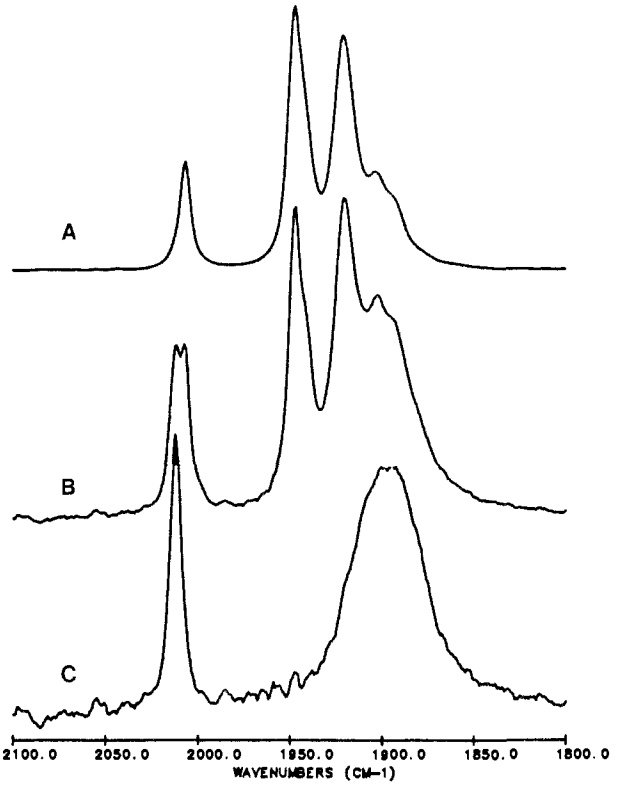

Figure 3. FTIR spectra of **1** in THF: (a) 0.005 M, (b) 0.0005 M, (c) subtraction B-(SF)A.

is in good agreement with the results of UV experiments, thus confirming our equilibrium model (Table I). As the temperature is increased, IR spectra show a shift in the equilibrium toward **2**. At 92 °C, the equilibrium is shifted almost entirely to **2**, and the IR spectrum resembles Figure 3c.

The thermodynamic parameters indicate an extremely weak Cr–Cr bond for **1**. The amount of radical **2** present in solutions of **1** at room temperature is much greater than previously estimated.[2] For example, a 0.01 M solution of **1** at 25 °C is about 10% dissociated to **2**. The large positive value of ΔS and its insensitivity to solvent (toluene versus THF) both argue against any direct participation of solvent in reaction 1. Similar values of ΔS have been reported for Fe–Fe bond cleavage in $[(allyl)Fe(CO)_3]_2$.[10] Upon the basis of the heat of hydrogenation of **1** and an estimate of the Cr–H bond strength, Hoff had previously estimated the enthalpy of reaction 1 to be 12.7 kcal/mol.[11] Considering the approximation use by Hoff, his estimate is in good agreement with our results.

Upon the basis of the known lability of 17-electron radicals,[12] solutions of **1**/**2** are expected to react readily with donor ligands. Indeed, the carbonyl ligands of **1** exchange with ^{13}CO at 25 °C and subatmospheric pressure! Reaction with Me_3CNC yields the stable monomeric 17-electron complex $CpCr(CO)_2(CNCMe_3)$.[13]

Registry No. $[CpCr(CO)_3]_2$, 12194-12-6; $CpCr(CO)_3$, 12079-91-3; $CpCr(CO)_2(CNCMe_3)$, 112043-97-7; Me_3CNC, 7188-38-7.

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(13) *$CpCr(CO)_2(CNCMe_3)$*. A solution of Me_3CNC (0.083 g, 1.00 mmol) in 25 mL of pentane was added dropwise to a rapidly stirred suspension of $[CpCr(CO)_3]_2$ (0.201 g, 0.50 mmol) in 75 mL of pentane over a period of 30 min. After having been stirred an additional 10 min, the mixture was filtered and cooled to −40 °C to give dark red-brown needles, 0.176 g (69%): IR (pentane solution, cm^{-1}) 2096 (w), 2071 (vw), 1938 (vs), 1842 (s); ESR (3-methylpentane, −80 °C) 2.0423. Anal. Calcd for $C_{12}H_{14}CrNO_2$: C, 56.25; H, 5.51; Cr, 20.3; N, 5.47. Found: C, 56.19; H, 5.46; Cr, 19.6; N, 5.63.

DNA Strand Scission by (−)-Epicatechin and Procyanidin B_2

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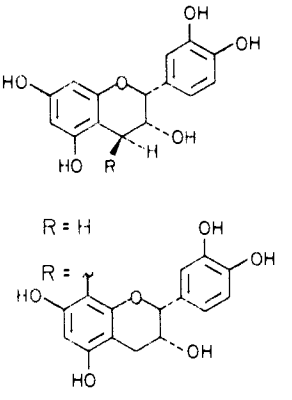
In recent years, considerable effort has been made to identify and characterize molecules capable of mediating nucleic acid strand scission. These include natural[1] and synthetically derived[2] products as well as known DNA binders that have been modified with adjuvants capable of "sequence-neutral" cleavage.[3] Interestingly, in spite of the natural origin of many of these species, we are unaware of any systematic effort to identify additional natural products that mediate nucleic acid strand scission. Reported herein is the identification of two plant-derived natural products that mediate DNA strand scission at micromolar concentrations.

(−)-Epicatechin (**1a**)[4] and (−)-epicatechin-[4β-8]-(−)-epicatechin (**1b**) (procyanidin B_2[5]) were isolated from an extract of *Celastrus*



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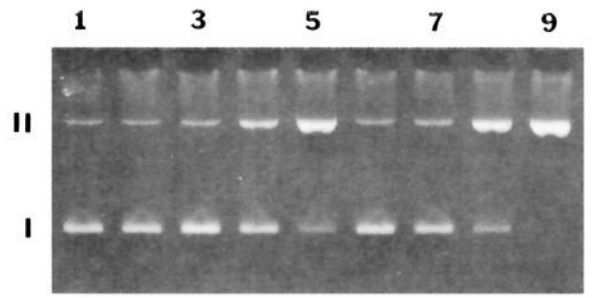

Figure 1. Relaxation of supercoiled cccDNA in the presence of **1a** and **1b**. ΦX174 Form I DNA (15 μM DNA nucleotide concentration) was incubated with 10 μM compound **1a** or **1b** + 10 μM $CuCl_2$ in a reaction mixture (40 μL total volume) containing 1.25 mM sodium cacodylate, pH 7.8. Incubation mixtures were maintained at 25 °C for the times indicated and then analyzed by agarose gel electrophoresis.[6] Lane 1, Cu(II) (30 min); lanes 2–5, **1a** + Cu(II) for 0, 5, 15 and 30 min, respectively; lanes 6–9, **1b** + Cu(II) for 0, 5, 15 and 30 min, respectively.

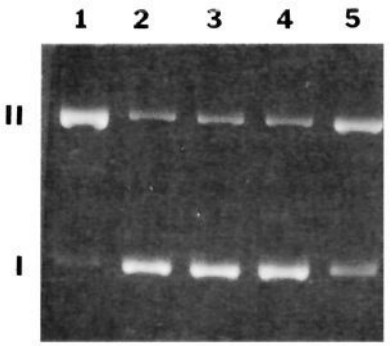

Figure 2. Cu(II) dependence of DNA strand scission by epicatechin (**1a**). ΦX174 Form I DNA was incubated with **1a** for 30 min at 25 °C, as described in the legend to Figure 1. Lane 1, 10 μM $Fe(NH_4)_2(SO_4)_2$ + 0.1% H_2O_2; lane 2, ΦX174 DNA alone; lane 3, 10 μM Cu(II); lane 4, 10 μM epicatechin (**1a**); lane 5, 10 μM **1a** + 10 μM Cu(II).

pringli Rose guided by an in vitro assay designed to detect molecules that cleave DNA.[6] Incubation of 10 μM **1a** or **1b** with ΦX174 Form I DNA under ambient conditions in the presence of Cu(II) produced Form II DNA; the extent of DNA relaxation was shown to increase steadily as a function of time (Figure 1). The Cu(II) dependence of DNA cleavage by **1a** and **1b** was demonstrated directly (Figure 2), as was the inability of Fe(II), Fe(III), Mn(II), Co(II), Ag(I), Zn(II), Al(III), or Mg(II) cations to mediate DNA strand scission under analogous conditions (data not shown).

In common with DNA strand scission mediated by Cu ions + bleomycin,[7] hemin,[1d] and 1,10-phenanthrolines,[2a,b,k,8] DNA cleavage obtained with Cu(II) + **1a** or **1b** required O_2.[9] However, in contrast to these agents, DNA cleavage by **1a** or **1b** occurred readily in the absence of any reductant and was actually diminished in the presence of thiols (unpublished results). These observations suggest that **1a** and **1b** act in a fashion mechanistically dissimilar to the aforementioned agents.

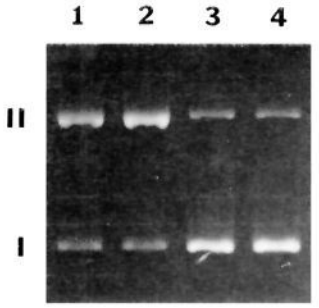

Figure 3. Effect of Cu(II) concentration on DNA cleavage by procyanidin B_2. ΦX174 Form I DNA was incubated with 10 μM (−)-epicatechin + 10 μM Cu(II) (lane 1) or 5 μM procyanidin + 10 μM Cu(II) (lane 2) at 25 °C for 30 min as described in the legend to Figure 1. Lane 3 contained ΦX174 DNA + 10 μM Cu(II); lane 4 contained DNA alone.

As reflected in Figure 1, the dimeric flavanoid **1b** was found to produce more DNA damage than **1a** when the two were employed at the same concentration in the presence of equimolar Cu(II). Addition of a second equivalent of Cu(II) to **1b** significantly increased the extent of DNA cleavage produced by **1b**. In fact 5 μM **1b** + 10 μM Cu(II) produced DNA cleavage to the same extent as 10 μM Cu(II) + 10 μM **1a**, suggesting that both epicatechin moieties in the dimer may participate in DNA degradation (Figure 3). The increased activity of **1b** relative to **1a** is of interest because of the known restricted rotation between oligomeric (epi)catechin moieties, and hence the apparent ability of homopolymers of epicatechin or catechin to form helices whose chirality is determined by the nature of the monomers.[5c,10] The structures of these helices may bear relevance to the nature of the presumptive binding of epicatechin and procyanidin B_2 to DNA.

The requirements for Cu(II) and O_2 in DNA cleavage mediated by **1a** and **1b** are consistent with a mechanism involving Cu-catalyzed oxidation of the catechol moiety with concomitant production of oxygen free radicals.[11,12] There is considerable evidence that diffusible oxygen radicals can mediate DNA strand scission.[13] That **1a** and **1b** associate with DNA prior to production of such oxygen radicals is suggested by the less efficient DNA cleavage produced under comparable conditions by the structurally related flavanoids quercetin, myricetin, fisetin, and (+)-catechin[14] and also by significant alteration of the circular dichroism spectrum of DNA and the UV spectrum of epicatechin upon admixture of the two.

The specific requirement for Cu(II) as a cofactor in DNA cleavage is intriguing and prompted the measurement of certain spectral parameters of **1a** in the presence of Cu(II). Both the UV–vis and ESR spectra indicated that a complex was formed.[15]

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(11) In this context it is of interest that certain structurally related compounds lacking a catechol moiety (e.g., morin, naringenin, and chromanol) were also inactive in DNA cleavage when tested under comparable conditions.

(12) Also consistent with this type of mechanism was the diminution of strand scission by agents known to quench reactive forms of oxygen such as 4,5-dihydroxy-1,3-benzenedisulfonate (Tiron), DMSO, and catalase.[2g]

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(14) Presumably, any of these species should be able to mediate oxygen radical production to the same extent as **1a** and **1b**, although it is recognized that some of these compounds may chelate metal ions differently than epicatechin.

The nature of this complex and the mode of its presumed association with the DNA substrate are under investigation.

Acknowledgment. We thank Dr. Herbert Kolodziej (Wilhelms-Universität, Münster) for an authentic sample of procyanidin B_2, Dr. V. S. Murty for helpful assistance with some of the initial bioassays, and Dr. Reuel Van Atta for assistance with ESR measurements. This work was supported by P.H.S. Grant CA40291, awarded by the National Cancer Institute, D.H.H.S.

(15) A solution of 10 mM (-)-epicatechin and 1 mM $Cu(ClO_4)_2$ (50 mM sodium cacodylate, pH 7.0; -140 °C) gave an EPR signal indicative of Cu(II) complex formation, $g_\perp \approx 2.04$; $g_\parallel \approx 2.28$, as evidenced by splitting of the Cu(II) signal. No EPR signal was observed in the absence of Cu(II). The UV absorption maximum shifted from 280 nm to 295 nm upon addition of equimolar $CuCl_2$.

Novel 1,2-Migration Reactions of Organometals Containing Aluminum, Zinc, and Other Main Group Metals with α-Haloorganolithiums

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1,2-Migration or migratory insertion is, in principle, one of the most fundamental patterns for carbon–carbon and carbon–hetero atom bond formation. Indeed, the majority of carbon–carbon bond-forming reactions of organoboron compounds proceed via 1,2-migration.[2] Carbonylation and related reactions of organo transition metals are representative examples of the 1,2-migration reactions involving transition metals.[3] At present, however, relatively little is known about 1,2-migration reactions involving main group metals other than boron. For example, although the reaction of organoalanes with diazomethane to give homologated organoalanes[4] most likely involves 1,2-migration, virtually no other 1,2-migration reactions of organoalanes are known.[5] We now wish to present experimental data which suggest that the 1,2-migration reactions of organo main group metals are much more widespread than the previously available data indicated.

Typically, addition of *i*-Bu_3Al (0.505 mL, 2.0 mmol) to $LiCH(Cl)SiMe_2Ph$[6] (**1**) at -78 °C, generated in situ by treating $ClCH_2SiMe_2Ph$ (0.554 g, 3.0 mmol) and 0.452 mL (3.0 mmol) of tetramethylethylenediamine (TMEDA) in 9.2 mL of THF with 2.3 mL (1.3 M, 3.0 mmol) of *sec*-BuLi in cyclohexane at -78 °C, followed by warming the mixture to 23 °C, stirring at this temperature for 6 h, treatment with water at 0 °C, and the usual extractive workup and chromatography (silica gel, pentane) provided an 80% GLC yield (62% isolated) of *i*-$BuCH_2SiMe_2Ph$[7] (**2**): ^1H NMR ($CDCl_3$, Me_4Si) δ 0.21 (s, 6 H), 0.5–0.8 (m, 2 H), 0.83 (d, J = 6.5 Hz, 6 H), 1.0–1.7 (m, 3 H), 7.3–7.7 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ -3.10, 13.07, 22.12, 30.92, 32.85, 127.69, 128.71, 133.55, 139.52; IR (neat) 1250 (s), 1110 (s), 840 (s) cm^{-1}; high resolution MS calcd for $C_{13}H_{22}Si$ 206.1491, found 206.1478. Also obtained was Me_3SiPh (0.45 equiv out of 1.5 equiv of $ClCH_2SiMe_2Ph$). Little or no $ClCH_2SiMe_2Ph$ was recovered. As shown in Table I not only some other organoalanes, such as *n*-Pr_3Al (77%, 6 h) and Me_3Al (83%, 6 h), but also organometals containing Mg, Zn, and Cd, such as *n*-Bu_2Mg (72%, 0.5 h), *n*-Bu_2Zn (61%, 0.5 h), and *n*-Bu_2Cd (55%, 1 h), have produced the corresponding RCH_2SiMe_2Ph in the yields indicated in parentheses within the indicated reaction times under otherwise the same conditions (eq 1). On the other hand, the reaction of Me_3SnCl with **1** merely gave $Me_3SnCH(Cl)SiMe_2Ph$ in 75% yield.

Table I. 1,2-Migration Reactions of Organometals Containing Aluminum and Other Main Group Metals with $LiCH(Cl)SiMe_2Ph$ (**1**)[a]

organometals	products	time, h	yield,[b] %
i-Bu_3Al	*i*-$BuCH_2SiMe_2Ph$	6	80 (62)
i-Bu_2AlCl	*i*-$BuCH_2SiMe_2Ph$	48	5
n-Pr_3Al	*n*-$PrCH_2SiMe_2Ph$	6	77 (53)
Me_3Al	$MeCH_2SiMe_2Ph$	6	83
(*E*)-*n*-HeptCH=CHAl(Bu-*i*)$_2$[c]	(*E*)-*n*-HeptCH=CHSiMe$_2$Ph and *i*-$BuCH_2SiMe_2Ph$	1	85 (65) 9
i-Bu_2AlPh[d]	$PhCH_2SiMe_2Ph$ and *i*-$BuCH_2SiMe_2Ph$	6	48 31
n-Bu_2Mg[e]	*n*-$BuCH_2SiMe_2Ph$	0.5	72
n-Bu_2Zn[e]	*n*-$BuCH_2SiMe_2Ph$	0.5	61
n-BuZnCl[e]	*n*-$BuCH_2SiMe_2Ph$	24	10
n-Bu_2Cd[e]	*n*-$BuCH_2SiMe_2Ph$	1	55

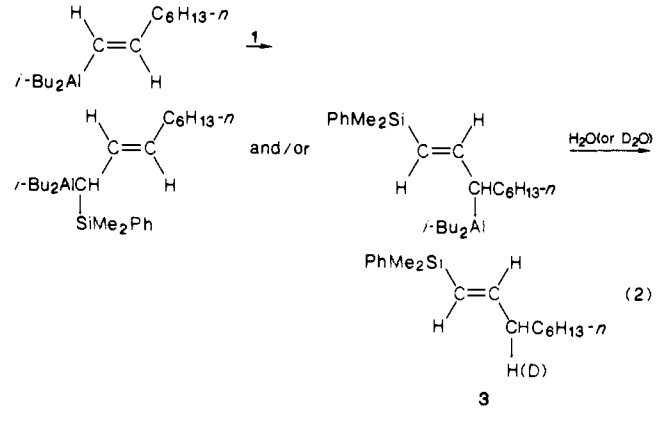
[a] Unless otherwise mentioned, all reactions were carried out under the standard conditions reported in the text. [b] By GLC based on an organometal. The numbers in parentheses are isolated yield. [c] Prepared by the reaction of DIBAH with 1-octyne. [d] Prepared by the reaction of *i*-Bu_2AlCl with 1 equiv of PhLi. [e] Prepared by the reaction of the corresponding metal dichloride with *n*-BuLi.

$$L_nMR \xrightarrow[2.\ H_2O]{1.\ LiCH(Cl)SiMe_2Ph\ (1)} RCH_2SiMe_2Ph \qquad (1)$$

R = Me, *n*-Pr, *n*-Bu, or *i*-Bu; ML_n = Al-, Mg-, Zn, or Cd-containing group

The reaction of (*E*)-*n*-HexCH=CHAl(Bu-*i*)$_2$ with **1** under the above-mentioned conditions gave isomerically >98% pure (*E*)-*n*-HeptCH=CHSiMe$_2$Ph (**3**) in 85% yield along with a 9% yield of **2**. The same reaction run at 0 °C under otherwise the same conditions produced **2** and **3** in 4% and 75% yields, respectively. Thus, the reactivity of the (*E*)-1-octenyl group relative to the *i*-Bu group at 23 or 0 °C is 19 or 38, respectively. Workup with D_2O gave essentially pure (*E*)-3-deuterio-1-nonenyldimethylphenylsilane (**4**) in 80% yield, indicating that an Al atom was bonded to the C-1 or C-3 atom of the alkenyl group (eq 2). The reaction of *i*-Bu_2AlPh with **1** gave within 6 h at 23 °C $PhCH_2SiMe_2Ph$ and **2** in 48% and 31% yields, respectively. Thus, the Ph/Bu-*i* reactivity ratio is 3.1.

The above described reactions can, in principle, proceed by various mechanisms. The three most likely paths deserving our attention are those involving (i) 1,2-migration (eq 3), (ii) direct displacement (eq 4), and (iii) carbene insertion (eq 5).



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(7) All new isolated products have been adequately characterized by ^1H and ^{13}C NMR, IR, and mass spectrometries. All new isomerically homogeneous compounds have been further characterized by elemental analyses.

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