Syntheses of Armed-Macrocycles by Reductive Amination using $NaBH(OAc)_3$ under 1 MPa

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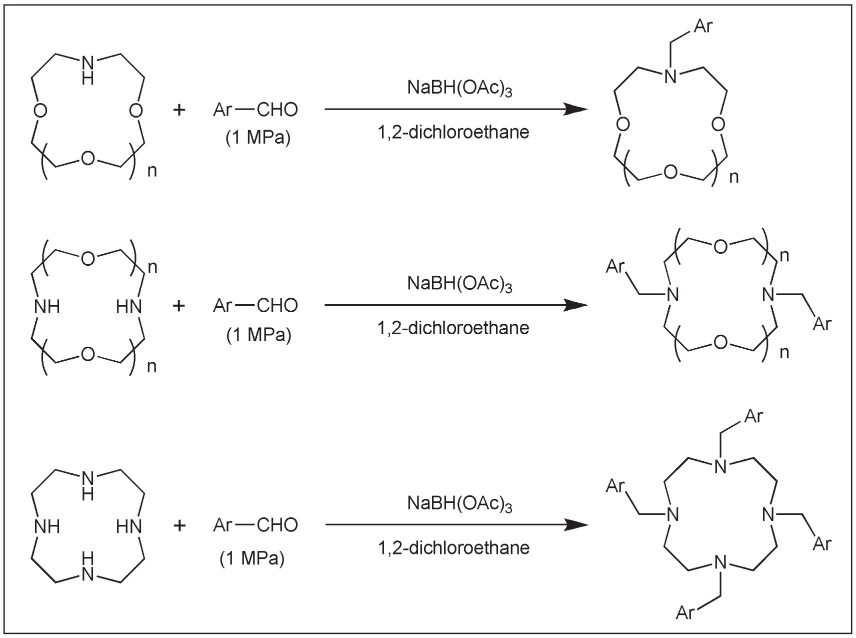

Armed-monoaza-12-crown-4, monoaza-15-crown-5, diaza-12-crown-4, diaza-18-crown-6 ethers, and 1,4,7,10-tetraazacyclododecane having aromatic pendants were prepared by the reductive amination of the corresponding macrocycles with aromatic carboxyaldehydes in the presence of $NaBH(OAc)_3$. Reductive amination under 1 MPa conditions provided significant shortening of the reaction time and yield enhancements.

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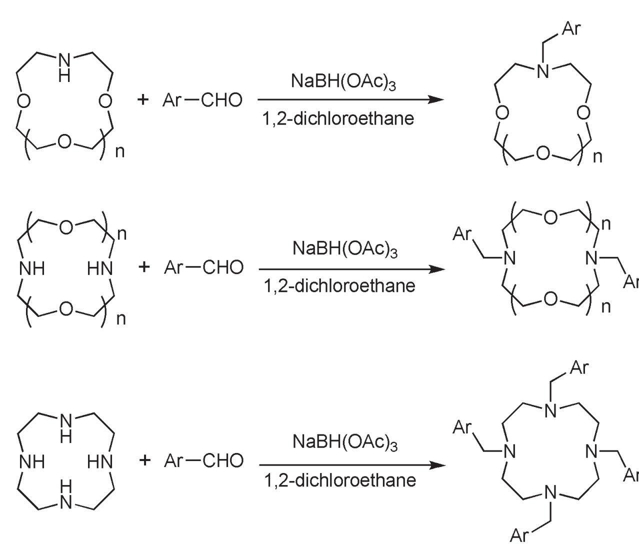
The reductive amination using $NaBH(OAc)_3$ as a reducing agent has been used to prepare many primary-, secondary- and tertiary-aliphatic, aromatic, and aliphatic-aromatic amines [1]. Recently, reductive amination was applied to prepare armed-azacrown ethers having aromatic pendants as additional binding sites, and those ligands showed specific cation binding abilities toward several metal ions [2]. We also have reported that 4-pyridylmethyl armed-monoaza-15-crown-5 ether, which was prepared by the reductive amination of monoaza-15-crown-5 with 4-pyridinecarboxyaldehyde in the presence of $NaBH(OAc)_3$, formed a [3.3]paracyclophane-like silver complex [3]. In order to further investigate effects of crown ring size, number of side-arms and structures of the side-arms of metal complexes, we have prepared new armed-monoaza- and diazacrown ethers, and cyclens having aromatic side arms. When diazacrown ethers and 1,4,7,10-tetraazacyclododecane were reacted with aromatic carbaldehydes in the presence of $NaBH(OAc)_3$ in 1,2-dichloroethane, long reaction times were required to finish the reaction. It is known that

Scheme 1



the reductive amination using NH_3 and H_2/Ni can be carried out under high pressure [4]. This prompted us to carry out the reductive amination using $NaBH(OAc)_3$ under high pressure conditions. Here, we report that the reductive amination under 1 MPa pressure is a useful procedure to synthesize the armed-macrocycles (**1**-**15**).

The experimental procedures are very simple and involve stirring aromatic carbaldehydes, amines, and $NaBH(OAc)_3$ in 1,2-dichloroethane at rt under 1 MPa (Argon atmosphere) as shown in Scheme 1. Reaction end times were checked by TLC. Structures of new compounds were confirmed by ^{1}H NMR, FABMS and elemental analyses.

The results are summarized in Table 1. When monoaza-12-crown-4 and monoaza-15-crown-4 ethers were used as the amine (entries 1-4 and 6-7), yields of the corresponding armed-azacrown ethers were increased about 1.1-1.9 times over those at atmospheric conditions at the same reaction time. Reaction times were reduced to half in the case of the reaction of monoaza-15-crown-5 with 3,5- difluorobenzenecarbaldehyde (entry 5). Preparation of double armed-diazacrown ethers required longer reaction times (72-144 h) than those of the monoazacrown derivatives. In all cases (entries 8-13), reaction times were shortened using the higher pressure. Especially, yields of diaza-18-crown-6 derivatives having 4-pyridylmethyl and 3-pyridylmethyl groups as side arms (entries 12 and 13) were significantly increased by 3.3 and 3.9 times, respectively, than under atmospheric conditions. When 1,4,7,10-tetraazacyclododecane was used as an amine under 1 MPa pressure conditions, reaction time was significantly shortened (72 h $\rightarrow$ 24 h) and yields increased about 1.2-1.4 times (entries 14 and 15). Yields of compounds 14 and 15 increased about 1.7 times, when the reaction times were elongated for 72 h under 1 MPa.

In addition, using the 1 MPa conditions also simplified the workup procedure. The aromatic carbaldehydes in the reaction mixtures completely disappeared as the reaction finished, which facilitated the separation and purification of the product.

In conclusion, we demonstrated that reductive amination using $NaBH(OAc)_3$ under 1 MPa provided significant reduction in the reaction time and yields of the addition products were enhanced especially for reactions requiring long reaction times.

EXPEERIMENTAL

^{1}H and ^{13}C nmr spectra were recorded in deuteriochloroform at 400 and 100 MHz, respectively. 1,4,7-Trioxa-10-azacyclododecane, 1,4,7,10-tetraoxa-13-azacyclopentadecane, 1,4,7,10,13-pentaoxa-16- azacyclooctadecane, 1,7-dioxa-4,10- diazacyclododecane, 1,4,10,13-tetraoxa-7,16- diazacyclooctadecane, 1,4,7,10-tetraazadodecane were used as purchased.

General Procedures for the Reaction of Monoazacrown Ethers with Pyridinecarbaldehydes or 3,5-Difluorobenzenecarblaldehyde.

After a mixture of monoazacrown ethers (10.0 mmol), aromatic aldehydes (15.1 mmol), $NaBH(OAc)_3$ (20.2 mmol) in 1,2-dichloroethane was stirred for 24 hours at rt under atmospheric pressure or 1 MPa (Argon atmosphere), saturated aqueous $NaHCO_3$ was added. The organic layer was separated, and the aqueous layer was extracted with chloroform (40 mL x 3). The combined organic layer was washed with water, dried over sodium sulfate, and concentrated. The residual yellow oil was separated and purified by gel-permiation column chromatography to give the following products.

N-(4-Pyridylmethyl)-1,4,7-trioxa-10-azacyclododecane (**1**).

Colorless crystals; mp 54.0-55.0 °C (recrystallized from hexane); ^{1}H nmr (deuteriochloroform): δ 8.53 (d, 2H, *J* = 5.9 Hz, 2H), 7.37 (d, *J* = 5.9 Hz, 2H), 3.80-3.69 (m, 10H), 3.67 (t, *J* = 5.0 Hz, 4H), 2.78 (t, *J* = 5.0 Hz, 4H); FABMS (NBA as a matrix): 266 ($[M+1]^+$, 100 %).

Anal. Calcd. for $C_{14}H_{22}N_2O_3$: C, 63.14; H, 8.33; N, 10.52. Found: C, 62.99; H, 8.46; N, 10.43.

N-(3-Pyridylmethyl)-1,4,7-trioxa-10-azacyclododecane (**2**).

Hygroscopic yellow oil; ^{1}H nmr (deuteriochloroform): δ 8.58 (d, *J* = 1.8 Hz, 1H), 8.50 (dd, *J* = 4.9 and 1.8 Hz, 1H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.22-7.28 (dd, *J* = 7.7 and 4.9 Hz, 1H), 3.74-3.61 (m, 14H), 2.74 (t, *J* = 4.8 Hz, 4H); FABMS (NBA as a matrix): 266 ($[M+1]^+$, 100 %).

Anal. Calcd. for $C_{14}H_{22}N_2O_3$+1/3H_2O: C, 61.74; H, 8.39; N, 10.29. Found: C, 61.57; H, 8.17; N, 10.03.

N-(3,5-Difluorobenzyl)-1,4,7-trioxa-10-azacyclododecane (**3**).

Yellow oil; ^{1}H nmr (deuteriochloroform): δ 6.96 (dd, *J* = 8.5 and 2.4 Hz, 2H), 6.66 (triple triplet, *J* = 8.5 Hz, 2.4 Hz, 1H), 3.74-3.68 (m, 8H), 3.65 (t, *J* = 4.8 Hz, 4H), 3.65 (s, 2H), 2.74 (t, *J* = 4.7 Hz, 4H); FABMS (NBA as a matrix): 300 ($[M+1]^+$, 100 %).

Anal. Calcd. for $C_{15}H_{21}NO_3F_2$: C, 59.79; H, 7.02; N, 4.65. Found: C, 59.52; H, 7.25; N, 4.68.

N-(3-Pyridylmethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (**4**).

Hygroscopic yellow oil; ^{1}H nmr (deuteriochloroform): δ 8.56 (d, *J* = 1.6 Hz, 1H), 8.50 (dd, *J* = 4.6 Hz, 1.6 Hz, 2H), 7.78 (d, *J* = 7.2 Hz, 1H), 7.26 (dd, *J* = 7.7 and 4.9 Hz, 1H), 3.77 (s, 2H), 3.68-3.63 (m, 16H), 2.84 (t, *J* = 5.6 Hz, 4H); FABMS (NBA as a matrix): 311 ($[M+1]^+$, 100 %).

Anal. Calcd. for $C_{16}H_{26}N_2O_4$+1/2H_2O: C, 60.17; H, 8.52; N, 8.77. Found: C, 60.02; H, 8.28; N, 8.74.

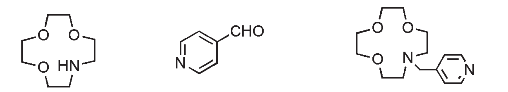
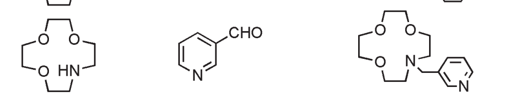
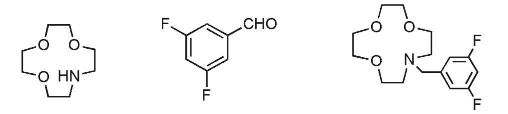
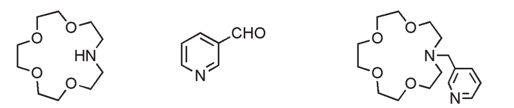
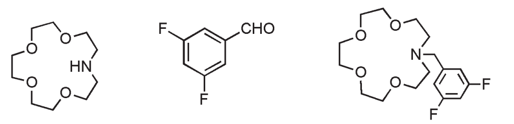
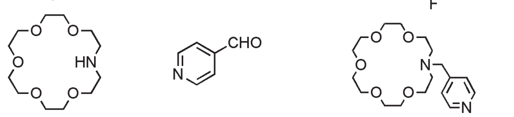
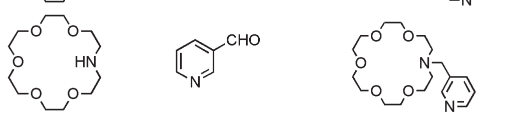
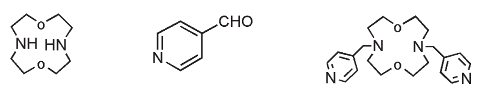
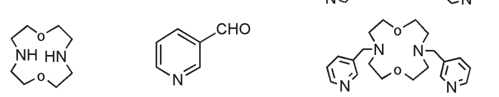
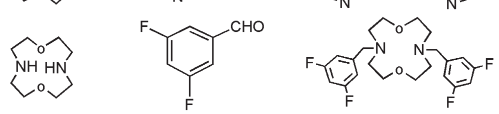
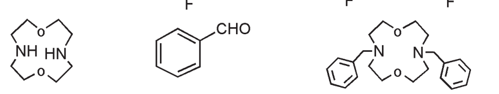
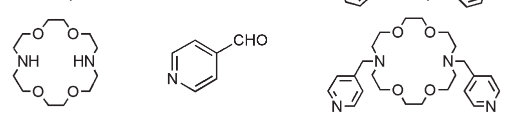
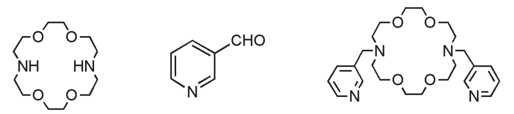
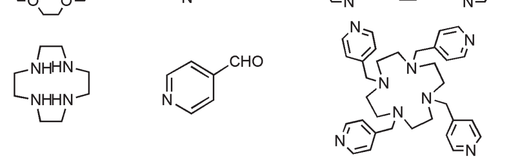
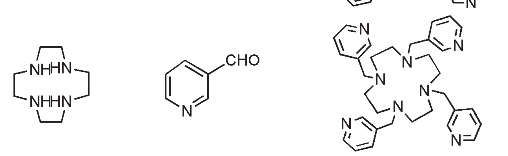
N-(3,5-Difluorobenzyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (**5**).

Yellow oil; ^{1}H nmr (deuteriochloroform): δ 6.93 (d, *J* = 6.4 Hz, 2H), 6.66 (triple triplet, *J* = 9.0 Hz, 2.2 Hz, 1H), 3.69 (s, 2H), 3.70-3.64 (m, 16H), 2.81 (t, *J* = 5.9 Hz, 4H); FABMS (NBA as a matrix): 346 ($[M+1]^+$, 100 %).

Anal. Calcd. for $C_{17}H_{25}NO_4F_2$: C, 59.12; H, 7.30; N, 4.06. Found: C, 59.25; H, 7.48; N, 3.93.

N-(4-Pyridylmethyl)-1,4,7,10,13-pentaoxa-16-azacyclooctadecane (**6**).

Table 1. Yields and reaction conditions.

Entry	Amine / Aldehyde / Product	(No.)	Time (h), pressure[1]	Yield (%)
1		(**1**)	24, a.p. 24, 1 MPa	21 36
2		(**2**)	24, a.p. 24, 1 MPa	36 48
3		(**3**)	24, a.p. 24, 1 MPa	31 58
4		(**4**)	24, a.p. 24, 1 MPa	49 56
5		(**5**)	48, a.p. 24, 1 MPa	75 77
6		(**6**)	24, a.p. 24, 1 MPa	35 56
7		(**7**)	24, a.p. 24, 1 MPa	32 44
8		(**8**)	72, a.p. 48, 1 MPa	64 82
9		(**9**)	72, a.p. 48, 1 MPa	49 50
10		(**10**)	96, a.p. 72, 1 MPa	76 83
11		(**11**)	96, a.p. 72, 1 MPa	26 41
12		(**12**)	144, a.p. 72, 1 MPa	20 66
13		(**13**)	144, a.p. 72, 1 MPa	14 55
14		(**14**)	72, a.p. 24, 1 MPa 72, 1 MPa	30 41 51
15		(**15**)	72, a.p. 24, 1 MPa 72, 1 MPa	31 36 53

1) The a.p. means atomospheric pressure.

Hygroscopic yellow oil; ^{1}H nmr (deuteriochloroform): δ 8.51 (d, *J* = 5.7 Hz, 2H), 7.32 (d, *J* = 5.7 Hz, 2H), 3.74-3.62 (m, 18H), 3.63 (t, *J* = 5.9 Hz, 4H), 2.81 (t, *J* = 5.9 Hz, 4H); FABMS (NBA as a matrix): 354 ($[M+1]^+$, 100 %).

Anal. Calcd. for $C_{18}H_{30}N_2O_5$+1/2H_2O: C, 59.48; H, 8.53; N, 7.90. Found: C, 59.79; H, 8.40; N, 7.75.

N-(3-Pyridylmethyl)-1,4,7,10,13-pentaoxa-16-azacyclooctadecane (**7**).

Hygroscopic yellow oil; ^{1}H nmr (deuteriochloroform): δ 8.54 (d, *J* = 1.8 Hz, 1H), 8.48 (dd, *J* = 4.8 and 1.8 Hz, 1H), 7.72 (d, *J* = 7.7, 1H), 7.24 (dd, *J* = 7.7 and 4.8 Hz, 1H), 3.73-3.65 (m, 18H), 3.63 (t, *J* = 5.5 Hz, 4H), 2.80 (t, *J* = 5.5 Hz, 4H); FABMS (NBA as a matrix): 354 ($[M+1]^+$, 100 %).

Anal. Calcd. for $C_{18}H_{30}N_2O_5$+1/2H_2O: C, 60.13; H, 8.63; N, 7.73. Found: C, 60.10; H, 8.47; N, 7.91.

General Procedures for the Reaction of Diazacrown Ethers with Pyridinecarbaldehydes or 3,5-Difluorobenzenecarbaldehyde.

After a mixture of diazacrown ethers (0.6 mmol), aromatic aldehydes (2.3 mmol), and $NaBH(OAc)_3$ (2.3 mmol) in 1,2-dichloroethane was stirred for 48-144 hours at rt under atmospheric pressure or 1 MPa (Argon atmosphere), saturated aqueous $NaHCO_3$ was added. The organic layer was separated, and the aqueous layer was extracted with chloroform (20 mL x 3). The combined organic layer was washed with water, dried over sodium sulfate, and concentrated. The residual yellow oil was separated and purified by gel-permiation column chromatography to give the following products.

N,N′-Bis(4-pyridylmethyl)-1,7-dioxa-4,10-diazacyclododecane (**8**).

Colorless crystals; mp 108.5-109.5 °C (recrystallized from acetonitrile); ^{1}H nmr (deuteriochloroform): δ 8.60 (d, *J* = 5.3 Hz, 4H), 7.45 (d, *J* = 5.3 Hz, 4H), 3.78 (s, 4H), 3.65 (t, *J* = 4.6 Hz, 8H), 2.85 (s, 8H); FABMS (NBA as a matrix): 357 ($[M+1]^+$, 100 %).

Anal. Calcd. for $C_{20}H_{28}N_4O_2$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.30; H, 7.88; N, 15.73.

N,N′-Bis(3-pyridylmethyl)-1,7-dioxa-4,10-diazacyclododecane (**9**).

Colorless crystals; mp 99.0-100.0 °C (recrystallized from acetonitrile); ^{1}H nmr (deuteriochloroform): δ 8.60 (s, 2H), 8.52 (dd, *J* = 4.7 and 1.6 Hz, 2H), 7.87 (d, *J* = 7.0 Hz, 2H), 7.29(dd, *J* = 7.7 and 4.7 Hz, 2H), 3.75 (s, 4H), 3.62 (t, *J* = 5.1 Hz, 8H), 2.81 (s, 8H); FABMS (NBA as a matrix): 357 ($[M+1]^+$, 100 %).

Anal. Calcd. for $C_{20}H_{28}N_4O_2$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.63; H, 8.10; N, 15.72.

N,N′-Bis(3,5-difluorobenzyl)-1,7-dioxa-4,10-diazacyclododecane (**10**).

Colorless crystals; mp 128.0-129.0 °C (recrystallized from acetonitrile); ^{1}H nmr (deuteriochloroform): δ 7.02 (d, *J* = 7.6 Hz, 4H), 6.68 (t, *J* = 7.6 Hz, 2H), 3.69 (s, 4H), 3.62 (s, 8H), 2.78 (s, 8H); FABMS (NBA as a matrix): 426 ($[M+1]^+$, 100 %).

Anal. Calcd. for $C_{22}H_{26}N_2O_2F_4$+1/4CH_3CN: C, 61.88; H, 6.17; N, 7.22. Found: C, 61.90; H, 6.37; N, 7.17.

N,N′-Dibenzyl-1,7-dioxa-4,10-diazacyclododecane (**11**).

Colorless crystals; mp 88.5-89.5 °C (recrystallized from acetonitrile) (lit.,[5] 89-90 °C (recrystallized from *n*-hexane)); ^{1}H nmr (deuteriochloroform): δ 7.48-7.11 (m, 10H), 3.74-3.47 (m, 12H), 2.79 (s, 8H); FABMS (NBA as a matrix): 355 ($[M+1]^+$, 100 %).

Anal. Calcd. for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.40; H, 8.77; N, 7.95.

N,N′-Bis(4-pyridylmethyl)-1,4,10,13-tetraoxa-7,16-diazacyclododecane (**12**).

Colorless crystals; mp 63.0-64.0 °C (recrystallized from heptane) (lit.,[6] 60-61 °C, recrystallized from ether); ^{1}H nmr (deuteriochloroform): δ 8.52 (d, *J* = 5.9 Hz, 4H), 7.33 (d, *J* = 5.9 Hz, 4H), 3.70 (s, 4H), 3.63 (t, *J* = 5.6 Hz, 8H), 3.60 (s, 8H), 2.84 (t, J = 5.6 Hz, 8H); FABMS (NBA as a matrix): 445 ($[M+1]^+$, 100 %).

Anal. Calcd. for $C_{24}H_{36}N_4O_4$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.54; H, 8.38; N, 12.44.

N,N′-Bis(3-pyridylmethyl)-1,4,10,13-tetraoxa-7,16-diazacyclododecane (**13**).

Colorless crystals; mp 69.5-70.0 °C (recrystallized from heptane); ^{1}H nmr (deuteriochloroform): δ 8.58 (s, 2H), 8.52 (d, *J* = 4.0 Hz, 2H), 7.85 (s, 2H), 7.27 (s, 2H), 3.86 (s, 4H), 3.69 (t, *J* = 5.1 Hz, 8H), 3.60 (s, 8H), 2.92 (s, 8H); FABMS (NBA as a matrix): 445 ($[M+1]^+$, 100 %).

Anal. Calcd. for $C_{24}H_{36}N_4O_4$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.62; H, 8.25; N, 12.48.

General Procedures for the Reaction of 1,4,7,10-Tetraazacyclododecane with Pyridinecarbaldehydes.

After a mixture of 1,4,7,10-tetraazacyclododecane (1.9 mmol), aromatic aldehydes (2.3 mmol), and $NaBH(OAc)_3$ (2.3 mmol) in 1,2-dichloroethane was stirred for 48-144 hours at rt under atmospheric pressure or 1 MPa (Argon atmosphere), saturated aqueous $NaHCO_3$ was added. The organic layer was separated, and the aqueous layer was extracted with chloroform (20 mL x 3). The combined organic layer was washed with water, dried over sodium sulfate, and concentrated. The residual yellow oil was separated and purified by gel-permeation column chromatography to give the following products.

N,N′,N′′,N′′′-Tetrakis(4-pyridylmethyl)-1,4,7,10-tetraazacyclododecane (**14**).

Orange crystals; mp 158.0-159.0 °C (recrystallized from acetonitrile); ^{1}H nmr (deuteriochloroform): δ 8.53 (d, *J* = 5.6 Hz, 8H), 7.30 (d, *J* = 5.6 Hz, 8H), 3.59 (s, 8H), 2.95 (s, 16H); FABMS (NBA as a matrix): 537 ($[M+1]^+$, 100 %).

Anal. Calcd. for $C_{32}H_{40}N_8$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.69; H, 7.59; N, 20.83.

N,N′,N′′,N′′′-Tetrakis(3-pyridylmethyl)-1,4,7,10-tetraazacyclododecane (**15**).

Colorless crystals; mp 151.0-152.0 °C (recrystallized from acetonitrile); ^{1}H nmr (deuteriochloroform): δ 8.54 (d, *J* = 4.0 Hz, 4H), 8.47 (s, 4H), 7.68 (d, *J* = 7.6 Hz, 4H), 7.25 (dd, *J* = 7.7 and 4.7 Hz, 4H), 3.58 (s, 8H), 2.93 (s, 16H); FABMS (NBA as a matrix): 537 ($[M+1]^+$, 100 %).

Anal. Calcd. for $C_{32}H_{40}N_8$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.87; H, 7.63; N, 20.82.

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