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Synthesis of New Lariat Cyclicdiamides and Their Metal Complexes

ÜMIT ÇAKIR,* MEHMET KARAKAPLAN, HAMDI TEMEL, HALIL HOŞGÖREN and ÇAKIL ERK**
Department of Chemistry, Faculty of Arts and Sciences, University of Dicle, 21280, Diyarbakir, Turkey

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Abstract. Three new lariat dilactam host molecules were prepared by the reaction of triethyleneglycol dicarboxylic acid dichloride with N,N'-disubstituted-4,7-dioxa-1,10-diazadecane precursors. The amide nitrogen pivot of such compounds are substituted with the benzyl, octyl and dodecyl groups. The complexing ability of these dilactams is displayed with a series of metal complexes of Na^+, K^+, Ca^{2+}, Sr^{2+}, Pb^{2+} and Ag^+ ions. The structures determined are consistent with the data of ^{1}H-NMR, ^{13}C-NMR, IR spectra and elemental analyses.

Key words: Macrocylic diazadioxo ethers, cation complexation.

1. Introduction

There is continuing interest in the preparation of diaza-lactams which have important uses as macrocyclic molecular receptors [1] as well as being valuable intermediates for the synthesis of cryptands [2] and related compounds. Preparative methods have been extensively reviewed [3,4]. Macrocyclic ethers and diaza crown ethers are known to form strong complexes, preferably with alkali and alkaline earth metals. N-pivot lariat cyclicdiamides, however, are not well recognised although macrocycles containing ether-ester groups have been recognized as potential ligands [4–7]. We have previously prepared some polyoxalactam derivatives with N-alkyl chains [8], and now report novel macrocyclic polyether-amides with long chain alkyl moieties since the modified macrocyclic ligands could result in increased binding activity and ion selectivity.

In the present work the starting materials for the preparation of macrocyclic diamides, namely, α,ω-N,N'-disubstituted aliphatic ethers, were synthesised in our laboratory as reported recently [8,9] with N-substituted benzyl, octyl and dodecyl groups expecting to increase their lipophilic characters. Diaza-lactams were prepared by reaction of triethyleneglycol dicarboxylic acid dichloride with the

* *Present address*: Balikesir University, Department of Chemistry, Balikesir, Turkey.
** *Present address*: Technical University of Istanbul, Chemistry Department, Maslak, Istanbul, Turkey.
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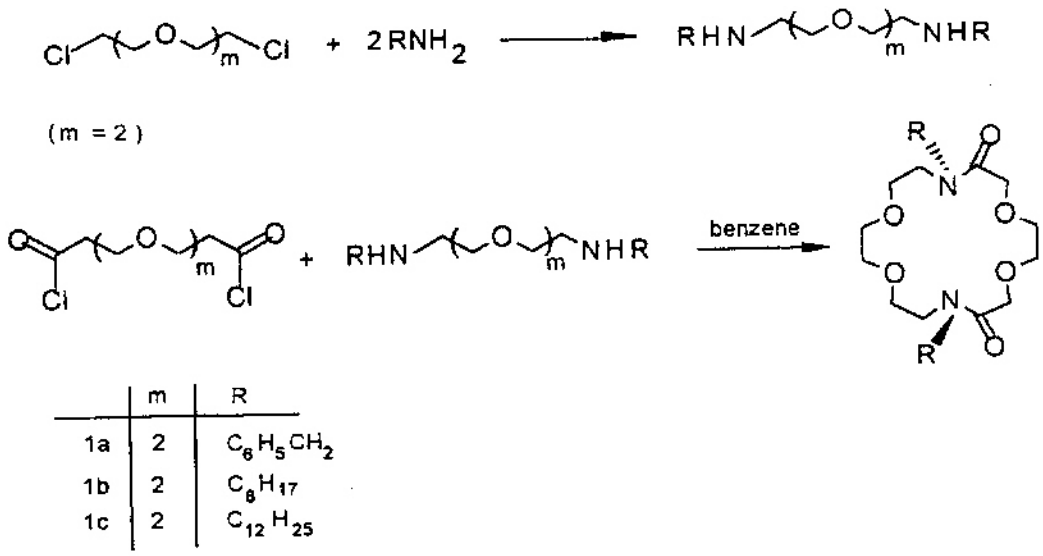
the respective N,N'-disubstituted-4,7-dioxa-1,10-diazadecane derivatives using the high dilution technique (Scheme I).



	m	R
1a	2	$C_6H_5CH_2$
1b	2	C_8H_{17}
1c	2	$C_{12}H_{25}$

Scheme 1.

2. Experimental

Chemicals used were from FLUKA unless otherwise cited and were used without further purification. Benzene was dried over metallic sodium. IR spectra were recorded on a Midac 1700 instrument in KBr pellets. ^{1}H and ^{13}C-NMR spectra at 200 and 50.2 MHz were recorded on a Bruker-AC 200 spectrometer in $CDCl_3$ and reported in ppm (δ) downfield from internal TMS. Elemental analyses were performed with a Carlo-Erba model 1200 instrument. Melting points given are uncorrected.

2.1. The Synthesis of N,N'-Bis-dialkyldiazapolyoxaalkanes

A solution of freshly distilled amine and 1,2-bis(2-chloroethoxy)ethane (Fluka, puriss) (mol ratio 4 : 1) was heated and stirred at 140–160 °C under a dry nitrogen atmosphere for 4 h. The glassy reaction mixture was then dissolved in hot benzene and cooled for some time. The precipitated starting amine salt was filtered off and the filtrate was treated with 10% aqueous sodium hydroxide. The benzene extracts were dried with anhydrous sodium sulfate, filtered and the solvent was removed. Unreacted excess amine was removed in vacuo and the product crystallised as the hydrochloride or picrate derivative, Table I.

Table I. Physical data of *N,N'*-dialkyldiazapolyoxaalkanes.

Compound	B.p., °C/ kPa Yield (%)	M.p[a]., °C (M.w.)	Formula[a]	Calculated/Found %C	%H	%N
1a	216/0.26	195–197[b]	$C_{20}H_{30}N_2O_2Cl_2$ [b]	59.85	7.48	6.98
	38	(391.4)		59.65	7.95	7.16
1b	194–201/0.11	99–103	$C_{34}H_{54}N_8O_{16}$	49.15	6.55	13.49
	46	(830.9)		49.53	6.80	14.02
1c	254–258/0.07	102–104	$C_{47}H_{70}N_8O_{16}$	53.50	7.48	11.88
	46	(943.1)		53.49	7.57	11.5

[a] Dipricate.
[b] Dihydrochloride.

2.2. THE SYNTHESIS OF 7,16-DIALKYL-7,16-DIAZA-1,4,10,13-TETRAOXACYCLOOCTADECANE-8,15-DIONE

Separate solutions of 0.002 mol triethyleneglycol dicarboxylic acid dichloride in benzene (250 mL) and 0.004 mol azadioxaalkane in benzene (250 mL) were added dropwise at the same rate to a rapidly stirred and refluxed benzene solution (1000 mL) during 3 h. The hydrochloride of the excess azadioxaalkane was filtered after cooling and benzene was removed under reduced pressure. Macrocyclic products were separated from open chain by-products by column chromatography on silicagel using benzene–methanol (5 : 1 to 10 : 1) as eluent; their purity was checked by TLC (detection using Dragendorffs reagent). The fractions collected were concentrated *in vacuo*. The residue was recrystallised from diethyl ether-benzene. Structural and spectral data are given below.

2.2.1. *7,16-Dibenzyl-7,16-diaza-1,4,10,13-tetraoxa cyclooctadecane-8,15-dione* (**IIa**) (LB)

Yield 28%, m.p. 93–96 °C; IR (cm^{-1}) 2965, 2938, 2882, 2857 (C—H); 1660, 1643 (CO); 1085, 1026 (C—O—C); ^{1}H-NMR (ppm) δ = 7.35 (s, 10H, Ar), 4.47 (m, 12H, OCH_2CH_2O, OCH_2CH_2N), 4.20 (s, 4H, OCH_2CO), 3.82 (s, 4H, NCH_2Ar), 3.41–3.60 (m, 4H, NCH); ^{13}C-NMR (ppm) δ = 46.23, 48.67 (C-(4), C-(7)), 69.59, 70.35 (C-(2), C-(6)), 70,69, 70.86 (C-(1), C-(5)), 127.27, 127.96, 128.45, 137.39, (C_6H_5), 170.13 (C-(3)), M.W. (468.5).

Anal. for $C_{26}H_{32}O_6N_2$ *calcd.* C%, 66.38; H%, 7.23; N%, 5.95; *found*: C%, 66.45; H%, 7.41; N%, 5.79.

2.2.2. *7,16-Dioctyl-7,16-diaza-1,4,10,13-tetraoxa cyclooctadecane-8,15-dione* (**IIb**) (LO)

Yield 45%, m.p. 63.5–64 °C; IR (cm^{-1}) 2949, 2927, 2857 (C—H), 1674, 1640(CO), 1121, 1133, 1084(C—O—C); ^{1}H-NMR (ppm) δ = 4.4 (s, 4H, —OCH_2CO—), 3.62

Table II. Characteristics of metal perchlorate complexes of diazalactams.

Compound	Formula M.w	M.p., °C Yield	Ratio M : L : H_2O	Calculated/Found %C	%H	%N
$NaClO_4 \cdot LB \cdot H_2O$	$C_{26}H_{34}N_2O_{11}ClNa$	77–79	1 : 1 : 1	51.10	5.89	4.58
	608.9	50		51.25	5.49	4.04
$Ba(ClO_4)_2 \cdot LB \cdot 2H_2O$	$C_{26}H_{36}N_2O_{16}Cl_2Ba$	107–109	1 : 1 : 2	47.56	5.49	4.27
	769.8	33		47.52	5.62	4.23
$NaClO_4 \cdot LO \cdot H_2O$	$C_{28}H_{56}N_2O_{11}ClNa$	78–80	1 : 1 : 1	51.33	8.55	4.27
	655.2	31		52.84	8.67	4.11
$Sr(ClO_4)_2 \cdot LO \cdot 4H_2O$	$C_{28}H_{62}N_2O_{18}Cl_2Sr$	129–131	2 : 1 : 4	51.34	8.56	4.03
	873.3	15		49.86	8.23	4.11
$AgClO_4 \cdot LO$	$C_{28}H_{54}N_2O_{10}ClAg$	18–20	1 : 1 : 0	46.58	7.49	3.88
	721.9	15		51.83	8.17	3.88
$Pb(ClO_4)_2 \cdot LO \cdot 3H_2O$	$C_{28}H_{60}N_2O_{17}Cl_2Pb$	65–67	1 : 1 : 3	34.50	6.16	2.78
	974.8	10		37.98	6.05	2.78
$NaClO_4 \cdot LD \cdot H_2O$	$C_{36}H_{72}N_2O_{11}ClNa$	115–118	1 : 1 : 1	56.36	9.39	3.66
	767.0	50		56.95	9.80	3.75
$Ba(ClO_4)_2 \cdot LD \cdot 3H_2O$	$C_{36}H_{76}N_2O_{17}Cl_2Ba$	29–30	2 : 1 : 3	52.61	8.91	3.41
	1016.7	75		51.37	8.66	3.03
$AgClO_4 \cdot LD$	$C_{36}H_{70}N_2O_{107}ClAg$	27–29	2 : 1 : 0	59.21	9.59	3.84
	833.7	29		59.53	9.78	3.67

(m, 20H, —CH_2N, —CH_2O—), 1.25 (s, 24H, —CH_2—), 0.86 (t, 6H, CH_3); ^{13}C-NMR (ppm) δ = 14.02 (CH_3C-(14)), 22.58, 26.94, 27.48, 29.35, 30.68, 31.74 $(CH_2)_6$(C-(8)···C-(13)), 46.14, 46.90 (C-(4), C-(7)), 69.48, 70.32 (C-(2), C-(6)), 70.25, 70.88 (C-(1), C-(5)), 169.58 (C-(3)); M.W. (514.7).

Anal. for $C_{28}H_{54}O_6N_2$ *calcd.* C%, 65.37; H%, 10.50; N%, 5.44; *found*: C%, 65.30; H%, 10.74; N%, 5.39.

2.2.3. *7.16-Didocdecyl-7,16-diaza-1,4,10,13-tetraoxacyclooctadecane-8,15-dione* (**IIc**) (LD)

Yield 50%, m.p. 70–72 °C, IR (cm^{-1}) 2954, 2914, 2850 (C—H), 1656 (CO), 1133, 1115, 1076 (C—O—C); ^{1}H-NMR (ppm) δ = 4.3 (s, 4H, —OCH_2CO—), 3.58 (m, 2OH, —NCH_2—, —CH_2O—), 0.24 (s, 40H, —CH_2—) 0.87 (t, 6H, —CH_3); ^{13}C-NMR (ppm) δ = 14.63 (CH_3, C-(18)), 23.18, 27.3, 27.5, 29.85, 29.95, 30.05, 30.12, 30.40 $(CH_2)_{10}$, (C-(8)—C-(17)), 46.58, 47.20 (C-(4), C-(7)), 68.26, 69.86 (C-(2), C-(6)), 70.23, 70.35 (C-(1), C-(5)), 172.52 (C-(3)); MW (626.5).

Anal. for $C_{36}H_{70}O_6N_2$ *calc.* C%, 69.00; H%, 11.18; N%, 4.47; *found*: C%, 68.91; H%, 11.30; N%, 4.28.

Table III. The common IR bands of salt complexes (cm^{-1}).

Compound	(R—O—R)	(CO)	(C—H)	(Ar—H)	(H_2O)	ClO_4
LB	1085	1660	2965			
	1026	1643	2938			
			2908			
			2882			
			2857			
$NaClO_4$·LB·H_2O	1093	1647	2918	3061	3528	623
			2877	3030		
LO	1121	1674	2949			
	1133	1640	2927			
	1084		2857			
$NaClO_4$·LO·H_2O	1121	1642	2927		3586	623
			2856			
$Sr(ClO_4)_2$·LO·4H_2O	1108	1636	2951		3420	622
	1084		2933			
			2857			
$AgClO_4$·LO·H_2O	1118	1650	2922		3468	623
	1088		2859			
LD	1133	1656	2954			
	1115		2914			
	1076		2850			
$NaClO_4$·LD·H_2O	1127	1637	2920		3427	622
	1112		2858			
$Ba(ClO_4)_2$·LD·3H_2O	1123	1654	2920		3474	622
	1083		2850			

2.3. The Preparation of Metal Complexes

$M^{n+}(ClO_4)_n$ (0.42 mmol) in CD_3CN (3 mL) was added to diazalactams (0.2 mmol) in CD_3CN (3 mL) and the precipitated solid was filtered after 24 h, washed and crystallised from CD_3CN, see Tables II, and III.

3. Results and Discussion

The synthesis of *N*,*N'*-dialkyl-4,7-dioxa-1,10-diazadecanes derived from 1,8-dichloro-3,6-dioxaoctane is shown in Scheme I. As seen in Table I, the yields are quite satisfactory, ranging from 38% to 46%. The procedure originally developed by Krespan [10] is more straightforward. The methods for the synthesis of dilactams are generally complicated [7,11] since they require a nitrogen protection/deprotection sequence [2–4]. The methods could involve the reaction of primary amines with diglycolicacid dichloride and reduction of bis-amides with

either lithium aluminium hydride ($LiAlH_4$) or diborane-tetrahydrofuran complexes ($BH_3 \cdot THF$).

Furthermore, acylation of the expensive 4,13-diaza-18-crown-6 would be required in order to prepare the lactams of interest to us [1–3]. The new approach of synthesis of diaza lactams and their precursors with high yields was more practical since the sidearms are incorporated prior to cyclization, eliminating the need for a protection scheme in the presence of excess of primary amine. Our expectation is that macrorings with combinations of side arms could give rise to good complexing behaviour and extraction abilities. Such work is in progress.

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