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Nitrogen- and sulphur-containing macroheterocycles and their complexes. New low molecular models of enzymes†

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ABSTRACT. Methods of synthesising *N,S*-containing macroheterocycles and their complexes with cations, anions and organic molecules are discussed. Complexes of copper(II) ions with thiazamacrocyclic ligands as low molecular structural models of the active centres of "blue" proteins are considered. The possibility of transporting metal ions through membranes by thiaza-crown compounds and the application of complexes of them in catalysis has been shown. Promising directions for using nitrogen- and sulphur-containing macroheterocycles in modelling enzymes are discussed.

The bibliography contains 98 references.

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I. Introduction

The vigorous development of the chemistry of macroheterocyclic compounds which has been observed in recent years is explained by the discovery of crown ethers and their ability to form stable complexes selectively with ions of the alkali and alkaline earth metals.[1–3] Further investigations in this area have shown that the macroheterocycles bind not only metal cations but also anions and even neutral organic molecules, forming complexes of the "host–guest" type.[2,3]

The study of nitrogen-sulphur-containing macroheterocycles and complexes of them as models of biological systems and processes occurring *in vivo* involving compounds of nitrogen and sulphur has become urgent. In particular, complexes of thiaza-crown compounds with copper(II) ions attract attention as models of copper proteins ("blue" proteins). The active centre of "blue" proteins is a complex of a copper(II) ion in an environment of nitrogen and sulphur atoms. It is characterised by spectral and oxidation–reduction properties unusual for copper(II) compounds. Investigation of the analogous physicochemical characteristics for complexes of macroheterocycles containing nitrogen and sulphur with copper(II) ions has shown that they are identical in this respect to a copper-containing "blue" protein. Copper proteins are important metal-containing enzymes for living organisms. They participate in electron-transfer, the metabolism of compounds and they catalyse oxidation–reduction functions of cell respiration. The study of copper(II) complexes with polythiazacrown compounds is urgent due to their use as low molecular models of metalloenzymes.

The metalloenzymes are highly organised systems possessing high substrate selectivity and catalytic activity. The further development of synthetic enzymes ("synzymes")[5,98] is only possible on continuing from simple monomolecular systems to oligomolecular systems, particularly to associates, bound by non-covalent interactions, i.e. by transferring from molecular chemistry to supramolecular chemistry.[4,5]

The development of supramolecular chemistry to date already enables the recognition and selective interaction of a macrocyclic receptor with various substrates to be effected.[5] This interaction is effected in two ways. Complex-formation may occur within the cavity of a macrocycle, when the receptor is able to "envelop" a substrate and retain it through the formation of many non-covalent bonds. Biological analogues of these endoreceptors may be found in the active centres of enzymes where a substrate insignificant in size is bound within the cavity of a large protein molecule. Another type of substrate binding uses the outer surface of the receptor. In this case complex-formation of the exoreceptor with the substrate occurs by surface–surface interaction. The biological analogy for this may be the protein–protein interactions occurring on the antigen–antibody interface, leading to immunological recognition processes.

N,S-Containing macroheterocycles display the properties of both endo- and exoreceptors in that they selectively bind cations, anions and organic substrates. The further development of the chemistry of nitrogen- and sulphur-containing macroheterocycles and their investigation as enzyme models may become the chief instrument for studying the structure and biological properties of many biopolymers.

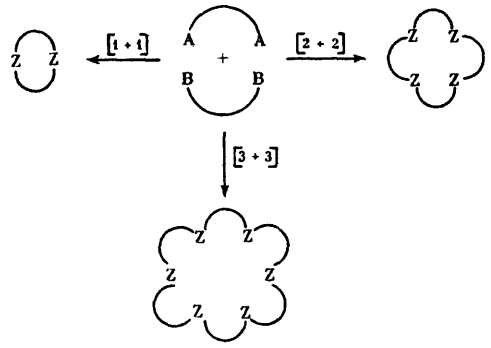
II. Synthesis of *N,S*-containing macroheterocycles

1. Aliphatic polythiaza crown compounds

The formation of macrocyclic compounds is complicated by the presence of secondary linear polycondensation products since the oligomers formed as intermediates may later take part in both intra- and intermolecular reactions at the same time. One further difficulty is the occurrence of cyclisation at several stoichiometric levels

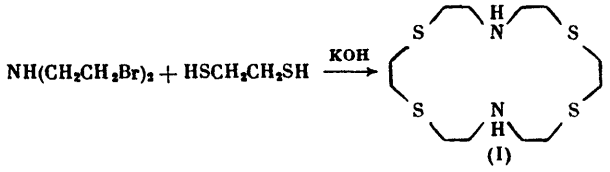
†Awarded first prize at the competition for reviews organised by section No. 4 "Organic and Hetero-organic Synthesis" of the Inter-departmental Scientific-Technical Bureau on the priority directions of chemical science and technology.

simultaneously. If one molecule of each starting material partakes in the formation of the macromolecule, that is designated a [1 + 1] condensation. There are also [2 + 2] and [3 + 3] condensations.



High dilution methods and template reactions are mainly used to prevent side reactions.

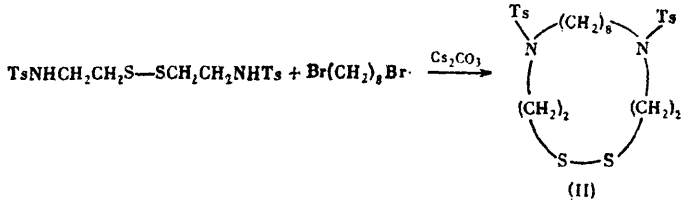
For example, the reaction of bis(2-bromoethyl)amine with ethane-1,2-dithiol takes place under conditions of high dilution by a [2 + 2] condensation.



(I)

The yield of 1,4,10,13-tetrathia-7,16-diazacyclo-octadecane (I) was 45%.[6,7]

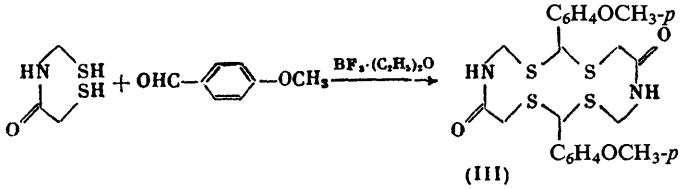
The macrocyclic disulphide (II) is obtained by the reaction of ditosylated cystamine with 1,8-dibromooctane in DMF in the presence of Cs_2CO_3.[8]



(II)

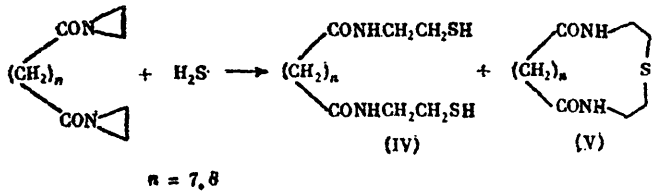
Reaction was carried out at room temperature for 24 h, the yield of macroheterocycle (II) was 20%.

The *N*-(mercaptomethyl)amide of thioglycolic acid reacts with anisaldehyde by a [2 + 2] condensation with the formation of the tetrathiadiaza crown compound (III) (61% yield).[9]



(III)

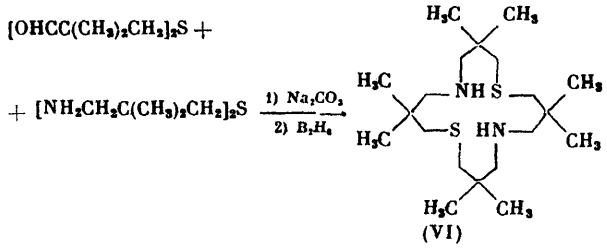
Fission of the aziridine rings of the bis-*N*-ethylenimides of azelaic and sebacic acids with hydrogen sulphide leads to a mixture of the linear bis(2-mercaptoethyl)diamides of the corresponding acids (IV) and the macrocyclic sulphide (V).[10]



(IV) (V)

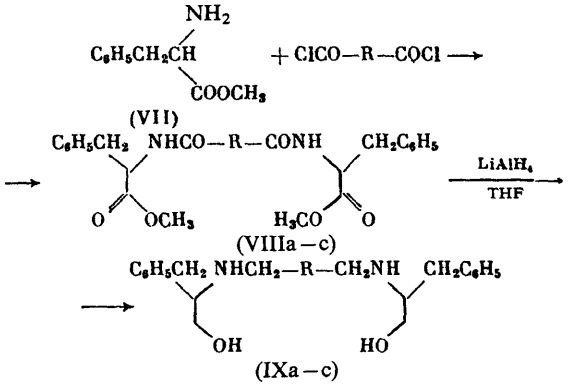
n = 7, 8

The dithiadiaza crown compound (VI), containing quaternary carbon atoms, is obtained by the reaction of 2,2,6,6-tetramethyl-4-thiaheptane-1,7-dial with 2,2,6,6-tetramethyl-4-thia-1,7-heptanediamine with subsequent treatment with diborane in THF.[11]



(VI)

The synthesis of chiral *N,S*-containing macrocycles is effected by the reaction of L-phenylalanine methyl ester (VII) with the diacid chlorides of dicarboxylic acids with several subsequent conversions.[12] On using the diacid chlorides of oxalic, succinic and diglycolic acids, the diamides (VIIIa–c) were obtained in 68–90% yield. Reduction of them with $LiAlH_4$ in THF leads to the diaminoalcohols (IXa–c).

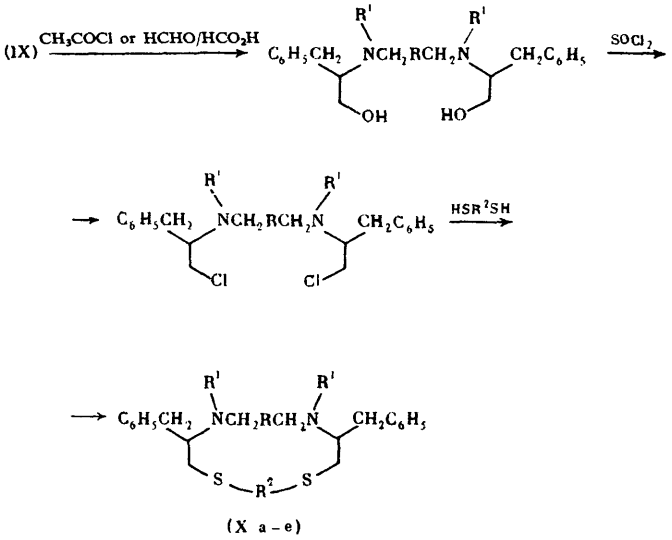


(IXa–c)

R = a bond (a), $-(CH_2)_2-$ (b), $-CH_2OCH_2-$ (c)

Treatment with CH_3COCl or $HCHO/HCO_2H$ and subsequent reduction gives the alkyl substituted diaminoalcohols. Reaction of the latter with $SOCl_2$ and subsequent cyclisation with α,ω-alkane-

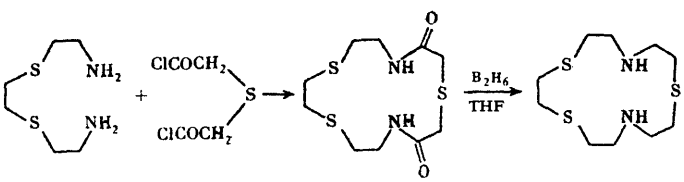
dithiols leads to the chiral *C*- and *N*-substituted *N,S*-containing macrocycles (Xa–f) in 16–26% yield.



(X a–e)

(Xa): R = a bond, $R^1 = C_2H_5$, $R^2 = -(CH_2)_2-$;
(Xb): R = a bond, $R^1 = C_2H_5$, $R^2 = -(CH_2)_3-$;
(Xc): R = a bond, $R^1 = C_2H_5$, $R^2 = -(CH_2)_4-$;
(Xd): $R = -(CH_2)_2-$, $R^1 = C_2H_5$, $R^2 = -(CH_2)_3-$;
(Xe): $R = -(CH_2)_2-$, $R^1 = CH_3$, $R^2 = -(CH_2)_3-$;
(Xf): $R = -CH_2OCH_2-$, $R^1 = CH_3$,
$R^2 = -(CH_2)_2S(CH_2)_2S(CH_2)_2-$

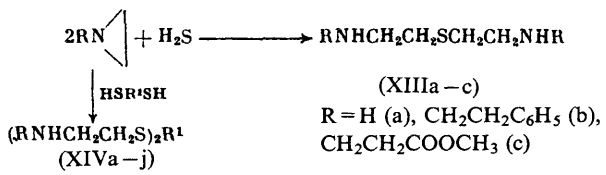
The most accessible method of synthesis of *N,S*-containing macroheterocycles is the acylation of open chain sulphur-containing diamines with diacid chlorides of dicarboxylic acids. On reacting 1,8-diamino-3,6-dithiaoctane with the diacid chloride of thiodiglycolic acid, a cyclocondensation of the [1 + 1] type takes place with the formation of the macroheterocycle (XI).[13]



(XI) (XII)

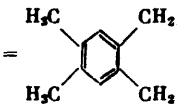
Reduction of the amide groups of the macrocycle (XI) with diborane leads to the crown compound (XII) in 57% yield.

Methods have been developed for obtaining polycarbo-functional *N,S*-containing open chain compounds (XIIIa–c) and (XIVa–j) on the basis of which macroheterocycles with the same various exocyclic functional groups have been synthesised.[14–27]

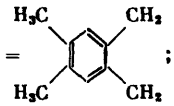


(XIIIa–c)
R = H (a), $CH_2CH_2C_6H_5$ (b), $CH_2CH_2COOCH_3$ (c)

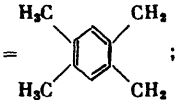
(XIVa): R=H, $R^1=CH_2CH_2$;

(XIVb): R = H, R^1 = ,

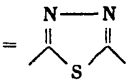
(XIVc): $R = CH_2CH_2C_6H_5$, $R^1 = CH_2CH_2$;

(XIVd): $R = CH_2CH_2C_6H_5$, R^1 = ;

(XIVe): $R = CH_2CH_2COOCH_3$, $R^1 = CH_2CH_2$;

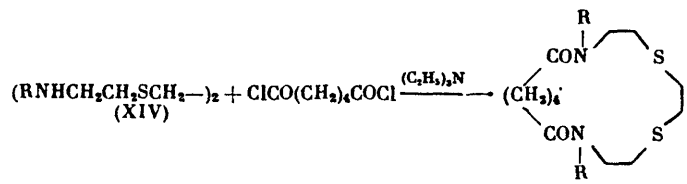
(XIVf): $R = CH_2CH_2COOCH_3$, R^1 = ;

(XIVg): $R = CH(COOCH_3)CH_2COOCH_3$, $R^1 = CH_2CH_2$;
(XIVh): $R = CH(COOC_2H_5)CH_2COOC_2H_5$, $R^1 = CH_2CH_2$;
(XIVi): $R = CH_2CH_2CN$, $R^1 = CH_2CH_2$;

(XIVj): $R = CH_2CH_2COOCH_3$, R^1 = 

The sulphur-containing diamides are obtained by the reaction of ethylenimine or its *N*-substituted derivatives with hydrogen sulphide or α,ω-aliphatic, aromatic and heterocyclic dithiols.[14–27] The reaction with H_2S proceeds in methanol at room temperature and with α,ω-dithiols at 60 °C. The yields of diamines (XIIIa–c) and (XIVa–j) were 80–90%.

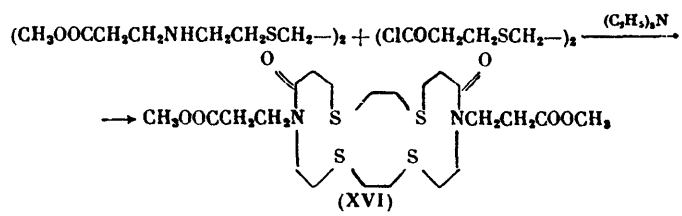
The cyclocondensation of diamines (XIVa), (XIVc), (XIVe) and (XIVi) with the diacid chloride of adipic acid leads to the 16-membered macroheterocycles (XV) in 70% yield.[16]



(XV)

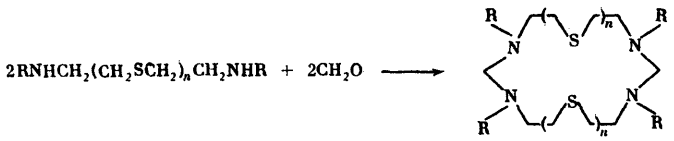
R = H, $CH_2CH_2C_6H_5$, $CH_2CH_2COOCH_3$, CH_2CH_2CN

The 20-membered macrocycle (XVI) containing exocyclic methoxycarbonylethyl groups is obtained by the reaction of diamine (XIVe) with the diacid chloride of dithiaoctane-dicarboxylic acid.[17]



(XVI)

The macroheterocycles (XV) and (XVI) were synthesised in dry benzene under high dilution conditions. The secondary diamines (XIIIb, c) and (XIVc, e, g, i) form a 22-membered polythiaza-crown compound (XVII) with formaldehyde.[25-27]



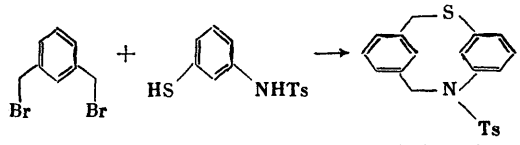
(XVII), 60 – 70%

n=1: R=$CH_2CH_2C_6H_5$, $CH_2CH_2COOCH_3$; n=2: R=$CH_2CH_2C_6H_5$, $CH_2CH_2COOCH_3$, $CH(COOCH_3)CH_2COOCH_3$, CH_2CH_2CN.

The cyclocondensation proceeds in methanol under high dilution conditions according to a [2 + 2] type.

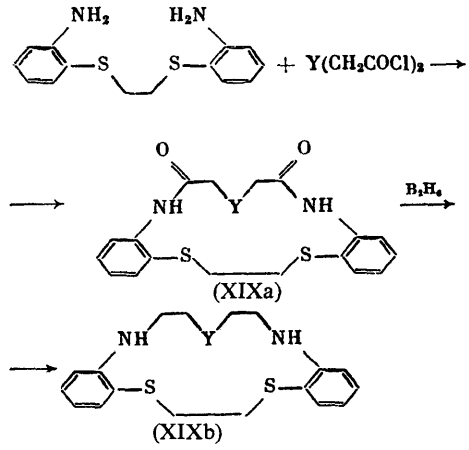
2. *N,S*-containing cyclophanes

Thiazamacrocycles containing a benzene ring in the molecule possess a stable cyclic skeleton which is important on complex-formation with metal ions and organic molecules. For example, the 10-membered cyclophane (XVIII) is obtained by the reaction of 1,3-bis(bromomethyl)benzene with 1-[(*p*-toluenesulphonyl)amino]-3-mercaptobenzene in the presence of caesium hydroxide under high dilution conditions.[28]



(XVIII), 9%

The acylation of 1,4-bis(2-aminophenyl)-1,4-dithiabutane with the diacid chlorides of glutaric and thiodiglycolic acids proceeds more successfully.[29] Reaction is effected under high dilution conditions in benzene, the yield of sulphur-containing diamides (XIXa) was 64–90%.



(XIXa)

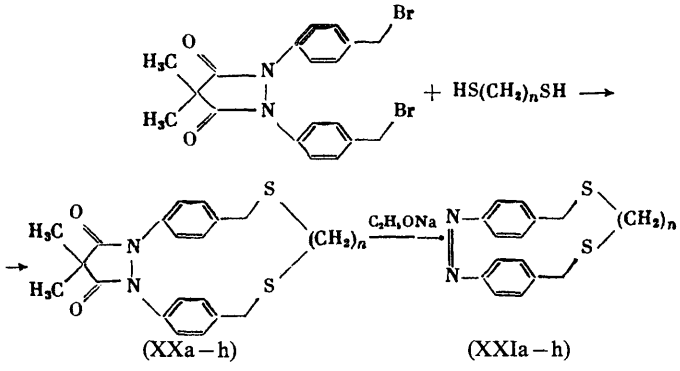
(XIXb)

Y = CH_2, S

Reduction of the amide groups with boron hydride leads to the macroheterocycle (XIXb) in 78–95% yield.

Crown compounds containing chromophoric groups are of interest as new types of macroheterocycle dyestuffs, organic reagents and extracting agents. One of the methods of synthesis of such chromophoric crown compounds is the introduction of an azo group into the molecule. An endocyclic azo group not only does not impair the complex-forming properties of crown compounds but also confers on them new interesting properties such as rigidity of the cyclic skeleton and the possibility of changing their ability towards complex formation under the action of irradiation due to *cis-trans*-isomerisation.

Dithiadiaza[2.n]paracyclophanes (XXa–h) are obtained by the reaction of the appropriate dibromides with α,ω-alkanedithiols. Treatment of them with sodium ethoxide leads to the *N,S*-containing macroheterocycles (XXIa–h) containing an endocyclic azo group.[30]

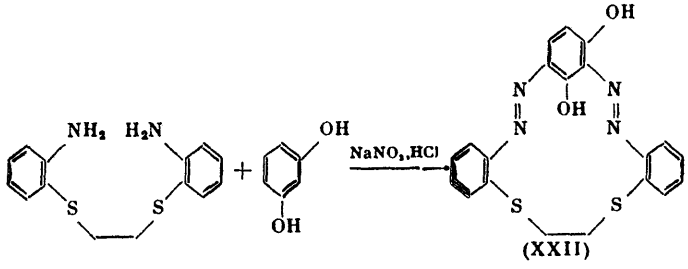


(XXa–h) (XXIa–h)

n=2 (a), 3 (b), 4 (c), 6 (d), 7 (e), 8 (f), 9 (g), 12 (h).

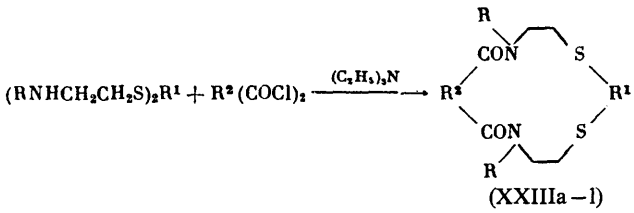
It was found that the macroheterocycles (XXIa–c) have the *cis* geometry while the cyclophanes of larger dimensions (XXIg, h) are more inclined to form *trans* isomers. The macrocycles (XXId–f) have both *cis* and *trans* configurations.

The azo coupling reaction of 1,4-bis(2-aminophenyl)-1,4-dithiabutane with resorcinol has been studied. It leads to a sulphur-containing cyclophane with two azo groups in the macrocycle (XXII).[31]



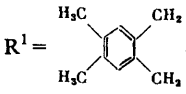
(XXII)

The synthesis of the *N,S*-containing macrocycles (XXIIIa–l) containing aromatic rings and exocyclic functional groups has been effected by the reaction of α,ω-diamines (XIVa–j) with the diacid chlorides of phthalic and terephthalic acids.[14–27,33–37]



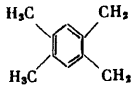
(XXIIIa–l)

(XXIIIa): R = H, $R^1 = CH_2CH_2$, $R^2 = 1,2\text{-}C_6H_4$;
(XXIIIb): $R = CH_2CH_2C_6H_5$, $R^1 = CH_2CH_2$, $R^2 = 1,2\text{-}C_6H_4$;
(XXIIIc): $R = CH_2CH_2COOCH_3$, $R^1 = CH_2CH_2$, $R^2 = 1,2\text{-}C_6H_4$;
(XXIIId): $R = CH(COOCH_3)CH_2COOCH_3$, $R^1 = CH_2CH_2$, $R^2 = 1,2\text{-}C_6H_4$; (XXIIIe): $R = CH(COOC_2H_5)CH_2COOC_2H_5$, $R^1 = CH_2CH_2$; $R^2 = 1,2\text{-}C_6H_4$; (XXIIIf): R = H,



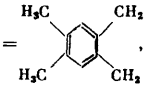
$R^2 = 1,2\text{-}C_6H_4$;

(XXIIIg): $R = CH_2CH_2COOCH_3$, $R^1 =$



$R^2 = 1,2\text{-}C_6H_4$; (XXIIIh): $R = CH_2CH_2COOCH_3$, $R^1 = CH_2CH_2$, $R^2 = 1,4\text{-}C_6H_4$; (XXIIIi): $R = CH_2CH_2C_6H_5$, $R^1 = CH_2CH_2$, $R^2 = 1,4\text{-}C_6H_4$; (XXIIIj): $R = CH(COOCH_3)CH_2COOCH_3$, $R^1 = CH_2CH_2$, $R^2 = 1,4\text{-}C_6H_4$;

(XXIIIk): $R = CH_2CH_2COOCH_3$, $R^1 =$



$R^2 = 1,4\text{-}C_6H_4$;

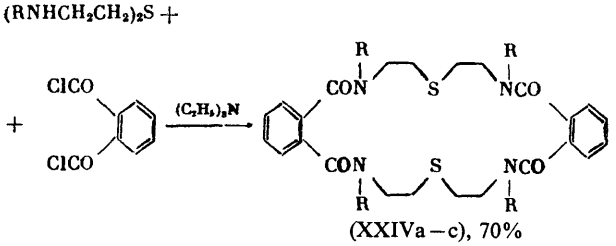
(XXIIIl): $R = CH_2CH_2COOCH_3$ $R^1 =$



$R^2 = 1,2\text{-}C_6H_4$.

Cyclocondensation occurs according to the [1 + 1] type in dry benzene under high dilution conditions. The yields of the *N,S*-containing macroheterocycles (XXIIIa–l) were 70–80%.

Under analogous conditions the reaction of diamines (XIIIa–c) with the phthaloyl chloride was effected according to a [2 + 2] type with the formation of the 22-membered macroheterocycles (XXIVa–c).[32]

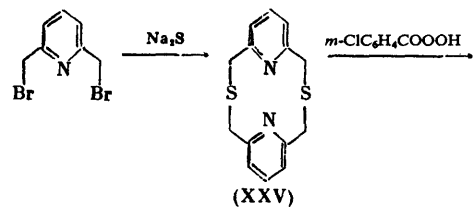


(XXIVa–c), 70%

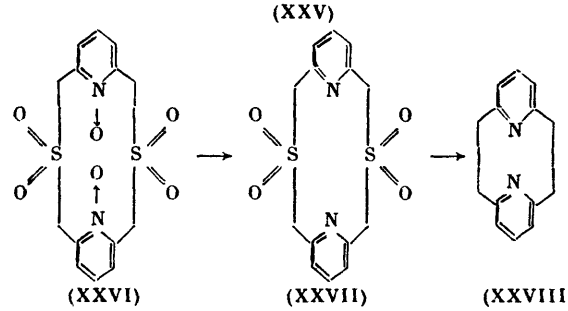
R = H (a), $CH_2CH_2C_6H_5$ (b), $CH_2CH_2COOCH_3$ (c)

3. Sulphur-containing pyridinophans

The synthesis of pyridinophan (XXV) is effected by the reaction of 2,6-bis(bromomethyl)pyridine with sodium sulphide by a [2 + 2] condensation.[38]



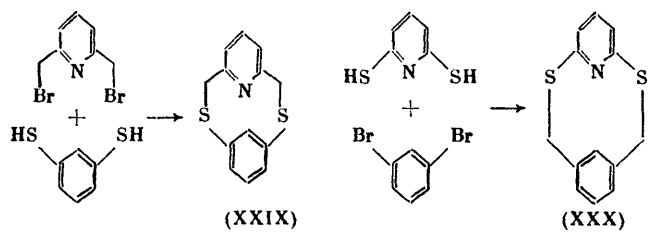
(XXV)



(XXVI) (XXVII) (XXVIII)

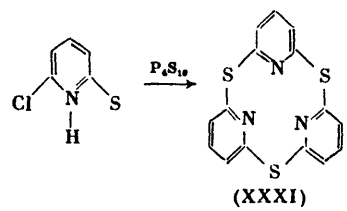
Oxidation of pyridinophan (XXV) leads to its bis-sulphone bis-*N*-oxide (XXVI). The selective reduction of the *N*-oxide groups with iron in trifluoroacetic acid gives the bis-sulphone (XXVII), pyrolysis of which leads to pyridinophan (XXVIII) in 46% yield.[39]

A series of pyridinophans such as (XXIX) or (XXX) containing bridge carbon–sulphur bonds is obtained by the reaction of 2,6-bis(bromomethyl)pyridine with dithioresorcinol[40] and other dithiols,[41–44] and also by the reaction of 2,6-bis(mercaptomethyl)pyridine or 2,6-pyridinedithiol with 1,3-dihaloalkylbenzenes.[45–50] Other methods of synthesis of such pyridinophans have also been described.[51,58]



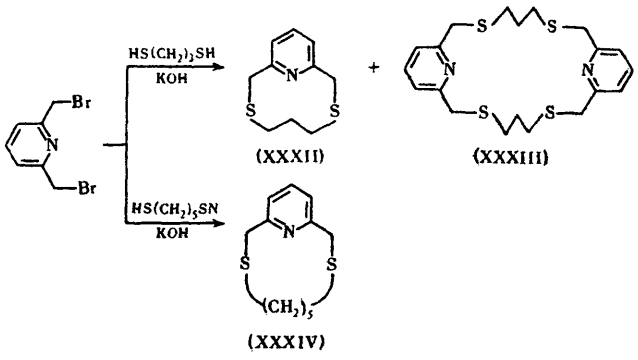
(XXIX) (XXX)

The pyridinophan (XXXI) with bridging sulphur atoms is obtained by intramolecular condensation of 6-chloropyridine-2-thione in the presence of P_4S_{10}.[52]



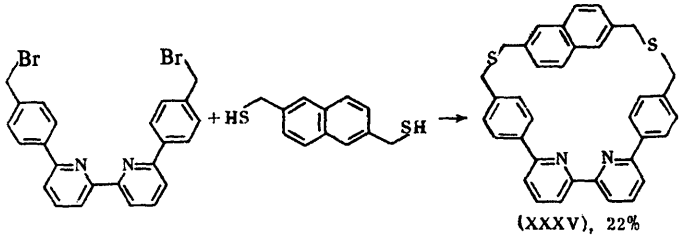
(XXXI)

The reaction of 2,6-bis(bromomethyl)pyridine with 1,3-propanedithiol occurs by a [1 + 1] and a [2 + 2] condensation simultaneously and leads to a mixture of the ten (XXXII) and twenty-membered pyridinophans (XXXIII) respectively.[53]



The analogous reaction with 1,5-pentanedithiol leads exclusively to the twelve-membered macroheterocycle (XXXIV), the formation of the dimeric macrocycle was not observed.

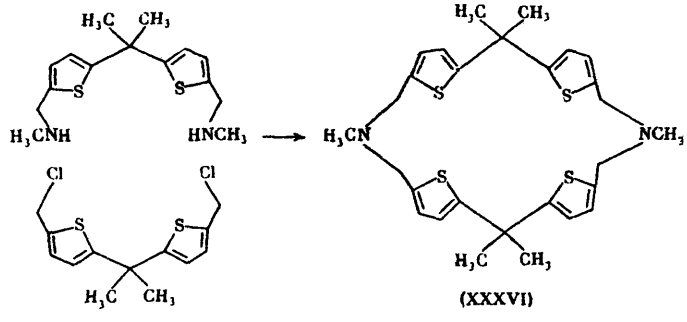
The thiaza crown compound (XXXV) containing a bipyridyl fragment is obtained by the reaction of 6,6′-di-(4-bromomethylphenyl)-2,2′-bipyridyl with 2,6-bis(mercaptomethyl)naphthalene under conditions of high dilution.[54,55]



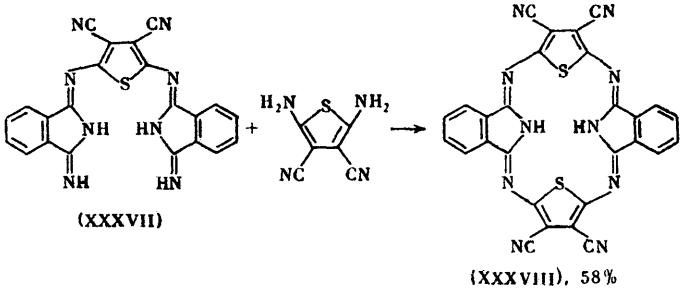
The reaction occurs in the presence of Cs_2CO_3 at 50 °C in DMF.

4. Nitrogen-containing thiophenophans

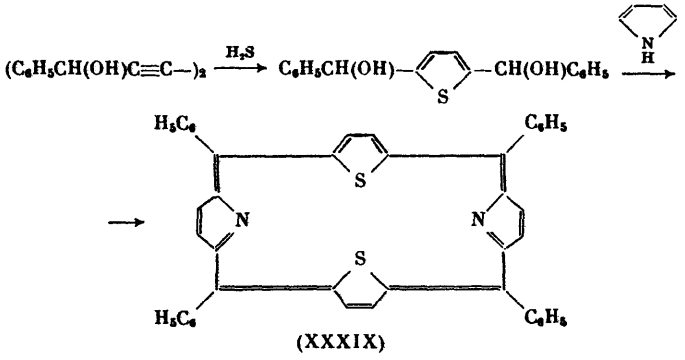
Methods have been developed for the synthesis of macroheterocycles in which thiophene rings are included as structural subunits and chains of C–N–C fragments form bridges. For example, the reaction of 2,2-bis(5′-methylaminomethyl-2′-thienyl)propane with 2,2-bis(5′-chloromethyl-2′-thienyl)propane in benzene at 40 °C leads to the *N,S*-containing macrocycle (XXXVI).[56]



The macroheterocyclic compound (XXXVIII) is formed on treatment of the derivative (XXXVII) with 2,5-diamino-3,4-dicyanothiophene.[57,58]

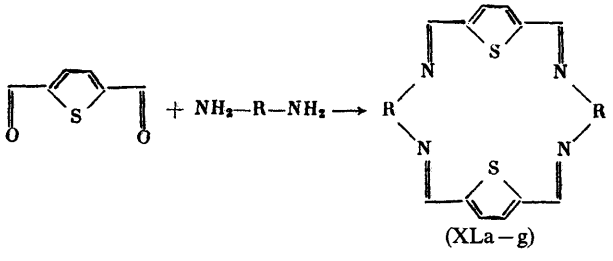


The dithiaporphyrin (XXXIX) is synthesised from 2,5-bis(phenylhydroxymethyl)thiophene and pyrrole.[59]



2,5-Bis(phenylhydroxymethyl)thiophene was obtained by the reaction of the corresponding diacetylene with hydrogen sulphide. Cyclisation was effected in a mixture of chloroacetic acid–benzene, chloroacetic acid–toluene or in propionic acid. The yield of compound (XXXXIX) was 4–10%.

The reaction of thiophene-2,5-dicarbaldehyde with α,ω-alkylenediamines has been studied.[60]



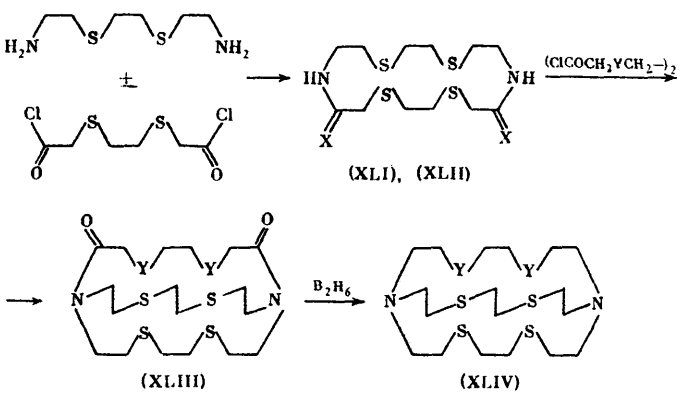
R = $(CH_2)_3$ (a), $(CH_2)_4$ (b), $(CH_2)_5$ (c), $(CH_2)_6$ (d), $(CH_2)_2S(CH_2)_2$ (e), $(CH_2)_2NH(CH_2)_2$ (f), $(CH_2)_3NH(CH_2)_3$ (g).

The reaction occurs in methanol at room temperature in 2.5 h or on heating in 0.5 h with the formation of the dimeric product ([2 + 2] condensation). The yield of *N,S*-containing macrocycles (XLa–g) varied from 50 to 90%.

5. *N,S*-Containing trimeric macroheterocyles

Trimeric macroheterocycles, cryptands, clathrochelants, form exceptionally stable complexes with a wide range of cations. They are capable of completely encapsulating a metal ion. Consequently there is undoubted interest in *N,S*-containing macrobicycles (cryptands) which form stable complexes with transition metals.[61]

The reaction of 1,8-diamino-3,6-dithioctane with the diacid chloride of 3,6-dithioctanedicarboxylic acid leads to the diamide (XLI). The subsequent reduction of diamide (XLI) with diborane gives the *N,S*-containing macrocycle (XLII). The macrobicyclic diamides (XLIII) are obtained by the condensation of the latter with diacid chlorides of dicarboxylic acids. The cryptands (XLIV) are obtained in 30% yield by reduction of the diamides with diborane.

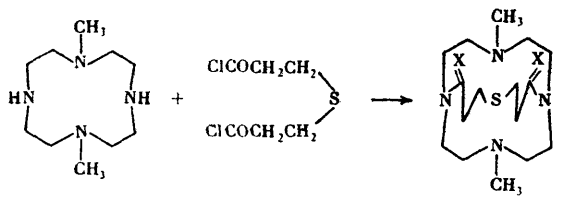


(XLI), (XLII)

(XLIII) (XLIV)

(XLI): X = O; (XLII): X = H_2; (XLIII), (XLIV): Y = S, N—Ts, NH.

The synthesis of cryptand (XLVII), containing four nitrogen atoms and one sulphur atom in the molecule has been carried out.[62]

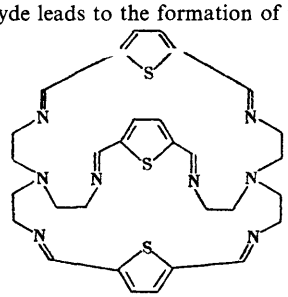


(XLVI), (XLVII)

(XLVI): X = O; (XLVII): X = H_2.

The basis of the preparation of (XLVII) is the reaction of the monomacrocyclic compound 1,7-dimethyl-1,4,7,10-tetraazacyclododecane with the diacid chloride of 3,3'-thiodipropionic acid. The macrobicyclic diamide (XLVI), formed in 75% yield, is reduced in diborane in THF. The cryptand (XLVII) is isolated in 68% yield.

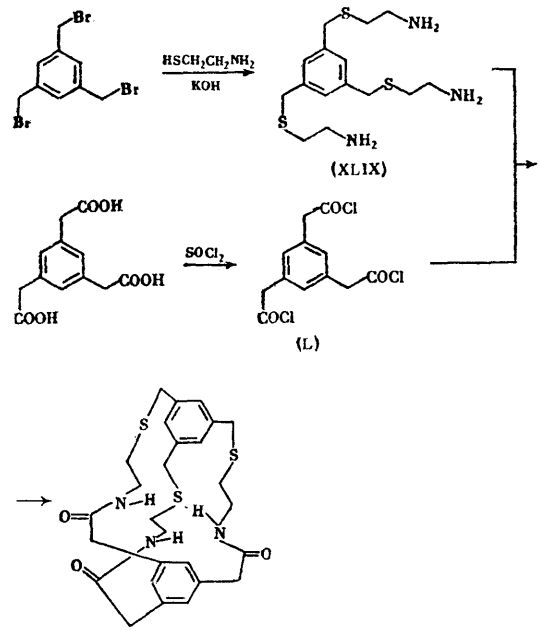
Treatment of tris(2-aminoethyl)amine with thiophene-2,5-dicarbaldehyde leads to the formation of the cage molecule (XLVIII).[63]



(XLVIII)

The reaction occurs at a molar ratio of trisamine and dialdehyde of 2:3 [yield of the macrobicycle (XLVIII) was 56%].

The synthesis of trithiacyclophan (LI) containing three amide groups is effected by the condensation of the triamine (XLIX) with the triacid chloride (L) by the following scheme.[64]



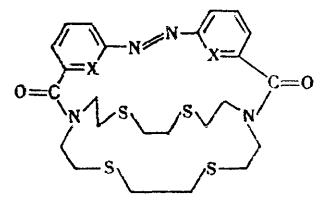
(XLIX)

(L)

(LI)

The triamine (XLIX) is obtained by the reaction of 1,3,5-tris-(bromomethyl)benzene with cysteamine in the presence of KOH in methanol and the triacid chloride of benzene-1,3,5-triacetic acid (L) is synthesised by reaction with thionyl chloride in toluene. Reaction of the triamine (XLIX) with the triacid chloride (L) occurs in dry THF [yield of macrobicycle (LI) is 11%].

The photosensitive *N,S*-containing cryptands (LII) and (LIII) are synthesised by the cyclocondensation of the triaza-crown compound (XLII), with 6,6'-bis(chloroformyl)-2,2'-azopyridine and with 3,3'-bis(chloroformyl)azobenzene respectively under high dilution conditions.[65]



(LII): X = N;
(LIII): X = CH.

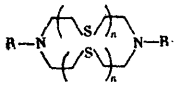
(LII), (LIII)

The yields of *trans*-cryptands (LII) and (LIII) were 33 and 24% respectively.

Polymacrocyclic systems may enclose two or more metal cations in the internal cavity of the molecule. Such cryptates are of interest as models of polynuclear biological complexes or as polynuclear catalysts.

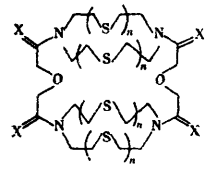
A general method of constructing cylindrical polymacrocyclic systems has been proposed.[66,67] Synthesis of the sulphur-containing trimacrocyclic tetraamide (LVa) is based on the condensation of the

macrocycle (LIVd), containing reactive substituents at the nitrogen atoms, with the macroheterocycle (LIVa). Subsequent reduction of the tetraamide (LVa) with diborane leads to the cylindrical trimacrocyclic tetrathiatetraamine (LVb).



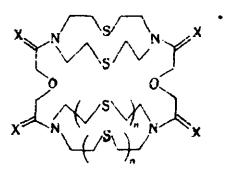
(LIVa–g)

(LIVa): $n=1$, R = H;
(LIVb): $n=1$, R = CH_3;
(LIVc) $n=1$, R = $COCH_2OCH_2COOH$;
(LIVd): $n=1$, R = $COCH_2OCH_2COOC_6H_4NO_2$-*p*;
(LIVe): $n=2$, R = CH_3;
(LIVf): $n=2$, R = $COCH_2OCH_2COOH$;
(LIVg): $n=2$, R = $COCH_2OCH_2COOC_6H_4NO_2$-*p*;



(LVa–d)

(LVa): $n=1$, X = O;
(LVb): $n=1$, X = H_2;
(LVc): $n=2$, X = O;
(LVd): $n=2$, X = H_2;



(LVIa, b)

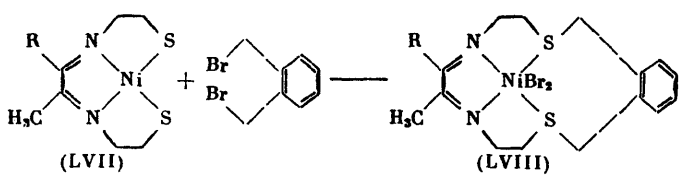
(LVIa): $n=2$, X = O;
(LVIb): $n=2$, X = H_2

The trimacrocycles (LVc) and (LVIb) are obtained in a similar manner.

6. Template synthesis of *N,S*-containing macroheterocycles

The basis of the template method of synthesis is the stereochemical organisation and orientation of reactants by a metal ion or by a metal-containing molecule. This leads to reaction of functional groups which under normal conditions is either difficult or generally impossible.[68]

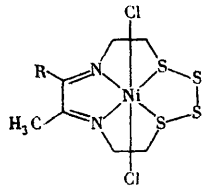
One example of template synthesis is the condensation of α-diketones with mercaptoamines in the presence of nickel salts leading to the complex (LVII) which may in its turn serve as a matrix for the formation of the macrocyclic compounds (LVIII) under the action of α,α′-dibromo-*o*-xylene.[69]



(LVII) (LVIII)

R = CH_3, C_2H_5, C_5H_{11}

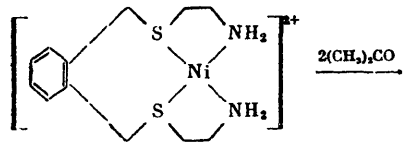
The reaction of the complex compounds (LVII) with sulphur monochloride proceeds in a similar manner and leads to the nickel-containing tetrathiadiazamacrocycle (LIX).[70]



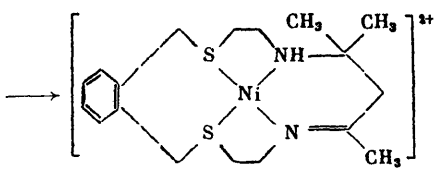
(LIX)

R = CH_3, C_2H_5, C_5H_{11}

The nickel chelate (LX) reacts with two molecules of acetone with the formation of the complex (LXI).[71]

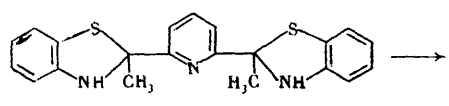


(LX)

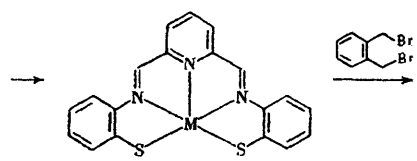


(LXI)

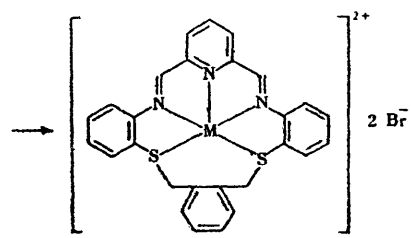
The product (LXII) of the condensation of 2,6-diacetylpyridine with 2-aminothiophenol undergoes an intramolecular rearrangement on reaction with zinc and cadmium acetates being converted into the complex (LXIII). Subsequent template reaction of it with α,α′-dibromo-*o*-xylene in acetone leads to the metal-containing macrocycle (LXIV).[72,73]



(LXII)



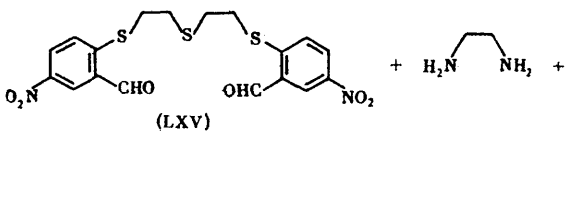
(LXIII)



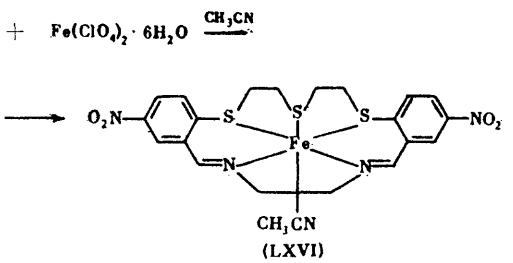
(LXIV)

M = Zn, Cd

A complex of iron ion with the *N,S*-containing macrocycle (LXVI) is obtained by the condensation of the dialdehyde (LXV) with ethylenediamine in acetonitrile in the presence of $Fe(ClO_4)_2.6H_2O$.[74]

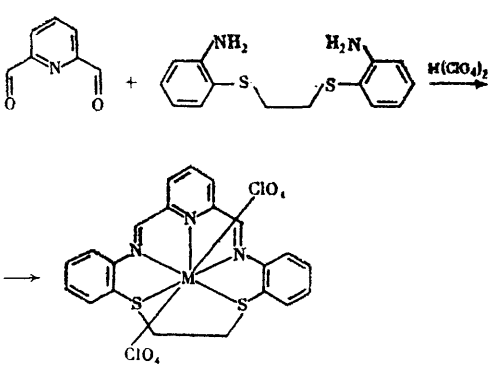


(LXV)



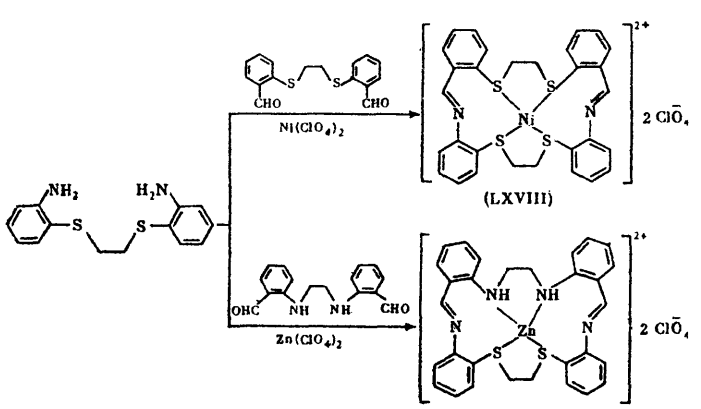
(LXVI)

The coordination compound (LXVII) with a pentadentate *N,S*-containing macrocyclic ligand was obtained according to the following scheme.[75]



(LXVII)
M = Mn, Zn

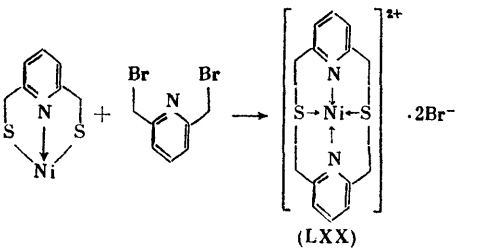
Condensation of 1,2-bis(2-aminophenylthio)ethane with 1,4-bis-(2-formylphenyl)-1,4-dithiabutane or 1,4-bis(2-formylphenyl)-1,4-diazabutane in the presence of nickel or zinc perchlorates leads to the complexes (LXVIII) and (LXIX) respectively.[76–78]



(LXVIII)

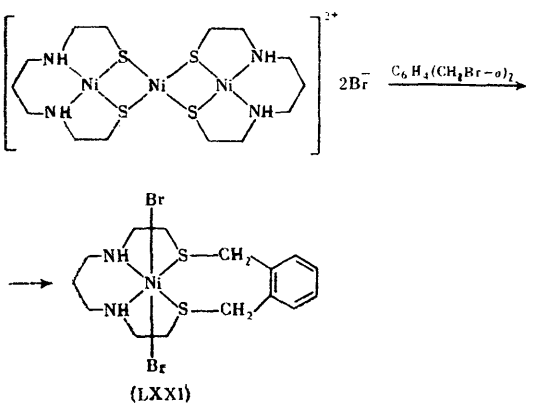
(LXIX)

The complex (LXX) of a sulphur-containing pyridinophan with nickel ion is obtained in 86% yield by the reaction of the nickel(II) complex of 2,6-bis(mercaptomethyl)pyridine with 2,6-bis(bromomethyl)pyridine in DMF.[79]



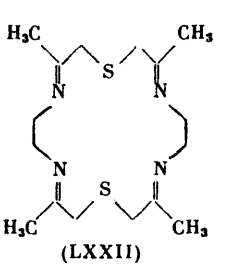
(LXX)

The reaction of α,α′-dibromo-*o*-xylene with bis(3,7-diazanonane-1,4-dithiolate)trinickel(II) bromide leads to the formation of the nickel complex of 3,13-dithia-6,10-diazabicyclo[13.4.0]nonadeca-(15),16,18-triene (LXXI).[80]

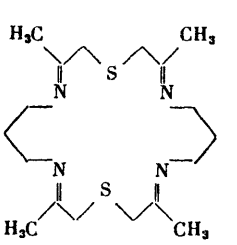


(LXXI)

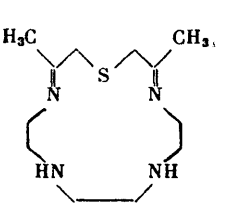
A series of nickel complexes containing macrocyclic Schiff's bases as ligands (LXXII)–(LXXIV) are obtained by the condensation of 1,2-diaminoethane, 1,3-diaminopropane or triethylenetetramine with 4-thiaheptane-2,6-dione in the presence of a nickel(II) salt.[81]



(LXXII)



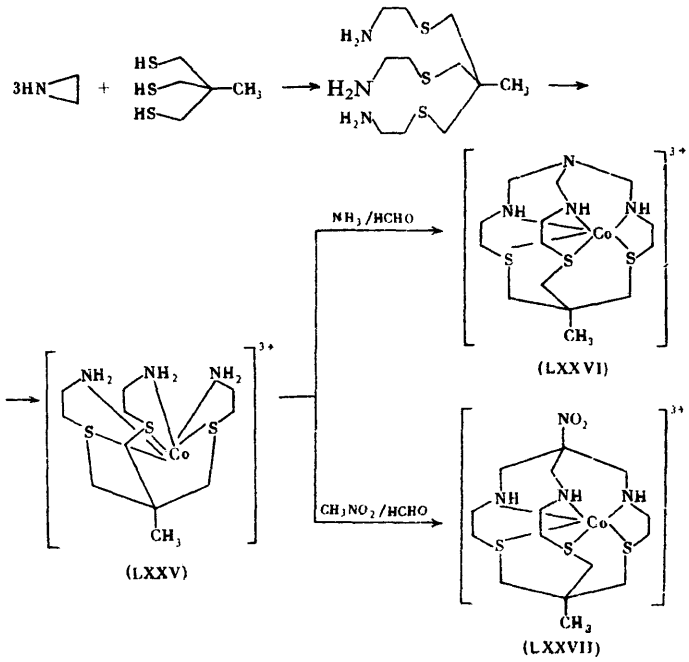
(LXXIII)



(LXXIV)

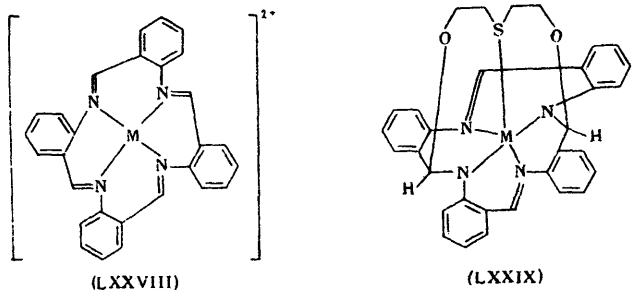
The macrocycles (LXXII)–(LXXIV) are not formed in the absence of nickel(II) ions. The reaction occurs on heating a mixture of diamine, 4-thiaheptane-2,6-dione and the nickel salt in dry ethanol for 0.5–4.0 h. The yield of complexes was 70%.

The template method of synthesising cage-like molecules (sepulchrates, sarcophagins) has been successfully effected in the presence of ions of cobalt(III), rhodium(III), iridium(III) and platinum(IV).[82] The sepulchrate (LXXVI) with an encapsulated cobalt(III) ion is formed on reaction of the hexadentate complex (LXXV) with formaldehyde and ammonia. Reaction of the same complex with nitromethane and formaldehyde leads to the sarcophagin (LXXVII).



(LXXV) (LXXVI) (LXXVII)

The synthesis of "basket-like" complexes with bicyclic ligands (LXXIX) has been effected by the reaction of compounds (LXXVIII) with bis(2-hydroxyethyl) sulphide.[83]



(LXXVIII) (LXXIX)

M = Ni, Cu

In such complexes the central sulphur atom is sterically located so as to occupy an axial position in the coordination sphere of the metal atom, as a result of which the square pyramidal pentacoordination complex (LXXIX) is formed.

III. *N,S*-containing receptors binding cations, anions and neutral organic molecules

1. Cation-binding receptors

N,S-Containing macrocycles form complexes with copper(II) ions which may be considered as low molecular structural models of the active centres of copper-containing "blue" proteins. The copper(II) ion in these proteins is in an environment of donor atoms of nitrogen and sulphur.[84,85] Investigation of the physicochemical characteristics of low molecular complexes showed that they possess the unusual spectral and oxidation–reduction properties characteristic of many copper-containing proteins. The electronic spectra of blue proteins have a strong absorption band in the 600 nm region and a high Cu(II)/Cu(I) oxidation–reduction potential (0.2–0.8 V). The copper-containing proteins, such as plastocyanin, azurin, etc., contain blue copper which is coordination bound with two histidine groups and the sulphur atoms of cysteine and methionine [the coordination polyhedron of copper is a distorted tetrahedron (Fig. 1)].[85,86]

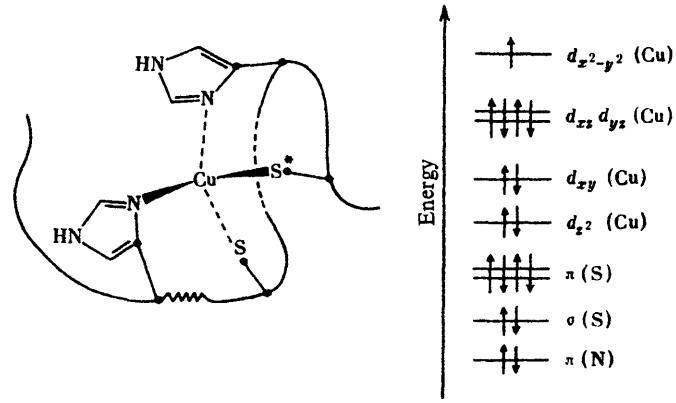


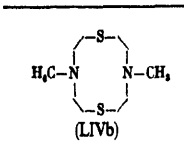
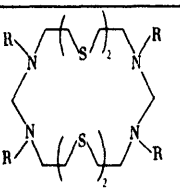
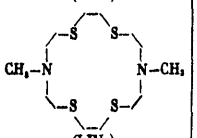
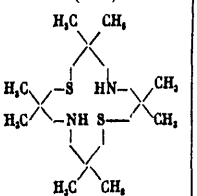
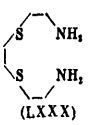
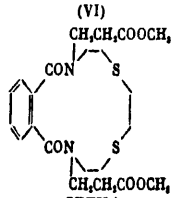
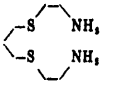
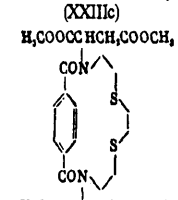
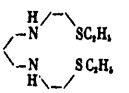
Figure 1. Structural representation of the distorted tetrahedral CuN_2SS^* centre (S is S of Cys; S* is S of Met) in plastocyanin and azurin.[85]

The parameters of the electronic spectra and the oxidation–reduction potentials of the complexes of *N,S*-containing macrocycles and of their open chain analogues and also of plastocyanin and azurin are given in Table 1.

The high intensity absorption bands in the spectra of plastocyanin and azurin with maxima at 752 and 778 nm belong to the charge transfer band (CTB) $\pi(S) \rightarrow d_{x^2-y^2}(Cu)$. The absorption bands at 606 and 552 nm in the spetrum of plastocyanine and at 631 and 567 nm in the spectrum of azurin also belong to CTB $\sigma(S) \rightarrow d_{x^2-y^2}(Cu)$. The absorption bands in the 428–481 nm region are linked with transitions occurring in the highest occupied π-orbitals of the imidazole ring [$\pi(N) \rightarrow d_{x^2-y^2}(Cu)$].[85]

The complexes of the copper(II) ion with *N,S*-containing macrocycles and open chain ligands have absorption bands with a maximum at $\lambda < 300$ nm caused by intraligand transitions, the absorption at 300–400 nm belongs to the CTB $\sigma(S) \rightarrow d(Cu)$ and that in the 650–850 nm region to a $d-d$ transition.[84]

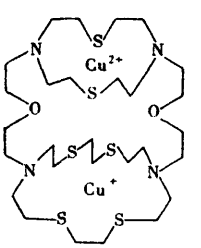
Table 1. Parameters of the electronic absorption spectra and oxidation–reduction potentials of CuL^{2+} at 25 °C.

Ligand L	Solvent	λ_{max}, nm(ε)	$E_{1/2}$, mV	Refs.	Ligand L	Solvent	λ_{max}, nm (ε)	$E_{1/2}$, mV	Refs.
 (LIVb)	80% CH_3OH+ +20% H_2O	370 (5000) 605 (1200)	495	[66]	 (XVIc)	CH_3CN	282 (3840) 333 (2150) 666 (52)	–	[84]
 (LIVe)	80% CH_3OH+ +20% H_2O	415 (2600) 695 (600)	695	[66]	 (XIIIg)	CH_3CN	289 (5200) 333 (3900) 685 (152)	–	[84]
 (VI)	80% CH_3OH+ +20% H_2O	251 (2030) 325 (4150) 390 (5510) 720 (385)	–	[11]	 (LXXX)	80% CH_3OH+ +20% H_2O	–	361	[87]
 (XXIIIc)	CH_3CN	275 sh (2100) 385 sh (1200) 833 (40)	790	[84]	 (LXXXI)	80% CH_3OH+ +20% H_2O	–	312	[87]
 (XXVIj)	CH_3CN	232 (2100) 275 (1200) 787 (45)	940	[84]	 (LXXXII)	80% CH_3OH+ +20% H_2O	–	342	[87]
					Plastocyanin	Thin film	428 (100) 450 (300) 552 (1163) 606 (4364) 752 (1289)	347	[85]
					Azurin	ditto	481 (198) 567 (504) 631 (3798) 779 (686)	330	[85]

The oxidation–reduction potentials of "blue" proteins, *N,S*-containing macrocycles and open chain analogues with the copper(II) ion are 312–940 mV, but for Cu^{2+}(aq) this value is 150 mV (see Table 1).

The copper complexes of the macrotricyclic ligands (LVb, d) and (LVIb) may be considered as binuclear models of copper proteins.[66,67] They have intense absorption near 400 and near 600 nm (375, 565, 430, 590, 375, 563 nm respectively). The oxidation–reduction potential of the copper complex (LVb) is 445 mV.

A mixed complex (LVIc) is formed by the reaction of copper(I) and copper(II) perchlorates (1 : 1) with the unsymmetrical macrotricycle (LVIb).[66] The electronic spectra of the complex indicate that the copper(I) and copper(II) cations are located in the 18- and 12-membered rings of the macrocycle respectively.



(LVIc)

According to the data of X-ray structural analysis the distance between the copper ions in the binuclear complex compounds (LVb, d) and (LVIb) is 5.7–6.0 Å. The macrotricyclic cryptates therefore possess a free space into which a molecule of oxygen or nitrogen may be introduced. Introduction of a molecule of oxygen or nitrogen between the two cations leads to a cascade complex

which may be used in binuclear catalysis or for the fixation of molecules of oxygen or nitrogen. On adding KO_2 or O_2 to the complex of macrotricycles, absorption bands appear at 330 and 370 nm respectively in addition to a wide absorption band at 550–850 nm. These changes in spectra are possible when superoxides or oxygen are included in the binuclear complex. Copper complexes with macrotricyclic ligands are therefore a new type of transition metal polynuclear complex and are potential bioinorganic models of biological processes occurring, for example, with the participation of copper proteins, superoxide dismutase, etc.[66]

N,S-Containing macrocycles also form complexes with cations of silver(I),[88–90] mercury(II),[89–90] nickel(II),[81,88] cobalt(II),[88] palladium(II)[53,88–90] and rhodium(III).[53,88]

2. Anion-binding receptors

Receptor molecules containing positively charged groups, neutral electron-deficient atoms (boron, silicon, tin, etc.), amide or carboxyl groups are capable of binding halide, azide and other anions.[3]

The trithiacyclophan (LI) containing three amide groups is able to form complexes with small-sized anions.[64] According to the data of X-ray structural analysis the size of the cavity of the macrobicycle corresponds to the size of a fluoride or hydroxide anion. In addition the hydrogen atoms of the N–H groups are directed into the ring which aids complex-formation due to the generation of three hydrogen bonds. This type of binding, which was confirmed by ^1H and ^{19}F NMR data, was established in the reaction of tetrabutylammonium fluoride with the macrobicycle (LI).

A cascade type of complex-formation is recorded in the reaction of the macrocyclic receptor (LXXXIII) with copper nitrate and sodium azide.[91] The structure of the complex $Cu_2^{2+}(N_3^-)_4L$ [L is the macrocyclic ligand (LXXXIII)] is shown in Fig. 2.

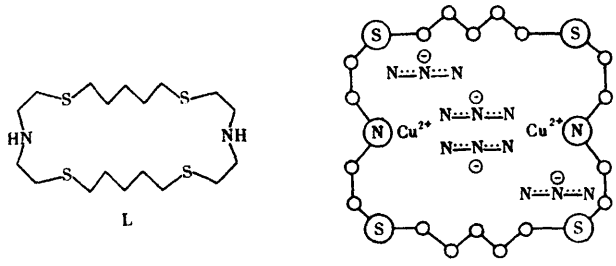


Figure 2. Schematic representation of the $Cu_2^{2+}(N_3^-)_4L$ complex (L is a macrocyclic ligand).[91]

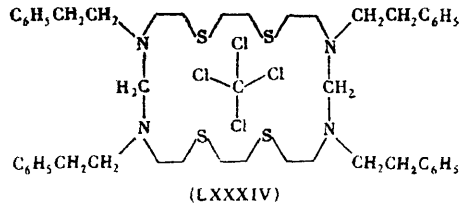
The principle of the cascade complex formation consists of a stepwise reaction. Initially the receptor binds the metal cations which then themselves become centres of association for anions.

3. Receptors forming complexes with neutral molecules

Crown ethers and cryptands form molecular complexes with various neutral molecules. Complex formation has been established with water, molecular bromine, methanol, ethanol, chloroform, urea, acetonitrile, acetylene-dicarboxylic acid dimethyl ester, malonodinitrile, phenylhydrazine, 2,4-dinitrophenylhydrazine, 2,4-dinitroaniline, 3-nitrophenol, etc.[3] Complex formation is effected by all three forms of intermolecular reaction, viz. hydrogen bonds, dipole–dipole interactions, van der Waals forces and hydrophobic binding. Selective binding of the receptor with the substrate leads to a supermolecule, which may consist of an associate of two or more molecular particles. This type of complex formation plays a basic role in such biochemical processes as enzyme–substrate reactions or drug–receptor interactions, etc.

The *N,S*-containing macrocycle (XXXV) forms a molecular complex with CH_3SnCl_3 of composition 1:1 in a mixture of $CDCl_3–CD_3CN$ as solvent. The formation of the complex was established by ^1H NMR spectral data.[54]

The 22-membered macroheterocyclic receptor (XVIIc), containing four exocyclic phenylethyl groups, binds a molecule of chloroform to form the crystalline complex (LXXXIV) which is stable on storage and on heating.[27]



Complex formation with chloroform did not take place on replacing the phenylethyl groups in the macrocycle (XVIIc) by methoxycarbonylethyl or cyanoethyl groups. The main factor in the reaction of this macromolecule with chloroform is therefore of a stereochemical nature created by the bulky phenyl groups.

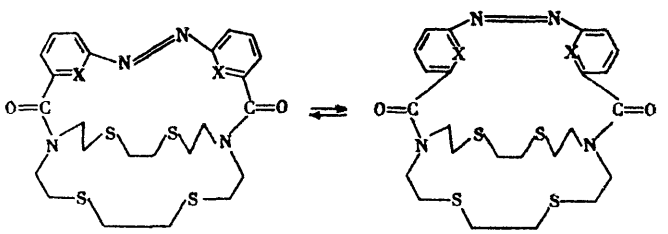
The macrocycle (XVIId), containing exocyclic ester groups, is capable of binding six molecules of urea by a type of complex-formation occurring on the receptor surface.[32] Reaction is effected by the formation of hydrogen bonds of the urea amino groups with the carbonyl oxygen atoms of the ester fragments of the macrocycle.

IV. Transport of metal ions by *N,S*-containing receptors through membranes, catalysis

Crown ethers and cryptands are capable of transferring metal cations through synthetic or natural membranes. It is possible to consider them as simplified models of natural ionophores such as valinomycin, nonactin, etc.[92]

The transport of metal cations through membranes is caused by the extraction of ions from the first aqueous phase due to complex-formation with the carrier and rapid release of them from the complex, which is in the membrane, into the second aqueous phase. The best carriers are therefore ligands forming complexes of average stability. Photoreversible macroheterocycles are attractive for this purpose, as they are capable, under the action of UV irradiation, of reversibly changing the ionophore structure and therefore its stability in complex-formation.[3]

The cryptands (LII) and (LIII), containing azopyridine and azobenzene groups respectively, are such photoreversible carriers.[65]

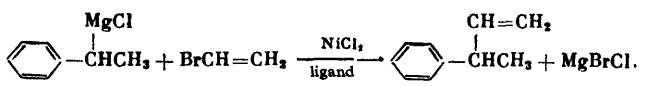


trans-(LII), (LIII) *cis*-(LII), (LIII)

(LII): X = N; (LIII): X = CH

The *cis*—*trans*-isomerisation of these compounds occurs reversibly under photoirradiation. The extraction of the Hg^{2+} ion is effected most efficiently in the presence of the *cis*-isomer of the macrobicycle (LII) compared to the *trans*-isomer, and also by the *cis*- and *trans*-isomers of the cryptand (LIII). The *trans*-isomer of (LIII) does show an appreciable affinity for ions of Cu^{2+}, Co^{2+}, Ni^{2+} and Pb^{2+}. The *trans*-isomer of cryptand (LII) does not react significantly with Cu^{2+} ions while the *cis*-isomer extracts copper(II) ion almost quantitatively. This circumstance enables the transfer of Cu^{2+} ion by the macrobicycle (LII) through a liquid membrane (*o*-dichlorobenzene—n-butanol, 4:1) to be studied. The investigations showed that the rate of transfer of the ion through the membrane was increased significantly by UV irradiation.

The cross-coupling reaction of the Grignard reagent (LXXXV) with vinyl bromide (LXXXVI) proceeds with the formation of (but-1-en-3-yl)benzene (LXXXVII).[12]



(LXXXV) (LXXXVI) (LXXXVII)

The yield of (but-1-en-3-yl)benzene was 10% in the presence of $NiCl_2$. The yield of compound (LXXXVII) was increased to 74—100% on using the complex of $NiCl_2$ with the chiral *N,S*-containing macrocycles (Xa—e) as catalyst.

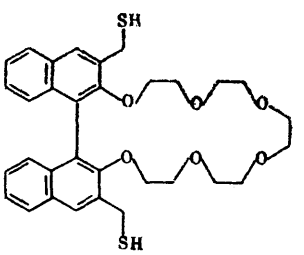
The complexes of copper(II) with the *N,S*-containing macrocycles (XXIII) proved to be efficient catalysts for the oxidation of thiols by oxygen in the air.[93]

V. Conclusion

The design and synthesis of compounds imitating the action of enzymes is one of the most complex and important problems of organic chemistry. Certain successes have been achieved in this direction during the years of development of the chemistry of macroheterocyclic compounds.

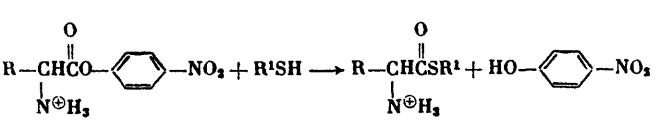
The proteolytic enzymes catalysing the hydrolysis of peptide and ester bonds are the most widely studied among the large number of enzyme systems. The basic conditions for enzymic catalysis are desolvation of the reaction centres of the enzyme—substrate complex[94] and stabilisation of the transition state or reactive form of the substrate.[95] Quantum chemical investigations carried out on the reaction of formamide with the CH_3O^- anion in the active centre of α-chymotrypsin ("the catalytic triad" Ser-195—His-57—Asp-102) confirmed these conclusions. Stabilisation of the transition state of the active centre of α-chymotrypsin may be effected by the formation of hydrogen bonds between the oxygen atom of the substrate carbonyl group and the NH groups of the polypeptide chain amides. Another important factor is the stabilisation of the reactive form of the substrate which leads to significant acceleration of the reaction.

Macroheterocyclic compounds containing donor oxygen atoms in the ring may serve as the cavity in which substrate binding occurs. At present the most studied is the three-point model of binding ammonium ion acting as guest, by a crown ether.[3] The next stage of developing "synzymes" is the synthesis of macrocycles containing a cysteine sulphur atom as active nucleophile. This is used as a model of SH-enzymes of the papain type (LXXXVIII).[3]

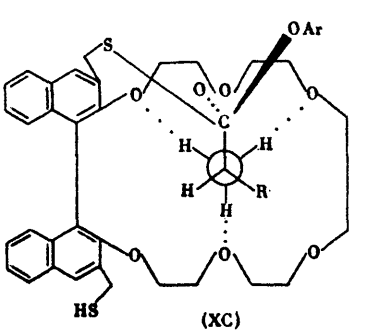


(LXXXVIII)

The crown ether ring serves as the "cavity" and the substrate is the ammonium salt (LXXXIX) which forms a three-point bond with the oxygen atoms of the polyether (XC).



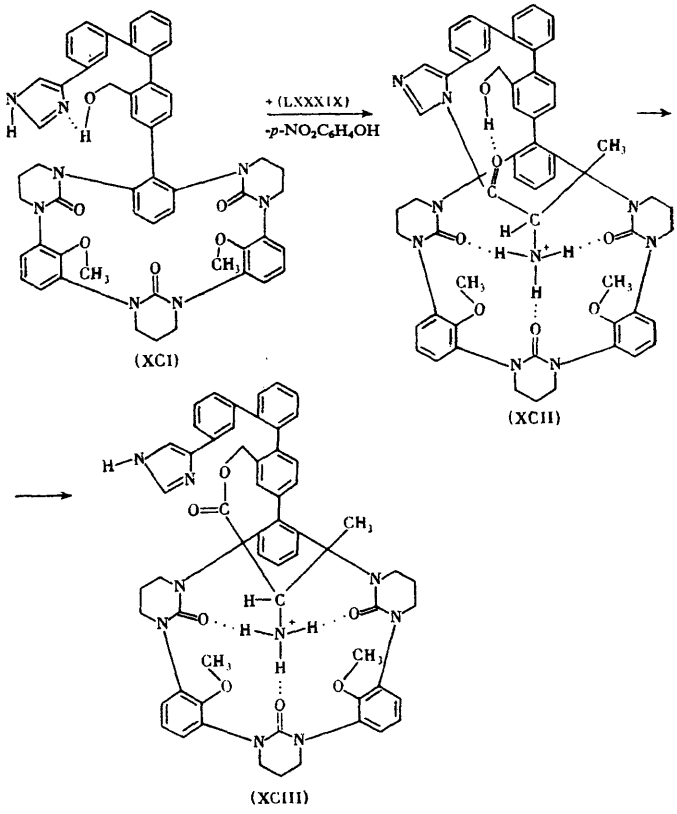
(LXXXIX)



(XC)

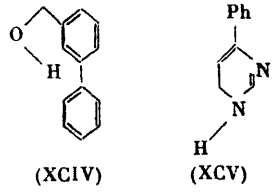
A comparison of the rate constants for the transacylation of the amino acid salts (LXXXIX) showed that the reaction occurs more rapidly with the macrocyclic compound (LXXXVIII) than with its open chain analogue.

A multistage synthesis has been developed for the macrocycle (XCI), which has a complex-forming centre, a nucleophilic hydroxyl and an imidazole proton-transfer agent.[96]



(XCI) (XCII) (XCIII)

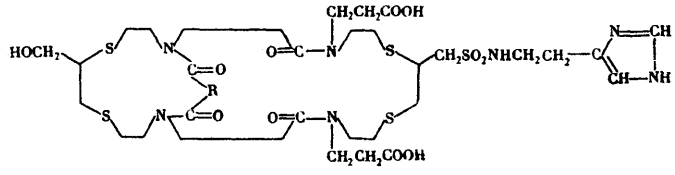
The salt of the amino ester (LXXXIX), which forms a complex with the crown compound (XCI), instantaneously acylates the imidazole group giving the complex (XCII), which is then converted into the more stable complex (XCIII). Acylation has also been studied in the presence of the non-complexing compounds (XCIV) and (XCV).



(XCIV) (XCV)

The rate constant for acylation of the macrocyclic complex is 10^{10} times higher than the rate of acylation with compounds (XCIV) and (XCV). This investigation shows that complex-formation of the receptor with the substrate stabilises the transition state and the reactive form of the substrate, thereby increasing the reaction rate appreciably.[96]

In order to construct new synthetic biomimetic systems as catalysts for the hydrolysis of polypeptides and polyesters, high molecular compounds are required which contain functional groups capable of binding substrates and of catalysing their reactions. We have developed methods of synthesis of the thiazacrown compounds (XCVI). These contain exocyclic hydroxyl, carboxyl and imidazole groups, prearranged for hydrogen bonds, imitating the active centre of the enzyme α-chymotrypsin.[97]



(XCVI)

R = $-(CH_2)_4-$, 1,2-C_6H_4

Further investigations in this region of chemistry will enable, even in the near future, the preparation of the most varied types of "synzymes" based on macroheterocycles and the development of vaccine-like and other biologically important materials.

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