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Association Constants of Alkaline Complexes of Macrolactones and Crown Ethers Derived from Biphenyl. Influence of the Position and Characteristics of Biphenyl Substituents

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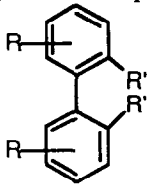
Abstract: The influence that substituents in the biphenyl moiety have on the association constants of several macrolactones and crown ether derived from biphenyl have been studied. The steric hindrance produced by the presence of substituents in 6,6' makes some crown ethers less suitable to complex alkaline cations. Carbonyl groups present in macrolactones reduce the effective space inside the hole and smaller cations are better fitted.

Several crown ethers containing biphenyl subunits have been synthesized with different goals. Thus 6,6'-dimethyl-19-crown-5 and 6,6'-dimethybiphenyl-21-crown-7 were prepared by Rebek[1] to be used as controls in his studies about allosteric cooperativity. Other related compounds have been utilized by Diederich to carry out experiments of chiral recognition in an aqueous solution[2]. Hence, it has been demonstrated that biphenyls are very interesting constituent parts of macrocyclic systems because they can be used to insert chiral barriers in macrocyclic hosts. That was the reason why we decided to study the influence of different substituents in the biphenyl moiety on the ability of these compounds to make complexes with different cations.

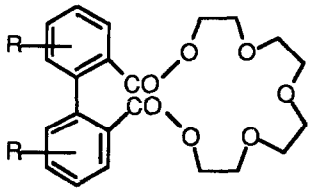


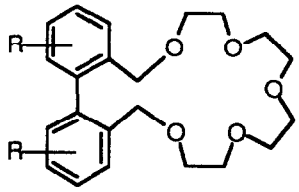
1a R'=COOH R=4-NO_2

1b R'=COOH R=6-OMe

1c R'=CH_2OH R=6-OMe

The studied crown ethers were prepared by a cyclization of biphenyl derivatives **1a-c**. Compound **1a** has been prepared from 9,10-phenanthrenequinone through its 2,7-dinitro derivative[3]; this nitrocompound can be oxidized with hydrogen peroxide to give **1a** in a very high yield. Compounds **1b-c** had been prepared by our group from 2-amine-3-methoxybenzoic acid[4]. Cyclization reactions have been carried out by using the corresponding acid chloride and the appropriate polyethylene glycol to give macrolactones[5], and from benzylic alcohol and polyethylene glycol distosylates to yield crown ethers[6]. This leads to compounds that have substituents at different positions and with different electronic characteristics.

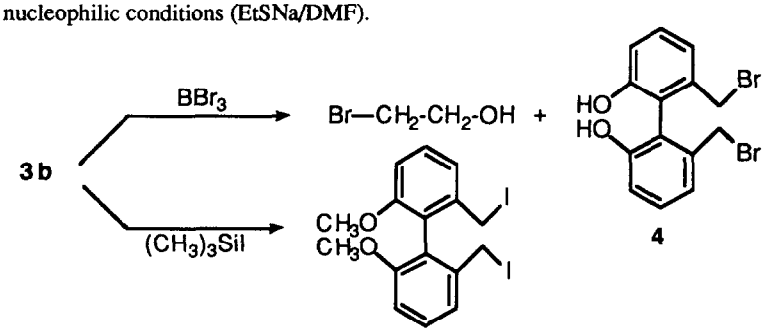




2a R=4-NO_2
2b R=6-OCH_3

3a R=4-NO_2
3b R=6-OCH_3
3c R=6-OH

Compound **3c** was obtained through demethylation of **3b**; this reaction was unsatisfactory when Lewis acids were used as demethylating agents. Thus treatment with $SnCl_4$ led to the recovery of unchanged starting material; in the reaction of **3b** with BBr_3[7], the macrocyclic system was broken and compound **4** and 2-bromoethanol were isolated in quantitative yields. On the other hand, when trimethylsilyl iodide[8] was used, the diiodo derivative **5** was isolated from the reaction. The desired **3c** was obtained[9] only when demethylation was carried out by using nucleophilic conditions (EtSNa/DMF).



As Sutherland and Ager[10] had described a direct high-yielding procedure for reduction of crown lactones to crown ethers, we decided to use the corresponding lactone **2b** to prepare compound **3b**. However, this reaction did not result in anything useful even though different reaction conditions were used. Similar results were observed when **2a** was used as starting material; attempts to reduce **2a** to the corresponding crown ether by using $LiAlH_4$ were unsuccessful and we observed different results depending on the temperature. Thus, when the reduction was carried out at -23°C, the starting material was completely recovered. At -14°C the desired crown ether was obtained, in very low yield (<10%) and it was impossible to purify it completly. In order to improve this yield, the reaction was repeated at 0°C. A complex mixture of compounds was obtained in which 4,4'-dinitro-2,2'-dihydroxybiphenyl seemed to be present (^1H NMR).

Determination of Association Constants

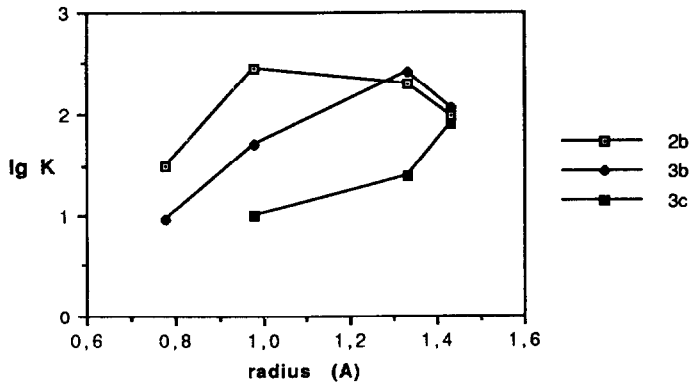
As established above, we had a series of compounds available which have different electronic and steric characteristics; so, we studied the influence of the substituent on the macrocycles ability to complex alkaline cations. The picrate extraction technique[11] was used to determine association constants and all variables were kept constant in order to have comparable results.

The results shown in Table 1 allow us to affirm that steric hindrance has a strong influence on the association constant values. Thus, compound **3b** complexed Na^+ as was expected but its association constant (log K=1.7) is lower than that obtained for 6,6'-dimethyl-2,2'-BF-19-C-5 (log K= 2.08)[1] and biphenyl-19-C-5 (log K=1.84 MeOH:H_2O, 8:2), although determination conditions were not the same in these experiments as in ours. Nevertheless, the results observed for **3b** and **3c** show that bulky groups in 6,6'-positions fix a conformation suitable to complex alkaline cations. As a consequence of the hole size and the oxygen number, both compounds complex K^+ better than Na^+. The lower ability present in **3c** could be explained by the presence of the hydroxy groups which can form intramolecular hydrogen bonds that make it more difficult to get the suitable conformation.

Table 1. Association Constants

		log K		
Cation	ionic radius (A)	**2b**	**3b**	**3c**
Li^+	0.78	1.5	0.97	
Na^+	0.98	2.45	1.7	1.0
K^+	1.33	2.30	2.41	1.4
NH_4^+	1.43	1.99	2.05	1.9

On the other hand, compound **3c** shows surprising behaviour because of the big association constant observed when ammonium was used. A reason for this fact could be found in the presence of both hydroxy groups which could take part in the complexation process. **2b** fits Na^+ better than K^+, meaning the effective hole for the macrolactone is smaller than in the crown ether, and Na^+ which has an ionic radius of 0.98 is complexed in a stronger way than the larger cation K^+. Experiments carried out using 4,4'-dinitromacrolactone, **2a**, demonstrated that this system is completly incapable of complexing any alkaline cation under the usual conditions. As there are no steric reasons[6], only electronic effects could be responsible for this behaviour, since compound **2b** shows the expected ability in complexation experiments.



Conclusions

From the results of the experiments carried out it is possible to conclude that a reduction reaction of macrolactones with $LiAlH_4$ is not a suitable process to obtain crown ether. On the other hand, the reactivity of

benzylic crown ethers in the presence of Lewis acids is higher than that of the methyl ether, and under these conditions, the crown is broken and biphenyl derivatives are isolated.

According to the complexation experiments, the ability to form complexes with alkaline cations increases when the conformation is fixed by steric or electronic effects. When macrolactones are used in these experiments, the influence of electronic effects is even higher, and in the presence of nitro groups, the complexation ability vanishes.

Experimental Section

General Methods. The products whose syntheses are not described were purchased from Aldrich Chemical Co. and used without further purification. Proton NMR spectra were recorded on a Hitachi Perkin Elmer R-24 B, Brucker AC-200, Varian Gemini-200, Varian Unity-300 and 400. ^{13}C NMR spectra were recorded on a Brucker WP 80 SY, Brucker AC-200, Varian Gemini-200, Varian Unity-300 and 400. Chemical shifts were reported from internal TMS. IR spectra were obtained on a Perkin Elmer 843 spectometer with KBr pellets. Mass spectra were taken on a MS-9-VG mass spectometer. Melting points were determined on a Cambridge Instrument and a Reichert Thermovar. TLC analyses were carried out on 0.2 mm Merck PC 60 F 245 silica gel plates. Column chromatographies were carried out on Merck 60 A-CC silica gel. Microanalyses were determined by Servicio de Microanálisis (C.S.I.C.). Ultraviolet measurements were made with a Spectrometer Shimadzu UV-240.

Reaction of 3b with boron tribromide. A solution of **3b** (0.2 g, 0.463 mmol) in 25 mL of dichloromethane was cooled at - 80°C in an dry ice acetone bath. Boron tribromide (0.34 mL, 3.565 mmol) was carefully added to the cool solution with a dry syringe. After addition, a calcium chloride tube was placed at the top of the flask to protect the reaction mixture from moisture. The solution was brought to room temperature and stirred overnight. Water (10 mL) was carefully added, and after separation of the precipitate, the liquid phase was shaken with water (2 x 20 mL) , dried ($MgSO_4$) and concentrated. **4** (0.17 g, 99%) was obtained as brown crystals. mp = 93°C. 200 MHz ^1H NMR ($CDCl_3$): d7.37 (1 H, t, Ar-H, J= 4.0 Hz); 7.18 (1 H, dd, Ar-H, J= 4.0 Hz, J= 0.01 Hz); 7.02 (1 H, dd, Ar-H, J= 4.0 Hz, J= 0.01 Hz); 4.30 (1 H, s, OH); 4.18 (2 H, s, CH_2). 200 MHz ^{13}C NMR ($CDCl_3$): d 154.0 (s), 138.5 (s), 131.0 (d), 123.2 (d), 118.6 (s), 116.5 (d), 31.4 (t). MS: m/e 372 (M^+), 292 (M^+ - Br), 291 (M^+ - Br), 211 (M^+ - Br_2). Anal. Calcd. for $C_{14}H_{12}O_2Br_2$: C, 45.16%; H, 3.22%; Br, 43.0%. Found : C, 45.15%; H, 3.39%; Br, 42.7%. In the aqueous phase, variable quantities of 2-Bromoethanol were identified.

Demethylation of 3b with iodotrimethylsilane. Trimethylsilyliodide (1.3 equiv) was added via a dry syringe into a NMR tube containing **3b** (0.016 g, 0.037 mmol) and a suitable quantity of $CDCl_3$ (0.55 mL). The closed tube was kept at room temperature for 24 h. The reaction was monitored by ^1H NMR analysis. The product obtained after purification by silica gel column chromatography (hexane - ethyl acetate rising polarity) was **5** (9 mg, 60%). 200 MHz ^1H NMR ($CDCl_3$): d 7.35 (1 H, t, Ar-H, J= 8.0 Hz); 7.19 (1 H, d, Ar-H, J= 8.0 Hz); 6.88 (1 H, d, Ar- H, J= 8.0 Hz); 4.14 (2 H, dd, CH_2, J= 23.2 Hz, J= 9.4 Hz). 200 MHz ^{13}C NMR ($CDCl_3$): d 153.8 (s), 138.5 (s), 129.4 (d), 123.6 (s), 122.8 (d), 110.2 (d), 55.8 (q), 4.3 (t).

Synthesis of dimethoxymacrolactone 2b. 6,6'- dimethoxy-2,2'-diphenic acid (0.35 g, 0.011 mmol) was added to an excess of thionyl chloride (1.5 mL). The suspension was refluxed under magnetic stirring until it became a clear solution. After 2 h the excess of thionyl chloride was distilled. The solid residue was dissolved in dry THF (35 mL) and treated with pyridine (0.5 mL). The solution was refluxed while a tetraethylene glycol solution in THF (0.20 g in 25 mL of dry THF) was very carefully added. After addition, the reaction mixture was refluxed for 12 additional hours. After filtration the liquid phase was evaporated. The solid obtained was dissolved again in CH_2Cl_2 and washed, with a sodium hydrogen carbonate solution, HCl solution (pH= 2) and water and then dried ($MgSO_4$). After evaporation a solid was obtained (560 mg); purification through silica gel chromatography column (hexane:ethyl acetate 3:2) gave **2b** as a solid (100 mg. 20%). m. p. 111-112°C. 300 MHz ^{1}H NMR ($CDCl_3$): d 7.6 (1 H, dd, Ar-H, J_1= 8.1Hz, J_2=2.1); 7.3 (1 H, t, Ar-H, J= 8.1Hz); 7.0(1 H, dd, Ar-H, J_1= 8.1Hz, J_2=2.1); 4.0 (2 H, t, Ar-COO-CH_2, J= 5.1); 3.5 (3H, s, CH_3). 3.5-3.3 (5H, m, CH_2); 3.2-3.1 (1H, m, CH_2). 200 MHz ^{13}C NMR ($CDCl_3$): d 167.15 (s), 156.92 (s), 131.68(s), 130.8 (s) 128.06(d), 127.88(s), 122.50(d), 114.23(d), 70.87 (t), 70.55 (t), 68.71 (t), 63.55(t), 56.20(q). Anal. Calcd. for $C_{24}H_{28}O_9$: C, 62.60%; H, 6.13%. Found : C, 62.63%; H, 6.11%.

Synthesis of dinitromacrolactone 2a. 2,7- dinitrodiphenic acid (0.3 g, 0.92 mmol) was added to an excess of thionyl chloride (1.4 mL). The suspension was refluxed under magnetic stirring till it became a clear solution. After 2 h the excess thionyl chloride was distilled. The solid obtained was dissolved in dry THF (35 mL) and pyridine (0.5 mL) was added. The solution was refluxed while a tetraethylene glycol solution in THF (0.15 g in 15 mL of dry THF) was very carefully added. After addition, the reaction mixture was refluxed for 2 additional hours. After filtration the liquid phase was evaporated. The solid obtained was dissolved again in chloroform and washed, with a sodium hydrogen carbonate solution, HCl solution (pH= 4) and water and then dried ($MgSO_4$). After evaporation **2a** (0.225 g, 76.5%) was obtained as a dense oil. IR (KBr): 2830, 1720, 1605, 1520, 1344, 1260, 1120, 650 cm^{-1}. 200 MHz ^{1}H NMR ($CDCl_3$): d 8.95 (1 H, d, Ar-H, J= 2.28 Hz); 8.38 (1 H, dd, Ar-H, J= 8.43Hz , J= 2.28 Hz); 7.38 (1 H, d, Ar-H, J= 8.43 Hz); 4.22 (2 H, m, CH_2); 3.5 (6 H, m, CH_2). 200 MHz ^{13}C NMR ($CDCl_3$): d 164.1 (s), 147.7 (s), 147.3 (q), 130.8 (s) 130.5 (d), 126.0 (d), 125.8 (d), 71.0 (t), 70.3 (t), 70.1 (t), 64.7 (t).

Reduction of 2a with $LiAlH_4$. General procedure. A solution of **2a** (0.5 g in 20 mL of dry THF) was added to a suspension of $LiAlH_4$ (150 mg in 30 mL of dry THF). The reactions were stopped by adding 15 mL of water, and the suspension obtained was filtered. The solid was extracted with ethyl acetate using a Soxhlet, and the organic phase was concentrated. After silica gel column chromatography (dichloromethane - ethyl acetate 1/1) different products were obtained: **At -23°C after 2h** starting material was recovered unchanged. **At -14°C after 2.15 h** 4,4´-dinitro-2,2´-biphenyl-19-C-5 (0.105 g, 9.5%). 200 MHz ^{1}H NMR ($CDCl_3$): d 8.5 (1 H, d, Ar-H, J= 2.3 Hz); 8.2 (1 H, dd, Ar-H, J= 8.5 Hz, J= 2.3 Hz); 7.3 (1 H, d, Ar-H, J= 8.5 Hz); 4.4 (2 H, m, CH_2); 3.6 (8 H, m, CH_2). 200 MHz ^{13}C NMR ($CDCl_3$): d 148.1 (s), 143.4 (s), 140.9 (s), 129.9 (d), 123.8 (d), 122.3 (d), 72.7 (t), 70.4 (t), 69.8 (t), 62.6 (t), 61.4 (t). **At 0°C after 2 h** 4,4´-dinitro-2,2´-hydroxymethylbiphenyl (traces). 200 MHz ^{1}H NMR ($CDCl_3$): d 8.55 (1 H, d, Ar-H, J= 2Hz); 8.24 (1 H, dd, Ar-H, J= 8 Hz, J= 2 Hz); 7.48 (1 H, d, Ar-H, J= 8 Hz); 4.42 (2 H, d, CH_2, J= 7Hz); 3.6 (1 H, s, OH).

Determination of given Association Constants by Ultraviolet Method._ All ultraviolet measurements were made at 380 nm. and 24-26ºC. Typically , 5 to 7 complexation experiments were run simultaneously with a given host.

0.5 mL of a 0.05 M picrate solution in distilled water was introduced in a tube. To one tube 1.0 mL of water was added to be used as a blank. 0.2 mL of the host solution (0.075 M in $CHCl_3$) was added to each of the tubes, including the one containing water. The contents of each tube were then stirred vigorously for 3 min. with a magnetic stirrer, and separated into clear layers by centrifugation.

An aliquot of 0.01 mL of $CHCl_3$ layer (or 0.05 mL if the colour intensity is too weak) was transferred by microsyringe into a 5-mL volumetric flask and diluted with CH_3CN. For each size of aliquot a blank was also made by measuring the desired volume from the $CHCl_3$ layer of the H_2O blank and diluting with CH_3CN in a 10-mL volumetric flask. The UV absorption of each solution was measured against the appropriate blank solution at 380 nm. The absorbance of the sample cell at 380 nm. relative to the absorbance of the blank cell when both were filled with CH_3CN was measured prior to each series of extractions. Calculations were based on Beer's law relationship and on Cram's equations. Extinction coefficients for each salt in CH_3CN were determined in the range of 10^{-4}-10^{-6}M of standard solutions prepared directly from the pure salts. The average values were used in the calculations.

Acknowledgements

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