data, the molecule of ligand **26a** has the following peculiarity: one of oxyethoxybenzyl fragments bound to the apical tertiary nitrogen atom threads through the cavity formed by the other two oxyethoxybenzyl chains. The attempts to perform X-ray diffraction for ligand **26b** failed, but the ^1H NMR data showed[42] that its glycolic fragments are oriented more symmetrically than in the molecule **26a**.

Binding of spherical (F^-, Br^- and I^-), planar triangular (CO_3^{2-}), angular (AsO_2^-) and tetrahedral ($H_2PO_4^-$, HPO_4^{2-}, SO_4^{2-} and PO_4^{3-}) anions by ligands **26a**,**b** has been studied by ^1H NMR titration. Upon addition of an excess of NaF or Na_2SO_4 to solutions of ligands **26a**,**b**, chemical shifts in their ^1H NMR spectra did not change, which was explained[42] by misfit of the sizes of the F^- and SO_4^{2-} anions and the macrobicyclic cavities of the ligands.

Upon addition of an excess of $NaAsO_2$, Na_2CO_3 and Na_3PO_4 to a solution of macrobicyclic ligand **26a** in DMSO-d_6, white complexes of the ligand with these anions precipitated, which precluded determination of the stability constants for these complexes by NMR titration. The addition of $H_2PO_4^-$ and HPO_4^{2-} salts to a solution of receptor **26a** caused a downfield shift of the signals for its protons. When the anion concentration increased, the spectrum changed and coincided with that for neutral macrobicycle **27a** thus indicating deprotonation of ligand **26a** upon complexation; the stability constants of complexes with these anions have not been determined. Similar phenomenon was observed for ligand **26b**: complexation with anions AsO_2^-, CO_3^{2-} and PO_4^{3-} was accompanied by deprotonation giving a neutral complex of ligand **27b**, which precluded the determination of stability constants of the complexes. In the case of the dihydrophosphate ion, no complexation was observed.

The addition of NaBr, NaI and $NaNO_3$ to the solution of ligand **26a** resulted in slight changes in chemical shifts of the signals for the NH_2^+ protons indicating the formation of 1 : 1 complexes with the anion encapsulated into the cavity of the ligand. The complexes are stabilised through electrostatic interaction with the tripodal fragment containing protonated

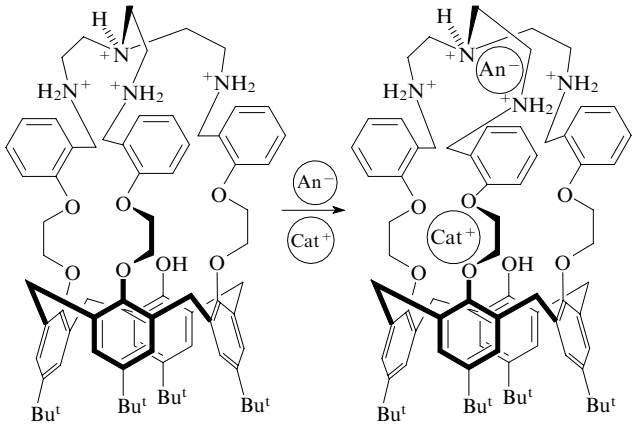
Scheme 3



Isomers: *ortho* (**a**), *para* (**b**).

amino groups. Compounds with this composition were also detected for macrobicycle **26b**. For both ligands, when using the Na^+ ion as a counter-ion, the complex stability decreased in the series $NO_3^- > I^- > Br^-$, ligand **26a** binding the nitrate ion stronger than macrobicycle **26b**.

The dependence of the degree of binding of spherically symmetrical bromide and iodide ions to ligands **26a**,**b** in the presence of alkali metal and organic cations has been studied.[42] The use of tetra-n-butylammonium cation as a counter-ion increases the stability of complexes of macrobicycles **26a**,**b** with the iodide ion, the complex of ligand **26b** being more stable than that of ligand **26a**. In the presence of K^+, the binding constant of bromide ion by ligand **26b** is ~ 1.5 times higher as compared to that with Na^+. At the same time, the addition of Na^+ does not influence receptor properties of compound **26a**. Thus, the crown-ether fragment of ligand **26a** prefes K^+ over Na^+. As follows from the X-ray data for macrobicycle **26a**, alkali metal ion can coordinate crown-ether fragment and causes the structural rearrangement of the macrobicyclic framework making ligand **26a** more appropriate for binding anions.



26a

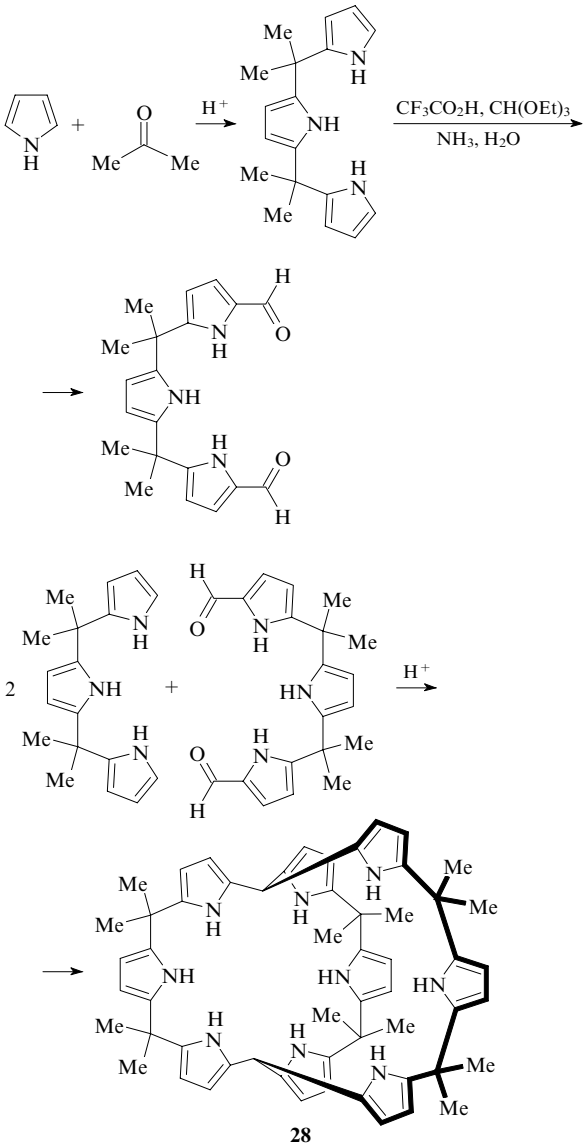
At the same time, the presence of Na^+ and K^+ cations diminishes the receptor ability of macrobicycle **26b** with respect to anions Br^- and I^-. Probably, an alkali metal cation that does not fit the cavity of the macrobicyclic fragment, retains the cation–anion pairs that compete in binding with the tripodal amine-containing fragment of the cage ligand.

IX. Macrobicyclic calixpyrroles and their anion-receptor properties

The first representative of this type of macrobicyclic ligands (compound **28**) was synthesised[43] according to Scheme 4. The presence of the bridgehead carbon atoms implies the existence of three configurational isomers of ligand **28**, however, only one of them was isolated. The ^1H NMR spectrum of this isomer corresponded to the highly symmetrical molecule **28** with a pseudo-C_3-symmetry going through the bridgehead carbon atoms. The structure of macrobicycle **28** was established by X-ray diffraction: the molecule in crystal has the configuration with both *meso*-carbon atoms being directed toward the centre of the macrobicyclic core.

A preliminary study of binding of anions as their tetra-n-butylammonium salts by ligand **28** showed that under anaerobic conditions, this macrobicycle encapsulates a wide range of anions: in the presence of fluoride, chloride, bromide, nitrate, dihydrophosphate and thiocyanate ions, the ^1H NMR spectra

Scheme 4



28

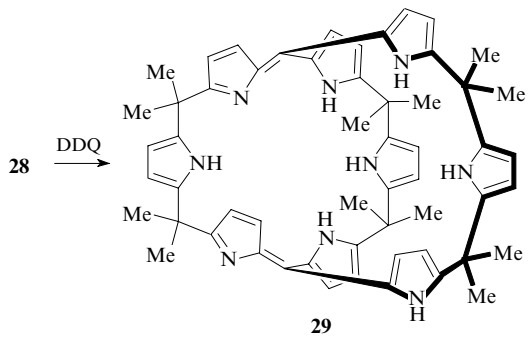
of the ligand change. The presence of three identical calixpyrrole cavities in ligand **28** gave the reason to suggest that in solution it can form 1 : 1, 1 : 2 and 1 : 3 anionic complexes . This fact as well as the possibility of the existence of a significant number of equilibrium forms prevented quantitative analysis for these systems. In addition, depending on the anion nature, the equilibrium was established in solution slower or faster (within the ^1H NMR time scale). In particular, for the nitrate ion, 1 : 2 complexes were readily formed. Attempts to obtain trianionic complex $[\mathbf{28} \cdot 3\,NO_3]^{3-}$ by addition of a large excess of tetra-n-butylammonium nitrate failed: only complicated spectroscopic pattern was observed reflecting the binding of several anions to one calixpyrrole fragment or, on the contrary, formation of complexes with one nitrate ion bound to a larger number of ligands **28**.[43]

Evidence for different types of binding were obtained in studies of the interaction of receptor **28** with the fluoride anion. The ^1H NMR spectrum of ligand **28** contains the signals for two types of protons of the NH groups, the ratio of their integral intensity being 2 : 1. These signals disappear after addition of 0.3 equiv. of tetra-n-butylammonium fluoride, but after addition of 3 equiv. of this salt, four new signals

appear with integral intensity ratio of 1 : 2 : 2 : 4. Only the two latter signals are downfield shifted indicating the involvement of the corresponding protons in anion binding. The ratio of signal integral intensities points to the formation of 1 : 1 complexes. In this case, two of three 'arms' of calixpyrrole form a single large cavity, in which six protons of the pyrrole NH groups are hydrogen-bonded to the anion. This hypothesis was confirmed by the low-temperature ^{1}H NMR study: only the signals for these groups were split due to ^{19}F – ^{1}H spin – spin coupling; the signals for the other three protons of the NH groups manifested themselves as broadened singlets. However, even at low temperature, the signals of the parent ligand **28** and its complex with the fluoride ion were not simultaneously present in the spectrum, therefore, it was impossible to determine the stability constant for the complex.

Similar picture was observed upon addition of tetra-n-butylammonium chloride to a solution of ligand **28** under anaerobic condition. With an increase in Cl^- ion concentration, the intensities of two signals for NH protons of the parent ligand decreased and simultaneously four new signals appeared. According to the NMR titration data, saturation occurs after addition of only 0.7 equiv. of chloride ion. This is the reason to suppose that one Cl^- anion is encapsulated between two molecules of ligand **28**, which adopt the same conformation as in the complex with F^- ion. Thus, Cl^- anion interacts with twelve protons of the NH groups.

Calixpyrrole macrobicycle **28** is light-sensitive and air-sensitive. Oxidation processes leading to colour changes have been studied in detail.[44] Taking into consideration the rigid structure of the parent macrobicyclic system and the red colour of its oxidation product, it was supposed that oxidation gives the compound containing sp^2-hybridised bridgehead carbon atoms. The oxidation by atmospheric oxygen was a slow process. When 2 equiv. of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) were added to a solution of the parent macrobicycle **28**, quick colouration of the solution occured, and product **29** was isolated. Its UV-Vis spectrum was comparable to those for partially oxidised calix[*p*]phyrin-type macrocycles.

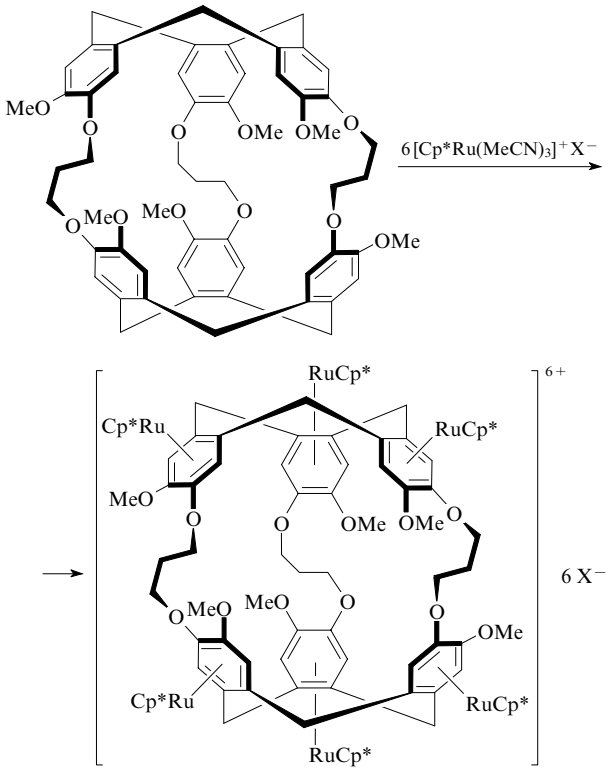


29

In particular, in the UV-Vis spectrum, the Soret band typical of porphyrins and the accompanying weak Q-band were absent. The ^{1}H NMR spectrum of the oxidation product corresponded to non-symmetric compound **29**. The signals characteristic of the protons of the bridging methine groups, which were present in the spectrum of the starting macrobicycle **28**, were absent. Crystal and molecular structures of compound **29** were established by X-ray diffraction. Unlike parent ligand **28**, where the bridging CH groups are oriented inward, compound **29** has a more open cavity suitable for binding of water or other substrate molecules.[44]

X. Binding of anions to metallated cryptophanes

Anions can be bound not only to positively charged species, *i.e.*, proton donors for hydrogen bonding and metal sites with Lewis acidity, but also to π-acidic arenes. Starting from well-known cryptophane-E,[46] which binds small organic cations and neutral molecules, Fairchild and Holman[45] synthesised macropolycycle **30** permetallated on all six arene fragments.



30

X = CF_3SO_3, SbF_6; Cp* = η^5-C_5Me_5.

Metallation results in increased electrophilicity of the arene fragments, therefore, the ligand acquires a weak π-acidic character; the macropolycycle cavity size is increased. The six-charge cage ligand obtained is capable of encapsulating sufficiently bulky anions, for instance, $CF_3SO_3^-$ and SbF_6^-. According to the X-ray data, in the $[\mathbf{30}\cdot CF_3SO_3]^{5+}$ and $[\mathbf{30}\cdot SbF_6]^{5+}$ cations, the encapsulated anions are located in the centre of the cavity, the 'axial' fluorine atoms of the SbF_6^- anion in the latter having shortened contacts with the arene carbon atoms.

The NMR spectra also confirmed encapsulation of anions by ligand **30** in solution. In the ^{19}F NMR spectrum of system **30** – 6 $CF_3SO_3^-$ in CD_3NO_2, two signals with an integral intensity ratio of 1 : 5 were observed. This is associated with one encapsulated and five outer-sphere $CF_3SO_3^-$ anions. In CD_2Cl_2 this ratio is slowly (for about three weeks) increased, which was explained by partial replacement of the $CF_3SO_3^-$ anion by CD_2Cl_2 molecules. In the presence of other anions, competitive complexation is observed in CD_3NO_2. The PF_6^- and SbF_6- ions extrude the triflate anion from the ligand cavity, however, the equilibrium is established extremely slow (it takes several weeks); the relative stability constants (with respect to that for the triflate ion) are equal to 1.18 and 0.30 for PF_6^- and SbF_6^-, respectively. The BF_4^- anion has no effect on

the NMR spectra. These results are typical of complexation by cryptophanes: too large or too small species as compared to the size of the ligand cavity are bound less efficiently that the anions fit the cavity, in this case, PF_6^-. Binding of other anions is more complicated, various allosteric effects are observed. Reversible binding of anions with cationic centres outside the cavity hinders the inclusion of anions into the cavity due to electrostatic repulsion between outer-sphere and encapsulated ions. Some anions ($CF_3CO_2^-$, $MeSO_3^-$, $EtSO_3^-$) simultaneously compete with the triflate ion for inclusion into the cavity of the macropolycyclic ligand and decrease therefore the binding ability of this cavity, whereas other anions (halide ions, NO_3^- and HCO_2^-) only hamper their encapsulation by the macrobicyclic ligand.[45]

* * *

The data considered in this review clearly demonstrate that diversity of macropolycyclic ligands and their structural modification allow the creation of new type receptors for recognition and selective separation of anions. Coordination and chemical properties of these receptors can be controlled by chemical modifications, coordination to metal ions, changing pH, *etc*. The complexes with encapsulated anions can serve as a basis for preparation of novel physiologically active, diagnostic, pharmaceutical and radiopharmaceutical compounds as well as biomimetics for studies of biochemical processes. Macropolycyclic ligands can also be applied for the target delivery of organic and inorganic anions to biological systems.

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