3-(4-Thiocarbamoyl-1,2,3-triazol-1-yl)benzo-15-crown-5: synthesis and properties

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A reaction of 1,2,3-thiadiazole-4-carbaldehyde with 3-aminobenzo-15-crown-5 involves the Cornforth rearrangement of the 1,2,3-thiadiazole ring, which leads to 1,2,3-triazole-4-carbothioamide containing the benzocrown ether substituent in position 1 of the triazole ring. Reversible formation of the isomeric thiadiazole occurs in aprotic nonpolar solvents such as deuterated chloroform. These compounds are suitable for extraction of α-amino acids from an aqueous phase.

Key words: rearrangement, nitrogen-containing heterocycles, crown ether, extraction, α-amino acids.

Recent increased interest in macroheterocyclic compounds is due not only to their fundamental importance but also to their possible practical applications in organic synthesis, monitoring of biological systems and the environment (as sensors), selective extraction and transfer of salts across lipophilic membranes, and recognition of ionic pairs.[1—3] Much attention is attracted to the synthesis of extractants that possess the ability to selectively bind such bipolar organic molecules as amino acids.[4]

The present work is concerned with the synthesis of benzo-15-crown-5 ethers containing a thiocarbamoyl-1,2,3-triazolyl substituent and with the extraction of α-amino acids from water using target compounds.

Earlier,[5,6] we have demonstrated that reactions of 1,2,3-thiadiazole-4-carbaldehyde with amines initially produce the corresponding imines, which *in situ* undergo the Cornforth rearrangement to give 1-substituted 1,2,3-triazole-4-carbothioamides. We used this reaction to obtain benzocrown ethers containing the 1,2,3-triazole ring linked *via* the thiocarbamoyl group. For instance, 3-aminobenzo-15-crown-5 (**1**) reacts with 5-morpholino-1,2,3-thiadiazole-4-carbaldehydes (**2a,b**) to give individual compounds **3a,b** in 85—92% yields (Scheme 1). The products were identified as 1-substituted 1,2,3-triazole-4-carbothioamides **3** (NMR data). Their ^{13}C NMR spectra show the signals of the thioamide C atom at δ 186.

It should be noted that the NMR spectra recorded in polar solvents such as DMSO (E_T = 0.444),[7] acetone (E_T = 0.355),[7] and ethanol (E_T = 0.654)[7] contain signals only for compounds **3a,b**. At the same time, the NMR spectra of the same samples in $CDCl_3$ (E_T = 0.259)[7] reveal the presence of isomeric imines **4a,b** (up to 10%).

In the ^1H NMR spectrum of compound **4**, the signal of the methine proton of the imino group appears at δ 8.65; *i.e.*, it is shifted downfield by 0.5 ppm compared to the signal of the H(5) proton of triazole **3**. In the ^{13}C NMR spectrum, the signal of the C(5) atom of thiadiazole **4** (δ 168.1) is shifted upfield by 16.9 ppm compared to the signal of the thioamide C atom in triazole **3** (δ 186.0). In contrast, the signal of the imino C atom in 1,2,3-thiadiazole **4** is shifted upfield by 20 ppm compared to the signal of the C(5) atom in triazole **3**. At the same time, the signal of the C(4) atom in the thiadiazole ring of compound **4** is slightly shifted downfield compared to the signal of the C(4) atom in triazole isomer **3** (δ 139 and 142, respectively).

Therefore, the equilibrium[8] between compounds **3** and **4** in polar solvents is shifted virtually completely toward triazole structure **3**, while in nonpolar solvents, the fraction of thiadiazole isomer **4** increases to 10%.

We studied liquid extraction of amino acids from an aqueous phase to CH_2Cl_2 using crown ether **3a**. Provided the complex crown ether—amino acid (*n***3a** ∈ aa) has a ratio of *n* : 1, the coefficient of partition of amino acids between the organic and aqueous phases (D_s) should be a linear function of the ligand concentration in logarithmic coordinates. This function can be used to determine

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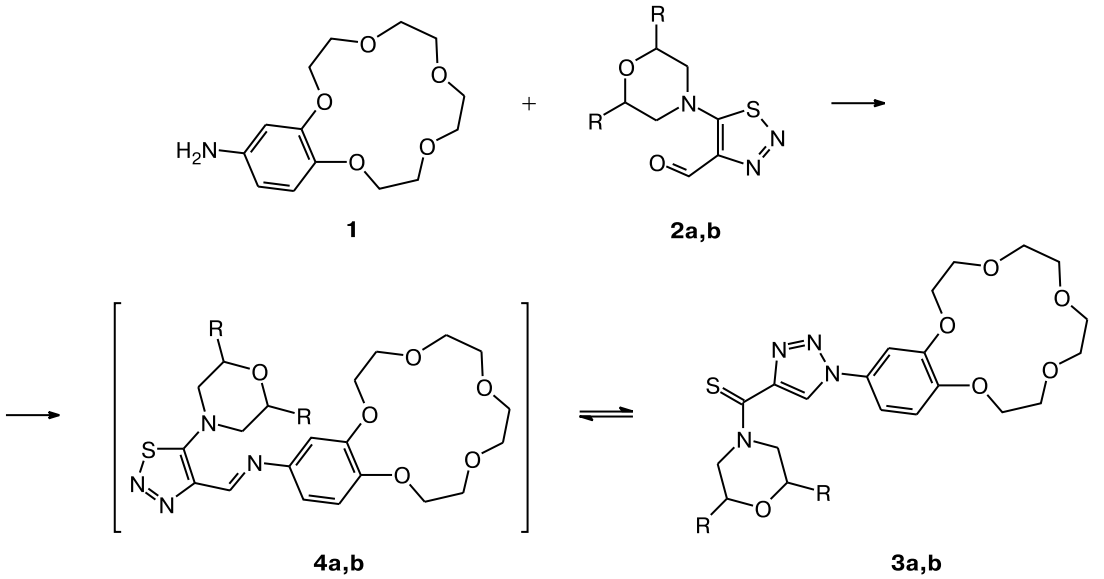
Scheme 1



2—4: R = H (**a**), Me (**b**)

the stoichiometric formula of the complex and the extraction constant K_{ex}:

$$n[L]_{org} + [aa]_{H_2O} = [aa \in L_n],$$

$$K_{ex} = [aa \in L_n]_{org}/([L]^n[aa]_{H_2O}),\ D_s = [aa]_{org}/[aa]_{H_2O},$$

$$\log D_s = n\log[L] + \log K_{ex}, \qquad (1)$$

where [L] is the ligand concentration in the organic phase, $[aa \in L_n]_{org}$ is the concentration of the amino acid—ligand complex in the organic phase, and $[aa]_{org}$ and $[aa]_{H_2O}$ are the concentrations of the amino acid in the organic and aqueous phases, respectively.

We found that 1 : 1 complexes are always formed in the extraction of the amino acids from aqueous solutions at pH 5.8 (Fig. 1) and 9.1. The K_{ex} values are given in Table 1.

From the data obtained it can be seen that the extraction constant for L-glutamine is much higher than those for the other α-amino acids. Apparently, this is due to the coordination of the ω-carbamoyl group of the amino acid to the heterocyclic fragment of benzocrown ether **3a**.

To sum up, the complexing abilities of 1,2,3-triazolylbenzocrown ethers allow one to regard them as potential amino acid receptors.

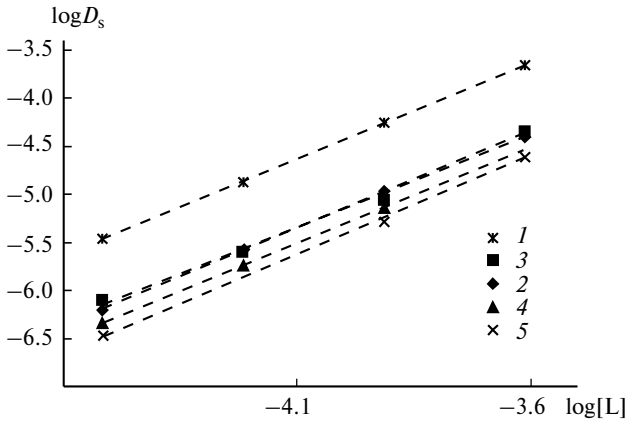


Fig. 1. Distribution of the amino acids ($c = 1.0 \cdot 10^{-4}$ mol L^{-1}) between the aqueous solution (pH 5.8) and CH_2Cl_2 for different concentrations of crown ether **3a**: L-glutamine (*1*), D-tryptophan (*2*), D,L-tyrosine (*3*), L-cysteine (*4*), and L-serine (*5*).

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 instrument (400 and 100 MHz, respectively) in DMSO-d_6 with

Table 1. Extraction constants K_{ex} for the extraction of the amino acids from the aqueous phase with crown ether **3a** at pH 5.8 (I) and 9.1 (II)

Amino acid	K_{ex}/L mol^{-1}	
	I	II
D-trp	678	1163
D,L-tyr	788	986
L-cys	485	1001
L-ser	384	961
L-gln	3762	4352

Me_4Si as the internal standard. Mass spectra were recorded on a MAT-11 instrument (EI, 70 eV). The course of the reactions was monitored and the purity of the compounds obtained was checked by TLC on DC-Plastikfolen Kieselgel 60 F 254 plates in CH_2Cl_2—C_6H_{14} (15 : 1) and EtOAc—C_6H_{14} (1 : 2). 3-Aminobenzo-15-crown-5 (**1**) (Acros) was used. Compounds **2a**,**b** were prepared as described earlier.[5]

3-(4-Morpholinothiocarbonyl-1,2,3-triazol-1-yl)benzo-15-crown-5 (3a). Crown ether **1** (0.28 g, 1 mmol) was added to a solution of 5-morpholino-1,2,3-thiadiazole-4-carbaldehyde (**2a**) (0.20 g, 1 mmol) in ethanol (2 mL). The reaction mixture was kept at ~20 °C for 1 h and then cooled down. The precipitate that formed was filtered off and recrystallized from ethanol. Yield 0.29 g (63%), m.p. 182.2—182.8 °C. ^{1}H NMR, δ: 3.73 (s, 8 H, CH_2O); 3.76 (t, 2 H, NCH_2, J = 4.8 Hz); 3.81 (t, 2 H, NCH_2, J = 4.6 Hz); 3.91 (m, 4 H, CH_2O); 4.12 (t, 2 H, OCH_2, J = 4.6 Hz); 4.35 (m, 6 H, OCH_2); 7.10 (d, 1 H, Ar, J = 8.3 Hz); 7.40 (d, 1 H, Ar, J = 8.3 Hz); 7.62 (s, 1 H, Ar). ^{13}C NMR, δ: 51.1, 53.6, 66.7, 67.2, 68.6, 69.1, 69.6, 69.7, 70.5, 70.6, 71.0, 71.1, 113.36, 115.8, 119.4, 127.4, 130.8, 146.4, 148.5, 149.6, 185.6. MS, m/z (I_{rel} (%)): 464 $[M]^{+\cdot}$ (3). Found (%): C, 54.4; H, 6.3; N, 12.1; S, 6.7. $C_{21}H_{28}N_4O_6S$. Calculated (%): C, 54.3; H, 6.1; N, 12.1; S, 6.9.

3-[4-(2,6-Dimethylmorpholino)thiocarbonyl-1,2,3-triazol-1-yl]benzo-15-crown-5 (3b) was obtained as described for compound **3a**. Yield 0.38 g (77%), m.p. 130.1—130.8 °C. ^{1}H NMR, δ: 1.22 (d, 3 H, CH_3, J = 6.4 Hz); 1.19 (d, 3 H, Me, J = 6.1 Hz); 2.93 (dd, 1 H, NCH, J = 12.8 Hz, J = 10.7 Hz); 3.13 (dd, 1 H, NCH, J = 12.8 Hz, J = 10.7 Hz); 3.63—3.74 (m, 10 H, OCH_2); 3.91 (m, 4 H, CH_2O); 4.20, 4.30 (m, 4 H, CH_2O); 4.54 (m, 1 H, NCH); 5.36 (m, 1 H, NCH); 7.08 (d, 1 H, Ar, J = 8.3 Hz); 7.40 (d, 1 H, Ar, J = 8.3 Hz); 7.65 (s, 1 H, Ar). Found (%): C, 56.0; H, 6.7; N, 11.6; S, 6.8. $C_{23}H_{32}N_4O_6S$. Calculated (%): C, 56.08; H, 6.55; N, 11.37; S, 6.51.

Determination of extraction constants. Extraction was carried out at different concentrations of the crown ether and at a constant concentration of the amino acid. An aqueous solution of an amino acid (4 mL, $1.0 \cdot 10^{-4}$ mol L^{-1}) and a solution of crown ether **3a** in CH_2Cl_2 (4 mL, $2.5 \cdot 10^{-5}$—$5.2 \cdot 10^{-4}$ mol L^{-1}) were stirred at ~20 °C for 2 min and then left quiet for 5 min. The phases were separated. The concentration of the amino acid in the aqueous phase before and after the extraction was measured conductometrically on a Radelkis OK-102 instrument. The extraction constant and the composition of the complex were determined from the plots of Eq. (1).

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