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COMMUNICATION

Synthesis and Complexation of an Optically Active Aza-Crown Ether

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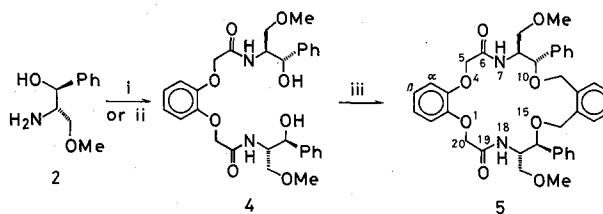
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A variety of macrocyclic polyethers have been synthesized and investigated since the discovery of the excellent chemical performances of crown ethers.¹⁾ Among them, chiral macrocyclic polyethers²⁾ which have been the target of artificial enzymes are also of interest from the viewpoint of ionophore models; cyclic polypeptides like crown ethers exhibit the selectivity toward specific metal cations and associate with such biological activities as antibiotics. We wish to report here the synthesis and the cation-binding ability of an optically active aza-crown ether **5** from (1*S*, 2*S*)-(+)-2-amino-1-phenyl-1,3-propandiol (**1**).

The O-methyl amino-alcohol **2** was prepared from **1** via oxazoline derivatives according to Meyers.³⁾ The DCC condensation of **2** and *o*-phenylenedioxydiacetic acid (**3**) derived from pyrocatechol and chloroacetic acid⁴⁾ gave the dihydroxy-diamide **4** in 34% yield; mp 111–112°C, $[\alpha]_D^{20} +63.7^\circ$ ($c=1.01$, CHCl₃), IR ν_{\max}^{KBr} cm⁻¹: 3400(OH), 1670 (N–C=O), 740 and 705 (phenyl), ¹H NMR(CDCl₃) δ : 3.27, (6H, singlet), 4.50 (4H, singlet), 4.90 (2H, doublet), 6.64–7.00 (4H, multiplet), 7.27 (10H, singlet). Alternatively, **4** was also prepared through the *p*-nitrophenyl ester of **3** in 47% yield. By the action of sodium hydride and α, α' -dibromo-*o*-xylene in DMSO, **4** was converted to the macrocyclic amide polyether, (8*S*, 9*S*, 16*S*, 17*S*)-8, 17-bis (methoxymethyl)-9, 16-diphenyl-2, 3, 12, 13-dibenzo-6, 19-dioxa-7, 18-diaza-1, 4, 10, 15-tetraoxy-2, 12-cycloeicosadiene, (**5**) in 40% yield; glass, $[\alpha]_D^{20} +103.3^\circ$ ($c=1.2$, CHCl₃), MS m/z : 654 (M⁺), IR ν_{\max}^{KBr} cm⁻¹: 2940 (CH), 1690 (N–C=O), ¹H NMR (CD₃CN) δ : 3.16–3.29 (2H, multiplet), 3.19 (6H, singlet, OCH₃), 4.12–4.61 (6H, multiplet), 4.43 (4H, singlet, H-11 and 14), 4.49 (4H, singlet, H-5 and 20), 7.00 (4H, singlet, H- α and β), 7.00–7.20 (2H, broad singlet, H-7 and 18), 7.23 (4H, singlet, phenylene with C-12 and 13), 7.36 (10H, singlet, phenyl at C-9 and 16), ¹³C NMR (CD₃CN) δ : 55.05 (C-8 and 17), 59.02 (OCH₃), 69.79 (C-11 and 14), 70.32 (methylene at C-8 and 17), 72.48 (C-9 and 16), 81.43 (C-5 and 20), 116.01, 123.73, 148.89 (phenylene with C-2 and 3), 128.41, 128.65, 129.46, 140.35 (phenyl at C-9 and 16), 129.15, 129.88, 137.36 (phenylene with C-12 and 13), 168.84 (C-6 and 19).

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Scheme 1. i, *o*-phenylenedioxydiacetic acid, DCC; ii, di-*p*-nitrophenyl *o*-phenylenedioxydiacetate; iii, NaH, α, α' -dibromo-*o*-xylene.

The cation-binding ability of the amide crown ether **5** with lithium, sodium, and magnesium perchlorates was assessed by CD and NMR spectroscopies in acetonitrile. In CD spectra, the ellipticity for the native **5** was 4.6×10^4 degree·cm²/dmol (217 nm) and complexation with magnesium and lithium ions increased the molar ellipticity up to 20%. The association constants, log *K*_a, were estimated to be 2.5 and 1.9 to magnesium and lithium ions, respectively, according to the literature⁵ which assumed a complex composed of one metal ion and one ligand.⁶ On the other hand, sodium ion formed no complex with **5**.⁷ The induced shift by adding equimolar amounts of the metal perchlorates in ¹³C NMR and ¹H NMR spectra also supported the above trend. Not only carbonyl oxygens (C-6 and 19) but also oxygens (O-1 and 4) of phenolic function participated with the complexation because the peaks of carbonyl oxygens (C-6 and 19), aromatic carbons and protons (C- α and C- β), and methylene protons (at C-5 and 20) adjacent to carbonyl groups shifted toward downfield.⁹ The oxygen atoms sticking out of the ring turned out to be irrelevant to the complexation.

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- (6) The concentration of **5** was 1.63×10^{-6} mol/l and the salts were added up to 5000-fold amounts.
- (7) The association constant, log *K*_a, of **5** and *t*-butylammonium thiocyanate in CDCl₃ measured according to Cram's procedure⁸ was shown to be less than 2.4.
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- (9) With magnesium ion, downfield shifts of 1.87 ppm (C-6 and 19), 0.53 ppm, and 0.47 ppm (C- α and β) in ^{13}C NMR and 0.083 ppm (protons at C-5 and 20) and 0.067 ppm (protons at C- α and β) in ^1H NMR. With lithium ion, downfield shifts of 1.05 ppm (C-6 and 19) and 0.24 ppm (C- α and β) in ^{13}C NMR and 0.017 ppm (C-5 and 20) and 0.033 ppm (protons at C- α and β) in ^1H NMR.