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MACROCYCLIC TETRALACTAMS : STRUCTURAL BEHAVIOUR OF THREE 21-MEMBERED RINGS AND THEIR Ca^{2+} COMPLEXES AS EVIDENCED BY ^{13}C AND ^{19}F NMR

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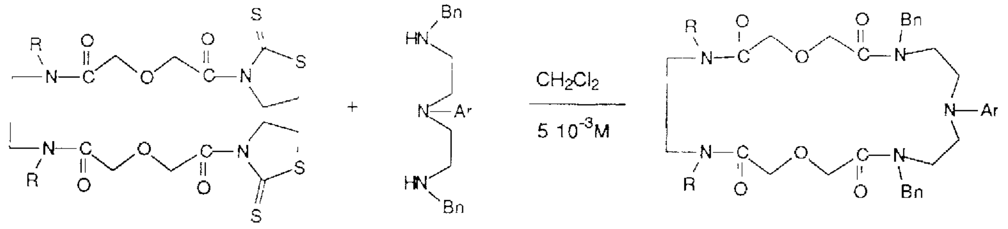
Abstract a stepwise synthesis of three macrocyclic tetralactams selective complexants of Ca^{2+} vs alkali and Mg^{2+} ions is reported The multiplicity of the resonances in ^{13}C and ^{19}F n m r spectroscopy is related to the restricted rotations around the carbon-nitrogen bond of the four amide moieties The 1/1 complexes formed by addition of one equivalent of $Ca(ClO_4)_2$ exhibit very simple spectra which are assigned to the existence of a single form in the complex with the carbonyl oxygen atoms in the same orientation

Among neutral Ca^{2+} selective systems (1), macrocyclic polyether tetramides show a high selectivity for calcium cation with respect to alkaline and Mg^{2+} ions (2, 3, 4), but so far no evidence has been reported for the structure of these complexes In this paper we describe the synthesis of three 21-membered macrocyclic tetralactams which exhibit high stability constants for Ca^{2+} and discuss the deep nmr spectral changes occuring when they are complexed with Ca^{2+} ion

Synthesis

Macrocyclic tetralactams were synthesized following a stepwise procedure (3) , the cyclisation step is depicted in the following scheme



R = H, Bn

1 Ar = Ph, R = Bn (58%)
2 Ar = Ph, R = H (62%)
3 Ar = 4F-C_6H_4, R = Bn (42%)

N,N' dibenzyl diethylene triamine derivatives (Ar = Ph, 4F-C6H4) were prepared in a three step synthesis by standard procedures (5, 6, 7) involving the dialkylation of an arylamine by methyl bromoacetate, then the amidation of the resulting diester by benzylamine and finally the reduction of the bisamide by borane Overall yields of 40% were thus obtained

The stepwise synthesis of the macrocycles involves condensation of diglycolic anhydride to ethylenediamine derivatives. The intermediate diamid diacids were activated by the 2-mercaptothiazoline group and condensed to two corresponding diethylene triamine derivatives following the procedure described by E Fujita (8), affording the three tetralactams 1-3 in a good overall yield

Compounds **1**-**3** were purified on silicagel column (CH_2Cl_2/CH_3CH_2OH)

1 white solid, m.p. = 119-120°C , IR (KBr) : ν(C=O) = 1662 cm^{-1} , RMN ^1H (CD_3CN) δ 3.12-3.77(m, 12H), 4.22- 4.60 (m, 16H), 6.26-6.70(m, 3H), 7.00-7.50(m, 22H) ; MS (FAB/MNBA matrix) : $C_{48}H_{53}N_5O_6$(m/e 796 (100) $[M+H]^+$)

2 white solid, m.p. = 95-97°C , IR (KBr) ν (NH) = 3260 cm^{-1}, ν(C=O) = 1652 cm^{-1} , RMN ^1H (CD_3CN) . δ 3.22-3.46(m, 12H), 3.86-4.05(m, 4H), 4.22-4.63(m, 8H), 6.36-6.77(m, 3H), 7.04-7.41(m, 12H), 7.50-7.70(m, 2H) ; MS (FAB/MNBA matrix) $C_{34}H_{41}N_5O_6$ (m/e 616 (100) $[M+H]^+$)

3 white solid, m.p. = 122-124°C ; IR (KBr) : ν(C=O) = 1654cm^{-1} , RMN ^1H ($CDCl_3$) δ 3.16-3.73(m, 12H), 4.20-4.78 (m, 16H), 6.04-6.92(m, 3H), 6.96-7.54(m, 21H) , MS (FAB/MNBA matrix) $C_{48}H_{52}N_5O_6F$ (m/e 814 (100) $[M+H]^+$)

Stability constants

*They were measured in THF solutions by ultraviolet spectrophotometry using calcium picrate.*The spectral changes were interpreted by the intervention of two equilibria involving ML and ML_2 complexes where M = Ca^{2+} and L = ligand The values of the calculated constants for the three complexes are given in the table

	1	**2**	**3**
log K_1	6.19	5.54	6.20
log K_2	4.04	3.88	4.59

$M + L \rightleftharpoons ML \quad K_1$

$ML + L \rightleftharpoons ML_2 \quad K_2$

The existence of a strong 1/1 complex was verified by elemental analysis (9) of the complexes which crystallize from methanol

nmr spectroscopy

62.9 MHz ^1H-decoupled ^{13}C spectra exhibit a high complexity for each type of carbon atom related to the phenomenon of restricted rotation around the carbon-nitrogen bond of each of the four amide moieties The interconversion between the various rotamers is slow relative to the nmr time scale and the spectrum represents the mixture of these forms Similar results were observed by Shanzer (10) for macrocyclic tetralactams possessing reflexion symmetry For instance we observed in $CDCl_3$ up to eight distinct carbonyl resonances for compound **1**, five for **2** and eight for **3** A high multiplicity is also clearly seen for the other carbon resonances in $CDCl_3$ as well as in CD_3CN solutions as shown in figure 1a

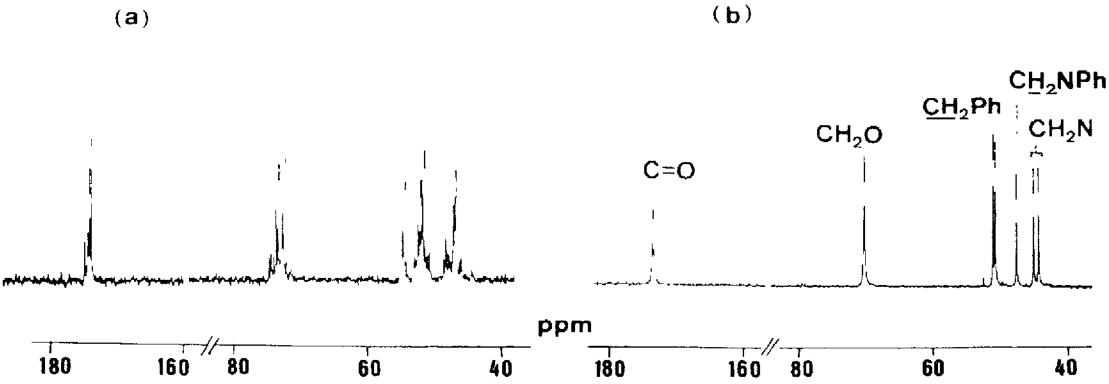
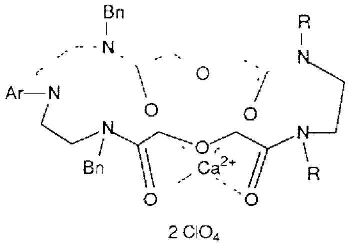


Figure 1 · ^{1}H-Decoupled ^{13}C-nmr spectra of 1 in CD_3CN at 62 9 MHz
(a) free ligand , (b) 1 / Ca^{2+} complex (1 1 stoichiometry)

When an equimolecular amount of calcium perchlorate is added to the acetonitrile solutions of the tetralactams, a dramatic change in the spectrum occurs Only one signal for each carbon atom is observed suggesting the stabilization of one rotamer able to form a 1/1 complex (Figure 1b) This rotamer has a mirror symmetry and among the four possible symmetry isomers the structure represented in figure 2 is the most likely to provide the best geometry giving a strong 1/1 complex

Figure 2 - a schematic view of 1 1 complexes
(1 - 3/Ca^{2+})



The carbonyl resonances are shifted downfield in relation with the participation of the oxygen atoms to the complexation An analogous result was observed for compound 3 using 282 4 MHz ^{1}H decoupled ^{19}F nmr spectroscopy By adding one equivalent of calcium perchlorate, the number of ^{19}F resonances change from eight to one indicating the same disappearance of structural heterogeneity (Figure 3).

The participation of the ether oxygen atoms to the complexation cannot be established soundly from the nmr data due to the structural heterogeneity of the uncomplexed ligands for ^{1}H and ^{13}C nmr spectroscopies the signals of CH_2-O nuclei in the 1/1 complex appear in the same range of chemical shifts that the multi-resonance systems in the uncomplexed ligands So a downfield or a high field shift cannot be determined clearly

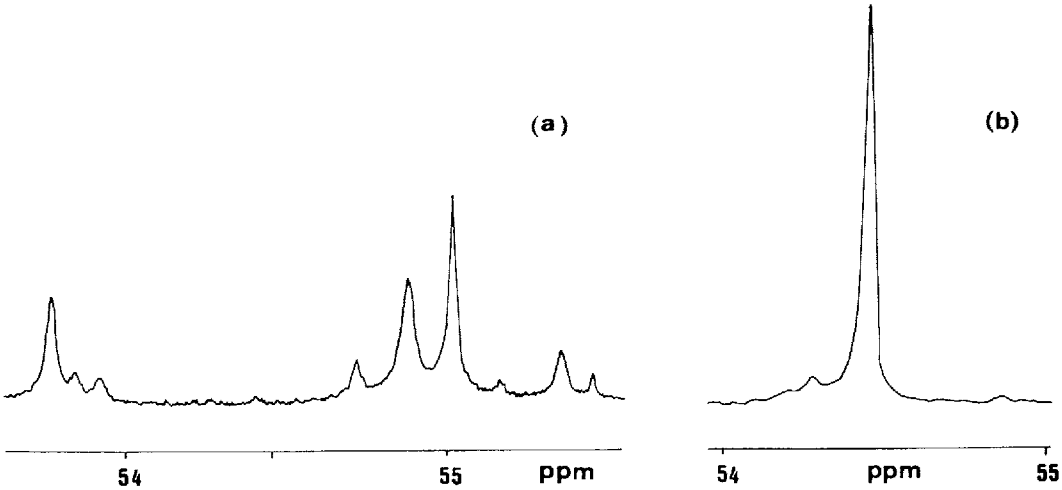


Figure 3 - ^1H decoupled ^{19}F-nmr spectrum of 3 in CD_3CN at 282 4 MHz
(a) free ligand , (b) 3 / Ca^{2+} complexe (1/1 stoichiometry)

The stability constants were measured in THF solutions Although their values in acetonitrile solvent, which was used in nmr spectroscopy, may be quite different, they can be indicative of observed very little differences between the behaviour of compounds 1, 3 in one hand and 2 on the other hand For compounds 1 and 3 only one symmetric rotamer was evidenced for each complex, while for compound 2 a limited number of very weak additional lines appear besides those of the major rotamer For instance three distinct lines are present for the carbonyl resonances one of them being of very little intensity This phenomenon can be related to the weaker value of K_1 compared to those of 1 and 3

References and Note

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(4) For the title compounds following selectivities measured by extraction experiments (% E) were found 1 Ca^{2+} (88%), Mg^{2+} (2,5%), alkaline (<1%) , 2 Ca^{2+} (18%), Mg^{2+} (1 2%), alkaline (0%) , 3 Ca^{2+} (90,0%), Mg^{2+} (1,6%), alkaline (3,4%)

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(9) elemental analysis % found (% calculated) 1-$Ca(ClO_4)_2$ $2H_2O$ C 53 92 (53 82), H 6 47 (6 54), N 5 24 (5 36) , 2-$Ca(ClO_4)_2.6H_2O$ C 42 14 (42 41), H 5.37 (5 54), N 7.12 (7 27) , 3-$Ca(ClO_4)_2$ C 54 98 (54 75), H 5 20 (4 98), N 6 59 (6.65)

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