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Oxidovanadium Complexes for the Consumption of Alkylating Toxins

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Carcinogens found in cooked foods, tobacco smoke, and vehicle exhaust undergo metabolic activation to pernicious alkylating toxins, yield damaged DNA, and promote cancerous growth. Vanadium has been shown to decrease the occurrence of cancers, possibly by intercepting such toxins before DNA damage can occur. According to recent results, nucleophilic oxido salts of vanadium can prevent this DNA alkylation. Although effective at detoxification and preventing DNA damage, vanadate salts equilibrate in solution to multiple coexisting species and can exhibit toxicity. Ligand-enforced coordination geometries may minimize such equilibrations, thereby decreasing toxicity and providing a means to control reactivity. As part of our efforts to detoxify alkylating agents, here we are studying reactions between oxidovanadium complexes and toxins. Alkylating agents such as diethyl sulfate were treated with a series of new oxidovanadium complexes of the salicylidenehydrazide ligand, $[VO_2(salhyph(R)_2)]^-$. These complexes consumed a collection of alkylating agents and brought about transformation to alcohols. Changing the ligand substituents (R = $-OCH_3$, $-CH_3$, –H, $-NO_2$) yielded a series of compounds with varied degrees of electron density. Kinetic experiments indicated that there may be a correlation between electron density and reactivity with alkylating toxins. The design and reactivity of these compounds indicate that we may be able to exert control over interactions between carcinogens and metal complexes. Such principles may be helpful in developing new compounds for the prevention of cancer.

Introduction

We are constantly exposed to carcinogens resulting from the combustion of organic matter. Cooked food, tobacco smoke, and vehicle exhaust all contain alkylating carcinogens such as the polycyclic aromatic hydrocarbons (PAHs) and nitrosamines.[1–3] Toxicity of these compounds is a result of enzymatic oxidation into electrophiles that attack nucleophilic positions on DNA. The resulting alkylated bases can mispair during replication, yield mutations, and bring about cancerous growth.[4,5] In order to develop new approaches to cancer prevention, we are focusing attention on ways to minimize such DNA damage. Recent studies have shown that salts of vanadium[6–10] and selenium[11–13] prevent cancers induced by alkylating toxins. In aqueous solutions vanadium[14,15] and selenium[16] equilibrate to anionic metal-oxido species such as $(H_2VO_4)^-$ and $(SeO_4)^{2-}$. From a mechanistic perspective, however, few detailed insights are available to explain the anticancer properties of vanadium or selenium. We have previously proposed, and provided evidence to show, that the cancer preventing properties of vanadium may result from a "carcinogen interception" process.[17] Nucleophilic metal-oxido species can react directly with electrophilic alkylating carcinogens, thereby consuming the toxin prior to the onset of DNA damage.[17,18] Although a new mechanism for preventing DNA damage is exciting, concentrating efforts on simple metal-oxido salts will not permit control over reactivity and toxicity. Problems with using simple salts include solution equilibration to multiple coexisting species, thus enhancing toxicity and complicating mechanistic studies. Introduction of chelating ligands to the metal-oxido moiety will minimize such equilibria and also facilitate the design of chemopreventative metal complexes with controllable chemistry.

A rich history surrounds complexes in which vanadium is bound by organic ligands. Perhaps the most widely known examples are those of the insulin mimetic vanadium compounds.[19–22] Other prominent examples of oxidovanadium complexes include oxidation catalysts, photocatalysts, and model complexes for vanadium-containing enzymes.[23–27] Use of organic ligands to bind metals can provide control over the compound charge, nuclearity, metal coordination number, nature of the ligand donor atoms, and the extent of ligand electron donation to the metal center. Occupation of multiple coordination sites about vanadium centers minimizes unwanted reactions and interconversions (e.g., monomer ↔ dimer ↔ trimer), consequently simplifying the mechanistic chemistry at hand. Greater complex stability may also reduce toxicity by preventing vanadium from mimicking phosphate [i.e., $(VO_4)^{3-}$ vs. $(PO_4)^{3-}$] and inhibiting phosphate-processing enzymes.[28] Proper choice and design of ligands provides us with inroads to developing cancer preventing complexes with controlled reac-

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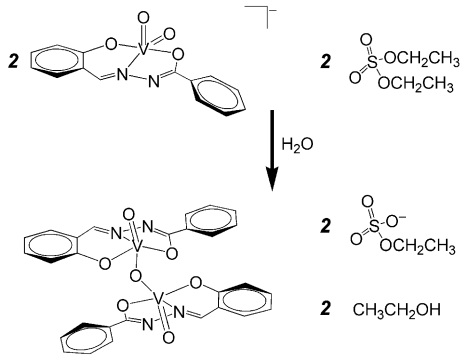
tivity toward toxins. In this report we describe a series of new oxidovanadium complexes and reactions with alkylating agents.

Results and Discussion

Dioxidovanadium(V) compounds of the salicylidenehydrazide ("salhyph") ligand provide an excellent entry into alkylation studies of oxidovanadium compounds (Scheme 1). Two terminal oxido ligands are present for reactions with alkylating agents and, overall, $[VO_2(salhyph)]^-$ is anionic, thereby indicating potential nucleophilicity. The starting $K[VO_2(salhyph)]\cdot CH_3OH$[29] was combined 1:1 with the alkylating toxin diethyl sulfate, $(CH_3CH_2O)_2SO_2$. Diethyl sulfate is a reagent used commonly in carcinogenesis studies.[30] This reaction was carried out in distilled $[D_6]$-DMSO and monitored by ^1H NMR spectroscopy. Figure 1 shows a ^1H NMR spectrum of this reaction in progress, focusing on the aliphatic resonances. Full spectroscopic data are provided in the Supporting Information. The starting $(CH_3CH_2O)_2SO_2$ was consumed while the products $(CH_3CH_2O)SO_3^-$ and CH_3CH_2OH were formed. Methanol was also observed, persisting from the crystallization of the starting $K[VO_2(salhyph)]\cdot CH_3OH$. Control solutions of $(CH_3CH_2O)_2SO_2$ in $[D_6]$DMSO did not yield CH_3CH_2OH on a comparable time scale.



Scheme 1. Proposed alkylation reaction of $[VO_2(salhyph)]^-$.

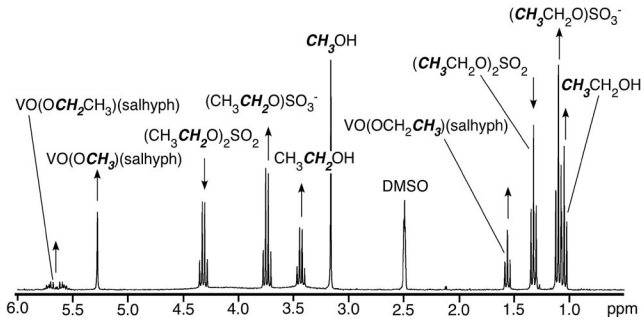


Figure 1. A ^1H NMR spectrum in $[D_6]$DMSO of the 1:1 reaction, in progress at approximately 8 h, between $K[VO_2(salhyph)]\cdot CH_3OH$ and $(CH_3CH_2O)_2SO_2$. Arrows indicate peak intensity changes during the course of the reaction.

These results indicate that this oxidovanadium compound can promote detoxification by transforming this alkylating agent into an alcohol. Such reactivity appears to be a general phenomenon for $[VO_2(salhyph)]^-$. Analogous experiments showed that the alkylating agents CH_3CH_2–I, CF_3SO_2O–CH_2CH_3, $NH_2CON(NO)$–CH_3, and CH_3SO_2O–CH_3 were each consumed by $[VO_2(salhyph)]^-$ and yielded the less toxic alcohols CH_3OH or CH_2CH_3OH. A proposed mechanism is electrophilic attack of an alkyl cation onto a nucleophilic terminal oxido of $[VO_2(salhyph)]^-$. Support for this mechanism comes from observations of the $VO(OCH_2CH_3)(salhyph)$ intermediate at δ = 1.56 and 5.62 ppm in the ^1H NMR spectra.[31] Subsequent protonation from residual water may then release CH_3CH_2OH.

In order to gain insights on the vanadium-containing product of this process, a reaction was run in acetone and then ether was diffused therein. Large, red-brown crystals resulted and were examined by single-crystal X-ray diffraction methods (see Supporting Information). The structure found was that of $\{[VO(salhyph)]_2O\}$, a known compound prepared previously via an unrelated route.[32] Scheme 1 shows a proposed reaction in which $\{[VO(salhyph)]_2O\}$ is produced from $[VO_2(salhyph)]^-$ and $(CH_3CH_2O)_2SO_2$. This reaction product resembles a dimer of the starting $[VO_2(salhyph)]^-$, however one oxygen short. This "missing" oxygen was likely extracted during formation of the ethanol product. Such results are consistent with our prior work wherein simple vanadates such as $(V_3O_9)^{3-}$ [i.e. $(VO_3^-)_3$] reacted with alkylating agents to yield alcohols and $(V_5O_{14})^{3-}$ [i.e. one oxygen "missing" from $(VO_3^-)_5$].[17,33] Inclusion of a ligand system here preserves the nucleophilic reactivity of the oxidovanadium moiety and provides a platform for subsequent modifications.

Electron donating (–OCH_3, –CH_3) and withdrawing (–NO_2) substituents were placed onto the salhyph ligand framework.[34] The resulting new $K[VO_2(salhyph(R)_2)]$ compounds, where R = H is the parent $[VO_2(salhyph)]^-$, were prepared and are depicted in Figure 2. Substituent electron donation into the aromatic rings may then increase electron density on the O and N ligand donor atoms. The central metal ion would exhibit enhanced electron density and may then increase nucleophilicity of the terminal oxygen ligands. As a consequence, reactivity toward alkylating agents could be enhanced. Given the long distances between added substituents and the terminal oxidos, such electronic effects are expected to be subtle, but may serve to indicate that limited control over reactivity is possible.

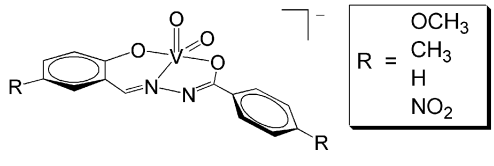


Figure 2. Electron-donating and -withdrawing substituents on $[VO_2(salhyph(R)_2)]^-$.

Each of the substituted $[VO_2(salhyph(R)_2)]^-$ compounds reacted readily with $(CH_3CH_2O)_2SO_2$, as well as all of the other alkylating agents mentioned above. Product characterization by ^1H NMR spectroscopy showed formation of CH_3CH_2OH from ethylating toxins or CH_3OH from methylating toxins, similar to experiments with the parent, unsubstituted $[VO_2(salhyph)]^-$ compound. Next we examined kinetics of the reactions between the $[VO_2(salhyph(R)_2)]^-$ compounds and $(CH_3CH_2O)_2SO_2$. Pseudo-first-order conditions were employed with a 10 : 1 $[VO_2(salhyph(R)_2)]^-$/$(CH_3CH_2O)_2SO_2$ ratio and concentrations of 200 mM and 20 mM, respectively. Rate constants, each determined in triplicate, were obtained by following the reduction of resonances from $(CH_3CH_2O)_2SO_2$ and plotting concentration vs. time. The methylene resonances of $(CH_3CH_2O)_2SO_2$ were monitored owing to a clear baseline on either side of the peak. Two processes may be noted in the plot (see Supporting Information), one of which is background hydrolysis of $(CH_3CH_2O)_2SO_2$ in distilled [D$_6$]DMSO, measured independently to be $k_{obsd.} = 1.1 \times 10^{-5}\ s^{-1}$. Although reagent decomposition is significant under these conditions, use of dmso was dictated by finding one solvent in which all derivatives of $[VO_2(salhyph(R)_2)]^-$ are soluble. Kinetic data were fit to a biexponential containing a fixed component to account for the hydrolysis. Figure 3 shows typical kinetic data along with a curve fit. The rate constants presented in Table 1 indicate subtle differences in reactivity between these complexes. The degree of electron donation or withdrawal from the aryl ring substituents may correlate with alkylation reactivity.

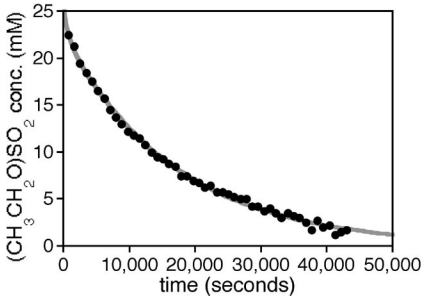


Figure 3. Plot of $(CH_3CH_2O)_2SO_2$ concentrations vs. time for the 10:1 (200:20 mM) reaction of $[VO_2(salhyph(H)_2)]^-$ and $(CH_3CH_2O)_2SO_2$.

Table 1. Pseudo-first-order rate constants for the alkylation reactions of $[VO_2(salhyph(R)_2)]^-$ compounds with $(CH_3CH_2O)_2SO_2$.

Substituent R	Hammett value σ	Rate constant[a] $k_{obsd.}$ [s^{-1}]
$-NO_2$	+0.78	$(4.3 \pm 0.7) \times 10^{-5}$
–H	0	$(5.5 \pm 1.5) \times 10^{-5}$
$-CH_3$	–0.17	$(6.3 \pm 1.1) \times 10^{-5}$
$-OCH_3$	–0.27	$(6.5 \pm 0.3) \times 10^{-5}$

[a] Each rate constant is an average of three runs. The error shows one standard deviation.

Conclusions

Here we have shown that a family of oxidovanadium complexes reacts with alkylating carcinogens and yields alcohols. Introduction of ligands can be a useful tool in moderating the nucleophilicity of metal oxides. Thus changes in ligand architecture may provide an avenue toward nucleophilic compounds for consuming toxins.

Experimental Section

H_2salhyph$(OCH_3)_2$: This compound was prepared by modifying a published procedure for the unsubstituted salhyph ligand.[35] In a round-bottomed flask, 4-methoxybenzhydrazide (1.734 g, 10.44 mmol) was dissolved in 1-propanol (40 mL) and 2-hydroxy-5-methoxybenzaldehyde (1.30 mL, 10.43 mmol) was added with stirring. The yellow reaction mixture was heated at reflux for 17 h, cooled, and left to stand for 6 h. Light yellow crystals precipitated, were removed by gravity filtration, and dried under vacuum (2.80 g, 89.6%). ^1H NMR (200 MHz, [D$_6$]DMSO, 22 °C): δ = 3.72 (s, 3 H, $-OCH_3$), 3.82 (s, 1 H, $-OCH_3$), 6.85 (br. m, 2 H, ar), 7.05 (br. m, 3 H, ar), 7.90 (d, $^3J_{H-H}$ = 8.6 Hz, 2 H, ar), 8.58 (s, 1 H, N=C–H), 10.78 (br. s, 1 H, –OH), 11.99 (br. s, 1 H, –NH) ppm.

H_2salhyph$(CH_3)_2$: In 1-propanol (40 mL), *p*-toluic hydrazide (1.803 g, 12.0 mmol) was dissolved slightly and 2-hydroxy-5-methylbenzaldehyde (1.633 g, 12.0 mmol) added with stirring. The reaction mixture was heated at reflux for 21 h. The solution was cooled and left to stand for 19 h. Off-white crystals precipitated and were removed by gravity filtration and dried under vacuum (2.70 g, 83.8%). ^1H NMR (300 MHz, [D$_6$]DMSO, 22 °C): δ = 2.24 (s, 3 H, $-CH_3$), 2.37 (s, 1 H, $-CH_3$), 6.82 (d, $^3J_{H-H}$ = 8.4 Hz, 1 H, ar), 7.09 (d, $^3J_{H-H}$ = 8.1 Hz, 1 H, ar), 7.35 (m, 3 H, ar), 7.84 (d, $^3J_{H-H}$ = 8.1 Hz, 2 H, ar), 8.58 (s, 1 H, N=C–H), 11.1 (br. s, 1 H, –OH), 12.0 (br. s, 1 H, –NH) ppm.

H_2salhyph$(NO_2)_2$: To a solution of 4-nitrobenzhydrazide (1.812 g, 10.0 mmol) in 1-propanol (40 mL), 2-hydroxy-5-nitrosalicylaldehyde (1.672 g, 10.0 mmol) was added with stirring. The reaction mixture was heated at reflux for 5 h, cooled, and left to stand overnight. A yellow solid was removed by gravity filtration and dried under vacuum (3.48 g, 90.4%). ^1H NMR (200 MHz, [D$_6$]DMSO, 22 °C): δ = 7.09 (d, $^3J_{H-H}$ = 8.8 Hz, 1 H, ar), 8.15 (br. m, 3 H, ar), 8.36 (d, $^3J_{H-H}$ = 8.2 Hz, 2 H, ar), 8.58 (s, 1 H, ar), 8.73 (s, 1 H, N=C–H), 12.2 (br. s, 1 H, –OH), 12.43 (br. s, 1 H, –NH) ppm.

K[VO_2(salhyph$(OCH_3)_2$)]: This compound was prepared as described previously for the unsubstituted K[VO_2(salhyph)] compound.[29] Potassium metavanadate, KVO_3 (0.5518 g, 4.0 mmol), was stirred in methanol (50 mL) to which H_2salhyph$(OCH_3)_2$ (1.202 g, 4.0 mmol) was added and the mixture was heated at reflux for 5 h. Crude yellow product was collected by gravity filtration from the hot reaction mixture and dried under vacuum (1.01 g, 60.1%). Needle-like crystals were obtained when the crude product was dissolved in *N*,*N*-dimethylformamide, followed by slow vapor diffusion of diethyl ether for ten days. Crystals were isolated by gravity filtration, rinsed with diethyl ether, and dried in vacuo. ^1H NMR (300 MHz, [D$_6$]DMSO, 22 °C): δ = 3.72 (s, 3 H, $-OCH_3$), 3.81 (s, 3 H, $-OCH_3$), 6.70 (d, $^3J_{H-H}$ = 9.3 Hz, 1 H, ar), 6.9–7.0 (m, 3 H, ar), 7.11 (d, $^3J_{H-H}$ = 3.0 Hz, 1 H, ar), 7.93 (d, $^3J_{H-H}$ = 8.7 Hz, 2 H, ar), 8.88 (s, 1 H, C=N–H) ppm. K[$C_{16}H_{14}N_2O_6V$] (420.34): calcd. C 45.72, H 3.36, N 6.66; found C 45.43, H 3.38, N 6.53.

$K[VO_2(salhyph(CH_3)_2)]$: This compound was prepared as described for $K[VO_2(salhyph(OCH_3)_2)]$, using the appropriate starting ligand, $H_2salhyph(CH_3)_2$. After 4 h of reflux the solution was filtered while hot. Upon standing, yellow needles precipitated. After cooling to room temperature, crystals of the desired compound were filtered by gravity and dried in vacuo (1.07 g, 68.9%). ^1H NMR (300 MHz, [D$_6$]DMSO, 22 °C): δ = 2.24 (s, 3 H, –CH$_3$), 2.35 (s, 3 H, –CH$_3$), 6.67 (d, $^3J_{H–H}$ = 8.1 Hz 1 H, ar), 7.15 (d, $^3J_{H–H}$ = 8.1 Hz, 1 H, ar), 7.24 (d, $^3J_{H–H}$ = 7.8 Hz, 2 H, ar), 7.31 (s, 1 H, ar), 7.88 (d, $^3J_{H–H}$ = 8.1, Hz, 2 H, ar), 8.86 (s, 1 H, C=N–H) ppm. $K[C_{16}H_{14}N_2O_4V]$ (388.34): calcd. C 49.49, H 3.63, N 7.21; found C 49.11, H 3.62, N 7.06.

$K[VO_2(salhyph(NO_2)_2)]\cdot H_2O$: This compound was prepared as described for $K[VO_2(salhyph(OCH_3)_2)]$, using the appropriate starting ligand, $H_2salhyph(NO_2)_2$. The pale yellow slurry was heated at reflux for 4.5 h and cooled to room temperature. A yellow solid was filtered by gravity and dried under vacuum (1.59 g, 84.9%). The product was recrystallized from nearly boiling acetonitrile. ^1H NMR (300 MHz, [D$_6$]DMSO, 22 °C): δ = 6.94 (d, $^3J_{H–H}$ = 9.3 Hz, 1 H, ar), 8.1–8.4 (m, 5 H, ar), 8.71 (s, 1 H, ar), 9.27 (s, 1 H, C=N–H) ppm. $K[C_{14}H_8N_4O_8V]\cdot H_2O$ (468.29): calcd. C 35.91, H 2.15, N 11.96; found C 35.91, H 1.99, N 11.80.

{[VO(salhyph)]$_2$O}: Under an inert argon atmosphere, $K[VO_2(salhyph)]\cdot CH_3OH$ (0.393 g, 1.0 mmol), was added to acetone (20 mL) and diethyl sulfate, $(CH_3CH_2O)_2SO_2$, (131 μL, 1.0 mmol), was added to the reaction flask. The pale yellow reaction was stirred under argon for 5 d, resulting in a dark black-brown solution. A small portion (appoximately 5 mL) of the acetone reaction mixture was removed. Diethyl ether was vapor diffused into the solution for 4 d. The vapor diffusion yielded yellow solids and large ($0.4 \times 0.4 \times 0.4$ mm), dark brown-black cubes. After gravity filtration of the mixture, the cubes were separated from the yellow solids using tweezers. The cubes were then rinsed with hexanes, dichloromethane, and water to dissolve residual yellow solids. The resulting X-ray quality crystals, {[VO$_2$(salhyph)]$_2$O}, were dried in vacuo. Given that only a portion of the reaction solution was subjected to vapor diffusion, an exact yield cannot be determined. However, back calculation from the approximately 81 mg of brown-black cubes indicates that {[VO(salhyph)]$_2$O} can be formed and crystallized with a rough yield of 324 mg, 52%. ^1H NMR (300 MHz, [D$_6$]DMSO, 22 °C): δ = 6.90 (d, $^3J_{H–H}$ = 8.7 Hz, 2 H, ar), 7.05 (t, $^3J_{H–H}$ = 7.8 Hz, 2 H, ar), 7.3–7.6 (m, 8 H, ar), 7.79 (d, $^3J_{H–H}$ = 7.2 Hz, 2 H, ar), 8.01 (d, $^3J_{H–H}$ = 7.8 Hz, 4 H, ar), 9.02 (s, 2 H, C=N–H) ppm. $C_{28}H_{20}N_4O_7V_2$ (626.37): calcd. C 53.69, H 3.22, N 8.94; found C 53.53, H 3.24, N 8.71.

Kinetic Experiments: Each of the $K[VO_2\{salhyph(R)_2\}]$ compounds was combined with diethyl sulfate (DES), $(CH_3CH_2O)_2SO_2$, in distilled [D$_6$]DMSO. Dimethylformamide (dmf) was used for an internal concentration standard. Pseudo-first-order reaction conditions were employed with a 10:1:5 ratio of V/DES/dmf. Concentrations were 200 mM, 20 mM, and 100 mM, respectively. The ^1H NMR spectra at 22 °C were acquired every 12 min. Kinetic data were examined by monitoring the reduction of the $(CH_3CH_2O)_2SO_2$ methylene resonances over time. This resonance was used consistently, owing to a clear baseline on both sides for each $[VO_2(salhyph(R)_2)]^-$ (R = H, NO$_2$, OCH$_3$, CH$_3$) compound (cf., Figure 1 at approximately 4.3 ppm). We could monitor the peak changes associated with production of $(CH_3CH_2O)SO_3^-$ and CH_3CH_2OH, however, the concentration vs. time plots were not nearly as clean owing to peaks overlapping with other species. Control kinetic runs of $(CH_3CH_2O)_2SO_2$ in [D$_6$]DMSO alone, without a vanadium complex, yielded a $k_{obsd.} = (1.1 \pm 0.1) \times 10^{-5}$ s^{-1}.

Supporting Information (see also the footnote on the first page of this article): Complete ^1H NMR spectra for select alkylation reactions and controls, and crystal structure data for {[VO(salhyph)]$_2$O}.

Acknowledgments

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