We have found that the HMQC NMR technique in a one-dimensional format[11] can be used to visualize the methylene protons directly bonded to the labeled allylic ^{13}C carbon atom of metabolite **7**, without interference from matrix resonances arising from protons attached to ^{12}C and natural abundance ^{13}C carbon atoms. The same metabolite sample as illustrated in Figure 1b was analyzed with a Varian VXR 500 FT NMR spectrometer equipped with an indirect-detection probe. Acquisition of the HMQC carbon-coupled proton spectrum (Figure 1c) was completed in 6 h, much less than the time required for a conventional proton-coupled ^{13}C NMR spectrum. The methylene protons attached to the ^{13}C-labeled carbon of **7** appear as a doublet of multiplets centered about 4.53 ppm (J_{CH} = 148.5 Hz), while the HOD and other extraneous peaks are completely filtered out. Acquisition with WALTZ carbon decoupling eliminated one-bond heteronuclear coupling and provided the expected single multiplet at 4.53 ppm (Figure 1d). These spectra unambiguously confirm the structure of the isotopically labeled metabolite **7**, enabling us to demonstrate that trichloroacrolein (**2**) is generated metabolically from triallate (**1**). Further studies elucidating the in vitro and in vivo metabolic pathways of triallate xenobiotic metabolism are in progress and will be reported in detail elsewhere.

In conclusion, we have shown that the proton-detected HMQC ^{13}C NMR experiment can be used to elucidate metabolite structures on a sample scale previously unattainable by conventional NMR techniques. This method provides important data on proton connectivity and heteronuclear coupling in the context of a simple experimental design which has the advantages of matrix transparency as well as greatly enhanced sensitivity relative to ordinary ^{13}C NMR spectroscopy. We anticipate that the HMQC ^{13}C NMR experiment will complement mass spectrometry as a major research tool in metabolism chemistry.

Acknowledgment. We thank Dr. Sastry Kunda for providing us with samples of isotopically labeled triallate.

(11) Applied with a nonincremental evolution time of 0.

Direct Selective Acylation of an Unactivated C-H Bond in a Caged Hydrocarbon. Approach to Systems for C-H Bond Functionalization That Proceed Catalytically and Selectively at High Substrate Conversion

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Homogeneous or heterogeneous systems that effect the replacement of unactivated C-H bonds catalytically and with high selectivity at high conversion of substrate are virtually unknown. In nearly all systems that effect oxidative functionalization of unactivated C-H bonds, the products are more reactive than the substrate.[1-11] We report here a systematic exploitation of the relative rates of photooxidation and quenching of the excited state of a complex, $W_{10}O_{32}^{4-}$, by different organic functions to effect the replacement of unactivated C-H bonds with C-C bonds in high selectivity at a reasonable conversion of substrate. Since derivatives of caged hydrocarbons are of current interest as medicinals[12] and energetic materials,[13] we chose the compound heptacyclo[6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}.0^{10,14}]tetradecane, commonly referred to as HCTD (**1**), as the substrate. Direct functionalization of this strained polycyclic hydrocarbon represents a formidable challenge as its C-H bonds are stronger than those in acyclic alkanes and its carbocyclic skeleton is susceptible to oxidative degradation. Although stoichiometric oxidation of **1** to a mixture of alcohols has recently been achieved using $Pb(OAc)_4$,[14] other attempts thus far to effect a clean direct functionalization of **1** in our laboratory and elsewhere using conventional methods have failed.[15]

Table I. Photochemical Functionalization of a Caged Hydrocarbon, **1**, by $Na_4W_{10}O_{32}$ and $Q_4W_{10}O_{32}$ under Anaerobic and Aerobic Conditions

	polyoxometalate[a]	% conversion[b]	product (selectivity)[c]
	I. Single Irradiation, Anaerobic Conditions[d]		
1	$Na_4W_{10}O_{32}$	53	**2** (81)
2	$Q_4W_{10}O_{32}$	24	**2** (84)
	II. Irradiation, Anaerobic Conditions/Dark O_2 Reoxidation Cycles[e]		
3[f]	$Na_4W_{10}O_{32}$	62	**2** (77)
4[f]	$Q_4W_{10}O_{32}$	38	**2** (88)

[a] Q = *n*-Bu_4N^+. [b] (Moles of **1** consumed/moles of **1** before reaction) × 100. [c] Selectivity defined as moles of **2** produced/moles of all detectable HCTD-derived products. [d] Reaction conditions: 10 mL of a slightly wet acetonitrile solution 27 mM in **1** and 5.4 mM in polyoxometalate catalyst with 3 mg of Pt under argon at ~15 °C was irradiated with a 550-W Hg lamp (λ > 280 Pyrex cutoff) for *x* h; products identified and quantified by gas chromatography and GC/MS. Reaction 1: *x* = 128 h; catalyst partially soluble. Reaction 2: 112 h. [e] Reaction conditions were the same as those for part I. Irradiation was terminated at 16-h intervals. The reactions were sequentially (a) placed under air to reoxidize the catalyst, (b) degassed and placed under argon, and then (c) irradiated again. [f] Reactions 3 and 4 run for seven 16-h cycles, total time 112 h; reaction 3 catalyst partially soluble.

Irradiation of acetonitrile solutions of **1** containing Na^+ or *n*-Bu_4N^+ salts of decatungstate, $W_{10}O_{32}^{4-}$, under Ar at 15 °C leads

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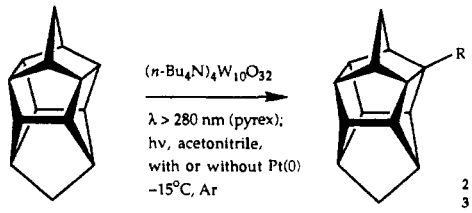
not only to direct functionalization of this very unreactive molecule but also to the selective production of the 1-acetyl derivative, **2**, a type of product not reported in any other homogeneous reaction for the replacement of unactivated C–H bonds. Ketone **2** was isolated, purified (neutral Al_2O_3, elution with hexane), and identified by its spectral properties.[16] Several other polyoxometalates of W and Mo are ineffective for this reaction.[17] These acylation processes (Table I) represent a one-electron oxidation of the carbon atom of the hydrocarbon, **1**, and a one-electron reduction of the carbon atom of the acetonitrile; the net reaction is a nonredox process.

During the course of reaction 1, Table I, there is some net redox chemistry: succinonitrile from acetonitrile oxidation and reduced polyoxotungstate are generated. Succinonitrile and **2** are produced



1

2 (R = $COCH_3$)
3 (R = $COCD_3$)
4 (R = $CH_2CH_2COCH_3$)

(1)

in a molar ratio of 1.1–1.0. The $W_{10}O_{32}^{4-}$ catalyst consumed by photoreduction can be reoxidized in the dark by O_2, and the photoreduction/reoxidation cycles can be repeated, producing **2** with a selectivity of >85% and at conversions in excess of 38% (Table I, part II). Such selectivities at these conversions are simply not seen in any alkane oxidation reaction dominated by radical cage or radical chain processes where steric environment and active site binding effects do not alter the relative reactivities of substrate and product. These effects clearly do alter the reactivities in the cases of cytochrome P-450[18] and methane monooxygenase.[19] The nonredox products, 1-butene and tributylamine, are also produced from the tetra-*n*-butylammonium cation.

Equations 2–8 illustrate processes pertinent to the observed C–C bond formation. A number of kinetic, product distribution, and spectroscopic studies published elsewhere establish that eqs 2 and 3 are operable in alkane photooxidation by polyoxometalates in general.[11,20] The principal origin of the simultaneous high selectivity and conversion lies in the inherent kinetics: alkane **1** is twice as reactive as **2** under the reaction conditions! This in turn is likely modulated in part by the relative rates of two key types of processes involving the excited state: substrate photooxidation, eq 3, and quenching not leading to net redox chemistry, eq 4. A defensible rationale for the observed reactivities (alkane > alkane-derived product) is that the rates of photooxidation, e.g., eq 3, are not greatly different for **1** and **2**, but quenching, eq 4, is substantially more efficient by **2** than **1**.[21] The other unusual if not unprecedented aspect of the overall process is the step forming the C–C bond itself. Radicals do not attack unactivated nitrile carbon atoms.[22] Two alternative mechanisms for C–C bond formation are radical attack at a nitrile that is weakly activated by ligation to W or the countercations present to generate the iminium radical, which then abstracts hydrogen. The resulting imine is then rapidly hydrolyzed by the water present, eqs 5 and 6. Alternatively, reduction of the alkyl radical derived from **1** to the corresponding carbanion followed by rapid electrophilic capture by the nitrile carbon may be operable. Protonation of the resulting anion and imine hydrolysis complete the process (eqs 7 and 8). Neither of these C–C bond forming scenarios is likely on the basis of literature precedence. At the present time, we favor eqs 7 and 8. Radicals are oxidized to carbonium ions by oxidized polyoxotungstates;[23] reduction of radicals has not heretofore been documented in either thermal or photochemical organic oxidation processes mediated by polyoxometalates.[20] On the basis of redox potentials, the equilibrium in eq 7 is quite unfavorable, but a small quantity of the carbanion could exist. The trapping by any carbanion that is formed to produce the anion of the imine, however, would be an exothermic and rapid process. The experimental observations are in accord with eqs 7 and 8: (1) production of cyclohexyl methyl ketone byproduct during the catalytic photochemical dehydrogenation of cyclohexane to cyclohexene by $W_{10}O_{32}^{4-}$ correlates with concentration of the reduced polyoxotungstate present,[24] (2) **3** is confirmed to be the product when CD_3CN is used as a solvent, and (3) **1** reisolated after reaction (eq 1) in the presence of 5 mol % D_2O contains deuterium.[25]

$$W_{10}O_{32}^{4-} + h\nu \rightarrow W_{10}O_{32}^{4-*} \quad (2)$$

$$W_{10}O_{32}^{4-*} + \mathbf{1} \rightarrow W_{10}O_{32}^{5-} + \mathbf{1}(-H)^{\bullet} + H^{+} \quad (3)$$

$$W_{10}O_{32}^{4-*} + \mathbf{1} \text{ or } \mathbf{2} \rightarrow W_{10}O_{32}^{4-} + \mathbf{1} \text{ or } \mathbf{2} \quad (4)$$

$$\mathbf{1}(-H)^{\bullet} + (CH_3CN)M^{+} \rightarrow M^{+} + \mathbf{1}(-H)(CH_3)C{=}N^{\bullet} \quad (5)$$

$$\mathbf{1}(-H)(CH_3)C{=}N^{\bullet} \xrightarrow{\text{hydrolysis of imine}} \mathbf{2} \quad (6)$$

$$\mathbf{1}(-H)^{\bullet} + W_{10}O_{32}^{5-} \underset{K \ll 1}{\longleftarrow} \mathbf{1}(-H)^{-} + W_{10}O_{32}^{4-} \quad (7)$$

$$\mathbf{1}(-H)^{-} + CH_3CN \xrightarrow{\text{rapid}} \mathbf{1}(-H)(CH_3)C{=}N^{-} \xrightarrow[\text{hydrolysis of amine}]{\text{protonation and}} \mathbf{2} \quad (8)$$

The products generated upon irradiation of **1** in the presence of O_2 were also examined. Again, the products are unusual. Whereas autoxidation of **1** in the presence of $Na_4W_{10}O_{32}$ produced an alcohol (9%), a ketone (1%), and other oxygenated products,[26] the presence of $Q_4W_{10}O_{32}$ not only suppressed these products but led to formation of only two major products, **2** (56%) and **4** (41%). The yields in parentheses are based on substrate consumed. Isolation and extensive spectral characterization led to the structural assignment for **4**[27] given in eq 1.

(16) For **2**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.78 (s), 1.83 (s) (4H, CH_2), 2.15 (s, 3 H, CH_3), 2.48–2.68, 2.80–2.84 (m, 11 H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.77 (CH_3); 42.04, 42.49 (CH_2), 50.84, 51.07, 51.21, 52.50, 52.99, 53.14, 53.25, 53.52, 53.81, 56.78, 57.77 (CH), 76.48, (C), 211.24 (C=O); MS, m/z 226 (M^+, 3.5), 211 (M – 15, 52), 183 (M – 43, 100).

(17) Reaction conditions: 5 mL of an acetonitrile solution 17 mM in **1** and 3.3 mM in catalyst with 3 mg of Pt under argon at 60 °C was irradiated with a 550-W Hg lamp for 24 h in a Pyrex Schlenk flask. **2** was not detected by GC using $H_3PW_{12}O_{40}$, $H_3PMo_{12}O_{40}$, $Q_3PMo_{12}O_{40}$, $Q_2W_6O_{19}$, $Q_2Mo_6O_{19}$, $(NH_4)_6P_2W_{18}O_{62}$, or $H_4SiW_{12}O_{40}$ as catalyst (Q = *n*-Bu_4N^+).

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(25) **1** before reaction: MS, m/z 183 (M – 1, 0.7), 184 (M, 100.0), 185 (M + 1, 16.2), 186 (M + 2, 1.0). **1** reisolated after partial reaction: MS, m/z 183 (0.7), 184 (53.3), 185 (100.0), 186 (50.0), 187 (14.3), 188 (2.0). (Both **2** and the tributylamine byproduct also show deuterium incorporation.)

(26) Heptacyclo[6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}.0^{10,14}]tetradecan-1-ol: MS, m/z 200 (M^+, 100).[14] Heptacyclo[6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}.0^{10,14}]tetradecanone: MS, m/z 198 (M^+, 100), 170 (M – 28, 46).

The major products generated upon irradiation of adamantane under anaerobic conditions[28] were analyzed by GC/MS and determined to be 1-acetyladamantane, 1,3-diacetyladamantane, and 1,3,5-triacetyladamantane. The processes reported here break ground on several fronts. We feel that further detailed evaluation of the energetic and mechanistic features of such processes is warranted.

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(27) For **4**: ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.83 (CH_3), 30.47, 40.56, 41.13, 42.81 (CH_2), 50.25, 51.11, 51.46, 51.60, 52.71, 53.12, 53.12, 53.40, 54.64, 56.78, 58.41 (*C*H), 62.96 (*C*), 209.71 (C=O); MS, m/z 254 (M^+, 19), 239 (M - 15, 59), 211 (M - 43, 100), 197 (M - 57, 7), 183 (M - 71, 19).

(28) Reaction conditions: see Table I, footnote *d*. Reaction run for three 16-h cycles, total time 48 h. Adamantane: MS, m/z 136 (M^+, 100). 1-Acetyladamantane: MS, m/z 178 (M^+, 7), 135 (M - 43, 100), 43 (M - 135, 10). 1,3-Diacetyladamantane: MS, m/z 220 (M^+, 8), 177 (M - 43, 84), 43 (M - 177, 100). 1,3,5-Triacetyladamantane: MS, m/z 262 (M^+, 8), 219 (M - 43, 58), 43 (M - 219, 100).

Sodium Cyanide: A Chemical Probe of the Conformation of DNA Modified by the Antitumor Drug *cis*-Diamminedichloroplatinum(II)

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It is generally accepted that the antitumor drug *cis*-diamminedichloroplatinum(II) (*cis*-DDP) exhibits its toxicity by reacting with DNA. Most of the adducts formed in the reaction of *cis*-DDP with DNA have been identified. The two major adducts arise from intrastrand cross-links between two adjacent guanine residues (d(G*G*) adduct) and between the adjacent adenine and guanine residues (d(A*G*) adduct).[1] Under physiological conditions, the adducts are stable over a large period of time, while in the presence of cyanide ions, most of the bound platinum residues, but not all of them, are rapidly removed.[2] Immunological analysis of the platinated DNA after treatment with cyanide ions suggests a preferential removal of d(G*G*) and the d(A*G*) adducts.[3] Studies of model nucleobase complexes of *cis*-DDP have shown that the conformation of the complexes and the nature of the bases play a key role in the cyanide substitution kinetics.[4] We herewith report that the kinetics of the reaction between cyanide ions and the two major adducts d(G*G*) and d(A*G*) is strongly dependent upon the DNA conformation.

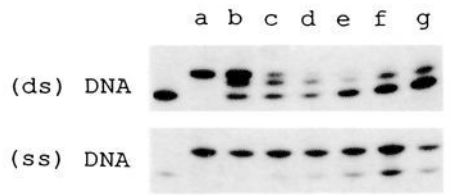

Figure 1. Autoradiogram of a denaturing 24% polyacrylamide gel of the products of the reaction between cyanide ions and ds or ss oligonucleotides containing a single d(G*G*) adduct. The platinated samples ($c \simeq 3 \times 10^{-6}$ M) were incubated at 37 °C and in 0.2 M NaCN, 20 mM Tris·HCl adjusted at pH 8.3 by addition of HCl. At various times, the samples were precipitated with ethanol, washed three times with ethanol, and then electrophoresed. Lanes a-g correspond to the following times of incubation: 0, 0.25, 0.50, 0.75, 1, 1.5, and 2 h for the ds oligonucleotide and 0, 1, 2, 3, 5, 7, and 9 h for the ss oligonucleotide, respectively. The two bands on the left of the autoradiograms correspond to the unplatinated oligonucleotide. The oligonucleotide d(CTTCTCTTCTGGTCTTCTCT) containing a single d(G*G*) adduct is ^{32}P-labeled at the 5′ end.

We first compared the relative resistance of a d(G*G*) adduct either in a single-stranded (ss) oligonucleotide or in a double-stranded (ds) oligonucleotide to the reaction with cyanide ions. The ss oligonucleotide d(CTTCTCTTCTGGTCTTCTCT) was reacted with *cis*-DDP and then ^{32}P labeled at the 5′ end.[5] The corresponding ds oligonucleotide was obtained by mixing the ss oligonucleotide containing a single d(G*G*) adduct with the complementary unplatinated strand. Both the platinated samples were treated with a large excess of cyanide ions. At various times, aliquots were withdrawn and analyzed by gel electrophoresis under denaturing conditions.[6] The ss and ds platinated oligonucleotides behave quite differently (Figure 1). As judged by the disappearance of the starting products (upper bands), cyanide ions are much less reactive with the ss oligonucleotide than with the ds oligonucleotide, the half-lives being 720 and 20 min (precision 10%), respectively. Moreover, only two products (the platinated and the unplatinated oligonucleotides) are detected by gel electrophoresis in the case of the ss oligonucleotide while, in the case of the ds oligonucleotide, three products (the platinated oligonucleotide, the unplatinated oligonucleotide, and an intermediate species) are detected.

Since, in ss and ds oligonucleotides, the two platinated G* residues are in a head-to-head, anti conformation,[7,8] we assume that the difference in the kinetics cannot be due essentially to a different protective effect of the exocyclic oxygens of the platinated bases.[4] The neighboring nucleotide residues could be responsible for a large protective effect in the ss oligonucleotide (structural distortions and even folded back structure (on the 5′ side of the adduct) have been proposed for platinated ss oligonucleotides[8,9]), and/or the double helix, by its surface properties, could favor the

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