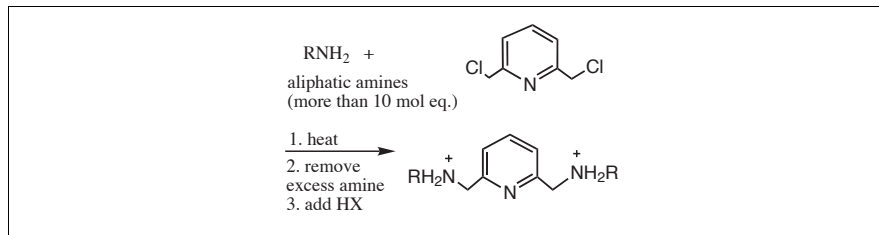


Facile Preparation and the Crystal Structure of *N,N'*-Dialkyl-2,6-pyridinedimethanaminium Halide

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Received June 9, 2005



A facile preparation and the crystal structures of *N,N'*-dialkyl-2,6-pyridinedimethanaminium halides were described. Direct substitution reactions were convenient to prepare specifically secondary diamines using 2,6-bis(chloromethyl)-pyridine and 10 equivalents molar of primary alkylamines. Hydrogen halide salts were obtained in good yields and the crystal structures of three *N,N'*-dialkyl-2,6-pyridinedimethanaminium salts were determined by the X-ray diffraction method. A concoid structure around the pyridine ring was observed commonly in the three salts. Acidity constants of the three salts were determined. Since the pKa values of the salts were slightly smaller than those of several common triamines previously reported, the acidities did not correlate with the concoid structure directly. This is probably due to electrostatic interaction of the two protonated amino groups, furthermore the central pyridine nitrogen was not protonated in all the ligands,

J. Heterocyclic Chem., **43**, 549 (2006).

Many catalysts or enzymes in biological systems efficiently work and perform various kinds of reactions in nearly neutral conditions and at body temperature. R. H. Holm reviewed structural and functional aspects of metal sites in detail [1]. At the reaction site in most biological systems, specific metal ions perform an essential role in biological processes with great efficiency. Imitating biological systems, biomimetic chemistry developed very much in coordination chemistry using tridentate or tetradentate ligands. These ligands were expected to form metal complexes in various reactions similar to biological systems, because such systems have to form reactive intermediates and work even in low concentrations such as *in vivo*. Since the metal complexes in the intermediates have to be reactive, they should be relatively labile and not too stable. Proper three dimensional structures of intermediates are essential in such biomimetic systems. Since metal ion competes with proton for ligands in order to form intermediates and then nucleophilic reactions on the intermediates proceed in many biological systems, protonation processes are also very important.

Here we report acidity constants and crystal structures of *N,N'*-dialkyl-2,6-bis(aminomethyl)pyridines containing pyridine rings. These basic data are expected to contribute

to knowledge in biomimetic model. Since the pyridine nitrogen atoms are very weak base and protected by adjacent positive charges of aminium ions, deprotonated forms are assumed to predominate in neutral conditions as disclosed by the crystal structures of present study. *N,N'*-Dialkyl-2,6-pyridinedimethanamines (**IIIa-IIIg**) were prepared *via* facile experimental processes as shown in Figure 1. Due to high substitution reactivity of the specific position activated by the electron withdrawing pyridine ring, *N,N'*-dialkyl-2,6-pyridinedimethanamines could be obtained as hydrogen halide salts in good yields. These difunctionalized pyridine derivatives are widely used as versatile building blocks for the syntheses of macrocyclic compounds and their metal complexes [2-5].

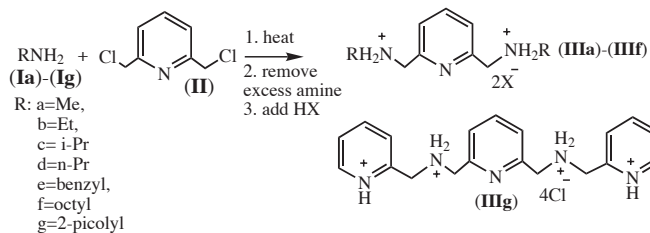


Figure 1. Substitution reaction of 2,6-bis(chloromethyl)pyridine with primary aliphatic amines

Results and Discussion.

I. Synthesis.

In order to obtain specifically alkylated amines, sure synthetic processes had been utilized generally in which metal diethylphosphoylamidate or tosylamidate were alkylated and deprotected. These processes are sound routes, but need 4 steps starting from primary amines and hard works in deprotection steps. Marchand *et al.* described direct substitution reaction of 2,6-bis(chloromethyl)pyridine with benzylamine to prepare *N,N'*-dibenzyl-2,6-pyridinedimethamine [6]. They used 6 equivalents of benzylamine against 2,6-bis(chloromethyl)pyridine and excess amine was removed under reduced pressure after a period of reaction and the liquid material was used for the next synthetic steps. We applied this direct substitution reaction to other aliphatic amines for the preparation of a series of *N,N'*-dialkyl-2,6-pyridine-dimethanaminium salts using ten equivalent of primary amines (5 equivalent per one reaction site). Using various primary amines, we could prepare the hydrogen halide salts of the ligands in good yields (**IIIa-IIIg**). This direct substitution reaction followed by isolation of halide salts is expected to be also applicable to prepare other *N,N'*-dialkyl-2,6-pyridinedimethanaminium salts. Primary textbooks of organic chemistry tell us that general alkylation reactions of primary amines with alkyl halide will give a complex mixture of variously alkylated products. Since primary alkyl amines are generally cheap and available in excess amount, direct substitution reaction is advantageous. Using large excess primary amines as described here makes possible the substitution reaction while avoiding the formation of a variously alkylated mixture. Similar substitution reactions at the positions activated by aromatic groups are expected to be successful as in such case. Similar attempts to prepare *N,N'*-diphenyl-2,6-pyridine-dimethanaminium salts with aniline were unsuccessful resulting in black colored materials.

2. Acidity of *N,N'*-Dialkyl-2,6-pyridinedimethanaminium Salts.

Acidity constants of the three salts were determined with potentiometric method.

Typical titration curves of **IIIb** and **IIIg** are shown in Figure 2a and Figure 2b. Since basicity of central pyridine nitrogens are very weak, the ligands are not protonated and free. But in the case of **IIIg**, two pyridine nitrogens on branch are protonated as confirmed by X-ray analysis and elemental analysis (pK_{a3} and pK_{a4} of **IIIg** had been reported already by Gruenwedel [7]). The pK_a values of three ligands (**IIIb**, **IIId** and **IIIg**) are listed in Table 1. Although all the N-H protons form hydrogen

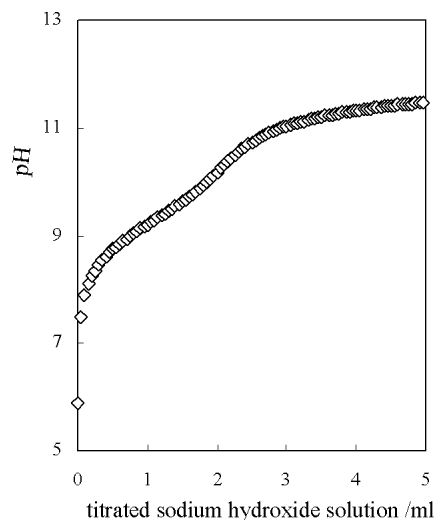


Figure 2a. The titration curve of py-2et • 2HBr (**IIIb**).

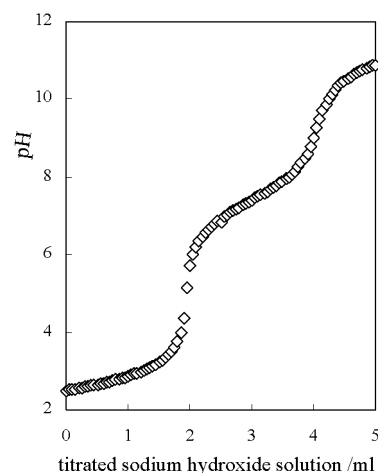


Figure 2b. The titration curve of py-2pic • 4HCl (**IIIg**).

bonds with halides or water and are stabilized forming cancroid crystal structure, the stabilized effects are not assumed to affect pK_a values. We expected that these ligands could catch protons more strongly than open triamines due to their unique structure. On the contrary to our expectation, pK_a values of **IIIa-IIIf** are slightly smaller than those of open chain triamine [8]. In the case

Table 1
 pK_a values determined by the titration method

	py-2et	py-2pr	py-2pic
pK_{a1}	8.84	8.85	—
pK_{a2}	9.59	9.36	2.43
pK_{a3}	—	—	7.09
pK_{a4}	—	—	7.70

of **IIIg**, two pyridine rings on the side chain are protonated. When **IIIg** was dissolved in water, the first proton dissociated completely and pK_{a1} was not observed. We could determine pK_{a2} in addition to Gruenwedel's results. The difference between the two kinds of pyridine rings is assumed to be due to electrostatic repulsion. In protonation reactions, the two aliphatic nitrogen atoms will be protonated preferentially and the central pyridine nitrogen atom last. Furthermore, the central pyridine rings are surrounded by two positive charges in **IIIa-IIIg** and cannot be protonated. Since similar strong prohibitions of protonation by electrostatic repulsion had been also reported in quinoxaline derivatives [9], it is true in our case. Since the two pyridine rings on the side chain are prohibited only very weakly, they are protonated easily.

3. Crystal Structure of **IIIc**, **IIIe**, and **IIIg**.

Hydrogen halide salts of all the ligands were crystallized in ethanol or methanol and could be isolated easily. Three of them gave single crystals and their crystal structures could be determined by the X-ray diffraction method. The crystallographic data are summarized in Table 2. The atomic coordinates of all atoms are listed in Table 3-5. Essential bond distances and angles, torsion angles and hydrogen bonds are listed

in Table 6-8. The three ORTEP drawings of **IIIc**, **IIIe**, and **IIIg** are shown in Figure 4-6 and the cancriod structures surrounding the central pyridine ring of the ligands are shown. In Figure 6a and 6b are also shown two drawings (one is perpendicular to molecular plane and another one along the plane). In all the drawings amino hydrogen atoms relating to hydrogen bonds are shown. Assuming that negative pole in the pyridine ring orients to the nitrogen atom, positive pole in two $N-H_2^+$ bonds on the side chain orient in the reverse direction. Thus the dipole of pyridine ring and the summated dipole of two dipole of $N-H_2^+$ bonds cancel each other out. As a whole, the hydrogen halide salts are assumed to be stabilized. These dipole-dipole electrostatic interactions result in the cancriod structure common to **IIIc-IIIg**. The ligands have a vacant space at the central part. In the case of **IIIc** and **IIIe**, halide ions are fixed above and below holding the molecular plane and form hydrogen bonds between $N-H$ groups and halide ions. In the case of **IIIg**, three chloride ions guard the "bottom" side of the molecular plane and one chloride the "upper" side. Interatomic distances between the nitrogen(D) and halide ions(A) are 2.97-3.13($N---Cl$) and 3.2-3.4 angstrom ($N---Br$) and bond angles($N-H---A$) are 160-176 degrees. Torsion angles around the the central pyridine ring disclose the conformation in detail. In **IIIe**, one benzene

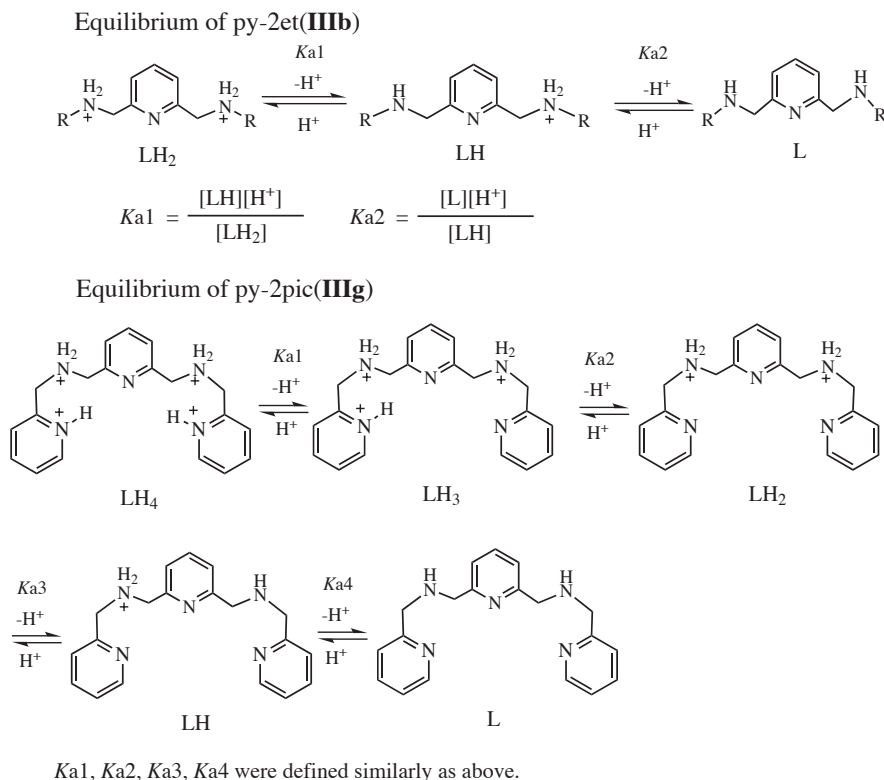


Figure 3. Equilibrium of variously protonated species.

Table 2
Crystallographic Data

Pyridinium salts	IIIc (R=CH(CH ₃) ₂)	IIIe (R=CH ₂ Ph)	IIIg (R=CH ₂ Py)
Formula	C ₁₃ H ₂₅ N ₃ Br ₂	C ₂₁ H ₂₅ N ₃ Br ₂	C ₁₉ H ₂₇ Cl ₄ N ₅ O
fw	383.17	479.26	483.27
Crystal system	monoclinic	triclinic	orthorhombic
space group	C2/c(#15)	P $\bar{1}$ (#2)	Pbcn(#60)
a/Å	18.035(5)	10.328(6)	16.439(8)
b/Å	13.765(5)	10.904(8)	21.010(9)
c/Å	17.054(5)	10.044(6)	13.404(6)
α /deg	90.0	93.03(7)	90.0
β /deg	127.44(2)	106.40(5)	90.0
γ /deg	90.0	87.02(5)	90.0
V/Å ³	3361(2)	3361(1)	4630(4)
Z	8	2	8
Dcalcd/g cm ⁻³	1.51	1.47	1.39
R ^a , Rw ^b	0.032, 0.040	0.035, 0.053	0.035, 0.050
No. of unique refl.(Rint=)	3855(0.034)	4967(0.021)	5334(0.011)
No. of observation(I>3 σ (I))	2513	3367	2717
($\Delta\rho$) _{max} /eÅ ⁻³	0.31	0.48	0.37
($\Delta\rho$) _{min} /eÅ ⁻³	-0.55	-0.99	-0.30
Crystal sizes/mm	0.25X0.70X0.60	0.55X0.60X0.40	0.80X0.10X0.30

$$^aR = (\|F_o - |F_c|| / \Sigma |F_o|), ^bR_w = [(\Sigma w(|F_o - |F_c||)^2 / \Sigma w F_o^2)^{1/2}], w = [\sigma_c^2(F_o) + (p^2/4)F_o^2]^{-1}, p = p\text{-factor}$$

ring orient itself in a perpendicular conformation and another ring inclines from the plane of central pyridine ring by about 33°. In **IIIg**, one pyridine ring has a perpendicular conformation and another one has a parallel conformation just "downstairs" from the plane. These two pyridine rings are protonated and the chloride ion held to the former one guards "upper" side of the plane. These structural details are shown in two ORTEP drawings (Figure 6a and 6b). One water molecule on a special position forms a hydrogen bond with a chloride ion. Consequently, all the hydrogen atoms in N-H and O-H groups of **IIIc-IIIg** are used to form hydrogen bonds with halide ions.

Table 3
Atomic coordinates and B_{eq}/B_{iso} of **IIIc**.

atom	x	y	z	B _{eq} /B _{iso}
Br(1)	0.82193(3)	0.17078(3)	0.70059(3)	3.478(8)
Br(2)	0.42293(3)	0.19116(3)	0.50836(3)	3.791(8)
N(1)	0.5994(2)	0.1779(2)	0.4942(2)	2.98(6)
N(2)	0.64464(19)	0.3524(2)	0.5786(2)	2.90(5)
N(3)	0.7330(2)	0.3284(2)	0.7751(2)	3.32(6)
C(1)	0.5964(2)	0.0790(2)	0.4546(2)	3.57(8)
C(2)	0.4979(2)	0.0547(3)	0.3659(3)	4.77(10)
C(3)	0.6674(2)	0.0712(3)	0.4344(3)	5.02(11)
C(4)	0.5712(2)	0.2622(2)	0.4260(2)	3.36(8)
C(5)	0.5924(2)	0.3569(2)	0.4803(2)	2.83(7)
C(6)	0.5599(2)	0.4436(2)	0.4283(2)	3.59(8)
C(7)	0.5828(2)	0.5282(2)	0.4809(3)	3.87(9)
C(8)	0.6365(2)	0.5252(2)	0.5828(2)	3.39(8)
C(9)	0.6673(2)	0.4355(2)	0.6286(2)	2.97(7)
C(10)	0.7334(2)	0.4274(2)	0.7399(2)	3.76(8)
C(11)	0.6478(2)	0.3005(2)	0.7668(2)	3.72(8)
C(12)	0.6554(3)	0.1945(3)	0.7913(4)	5.68(13)

Table 3 (continued)

atom	x	y	z	B _{eq} /B _{iso}
C(13)	0.6403(3)	0.3644(4)	0.8335(4)	6.48(15)
H(1)	0.6176	0.0360	0.5116	4.01
H(2)	0.4565	0.0551	0.3897	5.17
H(3)	0.4995	-0.0103	0.3451	5.17
H(4)	0.4740	0.0921	0.3083	5.16
H(5)	0.7274	0.0778	0.4948	5.96
H(6)	0.6502	0.1174	0.3869	5.97
H(7)	0.6683	0.0049	0.4112	5.97
H(8)	0.5633	0.1773	0.5137	3.47
H(9)	0.6578	0.1917	0.5452	3.45
H(10)	0.5102	0.2538	0.3811	3.93
H(11)	0.6063	0.2532	0.4004	3.94
H(12)	0.5313	0.4447	0.3659	4.36
H(13)	0.5593	0.5971	0.4501	4.77
H(14)	0.7206	0.4700	0.7744	4.26
H(15)	0.7976	0.4475	0.7601	4.25
H(16)	0.7843	0.3197	0.8373	3.75
H(17)	0.7400	0.2874	0.7440	3.75
H(18)	0.5976	0.3165	0.7005	4.36
H(19)	0.6558	0.1550	0.7398	6.95
H(20)	0.6067	0.1727	0.7871	6.95
H(21)	0.7076	0.1895	0.8535	6.95
H(22)	0.5933	0.3395	0.8340	8.81
H(23)	0.6980	0.3635	0.9007	8.81
H(24)	0.6312	0.4330	0.8145	8.81
H(25)	0.6553	0.5805	0.6180	4.18

$$B_{eq} = 8/3 \pi^2 (U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos \gamma + 2U_{13}(aa^*cc^*)\cos \beta + 2U_{23}(bb^*cc^*)\cos \alpha)$$

EXPERIMENTAL

Materials and Instruments. The necessary primary amines (**I**) were purchased from chemical companies and were used

Table 4
Atomic coordinates and B_{eq}/B_{iso} of **IIIe**.

atom	x	y	z	B_{eq}/B_{iso}
Br(1)	0.18195(4)	-0.02402(3)	0.37750(5)	4.736(9)
Br(2)	0.23655(4)	0.50615(3)	0.42850(5)	4.701(9)
N(1)	0.0741(2)	0.2497(2)	0.4442(3)	3.92(6)
N(2)	0.3245(3)	0.2384(2)	0.6455(3)	4.15(6)
N(3)	0.5161(2)	0.3047(2)	0.5295(3)	4.16(6)
C(1)	-0.0783(3)	0.2833(3)	0.2070(4)	4.47(8)
C(2)	-0.0663(4)	0.1785(3)	0.1258(5)	5.35(10)
C(3)	-0.0824(5)	0.1862(5)	-0.0157(5)	6.59(13)
C(4)	-0.1130(4)	0.2944(5)	-0.0794(5)	6.71(13)
C(5)	-0.1262(5)	0.3983(5)	-0.0029(6)	7.26(14)
C(6)	-0.1076(5)	0.3945(4)	0.1408(6)	6.94(13)
C(7)	-0.0672(3)	0.2746(4)	0.3571(4)	5.43(10)
C(8)	0.0835(4)	0.2362(4)	0.5941(4)	4.94(9)
C(9)	0.2199(4)	0.1852(3)	0.6695(3)	4.37(8)
C(10)	0.2370(5)	0.0875(4)	0.7553(5)	6.03(12)
C(11)	0.3650(6)	0.0414(4)	0.8140(5)	6.87(14)
C(12)	0.4759(5)	0.0945(4)	0.7906(4)	6.10(11)
C(13)	0.4500(3)	0.1942(3)	0.7048(3)	4.24(7)
C(14)	0.5608(3)	0.2618(4)	0.6747(4)	4.74(8)
C(15)	0.5037(4)	0.2012(3)	0.4205(4)	4.63(8)
C(16)	0.4612(3)	0.2497(3)	0.2787(4)	4.23(8)
C(17)	0.3314(4)	0.2342(4)	0.1938(5)	5.25(9)
C(18)	0.2929(4)	0.2793(4)	0.0618(4)	5.99(11)
C(19)	0.3820(5)	0.3370(4)	0.0105(5)	6.07(11)
C(20)	0.5108(5)	0.3520(4)	0.0927(5)	6.55(13)
C(21)	0.5502(4)	0.3105(4)	0.2264(5)	5.68(10)
H(1)	-0.0375	0.1052	0.1750	6.27
H(2)	-0.1038	0.1159	-0.0696	7.66
H(3)	-0.1120	0.3095	-0.1917	7.84
H(4)	-0.1418	0.4883	-0.0465	8.33
H(5)	-0.1174	0.4542	0.1890	7.95
H(6)	-0.0864	0.3499	0.4078	6.40
H(7)	-0.1022	0.2072	0.3847	6.39
H(10)	0.0678	0.3231	0.6380	6.11
H(11)	0.0174	0.1775	0.5994	6.09
H(8)	0.1321	0.3111	0.4353	4.77
H(9)	0.1131	0.1807	0.4172	4.77
H(12)	0.1509	0.0589	0.7709	7.44
H(13)	0.3810	-0.0232	0.8774	8.27
H(14)	0.5767	0.0637	0.8172	7.06
H(17)	0.4353	0.3477	0.5114	5.00
H(18)	0.5737	0.3590	0.5213	4.99
H(19)	0.4405	0.1404	0.4380	5.59
H(20)	0.6020	0.1564	0.4485	5.60
H(21)	0.2540	0.1945	0.2351	6.28
H(22)	0.1982	0.2566	0.0110	6.92
H(23)	0.3410	0.3822	-0.0865	7.15
H(24)	0.5659	0.3909	0.0602	8.08
H(25)	0.6386	0.3156	0.2826	6.79
H(15)	0.5768	0.3413	0.7356	5.53
H(16)	0.6429	0.2080	0.6763	5.53

without further purification. 2,6-Bis(chloromethyl)pyridine(**II**) were obtained from Tokyo Kasei Kogyo Co. Ltd. Infrared spectra were recorded on a JASCO FT/IR 300E spectrometer. ^1H and ^{13}C NMR spectra were obtained on a JEOL GSX-400 spectrometer at 400 MHz and 100 MHz, respectively. The chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane in CDCl_3 , DSS or dioxane in D_2O . As many assignments as possible of the peaks in spectral data are shown. Elemental analyses were performed at the Ibaraki University

Instrumental Analysis Center with YANACO MT-5 CHN Corder.

Table 5
Atomic coordinates and B_{eq}/B_{iso} and occupancy of **IIIg**

atom	x	y	z	B_{eq}	occ
Cl(1)	0.68451(5)	0.06252(4)	0.05796(6)	4.344(19)	
Cl(2)	0.81410(6)	0.13776(4)	0.36412(6)	4.68(2)	
Cl(3)	0.86668(6)	0.18829(5)	-0.13018(8)	5.60(2)	
Cl(4)	0.60430(6)	-0.14760(4)	0.12927(9)	5.29(2)	
O(1)	0.50000(10)	-0.2455(2)	0.25000(10)	8.89(15)	1/2
N(1)	0.71219(19)	0.21520(12)	-0.0095(2)	4.22(7)	
N(2)	0.8373(2)	0.13824(13)	0.1243(2)	6.00(9)	
N(3)	0.87260(14)	0.01537(12)	0.1387(2)	3.38(5)	
N(4)	0.73577(16)	-0.05280(12)	0.18334(19)	3.27(5)	
N(5)	0.66599(17)	0.05662(13)	0.3513(2)	4.13(6)	
C(1)	0.7287(2)	0.21588(14)	0.0883(2)	4.14(8)	
C(2)	0.6665(3)	0.2261(2)	0.1529(3)	6.11(11)	
C(3)	0.5898(3)	0.2340(2)	0.1179(4)	7.53(15)	
C(4)	0.5733(2)	0.2305(2)	0.0180(5)	7.25(14)	
C(5)	0.6369(2)	0.2217(2)	-0.0462(3)	5.87(11)	
C(6)	0.8153(2)	0.20541(16)	0.1191(2)	4.64(8)	
C(7)	0.9233(2)	0.12222(18)	0.1240(2)	4.72(8)	
C(8)	0.9386(2)	0.05218(16)	0.1288(2)	3.53(7)	
C(9)	1.01618(19)	0.0276(2)	0.1216(2)	4.09(8)	
C(10)	1.0259(2)	-0.0369(2)	0.1236(2)	4.48(9)	
C(11)	0.9593(2)	-0.07527(18)	0.1332(2)	4.18(8)	
C(12)	0.8834(2)	-0.04766(14)	0.1407(2)	3.35(6)	
C(13)	0.8085(2)	-0.08813(14)	0.1467(2)	3.95(7)	
C(14)	0.7384(2)	-0.03645(16)	0.2914(2)	3.87(7)	
C(15)	0.6613(2)	-0.00521(17)	0.3248(2)	3.50(7)	
C(16)	0.5873(2)	-0.03503(18)	0.3348(2)	4.11(8)	
C(17)	0.5210(2)	-0.0010(2)	0.3705(2)	4.67(8)	
C(18)	0.5291(2)	0.0615(2)	0.3961(2)	5.28(10)	
C(19)	0.6032(2)	0.0895(2)	0.3867(2)	5.18(10)	
H(1)	0.6751	0.2217	0.2224	7.33	
H(2)	0.5483	0.2398	0.1548	9.04	
H(3)	0.5214	0.2311	-0.0084	8.69	
H(4)	0.6281	0.2167	-0.1149	7.04	
H(5)	0.7544	0.2054	-0.0455	5.06	
H(6)	0.8511	0.2289	0.0741	5.58	
H(7)	0.8221	0.2209	0.1830	5.59	
H(8)	0.8474	0.1388	0.0406	7.23	
H(9)	0.8031	0.1126	0.1036	7.19	
H(10)	0.9403	0.1411	0.1718	5.67	
H(11)	0.9520	0.1447	0.0644	5.68	
H(12)	1.0582	0.0560	0.1126	4.90	
H(13)	1.0765	-0.0529	0.1167	5.37	
H(14)	0.9665	-0.1187	0.1326	5.01	
H(15)	0.8193	-0.1242	0.1971	4.74	
H(16)	0.7922	-0.1033	0.0868	4.72	
H(17)	0.7300	-0.0181	0.1461	3.93	
H(18)	0.6811	-0.0806	0.1742	3.95	
H(19)	0.7423	-0.0751	0.3255	4.64	
H(20)	0.7854	-0.0093	0.3015	4.64	
H(21)	0.5829	-0.0802	0.3178	4.93	
H(22)	0.4692	-0.0194	0.3812	5.61	
H(23)	0.4886	0.0812	0.4242	6.33	
H(24)	0.6151	0.1336	0.4000	6.22	
H(25)	0.7187	0.0761	0.3536	4.96	
H(26)	0.5368	-0.2218	0.2167	10.66	

$$B_{eq} = 8/3 \pi^2 (U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*) \cos \gamma + 2U_{13}(aa^*cc^*) \cos \beta + 2U_{23}(bb^*cc^*) \cos \alpha)$$

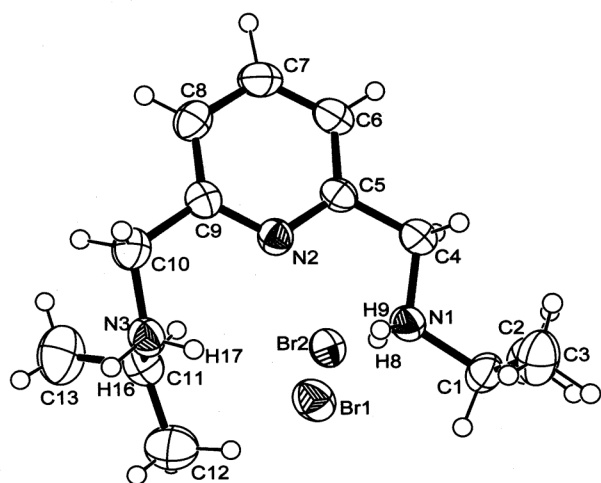
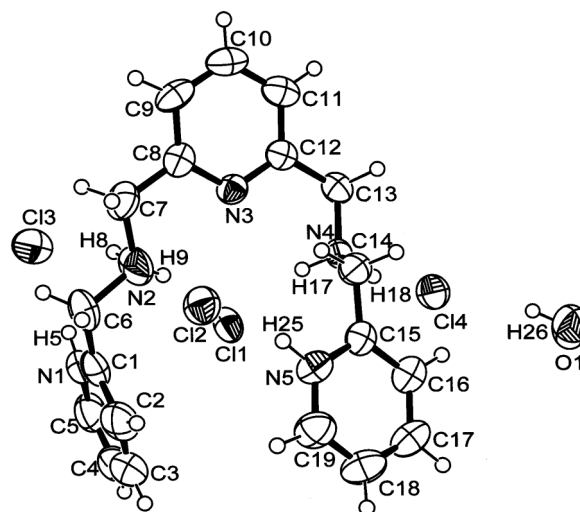
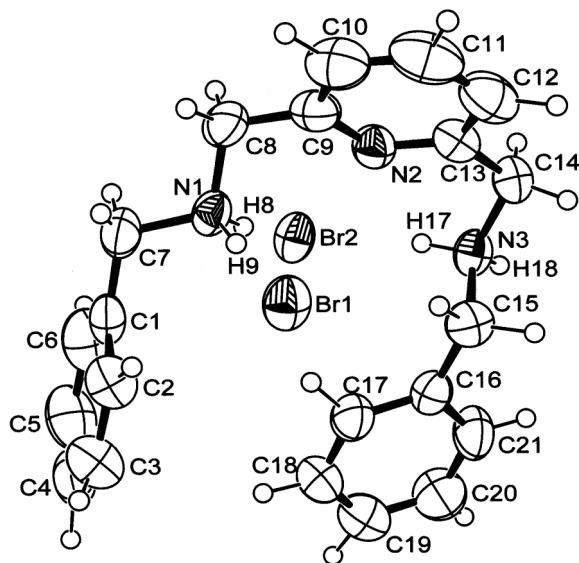
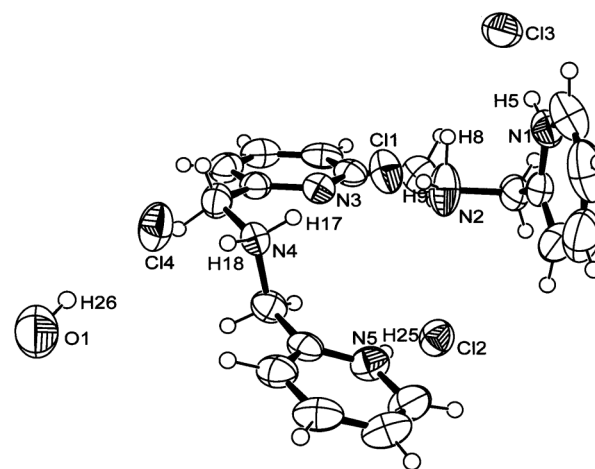
Figure 4. ORTEP drawing and numbering systems of **IIIc**.Figure 6a. ORTEP drawing of **IIIg** perpendicular to molecular plane and numbering systemFigure 5. ORTEP drawing and numbering systems of **IIIe**.Figure 6b. ORTEP drawing of **IIIg** along the molecular plane and groups relating to hydrogen bonds.

Table 6

Bond lengths (Å), angles(°), torsion angles(°) and hydrogen bonds of **IIIc**.

atom	atom	distance	atom	atom	distance
N(1)	C(4)	1.496(4)	N(2)	C(5)	1.335(4)
N(2)	C(9)	1.334(4)	N(3)	C(10)	1.492(5)
C(4)	C(5)	1.507(5)	C(9)	C(10)	1.512(5)

atom	atom	atom	angle	atom	atom	atom	angle
C(4)	N(1)	C(1)	116.7(3)	N(1)	C(4)	C(5)	110.7(3)
N(2)	C(5)	C(4)	116.9(3)	C(9)	N(2)	C(5)	118.1(3)
N(2)	C(9)	C(10)	116.1(3)	N(3)	C(10)	C(9)	112.3(2)

atom1	atom2	atom3	atom4	angle	atom1	atom2	atom3	atom4	angle
C(9)	N(2)	C(5)	C(4)	177.6(4)	C(5)	N(2)	C(9)	C(10)	-174.8(4)
N(1)	C(4)	C(5)	N(2)	10.6(5)	N(2)	C(9)	C(10)	N(3)	-22.3(6)

The sign is positive if when looking from atom 2 to atom 3 a clock-wise motion of atom 1 would superimpose it on atom 4.

Table 6 (continued)

Possible hydrogen bonds						
D	H	A	D...A	D-H	H...A	D-H...A
N(1)	H(8)	Br(2)	3.338(6)	0.893	2.485	160.5(2)
N(1)	H(9)	Br(1)	3.364(3)	0.888	2.516	160.5(3)
N(3)	H(16)	Br(2) ¹	3.325(3)	0.895	2.432	175.8(4)
N(3)	H(17)	Br(1)	3.372(5)	0.835	2.577	159.7(2)

Note. 1. Symmetry operator: X+1/2,-Y+1/2,Z+1/2. 2. Estimated standard deviations (esd's) are shown in the parentheses.

Acidity constants were determined by potentiometric measurements with a Horiba pH meter F-13 [9]. Protonated crystals were dissolved in water and NaOH solution (0.02 M) was titrated. At least three titration experiments (of about 100 data points each) were performed in the pH range 5.5-11.5. The computer program HYPERQUAD was used to calculate the equilibrium constants from electromotive force data. All titrations were treated either as separate entities for each system without significant variation in values of determined constants.

X-Ray diffraction data were obtained at room temperature with a Rigaku AFC7R diffractometer with graphite monochromated Mo-K α (0.71069 Å) radiation and a rotating anode generator. Single crystals of the hydrochlorides or hydrobromides salts were obtained from a mixed solvent of methanol and ethanol and all of them were stable during measurement. In the case of **IIIc** and **IIIe**, absorption correction could not be done. All the crystal structures were solved by the direct method [10] and refined using a package program,

Table 7

Bond lengths (Å), angles(°), torsion angles and hydrogen bonds of **IIIe**.

Atom	atom	distance	atom	atom	distance
N(1)	C(7)	1.494(4)	N(1)	C(8)	1.496(5)
N(2)	C(9)	1.338(5)	N(2)	C(13)	1.340(5)
N(3)	C(14)	1.493(5)	N(3)	C(15)	1.514(5)
C(1)	C(7)	1.487(6)	C(8)	C(9)	1.492(5)
C(13)	C(14)	1.501(6)	C(15)	C(16)	1.485(5)
C(16)	C(15)	1.485(5)			

Bond angles (°)

atom	atom	atom	angle	atom	atom	atom	angle
N(1)	C(7)	C(1)	113.3(3)	C(8)	N(1)	C(7)	112.9(3)
N(1)	C(8)	C(9)	110.3(3)	N(2)	C(9)	C(8)	115.6(3)
C(13)	N(2)	C(9)	119.1(3)	N(2)	C(13)	C(14)	115.2(3)
N(3)	C(14)	C(13)	109.9(2)	C(15)	N(3)	C(14)	113.3(3)
N(3)	C(15)	C(16)	110.8(3)				

Torsion Angles(°)

atom1	atom2	atom3	atom4	angle	atom1	atom2	atom3	atom4	angle
C(8)	N(1)	C(7)	C(1)	-177.8(3)	C(7)	N(1)	C(8)	C(9)	167.8(3)
C(13)	N(2)	C(9)	C(8)	-177.2(3)	C(9)	N(2)	C(13)	C(14)	-178.5(3)
C(15)	N(3)	C(14)	C(13)	-70.3(4)	C(14)	N(3)	C(15)	C(16)	-179.1(3)
N(1)	C(8)	C(9)	N(2)	47.2(4)	N(2)	C(13)	C(14)	N(3)	-35.8(4)

The sign is positive if when looking from atom 2 to atom 3 a clock-wise motion of atom 1 would superimpose it on atom 4.

Possible Hydrogen bonds

D	H	A	D...A	D-H	H...A	D-H...A
N(1)	H(8)	Br(2)	3.367(3)	0.945	2.447	164.8(3)
N(1)	H(9)	Br(1)	3.236(3)	0.900	2.356	165.4(3)
N(3)	H(17)	Br(2)	3.480(2)	0.912	2.590	165.3(3)
N(3)	H(18)	Br(2) ¹	3.287(3)	0.884	2.433	162.7(3)

Note) 1. Symmetry operator: -X+1, -Y+1, -Z+1. 2. Estimated standard deviations (esd's) are shown in the parentheses.

Table 8
Bond lengths (Å), bond angles(°), torsion angles and hydrogen bonds of **IIIg**.

atom	atom	distance	atom	atom	distance
N(1)	C(1)	1.339(4)	N(1)	C(5)	1.338(5)
N(2)	C(6)	1.459(4)	N(2)	C(7)	1.453(4)
N(3)	C(8)	1.338(4)	N(3)	C(12)	1.336(4)
N(4)	C(13)	1.491(4)	N(4)	C(14)	1.489(4)
N(5)	C(15)	1.349(4)	N(5)	C(19)	1.330(4)
C(1)	C(2)	1.357(6)	C(1)	C(6)	1.499(5)
C(7)	C(8)	1.494(5)	C(12)	C(13)	1.498(4)
C(14)	C(15)	1.496(4)	C(15)	C(16)	1.376(4)

atom	atom	atom	angle	atom	atom	atom	angle
N(2)	C(6)	C(1)	113.0(2)	C(7)	N(2)	C(6)	117.7(2)
N(2)	C(7)	C(8)	113.0(2)	N(3)	C(8)	C(7)	116.0(2)
C(12)	N(3)	C(8)	117.8(2)	N(3)	C(12)	C(13)	117.0(2)
N(4)	C(13)	C(12)	113.2(2)	C(14)	N(4)	C(13)	114.3(2)
N(4)	C(14)	C(15)	111.5(2)	N(5)	C(15)	C(14)	116.9(2)

atom1	atom2	atom3	atom4	angle	atom1	atom2	atom3	atom4	angle
C(6)	N(2)	C(7)	C(8)	-179.6(3)	C(12)	N(3)	C(8)	C(7)	178.3(2)
C(8)	N(3)	C(12)	C(13)	-177.1(2)	C(14)	N(4)	C(13)	C(12)	-71.6(3)
C(13)	N(4)	C(14)	C(15)	-176.0(2)	N(1)	C(1)	C(6)	N(2)	-83.5(3)
C(2)	C(1)	C(6)	N(2)	96.7(4)	C(1)	C(2)	C(3)	C(4)	1.5(6)
N(2)	C(7)	C(8)	N(3)	-3.8(4)	N(3)	C(12)	C(13)	N(4)	-19.3(4)
C(11)	C(12)	C(13)	N(4)	163.5(2)	N(4)	C(14)	C(15)	N(5)	-112.2(3)

The sign is positive if when looking from atom 2 to atom 3 a clock-wise motion of atom 1 would superimpose it on atom 4.

Possible hydrogen bonds

D	H	A	D...A	D-H	H...A	D-H...A
N(5)	H(25)	Cl(2)	2.977(2)	0.959	2.039	165.5(3)
N(2)	H(9)	Cl(1)	3.104(3)	0.826	2.299	164.8(3)
N(1)	H(5)	Cl(3)	3.064(3)	0.869	2.197	174.8(3)
N(4)	H(18)	Cl(4)	3.027(2)	1.079	1.984	161.6(2)
N(4)	H(17)	Cl(1)	3.067(2)	0.889	2.196	166.2(2)
O(1)	H(26)	Cl(4)	3.129(2)	0.903	2.243	166.9(3)

Note. Estimated standard deviations (esd's) are shown in the parentheses. They are not calculated when all atoms have an esd=0.0.

CrystalStructure [11]. All the non-hydrogen atoms were refined anisotropically. Although the positions of almost all the hydrogen atoms were determined from a difference Fourier maps, all the hydrogen atoms were refined using a riding model at the final stage of refinement.

Preparation of *N,N'*-Dimethyl-2,6-bis(aminomethyl)pyridine and the Hydrogen Chloride Salt.

Aqueous methylamine (40 %) (15 ml, about 30 mmol) was added to 2,6-bis(chloromethyl)pyridine (0.176 g, 1 mmol) in a flask and the flask was capped with a glass stopper. The solid, bis(chloromethyl)pyridine, dissolved completely after 2 h. The mixture was stirred at room temperature (1-2 days). Since the spot of bis(chloromethyl)pyridine disappeared on TLC, the reaction is assumed to end. Aqueous solution of NaOH (0.865 g in 20 ml of water) was added and the organic phase separated. The mixture was concentrated under a reduced pressure with an evaporator in a water bath. The organic component was extracted completely with chloroform. After the chloroform solution was filtered and the solvent was evaporated, the residual oil was found to be almost pure *N,N'*-dimethyl-2,6-

bis(aminomethyl)pyridine as confirmed by ¹H NMR. Yield 0.165 g (65 %).

Conc. HCl solution (2 ml) was added to the above obtained oil and the mixture was dissolved in ethanol. Diethyl ether was added to the ethanol solution. After a period, the hydrochloride salt was crystallized and filtered to yield 2.0 g (84 %) of **IIIa**. IR (KBr, cm⁻¹): 2647-2422(many peaks, ν_{NH₂⁺}), 1598-1576(two peaks) and 1466-1413(three peaks, δ_{NH₂⁺}). ¹H-NMR(DMSO): 2.60(s,6H), 4.35(s,4H), 7.48(d, *J*=7.9, 2H), 7.95(t, *J*=7.9, 1H). ¹³C-NMR(DMSO): 32.3, 51.0, 122.1, 138.4, 151.1.

Anal. Calcd. for C₉H₁₇N₃Cl₂: C, 45.39; H, 7.19; N, 17.64. Found: C, 45.42; H, 7.09; N, 17.65.

General Procedure for the Preparation of *N,N'*-Dialkyl-2,6-bis(aminomethyl)pyridine (**IIIb-IIIg**).

A mixture of 2,6-bis(chloromethyl)pyridine(1 eq.) and primary amines(10-20 mol eq.) in benzene was stirred overnight at room temperature. In the case of **IIIb**, benzene solution of ethylamine (70 %) was prepared using anhydrous ethylamine (purchased from Tokyo Kasei Kogyo) and dry benzene. More than five molar equivalents of amine were used for each reaction

site. After the spot of 2,6-bis(chloromethyl)pyridine disappeared on TLC, the reaction mixture was concentrated under reduced pressure until all the volatile materials were removed up to 100 °C. From the residual materials were obtained hydrochloride or hydrobromide salts in good yields (more than 80 %) in different ways as follows. 1) To the residual materials was added excess hydrochloric acid. Obtained salts were recrystallized from methanol or from a mixture of methanol and ethanol to give colorless crystals of hydrochloride salts. 2) To the residual materials was added more than five times the HBr molar equivalents using a 48 % HBr aqueous solution. The crude HBr salts were warmed in a water bath and the mixture dissolved once. The solution was concentrated to about half volume and ethanol was added. From the cooled solution colorless crystal were obtained. Recrystallization from ethanol gave pure sample. In many cases, addition of ether to an ethanolic solution of hydrogen halide salts gave also good results.

N, N'-Diethyl-2,6-bis(aminomethyl)pyridinium bromide **IIIb**.

IR(cm^{-1}): 2801-2439(many peaks, $\nu_{\text{NH}_2^+}$), 1590-1556(three peaks) and 1440($\delta_{\text{NH}_2^+}$). $^1\text{H-NMR}$ (D_2O): 1.29(t, $J=6.8$, 6H), 3.14(q, $J=6.8$, 4H), 4.35(s, 4H), 7.38(d, $J=7.4$, 2H), 7.84(t, $J=7.4$, 1H). $^{13}\text{C-NMR}$ (D_2O): 11.4, 43.6, 50.8, 123.6, 139.9, 151.5.

Anal. Calcd. for $\text{C}_{11}\text{H}_{21}\text{N}_3\text{Br}_2$: C, 37.21; H, 5.96; N, 11.83. Found: C, 37.03; H, 5.87; N, 11.66

N, N'-Diisopropyl-2,6-bis(aminomethyl)pyridinium bromide **IIIc**.

IR(cm^{-1}): 2815-2434(many peaks, $\nu_{\text{NH}_2^+}$), 1593-1553(three peaks) and 1446($\nu_{\text{NH}_2^+}$); $^1\text{H-NMR}$ (D_2O): 1.42 (d, $J=6.5$, 12H), 3.57 (se, $J=6.5$, 2H), 4.45 (s, 4H), 7.48 (d, $J=7.5$, 2H), 7.93 (t, $J=7.5$, 1H). $^{13}\text{C-NMR}$ (DMSO): 18.5, 46.8, 49.6, 122.2, 138.3, 151.5.

Anal. Calcd. for $\text{C}_{13}\text{H}_{25}\text{N}_3\text{Br}_2$: C, 40.75; H, 6.05; N, 10.97. Found: C, 40.47; H, 6.40; N, 10.84.

N, N'-Di(1-propyl)-2,6-bis(aminomethyl)pyridinium bromide **III d**.

IR(cm^{-1}): 2940-2408(many peaks, $\nu_{\text{NH}_2^+}$), 1601-1558(three peaks) and 1428($\delta_{\text{NH}_2^+}$). $^1\text{H-NMR}$ (D_2O): 1.00 (t, $J=5$, 6H), 1.79 (sextet, $J=5$, 4H), 3.15 (t, $J=5$, 4H), 4.50 (s, 4H), 7.48 (d, $J=7.7$, 2H), 7.94 (t, $J=7.7$, 1H). $^{13}\text{C-NMR}$ (DMSO): 11.0, 18.9, 48.4, 49.6, 122.4, 138.5, 151.2.

Anal. Calcd. for $\text{C}_{13}\text{H}_{25}\text{N}_3\text{Br}_2$: C, 40.75; H, 6.05; N, 10.97. Found: C, 40.45; H, 6.47; N, 10.87.

N, N'-Dibenzyl-2,6-bis(aminomethyl)pyridinium chloride **IIIe**.

IR (cm^{-1}): 2817-2410(many peaks, $\nu_{\text{NH}_2^+}$), 1599-1555(three peaks) and 1455-1442(two peaks, $\nu_{\text{NH}_2^+}$). $^1\text{H-NMR}$ (DMSO): 4.27(s, 8H), 7.39(t, $J=6.4$, 6H), 7.42(d, $J=8.0$, 2H), 7.67 (m, 4H), 7.86 (t, $J=8.0$, 1H), 10.26 (s, 2H). $^{13}\text{C-NMR}$ (DMSO): 48.8, 49.5, 122.2, 128.3, 128.7, 130.4, 131.4, 138.2, 150.9.

Anal. Calcd. for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{Cl}_2$: C, 64.62; H, 6.46; N, 10.76. Found: C, 64.45; H, 6.50; N, 10.74.

N, N'-Dioctyl-2,6-bis(aminomethyl)pyridinium bromide **III f**.

IR (cm^{-1}): 2920, 2801-2439(broad peaks, $\nu_{\text{NH}_2^+}$), 1610-1559(three peaks) and 1440($\nu_{\text{NH}_2^+}$). $^1\text{H-NMR}$ (DMSO- d_6): 0.86

(t, $J=6.6$, 6H), 1.32 (broad singlet, 20H), 1.77 (quintet, $J=7.6$, 4H), 3.05 (quartet, $J=6.0$, 4H), 4.42 (t, $J=5.6$, 4H), 7.52 (d, $J=8$, 2H), 7.97 (t, $J=8$, 1H). $^{13}\text{C-NMR}$ (DMSO- d_6): 13.9, 22.1, 26.0, 28.5, 28.53, 31.2, 46.8, 49.6, 122.4, 138.5, 151.1.

Anal. Calcd for $\text{C}_{23}\text{H}_{45}\text{N}_3\text{Br}_2$: C, 52.78; H, 8.67; N, 8.03. Found: C, 52.75; H, 8.60; N, 7.97.

N, N'-Bis(2-picoly)l-2,6-bis(aminomethyl)pyridinium hydrochloride **IIIg**.

To a solution of 2,6-bis(chloromethyl)pyridine(1.764 g, 10 mmol) in DMF (20 ml) was added picolyl amine (10 ml, 0.097 mol) below 5 °C. The pink mixture was stirred for 2 days. Excess picolylamine was removed in a oil bath at 100 °C under reduced pressure(less than 10 mmHg). To the residual materials was added 1 ml of conc HCl. The hydrochloride salt crystallized from ethanol solution to yield 2.16 g(46 %). IR (cm^{-1}): 3045($\nu_{\text{aromatic C-H}}$), 2817-2410(many peaks, $\nu_{\text{NH}_2^+}$), 1640-1620(two peaks) and 1470-1442(two peaks, $\nu_{\text{NH}_2^+}$). $^1\text{H-NMR}$ (D_2O): 4.46(s, 4H), 4.62(s, 4H), 7.31(d, $J=8$, 2H), 7.76(t, $J=7.6$, 1H), 7.83(t, $J=6.4$, 2H), 7.97(d, $J=8.4$, 2H), 8.35(d, $J=8.0$, 2H), 8.64(d, $J=5.2$, 2H). $^{13}\text{C-NMR}$ (D_2O): 48.4, 51.5, 124.0, 128.1, 128.6, 140.2, 144.9, 146.0, 146.7, 150.7.

Anal. Calcd. for $\text{C}_{19}\text{H}_{25}\text{N}_3\text{Cl}_4 \cdot 0.5\text{H}_2\text{O}$: C, 48.12; H, 5.53; N, 14.77. Found: C, 48.05; H, 5.44; N, 14.64.

Acknowledgement.

A major part of this work was supported by a grant-in aid from the Ministry of Education, Science and Culture (Japan).

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