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The Peculiarities of the Reaction of Benzo– and Dibenzocrown Ethers with N–Halogenosuccinimides

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The aromatic halogenation of benzo- and dibenzocrown ethers by N-halogenosuccinimides in solid phase, water or organic medium was researched for the first time. Under mechanochemical activation depending on stoichiometry of the process, benzocrown ethers smoothly and selectively transform into corresponding mono or dihalogeno derivatives. Addition of solid N-halogenosuccinimides to benzocrown ethers' water solutions with high yields leads to mono halogenation products. At that, the process proceeds under the action of hypohalogenous acids, i.e. imide hydrolysis products. However, only $4^I,5^I$-dibromo- or -diiodobenzocrown ethers were selectively obtained in 20% solutions of sulphuric acid. In similar conditions, dibenzocrown ethers in solid phase form mixtures of products and do not react with N-halogenosuccinimides in water solutions. In the boiling chloroform medium, the reactivity of investigated macrocycles is vastly varying. If bromination of benzo- and dibenzocrown ethers proceeds easily and with good yields, then under chlorination similar products form with low yields during significantly longer period of time. Only benzocrown ethers out of researched compounds undergo mono iodination at the influence of N-iodosuccinimide.

Introduction

Bromo- and iodosubstituted benzo- (BCE) and dibenzocrown ethers (DBCE) easily transform into either hardly obtainable or unavailable by other methods acetylenic,[1-3] vinyl,[4,5] *n*-alkyl, *n*-hydroxyalkyl,[6] phosphorus containing derivatives,[7] and also crown heterocycles,[8] *bis*-benzocrown ethers,[3,6] *etc*. Synthesis and properties of corresponding chloroanalogues are almost not researched.

Chlorination of BCE and DBCE by molecular chlorine is not selective and leads exceptionally to the products of aromatic perchlorination.[9,10] Molecular bromine,[11-15] rarely - N-bromosuccinimide[16] are commonly employed for the bromination, and as for iodination, oxidants are necessary. Therefore, it is carried out in the systems: I_2–HIO_3–H_2SO_4,[17,18] I_2–CF_3COOAg,[5] $I_2(HI)$–H_2O_2[19] or trimethyl-benzylammonium iodine dichloride–$ZnCl_2$–CH_3COOH.[20]

Intensification of substance transformation relates to one of the main problems of contemporary organic chemistry. Aiming at development of the obtaining methods and enhancing of the "family" of these compounds, continuing the search for new ligands,[21-25] extragents[26,27] and biologically active molecules,[28,29] we have researched for the first time[30-32] the interaction of some BCE and DBCE with N-chloro- (NCS), N-bromo-, (NBS) and N-iodosuccinimides (NIS) in solid, water and organic phases. Here we report the main results of recently carried out researches.

Experimental

Macrocycles **1**–**5** (Schemes 1 and 2) were purified by crystallization to the 98% purity (GLC). Due to the fact, that N-halogenosuccinimides (NHS) at standing liberate and sorb halogens, we subjected them to additional purification and used only fresh ones. Commercially availables NCS and NBS (Acros Organics) were purified to m. p. 144–150 °C and 175–178 °C, correspondingly, by crystallization from benzene (NCS) and water (NBS). NIS (m. p. 200–201 °C) was synthesized and purified similarly.[34] Used NHS represented white crystals with purity not less than 98–99% (titrimetrically). H_2SO_4 (Aldrich Chemical Co) contained no more than 2% of water.

Solid phase synthesis was performed in electromechanic hermetical vibratory pounder «KM–1» (Germany). ^{1}H NMR spectra were recorded in $CDCl_3$ (99.8%) on the 299.95 MHz Varian WXP 300 instrument using Me_4Si as internal standard. Mass spectra were obtained with a MX 1321 spectrometer equipped with a direct inlet; ionization voltage 70 eV and ionization chamber temperature 200 °C. The thin layer chromatographic control of the substances purity was performed on Silufol UV 254 plates using halogenated BCE and DBCE, synthesized (see Introduction) according to well–known methods, as reference compounds.

In a series of cases (for example, method B), the necessity to purify the products by crystallization was no longer relevant. The products **6**-**26** were obtained as stable white crystals. Interval of temperature values of melting is provided for all methods A–D, and data on elemental analysis is introduced for one of them.

Method A. General Procedure. The mixture of 5 mmol of BCE **1**–**3**, 5 (or 10) mmol of NHS and equimolar amount of *p*-toluene sulphuric acid (PTSA) monohydrate was mechanochemically poundered for 1 h (amplitude 14). After that, reaction mixture was thoroughly washed with 2x5 ml of cold water. The precipitate was filtered and dried at lowered (40-60 mm Hg) pressure to constant mass, and, if necessary, was crystallized from *n*-hexane or *n*-heptane. Dichlorides **15**–**17** were isolated with fractional crystallization.

Method B. Well-graunted NHS (5 mmol) was added in small portions to the BCE solution (5 mmol in 50 ml of distilled water). The mixture was stirred for 2 h at room temperature and cooled to 10 °C. The solution was neutrolized by $NaHCO_3$ till pH 7. Precipitated crystals were filtered, thoroughly washed with water (3×5 ml, 10 °C) and treated as described for method A.

Method C. Concentrated H_2SO_4 (~5 ml) was added to the solution of 5 mmol of BCE **1**–**3** in 50 ml of distilled water while stirring and cooling. Well-grounded NCS or NBS (10 mmol) was added by small portions (during 15-20 min) to the obtained solution at intensive stirring. The mixture was stirred for 2 h at 20 ^{o}C. After that 10 ml of 3% Na_2SO_3 water solution was added and the reaction mixture was stirred for ~15 min untill decolorization. The solution was neutrolized by 10% $NaHCO_3$ water solution till pH 7. The precipitate was filtered, washed with 3x10 ml of warm water and treated as described for method A.

*Method D. General Procedure for BCE **1-3**.* Solid NBS (10 or 20 mmol) was added to the solution of 10 mmol of BCE **1**–**3** in 20–40 ml of $CHCl_3$ The mixture was refluxed at stirring for 0.5–1 h, cooled to 20 °C. The solution of product in $CHCl_3$ was filtered through wet neutral Al_2O_3 till obtaining of colorless solution. Solvent was evaporated completely, the residue was dried, the products (compounds **9**–**14**) were crystallized from *n*-hexane, *n*-heptane or light petroleum. Macrocycles **6**–**8**, **15**–**17** were additionally purified by fractional crystallization.

Method D. 4^I,4^{II},(5^{II})-Dichloro[3.3]dibenzo-18-crown-6, mixture of cis- and trans-isomers (24). Macrocycle **4** (3.0 g, 8 mmol) was dissolved in chloroform (25 ml), heate to 50 °C. Then solid NCS (2.23 g, 16 mmol) was added. The reaction mixture was refluxed at stirring for 10 h and cooled. The obtained precipitate was filtered, washed with 10 ml of 3% Na_2SO_3 solution of and hot water and dried to constant mass. According to ^{1}H NMR and mass spectroscopy data, the obtained compound **24** contained impurities of mono- and trichlorides. The impure product was suspended in 150 ml of *n*-hexane and refluxed for 1 h. Then the mixture was filtered. The precipitation of the product **24** was dried and crystallized from 1.4-dioxane (yield 2.82 g, 82%). m. p. 177–184 °C. Found: C 55.92, H 5.08, Cl 16.47 %. $C_{20}H_{22}Cl_2O_6$ requires C 55.96, H 5.17, Cl 16.52. ***m/z*** (ESI) (%) 428 (21); 430 (14) [M$^+$], 214 (6) [1/2M$^+$]; 170 (100), 171 (34), 172 (34). δ_H ($CDCl_3$, 298 K) 7.15–6.71 (6H, m, Ar), 4.29–4.21, 4.19–4.06, 4.00 (16H, m, OCH_2CH_2O).

Method D. 4^I,4^{II},(5^{II})-Dibromoro[3.3]dibenzo-18-crown-6, mixture of cis- and trans-isomers (25). 71.2 g (0.4 mmol) of NBS was added by small portions to the stirring suspension of macrocyle **4** (72.1 g, 0.2 mmol) in 350 ml of $CHCl_3$. The reaction mixture quickly became warm and transparent. After adding NBS thick suspension is formed in 15-20 min. This mixture was refluxed while stirring for 30 min, then cooled to 20 °C. The precipitate obtained was filtered and mixed with 1 l of water. Suspension was stirred at 90–95 °C and filtered. Dry product was added to 1.4 l of 1.4-dioxane and boiled for 15 min. Hot solution was quickly filtered. Filtrate was cooled to 20 °C, the precipitate obtained was filtered. 1200 ml of 1.4-dioxane was deleted at lowered pressure; precipitate was cooled to 20 °C and filtered. Combined precipitates of **25** were dried at 60–80 °C (yield 93.3 g, 90%). m. p. 183–186 °C. Found: C 46.31, H 4.21, Br 30.80 %. $C_{20}H_{22}Br_2O_6$ requires C 46.36, H 4.28, Br 30.84. ^{1}H NMR: unsoluble.

4^I-Chlorobenzo-12-crown-4 (6). Method–yield, %: A 71, B (at heating) 75, D 23, m. p. 56.5–58.5 °C. Found: C 55.67, H 5.69, Cl 13.56 %. $C_{12}H_{15}ClO_4$ requires C 55.71, H 5.84, Cl 13.70. ***m/z*** (ESI) (%) 258 (48), 260 (15) [M$^+$]; 169 (3), 170 (100), 171 (12), 172 (27) [(M– $(CH_2CH_2O)_2$)]$^+$. δ_H ($CDCl_3$, 298 K) 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, OCH_2), 4.19–4.06 (4H, t, *J*=4.5 Hz, CH_2O), 3.78 (4H, s, OCH_2CH_2O).

4^I-Chlorobenzo-15-crown-5 (7). Method–yield, %: A 80, B (at heating) 83, D 41, m. p. 83–86 °C. Found: C 55.48, H 6.23, Cl 11.65 %. $C_{14}H_{19}ClO_5$ requires C 55.54, H 6.33, Cl 11.71. ***m/z*** (ESI) (%) 302 (22) 304(7) [M$^+$], 170 (94) 172(31) [(M–$(CH_2CH_2O)_3$)]$^+$.δ_H ($CDCl_3$, 298 K) 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, OCH_2), 3.92–3.87 (4H, t, *J*=4.2 Hz, CH_2O), 3.75 (8H, s, OCH_2CH_2O).

4^I-Chlorobenzo-18-crown-6 (8). Method–yield, %: A 73, B (at heating) 80, D 30, m. p. 58–60.5 °C. Found: C 55.36, H 6.53, Cl 10.17 %. $C_{16}H_{23}ClO_6$ requires C 55.41, H 6.68, Cl 10.22. ***m/z*** (ESI) (%) 346 (9), 348 (3), [M$^+$]; 170 (100), 171 (7), 172 (29) [(M–$(CH_2CH_2O)_4$)]$^+$. δ_H ($CDCl_3$, 298 K) 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, OCH_2), 3.92–3.90 (4H, t, *J*=4.1 Hz, CH_2O), 3.70–3.76 (8H, m, OCH_2CH_2O), 3.68 (4H, s, OCH_2CH_2O).

4^I-Bromobenzo-12-crown-4 (9). Method–yield, %: A 91, B 76, D 69, m. p. 58–60 °C. Found: C 47.50, H 4.80, Br 26.25 %. $C_{12}H_{15}BrO_4$ 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–$(CH_2CH_2O)_2$)]$^+$. δ_H ($CDCl_3$, 298 K) 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, OCH_2), 3.87–3.81 (4H, m, CH_2O), 3.77 (4H, s, OCH_2CH_2O).

4^I-Bromobenzo-15-crown-5 (10). Method–yield, %: A 95, B 80, D 72, m. p. 69–71 °C. Found: C 48.40, H 5.41, Br 22.98 %. $C_{14}H_{19}BrO_5$ 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–$(CH_2CH_2O)_3$)]$^+$. δ_H ($CDCl_3$, 298 K) 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, OCH_2), 3.91–3.88 (4H, t, *J*=4.4 Hz, CH_2O), 3.75 (8H, s, OCH_2CH_2O).

4^I-Bromobenzo-18-crown-6 (11). Method–yield, %: A 92, B 81, D 78, m. p. 80–82 °C. Found: C 48.40, H 5.41, Br 22.94 %. $C_{16}H_{23}BrO_6$ requires C 48.43, H 5.52, Br 23.01. ***m/z*** (ESI) (%) 390 (45), 392 (46) [M$^+$]; 216 (99), 214 (100) [(M–$(CH_2CH_2O)_4$)]$^+$. δ_H ($CDCl_3$, 298 K) 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, OCH_2), 3.92–3.89 (4H, t, *J*=4.0 Hz, CH_2O), 3.77–3.70 (8H, m, OCH_2CH_2O), 3.68 (4H, s, OCH_2CH_2O).

4^I-Iodobenzo-12-crown-4 (12). Method–yield, %: A 83, B 81, D 12, m. p. 71–73.5 °C. Found: C 41.12, H 4.13, I 36.10 %. $C_{12}H_{15}IO_4$ requires C 41.16, H 4.32, I 36.24. ***m/z*** (ESI) (%), 350 (100) [M$^+$]; 262 (96), 263 (11) [(M–$(CH_2CH_2O)_2$)]$^+$. δ_H ($CDCl_3$, 298 K) 7.28–7.24 (2H, d, *J*=9.0 Hz, Ar), 6.74–6.71 (1H, d, *J*=9.0 Hz, Ar), 4.17–4.14 (4H, t, *J*=4.4 Hz, OCH_2), 3.86–3.84 (4H, t, *J*=4.4 Hz, CH_2O), 3.78 (4H, s, OCH_2CH_2O).

4^I-Iodobenzo-15-crown-5 (13). Method–yield, %: A 90, B 76, D 20, m. p. 79.5–82 °C. Found: C 42.62, H 4.70, I 32.07 %. $C_{14}H_{19}IO_5$ requires C 42.66, H 4.86, I 32.19. ***m/z*** (ESI) (%) 394 (49) [M$^+$]; 262 (100) [(M–$(CH_2CH_2O)_3$)]$^+$. δ_H ($CDCl_3$, 298 K) 7.22–7.18 (1H, dd, *J*=8.4 Hz, *J*$'$=1.85 Hz, Ar), 7.13–7.12 (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, CH_2CH_2O), 3.91–3.88 (4H, t, *J*=4.4 Hz, CH_2CH_2O), 3.75 (8H, s, CH_2CH_2O).

4^I-Iodobenzo-18-crown-6 (14). Method–yield, %: A 95, B 79, D 15, m. p.107–109 °C. Found: C 43.71, H 5.18, I 28.81 %. $C_{16}H_{23}IO_6$ requires C 43.85, H 5.29, I 28.96. ***m/z*** (ESI) (%) 438 (43) [M$^+$], 262 (100) [(M–$(CH_2CH_2O)_4$)]$^+$. δ_H ($CDCl_3$, 298 K) 7.24 (1H, s, Ar), 7.12–7.08 (1H, d, *J*=8.4 Hz, Ar), 6.82–6.78 (1H, d, *J*=8.4 Hz, Ar), 4.15–4.12 (4H, t, *J*=4.4 Hz, OCH_2), 3.92–3.90 (4H, t, *J*=4.4 Hz, CH_2O), 3.86–3.80 (8H, m, OCH_2CH_2O), 3.68 (4H, s, OCH_2CH_2O).

4^I,5^I-Dichlorobenzo-12-crown-4 (15). Method–yield, %: A 22, D 27, m. p. 86–87.5 °C. Found: C 49.11, H 4.66, Cl 24.07 %. $C_{12}H_{14}Cl_2O_4$ requires C 49.17, H 4.81, Cl 24.19. ***m/z*** (ESI) (%) 292 (39), 293 (7), 294 (25) [M$^+$]; 203 (3), 204 (100), 205 (13), 206 (65), 207 (7), 208 (10) [(M–$(CH_2CH_2O)_2$)]$^+$. δ_H ($CDCl_3$, 298 K) 7.05 (2H, s, Ar), 4.17–4.14 (4H, t, *J*=4.2 Hz, OCH_2), 3.86–3.83 (4H, t, *J*=4.2 Hz, CH_2O), 3.76 (4H, s, OCH_2CH_2O).

4^I,5^I-Dichlorobenzo-15-crown-5 (16). Method–yield, %: A 16, D 45, m. p. 93–95 °C. Found: C 49.81, H 5.20, Cl 20.88 %. $C_{14}H_{18}Cl_2O_5$ requires C 49.87, H 5.38, Cl 21.03. ***m/z*** (ESI) (%) 336 (4), 338 (3) [M$^+$], 204 (21), 206 (14) [(M– $(CH_2CH_2O)_3$)]$^+$. δ_H ($CDCl_3$, 298 K) 6.92 (2H, s, Ar), 4.25–4.08 (4H, t, *J*=5.2 Hz, OCH_2), 3.99–3.89 (4H, t, *J*=5.2 Hz, CH_2O), 3.74 (8H, s, OCH_2CH_2O).

4^I,5^I-Dichlorobenzo-18-crown-6 (17). Method–yield, %: A 31, D 33, m. p. 74–74.5 °C. Found: C 50.32, H 5.70, Cl 18.56 %. $C_{16}H_{22}Cl_2O_6$ requires C 50.41, H 5.82, Cl 18.60. ***m/z*** (ESI) (%) 380 (11), 381 (1) 382 (6), 383 (1) [M$^+$]; 204 (99), 205 (13), 206 (62), 207 (6), 208 (9), 209 (1) [(M–$(CH_2CH_2O)_4$)]$^+$. δ_H ($CDCl_3$, 298 K) 6.92 (2H, s, Ar), 4.13–4.11 (4H, t, *J*=4.3 Hz, OCH_2), 3.92–

3.89 (4H, t, J=4.3 Hz, CH_2O), 3.77–3.70 (8H, m, OCH_2CH_2O), 3.68 (4H, s, OCH_2CH_2O).

*$4^I,5^I$-Dibromobenzo-12-crown-4 (**18**)*. Method–yield, %: A 89, C 90, D 75, m. p. 79–80 °C. Found: C 37.68, H 3.51, Br 41.70 %. $C_{12}H_{14}Br_2O_4$ 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), $[(M–(CH_2CH_2O)_2)]^+$. δ_H ($CDCl_3$, 298 K) 7.15 (2H, s, Ar), 4.15–4.10 (4H, t, J=5.0 Hz, OCH_2), 3.97–3.87 (4H, t, J=5.0 Hz, CH_2O), 3.72 (4H, s, OCH_2CH_2O).

*$4^I,5^I$-Dibromobenzo-15-crown-5 (**19**)*. Method–yield, %: A 94, C 91, D 85, m. p. 84.5–85°C. Found: C 39.36, H 4.22, Br 37.42 %. $C_{14}H_{18}Br_2O_5$ requires C 39.46, H 4.26, Br 37.51. *m/z* (ESI) (%) 424 (19), 426 (37), 428 (17), $[M^+]$; 291 (1.5), 292 (49), 293 (7), 294 (100), 295 (11), 296 (49), $[(M–(CH_2CH_2O)_3)]^+$. δ_H ($CDCl_3$, 298 K) 6.92 (2H, s, Ar), 4.06–4.02 (4H, t, J=4.3 Hz, OCH_2), 3.83–3.81 (4H, t, J=4.3 Hz, CH_2O), 3.66 (8H, s, OCH_2CH_2O).

*$4^I,5^I$-Dibromobenzo-18-crown-6 (**20**)*. Method–yield, %: A 90, C 94, D 90, m. p. 89–90 °C. Found: C 40.81, H 4.63, Br 33.87 %. $C_{16}H_{22}Br_2O_6$ requires C 40.87, 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) $[(M–(CH_2CH_2O)_4)]^+$. δ_H ($CDCl_3$, 298 K) 7.08 (2H, s, Ar), 4.13–4.10 (4H, t, J=4.3 Hz, OCH_2), 3.91–3.88 (4H, t, J=4.3 Hz, CH_2O), 3.76–3.69 (8H, m, OCH_2CH_2O), 3.67 (4H, s, OCH_2CH_2O).

$4^I,5^I$-Diiodobenzo-12-crown-4 (21). Method–yield, %: A 94, C 90, m. p. 104–105.5 °C. Found: C 30.24, H 2.78, I 53.24 %. $C_{12}H_{14}I_2O_4$ requires C 30.28, H 2.96, I 53.32. *m/z* (ESI) (%) 476 (40), $[M^+]$; 388 (31) $[(M–(CH_2CH_2O)_2)]^+$; 350 (76) $[(M–I]^+$; 262 (100) $[(M–I–(CH_2CH_2O)_2]^+$. δ_H ($CDCl_3$, 298 K) 7.41 (2H, s, Ar), 4.16–4.13 (4H, t, J=4.0 Hz, OCH_2), 3.85–3.82 (4H, t, J=4.0 Hz, CH_2O), 3.78 (4H, s, OCH_2CH_2O).

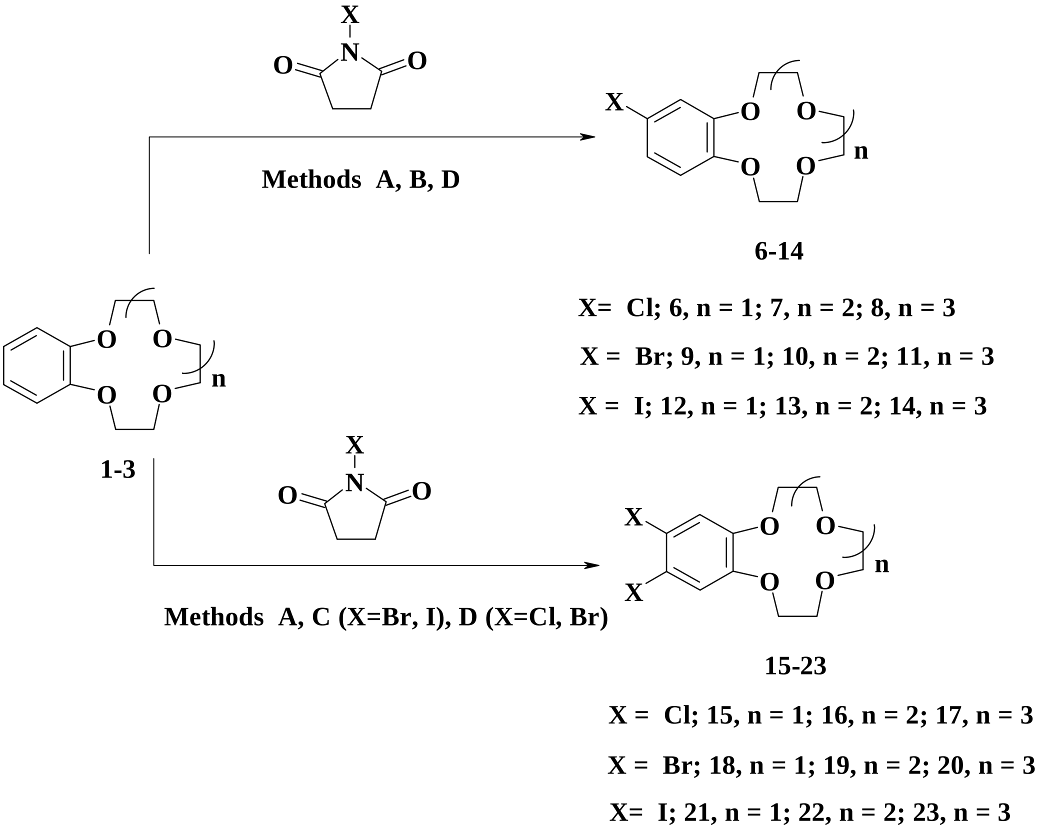
$4^I,5^I$-Diiodobenzo-15-crown-5 (22). Method–yield, %: A 87, C 91, m. p. 98–99.5 °C. Found: C 32.30, H 3.30, I 48.67 %. $C_{14}H_{18}I_2O_5$ requires C 32.33, H 3.49, I 48.80. *m/z* (ESI) (%) 520 (17) $[M^+]$; 388 (100) $[(M–(CH_2CH_2O)_3)]^+$. δ_H ($CDCl_3$, 298 K) 6.91 (2H, s, Ar), 4.20–4.10 (4H, t, J=4.4 Hz, OCH_2), 3.85–3.76 (4H, t, J=4.4 Hz, CH_2O), 3.67 (8H, s, OCH_2CH_2O).

*$4^I,5^I$-Diiodobenzo-18-crown-6 (**23**)*. Method–yield, %: A 93, C 94, m. p. 91–93 °C. Found: C 33.00, H 3.73, I 44.91 %. $C_{16}H_{22}I_2O_6$ requires C 34.06, H 3.86, I 44.99. *m/z* (ESI) (%) 564 (55) $[M^+]$; 388 (100), 389 (11), $[(M–(CH_2CH_2O)_4)]^+$. δ_H ($CDCl_3$, 298 K) 7.26 (2H, s, Ar), 4.11–4.09 (4H, t, J_1=5.6 Hz, OCH_2), 3.90–3.87 (4H, t, J_1=5.6 Hz, CH_2O), 3.75–3.70 (8H, m, J=4.7 Hz, OCH_2CH_2O).

Results and Discussions

The replacement of fluid technologies on “dry” ones, which are not requiring usage of various solvents and their following removal and regeneration, is relevant in fine organic synthesis. Previously, mechanochemical activation of solid reagents at the absence of solvent was not employed in preparing of crown ethers. Their interaction with N-halogenosuccinimides (NHS) was performed by us in electromechanical hermetical vibratory agathic pounder under fixed time and intensity of ball’s amplitude of oscillation.

It was discovered, that benzo-12-crown-4 (**1**), benzo-15-crown-5 (**2**), benzo-18-crown-6 (**3**), [3.3]dibenzo-18-crown-6 (**4**) and [4.4]dibenzo-24-crown-8 (**5**) halogenation with any ratios of reagents leads only to the mixture of products. At the same time, in the presence of *p*-toluene sulfonic acid monohydrate (TSA, it is significant, that it was already used in solid-phase synthesis[34]), BCE **1–3** quickly (1 h) and selectively react with either NBS or NIS, depending on the stoichiometry of the reaction (BCE:NHS = 1:1 or 1:2), forming the products of 4^I- (**9–14**) or $4^I,5^I$-substitution (**18–23**), correspondingly (Method A, Scheme 1). These compounds are isolated with 83–95% yields after simple purification.



Scheme 1. Method A: solid phase, in presence of TSA; method B: water solution; method C: 20% H_2SO_4 solution; method D: boiling $CHCl_3$ medium.

Selective chlorination of polyethers **1**–**3** to monochlorides **6**–**8** (yields 71-80%) was realized for the first time and passes smoothly only at equimolar ratio of reagents. The increase of BCE:NCS ratio up to 1:2, unlike NBS and NIS, yields in the mixture of chlorinated macrocyles. Therefore, we could isolate dichlorides **15**–**17** with low yields of 16–31% only under fractional crystallization.

However it is impossible to isolate in the same way the halogenation products of DBCE **4** and **5** in pure form. Analysis of resulting mixtures points at significantly larger reactivity of polyether **5** comparing to **4**.

The examples of CE halogenation in their water solutions, not containing organic solvents as addition agents, are not known to us. Compounds **1-3** form ~3–5% water solutions, which allowed to carry out this process in homogeneous conditions. It was discovered, that addition of equimolar quantities of solid NBS or NIS to water solution of macrocycles **1**–**3** at room temperature and intensive stirring quickly and selectively leads (Method B, Scheme 1) exceptionally to corresponding 4^{I}-substituted BCE **9**–**14** with 76–81% yields. These products crystallize from water solution and are isolated by simple filtration. Their little solubility in water is the reason of observed selectivity. Such conclusion (^{1}H NMR spectroscopy, mass spectrometry, TLC) is proved by the absence of corresponding $4^{\mathrm{I}},5^{\mathrm{I}}$-diiodoBCE in the reaction mixture and products.

Unlike its analogues, NCS does not react at room temperature with compounds **1**–**3**, and such transformation is observed only into 4^{I}-chloro derivatives **6**–**8** with 75–83% yields at 55–60 °C (Scheme 1).

Obviously, the route of reaction includes quick NHS hydrolysis to corresponding hypohalogenous acids HXO (X = Cl, Br, I) and following oxidizing halogenation of the BCE.

The addition of catalytic quantities (1 drop) of concentrated H_2SO_4 insignificantly accelerates the process, not influencing the selectivity and the yield of compounds **9**–**14**. Under interaction of polyethers **1-3** with equimolar quantities of NIS in 10–20% H_2SO_4 water solutions, we obtained corresponding mono- and diiodo derivatives with prevailing of the first ones.

However, bromination and iodination of BCE **1**–**3** in ~20% H_2SO_4 water solutions (BCE:NHS = 1:2, 20 °C) allows selective synthesis of $4^{\mathrm{I}},5^{\mathrm{I}}$-disubstituted BCE **18**–**23** with 90–94% yields (Method C, Scheme 1). It is possible to make a certain assumption, that intermediates **9**–**14** as oxonium ion adducts dissolve in strong-acid water medium, and this fact provides their smooth homogeneous halogenation to the finishing products **18**–**23**. It is important to mention, that in these conditions NCS doesn't react with compounds **1**–**3**, *i.e.* at room temperature semi-products **6**–**8** do not form even in acid solution. Resinification of the reaction mixture starts when heating.

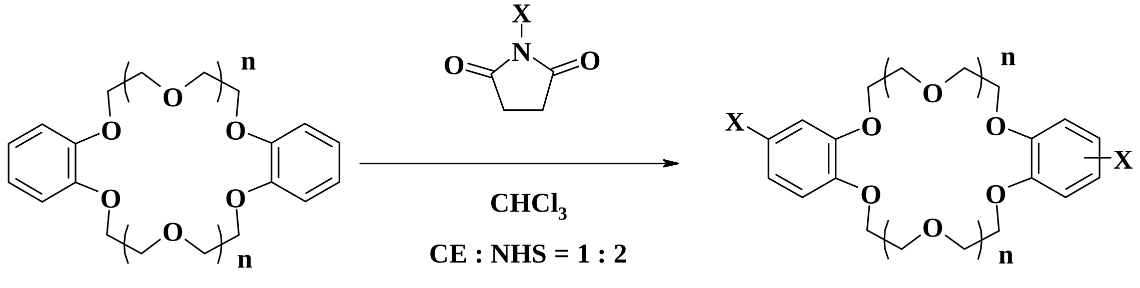
In all cases, while conveying the process in water solutions, macrocycles **4** and **5** almost do not react with NHS.

Considerable differences in crown compounds reactivity exhibit at halogenation in the halogenohydrocarbon medium (Method D, Scheme 2), from which $CHCl_3$ seems to be optimal.

It was found, that addition of stoichiometric quantity of solid NBS to polyether **4** suspension in $CHCl_3$ (20 °C) leads to quick (5–15 min) warming of reaction mixture and extensive precipitation of dibromide **25** (mixture of *cis*- and *trans*-isomers), which was obtained with 90% yield (Scheme 2).

At the same time, for DBCE **5** such effect is less noticeable and additional short boiling of reaction mixture is necessary for obtaining corresponding dibromide **27**. Even smaller reactivity is observed for [2.3]dibenzo-15-crown-5. It is possible to exclude that in the case of 18-member macrocycle **4,** the DBCE:NBS complex is formed most easily, which provide to significant polarization of the N–Br bond. This assumption is proved by the fact that, under similar bromination of DBCE containing biphenyl and diphenyl oxide fragments, the speed of reaction is in 5–30 times higher, than for model non-cyclic biphenyls and diphenyl oxides and also depends on the size of macrocycle. Synthesis and properties of these bromo compounds will be considered by us in a separate paper.

Interaction of polyethers **1**–**3** with NBS smoothly and quickly (30 min–1 h) proceeds in boiling $CHCl_3$, what (depending on the reagents ratio) allows preparing of derivatives **9**–**11** or **18**–**20** (Scheme 1) with 69–90% yields.



Method D

mixture of isomers

4, n = 1; 5, n = 2

R= Cl, 24, n = 1

R= Br, 25, n = 1; 26, n = 2

R= I, n = 1, 2 not isolated

Scheme 2.

We should mention, that by-products which are connected with the participation of solvent were not found even in the traces.

Absolutely opposite results were obtained for NIS. Incomplete conversion was fixed for all BCE, and due to this, products **12–14** were obtained with yields not higher than 20% but diiodides **21–23** do not form at all. Conversion is even lower under iodination of DBCE **4** and **5**, so it is impossible to separate mono and diiodo derivatives.

At the same time, long-lasting (8-10 h) boiling is necessary for chlorination of compounds **1-3,** what also leads to the formation of impurities. Thus, the obtained chlorides **6–8** contain impurities of the substrate and corresponding dichloro- derivatives and were isolated in pure form only with 23–41% yields after fractional crystallization. Products **15–17,** yields of which do not exceed 50%, were purified by the similar method. Nevertheless, durational chlorination of DBCE **4**, as for NBS**,** allowed preparing dichloride **24** with 82% yield.

The structure of synthesized compounds **6–26** was defined by ^{1}H NMR spectroscopy, mass spectrometry and the composition was determined by elemental analysis. Individuality of the products was controlled by TLC using crown compounds synthesized by common methods (see Introduction) as the standards. Melting points and other physicochemical characteristics of the prepared macrocycles agreed with that described in literature.

Conclusions

Consequently, using reagents of the same type, namely NHS, we for the first time carried out selective chlorination, bromination and iodination of BCE and partially, DBCE and compared their reactivity. Developed methods of BCE halogenation in solid state and water are simple and, from our view, they offer an obvious advantage to the known ones.

It is worthwhile of mentioning, that in the conditions of B and C methods, NHS actually are the only sources of halogen because of being easily hydrolyzed, what is proved by additional experiments. At the same time, hypohalogenous acids proved themselves as efficient halogenating agents for BCE.

The macrocycles studied often demonstrate noticeable differences in reactivity, which not always may be explained now and needs in performance of additional experiments.

Some of reported results put an idea to investigate the possibility of preparing crown ether “host-guest” complexes with ionic compounds or neutral organic molecules in solid phase under mechanochemical activation.

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Received 05.05.2008
Accepted 03.06.2008