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Selective One-Electron Reduction of a Cationic Substrate, 10-Methylacridinium Ion, by Group 4B Dimetals, Me_3SnMMe_3 (M = Sn, Ge, Si), via Radical Chain Reactions

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One-electron reduction of cationic substrates (C^+) such as pyridinium ions has so far been made possible by electrochemical methods or by electron transfer from one-electron reductants to C^+, followed by the dimerization of the resulting radicals ($C^\bullet$) to yield the corresponding dimer (C–C), eq 1.[1,2] On the other

$$C^+ \xrightarrow{-e} C^\bullet \rightarrow \tfrac{1}{2}(C\text{–}C) \qquad (1)$$

hand, the reduction of C^+ by two-electron reductants (A–B) generally results in the two-electron reduction of C^+, which involves transfer of A^- (or B^-) to C^+ (eq 2).[3] When one-electron reduction

$$A\text{–}B + C^+ \rightarrow A\text{–}C \text{ (or B–C)} + B^+ \text{ (or } A^+) \qquad (2)$$

of C^+ by two-electron reductants (A–B) is forced to occur by electron transfer from A–B to C^+, the resulting $A\text{–}B^{\bullet+}$ radicals may dissociate to give $A^\bullet$ (or $B^\bullet$). The coupling of $C^\bullet$ to yield the one-electron-reduced product (C–C) is generally accompanied by the cross-coupling of $C^\bullet$ with $A^\bullet$ (or $B^\bullet$) to yield the two-electron-reduced product, A–C (or B–C).[4,5] Thus, there has so far been no report on selective one-electron reduction of cationic substrates by two-electron reductants, which may require a novel reaction pathway to avoid the cross-coupling of the radicals.

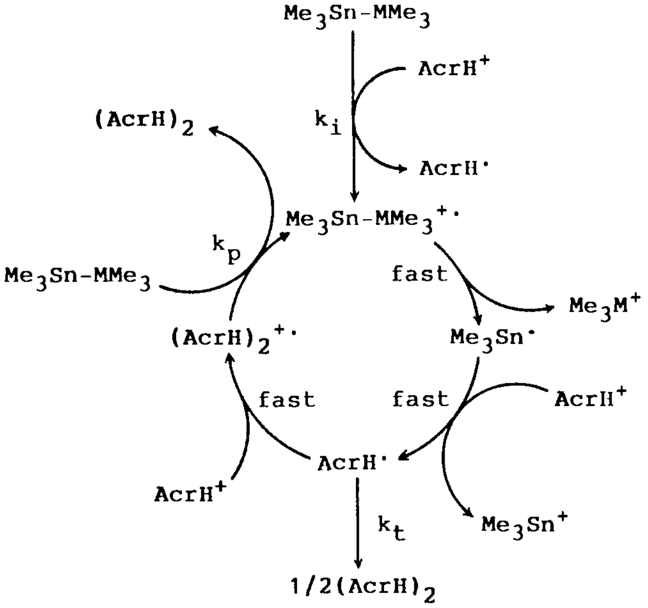
This study reports that group 4B dimetals, which are known as two-electron σ-donors,[6,7] can reduce a cationic substrate, 10-methylacridinium ion ($AcrH^+$), via novel radical chain reactions to yield the one-electron-reduced product, i.e., 10,10′-dimethyl-9,9′-biacridine [$(AcrH)_2$] selectively.

Table I. Observed Second-Order Rate Constants (k_{obsd}) for the One-Electron Reduction of $AcrH^+$ by Group 4B Dimetals $Me_3MM'Me_3$ (M, M′ = Sn, Ge, Sn) in Deaerated MeCN at 333 K and the Ionization Potentials (I_D) of $Me_3MM'Me_3$

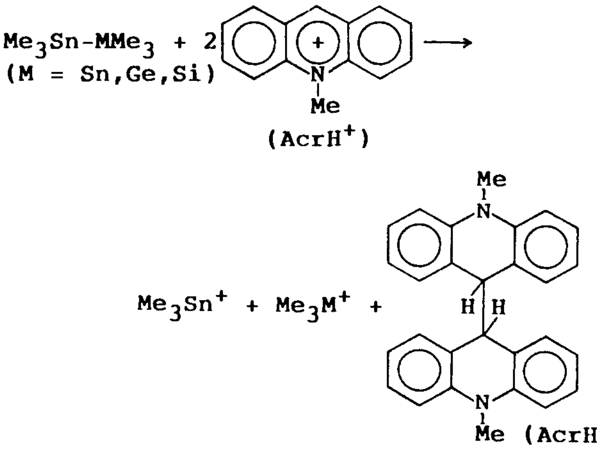
$Me_3MM'Me_3$	I_D,[a] eV	k_{obsd},[b] $M^{-1}\ s^{-1}$
$Me_3SnSnMe_3$	8.20	5.6×10^{-2}
$Me_3SnGeMe_3$	8.36	4.6×10^{-2}
$Me_3SnSiMe_3$	8.39	3.6×10^{-2}
$Me_3GeGeMe_3$	8.60	*c*
$Me_3GeSiMe_3$	8.62	*c*
$Me_3SiSiMe_3$	8.68	*c*

[a] Reference 8. [b] The experimental errors are ±5%. [c] No reaction.

Scheme I



The group 4B dimetals ($Me_3GeGeMe_3$, $Me_3SiGeMe_3$, and $Me_3SiSiMe_3$), which have higher ionization potentials compared with those involving Sn ($Me_3SnSnMe_3$, $Me_3SnGeMe_3$, and $Me_3SnSiMe_3$),[8] showed no reactivity toward $AcrH^+$ in deaerated acetonitrile (MeCN) in the dark. However, $AcrH^+$ is reduced readily by Me_3SnMMe_3 (M = Sn, Ge, Si) in deaerated MeCN to yield the corresponding dimer, 10,10′-dimethyl-9,9′-biacridine [$(AcrH)_2$] selectively (eq 3). Since the dimer $(AcrH)_2$ is sparingly soluble in MeCN, it can be readily isolated quantitatively and identified by the elementary analysis and ^1H NMR spectrum in $CDCl_3$.[9] The formation of Me_3MClO_4 (M = Sn, Ge, Si) is also



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confirmed by the ^{1}H NMR spectra.[9,10] When $AcrH^+$ has been replaced by a common NAD$^+$ analogue, 1-benzylnicotinamidium ion (BNA^+), which is a much weaker oxidant than $AcrH^+$,[2a,11] however, no reduction of BNA^+ by Me_3SnMMe_3 has occurred in deaerated MeCN at 333 K. On the other hand, the reduction of $AcrH^+$ by Me_3SnMMe_3 (eq 3) is strongly inhibited by the presence of oxygen. As such, essentially no reaction has occurred in aerated MeCN at 333 K.

Rates of the reduction of $AcrH^+$ by Me_3SnMMe_3 in deaerated MeCN were followed by the decay of the absorption band due to $AcrH^+$ (λ_{max} 358 nm) under conditions in which the concentrations of Me_3SnMMe_3 [$(4.8 \times 10^{-3}) - (1.4 \times 10^{-2})$ M] were maintained in large excess of $AcrH^+$ (e.g., 1.0×10^{-4} M) at 333 K. The rates obey pseudo-one-half-order kinetics, when $[AcrH^+]^{1/2}$ decreases linearly with an increase in the reaction time. The observed pseudo-one-half order rate constants ($k_{1/2}$) are proportional to $[Me_3SnMMe_3]^{3/2}$. Thus, the kinetic formulation is given by eq 4. The observed overall second-order rate constants

$$-d[AcrH^+]/dt = k_{obsd}[Me_3SnMMe_3]^{3/2}[AcrH^+]^{1/2} \quad (4)$$

(k_{obsd}) in deaerated MeCN at 333 K are listed in Table I, together with the ionization potentials of $Me_3MM'Me_3$.[7] The k_{obsd} value decreases in the order $Me_3SnSnMe_3 > Me_3SnGeMe_3 > Me_3SnSiMe_3$, when the donor ability of $Me_3MM'Me_3$ decreases as indicated by the increase in the I_D value (Table I).

The strong inhibitory effect of oxygen and the unusual kinetic formulation (eq 4) indicate that the one-electron reduction of $AcrH^+$ by Me_3SnMMe_3 proceeds via electron-transfer radical chain processes as shown in Scheme I.[12] The reaction may be initiated by electron transfer (k_i) from Me_3SnMMe_3 to $AcrH^+$ to produce $Me_3SnMMe_3^{\bullet+}$ and $AcrH^\bullet$.[13] The Sn–M bond of $Me_3SnMMe_3^{\bullet+}$ (M = Sn, Ge, Si) is known to be readily cleaved to give mainly $Me_3Sn^\bullet$ and Me_3M^+.[8,14] Then, electron transfer from $Me_3Sn^\bullet$ to $AcrH^+$ may occur to give acridinyl radical $AcrH^\bullet$, which may react with $AcrH^+$ to form the dimer radical cation $(AcrH)_2^{\bullet+}$. The electron transfer from Me_3SnMMe_3 to $(AcrH)_2^{\bullet+}$ (k_p) may be the rate-determining step to yield $(AcrH)_2$, accompanied by regeneration of $Me_3SnMMe_3^{\bullet+}$ (Scheme I). The chain carrier radical $AcrH^\bullet$ may be coupled in the termination step (k_t) to yield $(AcrH)_2$.[15] The steady-state approximation is applied to the reactive intermediates in Scheme I to derive the kinetic formulation which agrees with eq 4, where k_{obsd} corresponds to $k_p(k_i/k_t)^{1/2}$. The strong inhibitory effect of oxygen, which may be ascribed to the efficient trap of the chain carrier radical $AcrH^\bullet$ by oxygen,[2a,16] indicates a long chain length of the radical chain reactions.[15] Such a long chain length causes the highly selective formation of the dimer $(AcrH)_2$, in contrast with usual radical reactions. The unreactivity of the group 4B dimetals $Me_3MM'Me_3$ (M, M′ = Ge, Si) that do not contain Sn may be ascribed to the much less reducing ability of $Me_3Ge^\bullet$ or $Me_3Si^\bullet$ in the propagation step (k_p) compared with $Me_3Sn^\bullet$, combined with the less reducing ability of $Me_3MM'Me_3$ compared to Me_3SnMMe_3 (M = Sn, Ge, Si) in the initiation step (k_i), as indicated by the I_D values in Table I. By the same token, BNA^+, which is a much weaker oxidant than $AcrH^+$,[11] has no ability to start or to continue the chain reactions with Me_3SnMMe_3.

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Supplementary Material Available: Kinetic data for the derivation of eq 4 (1 page). Ordering information is given on any current masthead page.

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(9) Typically, a deaerated MeCN solution containing 19.6 mg of $Me_3SnSnMe_3$ (3.0×10^{-2} M) and 35.2 mg of $AcrH^+ClO_4^-$ (6.0×10^{-2} M) was heated at 333 K for 30 min and filtered to yield 23.3 mg (79%) of $(AcrH)_2$, when the conversion of $AcrH^+$ was 80%. Analytical and spectral data found for $(AcrH)_2$: C, 86.4; H, 6.1; N, 7.2. Calcd for $C_{28}H_{24}N_2$: C, 86.6; H, 6.2; N, 7.2. ^{1}H NMR (100 MHz): $(AcrH)_2$ $\delta(CDCl_3)$ 3.06 (6 H, s), 3.99 (2 H, s), 6.5–7.3 (16 H, m); Me_3SnClO_4 $\delta(CD_3CN)$ 0.63 (9 H, s); Me_3GeClO_4 δ 0.79 (9 H, s); Me_3SiClO_4 δ 0.36 (9 H, s).

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(13) Alternatively, the homolytic cleavage of the Sn–M bond of Me_3SnMMe_3, followed by electron transfer from $Me_3Sn^\bullet$ to $AcrH^+$, may initiate the chain reaction. However, electron transfer from Me_3SnMMe_3 to $AcrH^+$ may be much faster than the homolytic cleavage, since the activation Gibbs energy of the electron transfer from Me_3SnMMe_3 to $AcrH^+$ (e.g., $\Delta G^{\ddagger} = 25.8$ kcal mol^{-1} for $Me_3SnSnMe_3$), which is calculated by using the Marcus theory (Marcus, R. A. *Annu. Rev. Phys. Chem.* **1964**, *15*, 155), is much smaller than the Sn–M bond dissociation energy (e.g., 39 kcal mol^{-1} for $Me_3SnSnMe_3$; cf.: Keiser, D.; Kana'an, A. S. *J. Phys. Chem.* **1969**, *73*, 4264). The parameters used for the calculation were determined by the analyses of the cyclic voltammograms according to the method reported previously.[11]

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Site-Specific Cleavage of the Protein Calmodulin Using a Trifluoperazine-Based Affinity Reagent

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Reagents that react specifically with protein chains are extremely useful in chemistry and biology. Affinity labeling reagents react covalently with proteins and enable identification and modification of receptor sites.[1] Cleavage of the protein chain may be achieved with proteolytic enzymes or small molecules (such as cyanogen bromide).[2] Protein cleavage reagents permit sequence analysis of large or blocked proteins, functional analysis of protein domains, and structural analysis of receptors. In this communication, we describe the synthesis and evaluation of a molecule that combines the properties of both classes of protein probes: *an active site specific protein cleaving molecule.* Our target was trifluoperazine–EDTA (TFE (**1**), see Figure 1), which consists of the iron chelate ethylenediaminetetraacetic acid (EDTA) covalently tethered to the calmodulin antagonist trifluoperazine (TFP). TFE binds calmodulin under physiological conditions and, in the presence of Fe, O_2, and dithiothreitol (DTT), cleaves calmodulin to produce six major cleavage fragments. The appearance of these fragments is blocked by TFP and requires calmodulin to exist in an active conformation. *TFE is an affinity*

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