Synthesis and ESI-MS Complexation Studies of New Macrocyclic Bisamides Containing Binaphthyl Unit

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Abstract

Eight new chiral macrocyclic bisamides, containing binaphthyl and some other aromatic (phenyl or naphthyl) subunits, are obtained in racemic form. Preliminary results concerning their ability for complexation of alkali metal cations, using ESI-MS technique, are presented.

Introduction

Optically active 1,1′-binaphthyl unit is very well known as an efficient chiral auxiliary as well as an outstanding controller of chiral recognition [1]. The catalysts built on the basis of this rigid chiral molecule are successfully applied in catalytic asymmetric hydrogenation [2], reduction of carbonyl compounds [3], and in many other enantioselective processes such as aldol addition [4] ene reaction [5], [4 + 2] cycloaddition [6], skeleton rearrangements [7]. In 1970s many 1,1′-binaphthyl-2,2′-diol crown ethers have been also prepared [8, 9] and applied to stereocontrolled organic synthesis [10].

Owing to the attractive properties of the 1,1′-binaphthyl unit, we turn our attention to its incorporation into macrocyclic bisamide type synthetic receptors.

Recently, we found that α,ω-diamino aliphatic ethers react under ambient conditions with dimethyl α,ω-dicarboxylates in methanol as a solvent, to give macrocyclic diamides in moderate yields [11], however, addition of sodium methoxide improves kinetics, and to some extent the yield of macrocyclization reaction [12]. This finding constitutes a very efficient and versatile procedure for the synthesis of various macrocyclic diamides, as shown in Scheme 1.

In this paper we present applications of the method for the preparation of eight macrocyclic receptors containing the 1,1′-binaphthyl unit, which were further subjected to the preliminary studies of their ability for complexation of alkali metal cations, using the ESI-MS technique. Up to now there are only several reports using ESI-MS for the determination of the binding selectivities of crown ethers and related compounds for

alkali metal cations [13–16]. The results presented in these papers encouraged us to evaluate the alkali metal binding selectivities and estimate the relations between the structure and the observed binding strengths.

Experimental

Melting points were taken on a Köfler-type (Boetius) hot-stage apparatus and are not corrected. ^{1}H NMR spectra were recorded with a Varian Gemini (200 MHz) spectrometer in CDCl$_3$ using tetramethylsilane as an internal standard. ^{13}C NMR spectra were also recorded using a Varian Gemini (50 MHz) spectrometer. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ 0.00 ppm), and coupling constants (J) are measured in Hertz. The high-resolution mass spectrometry (HRMS) experiments were performed on an Quattro LC Micromass instrument using the ESI technique. The column chromatography was carried out on silica gel (Kieselgel-60, 200–400 mesh). Methanol was freshly distilled from Mg/I$_2$ under Ar. Amines **1**–**3** were obtained *via* BMS reduction of appropriate nitriles [17]. Esters **4**–**9** were synthesized according to the general literature method [12] (Figure 1).

General procedure for the macrocyclization reaction

One equivalent of an appropriate diamine and one equivalent of a diester were dissolved in dry methanol (∼0.1 M). To this solution 1 equiv of metallic sodium was added and the mixture was stirred for a few days (monitoring by TLC) at room temperature. After completion of the reaction, the solvent was evaporated

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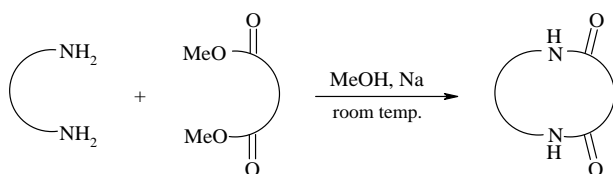
Scheme 1. A general route to macrocyclic bisamides.

and the product was purified by column chromatography (CH$_2$Cl$_2$/MeOH 1–5%).

Macrocyclic bisamide rac-10

Yield: 64%, mp 146–150 °C. ^{1}H NMR (200 MHz, CDCl$_3$), δ: 3.10–3.16 (2H, m), 3.56–3.60 (2H, m), 3.71–3.77 (2H, m), 4.00–4.04 (2H, m), 4.41 (2H, AB/2, $J = 15.6$), 4.54 (2H, AB/2, $J = 15.6$), 6.70 (2H, bt, $J = 5.5$), 6.82–6.86 (2H, m), 7.00–7.04 (2H, m), 7.10–7.40 (8H, m), 7.60 (2H, d, $J = 9$), 7.79 (2H, d, $J = 7.9$). ^{13}C NMR (50 MHz, CDCl$_3$): 38.7, 66.8, 69.0, 113.2, 114.5, 119.5, 121.5, 124.4, 125.0, 127.0, 128.2, 129.8, 130.3, 133.3, 148.1, 152.8, 168.7. HR ESI-MS: calcd for C$_{34}$H$_{31}$N$_2$O$_6$[M + H]$^+$ 563.2182, found: 563.2172.

Macrocyclic bisamide rac-11

Yield: 15%, mp 217–221 °C. ^{1}H NMR (200 MHz, CDCl$_3$), δ: 2.93–3.07 (2H, m), 3.6–3.76 (2H, m), 3.79–3.88 (2H, m), 3.94–4.04 (2H, m), 4.30 (2H, AB/2, $J = 15.2$), 4.40 (2H, AB/2, $J = 15.2$), 6.13 (1H, t, $J = 2.3$), 6.33 (2H, bt, $J = 5.4$), 6.47 (2H, dd, $J = 8.2$,

$J = 2.5$), 7.09–7.44 (9H, m), 7.82–7.89 (4H, m). ^{13}C NMR (50 MHz, CDCl$_3$): 39.0, 66.6, 69.5, 104.3, 107.7, 115.7, 119.8, 124.7, 125.0, 127.2, 128.3, 130.0, 130.2, 130.4, 133.2, 153.2, 160.0, 168.7. HR ESI-MS: calcd for C$_{34}$H$_{31}$N$_2$O$_6$[M + H]$^+$ 563.2182, found: 563.2206.

A mixture of macrocyclic bisamides rac-12

Yield: 48%, mp 151–168 °C. ^{1}H NMR (200 MHz, CDCl$_3$), δ: 2.67–2.87 (1H, m), 3.03–3.22 (1H, m), 3.26–3.44 (1H, m), 3.51–4.03 (5H, m), 4.06–4.48 (4H, m), 6.58–6.70 (2H, bm), 6.92–7.61 (16H, m), 7.78–8.02 (8H, m), ^{13}C NMR (50 MHz, CDCl$_3$): 38.3, 39.3, 69.8, 70.1, 115.7, 116.6, 117.4, 117.7, 120.2, 121.1, 121.5, 121.6, 124.4, 124.7, 124.9, 125.35, 125.40, 125.40, 125.5, 126.6, 126.8, 127.2, 127.3, 128.0, 128.1, 128.2, 129.8, 129.9, 129.88, 130.0, 130.1, 130.3, 130.5, 133.7, 133.8, 134.1, 153.3, 153.4, 153.6, 154.0, 168.8, 169.0. HR ESI-MS: calcd for C$_{48}$H$_{38}$N$_2$O$_6$Na[M + Na]$^+$ 761.2628, found: 761.2648.

Macrocyclic bisamide rac-13

Yield: 40%, mp 239–241 °C. ^{1}H NMR (200 mHz, CDCl$_3$), δ: 3.14–3.29 (2H, m), 3.51–3.71 (2H, m), 3.87–3.97 (2H, m), 4.08–4.19 (2H, m), 4.34 (2H, AB/2, $J = 15.6$), 4.50 (2H, AB/2, $J = 15.6$), 6.93–7.39 (14H, m), 7.75–7.84 (4H, m). ^{13}C NMR (50 MHz, CDCl$_3$): 39.2, 69.8, 69.8, 116.6, 117.3, 122.0, 123.8, 124.6, 125.5, 127.0, 128.3, 130.0, 130.2, 134.2, 148.1, 153.4, 168.4. HR ESI-MS: calcd for C34H$_{31}$N$_2$O$_6$[M + H]$^+$ 563.2182, found: 563.2198.
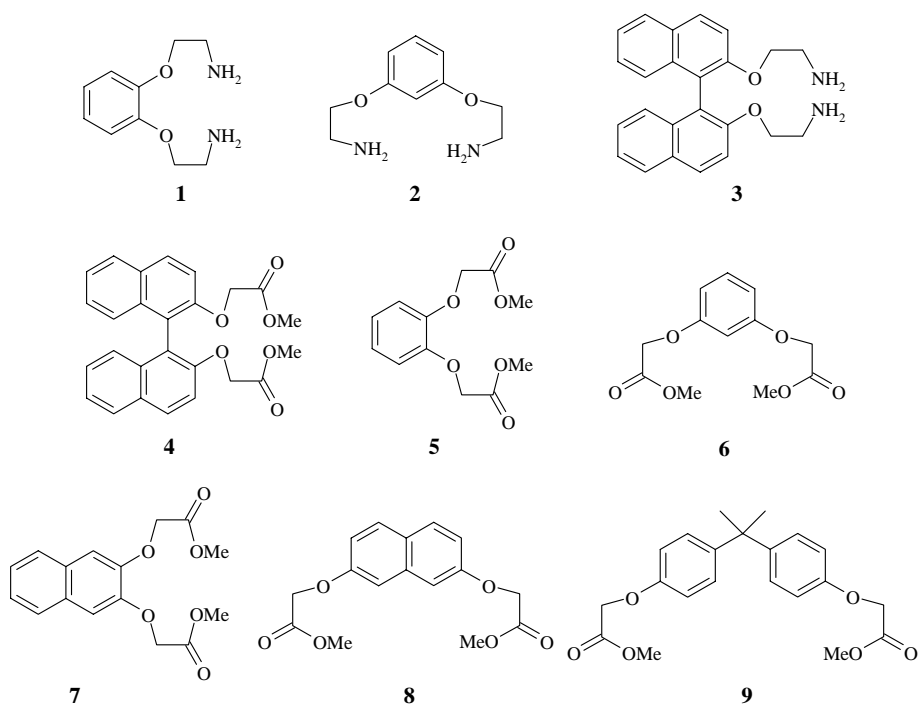

Figure 1. Structure of the substrates used.

Macrocyclic bisamide rac-14

Yield: 19%, mp 227–229 °C. ^{1}H NMR (200 mHz, CDCl$_3$), δ: 2.93–3.08 (2H, m), 3.43–5.7 (2H, m), 3.75–3.85 (2H, m), 3.91–4.02 (2H, m), 4.12 (2H, AB/2, $J = 15.6$), 4.42 (2H, AB/2, $J = 15.6$), 6.34 (1H, t, $J = 2.5$), 6.40 (1H, bt, $J = 5.3$), 6.56 (2H, dd, $J = 2.4$, $J = 8.4$), 7.11–7.41 (9H, m), 7.85–7.90 (4H, m). ^{13}C NMR (50 MHz, CDCl$_3$): 39.0, 68.2, 69.8, 103.9, 108.6, 118.1, 121.7, 124.7, 125.3, 126.9, 128.3, 130.0, 130.1, 130.8, 134.0. HR ESI-MS: calcd for C$_{34}$H$_{32}$N$_2$O$_6$[M + H]$^+$ 563.2182, found: 563.2206.

Macrocyclic bisamide rac-15

Yield: 70%, mp 136–139 °C. ^{1}H NMR (200 mHz, CDCl$_3$), δ: 3.15–3.35 (2H, m), 3.56–3.77 (2H, m), 3.92–4.06 (2H, m), 4.14–4.28 (2H, m), 4.38 (2H, AB/2, $J = 14.6$), 4.57 (2H, AB/2, $J = 14.6$), 6.82–6.96 (2H, bm), 6.98–7.53 (12H, m), 7.64–7.82 (6H, m). ^{13}C NMR (50 MHz, CDCl$_3$): 39.3, 68.4, 69.1, 110.0, 116.8, 121.7, 124.4, 125.2, 125.4, 126.7, 128.06, 129.7, 129.9, 134.0, 147.0, 153.2, 167.8. HR ESI-MS: calcd for C$_{38}$H$_{32}$N$_2$O$_6$Na[M + Na]$^+$ 635.2158, found: 635.2167.

Macrocyclic bisamide rac-16

Yield: 8%, mp 229–233 °C. ^{1}H NMR (200 mHz, CDCl$_3$), δ: 2.95–3.12 (2H, m), 3.38–3.52 (2H, m), 3.72–3.99 (4H, m), 4.31 (2H, AB/2, $J = 16$), 4.47 (2H, AB/2, $J = 16$), 5.95–6.05 (2H, bm), 6.60–7.83 (18H, m), ^{13}C NMR (50 MHz, CDCl$_3$): 39.7, 69.2, 69.6, 109.1, 117.0, 117.1, 117.7, 120.6, 124.3, 124.79, 126.1, 126.61, 128.2, 129.5, 129.7, 133.5, 135.5, 154.0, 156.7, 168. 8. HR ESI-MS: calcd for C$_{38}$H$_{32}$N$_2$O$_6$Na[M + Na]$^+$ 635.2158, found: 635.2152.

Macrocyclic bisamide rac-17

Yield: 7%, mp 124–128 °C. ^{1}H NMR (200 mHz, CDCl$_3$), δ: 1.69 (6H, s), 2.97–3.07 (2H, m), 3.33–3.47 (2H, m), 3.61–3.72 (2H, m), 3.80–3.90 (2H, m), 4.22 (2H, AB/2, $J = 15.8$), 4.37 (2H, AB/2, $J = 15.8$), 5.92–5.98 (2H, bm), 6.49–7.99 (20H, m), ^{13}C NMR (50 MHz, CDCl$_3$): 30.0, 38.2, 41.5, 67.8, 68.8, 114.39, 116.1, 120.9, 124.3, 125.1, 126.5, 126.7, 127.8, 128.2, 129.7, 129.8, 133.7, 144.7, 153.4, 155.1, 168.7. HR ESI-MS: calcd for C$_{43}$H$_{40}$N$_2$O$_6$Na[M + Na]$^+$ 703.2784, found: 703.2811.

ESI-MS measurements

All electrospray ionization mass spectra were recorded on a LCT (TOF) Micromass instrument equipped with an ESI source. Electrospray ionization was achieved by application of a potential of 3.5 kV to a stainless needle. A Harvard apparatus syringe pump system was set at 10.0 mL/min. Nitrogen as a nebulizer gas was delivered to the spectrometer by a nitrogen line.

All solutions were made with methanol of HPLC purity and consisted of either one host and multiple guests or two hosts and one guest. The concentration ratios were either 1:1:1:1:1:1 for the one host–five guests mixture, and the concentration of each component was 1.0×10^{-4} M. The alkali metal guests (Li, Na, K, Rb, and Cs) were added to the solution as their chloride salts.

Solutions were filled up to 1mL and after 30 min a spectrum scanned in the range of 50–1500 Da was recorded. The time of a single scan was 1 s. Average intensities from 30 s acquisition were taken to calculations. Corrections for natural abundance of isotopes were considered. The resulting intensities were multiplied by 1.08 for lithium, 1.0722 for potassium, and by 1.3856 for rubidium. The signal intensities in a modified spectrum were normalized against the strongest signal having 100% intensity.

Results and discussion

The macrocyclization reaction of α,ω-diamines with dimethyl α,ω-dicarboxylates were carried out in dry

Table 1. The isolated and identified products **10**–**12**
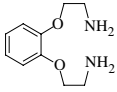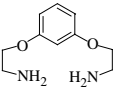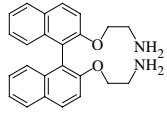
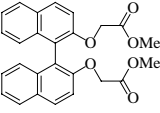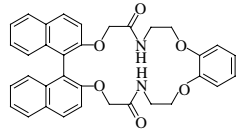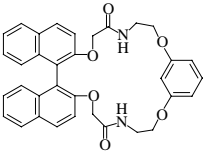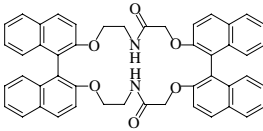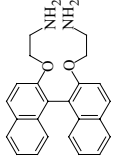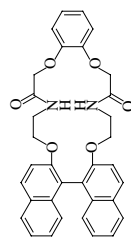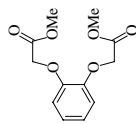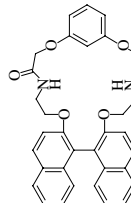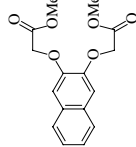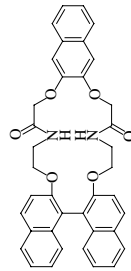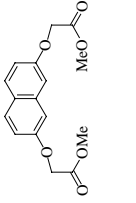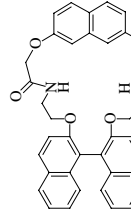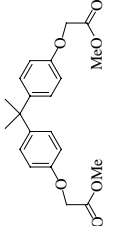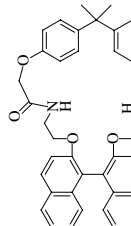| **1**	**2**	**3**
4		
10 64%	**11** 15%	**12** 48%

Table 2. The isolated and identified products **13–17**

methanol in the presence of sodium methoxide (1 equivalent). In the first preparation series, the reactions of dimethyl α,ω-dicarboxylate **4** with three various α,ω-diamines **1**, **2**, **3** were applied. The results of these macrocyclization reactions are listed in Table 1. The macrocyclic bisamides **10** and **12** were obtained in good yields, whereas compound **11** was formed in rather low yield.

In the second synthetic series, reaction of α,ω-diamine **3** with five various dicarboxylates **5–9** was used, and the results are listed in Table 2. Also in these cases, macrocyclic products were obtained in different yields, high for **15**, moderate for **13**, low for **14**, and very low for **16** and **17**.

In turn, we commenced the study on selectivity of the prepared ligands towards the alkali metal cations using ESI-MS technique. The investigations concerned competition of alkali metal cations towards one ligand, and the results are presented in Table 3.

The selectivities of almost all investigated macrocyclic bisamides are poor. However, ligands **12**, **15** and **17** exhibit relatively high selectivity against Cs^+. Compound **10** complexes Li^+ clearly better than remaining cations, except of Cs^+. Similar results were observed for ligand **13**. On the other hand, compounds **14** and **16** form similarly strong complexes with three cations: Li^+, Na^+, K^+ and K^+, Rb^+, Cs^+ respectively.

Table 3. The ESI-MS study of the system comprising one ligand and series of alkali metal cations

Ligand		Distribution of (1:1) complexes with alkali metal cations M^+ [%]				
		Li^+	Na^+	K^+	Rb^+	Cs^+
10	A	**100.0**	64.2	66.4	56.7	85.4
	B	26.8	17.2	17.8	15.2	22.9
11	A	**100.0**	90.7	78.2	60.0	51.8
	B	26.3	23.8	20.5	15.8	13.6
12	A	36.7	30.9	54.9	56.8	**100.0**
	B	13.1	11.1	19.7	20.3	35.8
13	A	**100.0**	61.0	68.5	64.2	94.1
	B	25.8	15.7	17.7	16.6	24.3
14	A	90.9	**100.0**	87.9	65.5	61.0
	B	22.4	24.7	21.7	16.2	15.1
15	A	50.2	42.6	61.4	63.8	**100.0**
	B	15.8	13.4	19.3	20.1	31.4
16	A	52.0	67.5	97.8	97.4	**100.0**
	B	12.5	16.3	23.6	23.5	24.1
17	A	56.1	40.3	49.5	60.1	**100.0**
	B	18.3	13.2	16.2	19.6	32.7

A – *intensities from spectra*, B – *complete percentage*.

Conclusions

Our results indicate the usefulness of the macrocyclization reaction of α,ω-diamines with methyl α,ω-dicarboxylates, carried out in the presence of sodium methoxide, for systems containing various aromatic moieties, including binaphthyl units. We also demonstrated that the ESI-MS technique can be successfully used for preliminary determination of the selectivity of binding of alkali metal cations by the above-mentioned macrocyclic bisamides.

Acknowledgements

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