DIPYRIDINE CROWN ETHERS. SYNTHESIS AND CONFORMATIONAL ASPECTS OF A TETRAAZADITHIA-18-CROWN-6 ANALOG.†

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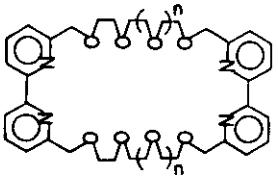
Abstract. The synthesis and conformational analysis by VTNMR of a bis-dipyridylthia-18-crown-6-ether (4) are described. The energy barrier of inversion $\Delta G^{\ddagger}$ is 10.4 kcal/mol and measures a transverse isomerization inversion process.

The chemistry of macrocyclic molecules possessing subheterocyclic rings within the crown ether framework has received considerable attention in past few years[1]. During our studies related with the synthesis and complexation of 2,2'-dipyridine crown ethers, e.g., 1, we observed that the conformational preferences of these molecules are dictated by the size of the bridge connecting the two dipyridine subunits[1b,2]. As part of our continuing investigation in the area of



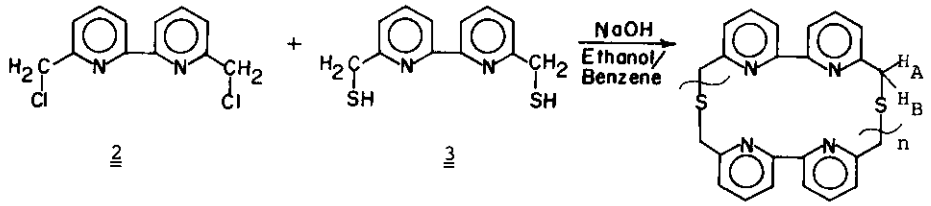
1 a, n=2
b, n=3
c, n=4

binuclear complexes, we synthesized macrocycles in which the two dipyridine units are held as close to one another as possible. In this communication, we wish to report the synthesis and NMR study of 4, which is an analog of 18-crown-6 as well as a novel [3:3]dithiametacyclophane.

The 6,6'-dichloromethyl-2,2'-dipyridine[1c] (2) was treated with thiourea followed by base hydrolysis to provide the dithiol 3[4], as a white solid: mp 107-108°C (hexane); NMR ($CDCl_3$) δ 2.1 (t, -S<u>H</u>, J = 8.0Hz, 1H), 3.92 (d, -C<u>H</u>$_2$SH, J = 8.0 Hz, 2H), 7.35 (d, 5-Pyr-H, J = 7.5Hz, 1H), 7.78 (t, 4-Pyr-H, J = 7.5Hz, 1H), 8.37

†Dedicated to Professor Tetsuji Kametani on the occasion of his retirement.

(d, 3-Pyr-H, J = 7.5Hz, 1H). The high dilution[5] reaction between 2 and 3 in presence of sodium hydroxide gave (15%), after preparative thick layer chromatography on neutral alumina [ethyl acetate-cyclohexane (1:10)], 4[4] as a white crystalline solid: mp 234-235°C; R_f = 0.36; NMR ($CDCl_3$) δ 4.07 (s, Pyr-CH_2, 2H), 7.12 (d, 5-Pyr-H, J = 7.5Hz, 1H), 7.32 (t, 4-Pyr-H, $J_{4,5} = J_{4,3}$ = 7.5Hz, 1H), 7.72 (d, 3-Pyr-H, $J_{3,4}$ = 7.5Hz, 1H); IR (KBr) 1565 (vs), 1430 (vs) cm^{-1}; MS (m/e, rel. int.) 428 (M^+, 12.7), 395 (100), 245 (52), 229 (37), 214 (72). Also obtained from this reaction was the 3:3-macrocycle 5[4], as colorless crystals (methylene



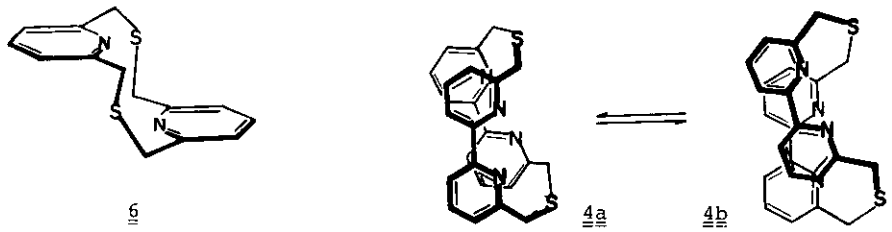
2 + 3 → 4; n=1 (15%), 5; n=2 (4%)

chloride): mp 172-173°C; R_f 0.05; NMR ($CDCl_3$) δ 3.97 (s, Pyr-CH_2, 2H), 7.31 (d, 5-Pyr-H, $J_{5,4}$ = 7.5Hz, 1H), 7.47 (t, 4-Pyr-H, $J_{4,3} = J_{4,5}$ = 7.5Hz, 1H), 7.95 (d, 3-Pyr-H, $J_{3,4}$ = 7.5Hz, 1H); IR (KBr) 1555 (vs), 1425 (vs) cm^{-1}; MS (m/e, rel. int.) 642 (M^+, 0.2), 245 (67), 215 (78), 214 (69), and 184 (100). The dithiacyclophane 4 could also be prepared in lower yield by the reaction of 2 with sodium sulfide under high dilution conditions[5]; however in this case, 5 was obtained as the major macrocyclic product.

The 200 MHz H^1 spectrum of crown 4 is shown in Figure 1. It is interesting to note that all aromatic hydrogens in 4 are shifted to higher field as compared to the open chain analog 3; the most dramatic change observed is in the resonance of H-3, which absorbs at δ 7.72 for 4 as compared to δ 8.37 for 3. This shift to high field for H-3 in 4 *clearly demonstrates that the orientation of the pyridine rings is approaching a syn configuration.* Obviously, 3 is assumed to have the dipyridine moiety in an anti orientation on the basis of chemical shift for H-3.[6] The methylene protons (H_A, H_B) in 4 are found to be equivalent at room temperature as suggested by the singlet at δ 4.07. However, the variable temperature NMR (Fig. 1) shows that the geminal methylene hydrogens becoming nonequivalent at lower temperatures and appear as a doublet at 190°K. The coalescent temperature is found to be 205°K, from which the energy barrier ($\Delta G^{\ddagger}$) for the inversion of the

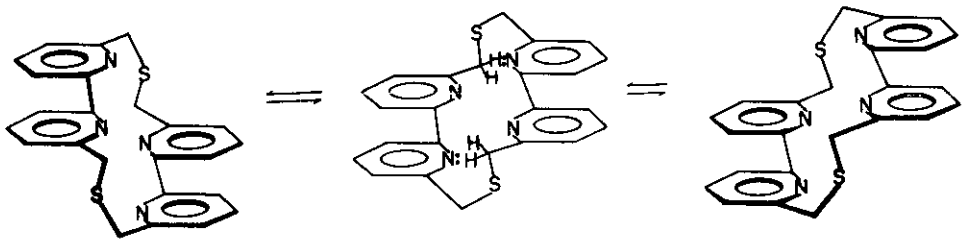
macrocycle is calculated to be 10.4 kcal/mole. This high energy barrier for the transverse isomerization process[7] in 4 is in contrast to the case of the related pyridine dithiacyclophane 6, in which the inversion of the central ring is found to be too fast for dynamic NMR.[8]

Examination of the molecular models of 4 reveals a number of probable conformations, in which the dipyridyl moiety can exist in an anti conformation;



6 4a 4b

however, these anti structures can be disregarded on the basis of the chemical shift for the 3-pyridine hydrogen. Conformations 4a and 4b will account for the upfield shift of all aromatic hydrogens but they do not account for a high barrier



4c 4f 4d

for the ring inversion in 4. Two chair conformations, 4c and 4d, are possible for 4, which must interconvert via a near planar, strained conformation 4f. In this transitional conformation the two α-methylene hydrogens are thrust into the immediate proximity of the pyridine N-electrons. This unfavorable interaction during the interconversion of 4c and 4d may account for a high $\Delta G^{\#}_{inversion}$ observed for 4, as compared to similar systems.

We are currently investigating the x-ray crystal structure of 4, its conversion into the corresponding [2:2]-metacyclophane, and the complexation behavior of these 18-crown-6 analogs.

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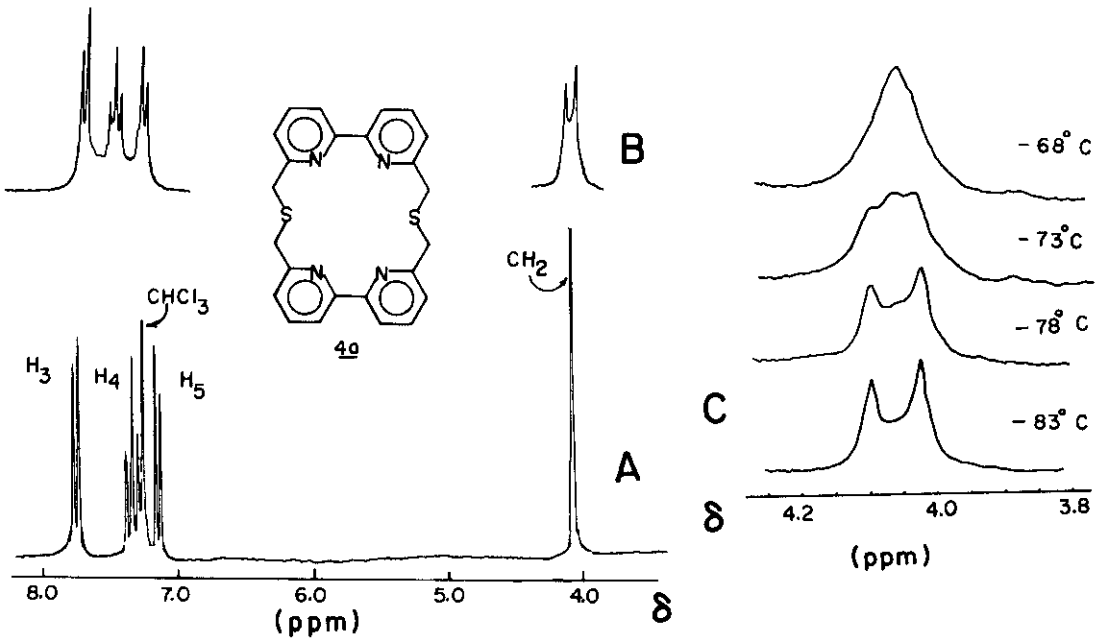

Figure 1. A. 200 MHz NMR of 4 in $CDCl_3$. B. NMR spectrum at 190°K.
C. VTNMR spectrum of 4 methylene region.

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