# Macrocycle opening in formyl derivatives of benzocrown ethers under the action of methylamine

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A new method for synthesizing nitrogen-containing podands by nucleophilic regioselective cleavage of the macrocycle in formyl derivatives of benzocrown ethers by heating with methylamine and methylammonium chloride has been developed. This reaction is the first example of crown ether opening by a nitrogen-containing nucleophile.

**Key words:** 4′-formylbenzocrown ethers, macrocycle opening; methylamine.

The known methods for synthesizing open-chain analogs of crown-containing compounds, podands,[1] which possess high complexing ability toward alkaline and alkaline-earth metal ions, are mostly based on condensation of two fragments. In this work we studied the possibility of synthesizing podands from substituted benzocrown ethers.

Previously, treatment with an alkali has been observed to cause macrocycle opening in nitro-derivatives of benzocrown ethers.[2] However, the presence of a nitro group at a benzene ring weakens the complexing ability of compounds. In addition, the limited choice of suitable methods for the transformation of this group decreases the synthetic value of the above reaction. On the other hand, a number of other electron-withdrawing groups are known that can activate the nucleophilic substitution at an aromatic ring[3] and hence favor opening of the macrocycle in benzocrown ethers. In the context of the problem considered, the nucleophilic substitution in benzaldehyde derivatives[4] is the most interesting, since the formyl group is one of the most valuable groups for synthesis. In addition, the use of amines instead of alkali for macrocycle opening also seems to be favorable, since nitrogen-containing podands offers a number of advantages.

We assumed that crown-containing benzaldehydes, in which the formyl group is located *para* to one of the O atoms in the crown ether moiety, should undergo nucleophilic macrocycle opening by methylamine.

The 4′-formylbenzocrown ethers (**1a—c**) and 4′,4″(5″)-diformyldibenzo-18-crown-6 (**1d**) required for this study were obtained by the known methods.[5—7]

It was found that heating of formylbenzocrown ethers **1a—c** with an ethanolic solution of $MeNH_2$ and $MeNH_2 \cdot HCl$ followed by hydrolyzing the reaction mixture with a dilute acid results in podands **2a—c** in up to 80 % yields (Scheme 1, Table 1).

It is known that benzaldehyde derivatives readily undergo condensation with amines to give Schiff bases.[8] It may therefore be assumed that when excess amine is present, an azomethine derivative of a crown-containing benzaldehyde is initially formed. The protonated form of the latter (**3**, see Scheme 1) is more strongly activated toward nucleophilic substitution at the *para* position than the starting compound. On the other hand, crown ethers readily form complex compounds with ammonium ions. In these complexes, the "host" and "guest" molecules are linked by hydrogen bonds.[9,10] In view of this, we assumed that the macrocycle can be additionally activated toward nucleophilic opening by complexing as mentioned above. One piece of indirect evidence for this assumption is that the yield of podand **2a**, which results from macrocycle opening in 4′-formylbenzo-12-crown-4 (**1a**) characterized by lower constants of complexing with ammonium salts, is somewhat lower.[9]

**Table 1.** Characteristics of podands **2a—e** synthesized

| Podand | Yield (%) | $[M]^+$,* found / calculated | Molecular formula |
|---|---|---|---|
| **2a** | 66 | 283.1404 / 283.1419 | $C_{14}H_{21}NO_5$ |
| **2b** | 79 | 327.1671 / 327.1682 | $C_{16}H_{25}NO_6$ |
| **2c** | 80 | 371.1951 / 371.1944 | $C_{18}H_{29}NO_7$ |
| **2d** | 41 | 239.1168 / 239.1157 | $C_{12}H_{17}NO_4$ |
| **2e** | 36 | — | $C_{20}H_{24}N_2O_5$ |

* Mass spectrometry data.

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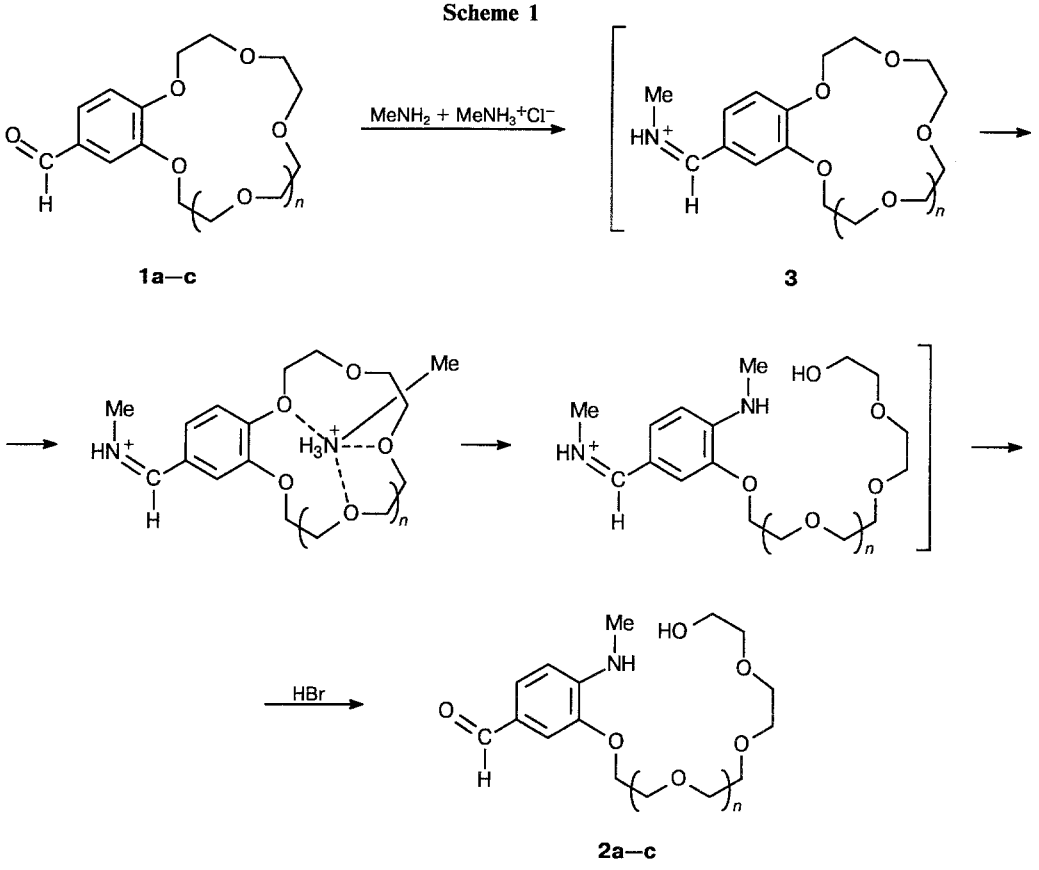
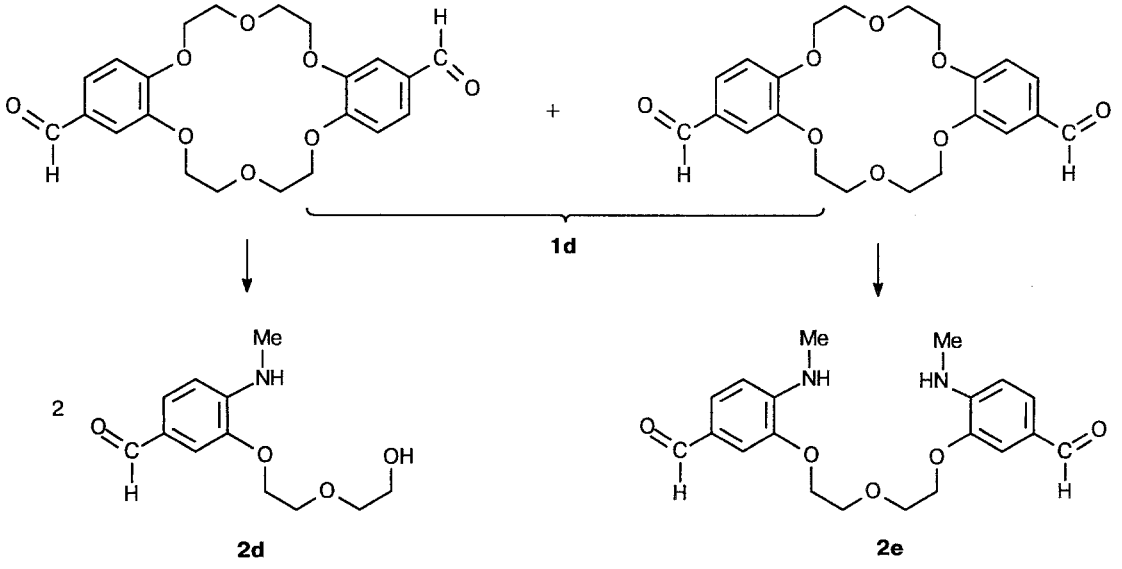
**Scheme 1**




**1a–c** **3** **2a–c**

**1, 2:** $n$ = 0 (**a**), 1 (**b**), 2 (**c**)

**Scheme 2**



**1d** **2d** **2e**

**Reagents:** 1) $MeNH_2$ + $MeNH_3^+Cl^-$; 2) dilute HBr.

The method found was expanded for compounds with two reaction centers, *e.g.*, 4′,4″(5″)-diformyldibenzo-18-crown-6 **1d** (Scheme 2, see Table 1).

Electrophilic substitution in dibenzo-18-crown-6 ethers generally gives almost unseparable mixtures of two isomers in approximately equal amounts. Therefore,

**Table 2.** Mass spectra of podands **2a—e**

| Podand | $m/z$ ($I_{rel}$ (%))* |
|---|---|
| **2a** | 283 (100), 219 (8), 195 (10), 152 (8), 151 (71), 150 (60), 148 (9), 133 (14), 122 (13), 94 (12), 89 (30) |
| **2b** | 327 (88), 239 (16), 221 (15), 219 (14), 195 (18), 178 (15), 177 (19), 151 (100), 150 (70), 94 (15), 89 (59) |
| **2c** | 371 (100), 178 (19), 164 (35), 163 (50), 151 (84), 150 (83), 149 (25), 136 (75), 121 (29), 89 (33), 80 (18) |
| **2d** | 239 (100), 208 (9), 177 (8), 152 (15), 151 (100), 150 (99), 148 (11), 122 (21), 94 (21), 78 (7), 77 (7) |
| **2e** | 372 (100), 342 (39), 194 (26), 178 (30), 151 (30), 150 (85), 149 (21), 148 (21), 123 (24), 122 (41), 94 (21) |

* The molecular ion peak and 10 most intense peaks are presented.

could expect that the reaction of compound **1d** with $MeNH_2$ would give two nucleophilic substitution products corresponding to macrocycle opening in the two isomers. In fact, such podands (**2d,e**) were isolated in 77 % overall yield (see Table 1). The molar ratio was found to be 2 : 1, which shows that the two isomers of **1d** in this reaction have approximately the same reactivity.

The structures of the compounds obtained were established by $^1H$ NMR and IR spectroscopy and by mass spectrometry (Tables 1—3) and confirmed by elemental analyses.

Thus, a new method for synthesizing nitrogen-containing podands has been elaborated. The method is based on nucleophilic regioselective macrocycle opening by methylamine in readily accessible formyl derivatives of oxygen-containing benzocrown ethers. The reaction found is the first example of crown ether opening by a nitrogen-containing nucleophile.

## Experimental

$^1H$ NMR spectra were obtained on a Bruker AC-200p spectrometer using $CDCl_3$—$CCl_4$ (1 : 2) and DMSO-$d_6$ as solvents and $SiMe_4$ as the internal standard. IR spectra were recorded in thin films and in KBr on a Shimadzu IR-470 spectrophotometer. Mass spectra were obtained on a Varian MAT-311A instrument at an ionization energy of 70 eV using direct injection of samples into the ionization source. The reactions were monitored by TLC on DC-Alufolien Kieselgel 60 $F_{254}$ plates.

**Synthesis of podands 2a—e (general procedure).** $MeNH_2 \cdot HCl$ (10 mmol, or 20 mmol in the case of **1d**) and a 38 % solution of $MeNH_2$ in dry EtOH (6 mL) were added to 4′-formylbenzocrown ether **1a—c** or 4′,4″(5″)-diformyldibenzo-18-crown-6 ether **1d** (1 mmol), and the reaction mixture was heated for 60 h at 200 °C (a bath with Wood's alloy) in a sealed tube. The tube was then opened, and the solvent was evaporated *in vacuo*. Aqueous HBr (30 : 1, 60 mL) was added to the residue, and the mixture was kept for 3 h. Dilute KOH was then added until pH 10 was attained, and the mixture was extracted with chloroform. The extract was concentrated *in vacuo*, and the residue was purified by dry flash chromatography on $Al_2O_3$ (L 5/40, alkaline, Chemapol). Gradient elution from benzene to MeOH (up to 7 % of the latter) gave podands **2a—d** as light yellow oils. **Compound 2e:** m.p. 84—86 °C after recrystallization from heptane. Found (%): C, 64.36; H, 6.77; N, 7.53. $C_{20}H_{24}N_2O_5$. Calculated (%): C, 64.50; H, 6.50; N, 7.52.

**Table 3.** IR and $^1H$ NMR spectra of podands **2a—e**

| Podand | IR (film), $\nu/cm^{-1}$ | $^1H$ NMR ($CDCl_3$—$CCl_4$, 1 : 2), $\delta$ ($J$/Hz) |
|---|---|---|
| **2a** | 3392(N—H, OH); 1664 (C=O) | 2.92 (d, 3 H, NMe, $J$ = 5.1); 3.24 (br.s, 1 H, OH); 3.55—3.71 (m, 8 H, 4 $CH_2O$); 3.83 (m, 2 H, $CH_2O$); 4.20 (m, 2 H, $CH_2O$); 5.63 (br.q, 1 H, NH, $J$ = 5.1); 6.50 (d, 1 H, H-3, $J$ = 8.1); 7.22 (s, 1 H, H-6); 7.33 (d, 1 H, H-4, $J$ = 8.1); 9.63 (s, 1 H, CH=O) |
| **2b** | 3392 (N—H, OH); 1662 (C=O) | 2.85 (d, 3 H, NMe, $J$ = 5.2); 3.31 (br.s, 1 H, OH); 3.45—3.69 (m, 12 H, 6 $CH_2O$); 3.75 (m, 2 H, $CH_2O$); 4.09 (m, 2 H, $CH_2O$); 5.61 (br.q, 1 H, NH, $J$ = 5.2); 6.42 (d, 1 H, H-3, $J$ = 8.1); 7.13 (s, 1 H, H-6); 7.26 (d, 1 H, H-4, $J$ = 8.1); 9.55 (s, 1 H, CH=O) |
| **2c** | 3392 (N—H, OH); 1662 (C=O) | 2.87 (d, 3 H, NMe, $J$ = 5.2); 3.09 (br.s, 1 H, OH); 3.45—3.71 (m, 16 H, 8 $CH_2O$); 3.78 (m, 2 H, $CH_2O$); 4.12 (m, 2 H, $CH_2O$); 5.59 (br.q, 1 H, NH, $J$ = 5.2); 6.43 (d, 1 H, H-3, $J$ = 8.1); 7.16 (s, 1 H, H-6); 7.27 (d, 1 H, H-4, $J$ = 8.1); 9.57 (s, 1 H, CH=O) |
| **2d** | 3408 (N—H, OH); 1661 (C=O) | 2.88 (s, 3 H, NMe); 3.13 (br.s, 1 H, OH); 3.58 (m, 2 H, $CH_2O$); 3.68 (m, 2 H, $CH_2O$); 3.77 (m, 2 H, $CH_2O$); 4.11 (m, 2 H, $CH_2O$); 5.38 (br.s, 1 H, NH); 6.46 (d, 1 H, H-3, $J$ = 8.1); 7.20 (s, 1 H, H-6); 7.29 (d, 1 H, H-4, $J$ = 8.1); 9.59 (s, 1 H, CH=O) |
| **2e*** | 3440 (N—H)**; 1658 (C=O) | 2.81 (s, 6 H, 2 NMe); 3.88 (m, 4 H, 2 $CH_2O$); 4.19 (m, 4 H, 2 $CH_2O$); 6.12 (br.s, 2 H, 2 NH); 6.58 (d, 2 H, H-3, H-3′, $J$ = 8.2); 7.21 (s, 2 H, H-6, H-6′); 7.42 (d, 2 H, H-4, H-4′, $J$ = 8.2); 9.61 (s, 2 H, 2 CH=O) |

* The $^1H$ NMR spectrum was obtained in DMSO-$d_6$. ** In KBr.

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