Inorganica Chimica Acta, 210 (1993) 7–9

Inorganica Chimica Acta

LETTER

The high yield synthesis of *N*-tetrapropionic methyl ester, acid and carboxylate derivatives of 1,4,8,11-tetraazacyclotetradecane, and molecular structure of the tetramethylpropionate ester dication

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(Received April 14, 1993)

Functionalization of cyclic polyamines allows preparation of multichelating macrocycles with selectivities and stabilities which may vary with the nature of their substituents [1]. With the 1,4,8,11-tetraazacyclotetradecane ligand (cyclam), many examples have been reported yielding macrocycles with multi chelating properties [2], or with functionalities which might provide access to superstructured compounds. In relation to a previous work [3], we have been looking for the preparation of the methyl propionate compound **1**, the formula of which had been mentioned once in the literature [4], but were unable to find any synthetic details; therefore we undertook its preparation as well as that of its tetraacid (carboxylate) derivative **2a** (**2b**), and the nickel salt [NiI$_2$**1**], by soft and clean methods. The syntheses of **1**, **2** and [NiI$_2$**1**] (Scheme 1), along with the crystal structure of the diprotonated form of the tetraester [H$_2$**1**]I$_2$ are reported hereafter**.

The synthesis of the tetraacetic derivative of cyclam is well known and involves substitution with 1-bromoacetic acid [5]; with 1-bromopropionic acid, no tractable product could be obtained by following this procedure. We found that **1** could easily be obtained by reacting cyclam with methylacrylate in milder conditions than those described in the synthesis of the monosubstituted derivative of tetramethylcyclam [6], using this activated olefin as the solvent: stirring a suspension of the macrocycle in methylacrylate for two days at room temperature afforded a pale yellow solution. Evaporation of the solvent gave a yellowish oil having an NMR spectrum which was that of the clean substituted macrocycle. Subsequent extraction with pentane followed by crystallization yielded 70% of **1** as a colorless, hygroscopic and analytically pure solid compound. In ^{1}H NMR (CDCl$_3$), **1** displays the typical features of tetrasubstituted cyclam derivatives: the quintuplet (γ CH$_2$) appears at $\delta = 1.68$ ppm, whereas the singlet and the triplet (β, β') are located at 2.55 and 2.46 ppm. Three additional resonances appear at $\delta = 3.74$(s), 2.77(t) and 2.46(t) ppm, and stand for the methoxy and methylene substituent signals, respectively. The ν(CO) vibration is observed at 1720 cm^{-1} by IR spectroscopy (KBr). Acidification of a methanol solution of **1** with aqueous HCl resulted in precipitation of the tetra hydrochloride derivative [H$_4$**1**]Cl$_4$ in quantitative yield; again ^{1}H NMR and IR spectroscopies (ν(NH$^+$) = 2300–2500 cm^{-1}) are in complete agreement with the proposed structure. Wishing to avoid heating the macrocycle, we hydrolyzed the four ester functions at room temperature: evaporation of a solution of **1** stirred 4 days at ambient temperature in 20% aqueous HCl, afforded, after washing with methanol, 90% of [H$_4$**2**]Cl$_4$. ^{1}H NMR spectroscopy (D$_2$O, tBuOH) revealed a complete loss of the methoxy groups and the preservation of the macrocyclic structure $\delta = 2.00$(q), 3.30(s) and 3.00(t) ppm; two doublets at $\delta = 3.20$ and 2.80 ppm (substituents). The carboxylate form [**2**]Na$_4$ can be obtained by reaction of sodium hydroxide with [H$_4$**2**]Cl$_4$ or by stirring **1** for 10 days in aqueous sodium hydroxide; the ν(CO) frequency shifts from 1730 and 1710 cm^{-1} for [H$_4$**2**]Cl$_4$ to 1560 cm^{-1} for [**2**]Na$_4$.

Metalation of **1** by NiI$_2$ was achieved according to a published procedure [7], and yields a one-to-one metal–ligand complex. After washing with diethyl ether and extraction with THF, [NiI$_2$**1**] was obtained in 45% yield as a brown, analytically pure solid. The single ν(CO) vibration observed for **1** in IR spectroscopy (KBr) is now split and appears at 1702 and 1738 cm^{-1} indicating two different types of carbonyl groups. It is already known that isomerization as well as dealkylation reactions occur when heating nickel complexes of some tetrafunctional macrocycles [4]. In the case of [NiI$_2$**1**] which was obtained as a clean compound, and contrary to the solid state in which it is thermally stable, we observed slow demetalation in solution at room temperature, yielding the diprotonated free macrocycle [H$_2$**1**]I$_2$. Attempts to obtain single crystals of [NiI$_2$**1**] by slow diffusion of CH$_3$OH into a CH$_2$Cl$_2$ solution resulted in the formation of colorless crystals of [H$_2$**1**]I$_2$ solvated with one CH$_2$Cl$_2$ molecule.

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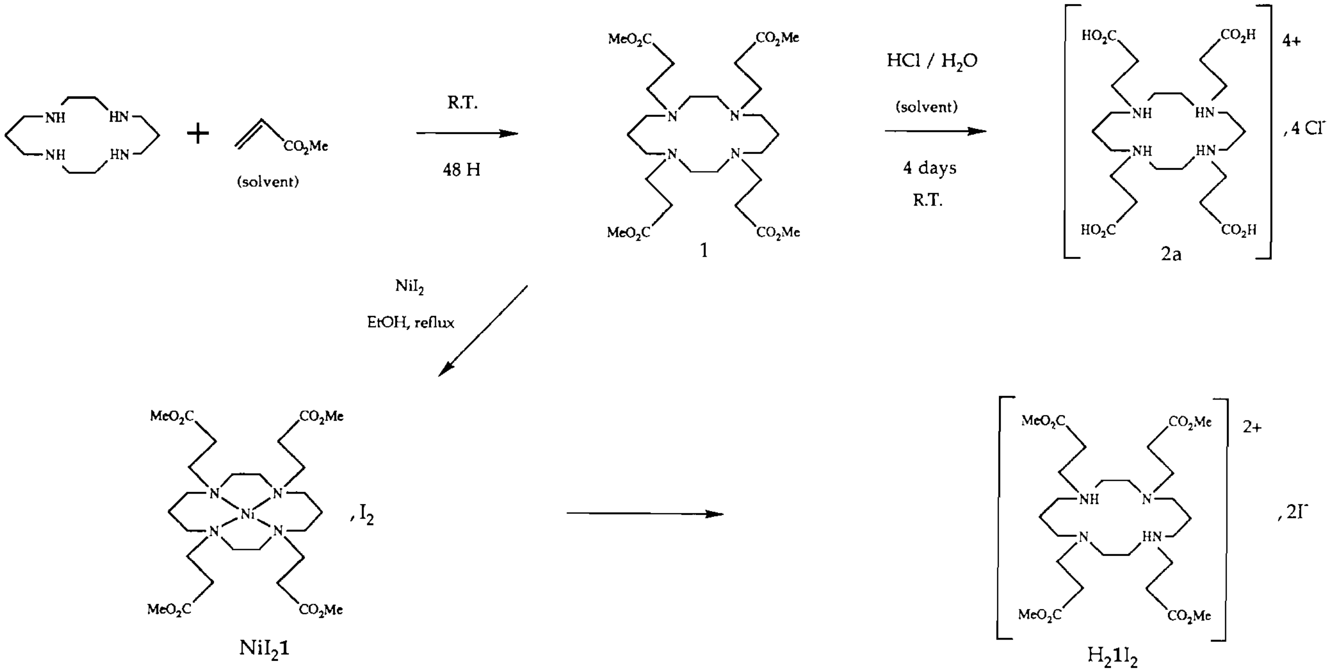
All compounds described in this communication were characterized by ^{1}H, ^{13}C, IR spectroscopies and, except for **2b, gave satisfactory elemental analyses.

0020-1693/93/$6.00

The crystal structure of $[H_2\mathbf{1}]I_2\cdot CH_2Cl_2$ was determined*. The ORTEP diagram of the dication is shown in Fig. 1, and a stick plot is given in Fig. 2. The macrocyclic ring is centered on a crystallographic inversion center, so that only half of the atoms of the formula are independent, the other half being symmetry related. The ring adopts a rectangular conformation [9] where C1 and C5 mark corner positions. The methyl propionate on N1 extends laterally from the ring, whereas the two other substituents extend up and down



Scheme 1. Synthesis of the macrocycle derivatives.

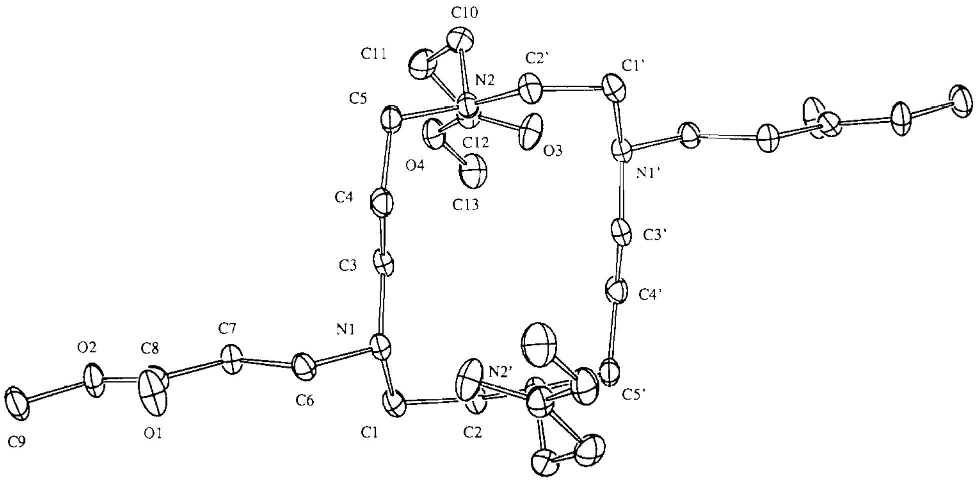


Fig. 1. ORTEP plot of the $H_2\mathbf{1}I_2$ dication with numbering. Thermal ellipsoïds are drawn at 50% probability level. Hydrogen atoms are omitted for clarity.

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*Crystal data for $[H_2\mathbf{1}]I_2\cdot CH_2Cl_2$: $C_{27}H_{52}N_4O_8Cl_2I_2$, molecular weight = 885.5, monoclinic, $C2/c$, $a = 20.915(6)$, $b = 11.442(3)$, $c = 15.970(4)$ Å, $\beta = 98.28(2)°$, $V = 3782$ Å^3, $Z = 4$, $D_{calc} = 1.555$ g cm^{-3}, λ(Mo Kα) = 0.7107 Å (graphite monochromator), $T = 20$ °C. An Enraf-Nonius CAD4-F diffractometer was used to collect 3620 reflections ($4 < 2\theta < 50°$) on a colorless crystal $0.10 \times 0.20 \times 0.25$ mm. Of these, 2040 were observed ($I > 3\sigma(I)$). Semi empirical absorption corrections based on ψ scans of 4 reflections and Lorentz and polarization corrections were applied to the data. All non-hydrogen atoms were located by direct methods, and they were refined anisotropically. The hydrogen atoms were included as idealized contributions. $R = 0.040$, $R_w = 0.060$, $GOF = 1.27$, final residual = 0.28 e Å^{-3}. All computations used MOLEN on a VAX computer using the Enraf-Nonius CAD4-SDP package [8].

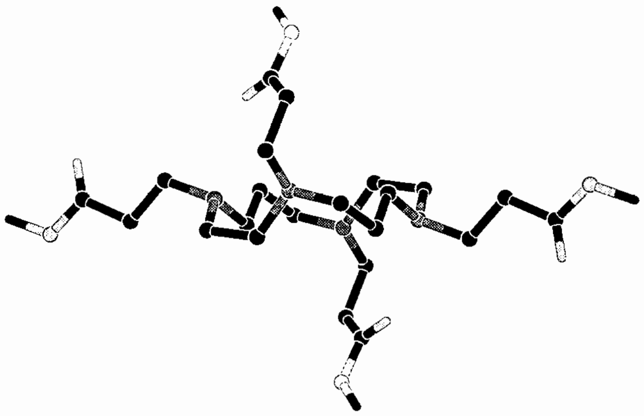

Fig. 2. Stick plot of the $H_2 1 I_2$ dication showing the flexibility of the ligand.

the mean plane of the macrocycle. The bond lengths and angles are here less accurate than those reported for the protonated cyclam [10] and its tetraacetic acid derivative [11]. Nevertheless, the elongation of thc average N1–C distance with respect to the average N2–C distance (1.510(4) and 1.467(5) Å, respectively) is also observed and indicates protonation at N1. Since the distance of 2.750(7) Å between N1 and O3 is short, it is likely than hydrogen bonding occurs between the carbonyl and the proton located on this nitrogen, thus being responsible for the conformation of this substituent. The carbonyl C18 lies in the plane defined by the four nitrogen atoms, whereas C12 lies at 2.986(6) Å above this plane. The distances between the carbonyl oxygens O1 and O3 to the inversion center are 6.684(5) and 3.597(5) Å, respectively. No unusual distances could be seen between the independent iodides and the diprotonated ring.

In summary, we have shown that tetrapropionic derivatives of 1,4,8,11-tetraazacyclotetradecane can be obtained in high yield at room temperature. The one-to-one nickel ligand complex of the ester is obtained by regular procedures, but has to be kept in the solid state to avoid demetalation. In the field of multi chelating cyclic polyamines, **1** and **2** may find applications where more flexible substituents than acetates are required.

Supplementary material

Tables of X-ray experimental data, atomic positional and isotropic equivalent thermal parameters, anisotropic thermal parameters, and bond distances and angles, and listings of observed and calculated structure factors (14 pages) are available from the authors on request.

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