Russian Chemical Reviews **85** (2) 172 – 203 (2016) © 2016 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RCR4483

Halogen derivatives of benzo- and dibenzocrown ethers: synthesis, structure, properties and application

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Methods of synthesis of halogenated benzo- and dibenzocrown ether derivatives are surveyed: halogenation of benzo- and dibenzocrown ethers with molecular halogens, *N*-halosuccinimides in the solid phase and different media (water, ethanol, halohydrocarbons) and hypohalites in water, as well as the 'assembly' method. Reactions of these compounds are considered: synthesis of phosphorus-containing crown ethers, organometallic synthesis, the Heck and Sonogashira reactions, synthesis of acetylene derivatives and other reactions. Special attention is focused on the complexing properties of halogenated benzocrown ethers with respect to ionic guests and neutral organic molecules. The possibility of synthesis of complexes of such compounds in the solid phase is demonstrated. The extraction and sorption properties of halogenated benzo- and dibenzocrown ethers are considered. Examples of practical use of these compounds are presented.
The bibliography includes 203 references.

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I. Introduction

Crown ether are widely used in organic, inorganic, coordination, analytical and supramolecular chemistry, first of all, for phase transfer catalysis and extraction, as well as in biology and medicine.[1–15] Nowadays, many of crown ethers are commercially available. Further expansion of application areas in science and engineering can be achieved by modifying crown ethers, which implies molecular design and development of efficient methods of synthesis.

Because of the relative ease of synthesis, crown ethers containing endocyclic aromatic moieties hold a special position in the chemistry of macroheterocycles. Benzo- (BCEs) and dibenzocrown ethers (DBCEs) with one or several halogen atoms in the benzene ring are reasonably believed to be among the most important reagents. A rather high mobility of bromine and iodine atoms in the aromatic moieties is responsible for easy transformation of these macrocycles into compounds otherwise hardly available or unavailable: biologically active acetylene,[16–18] vinyl,[17,18] n-alkyl, n-hydroxyalkyl,[19] ammonium and phosphonium derivatives,[20] as well as into crown ether heteroanalogues,[21] bis(benzocrown ether)s,[16,19] *etc*. Halogenated benzo- and dibenzocrown ethers (HBCEs) are of interest as initial compounds for synthesis of new types of selective sorption polymers,[22] original nanofilms that considerably enhance the wear resistance of articles,[23] *etc*.

The present review covers the 40-year period — from the first publications of the early 1970s to modern studies, including original works of the author, dealing with the methods of synthesis and transformation, complexing properties, examples of commercial production and areas of application of HBCEs. These issues have not been reviewed. Although electrophilic halogenation of aromatic compounds have been well studied and described in a rather large number of publications, including reviews (see, *e.g.*, reviews[24–26]), similar reactions with BCEs and DBCEs have specific features. (In the infancy of the chemistry of crown ethers, common methods of BCE and DBCE halogenation were used; however, it turned out soon that the presence of the polyether ring in a molecule had an effect on the properties of these compounds and required a special approach.) There are several reviews (for example, recent

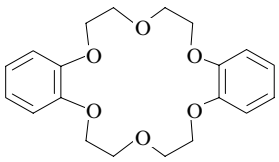
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Current research interests: macrocyclic complexones, host–guest chemistry, solid-phase organic reactions.

Received 7 June 2014
Uspekhi Khimii **85** (2) 172–203 (2016); translated by G A Kirakosyan

reviews[27,28]) focusing on different aspects of the chemistry of macrocyclic complexones, including mono(di)benzo-crown ethers and their halogenated derivatives. However, these data are fragmentary. Therefore, it is necessary to systemize all available data on the synthesis and properties of halogenated crown ether derivatives.

Because of specific properties of fluorinated BCEs and DBCEs, their synthesis and properties are not considered in detail in this review. It is only worth noting that the fluorination of crown ethers with fluorine gas (in the presence of SbF_5, HF and similar reagents) is unselective and leads exclusively to the corresponding perfluorinated derivatives.[29–36] In most cases, this pertains to aliphatic crown ethers; only one example of direct fluorination of their aromatic analogues, namely, [3.3]dibenzo-18-crown-6 (**1**), is known.

Structure 1



1

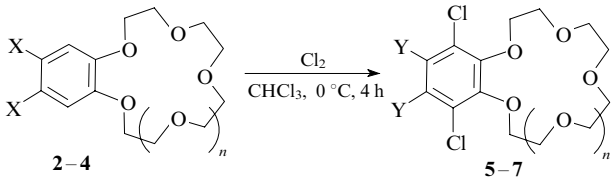
In the other cases, target products are assembled with the use of corresponding fluoro-substituted aromatic reagents.[37–40]

II. Methods of synthesis of halogenated benzo- and dibenzocrown ethers

II.1. Halogenation with molecular halogens

Biernat with co-workers[41] have chlorinated benzo-15-crown-5 (**2**), benzo-18-crown-6 (**3**) and 4′,5′-dibromo-benzo-15-crown-5 (**4**) with chlorine gas in chloroform in the cold and in the dark. The reactions led to di- and tetrahalogenated compounds **5**–**7** in 56%–70% yield (Scheme 1).

Scheme 1



2–**4** **5**–**7**

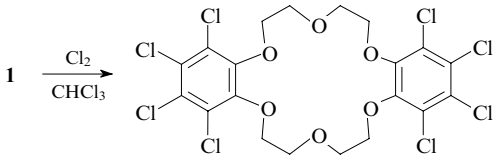
n	Substrate	X	Product	Y	Yield (%)
1	**2**	H	**5**	Cl	66
2	**3**	H	**6**	Cl	56
1	**4**	Br	**7**	Br	70

The reaction products were isolated by conventional crystallization. No properties of these chloro derivatives (except melting point) have been reported.

According to Pannell *et al.*,[42] the chlorination of DBCE **1** with chlorine in $CHCl_3$ at 25 °C is unselective (Scheme 2).

Only one product was isolated from the reaction mixture in 25% yield: high-meting (m.p. 283 °C) octachloro[3.3]dibenzo-18-crown-6 (**8**). He was poorly soluble in organic solvents, which prevented the recording of its ^{1}H NMR spectrum.

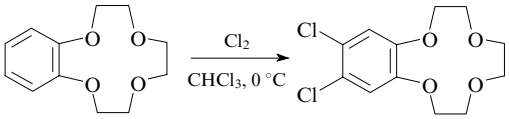
Scheme 2



8

We have chlorinated BCEs by bubbling gaseous chlorine through a solution of macrocycles **2**, **3** and benzo-12-crown-4 (**9**) in $CHCl_3$ at 0 °C in the dark up to saturation.[43] Compounds **2** and **3** give exclusively corresponding tetrachlorides **5** and **6** in 66% and 56% yield, respectively, which is supported by the data of Ref. 41. The resulting perchlorinated derivatives are poorly soluble and crystallize partially or almost completely from a solution. At close yields, the chlorination rate is maximal for BCE **3** and minimal for macrocycle **9**; in the latter case, we failed to isolate the pure product — 3′,4′,5′,6′-tetrachlorobenzo-12-crown-4 (**10**). Therefore, we did not carry out complete chlorination; rather, we filtered the reaction mixture and subjected the residue to fractional crystallization to isolate 4′,5′-dibenzo-chloro-12-crown-4 (**11**) in 21% yield (Scheme 3).

Scheme 3



9 **11** (21%)

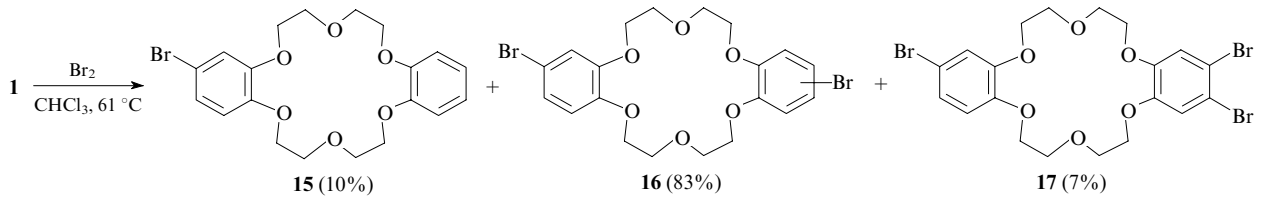
However, this procedure is inapplicable to BCEs **2** and **3**. Thus, the chlorination of BCEs with molecular chlorine leads to products with the perchlorinated aromatic nucleus, and the synthesis of dichloro-subsituted BCE **11** can be treated as an exception.

We synthesized perchlorinated derivative **8** by chlorination of DBCE **1** with chlorine in the presence of catalysts — 12-crown-4 (**12**), 15-crown-5 (**13**) and 18-crown-6 (**14**).[43] It turned out that, in the presence of 20 mol.% of compound **14**, the time of chlorination of polyether **1** decreases ~2-fold, and the yield of the target product increases ~2-fold (53%) as compared with the reaction in the absence of a catalyst (the reaction gives compound **8** with m.p. 282–285 °C). However, the addition of polyether **13** under analogous conditions leads to the increase in the chlorination duration, whereas macrocycle **12** [as well as n-butyltriethylammonium chloride (BTEAC)] has almost no effect on the reaction course.

Thus, chlorine gas is not a very good reagent for synthesis of HBCEs because of its high chemical activity and nonselective action.

The first bromination of DBCEs with molecular bromine was carried out by Shchori and Jagur-Crodzinski.[44] The reaction of macrocycle **1** with bromine was carried out in boiling $CHCl_3$, and crystallization led to a mixture of compounds **15**–**17** (Scheme 4). The major product was named as 4,4′-dibromo[3.3]dibenzo-18-crown-6 (**16**), although the location of the second bromine atom was not determined. The method used for determining the ratio of

Scheme 4



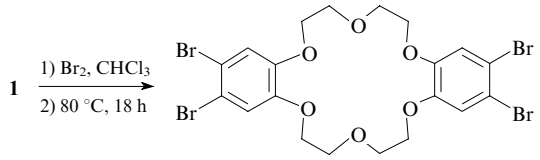
15 (10%) **16** (83%) **17** (7%)

products **15**–**17** in the mixture, as well as their physicochemical characteristics, have not been reported.

The method of bromination of polyether **1** with bromine in formic acid at 85–95 °C has been patented.[45] Under these conditions in the presence of catalytic amounts of iron, macrocycle **16** (m.p. 180–182 °C), named by the authors as di(*m*-bromobenzo)-18-crown-6, is formed in 90% yield. However, this patent, as well, presents no data supporting the structure of the product and its purity.

According to Pannell *et al.*,[42] bromination with molecular bromine also gives 4′,4″,5′,5″-tetrabromo[3.3]dibenzo-18-crown-6 (**18**, Scheme 5). The addition of a stoichiometric amount of bromine to a solution of compound **1** in $CHCl_3$ leads to crystalline complex of indefinite composition **18**·$x\,Br_2$ (m.p. 200–210 °C) in 50% yield by analogy with the bromine complex with 1,4-dioxane (dioxane dibromide, DDB).[46–49] In the course of long-term heating (80 °C, 18 h) at reduced pressure, this complex is converted into product **18** (m.p. 212–215 °C).

Scheme 5

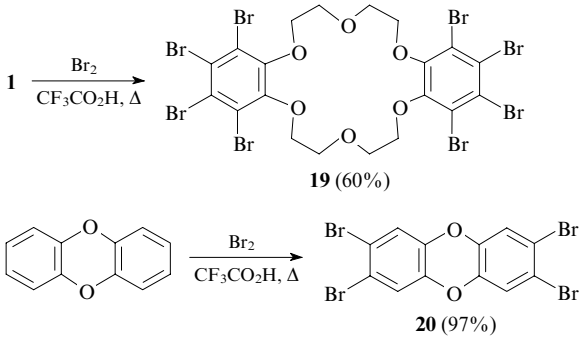


18 (25%)

Kuntsevich *et al.*[50] have carried out the exhaustive bromination of the aromatic moieties of DBCE **1**. Long-term boiling under reflux of compound **1** with a 20-fold excess of bromine in trifluoroacetic acid afforded high-melting (m.p. 293–295 °C) octabromo[3.3]dibenzo-18-crown-6 (**19**) in 60% yield (Scheme 6). Under the same conditions, dibenzo-*p*-dioxin, a formal analogue of crown ether **1**, is converted into 2,3,7,8-tetrabromodibenzo-*p*-dioxin (**20**) nearly quantitatively.[50, 51] Octabromide **19** is highly toxic [the half-lethal dose (LD_{50}) is 0.12 mg kg^{-1}],[51] being more than three times more toxic than dioxin **20** (LD_{50} = 0.45 mg kg^{-1}) and other compounds of this class.[52, 53] As is known, halogenated dibenzo-*p*-dioxins are currently the most dangerous among man-made environmental toxicants.

It has been revealed for the reaction of bromine with the copolymer of dibenzo-18-crown-6 with formaldehyde (its

Scheme 6



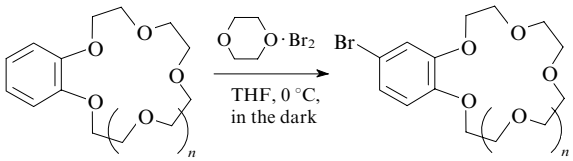
19 (60%)

20 (97%)

fragment **21** is shown in Scheme 7) produced by Parish Chem that the oxidative bromination involves the dihydroanthracene moiety.[54] The product is able to form a 1 : 1 complex with bromine insoluble in organic solvents. However, the heterogeneous bromination of some alkenes with the use of such a complex is highly selective.[54]

Okano *et al.*[55–57] have found that DDB under mild conditions selectively brominates BCEs **2**, **3**, **9** and benzo-21-crown-7 (**22**) if the reaction is carried out in the cold and in the dark (Scheme 8).

Scheme 8

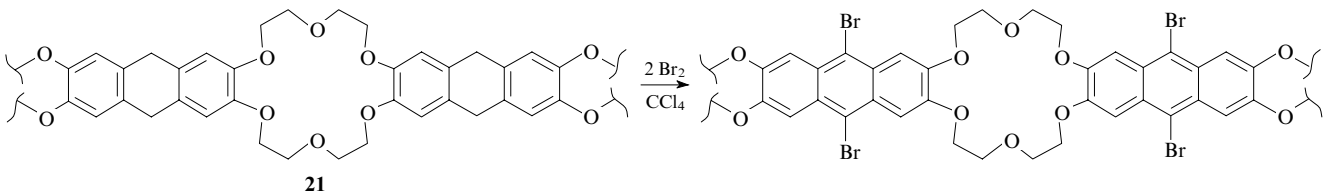


2, **3**, **9**, **22** **23**–**26**

n	Substrate	Product	Yield (%)
0	**9**	**23**	78
1	**2**	**24**	76
2	**3**	**25**	78
3	**22**	**26**	62

The structure and purity of compounds **23**–**26** have been determined only by ^1H NMR. It is worth noting that a melting point of 72.5–73.5 °C has been reported for bro-

Scheme 7



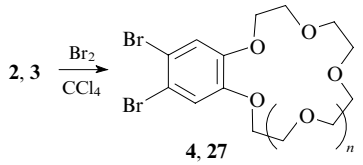
21

mide **25**,[58] whereas the companies producing this crown ether provide other data (80–82 °C for the product of 98% purity in the Acros Organic and Aldrich Chemical catalogues, 78–80 °C for the compound of 97% purity in the Fluka Chemical catalogue). The authors also do not explain the low melting point of product **23** (37.5–38.5 °C).

Bromination of BCEs with a bromine excess gives dibromo derivatives in moderate to high yield; these derivatives are easy to purify. In particular, the reaction of bromine with a solution of BCE **2** in boiling CCl_4 afforded 4′,5′-dibromobenzo-15-crown-5 (**4**) in 84% yield.

Tsivadze with co-workers[60,61] have suggested synthesizing dibromides **4** and **27** through the bromination of corresponding crown ethers in glacial acetic acid at room temperature in the presence of catalytic amounts of iodine (58% and 89% yield, respectively). The structures of the dibromides have been determined by ^1H and ^{13}C NMR and IR spectroscopy, as well as with the use of elemental analysis (Scheme 9).[59]

Scheme 9



n = 1 (**2**, **4**), 2 (**3**, **27**)

The bromination of BCEs **2**, **3** and **9** with bromine at the stoichiometric ratio substrate : bromine = 1 : 1 was studied in different solvents. The best solvent turned out to be $CHCl_3$ — the products were obtained in 50%–75% yield as calculated for the monobromo derivative. Even in CCl_4, the reaction proceeded more slowly and in lower yield (Scheme 10).[43] The reaction was carried out on heating the reaction mixture or at room temperature, varying the order of addition of the reactants.

The composition of the resulting crystalline compounds was determined by chromatography–mass spectrometry. In addition to the target products — 4′-monobromo-substituted BCEs **23**–**25**, not only expected dibromo derivatives **4**, **27** and **28**, but also small amounts of *ortho*-bromo isomers **23′**–**25′**,† as well as corresponding tribromo derivatives, were identified.

Not only the isolated crystalline products, but also the reaction mixture were analyzed. For example, after mixing solutions of polyether **3** with bromine (1 : 1) in $CHCl_3$, the reaction mixture, according to chromatography–mass spectrometry, contained ~10%–15% of initial compound **3**, 50%–60% of 4′-bromo derivative **25**, 10–20% of dibromide **4** and trace amounts of *ortho* isomer **25′**.

An analogous reaction of crown ethers **2**, **3** and **9** with a twofold bromine excess gives dibromo derivatives **4** , **27** and **28** in rather high yield (60%–85%) and, as in the above case, monobrominated products **23**–**25** (~15%–30%) and trace amounts of the corresponding tribromides as impurities.

The bromination of BCEs with the DDB complex (both separately prepared and synthesized *in situ*) in dioxane at 25 °C leads to almost the same products as the bromination with molecular bromine: the reaction gives a mixture of monobromo products (85%) and their *ortho* isomers (1%–3%), as well as di- (10%) and tribromides (≪ 1%).[43] The overall yield of the products is 60%–80% as calculated for the monobrominated derivative.

The bromination of DBCE **1** with molecular bromine or DDB leads to dibromo derivative **16** with small impurities of compounds **15** and **17** (according to mass spectrometry data).[43] We failed to completely purify macrocycle **16** to the chemically pure grade.

Summarizing the above, we can state that the bromination of aromatic crown ethers with molecular bromine can be successfully used only for synthesis of dibromo derivatives. This conclusion explains, to an extent, the inconsistency between the literature melting point values for HBCEs, first of all, for 4′-bromo derivatives. In some cases, the reported values considerably differ from the constants presented in the catalogues of the largest chemical companies.

Note that the mechanism of iodination of aromatic substrates with molecular iodine in the presence of oxidants has been addressed in a much smaller number of publications than the synthesis of the corresponding derivatives. It is believed that such electrophilic substitution reactions are of complex character.[24–26,62–64] The behaviour of reagents during iodination is largely determined by the ease of homolysis of the chemical bond to give atomic and molecular iodine and, then, triiodide cation I_3^+ through heterolysis of the iodine–hetero atom bond.[65,66]

The clearest situation is observed only for the classical Tronov–Novikov system ($I_2-HNO_3-H_2SO_4$),[62,64,67] where the route of formation of the iodine cation[68] has been proven by kinetic and other studies. By the same reason, the reaction of stoichiometric (or nearly stoichiometric) amounts of the reactants leads to monoiodination rather than to nitration [reactions (1) and (2)].

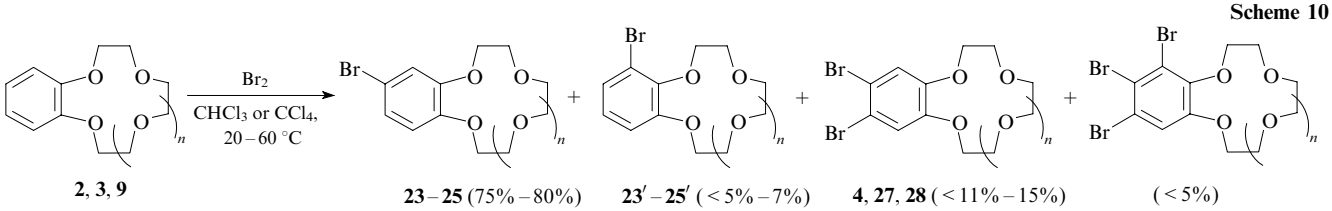
$$2H_2SO_4 + HNO_3 \longrightarrow NO_2^+ + H_3O^+ + 2HSO_4^- \quad (1)$$

$$I_2 + 2NO_2^+ \longrightarrow 2I^+ + 2NO_2 \quad (2)$$

In the $I_2-HIO_3-H_2SO_4$ system, depending on the H_2SO_4 concentration, the reaction can proceed along at least two pathways; in addition, hydroiodic acid formed as a

† In this review, geometric isomers are, in some cases, denoted by identical numbers; if the configuration of the substituents in isomers has been determined, a primed number is introduced to discern between them.

Scheme 10



n = 1 (**9**, **23**, **23′**, **28**), 2 (**2**, **4**, **24**, **24′**), 3 (**3**, **25**, **25′**, **27**)

side product can be involved in the process.[62, 64] The use of concentrated H_2SO_4 (which is, however, impossible for BCEs) affords the generation of highly electrophilic iodine cation incorporated in the probable iodinating agent $I^+HSO_4^-$ [reaction (3)], which is able to attack arenes [reaction (4)].

$$2I_2 + HIO_3 + 5\,H_2SO_4 \longrightarrow 5\,I^+HSO_4^- + 3\,H_2O \quad (3)$$

$$Ar-H + I^+HSO_4^- \longrightarrow Ar-I + H_2SO_4 \quad (4)$$

The participation of the highly active iodinating intermediate $I_3^+HSO_4^-$ in this reaction is not ruled out [reactions (5) and (6)].

$$7I_2 + HIO_3 + 5\,H_2SO_4 \longrightarrow 5\,I_3^+\,HSO_4^- + 3\,H_2O \quad (5)$$

$$Ar-H + I_3^+HSO_4^- \longrightarrow Ar-I + I_2 + H_2SO_4 \quad (6)$$

Thus, the overall process can be described by Eqn (7).

$$5\,Ar-H + 2\,I_2 + HIO_3 \longrightarrow 5\,Ar-I + 3\,H_2O \quad (7)$$

In the presence of water and sulfuric acid in this system, reactions (8)–(10) are possible.

$$2I_2 + HIO_3 + 2\,H_2O \longrightarrow 5\,HIO \quad (8)$$

$$HIO + H_2SO_4 \longrightarrow H_2IO^+HSO_4^- \quad (9)$$

$$H_2IO^+ \longrightarrow I^+ + H_2O \quad (10)$$

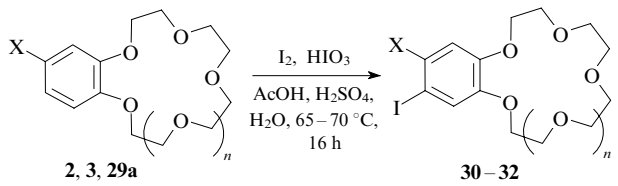
The iodinating agent is, most likely, the iodine cation [reaction (11)].

$$Ar-H + I^+ \longrightarrow Ar-I + H^+ \quad (11)$$

In the $I_2-HIO_3-H_2SO_4-AcOH$ system, the organic acid promotes the dissolution of HIO_3 and homogenization of the reaction mixture as a whole. In addition, acyl hypoiodite (AcOI) can also act as a iodinating agent.[62, 64] It should be noted that many of the modern concepts of iodination mechanisms of aromatic compounds are based on the works of the scientific school of Tomsk Polytechnic University. Such investigations are currently continued, and there is every reason to believe that the mechanism of the processes under consideration will be proved.

The iodination of BCEs was studied for the first time by Hyde *et al.*[69] Benzocrown ethers **2**, **3** and **29a** react with iodine in the presence of an oxidant (HIO_3) in a mixture of glacial AcOH and H_2SO_4 with water addition to give monoiodides **30**–**32**. Compound **32** is formed in 88% yield after long-term heating (65–70 °C, 16 h); for the other products, the yields have not been reported (Scheme 11). Later, the Hyde method has been used to produce iodinated BCEs on the preparative scale.

Scheme 11

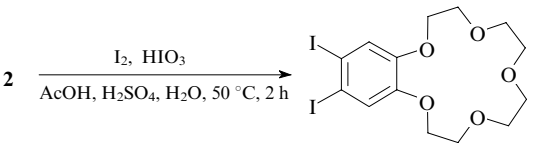


2, **3**, **29a** **30**–**32**

X = H: n = 1 (**2**, **30**), 2 (**3**, **31**); X = Me, n = 2 (**29a**, **32**)

Recently, Klyatskaya *et al.*[70, 71] have successfully modified this method, significantly decreasing the reaction duration (6–8-fold). The iodination was carried out by slowly adding I_2 and HIO_3 to a solution of BCEs in a mixture of 80% acetic and 30% sulfuric acids at 50–55 °C. It turned out that this reaction affords diiodo derivatives of not only BCEs but also DBCEs. For example, 4′,5′-diiodobenzo-15-crown-5 (**33**) is formed under these conditions in 75% yield (Scheme 12).

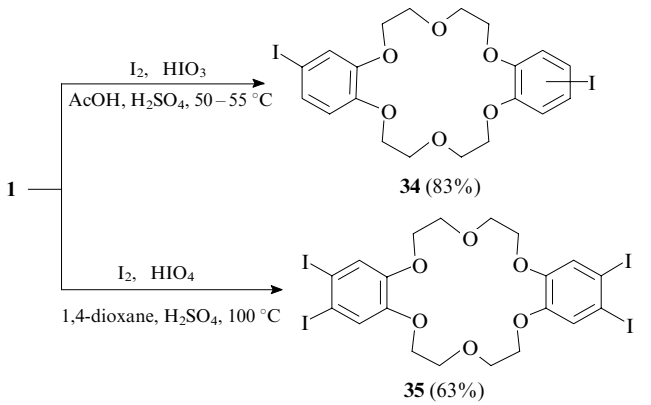
Scheme 12



33 (75%)

An analogous reaction converts compound **1** into diiodide **34** as a mixture of two geometric isomers; under more severe conditions in the presence of sodium periodate, the reaction yields tetraiodo derivative **35** (Scheme 13).[70]

Scheme 13

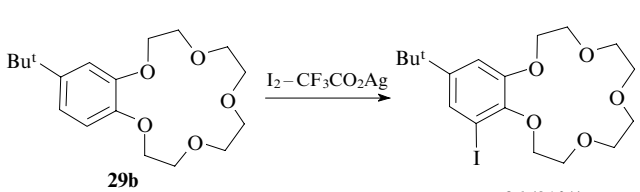


34 (83%)

35 (63%)

If the benzene ring of BCEs (for example, in compound **29b**) has a *tert*-butyl group in the 4-position, which is the most active in electrophilic substitution, the I^+ cation is directed to the *meta*-position to this substituent. The best results (yield of **36** of 81%) have been achieved with the use of an excess of the $I_2-CF_3CO_2Ag$ reagent (Scheme 14).[18] According to the authors, the iodinating agent is trifluoroacetyl hypoiodite forming *in situ*. The reaction of stoichiometric amounts of the reactants leads to a 9 : 1 oily mixture of the product and substrate, which cannot be separated even by column chromatography.

Scheme 14

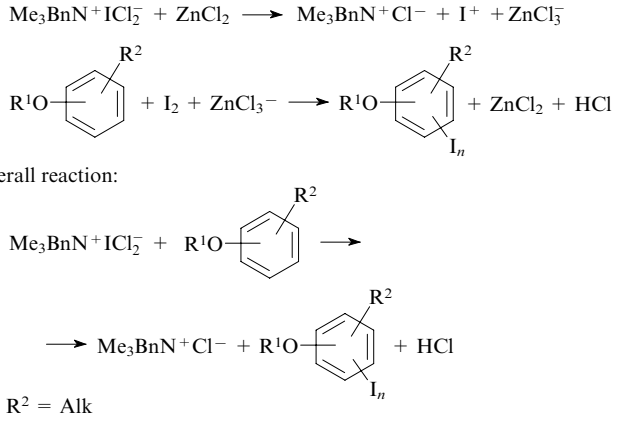


29b **36** (81%)

Benzyltrimethylammonium dichloroiodate(I) ($Me_3BnN^+ICl_2^-$, TMBADCI) is widely used for iodination of different phenol ethers.[72] This reagent is synthesized from benzyltrimethylammonium chloride and ICl. It is stable in the solid state and is easy to dispense. The

iodination of aromatic phenols with TMBADCI is carried out in the presence of anhydrous $ZnCl_2$ at 20 °C, whereas pure ICl is used, as a rule, at elevated temperatures in glacial AcOH. The probable reaction mechanism is shown in Scheme 15.

Scheme 15

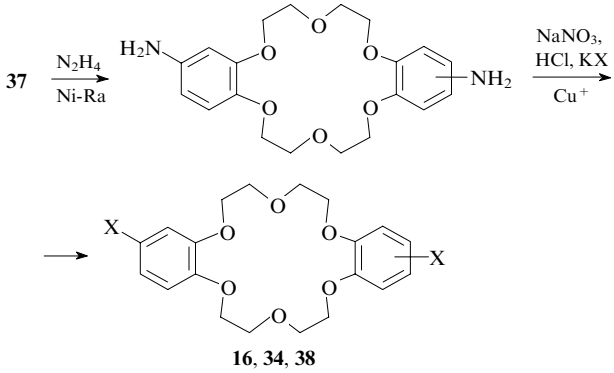


There is only one example of using TMBADCI for synthesis of an iodinated benzocrown ether:[73] monoiodide **31** has been synthesized from BCE **3** in 81% yield. However, no physicochemical characteristics of the product and proofs of its structure have been reported in Ref. 73 (as well as in Refs 74 and 75).

Noteworthy is the original method developed by Klyatskay *et al.*[70,71] for synthesis of individual isomers of diiodide **34**. The method is based on the considerable difference in solubility between the isomeric products of nitration of macrocycle **1** — 4′,4″-dinitro[3.3]dibenzo-18-crown-6 ('*cis*' isomer, **37**) and 4′,5″-dinitro[3.3]dibenzo-18-crown-6 ('*trans*' isomer, **37′**). These isomers (as distinct from the other known dinitro DBCE derivatives) have been obtained in the pure form by crystallization from DMF, reduced by hydrazine hydrate in the presence of a palladium catalyst, and the resulting diamino derivatives have been introduced into the Sandmeyer reaction (Scheme 16).

It has been recently reported that an analogous approach was used for synthesis of dichloro- (**38**), dibromo- (**16**) and diiodo-substituted (**34**) DBCEs (Scheme 17).[76] However, the yields of the products have not been reported.

Scheme 17



Ni-Ra is Raney nickel; X = Cl (**38**), Br (**16**), I (**34**)

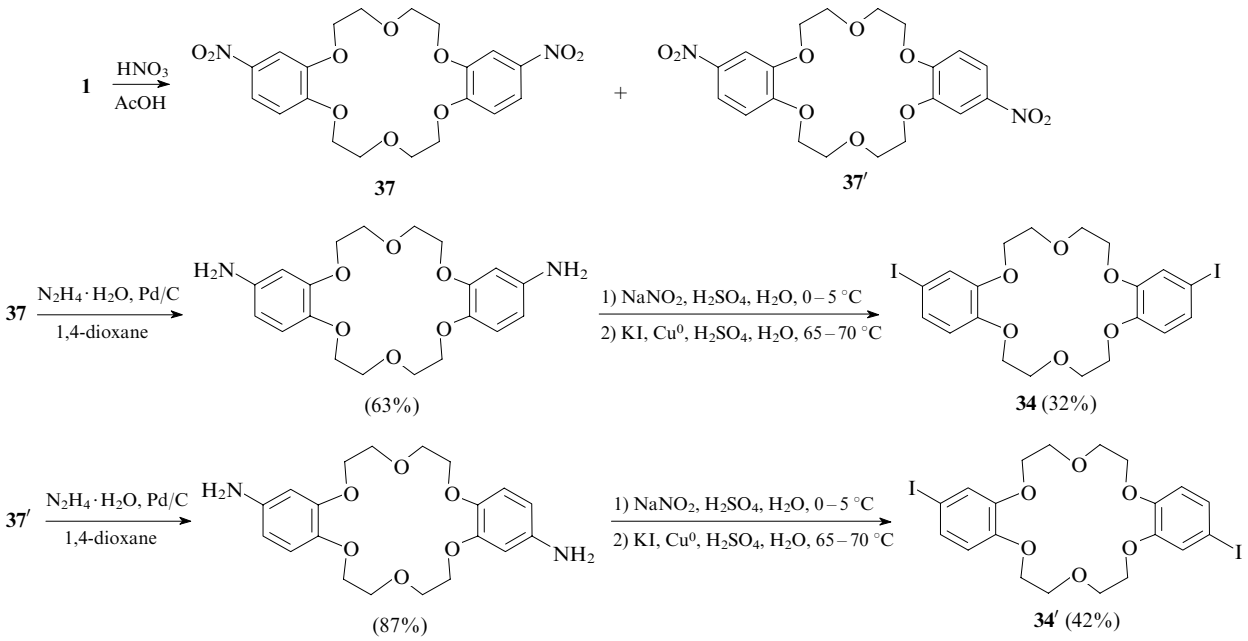
A mixture of isomers **37** containing 78% of the *cis* form was used as the initial compound. Therefore, mixtures of products **16**, **34** and **38** enriched in *cis* isomers have been actually produced.

Thus, molecular iodine in the presence of strong oxidants or expensive exotic reagents have been most frequently used for iodination of BCEs and DBCEs. At the same time, rather available compounds, such as *N*-iodosuccinimide (NIS),[77–79] iodine chloride, hypoiodites *etc.*, have not been used in this reaction before our studies.

II.2. Halogenation with *N*-halosuccinimides in different media

The above procedures of nonselective halogenation of BCEs and DBCEs with molecular chlorine, bromine and iodine

Scheme 16



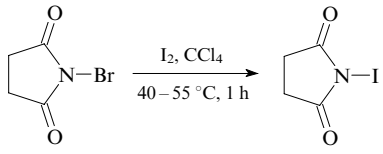
can hardly be considered as a general usable method of synthesis of a wide variety of HBCEs suitable for further transformations. That is why we have focused our attention on *N*-halosuccinimides (NHSs) — rather stable, available and easy-to dispense crystalline compounds. To the best of our knowledge, no examples of using *N*-chlorosuccinimide (NCS) and NIS for halogenation of BCEs and DBCEs are available, although using *N*-bromosuccinimide (NBS) for these purposes is known.[80,81]

By their properties, NHSs are close to *N*-haloimides of carboxylic and sulfonic acids since they contain the reactive halogen atom readily eliminated in the presence of water to give hypohalogenous acid HOHal. Owing to these properties, NHSs are used as mild halogenating agents or oxidants.[82–94]

In nonaqueous aprotic media (for example, in CCl_4), NCS and NBS halogenate alkenes through a radical pathway at the allyl position, while the double bond remains intact (Wohl–Ziegler reaction); for alkylarenes, the halogenation occurs at the side chain. In the presence of protic or aprotic acids, NHSs halogenate the aromatic nucleus of aromatic and heteroaromatic compounds basically by the ionic mechanism. In protic solvents (alcohols or acetic acid), the NHS reaction with alkenes leads to α-bromoesters.

It is worth noting that NCS and NBS are relatively available: at the moment of writing this review, the price of reagent grade NCS and NBS in the catalogues of largest chemical companies was 100–150 EUR per kg. At the same time, NIS, used for iodination of aldehydes, ketones, alkenes and aromatic compounds,[92,94,95] is essentially more expensive (530–650 EUR per 100 g) than the chloro- and bromo-containing analogues. A common method of synthesis of NIS, consisting in the reaction of iodine with silver succinimide,[78] is rather expensive. It has been reported that NIS with a purity no worse than 97%–98% is smoothly obtained in good yield by short-term heating of equimolar amounts of technical grade NBS and iodine in CCl_4 (Scheme 18).[79]

Scheme 18



It should be noted that pure NBS almost does not enter into the exchange reaction (see Scheme 18). The substitution of a bromine atom for the chlorine atom in NCS under analogous conditions also fails. The above method of synthesis of NIS extends its possibilities of use. It is a good electrophilic agent for iodination of aromatic systems.[96]

II.2.a. Solid-phase halogenation

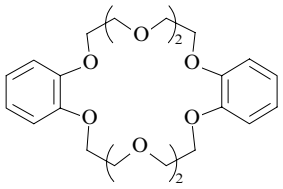
The major trend in the development of modern organic synthesis is to search for solvent-free procedures,[97] which makes it possible to develop technologies radically distinguished from conventional methods by environmental and engineering safety and efficiency. The replacement of liquid methods by dry procedures that do not require solvents and their subsequent removal and regeneration is important for synthesis of complexes and other compounds, which meets the green chemistry conditions.

Mechanochemistry — a currently rapidly developing area of modern chemistry — studies processes induced by mechanical activation of solid mixtures. Mechanical treatment enhances the reactivity of solid compounds and promotes chemical reactions between the components, and the solid-phase reaction itself proceeds during mechanochemical treatment.[98–101] These processes lead to the formation of a new phase, and specific features of its formation dictate the reaction course. It is known that mechanochemical treatment initiates new phase transitions and leads to accumulation of different structural defects. According to modern concepts,[99–101] it is precisely these processes that are responsible for the sharp increase in the reactivity of a solid compound and its transformations.

For electrophilic aromatic halogenation, there are a few examples of efficient solvent-free reactions. We can mention the solid-phase iodination of arenes with tetramethylammonium dichloroiodate(I) ($Me_4N^+ICl_2^-$) or iodine in the presence of bismuth nitrate,[102,103] as well as with ICl, phenyliodosoacetate and NIS.[95] The solid-phase synthesis of the known drug 4-iodoantipyrine with the use of tetraalkylammonium dichloroiodate(I) has been reported.[104]

We have pioneered the use of mechanochemical activation (method A) for solvent-free halogenation of BCEs and DBCEs.[105,106] The solid-phase reaction with NHS has been carried out not only with BCEs **2**, **3** and **9**, but also with DBCEs **1** and **39**.

Structure 39



39

(It should be noted that we are not aware of other examples of using mechanochemical treatment (activation) in synthesis and functionalization of crown ethers.)

The process was carried out in a sealed electromechanical vibrating mortar at fixed vibration time and amplitude, which made it possible to correctly reproduce experimental results obtained with thoroughly purified crown ethers and halosuccinimides. For all BCEs under consideration, the reaction of equimolar amounts of the reactants does not lead to complete substitution and gives mixtures of 4′-substituted and 4′,5′-disubstituted HBCEs.

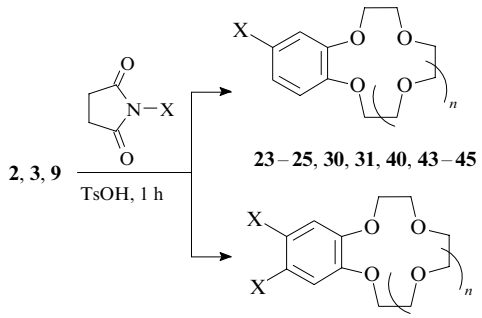
The reactivity of DBCEs **1** and **39** towards NHSs taken in a two- or fourfold excess is different over a period of time of 1–4 h. The largest conversion (leading to the formation of a mixture of mono- and dibromo derivatives) has been observed only in the case of NBS. The reaction with NCS and NIS gives a mixture of starting DBCEs, monosubsituted HBCEs and trace amounts of dihalogenated derivatives. For example, NIS almost does not iodinate 18-membered DBCE **1**, while 24-membered macrocycle **39** completely reacts under these conditions to give an inseparable mixture of mono-, di- and triiodides. We have studied the effect of different solid additives (Al_2O_3, silica gel, activated carbon, solid organic acids, *etc.*) on the conver-

sion of the substrate and the process selectivity. In some cases, an increase in conversion has been observed.

The best results have been achieved with addition of *p*-toluenesulfonic acid monohydrate (TsOH), which was previously already used in solid-phase aromatic halogenation.[95] Under the experimental conditions (20 °C, 1–2 h), TsOH does not react with NHSs; only after the reaction with NCS in the absence of another substrate for 4 h, mass spectrometry has detected insignificant amounts of aromatic chlorination products.

In the presence of TsOH, compounds **2**, **3** and **9** rapidly (in 1 h) and selectively react with NHSs to give, depending on stoichiometry (BCE : NHS = 1 : 1 or 1 : 2), 4′- or 4′,5′-substituted products, respectively (method A, Scheme 19). The bromination and iodination of these BCEs by method A gives bromides **23**–**25** and iodides **30**, **31** and **40**, as well as dihalides **4**, **27**, **28**, **33**, **41** and **42** of acceptable purity in good yield.

Scheme 19



Substrate	*n*	X	NHS quantity /equiv.	Product	Yield (%)
9	1	Br	1	**23**	91
2	2	Br	1	**24**	95
3	3	Br	1	**25**	92
9	1	Br	2	**28**	89
2	2	Br	2	**4**	94
3	3	Br	2	**27**	90
9	1	I	1	**40**	90
2	2	I	1	**30**	95
3	3	I	1	**31**	93
9	1	I	2	**41**	94
2	2	I	2	**33**	87
3	3	I	2	**42**	93
9	1	Cl	1	**43**	71
2	2	Cl	1	**44**	80
3	3	Cl	1	**45**	70
9	1	Cl	2	**11**	22
2	2	Cl	2	**46**	16
3	3	Cl	2	**47**	31

We have pioneered the selective monochlorination of BCEs to give products **43**–**45**. However, at BCE : NCS = 1 : 2, the reaction gave a mixture of chloro derivatives, and fractional crystallization of this mixture afforded the isolation of only dichlorides **11**, **46** and **47** in 16%–31% yield. Except these compounds, no products of alternative halogenation of BCEs have been detected by mass spectrometry and thin layer chromatography (TLC), which considerably simplifies purification of the target compounds.

Thus, the in-principle possibility of using mechanochemical activation for solid-phase synthesis of HBCEs has been demonstrated.

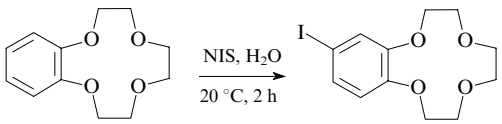
II.2.b. Halogenation in an aqueous medium

We have studied the reaction of BCEs with NHSs in an aqueous medium in the absence of oxidants and mineral acids.[105, 107] Let us recall that compounds **2**, **3** and **9** readily form ~3%–5% aqueous solutions, which makes it possibly to carry out the reaction under homogeneous conditions. Other examples of BCE halogenation in aqueous solutions are absent in the literature.

It is known that NHSs in an aqueous medium are hydrolyzed to succinimide and corresponding hypohalogenous acids (HOHal) exhibiting oxidative and halogenating properties.[98, 108] The oxidative iodination with hypoiodites formed *in situ* is one of the widely used methods of introduction of an iodine atom into phenols, naphthols, aromatic hydroxycarboxylic acids and some heterocycles.[109, 110]

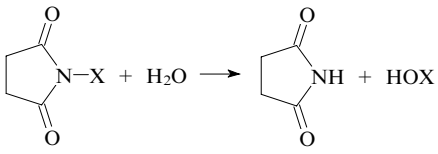
Adding thoroughly ground solid NIS to an aqueous solution of crown ether **9** (1 : 1) at 20 °C in 15 min leads exclusively to corresponding 4′-iodo derivative **40** (method B, Scheme 20).[105, 107]

Scheme 20



By analogy with the reported data,[83, 84, 96] we can assume that the iodination of BCEs follows a pathway involving NIS hydrolysis in an aqueous solution to the HOI acid (Scheme 21 for X = I), which then enters into the reaction of oxidative iodination of the substrate. Halogenation of other BCEs occurs in a similar way to give the corresponding monohalo derivatives.

Scheme 21



X = Cl, Br, I

The possibility of formation of the I^+ cation upon dissociation of weak acid HOI in dilute solutions as a weak base [reaction (12)][83]

$$HOI \rightleftharpoons OH^- + I^+ \qquad (12)$$

is not considered since all reaction mixtures after the end of reaction have pH ~2.8–3.5, according to potentiometric data.

Compounds **30** and **31** have been obtained from crown ethers **2** and **3** in a similar way (in 76%–84% yield). Iodinated derivatives **30**, **31** and **40** rapidly crystallize from an aqueous solution and are isolated merely by filtration. As a rule, after washing with water, solid residues do not

contain impurities of the initial crown ether or corresponding 4′,5′-diiodide. In most cases, crystallization of the products from organic solvents (usually, a mixture of n-hexane and n-heptane) is not necessary. The observed iodination selectivity is presumably caused by the low solubility of iodides **30**, **31** and **40** in water so that they are transferred from the solution to the solid phase and, thus, monohalogenated derivatives are not subjected to further iodination. It should be noted that different physicochemical methods (^{1}H NMR, mass spectrometry, TLC) have not detected diiodides **33**, **41** and **42** in the reaction mixture even at the ratio BCE : NIS = 1 : 4.

At the same time, crown ethers **2**, **3** and **9** at room temperature do not react with NCS, and their transformation into 4′-chloro derivatives **43**–**45** (yield 75%–83%) is observed only at 60 °C. NBS exhibits the highest reactivity in method B. Like the above reaction with NIS (see Scheme 20), the reaction of NBS with compounds **2**, **3** and **9** gives corresponding 4′-bromo derivatives **23**–**25** in 72%–86% yield.

Under the above conditions, the studied DBCEs do not react with NHSs, which is likely due to their much lower solubility in water as compared with BCEs.

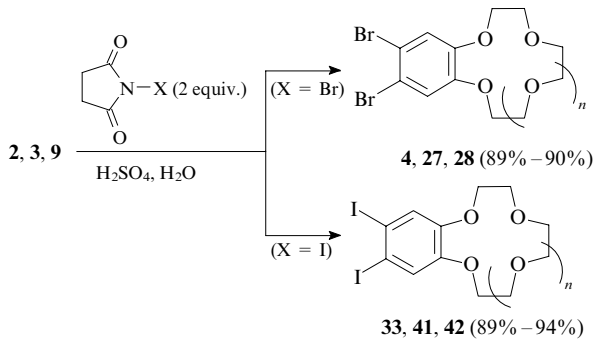
In our opinion, method B, along with solid-phase synthesis, is the simplest one among the methods described in the literature and offers many advantages: selectivity, versatility, simplicity, explosion and fire safety, as well as the ease of isolation of target products.

II.2.c. Halogenation in acidic aqueous media

Whereas the use of strong mineral acids for chlorination and bromination of aromatic compounds is not necessary, the iodination of arenes with NIS or *N*-iodoamides is strongly promoted in the presence of sulfuric or trifluoroacetic acid.[108]

We have found that the addition of NHSs to an aqueous solution of BCEs **2**, **3** and **9** containing catalytic amounts (1 drop) of concentrated H_2SO_4 has nearly no effect on the selectivity of the process and on the yield of target products.[105, 107] At the same time, the iodination of these compounds in an 18%–20% H_2SO_4 solution at the equimolar reactant ratio leads to a mixture of mono- and diiodides. Corresponding 4′,5′-diiodo derivatives **33**, **41** and **42** are obtained in high yield only at a twofold NIS excess (method C, Scheme 22).

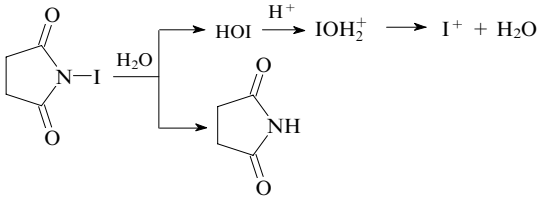
Scheme 22



n = 1 (**9**, **28**, **41**), 2 (**2**, **4**, **33**), 3 (**3**, **27**, **42**)

According to the known hypotheses (see, *e.g.*, Refs 62, 83 and 108), the presence of a strong mineral acid generally facilitates the formation of an electrophilic iodine cation in the reaction mixture (Scheme 23). However, similar assumptions should be taken with caution since the existence of such a cation as a kinetically independent species has been proved only in strong acid solutions,[62] although the lower concentration threshold of a mineral acid is still not determined.

Scheme 23



It is likely that monoiodides **30**, **31** and **40** are soluble in an H_2SO_4 solution (as in a strong acid aqueous medium) as adducts with hydroxonium ion,[111] which is responsible for their selective homogeneous iodination to diiodides **33**, **41** and **42**. This assumption is supported by the fact that compound **30** under the experimental conditions is smoothly iodinated with an equimolar NIS amount to diiodide **33**.

The reaction of BCEs with NBS occurs in a similar way and gives 4′,5′-dibromo derivatives **4**, **27** and **28** in high yield (up to 90%) (see Scheme 22).

As distinct from their bromo- and iodo-containing analogues, NCS under the described conditions at room temperature almost does not react with BCEs **2**, **3** and **9** (only traces of the products have been detected), while on heating, the reaction mixture starts noticeably resinifying. The same situation is also observed at elevated temperatures for the other NHSs.

As is known, hypohalogenous acids are unstable and can disproportionate by reaction (13).[112]

$$3\,HOX \longrightarrow 2\,HX + HXO_3 \qquad (13)$$

The rate of this reaction is low at room temperature and sharply increases on heating, especially for X = Br and I. The use of H_2SO_4 of relatively low concentration (18%–20%) presumably minimizes all possible side reactions. The necessity of neutralization of sulfuric acid after the end of reaction in order to maximize the product yield should be recognized to be a relative disadvantage of this procedure.

Inasmuch as elevated temperatures and acid media promote the side reaction of disproportionation of hypohalogenous acids, which leads to a decrease in the yield of the target product and its contamination with resins, halogenation should be carried out at temperatures as low as possible. *N*-Chlorosuccinimide is the worse reagent for BCE halogenation in an aqueous medium as compared with the other NHSs, since its hydrolysis in water to give noticeable amounts of hypochlorite begins only at 60 °C. In addition, under the same conditions, the resulting hypochlorite partially decomposes, which leads to contamination of the target product with resins, and in an acid medium at this temperature, the resulting hypochlorite decomposes faster than it reacts with BCEs.

It is worth noting that DBCEs **1** and **39** do not react with NHSs under similar conditions.

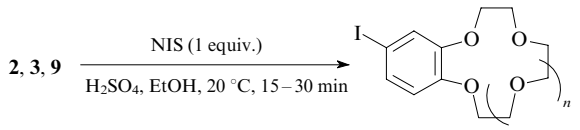
II.2.d. Iodination with *N*-iodosuccinimide in ethanol

It is known that superelectrophilic iodine capable of easily iodinating strongly deactivated arenes readily forms in H_2SO_4 from a mixture of iodine chloride and Ag_2SO_4 or 2,4,6,8-tetraiodo-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (tetraiodoglycoluril, TIG).[113–116] The iodine cation is generated exclusively in concentrated H_2SO_4 (90%–95%). Analogously, when dissolved in concentrated H_2SO_4, NIS forms a superelectrophilic iodine-containing intermediate iodinating nitrobenzene in 77%–79% yield at 20 °C in 20 min and at 0 °C in 90 min.[108]

However, compounds containing electron-donating groups (crown ethers, alkylbenzenes, aromatic amines, polycyclic hydrocarbons, *etc.*) cannot be successfully iodinated in concentrated H_2SO_4 since the iodination is accompanied by side reactions of protonation, resinification, sulfonation, *etc.*

We have developed a general method of selective iodination of both benzo- and dibenzocrown ethers (method D), which distinguishes it from methods A–C.[117] In particular, macrocycles **2**, **3** and 9 rapidly react with a stoichiometric amount of NIS in ethanol in the presence of H_2SO_4 to give 4′-iodo derivatives **30**, **31** and **40** in high yield (method D, Scheme 24).

Scheme 24

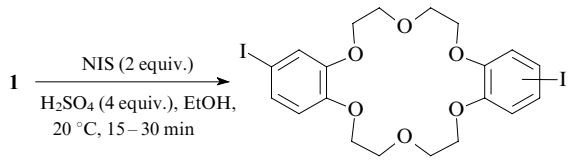


30, **31**, **40** (76%–86%)

n = 1 (**9**, **40**), 2 (**2**, **30**), 3 (**3**, **31**)

Under analogous conditions, the iodination of polyether **1** (DBCE : NIS = 1 : 2) leads to diiodide **34** as a mixture of *cis* and *trans* isomers (Scheme 25).

Scheme 25



34 (76%)

The reaction is carried out by stirring a reaction mixture at 20 °C for 15–30 min. The EtOH : H_2SO_4 (v/v) ratio is 10 : 1 for compounds **2**, **3** and **9** and ~15 : 1 for macrocycle **1**. It is worth noting that, as distinct from the above reactions, the reactivity of BCEs and DBCEs under the conditions of this experiment is roughly the same.

Since the reaction of a solvent with NIS is possible, we have initially used a 20%–25% excess of succinimide. However, over the short time it takes the reaction to complete, no ethanol oxidation is observed at room temperature.

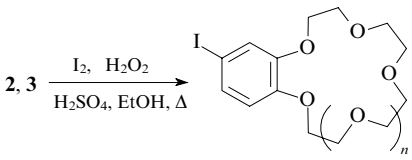
The suggested method of isolation of products **30**, **31**, **34** and **40** is rather simple, and neutralization of a solution and removal of the alcohol from the reaction mixture rule out the losses related to the solubility of products in water (in the protonated form) or in an aqueous alcohol medium.

The twofold increase in the NIS : substrate ratio affords mixtures of corresponding 4′-iodo- and 4′,5′-diiodo-substituted BCEs with a predominance of the former, and the reaction with macrocycle **1** gives diiodide **34** in ~70% yield with noticeable impurities of the starting compound and mono- and triiodides.

Recall that design of systems with the adjustable activity of electrophilic iodine tuned for definite groups of substrates is currently a topical problem of organic chemistry. The iodinating system described in this section has shown acceptable selectivity for iodination of both BCEs and DBCEs at room temperature for a short period of time.

We have also studied the iodination of crown ethers in the I_2–H_2O_2–EtOH–H_2SO_4 system at different temperatures and reactant ratios and concentrations (method E).[43] It has been demonstrated that, with the use of finely ground iodine, 30% aqueous hydrogen peroxide and concentrated H_2SO_4, macrocycles **2** and **3** are iodinated rather smoothly on heating to give the corresponding BCE monoiodides in modest yield (Scheme 26).

Scheme 26

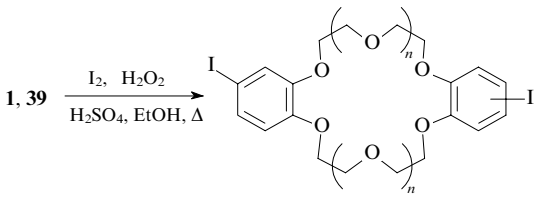


30, **31** (< 75%)

n = 1 (**2**, **30**), 2 (**3**, **31**)

The reactions with dibenzocrown ethers **1** and **39** under analogous conditions lead to diiodides **34** and **48** (Scheme 27). It should be noted that these reactions also give up to 10%–15% of impurities of alternative iodination products, which are separated in the course of purification.

Scheme 27



34, **48**

n = 1 (**1**, **34**; yield 66%), 2 (**39**, **48**; 70%)

A version of method E is also the iodination in the same system but in the absence of hydrogen peroxide. In this case, the reaction of BCEs **2** and **3** with thoroughly ground crystalline iodine leads to the monoiodides in up to 50%–60% yield; however, the content of impurities is considerably higher than in the previous case, which complicates the purification of target compounds and makes this method less acceptable.

II.2.e. Halogenation in halohydrocarbons

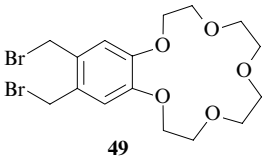
N-Bromosuccinimide is widely used in fine organic synthesis (see, *e.g.*, Refs 118 and 119) for allyl bromination of saturated hydrocarbons, unsaturated aliphatic and alicyclic compounds, polyolefins with isolated or conjugated double bonds, carbonyl compounds, steroids, and terpenes, as well as a broad spectrum of aromatic and heteroaromatic compounds.

Smid and co-workers[80] have pioneered the use of NBS for bromination of BCE **2**. It is a difficult task to assess the

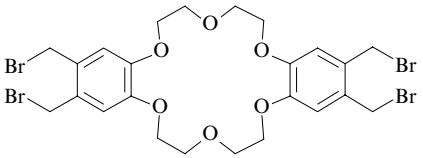
selectivity of the process carried out in boiling CCl_4 since 4′-bromo derivative **24** is formed in modest yield (57%). Later, the above procedure has afforded bromide **25** in 70% yield.[81]

Bromomethyl derivatives **49** and **50** were synthesized in 85% and 75% yield, respectively, by Biernat and co-workers[120] through the reaction of compounds **2** and **1** with paraform and a 36% HBr solution in AcOH. This procedure is currently conventional.

Structures 49, 50



49



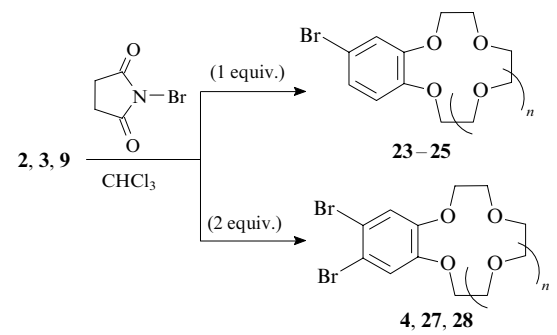
50

At the same time, tetrakis(bromomethyl)cavitands are synthesized in good yield (up to 80%) by the reaction of NBS with the corresponding tetramethylcavitands.[121]

We have compared the reactivities of BCEs and DBCEs in halogenation reactions with *N*-halosuccinimides in chloroform (method F) and have revealed significant differences.[43, 105, 122]

When NBS of technical grade (Acros Organics, orange crystalline powder with mp 175–178 °C) is used, BCEs **2**, **3** and **9** are selectively brominated to the corresponding mono- (**23**–**25**) or dibromides (**4**, **27** and **28**), depending on the stoichiometry (method F, Scheme 28). The yields of the products are 76%–93%.

Scheme 28

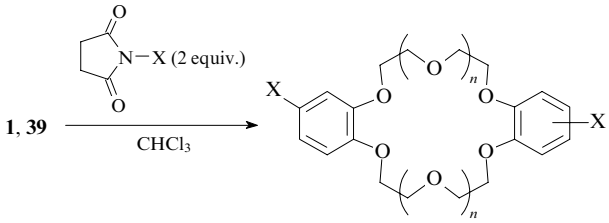


2, 3, 9 → (1 equiv.), $CHCl_3$ → **23**–**25**; (2 equiv.), $CHCl_3$ → **4, 27, 28**

n = 1 (**9**, **23**, **28**), 2 (**2**, **4**, **24**), 3 (**3**, **25**, **27**)

The bromination of polyether **1** proceeds much more readily (without heating in 15–30 min) when it reacts with solid NBS of technical grade at 20 °C. On heating, the reaction of thoroughly purified NBS with macrocycle **1** is 1.5–2 times slower but gives product **16** in nearly the same yield (~90%) (Scheme 29). (It should be noted that halogenated derivatives **51** and **52** have been synthesized from-crown ethers **1** and **39**, respectively, under analogous conditions.)

Scheme 29



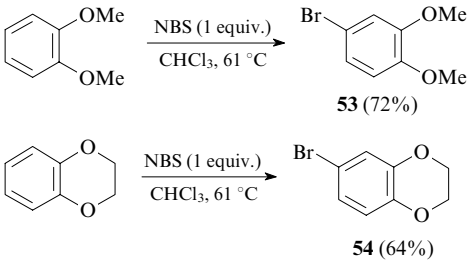
1, 39 → N–X (2 equiv.), $CHCl_3$ → **16, 51, 52**

X = Cl (**51**), Br (**16**, **52**); n = 1 (**16**, **51**), 2 (**52**)

When comparing the behaviour of technical grade and purified NBS in this reaction, it should be taken into account that the former contains impurities of Br_2 and HBr, the products of hydrolysis of bromoimide exposed to air moisture. It is known that HBr replaces Br_2 in the NBS molecule.[119] In addition, the H–Br and Br–Br bond cleavage in $CHCl_3$ can also be facilitated by complexation with a macrocycle. It is likely that these processes are responsible for the appearance of the reactive Br^+ cation, which triggers the fast bromination process. Hence, for the thoroughly NBS free of the above impurities, only the N–Br bond polarization is possible, which accounts for the differences in reactivity of succinimides of different grades of purity.

This assumption is supported by the bromination of formal benzocrown analogues — acyclic (1,2-dimethoxybenzene) and cyclic ('benzo-6-crown-2', 2,3-benzo-1,4-dioxane). The bromination of these compounds with NBS (both of technical grade and purified) under the given conditions to form 4-bromobenzenes **53** and **54** occurs much more slowly than in the case of BCEs **1**–**3**, **9** and **39** (Scheme 30).

Scheme 30



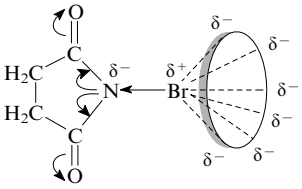
NBS (1 equiv.), $CHCl_3$, 61 °C → **53** (72%)

NBS (1 equiv.), $CHCl_3$, 61 °C → **54** (64%)

Thus, the NBS purity has an effect on the bromination rate of benzocrown ethers and is not important for the reaction with other compounds. The behaviour of the purified reagent enables the assumption that in the course of bromination the macrocyclic substrate increases the degree of polarization of the N–Br bond, which facilitates its cleavage.

Since the bromination follows an ionic mechanism,[83, 84, 119] let us recall that, as a result of σ,π-conjugation with a macrocycle (shown as the ring) in the transition state NBS$^{\neq}$, electron density can be strongly shifted from the bromine atom to the nitrogen atom so that the bromine atom acquires a partial positive charge.

Structure of NBS[≠]



The denticity of a crown compound presumably plays a certain role in its bromination with NBS in chloroform since hexadentate macrocycles **1** and **3** are most active in this reaction. At the same time, for octadentate macrocycle **39**, this effect is less pronounced: completion of the reaction requires heating, and dibromide **52** forms in 84% yield (see Scheme 29).

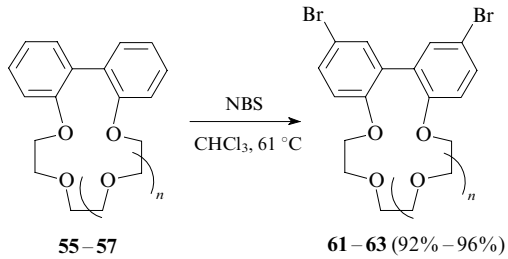
The strongest effect is observed in $CHCl_3$; in CCl_4, the bromination of BCEs with NBS, both of technical grade and purified, proceeds more slowly. Compound **1** reacts with NBS in CCl_4 for 1 h to transform into product **16** in ~85% yield (calculated for dibromide). However, the melting point of the resulting sample was 176–180 °C (for pure macrocycle **16**, m.p. 182–184 °C), and mass spectrometry detected mono-, tri- and even tetrabromides as impurities.

At the same time, mass spectrometry does not reveal side products resulting from the participation of the solvent in the reaction (*i.e.*, the products of the reaction of the solvent with the radicals generated in the course of homolytic dissociation of NBS). This fact is consistent with the known concepts (see Refs 119, 123 and 124) implying that free radicals of succinimidyl and bromine generated in the course of thermal dissociation of NBS are not reactive and do not react with solvents; however, this fact does not answer the question whether such dissociation occurs in this case.

Interesting objects for halogenation are proximal dibenzocrown compounds containing a biphenyl (**55**–**57**) or diphenyl oxide (**58**–**60**) moiety.

It has been demonstrated that the bromination of compounds **55**–**60**, as distinct from that of distal crown ethers **1** and **39** leading to mixtures of isomers, gives exclusively the products of substitution at the 5- and 4-positions of the aromatic moiety.[125] This fact has been proved by ^{1}H NMR, mass spectrometry and X-ray crystallography. In particular, under analogous conditions, [0.4]dibenzo-14-crown-4 (**55**), [0.5]dibenzo-17-crown-5 (**56**) and [0.6]dibenzo-20-crown-6 (**57**) give 5,5′-dibromo derivatives **61**–**63** in 92%–96% yield (Scheme 31).

Scheme 31

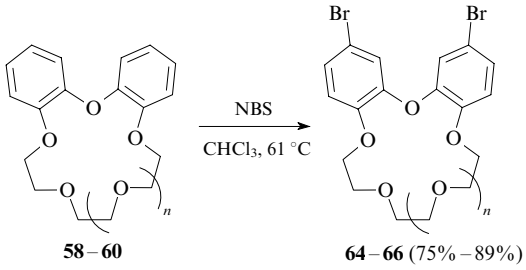


55–**57** **61**–**63** (92%–96%)

n = 1 (**55**, **61**), 2 (**56**, **62**), 3 (**57**, **63**)

The bromination of [1.4]dibenzo-15-crown-5 (**58**), [1.5]dibenzo-18-crown-6 (**59**) and [1.6]dibenzo-21-crown-7 (**60**) leads to 4,4′-dibromides **64**–**66** in 75%–89% yield (Scheme 32).

Scheme 32

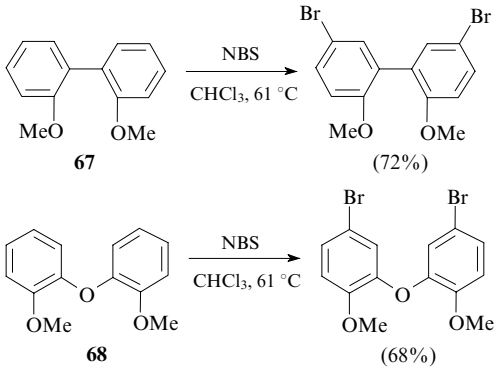


58–**60** **64**–**66** (75%–89%)

n = 1 (**58**, **64**), 2 (**59**, **65**), 3 (**60**, **66**)

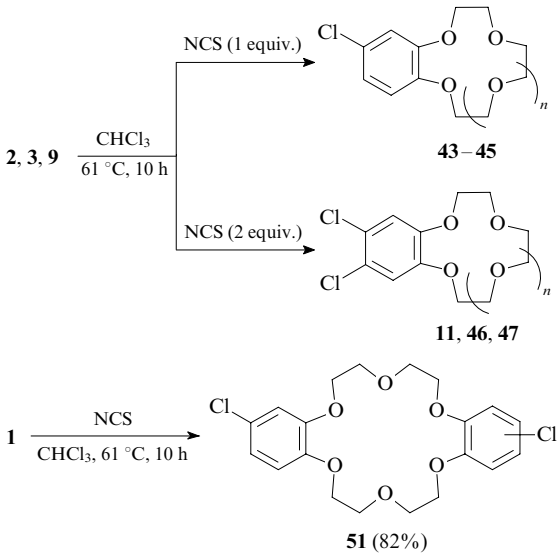
The fact that compounds **55**–**60** react with NBS 5–30 times faster than acyclic compounds **67** and **68** (Scheme 33) points to the possibility of formation, in such reactions, of a crown ether–NBS intermediate complex with the N—Br bond activated by the macrocycle. It is also worth noting that the bromination proceeds most readily in the case of hexadentate macrocycles.

Scheme 33



Long-term refluxing (8–10 h) turned out to be necessary for chlorination of macrocycles **2**, **3** and **9** with NCS (Scheme 34).[105]

Scheme 34

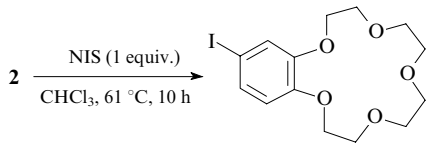


n = 1 (**9**; **43**, 23% yield; **11**, 27%), 2 (**2**; **44**, 41 %; **46**, 45%), 3 (**3**; **45**, 30%; **47**, 33%)

In particular, in addition to monochlorides **43**–**45**, the reaction mixture contained impurities of the initial compound and the corresponding dichloro derivatives. Pure target products **43**–**45** were isolated by fractional crystallization. Analogously, dichlorides **11**, **46** and **47** were synthesized in 27%–45% yield, and the long-term chlorination of compound **1** made it possible for the first time to synthesize dichloride **51** as a mixture of *cis* and *trans* isomers by direct chlorination (see Scheme 34). It should be noted that, according to TLC, substrate **1** is almost completely consumed even within 6–7 h of refluxing.

Radically different results have been obtained for the iodination reaction under analogous conditions.[105] Low conversion under the action of NIS in chloroform has been observed for all BCEs; however, even after the long-term heating of the reaction mixture, the maximal yield of the product (30%) has been achieved for iodide **30**, while the formation of diiodide has not been observed (Scheme 35).

Scheme 35



30 (23%)

It is worth noting that, under these conditions, conversion of DBCEs is also low, and individual products are not isolated.

Thus, there are essential differences in the reactivity of *N*-halosuccinimides in their reactions with BCEs and DBCEs in halohydrocarbons, for example, in $CHCl_3$. Whereas the bromination reaction can be recommended as a convenient selective method of synthesis of corresponding mono- and dibromo derivatives, chlorination smoothly proceeds only for DBCEs, and iodination is inefficient at all.

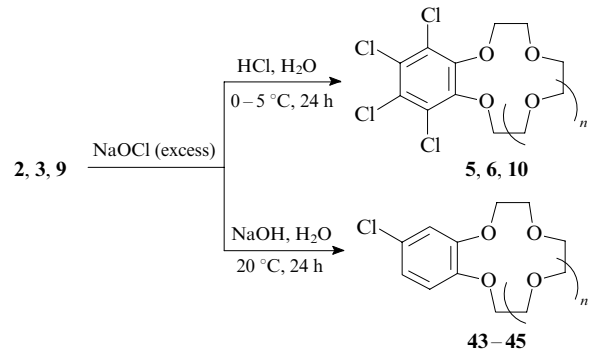
II.3. Halogenation with hypohalites in aqueous solutions

Experimental data reported in Sections II.2.a–d allow us to assume that the halogenating agents for BCEs in aqueous solutions are hypohalites formed by hydrolysis of NHSs. Therefore, it is reasonable to use aqueous solutions of easily available hypochlorites and hypobromites for halogenation of BCEs in aqueous solutions.[126]

It has been revealed that sodium hypochlorite (NaOCl) can be used as a mild and selective agent for chlorination of BCEs in aqueous solutions. In particular, compounds **2**, **3** and **9** are readily chlorinated by NaOCl taken in a threefold excess at 20 °C for 24 h in an aqueous alkaline solution (pH 10). The reaction leads to 4′-chlorides **43**–**45** containing insignificant impurities of the initial BCEs and traces of the corresponding dichlorides. Chlorides **43**–**45** are almost insoluble in an aqueous alkaline solution, rapidly crystallize, and become inaccessible for further attack of the chlorinating agent.

BCEs have been successfully chlorinated with sodium hypochlorite in a strongly acidic solution. The reaction is carried out by carefully adding an NaOCl solution to a solution of BCEs in concentrated hydrochloric acid. Our experimental data are consistent well with the aforementioned lability of hypochlorites in an acidic medium at elevated temperatures. At 55 °C, the reaction leads mainly to resinous chlorination products, from which dichlorides (**11**, **46**, **47**) and monochlorides (**43**–**45**) are isolated in a ~3 : 1 ratio in low yield by crystallization. If a solution of NaOCl is added to a solution of BCEs in hydrochloric acid at room temperature without cooling the reaction mixture, the latter warms up to 40 °C. In this case, sticky crystalline products are formed, from which dichlorides (**11**, **46**, **47**) and monochlorides (**43**–**45**) are isolated in a 10 : 1 ratio by fractional crystallization. Preliminary cooling of a BCE solution in HCl to 0 °C and careful addition of a cooled NaOCl at a rate at which the temperature of the reaction mixture does not exceed 5 °C lead to easily crystallizable compounds. However, contrary to expectation, the reaction does not lead to dichlorides; rather, it gives products with a perchlorinated aromatic nucleus of BCEs — 3′4′,5′,6′-tetrachlorides **5**, **6** and **10**. Thus, the optimal reaction conditions — an excess of NaOCl in HCl (pH < 1), 0–5 °C, 24 h — are necessary for hypochlorite to realize its chlorinating potential (Scheme 36).

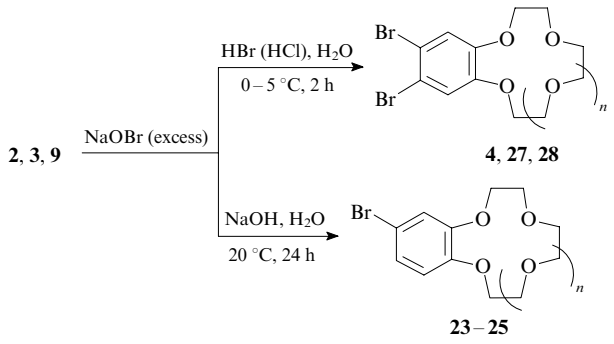
Scheme 36



n = 1 (**9**; **43**, yield 63%; **10**, 48%), 2 (**2**; **44**, 75%; **5**, 45%), 3 (**3**; **45**, 75%; **6**, 76%)

It has been revealed that sodium hypobromite (NaOBr) is also a selective reagent for bromination of BCEs in an aqueous solution. In particular, compounds **2**, **3** and **9** are readily brominated (substrate : NaOBr = 1 : 3, 20 °C, 24 h) in water to form corresponding 4′-bromides **23**–**25**, which contain traces of dibromides. However, NaOBr is a more reactive and more selective reagent as compared with NaOCl. This is supported by the fact that the use of NaOBr in HBr under similar conditions (pH < 1, 0–5 °C,

Scheme 37



n = 1 (**9**; **23**, 72% yield; **28**, 84%), 2 (**2**; **4**, 45%; **24**, 80 %), 3 (**3**; **25**, 80%; **27**, 82%)

2 h) affords exclusively dibromides **4**, **27** and **28**, while the corresponding tetrabromides do not form (Scheme 37).

It is known that, as distinct from hypochlorites and hypobromites, hypoiodites are very unstable in aqueous solutions.[112] Dissolving iodine in aqueous sodium hydroxide even at temperatures close to the freezing point of the solution immediately leads to a mixture of sodium iodide (NaI) and iodate ($NaIO_3$). Attempts to obtain iodinated BCEs through careful addition of iodine to a cooled alkaline solution of a crown ether always lead to the isolation of the starting compound. At the same time, as shown above, hypoiodites generated *in situ* from NIS successfully iodinate BCEs to iodides in aqueous solutions.

In iodination of aromatic compounds with iodine, mercury oxide is often used.[127] It acts as an oxidant and an agent that binds iodide forming in the equilibrium reaction and, thus, favours the accumulation of hypoiodite. This system turns out to be suitable for iodination of BCEs as well. In particular, within 24 h after the addition of crystalline iodine to a suspension of mercury oxide in an aqueous solution of benzocrown ether **2** at room temperature, iodide **30** was isolated from the reaction mixture in 52% yield. Mercury oxide can be easily regenerated by treating the resulting mercury iodide with an alkali solution.

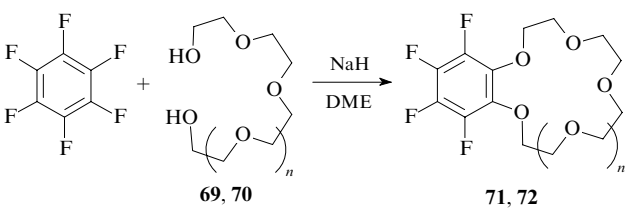
Thus, the suggested pH-controlled methods of halogenation of BCEs with hypohalites in an aqueous medium are available, fire-safe and rather simple. Changing the acidity of a medium in these processes makes it possible to control the number of halogen atoms in the aromatic moiety of BCEs. It has been demonstrated that elemental iodine can be in principle used in an aqueous medium for iodination of BCEs with hypoiodites forming *in situ*. The above-mentioned low solubility of DBCEs in water prevents the synthesis of their halides by this method. However, the solubility of DBCEs can be improved by selecting a combination of solvents miscible with water so that the former enter into this reaction.

II.4. Synthesis of halogenated benzocrown ethers by the 'assembly' method

It has been noted in the Introduction that, for synthesis of fluorinated BCEs, these macrocycles are constructed from the corresponding acyclic blocks. Since the fluorine atom is much more mobile than chlorine and bromine atoms in the reactions of nucleophilic aromatic substitution, dinucleophiles should react with perfluoroaromatic compounds to form crown compounds.

In particular, stirring a mixture of hexafluorobenzene and tetra- (**69**) or pentaethylene glycol (**70**) in 1,2-dimethoxyethane (DME) at room temperature in the presence of sodium hydride leads to tetrafluorobenzocrown ethers **71** and **72** (Scheme 38).[37]

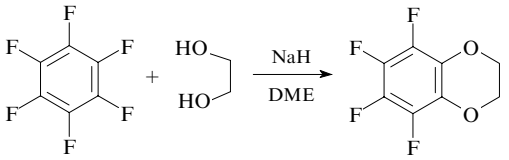
Scheme 38



n = 1 (**69**; **71**, yield 37%), 2 (**70**; **72**, 45%)

However, an analogous derivative of crown ether **9** (n = 0) was not obtained by this method (under the action of NaH or Bu^nLi, only one fluorine atom was substituted), although the formation of tetrafluorobenzo-1,4-dioxane was observed for ethylene glycol (Scheme 39).

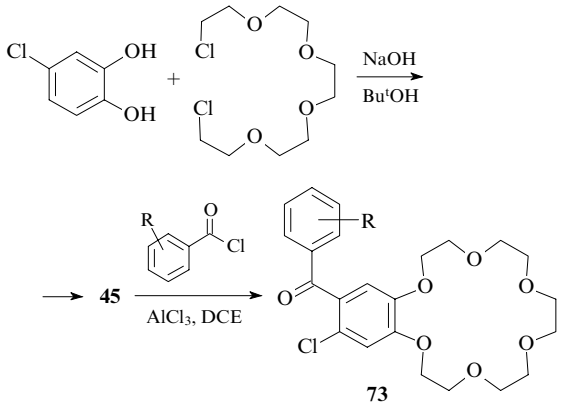
Scheme 39



Fluorine-containing BCEs have been studied as extractants of alkali metal picrates in the methylene chloride–water system.[37]

In some cases, BCE chlorides have been synthesized from chloropyrocatechol and oligo(ethylene glycol)s or their derivatives. The synthesis of compound **44** by the Pedersen method has been described:[41] long-term (30 h) refluxing of 4-chloropyrocatechol with 1,11-dichloro-3,6,9-trioxaundecane in the presence of NaOH in n-butanol leads to the product in 55% yield. An analogous method of synthesis of macrocycle **45** as the initial compound for synthesis of biologically active crown ethers **73** has been patented (Scheme 40).[128, 129]

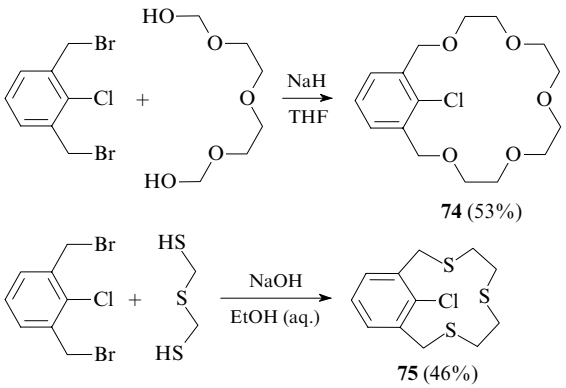
Scheme 40



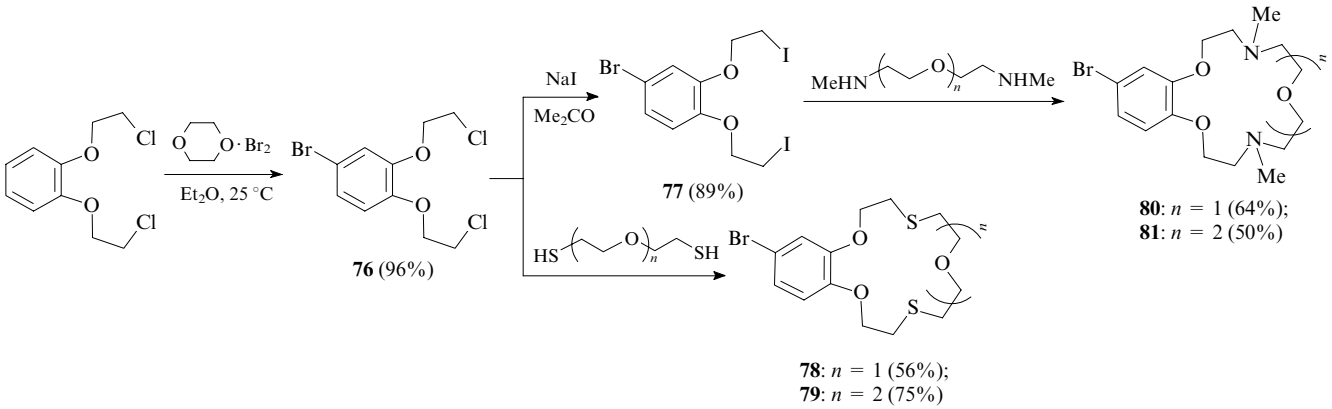
R = 2-Me, 2-F, 2-Cl, 4-Me, 4-F, 4-Cl, 3-F, 3-Br;
DCE is 1,2-dichloroethane

Other macroheterocycles containing a chlorine atom in the benzene ring (for example, compounds **74**, **75**) have also been synthesized from the corresponding reagents.[130–135] In

Scheme 41



Scheme 42

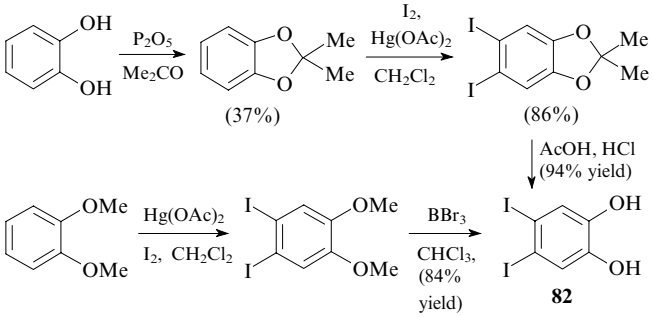


addition to the classical Pedersen method, the cyclization has been carried out under high dilution conditions, using sodium hydride as a base (Scheme 41).

Gromov *et al.*[136] tried to use DDB for bromination of crown ether heteroanalogues. However, it turns out that, under such conditions, the reaction mixture is strongly resinified. At the same time, cyclization of 4-bromo-1,2-bis(2-chloroethoxy)benzene (**76**) and 4-bromo-1,2-bis(2-iodoethoxy)benzene (**77**) with polyoxaalkanes containing terminal containing terminal SH and NHMe groups leads to bromo derivatives of thia- and azacrown ethers — macrocycles **78**–**81** — in satisfactory yield (Scheme 42).

The alternative 'assembly' of such compounds is a multistage and complex process, which has been clearly demonstrated by Pak *et al.*[137] From 4,5-diiodopurocatechol (**82**), prepared by two methods from pyrocatechol (Scheme 43), the authors have synthesized 4′,4″,5′,5″-tetraiodo[4.4]dibenzo-24-crown-8 (**83**) (Scheme 44).

Scheme 43



It is worth noting that some of intermediate products have been isolated in the individual form by means of column chromatography.

Thus, the laborious method of assembly of HBCEs is still relevant when direct halogenation of benzocrown compounds cannot be applied for some reasons.

III. Reactions of halogenated benzo- and dibenzocrown ether derivatives

III.1. Synthesis of phosphorus-containing crown compounds

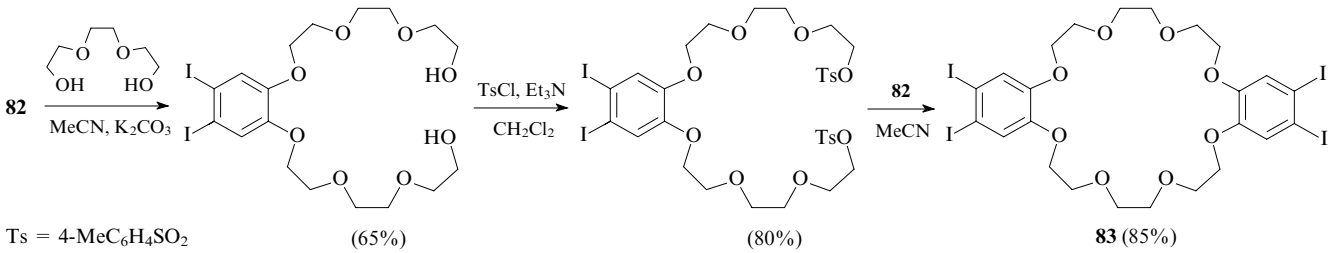
Phosphorus-containing aromatic crown ethers (PCEs) are promising from the practical point of view since exocyclic P-substituents can significantly increase the selectivity of complexation due to the cooperative interaction with donor heteroatoms of the macrocycle.[138] Such compounds have become available precisely due to the use of bromo and iodo derivatives of BCEs and DBCEs as initial compounds for the phosphorylation reaction since numerous attempts to produce them by direct phosphorylation of unsubstituted benzocrown compounds failed.

The chemistry of PCEs originated in the 1980s in pioneering investigations of the Kiev school of organic chemists headed by Academician of the National Academy of Sciences of Ukraine L N Markovskii and Corresponding Member of the National Academy of Sciences of Ukraine V I Kal'chenko.[138] The introduction of phosphoryl substituents into benzene rings of BCEs to form a $P-C_{arom}$ bond is based on the $NiBr_2$ -catalyzed reaction of BCE and DBCE bromides with trialkyl phosphites (the Arbuzov reaction).[139, 140]

In particular, the reaction of dibromide **16** (a mixture of the *cis* and *trans* isomers) with trialkyl phosphites in the presence of 10 mol.% – 15 mol.% of anhydrous $NiBr_2$ gives corresponding 4,4′(5′)-dialkoxyphosphoryl[3.3]dibenzo-18-crown-6 derivatives **84** (Scheme 45).[141]

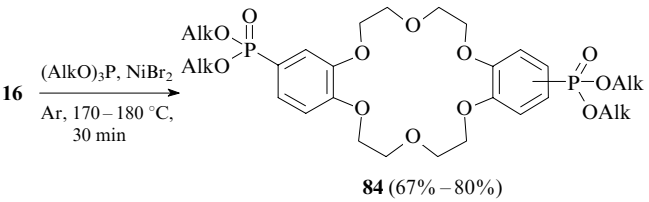
Individual isomers have been isolated by fractional crystallization. Some of them have been characterized by X-ray crystallography.[142]

Scheme 44



Ts = 4-$MeC_6H_4SO_2$

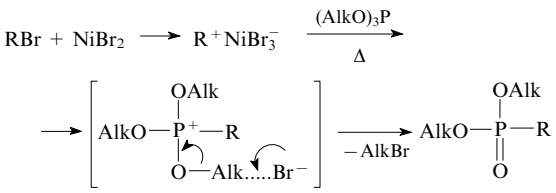
Scheme 45



84 (67%–80%)

The putative reaction mechanism, described, for example in Refs 139 and 140, is presented in Scheme 46.

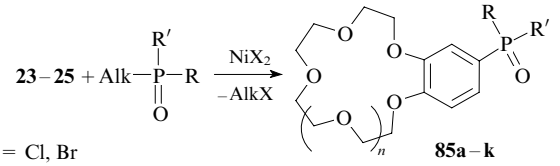
Scheme 46



R is crown ether moiety

Later, the range of HBCEs introduced into the phosphorylation reaction has been considerably extended.[143–147] For example, for BCE monobromides **23**–**25**, different phosphonates, phosphonites and phosphinites in the presence of nickel chloride or bromide have been used as phosphorylating agents (Scheme 47).

Scheme 47



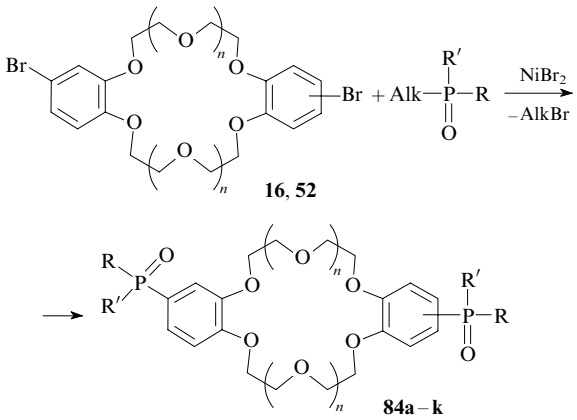
X = Cl, Br **85a**–**k**

Substrate	Product **85**	*n*	R	R′	Yield (%)
23	**a**	0	EtO	EtO	49
23	**b**	0	Bu^nO	Bu^nO	52
23	**c**	0	Ph	Ph	52
23	**d**	0	Ph	Pr^iO	63
24	**e**	1	EtO	EtO	65
24	**f**	1	Pr^nO	Pr^nO	72
24	**g**	1	Bu^nO	Bu^nO	33
24	**h**	1	Ph	Ph	50
24	**i**	1	Ph	EtO	44
24	**j**	1	Ph	Pr^iO	42
25	**k**	2	Ph	Pr^iO	47

DBCE dihalides, for example, compounds **16** and **52**, react under analogous conditions (Scheme 48).

An increase in reaction temperature or long-term heating reduce the yields of target products **84a**–**k**, **85a**–**k** because of polymerization of both HBCEs and PCEs. Maximal yields of PCEs **84** and **85** (R, R′ = Alk) have been achieved by using dialkyl phosphonates (see Schemes 45, 47, 48). With more nucleophilic phosphonites and phosphinites, the yields of PCEs decrease since they react with the forming alkyl halides. Substituents significantly reducing the nucleophilicity of trivalent phosphorus hinder the phosphorylation reaction.[143–147]

Scheme 48

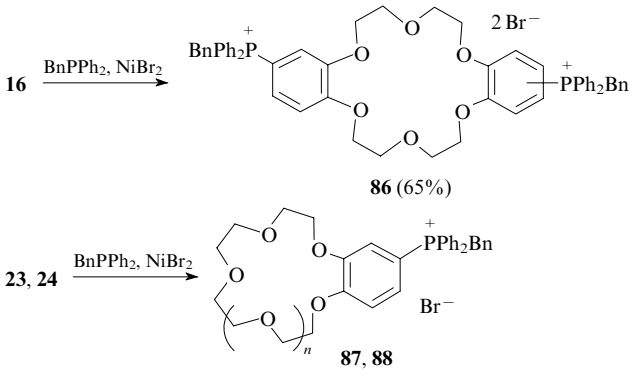


Substrate	Product **84**	*n*	R	R′	Yield (%)
16	**a**	1	EtO	EtO	73
16	**b**	1	Pr^nO	Pr^nO	80
16	**c**	1	Bu^nO	Bu^nO	72
16	**d**	1	Bu^n	Bu^n	30
16	**e**	1	Ph	Ph	66
16	**f**	1	Ph	EtO	53
16	**g**	1	Ph	Pr^iO	70
16	**h**	1	Pr^nO	$CHF_2CF_2CH_2O$	36
52	**i**	2	Pr^iO	Pr^iO	68
52	**j**	2	Ph	Ph	85
52	**k**	2	Ph	Pr^iO	47

It has been demonstrated that the possibility of using phosphorylating agents depends on their thermal stability. Because of dominating processes of isomerization, methyl esters of trivalent phosphorus acids, 2-dimethylamino-1,3,2-dioxaphosphorolane, triallyl phosphite, and butyl diphenylthiophosphinite do not react or form target products in low yield.

Even under severe conditions, triphenylphosphine reacts with BCE bromides very slowly, so that the reaction mixture accumulates polymerization products, which cannot be separated from the resulting phosphonates. Bromides **16**, **23** and **24** react much more readily with more nucleophilic benzyldiphenylphosphine to form corresponding benzyldiphenylphosphonium salts **86**–**88** (Scheme 49).[143]

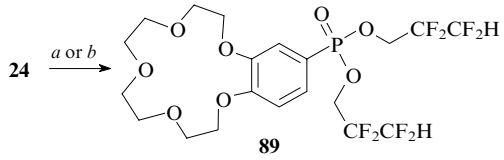
Scheme 49



n = 0 (**87**, 65% yield), 1 (**88**, 70%)

Macrocycles with acceptor substituents at the phosphorus atom have been synthesized by the Michaelis–Becker reaction catalyzed by metal salts.[148] It has been found that bromide **24** reacts with sodium bis(tetrafluoro-n-propyl) phosphite in the presence of an equimolar amount of Cu_2I_2 to give bis(tetrafluoro-n-propoxy)phosphoryl-benzo-15-crown-5 (**89**) in 20% yield (Scheme 50).

Scheme 50

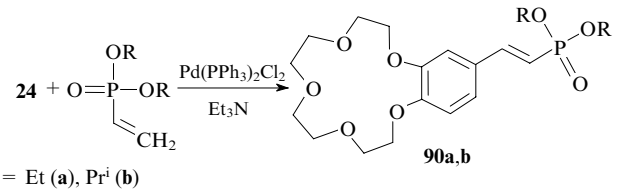


(*a*) $(HCF_2CF_2CH_2O)_2P(O)Na$, Cu_2I_2;
(*b*) $(HCF_2CF_2CH_2O)_2P(O)H$, $(Ph_3P)_4Pd$, Et_3N

The yield of product **89** builds up to 53% if a mixture of the corresponding phosphite, triethylamine and the catalyst — tetrakis(triphenylphosphino)palladium — is used instead of the sodium salt.

Markovskii and co-workers [144] accomplished palladium-catalyzed vinylation of bromide **24** with vinyl phosphonates under the Heck reaction conditions [149, 150] (Scheme 51). The target products — *meta*-(β -dialkoxyphosphorylvinyl) derivatives **90a** and **90b** were obtained in 40%–50% yield and isolated by column chromatography. Their structures has been proved not only by spectral methods but also by X-ray crystallography (for R = Pr^i).[151]

Scheme 51



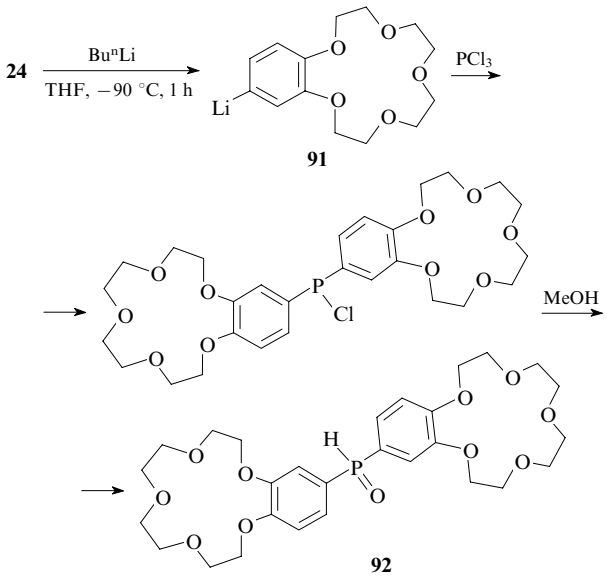
R = Et (**a**), Pr^i (**b**)

It should be noted that most of the described methods of phosphorylation of HBCEs are based on the reactions that occur with a change in the valence or configuration of the phosphorus atom in a reagent molecule. The approach suggested by Markovskii and co-workers [144] rules out similar transformations, which makes it possible to introduce even chiral phosphorus-containing groups into such reactions.

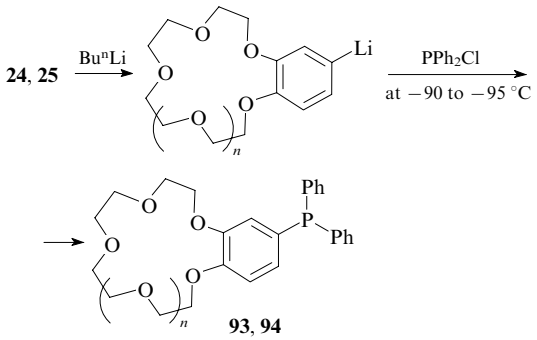
Markovskii and co-workers [152] have described the reaction of macrocycle **24** with n-butyllithium and cross-linking of the resulting lithium derivative **91** under the action of PCl_3 (Scheme 52). Treatment of the reaction mixture with methanol leads to bis(benzocrown)phosphine oxide **92** in 35% yield. The attempt to synthesize tris(crown ethers) by the same procedure by changing the stoichiometric reactant ratios failed.

It is worth noting that, under analogous very mild conditions, Okano *et al.*[57] have synthesized crown-containing phosphines **93** and **94** (Scheme 53). The authors underline that the yields of target products in this reaction strongly depend on the reaction temperature. In particular, at −78 °C, the yield of compound **93** did not exceed 30%.

Scheme 52



Scheme 53



n = 1 (**24**; **93**, yield 92%), 2 (**25**; **94**, 76%)

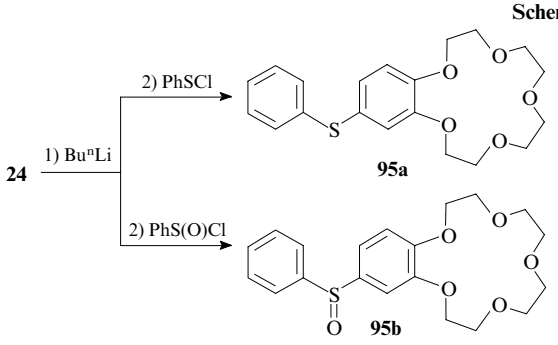
Physicochemical, complexing (including solubilizing) and ionophore properties of the synthesized macrocycles,[147, 152–154] as well as their spectral and proton-acceptor characteristics,[155] have been comprehensively studied.

III.2. Organometallic synthesis

Organometallic synthesis as an area of the chemistry of crown ethers has been developed largely because of the availability of HBCEs.

Using such an approach, Markovskii *et al.*[156, 157] have pioneered the synthesis of BCE **2** derivatives functionalized by coordinatively unsaturated phenylsulfanyl and phenylsulfinyl groups (Scheme 54).

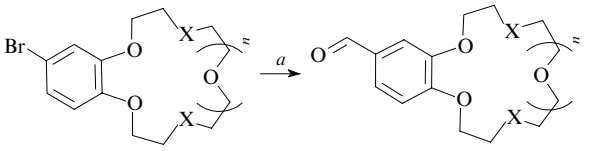
Scheme 54



Treatment with n-butyllithium of initial bromide **24** at −95 °C generates the corresponding lithium derivative, which is introduced into the reaction with phenylsulfanyl and phenylsulfinyl chlorides. Macrocycles **95a** and **95b** are formed in 50%–60% yield.

Gromov *et al.*[158] have found that treatment of bromides **24**, **25**, **78** and **79** with n-butyllithium in an Et_2O–THF mixture (5 : 3), the subsequent reaction of the resulting organolithium intermediates with DMF and the acid hydrolysis of the reaction mixture lead to the formyl derivatives of benzocrown ethers and their heteroanalogues — compounds **96**–**99** (Scheme 55).

Scheme 55



24, **25**, **78**, **79** **96**–**99**

X = O (**24**, **25**, **96**, **97**), S (**78**, **79**, **98**, **99**); *n* = 1 (**24**, **78**, **96**, **98**), 2 (**25**, **79**, **97**, **99**);
(*a*) 1) Bu^nLi, Et_2O–THF (5 : 3); 2) DMF; 3) HCl

The yields of target products depend on the reaction temperature and durations of the metallation and reaction with DMF. Under optimal conditions (60 °C for oxygen-containing and −100 °C for sulfur-containing macrocycles, metallation time 2–3 h, time of the reaction with DMF 4 h), formyl derivatives **96**–**99** are obtained in 61%–80% yield. For oxygen-containing BCEs **96** and **97**, the yields exceed those reported in Refs 42, 78 and 95.

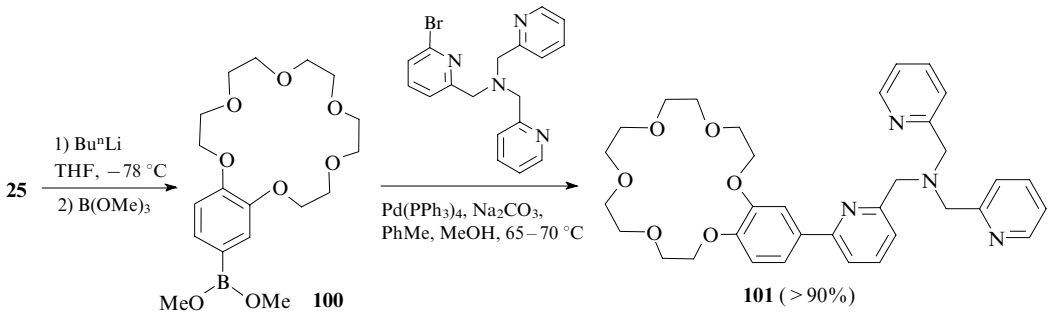
Boron derivative **100** has been synthesized by careful lithiation of bromide **25** with n-butyllithium in THF at low temperature followed by treatment of the reaction mixture with trimethyl borate.[159] Compound **100** has been then transformed into macrocycle **101** of lariat type, which exhibits high selectivity in complexation with some metal cations (Scheme 56).

A series of thiophene-containing benzocrown ethers **102** have been described. It has been demonstrated that bromides **24** and **25** in the presence of 10% $Pd(PPh_3)_4$ react with organotin derivatives **103**, combining thiophene and isophthalic acid moieties, to form crown-containing heterocycles **102a** and **102b** in 79% and 82% yield, respectively [160] (Scheme 57). From these heterocycles, efficient fluorescent Na^+ and K^+ indicators — compounds **102c** and **102d** — and diacids **102e** and **102f** (yield ~90%) have been synthesized.

Dimethyl ester **102b** has also been synthesized by an alternative method, and crown ethers **102g** and **102h** have been isolated as intermediate products (Scheme 58).

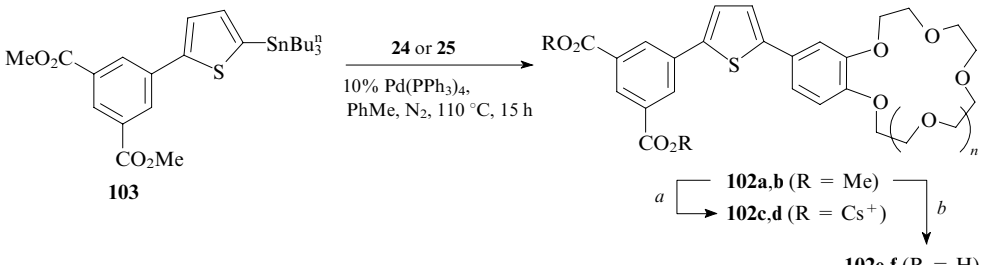
With the use of the same approach, a series of ionochromic copolymers **104** have been obtained for the first time in average yield of 90% by copolymerization of macrocycle **16**

Scheme 56



100 **101** (>90%)

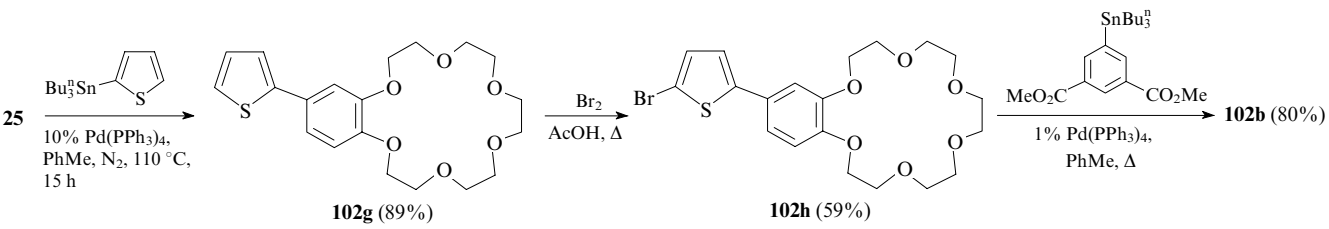
Scheme 57



103

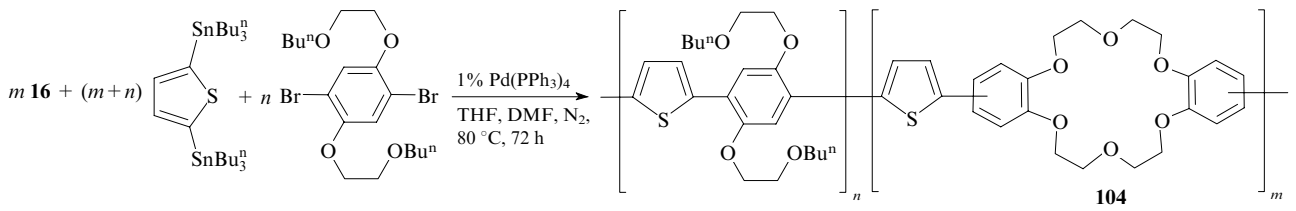
n = 1 (**24**, **102a**, **102c**, **102e**), 2 (**25**, **102b**, **102d**, **102f**);
(*a*) CsOH (10 equiv.), MeOH, Δ; (*b*) $KOSiMe_3$, THF, Δ

Scheme 58



102g (89%) **102h** (59%) **102b** (80%)

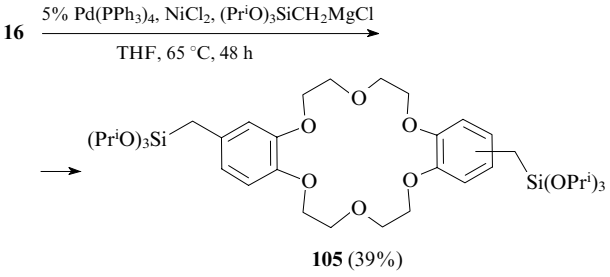
Scheme 59



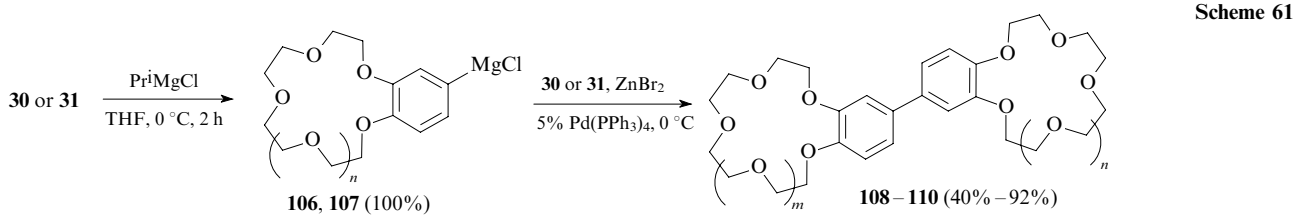
with 2,5-bis(tri-n-butylstannyl)thiophene and 1,4-dibromo-2,5-bis(2-n-butoxyethoxy)benzene (the monomer ratio (m : n) varied from 1 : 5 to 1 : 50) (Scheme 59).[161]

Reactions of HBCEs with organomagnesium compounds are of considerable interest. In particular, the reaction of DBCE **16** with $(Pr^iO)_3SiCH_2MgCl$ in the presence of a palladium complex and nickel chlorides gives compound **105** containing two readily hydrolysable $(Pr^iO)_3Si$ groups (Scheme 60).[162] Hydrolysis and subsequent polycondensation of crown ether **105** lead to so-called xerogels — promising hybrid materials for commercial use as indicators of humidity or air dehumidifiers for high technologies (similar to the use of tightness indicators and residual gas absorbers — getters — in the manufacture of vacuum electronic devices).

Scheme 60

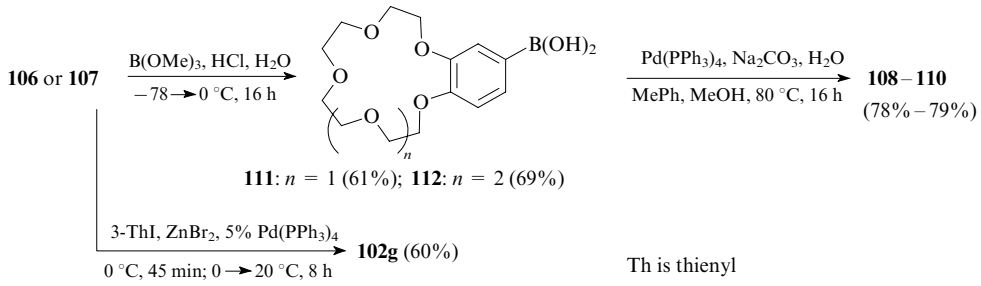


Scheme 61

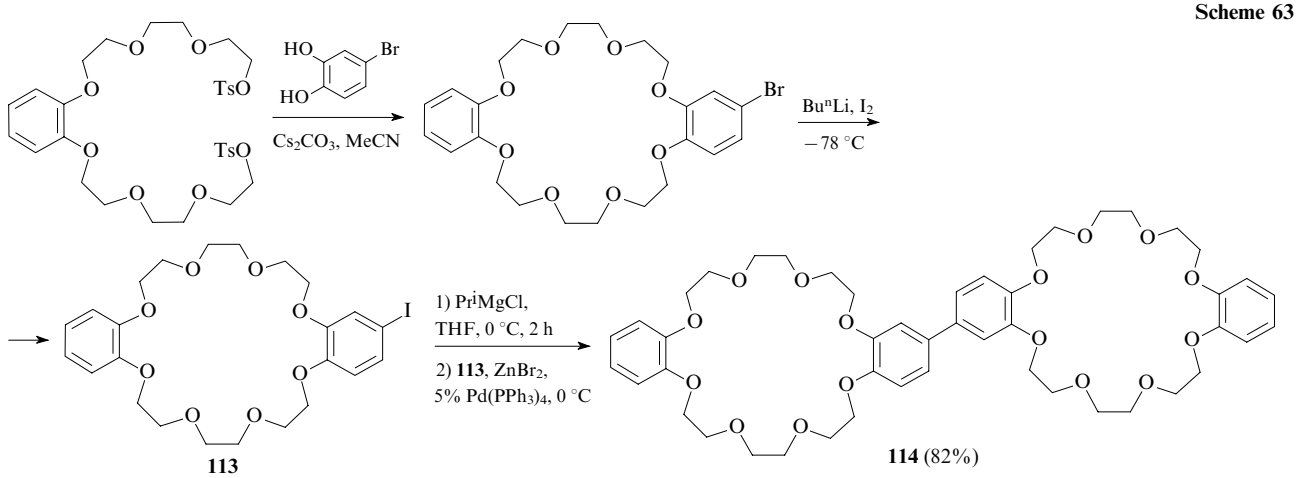


n = 1 (**30**, **106**, **108**, **110**), 2 (**31**, **107**, **109**); m = 1 (**108**), 2 (**109**, **110**)

Scheme 62



Scheme 63



Dixon *et al.*[163] have successfully accomplished classical Grignard reactions with BCE iodides leading to organomagnesium crown ethers **106** and **107** and bis(crown) compounds **108**–**110** (Scheme 61).

It should be emphasized that the suggested procedure affords crown-containing Grignard reagents (compounds **106**, **107**) in quantitative yield. They have been isolated and identified by physicochemical methods. Such compounds are readily soluble in THF even at −78 °C. Using another strategy, the same authors have synthesized crown derivatives of boronic acid (**111**, **112**), which have been converted into dimers **108**–**110** and crown ether **102g**, containing the thiophene moiety (Scheme 62).[163]

With the use of organometallic reagents, through the intermediate formation of DBCE iodide **113**, the first representative of bis(dibenzocrown ether) family — macrocycle **114** — has also been synthesized (Scheme 63).[163]

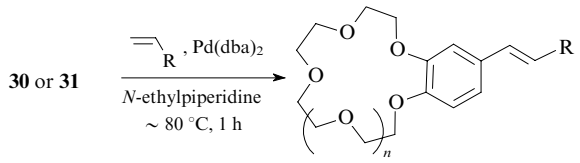
Thus, the above data demonstrate that on the basis of HBCEs, novel macrocyclic systems containing (di)benzocrown ether moieties have recently become available.

III.3. Heck and Sonogashira reactions

Different transformations of HBCEs under the Heck and Sonogashira reaction conditions have been studied. Here, we dwell on the most interesting among them.

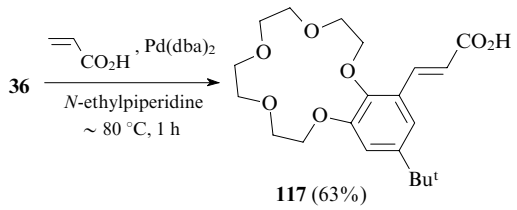
Because of the higher mobility of a iodine atom as compared with a bromine atom, BCE iodides enter into the Heck vinylation reaction under much milder conditions. There has been described a convenient procedure of alkenylation of 3′- and 4′-iodobenzocrown ethers **30**, **31** and **36** affording macrocycles **115**–**117** in acceptable yields[18] (Scheme 64).

Scheme 64



115a–**c**, **116a**–**c** (79%–98%)

n = 1 (**115**), 2 (**116**); R = Ph (**a**), CO_2Et (**b**), CO_2H (**c**)



117 (63%)

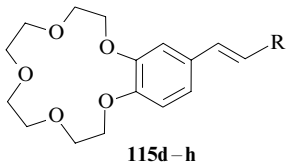
dba is dibenzylideneacetone

For the same reaction with BCE bromides, the yield of target products does not exceed 40%–50%. However, it is a challenging task to ultimately purify the resulting crown ethers from the catalyst.

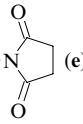
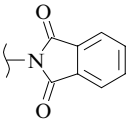
This problem has been successfully solved by Liao *et al.*,[17] who used polymer-supported palladium catalysts.[164–167] By this procedure, iodide **30** has been converted not only into derivatives **115a**–**115g** but also into bis(crown-ether) **115h**.

Vinylation of iodide **30** was carried out for 5–24 h in the presence of a catalyst and tri-n-butylamine at 100–150 °C. The yields of products **115** were 45%–85% depending on the vinyl component and the catalyst nature (Table 1).

Structures 115



115d–**h**

R = C(O)NH_2 (**d**),  (**e**),  (**f**),

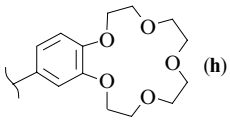
$(CH_2)_8CO_2H$ (**g**),  (**h**)

Table 1. Yields of vinylation products of iodide **30** under the Heck reaction conditions in the presence of different catalysts.

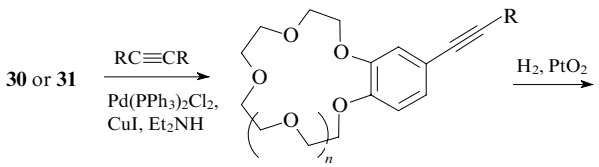
Compound **115**	Yield (%)			Ref.
	$Pd(dba)_2$	P-Ph-Phen-Pd(red) [a]	P-Ph-bipy-Pd^0 (see [b])	
a	97	80	82	17, 18
b	98	82	79	17, 18
c	79	67	45	17, 18
d	—	85	82	17
e	—	65	67	17
f	—	85	82	17
g	—	63	65	17
h	—	50	50	17

Note. The dash means that the product was not synthesized by this method. [a] Complex of palladium acetate with a copolymer of styrene and 2% divinylbenzene with grafted 1,10-phenanthroline reduced by $LiAlH_4$; [b] complex of $Pd(OAc)_2$ with a copolymer of styrene and 2% divinylbenzene with grafted 4,4′-bipyridine.

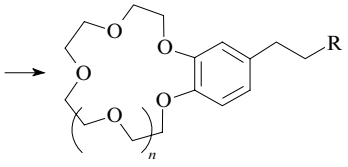
Hydrogenation of alkenyl moieties on macrocycles **115** (H_2, Pd/C, 100 °C, 10 atm) gave in high yield (88%–98%) the corresponding alkyl derivatives not otherwise available.

The use of iodinated benzocrown ethers made it possible to successfully carry out these reactions with alkynes (Sonogashira modification[168]). Kikukawa *et al.*[19] introduced BCEs **30** and **31** into the reaction of alkynylation

Scheme 65



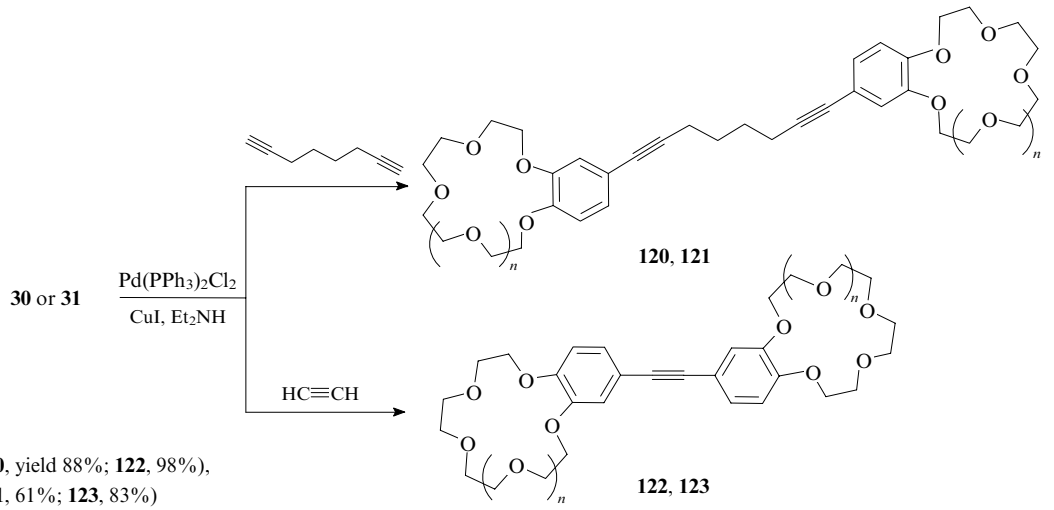
n = 1: **118a** (87%), **118b** (73%);
n = 2: **119a**,**b**



n = 1: **124a** (76%), **124b** (70%);
n = 2: **125a** (84%), **125b** (68%)

R = n-C_5H_{11} (**a**), CH_2OH (**b**)

Scheme 66

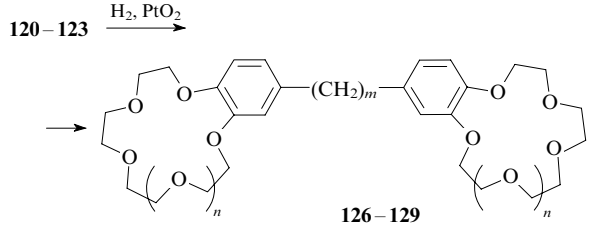


n = 1 (**120**, yield 88%; **122**, 98%),
n = 2 (**121**, 61%; **123**, 83%)

with hept-1-yne, propargyl alcohol, octa-1,7-diyne and acetylene leading to macrocycles **118**–**123** (Schemes 65 and 66). The reaction was catalyzed by the $Pd(PPh_3)_2Cl_2$–CuI system.

Hydrogenation of corresponding alkynyl BCEs leads to 4′-heptyl- and 4′-(3-hydroxypropyl)benzocrown compounds **124** and **125** (see Scheme 65), as well as to hardly available bis(crown ethers) **126**–**129**, in which the benzocrown moieties are linked by oligomethylene bridges of different length (Scheme 67).

Scheme 67



n = 1: m = 2 (**126**, yield 75%), 8 (**127**, 76%);
n = 2: m = 2 (**128**, 69%), 8 (**129**, 69%)

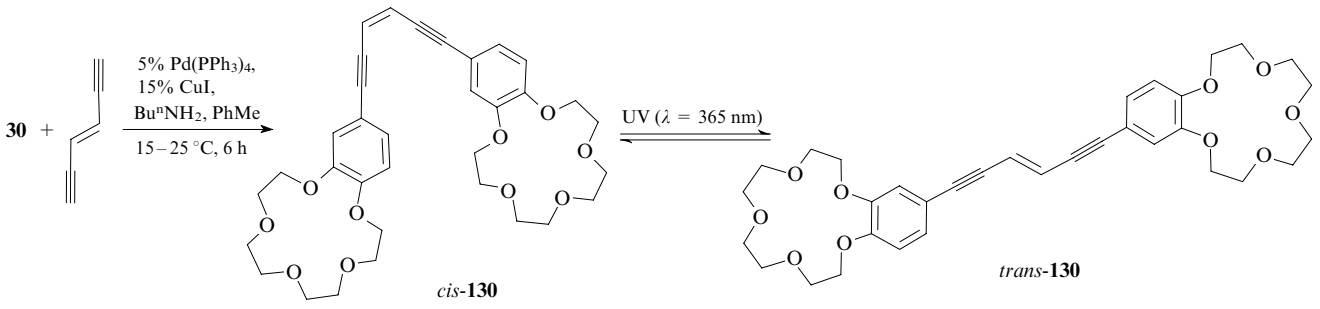
Using a similar procedure, BCE iodide **30** has been transformed in 61% yield into 4′-ethynylbenzo-15-crown-5, which has been subjected to polymerization.[169] The yield of the polymer (45%–78%) and reaction time (1 or 20 h) essentially depend on the nature of the metal complex catalyst and solvent.

Similar transformations of BCE bromides lead to alkynylbenzocrown ethers in yields not exceeding 60%.[170]

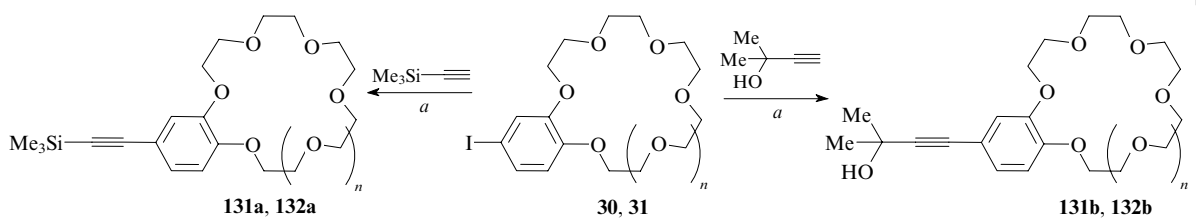
Bis(crown ether) **130** (65% yield) synthesized for the first time by Koenig *et al.*[16] and analogous macrocycles are used as traps for cations or as photoswitchable compounds (Scheme 68).

Klyatskaya *et al.*[171,172] have synthesized alkynylation products **131** and **132** by the reaction of iodides **30** and **31** with 2-methylbut-3-yn-2-ol and trimethylsilylacetylene (Scheme 69). In addition to moniodides,[121] the reaction proceeds rather smoothly with diiodo- and tetraiodoben-

Scheme 68

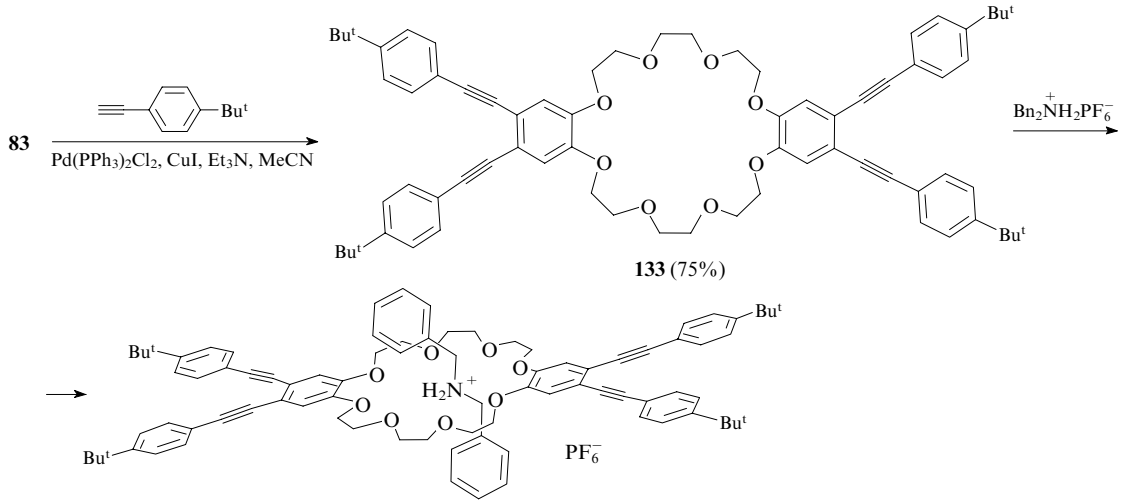


Scheme 69

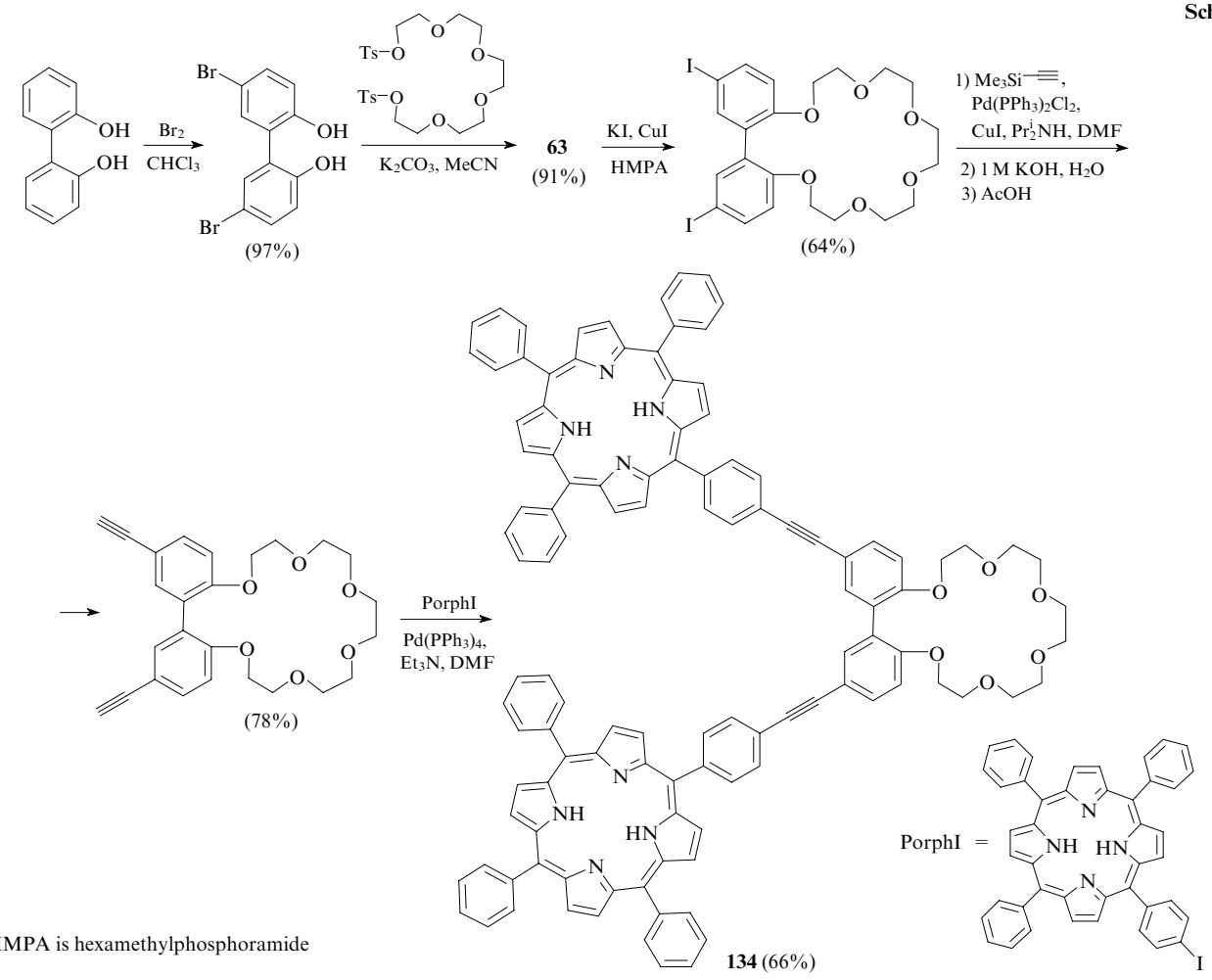


n = 0 (**131a**, yield 85%; **131b**, 96%), 1 (**132a**, 96%; **132b**, 69%); (*a*) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, PhH, Ar, 70–75 °C, 1 h

Scheme 70



Scheme 71



HMPA is hexamethylphosphoramide

zocrown ethers (as distinct from their brominated analogues) to form the target products in 50% to 90% yield.[70]

It has been found that tetraiodide **83** under the Sonogashira coupling conditions is converted into conjugated crown tetraacetylene **133**, which reacts with dibenzylammonium hexafluorophosphate to give a 1 : 1 complex — pseudorotoxane[137] (Scheme 70).[21]

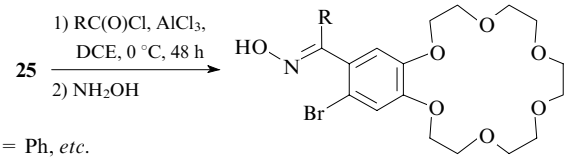
An elegant synthesis of bisporphyrin **134**, containing BCE moieties has been accomplished by Kubo *et al.*[173] through a series of transformations of dibromide **63** (Scheme 71).

III.4. Other transformations

Acylation of bromide **25** with acyl chlorides with the subsequent treatment of the reaction mixture with hydrox-

ylamine leads to the corresponding oximes (Scheme 72), which exhibit antiviral activity and are used as chelating agents for metal cations.[174]

Scheme 72



R = Ph, *etc.*

Macrocycle **25** has also been used as the initial compound for synthesis of cyanine dyes, for example, compound **135** (Scheme 73).[81] In the course of this synthesis, the authors obtained different benzocrown ether derivatives, including heterocyclic ones.

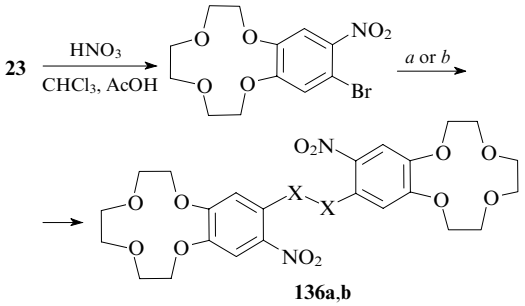
The substitution of sulfur and selenium atoms for the bromine atoms in HBCEs proceeds rather easily. For example, the synthesis of bis(benzo-12-crown-4) compounds linked by a disulfide (**136a**, yield 71%) or diselenide (**136b**, yield 31%) bridges (Scheme 74) has been reported.[175] Similar crown ethers are used in ion-selective electrodes for quantification of Ag^+ in the presence of a large range of impurity cations.

Owing to the ease of cyanation, BCE dibromides are almost the only initial compounds for synthesis of exotic crown-phthalocyanines and related structures. In particular, treatment of bromide **4** with copper(I) cyanide in DMF under different conditions afforded dicyano derivative **137** (Scheme 75). The yields of the product were 66%[176] and 31%[177] depending on the reaction temperature (150 and 180 °C) and duration (5 and 24 h).

Tsivadze with co-workers[60] have made a definite contribution to the solution of this problem by modifying the procedure of synthesis of macrocycle **137** . The authors have subjected bromide **4** to Rosenmund–von Braun cyanation and, after long processing of the reaction mixture, involving decomposition of the resulting copper complexes and column chromatography, have obtained rather pure target product in 77% yield.

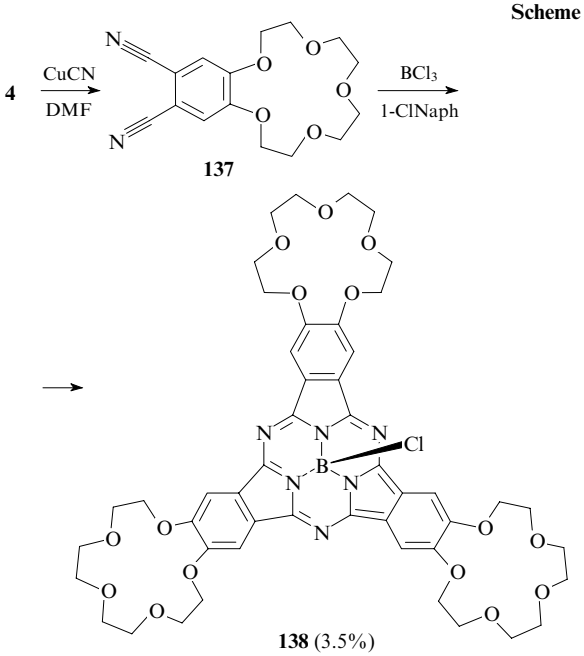
Subphthalocyanine **138** results from cyclotrimerization of dinitrile **137** under the action of boron trichloride (see Scheme 75).[59] Crown-containing phthalocyanine **139a**, as well as its copper and zinc complexes (**139b**,**c**), have been synthesized from dibromide **27** by an analogous procedure.[61]

Scheme 74



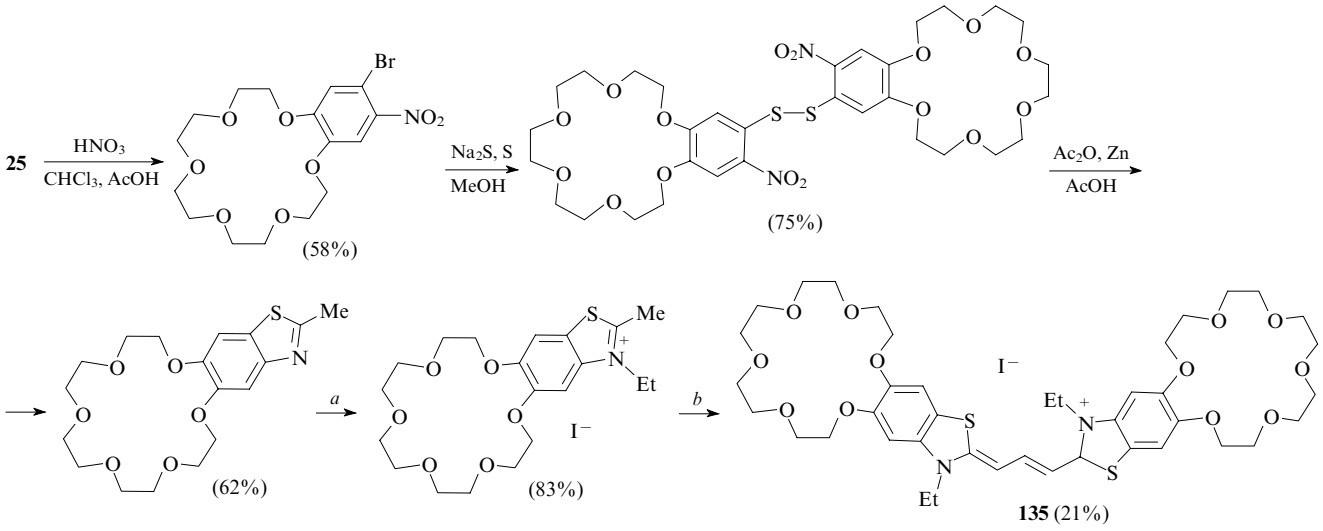
X = S (**136a**), Se (**136b**); (*a*) Na_2S_2, MeOH; (*b*) K_2Se_2, EtOH, N_2

Scheme 75



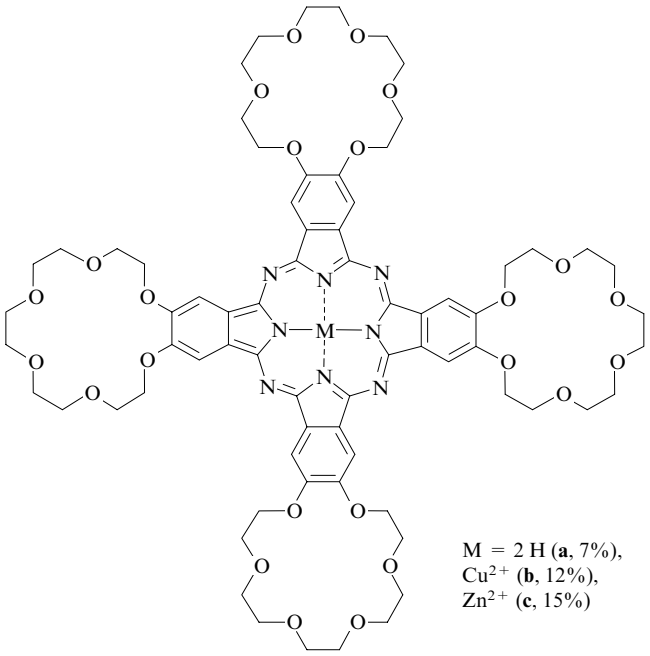
1-ClNaph is 1-chloronaphthalene

Scheme 73



(*a*) EtI, 120 °C, 4 h; (*b*) $HC(OEt)_3$, Py, Et_3N, 80 °C, 2 h; Py is pyridine

Structures 139



139a–c

IV. Complexing properties

IV.1. Complexes with ionic guests

The complexing properties of BCE and DBCE halides have not been systematically studied; at the same time, separate results discussed below have become a surprise.

For 4′-bromo-substituted crown **24** as an example, it has been demonstrated that the stability constants of HBCE complexes with NaI correlate satisfactorily with Hammett constants (σ) for exocyclic substituents and decrease in the series $NH_2 > Me > H > Br > CO_2H > CHO > NO_2$.[147] The complexing properties of bromide **24** differ only slightly from those for unsubstituted BCE **2**. A similar, even if less pronounced, dependence is also observed for the complexation of analogous derivatives **1** and **3** with potassium salts.[176]

The synthesis of complexes of dibromide **4** and 4′-bromo-5′-nitrobenzo-15-crown-5 (**140**) with triply charged lanthanide nitrates (La^{3+}, Ce^{3+}, Pr^{3+}, Sm^{3+}, Eu^{3+}), as well as with hydrated thorium nitrate in chloroform or in a chloroform–acetonitrile mixed solvent (the yields of the products, 25%–88%), has been described.[177–179] The synthesis of 19 complexes of crown ethers **4**, **18**, **33** and **140** with Mn^{II}, Co^{II}, Cu^{II}, Zn^{II}, Ag^{I} and Cd^{II} nitrates, perchlorates and chlorides in a chloroform–methanol or chloroform–acetone mixtures has been reported.[180,181] Physicochemical properties of such complexes (IR and UV spectra, thermogravimetric characteristics, *etc.*) have been studied. The complexes of substituted BCEs, including compounds **4** and **30**, with sodium picrate and picric acid have been synthesized by Izatt and co-workers[182] in a chloroform–methanol mixture (yield, 92%–99%).

Tashmukhamedova with co-workers[183] have synthesized a complex of macrocycle **4** with KSCN and characterized it by X-ray crystallography data. According to the latter, such a complex is a typical 2 : 1 sandwich (Fig. 1). The K–O distances are within 2.75–3. 06 Å. The Br···Br

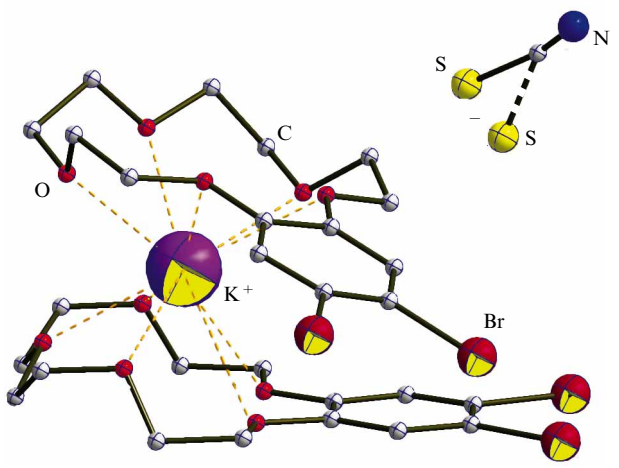


Figure 1. Structure of complex $(4)_2 \cdot KSCN$ in crystal.[183] (The S atoms are disordered.)

interactions (3.70–3.93 Å) link the complex cations to form bands along one of the crystallographic axes, and the free space between them is filled with NCS^- anions.

As distinct from the complex of pentadentate macrocycle **4**, the complex of tetradentate ether **28** with NaBr, synthesized and studied by the same authors,[184] contains water molecules and has the composition $(28)_2 \cdot NaBr \cdot 2\,H_2O$ (Fig. 2).

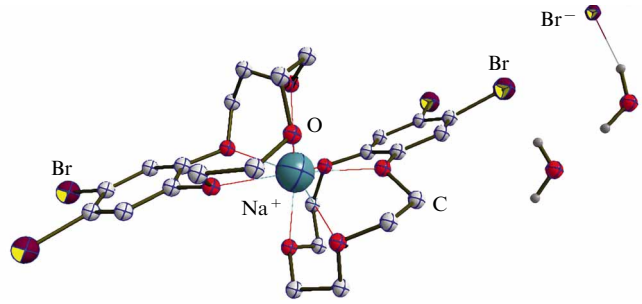


Figure 2. Structure of complex $(28)_2 \cdot NaBr \cdot 2\,H_2O$ in crystal.[184]

An unusual complex has been described by Calleja *et al.*[185] Mixing a concentrated solution of $HAuCl_4$ in aqua regia with DBCE **1** led to the formation of four crystalline products, one of which was identified by X-ray crystallography as the onium complex $[(H_{11}O_5)(TCDB\text{-}18C6)_2][AuCl_4]$ (**141**, TCDB-18C6 is tetrachlrodibenzo-18-crown-6) (Fig. 3). A specific feature of the structure is that the oxonium ion passes through one of the macrocycles. It should be noted that there are about ten crown ether complexes with $(H_{11}O_5)^+$, and DBCEs have not been used as ligands so far.

There is not a single fact that the ligand is halogenated under the conditions of oxonium complex formation. In particular, it has been revealed that stirring macrocycle **2** with europium nitrate in an organic phase with a subsequent slow addition of HBr leads, in 70% yield, to complex **142**, composed of dibromide **4** and $(H_3O)^+Br_3^-$ in the 2 : 1 ratio, (Fig. 4).[186] The complex cation of the sandwich biligand type is asymmetric and is formed due to

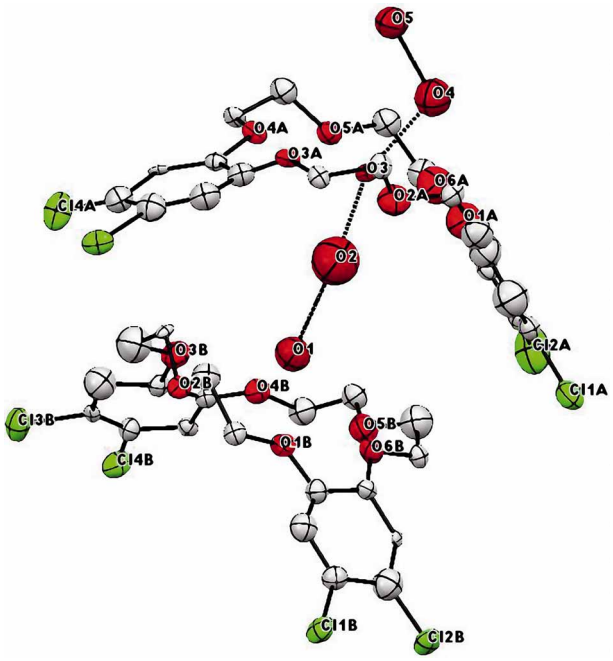


Figure 3. Structure of the cation of complex **141** in crystal.[185]

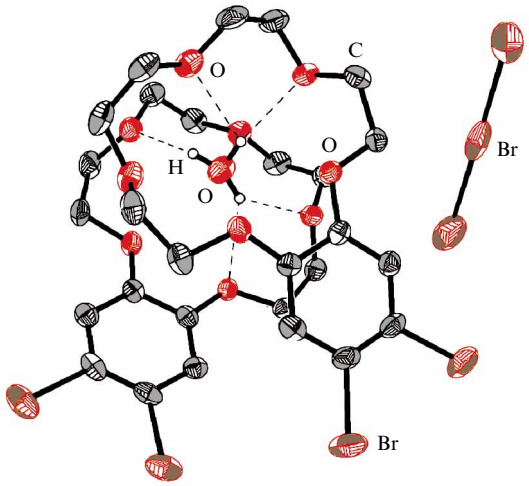


Figure 4. Structure of complex **142** in crystal (hereinafter, dashed lines denote hydrogen bonds).[186]

O–H···O hydrogen bonds. It should be noted that, by its supramolecular architecture, conformation of the ligands (containing *gauche*-C–C and *anti*-C–O moieties), bond lengths and torsion angles, the complex largely resembles the sandwich complexes of unsubstituted benzocrown ether **2**.[187] The C–H···Br intermolecular bonds play a noticeable role and, along with common O–H···O contacts, stabilize the crystal structure.

A similar situation has been observed for the reaction of unsubstituted BCE **2** with selenium(IV) bromide in an HBr solution. As a result, hexabromoselenate(IV) complex **143** of composition $[H_3O(\mathbf{4})]_2[SeBr_6]$ has been isolated.[188, 189] The crystal structure of the complex is composed of octahedral $[SeBr_6]^{2-}$ anions and oxonium cations (Fig. 5) each of which is stabilized by two BCE molecules.

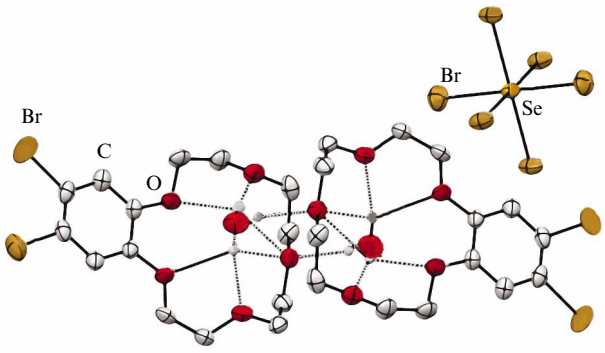


Figure 5. Structure of complex **143** in crystal.[188, 189]

We have also observed the formation of an oxonium complex with a halogen-containing ligand on dissolving unsubstituted BCE in an aqueous solution of $HAuCl_4$.[190] Interaction of macrocycles **3** and **25** with concentrated and dilute $HAuCl_4$ and $HAuBr_4$ solutions (to prevent nitration of BCEs, nitrate-free solutions were used) resulted in corresponding complexes **144** –**147**, which were studied by X-ray crystallography. It took about a day for crystals of complexes **145**–**147** to grow. X-Ray crystallography confirmed the following formulas determined by elemental analysis: $(H_3O(\mathbf{25})][AuCl_4]$ (**145**), $[H_3O(\mathbf{25})][AuBr_4]$ (**146**) and $[H_3O(\mathbf{3})][AuBr_4]$ (**147**) (Fig. 6 *b*–*d*). The BCE complexes with $HAuCl_4$ are bright yellow and those with $HAuBr_4$ are deep red-brown. Crystals of complex **144** suitable for X-ray crystallographic analysis were obtained only several months later by alternating operations of its dissolution in an ethyl acetate–ethanol mixture and subsequent slow evaporation of the solvent. A combination of X-ray crystallography, elemental analysis, mass spectrome-

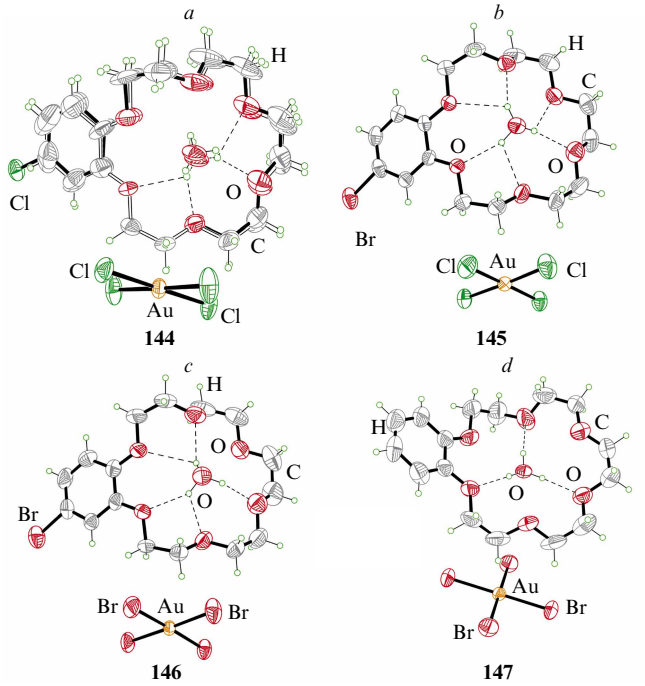


Figure 6. Structure of complexes **144** (*a*), **145** (*b*), **146** (*c*) and **147** (*d*) in crystal.[190]

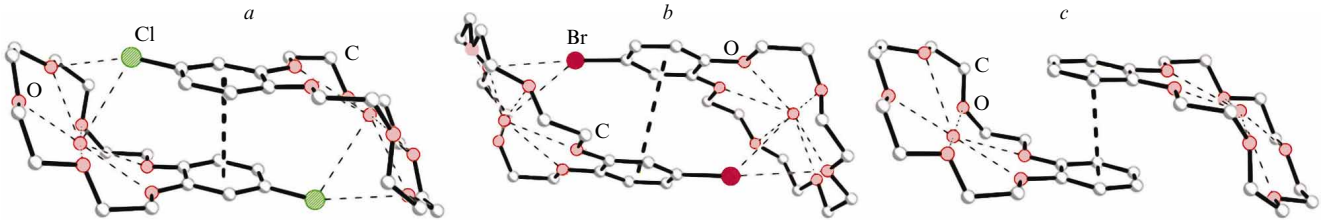


Figure 7. Stabilization of dimers of complex **144** (*a*), **146** (*b*) and **147** (*c*) by π–π-stacking and extra interactions.[190] Anions and hydrogen atoms are omitted.

try and ^{1}H and ^{13}C NMR data demonstrates that complex **144** is described by the formula $[H_3O(\mathbf{3})]_{0.52}[H_3O(\mathbf{45})]_{0.48}[AuCl_4]$. The structure of complex **144** is shown in Fig. 6 *a* (the chlorinated ring is shown, and unchlorinated rings have the same positions).

We have shown [190] that complex **145** in the presence of HBr is rapidly and quantitavely converted into complex **146**. The bright yellow crystalline compound obtained through interaction of macrocycle **3** with $HAuCl_4$ (Structure **144′**) was treated with an HBr solution immediately after isolation. X-Ray crystallographic analysis of the resulting red-brown crystals demonstrated its complete identity with complex **147**. This allowed us to assume that, immediately after the formation, compound **144′** has the composition $[H_3O(\mathbf{3})][AuCl_4]$, and only after exposure of its solution to air for several months, it is converted into structure **144**. Thus, we have demonstrated that the ligand is chlorinated upon long-term exposure of a solution of the BCE complex to $HAuCl_4$ and air. The chlorine cation required for chlorination can form through a series of reactions (14)–(16).

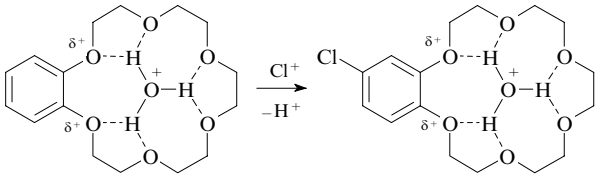
$$4\,HCl + O_2 \longrightarrow 2\,H_2O + 2\,Cl_2 \qquad (14)$$

$$HAuCl_4 \rightleftharpoons HCl + AuCl_3 \qquad (15)$$

$$AuCl_3 + Cl_2 \rightleftharpoons [AuCl_4]^- + Cl^+ \qquad (16)$$

It is likely that complexation of BCEs with oxonium ion facilitates chlorination (Scheme 76).

Scheme 76



Complexes **144**–**147** are centrosymmetric dimers stabilized by π–π-stacking interactions. The presence of the halogen atom in the 4′-position leads to their additional stabilization (Fig. 7 *a*–*c*).

The reactions of 4′-halo derivatives of macrocycle **3** containing chlorine (**45**), bromine (**25**) or iodine atoms (**31**) with potassium chlorochromate ($KCrO_3Cl$) giving 1 : 1 complexes — compounds **148**–**150** — have been studied (Scheme 77).[191–193]

Complexes have been synthesized by mixing solutions of the reactants in dry ethyl acetate at room temperature.[194] Attempts to synthesize an analogous complex of dibromide **16** failed presumably due to the low solubility of the ligand in organic solvents.

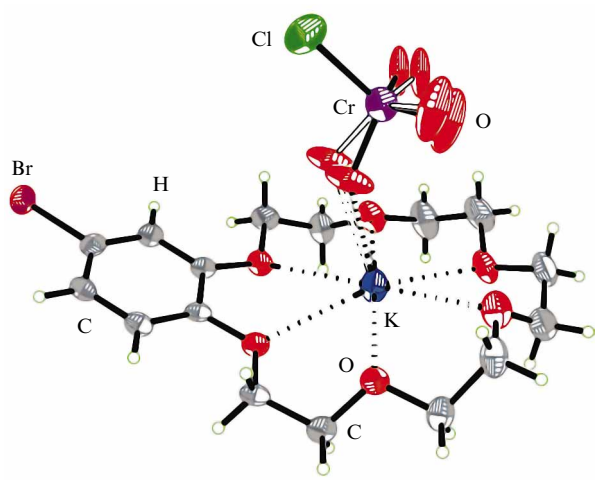
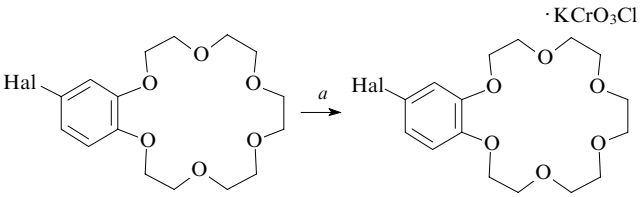


Figure 8. Structure of complex **149** in crystal.[191] (The anions are disordered.)

Scheme 77



25, **31**, **45** **148**–**150** (78%–93%)

Hal = Cl (**45**, **148**), Br (**25**, **149**), I (**31**, **150**);
(*a*) $KCrO_3Cl$, EtOAc, 20 °C, 5–15 min

For complex **149**, X-ray crystallography has confirmed the 1 : 1 composition determined by elemental analysis (Fig. 8).[191]

Thus, benzocrown ether halides, like unsubstituted BCEs and DBCEs, are able to efficiently form complexes with ionic guests. A halogen atom as the substituent in the aryl moiety additionally stabilizes the complex structure through the formation of extra electrostatic bonds and bonds involving the halogen atom.

IV.2. Complexes with neutral organic molecules

In the past two decades, the host–guest chemistry as applied to crown ethers and neutral organic compounds has been mainly studied for biologically active molecules (drugs, heterocyclic bases, *etc.*). This application is based on the unique ability of crown ethers as two-end spacers able to form a large number of hydrogen bonds for the formation

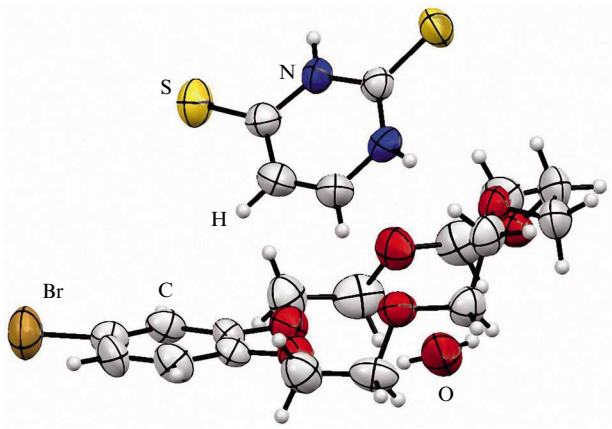
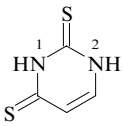


Figure 9. Structure of complex **151** in crystal.[195]

of a crystalline complex with a guest. First of all, of interest are different H-donors containing NH_2, $C(=S)NH_2$, $C(=O)NH_2$, *etc.* groups and crown ethers as candidates for creation of supramolecular architectures.

Crystalline complex **151** (Fig. 9) has been obtained in high yield (> 80%) by mixing solutions of 2,4-dithiouracil (DTU) and ligand **25** in organic solvents (MeOH, EtOAc, Bu^nOH) at room temperature followed by spontaneous solvent evaporation.[195]

Structure of DTU



According to X-ray crystallographic data, the host and guest molecules in the crystal of complex **151** are held together exclusively by weak hydrogen bonds.

IV.3. Solid-phase synthesis of complexes

In searching for new synthetic routes for host–guest complexes containing crown ethers, the potential of mechanochemical activation has been studied. The $KCrO_3Cl$ complexes with aliphatic, cyclo- and dicycloaliphatic crown ethers, as well as with BCEs and DBCEs, are usually synthesized in aqueous acid solutions, two-phase systems or organic media.[194] The composition and structure of more than 20 similar complexes have been determined by X-ray crystallography.

The complexation of halogenated crown ethers **4**, **24**, **25**, **27**, **30**, **31**, **44**, **45**, **63** and **65** with $KCrO_3C$ has been studied under identical conditions of solvent-free mechanochemical activation. It has been .elucidated that solid-phase synthesis can be successfully used for producing crown ether complexes with ionic guests.[109, 110, 174, 176, 196] The reactions were carried out as described above (see Section II.2.a) in a sealed electromechanical vibrating mortar.

Hexadentate ligands and metal salts form 1 : 1 complexes, while pentadentate macrocycles give 2 : 1 sandwich complexes. It has been found that the yield of complexes essentially depends on the ligand nature. In particular, the maximal yields of the products (81% – 100%) have been achieved for BCE bromides **24** and **25** and DBCE dibromides **63** and **65**. Crown ether **25** forms complex **149** with $KCrO_3Cl$ in nearly quantitative yield; its structure and composition (1 : 1)[191] have been described in Section IV.1. DBCE dibromides **63** and **65** form 1 : 1 complexes with $KCrO_3Cl$ in ~90%. The simple method of ultimate purification of the product that we proposed makes it possible to easily and without loss isolate complexes of reagent grade from the reaction mixture, even in the case of their low yields. The complexes have been isolated by successive treatment of the solid reaction mixture with n-hexane, in which the unreacted ligand is readily soluble while the target complex is almost insoluble, and ethyl acetate, which dissolves unreacted $KCrO_3Cl$ and does not dissolve the target complex. The high efficiency of this purification procedure allows one to correctly compare the yields of complexes obtained with different macrocyclic ligands.

Under these conditions, benzo-15-crown-5 4′-halides **24**, **30** and **44** react with $KCrO_3Cl$ to give 2 : 1 sandwich complexes. The complexes of chloride **44** and iodide **30** have been obtained in 15% and 37% yield, respectively, whereas bromide **24** is much more reactive, and the yield of its complex vary in different experiments from 72% to 81%. An analogous situation is also observed for 4′-halo derivatives of BCE **3** — compounds **25**, **31** and **45**, which form 1 : 1 complexes. In the case of 15- and 18-membered dibromides **4** and **27**, complexes of different composition (2 : 1 and 1 : 1) have been obtained in nearly the same yield — 43% and 50%. At the same time, unsubstituted macrocycle **1** does not react with $KCrO_3Cl$, BCE **3** being converted into oil in the course of mechanochemical process because of the low melting point (~40 °C). As distinct from the solid-phase synthesis, all HBCEs that we studied in ethyl acetate exhibit roughly the same reactivity toward metal salts, and target complexes are formed in 73% – 92% yield. Physicochemical characteristics and elemental analysis data of the complexes obtained by two different methods are nearly the same.

IV.4. Extraction properties of halogenated benzocrown ethers

Extraction of metal ions with HBCEs has been described. In particular, lanthanide picrate complexes have been extracted with bromide **24** and 4-*tert*-butyl-substituted crown ether **29b** (see Scheme 14) in a water–nitrobenzene (or $CHCl_3$) two-phase system.[197] The series of the extraction activity of metals for both macrocycles is as follows: Ce > Eu > Tm > Yb > Lu, with maximal values for Sm. The crown ether : salt ratio in all extracted complexes is 2 : 1, and the distribution ratios (D_M) in nitrobenzene for lanthanide complexes of macrocycle **29b** are approximately two times as high as for complexes of macrocycle **24**. Noticeable dilution of nitrobenzene with chloroform leads to a 20-fold increase in D_M value.

Extraction of ~30 metal cations with bromide **25** and macrocycles **3** and **1** (as reference compounds) into the organic phase ($CHCl_3$) from aqueous HNO_3 solutions has been studied.[198] In contrast to expectation, macrocycle **25** almost always exceeds in extraction properties compound **3**, and for extraction of Pb^{II} ions, the distribution ratio of extractant **25** turns out to be five times higher. Hence, bromide **25** is a highly selective extractant of Pb^{II} ions from nitric acid solutions.

Even more interesting results have been obtained for extraction of metal ions in an acid solution (5 M HCl). It has been shown that compound **25** in most cases has better extraction properties than not only extractant **3** but also dibenzocrown ether **1**. In extraction of Au^I, the D_M value

for compound **25** is very large (15.2) and is almost four times higher than the value for macrocycle **3** (D_M = 4.20) and seven times higher than that for macrocycle **1** (D_M = 2.20). The other metals are almost not extracted by crown ether **25** (D_M = 0–0.5); *i.e.*, this compound is a highly selective extractant of Au^I ions. It is worth noting that, for benzocrown ethers studied in similar processes, such high selectivity toward Au^I and Pb^{II} ions with almost complete absence of extraction properties toward the other elements has not been observed previously.

We have studied the extraction of the same metals with halides of tetra- (**23** and **40**) and pentadentate BCEs (**4**, **24** and **30**) from HNO_3 and HCl solutions.[198] As reference compounds, unsubstituted BCEs have been used. In an HNO_3 solutions, the macrocycles nearly do not exhibit extraction properties, and no noticeable differences between HBCEs and unsubstituted BCEs **2** and **9** have been observed. As analogous situation is observed for hydrochloric acid solutions, with exception of Au^I ion. The increased distribution ratios of this metal are shown by all HBCEs under consideration. In particular, for unsubstituted macrocycle **9** the D_M value is only 0.21, whereas for bromide **23** this value is 27-fold higher (D_M = 5.70), and for dichloride **11**, it is 64-fold higher (D_M = 13.50).

Among derivatives of unsubstituted BCE **2**, the extraction properties increase in the series unsubstituted macrocycle **2** (D_M = 5.50) < bromide **24** (D_M = 6.10) < iodide **30** (D_M = 10.50) and decrease on going to dibromide **4** (D_M = 3.00). It is worth noting that, whereas the introduction of a bromine atom (polyether **23**) or two chlorine atoms (polyether **11**) into molecule **9** leads to a sharp increase in D_{Au} (by a factor of 27 and 64, respectively), in the series of derivatives of macrocycle **2** with similar lipophilicities, a noticeable D_{Au} increase is observed only for iodide **30**, while the extraction activity of dibromide **4** decreases nearly twofold. The data on extraction with HBCEs are of practical interest since they make it possible to use such macrocycles as highly selective extractants for Au or Pb ions in the nearly complete absence of extraction of background metals.

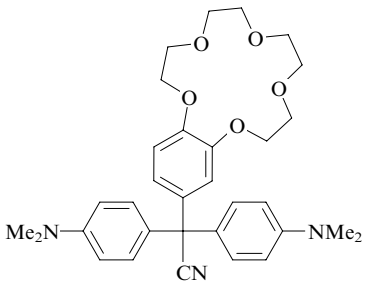
IV.5. Sorption properties of halogenated benzocrown ethers

DBCEs and HBCEs insoluble in aqueous and acid solutions can serve as selective sorbents of different metal ions. Our studies have demonstrated that the introduction of bromine atoms into benzene rings of polyether **39** leads to a sharp (hundredfold) increase in sorption properties of resulting dibromide **52** toward some elements in aqueous hydrochloric acid solutions.[199, 200] Maximal distribution ratios are observed for Au, Ga, Sb, Fe, Sn and Mo, *i.e.*, for elements that form complex metal acids in hydrochloric acid solutions. The above results reasonably suggest that HBCE **52** is a new highly selective reagent for extraction and separation of elements from multicomponent mixtures.

V. Application and commercial production of halogenated benzocrown ethers

Materials produced from HBCEs often have a set of unique valuable properties. For example, the ease of lithiation of macrocyclic bromides enables the synthesis of photochromic macrocycles similar to those described in Ref. 201. The synthesis of leucomalachite green **152** containing a crown ether moiety is based on the reaction of the corresponding lithium derivative of ether **24** with 4,4′-bis(*N*,*N*-dimethylamino)benzophenone (Michler's ketone). It is worth noting that similar photosensitive ion-conducting materials can hardly be obtained by other methods.

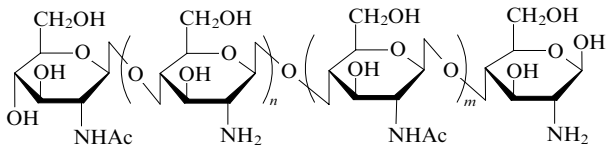
Structure 152



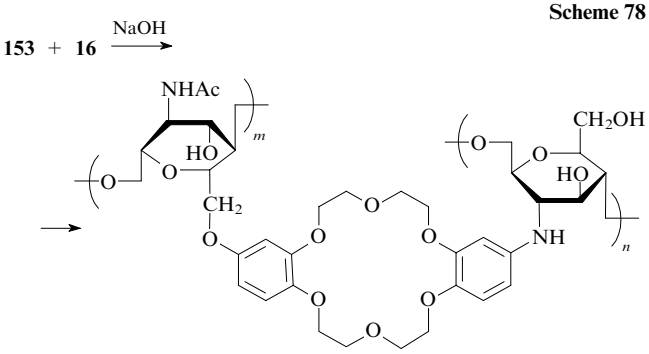
152

It has been revealed that chitosan (**153**), composed of randomly alternating β-(1-4)-D-glucosamine and *N*-acetyl-D-glucosamine units, and DBCE dibromide **16** can form a copolymer (Scheme 78).[202]

Structure 153



Scheme 78



The resulting polymeric material extracts Ag^+, Cu^{2+}, Pb^{2+} and Ni^{2+} ions better than crown ethers and much more efficiently as compared with other chitosan-based polymeric materials. Polymers produced from crown ether **16** turn out to be even more efficient for extraction of microimpurities of elements from Antarctic meltwater.[22] It has been demonstrated that adsorption of such elements (including As, Pb, Cu, Zn, Cr, Cd *etc.*) is 97% at water pH 7.5.

Adsorption on a sliding surface associated with chemical changes that occur within a few nanometres is the basis of action of lubricants and lubricant additives under so-called boundary lubrication conditions. It has been shown that macrocycle **24** is a new highly efficient, antioxidant and antifriction additive for protection of metal surfaces, which considerably enhance the resistance of the latter to oxidation and wear.[23] Spreading a solution of macrocycle **24** in kerosene onto the metal surface and subsequent spontaneous evaporation of the solvent leave a thin (no more than 2 nm) but extremely chemically stable layer on the surface. The latter is formed due to the interaction of compound **24**

with iron ions, which imparts the specified properties to the product. As compared with the properties of analogues used in engineering, the properties of macrocycle **24** are accepted as unique and are essentially superior to those for zinc dialkyl dithiophosphate.

Commercial production of BCE bromides **24** and **25** was started in the late 1980s – early 1990s. Later, this range was extended to macrocycle **16** (it was manufactured, in particular, at Cherkassy chemical plant (Ministry of Chemical Industry of the USSR, specification TU 6-09-20-93-87). However, this range of HBCEs was exhaustive. It is worth noting that, despite the great demand for BCE iodides in economy, their commercial production has not been implemented thus far, which is likely associated with the difficulty of their purification (to 96% – 98% required for the reagent grade).

Among the major manufacturers of crown ethers **16**, **24** and **25** are giant companies, such as Merck, Fluka, Sigma-Aldrich, Acros, and TCI, as well as little known companies Cole-Parmer and Chemos and a number of Chinese manufacturers. The cost of the product is sometimes as high as 100 USD per gramme.

VI. Conclusion

As part of work on the chemistry of crown ethers, studies of synthesis and properties of halogenated BCEs and DBCEs have passed relevant stages of development and formation. With accumulation of comprehensive information on the specific methods of synthesis and specific properties of HBCEs, their role and place in organic chemistry, as well as prospects for practical application, have become more concrete.

At the same time, presented examples of use of HBCEs for solving applied problems show that their applications can be diverse — from quite expected (extraction and sorption in processes of preconcentration and recovery of elements even from very dilute solutions, water purification, deactivation, *etc*.) to unexpected (for example, as antioxidant and antifriction additives). The discovered antimicrobial and, presumably, fungicidal properties of HBCEs [43, 203] can be relevant to industrial hygiene. The reported examples of using such compounds in organic synthesis also demonstrate their considerable potential as building blocks.

However, it is evident that not all of the problems of synthesis of various HBCEs have been solved optimally. The reviewed data demonstrate that methods of halogenation of BCEs and aromatic alkoxy compounds have differences. The crown ether moiety introduces specific features into aryl halogenation procedures, and some halogenation methods become applicable only for BCEs. Although the suggested methods of their synthesis in the solid phase and aqueous and organic media cover almost all range of BCE and DBCE chlorides, bromides and iodides, some of them should be optimized. In particular, selective methods of synthesis have been well developed for BCE bromides in aqueous solutions with the use of NBS and $NaBrO_3$ as brominating agents and for DBCE bromides with the use of NBS in chloroform. Selective iodination of BCEs proceeds most smoothly with NIS in water or ethanol. Controlled change in pH during chlorination, bromination and iodination in aqueous solutions makes it possible to regulate the number of introduced halogen atoms. For iodination of DBCEs, the modified Hyde system, consisting of a iodine solution in acetic acid or 1,4-dioxane in the presence of iodates or periodates and sulfuric acid, is rather efficient. At the same time, the iodinating system consisting of TMBADCI (see above) and zinc chloride in glacial acetic acid seems to be unfairly bypassed. It is also worth noting that although the chlorination of BCEs (except BCE **9**) and DBCEs with chlorine gas is almost exhaustive, and BCE monochlorides are obtained in good yield in the case of an aqueous solution of NaClO, methods of synthesis of individual BCE and DBCE dichlorides need to be improved. For example, the halogenation of BCEs and DBCEs with *N*-haloacetamides and N,N',N'',N'''-tetrahaloglycolurils has not been studied. There are similar unresolved issues, and some aspects of the chemistry of HBCEs touched on in this review still await their researchers.

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