Acta Chimica and Pharmaceutica Indica

Research | Vol 8 Issue 3

Some Aspects of the Synthesis of Crown Ethers

Gasan Kh Khojayev[1], Raya A Najafova[2], Afag Y Melikova[1] and Sabir A Mammadov[2*]

[1]Azerbaijan State University of Oil and Industry, Baku, Azerbaijan

[2]Institute of Chemistry of Additives, Azerbaijan National Academy of Sciences, Baku, Azerbaijan

[*]**Corresponding author:** Sabir A Mammadov, Institute of Chemistry of Additives, Azerbaijan National Academy of Sciences, Baku, Azerbaijan, E-Mail: nina62_62@mail.ru

Received: February 03, 2018; **Accepted:** March 14, 2018; **Published:** September 10, 2018

Abstract

As a result of this study, we have developed a new method for the synthesis of dibenzo-, benzoaza-, spiroaza-, benzthio- and other crown-ethers. High selective yields of crown-ethers have been obtained due to change in ratio of reacting components and use of different catalysts (ammonium, boron trifluoride etherate), as well as reaction conditions. Interphase debromation of dibroalkanes with crown-ethers has been studied.

***Keywords**: 18-Crown-6 (18C6); Catalysis of interphase transition (CMPhT);Dibenzo-18-crown-6 (DBC); Pentamethyl-15-crown-5 (PM15L5); Tetramethylbenzylammonium chloride (TEBA); Tetramethyl-12-crown-4 (TM12C4), Dichlordiethyl ether (chlorex), n-Methylbenzeneamine (toluidine.*

Introduction

With an increase of application area of macro cyclic crown-ethers the interest in development of new methods of their synthesis by using new sintons has been increased. These compounds have unusual chemical properties, in particular, high ability to complexation. Their metal complexes find wide application in separation of metal ions, in various extraction processes, interphase catalysis, as well as in catalysis of redox and biochemical processes [1-4]. It is expected that such compounds will be used in devices for photometric and luminescent determination of metal cations, ammonium ions and some organic cations.

Most of ionic compounds are restrictedly soluble in nonpolar aprotic solvents. Realization of a significant increase in nucleophility of anions in a polar aprotic solvent has led to essential improvement of nucleophilic substitution or connection. Macrocyclic poly ethers can solvate specifically such cations like Na^+ and K^+. For example, with 18-crown-6 potassium fluoride is soluble in benzene or acetonitrile and acts as a reactive nucleophile which causes the substitution of haloids with fluorine ion. Therefore, nucleophility of anion strongly depends on the degree of its solvation.

The most adverse factor for a research in bipolar aprotic solvents unlike proton environments is a solubility of salts of alkaline metals. In the solution of this problem considerable achievement was the use of crown-ether of 18-crown-6.

Experimental Part

Citation: Khojayev KG, Raya A Najafova AR, Melikova YA, et al. Some Aspects of the Synthesis of Crown Ethers. Acta Chim Pharm Indica, 2018; 8(3):131

Synthesis of crown-ethers on the basis of cyclohexanedionedioxime-1,2 (I)

The reaction was conducted at constant excess of ethylene oxide and in diethyl ether in a range of 0-20°C where Boron trifluoride etherate was used as a catalyst. Reaction time was 10-12 hours. Then the mixture was washed with water, dried, diethyl ether was distilled, the residue was crystallized with heptane T_{melt} 85-89°C.

Synthesis of crown-ethers of α-furyldioxime (II)

Synthesis method is similar to obtaining of compound III. However, depending on mol ratio of furyldioxime and dichlordiethyl ether we may control the amount of oxyethylene fragments T_{melt} 98-110.

Spiroarylaminocrown ethers (III a, b)

16-fold excess of aniline or toluidine was dissolved in o- or n-xylol. The solution was heated up to 140°C and 20-fold excess of cghlorex was added drop by drop within an hour. Mixing was continued at 140°C for 10-11 hours. After the reaction was completed solvent and unreacted amine were dissolved. Remaining mass was washed with water and crystallized with hexane or heptane. T_{melt} of aniline-18-crown-6-ether is 47°C (V_a), but T_{melt} of toluidine-18-crown-6- ether is at 82°C.
In PMR-spectrum protons of methylene groups connected with amine group appear in 3.52-3.54 ppm, but protons of the rest methylene groups are in a weaker field. Protons of mono-substituted aromatic fragments appear in 4.2 ppm.

Synthesis of crown-ethers on the basis of salicylic or thiosalicylic acids and ethylenechlorhydrine (IV a,b)

The reaction was conducted in steel autoclave at an excess of ethylenchlorhydrine. Solution of salicylic to thiosalicylic acids and ethylenechlorhydrine were loaded in an autoclave in benzene by adding alkali catalyst. The mixture was heated up to 70-75°C until pressure suppression is stopped. After cooling, benzene was removed from the mass. The remaining mass was washed with water and crystallized from n-heptane. Yields of crown-ethers make 51-75 %. Melting temperature range is very wide (beginning from 91°C) due to the amount of ethylene groups.

Allylaminocrown-ether (V)

Ethylene oxide in mol ratio of allyl amine and ethylene oxide 1: 25÷30 were passed through the mixture of allylamine and benzene at 20°C. Reaction time was 10-12 hours. Then the mixture was boiled till complete extraction of water in Dean-Stark trap. Reaction mixture was cooled, washed and the residue was crystallized with hexane T_{melt} 65-68°C.

Results and Discussion

When studying relative rates of nucleophilic substitution of benzyltosylate with potassium salts in acetonitrile with 18-crown-6 we established obviously expressed smoothing effect [5,6]. In certain cases crown-ether modified by silica gel are used to separate sulfate salts of alkali metals in water flow. Perhydrodibenzo-18-crown-6 is used as crown ether (isomer A) [7]. The offered method 2.5 times exceeds in efficiency the known separation method.

The purpose of this work is to develop new synthesis methods of aza-and thiocrown-ethers and to study them in catalysis of dehydrobromation of 1,2-dibromalkanes.

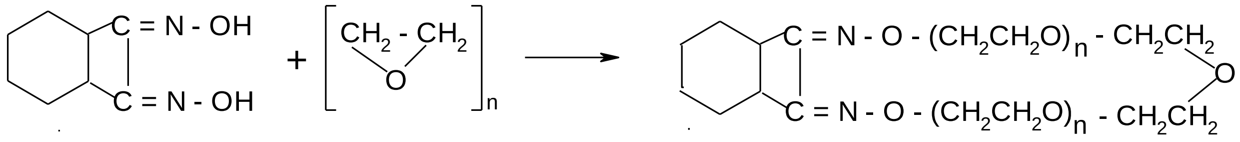
Among crown-ethers azacrown compound which contains one nitrogen atom is of considerable interest for obtaining photoactive crown-ethers. At present derivatives of phenylazacrown ethers have been widely used. However they have one essential shortcoming: their constants of complexation with metal ions are low. In this regard the synthesis and development of new synthesis methods which lead to high yields of azacrown-ethers are urgent tasks.

Such crown-ethers were obtained by the condensation of two acyclic fragments [8-10]. There are practically no synthesis methods of azacrown-ethers by cyclization of suitable acyclic predecessor due to unavailability of sintons. However it is known that many available derivatives of heterocycles are formed from more available predecessors using transformation reaction of cycles [11]. Aliphatic amines and alkyl ammonium chloride are used as primary compounds for the synthesis of azacrown-ethers [12,13].

Synthesis methods of azacrown-ethers containing aryl-, furyl-and thienyl fragments were developed [14]. It was established that synthesized imidazobenzo-15-crown-5-ether which contains arylthienyl or bisthienyl forms resistant compound with Pd^{+2} and Cu^{+2} [15]. Alkali element alkoxides are used as a catalyst in the synthesis of crown-ethers by using the reaction of polyethylene glycol with dichlorides of glycols. Obtained crown-ethers are selected in the form of a complex with alkaline ions, and output of target products is low. Ammonia solution is taken instead of alkali metal alkoxides in our method. The reaction was conducted between ethylene glycol or diethylene glycol with dichlordiethyl oxide. When using ammonia solution the output of crown-ether reaches 85.8%.

We used substituted aromatic diatomic alcohols, diatomic phenols and other compounds for the synthesis of aromatic crown-ethers. Typical aromatic crown-ethers are benzo-and dibenzosubstituted crown-ethers, including dibenzo-18-crown-6.

We have developed a method for obtaining new crown-ethers by polycondensation reaction of dioximes with ethylene oxide in diethyl ether. As primary dioximes we used cyclohexanediondioxime-1,2. Reaction was conducted with the catalyst – boron trifluoride etherate in the range of 0 ÷ 20°C at constant addition of excess ethylene oxide:



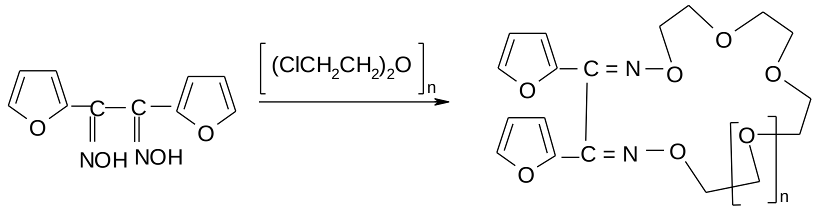
n = 3, 4

I

Bifunctional initial substances leading to the formation of oligomers, participate in reaction of intramolecular cyclization. The side reactions related to condensation of macro cycle with initial substances may also proceed. Such processes have a peculiar character and are only related to the properties of initial substances, namely – oligomerization reaction of ethylene oxide and Beckmann rearrangement of dioximes.

The most universal template agents for the synthesis of nitrogen-containing macro cycles are ions of alkaline metals.

The nature of anions has a certain impact on the yield of products of template synthesis. When replacing NaOH by NaOMe the yield of ethers has doubled. It can be explained with the increase in nucleophility of anion that facilitates the transformation of OH group in primary polyethylene glycol alkoxide-ion. We have studied that the condensation reaction of α-furyldioxime with dichloralkyl ether in excess of the latter:

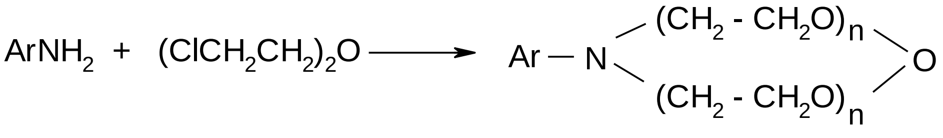


II

n= 2 - 4

Depending on mol ratio of primary components synthesized compounds allows us to obtain nitrogen-containing crown-ethers with various amounts of oxyethylene groups.

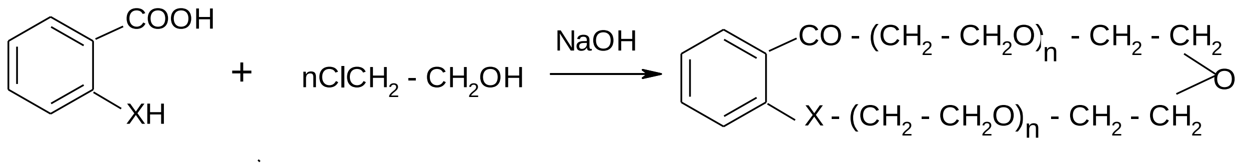
We have studied the condensation reaction of aniline and toluidine with dichlordiethyl ether (chlorex) in the presence of alkali. As it is a known reaction of chlorex with amines proceeds by SN_2 nucleophilic substitution mechanism of chlorine atom with amine group. It was found that in case of great excess of chlorex the reaction does not stop in terminations of monochlordialkylamines. The use of aniline and o-toluidine in reaction with chlorex in excess amines at 140- 150°C for 10-12 hours results in the formation of spiro-crown-ethers:



$$ArNH_2 + (ClCH_2CH_2)_2O \longrightarrow Ar-N\begin{matrix}(CH_2-CH_2O)_n \\ (CH_2-CH_2O)_n\end{matrix}O$$

Ar = Ph (IIIa), Tol (IIIb) n =6 - 18

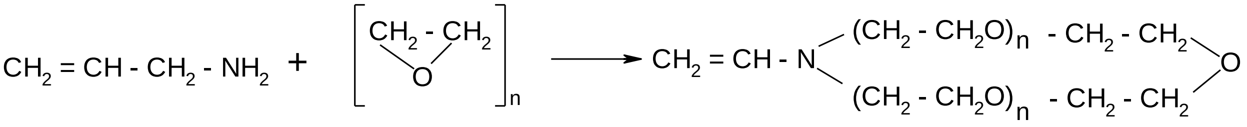
To obtain benzthiocrown-ethers we have developed an effective synthesis method of ethers which differ by the size of heterocycle and combination of atoms O and S. The synthesis of such thiocrown-ethers is known from literature [16] and the structures of their complexes were studied by the methods of NMR and RSA [17]. We obtained benzthiocrownethers by the condensation of salicylic and thiosalicylic acids with ethylenechlorhydrine in benzene with the basis in autoclave at 70 – 75 °C. Benz crown- and benzthiocrownethers were obtained with high yield:



n = 6 - 14 ; X=O (IVa), X=S (IVb)

Investigation of properties of crown-ethers showed that polymer derivatives, particularly, polyvinyl-18-crownethers ($P_{18}C_6$) form more resistant complexes. They connect sodium picrate, methyl orange and others into the complex. Besides, they are more stable than the complexes of polyvinylpyrrolidon and bovine serum albumin [18,19].

For the synthesis of polyvinyl crown-ethers we studied the reaction of allylamine with ethylene oxide with excess of the last:



n= 6 - 14 (V)

Great progress has been made in the organic synthesis among various application fields of crown-compounds. The reaction with crown-ethers includes different types of conversions such as neutralization, etherification, oxidation, reduction, nucleophilic substitution, peeling reaction and so on. The use of crown-ethers in organic reactions is conditioned by a number of important reasons like the formation of cationic complexes with inorganic salts, solution in non-polar solvents by obtaining of «fresh active unsolvated ion» and so on. This results in the increase of an electro donor ability of anion and, correspondingly, the rise of its nucleophility and basicity. Among many literature data on these studies peeling reaction is the most important for synthesis of unsaturated compounds [20].

In the solution alkoxides are associated, but under the action of crown-ethers they are dissociated and their reactivity increases several times. Continuing the researches in this field we conducted the catalysis of dehydrobromation of 1,2-dibromoctane (DBO) with crown-ethers.

We studied the reaction of exhaustive alkali dehydrobromation of 1,2-dibromoctane by interphase catalysis. The reaction was conducted in double-phase heterogeneous system consisting of anhydrous powder alkali, solution of DBO in organic solvents and catalysts of interphase transition (CIT). For comparison we obtained and studied the following crown-ethers:

- Dibenzocrown-ether (DBC), synthesized by interaction reaction of pyrocatechin with dichlordiethyl ether in the presence of aqueous ammonia ($T_{melt.}$= 125-126°C);
- Cyclohexane crown-ether (CHC), obtained by the reaction of cyclohexanediol with chlorex in the presence of ammonia ($_{Tboil.}$= 175-177°C / 1 mm of mercury);

- Pentaethylene 15C-5 (PEC15C-5), synthesized by the reaction of diethyleneglycole with chlorex in the presence of ammonia c ($T_{melt.}$= 22°C)
- Salicylthiocrown-ether (STC), obtained by the reaction of thiosalicylic acid with ethylenechlorhydrine in the presence of a base [21]
- Spiro- and ansa-crown-ethers (SAC), obtained by the reaction of quinone (spiro-) or hydroquinone with ethylene oxide in the presence of catalyst – boron trifluoride etherate [22]
- Furyldioxime Crown-ethers (FDOC), obtained by the reaction of furyldioxime with dichlorethyl ether in the presence of a base

For comparison we used clay and chloro triethylbenzylammonium (TEBA). It was shown that the activity of a super basic dehydrohalogenating system (DHS) and yield of end product of octyne is primarily controlled by the transition rate of alkali molecules to organic phase, but the latter depends on the complexation of crown-ether and solubility of this complex. Maximum yield of octyne is observed in polar protic solvents in which solvation of hydroxyl anion is absent in solvation of cation. That’s why depending on a solvent the yield of a product decreases:

Without solvent > in simple ethers > in alcohols > in glycoles > in hydrocarbons

Crown-ethers have appeared highly effective among three classes of CIPT. The least active CITP is TEBA. In the series of crown ethers relative to potassium alkali beginning from six (-CH_2 – CH_2O) groups in macro cycle the activity decreases as the sizes of cavity of crown-ethers decreases. Activity of CITP changes in the following way:

DBC > STC > FDC > SAC > CHC > PE15C-5 > clay > TEBA

It is assumed that furyldioxime crown-ether has a high degree of tension in nitrogen atoms which makes it less effective complexing agent than dibenzocrown-ether. Such tension is also observed in benzoazacrown-ethers [23].

It was noted in literature [24] that sulphur atom in thiocrown-ethers have an adverse effect on the coordination of metals, but depending on a solvent flexible macro heterocyclic fragment is capable of conformation reconstruction. During catalysis of debromation reaction of 1,2-dibromoctane synthesized thiocrown-ethers showed high effectiveness. Probably, this is related to mutual influence of thio- and carbonyl groups of thiosalicylic acid.

Activity of DHS and yield of 1-octyne rise with the increase of alkali concentration and CITP. However, after certain concentration side effects occur, such as isomerization of octyne to 1,2-octadiene and partial resinification. Used bases are disposed on activity in the following row:

KOH > NaOH > LiOH = Ca $(OH)_2$

Maximum activity of KOH is due to affinity of DBC to K^+ ion in solvent which provides the best transition of KOH to organic phase. The influence of water on activity of double-phase heterogeneous system and yield of 1-octyne indicates high activity of quaternary base as compared to crown-ether in aqueous medium.

Thus, as a result of researches we have developed a new synthesis method of new dibenzo-, benzoaza-, spiroaza-, benzthiocrown- and other ethers. They have been studied as catalysts in interphase catalysis of debromation of 1,2-

dibromoctane. It was established that activity of double-phase super basic DHS and yield of end product is defined by a number of factors, each of which, depending on specific conditions, can be dominant.

REFERENCES

1. Bogatskiy AV. Bioorganic chemistry 1986, 31:1445-1482.
2. Ushakov EN. Russian nanotechnologies 2008, 1:42-59.
3. Minkin VI. Proceedings of Academy of Sciences, 2008, 4:673-703.
4. Mizerov AA, Lukovskaya EV, Bobileva AA, et al. Collection of scientific works of Dmitry Mendeleev University of Chemical Technology of Russia. Chemical Technology of Russia, 2010; 25:89-92.
5. Liotta CL, Harris HP. Chemistry of naked anions. I. Reactions of the 18-crown-6 complex of potassium fluoride with organic substrates in aprotic organic solvents. J Am Chem Soc, 1974,96: 2250-2255.
6. Klimenko LS, Martyanov TP. Herald of Chemical. Yugra State University, 2009;3:37-42.
7. Karaev SF, Habibova AK, Kazimov AS. Reports of conference «Organic reagents in analytical chemistry», Baku, 2009.
8. Rusalov MV, Ujinov BM, Alfimov MB, et al. Photoinduced recoordination of metal cations in complexes with chromogenic crown ethers. Uspekhi Khimii, 2010;79:1193-1197.
9. Lockhart JC, Robson AC, Thompson SD, et al. Catalysis of .alpha.-hydrogen exchange. XII. Catalysis of the dedeuteration of isobutyraldehyde-2-d by linear diamines including 1-dimethylamino-8-amino-2-octyne, a bifunctional catalyst. J Am Chem Soc, 1973;95:1577-1582.
10. Van der Plas HC. Ring transformations of Heterocycles. Academic Press. London-New York, USA.
11. Gromov SP. Ring Transformation of Pyridines and Benzo Derivatives under the Action of C-Nucleophiles. Heterocycles, 2000;53:1607-1612.
12. Dmirtieva SN, Churakova MV, Gromov SP. Phenylaza- and benzoazacrown compounds with a nitrogen atom conjugated with a benzene ring. Journal of Organic chemistry, 2005,41,3:468-471.
13. Gromov SP, Dmitrieva SN, Vedernikov AI, et al. N-Methylbenzoazacrown ethers with the nitrogen atom conjugated with the benzene ring: the improved synthesis and the reasons for the high stability of complexes with metal and ammonium cations. J Phys Org Chem, 2009;22:823-826.
14. Oliveira E, Batista RMF, Costa SPG, et al. Exploring the Emissive Properties of New Azacrown Compounds Bearing Aryl, Furyl, or Thienyl Moieties: A Special Case of Chelation Enhancement of Fluorescence upon Interaction with Ca2+, Cu2+, or Ni2+. J Inorganic Chem. 2010,49;23:10847-10857.
15. Batista RMF, Oliveira E, Costa SPG, et al. Imidazo-benzo-15-crown-5 ethers bearing arylthienyl and bithienyl moieties as novel fluorescent chemosensors for Pd* and Cu. Tetrahedron, 2011, 67,37:7106-7113.
16. Dmitrieva SN, Siderenko NI, Vedernikov AI, et al. Proceedings of Academy of Sciences (Russian). Chem Serie, 2007;58:56-61.
17. Dmitrieva SN, Siderenko NI, Kurchavov NA, et al. Macrocyclic Complexes of Palladium (II) with Benzothiacrown Ethers: Synthesis, Characterization, and Structure of cis and Trans Isomers. J Inorganic Chem, 2011; 50: 7500-7510.

18. Zeynalov SB. Ethers of alicyclic serie. Baku, Elm, 1996.
19. Nakatsuji Y, Mori T, Okahoma M. Tetrahedron Lett, 1984;25:2171-2174.
20. Maeda H, Kikui T, Nakatsuji Y. Synthesis of Bis (Aminomethyl) Crown Ethers. Synthesis, 1983;3:185-187.
21. Budagova RN, Zeynalov SB, Xocayev HX. Patent a 2015 0031. Azerbaijan.
22. Budagova RN, Zeynalov SB, Sadikhova GK, et al. Spiro- and ansa-macrocyc-lic polyethers. Austrian J Tech Nat Sci, 2015,3:128-130.
23. Gromov SP, Dmitrieva SN, Vedernikov AI, et al. New Synthesis of Formyl benzoazacrown Ethers. Rus J Org Chem, 2005;41:1387-1389.
24. Kuzmina LG, Vedernikov AI, Dmitriyeva SN, et al. Proceedings of Academy of Sciences (Russia). Serie Chem, 2007;57:967-970.