

Halogenation of Benzocrown Ethers by Hypohalites in Aqueous Solutions

Sergei M. Pluzhnik-Gladyr

Dedicated to Academician Aslan Yu. Tsivadze on the occasion of his 70th birthday

*A.V. Bogatsky Physico-Chemical Institute of National Academy of Sciences of Ukraine, 65080 Odessa, Ukraine
E-mail: sergey_pluzhnik@ukr.net*

It was found that both sodium hypochlorite and hypobromite can be used as mild and selective reagents for chlorination and bromination of benzocrown ethers (BCE) in water medium. The adjustment of pH in these processes enables the control of the resulting number of atoms of halogens in the aromatic fragment of BCE. Only mono halogen-BCE are found in the alkaline environment, while in the acidic medium there are only tetrachloride and dibromide BCE. The possibility of the use of elementary iodine in aqueous solution for the iodination of BCE by hypoiodite in situ was also demonstrated.

Keywords: Benzocrown ethers, halogeno derivatives, synthesis, selective halogenation, hypohalites, aqueous solutions.

Галогенирование бензокраун-эфиров гипогалогенитами в водных растворах

С. М. Плужник-Гладырь

Посвящается академику Аслану Юсуповичу Цивадзе по случаю его 70-летнего юбилея

*Физико-химический институт им. А.В. Богатского НАН Украины, 65080 Одесса, Украина
E-mail: sergey_pluzhnik@ukr.net*

NaClO и NaBrO могут быть использованы в качестве селективных реагентов для хлорирования и бромирования бензокраун-эфиров (БКЭ) в водной среде. Регулирование pH в этих процессах позволяет контролировать число атомов галогенов в ароматическом фрагменте БКЭ.

Ключевые слова: Бензокраун-эфиры, галогенпроизводные, синтез, селективное галогенирование, гипогалогениты, водные растворы.

Introduction

The halogen containing benzocrown ethers (HBCE) are used in applied,^[1] technological^[2] and synthetic chemistry. Sufficient mobility of bromine and iodine atoms in the aromatic fragments of these macrocycles enables ease of further transformations into acetylene,^[3-5] vinyl,^[4-5] *n*-alkyl, *n*-hydroxyalkyl,^[6] bioactive ammonium and phosphonium^[7] derivatives, which are hard or inaccessible by other ways,

and also crown heterocycles,^[8] bis-benzocrown ethers,^[3,6] *etc.* HBCE have great potential as materials for the synthesis of new types of polymers with selective sorption,^[9] original nanolayers,^[1] considerably increasing products' wear resistance, *etc.* The iodination usually is conducted in the systems, containing strong oxidants or expensive reagents, namely, I₂-HIO₃-H₂SO₄,^[10,11] I₂-CF₃COOAg,^[5] trimethylbenzylammonium dichloro iodide-CH₃COOH-ZnCl₂.^[12] In the bromination process the molecular bromine (Br₂) is

used or, in some cases, *N*-bromosuccinimide (NBS).^[13-16] The process of chlorination by molecular chlorine is not selective enough and produces only perchlorinated aromatic products.^[17] The abilities of the other halogenating agents are not yet known. Therefore, the known methods of synthesis of HBCE are using toxic, explosive or exotic reagents, and organic solvents, requiring evaporation and regeneration.

In order to reduce the cost of HBCE, reduce the fire hazard and to simplify the production, we suggested a number of laboratory methods of halogenation of BCE, with the use of *N*-halogenosuccinimides (NHS) as the halogenating agent. The halogenation of BCE was performed both in water solutions,^[18-20] and without any solvent, with the use of principles of «green chemistry».^[18,21] There are no documented methods of halogenation of BCE or its derivatives (other crown compounds) in a water medium prior to our study.

It is the fact that BCE are capable to form 3-5% water solutions that enables the reaction in homogeneous conditions. Dibenzocrown ethers (DBCE) unlike BCE are practically insoluble in water.

It was found that the gradual addition of finely ground powder of NHS to the stirred aqueous solution of BCE, smoothly, selectively and in high yields resulted in mono-bromo or mono-iodo derivatives at room temperature. In order to get monochloride derivatives of BCE, however, it was necessary to raise the temperature of the reaction up to 60 °C. We assume that the route of the reaction involves rapid hydrolysis of NHS to the corresponding hypohalite acids, followed by in situ oxidative halogenation of the substrate (Figure 1).

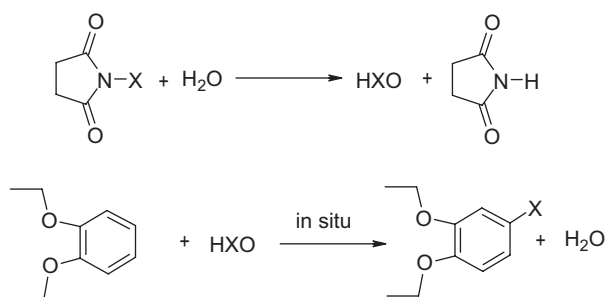


Figure 1. X = Cl; Br; I.

The observed changes of acidity of the freshly prepared aqueous solutions of NHS confirm their rapid hydrolysis. So the *pH* of solutions at the time of preparation equal to 3.79; 4.71; 4.12 for *N*-chloro- (NCS); *N*-bromo- (NBS); and *N*-iodosuccinimide (NIS) accordingly. After 30 minutes this index became equal to 3.74; 4.45; 3.35, and after 24 hours - 2.8; 4.2; 3.3.

The observed selectivity of BCE halogenation is apparently stipulated by the low solubility of the target HBCE in water and their rapid crystallization. For example diiodides are not detected among products of reaction even at a quadruple excess of NIS.

BCE's solubility in acidic aqueous medium increases greatly. It has been found that BCE are easily brominated and iodinated by NHS in 20% aqueous solution of sulfuric acid

at the room temperature forming exclusively disubstituted products with the high yields.

Apparently, in H_2SO_4 solution, intermediates (monobromides and monoiodides) are soluble in the forms of complexes with hydronium ions,^[22] which ensure homogeneous selective halogenation to dibromides and diiodide. This assumption is confirmed by the fact that Br-BCE and I-BCE in the 20 % aqueous solution of H_2SO_4 are smoothly brominated at the room temperature and are iodinated with equimolar amount of the appropriate NHS to dihalogenoderivates.

In contrast with the NBS and NIS, the hydrolysis rate of NCS in aqueous solution at room temperature is not sufficient to generate hypochlorite and becomes significant only at 60 °C. Under acidic conditions, at room temperature, NCS also does not react with BCE (products found only in trace amounts), and the heating of the reaction mixture begins the side effect resinification noticeably. The same strong resinification reaction at elevated temperatures is observed in acidic water solution during the BCE halogenation using NBS and NIS.

It is a well-known fact that hypohalogen acids are unstable and easily undergo disproportionation^[23] as per scheme: $3HXO = 2HX + HXO_3$, the reaction rate is low at room temperature and increases rapidly when heated, especially for X = Br and I. The use of H_2SO_4 in relatively low (18-20 %) concentrations, apparently reduces the possible side effects to a minimum.

The experimental results confirm our hypothesis about the mechanism of halogenation of BCE by NHS in neutral or acidic aqueous solutions. Therefore with regard to the discussed halogenating systems the author can conclude the following:

1. The halogenating agent of BCE in an aqueous solution is hypohalite formed by the hydrolysis of the NHS.
2. The use of NHS for halogenation of BCE in an aqueous solution leads exclusively to the monosubstitution products.
3. A solubility of both BCE and their monohalogeno derivatives increases rapidly in 20 % aqueous solution of H_2SO_4 , and allows the further halogenation of corresponding halogen-BCE.
4. The halogenation of BCE by NHS should be done at the lowest possible temperature.
5. The NCS is the least successful reagent for BCE halogenation in an aqueous solution in comparison with NBS and NIS.

The experimental results and the mentioned above arguments allow us to conclude that for the BCE halogenation it is advisable to use water solutions of widely available hypochlorites and hypobromites.

Experimental

The trade acids, sodium hydroxide, crown ether **1** (98 %, «TCI America»), bromine and iodine were used without additional purification. Commercially available 10 % water solution of NaClO («Belizna-Kalushanka», Oniks, Ukraine) were used. Macrocyces **2**^[24] and **3**^[25] were prepared according to the known methods and purified by crystallization to the 98 % purity (GLC). ¹H NMR spectra were recorded on the Varian VXR-300 (299.94 MHz) spectrometer. All chemical shifts are quoted in ppm on the δ scale with TMS as an

internal standard. The melting points were determined by the open capillary tube method and were uncorrected. Fast atom bombardment (FAB) mass spectrometry was performed on a VG 70-70EQ mass spectrometer, equipped with an argon primary atom beam, and an *m*-nitrobenzyl alcohol matrix was utilized. EI-Mass spectra were obtained with a MX 1321 spectrometer equipped with a direct inlet; ionization voltage 70 eV and ionization chamber temperature 200 °C. Elemental analysis was carried out on a EuroVector EA3000 CHNS elemental analyzer. The sum of halogens was determined by the Schöniger flask test by the sample burning in the oxygen atmosphere using platinum catalyst, followed by mercurimetric titration of the halogenated combustion products in the presence of diphenylcarbazone.^[26] The thin layer chromatographic control of the substances purity was performed on Silufol UV 254 plates using halogenated BCE, synthesized (see Introduction) according to well-known methods, as reference compounds.

Chlorination in alkaline aqueous medium. General procedure.

3.73 mmol of crown ether (**1-3**) at room temperature (20 °C) was placed in a 10 ml (14.38 mmol) of 10 % aqueous solution (density 1.071) of sodium hypochlorite. The reaction mixture was stirred for 5 min, and the resulting clear solution was left for 24 hours. The precipitated crystals were filtered and washed on the filter with water (1 ml×3) and air-dried to constant weight, if necessary, was crystallized from a minimum amount of *n*-hexane.

4'-Chlorobenzo-12-crown-4 (4): Obtained 0.63 g (65 %), m.p. 56 °C. Found, %: C 55.66, H 5.73, Cl 13.57. C₁₂H₁₅ClO₄ requires, %: C 55.71, H 5.84, Cl 13.7. *m/z* (ESI) (%): 258 (46), 260 (12) [M⁺]; 170 (100), 171 (14), 172 (29) [(M-(CH₂CH₂O)₂]⁺. ¹H NMR (CDCl₃, 298 K) δ_H ppm: 7.05 (1H, s, Ar), 6.96-6.94 (1H, d, *J* = 9.2 Hz, Ar), 6.92-6.90 (1H, d, *J* = 9.2 Hz, Ar), 4.29-4.21 (4H, t, *J* = 4.5 Hz, OCH₂), 4.19-4.06 (4H, t, *J* = 4.5 Hz, CH₂O), 3.78 (4H, s, OCH₂CH₂O).

4'-Chlorobenzo-15-crown-5 (5): Obtained 0.85 g (75 %), m.p. 84 °C. Found, %: C 55.61, H 6.22, Cl 11.81. C₁₄H₁₉ClO₅ requires, %: C 55.54, H 6.33, Cl 11.71. *m/z* (ESI) (%): 302 (34) [M⁺]; 170 (100) [(M-(CH₂CH₂O)₃]⁺. ¹H NMR (CDCl₃, 298 K) δ_H ppm: 6.92 (1H, s, Ar), 6.87-6.85 (1H, d, *J* = 8.4 Hz, Ar), 6.79-6.77 (1H, d, *J* = 8.4 Hz, Ar), 4.13-4.08 (4H, t, *J* = 4.2 Hz, OCH₂), 3.92-3.87 (4H, t, *J* = 4.2 Hz, CH₂O), 3.75 (8H, s, OCH₂CH₂O).

4'-Chlorobenzo-18-crown-6 (6): Obtained 0.97 g (75 %), m.p. 59 °C. Found, %: C 55.35, H 6.55, Cl 10.17. C₁₆H₂₃ClO₆ requires, %: C 55.41, H 6.68, Cl 10.22. *m/z* (ESI) (%): 346 (9), 348 (3), [M⁺]; 170 (100), 171 (9), 172 (31) [(M-(CH₂CH₂O)₄]⁺. ¹H NMR (CDCl₃, 298 K) δ_H ppm: 6.87-6.89 (1H, d, *J* = 8.1 Hz, Ar), 6.84 (1H, s, Ar), 6.76-6.79 (1H, d, *J* = 8.1 Hz, Ar), 4.14-4.12 (4H, t, *J* = 4.1 Hz, OCH₂), 3.92-3.90 (4H, t, *J* = 4.1 Hz, CH₂O), 3.70-3.76 (8H, m, OCH₂CH₂O), 3.68 (4H, s, OCH₂CH₂O).

Chlorination in acidic aqueous medium. General procedure.

3.73 mmol of crown ether (**1-3**) at 0-5 °C was dissolved in 50 ml of concentrated hydrochloric acid. To this solution at 0-5 °C for 15-20 minutes with vigorous stirring, 50 ml of 10 % aqueous solution (density 1.071), sodium hypochlorite and the resulting clear solution was left for 24 hours. Slightly sticky fallen crystals were filtered and washed on the filter with water (1 ml×3) and dried on air to constant weight, crystallized from a minimum amount of ethanol.

3',4',5',6'-Tetrachlorobenzo-12-crown-4 (7): Obtained 0.65 g (48 %), m.p. 165 °C. Found, %: C 39.68, H 3.31, Cl 39.06. C₁₂H₁₂Cl₄O₄ requires, %: C 39.81, H 3.34, Cl 39.17. *m/z* (FAB) (%): 360 (14), 361 (59), 362 (23), 363 (60), 364 (19), 365 (24), 366 (2), 367 (6) [M⁺]; 271 (4), 272 (50), 273 (32), 274 (61), 275 (38), 276 (26), 277 (23) [(M-(CH₂CH₂O)₂]⁺. ¹H NMR (CDCl₃, 298 K) δ_H ppm: 4.26-4.23 (4H, e, *J* = 4.05 Hz, OCH₂), 3.94-3.91 (4H, t, *J* = 4.05 Hz, CH₂O), 3.81 (4H, s, OCH₂CH₂O).

3',4',5',6'-Tetrachlorobenzo-15-crown-5 (8): Obtained 1.18 g (78 %), m.p. 112 °C. Found, %: C 41.29, H 4.01, Cl 34.77. C₁₄H₁₆Cl₄O₅ requires, %: C 41.41, H 3.97, Cl 34.92. *m/z* (FAB) (%): 404 (12), 405 (52), 406 (23), 407 (59), 408 (19), 409 (32), 410

(3), 411 (4); [M⁺]; 271 (1), 272 (53), 273 (35), 274 (68), 275 (30), 276 (23), 277 (15), 278 (3), 279 (6); [(M-(CH₂CH₂O)₃]⁺. ¹H NMR (CDCl₃, 298 K) δ_H ppm: 4.25-4.22 (4H, t, *J* = 4.98 Hz, OCH₂), 3.99-3.96 (4H, t, *J* = 4.98 Hz, CH₂O), 3.74 (8H, s, OCH₂CH₂O).

3',4',5',6'-Tetrachlorobenzo-18-crown-6 (9): Obtained 1.28 g (76 %), m.p. 94 °C. Found, %: C 42.52, H 4.57, Cl 31.37. C₁₆H₂₀Cl₄O₆ requires, %: C 42.69, H 4.48, Cl 31.50. *m/z* (FAB) (%): 448(18), 449 (66), 450 (27), 451 (70), 452 (23), 453 (35), 454 (4), 455 (5); [M⁺]; 272 (59), 273 (41), 274 (78), 275 (36), 276 (28), 277 (21), 279 (8); [(M-(CH₂CH₂O)₄]⁺. ¹H NMR (CDCl₃, 298 K) δ_H ppm: 4.12-4.10 (4H, t, *J* = 4.4 Hz, OCH₂), 3.91-3.88 (4H, t, *J* = 4.4 Hz, CH₂O), 3.76-3.70 (8H, m, OCH₂CH₂O), 3.68 (4H, s, OCH₂CH₂O).

Bromination. General procedure a) Preparation of sodium hypobromite solution. 7.11 g (177 mmol) of sodium hydroxide dissolved in 50 ml of water. To this solution at a temperature of 0 °C and vigorous stirring gently added 14.22 g (88 mmol) of bromine.

b) BCE bromination in alkaline aqueous medium. 5 mmol of crown ether (**1-3**) was dissolved in 50 ml of water and to the solution at 0 °C and vigorous stirring was added a freshly prepared solution of sodium hypobromite. After 24 hours, the precipitated crystalline precipitate was filtered off, washed on the filter with water (1 ml×3), air-dried to constant weight, and crystallized from a minimum amount of *n*-hexane.

c) BCE bromination in acidic aqueous medium. 5 mmol of crown ether (**1-3**) was dissolved in 50 ml of concentrated hydrobromic or hydrochloric acid. To this solution at 0 °C was carefully added a freshly prepared solution of sodium hypobromite. After 2 hours, the reaction mixture was added 3 % aqueous solution of sodium sulfite prior to bleaching. The precipitated crystalline precipitate was filtered off, washed on the filter with three portions of water (1 ml×3) and crystallized from *n*-hexane.

4'-Bromobenzo-12-crown-4 (10): Obtained 1.09 g (72 %), m.p. 57.5-58 °C. Found, %: C 47.52, H 4.82, Br 26.25. C₁₂H₁₅BrO₄ requires, %: C 47.54, H 4.99, Br 26.36. *m/z* (ESI) (%): 302 (52) 303 (4), 304 (56), [M⁺]; 214 (94), 215 (2), 216 (100) [(M-(CH₂CH₂O)₂]⁺. ¹H NMR (CDCl₃, 298 K) δ_H ppm: 7.20 (1H, s, Ar), 7.08-7.04 (1H, d, *J* = 8.1 Hz, Ar), 6.74-6.71 (1H, d, *J* = 8.1 Hz, Ar), 4.18-4.12 (4H, m, OCH₂), 3.87-3.81 (4H, m, CH₂O), 3.77 (4H, s, OCH₂CH₂O).

4'-Bromobenzo-15-crown-5 (11): Obtained 1.39 g (80 %), m.p. 68 °C. Found, %: C 48.42, H 5.44, Br 23.00. C₁₄H₁₉BrO₅ requires, %: C 48.43, H 5.52, Br 23.01. *m/z* (ESI) (%): 347 (25) 349 (27), [M⁺]; 215 (100), 216 (12), 217 (97) [(M-(CH₂CH₂O)₃]⁺. ¹H NMR (CDCl₃, 298 K) δ_H ppm: 7.07 (1H, dd, Ar), 7.03-6.97 (1H, d, *J* = 8.45 Hz, Ar), 6.75-6.72 (1H, d, *J* = 8.45 Hz, Ar), 4.11-4.09 (4H, t, *J* = 4.4 Hz, OCH₂), 3.91-3.88 (4H, t, *J* = 4.4 Hz, CH₂O), 3.75 (8H, s, OCH₂CH₂O).

4'-Bromobenzo-18-crown-6 (12): Obtained 1.64 g (84 %), m.p. 79-80 °C. Found, %: C 49.05, H 5.99, Br 20.36. C₁₆H₂₃BrO₆ requires, %: C 49.12, H 5.93, Br 20.42. *m/z* (ESI) (%): 390 (45), 392 (46) [M⁺]; 216 (99), 214 (100) [(M-(CH₂CH₂O)₄]⁺. ¹H NMR (CDCl₃, 298 K) δ_H ppm: 7.02 (1H, s, Ar), 7.02-6.98 (1H, d, *J* = 7.8 Hz, Ar), 6.76-6.73 (1H, d, *J* = 7.8 Hz, Ar), 4.15-4.11 (4H, t, *J* = 4.0 Hz, OCH₂), 3.92-3.89 (4H, t, *J* = 4.0 Hz, CH₂O), 3.77-3.70 (8H, m, OCH₂CH₂O), 3.68 (4H, s, OCH₂CH₂O).

4',5'-Dibromobenzo-12-crown-4 (13): Obtained 1.45 g (76 %), m.p. 80 °C. Found, %: C 37.66, H 3.50, Br 41.68. C₁₂H₁₄Br₂O₄ requires, %: C 37.73, H 3.69, Br 41.83. *m/z* (ESI) (%): 380 (15), 382 (7), 384 (10) [M⁺]; 291 (5), 292 (60), 293 (3), 294 (100), 295 (12), 296 (53), 297 (5), [(M-(CH₂CH₂O)₂]⁺. ¹H NMR (CDCl₃, 298 K) δ_H ppm: 7.15 (2H, s, Ar), 4.15-4.10 (4H, t, *J* = 5.0 Hz, OCH₂), 3.97-3.87 (4H, t, *J* = 5.0 Hz, CH₂O), 3.72 (4H, s, OCH₂CH₂O).

4',5'-Dibromobenzo-15-crown-5 (14): Obtained 1.70 g (80 %), m.p. 85 °C. Found, %: C 39.37, H 4.21, Br 37.40. C₁₄H₁₈Br₂O₅ requires, %: C 39.46, H 4.26, Br 37.50; *m/z* (ESI) (%): 424 (19), 426 (37), 428 (17), [M⁺]; 291 (1.5), 292 (49), 293 (7), 294 (100), 295 (11), 296 (49), [(M-(CH₂CH₂O)₃]⁺. ¹H NMR (CDCl₃, 298 K) δ_H ppm: 6.92 (2H, s, Ar), 4.06-4.02 (4H, t, *J* = 4.3 Hz, OCH₂), 3.83-3.81 (4H, t, *J* = 4.3 Hz, CH₂O), 3.66 (8H, s, OCH₂CH₂O).

4',5'-Dibromobenzo-18-crown-6 (15): Obtained 1.93 g (82 %), m.p. 92 °C. Found, %: C 40.79, H 4.61, Br 33.87. $C_{16}H_{22}Br_2O_6$ requires, %: C 40.88, H 4.72, Br 33.99; m/z (ESI), %: 468 (8), 470 (16), 472 (8), [M+]; 292 (46), 293 (7), 294 (100), 295 (12), 296 (50) [(M-(CH₂CH₂O)₄)]+. ¹H NMR (CDCl₃, 298 K) δ_H , ppm: 7.08 (2H, s, Ar), 4.13-4.10 (4H, t, $J = 4.3$ Hz, OCH₂), 3.91-3.88 (4H, t, $J = 4.3$ Hz, CH₂O), 3.76-3.69 (8H, m, OCH₂CH₂O), 3.67 (4H, s, OCH₂CH₂O).

Iodination. 3.73 mmol of crown ether **2** at room temperature was dissolved in 50 ml of distilled water 2.0 g (9.22 mmol) of mercury oxide powder and 1.13 g (4.44 mmol) of fine powder iodine were added to the stirred solution. After 24 hours on the Schott filter solid portion was separated from the aqueous phase. The filtrate was treated with chloroform (25 ml×3). The filter cake was washed with chloroform. Chloroform extracts were combined, chloroform was removed under reduced pressure. The solid residue was crystallized from *n*-hexane.

4'-Iodobenzo-15-crown-5 (16): Obtained 0.76 g (52.%), m.p. 87 °C. Found, %: C 42.56, H 4.94, I 32.26. $C_{14}H_{19}IO_5$ requires, %: C 42.66, H 4.86, I 32.19; m/z (ESI), %: 394 (44), [M+]; 306 (7) [(M-(CH₂CH₂O)₂)]+; 262 (100) [(M-(CH₂CH₂O)₃)]+. ¹H NMR (CDCl₃, 298 K) δ_H , ppm: 7.22-7.18 (1H, dd, $J = 8.4$ Hz, $J' = 1.85$ Hz, Ar), 7.13-7.127 (1H, d, $J = 1.85$ Hz, Ar), 6.63-6.60 (1H, d, $J = 8.4$ Hz, Ar), 4.11-4.09 (4H, t, $J = 4.4$ Hz, OCH₂), 3.91-3.88 (4H, t, $J = 4.4$ Hz, CH₂O), 3.75 (8H, s, OCH₂CH₂O).

Results and Discussion

It was found that sodium hypochlorite NaClO can be used as a mild and selective agent in the chlorination of BCE in water solutions. So, benzo-12-crown-4 (**1**) -15-crown-5 (**2**) and -18-crown-6 (**3**) smoothly chlorinated (ratio BCE: NaClO = 1:3, 20 °C, 24 h) in an alkaline ($pH = 10$) aqueous solution of NaClO, as expected, producing only to the corresponding 4'-chloroBCE (**4-6**), which also contain minor impurities in the form of original substrates and the traces of dichlorides. The resulting 4'-chloroBCE are practically insoluble in a alkaline aqueous solution. They quickly crystallize and become unavailable for the further attacks by a chlorinating agent. Pure 4'-BCE were obtained using the developed method with yields of 65-75 %.

The BCE chlorination by hypochlorite in a strongly acidic medium was also successful. The process was performed by carefully adding sodium hypochlorite

solution to the BCE in concentrated hydrochloric acid. Our experimental data confirmed the above-mentioned fact: the hypochlorite instability in acidic medium at high temperatures. The resinous by-products are the main products of the BCE chlorination at 55 °C. The 4',5'-dichloroBCE and 4'-chloroBCE were isolated by crystallization with the ratio about 3:1 and with low yields. When the sodium hypochlorite solution was added at room temperature to a solution of BCE in hydrochloric acid, the mix was self-heating up to 40 °C if no measures were taken to cool down the reaction mixture. The sticky crystalline product was obtained in this case, from which, by fractional crystallization, 4',5'-dichloroBCE and 4'-chloroBCE were separated, but with the 10:1 ratio. Precooling BCE hydrochloric acid solution to 0 °C, and the careful addition to it the chilled sodium hypochlorite solution at a rate at which the temperature of the reaction mixture did not exceed 5 °C yielded good crystallized products. But contrary to the expected, dichlorides were absent and pure products of aromatic ring exhaustive chlorination were formed – 3',4',5',6'-tetrachloroBCE (**7-9**). Therefore the optimized reaction conditions (excess NaClO in solution of HCl ($pH < 1$, 0-5 °C, 24 h) allowed hypochlorite to use the most of it's chlorinating potential. Tetrachloroderivatives **7-9** were isolated with 48-78 % yields and purity >97 %. The results are shown in Figure 2.

Sodium hypobromite NaBrO also leads to a selective bromination of BCE in the water solution – *e.g.* crown ethers **1-3** were smoothly brominated (BCE:NaBrO=1:3, 20 °C, 24 h) to corresponding 4'-bromoBCE (**10-12**) containing trace amount of BCE dibromides as impurities. Using the developed method the pure Br-BCE were synthesised with 72-84 % yields. The hypobromite however is more active and more selective in comparison with the hypochlorite – the use of the excess of NaBrO in HBr solution in similar conditions ($pH < 1$, 0-5 °C, 2 h) leads only to dibromides **13-15** (76-82 %) and the corresponding tetrabromides are not formed (Figure 3).

It is well known,^[23] that in contrast to hypochlorite and hypobromite, hypoiodite is extremely unstable in aqueous solutions and cannot exist independently. When dissolving iodine in an aqueous sodium hydroxide solution at the temperature close to the freezing point of the solution, a

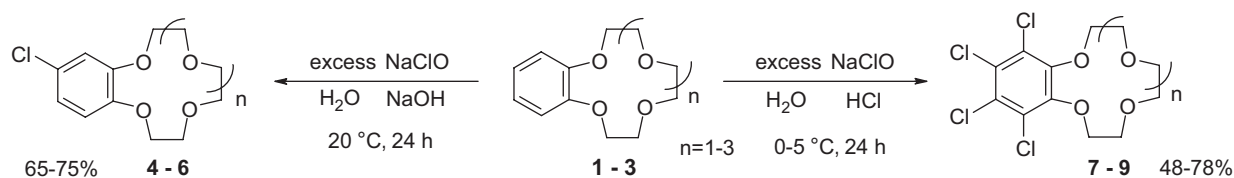


Figure 2.

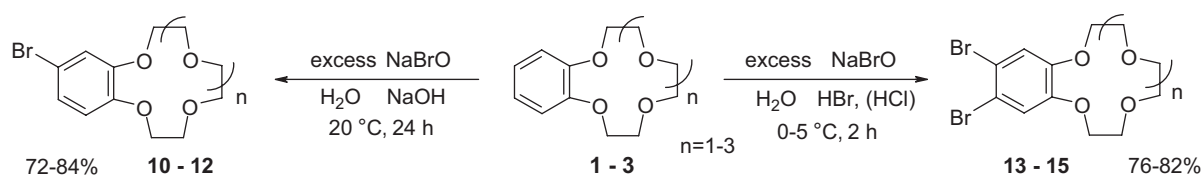


Figure 3.

mixture of sodium iodide (NaI) and iodate (NaIO₃) appear at once. The attempt to get iodo-BCE by cautious addition of iodine to the cooling of the aqueous alkaline solution of BCE invariably leads to the precipitation of the initial BCE. As we have shown previously (see above) the hypiodites successfully iodinate the BCE *in situ* when NIS was added to an aqueous solution of the BCE.

It is known,^[27] that the mercury oxide is used for iodination of aromatic compounds with iodine as an oxidizing agent and as an agent binding the iodide which is formed in an equilibrium reaction and thus contribute to the accumulation of hypiodite. This technique has been successful in our case. As a result of the addition of iodine to the suspension of crystalline mercury oxide in aqueous crown ether **2**, at the room temperature after 24 hours, 4'-iodobenzo-15-crown-5 (**16**) was isolated with 52 % yield (Figure 4).

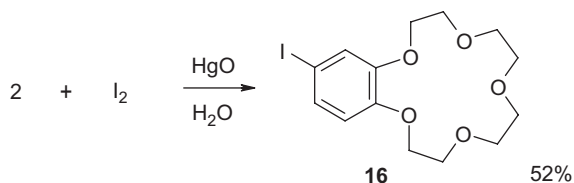


Figure 4.

Mercury oxide can be easily regenerated from the mercury iodide by an alkaline solution.

Conclusions

Thus, the proposed techniques of BCE halogenation by hypohalites in aqueous solutions are available, free of fire hazard and very simple. The control of acidity of the medium in this process allows the control of the number of halogen atoms in the benzene ring of BCE. In the alkaline medium, monohalogen-BCEs are formed exclusively, while in the acidic medium there are only tetrachlorides and dibromides. The possibility to use elemental iodine in water for BCE iodination *in situ* by hypiodites is demonstrated. The above-noted DBCE low solubility in water does not allow applying the described approaches for them. However, it seems to us that this problem is solvable in principle.

Acknowledgements. Ildar M. Rakipov, Ph.D for recording and help for interpretation of mass spectra.

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Received 23.11.2012

Accepted 03.12.2012