cal/(mol K), respectively, in only 0.1 N NaClO$_4$[10] as compared to the 6 N NaClO$_4$ employed in our experiment. (As the concentration of salt increases, so does K_{eq} and ΔS.) A plausible explanation for the relatively low entropy term for the reaction involving the Ni[12]aneN$_4$ complex is that a five-coordinate complex is formed rather than the four-coordinate species. As a consequence of forming a five-coordinate species, fewer water molecules are lost. It is also possible that the small ΔS value is somehow related to the ligand's rearrangement from cis octahedral to square planar. A lower endothermicity of the blue to yellow conversion for [Ni([12]aneN$_4$)]X$_2$ complexes compared with the nickel(II) species containing 14-membered tetraaza macrocyclic ligand in 0.1 N NaClO$_4$ can be rationalized if the former complexes are converted from a cis-octahedral nickel(II) compound to a five-coordinate compound while the latter complexes involve a trans-octahedral to square-planar conversion. The conversion of a six-coordinate metal complex to a square-planar complex involves the contraction of all the in-plane metal to donor bonds. However, a conversion from a cis-octahedral species to either a trigonal bipyramid or a square pyramid with the metal extruded out of the plane of the donor atoms should involve only minor bond and angle alterations.

It has been shown that the stronger the ligand-field strength of a given ligand, the more it will stabilize the square-planar nickel(II) species over the octahedral species.[11] The smaller the size of the N$_4$ macrocycle coordinating to a metal ion in a planar fashion the higher its ligand-field strength.[1,12] Consequently, a 12-membered N$_4$ ring should exert an abnormally high ligand-field effect on the nickel(II), thereby stabilizing the square-planar geometry. This high ligand-field strength would be due to a mechanical constrictive effect which would result in shortening the nickel–nitrogen bond distance.[1] Assuming this mechanical constrictive effect to be the only operational factor determining the magnitude of K_{eq} and that the [12]aneN$_4$ could and did bond in a coplanar manner with the nickel(II), we would therefore expect higher K_{eq} values for the Ni([12]aneN$_4$) systems compared to those of nickel(II) complexes containing larger macrocyclic ligands. Since the K_{eq} is smaller for the [12]aneN$_4$ compared to larger size macrocycles, we believe that the [12]aneN$_4$ does not chelate in a planar fashion with the nickel(II) ion. It is also possible that the relatively low K_{eq} value found for the [Ni([12]aneN$_4$)]$^{2+}$ system may be due to a large increase in the strain energy of square-planar [Ni([12]aneN$_4$)]$^{2+}$ compared to that in nickel(II) complexes with larger macrocyclic ligands. However, [13]aneN$_4$ should impose a larger mechanical constrictive effect (thereby stabilizing the square-planar geometry) and also more strain energy (thereby stabilizing the six-coordinate species) than the [14]aneN$_4$ ligand.[1] The fact that the square-planar nickel(II) complex containing [13]aneN$_4$ was isolated from water and not the trans six-coordinate complex[13] suggests that the mechanical constrictive effect is a more important parameter in determining the position for the above paramagnetic–diamagnetic equilibrium than the strain energy. Also the more favorable ΔH values (less endothermic) for Ni([12]aneN$_4$)X$_2$ compounds compared to those of similar reactions in which larger macrocycles were employed suggest that it is not likely that a highly strained square-planar [Ni([12]aneN$_4$)]$^{2+}$ complex is formed. It is more likely that the complex is five-coordinate.

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Mutagenicity and Modes of Metal Binding to Nucleic Acids

Sir:

Recent work in this laboratory has shown that adenine and cytosine are capable of forming stable bonds to transition metals through their exocyclic nitrogens.[1,2] Unequivocal verification of this has now been made by Graves and Hodgson[3] utilizing crystals of [(1-MeCyt$^-$)(NH$_3$)$_5$Ru](PF$_6$)$_2$ prepared here. Metal coordination in this fashion makes available stable modes of metal–nucleic acid interaction, including cross-linking possibilities which have not hitherto been considered in the design of transition-metal anticancer drugs.[4] Moreover, it suggests alternative mechanisms to account for the mutagenicity of ammineruthenium(III) complexes[2,5] and perhaps that of other metal ions as well.[6,7]

Attack by ruthenium on adenosine (Ado) or cytidine (Cyd) is greatly facilitated by reduction of the metal to the more labile dipositive oxidation state.[2] Initial binding on Ado and possibly Cyd appears to occur on the pyrimidine-ring nitrogen adjacent to the exocyclic amine,[1] but some interaction may also occur at the N(7) site of Ado. Subsequent oxidation of the metal to the tripositive state probably facilitates deprotonation of the nearby exocyclic amine and so converts this nitrogen from a poor to an excellent coordination site.[1] Linkage isomerization can then take place from the ring to the exocyclic nitrogen. Abundant evidence exists for the relatively rapid linkage isomerization of (NH$_3$)$_5$Ru^{II} and -Ru^{III} complexes upon changing either the oxidation state of the metal or the protonation state of the ligand.[2,8] Furthermore, it should be noted that this mechanism is applicable to other metal complexes initially binding at a ring nitrogen proximal to an exocyclic amine, providing these can also significantly increase the acidity of this group and will firmly coordinate the resulting amide.

Contrary to the interpretation of Graves and Hodgson,[3] it is likely that the thermodynamic stability of complexes involving Ru(III) coordinated to the deprotonated exocyclic nitrogen of nucleosides is in good part due to π interactions. Evidence of the π-acceptor ability of Ru(III) was first indicated by Brown, Sutton, and Taube,[9] and thermodynamic

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results of Shepherd now corroborate this.[10] The present case offers structural evidence for Ru(III) π bonding in that the geometry around the metal ion in $(1\text{-MeCyt})^-(NH_3)_5Ru^{III}$ is nearly identical with that of an ammineruthenium–flavin complex in which strong π interactions can be well established.[11] In both instances the metal is approximately 0.5 Å out of the plane of the heterocyclic ligand and is bound to it by a short Ru–N bond distance of 1.98 Å. Moreover, the ligand nitrogen–carbon bonds which have considerable double-bond character in the free molecules are significantly lengthened in both complexes. In the cytosinato case, this suggests that much of the π-electron density from the exocyclic nitrogen, which is normally taken into the ring, is now diverted to interaction with the partially filled d orbital on the metal ion. The intense visible bands of both the flavin and cytosinato species, which behave as ligand to metal charge-transfer transitions on protonation of the ligand, further indicate substantial π interaction. A priori, however, these compounds would usually be considered to contain the metal in different oxidation states, so that the flavin complex would represent a Ru(II) species with a strong π-acceptor ligand and the cytosinato complex would represent a Ru(III) species with a good π-donor ligand. Therefore, it appears in both instances that, owing to strong π interactions, the metal is behaving in a manner intermediate between the two oxidation states.

Earlier work with DNA complexes of $(NH_3)_5Ru^{III}$ can now safely be interpreted as showing coordination to the exocyclic-N sites of Ade and Cyt residues as well as to the N(7) of guanine.[12] Thus binding to these sites constitutes a means whereby substitution-inert metal ions can cause recognizable lesions in cellular chromatin and so induce the cell to attempt to repair its DNA by error-prone methods. It is the error-prone repair response that finally results in observable bacterial mutations caused by most substitution-inert metal ions.[5,6,13]

While the mechanisms of metal-induced mutagenicity are now a matter of considerable investigative effort, it is becoming apparent that many commonly used metal ion complexes are mutagenic and that intracellular electron transfer involving metal ions may serve to activate some species in this regard.[14] Workers handling these materials might be well-advised to use a bit more caution than has customarily been the case.

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Additions and Corrections

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Kenneth R. Poeppelmeier, John D. Corbett,* Tom P. McMullen, David R. Torgeson, and Richard G. Barnes: Study of the Crystal Structures and Nonstoichiometry in the System $Cs_3Sc_2Cl_9$–$CsScCl_3$.

Page 131. In Table I the units for the *d* values are incorrect. These are lattice distances—not densities—and should not be given in g/cm^3.—John D. Corbett