Macrocycle opening in crown compounds
4.* Steric effects in the ring-opening reaction of the macrocycle of 4′-nitrobenzo-15-crown-5 ether under the action of amines to form podands

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The regioselective nucleophilic opening of the macrocycle of 4′-nitrobenzo-15-crown-5 ether under the action of amines with various structures to form nitrogen-containing podands was studied. A distinguishing characteristic feature of this reaction with aminoalcohols is the ability of the latter to form hydrogen bonds, resulting in an increase in the degree of conversion into podands.

Key words: 4′-nitrobenzo-15-crown-5 ether, opening of the macrocycle, amines, podands.

Previously, we have reported the nucleophilic opening of the macrocycle of formylbenzocrown and nitrobenzocrown ethers under the action of alkylamines (RNH_2 and $RNH_3^+Cl^-$)[2,3] and methylamine,[1] respectively, to form acyclic analogs of benzocrown ethers (podands) in high yields. It was suggested that the structure and nucleophilicity of amines can substantially affect the pathway of the latter reaction.

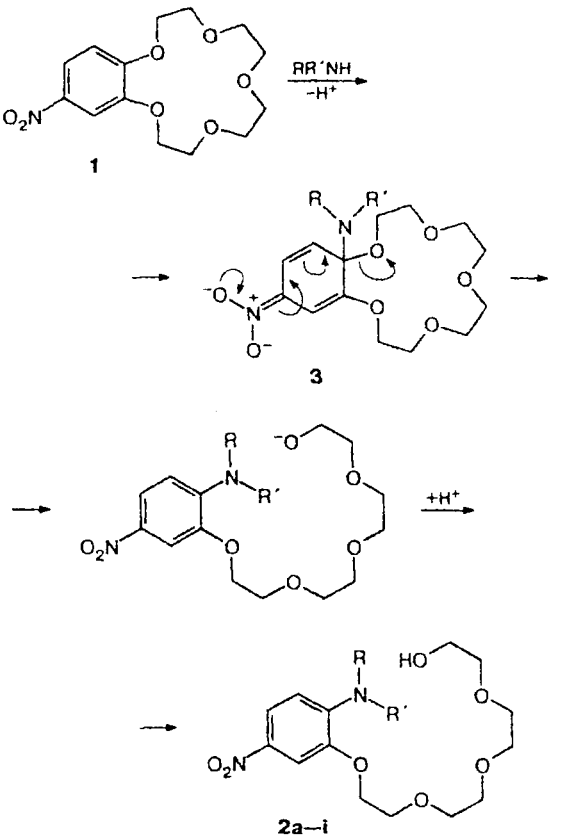
In this work, we studied the synthesis of nitrogen-containing podands from 4′-nitrobenzo-15-crown-5 ether (**1**). The starting compound **1** was prepared according to a known procedure.[4]

It was established that in most instances heating of 4′-nitrobenzo-15-crown-5 ether (**1**) with alcoholic solutions of amines afforded podands **2a—i** in virtually quantitative yields without the formation of by-products (Scheme 1, Table 1).

It is known that the nature of the N-nucleophile substantially affects the efficiency of opening of the heterocycle (see, for example, Refs. 5 and 6). With the aim of revealing the mechanism, we performed a series of experiments under comparable conditions over a period of time, which in most cases was undoubtedly insufficient (100 h) for complete conversion of **1** into the reaction products. The degree of conversion increases as the duration of the reaction increases, and if required, it can be brought up to 100% (see Table 1).

One would expect that an increase in the size and the number of radicals in amine RR′NH will hinder its addition to compound **1** to form the Meisenheimer σ-complex (**3**) and, consequently, will inhibit the reaction of nucleophilic substitution. Actually, it was experimentally found that in the case of R′ = H, the use of alkyl substituents other than R = Me leads to a gradual (as the lengths of the alkyl radicals at the amine nitrogen atom increase and they become more branched) decrease in the degree of conversion of compound **1** into

Scheme 1



2: R = Me (**a**, **e**), Et (**b**), Pr^n (**c**), Pr^i (**d**), $PhCH_2$ (**f**), $HOCH_2CH_2$ (**g**, **i**), $HOCH_2CH_2CH_2$ (**h**); R′ = H (**a—d**, **f—h**), Me (**e**, **i**)

* For Part 3, see Ref. 1.

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Table 1. Reaction conditions of opening of the macrocyle of crown ether **1** under the action of amines at 100 °C and the yields of podands **2a—i**

Amine	Podand	τ/h	Yield[a] (%)	α[b] (%)	Recovery of **1** (%)
$MeNH_2$[c]	**2a**	20	98	100	0
$EtNH_2$	**2b**	100	100	97	3
Pr^nNH_2	**2c**	100	100	84	16
		150	100	96	4
Pr^iNH_2	**2d**	100	95	19	80
		200	97	38	61
Bu^tNH_2		100	0	0	100
Me_2NH	**2e**	100	100	88	12
		150	100	100	0
$PhCH_2NH_2$	**2f**	100	93	34	63
		300	100	71	29
$HOCH_2CH_2NH_2$	**2g**	100	100	100	0
$HO(CH_2)_3NH_2$	**2h**	100	100	100	0
$HSCH_2CH_2NH_2$		100	0	0	0
$HO(CH_2)_2O(CH_2)_2NH_2$		100	0	0	95
$HOCH_2CH_2NHMe$	**2i**	100	100	17	83

Note. τ is the duration of the reaction.
[a] With respect to consumed **1**. [b] The degree of conversion (α) was determined from the ^1H NMR spectra. [c] See Ref. 1.

podands from 97% for R = Et (**2b**) to 19% for R = Pr^i (**2d**). In the case of R = Bu^t, the corresponding podand was not detected (see Table 1).

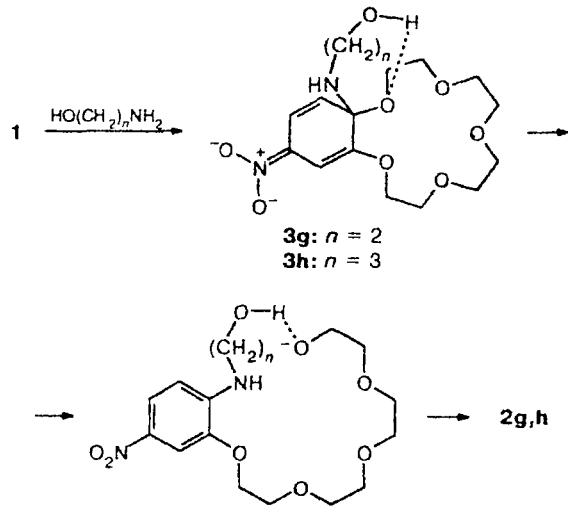
In the reaction of compound **1** with Me_2NH, the degree of conversion is higher than that observed in the reactions with primary alkylamines (except for the conversion of **1** into **2a,b**) in spite of substantial steric hindrances that occur when the amine (branched at the nitrogen atom) approaches the reaction center.

It was of interest to study the reaction of opening of the macrocycle of compound **1** under the action of functionalized derivatives of alkylamines, for example, of primary β- and γ-aminoalcohols. In this case, the degree of conversion of **1** into podands **2g,h** (100%) was the highest achieved for the studied amines, except for $MeNH_2$, though the radicals at the N atom of the amines are rather bulky and the negative inductive effect of the hydroxyl group should decrease their nucleophilicity. Apparently, this reaction is favored by the formation of a hydrogen bond between the hydroxyl group of the aminoalcohol and the oxygen atom of the crown ether, which stabilizes σ-complexes **3g,h** and promotes intramolecular elimination of the alkoxy anion.

Actually, β-aminoethanethiol that is incapable of participating in a hydrogen bond is nonreactive, like $NH_2(CH_2)_2O(CH_2)_2OH$ for which hydrogen bonding is highly improbable.

Apparently, the appearance of the second substituent R′ = Me at the nitrogen atom of aminoalcohol results in strong steric interactions with the *ortho* alkoxy substituents, which hinder the formation of a strong hydrogen bond. Hence, in this case the degree of conversion of compound **1** into **2i** was substantially smaller (17%)

Scheme 2



than that in the case of primary aminoalcohols.

The structures of the resulting compounds were confirmed by spectral methods (Tables 2 and 3).

Therefore, the course of the reaction of nucleophilic opening of the macrocycle of nitrobenzo-15-crown-5 ether under the action of amines depends on the length, the nature, and the number of radicals at the nitrogen atom in amines, as well as on their branching, in particular, at the α-carbon atom and, to a lesser degree, at the β-carbon atom. The data obtained count in favor of the suggested scheme of opening of the macrocycle of nitrobenzocrown ether.

Table 2. Mass spectra of podands **2b—i**

Podand	*m/z* (I_{rel} (%))*
2b	358 (10), 182 (35), 181 (29), 167 (42), 165 (29), 151 (29), 149 (24), 135 (52), 89 (100), 78 (46), 73 (29)
2c	372 (32), 196 (27), 193 (65), 167 (64), 165 (28), 149 (33),147 (48), 135 (28), 89 (100), 87 (27), 78 (24)
2d	372 (21), 207 (57), 181 (67), 179 (30), 165 (36), 148 (37),133 (32), 89 (100), 78 (44), 73 (34), 57 (30)
2e	358 (15), 209 (18), 182 (100), 181 (23), 164 (13), 163 (13), 149 (11), 136 (13), 135 (26), 92 (16), 89 (23)
2f	420 (2), 403 (23), 197 (6), 165 (6), 92 (13), 91 (100), 89 (26), 78 (8), 77 (6), 65 (8), 51 (6)
2g	374 (10), 193 (100), 167 (47), 165 (58), 147 (57), 119 (44), 91 (66), 89 (93), 87 (38), 78 (39), 73 (49)
2h	388 (100), 357 (27), 343 (34), 212 (55), 211 (32), 193 (84), 181 (29), 167 (80), 165 (58), 147 (35), 89 (38)
2i	388 (3), 357 (100), 181 (41), 179 (20), 165 (9), 149 (15), 111 (11), 97 (17), 83 (16), 69 (21), 57 (19)

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

Table 3. IR spectra (films) and ^1H NMR spectra ($CDCl_3$) of podands **2b—i**

Podand	IR, ν/cm^{-1}	^1H NMR, δ (J/Hz)
2b	3387 (NH, OH); 1539 (NO_2)	1.32 (t, 3 H, Me); 3.29 (m, 2 H, CH_2N); 3.62 (m, 2 H, CH_2O); 3.67—3.76 (m, 10 H, 5 CH_2O); 3.90 (m, 2 H, CH_2O); 4.23 (m, 2 H, CH_2O); 5.50 (br.s, 1 H, NH); 6.48 (d, 1 H, H-3, $J_{H-3,H-4}$ = 9.0); 7.64 (d, 1 H, H-6, $J_{H-6,H-4}$ = 2.5); 7.91 (dd, 1 H, H-4, $J_{H-4,H-3}$ = 9.0, $J_{H-4,H-6}$ = 2.5)
2c	3421 (NH, OH); 1539 (NO_2)	1.02 (t, 3 H, Me, J = 7.3); 1.71 (m, 2 H, CH_2); 3.22 (m, 2 H, CH_2N); 3.62 (m, 2 H, CH_2O); 3.63—3.74 (m, 10 H, 5 CH_2O); 3.90 (m, 2 H, CH_2O); 4.25 (m, 2 H, CH_2O); 5.44 (br.s, 1 H, NH); 6.49 (d, 1 H, H-3, $J_{H-3,H-4}$ = 8.9); 7.66 (d, 1 H, H-6, $J_{H-6,H-4}$ = 2.2); 7.91 (dd, 1 H, H-4, $J_{H-4,H-3}$ = 8.9, $J_{H-4,H-6}$ = 2.2)
2d	3380 (NH, OH); 1535 (NO_2)	1.29 (d, 6 H, 2 Me, J = 6.2); 3.61 (m, 2 H, CH_2O); 3.67—3.75 (m, 11 H, CH, 5 CH_2O); 3.90 (m, 2 H, CH_2O); 4.25 (m, 2 H, CH_2O); 5.12 (br.d, 1 H, NH, J = 7.2); 6.50 (d, 1 H, H-3, $J_{H-3,H-4}$ = 8.8); 7.68 (d, 1 H, H-6, $J_{H-6,H-4}$ = 2.5); 7.90 (dd, 1 H, H-4, $J_{H-4,H-3}$ = 8.8, $J_{H-4,H-6}$ = 2.5)
2e	3325 (OH); 1518 (NO_2)	3.01 (s, 6 H, NMe_2); 3.61 (m, 2 H, CH_2O); 3.67—3.74 (m, 10 H, 5 CH_2O); 3.92 (m, 2 H, CH_2O); 4.23 (m, 2 H, CH_2O); 6.76 (d, 1 H, H-3, $J_{H-3,H-4}$ = 9.0); 7.73 (d, 1 H, H-6, $J_{H-6,H-4}$ = 2.5); 7.85 (dd, 1 H, H-4, $J_{H-4,H-3}$ = 9.0, $J_{H-4,H-6}$ = 2.5)
2f	3380 (NH, OH); 1539 (NO_2)	3.56 (m, 2 H, CH_2O); 3.63—3.72 (m, 10 H, 5 CH_2O); 3.91 (m, 2 H, CH_2O); 4.27 (m, 2 H, CH_2O); 4.50 (d, 2 H, $\underline{CH_2}Ph$, J = 5.6); 6.16 (br.s, 1 H, NH); 6.44 (d, 1 H, H-3, $J_{H-3,H-4}$ = 9.0); 7.28—7.39 (m, 5 H, Ph); 7.67 (d, 1 H, H-6, $J_{H-6,H-4}$ = 2.3); 7.84 (dd, 1 H, H-4, $J_{H-4,H-3}$ = 9.0, $J_{H-4,H-6}$ = 2.3)
2g	3379 (NH, OH); 1539 (NO_2)	3.40 (m, 2 H, CH_2N); 3.61 (m, 2 H, CH_2O); 3.66—3.76 (m, 10 H, 5 CH_2O); 3.86 (m, 2 H, $\underline{CH_2}OH$); 3.89 (m, 2 H, CH_2O); 4.23 (m, 2 H, CH_2O); 5.91 (br.s, 1 H, NH); 6.52 (d, 1 H, H-3, $J_{H-3,H-4}$ = 9.0); 7.65 (d, 1 H, H-6, $J_{H-6,H-4}$ = 2.3); 7.92 (dd, 1 H, H-4, $J_{H-4,H-3}$ = 9.0, $J_{H-4,H-6}$ = 2.3)
2h	3379 (NH, OH); 1539 (NO_2)	1.91 (m, 2 H, CH_2); 3.40 (m, 2 H, CH_2N); 3.61 (m, 2 H, CH_2O); 3.68—3.73 (m, 10 H, 5 CH_2O); 3.79 (m, 2 H, $\underline{CH_2}OH$); 3.88 (m, 2 H, CH_2O); 4.21 (m, 2 H, CH_2O); 6.22 (br.s, 1 H, NH); 6.49 (d, 1 H, H-3, $J_{H-3,H-4}$ = 9.0); 7.61 (d, 1 H, H-6, $J_{H-6,H-4}$ = 2.2); 7.91 (dd, 1 H, H-4, $J_{H-4,H-3}$ = 9.0, $J_{H-4,H-6}$ = 2.2)
2i	3390 (OH); 1516 (NO_2)	2.96 (s, 3 H, NMe); 3.44 (t, 2 H, CH_2N); 3.58 (m, 2 H, CH_2O); 3.64—3.75 (m, 10 H, 5 CH_2O); 3.88—3.93 (m, 4 H, $\underline{CH_2}OH$, CH_2O); 4.22 (m, 2 H, CH_2O); 6.77 (d, 1 H, H-3, $J_{H-3,H-4}$ = 8.9); 7.64 (d, 1 H, H-6, $J_{H-6,H-4}$ = 2.3); 7.85 (dd, 1 H, H-4, $J_{H-4,H-3}$ = 8.9, $J_{H-4,H-6}$ = 2.3)

Experimental

The ^1H NMR spectra were recorded on a Bruker AMX-400 spectrometer in $CDCl_3$ with Me_4Si as the internal standard. The IR spectra were obtained on a Bruker IFS-113v spectrophotometer in films. The mass spectra (EI) were measured on a Varian MAT-311A instrument with direct inlet of the sample into the ionization zone; the energy of ionizing electrons was 70 eV. The course of the reaction was monitored by TLC on DC-Alufolien Kieselgel 60 F_{254} plates.

Synthesis of podands 2b—i (general procedure). A mixture of 4′-nitrobenzo-15-crown-5 ether (**1**) (0.25 mmol) and a 45% solution of amine (0.04 mol) in anhydrous EtOH was heated in a sealed tube at 100 °C (water bath) for 100—300 h. Then the tube was opened and the reaction mixture was concentrated *in vacuo*. The podands were isolated from mixtures of the reaction products according to one of the following procedures.

A. The residue containing **2b—e** was purified by column chromatography on SiO_2 (Kieselgel 60, 0.063—0.100 μm, Merck); a 5 : 1 AcOEt : EtOH mixture was used as the eluent.

B. Water (50 mL) was added to the residue containing **2f—i** and then a concentrated HCl solution was added dropwise to pH 3. The aqueous solution was extracted with AcOEt, the extract was concentrated *in vacuo*, and the residue was purified analogously to procedure ***A***. In the case of **2i**, a 20 : 1 C_6H_6 : EtOH mixture was used as the eluent.

Podands **2b—i** were isolated as yellow oils.

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