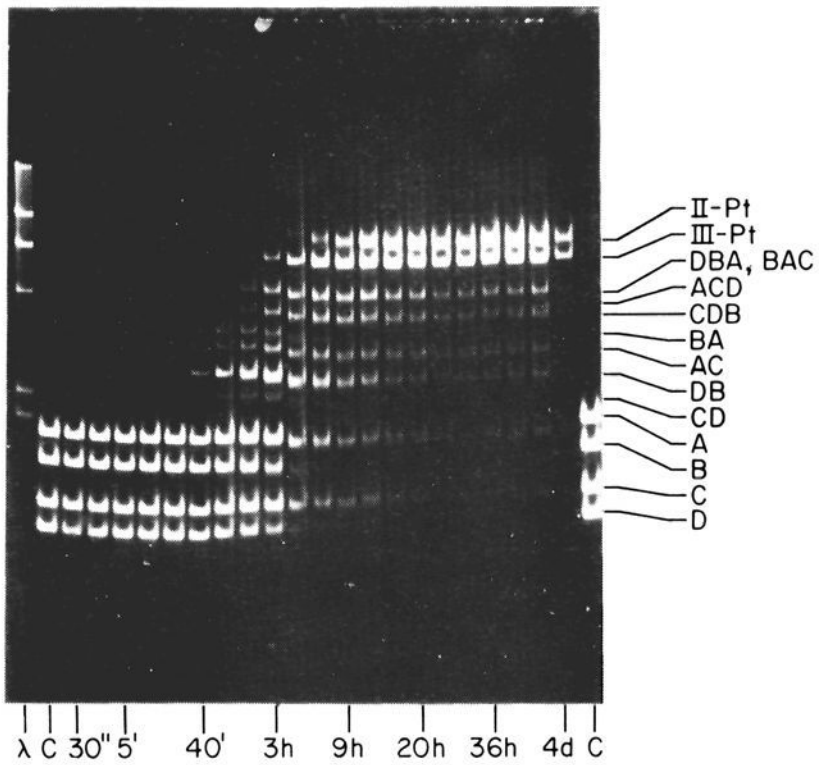


**Figure 2.** Electrophoresis in 1% agarose gels of a mixture of closed and nicked circular pSM1 DNAs incubated with *cis*-DDP for various time intervals and treated with Pst I restriction endonuclease. Channels 2–24 correspond to incubation times of 0 (C, control) and 30 s, 1.5, 5, 10, 20, and 40 min, 1.3, 2, 3, 5, 7, 9, 12, 16, 20, 24, 30, 36, 48, 72, 96, and 0 (C) h. The amount of platinum bound per nucleotide for channels 3–23 was determined by AA to rise from $3.63 \times 10^{-3}$ after 20 min to 0.070 near the end of the incubation period. Labels refer to fragments identified in Figure 1; the symbols II-Pt and III-Pt refer to nicked circular and linear DNAs, respectively, produced following long time incubation with *cis*-DDP (see ref 15). Channel 1 contains λ DNA cut with Hind III as an internal standard for sizing the pSM1 DNA fragments. Further experimental details and results will be reported elsewhere.

quence, the selective inhibition by *cis*-DDP of cleavage at the D–B junction must involve base pairs adjacent to the restriction sequence. Figure 1 displays the sequences[6] of pSM1 DNA surrounding the four Pst I restriction sites. Examination of the region around the D–B junction reveals the occurrence of a unique $(dG)_4(dC)_4$ cluster to which we ascribe the selectivity of cleavage inhibition.[7] The other three cutting sites are not adjacent to an oligo(dG)·(dC) sequence. Studies of the reaction of *cis*-DDP with DNAs of varying (G + C)/(A + T) ratios have shown that the extent of binding increases with the (G + C) content; moreover, binding to poly(dG)·poly(dC) is substantially greater than to poly(dG·dC).[8] A study of *cis*-DDP with various nucleotides showed the rate of reaction with 5′-GMP to be the most rapid.[9] A previous investigation of the effect of *cis*-DDP on the Bam H1 restriction enzyme digest of λ DNA was interpreted as evidence for binding to adjacent guanine bases, although this was not a unique interpretation.[10] The present results are the first demonstration of selective binding of *cis*-DDP to a specific sequence in a naturally occurring DNA. It is also noteworthy that the effect occurs with as little as four bound platinum atoms per thousand nucleotides.

An examination of a CPK space filling model of $(dC)_4(dG)_4$ reveals that *cis*-DDP can bind two adjacent guanine bases at N-7, or two adjacent cytosine bases at N-3, if base pairing is disrupted. The models indicate that such binding could produce a twofold shortening of the DNA measured along the original helix axis, as found by electron microscopy.[3,11] Numerous X-ray diffraction studies of guanine or cytosine containing DNA fragments coordinated to *cis*-DDP support the likelihood of N-7 (G) or N-3 (C) coordination.[2,12] It is interesting that the two guanine N-7 atoms of the d(pGpG) unit cannot bind the inactive *trans*-diammineplatinum(II) moiety as revealed by studying CPK models of the dinucleotide and the platinum complex. The difficulty of coordinating a *trans*-diammineplatinum(II) complex to adjacent guanine bases on a DNA strand was noted previously.[8b] Thus, of the various candidates for the *cis*-DDP recognition site on DNA,[2,13] intrastrand cross-linking of nearest neighbor guanine[10,14] or cytosine bases by the drug is strongly supported by the present results.

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## Mechanism of Oxidative Cleavage of α-Hydroxyalkylchromium Complexes

*Sir:*

One key intermediate in the Fischer–Tropsch process may be a metal-bound α-hydroxyalkyl group.[1,2] Transition metal complexes containing this group[3–5] are relatively rare and often quite unstable, and thus their chemistry has not been extensively explored. Hydroxymethyl complexes of cobalt(III) macrocycles,[3,4] for example, undergo unimolecular decomposition in aqueous solution by an internal two-electron process (eq 1) preventing an examination of their chemical reactions.

$$[Co^{III}(N_4chel)CH_2OH]^{n+} + H_2O \rightarrow [Co^{I}(N_4chel)]^{n-1} + HCHO + H_3O^+ \quad (1)$$

The closely related chromium(III) analogues[6,7] such as $(H_2O)_5CrCH_2OH^{2+}$ and other $(H_2O)_5CrCRR'OH^{2+}$ cations are stable to decomposition in this manner.[8] We have found that these complexes, prepared by the published methods,[6] are very powerful but selective reducing agents. They react with

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the mild and substitution-labile one-electron oxidants $Fe^{3+}$ and $Cu^{2+}$, whereas the analogous chromium alkyls do not. The exceptional chemistry of the hydroxyalkylchromium cations is shown not only by the formation of the reduced metal ion ($Cu^{+}$ or $Fe^{2+}$), but also by the net reduction of chromium to its divalent state, as shown in eq 2.

$$CrCRR'OH^{2+} + Cu^{2+}(\text{or } Fe^{3+}) = Cr^{2+} + Cu^{+}(\text{or } Fe^{2+}) + RR'CO + H^{+} \quad (2)$$

The $Cr^{2+}$ produced, unless specifically scavenged,[9] is subsequently oxidized[10] by a second mole of $Fe^{3+}$ (rapidly) or $Cu^{2+}$ (slowly). In each case, the stoichiometry of the reactions and the yields and identities of the organic and inorganic products as given in this equation were unambiguously determined.[11] The mechanism of these intriguing reactions was investigated by kinetic studies over a wide range of concentrations.[12] A small sample of the data for $CrCH(CH_3)OH^{2+}$ is shown in Figure 1. These results were used to establish the rate equation

$$-d[CrCRR'OH^{2+}]/dt = \{k_d + (k + k'[H^{+}]^{-1})[M]\}[CrCRR'OH^{2+}] \quad (3)$$

where $k_d$ is the rate of spontaneous acidolysis[6,7,13] and M represents $Cu^{2+}$ or $Fe^{3+}$. The rate constants[12] for $CrCH_2OH^{2+}$ are $k$ ($M^{-1}$ $s^{-1}$) = 0.036 ± 0.007 ($Cu^{2+}$), 0.22 ± 0.01 ($Fe^{3+}$); $k'$ ($s^{-1}$) = 0.251 ± 0.003 ($Cu^{2+}$), 0.496 ± 0.006 ($Fe^{3+}$). These values are such that the pathway represented by the rate constant $k'$ predominates under the conditions employed. Values of $k'$ for the related complex $CrCH(CH_3)OH^{2+}$ are 1.46 ± 0.05 ($Cu^{2+}$) and 0.481 ± 0.005 ($Fe^{3+}$) $s^{-1}$ and for $CrC(CH_3)_2OH^{2+}$ are 0.574 ± 0.013 ($Cu^{2+}$) and 1.90 ± 0.08 ($Fe^{3+}$) $s^{-1}$.

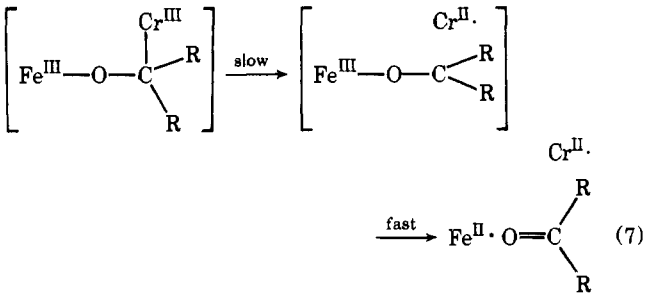
The mechanism proposed to account for the major pathway consists of a rapidly established preequilibrium[14] in which the proton of the C-bonded alcohol is replaced by the metal ion oxidant. For $Fe^{3+}$, for example,

$$Fe^{3+}_{aq} + H_2O \rightleftharpoons FeOH^{2+} + H^{+} \quad (4)$$

$$(H_2O)_5CrCH_2OH^{2+} + FeOH^{2+} \rightleftharpoons [(H_2O)_5CrCH_2OFe^{4+}] \quad (5)$$

$$[(H_2O)_5CrCH_2OFe^{4+}] \rightarrow Cr^{2+}_{aq} + Fe^{2+}_{aq} + HCHO \quad (6)$$

According to this mechanism, if the intermediate is assumed to follow the steady-state approximation and reaction 6 is taken to be rate limiting, $k' = K_4K_5k_6$. Values of $k'$ for the three complexes studied are quite similar for both $Cu^{2+}$ and $Fe^{3+}$, all lying within the range 0.25–1.9 $s^{-1}$. This suggests that the rate in every case may be governed by a similar process, most likely electron transfer to chromium(III). This idea is incorporated into the scheme shown in eq 7. Clearly ruled out by the




(7)

nature of the organochromium complexes is a mechanism similar to that found for free ·ROH radicals by copper(II) ions, involving an organocopper intermediate.[15,16] An examination was also made of the two closely related complexes $CrCH(CH_3)OC_2H_5^{2+}$ and $CrCH(CF_3)OH^{2+}$. The former does not react with $Cu^{2+}$ at all and the latter reacts so slowly that only an approximate value, $k' < 2 \times 10^{-4}$ $s^{-1}$, can be cited. Both findings are consistent with the formulation given in eq 7, in that the very electronegative substituent would be expected to greatly reduce electron transfer from coordinated alcohol to chromium, and an OR group in place of OH would be expected to prevent reaction by this pathway.

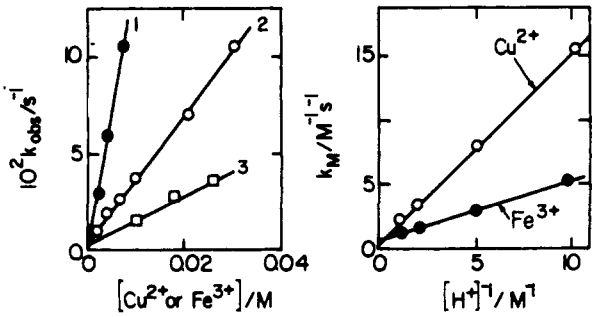



**Figure 1.** Representative kinetic data for the oxidation of $CrCH(CH_3)OH^{2+}$ by $Cu^{2+}$ and $Fe^{3+}$ showing (left) the linear variation of the pseudo-first-order rate constant with the concentration of oxidant at constant $[H^+]$ (line 1, $Cu^{2+}$ at 0.1 M $H^+$; 2, $Cu^{2+}$ at 0.5 M $H^+$; 3, $Fe^{3+}$ at 0.8 M $H^+$) and (right) the variation of the second-order rate constant with $[H^+]^{-1}$.

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(10) In the case of $Fe^{3+}$, oxidation of $Cr^{2+}$ occurs rapidly compared with the rate of eq 2, although not so rapidly as to prevent scavenging of $Cr^{2+}$ by $Co(NH_3)_5Br^{2+}$.[9] The reoxidation of $Cr^{2+}$ by $Cu^{2+}$ occurs more slowly and is competitive with the rate of eq 2.
(11) The organic products for the three $CrCRR'OH^{2+}$ complexes with CRR'OH = $CH_2OH$, $CH(CH_3)OH$, and $C(CH_3)_2OH$ are, respectively, formaldehyde, acetaldehyde, and acetone; these products support the formulations of the complexes themselves as given previously[6,7] and are consistent with the stoichiometric requirements of eq 2.
(12) Kinetic data were evaluated spectrophotometrically at 24.8 °C, 1.00 M ionic strength, in 1 M (~4–8 vol. %) aqueous alcohol (methanol, ethanol, or 2-propanol, respectively). Reactions conducted using a large stoichiometric excess of $Cu^{2+}$ or $Fe^{3+}$ followed pseudo-first-order kinetics, with $k_{obsd}$ dependent on $[H^+]$ and $[Cu^{2+}]$ or $[Fe^{3+}]$ as shown in Figure 1. A small excess of $Cr^{2+}$ was usually employed in the preparation of $CrROH^{2+}$; excess hydrogen peroxide was occasionally used, but this proved immaterial as $H_2O_2$ does not react with the $CrCRR'OH^{2+}$ complexes.
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