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^{1}H, ^{13}C, ^{15}N NMR and X-Ray Diffractometry in Structural Studies of Macrocyclic Lactams Containing Pyridine Moiety

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We examined complexing sites of the Pb^{2+} complex of the macrocyclic lactam 1 using ^{15}N NMR and other spectroscopies and we have found that the amide groups undergo conformational changes to allow the complexation process to proceed *via* the pyridine nitrogen atom and carbonyl and ethereal oxygen atoms. X-Ray analysis of compound 1 was carried out successfully. Space group $I4_1/a$, a=28.332(4)Å, b=28.332(4)Å, c=10.7379(4)Å, Z=16, V=8619.3(18)Å^3, D_c=1.197gcm^{-3}, R1=0.0479 (based on 2510 reflections $I>2\sigma(I)$. It shows presence of intramolecular hydrogen bonds, which are broken during the complexation. Molecules form supramolecular tetragonal assemblies in the crystal, which form channels the walls of which are 7.42 Å apart.

Keywords: Macrocyclic lactam, X-ray diffractometry, ^{15}N NMR, complexation

Continuing our study concerning the synthesis of various diazacoronands[1],[2], we considered the conditions which should be fulfilled in order to render the intermediate diamides to be good receptors for cations. Relatively high stability constants were reported for ternary macrocyclic amides in some cases[3]. However, complexing properties of secondary macrocyclic amides have not been very often studied because stability constants are usually not measurable[4]. Pyridine-amide based macrocycles for selective recognition of metal cations[5], anions[6],[7],[8] and neutral organic molecules[9],[10] adopt preorganization of their binding sites through hydrogen bonding as well as configurational rigidity of the amide carbon-nitrogen bond. We carried out preliminary investigations of binding behavior of several representative macrocyclic diamides which we obtained in the reaction of pyridine-2,6-dicarboxylic acid dimethyl ester **4** with α,ω-diaminoaliphatic ethers[11]. During the above-mentioned study, we found that stability constants of complexes of diamide **1** with various metal cations are relatively high[11]† as compared with complexes of other synthetic macrocyclic amides[4]. For structural studies, we have chosen the strongest complex **1a** with Pb(II) ion. The chemistry of lead is of interest in rela-

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† Stability constants for complexes of diamide **1** are as follows: $\log\beta(1+Pb^{2+})=5.0$, $\log\beta(1+Cd^{2+})=2.6$, $\log\beta(1+Na^{+})=2.8$, $\log\beta(1+K^{+})=2.4$.

tion to its toxicity and the problem of stereochemical activity of the lone electron pair[12]. The coordination number for stereochemical active complexes tends to be 7 or less[13], while stereochemical inactive complexes are considered to have higher coordination numbers (even as high as 10[14]). Generally lead ions prefer coordination through nitrogen atoms; however, coordination through amide[15] or etheral[16] oxygen atoms is also common.

It seems that, in studies of complexes of macrocyclic azacoronands, ^{15}N NMR is an excellent method. We could have splendid insight into host-guest type interactions, observing spectra of nuclei which might directly participate in a complexation process. The natural-abundance study was greatly helped by the HMQC[17] and HSQC[18] experiments with B_0 gradient coherence selection, which provide a theoretical enhancement of $(\gamma^1H/\gamma^{15}N)^{5/2}$ relative to conventional 1-D measurements[19]. For the case of N_{am} in the presence of a relatively large one-bond coupling constant (ca. 90 Hz), phase-sensitive HSQC experiment is a method of choice. However, for quaternary nitrogen atoms where only small long range N-H couplings are available, HMQC type experiments should be preferred. Although ^{15}N NMR was recently used in the investigation of complexes[20],[21], this is the first example, to our best knowledge, of using ^{15}N NMR in the investigation of macrocyclic amides complexes. ^{15}N NMR data were successfully obtained for ligands **1, 2** and **3**[*] and their complexes **1a, 2a** and **3a** (Table I). [†] In order to facilitate the interpretation, we also obtained the ^{15}N NMR data for pyridine-2,6-dicarboxylic acid dimethyl ester (**4**). The conformation of diamide **1** and its complex with Pb^{2+} in solution was examined by NMR.

The X-ray structure of lactam **1** (Fig. 1) showed amide NH involvement in the intramolecular hydrogen bonding and carbonyl oxygen atoms positioned outside of the cavity with an additional water molecule bound inside (hydrogen bond geometry D-H...A(Å), D....A(Å) distances and D-H...A(°) angles are: 2.26(2), 2.671(3) and 108.8(19) for N1-H1N...N4, 2.34(3), 2.694(3) and 105(2) for N7-H7N...N4, 2.11(3), 2.912(3) and 154(2) for N1-H1N...O1W, 2.11(3), 2.943(3) and 160(3) for N7-H7N...O1W, 2.03(4), 2.793(3) and 164(3) for O1W-H2W...O4, 1.94(5), 2.739(3) and 175(4) for O1W-H1W...O2(-.25+Y, 2.25-X,1.25-Z)). This suggests that N_{Py} is blocked as a potential donor atom and that the cavity is small.

TABLE I ^{15}N NMR data (δ, ppm)

	No.	*-^{15}NH-CO*	*-$^{15}N_{Py}$*
1		–273.4	–90.5
1a	(**1**+Pb^{2+})	–255.3	–83.4
2		–269.0 –	-
2a	(**2**Pb^{2+})	–263.5 –	-
3		–272.3	–90.9
3a	(**3**+Pb^{2+})	–269.5	–90.1
5		-	–65.3
5a	(**5**+Pb^{2+})	-	–76.4

[*] Synthesis: Ligand **2** was obtained from dimethyl isophtalate and 4,7,10-trioxa-1,13-diaminotridecane under high-pressure in a yield of 23.7 %. Colorless crystals; m.p. 146–147°C; ^1H NMR (500 MHz, CD_3CN) δ 8.03 (dd, J_1=7.5 Hz, J_2=1.5 Hz, 2H), 7.97 (d, J=1.5 Hz, 1H), 7.66 (bs, 2H), 7.55 (t, J=7.5 Hz, 1H), 3.66–3.58 (m, 12H), 3.56–3.51 (m, 4H), 1.84–1.76 (m, 4H); ^{13}C NMR (125 MHz, CD_3CN) δ 166.8, 136.3, 131.9, 130.1, 123.6, 71.0, 69.8, 69.3, 40.0, 29.5; HRMS m/z calcd. for $C_{18}H_{26}N_2O_5$ $(M)^+$ 350.1842, found 350.1851; Anal. calcd. for $C_{18}H_{26}N_2O_5$: C, 61.70; H, 7.48; N, 7.99; found: C, 61.64; H, 7.43; N, 7.81. Ligand **3** was obtained from dimethyl pyridine-2,6-dicarboxylate **5** and 1,12-dodecanediamine using conditions described by us previously (yield 11.8%). Colorless crystals; m.p. 247–250°C; ^1H NMR (500 MHz, CD_3CN) δ 8.36 (bs, 2H), 8.24 (d, J=7.5 Hz, 2H), 8.05 (t, J=7.5 Hz, 1H), 3.5–3.4 (m, 4H), 1.7–1.6 (m, 4H), 1.5–1.2 (m, 16H); ^{13}C NMR (125 MHz, CD_3CN) δ 164.2, 149.8, 139.8, 125.0, 39.7, 29.4, 28.9, 28.5, 28.0, 26.8; Anal. calcd. for $C_{19}H_{29}N_3O_2$: C, 68.85; H, 8.82; N, 12.68; found: C, 68.91; H, 9.02; N, 12.68.

† All spectra were measured for ca. 0.05 M solutions of free ligand and its 1 : 1 complex in CD_3CN at 300K, using a Varian Unity Plus 500 MHz spectrometer equipped with ID-PFG probe. The ^{15}N chemical shifts of N_{am} were obtained from phase-sensitive HSQC experiments with gradient echo-antiecho coherence selection optimized for $^1J(^{15}N\text{-}^1H)$ (ca. 90 Hz). For the N_{Py}, long-range HMQC optimised for $^3J(^{15}N\text{-}^1H)$ (ca. 2 Hz) was employed. In all cases measuring time was less than one hour. Ligand 1+$Pb(ClO_4)_2$: ^1H NMR (500 MHz, CD_3CN) δ 9.02 (bs, 2H) 8.52 (t, J=8.2Hz, 1H), 8.35(d, J=8.2 Hz, 2H), 3.73 (bs, 8H), 3.35 (t, J=4.5Hz, 4H), 2.76 (bs, H_2O), 1.88 (m, 4H); ^{13}C NMR (125 MHz, CD_3CN) δ 169.8, 149.3, 143.8, 127.3, 71.4, 70.9, 68.7, 41.4, 27.5.

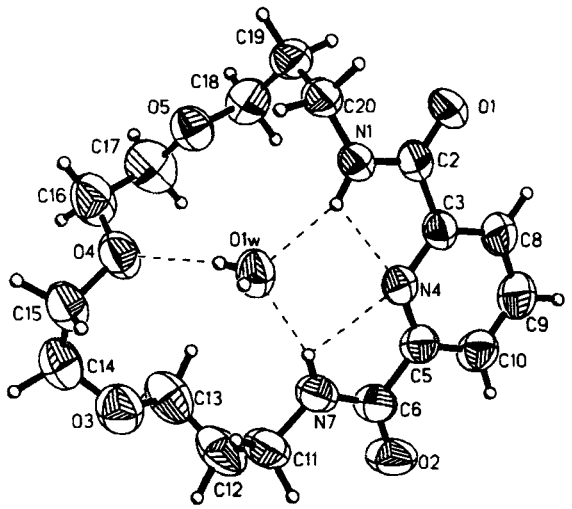

FIGURE 1 ORTEP view of the crystal structure of macrocyclic bisamide **1**

The very interesting packing diagram of **1** is showed in Fig. 2. During our investigation of 2,6 pyridine-amide based macrocycles we observed their tendency to form teragonal assemblies in the crystal. However, this is the most spectacular example. Supramolecular square voids consist of four macromolecules arranged by water molecules, which are positioned in the corners (Fig. 3). The channel formed in such a way is filled with highly disordered linear molecules, which are probably acetonitrille ones, but we were unable to recognize the type of disorder. The diameter of the channel was 7.42Å.

In the solution an amide proton signal in ^{1}H NMR spectrum is shifted downfield by ca. 0.8 ppm, which suggests that the structure resembles the solid state structure. This was also supported by the absence of any NOE enhancements between amide NH and aromatic protons.

TABLE II Crystal data and structure refinement for **1**

Empirical formula	$C_{18}H_{25}N_3O_5 \cdot H_2O$
Formula weight	388.43
Temperature (K)	293(2)
Wavelength (Å)	1.54178
Crystal system	tetragonal
Space group	$I4_1/a$
a (Å)	28.332(4)
b (Å)	28.332(4)
c (Å)	10.7379(4)
Volume (Å^3)	8619.3(18)
Z	16
Calculated density (Mg/m^3)	1.197
Absorption coefficient mm^{-1}	0.755
F(000)	3320
Crystal size (mm)	0.32x 0.32 × 0.17
θ range for data collect. (°)	4.40 to 74.06
Index ranges h, k, l	0–34, 0–34, –13-0
Refl. collected / unique	2747/2623 [R(int)=0.0141]
Completeness to 2θ = 74.06	28.3%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2623 / 0 / 266
Goodness-of-fit on F^2	0.963
Final R indices	[I>2σ(I)] R1 = 0.0479, wR2 = 0.1422
R indices (all data)	R1=0.0496, wR2=0.1453
Largest diff. peak and hole (eA^{-3})	0.195 and –0.187

Addition of one equiv. of $Pb(ClO_4)_2$ aq. to a CD_3CN solution of **4** resulted in considerable changes in the ^{1}H, ^{13}C and ^{15}N NMR spectra. Control experiments disqualified changes as being the effect of water. ^{15}N NMR spectrum showed upfield shift (-11.1 ppm) on the N_{Py}. This is in good agreement with the general effect of complexation on N_{py}[22]. However, in the case of amide **1**, we observed an opposite, deshielding effect (7.1 ppm), which raises the question regarding the participation of N_{Py} in the complexation. On the other hand the participation of $N_{Py}$is supported by the fact that voltammetric studies of stability constant for **2a** showed that it is over 100 times lower than that for **1a**. Such a direction of changes could be attributed to the fact that intramolecular NH....N_{Py} hydrogen bonds present in ligand **1** are broken during the complexation, which

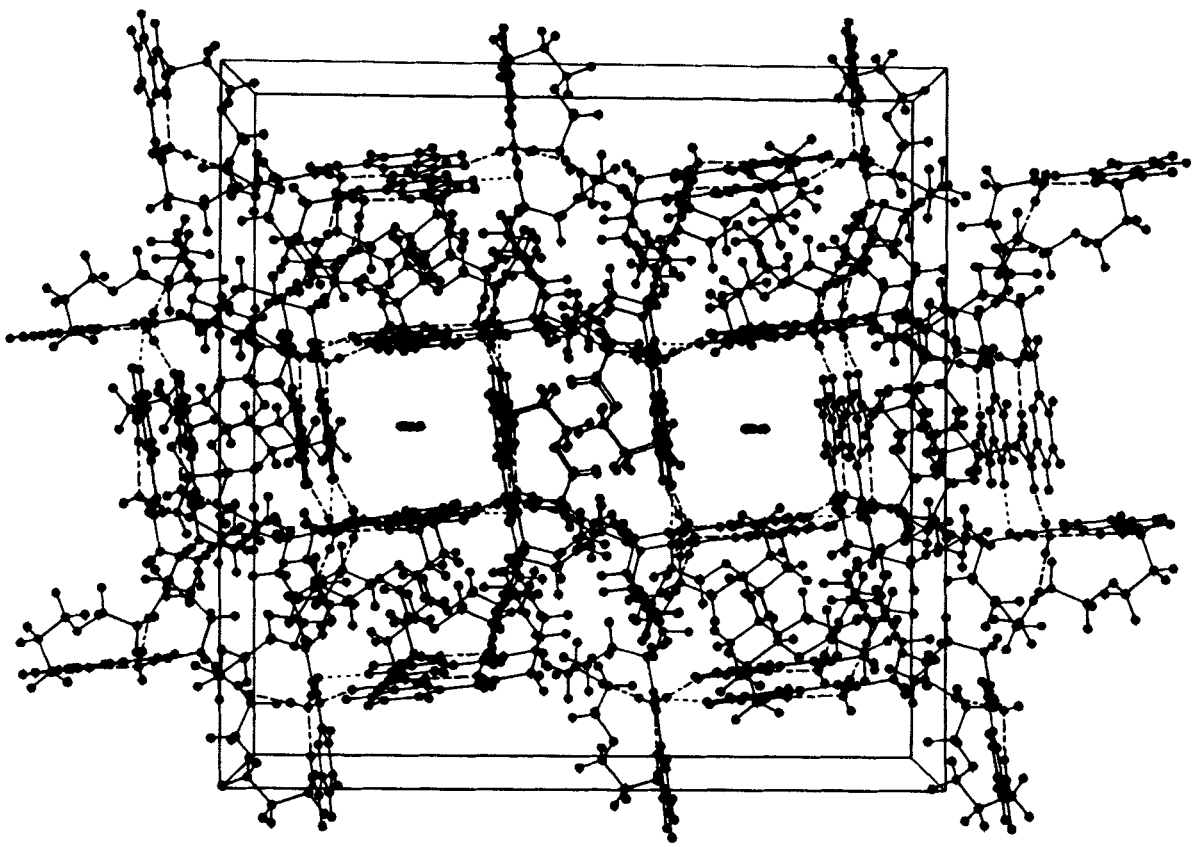

FIGURE 2 A packing diagram of **1**. A view normal to the C axis with acetnitrille molecules inside of the channels

causes a deshielding effect on N_{Py}[22]. In this light, we can assume that N_{Py} participates in the binding of Pb^{2+} but its effect on ^{15}N NMR spectrum is a resultant of two components: the deshielding effect upon hydrogen bond breaking (the larger one) and shielding effect of the complexation (the smaller one).

Although binding of Pb^{2+} by ethereal oxygen atoms seems to be evident, we examined ligand **3**, of similar cavity from the geometrical viewpoint, but with lacking ethereal oxygen atoms. Very small changes (on both N_{Py} and N_{am}) are indicative that ligand **3** does not complex Pb^{2+}.

It is known that noncyclic derivatives of picolinic acid usually coordinate through $N_{Py}$and O_{am} [23],[24]. Sometimes, coordination through N_{am} accompanied by the spontaneous dissociation of an amide proton, was also observed[25]. In our case, ^1H NMR spectrum of **1a** undoubtly indicates the presence of amide protons in the molecule[26]. Participation of carbonyl oxygen atoms in complexation is confirmed by ^{13}C NMR which shows +5.4 ppm shift upon addition of Pb^{2+}, although the value of $^1J(^{15}N,^1H)$ on going from the free ligand **1** to the Pb^{2+} complex **1a** does not change significantly (93.5 Hz and

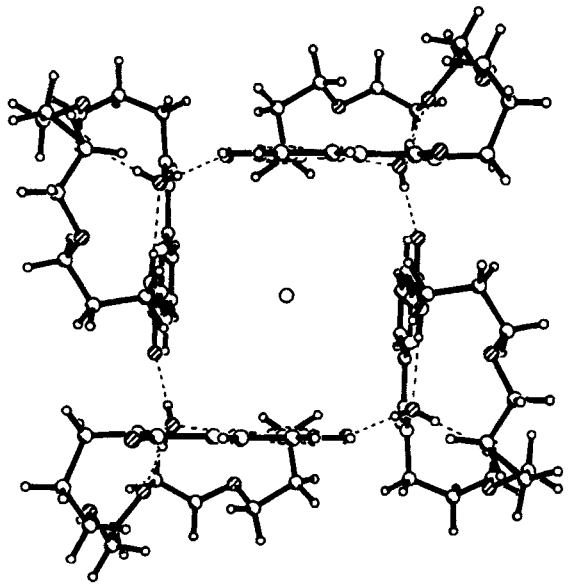

FIGURE 3 The struture of the tetragonal assemblies. Water molecules are in the corners of the channel

93.7 Hz, respectively). The most important structural data were obtained from a NOE experiment. It shows in compound **1a** a substantial NOE between the amide NH and H-3,5 of pyridine. Such an effect could only take place if the macrocyclic ring undergoes substantial conformational changes so that amide oxygen atoms are positioned inside the cavity while amide NHs remain outside. In the ^{15}N NMR spectrum for **1a** we observed downfield shift (18.1ppm) of the N_{am} signal. It seems that changes on N_{am} are also a resultant of a few component processes namely complexation through an amide oxygen atom (deshielding effect), hydrogen bond N-H....N_{Py} breakage (shielding effect) and also resonant connection breakage (deshielding effect). Summing up, we can state that for **1a**, the coordination proceeds *via* N_{Py}, ethereal and amide oxygen atoms. Neutral amide groups undergo rearrangement in that way to allow coordination through N_{Py} and oxygen atoms. Further, more detailed studies on the structure of complexes of pyridinophanes with various cations are in progress.

TABLE III Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2x10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij}tensor

	x	*y*	*z*	*U(eq)*
O(1)	8763(1)	11004(1)	1222(2)	76(1)
O(2)	10789(1)	11201(1)	4939(2)	100(1)
O(3)	9709(1)	10438(1)	8768(2)	97(1)
O(4)	8779(1)	10279(1)	7460(2)	83(1)
O(5)	8325(1)	10109(1)	5135(2)	75(1)
O(1W)	9023(1)	11039(1)	5937(2)	67(1)
N(1)	8748(1)	10996(1)	3326(2)	60(1)
C(2)	8967(1)	11027(1)	2235(2)	59(1)
C(3)	9492(1)	11096(1)	2300(2)	56(1)
N(4)	9685(1)	11091(1)	3438(2)	57(1)
C(5)	10150(1)	11149(1)	3523(2)	62(1)
C(6)	10360(1)	11148(1)	4806(3)	72(1)
N(7)	10059(1)	11084(1)	5745(2)	73(1)
C(8)	9755(1)	11155(1)	1225(3)	72(1)
C(9)	10231(1)	11216(1)	1327(3)	83(1)
C(10)	10439(1)	11210(1)	2495(3)	76(1)
C(11)	10210(1)	11083(1)	7046(3)	87(1)
C(12)	10357(1)	10593(2)	7478(3)	109(1)
C(13)	9949(1)	10264(1)	7723(3)	97(1)
C(14)	9315(1)	10166(1)	9197(3)	94(1)
C(15)	8861(1)	10360(1)	8748(3)	83(1)
C(16)	8527(2)	9859(1)	7179(3)	100(1)
C(17)	8575(2)	9762(1)	5833(3)	102(1)
C(18)	8388(1)	10036(1)	3841(3)	81(1)
C(19)	8114(1)	10397(1)	3124(3)	77(1)
C(20)	8248(1)	10902(1)	3434(2)	67(1)

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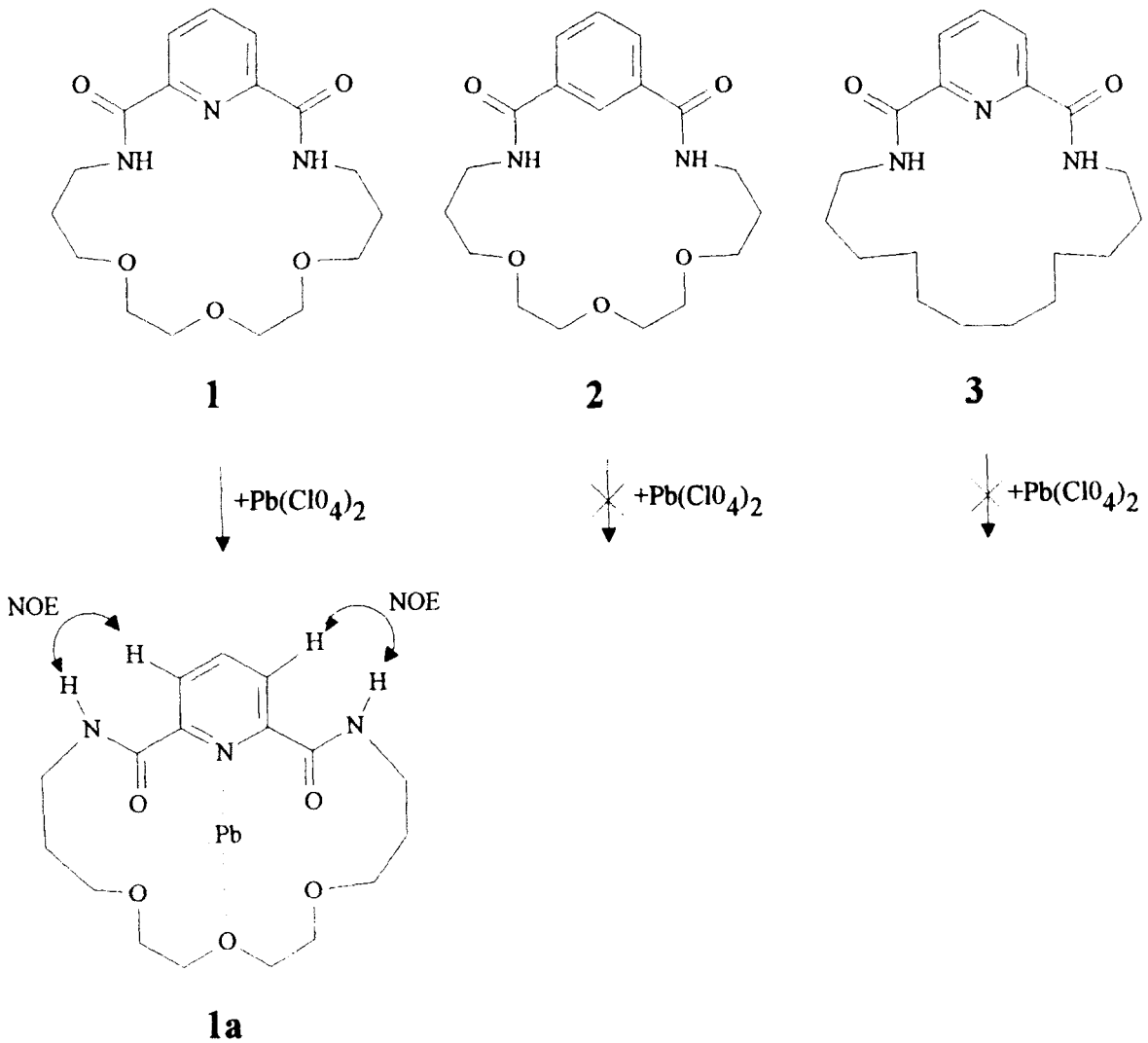

SCHEME 1

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