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Synthesis of the First Lariat Crown-Formazan, Prototype of a New Series of Podandocoronands

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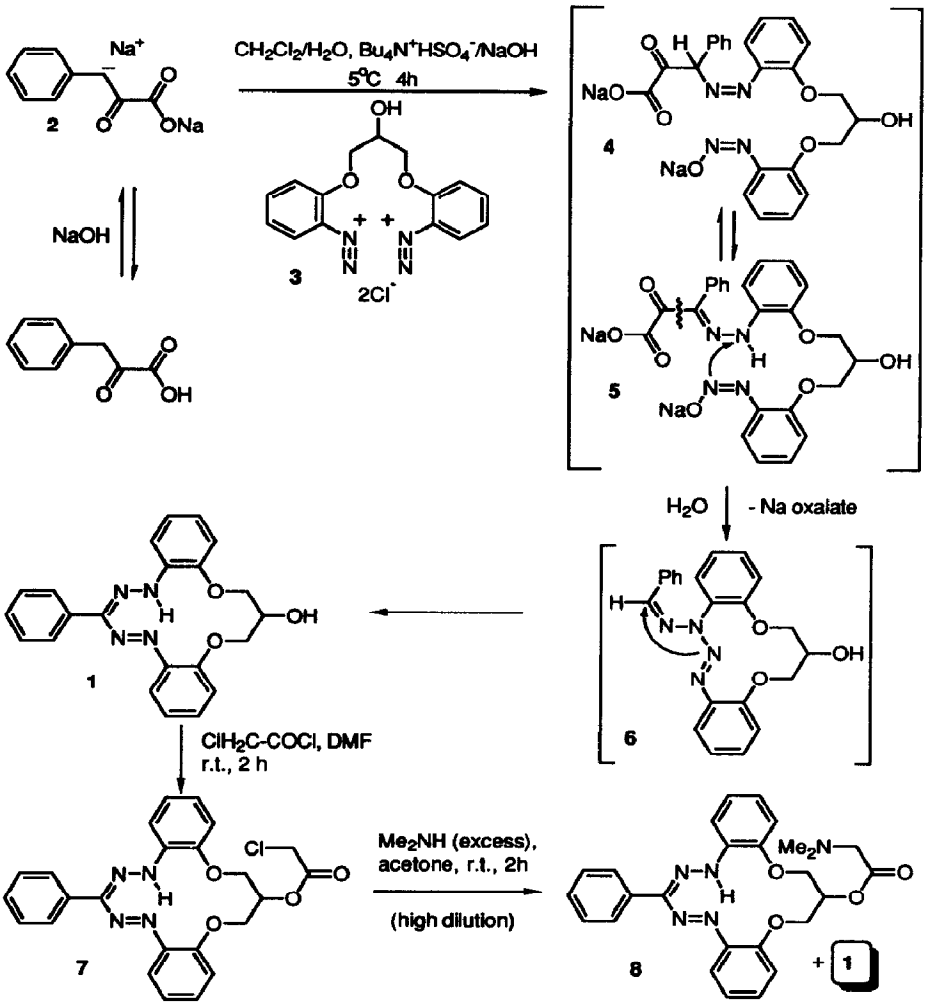
Abstract: Crown-formazan (**1**) with a pendant hydroxy group was obtained by a phase-transfer assisted azo-coupling reaction. Acylation of the hydroxy group of (**1**) with 2-chloroacetyl chloride followed by reaction with dimethylamine afforded 13-[2-(*N*,*N*-dimethylamino)acetoxy]-16,17-dihydro-7-phenyl-5H,15-dibenzo[b,i][1,11,4,5,7,8]dioxatetraazacyclotetradecyne (**8**), the first lariat crown-formazan containing a strong donor group as a supporting ligand at the end of the side arm.

Of the wide variety of macrocyclic ethers, the lariat crown ethers (podandocoronands[1]) possess unique properties from the combination of the advantages of their three topological precursors (coronands, cryptands and podands). As efficient organic ligands, they meet the requirements of rapid, strong, and three-dimensional cation binding and can mimic the properties of natural ionophores.[2] The chemistry of lariat crown ethers was mostly focused on side-arm analogs of known oxygen-containing crown ethers because of the easy comparisons of cation binding data. Nitrogen-containing lariats are less documented, among them derivatives of azacrown ethers dominate.[2,3] A disadvantage of azacrown ethers is the decreased hydrolytic stability of their metal complexes compared to non- nitrogen-containing related structures, which was explained by the rapid inversion of the nitrogen atoms in macrocyclic rings.[2]

Other oxazacoronands, so-called "crown-formazans",[4] contain a rigid formazan block with one carbon and four nitrogens linked in a cyanine-like system incapable of inversion, and a flexible crown-like bridge which consists of oligo-oxyethylene or -oxypropylene units. Crown-formazans (multidentate formazans[5,6]) have recently been intensively studied as potential chromogenic chelates for transition and post-transition metals. Some have shown excellent selectivity towards copper (II) and mercury (II) and were recommended as selective extractants for these metal cations.[7] In this series of crown-formazans, the 14-membered macrocycles of the tetradecyne system were found to be the most stable and correspond to the most favorable (planar) conformation of the macrocyclic ring.[5] Unfortunately, the high rigidity of the formazan component in such macrocycles results, as is to be expected, in the weakening of complexing ability by reduction of the cavity size due to intramolecular hydrogen bonding and the shortening of bond distances because of strong conjugation. Therefore, to improve the potential complexing ability of crown-formazans, we have examined the introduction of additional donor groups capable of providing three-dimentional cation solvation.

Based on the "Lariat ether concept",[2] we designed the structure of macrocycle (**1**) (Scheme) as a basic model for the preparation of the new formazan series, the lariat crown-formazans.

The following sequence of reactions was employed to obtain tetrazo compound (**3**), a major component in



the construction of the macrocyclic ring. Reaction of 1,3-dibromopropan-2-ol with potassium 2-nitrophenolate (molar ratio 1 : 2) in DMF for 4h with stirring at 70-80°C gave 1,3-di-(2-nitrophenyl)propan-2-ol in 66% yield.[8] Reduction of this dinitro compound with hydrazine hydrate in methanol in the presence of Pd/C (reflux, 1h) afforded 1,3-di-(2-aminophenyl)propan-2-ol in 65% yield,[9] which was then bis-diazotized in accordance with the literature procedure[5] to give bis-diazonium salt (3).

We initially attempted a synthesis of macrocycle (1) in accordance with the literature procedure for related macrocycles.[5] However, cyclization of salt (3) with the *CH*-active compound, phenylmalonic acid, using an equimolar ratio of reagents at high dilution under basic conditions, gave only *ca.* 13% of azacrown (1). A considerable amount of deeply colored side products was also formed, apparently, as a result of a preferable linear azo-coupling which stops the reaction at the azo-compound stage, *i. e.*, decarboxylation of the diazo derivative of phenylmalonic acid followed by *Japp-Klingemann* rearrangement into the phenylhydrazone

derivative, does not proceed easily in this particular case. The template method,[5] employing Cu^{2+} as an assembling cation, gave a still smaller yield of macrocycle (**1**), probably because of the unfavorable competitive involvement of the pendant hydroxy group of (**3**) in complex formation leading to linear products.

Recently we found that phase-transfer catalysis in the syntheses of formazans offers certain advantages.[10] Application of this methodology resulted in a successful synthesis of crown-formazan (**1**) in the two phase liquid-liquid system starting from the same bis-diazonium component (**3**) and β-phenylpyruvic acid as the *CH*-active compound. An aqueous solution of the disodium salt of β-phenylpyruvic acid (**2**) was added simultaneously with a solution of tetrazotized 1,3-di-(2-aminophenoxy)propan-2-ol (**3**) to a vigorously stirred mixture containing tetrabutylammonium bisulfate (phase-transfer catalyst), sodium hydroxide, methylene chloride and water. Apparently, the intermediate hydrazone (**5**), which exists in equilibrium with the related azo-compound (**4**), first affords a 12-membered macrocyclic triazene (**6**) as a result of intramolecular azo-coupling which is consistent with the suggested mechanism of formazan formation.[11] An analog of compound (**6**), a 17-membered triazene, was isolated as a side product in the reaction of tetrazotized 1,10-di-(2-aminophenyl)-1,4,7,10-tetraoxadecane with malonic acid.[6] In our case, intramolecular cyclization is accompanied by loss of the hydrophilic portion of the triazene (**6**), which forces the transfer of the macrocycle into the organic phase with subsequent rearrangement into formazan (**1**). A simple work-up procedure, usual when employing the PTC technique, followed by flash column chromatography (silica gel, eluent - chloroform), afforded the target macrocycle (**1**) in 36% yield.[12]

Reaction of azacrown (**1**) with 2-chloroacetyl chloride in DMF after 2h of stirring at room temperature gave the corresponding ester (**7**) in 94% yield.[13] When ester (**7**) reacted with an excess of dimethylamine in acetone under high dilution conditions at room temperature, the crude dimethylamino derivative (**8**) was formed. After column chromatography (silica gel, eluent - chloroform : hexane 4 : 1), pure lariat crown-formazan (**8**) was isolated in 52% yield.[14] A partial aminolysis of formazan (**7**) during the reaction led to recovery of the parent macrocycle (**1**) (*ca.* 30%).

Development of this topological approach offers much potential for the preparation of a wide variety of useful lariat crown-formazans, novel podandocoronands having a variety of donor/acceptor end groups and varying length side arms.

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8. mp 114-116°C; ^{1}H NMR, 300 MHz ($CDCl_3$/DMSO-d_6 1:1 v/v), δ, ppm: 3.30 (s, 1H); 4.28-4.36 (m, 4H); 5.42 (br. s, 1H); 7.06 (t, 9.4 Hz, 2H); 7.26 (d, 9.4 Hz, 2H); 7.58 (t, 9.4 Hz, 2H); 7.81 (d, 9.4 Hz, 2H); ^{13}C NMR, 75 MHz ($CDCl_3$/DMSO-d_6 1:1 v/v), δ, ppm: 65.9; 68.7; 113.6; 119.2; 124.0; 133.1; 138.2; 150.6. Anal. Calcd. for $C_{15}H_{14}N_2O_7$: C, 53.90%; H, 4.22%; N, 8.38%. Found: C, 53.97%; H, 4.18%; N, 8.35%.
9. mp 85°C; ^{1}H NMR, 300 MHz ($CDCl_3$), δ, ppm: 3.81 (br. s, 1H); 4.07-4.15 (m, 4H); 4.29-4.36 (m, 1H); 6.65-6.84 (m, 8H); ^{13}C NMR, 75 MHz ($CDCl_3$), δ, ppm: 68.5; 69.6; 112.2; 115.5; 118.6; 121.6; 136.1; 146.1. Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.68%; H, 6.61%; N, 10.21%. Found: C, 65.59%; H, 6.57%; N, 10.18%.
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12. mp 213-214°C; ^{1}H NMR, 300 MHz ($CDCl_3$), δ, ppm: 3.24 (d, 9.6 Hz, 1H); 4.21-4.27 (m, 1H); 4.31 (d, 9.6 Hz, 2H); 4.64 (dd, 4.3 Hz, 9.6 Hz, 2H); 6.99 (d, 8 Hz, 2H); 7.07 (t, 8 Hz, 2H); 7.24 (t, 8 Hz, 2H); 7.35 (t, 8 Hz, 2H); 7.46 (t, 8 Hz, 2H); 8.05 (d, 8 Hz, 2H); 8.21 (d, 8 Hz, 2H); ^{13}C NMR, 75 MHz ($CDCl_3$), δ, ppm: 67.4; 70.5; 111.0; 114.5; 121.4; 125.5; 127.2; 127.9; 128.1; 136.8; 137.7; 142.5; 150.6. Anal. Calcd. for $C_{22}H_{20}N_4O_3$: C, 68.03%; H, 5.19%; N, 14.42%. Found: C, 68.33%; H, 5.23%; N, 14.43%.
13. mp 207-209°C; ^{1}H NMR, 300 MHz ($CDCl_3$), δ, ppm: 4.02 (s, 2H); 4.38 (d, 9.6 Hz, 2H); 4.53 (dd, 4.9 Hz, 9.6 Hz, 2H); 5.37-5.45 (m, 1H); 6.91 (d, 8 Hz, 2H); 7.05 (t, 8 Hz, 2H); 7.19 (t, 8 Hz, 2H); 7.33 (t, 8 Hz, 2H); 7.44 (t, 8 Hz, 2H); 8.01 (d, 8 Hz, 2H); 8.19 (d, 8 Hz, 2H); ^{13}C NMR, 75 MHz ($CDCl_3$), δ, ppm: 40.5; 67.9; 70.7; 111.7; 114.6; 121.7; 125.4; 127.2; 127.8; 128.1; 137.1; 137.5; 142.5; 150.3; 165.6. Anal. Calcd. for $C_{24}H_{21}ClN_4O_4$: C, 62.00%; H, 4.55%; N, 12.05%. Found: C, 61.62%; H, 4.72%; N, 12.31%.
14. mp 203-204°C; ^{1}H NMR, 300 MHz ($CDCl_3$), δ, ppm: 2.30 (s, 6H); 3.17 (s, 2H); 4.42 (dd, 2.2 Hz, 9.6 Hz, 2H); 4.54 (dd, 4.9 Hz, 9.6 Hz, 2H); 5.37-5.45 (m, 1H); 6.94 (d, 8 Hz, 2H); 7.06 (t, 8 Hz, 2H); 7.21 (t, 8 Hz, 2H); 7.34 (t, 8 Hz, 2H); 7.44 (t, 8 Hz, 2H); 8.03 (d, 8 Hz, 2H); 8.20 (d, 8 Hz, 2H); ^{13}C NMR, 75 MHz ($CDCl_3$), δ, ppm: 44.9; 59.6; 68.2; 69.0; 111.6; 114.5; 121.6; 125.4; 127.2; 127.8; 128.1; 137.1; 137.6; 142.3; 150.5; 169.7. Anal. Calcd. for $C_{26}H_{27}N_5O_4$: C, 65.95%; H, 5.75%; N, 14.79%. Found: C, 65.73%; H, 5.71%; N, 14.97%.

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