SYNTHESIS AND ^{1}H NMR COMPLEXATION STUDY OF A NOVEL MACROCYCLIC POLYETHER CONTAINING 1,1'-BIAZULENE UNIT

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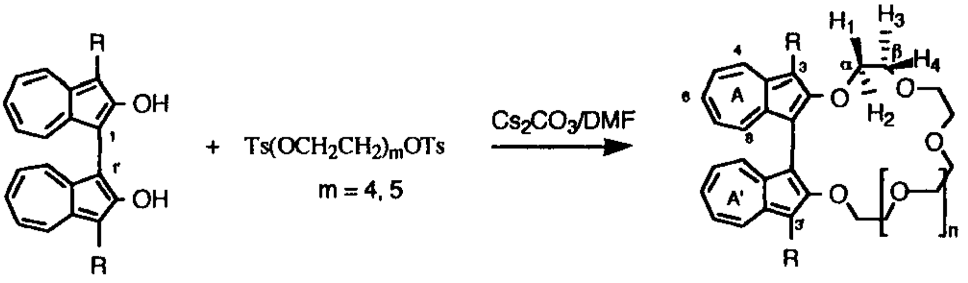
Abstract - A new class of chiral macrocyclic polyethers containing 1,1'-biazulene unit was prepared from the reaction of 2,2'-dihydroxy-3,3'-bis(methoxycarbonyl)-1,1'-biazulene with tetra- or pentaethyleneglycol ditosylate by a high dilution technique. Complexation study with alkali metals by ^{1}H nmr indicated ion selectivity for these macrocycles. The crystal structure was studied by X-ray diffraction.

Synthetic macrocyclic molecules have been used in a variety of fields.[1a-d] One of the interesting area is the recognition behavior between hosts and guests. There has been much work in designing macrocyclic hosts which are able to recognize specific guests. Our interests have been focused on macrocylic polyethers containig azulene units because of its unique chromophore and rigid structure. Analogy to the binaphthyl system biazulenyl macrocycles are expected to be chiral. In this paper, we report their synthesis, selective ion complexation, and X-ray crystallography.

Tetra- (**2a**) and pentaethyleneglycol ethers (**2b**) of 2,2'-dihydroxy-3,3'-bis(methoxycarbonyl)-1,1'-biazulene (**1**) were synthesized according to Scheme 1.

Scheme 1



1 : R = CO_2Me

2a : R = CO_2Me, n = 1
2b : R = CO_2Me, n = 2

Typical synthetic procedure involves a high dilution technique: A solution prepared from equivalent molar of **1**[2] and 1 mM of polyethylene glycol di-*p*-tosylate in 12 ml of DMF was added at 90 °C under argon to a stirred solution of 3 molar equivalences of cesium carbonate in 3 ml of DMF[3] by using a syringe pump with flow system for 12 h.[4] The reaction mixture was stirred at 90 °C for another 12 h and cooled to room temperature before it was filtrated. The filtrate was diluted with water and extracted with chloroform. The combined extract was washed with water and dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the oily residue was purified by column chromatography (silica gel, methanol/chloroform = 2/98 v/v) to give **2a** and **2b**, in 25 and 30 % yields, respectively. The structures of **1**, **2a**, and **2b** were determined on the basis of their spectral data (ir, nmr, and ms).[2,5]

It has been reported that 2,2'-dimethoxy-1,1'-biazulene is comformationally unstable and racemerized rapidly at room temperature.[6] However, **2a** and **2b** are expected to be essentially chiral molecules because the C1-C1' bond is unable to rotate freely from molecular modelling study. In fact, the protons of α-methylene in their ^{1}H nmr spectra showed complicated splitting pattern. Namely, two hydrogens on α-carbon showed a *ddd* splitting pattern at δ 4.36 and 3.85 ppm for **2a** and 4.33 and 3.85 ppm for **2b**, respectively. The other methylene protons also showed a multiplet splitting pattern. The complicated splitting pattern resulted from its low symmetry and rigid structure. On the other hand, their ^{13}C nmr spectra showed three sharp peaks for **2a** (four peaks for **2b**) at *ca.* δ 70 ppm in the polyether region. These data indicate that there is an axis of symmetry (C_2) through the C1-C1' bond. In order to get better understanding of the conformational behavior, molecular modelling was performed using an insight II program.[7] Computer modelling study showed that the ring current of azulene ring A' made α H-1 so much more downfield shift than α H-2 in ^{1}H nmr. Salt complexations were studied by ^{1}H nmr spectra in $CDCl_3$. To a solution of host dissolving in $CDCl_3$ (*ca.* 10^{-4} M) different alkali salt (LiCl, NaSCN, KSCN, RbBr, or CsI) was added in excess.

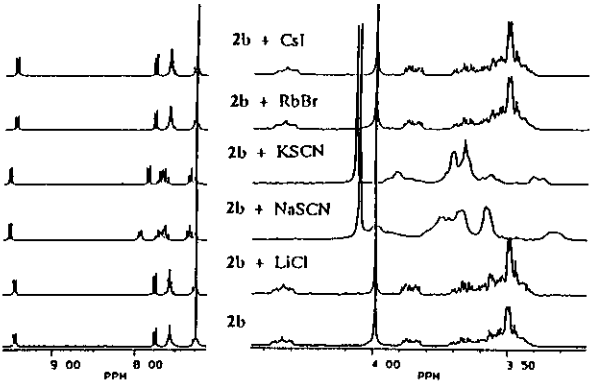


Figure 1. ^{1}H Nmr spectra of **2b** in $CDCl_3$ (300 MHz) with various alkali salts (LiCl, NaSCN, KSCN, RbBr, CsI).

After the mixture was shaken for 5-10 min, ^1H nmr spectrum was taken. The results are shown in Figure 1 and Table 1. An obvious change of the nmr spectra observed for **2b** with NaSCN or KSCN. The presence of the potassium or sodium salt induced spectral changes for not only the polyether ring but also the zulene ring and the methoxy group. It is interesting that **2a** has smaller cavity than **2b**, but the change of the spectra after adding NaCSN is not as remarkable as **2b**. It is worth noting that the cavity size is not the only reason for salt complexation; the ability of preorganization of host should play an important role in this case. The induced change in the chemical shift by a specific cation suggests that there is a special selectivity for each host molecule (for alkali salts: **2a** toward Na^+; **2b** toward Na^+ and K^+).

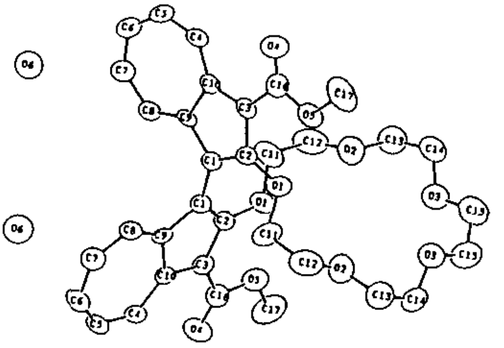
Table 1. Proton Chemical Shift Differences [$\Delta\delta = \delta$ (complex - host) x 300 MHz] between Host and Their Complexes in $CDCl_3$

	polyether ring				azulene ring			
Complex	α-H_1	β-H_2	OCH_2 (ppm)[b]	CO_2Me	H-4	H-8	H-6,7	H-5
2 a/NaSCN	-14 9	5.0	3.741-3.391	3.3	1.1	2.7	3.3	1.7
/KSCN	-6 0	1.1	3.732-3.360	0.6	0	0.5	0	2.9
/RbBr	0	0	3.737-3.345	0	0	0.5	0	0
/CsI	0.5	0.6	3.739-3.347	0.5	0.5	0.5	0.6	0.54
2 b/LiCl	-1.1	2.8	3.704-3.409	0	0	1.7	-0.6	0
/NaSCN	a	a	4.146-3.244	17.6	20.3	55.0	44.0, 17.6	24.8
/KSCN	a	a	3.983-3.338	22.0	19.2	26.9	38.6, 16.4	16.0
/RbBr	-1.7	1.7	3.708-3.411	0	0	0	-0.6	0
/CsI	-2.8	1.7	3.710-3.259	0.5	0	1.1	0	0.6

a . All peaks are shifted upfield (Figure 1).

b : The chemical shift of **2a** is 3.737-3.335; **2b**, 3.710-3.411 ppm.

X-Ray crystallography of **2b•2H$_2$O** is shown in Figure 2.[8] Bond alternation of the azulene ring is smaller in the 7 membered ring than that of the 5 membered ring. The dihedral angle between two azulene planes is 75 °, which is smaller than 94 ° for 3,3'-dimethyl-1,1'-binaphthalene-2,2'-crown-6-ether.[9]



Selective average bond lengths and angles: C-C of the 7 membered ring, 1.393; C-C of the 5 membered ring, 1.426; CH_2-O, 1.388; CH_2-CH_2, 1.437 Å. Interior angles: the 7 membered ring, 127.8; the 5 membered ring, 108; CH_2-O-CH_2, 116; O-CH_2-CH_2, 110 °.

Figure 2. Simplified view of X-ray crystallograpy of **2b•2H$_2$O**.

The diameter of the cavity formed among oxygen atoms in the polyether ring is estimated to be about 5 Å. The cavity size and dihydral angle between the two azulene rings appears to be optimal for the complexation of the host toward Na^+ (1.94 Å) and K^+ (2.99 Å) ions. **2a** may have a smaller cavity and will have better complexation toward the Na^+ or Li^+ ion. Although studies by molecular modelling showed the opposite. The more rigid polyether ring of **2a** causes it to have a larger cavity. The lower flexibility of the cavity is the reason which results in the low complexation of **2a** toward alkali cations.

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2. Compound (**1**) was prepared by oxidative coupling reaction of methyl 2-hydroxyazulene-1-carboxylate with ferric chloride in 40% yield by some modifications of the methods: T. Morita, S. Kosuge, K. Suzuki, and K. Takase, to be published. Methyl 2-hydroxyazulene-1-carboxylate was prepared according to the reported methods: T. Morita and K. Takase, *Sci. Rept.Tohoku Univ.* **1980**,*72*, 83-90; T. Nozoe, K. Takase, M. Kato, and T. Nogi, *Tetrahedron*, **1971**, *27*, 6032. Data of **1**: Deep red prisms, 230-231 °C (decomp.). Ir (KBr) 3400, 1633, 1218 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$): δ 11.04 (2H, s, OH), 9.03-8.98 (2H, m, H-4,4'), 7.94 (2H, d, $J =$ 10.1 Hz, H-8,8'), 7.52-7.47 (4H, m, H-5,5',6,6'), 7.35-7.24 (2H, m, H-7,7'), 4.07 (6H, s, 2 x COOMe); ^{13}C nmr (75 MHz, $CDCl_3$) δ 169.9, 169.2, 141.7, 139.9, 134.4, 133.7, 132.3, 129.4, 128.5, 107.7, 99.2, 51.4; EIms *m/z* 402 (M^+, 34), 370 (29), 338 (100), 310 (10), 282 (13); HRms: Calcd for $C_{24}H_{18}O_6$ 402.1103, found 402.1108.
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4. SAGE Instruments, Syringe Pump Model 314B.
5. **2a** : Reddish brown crystals, mp 226-227 °C, ir (KBr) 1671, 1212, 1130, 1097, 1040 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$): δ 9.45-9.40 (2H, m, H-4,4'), 7.77 (2H, d, $J =$ 9.7 Hz, H-8,8'),

7.59-7.53 (4H, m, H-5,5',6,6'), 7.30-7.20 (2H, m, H-7,7'), 4.37 (2H, ddd, *J* = 10.9, 7.6, 3.3 Hz, α-H-1), 3.85 (2H, ddd, *J* = 10.9, 4.0, 4.0 Hz, α-H-2), 3.99 (6H, s, 2 x COOMe), 3.74 -3.34 (12H, m, OCH_2); ^{13}C nmr (75 MHz, $CDCl_3$) δ 166.8, 165.5, 141.9, 140.6, 135.8, 134.5, 133.9, 128.9, 127.9, 109.7, 105.2, 72.4, 70.5, 70.2, 70.1, 51.1; EIms *m/z* 560 (M^+, 100); HRms: Calcd for $C_{32}H_{32}O_9$, 560.2047; found, 560.2047.

2b: Reddish brown crystals, mp 141-142 °C, ir (KBr) 1672, 1211, 1129, 1097, 1040 cm^{-1}.

^1H Nmr (300 MHz, $CDCl_3$) δ 9.46-9.43 (2H, m, H-4,4'), 7.74 (2H, d, *J* = 9.9 Hz, H-8,8'), 7.61-7.50 (4H, m, H-5,5',6,6'), 7.27-7.20 (2H, m, H-7,7'), 4.33 (2H, ddd, *J* = 10.8, 7.4, -3.3 Hz, α-H-1), 3.85 (2H, ddd, *J* = 10.8, 4.7, 3.3 Hz, α-H-2), 3.98 (6H, s, 2 x COOMe), 3.70 -3.43 (16H, m, OCH_2); ^{13}C nmr (75 MHz, $CDCl_3$) δ 166.7, 165.6, 142.1, 140.6, 135.8, 134.6, 133.8, 129.1, 128.1, 109.5, 105.2, 72.2, 70.5, 70.4, 70.3, 70.1, 51.1;
EIms *m/z* 604 (M^+, 100); HRms : Calcd for $C_{34}H_{36}O_{10}$, 604.2309; found, 604.2311.

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7. Insight II Program, Version, 2.3.0 (1993) from Biosym, San Diago, California, USA.
8. Crystal data for **2b**: $C_{34}H_{40}O_{12}$, F. M.= 640.68, monoclinic, space group C2/c, a = 494 (3), b = 20.038 (4), c = 17.387 (4) Å, β = 93.835 (21)°, V = 3300.3 (14) $Å^3$, Z = 4, D = 1.289 g cm^{-3}, Crystal dimensions 0.08 x 0.10 x 0.55 mm^3, Data were collected on a Nonius CAD4 diffractometer using Mo-Kα (0.7093 Å) radiation at 298 °K, no. of measured reflections: 2164, no. of observed reflections : 862 with $I > 2\sigma(I)$, no. of unique reflections: 2164. The refinement converted at R = 0.069, Rw = 0.071. NRCVAX was used as a refinement program.

   Bond lengths: C1-C1, 1.478 (13); C1-C2, 1.384(11); C1-C9, 1.413(11); C2-C3, 1.444(11); C2-O1, 1.349(10); C3-C10, 1.397(12); C3-C16, 1.471(12); C4-C5, 1.375(13); C4-C10, 1.384(11); C5-C6, 1.367(14); C6-C7, 1.409(12); C7-C8, 1.362(12); C8-C9, 1.367(11); C9-C10, 1.490(10); C11-C12, 1.508(15); C11-O1, 1.372(11); C12-O2, 1.367(15); C13-C14, 1.497(17); C13-O2, 1.429(12); C14-O3,1.385(12); C15-C15, 1.374(20); C15-O3, 1.432(14); C5-O3, 1.432(14); C16-O4, 1.188(10); C16-O5, 1.322(11); C17-O5, 1.439(12) Å. Bond angles: C1-C1-C2, 127.8(7); C1-C1-C9, 124.2(7); C1-C2-C3, 110.5(7); C1-C2-O1, 129.5(7); C3-C2-O1, 120.0(7); C2-C3-C10, 107.0(7); C2-C3-C16, 130.2(8); C10-C3-C16, 122.8(7); C5-C4-C10, 129.1(7); C4-C5-C6, 129.8(8); C5-C6-C7, 129.3(8); C6-C7-C8, 127.9(8); C7-C8-C9, 129.7(7); C1-C9-C8, 124.4(7); C1-C9-C10, 107.2(7); C8-C9-C10, 128.4(7); C3-C10-C4, 126.9(7); C3-C10-C9, 107.3(6); C4-C10-C9, 125.8(7); C12-C11-O1, 110.3(8); C11-C12-O2, 110.3(9); C14-C13-O2, 107.6(8); C13-C14-O3, 111.2(8); C15-C15-O3, 111.7(9); C3-C16-O4, 126.5(8); C3-C16-O5, 110.4(7); O4-C16-O5, 123.0(8), C2-O1-C11, 118.5(7); C12-O2-C13, 114.4(8); C14-O3-C15, 116.8(7); C16-O5-C17, 111.5(7)°.

   This molecule is conformationally disordered around the O3-C15-C15-O3 moiety.
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