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Synthesis and Determination of Alkali Metal Binding Selectivities of Chiral Macrocyclic Bisamides Derived from D-Mannitol and L-Threitol

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Abstract

Eight new chiral macrocyclic diamides derived from D-mannitol and L-threitol, possessing C_2 symmetry, are prepared. Their application for alkali metal binding processes is studied using the ESI-MS technique.

Introduction

The increasing interest in the chiral recognition and complexation properties of natural receptors has attracted much attention in the design and synthesis of new chiral macrocyclic polyaza- [1] as well as polyoxacoronands [2]. In the early 1990s, we found that α,ω-diamino aliphatic ethers react under ambient conditions with dimethyl α,ω-dicarboxylates in methanol as a solvent, to afford macrocyclic bisamides [3]. This method was extensively investigated, also using the high-pressure technique [4]. In this study, we report the application of this general approach to the synthesis of eight chiral diazacoronands **3** derived from D-mannitol and L-threitol (Scheme 1). Ligands **3**, differing in size of the macrocyclic gap, were tested as complexing agents to bind alkali metal cations using the electrospray-ionisation mass spectrometry (ESI-MS). These preliminary model studies are important for further chiral recognition investigations using enantiopure ammonium cations.

Experimental

Melting points were taken on a Köfler-type (Boetius) hot-stage apparatus and are not corrected. Optical rotations were measured using a Perkin-Elmer 241 polarimeter equipped with a thermally jacketed 10 cm cell. ^{1}H NMR spectra were recorded with a Varian Gemini 500 (500 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. ^{13}C NMR spectra were also recorded using a Varian Gemini 500 (125 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 a 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. THF and dioxane were freshly distilled from Na/benzophenone under Ar. The high-pressure reactions were conducted under 12 kbar pressure using a custom-made cylinder–piston type apparatus [5]. The elemental analyses (C, H, and N) were performed by the 'in-house' analytical service.

Diamines **1a–d** [6] and diesters **2a** [7] and **2b** [8] were synthesised according to the literature procedures.

General procedures for the syntheses of macrocycles **3**

Method A (in the presence of MeO^-): Sodium (1 mol equiv.) was added to a cooled (5 °C) solution (0.1 mol/L) of diester in dry methanol. Then an equal volume of a solution (0.1 mol/L) of diamine in dry methanol was added. The mixture was left at room temperature over a period of 5 – 8 days (monitored by TLC). Then the solvent was evaporated and the residue was purified by column chromatography using a gradient of toluene/chloroform, chloroform and chloroform/methanol mixtures as eluent.

Method B (under high pressure): An equimolar solution of the dimethyl α,ω-dicarboxylate (0.5 mmol) and the appropriate α,ω-diamine (0.5 mmol) in methanol (5 mL) was charged into a Teflon ampoule, sealed, placed in a high-pressure vessel filled with ligroin as a transmission medium, and compressed (12 kbar) at room temperature for 48 h. After decompression, the reaction mixture was transferred quantitatively to a round-bottomed flask and the solvent was evaporated.

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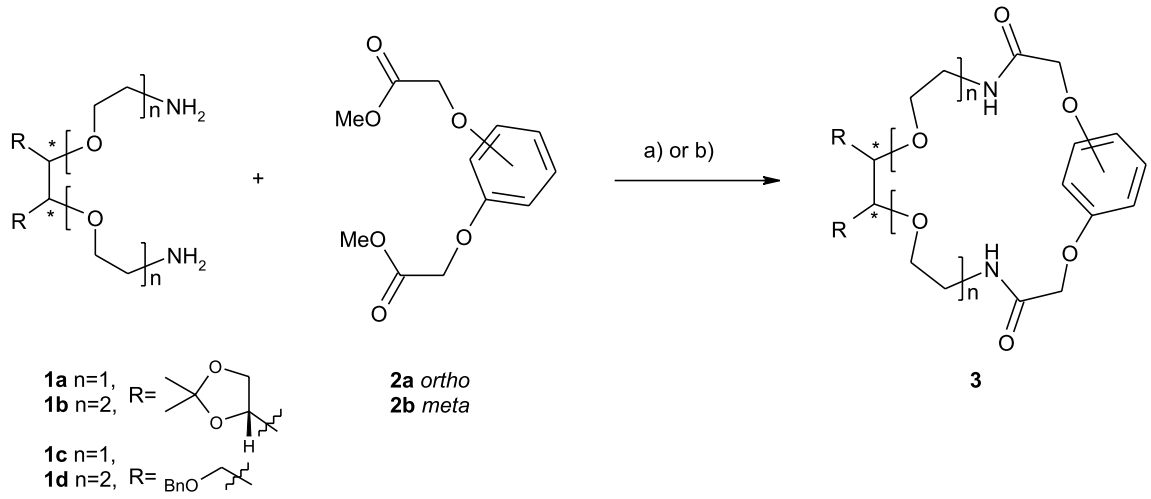

Scheme 1. Conditions of macrocyclisation: (a) MEeOH, MeONa,rt, 5–8 days; (b) MeOH, 12 kbar, rt, 48 h.

The residue was chromatographed on a silica gel column using 0.5–3% mixtures of methanol in chloroform.

*(6R,7R)-6,7-Bis-[(4R)-2,2-dimethyl-1,3-dioxalan-4-yl]-15,16-benzo-5,8,14,17-tetraoxa-2,11-diazaoctadeca-1,12-dione (***3aa***)*
Method A: 5 days, 58%, *method B:* 36%. Colourless glass (foam), mp 49–51 °C. $[\alpha]_D^{24} = +11.3$ (*c* 1.5, $CHCl_3$). ^1H NMR ($CDCl_3$), δ: 7.11 (2H, bt, $J = 5$, —NHCO—), 7.03–6.98 (2H, *AA′BB′/2*), 6.94–9.89 (2H, *AA′BB′/2*), 4.65 (2H, *AB/2*, $J = 15.6$), 4.60 (2H, *AB/2*, $J = 15.6$), 3.97–3.88 (4H, m), 3.82–3.75 (2H, m), 3.72–3.62 (4H, m), 3.62–3.46 (6H, m), 1.36 (6H, s), 1.31 (6H, s). ^{13}C NMR ($CDCl_3$), δ: 167.8, 146.6, 122.4, 112.8, 108.9, 79.3, 74.9, 70.3, 67.7, 67.1, 38.9, 26.7, 25.3. HR ESIMS calcd for $C_{26}H_{39}N_2O_{10}$ $[M+H]^+$ 539.2605. Found: 539.2595.

*(9R,10R)-9,10-Bis-[(4R)-2,2-dimethyl-[1,3]dioxolan-4-yl] -2,8,11,17-tetraoxa-5,14-diaza-bicyclo[16.3.1]docosa-1(21),18(22),19-triene-4,15-dione (***3ab***)*
Method A: 7 days, 54%, *method B:* 29%. Colourless crystals (hexane/acetone), mp 128–130 °C. $[\alpha]_D^{24} = +23.6$ (*c* 2.0, $CHCl_3$). ^1H NMR ($CDCl_3$), δ: 7.26 (1H, t, $J = 8.3$), 6.74 (2H, bt, $J = 6.7$, —NHCO—), 6.60–6.57 (3H, m), 4.60 (2H, *AB/2*, $J = 16.6$), 4.56 (2H, *AB/2*, $J = 16.1$), 3.88–3.83 (2H, m), 3.83–3.79 (2H, m), 3.75–3.71 (2H, m), 3.70–3.61 (4H, m), 3.37–3.50 (2H, m), 3.48 (2H, d, $J = 6.3$), 3.44–3.37 (2H, m), 1.36 (6H, s), 1.31 (6H, s). ^{13}C NMR ($CDCl_3$), δ: 168.5, 158.9, 130.8, 108.7, 107.3, 103.3, 79.9, 75.1, 70.3, 67.5, 66.7, 39.4, 26.6, 25.1. HR ESIMS calcd for $C_{26}H_{39}N_2O_{10}$ $[M+H]^+$ 539.2605. Found: 539.2614. Elemental analysis (%) calcd: C, 58.0, H, 7.1; N, 5.2. Found: C, 58.1; H, 7.1; N, 5.0.

*(9R,10R)-9,10-Bis-[(4R)-2,2-dimethyl-1,3-dioxalan-4-yl]-21,22-benzo-5,8,11,14,20,23-hexaoxa-2,17-diazatetracosa-1,18-dione (***3ba***)*
Method A: 7 days, 42.0%, *method B:* 25.4%. Colourless crystals (foam), mp 104–108 °C. $[\alpha]_D^{21} = +10.6$ (*c* 2.0, $CHCl_3$). ^1H NMR ($CDCl_3$), δ: 7.51 (2H, bs, —NHCO—), 7.02–6.92 (4H, *AB*), 4.61 (2H, *AB/2*, $J = 15.5$), 4.53 (2H, *AB/2*, $J = 15.5$), 4.21 (2H, q, $J = 6.5$), 4.08 (2H, dd, $J = 6$, $J = 8.5$), 3.95 (2H, dd, $J = 6$, $J = 8.5$), 3.82–3.71 (4H, m), 3.62–3.46 (14H, m), 1.37 (6H, s), 1.29 (6H, s). ^{13}C NMR ($CDCl_3$), δ: 168.7, 147.9, 122.9, 115.3, 108.7, 80.3, 75.3, 71.9, 70.4, 69.8, 69.4, 66.6, 39.2, 26.7, 25.3. HR ESIMS calcd for $C_{30}H_{47}O_{12}N_2$ $[M+H]^+$ 627.3129. Found: 627.3114.

*(12R, 13R)-12,13-Bis-[(4R)-2,2-dimethyl-[1,3]dioxalan-4-yl]-2,8,11,14,17,23-hexaoxa-5,20-diazabicyclo[22.3.1]octacosa-1(27),24(28),25-triene-4,21-dione (***3bb***)*
Method A: 8 days, 36%, *method B*: 19%. Colourless glass (foam), mp 48–49 °C. $[\alpha]_D^{24} = +7.4$ (*c* 2.1, $CHCl_3$). ^1H NMR ($CDCl_3$), δ: 7.26 (1H, t, $J = 8.5$), 7.13 (2H, bs, —NHCO—), 6.73 (1H, t, $J = 2.5$), 6.56 (2H, dd, $J = 2.5$, $J = 8.5$), 4.51 (4H, s), 4.21 (2H, q, $J = 6$), 4.11 (2H, dd, $J = 6$, $J = 8$), 4.00 (2H, dd, $J = 6$, $J = 8$), 3.84–3.74 (4H, m), 3.69–3.63 (2H, m), 3.48–3.60 (12H, m), 1.39 (6H, s), 1.31 (6H, s). ^{13}C NMR ($CDCl_3$), δ: 168.0, 158.5, 130.6, 108.5, 106.6, 105.3, 80.6, 76.0, 72.4, 70.8, 69.7, 67.3, 66.3, 38.9, 26.6, 25.3. HR ESI *m/z* calcd for $C_{30}H_{50}N_3O_{12}$ $[M+NH_4]^+$ 644.3394. Found: 644.3324. Elemental analysis (%) calcd: C, 57.5; H, 7.4; N, 4.45. Found: C, 57.3; H, 7.5; N, 4.6.

*(6S,7S)-6,7-Bis(benzyloxymethyl)-15,16-benzo-5,8,14,17-tetraoxa-2,11-diazaoctadeca-1,12-dione (***3ca***)*
Method A: 5 days, 38.5%, *method B*: 32.1%. Yellowish oil. $[\alpha]_D^{24} = +18.4$ (*c* 1.95, $CHCl_3$). ^1H NMR ($CDCl_3$), δ: 7.34-7.23 (10H, m, —Ph), 7.13 (2H, bt, —NHCO—), 6.99–6.95 (2H, *AA′BB′/2*, —Ar), 6.90–6.86 (2H, *AA′BB′/2*, —Ar), 4.55 (4H, s, $J = 3$), 4.44 (2H, *AB/2*, $J = 12$), 4.39 (2H, *AB/2*, $J = 12$), 3.72–3.66 (2H, m), 3.63–3.58 (2H, m), 3.55-3.46 (6H, m), 3.46–3.40 (4H, m). ^{13}C NMR ($CDCl_3$), δ: 167.8, 146.7, 137.7 (—Ph), 128.4 (—Ph), 127.8 (—Ph), 127.7 (—Ph), 122.4, 113.0, 77.6,

73.4, 69.5, 68.7, 67.7, 39.1. HR ESIMS calcd for $C_{32}H_{39}N_2O_8$ $[M + H]^+$ 579.2706. Found: 579.2700.

*(9S,10S)-9,10-Bis(benzyloxymethyl)-2,8,11,17-tetraoxa-5,14-diaza-bicyclo[16.3.1]docosa-1(21),18(22),19-triene-4,15-dione (***3cb***)*

Method A: 6 days, 34%, *method B*: 25%. Yellowish oil or glass. $[\alpha]_D^{20} = +9.0$ (*c* 2.0, $CHCl_3$). ^1H NMR ($CDCl_3$), δ: 7.37–7.26 (10H, m, —Ph), 7.17 (1H, t, $J = 8.3$), 6.91 (2H, bt, $J = \sim 5.1$, —NHCO—), 6.55 (1H, t, $J = 2.4$), 6.51 (2H, dd, $J = 2.4$, $J = 8.3$), 4.48 (5H, s + *AB*/2, H^3), 4.47 (1H, *AB*/2), 4.42 (2H, *AB*/2, $J = 11.7$), 3.65–3.60 (2H, m), 3.52–3.46 (4H, m), 3.44–3.38 (8H, m). ^{13}C NMR ($CDCl_3$), δ: 169.3, 158.8, 137.7 (—Ph), 130.6, 128.5 (—Ph), 127.9 (—Ph), 127.8 (—Ph), 107.1, 103.6, 77.9, 73.5, 69.9, 69.1, 67.4, 39.2. HR ESIMS calcd for $C_{32}H_{38}N_2O_8Na$ $[M + Na]^+$ 601.2526. Found: 601.2511.

*(9S,10S)-9,10-Bis(benzyloxymethyl)-21,22-benzo-5,8,11,14,20,23-hexaoxa-2,17-diazatetracosa-1,18-dione (***3da***)*

Method A: 7 days, 45%, *method B*: 31%. Yellowish oil. $[\alpha]_D^{24} = +14.9$ (*c* 2.1, $CHCl_3$). ^1H NMR ($CDCl_3$), δ: 7.57 (2H, bt, —NHCO—), 7.34–7.25 (10H, m, —Ph), 6.98–6.94 (2H, *AB*/2), 6.92–6.88 (2H, *AB*/2), 4.55 (2H, d *AB*/2, $J = 15$), 4.51 (2H, d *AB*/2, $J = 15$), 4.46 (4H, s), 3.77–3.72 (2H, m), 3.71–3.67 (2H, m), 3.67–3.62 (4H, m), 3.55–3.46 (14H, m). ^{13}C NMR ($CDCl_3$), δ: 168.6, 148.1, 138.1 (—Ph), 128.1 (—Ph), 127.71 (—Ph), 127.69 (—Ph), 123.0, 115.6, 79.0, 73.3, 70.7, 70.5, 69.7, 69.6, 69.5, 39.1. MS (HR ESI) *m*/*z* calcd for $C_{36}H_{47}N_2O_{10}$ $[M + H]^+$ 667.3231. Found: 667.3213.

*(12S, 13S)-12,13-Bis-benzyloxymethyl-2,8,11,14,17,23-hexaoxa-5,20-diaza-bicyclo[22.3.1]octacosa-1(27),24(28),25-triene-4,21-dione (***3db***)*

Method A: 7 days, 37%, *method B:* 23%. Thick colourless oil. $[\alpha]_D^{21} = +1.0$ (*c* 2.0, $CHCl_3$). ^1H NMR ($CDCl_3$), δ: 7.32–7.25 (10H, m, —Ph), 7.22 (1H, t, $J = 8.5$), 7.11 (2H, bt, —NHCO—), 6.65 (1H, t, $J = 2$), 6.52 (2H, dd, $J = 2.5$, $J = 8.5$), 4.48 (4H, s), 4.43 (4H, s), 3.77–3.66 (8H, m), 3.60–3.46 (14H, m). ^{13}C NMR ($CDCl_3$), δ: 67.8, 158.4, 138.6, 130.6, 128.4 (—Ph), 127.7 (—Ph), 106.5, 105.1, 79.1, 73.3, 70.8, 70.7, 69.7, 69.5, 67.2, 38.7. HR ESIMS calcd for $C_{36}H_{50}N_3O_{10}$ $[M + NH_4]^+$ 684.3496. Found: 684.3492.

Results and discussion

The macrocyclisation reactions were carried out in methanol at room temperature in two ways: (a) at atmospheric pressure in the presence of 1 mol equiv. of MeONa, and (b) under a pressure of 12 kbar without any additives. In the first method, the reaction time was variable, based on the reaction monitoring by TLC. In the latter method, the reaction time was always 48 h. In all cases, diamides were the almost exclusive products; the traces of higher macrocyclic oligomers were observed only using the spectrometric techniques and were not isolated.

The results of macrocyclisation reactions, comprising the yields of both methods, are listed in Table 1. In all cases, the method using MeONa gave higher yields. The particularly high differences in yields are observed for

Table 1. Results of macrocyclisation reaction of **1** and **2**. (a) MeOH, NaOMe, rt; (b) MeOH, rt, 12 kbar, 48 h

	1a	**1b**	**1c**	**1d**
2a	**3aa** 57.9%[a] 36.0%[b]	**3ba** 42.0%[a] 25.4%[b]	**3ca** 38.5%[a] 32.1%[b]	**3da** 44.5%[b] 31.1%[b]
2b	**3ab** 53.8%[a] 28.5%[b]	**3bb** 36.0%[a] 19.3%[b]	**3cb** 33.5%[a] 25.2%[b]	**3db** 36.7%[a] 22.6%[b]

Table 2. The ESI-MS study of the system comprising one ligand and a series of alkali metal cations

Ligand	Type of the complex	Signal intensities of the complexes with alkali metal cations M^+ (%)				
		Li^+	Na^+	K^+	Rb^+	Cs^+
3aa	$[L+M]^+$	69.7	100.0	97.7	94.8	41.9
	$[2L+M]^+$	0.9	0.8	0.9	1.1	0.4
	Complete percentage	17.3	24.7	24.1	23.5	10.4
3ba	$[L+M]^+$	67.5	100.0	79.5	45.5	25.7
	$[2L+M]^+$	0.7	0.7	0.7	0.7	0.6
	Complete percentage	21.2	31.3	25.0	14.4	8.2
3ab	$[L+M]^+$	73.7	90.8	100.0	88.6	59.5
	$[2L+M]^+$	1.5	1.3	1.2	1.2	0.7
	Complete percentage	18.0	22.0	24.2	21.5	14.4
3bb	$[L+M]^+$	100.0	98.0	91.8	58.3	37.5
	$[2L+M]^+$	0.6	0.4	0.4	0.6	0.5
	Complete percentage	25.9	25.3	23.8	15.2	9.8
3ca	$[L+M]^+$	59.0	78.1	100.0	80.8	38.0
	$[2L+M]^+$	0.6	0.5	0.5	0.5	0.3
	Complete percentage	16.6	21.9	28.0	22.7	10.7
3da	$[L+M]^+$	52.0	100.0	98.5	61.2	37.5
	$[2L+M]^+$	0.9	0.8	0.8	1.0	0.7
	Complete percentage	15.0	28.5	28.1	17.6	10.8
3cb	$[L+M]^+$	56.2	92.9	100.0	85.2	42.3
	$[2L+M]^+$	0.6	0.5	0.4	0.5	0.3
	Complete percentage	15.0	24.6	26.5	22.6	11.2
3db	$[L+M]^+$	88.3	92.6	100.0	77.7	58.4
	$[2L+M]^+$	1.1	0.9	0.9	1.2	0.9
	Complete percentage	21.2	22.2	23.9	18.7	14.0

Table 3. The ESI-MS study of the system comprising two ligands and one alkali metal cation

Ligands		Ratios of signal intensities in the ESI-MS spectra ($[L1+M]^+/[L2+M]^+$)				
L1	L2	Li^+	Na^+	K^+	Rb^+	Cs^+
3ba	**3aa**	3.4	3.3	2.3	1.8	2.0
3da	**3ca**	3.6	5.4	2.0	2.8	2.7
3bb	**3ab**	3.1	3.1	2.2	1.5	2.2
3db	**3cb**	2.8	1.6	1.6	1.9	2.6
3ca	**3aa**	2.4	2.6	2.6	1.9	1.6
3db	**3ba**	0.5 (2.1)[a]	0.9 (1.1)[a]	1.2	1.6	1.4
3cb	**3ab**	1.6	2.3	2.4	1.2	1.5
3db	**3bb**	0.9 (1.1)[a]	1.2	1.2	1.6	2.0
3bb	**3aa**	3.8	4.4	2.9	3.3	3.6
3ba	**3ab**	4.2	5.0	3.4	4.0	3.6
3db	**3ca**	4.3	3.5	2.4	3.4	4.1
3da	**3cb**	5.0	10.5	4.4	5.5	4.6

[a]The values in brackets are the reciprocal values for the cases when the calculated ratio is less than 1.

the D-mannitol derivatives. This phenomenon is related probably to the lower number of degrees of freedom for the D-mannitol derivatives, what makes it difficult to adopt the procyclic transition state under high-pressure conditions. The effect of high pressure is more advantageous in the case of macrocyclisation of the more labile L-threitol derivatives.

In turn, we commenced the studies 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,
- competition of two ligands towards one cation.

The results obtained for competition of alkali metal cations towards one ligand are presented in Table 2.

The selectivities of almost all investigated macrocycles were poor. Most of these ligands exhibit similar complexation (differences up to 10% of the signal intensity in the mass spectrum) for two or even three cations. The L-threitol derivatives form the most

stable complexes with Na^+ and K^+ cations, the complexation by macrocycles **3da**, **3cb**, **3db** being similar. Compound **3ca** complexes K^+ cation clearly better than Na^+ cation. The D-mannitol derivatives exhibit lower selectivities and bind similarly more cations. Out of this group, only one ligand, **3ba**, binds selectively Na^+ cation, the remaining ligands form similarly strong complexes with three cations, i.e., **3aa** and **3ab** bind Na^+, K^+, and Rb^+, whereas **3bb** binds Li^+, Na^+, and K^+, respectively.

The results obtained for competition of two ligands towards one cation are presented in Table 3.

Based on the presented evidence, one can conclude that all the investigated cations, irrespective of size of the macrocyclic gap, are better complexed by the ligands having the larger gap. By comparing results for ligands differing in the substituents at the stereogenic centres, one can see that, in general, the L-threitol derivatives have slightly better affinity to alkali metal cations than the D-mannitol derivatives. Only three cases depart from this trend.

The ESI-MS technique does not allow direct comparison of properties of isomeric compounds. Therefore, such an information was obtained indirectly, by comparison with the reference ligand. Based on feasible measurements for two groups of compounds (the D-mannitol derivatives: **3aa**, **3ab**, **3ba**, **3bb**, and the L-threitol derivatives: **3ca**, **3da**, **3cb**, **3db**, respectively) it was possible to determine which of the isomeric macrocycle forms, *ortho* or *meta*, exhibits the better complexation properties. In all cases but one, the *ortho* and *meta* isomers bind alkali metal cations similarly strong. Only compound **3da** binds the Li^+, Na^+, K^+, Rb^+ cations (especially Na^+ cation) clearly stronger than the corresponding compound **3db**.

Conclusions

Our results of the synthesis of macrocyclic diamides indicate the usefulness of the macrocyclisation using sodium methoxide as an accelerator of the reaction. Besides, we demonstrated that the ESI-MS technique can be successfully used for preliminary determination of the selectivity of binding of the alkali metal cations by the prepared macrocyclic compounds – this is useful for planning of the more precise, and therefore more expensive measurements of chiral recognition.

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