mal" intramolecular electron transfer by this mechanism; the value is 160-fold lower than that measured for k_a (0.18 s^{-1}).
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The Stabilization of Trivalent Nickel in Deprotonated-Peptide Complexes

Sir:

Trivalent nickel has been considered to be a relatively rare oxidation state until recently. Nickel(III) complexes of the macrocyclic tetraaza ligands have been prepared and characterized in acetonitrile solution[1,2] and as solids.[2] Complexes of Ni(III) cyclam and its derivatives are stable as solids in a dry atmosphere, but decompose rapidly in aqueous solution.[2,3] Pulse radiolysis has been used to generate the Ni(III) complexes of ethylenediamine and of glycine in aqueous solution where the complexes rapidly decompose.[4] On the other hand a Ni(III)-EDTA complex, also prepared by the reaction of hydroxyl radicals, has recently been reported to be stable in deoxygenated aqueous solution for several days.[5]

In the present work Ni(III) deprotonated-peptide complexes are prepared and characterized in aqueous solution. This laboratory recently reported[6] that the Cu(III) oxidation state is substantially stabilized, both thermodynamically and kinetically, by metal-ligand bonding involving deprotonated-peptide nitrogen coordination. We find similar behavior for Ni(III)-peptide complexes, where the electrode potentials are lower than for other Ni(III) complexes due to the strong electron-donor properties of the deprotonated-peptide nitrogens. The suggested coordination is the same as that proposed for Ni(III)-bis(biuret),[7] except that there cannot be as much π-delocalization. The magnetic susceptibility and the reflectance spectrum were reported for the highly insoluble $KNi^{III}(bi)_2$ compound,[7] but this complex could not be characterized in solution.

The crystal structure of the Ni(II) complex of tetraglycine (G_4) shows that $Na_2[Ni(H_{-3}G_4)]\cdot 8H_2O$ is a square-planar complex with four nitrogens coordinated to the metal ion (one amine N and three deprotonated-peptide N).[8] This complex can be oxidized electrochemically or chemically to the corresponding Ni(III) species, but it decomposes easily, oxidizing the ligand to triglycinamide (G_3a), formaldehyde, and carbon dioxide.[9,10] Hence, most of the present studies were carried out with the more stable G_3a complex. The $[Ni^{II}(H_{-3}G_3a)]^-$ complex is oxidized quantitatively, either electrochemically or chemically (with $Ir^{IV}Cl_6^{2-}$), to the corresponding $Ni^{III}(H_{-3}G_3a)$ species, which is relatively stable in slightly acidic solution, but decomposes rapidly in base. Electrochemical oxidation was performed with a flow system in which the electrode arrangement included a graphite powder working electrode packed in a porous glass column, wrapped externally with a Pt wire electrode.[11] Oxidation causes a change in the electronic spectrum from an absorption band of the $[Ni^{II}(H_{-3}G_3a)]^-$ at 410 nm, ϵ 140 M^{-1} cm^{-1}, to an intense charge-transfer absorption for the Ni(III) species with a band at 320 nm, ϵ 5360 ± 150 M^{-1} cm^{-1}. The molar absorptivity was determined by quantitative reactions between the trivalent nickel complex and several different reducing agents including di(*tert*-butyl)nitroxide, hydroquinone, and $Fe(CN)_6^{4-}$. Immediate quenching of the electrochemically generated $Ni^{III}(H_{-3}G_3a)$ complex by a reducing agent affords nearly quantitative recovery of the original peptide ligand. This reversible redox property provides one piece of evidence that it is the metal ion and not the ligand which has been oxidized.

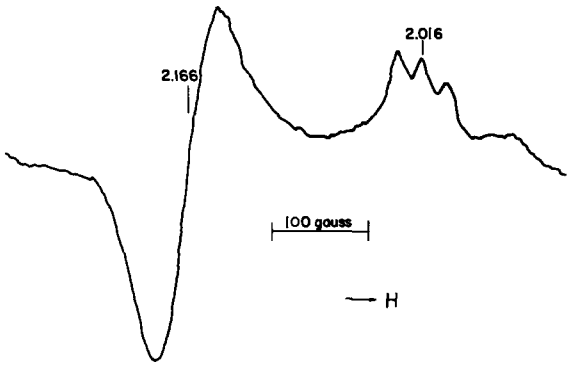

Figure 1. EPR spectrum of $Ni^{III}(H_{-3}G_3a)$. The Ni(II) complex (2.0×10^{-2} M, pH 9.5) was oxidized on a graphite column at 0.83 V vs. Ag|AgCl. The spectrum was obtained at 77 K and 9.074 GHz.

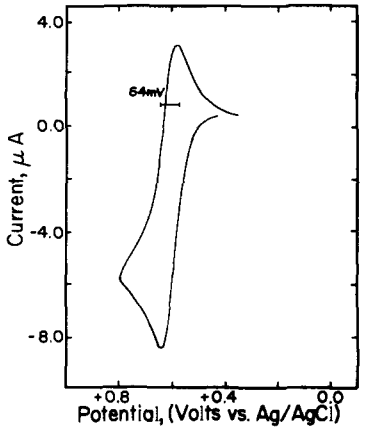

Figure 2. Cyclic voltammogram of $[Ni(H_{-3}G_3a)]^-$ in aqueous solution at a carbon paste electrode. $[NiG_3a]_T = 2.0 \times 10^{-3}$ M, μ = 0.1 M $NaClO_4$, scan rate = 20 mV s^{-1}. E^0 = 0.83 V vs. NHE.

The $Ni^{III}(H_{-3}G_3a)$ complex is much slower to decompose in acid than is the $[Ni^{II}(H_{-3}G_3a)]^-$ complex. The Ni(II) complex has a half-life of only 0.026 s at pH 3,[12] while the half-life of the Ni(III) complex is 900 s at this pH. Reduced lability of the metal-N(peptide) toward acid attack was also found in the case of Cu^{III}.[6]

More definitive evidence that the oxidized complex contains Ni^{III} is provided by its EPR spectrum. The $[Ni^{II}(H_{-3}G_3a)]^-$ complex is a low spin, d^8 species which is EPR inactive. After electrochemical oxidation an EPR spectrum was obtained at liquid nitrogen temperatures as shown in Figure 1. The spectrum with $g_\perp$ (2.166) greater than $g_\parallel$ (2.016) is similar to that found for Ni(III) complexes of the tetraaza macrocycles.[2,3,13] The existence and value of $g_\perp$ indicates that the initial oxidation gives a d^7, tetragonal nickel complex[13] rather than a nickel(II) ligand radical.[14] The value for $g_\parallel$ is a tentative assignment, and the factors contributing to its splitting are under investigation.

Cyclic voltammetry is used to characterize the triglycinamide and other peptide complexes of nickel. Figure 2 shows the current-voltage response for the nickel-triglycinamide complex. The voltammogram shows quasi-reversible behavior at slow scan rates, and therefore the potential of 0.83 V (vs. NHE), the midpoint between the oxidation peak and the reduction peak, is a reasonable estimate of E^0 for the $[Ni^{III,II}(H_{-3}G_3a)]^{0,-1}$ couple.

$$Ni^{III}(H_{-3}G_3a) + e \rightleftarrows Ni^{II}(H_{-3}G_3a)^- \quad E^0 = 0.83 \text{ V}$$

Table I lists the electrode potentials for a series of Ni(III) peptide complexes. Thermodynamic stability within this series

Table I. Standard Electrode Potentials of $Ni^{III,II}$–Peptide Complexes[a]

Ni(III) peptide	ΔmV[b]	E^0, V
Ni(H_{-2}glycylglycyl-L-histidine)	90	0.96
Ni(H_{-2}triglycine)	78	0.85
Ni(H_{-3}tetraglycinamide)	73	0.84
Ni(H_{-3}pentaglycine)$^-$	87	0.83
Ni(H_{-3}triglycinamide)	80	0.83
Ni(H_{-3}tetraglycine)$^-$	100	0.79

[a] Determined by cyclic voltammetry at 100 mV s^{-1} with a carbon paste working electrode, $[NiL]_T = 7.0 \times 10^{-4}$ M, 25 °C, $\mu = 0.1$ M $NaClO_4$, pH 9.3. [b] Peak to peak separation indicating the reversibility of the electrode reaction.

of trivalent nickel complexes increases with the number of deprotonated-peptide or deprotonated-amide nitrogen bonds. The proposed structure for the $[Ni^{III}(H_{-3}G_3a)]$ complex has two deprotonated-peptide nitrogens, one deprotonated-amide nitrogen and one amine nitrogen bound to the metal. Complexes of tetraglycine, pentaglycine, tetraglycinamide, and triglycinamide have similar metal–nitrogen bonding and correspondingly similar electrode potentials. The glycylglycyl-L-histidine complex, which has two deprotonated-peptide nitrogens, an amine nitrogen, and an imidazole nitrogen coordinated, is thermodynamically and kinetically much less stable in the higher oxidation state of nickel than the preceding complexes. On the other hand the triglycine complex (with an amine, a carboxylate, and two deprotonated-peptides coordinated) has an electrode potential only slightly higher than the triply deprotonated-peptide complexes and $Ni^{III}(H_{-2}G_3)$ is slower to decompose in acid than is $Ni^{III}(H_{-3}G_3a)$. In general the relatively low electrode potentials of the Ni(III)–peptide complexes can be attributed to the strong electron-donor properties of the deprotonated-peptide nitrogen.

The $Ni^{III,II}$ potentials for G_4 and G_3a are 0.16 and 0.19 V greater than the corresponding $Cu^{III,II}$ potentials for these peptide complexes. Direct chemical evidence of the difference in potential is seen in the quantitative oxidation of $Cu^{II}(H_{-3}G_3a)^-$ to $Cu^{III}(H_{-3}G_3a)$ by $Ni^{III}(H_{-3}G_3a)$. The difference in potential can be attributed in part to the relative advantages in ligand field stabilization of d^8 vs. d^9 and d^7 electronic configurations in the square-planar or tetragonal environment of the peptide complexes.

Nickel(II) catalyzes the reaction of molecular oxygen with some oligopeptides in neutral solution.[9,10] The reaction produces small amounts of Ni(III)–peptides which are intermediates in the oxidation of the peptides. An autocatalytic pathway by which O_2 reacts to give Ni(III) species is under investigation in this laboratory. The relatively mild conditions under which the Ni(III) state is attained suggests that this unusual oxidation state of the metal may be important in other nickel(II) catalyzed reactions.

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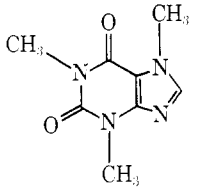
The Effect of Crystal Packing and Defects on Desolvation of Hydrate Crystals of Caffeine and L-(−)-1,4-Cyclohexadiene-1-alanine

Sir:

Numerous compounds are capable of existing in the solid state as hydrates and nonhydrated polymorphs.[1-12] Since the chemical[6] and physical properties[7] of crystal hydrates of drugs, e.g., caffeine[7] (I) and L-(−)-1,4-cyclohexadiene-1-alanine[6] (II) can differ markedly, crystal hydration may influence biological properties.[1,8,9] It is therefore important to understand what factors influence the solid state interconversion of such hydrates with their anhydrous forms.



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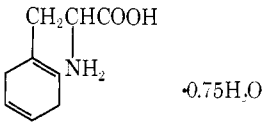

II

A typical crystal of caffeine hydrate (grown by slow evaporation of a water solution) and its anisotropic behavior upon dehydration is shown in Figure 1 (Ia through Id). The water

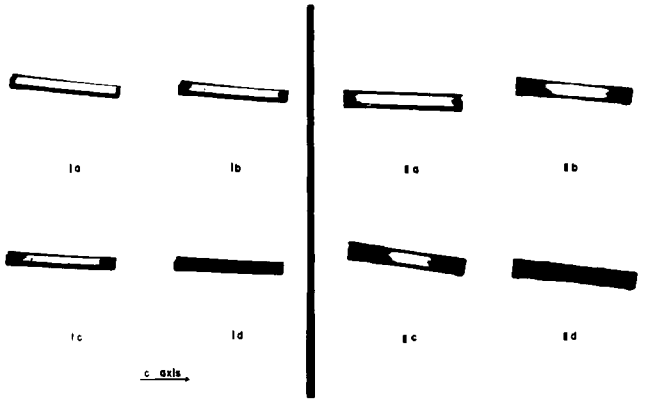

Figure 1. Behavior of a crystal (0.9 × 0.17 mm) of caffeine monohydrate (Ia through Id) in air at room temperature after both ends were cut off using a razor blade: (a) immediately after cutting; (b) after 4 h at room temperature; (c) after 24 h at room temperature; and (d) after 72 h at room temperature. Precession photography showed that the *c* axis paralleled the elongated direction of the crystal (horizontal axis in the photograph) and that the *a* axis was the vertical axis in the photograph. The nature of the crystals prevented goniometric determination of the Miller indices of the crystal faces but the precession studies showed that the end face approximated the (001) face while the top face approximated the (100) face. Photographs IIa through IId show the behavior of a crystal (1 × 0.2 mm) of L-(−)-1,4-cyclohexadiene-1-alanine·0.75H_2O in air at room temperature after both ends were cut off with a razor blade: (a) after 0.5 h; (b) after 2 h; (c) after 3 h, and (d) after 5 h.