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A BARIUM SELECTIVE MACROCYCLIC TETRALACTAM WITH DIMETHYLENEOXY MOIETIES

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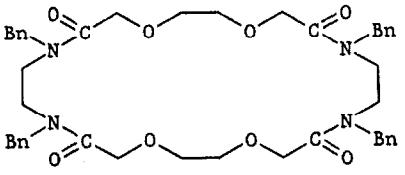
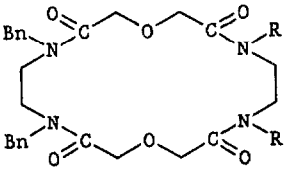
ABSTRACT : *Two new 18-membered tetralactams with two dimethyleneoxy moieties are synthesized by direct macrocyclization or steps reaction. In the latter case symmetrical or unsymmetrical compounds can be obtained. The unsymmetrical tetralactam shows a very high selectivity for barium vs. Na^+ and Zn^{2+} and to a lesser extent vs. K^+, Mg^{2+} and Ca^{2+} in the extraction procedure with picrates. In addition, the stability constants are determined for the two 1:1 tetralactam:Ba^{2+} complexes by UV spectrophotometry in THF solution.*

In a little documented series, the tetralactam 1 with an ethylenedioxy moiety, synthesized by direct macrocyclization, has shown interesting calcium selective complexing properties (1,2). By replacing this moiety by a dimethyleneoxy one, the tetralactams 2 were synthesized either by direct macrocyclization (compound 2a) either by stepwise reactions. In this latter approach, symmetrical (compound 2a) or dissymmetrical (compound 2b) macrocycles can be obtained.

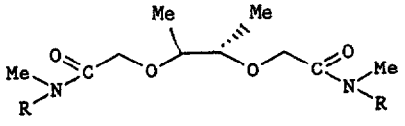
These two types of tetralactams parallel the linear diamides ETH 1001 and ETH 129, calcium selective neutral ionophores (3, 4). The stoichiometry of the complexes of these linear diamides with calcium picrate has been found to be mainly 2:1 in solution (3, 5).



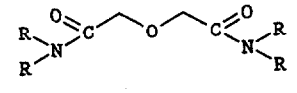
1 (Bn = $-CH_2-C_6H_5$)



2a R = Bn
2b R = H



ETH 1001 R = $(CH_2)_{11}COOEt$



ETH 129 R = cyclohexyl

The macrocyclic effect of compound 1 versus ETH 1001 has been evaluated (1) for the liquid-liquid extraction of metallic picrates. It results, in spite of a lower lipophilicity, in increased extraction and selectivity, particularly for Ca^{2+} versus Mg^{2+}.

When the ethylenedioxy moiety is replaced by a dimethyleneoxy moiety, both ring size (24 → 18-membered cycles) and complexation sites number (8 → 6) are reduced. On the other hand the absence of substituents on two nitrogen atoms in compound 2b weakens the lipophilicity.

In this paper we report the synthesis of the tetralactams 2a and 2b, and the analysis of their complexing properties, measured by the extraction technique, in relation with the macrocyclic effect, the ring size and the lipophilicity.

SYNTHESIS

Tetralactam 2a is synthesized by two methods : direct macrocyclization (scheme 1) or by steps reaction (scheme 2).

Direct macrocyclization is obtained by the reaction of an activated derivative of diglycolic acid with N,N'-dibenzyl ethylenediamine. The activation is achieved through the diacid chloride or the N-acyl thiazolidinethione derivative (6). In both cases the 18-membered tetralactam is prepared in acceptable yields (20-25%) beside 20% of the corresponding dilactam.

The stepwise synthesis involves an intermediate diamid diacid prepared from the diglycolic anhydride and the diamine (yield 96%). The acid functions are then activated by the 2-mercaptothiazoline group (yield 39%) and the cyclization with N,N'-dibenzylethylenediamine leads in low-dilution conditions to the tetralactam 2a in excellent yield (69%).

The overall yields for these two methods are comparable (~ 25%). However, for the direct macrocyclization the limiting step is the cyclization itself which seems difficult to optimize because of the competition di/tetralactam (7), while for the stepwise approach, the low-yield step is the activation of the diamid diacid which has not been optimized. Other advantages of this latter approach are a possible dissymmetrisation of the macrocycle and an easier purification of the desired tetralactam.

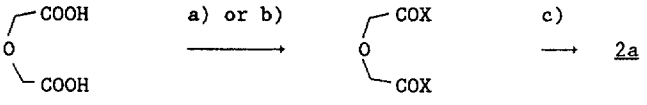
Tetralactam 2b is obtained following scheme 2 from the condensation product of diglycolic anhydride (yield = 32%). The cyclization step occurs in a good yield.

Compounds 2a and 2b are purified on silicagel column (CH_2Cl_2/CH_3CH_2OH)

2a white solid, m.p = 214-218°C ; IR ($CHCl_3$) : ν(C=O) = 1665 cm^{-1} : RMN ^1H ($CDCl_3$) : δ 3.36-3.73(8H, m), 4.23-4.69(16H, m), 7.0-7.45(20H, m) ; SM (DCI/NH_3) : $C_{40}H_{44}N_4O_6$ (m/e 677 (100) $[M+H]^+$)

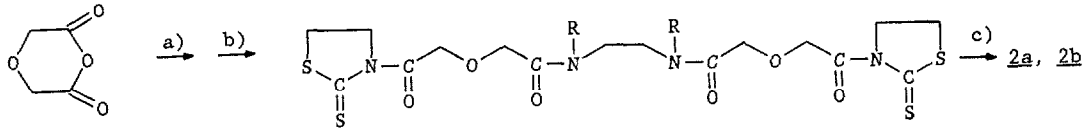
2b white solid, m.p = 150-152°C ; IR ($CHCl_3$) : ν(NH) = 3367 cm^{-1}, ν(C=O) = 1659 cm^{-1} ; RMN ^1H ($CDCl_3$) : δ 3.25-4.64(20H,m), 6.90-7.47(10H, m), 7.78(2H, m) ; SM (DCI/NH_3) : $C_{26}H_{32}N_4O_6$ (m/e 497(100) $[M+H]^+$).

Scheme 1



a) ClCOCOCl, C_6H_6 ; X = Cl (100%) ; b) 2-mercaptothiazoline, DCC, AcOEt, X =  (80%)
c) $BnHNCH_2CH_2NHBn$, $10^{-2}M$; X = Cl, C_6H_6, Et_3N (20%); X =  , CH_2Cl_2 (31,3%)

Scheme 2



a) $RNHCH_2CH_2NHR$, C_6H_6 ; R = Bn (96%), R = H (32%) ; b) 2-mercaptothiazoline, DCC, AcOEt ; R = Bn (39%), R = H (46%) ; c) $BnNHCH_2CH_2NHBn$, CH_2Cl_2, $4.10^{-3}M$; R = Bn (69%), R = H (70%).

COMPLEXING PROPERTIES

They were determined for the three macrocycles and for ETH 129 by extraction of alkaline (Na^+, K^+), alkaline-earth (Mg^{2+}, Ca^{2+}, Sr^{2+} and Ba^{2+}) and zinc picrates from an aqueous phase to a chloroformic phase (8). The percent of extraction and the lipophilicities as log P (9,10) are indicated in the table with literature data for ETH 1001 (3) and 18-c-6 crown ether (11).

ligand	Na	K	Mg	Ca	Sr	Ba	Zn	log P
1[a]	3.0	7.1	0	58.9	52.6	67.7	1.8	3.8
2a[a]	5.8	6.5	4.5	77.5	87.2	89.2	1.0	3.8
2b[a]	0	2.7	2.8	4.0	22.0	76.6	0	1.9
ETH 1001[b]	-	-	3	38	15	18	-	6.2
ETH 129 [c]	0	1	8.4	76.0	81.8	79.5	58.0	6.8
18-c-6[d]	6.3	69.0	2.5	26.2	69.0	75.8	-	0

a) $[picrate]_{aq} = [ligand]_{CHCl_3} = 1.5x10^{-2}M$

b) $[picrate]_{aq} = 6.5x10^{-3}M$, $[ligand]_{CH_2Cl_2} = 1.5x10^{-3}M$;

c) $[ligand]_{CHCl_3} = 2[picrate]_{aq} = 3x10^{-2}M$

d) $[picrate]_{aq} = [ligand]_{CH_2Cl_2} = 3x10^{-3}M$

The major results are the following :

1) The macrocyclization effect observed for macrocycle 1 versus ETH 1001 is evidenced by an increased selectivity for Ca^{2+}, Sr^{2+} and Ba^{2+} with respect to Mg^{2+}. The same effect, in a lesser extent however, exists between compound 2a and ETH 129, while it remains only for Ba^{2+} when compound 2b and ETH 129 are compared.

2) On the other hand, for this latter macrocycle a high selectivity for the extraction of alkaline-earth cations (Mg < Ca < Sr < Ba) is noticed ; it may be related to its weaker lipophilicity in relation with the hydration energy of cations and, thus, with their ionic radius. For ETH 129, which is more lipophilic (log P = 6.8), this selectivity remains only

versus Mg^{2+}, which is generally poorly extracted. A same conclusion can be drawn for ETH 1001 but Ca^{2+} is better extracted than Sr^{2+} or Ba^{2+} ; here a charge-charge interaction effect could favour the smallest cation.

3) For a same lipophilicity, but for a lower number of coordination sites (2 ether oxygen atom less) and different ring size, the 18-membered tetralactam 2a extracts the alkaline-earth cations better than the more flexible 24-membered homolog 1. In both cases the selectivity Ca/Sr/Ba is very low.

4) For same ring size and number of coordination sites, but for a different nature of coordination sites, tetralactams 2a and 2b and 18-crown-6, behave either similarly -very strong extraction of Ba^{2+} and weak Mg^{2+}, sequence Mg < Ca < Sr < Ba - either very differently with respect to the extraction of K^+ which has a size identical to that of Ba^{2+} ; very strong extraction of K^+, analogous to that of Ba^{2+} for the 18-crown-6 (11), and very weak for the two tetralactams. The replacement of 4 CH_2O moieties by 4 amide functions modify considerably the properties of the host. Particularly the presence of highly polar sites favour divalent cations versus monovalent cations (12) ; on another hand, the spatial arrangement of the coordination sites is different as it can be seen on CPK molecular models where they are not oriented inside the cavity for the tetralactams.

5) This spatial arrangement may be also invoked to explain the easy extraction of Ca^{2+}, Sr^{2+}, Ba^{2+} cations with a coordination number $\geqslant 8$ (favouring square antiprisms) , and the difficulty found for those (Na^+, K^+, Mg^{2+}, Zn^{2+}) where this number, generally equal to 6, leads to an octahedral geometry.

A 1:1 stoichiometry was found for the two complexes 2a, 2b : barium picrate by elemental analysis of the isolated complexes, and by UV spectrophotometry. The stability constants in tetrahydrofuran for 2a : $BaPic_2$ ($\log K_1 = 4.9$) and 2b : $BaPic_2$ ($\log K_1 = 3.8$) complexes were determined by this UV technique.

In conclusion, a 3 step synthesis leads to symmetrical and dissymmetrical tetralactams with dimethyleneoxy moieties. One of these is one of the most selective neutral ionophore of barium versus Na^+ and Zn^{2+}, but also K^+, Mg^{2+} and Ca^{2+}.

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