Pergamon

Polyhedron Vol. 14, No. 6, pp. 781–786, 1995
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0277–5387/95 $9.50+0.00

0277–5387(94)00299–1

SYNTHESIS, CHARACTERIZATION AND PROPERTIES OF NEW FULLY N-ALKYLATED 14-MEMBERED TETRAAZA MACROCYCLES AND THEIR COPPER(II) COMPLEXES

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(*Received* 12 *July* 1994; *accepted* 22 *July* 1994)

Abstract—New fully N-alkylated 14-membered tetraaza macrocycles 3,14-dimethyl-2,6,13,17-tetraethyl-2,6,13,17-tetraazatricyclo[16.4.0.^{1,18}0.^{7,12}]docosane (**3**) and 3,14-dimethyl-2,6,13,17-tetrakis(n-propyl)-2,6,13,17-tetraazatricyclo[16.4.0.^{1,18}0.^{7,12}]docosane (**4**) have been prepared from direct reactions of 3,14-dimethyl-2,6,13,17-tetraazatricyclo[16.4.0.^{1,18}0.^{7,12}]docosane (**1**) with appropriate alkyl bromides. The protonation constants of **3** and **4** were determined by a potentiometric method, and it was found that these ligands have a higher proton affinity than **1** and its tetra-N-methyl derivative (**2**). The new macrocycles react with the dehydrated copper(II) ion to form the stable complexes $[Cu(L)]^{2+}$ (L = **3** or **4**) in an ethanol solution, but do not react with hydrated copper(II) or nickel(II) ions in the same solution. The effects of the N-alkyl groups on the protonation and complexation behaviours of the macrocycles and on the spectroscopic and redox properties of their copper(II) complexes are presented.

Fully N-alkylated polyaza macrocyclic ligands and their transition metal complexes are of interest because of the effect of the N-alkyl groups upon the structures and/or chemical properties of the compounds.[1–11] Although various fully N-alkylated 14-membered tetraaza macrocyclic ligands have been prepared and investigated, most of them have N-methyl groups. However, such compounds with bulkier N-alkyl groups (e.g. Et, Pr etc.) have rarely been prepared.[11] One of the problems in the synthesis of polyaza macrocyclic ligands containing bulky N-alkyl groups is that the introduction of one alkyl group to each secondary amino group of polyaza macrocyclic ligands such as cyclam (**5**) is difficult or requires several steps; direct N-alkylation of **5** with ethyl or propyl bromide usually forms quaternary ammonium salts with no metal ligating properties.[11]

Recently, we reported the synthesis and properties of the 14-membered tetraaza macrocycles 3,14-dimethyl-2,6,13,17-tetraazatricyclo[16.4.0.^{1,18}0.^{7,12}]docosane (**1**)[12] and its tetra-N-methyl derivative (**2**)[9,10] containing cyclohexane rings and C-methyl groups. It has been observed that the N-methylated macrocyle **2** has a higher proton affinity than the unmethylated ligand **1** and exhibits an extraordinarily high selectivity for complex formation with copper(II) over nickel(II) ions in aqueous solutions.[9,10] In this work, we prepared new fully N-alkylated macrocyclic ligands 3,14-dimethyl-2,6,13,17-tetraethyl-2,6,13,17-tetra-

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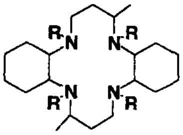
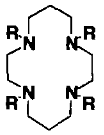


1: R = H
2: R = Me
3: R = Et
4: R = *n*-Pr



5: R= H
6: R= Me

azotricyclo[16.4.0.^{1,18}0.^{7,12}]docosane (**3**) and 3,14-dimethyl-2,6,13,17-tetrakis(n-propyl)-2,6,13,17-tetraazatricyclo[16.4.0.^{1,18}0.^{7,12}]docosane (**4**) to understand the effects of the bulky N-alkyl groups on the protonation and complexation behaviours of polyaza macrocycles. As far as we know, the effects of bulky N-alkyl groups of 14-membered polyaza macrocyclic compounds on such properties have not been reported. For the synthesis of the macrocycles, we utilized direct N-alkylations of **1** with the appropriate alkyl bromides. This paper reports the synthesis, characterization, protonation constants and complexation properties of the new macrocycles. The effects of the N-alkyl groups on the spectral and redox properties of their copper(II) complexes are also described.

EXPERIMENTAL

Measurements

IR spectra were recorded as either Nujol mulls or KBr pellets on a Shimadzu IR-440 spectrophotometer. Electronic spectra were obtained using a Shimadzu UV-160 spectrophotometer. Conductance measurements were made by using a Metrohm Herisau E518 Conductometer. NMR spectra were recorded with a Bruker WP 300 FT NMR spectrometer. Mass spectra were recorded on a Kratos 25-RFA GC-mass spectrometer. Elemental analyses were performed at the Kolon R & D Center, Kumi, Korea. Potentiometric titrations were carried out using an Orion Model 701 A/digital ion analyser. Cyclic voltammograms were recorded using a Yanaco Voltammetric Analyser p-1000 equipped with a FG-121B function generator and a Watanabe *X–Y* recorder. The working and reference electrodes were platinum and SCE, respectively. The electrochemical measurements were conducted in oxygen-free 0.1 M $(Bu^n)NClO_4$ acetonitrile solutions at 20°C.

Protonation constants for **3** and **4** were determined at 25 ± 0.1°C by potentiometric titration of the protonated ligands with 0.1 M Me_4NOH. Each titration was performed on a 90% (v/v) methanol–water solution (50 cm^3) of the ligand (2.5×10^{-3} M) and HCl (1.1×10^{-2} M) adjusted to 0.1 M ionic strength with Me_4NCl. The speciation curves for **3** and **4** are shown in Figs 1 and 2, respectively. The apparent protonation constants were determined using the program BEST.[13]

Materials

All chemicals used in syntheses were of reagent grade and were used without further purification. The macrocyclic ligands **1** and **2** and their copper(II) complexes were prepared as described previously.[9,10,12]

Synthesis

Compound **3**. A toluene (30 cm^3) suspension of **1** (1.0 g, 3.0 mmol), 99% ethyl bromide (1.8 cm^3, 24 mmol) and KOH (2.7 g, 47 mmol) was heated at reflux over 3 days. The reaction mixture was filtered and washed with chloroform. The mixture of the filtrate and washings was evaporated on a rotary evaporator until a semi-solid remained. The solid was dissolved in a minimum volume of ether and then an excess amount of methanol was added to the solution. After standing at room temperature for a few days, the white solid formed was filtered off. This solid often contains small amounts of partially N-ethylated derivatives of **1** as by-products. The pure product was obtained as a white solid by redissolving the crude product in a minimum volume of ether, followed by the addition of an excess volume of methanol. The product was filtered off, washed with methanol and dried in air. Yield: ~40%. Mass spectrum (*m*/*z*): 448 (M^+). Found: C, 74.1; H, 12.9; N, 12.1. Calc. for $C_{28}H_{56}N_4$: C, 74.9; H, 12.6; N, 12.5%.

Compound **4** · H_2O. This compound was prepared as a white solid by a method similar to that for **3** except that 98% n-propyl bromide (1.8 cm^3, 24 mmol) was reacted instead of ethyl bromide. Yield: ~30%. Mass spectrum (*m*/*z*): 504 (M^+). Found: C, 73.3; H, 13.0; N, 10.5. Calc. for $C_{32}H_{66}N_4O$: C, 73.5; H, 12.7; N, 10.7%.

$[Cu(3)](ClO_4)_2 \cdot H_2O$. An ethanol solution (20 cm^3) of $Cu(OAc)_2 \cdot H_2O$ (1.2 g) and $CH(OEt)_3$ (4.0 cm^3) was heated at reflux for 3 h. After **3** (1.2 g) dissolved in ether (10 cm^3) was added, the resulting solution was further refluxed for 24 h. Excess $NaClO_4$ dissolved in water was added to the solution, and then the mixture was stored in a refrigerator. The red crystals formed were filtered off, washed with a water–ethanol (1 : 1) mixture and dried in air. The product was recrystallized from methanol. Yield: >70%. Found: C, 45.7; H, 7.4;

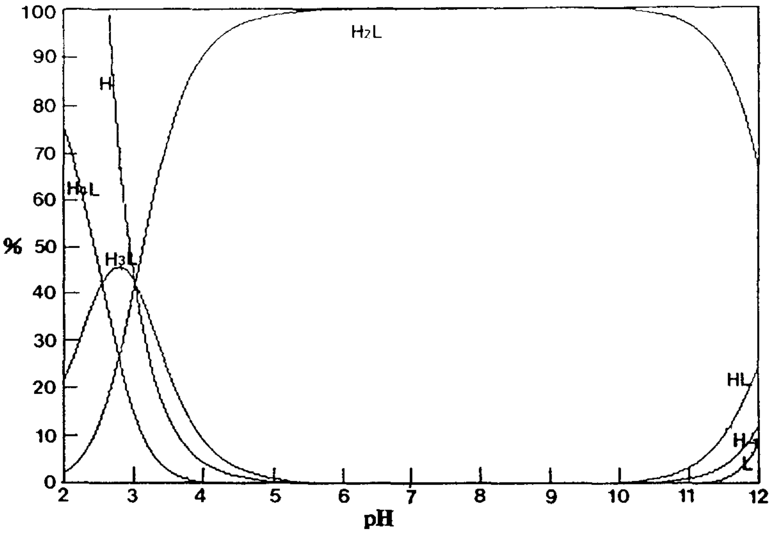


Fig. 1. Speciation curves for the protonated forms of **3** in 90% (v/v) methanol–water mixture at 25°C ($\mu = 0.1$ M).

N, 7.7. Calc for $CuC_{28}H_{58}N_4Cl_2O_9$: C, 46.1 ; H, 8.0 ; N, 7.7%.

$[Cu(4)](ClO_4)_2$. This complex was prepared by a method similar to that for $[Cu(3)](ClO_4)_2$ except that **4** was reacted instead of **3**. Yield: >70%. Found: C, 50.3; H, 7.8; N, 7.6. Calc. for $CuC_{32}H_{64}N_4Cl_2O_8$: C, 50.1 ; H, 8.4 ; N, 7.3%.

$L \cdot 2HClO_4$ (L = **3** or **4**). The addition of an excess amount of $NaClO_4 \cdot H_2O$ to a methanol solution of **3** or **4** produces a white solid. The product was filtered off, washed with methanol and dried in air. Found for $\mathbf{3} \cdot 2HClO_4$: C, 52.1 ; H, 8.9 ; N, 8.8. Calc. for $C_{28}H_{58}N_4Cl_2O_8$: C, 51.8 ; H, 9.0 ; N, 8.6%. Found for $\mathbf{4} \cdot 2HClO_4$: C, 53.9 ; H, 9.3 ; N, 7.8. Calc. for $C_{32}H_{66}N_4Cl_2O_8$: C, 54.5 ; H, 9.4 ; N, 8.0%. The same salts were also obtained in all attempts to prepare copper(II) and nickel(II) complexes of **3** and **4** from the reactions of the hydrated metal ions with the ligands in methanol.

RESULTS AND DISCUSSION

Syntheses of the ligands

Direct reaction of **1** with excess ethyl bromide or n-propyl bromide in the presence of KOH produced the fully N-alkylated macrocycle **3** or **4**, respectively. Although it has been reported that the direct

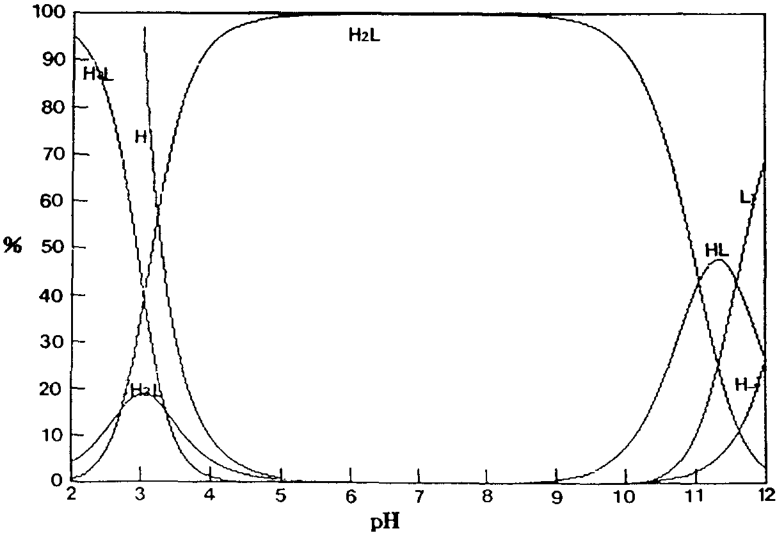


Fig. 2. Speciation curves for the protonated forms of **4** in 90% (v/v) methanol–water mixture at 25°C ($\mu = 0.1$ M).

N-alkylation of **5** usually produces quaternary ammonium salts,[11] such a quaternization was not observed in the present work; moreover, the crude products often contain some partially N-alkylated species as by-products. This may be attributed to the steric hindrance of the cyclohexane rings and the C-methyl groups. The products can be easily isolated by fractional recrystallizations of the crude products (see Experimental). The white solids **3** and **4** are freely soluble in chloroform and ether. They are slightly soluble in methanol, and the solubility order is found to be **1** > **2** ≫ **3** > **4**.

IR spectra of the macrocycles show no band around 3200 cm^{-1} assignable to ν(N—H). Mass spectra of **3** and **4** gave *m*/*z* values of 448 and 504, respectively, which are in accord with the molecular weight of the macrocycles. ^{13}C NMR spectra (Table 1) of the macrocycles measured in $CDCl_3$ show that **3** and **4** contain 14 and 16 pairs of non-equivalent carbon atoms, respectively. These are consistent with the ligand structures.

Protonation and complexation behaviours

The protonation equilibria of the fully N-alkylated macrocycles **3** and **4** were studied by potentiometric titration at 25±0.1°C and $\mu = 0.1$ M Me_4NCl. The speciation curves (Figs 1 and 2) show that the proportions of the deprotonated forms of the macrocycles are negligible, even at pH 10. The proportions of the diprotonated species H_2**3** and H_2**4** are *ca* 100 and 92%, respectively, of the total macrocycles at the same pH, showing that the proton affinity of **3** is higher than that of **4**. The protonation constants for the ligands are listed in Table 2, together with those for **1** and **2**.[10] These ligands exhibit two high and two low values of protonation constants. Table 2 shows that the introduction of the alkyl groups on the secondary amino groups of **1** to give **2**, **3** or **4** results in increased proton affinity. This trend is in sharp contrast to the orders $R_2NH > R_3N$ (R = Me, Et, Bu^i)[14] and **5** > **6**[7,8] measured in aqueous solutions, but is rather similar to the order $R_2NH < R_3N$ in the gas phase.[14] It is well known that both the inductive and solvation effects are important factors affecting the basicity of alkyl amines in aqueous solutions, whereas the inductive effect is the major factor in the gas phase.[14] The present result may indicate that the hydration of the protonated species of **3** and **4**, as well as **1** and **2**, is much restricted by the steric hindrance of the N- and/or C-substituents, and therefore the inductive effects of the substituents outweigh the solvation effects. This idea is in accord with the result that the proton affinity of the macrocycles are strongly affected by the nature of the N-alkyl groups; the stepwise protonation constant log K_1 and the overall protonation constant log β_4 values rise with increasing inductive effect of the alkyl group in the order **1** < **2** < **3**. However, in the case of **4**, the values are somewhat lower than those of **3**. This strongly indicates that the inductive effects of the propyl groups on **4** is exceeded by the back-strain[14] of the tertiary amino groups caused by the steric repulsion of the bulky alkyl groups, in contrast to **2** and **3**, where the inductive effects of the methyl or ethyl groups outweigh the back-strain.

It has been observed that, although both copper(II) and nickel(II) complexes of the unalkylated macrocycle **1** are easily prepared by the reactions of the hydrated metal ions with the ligand in methanol–water mixtures,[12] the fully N-methylated macrocycle **2** exhibits unusually high copper(II) ion selectivity in similar conditions;[9,10] the latter readily reacts with the copper(II) ion to form the complex $[Cu(\mathbf{2})]^{2+}$ but not with the nickel (II) ion in a methanol solution containing water. The synthesis of copper(II) and nickel(II) complexes of **3** and **4** was

Table 1. ^{13}C NMR spectral data of the macrocycles[a]

	δ (ppm)		
Compound	C-Me	N-Alkyl	Others
3	18.7	15.0 15.7 39.4 43.8	26.4 26.5 26.7 31.1 37.4 48.7 50.5 59.1 60.9
4	18.7	12.0 (d) 22.7 23.3 49.2 52.6	26.4 26.5 26.7 31.3 37.5 48.3 50.7 59.5 61.4

[a] Measured in $CDCl_3$.

Table 2. Protonation constants of the fully N-alkylated macrocycles at 25°C[a]

	1[b]	**2**[b]	**3**[c]	**4**[c]
log K_1	11.56	12.21	12.45	11.59
log K_2	9.83	9.58	12.44	11.00
log K_3	2.61	2.43	3.01	2.68
log K_4	2.60	3.00	2.55	3.41
log β_4	26.60	27.22	30.45	28.68

[a] In 0.1 M Me_4NCl. [b] Ref. 10. [c] This work.

attempted in various experimental conditions. However, all efforts to prepare both copper(II) and nickel(II) complexes of the macrocycles from the reactions of the hydrated metal ions with the ligands in methanol or methanol–water mixtures were unsuccessful. Even after prolonged heating (>3 days) at reflux of the mixtures, no spectral change was observed. In all cases, the addition of $NaClO_4$ to the reaction mixtures produced the white solid **3**·$2HClO_4$ or **4**·$2HClO_4$ instead of the complexes. Furthermore, we could not observe any evidence of complex formation even at the high pH at which the copper(II) or nickel(II) hydroxide precipitates. We were also unsuccessful in isolating any iron(II) or cobalt(II) complex of **3** or **4** from similar reactions. Such behaviours of **3** and **4** are different from those observed for **1** and **2**. However, interestingly, the macrocycles react with dehydrated copper(II) ion in a dehydrated methanol or ethanol solution (see Experimental)[10,15]* to form the stable complexes $[Cu(\mathbf{3})]^{2+}$ and $[Cu(\mathbf{4})]^{2+}$, but not with nickel (II) ion in similar conditions. This indicates that the macrocycles **3** and **4** are selective for complex formation with copper(II) over nickel(II) ions in the dehydrated condition. It is well known that the copper(II) ion is a stronger Lewis acid than the nickel(II) ion.[14,16] Therefore, the copper(II) ion selectivity of the macrocycles in the dehydrated condition may be attributed to the acidity difference between the two metal ions. The reasons for the lack of complexation of **3** and **4** with the copper(II) ion as well as nickel(II) in methanol solutions containing water are not clearly understood. However, the above results strongly indicate that the lack of complexation is caused in part by the high proton affinity of the macrocycles, together with the back-strain.

Properties of copper(II) complexes

The copper(II) complexes $[Cu(\mathbf{3})](ClO_4)_2$ and $[Cu(\mathbf{4})](ClO_4)_2$ are soluble in acetonitrile, nitromethane and methanol, but are insoluble in water. They are extremely stable in the solid state and relatively stable even in solutions containing nitric acid. The visible spectra of the complexes (1.0×10^{-3} M in 0.3 M HNO_3) in acetonitrile–water (1 : 1) mixture solution showed that only less than 5% of the complexes are decomposed in 15 h at 20°C. This result is quite similar to those observed for the copper(II) complexes of **1**[12] and **2**,[10] showing that the decomposition rate is rarely affected by the nature of the alkyl groups.

The values of molar conductance for the complexes $[Cu(\mathbf{3})](ClO_4)_2$ and $[Cu(\mathbf{4})](ClO_4)_2$ in acetonitrile are 288 and 292 Ω^{-1} mol^{-1} cm^2, respectively, showing that the complexes are 1 : 2 electrolytes. The electronic spectra and redox potentials of the copper(II) complexes are summarized in Table 3. The electronic absorption spectra of the complexes of **3** and **4** measured in nitromethane show *d–d* transition bands at 473 and 475 nm, respectively, indicating that the complexes are in square planar Cu^{II}–N_4 environments. Unexpectedly, the ligand field strength of the complexes is rarely affected by the nature of the N-alkyl groups; the wavelengths of the bands for the complexes of **3** and **4** are quite similar to those of $[Cu(\mathbf{2})]^{2+}$. However, the molar absorption coefficients of the complexes are strongly affected by the nature of the N-alkyl groups and show the order $\mathbf{1} < \mathbf{2} < \mathbf{3} < \mathbf{4}$. The larger value of molar absorption coefficient for $[Cu(\mathbf{4})]^{2+}$, compared to those for $[Cu(\mathbf{2})]^{2+}$ and $[Cu(\mathbf{3})]^{2+}$, may be attributed to the more distorted structure of the complex[10,17,18] due to the increased steric crowding caused by the presence of the bulky N-propyl groups. Cyclic voltammograms of the complexes of the copper(II) complexes of **3** and **4** obtained in 0.1 M $(Bu^n)_4NClO_4$ acetonitrile solutions exhibited one-electron oxidation and reduction peaks corresponding to Cu^{II}/Cu^{III} and Cu^{II}/Cu^{I} processes, respectively. The redox potentials (Table 3) for the complexes of **3** and **4** are more anodic than those for the complex of **1** but are quite similar to those for the complex of **2**. It is well known that alkylation on secondary amino groups of a 14-membered tetraaza macrocyclic copper(II) complex makes the attainment of the Cu^{III} state more difficult and the reduction to Cu^{I} easier.[2,10,18] However, the present result clearly shows that the redox potentials are rarely affected by the nature of the N-alkyl groups.

Summary

This work shows that the fully N-alkylated macrocycles **3** and **4** can be readily prepared by direct reactions of **1** with appropriate alkyl bromides. To our knowledge, **3** and **4** are rare fully N-alkylated 14-membered tetraaza macrocycles that are prepared by the direct alkylation of secondary amino groups on a macrocyclic compound. It is clear that, although the protonation constants and complexation behaviours of the macrocyclic ligands are strongly affected by the nature of the N-alkyl groups, the redox potentials and ligand fields of the copper(II) complexes are

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*The reagent $HC(OEt)_3$ reacts with H_2O to produce HCO_2Et and EtOH. See also Refs 10 and 15.

Table 3. Electronic spectra and cyclic voltammetric data for the copper(II) complexes

Compound	λ_{max}[a] nm (ε, M^{-1} cm^{-1})	Potentials[b] (V vs SCE)	
		Cu^{II}/Cu^{III}	Cu^{II}/Cu^{I}
$[Cu(\mathbf{1})](ClO_4)_2$[c]	487 (113)	+1.41	−0.92(i)
$[Cu(\mathbf{2})](ClO_4)_2$[d]	473 (235)	+1.91(i)[e]	−0.28
$[Cu(\mathbf{3})](ClO_4)_2$	473 (340)	+1.89(i)	−0.31
$[Cu(\mathbf{4})](ClO_4)_2$	476 (440)	+1.88(i)	−0.31

[a] In nitromethane at 20°C.

[b] Measured in 0.1 M $(Bu^n)_4NClO_4$ acetonitrile solution at 20°C.

[c] Ref. 12.

[d] Ref. 10.

[e] i = irreversible.

not affected significantly by the nature of the alkyl groups attached to the coordinated nitrogen atoms.

Acknowledgement—This work was supported by the Basic Science Research Program, the Ministry of Education of the Republic of Korea, 1994.

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