Journal of Inclusion Phenomena and Macrocyclic Chemistry **35:** 147–155, 1999.
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Complexation Studies Using Azamacrolactones Derived from Biphenyl

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Abstract. Steric effects must be considered in order to explain the ability of several macrolactones derived from biphenyl in complexing alkali cations and mercury compounds.

Key words: azamacrolactones, complexation, steric hindrance.

1. Introduction

During the last few years our research group has been interested in studying crown ethers and related compounds containing biphenyl units in their structures. Different reasons justify this interest: first, the rigidity of the biaryl framework could be used to design receptors presenting allosteric behaviour [1–3]. In addition, the chirality observed in some biphenyl derivatives could permit the preparation of ligands for chiral recognition [4].

Previous experiments [5] had showed that the ability of crown ethers and lactones to extract alkali picrates depends on steric and electronic effects. In addition complexation experiments with mercury thiocyanate had demonstrated that macrolactones containing only oxygen atoms in the crown (Chart 1) are unable to complex this metal. We now report the preparation of related lactones containing in their structure not only oxygen atoms but also a methylamine group. The preparation and study of these compounds seemed to be interesting in order to clarify why previously synthesized lactones did not form stable compounds with mercury compounds.

2. Experimental

2.1. SYNTHESIS OF *N*-METHYL-6-AZA-3,9-DIOXAUNDECANE-1,11-DIOL (**4**)

6-Aza-3,9-dioxaundecane-1,11-diol (2.0 g, 10.35 mmol) and an aqueous solution of formaldehyde (30%, 1.43 mL, 15.53 mmol) were dissolved in ethanol (100 mL) and Pd/C 10% (0.160 g) was added. The suspension was stirred under hydrogen

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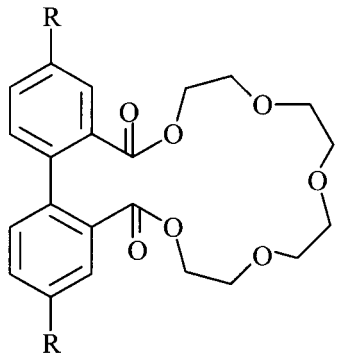
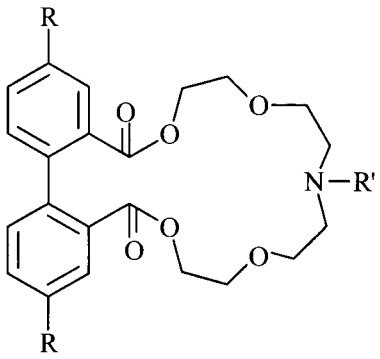


1a R=NO_2
1b R=$N(CH_3)_2$
1c R=NH_2



2a R=NO_2, R'=CH_3
2b R=$N(CH_3)_2$, R'=CH_3
2c R=NH_2, R'=H

Chart 1.

atmosphere at room temperature until the starting material was consumed. The suspension was quickly filtered up and the solvent was removed from the filtrate under vacuum to give **4** as a clear oil (2.112 g, 99%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.87 (2H, broad s, OH), 3.52–3.39 (12H, m, CH_2O), 2.46 (4H, t, J = 4.5 Hz, CH_2N), 2.15 (3H, s, NCH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 72.6 (t), 67.5 (t), 61.4 (t), 57.9 (t), 41.7 (q). HRMS (CI^+) calcd for $C_9H_{22}NO_4$ 208.1549; found 208.1542.

2.2. SYNTHESIS OF 4,4′-DINITRO-2,2′-BIPHENYL-3,17-DIOXO-10-(*N*-METHYL)AZA-19-CROWN-5 (**2a**)

A mixture of 4,4′-dinitrobiphenyl-2,2′-dicarboxylic acid (0.300 g, 0.90 mmol) and thionyl chloride was heated under reflux for 1.5 h. After addition of anhydrous THF (30 mL) the solution was distilled to dryness under argon. The residue was dissolved in dry TFH (50 mL) and anhydrous triethylamine (1 mL). The solution was heated under reflux while a solution of 6-(*N*-methyl)aza-3,9-dioxaundecane-1,11-diol (**4**) (0.187 g, 0.90 mmol) in dry THF (50 mL) was added dropwise for a period of 5 hours with a syringe pump. The reaction was stirred under argon overnight. After this time the solvent was distilled and the residue was dissolved in chloroform (75 mL) and washed with cold sodium bicarbonate solution (3 × 25 mL, 10%) and then with water (1 × 25 mL). The organic phase was dried over Na_2SO_4 and the solvent removed under vacuum. The crude product was purified by chromatography through a neutral alumina column (from hexane/ethyl acetate (2/8) to ethyl acetate/methanol (9/1)) to afford 0.077 g of **2a** (17% yield). m.p. 111–113 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.99 (2H, d, J = 2.4 Hz, Ar—H), 8.41 (2H, dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz. Ar—H), 7.35 (2H, d, J = 8.4 Hz, Ar—H), 4.30 (2H, ddd, J_1 = 12.2 Hz, J_2 = 6.2 Hz, J_3 = 2.4 Hz, CO_2CH_2), 4.21–4.09 (2H, m,

CO_2CH_2), 3.61–3.48 (4H, m, CH_2O), 3.36 (2H, ddd, J_1 = 10.8 Hz, J_2 = 6.5 Hz, J_3 = 3.2 Hz, OCH_2CH_2N), 3.24 (2H, ddd, J_1 = 10.8 Hz, J_2 = 6.5 Hz, J_3 = 3.2 Hz, OCH_2CH_2N), 2.90 (2H, ddd, J_1 = 14.0 Hz, J_2 = 6.5 Hz, J_3 = 3.2 Hz, CH_2N), 2.54 (2H, ddd, J_1 = 14.0 Hz, J_2 = 6.5 Hz, J_3 = 3.2 Hz, CHN), 2.28 (3H, s, N—CH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 164.1 (s), 148.0 (s), 147.3 (s), 130.5 (d), 130.2 (s), 126.1 (d), 125.9 (d), 69.5 (t), 68.3 (t), 64.8 (t), 56.3 (t), 43.7 (q). HRMS (CI^+) calcd. for $C_{23}H_{26}N_3O_{10}$, 504.1618; found 504.1621.

2.3. SYNTHESIS OF 2,2′-TETRAMETHYLBENZIDINE-3,17-DIOXO-10-(*N*-METHYL)AZA-19-CROWN-5 (**2b**)

2a (0.280 g, 0.56 mmol) and an aqueous solution of formaldehyde (30%, 1 mL, 10.99 mmol) were dissolved in ethanol (100 mL). Then 10% Pd-C (0.647 g) was added and the mixture was stirred under hydrogen atmosphere at room temperature until the starting material was consumed. The suspension was quickly filtered and the solvent removed from the filtrate under vacuum. The residue was dissolved in hydrochloric acid (15 mL, 10%) and the catalyst exhaustively washed with hydrochloric acid solution. The acidic solutions were treated with sodium hydroxide and extracted with ethyl acetate (3 × 5 mL). The organic solution was dried and the solvent evaporated under vacuum. The crude product was purified by chromatography through neutral alumina column to give **2b** (0.060 g, 21%). m.p. 90–91 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.32 (2H, d, J = 2.9 Hz, Ar—H), 7.01 (2H, d, J = 8.4 Hz, Ar-H), 6.82 (2H, dd, J_1 = 8.4 Hz, J_2 = 2.9 Hz, Ar—H), 4.22–4.10 (4H, m, CO_2CH_2), 3.55–3.46 (4H, m, CH_2O), 3.41 (2H, ddd, J_1 = 10.5 Hz, J_2 = 6.7 Hz, J_3 = 3.5 Hz, OCH_2CH_2N), 3.21 (2H, ddd, J_1=10.5 Hz, J_2=6.7 Hz, J_3=3.5 Hz, OCH_2CH_2N), 2.99 (12H, s, Ar—NCH_3), 2.90 (2H, ddd, J_1 = 13.7 Hz, J_2 = 6.7 Hz, J_3 = 3.5 Hz, CH_2N), 2.61 (2H, ddd, J_1 = 13.7 Hz, J_2 = 6.7 Hz, J_3 = 3.5 Hz, CH_2N), 2.34 (3H, s, N—CH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.2 (s), 149.0 (s), 131.6 (d), 131.4 (s), 130.1 (s), 115.1 (d), 113.5 (d), 68.7 (t), 68.6 (t), 63.7 (t), 55.7 (t), 43.6 (q), 40.6 (q). HRMS (CI^+) calcd. for $C_{27}H_{38}N_3O_6$, 500.2761; found 500.2753.

2.4. SYNTHESIS OF *N*-BENZYLOXYCARBONYL-6-AZA-3,9-DIOXA-UNDECANE-1,11-DIOL (**6**)

Benzyl chloroformate (0.41 mL, 2.87 mmol) was added at 0 °C and under inert atmosphere to a solution of 6-aza-3,9-undecane-1,11-diol (0.50 g, 2.59 mmol), 4-dimethylaminopiridine (0.032 g, 0.26 mmol) and dry triethylamine (1.08 mL, 7.75 mmol) in dry THF (11 mL). When the reaction reached room temperature, it was stirred for 6 additional hours. Then, the solution was evaporated and the residue was dissolved in ethyl acetate (60 mL) and washed with water (3 × 20 mL). The solution was dried and evaporated. The product was purified by column chromatography to give a colourless oil (0.526 g, 62%). ^{1}H NMR (250 MHz, $CDCl_3$) δ

7.33 (5H, bs, Ar—H), 5.12 (2H, s, CH_2—Ar), 3.90–3.55 (16H, m, CH_2O, CH_2N), 2.90 (2H, bs, OH). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 155.9 (s), 136.1 (s), 128.0 (d), 127.6 (d), 127.3 (d), 71.9 (t), 69.1 (t), 68.8 (t), 66.7 (t), 60.9 (t), 47.8 (t), 47.2 (t).

2.5. SYNTHESIS OF 4,4′-DINITRO-2,2′-BIPHENY-3,17-DIOXO-10-(*N*-BENZYLOXYCARBONYL)AZA-19-CROWN-5 (**7**)

This was synthesized under the same conditions described for **2a** from 4,4′-dinitrobiphenyl-2,2′-dicarboxylic acid (0.30 g, 0.90 mmol), thionyl chloride (3 mL) and 6-(*N*-benzyloxycarbonyl)aza-3,9-dioxaundecane-1,11-diol (**5**) (0.295 g, 0.90 mmol). The product was isolated as a solid (0.082 g, 15%). m.p. 129–130 °C. ^1H NMR (250 MHz, $CDCl_3$) δ 8.99 (2H, d, J = 2.4 Hz, Ar—H), 8.41 (2H, dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz Ar—H), 7.36 (2H, d, J = 8.4 Hz, Ar—H), 7.34–7.30 (5H, m, Ar—H), 5.09 (2H, s, CH_2—Ar), 4.43–4.27 (2H, m, Ar—CO_2CH_2), 4.12–4.05 (2H, m, Ar—CO_2CH), 3.65–3.39 (10H, m, CH_2O, CH_2NCO), 3.28–3.15 (2H, m, CH_2NCO). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 164.0 (s), 156.0 (s), 148.1 (s), 147.3 (s), 136.6 (s), 130.6 (d), 130.1 (s), 128.5 (d), 128.0 (d), 127.8 (d), 126.2 (d), 125.8 (d), 70.3 (t), 70.2 (t), 68.2 (t), 68.0 (t), 67.1 (t), 64.9 (t), 64.7 (t), 48.1 (t), 47.7 (t). HRMS (EI^+) calcd. for $C_{30}H_{29}N_3O_{12}$, 623.1751; found 623.1761.

2.6. SYNTHESIS OF 4,4′DINITRO-2,2′-BIPHENYL-3,17-DIOXO-10-AZA-19-CROWN-5 (**2c**) AND 4,4′-DINITRO-2,2′-BIPHENYL-3,17-DIOXO-10-(*N*-BENZYL)AZA-19-CROWN-5 (**8**)

Compound **7** (0.100 g, 0.16 mmol) was heated at 100° C with hydrobromic acid in acetic acid (0.3 mL, 30%) for 5 minutes. Then, water (10 mL) was added and the mixture was extracted with dichloromethane (2 × 5 mL). The organic phase was dried and the solvent evaporated to give **2c** as a white solid (0.064 g, 82%). m.p. 112–113 °C. ^1H NMR (250 MHz, $CDCl_3$) δ 8.78 (2H, d, J = 2.4 Hz, Ar—H), 8.35 (2H, dd, J_1 = 8.5 Hz, J_2=2.4 Hz, Ar—H), 7.39 (2H, d, J = 8.5 Hz, Ar—H), 4.19–4.06 (4H, m, CO_2CH_2), 3.58–4.38 (8H, m, CH_2O), 3.31–3.11 (5H, m, CH_2N, N—H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 165.7 (s), 149.6 (s), 148.9 (s), 132.6 (d), 131.2 (s), 127.5 (d), 126.3 (d), 69.9 (t), 66.1 (t), 65.3 (t), 47.5 (t). HRMS (EI^+) calcd. for $C_{20}H_{23}N_3O_{10}$, 489.1383; found 489.1390.

The aqueous phase was treated with sodium hydroxide (10 M) and then extracted with ethyl acetate (3 × 10 mL). The organic phase was dried with Na_2SO_4 and the solvent evaporated under vacuum. Compound **8** was isolated as a yellow oil that became solid by standing (6 mg, 7%). m.p. 94–95 °C. ^1H NMR (250 MHz, $CDCl_3$) δ 9.01 (2H, d, J = 2.4 Hz, Ar—H), 8.44 (2H, dd, J_1 = 8.5 Hz, J_2 = 2.4 Hz, Ar—H), 7.40 (2H, d, J = 2.4 Hz, Ar—H), 7.40–7.28 (5H, m, Ar—H), 4.30–4.10 (4H, m, CO_2CH_2), 3.60–3.29 (10H, m, CH_2O, CH_2—Ar), 3.10–2.65 (4H, m, CH_2N). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 164.3 (s), 147.7 (s), 147.4 (s), 137.0 (s), 130.6 (d), 130.2 (s), 128.9 (d), 128.2 (d), 127.0 (d), 126.1 (d), 125.9 (d), 68.5 (t), 68.3 (t),

64.8 (t), 53.4 (t), 47.3 (t). HRMS (EI^+) calcd. for $C_{29}H_{29}N_3O_{10}$, 579.1853; found 579.1818.

2.7. SYNTHESIS OF COMPLEXES. GENERAL PROCEDURE

One equivalent of the salt in acetone was added to one equivalent of the ligand in acetone. In each case the minimum amount of acetone to dissolve the ligand and the salt was employed. The mixture was stirred in a closed tube for 4 hours and then the solvent was slowly evaporated to give the different complexes.

2.7.1. *Complex* **2a**·$Hg(CN)_2$

Yellow solid. m.p. 180–181 °C. ^{1}H NMR (250 MHz, CD_3OD) δ 8.83 (2H, d, J = 1.6 Hz, Ar—H), 8.39 (2H, dd, J_1 = 7.7 Hz, J_2 = 1.6 Hz, Ar—H), 7.43 (2H, d, J = 7.7 Hz, Ar—H), 4.25–4.00 (4H, m, CO_2CH_2), 3.90–3.30 (8H, m, CH_2O), 3.10–2.60 (4H, m, CH_2N), 2.32 (3H, s, N—CH_3). ^{13}C NMR (62.5 MHz, CD_3OD) δ 165.7 (s), 149.4 (s), 148.9 (s), 143.5 (s, CN), 132.5 (d), 131.4 (s), 127.3 (d), 126.4 (d), 69.6 (t), 68.5 (t), 65.7 (t), 57.1 (t), 43.1 (q).

2.7.2. *Complex* **2a**·$Cd(NO_3)_2$

Yellow solid. m.p. 169–170 °C. ^{1}H NMR (250 MHz, CD_3OD) δ 8.71 (2H, d, J = 2.4 Hz, Ar—H), 8.36 (2H, dd, J_1 = 8.5 Hz, J_2 = 2.4 Hz, Ar—H), 7.39 (2H, d, J = 8.4 Hz, Ar—H), 4.30–4.00 (4H, m, CO_2CH_2), 3.90–3.30 (8H, m, CH_2O), 3.12 (3H, s, N—CH_3), 3.00–2.25 (4H, m, CH_2N). ^{13}C NMR (62.5 MHz, CD_3OD) δ 165.7 (s), 150.1 (s), 148.9 (s), 132.6 (s), 132.0 (s), 127.4 (d), 125.8 (d), 71.5 (t), 66.2 (t), 63.4 (t), 59.8 (t), 43.0 (q).

2.7.3. *Complex* **2a**·$Pb(NO_3)_2$

Yellow solid. m.p. 155–156 °C. ^{1}H NMR (250 MHz, CD_3OD) δ 8.85 (2H, d, J = 2.0 Hz, Ar—H), 8.43 (2H, dd, J_1 = 8.3 Hz, J_2 = 2.0 Hz, Ar—H), 7.47 (2H, d, J = 8.3 Hz, Ar—H), 4.43–4.09 (4H, m, CO_2CH_2), 4.04–3.40 (8H, m, CH_2O), 3.35–3.10 (4H, m, CH_2N), 2.74 (3H, s, N—CH_3). ^{13}C NMR (62.5 MHz, CD_3OD) δ 165.8 (s), 150.5 (s), 149.0 (s), 132.6 (d), 131.0 (s), 127.6 (d), 125.8 (d), 73.6 (t), 70.0 (t), 65.2 (t), 58.0 (t), 43.0 (q).

2.7.4. *Complex* **2b**·$Hg(CN)_2$

Yellow wax. ^{1}H NMR (250 MHz, CD_3OD) δ 7.21 (2H, d, J = 2.3 Hz, Ar—H), 6.90 (2H, d, J = 8.6 Hz, Ar—H), 6.83 (2H, dd, J_1 = 8.6 Hz, J_2 = 2.3 Hz, Ar—H), 4.25–3.85 (4H, m, CO_2CH_2), 3.60–2.50 (12H, m, CH_2O, CH_2N), 2.91 (12H, s, Ar—NCH_3), 2.31 (3H, s, N—CH_3). ^{13}C NMR (62.5 MHz, CD_3OD) δ 170.1 (s), 150.8 (s), 144.0 (s, CN), 132.9 (d, s), 131.5 (s), 116.7 (d), 114.7 (d), 69.8 (t), 68.7 (t), 64.8 (t), 57.1 (t), 43.6 (q), 40.9 (q).

2.7.5. *Complex* **2b**·$Cd(NO_3)_2$

Yellow wax. ^{1}H NMR (250 MHz, CD_3OD) δ 7.22 (2H, d, J = 2.7 Hz, Ar—H), 6.92 (2H, d, J = 8.6 Hz, Ar–H), 6.85 (2H, dd, J_1 = 8.6 Hz, J_2 = 2.7 Hz, Ar–H), 4.32–3.80 (4H, m, CO_2CH_2), 3.70–2.75 (12H, m, CH_2O, CH_2N), 2.91 (12H, s, Ar—NCH_3), 2.52 (3H, s, N—CH_3). ^{13}C NMR (62.5 MHz, CD_3OD) δ 170.1 (s), 150.8 (s), 133.0 (d, s), 131.4 (s), 116.7 (d), 114.4 (d), 70.2 (t), 65.4 (t), 64.2 (t), 56.4 (t), 42.1 (q), 40.8 (q).

2.7.6. *Complex* **2b**·$Pb(NO_3)_2$

Yellow wax. ^{1}H NMR (250 MHz, CD_3OD) δ 7.21 (2H, d, J = 2.8 Hz, Ar—H), 6.93 (2H, d, J = 8.5 Hz, Ar—H), 6.85 (2H, dd, J_1 = 8.5 Hz, J_2 = 2.8 Hz, Ar—H), 4.32–3.84 (4H, m, CO_2CH_2), 3.83–2.80 (12H, m, CH_2O, CH_2N), 2.92 (12H, s, Ar—NCH_3), 2.74 (3H, s, N—CH_3). ^{13}C NMR (62.5 MHz, CD_3OD) δ 170.1 (s), 150.8 (s), 133.0 (d, s), 131.4 (s), 116.8 (d), 114.4 (d), 70.3 (t), 65.0 (t), 64.2 (t), 56.5 (t), 42.0 (q), 40.8 (q).

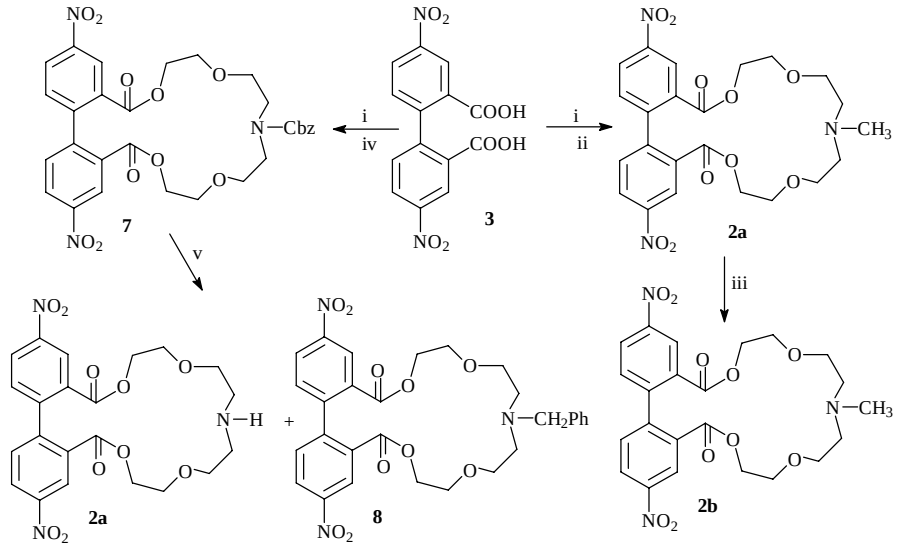
2.8. DETERMINATION OF THE ASSOCIATION CONSTANTS OF THE COMPLEXES WITH SODIUM PICRATE. GENERAL PROCEDURE

All titrations were done at constant host concentration. Aliquots of 50 μL of a 50 mM guest solution in acetone were added to a solution of the host (20 mmol) in acetone-d_6 (0.5 mL). The solvent level was kept constant by evaporation and the different spectra recorded at 298 K. The chemical shift (signals corresponding to the methylene group directly bound to the ester) were plotted against increasing concentrations of guest. This curve was fitted by using a non-linear least-squares regression analysis.

3. Results and Discussion

3.1. SYNTHESES OF LIGANDS

Ligands were synthesized as shown in Scheme 1. All the synthetical pathways used as starting material 4,4′-dinitrobiphenyl-2,2′-dicarboxylic acid (3), which was converted into the corresponding acyl chloride. From it, macrolactones could be prepared in low to moderate yields by reacting with the appropriate diols. In this sense, chain **4** was prepared from 6-aza-3,9-dioxaundecane-1,11-diol [7] through reductive methylation. Similarly, compound **6** was prepared from the same diol by reaction with benzylchloroformate.



i. Cl_2SO. ii. $(HOCH_2\text{-}CH_2\text{-}O\text{-}CH_2\text{-}CH_2)_2NCH_3$ (**4**)/Et_3N/THF. iii. H_2, Pd, H_2CO.
iv. $(HOCH_2\text{-}CH_2\text{-}O\text{-}CH_2\text{-}CH_2)_2N$-Cbz (**6**). v. HBr/AcOH.

Scheme 1.

3.2. COMPLEXATION STUDIES

3.2.1. *Complexation of transition metals*

Complexation studies carried out with compounds **1a–b** showed that these ligands were unsuitable for complexing $Hg(SCN)_2$ [6]. On the other hand, additional experiments demonstrated that $Hg(CN)_2$ was not complexed by these macrolactones. These results were explained on the basis of steric effects. Thus, macromodel studies of these compounds had shown that whereas one carbonyl group was coplanar to its aromatic ring, the other was almost perpendicular. These positions of the carbonyl groups not only produced a strong steric hindrance but also prevented one oxygen directing its lone pair towards the cavity. These two effects made the conformation unsuitable for complexing mercury atom since one of the SCN or CN groups would pass through the cavity which was hindered by the presence of one of the carbonyl groups.

By contrast, ligands now reported, **2a–b**, complex mercury compounds even in MeOH. Complexation constants with these ligands are so high that in the NMR spectrum only the signals corresponding to the complexes were observed. It is known that the presence of a nitrogen atom increases the strength of the complex with transition metals [8]. However, the difference observed between these compounds and those previously studied seems too big to be only due to the presence of a nitrogen atom.

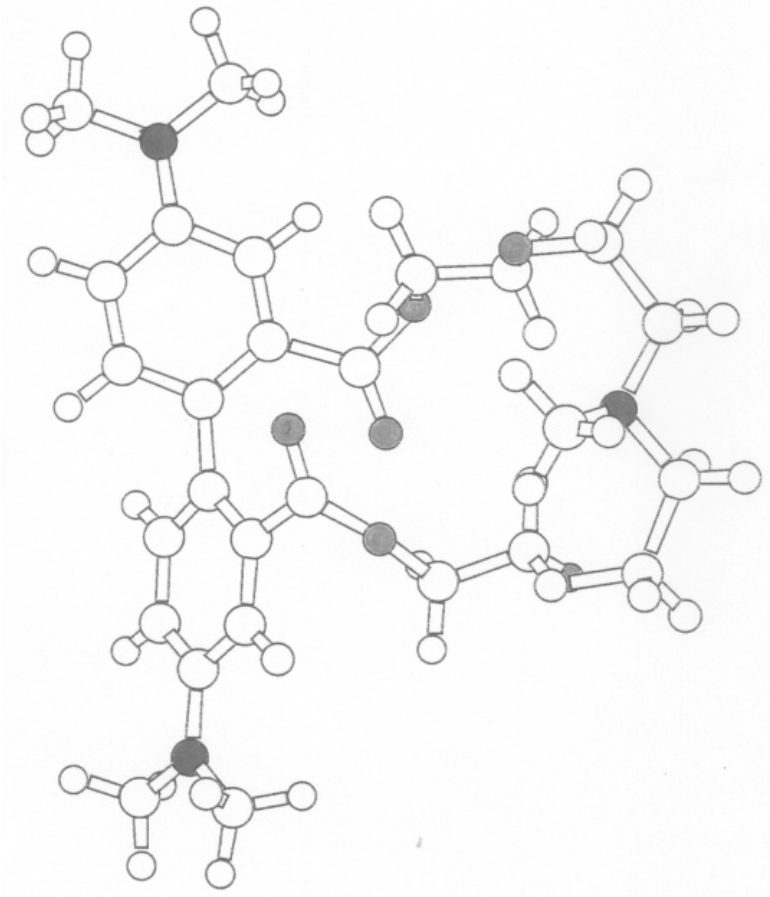


Figure 1. Molecular modeling structure of **2b**.

On the other hand, a wider study using other transition metal salts demonstrated that the synthesized compounds also complex cadmium and lead salts with high association constants. These experiments show that the ionic or covalent character of the guest was not very important in complexation.

3.2.2. *Complexation of sodium picrate*

The behaviour of the synthesized compounds in complexing sodium cation was even more interesting. Complexation constants determined through titration experiments are shown in Table I. The value summarized in the table demonstrated that compound **2a–b** complexed sodium cation better than compounds **1a–b**. The observed increment could not be due to the presence of the nitrogen atom, since an opposite effect would be observed. Thus, these observations, in addition to the

Table I. Complexation constants (K_a (M^{-1}) d_6-acetone 25 °C)

Ligand	**1a**	**1b**	**2a**	**2b**
Na^+	–	28	6	48

results obtained in mercury complexation, suggest that the methyl group must have an influence in the cavity that makes it more suitable for complexing guests.

Macromodel studies [9] with these new hosts demonstrated that both carbonyl groups are almost perpendicular to the corresponding aromatic rings. This fact could decrease steric hindrance and guests should be more easily complexed by the crown. In addition, this disposition of the carbonyl groups allows all the oxygens to direct their lone pairs toward the cavity which increases the host–guest interactions.

In order to confirm this supposition new lactones containing more nitrogen atoms in the crown are being prepared.

Acknowledgements

We thank the Dirección General de Investigación Científica y Técnica (PB95-1121-C02-01) for support. E. Monrabal is grateful to the Generalitat Valencia for a predoctoral fellowship.

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