and also a very good hydrogen abstractor for a number of saturated organic substances. These facts suggest that hydrogen abstraction is more plausible for the reaction of $[Co(en)_3]^{3+}$ with OH radical, different from that for Cu(II) or Ni(II) complexes.

Acknowledgment. The authors thank Professor A. Henglein for supporting this work.

Registry No. $[Co(en)_3]^{3+}$, 14878-41-2; $[Co(dien)_2]^{3+}$, 18703-28-1; $[CoCl_2(en)_2]^+$, 15275-04-4; $[CoCl_2(trien)]^+$, 46135-19-7; OH radical, 3352-57-6.

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Fitting of Nickel(II) Ion into the Two 14-Membered Tetraaza Macrocycles. Blue-to-Yellow Conversion and the Oxidation and Reduction Behavior

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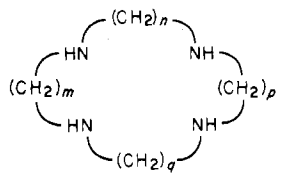
The novel saturated tetraaza macrocycle *isocyclam* (**2**) has been synthesized and the behavior of its nickel(II) complexes, which contain a 5,5,6,6 sequence of chelate rings, is compared with that of corresponding complexes of *cyclam* (**1**) (sequence: 5,6,5,6). These complexes exist in solution as a mixture of blue, octahedral, high-spin and yellow, planar, low-spin species; the thermodynamic parameters for the blue-to-yellow conversion depend upon the cyclic nature of the ligand. In analogy with $Ni(cyclam)^{2+}$, $Ni(isocyclam)^{2+}$ undergoes one-electron oxidation and reduction processes at a platinum electrode in acetonitrile. The easier reduction and more difficult oxidation of both blue and yellow 5,5,6,6 complexes with respect to the 5,6,5,6 analogues have been related to the differences in the in-plane Ni–N interaction parameters, as inferred from electronic spectra. General redox behavior of Ni(II) complexes with tetraaza macrocycles has been reconsidered and a linear correlation between oxidation and reduction potentials is presented.

Introduction

The growing interest in synthetic tetraaza macrocycles and their metal complexes depends (i) on the fact that they may mimic naturally occurring macrocyclic molecules in their structural and functional features and (ii) on their rich chemical behavior. Since the pioneering work of Curtis[1] and Busch[2] on the template syntheses of both saturated and unsaturated macrocycles, preparative improvements have now made available a complete series of saturated and unsubstituted 12- to 16-membered cyclic tetramine ligands.[3-5]



$m = n = p = q = 2$ [12]aneN$_4$
$m = n = p = 2; q = 3$ [13]aneN$_4$
$m = p = 2; n = q = 3$ [14]aneN$_4$ or *cyclam*
$m = 2; n = p = q = 3$ [15]aneN$_4$
$m = n = p = q = 3$ [16]aneN$_4$

These ligands have a strong tendency to encircle in a coplanar fashion 3d metal ions, forming a unique family of complexes in which the strength of the in-plane metal–nitrogen interactions is modulated according to the size of the ligand aperture. It has been predicted, on the basis of conformational arguments,[6] that the size of the 14-membered macrocycle, [14]-aneN$_4$, previously named *cyclam*,[7] is almost exactly that required by the divalent first-row transition-metal ions, larger and smaller ligands of the series being too large and too small. This prediction has been confirmed by both spectrochemical and thermochemical studies: in fact (i) cyclam establishes the highest in-plane *Dq* with copper(II)[8] and high-spin nickel(II),[5] and (ii) it gives the most exothermic metal–ligand enthalpies[9,10] (this latter property being coresponsible for the exceptionally high solution stablity, the so-called thermodynamic *macrocyclic effect*).[11]

The favorable size requirements and sequence of chelate rings of cyclam are further demonstrated by the fact that template syntheses work well mainly when a cyclam-like structure is involved.[12-14]

It must be pointed out that, in the series of cyclic tetraaza ligands under consideration, the 14-membered example is

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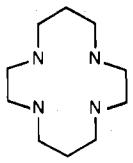
unique in that it can exist as *two* isomeric forms (provided that formation of chelate rings other than five- or six-membered is excluded): the first one (**1**), cyclam, gives a system of *alternating* five- and six-membered chelate rings (sequence 5,6,5,6) while the second one (**2**), gives a system in which the five- and six-membered rings are separately grouped (sequence 5,5,6,6).



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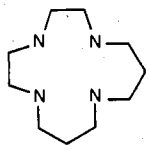

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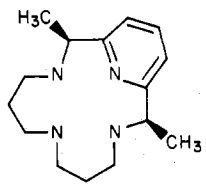
As **2** is isomeric with cyclam, it was named *isocyclam*. This novel macrocycle has been synthesized through condensation of the appropriate segments, in the absence of a templating metal ion. Previous studies on open-chain polyamines have shown that alternating consecutive five- and six-membered chelate rings favor the formation of strong coordinative interactions.[15] Comparison of cyclam and isocyclam should allow one to evaluate how the sequence of rings affects coordinating tendencies of cyclic ligands of the same size.

We report here the solution properties of nickel(II) complexes, with special regard to the oxidation and reduction behavior. For comparative purposes, the corresponding complexes with the two isomeric forms (meso and racemic) of the macrocycle CRH,[16,17] **3** and **4**, have been reconsidered.



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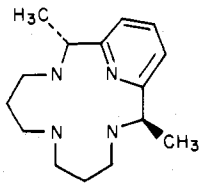

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In fact, in analogy with isocyclam, the ligand CRH forms complexes containing a 5,5,6,6 sequence of fused chelate rings.

It has been recently demonstrated, that, in the same way as open-chain tetramines, cyclic unsubstituted ligands, such as cyclam, can give in solution a mixture of high-spin (blue) and low-spin (yellow) nickel(II) complexes.[18] Therefore, an equilibrium study of the blue-to-yellow conversion was conducted and its thermochemical aspects elucidated. The inference of the above equilibrium on the nickel(II) redox processes has been discussed for the first time.

Experimental Section

Synthesis of the Ligand and Its Nickel(II) Complexes. 1,5,9-Tris(*p*-toluenesulfonyl)-1,5,9-triazanonane and Its Disodium Salt. A solution of 114.4 g (0.6 mol) of *p*-toluenesulfonyl chloride (Erba RPE, tosyl chloride) in 600 mL of diethyl ether was added dropwise (0.2 mL/min) to a vigorously stirred solution containing 26.3 g (0.2 mol) of dipropylenetriamine (Fluka, purum) and 40 g (0.6 mol) of NaOH in water (200 mL), at room temperature. When the addition was complete, the solution was further stirred for 1 h. The white solid was filtered and recrystallized from ethanol (yield 85%). Anal. Calcd for $C_{27}H_{35}N_3S_3O_6$: C, 55.17; H, 4.97; N, 7.15. Found C, 55.02; H, 4.81; N, 6.95. The tosylated triamine was added in small amounts to a stirred solution of sodium (0.2 mol) in 1 L of anhydrous ethanol. The white precipitate which formed was filtered under nitrogen, washed with absolute ethanol, and then washed with anhydrous ether (yield 65%). Anal. Calcd for $C_{27}H_{33}N_3S_3O_6Na_2$: C, 51.34; H, 4.31; N, 6.65. Found: C, 51.05; H, 4.15; N, 6.55.

***N,O,O*-Tris(*p*-toluenesulfonyl)bis(2-hydroxyethyl)amine.** Tosyl chloride, 114.4 g (0.6 mol), was added to an open-air stirred solution of 21.0 g (0.2 mol) of diethanolamine (Erba RPE) in 200 mL of triethylamine. Stirring was continued for 1 h after complete mixing of reagents. Water was then added in order to bring into solution unreacted substances and triethylamine in excess. The white solid residue was filtered and dissolved in the minimum amount of hot ethanol from which it crystallizes on cooling (yield 60%). Anal. Calcd for $C_{25}H_{29}NS_3O_8$: C, 52.85; H, 5.11; N, 2.50. Found: C, 52.22; H, 5.41; N, 2.59.

1,4,7,11-Tetrakis(*p*-toluenesulfonyl)-1,4,7,11-tetraazacyclotetradecane. To a stirred 0.1 M solution of tosylated triamine disodium salt in DMF (900 mL) maintained at 110 °C, 450 mL of a 0.2 M solution of tosylated diethanolamine, in DMF, was added dropwise over a period of 2 h. After complete addition, stirring was continued for 1 h. The clear bright yellow solution was evaporated at reduced pressure to 100 mL. Water, 1.5 L, was then added to give a noncrystalline white substance which was dissolved in 1 L of hot benzene. After filtration, the solution was kept for 7 h over anhydrous Na_2SO_4. The solution was filtered and rotoevaporated to 120 mL. This concentrated benzene solution was dissolved in 400 mL of hot absolute ethanol, to give white needles on cooling (yield 20%, mp 227–228 °C (lit. value:[3] 234–236 °C)). Anal. Calcd for $C_{38}H_{48}N_4O_8S_4$: C, 55.86; H, 5.92; N, 6.86. Found: C, 55.70; H, 6.12; N, 6.64.

1,4,7,11-Tetraazacyclotetradecane (Isocyclam). The tosylated macrocycle (0.022 mol) was dissolved in a mixture of 48% hydrobromic acid (1.1 L) and glacial acetic acid (0.6 L) and refluxed for 48 h. The filtered solution was rotoevaporated to 200 mL. One and one-half liters of a 25% ether–75% ethanol solution was added. The white precipitate (6.7 g) of amine tetrahydrobromide was recrystallized from aqueous ethanol and then dissolved in 50 mL of 1 M NaOH. The free ligand was extracted with fifteen 5-mL portions of chloroform, which was flashed evaporated, and then ether was added. After filtration, the macrocycle was obtained upon evaporation as a white powder (yield 60%, mp 75–76 °C). Anal. Calcd for $C_{10}H_{24}N_4$: C, 59.95; H, 12.08; N, 27.97. Found: C, 59.09; H, 11.74; N, 27.03.

Ni(isocyclam)$(ClO_4)_2$. A 20-mL hot ethanolic solution of $Ni(ClO_4)\cdot 6H_2O$ was added to a stirred 20-mL hot ethanolic solution of isocyclam (0.50 g). An orange crystalline product formed which was recrystallized from methanol (yield 70%). Anal. Calcd for $C_{10}H_{24}N_4O_8Cl_2Ni$: C, 26.22; H, 5.28; N, 12.24. Found: C, 26.43; H, 5.17; N, 12.06.

Ni(isocyclam)Cl_2. To a methanolic solution of Ni(isocyclam)-$(ClO_4)_2$ (0.5 g in 10 mL) was added a solution of KCl in methanol; precipitated $KClO_4$ was eliminated and the solution was rotoevaporated to give a purple solid, which was then dissolved in $CHCl_3$. The solid obtained from the solution after filtration and evaporation was recrystallized from acetonitrile (yield 30%). Anal. Calcd for $C_{10}H_{24}N_4Cl_2Ni$: C, 36.40; H, 7.33; N, 16.98. Found C, 36.25; H, 6.98; N, 16.55.

Ni(II) Complexes with *ms*- and *dl*-CRH. The procedure described by Karn and Busch[16] has been employed. 2,6-Diacetylpyridine (Aldrich, Europe), recrystallized from ethanol, and dipropylenetriamine (Fluka, purum) were used. In the present work, Ni(CR)$(ClO_4)_2$ was reduced with $NaBH_4$ in methanolic solution, rather than with H_2/Pt in water.[16] This method ensures a comparatively greater yield of *dl* isomer (15–20%). Complexes of the two isomeric forms were separated by the oxalate method[16] and were obtained as perchlorate salts.

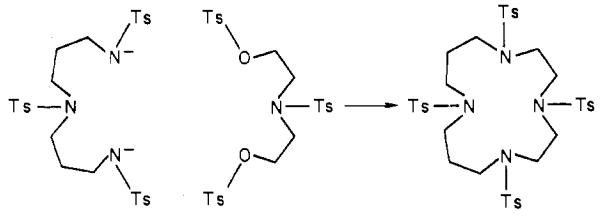
Electrochemical Measurements. Voltammetry and polarography were performed with the Electrochemolab System (Amel, Milan), consisting of a potentiostat (Model 552/MWR) and a function generator (Model 556), connected through a 563 multifunction interface. Current/potential curves were obtained on a Hewlett-Packard 7040 X-Y recorder or, at the highest scan rates, on an oscilloscope (HM 312 Hameg). Electrochemical measurements, in acetonitrile, made 0.1 M in Bu_4NClO_4, were carried out in a closed glass vessel, thermostated at 25.0 ± 0.1 °C, under a nitrogen atmosphere. A silver wire immersed in a CH_3CN solution, 0.01 M in $AgNO_3$ and 0.1 M Bu_4NClO_4, was used as a reference electrode. It was separated from the working electrode compartment by two medium glass frits, and contact was made through a capillary tip. A platinum microsphere or a rotating or a vibrating platinum wire (Metrhom) was used as a working electrode, according to the chosen technique. A platinum foil was used as the auxiliary electrode. Platinum working electrodes were pretreated through immersion in chromic acid and then were washed with water and acetonitrile and anodized at a small positive potential. Acetonitrile was purified through consecutive distillation over drying agents (CaH_2, P_4O_{10}, CaH_2) and then kept over molecular sieves (5 Å), in a nitrogen atmosphere. Bu_4NClO_4 was prepared by reaction in aqueous solution of Bu_4NOH (40% solution, Fluka, pract.) and $HClO_4$. The white precipitate was recrystallized twice from water and twice from

acetone/ether and then dried in vacuo over P_4O_{10}. Purity of the electrolyte was checked by exploring the electrochemical range of its acetonitrile solution. Commercial Bu_4NClO_4 (Fluka, purum), in spite of repeated crystallizations from water and acetone/ether, was found not suitable for electrochemical purposes, being electrochemically active between the potential limits of the solvent. High-purity nitrogen (IGT, UPP), used to deaerate solutions, was further purified by passing through two 1-m columns of BASF catalyst (R-3-11), to remove traces of oxygen, and then through columns of drying agents (H_2SO_4, KOH, molecular sieves). In a typical measurement, a weighed amount of the perchlorate complex was added to 30 mL of deaerated solution, to give a millimolar concentration.

Spectral Measurements. Electronic spectra were recorded on a Beckman DK-2A spectrophotometer. In the equilibrium measurements, the temperature of the solution, contained in an air-thermostated 1-cm silica cell, was measured through the resistance of a calibrated thermistor dipped in the solution.

Results and Discussion

1. Synthesis and Properties of the Ligand. Cyclam can be prepared in good yield through the nickel(II)-assisted condensation of the open-chain tetramine 3,2,3-tet[19] and glyoxal, followed by the hydrogenation of the two imine bonds of the unsaturated macrocycle.[20,21] This route was not attempted in the case of isocyclam, since the precursor open-chain tetramine, 2,3,3-tet, is not easily available. Therefore, isocyclam was synthesized through a nonmetal procedure, as outlined by Richman and Atkins.[3] The main reaction involves the condensation of the appropriate tosylated segments, as follows:



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Hydrolysis of **5** was carried out in CH_3COOH/HBr. The free ligand isocyclam is a white solid melting at 75 °C, i.e., more than 100 °C below cyclam (191 °C). Melting points of 12- to 16-membered saturated unsubstituted tetraaza macrocycles range from 40 to 90 °C,[5,22] testifying for comparatively weak intermolecular interactions. The anomalous stability of crystalline cyclam could be ascribed to its highly symmetrical framework, which allows a strong molecular packing, through hydrogen bonding. The comparatively low solubility in water of cyclam (about 10 times less soluble than other members of the series under consideration) was previously ascribed to the poor hydration of the ligand, due to its closed configuration.[23] The above data suggest that also an unusually high crystal lattice energy helps lower the solubility of cyclam, with respect to isocyclam and other saturated macrocycles.

2. Blue-to-Yellow Conversion in Aqueous Solution. Nickel(II) complexes with saturated tetramines (L) exist in aqueous solution as an equilibrium mixture of a blue, octahedral, high-spin species and a yellow, planar, low-spin species according to eq 1. Equilibrium 1 was first reported for L =

$$\underset{\text{octahedral}}{NiL(H_2O)_2^{2+}} \rightleftharpoons \underset{\text{planar}}{NiL^{2+}} + 2H_2O \qquad (1)$$

2,2,2-tet and was found to be displaced to the right both by increasing temperature ($\Delta H° > 0$) and by increasing concentrations of background electrolyte (e.g., $NaClO_4$).[24] Similar behavior was then reported for homologous open-chain tetramines (2,3,2-tet,[18,23] 3,2,3-tet,[25] 3,3,3-tet[26]) and the position of equilibrium 1 was found to be related to the ligand structure. It has been demonstrated recently that Ni(cyclam)$^{2+}$ also undergoes a blue-to-yellow conversion in water, and the thermodynamic quantities associated with eq 1 have been reported.[18] This type of study has now been extended to isocyclam. Spectra of aqueous Ni(isocyclam)$^{2+}$ (see Figure 1) show the absorption bands of the "octahedral" chromophore (in Figure 1 ν_2 and ν_3) and the band of the planar chromophore (at 463 nm). Increasing temperature and/or inert electrolyte concentration results in an increase in the intensity of the band due to the planar species, with a simultaneous decrease in the other ones. The thermodynamic study of eq 1 is carried out as follows: (1) $Ni(L)(ClO_4)_2$ complex is dissolved in 7.2 M $NaClO_4$ solution. Under these strong conditions, only the yellow species exists, as shown by definitive disappearance of the bands due to the blue form. A temperature increase of this strong solution does not cause any further increase of the band intensity, corroborating the existence of the 100% planar species. The molar extinction coefficient of the planar complex is then calculated (116.4 L mol^{-1} cm^{-1}, for Ni(isocyclam)$^{2+}$). This procedure assumes that ϵ_{yellow} is not ionic-strength dependent. In fact, Ni(tetramine)$^{2+}$ complexes in 100% yellow form, such as Ni(*ms*-CTH)$^{2+}$ and Ni(*dl*-CTH)$^{2+}$ (CTH = 5,7,7,12,14,14-hexamethyltetraazacyclotetradecane) exhibit the same ϵ value both in pure water and in 7.2 M $NaClO_4$ solution (their spectra being also temperature independent). (2) Visible spectra of $Ni(L)(ClO_4)_2$ at a fixed ionic strength (0.1 M $NaClO_4$) are recorded at different temperatures (see Figure 1). Since the molar absorptivity ϵ at 463 nm is known, the equilibrium constant K ($K = \epsilon/\epsilon_{yellow} - \epsilon$) is calculated at each temperature. A plot of ln K vs. $1/T$ makes $\Delta H°$ and $\Delta S°$ values available.

Thermodynamic quantities for the blue-to-yellow conversion of Ni(isocyclam)$^{2+}$ are compared in Table I with those for corresponding complexes of cyclam[18] and for the noncyclic

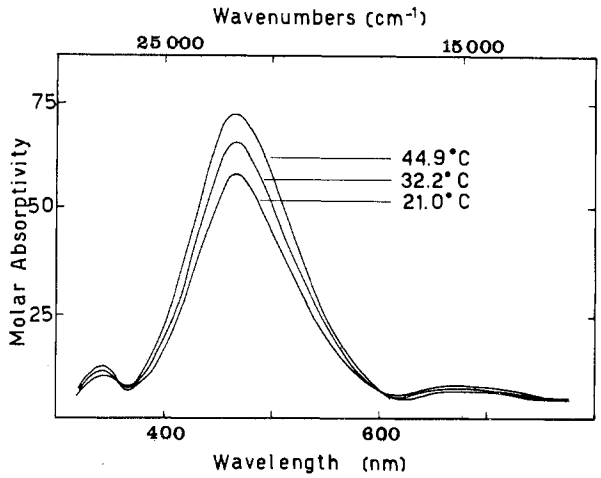

Figure 1. Visible absorption spectrum of Ni(isocyclam)$(ClO_4)_2$ in aqueous 0.1 M $NaClO_4$, recorded at different temperatures. The molar absorptivity of the planar complex, at 463 nm, is 116.4 L mol^{-1} cm^{-1}. For a complete entry of temperature-dependent equilibrium data, see Table I, footnote *b*.

Table I. Thermodynamic Quantities for the Blue-to-Yellow Conversion of Nickel(II) Complexes with Cyclic and Noncyclic Tetramines, at 25 °C in Aqueous 0.1 M $NaClO_4$[a]

ligand	$\Delta G°$, kcal mol^{-1}	$\Delta H°$, kcal mol^{-1}	$\Delta S°$, cal K^{-1} mol^{-1}
isocyclam	−0.26 ± 0.02	5.3 ± 0.1[b]	18.7 ± 0.5
cyclam[c]	−0.5	5.4	20
2,3,2-tet[c,d]	0.7	3.4	9
2,2,2-tet[d]	2.6	3.4	3

[a] For (2–4) × 10^{-2} M solution of perchlorate complex. [b] Calculated from the ln K vs. $1/T$ plot: 21.0 °C, ln K = 0.317; 28.0 °C, 0.529; 32.2 °C, 0.665; 35.6 °C, 0.738; 41.1 °C, 0.891; 44.9 °C, 1.013. Correlation coefficient for the least-squares straight line: 0.9993. [c] Reference 18. [d] Reference 23.

Table II. Spectroscopic Parameters of High- and Low-Spin Nickel(II) Complexes with 14-Membered Tetraaza Macrocycles

	low-spin[a] ν(d–d), cm^{-1}	high-spin[b] $\nu(^3B_{1g} \rightarrow {}^3B_{2g})$, cm^{-1}
Ni(isocyclam)$^{2+}$	21 600	13 700
Ni(cyclam)$^{2+}$	22 470[c]	14 750[d]

[a] Obtained from solution spectra, at 25 °C. [b] Ni(L)Cl_2 complex, 77 K. [c] Reference 40. [d] Reference 5.

tetramines 2,2,2-tet[23] and 2,3,2-tet.[18,23] It can be seen that $\Delta H°$ and $\Delta S°$ values for isocyclam are very similar to those found for cyclam but are remarkably different from those observed with noncyclic tetramines: in particular, the blue-to-yellow conversion is more endothermic (about 60%) for cyclic ligands than for their open-chain counterparts, but this enthalpic disadvantage is more than compensated by the entropy term, which is specially favorable for macrocyclic complexes. As a result, the equilibrium concentration of the yellow form (at 25 °C, 0.1 M $NaClO_4$, concentration of the complex (2–4) × 10^{-2} M) is remarkably larger when Ni(II) ion is incorporated in a macrocycle (cyclam, 71%; isocyclam, 61%; 2,3,2-tet, 23%; 2,2,2-tet, 1%).

The endothermicity of (1) reflects the endothermic release (or mobilization, see below) of the two apically coordinated water molecules, which is not fully compensated by the exothermic shortening of in-plane Ni–N bonds due to the spin reduction (from 2.07–2.10 Å (high spin)[27–31] to 1.88–1.91 Å (low spin)[24,32]). Because of the contraction of the central ion, tetramine ligands are forced to further fold themselves around the metal, to offer nitrogen atoms at required distances. This process should involve an increase of internal energy (and of enthalpy) of steric origin and is expected to be more conspicuous (more endothermic) for the more rigid, precyclized molecules cyclam and isocyclam, rather than for the flexible open-chain ligands 2,3,2-tet and 2,2,2-tet, accounting for the discrepancy of the experimental enthalpy behavior. It has been suggested that the spin interconversion of the above aqueous complexes does not necessarily involve a definitive release of the apical water molecules, but it may occur through a more or less conspicuous elongation of the axial Ni–OH_2 bonds.[23] This mechanism probably operates with open-chain complexes, where the measured entropy change is considerably lower than that expected for the effective liberation of two water molecules in aqueous solution (2 × 8–10 cal mol^{-1} K^{-1}).[23,33,34] The positive entropy change reflects the increased mobility of the weakly coordinated water molecules in the extremely tetragonally distorted octahedral complexes.[35] On the contrary, $\Delta S°$ values measured for cyclic complexes range between the predicted values, suggesting that, in this case, an effective liberation of the coordinated water molecules occurs. This is believed to originate from the increase of nonbonded repulsive interactions between apical water molecules and the aliphatic part of the ligand (for cyclam and isocyclam there is an additional trimethylenic chain compared to the case of 2,3,2-tet). The inference of ligand–apical water molecules interactions on the entropy change of equilibrium 1 has been demonstrated also with Ni(II) complexes with *C*-alkyl-substituted ethylenediamines.[36,37] It is comforting that the blue-to-yellow conversion for the Ni(II) complex with the 14-membered macrocycle *ms*-CRH (**3**) is regulated by thermodynamic quantities that are similar to those found for cyclam and isocyclam ($\Delta H°$ = 4.4 kcal mol^{-1}, $\Delta S°$ = 15.8 cal K^{-1} mol^{-1}).[16,38]

3. Ligand Structure and In-Plane Nickel(II)–Nitrogen Interactions. For low-spin Ni(II) tetramine complexes, the energy of the unique band in the visible region is a measure of the energy of the equatorial Ni–N interactions.[39,40] The absorption band maximum of Ni(isocyclam)$^{2+}$ (yellow) appears at a frequency (see Table II) remarkably lower (about 1000 cm^{-1}) than that for Ni(cyclam)$^{2+}$, demonstrating that the asymmetric macrocycle establishes weaker metal–donor atom interactions than its more symmetric homologue.

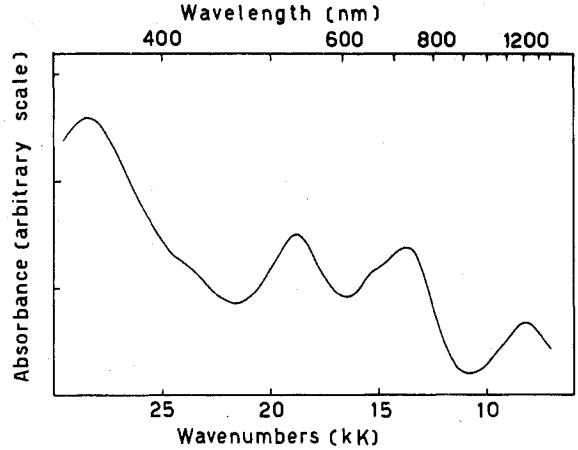

Figure 2. Electronic spectrum of Ni(isocyclam)Cl_2, at 77 K. The energy of the band at 13 700 cm^{-1} ($^3B_{1g} \rightarrow {}^3B_{2g}$) gives $10Dq^{xy}$.

Information about in-plane Ni–N interactions cannot be obtained for the high-spin Ni(L)$(H_2O)_2^{2+}$ species from solution spectra, because d–d bands are very weak and poorly resolved, due to the predominance of the low-spin complex. On the other hand, the hydrated chromophore cannot be isolated as a solid. Recently, a thorough study has been reported on the spectral properties of a series of complexes of formula Ni(L)X_2, in which L is a 14- (cyclam) to 16-membered tetraaza macrocycle and X is an inorganic counterion.[5] Detailed quantitative analysis allowed the determination of spectroscopic parameters; among those was $10Dq^{xy}$, which is exactly given by the energy of the $^3B_{1g} \rightarrow {}^3B_{2g}$ transition. Considering that chloride ion, among the counterions, is the closest ligand to water in the spectrochemical series, we have recorded the electronic spectrum of Ni(isocyclam)Cl_2 at liquid nitrogen temperature (Figure 2). It shows six bands in the 350–1200-nm region and they were fully defined through Gaussian analysis. The $^3B_{1g} \rightarrow {}^3B_{2g}$ band was identified according to the criteria developed in the previous treatment.[5,41] It appears at 13 700 cm^{-1}, i.e., at an energy value 1000 cm^{-1} lower than for corresponding cyclam complex in the same experimental conditions[5] (see Table II).

The two 14-membered macrocycles have a coordination cavity of comparable aperture, and the weaker coordinative interactions experienced by both low- and high-spin nickel(II) ion when incorporated in isocyclam, rather than in cyclam, cannot be merely ascribed to a mismatch in the size of macrocyclic hole and metal. The difference in behavior must lie in the ligand configuration and consequent orientation of donor atoms. In this connection, it must be considered that, whereas in cyclam complexes the two most hindering six-membered chelate rings, which are probably in the most stable chair form, are trans each other, in isocyclam complexes they are consecutively disposed. It is possible that, in order to reduce the steric repulsions between the two cis trimethylenic chains, the latter coordinated ligand experiences some distortion, which results in a displacement of donor atoms from the square (deviation toward a trapezoid) or, in any case, in a less favorable orientation of nitrogen atoms. This involves a reduction of Ni–N bond energy: this energy decrease is of the same order (~3 kcal mol^{-1}), as deduced from spectral parameters (Table II), and is independent of the spin state of the central Ni(II) ion.

A less symmetrical arrangement of donor atoms in Ni(isocyclam)$^{2+}$ with respect to Ni(cyclam)$^{2+}$ is also suggested by the remarkably larger value of the molar absorptivity of

Table III. Electrochemical Behavior of Nickel(II) Complexes with Tetraaza Macrocycles, in Acetonitrile and 0.1 M Bu_4NClO_4, at 25 °C

complex	oxidn potl[a,b]	reducn potl[a,b]
Ni(isocyclam)$^{2+}$ (mixture)[c]	0.838	−1.628[d]
Ni(isocyclam)$^{2+}$ (blue)[e]	0.85	−1.64
Ni(isocyclam)$^{2+}$ (yellow)[e]	0.81	−1.60
Ni(cyclam)$^{2+}$ (mixture)[f]	0.702	−1.714[g]
Ni(cyclam)$^{2+}$ (blue)[h]	0.71	−1.72
Ni(cyclam)$^{2+}$ (yellow)[h]	0.68	−1.69
Ni([15]aneN$_4$)$^{2+}$ (blue)[i]	1.012	
Ni(*dl*-CRH)$^{2+}$ (mixture)[j]	0.929	−1.462
Ni(*dl*-CRH)$^{2+}$ (blue)[k]	0.93	−1.46
Ni(*dl*-CRH)$^{2+}$ (yellow)[k]	0.93	−1.46
Ni(*ms*-CRH)$^{2+}$ (mixture)[l]	0.928	−1.450
Ni(*ms*-CRH)$^{2+}$ (blue)[m]	0.93	−1.45
Ni(*ms*-CRH)$^{2+}$ (yellow)[m]	0.93	−1.45

[a] E (V); vs. $Ag/AgNO_3$ 0.01 M; 0.1 M Bu_4NClO_4. [b] Measured at a platinum electrode (CV, dc, ac), ±0.005 V; ±0.01 V for potentials corrected to blue or yellow species. [c] 82% blue, 18% yellow. [d] Reduction potential at the hanging mercury drop (CV): −1.627 V. [e] Calculated through ΔG(blue-to-yellow) = 0.66 kcal mol^{-1}. [f] 78% blue, 22% yellow. [g] Reduction potential at the hanging mercury drop (CV): −1.713 V. [h] Calculated through ΔG(blue-to-yellow) = 0.75 kcal mol^{-1}. [i] 99% blue; distorted, irreversible voltammogram on reduction. [j] 45% blue, 55% yellow. [k] ΔG(blue-to-yellow) = −0.12 kcal mol^{-1}. [l] 55% blue, 45% yellow. [m] ΔG(blue-to-yellow) = 0.12 kcal mol^{-1}.

the low-spin form of the latter (116.4 and 64.5 L mol^{-1} cm^{-1}, respectively).

4. Oxidation and Reduction Behavior. Nickel(II) complexes with saturated tetraaza macrocycles undergo chemical and electrochemical oxidation and reduction in acetonitrile solution.[42,43] In a thorough paper on the electrochemistry of Ni(II) macrocyclic complexes,[44] it has been demonstrated by ESR studies that these redox processes involve the formation of authentic Ni(III) and Ni(I) species. We have now investigated the oxidation and reduction behavior of Ni(isocyclam)$^{2+}$ in acetonitrile solution. For comparative purposes, in view of the different conditions of temperature and/or reference electrode, the complexes with cyclam and other selected tetraaza macrocycles were reinvestigated. The redox behavior of Ni(*dl*-CRH)$^{2+}$ is reported for the first time.

In CV experiments i_{pa}/i_{pc} was unity and the $i_p/(\nu)^{1/2}$ ratio was constant and independent of the voltage scan speed, ν, (from 100 to 500 mV s^{-1});[45] peaks in the ac voltammograms (ν = 1–2 mV s^{-1}) were symmetrical and the half-peak width ranged between 90 and 95 mV;[46] dc voltammograms were typically S shaped, with comparable values of limiting current. All of this evidence establishes the simplicity of the electron transfer and is consistent with electrochemical reversibility. In the case of Ni(isocyclam)$^{2+}$ the one-electron stoichiometry was confirmed by controlled-potential coulometry, for both oxidation and reduction processes. Values of the redox potential were found to be coincident, within the experimental error, independent of the technique employed, and are reported in Table III.

Prior to comment on the electrochemical behavior, it is necessary to assess the nature of the solution species to be oxidized or reduced. In fact, Ni(II) complexes with tetraaza ligands also exist as an equilibrium mixture of blue and yellow forms in acetonitrile, as is clearly shown by the visible spectra of their solutions. The impossibility of obtaining only one form by either temperature change or addition of background electrolyte prevents a quantitative assessment of equilibrium 2. However, approximate values for log K of eq 2 can be

$$Ni(L)(CH_3CN)_2^{2+} \rightleftharpoons Ni(L)^{2+} + 2CH_3CN \qquad (2)$$

obtained, assuming that ϵ_{yellow} has the same value as in water or acetone (solvents in which 100% of the low-spin complex is easily achieved). This assumption is justified by the fact that for the reference complex Ni(*ms*-CTH)$^{2+}$ and Ni(*dl*-CTH)$^{2+}$ the variation of the ϵ_{yellow} value, changing from CH_3CN to H_2O and $(CH_3)_2CO$, is less than 10%. Therefore the equilibrium constant for (2), for L = isocyclam, cyclam, *ms*-CRH, and *dl*-CRH, has been evaluated, using the ϵ_{yellow} value measured in water or acetone. Log K values are reported in Table III (see footnotes *c*, *f*, *i*, and *l*). Ni([15]aneN$_4$)$^{2+}$ exists as more than 99% of the blue form. As a general behavior, in view of the stronger coordinating tendencies of axial CH_3CN molecules, the blue "octahedral" complex is expected to be favored, with respect to water. This is found true for the complexes with the unsubstituted macrocycles cyclam and isocyclam, where the concentration of the blue species is doubled or more than doubled. In the case of CRH complexes, the solvent change does not apparently modify the equilibrium (2); this is probably due to the presence of two methyl groups on the macrocyclic skeleton, which exert a mechanical resistance toward the axial coordination, independently from the nature of the apical ligands.

If $\Delta G°$ values for eq 2 are used, the electrode potentials, measured for the Ni(II) blue–yellow mixture, can be split into those referring to each species of different spin multiplicity. This correction, which is small, but not negligible, was not taken into account in the previous report.[44]

It is seen that for cyclam and isocyclam the oxidation and reduction of the most thermodynamically stable (in CH_3CN) blue form require more energy than corresponding oxidation and reduction of the yellow form. On the other hand, both octahedral and planar complexes of cyclam experience an *easier oxidation* (less positive potential) and a *more difficult reduction* (more negative potential) than corresponding ones of isocyclam. This behavior can be qualitatively justified by considering that cyclam, which exerts stronger Ni–N in-plane interactions, increases the energy of the Ni(II) complex antibonding orbital, from which the electron is abstracted (oxidation) or in which it is dropped (reduction), with respect to its less symmetrical and less strongly coordinating isomer isocyclam.

In the case of complexes with *ms*- and *dl*-CRH isomers, the blue and yellow forms have a comparable solution stability; therefore their redox potentials are nearly coincident. Noteworthy, configurational differences of the two isomeric ligands (i.e., the relative positions of the two CH_3 groups) provoke only small differences in the Ni(II) oxidation and reduction potentials. The same was previously observed with complexes of *ms*- and *dl*-CTH.[42] Finally, the CRH complexes have a chelate ring sequence analogous to isocyclam complexes (5,5,6,6) but undergo oxidation at higher potential and reduction at lower potential. Explanation is not straightforward, but it should be related to (i) the difference of in-plane interactions, due to the presence of a pyridine nitrogen atom, and (ii) different flexibility of the macrocyclic framework.

It is worthwhile to note that the algebraic difference, ΔE, of the oxidation and reduction potential for the Ni(II) complexes reported in Table III (i.e., the range of their electrochemical existence) is roughly constant (2.41 ± 0.08 V; this value is independent of the reference electrode potential). Moreover, this behavior is general, as shown in Figure 3, where the oxidation potential is plotted against the reduction potential for a complete series of nickel(II) complexes with saturated and unsaturated and substituted and unsubstituted tetraaza macrocycles, taken from literature.[44] It is seen that the plotted values are well behaved with respect to a straight line of slope 1 and an intercept = ΔE = 2.42 V. Good behavior requires that oxidation/reduction processes produce authentic Ni(III)/Ni(I) species. Two points have been reported (12 and

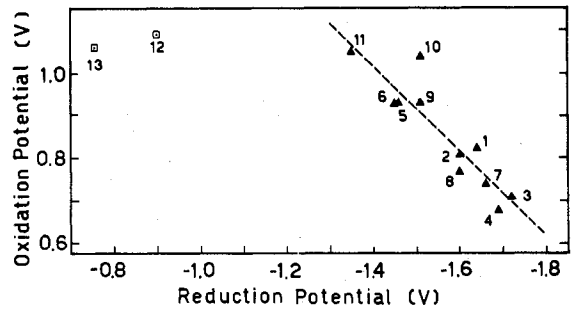

Figure 3. Correlation of oxidation and reduction potentials (vs. Ag/Ag^+ 0.01 M) of nickel(II) complexes with tetraaza macrocycles, in acetonitrile. Ligands: 1, isocyclam, blue; 2, isocyclam, yellow; 3, cyclam, blue; 4, cyclam, yellow; 5, *dl*-CRH; 6, *ms*-CRH; 7, Me_2-[14]aneN$_4$; 8, Me_4[14]aneN$_4$; 9, Me_6[14]aneN$_4$; 10, Me_6[14]-4,11-dieneN$_4$; 11, Me_6[14]-1,4,8,11-tetraeneN$_4$; 12, Me_4[14]-1,3,-8,10-tetraeneN$_4$; 13, CR. Values for complexes 7–13 are taken from ref 44. The dashed straight line has a slope of −1 and an intercept of 2.42 V (mean of $(E_{Ox} - E_{Red})$ for complexes 1–11).

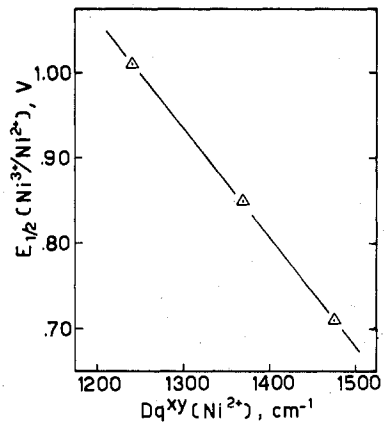

Figure 4. Correlation of the electrode potential of the Ni^{III}/Ni^{II} couple with $Dq^{xy}(Ni^{II})$ for three complexes with saturated tetraaza macrocycles (Dq^{xy} values, obtained from chloride complexes, at 77 K, for cyclam and [15]aneN$_4$ are taken from ref 5).

13) that do not absolutely fit the straight line: they refer to complexes in which the electron taken up on reduction does not lie on the metal but is delocalized on the ligand framework, as demonstrated by ESR analysis.[44] Therefore, the oxidation/reduction potential plot can be used as a quick (*only electrochemical*) test for the authenticity of the oxidation states of redox products of Ni(II) complexes with novel tetraaza macrocycles.

It is clear that the redox potential and the ligand field energy change associated with the electrode process are strictly correlated. Therefore, it is not surprising that a linear relationship exists between the oxidation potential and the Dq^{xy} for presently available high-spin nickel(II) complexes with tetramine macrocycles (Figure 4). In fact, to a fixed value of Dq^{xy} of Ni(II) complex, a highest Dq^{xy} value must correspond to a Ni(III) analogue, due to the increase of the positive charge. Linearity involves that all other terms than ligand field energy change in the oxidation process (the change of solvation energies) remain constant. A similar trend was found for six low-spin Ni(II) complexes with tetrapeptides in aqueous solution.[47] Furthermore, the potential of the Co^{III}/Co^{II} couple for a series of macrocyclic complexes was found linearly correlated to Dq^{xy} of the Co^{III} corresponding chromophore.[48]

Conclusions

Previous papers have shown how the energy of the metal–nitrogen bond is strictly dependent upon the size of the macrocyclic cavity.[5,6] We have demonstrated that, as far as the 14-membered macrocycles are concerned, where two different structures are possible, the distribution of nitrogen atoms in the ligand dramatically affects coordinative properties. The different ability to establish in-plane interactions with nickel(II) ions seems to be related to the ligand configuration, which influences position and orientation of the four coplanar donor atoms. Consequent alteration of in-plane bond strength determines the magnitude of electrode potentials, for both one-electron oxidation and reduction processes, in complete analogy with the general behavior of nickel(II) complexes with cyclic tetraaza ligands.

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Registry No. Ni(isocyclam)$(ClO_4)_2$, 68344-01-4; Ni(isocyclam)Cl_2, 68317-93-1; Ni(isocyclam)$(CH_3CN)_2^{2+}$, 68317-94-2; Ni(cyclam)$^{2+}$ (yellow), 46365-93-9; Ni(cyclam)$(CH_3CN)_2^{2+}$, 68317-95-3; Ni([15]aneN$_4$)$(CH_3CN)_2^{2+}$, 68317-96-4; Ni(*dl*-CRH)$(CH_3CN)_2^{2+}$, 68398-31-2; Ni(*dl*-CRH)$^{2+}$ (yellow), 47023-87-0; Ni(*ms*-CRH)-$(CH_3CN)_2^{2+}$, 68317-91-9; Ni(*ms*-CRH)$^{2+}$ (yellow), 53537-59-0; 1,5,9-tris(*p*-toluenesulfonyl)-1,5,9-triazanonane, 35980-64-4; 1,-5,9-tris(*p*-toluenesulfonyl)-1,5,9-triazanonane disodium salt, 56479-75-5; *p*-toluenesulfonyl chloride, 98-59-9; dipropylenetriamine, 27708-70-9; *N,O,O*-tris(*p*-toluenesulfonyl)bis(2-hydroxyethyl)amine, 16695-22-0; diethanolamine, 111-42-2; triethylamine, 121-44-8; 1,4,7,11-tetrakis(*p*-toluenesulfonyl)-1,4,7,11-tetraazacyclotetradecane, 52601-79-3; isocyclam, 52877-36-8; Ni(isocyclam)$(H_2O)_2^{2+}$, 68317-92-0.

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Amine Deprotonation in Copper(III)–Peptide Complexes

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Copper(III)–peptide complexes react rapidly with base, changing color from yellow to red (or to blue with a prolyl group at the amine terminal), prior to their redox decomposition. The initial Cu(III) complexes have three deprotonated peptide groups, and the proposed reaction with base is a deprotonation of the coordinated amine terminal of the peptide. Complexes in which the amine group has been N-formylated or dimethylated do not exhibit the effect and therefore it cannot be attributed to hydroxide addition to the metal. The reaction occurs only with the +3 oxidation state of copper. The pK_a values determined for complexes of eight peptides and peptide amides vary from 11.3 to 12.3.

Introduction

Coordination of deprotonated peptide nitrogens and deprotonated amide nitrogens to metal ions is well-known and occurs commonly with both copper(II)[1-4] and nickel(II)[1,5,6] complexes. This has been confirmed by a combination of potentiometric,[1,2,4,5] spectrophotometric,[4,6] and crystallographic[7] data. Similar reactions are found with cobalt(II)[8,9] and palladium(II).[10,11] The pH at which the metal-assisted deprotonation occurs varies according to the sequence Co(II), above pH 10 > Ni(II), pH 7–9 > Cu(II), pH 5–7 > Pd(II), pH 2–4.

In these studies the deprotonation of coordinated amine nitrogens has not been observed. Amine hydrogens are, of course, much less acidic than hydrogens on peptide or amide nitrogens. Deprotonation of amines coordinated to cobalt(III) has been proposed in the conjugate-base mechanism of cobalt(III) substitution reactions,[12,13] but the pK_a values are estimated to be well above 14.[14,15] On the other hand, gold(III)[16,17] and platinum(IV)[18] complexes have been observed to lose amine protons at much lower pH. In this work we find that copper(III)–peptide complexes undergo deprotonation of amine groups at pH 11–12.

The trivalent oxidation state of copper is stabilized in aqueous solution by peptide coordination.[19] Whereas other copper(III) species generated by electrochemical methods,[20] by pulsed radiolysis,[21] or by hypohalites[22] are relatively short-lived, copper(III)–peptide complexes can be kept from minutes to weeks, depending upon the peptide and the solution conditions.[23] The tetraglycine (G_4) complex of copper(II) reacts spontaneously with dioxygen[24] to generate $Cu^{III}(H_{-3}G_4)^-$, a complex with three deprotonated peptide groups coordinated to copper(III).[25] This complex and many other peptide complexes can be generated easily with oxidizing agents or by electrochemical means.[26]

The typical yellow color of the copper(III)–tetraglycine complex changes to red upon the addition of base. We propose that the reaction (eq 1) occurs with the loss of a fourth proton

$$\underset{\text{yellow}}{Cu^{III}(H_{-3}G_4)^-} + OH^- \rightleftarrows \underset{\text{red}}{Cu^{III}(H_{-4}G_4)^{2-}} + H_2O \quad (1)$$

from tetraglycine, caused by deprotonation of the coordinated amine group. The reaction is reversible with the addition of acid. Since base also catalyzes the oxidation of the ligand by copper(III), most of the copper(III) is destroyed after shifting back and forth between yellow and red several times. The products and stoichiometry of the oxidation–reduction reaction with tetraglycine are discussed elsewhere.[27] In order to be certain that the spectral changes are due to the loss of amine hydrogens and not to the addition of hydroxide ion to Cu(III), several *N*-formyl peptide complexes were prepared. These complexes have four deprotonated nitrogens coordinated (one formyl and three peptide groups) but they do not undergo the characteristic spectral shift in base. Spectra are obtained rapidly for all the complexes using a stopped-flow vidicon system.[28,29] The pH dependence of the electrode potential for the Cu(II)–Cu(III) reaction measured by cyclic voltammetry confirms the stoichiometry and equilibrium constant for eq 1. The nature of the observed spectral shifts suggests interesting changes in the nature of the bonding for the amine-deprotonated copper(III) complexes.

Experimental Section

Reagents. Chromatographically pure peptides were used in this work. Tetraglycine (G_4), pentaglycine (G_5), hexaglycine (G_6), and tetra-L-alanine (A_4) were obtained from Biosynthetika (Oberdorf, Switzerland). Triglycinamide (G_3a), tetraglycinamide (G_4a), L-prolylglycylglycinamide (PGGa), and L-phenylalanylglycylglycinamide (FGGa) were supplied as hydrochlorides from Vega-Fox (Tucson, Ariz.). The *N*-formyl peptides were prepared by dissolving 0.2 g of the parent peptide in 2.3 mL of formic acid and adding dropwise a twofold excess of acetic anhydride (~0.2 g). The *N*-formyl derivatives crystallized readily during 2–3 h of stirring of this mixture. The crystals were washed several times with ethanol and ether and dried. Anal. Calcd for *N*-fG_3 ($C_7H_{11}N_3O_5$): C, 38.5; H, 5.07; N, 19.4. Found: C, 38.7; H, 5.22; N, 19.3. Calcd for *N*-fG_4 ($C_9H_{14}N_4O_6$): C, 39.4; H, 5.11; N, 20.4. Found: C, 39.1; H, 5.15; N, 19.7. (*N*-f = *N*-formyl.)

Copper(II) perchlorate solutions were prepared from the twice-recrystallized salt and were standardized by EDTA titration using Murexide as an indicator. The copper(II)–peptide complexes were prepared in solution using 5–10% stoichiometric excess of the peptide. The pH was adjusted to about 10.8 to form the triply deprotonated complexes $Cu^{II}(H_{-3}L)$ or, in the case of *N*-fG_3a and *N*-fG_4, the quadruply deprotonated complexes $Cu^{II}(H_{-4}L)$. High pH (>10) is needed to form the copper(II) complexes of the *N*-formyl peptides; otherwise the mixture tends to precipitate. Table I summarizes some of the spectral and electrochemical data for the copper–peptide complexes. Most of the visible absorption maxima for the copper(II) complexes occur at slightly lower wavelength than that predicted by

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