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Studies on the Synthesis of bis(Benzo diaza 23-crown-7) and its Complexes with K^+, Mg^{2+}, Ca^{2+} and Ba^{2+} Perchlorates

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Abstract. A novel (E, E)-dioxime (**H_2L**) containing a 23-membered macrocyclic ionophore was synthesized from the reaction of 2,3-(4′-aminobenzo)-1,4,11,14,17-pentaoxa-6,22-dioxo-7,21-diaza-cyclotricosane-2-ene (**5**) prepared from 2,3-(4′-nitrobenzo)-1,4,11,14,17-pentaoxa-6,22-dioxo-7,21-diazacyclotricosane-2-ene (**4**) and cyanogen di-*N*-oxide (**6**). **H_2L** encapsulates and coordinates to alkaline earth metal cations via the oxygen atom to form complexes, **H_2L·2MX** (**M** = K^+, Mg^{2+}, Ca^{2+} and Ba^{2+}; **X** = ClO_4^-). After the complexation with alkaline earth metal cations, ^{1}H-NMR, ^{13}C-NMR and IR data were obtained and a comparison of these spectral data is presented.

Key words: Synthetic macrocyclic ionophores, *vic*-dioxime, alkali and earth alkaline metal complexes, NMR and IR shifts.

1. Introduction

Naturally occuring ionophores selectively transport alkali metal and alkaline earth metal cations across natural and artificial membranes. Although the antibiotics nigerisin and lasalocid, as first representatives of the naturally ionophores, were isolated as early as 1951 from *Streptomyces* cultures, it was only in the late sixties that the function of these membrane affecting compounds as complexing and transporting agents for some metal cations was established [1]. Ionophores can be characterized as receptors which form stable, lipophilic complexes with charged hydrophilic species for alkali or alkaline earth metal cations and, thus, are able to transport them into lipophilic phases, for instance across natural or artificial membranes. Generally, the complexation and transportation processes are highly specific; for instance, the antibiotic valinomycin has a 10^4 times greater affinity to potassium than to sodium.

vic-Dioximes have received considerable attention as model compounds to mimic biofunctions such as the reduction of vitamin B_{12} [2]. Because of the high stability of the complexes vicinal dioximes have been extensively used for various

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purposes, including trace metal analysis [3]. They have also been examined as compounds with columnar stacking, which is thought to be the reason for their semiconducting properties [4]. The presence of mildly acidic hydroxy groups and slightly basic nitrogen atoms makes *vic*-dioximes amphoteric compounds which form corrin-type square-planar, square-pyramidal or octahedral complexes with transition metal complexes [5].

In the present study, our goal has been to undertake the synthesis and characterization of an (E, E)-dioxime carrying a 23-membered N_2O_5 macrocyclic ionophore and precursor compounds. On the other hand, the interest in this system is aroused by the host peculiarities manifested in the macrocyclic ionophore cavity with alkali and alkaline earth metal cations which cause significant shifts in NMR and IR spectral data of vicinal dioxime ionophores.

2. Experimental

^{1}H- and ^{13}C-NMR spectra were obtained on a Varian XL-300 and Varian 200 FT spectrometer using $CDCl_3$ or DMSO-d_6 as solvents with TMS as the internal standard. IR spectra were recorded on a Perkin–Elmer 1600 FT-IR and ATIunicam Mattson 1000 FTIR spectrometers with the samples in compressed KBr discs. Electron impact (EI) and fast atom bombardment mass spectra were obtained on a VG AutoSpec from VG Analytical Instruments and a Concept H Series mass spectrometer. Elemental analyses were determined with a Hewlett-Packard 185 CHN analyzer. 1,2-Bis(ethoxycarbonylmethoxy)-benzene [6], (E, E)-dichloroglyoxime [7] and cyanogen di-N-oxide [8] were prepared according to the reported procedures. Commercially available pure grade solvents, dried and purified by conventional procedures [9], were used.

2.1. Preparation of 1,2-bis(ethoxycarbonylmethoxy)-4-nitrobenzene

Nitric acid (70%, 50 mL) was added dropwise over a 1 h period to 14.1 g (50 mmol) of 1,2-bis(ethoxycarbonylmethoxy)benzene (**1**) dissolved in a mixture of 312 mL of chloroform and 250 mL of acetic acid. The mixture was stirred for 24 h at room temperature, then neutralized with a saturated aqueous solution of $NaHCO_3$, and the chloroform layer was separated. The aqueous layer was extracted with chloroform, and the combined chloroform extracts were dried over anhydrous $MgSO_4$. After evaporation of chloroform, a pale yellow solid was obtained and dried *in vacuo*. Recrystallization of the pale yellow solid from ethanol gave 7.9 g (48%) white crystals, m.p. 82–83 °C (lit. [14] m.p. 74–76 °C); ^{1}H-NMR ($CDCl_3$): (δ) 7.82 (d, 1H, Ar—H), 7.66 (s, 1H, Ar—H), 6.83 (d, 1H, Ar—H), 4.72 (s, 4H, Ar—OCH_2), 4.19 (q, 4H, CH_2), 1.22 (t, 6H, CH_3);; ^{13}C-NMR ($CDCl_3$): (δ) 168.11, 153.29, 147.85, 142.35, 118.07, 113.40, 110.01, 66.25, 61.89, 14.15; IR (KBr pellets, cm^{-1}): 3095 (Ar—H), 2978 (C—H), 1742 (C=O), 1519 (Ar—$NO_2)_{asym}$, 1343 (Ar—$NO_2)_{sym}$, 1290 (Ar—OCH_2); MS (EI) *m/z* 327 $[M]^+$.

Anal. Calcd. for $C_{14}H_{17}NO_8$: C, 51.37; H, 5.19; N, 4.28; mol. wt. 327.3. *Found*: C, 51.35; H, 5.11; N, 4.08.

2.2. PREPARATION OF 2,3-(4′-NITROBENZO)-1, 4, 11, 14, 17-PENTAOXA-6, 22-DIOXO-7, 21-DIAZACYCLOTRICOSANE-2-ENE (**4**) AND 2, 3, 25, 26-BIS(4′-NITROBENZO)-1, 4, 11, 14, 24, 27, 34, 37, 40-OCTAOXA-6, 22, 29, 45-TETRAOXO-7, 21, 30, 44-TETRAAZACYCLOHEXATETRACONTANE-2, 25-ENE (**5**)

A solution of 4,7,10-trioxa-1,13-tridecanediamine (4.40 g 20 mmol) was added to a solution of 1,2-bis(etoxycarbonylmethoxy)-4-nitrobenzene (**2**) (6.54 g, 20 mmol) in absolute ethanol (550 mL) under an oxygen-free nitrogen atmosphere at room temperature. The reaction mixture was refluxed and stirred for 50 h and the reaction was monitored by TLC [R_f = 0.83, petroleum ether : ethanol]. The mixture was cooled and the solvent was removed *in vacuo*. After evaporation of the solvent, an oily product was obtained. The residue was passed through a silica gel column to remove polymeric product using dichloromethane as an eluent. A further purification was performed by chromatography on silica gel (70–230) using ethanol as the eluent to give 3.85 g (42%) of **4** as pale yellow needles, m.p. 165 °C; ^{1}H-NMR (DMSO-d_6): (δ) 8.10 (s, 2H, NH), 7.92 (d, 1H, Ar—H), 7.85 (s, 1H, Ar—H), 7.22 (d, 1H, Ar—H), 4.68 (s, 4H, Ar—OCH_2), 3.45–3.35 (m, 12H, CH_2O), 3.20 (m, 4H, $HNCH_2$), 1.67 (m, 4H, CH_2); ^{13}C-NMR (DMSO-d_6): (δ) 167.66, 153.36, 147.30, 141.30, 118.64, 113.44, 109.90, 69.85–68.58, 68.03, 36.37, 29.44; IR (KBr pellets, cm^{-1}): 3363 (N—H), 3076 (Ar—H), 2923–2853 (C—H), 1676 (HNC=O), 1518 (Ar—NO_2)$_{asym}$, 1337 (Ar—NO_2)$_{sym}$, 1268 (Ar—OCH_2), 1121 (CH_2OCH_2); MS (FAB positive) *m/z* 456 $[M + 1]^+$.

Anal. Calcd. for $C_{20}H_{29}N_3O_9$: C, 52.74; H, 6.37; N, 9.23; mol. wt. 455.5. *Found*: C, 52.58; H, 6.33; N, 9.18.

2,3,25,26 - Bis(4′ - nitrobenzo) - 1,4,11,14,24,27,34,37,40 - octaoxa - 6,22,29,45-tetraoxo-7,21,30,44-tetraazacyclohexatetracontane-2,25-ene (**5**) was eluted second by using ethanol and isolated as a white solid to give 0.65 g (12%), m.p. 277 °C; ^{1}H-NMR (DMSO-d_6): (δ) 8.03 (s, 4H, NH), 7.81–7.73 (m, 4H, Ar—H), 7.16 (d, 2H, Ar—H), 4.53 (m, 8H, Ar—CH_2), 3.55–3.24 (m, 24H, CH_2O), 3.11 (m, 8H, $NHCH_2$), 1.55 (m, 8H, CH_2); ^{13}C-NMR (DMSO-d_6): (δ) 167.43, 153.54, 147.38, 141.19, 119.01, 113.61, 110.08, 71.28–69.24, 68.27–67.51, 36.46, 29.63; IR (KBr pellets, cm^{-1}): 3397 (N—H), 3084 (Ar—H), 2969–2878 (C—H), 1684 (HNC=O), 1524 (Ar—NO_2)$_{asym}$, 1340 (Ar—NO_2)$_{sym}$, 1303 (Ar—OCH_2), 1148–1114 (CH_2OCH_2); MS (FAB positive) *m/z* 911 $[M + 1]^+$.

Anal. Calcd. for $C_{40}H_{58}N_6O_{18}$: C, 52.74; H, 6.37; N, 9.23; mol. wt.: 910.1. *Found*: C, 52.61; H, 6.29; N, 9.14.

2.3. PREPARATION OF 2, 3-(4′-AMINOBENZO)-1, 4, 11, 14, 17-PENTAOXA-6, 22-DIOXO-7, 21-DIAZACYCLOTRICOSANE-2-ENE (**6**)

A procedure reported for the synthesis of 4,5-diaminobenzo(15-crown-5) [10] was modified. A solution of 3.64 g (8 mmol) of precursor nitro compound (**4**) dissolved in n-butanol (300 mL) was heated to 100 °C. Palladium/activated carbon (10%) (0.70 g) was added to this solution at the same temperature and the reaction mixture was heated to 120 °C. 5.5 mL of hydrazine hydrate (98%) was added dropwise to this mixture and refluxed for 2 h. After having been cooled to room temperature, the mixture was filtered and concentrated to 25 mL *in vacuo*. The pale yellow solution was cooled in a refrigerator at −18 °C overnight, whereupon the product crystallized from the solution. Recrystallization of the white solid from a mixture of ethanol/diethyl ether gave 2.75 g (81%) of **5** as colourless needles, m.p. 161 °C; ^{1}H-NMR (DMSO-d_6): (δ) 8.03 (s, 2H, NH), 6.72 (d, IH, Ar—H), 6.22 (s, 1H, Ar—H), 6.09 (d, 1H, Ar—H), 4.78 (s, 2H, NH_2), 4.28 (s, 4H, Ar—OCH_2), 3.55–3.45 (m, 12H, CH_2O), 3.17 (m, 4H, $HNCH_2$), 1.65 (m, 4H, CH_2); ^{13}C-NMR (DMSO-d_6): (δ) 168.43, 149.55, 145.66, 139.22, 119.08, 107.44, 102.09, 71.30–69.08, 68.46, 37.24, 30.14; IR (KBr pellets, cm^{-1}): 3389 (N—H)$_{asym}$, 3295 (N—H)$_{sym}$, 3072 (Ar—H), 2931–2872 (C—H), 1654 (HOC=N), 1609 (N–H), 1290 (Ar—OCH_2), 1131 (CH_2OCH_2); MS (FAB positive) *m/z* 426 [M + 1]$^+$.

Anal. Calcd. for $C_{20}H_{31}N_3O_7$: C, 52.06; H, 7.59; N, 9.11; mol. wt. 425.5. *Found*: C, 51.92; H, 7.48; N, 8.99.

2.4. PREPARATION OF N,N'-BIS[2, 3-(4′-AMINOBENZO)-1,4, 11,14, 17-PENTAOXA-6, 22-DIOXO-7, 21-DIAZACYCLOTRICOSANE-2-ENE]DIAMINOGLYOXIME (**H_2L**)

A solution of cyanogen di-N-oxide which was prepared by treating a suspension of (E, E)-dichloroglyoxime (**7**) (0.785 g, 5 mmol) in dichloromethane (25 mL) with 25 mL of 0.5 M Na_2CO_3 at −10 °C was added to a solution of **5** (4.25 g, 10 mmol) in dichloromethane at the same temperature. The solution was stirred at −10 ° C for 10 h, then allowed to warm up to room temperature, dried over anhydrous $MgSO_4$ and evaporated. The oily residue was passed through neutral alumina by using chloroform as eluent and concentrated to dryness. The pale yellow solid product was recrystallized from ethanol to give 2.85 g (63%) of **H_2L** as pale yellow needles, m.p. 174 °C (dec.); ^{1}H-NMR (DMSO-d_6): (δ)11.07 (s, 2H, OH), 8.88 (s, 2H, NH), 8.12 (s, 4H, NH), 6.81 (d, 2H, Ar—H), 6.51 (s, 2H, Ar—H), 6.35 (d, 2H, Ar—H), 4.39 (s, 8H, Ar—OCH_2), 3.48–3.37 (m, 24H, CH_2O), 3.23 (m, 8H, $HNCH_2$), 1.67 (m, 8H, CH_2); ^{13}C-NMR (DMSO-d_6): (δ) 168.78, 147.11, 145.84, 143.67, 140.17, 120.11, 107.95, 102.87, 71.59–69.23, 68.54, 37.68, 30.71; IR (KBr pellets, cm^{-1}): 3361 (N—H), 3234 (O—H), 3080 (Ar—H), 2927–2851 (C—H), 1675 (HNC=O), 1625 (C=N), 1605 (N—H), 1265 (Ar—OCH_2), 1140 (CH_2OCH_2), 961 (N—O); MS (FAB positive): *m/z* = 935 [M + 1]$^+$.

Anal. Calcd. for $C_{42}H_{62}N_8O_{16}$: C, 53.96; H, 6.63; N, 11.99; mol. wt. 935.0. *Found*: C, 53.85; H, 6.48; N, 11.87.

2.5. PREPARATION OF HOST-GUEST COMPLEXES WITH ALKALI OR ALKALINE EARTH METALS (**8–11**)

A solution of the free ligand (**H_2L**) (0.467 g, 0.5 mmol) in ethanol (25 mL) was added to a refluxing solution of 1 mmol of alkali or alkaline earth metal perchlorates [$KClO_4$ (1.38 g), $Mg(ClO_4)_2$ (2.23 g), $Ca(ClO_4)_2$ (3.11 g), or $Ba(ClO_4)_2$ (3.36 g)] in ethanol (35 mL) over a period of 1 h. After the addition was complete, the mixture was refluxed for 30 min. The solution was concentrated to 15 mL, and after addition of 5 mL of petroleum ether (40–60) it was allowed to cool at -18 °C in a refrigerator overnight. The products were filtered off; washed with cold chloroform and diethyl ether then dried *in vacuo* over P_4O_{10}.

2.5.1. **H_2L**·*2KClO$_4$* (**8**)

Yield: 0.578 g (51%), m.p. 205 °C (dec.); ^{1}H-NMR (DMSO-d_6): (δ) 11.11 (s, 2H, OH), 8.93 (s, 2H, NH), 8.54 (s, 4H, NH), 6.79 (d, 2H, Ar—H), 6.54 (s, 2H, Ar—H), 6.33 (d, 2H, Ar—H), 4.57 (s, 8H, Ar—OCH_2), 3.62–3.46 (m, 24H, CH_2O), 3.34 (m, 8H, $HNCH_2$),1.46 (m, 8H, CH_2); ^{13}C-NMR (DMSO-d_6): (δ) 169.96, 147.22, 145.80, 143.81, 140.24, 120.28, 108.04, 102.94, 72.77–70.87, 68.71, 37.91, 30.43; IR (KBr pellets, cm^{-1}): 3342 (N—H), 3218 (O—H), 3080 (Ar—H), 2922–2855 (C—H), 1657 (HNC=O), 1623 (C=N), 1595 (N—H), 1237 (Ar—OCH_2), 1159–1093 $(ClO_4)^-$, 961 (N—O), 629 $(ClO_4)^-$; MS (FAB positive): *m/z* = 1211 $[M + 1]^+$, 1112 $[M - ClO_4 + 1]^+$, 1014 $[M - 2(ClO_4) + 2]^+$.

Anal. Calcd. for $C_{42}H_{62}N_8O_{24}Cl_2K_2$: C, 41.61; H, 5.11; N, 9.24; mol. wt. 1212.1. *Found*: C, 41.48; H, 4.97; N, 9.15.

2.5.2. **H_2L**·*2Mg(ClO$_4$)$_2$* (**9**)

Yield: 0.645 g (47%), m.p. 218 °C (dec.); ^{1}H-NMR (DMSO-d_6): (δ) 11.15 (s, 2H, OH), 8.90 (s, 2H, NH), 8.45 (s, 4H, NH), 6.79 (d, 2H, Ar—H), 6.54 (s, 2H, Ar—H), 6.33 (d, 2H, Ar—H), 4.65 (s, 8H, Ar—OCH_2), 3.59–3.45 (m, 24H, CH_2O), 3.39 (m, 8H, $HNCH_2$), 1.54 (m, 8H, CH_2); ^{13}C-NMR (DMSO-d_6): (δ) 170.18, 147.19, 145.89, 143.75, 140.27, 122.23, 108.10, 102.99, 72.87–70.48, 68.75, 37.93, 30.36; IR (KBr pellets, cm^{-1}): 3345 (N—H), 3231 (O—H), 3090 (Ar—H), 2953–2867 (C—H), 1650 (HNC=O), 1621 (C=N), 1597 (N—H), 1231 (Ar—OCH_2), 1165–1089 (ClO_4), 963 (N—O), 628 (ClO_4); MS (FAB positive): *m/z* = 1379 $[M + 1]^+$.

Anal. Calcd. for $C_{42}H_{62}N_8O_{32}Cl_4Mg_2$: C, 36.50; H, 4.49; N, 8.11; mol. wt. 1381.4. *Found*: C, 36.39; H, 4.35; N, 7.97.

2.5.3. **H_2L**·*2Ca(ClO_4)$_2$* (**10**)

Yield: 0.973 g (69%), m.p. 227 °C (dec.); ^{1}H-NMR (DMSO-d_6): (δ) 11.13 (s, 2H, OH), 8.91 (s, 2H, NH), 8.28 (s, 4H, NH), 6.94 (d, 2H, Ar—H), 6.60 (s, 2H, Ar—H), 6.39 (d, 2H, Ar—H), 4.52 (s, 8H, Ar—OCH_2), 3.61–3.48 (m, 24H, CH_2O), 3.34 (m, 8H, $HNCH_2$), 1.50 (m, 8H, CH_2); ^{13}C-NMR (DMSO-d_6): (δ) 170.51, 147.27, 145.94, 143.94, 143.79, 140.34, 120.19, 107.99, 102.95, 73.31–70.73, 68.82, 38.08, 30.28; IR (KBr pellets, cm^{-1}): 3338 (N—H), 3220 (O—H), 3093 (Ar—H), 2931–2898 (C—H), 1644 (HNC=O), 1620 (C=N), 1599 (N—H), 1217 (Ar—OCH_2), 1161–1092 (ClO_4), 964 (N—O), 627 (ClO_4); MS (FAB positive): *m/z* = 1411 $[M + 1]^+$, 1312 $[M - ClO_4 + 1]^+$.

Anal. Calcd. for $C_{42}H_{62}N_8O_{32}Cl_4Ca_2$: C, 35.69; H, 4.39; N, 7.93; mol. wt. 1412.95. *Found*: C, 35.53; H, 4.27; N, 7.80.

2.5.4. **H_2L**· *Ba(ClO_4)$_2$* (**11**)

Yield: 0.927 g (58%), m.p. 212 °C (dec.); ^{1}H-NMR (DMSO-d_6): 11.19 (s, 2H, OH), 8.82 (s, 2H, NH), 8.31 (s, 4H, NH), 7.01 (d, 2H, Ar—H), 6.62 (s, 2H, Ar—H), 6.42 (d, 2H, Ar—H), 4.77 (s, 8H, Ar—OCH_2), 3.57—3.48 (m, 24H, CH_2O), 3.32 (m, 8H, $HNCH_2$), 1.45 (m, 8H, CH_2). ^{13}C-NMR (DMSO-d_6): (δ) 170.51, 147.35, 146.04, 143.88, 140.41, 120.27, 108.05, 103.03, 73.05–70.42, 68.78, 37.98, 30.34; IR (KBr pellets, cm^{-1}): 3350 (N—H), 3228 (O—H), 3086 (Ar—H), 2927–2902 (C—H), 1648 (HNC=O), 1622 (C=N), 1600 (N—H), 1223 (Ar—OCH_2), 1165–1089 (ClO_4), 967 (N—O), 629 $(ClO_4)^-$; MS (FAB positive): *m/z* = 1605 $[M + 1]^+$, 1209 $[M - 2(ClO_4) + 1]^+$.

Anal. Calcd. for $C_{42}H_{62}N_8Cl_4O_{32}Ba_2$: C, 31.36; H, 3.85; N, 6.97; mol. wt. 1607.5. *Found*: C, 31.22; H, 3.68; N, 6.81.

3. Results and Discussion

2, 3-Bis(ethoxycarbonylmethoxy)-4-nitrobenzene (**2**) was prepared by the nitration of 2,3-bis-(ethoxycarbonylmethoxy)benzene (**1**) with nitric acid in a chloroform/acetic acid medium at room temperature. This method is convenient, simple and economic compared to the reported method [11]. The compound was obtained in the form of white flakes with a m.p. 82–83 °C, while that reported in [11] was in the form of light yellow crystals with a m.p. 74–76 °C. The ^{1}H-NMR spectral data of **2** are in accord with the above mentioned literature. The ^{13}C-NMR spectrum of **2** showed the expected amide carbon absorption at δ = 68.11 ppm and the chemical shifts for Ar—OCH_2, OCH_2— and —CH_3 carbons at δ = 66.25, 61.89 and 14.15 ppm, respectively (Table I). The mass spectrum (EI) of **2**, which showed a molecular ion at *m/z* = 327 $[M]^+$, confirms the proposed compound.

The condensation of **2** with diamine (**3**) gave nitrogen–oxygen mixed donor type macrocyclic ionophores **4** and **5**. The novel 23-membered macrocyclic ionophore (**4**) was obtained in sufficient yield for most practical purposes. However, the results

Table I. IR (ν_{max}/cm^{-1}) host–guest complexation shifts for $\mathbf{H_2L}$ and its complexes.

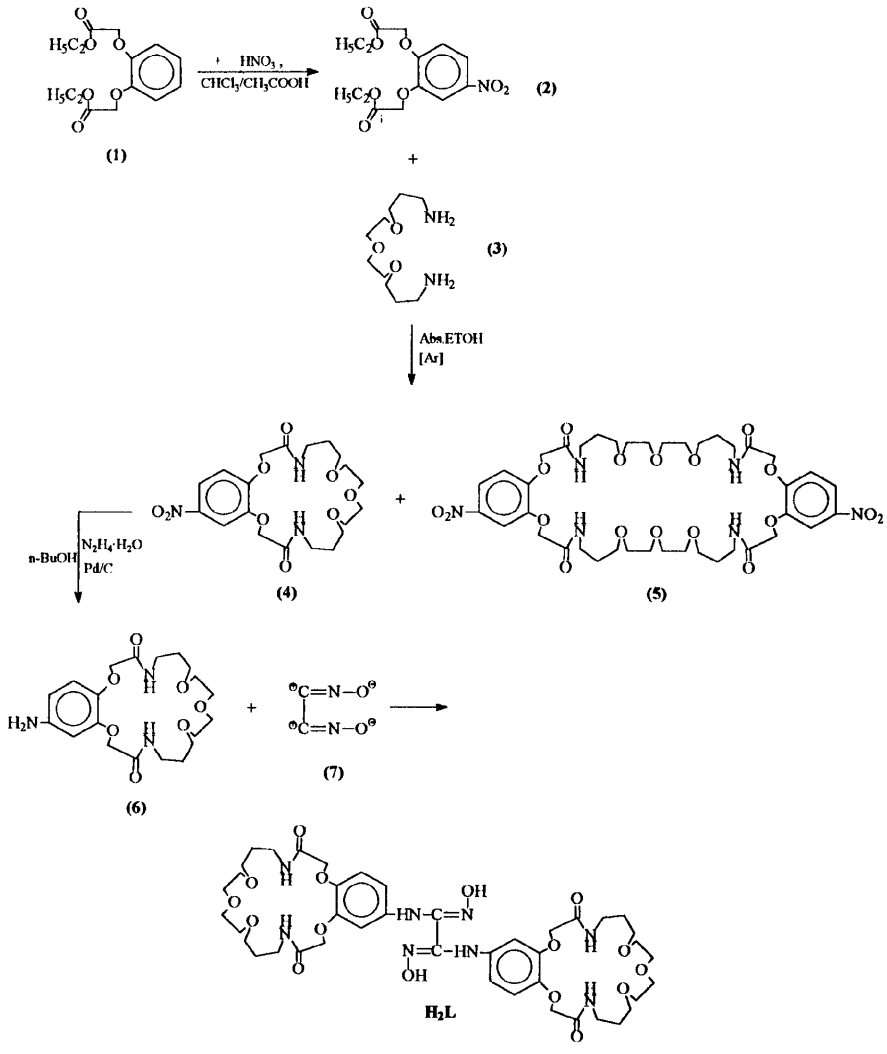
	Ar—OCH_2 (Ligand)	C=O (Ligand)	N—H (Ligand)
K^+	1237 (1265)	1657 (1675)	3342 (3361)
Mg^{2+}	1231 (1265)	1650 (1675)	3345 (3361)
Ca^{2+}	1217 (1265)	1654 (1675)	3338 (3361)
Ba^{2+}	1223 (1265)	1648 (1675)	3350 (3361)

indicate that the yields of the reactions do depend on the ring size of the products; the preference to form 17-membered rings is evidenced by the present and the previous series of reactions [10]. Even though a number of open-chain ionophores with various end groups [1c] and macrocyclic ionophore compounds containing various sizes of macrocyclic cavity have been reported [6, 12], the nitro substituted and fairly large sample was first synthesized in this study.

^{1}H-NMR analysis showed that the major by-product of this reaction consists of one subunit of diester and one subunit of diamine in the form of a 23-membered macrocyclic ionophore. In the reaction between **2** and **3**, giving **4** and **5**, the presence of the contaminating product **5** formed by the reaction of two subunit diesters and two subunit diamines in the form of a 46-membered macrocyclic ionophore (Scheme 1) was confirmed by ^{1}H-NMR, IR and MS data. The ^{1}H-NMR spectrum of a DMSO-d_6 solution of **4** was well resolved and obviously showed that the formation of this macrocycle was accomplished. The deuterium-exchangeable protons of —CONH— groups appear at δ = 8.10 ppm as a singlet. The four methylene protons adjacent to the —HNC=O bridgehead appeared at δ = 3.20 ppm, when protons next to oxygen were found between 3.45–3.35 ppm, in agreement with NMR data reported for this kind of compound [6]. In the ^{13}C-NMR spectrum of this compound, individual signals were observed for the equivalent methylene and amide carbon atoms. The chemical shifts of these carbons ranged from δ = 69.85–68.03 and 167.66 ppm, respectively. It is obvious that the chemical shifts at δ = 36.37 ppm indicate methylene carbons adjacent to the anilide group. The bridgehead carbon resonances between OCNH and ether groups (CH_2O) appear at δ = 29.44 ppm which is in accord with the proposed structure.

The IR spectrum of **4** exhibits sharp absorptions at 3363 and 1676 cm^{-1} indicating the stretching vibrations of N—H and C=O, respectively. The fast atom bombardment mass spectrum of this compound (**4**) showed an expected molecular ion peak at *m/z* = 456 $[M + 1]^+$.

Elemental analysis, ^{1}H- and ^{13}C-NMR, IR and MS spectral data confirmed the structure of the 46-membered macrocyclic ionophore (**5**). Fast atom bombardment mass spectrometry shows the molecular ion peak at *m/z* = 911 $[M + 1]^+$ which corresponds to **5**. The IR spectrum of this compound (**5**) confirms the presence of N—H (ca. 3397 cm^{-1}) and C=O (ca. 1684 cm^{-1}) and the absence of amine



Scheme 1.

functional groups of the starting material. The asym and sym stretching vibrations of Ar—NO_2 are at around 1524 and 1340 cm^{-1}, respectively. In the ^{1}H-NMR spectrum of **5**, the absence of amine functional groups and the presence of NH groups at δ = 8.03 ppm indicate the formation of a condensation reaction. The other chemical shifts belonging to aromatic and aliphatic protons are very similar to those of the 23-membered macrocyclic compound (**4**), as expected. On the other hand, the proton-decoupled ^{13}C- NMR spectrum of **5** is consistent with the proposed formulation. The chemical shifts for OCH_2CH_3 carbon atoms belonging to the starting material are found at δ = 61.94 and 14.43 ppm. The disappearance

of these resonances in the ^{13}C-NMR spectra of **5** can be attributed to the formation of the HNC=O group which indicates the proposed structure.

Several methods can be used for the reduction of nitro derivative **4**. Tin(II) chloride dihydrate in concentrated hydrochloric acid and palladium on charcoal hydrogenation using a Parr instrument were used for the reduction of **4** to amine **6** in low yield. So, this compound was reduced by palladium/activated carbon (10%) with hydrazine hydrate in n-butanol in 81% yield. In the ^{1}H-NMR spectrum of **6**, the chemical shift for the primary aromatic amine protons is observed at δ = 4.78 ppm. A comparison of the ^{1}H- NMR resonances of **4** and 6 resulted in an upfield shift of the aromatic protons from δ = 7.92, 7.85 and 7.22 ppm in **4** to δ = 6.72, 6.22 and 6.09 ppm in **6**. In the IR spectrum of **6**, the stretching and bending vibrations of the aromatic primary amine are observed at 3389ν_{asym}, 3295ν_{sym} and 1609 cm^{-1}, respectively. The disappearance of the (Ar—NO_2)$_{\text{asym}}$ and (Ar—NO_2)$_{\text{sym}}$ stretching vibrations in the IR spectrum of the nitro compound indicate the formation of the amine compound. This macrocycle shows a strong absorption at 1654 cm^{-1}. This is attributed to the strong hydrogen bonding between the amine N—H and C=O oxygen atoms, which forms a seven-membered ring. The other vibrations are very similar to those of **4** and **6**. The fast atom bombardment mass spectrum of this compound showed an expected molecular ion peak at *m/z* = 426 $[M + 1]^+$.

The preparation of the dioxime ligand (**H$_2$L**) has been accomplished as described [13] in 63% yield by the reaction of **6** with cyanogen di-N-oxide (**7**) at -10 °C in dichloromethane. Elemental analysis, NMR, IR and MS spectral data confirmed the **H$_2$L** structure. In the ^{1}H-NMR spectrum of **H$_2$L**, the expected hydroxyimino and NH absorptions appeared at δ = 11.07 and 8.12 ppm., respectively. On the other hand, a singlet which indicates the primary aromatic amine groups disappears and a new resonance at δ = 8.88 ppm, which can be assigned to the NH protons in the neighbourhood of hydroxyimino groups, appears. These singlets disappear on deuterium exchange. A single chemical shift for OH protons indicates that the oxime groups are in the (E, E) form [14] as expected. In the proton-decoupled ^{13}C-NMR spectrum of this compound, the carbon resonance of the hydroxyimino groups is found at δ = 143.67 ppm. This single carbon resonance can be interpreted as the geometrical isomers of the oxime groups in the (E, E) structure [15]. The chemical shifts belonging to the aromatic carbons were observed at δ = 145.84 (C_2), 102.87 (C_3), 147.11 (C_4'), 120.11 (C_5'), 107.95 (C_6'), and 140.17 (C_1') ppm. All the carbon atoms belonging to aliphatic ether groups show absorptions between δ = 71.59–69.23 ppm, as previously reported [16]. In the IR spectrum of **H$_2$L** the stretching vibrations belonging to the amino-substiuted macrocyclic ionophore moiety disappear after the addition reaction and new resonances, which indicate the O—H groups, appear at 3234 cm^{-1} as a broad band. The C=N and N—O stretching vibrations are at 1625 and 961 cm^{-1}, respectively. These values are consistent with the previously reported diaminoglyoxime derivatives [14, 17].

Table II. ^{13}C-NMR host–guest complexation shifts ($\Delta\delta$) for **H_2L** and its complexes.

	Induced chemical shifts[a]				
	C_7	C_8	C_9	C_{10}	C_{11-12}
K^+	+0.17	+1.18	+0.23	−0.28	+1.00–1.14
Mg^{2+}	+0.21	+1.40	+0.25	−0.35	+1.10–1.00
Ca^{2+}	+0.28	+1.73	+0.40	−0.43	+1.27–1.12
Ba^{2+}	+0.24	+1.60	+0.30	−0.37	+1.13–1.05

[a] Positive is downfield shift.

The fast atom bombardment mass spectrum of H_2L shows a molecular ion peak at *m/z* = 935 due to $[M + 1]^+$.

The high stability of the alkali and earth alkaline metal complexes of the macrocyclic ionophore (**H_2L**) has been confirmed during this work, since the alkali or alkaline earth complex did not change during the synthesis and characterization. The crystalline complexes of H_2L were obtained by adding saturated solution of salts [**MX** or **M′X$_2$**; **M** = K^+, **M′** = Mg^{2+}, Ca^{2+} and Ba^{2+}; **X** = ClO_4^-] to an absolute ethanol solution of the equivalent amount of **H_2L**. Elemental analysis and MS spectral data indicate the metal: ligand ratio of 2 : 1. For cations smaller than the internal ionophore cavity, the stoichiometry of complexation is known with certainty. Selective alkali or alkaline earth metal ion binding (or host–guest complexation properties) of ionophores, for example valinomycin, has been studied using many different methods including fluorescent probes [18], electrochemical reduction [19] and spectroscopy [20]. We have determined and investigated the relative alkali or alkaline earth metal cation affinity and the spectroscopic change of the macrocyclic ionophore by IR and NMR spectral techniques. The relative shifts in IR and ^{13}C-NMR spectral data of the compounds were also studied (Tables I, II).

The macrocycle containing a vicinal dioxime unit posesses ether and amide functionalities along with *vic*-dioxime functions in the side-chain. It is not known whether the extraction studies reflect the overall effect of all the functional groups on complexation. The comparison of IR and NMR spectral data of **H_2L** with the respective data of its complexes with metal perchlorates (K^+, Mg^{2+}, Ca^{2+}, and Ba^{2+}) could provide a closer scrutiny of the mode of complexation of this ionophore.

The IR spectra of complexes of **H_2L** (**H_2L·MX** or **H_2L·MX$_2$**) gave identical IR vibrations, except for some additional, low-intensity peaks in the latter due to the free ligand. The metal perchlorate complexes exhibit an amide absorption band (C=O) at 1650 ± 10 cm^{-1}. Therefore, in all metal complexes, the amide C=O stretching vibrations shift to lower frequency, which indicates that the complexation occurs through the C=O oxygen atoms (Table I). This indicates that the metal cations are connected via the amide oxygen atom and that a strong interaction

is present. The N—H stretching frequencies were observed at 3350–3332 cm^{-1} for these complexes, indicating that the N—H bonds are slightly affected by the complex formation. All of the perchlorate salts show a strong band near 1089–1165 cm^{-1} (antisymmeric stretch) and sharp bands at 628–630 cm^{-1} (antisymmetric bend), indicative of uncoordinated perchlorate anions [21].

In the ^{1}H-NMR spectra of the complexes, the influence of complexation in either of the cavities of the macrocycle is rather large. The NH signals adjacent to the C=O groups, which were observed at δ = 8.12 ppm for the free macrocycle $\mathbf{H_2L}$, shifted to slightly lower field, at δ = 8.54–8.31 ppm, upon complexation of metal perchlorate to give **7–10**. This may be due to the electron-withdrawing properties of metal cations [22] coordinated to the amide groups. The complexation of alkali or alkaline earth metal cations had little influence on the aromatic protons or on the protons of the polyether ring. The other chemical shifts belonging to hydroxyimino and oxime adjacent NH protons do not show any differences for the free ligand after complexation (Table II).

Comparison of ^{13}C-NMR spectra of the free ligand with the ^{13}C-NMR spectra of its complexes gives significant information about the complexation character of that macrocycle. The magnitudes of change in the chemical shifts show that these compounds complex with barium perchlorate slightly stronger than the other metal perchlorates where maximum complexation is also observed with the same metal cation. The free ligand shows maximum metal-induced changes in the ^{13}C-NMR chemical shifts of its C=O, OCH_2 and amide $NHCH_2$ resonances with metal perchlorate ($\Delta\delta$ = 0.42–1.73 ppm). However, alkaline earth cations show a greater shift in the C=O and $HNCH_2$ resonances. In the complexes, shifts in the amide NCH_2, Ar—OCH_2, CH_2OCH_2 and C=O resonances are downfield, but the CH_2 signals are shifted upfield. The amine CH_2 absorptions showed only marginal shifts, indicating that this group is not or only very weakly interacting with the guests. However, the maximum shift in the carbonyl resonance is observed in the case of Ba^{2+}. Therefore, the ethereal oxygen participates more effectively in complexation with alkaline earth cations. All these complexes show downfield chemical shifts for the C=O signals (Table II). This result indicates a major role of the amide C=O group in complexation with metal ions. Small changes in the ^{13}C-NMR spectral data are observed on formation of the complexes (**8–11**), indicating a fairly strong complexation of metal cations in the ionophore subunits. Further addition of metal cations do not modify the spectral data, indicating that two cations are complexed within each ionophore unit.

Although the size of the ionophore, as estimated by CPK models, is fairly large for some cations (Mg^{2+}, Ca^{2+}), it is clear that the ionophore ($\mathbf{H_2L}$) posseses no selectivity towards significant cations as evidenced by ^{13}C-NMR and IR spectral data.

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