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Solution Speciation, Kinetics, and Observing Reaction Intermediates in the Alkylation of Oxidovanadium Compounds

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Contact with environmental alkylating agents brings about modification of DNA bases, mispairing, mutations, and cancer. Nucleophilic compounds may be able to consume these toxins, thereby providing an alternative reaction pathway and preventing DNA damage. Owing to promising results from animal trials, oxidovanadium compounds present a potential class of nucleophilic complexes for preventing cancer. We are studying the reactivity of alkylating toxins with oxidovanadium-ligand compounds. The complexes $K[VO_2(salhyph(R)_2)]$, where salhyph is the salicylidenehydrazide ligand, are the focus of this study. By changing the electron donating or withdrawing ability of the -R substituents upon the salhyph$(R)_2$ ligand (R = $-NO_2$, -H, $-CH_3$, $-OCH_3$), a family of compounds is obtained to investigate. Conductivity measurements reveal significant ion-pairing of all compounds in dimethyl sulfoxide (DMSO) solutions. Kinetic analysis shows that this ion-pairing causes a reduction in reaction rates. Reactivity of $K[VO_2(salhyph(R)_2)]$ is attributed exclusively to the non-ion-paired "free" $[VO_2(salhyph(R)_2)]^-$ anion in solution. Both ^1H and ^{51}V NMR spectroscopic studies show that direct alkylation of $K[VO_2(salhyph(H)_2)]\cdot CH_3OH$ generates a $VO(OCH_2CH_3)(salhyph(H)_2)$ intermediate which then protonates to release CH_3CH_2OH and a proposed $[VO(salhyph(H)_2)]^+$ compound. Upon hydrolysis the dinuclear $\{[VO(salhyph(H)_2)]_2O\}$ end product is formed. This mechanistic understanding and ability to exert control over reactions between inorganic compounds and alkylating toxins may aid in the future development of pharmaceuticals for preventing DNA damage.

Introduction

Daily exposure to environmental carcinogens is nearly impossible to avoid. Common alkylating toxins include the nitrosamines and polycyclic aromatic hydrocarbons (PAHs). Foods such as hot dogs, beer, and even bread contain high levels of nitrosamines. The combustion of any organic matter in cooked foods,[1] tobacco smoke,[2] and vehicle exhaust[3] generates PAHs. Enzymatic oxidation of nitrosamines yields intermediates that decompose to alkyl diazoniums. The PAHs are also acted upon by oxidizing enzymes to form aromatic epoxides. Both the epoxide and alkyl diazonium electrophiles can alkylate DNA base nucleophiles, cause base mismatching during replication, generate mutations, and lead to the eventual formation of cancer.[4,5] Given that exposure to these carcinogens is so commonplace, it is essential to develop new methods for preventing DNA damage.

Many compounds have been investigated in the search for chemopreventive agents, including simple salts of vanadium[6−10] and selenium.[11−13] Beyond the many animal studies,[14−18] a large phase III clinical trial investigated the effect of dietary selenium on cancer. The Selenium and Vitamin E Chemoprevention Trial (SELECT) included over 30,000 men at risk for prostate cancer.[19] Preliminary results

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indicated that those participants taking 200 μg Se per day were half as likely to develop prostate cancer.[20]

Although less prominent in chemoprevention than selenium, vanadium has also shown a protective effect.[8,10,15,16,21] Most vanadium chemoprevention studies have been performed with rats. For example when rats were treated with NH_4VO_3 in drinking water, before exposure to alkylating toxins, fewer tumors formed relative to controls.[16] In these chemoprevention trials vanadium has shown an ability to prevent DNA strand breaks.[22] Further DNA lesion investigations indicated that vanadium halts formation of ethylated DNA after exposure to ethylating carcinogens.[23] With chemically induced mammary cancer in rats, vanadium can suppress cell proliferation and induce apoptosis.[9]

Despite these findings, few mechanistic insights are available to explain chemoprevention from vanadium. When placed in water, salts of vanadium[24,25] equilibrate to multiple anionic oxido species such as $H_2VO_4^-$. Previously we presented experiments with reactions between DNA, metal-oxido compounds, and carcinogens.[26] We found that vanadates and selenates prevent alkylation of DNA.[26] These results brought us to a proposed "carcinogen interception" mechanism in which nucleophilic metal-oxido groups attack electrophilic alkylating agents, thereby avoiding a deleterious reaction with DNA. We also showed that simple vanadates such as $V_3O_9^{3-}$ can transform alkylating agents (e.g., CH_3CH_2I) into alcohols (e.g., CH_3CH_2OH) rather than allowing formation of alkylated DNA lesions.[27,28]

In aqueous solutions many inorganic salts equilibrate to numerous species. The extent of equilibration depends on factors including pH, concentration, and dissolved oxygen content. The case of vanadium in water can be especially tricky when starting from vanadates (V^{5+}), with four or more species coexisting in the same solution (e.g., $H_2VO_4^-$, $H_2V_2O_7^{2-}$, $V_4O_{12}^{4-}$, and $V_5O_{15}^{5-}$). Beyond this complex speciation for simple solutions, in biological environments vanadate can mimic phosphate, thereby interfering with phosphate processing enzymes.[29] If we wish to facilitate the design of chemopreventative compounds, a good place to start is trying to simplify the solution speciation. One way to minimize equilibration between several oxidovanadium species is to chelate the metal center with an organic ligand. In addition to minimizing equilibrations, and hence toxicity, binding a ligand to the metal center may also allow for control of the overall compound charge, coordination number, and extent of electron donation from the ligand to the metal. With the metal compound less able to interconvert between several species, the efficacy of an administered regimen could also increase.

Oxidovanadium-ligand compounds are plentiful in the literature. Indeed, far more metal−ligand chemistry is known for vanadium than selenium. Hence we will focus on vanadium complexes. Insulin mimetics such as bis(picolinato)oxidovanadium(IV),[30] $[VO(OH_2)(5\text{-MeOdipic})_2]$,[31] and bis(maltolato)oxidovanadium(IV)[32] are widely known and have been studied extensively. Although chelating ligands tend to minimize solution speciation, once in a biological environment the ligand can be shed and vanadium may be bound by proteins such as transferrin.[33−38] Other prominent vanadium complexes include photocatalysts,[39] oxidation catalysts,[40] and synthetic models of vanadium-containing enzymes.[41]

In a preliminary report[42] we showed that anionic V^{5+} dioxido compounds of the salhyph (salicylidenehydrazide) ligand reacted readily with a series of alkylating agents. Electron donating and withdrawing substituents were placed on the ligand framework to generate the $K[VO_2(\text{salhyph-}(R)_2)]$ family of compounds. In this current report we investigate the mechanism of alkylation reactions and the origin of differences in nucleophilicity between these compounds. To gain mechanistic insights, we set out to determine the reaction order of each reagent, both the $(CH_3CH_2O)_2SO_2$ alkylating agent and vanadium. Consequently a kinetic study was performed. Somewhat unexpected results were found and led us to conductivity studies for determining the species present in solution. Conductivity showed that the $K[VO_2(\text{salhyph}(R)_2)]$ compounds ion-pair in dimethyl sulfoxide (DMSO) solvent. The degree of ion-pairing varies with the electron donating and withdrawing substituents. Ion-pairing equilibrium constants were determined. Reactivity of the $[VO_2(\text{salhyph}(R)_2)]^-$ anions was shown to be significant whereas the neutral, ion-paired species $K[VO_2(\text{salhyph}(R)_2)]$ were relatively unreactive. We explored the mechanism and products of the alkylation reactions. Vanadium-containing intermediates were formed during the course of alkylation. These detailed mechanistic insights may facilitate the design of improved compounds for preventing DNA damage and cancer.

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Experimental Section

Materials and Methods. Deuterated and non-deuterated DMSO were each dried over NaOH for at least 1 day, distilled over fresh NaOH at reduced pressure (~15 mmHg), and stored under argon. This drying process reduced the solvent water content from ~450 mM to ~45 mM. Final water content was determined by integrating the ^{1}H NMR water peak and comparing to an internal standard of $P(C_6H_5)_3$ at a known concentration. All NMR spectra were obtained at 25 ± 1 °C using a Varian INOVA 300 spectrometer at 300 MHz for ^{1}H, unless noted otherwise. The ^{51}V NMR spectra were acquired at 78.9 MHz, with ^{1}H decoupling. For ^{51}V NMR spectroscopy, chemical shift values were referenced to an external standard of neat $VOCl_3$ ($\delta = 0$ ppm). Typical ^{51}V NMR spectral parameters included 256 transients, 0.65 s acquisition time, 70 kHz spectral width, 13 μs pulse width, and 35 Hz line broadening.

Synthesis of K[VO_2(salhyph(R)$_2$)] Compounds. The parent K[VO_2(salhyph(H)$_2$)]·CH_3OH complex was synthesized using a published method.[43] This compound crystallizes with 1 equiv of methanol. It was noted that crushing and in vacuo drying of the crystals (e.g., 24 h) removed 20% of the methanol. All kinetic experiments reported below used crushed and dried K[VO_2(salhyph(H)$_2$)]·CH_3OH and molecular weights calculated account for this solvent loss. Other K[VO_2(salhyph(R)$_2$)] (R = -OCH_3, -CH_3, -NO_2) compounds were prepared by the methods reported previously.[42] The R = -OCH_3 and -CH_3 complexes contain no solvent molecules in the crystals. The R = -NO_2 compound crystallized with 1 equiv of H_2O.

Synthesis of {[VO(salhyph(H)$_2$)]$_2$O}. This known[44−46] compound was prepared as previously reported.[46] Briefly, the H_2salhyph ligand[47] was combined with $VO(acac)_2$ 1:1 in CH_3CN. This dinuclear species was also synthesized by our new method of alkylating K[VO_2(salhyph(H)$_2$)]·CH_3OH with $(CH_3CH_2O)_2SO_2$.

VO(OCH_3)(salhyph(H)$_2$). The compound was prepared by combining {[VO(salhyph(H)$_2$)]$_2$O} (2.00 g, 3.19 mmol) with an excess of boiling methanol (30 mL). The mixture was filtered while hot, and any insoluble solids were discarded. The clear, black filtrate was then allowed to cool to room temperature, followed by storage at −20 °C for 7 days. Black crystals formed in the solution, were collected by filtration, and dried in vacuo. This procedure is similar to that described previously for the ammonium salt.[48] ^{1}H NMR (ppm in DMSO-d_6): δ 5.28 (s, 3H), 6.90 (d, 1H), 6.98 (t, 1H), 7.45−7.46 (m, 4H), 7.71 (d, 1H), 8.04 (d, 2H), 8.90 (s, 1H). ^{51}V NMR (DMSO-d_6): δ −534 ppm. ^{51}V NMR (acetone-d_6): δ −541 ppm.

VO(OCH_2CH_3)(salhyph(H)$_2$). An equimolar mixture of H_2salhyph ligand (0.722 g, 3.00 mmol) and $VO(acac)_2$ (0.796 g, 3.00 mmol) was allowed to stir in absolute ethanol (20 mL) at room temperature while exposed to air for 4 days. The desired crude product was obtained by reducing the solution to dryness in vacuo. This method is similar to that described for an oxidovanadium compound involving the 2-hydroxybenzoylhydrazone of 2-hydroxybenzoylhydrazine ligand.[49] ^{1}H NMR (ppm in DMSO-d_6): δ 1.56 (t, 3H), 5.45−5.7 (m, 2H), 6.88 (d, 1H), 6.96 (t, 1H), 7.4−7.5 (m, 4H), 7.68 (d, 1H), 8.01 (d, 2H), 8.88 (s, 1H). ^{51}V NMR (DMSO-d_6): δ −541 ppm. ^{51}V NMR (acetone-d_6): δ −550 ppm.

Kinetic Reactions. Kinetics were monitored by ^{1}H NMR spectroscopy with a spectrum taken every 15 min, over 12 h. This 12 h reaction time provided data for approximately 3−4 half-lives, depending upon the reaction. Kinetic data were extracted from the reduction of $(CH_3CH_2O)_2SO_2$ methylene resonances over time, owing to a clear baseline on either side of the peaks. With the variety of compounds studied here, the resonances of CH_3CH_2OH and $(CH_3CH_2O)SO_3^-$ sometimes overlapped with other peaks and could not always be monitored cleanly. The integrals of $(CH_3CH_2O)_2SO_2$ peaks were referenced to a DMF internal standard at 100 mM, thereby providing concentrations of $(CH_3CH_2O)_2SO_2$ at each time point.

Kinetic reaction solutions were prepared under an argon blanket in oven- and flame-dried 1 mL volumetric flasks. Standard pseudo-first-order reaction conditions included a 10:1 ratio of vanadium compound:alkylating agent at concentrations of 200 mM and 20 mM, respectively. For example, K[VO_2(salhyph(H)$_2$)]·CH_3OH (0.0772 g, 0.200 mmol) was dissolved with stirring in approximately 0.5 mL of DMSO-d_6 in a 1 mL volumetric flask. The internal concentration standard DMF (7.74 μL, 0.100 mmol) was placed in the solution. The $(CH_3CH_2O)_2SO_2$ alkylating agent (2.6 μL, 0.020 mmol) was then syringed into the reaction mixture. Finally, DMSO-d_6 was added to bring the total sample volume to 1.00 mL. After mixing, the reaction was transferred to an argon-flushed NMR tube. The tube was flushed with argon, capped, sealed with Parafilm, and covered with foil to minimize light exposure. Kinetic reactions for each compound were repeated three times. Rate constants presented are an average of these three runs and show one standard deviation.

Kinetic Variation of Vanadium Concentrations. Pseudo-first-order conditions were used as described above. The concentration of K[VO_2(salhyph(H)$_2$)]·CH_3OH was varied (100, 200, 300, 400, or 500 mM) while the concentration of the $(CH_3CH_2O)_2SO_2$ alkylating agent was kept constant at 20 mM.

Kinetic Variation of K^+ Concentrations. Pseudo-first-order conditions were used as described above. The concentration of K[VO_2(salhyph(H)$_2$)]·CH_3OH remained at 200 mM, and the alkylating agent $(CH_3CH_2O)_2SO_2$ was also maintained at 20 mM. Varied concentrations of KPF_6 were added as desired (125, 250, 375, or 500 mM).

"Background" Reaction. A control involving 50 mM $(CH_3CH_2O)_2SO_2$ (6.5 μL) in 1.0 mL of dried and distilled DMSO-d_6, without any vanadium compound, was monitored by ^{1}H NMR spectroscopy approximately every 4 h using a Bruker Avance-III-800 spectrometer at 800 MHz. A solution of CH_3CH_2I at 100 mM (8.0 μL) in 1.00 mL of dried and distilled DMSO-d_6, without any vanadium compound, was also observed using ^{1}H NMR spectroscopy over the course of 3 days.

Conductivity. Conductivity measurements were recorded on an Oakton CON 100 Series Model 35607−10 conductivity/temperature meter equipped with a glass platinum electrode. The instrument was calibrated with KCl NIST conductivity calibration standards once per day, prior to experiments. All solutions were maintained at 22 ± 1 °C by use of a temperature-controlled water bath and kept under a blanket of argon. Initial solutions of 400 mM $(n\text{-}C_4H_9)_4NPF_6$ or K[VO_2(salhyph(R)$_2$)] were prepared from dried and distilled DMSO, and the conductivity was measured. These solutions were then diluted stepwise, and the conductivity was measured again, thereby providing conductivity data at a series of lower concentrations. The maximum solubility of K[VO_2(salhyph(NO_2)$_2$)]·H_2O in dry DMSO was only ~200 mM, thus limiting the range of conductivity data presented for this one compound.

Ultraviolet−Visible (UV−vis) Spectroscopy. Each K[VO_2(salhyph(R)$_2$)] compound (~0.01 g) was dissolved in 1 L of dry DMSO to a final concentration of 25.0 μM. A 3 mL aliquot was added to a 1 cm path length cuvette. Each spectrum was recorded on a Cary 100 Bio UV−vis dual-beam instrument.

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Table 1. Kinetic Data, Ion-Pairing Data, Adjustments, and Resulting Rate Constants for Alkylation of $K[VO_2(salhyph(R)_2)]$ Complexes

compound	initial conc. (mM)	"free" $[VO_2(salhyph(R)_2)]^-$ anion (mM)	K_{IP} (mM^{-1})	correction factor applied[a]	k_{obs} ($\times 10^{-5}$ s^{-1})	k_{obs} adjusted for ion pairing ($\times 10^{-4}$ s^{-1})
$K[VO_2(salhyph(NO_2)_2)]\cdot H_2O$	200			26.6%[b]	5.0 ± 0.5	1.7 ± 0.2
$K[VO_2(salhyph(H)_2)]\cdot CH_3OH$	200	58.7	0.041 ± 0.003	26.6%	5.3 ± 0.9	1.8 ± 0.3
$K[VO_2(salhyph(CH_3)_2)]$	200	52.3	0.054 ± 0.005	26.2%	5.5 ± 0.7	2.1 ± 0.3
$K[VO_2(salhyph(OCH_3)_2)]$	200	41.9	0.090 ± 0.018	21.0%	5.9 ± 0.3	2.8 ± 0.1

[a] The correction factor applied accounts for the quantity of non-ion-paired $[VO_2(salhyph(H)_2)]^-$ anion in solution and available to react with the alkylating agent. See the section "Ion-Pairing and Conductance" for details. [b] Note that the correction applied to the R = -NO_2 compound could not be measured experimentally and that used is from the parent R = -H species. A higher percent value may be expected given the electron withdrawing nature of -NO_2 groups.

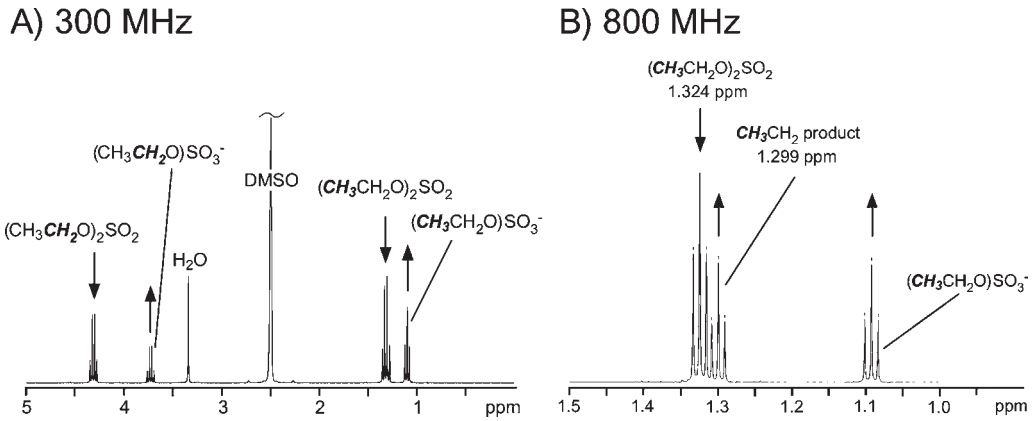

Figure 1. (**A**) ^1H NMR of the background reaction of $(CH_3CH_2O)_2SO_2$ in DMSO-d_6 at 8 h. Note that no ethanol is observed. (**B**) 800 MHz ^1H NMR spectrum of $(CH_3CH_2O)_2SO_2$ in DMSO-d_6. Notice the two different triplets at ~1.3 ppm.

Monitoring Alkylation Reactions by ^{51}V NMR Spectroscopy: Reactions Between $(CH_3CH_2O)_2SO_2$ and $K[VO_2(salhyph(H)_2)]\cdot CH_3OH$. Each reagent was combined 1:1 in DMSO-d_6 (50 mM each). The ^1H NMR and ^{51}V NMR spectra were taken at 4, 8, 23, 27 h and then 3, 6, 18 days. Analogous reactions were also carried out in acetone-d_6 (50 mM each reagent). These ^1H NMR and ^{51}V NMR spectra were taken at 4, 8, 24, 32, 48, 55 h and then 4, 9, 13, 22, 25, 30, 38 days.

Large Scale Reactions of $(CH_3CH_2O)_2SO_2$ and $K[VO_2(salhyph(H)_2)]\cdot CH_3OH$ in Acetone. A 1:1 reaction of $K[VO_2(salhyph(H)_2)]\cdot CH_3OH$ (0.391 g, 50.0 mM) and $(CH_3CH_2O)_2SO_2$ (130 μL, 50 mM) in 20 mL of acetone was stirred for 3 days in darkness. Solid products were collected by gravity filtration, dried under vacuum, and analyzed after that time.

Results and Discussion

Previously it was shown that the series of $K[VO_2(salhyph(R)_2)]$ (R = -H, -NO_2, -CH_3, or -OCH_3) compounds react with many different alkylating agents: CH_3CH_2I, CH_3CH_2Br, CH_3I, $H_2NCON(NO)CH_3$, $CH_3SO_2OCH_3$, $(CH_3CH_2O)_2SO_2$, and $(CH_3CH_2O)SO_2CF_3$.[42] Here the focus is on one reagent for consistency, $(CH_3CH_2O)_2SO_2$. Upon reaction with $K[VO_2(salhyph(R)_2]$ compounds, this diethyl sulfate, $(CH_3CH_2O)_2SO_2$, alkylating agent yields monoethyl sulfate, $(CH_3CH_2O)SO_3^-$, and the vanadium-containing products characterized below. Kinetic experiments were performed in dry DMSO-d_6 because it is the only solvent in which sufficient solubility was achieved for all substituted compounds being examined here. Kinetic data were obtained for the reaction between $K[VO_2(salhyph(R)_2)]$ (200 mM) and $(CH_3CH_2O)_2SO_2$ (20 mM) under pseudo-first-order conditions. Loss of $(CH_3CH_2O)_2SO_2$ was fit with monoexponential curves and shown to be first-order with respect to $(CH_3CH_2O)_2SO_2$ (See Supporting Information, Figure S1). Previously kinetic data were fit using a biexponential expression, accounting for the primary reaction as well as background decomposition of $(CH_3CH_2O)_2SO_2$.[42] As will be shown below, a monoexponential fit is more appropriate here. A reaction between $(CH_3CH_2O)_2SO_2$ and the DMSO solvent has since been found to be a part of the system. Prior to any corrections, the k_{obs} values measured for each of the four compounds, using monoexponential fits, are as follows (s^{-1}): R = -NO_2, $k_{obs} = 5.0 \times 10^{-5}$; R = -H, $k_{obs} = 5.3 \times 10^{-5}$; R = -$CH_3$, $k_{obs} = 5.5 \times 10^{-5}$; R = -$OCH_3$, $k_{obs} = 5.9 \times 10^{-5}$ s^{-1}. These rate constants are also provided in Table 1, in the next-to-last column. A mild trend may or may not be present in which electron donating groups increase nucleophilicity and thereby hasten the reactions. The converse could be true for an electron withdrawing group. However, such a trend may not be present given the small differences in rate constants and the associated standard deviations.

A background reaction was found to occur in which limited $(CH_3CH_2O)_2SO_2$ consumption takes place without a vanadium compound present. This background reaction appears to not be hydrolysis, rather a reaction between the DMSO solvent and $(CH_3CH_2O)_2SO_2$. Figure 1A shows the ^1H NMR spectrum of $(CH_3CH_2O)_2SO_2$ in DMSO-d_6 at 300 MHz. Loss of $(CH_3CH_2O)_2SO_2$ and formation of $(CH_3CH_2O)SO_3^-$ are both apparent. However, no CH_3CH_2OH or other ethyl-containing products are seen. It is plausible, then, to ask where the "missing" ethyl groups may have gone. One possible explanation is that there are overlapping peaks in the 300 MHz NMR spectrum. The ^1H NMR spectrum of $(CH_3CH_2O)_2SO_2$ in DMSO-d_6 was taken again, this time at 800 MHz. Figure 1B shows the expanded region near 1.3 ppm

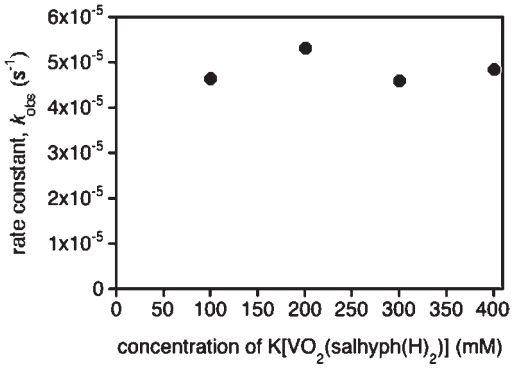

Figure 2. Kinetic data for the concentration of $K[VO_2(salhyph(H)_2)]\cdot CH_3OH$ versus observed rate constant in the reaction with $(CH_3CH_2O)_2SO_2$. The $(CH_3CH_2O)_2SO_2$ concentration was 20 mM.

at this higher field. Two distinct species are now visible at 1.299 and 1.324 ppm. The peak at 1.324 ppm is assigned to $(\boldsymbol{CH_3}CH_2O)_2SO_2$, and the peak at 1.299 ppm is a reaction product. These two separate species were not visible at 300 MHz.

An analogous experiment with CH_3CH_2I in DMSO-d_6 showed the same product growing in at 1.29 ppm, very close to the shift for $(CH_3CH_2O)_2SO_2$, thereby suggesting that CH_3CH_2I also alkylates DMSO in the same manner (data not shown). To investigate this DMSO alkylation product further, an analysis by gas chromatography/mass spectrometry (GC/MS) was attempted but did not provide useful data owing to the high temperature of the instrument and immediate formation of ethanol from $(CH_3CH_2O)_2SO_2$ and residual water. Alkyl triflate compounds are known to react with DMSO and yield $[(CH_3)_2S{-}O{-}R]^+$.[50] Consequently the "missing" ethyl group was attributed to formation of $[(CH_3)_2S{-}O{-}CH_2CH_3]^+$. The methylene resonances of alkylated DMSO were not observed, likely a result of overlap with those of the starting $(CH_3CH_2O)_2SO_2$, according to earlier studies.[51] This reaction of 50 mM $(CH_3CH_2O)_2SO_2$ in DMSO-d_6 consumes a maximum of ~50% starting DMSO, even after 21 days. The kinetics of this reaction were measured and k_{obs} was found to be 1.1 ($\pm$0.1) $\times 10^{-5}$ s^{-1}. This rate constant is lower than those measured for the $K[VO_2(salhyph(R)_2)]$ complexes ($k_{obs} \approx (5{-}6)\times 10^{-5}$ s^{-1}, Table 1).

Rate Law Investigations. After determining that the system is first-order with respect to $(CH_3CH_2O)_2SO_2$ (Supporting Information, Figure S1), the next step was to find out the reaction order with respect to vanadium and obtain the full rate law. If the concentration of total vanadium in the reaction is varied and 1:1 linear changes in the observed rate constants are found, a first-order dependence on vanadium can be surmised. Figure 2 shows the observed rate constants, with $(CH_3CH_2O)_2SO_2$ at 20 mM and $K[VO_2(salhyph(H)_2)]\cdot CH_3OH$ varied from 100 to 400 mM. A rather surprising result was found in that no major dependence upon vanadium concentration was observed. Additional examinations of 1:1 $(CH_3CH_2O)_2SO_2$: $K[VO_2(salhyph(H)_2)]\cdot CH_3OH$ (50 mM each) alkylation reactions in acetone-d_6 turned out to proceed much slower than the DMSO-d_6 counterparts. For example, a DMSO-d_6 reaction was complete in 27 h whereas the same reaction took greater than 38 days to finish in acetone-d_6.

Ion-Pairing and Conductance. Acetone is significantly less polar than DMSO. Thus a decreased reaction rate in acetone indicates that a key reactive species or intermediate is likely to be polar or charged. Ion-pairing of $K[VO_2(salhyph(R)_2)]$ in solution could influence reactivity. For example, one may anticipate the nucleophilicity of anionic "free" $[VO_2(salhyph(R)_2)]^-$ to be greater than that of a neutral $\{K[VO_2(salhyph(R)_2)]\}$ ion-pair. Such ion-pairing would occur more readily in acetone than DMSO, thereby explaining the differences in rate constants. Furthermore, ion-pairing typically increases at higher concentrations. This phenomenon could mask a potential dependence of the reaction upon $[VO_2(salhyph(R)_2)]^-$ concentration (c.f., Figure 2). Ion-pairing of other vanadates has been observed previously.[52]

Consequently conductivity experiments were chosen to determine if ion-pairing of $K[VO_2(salhyph(R)_2)]$ was, indeed, occurring. The salt $(n\text{-}C_4H_9)_4NPF_6$ was used for a 1:1 electrolyte standard. Figure 3A shows the concentration-versus-conductance data for three $K[VO_2(salhyph(R)_2)]$ complexes along with the $(n\text{-}C_4H_9)_4NPF_6$ standard. Conductivity for the R = -NO_2 compound is not shown. This compound was not soluble beyond 200 mM. After initial dissolution in DMSO at 200 mM, the R = -NO_2 compound changed from bright yellow flakes to a dark orange solution and then precipitated out of solution. Note that all compounds, including $(n\text{-}C_4H_9)_4NPF_6$, exhibit nonlinear conductivity curves. These data indicate the presence of significant ion-pairing, especially at the higher concentrations.

Determining the extent of ion-pairing requires comparison to an ideal 1:1 electrolyte. As can be seen in Figure 3A, even $(n\text{-}C_4H_9)_4NPF_6$ ion-pairs at the high concentrations used here (~100−400 mM). However, this ion-pairing is insignificant at very low concentrations, below 1 mM. The conductivity of $(n\text{-}C_4H_9)_4NPF_6$ was measured in the range of 0−0.5 mM and a linear relationship of concentration-versus-conductance (Figure 3B) was found. This line was plotted along with the conductance data of the $K[VO_2(salhyph(R)_2)]$ compounds and $(n\text{-}C_4H_9)_4NPF_6$ to indicate the degree of deviation from ideal behavior in each case (Figure 3A).

When examining conductivity of the vanadium complexes (R = -H, -CH_3, -OCH_3) a potential correlation with Hammett parameters could be noted. Electron donating compounds may provide greater electron density to the metal center and/or the oxido groups, thereby inducing more ion-pairing with the K^+ counterion. The conductivity data in Figure 3A show ion-pairing to follow a trend of R = -OCH_3 > -CH_3 > -H. This series correlates well with the electron donation ability of the ligands. For example, the most electron donating substituent, -OCH_3, shows the greatest degree of ion-pairing.

With the conductivity data in hand, it was desirable to determine the amount of "free" vanadium ("V^-_{free}"), or the $[VO_2(salhyph(R)_2)]^-$ anion which is not ion-paired in solution at a given concentration. These data will relay how much of the reactive V^-_{free} form is available versus

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(51) Olofson, R. A.; Marino, J. P. *Tetrahedron* **1971**, *27*, 4195–4208.
(52) Hamilton, E. E.; Fanwick, P. E.; Wilker, J. J. *J. Am. Chem. Soc.* **2002**, *124*, 78–82.

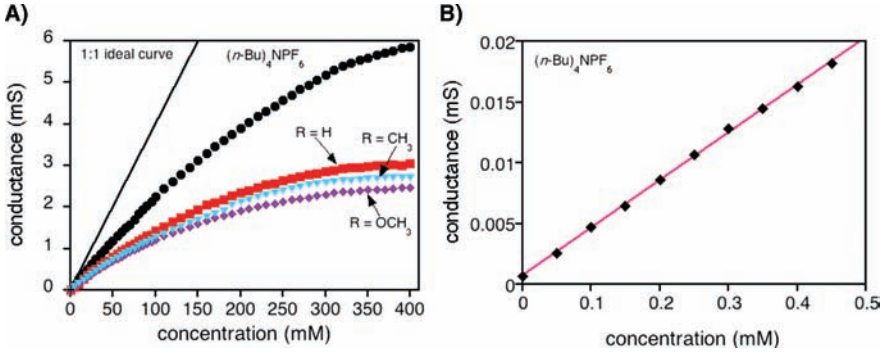

Figure 3. (**A**) Conductance-versus-concentration data for the R = -H, -CH_3, and -OCH_3 K[VO_2(salhyph(R)$_2$)] compounds as well as (n-C_4H_9)$_4$NPF_6. The ideal 1:1 line shown is extrapolated from the lower concentration (n-C_4H_9)$_4$NPF_6 data at 0−0.5 mM, shown in (**B**).

the neutral, unreactive, ion-paired "KV" form. Beginning with the "ideal" (i.e., not ion-paired) behavior of a line to determine 1:1 electrolyte we refer to the extrapolated line of (n-C_4H_9)$_4$NPF_6, in Figure 3A. The ideal conductivity at 200 mM was 7.78 mS, while the measured conductance for the parent compound K[VO_2(salhyph(H)$_2$)]·CH_3OH was 2.35 mS at 200 mM. Thus there was a 69.8% drop in conductivity, relative to the ideal, from ion-pairing. These data indicate that at 200 mM 69.8% of K[VO_2(salhyph(H)$_2$)]·CH_3OH is ion-paired and 30.2% is the "free" (or not ion-paired) [VO_2(salhyph(H)$_2$)]$^-$ anion. V_{total} is defined to be a sum of the concentrations of ion-paired K[VO_2(salhyph(H)$_2$)]·CH_3OH (or "KV") and the "free" anion [VO_2(salhyph(H)$_2$)]$^-$ or "V^-_{free}". Applying a "correction factor" to account for ion-pairing yields a V^-_{free} concentration of 60.4 mM when the starting KV (or V_{total}) is 200 mM. This correction factor is simply the percentage, at a given concentration, of the starting KV that is not ion paired, remaining in the V^-_{free} form. Correction factors at 200 mM for each compound and resulting concentrations of free vanadium available at 200 mM are reported in Table 1. Each of these values was determined by using the average ion pairing equilibrium constant (K_{IP}, vide infra), rather than conductivity data from a single point (e.g., 200 mM). Consequently the numbers vary slightly. For example, using average K_{IP} values the V^-_{free} concentration for the parent compound works out to be 58.7 mM. Given that the electron withdrawing nitro-substituted compound did not behave cleanly at high concentrations (>200 mM), the correction factor used in that case was from the parent compound (R = -H). However, one might expect the -NO_2 compound to ion-pair less than the other derivatives examined and follow a correlation of greater electron donation yielding greater ion-pairing. The observed reactivity can now be attributed to only the portion of V_{total} that is not ion-paired, that is, V^-_{free}. Dividing the observed rate constants by the correction factor provides adjusted rate constants. Taking the R = -H derivative for an example, the observed rate constant of 5.3×10^{-5} s^{-1} divided by the 26.6% correction factor (i.e., 0.266) provides an adjusted rate constant of $k_{obs} = 1.8 \times 10^{-4}$ s^{-1} (Table 1).

Two parallel processes are present to consume the starting (CH_3CH_2O)$_2SO_2$ alkylating agent: Reaction with the V^-_{free} anions and the background reaction with DMSO solvent (c.f., Figure 1). Both reactions are pseudo-first-order processes, with V^-_{free} anions and DMSO in excess relative to (CH_3CH_2O)$_2SO_2$. Consequently mono-exponential fitting is appropriate for the kinetic plots of (CH_3CH_2O)$_2SO_2$ loss over time, shown in Supporting Information, Figure S1. Pseudo-first-order rate constants for the reactions of (CH_3CH_2O)$_2SO_2$ with the V^-_{free} anions are in the range of $(1.7-2.8) \times 10^{-4}$ s^{-1} (Table 1), approximately 15−25 times that of the pseudo-first-order rate constant of 1.1 ($\pm$0.1)$\times 10^{-5}$ s^{-1} for the background consumption of (CH_3CH_2O)$_2SO_2$ by solvent. Relative to (CH_3CH_2O)$_2SO_2$ loss from V^-_{free} anions, we can consider the background reaction with DMSO to be negligible.

Next K_{IP}, the equilibrium constant of ion-pairing, was found for the oxidovanadium compounds (R = -H, -CH_3, -OCH_3). These K_{IP} values were calculated at each concentration for which conductivity data were obtained between 100 and 350 mM and then averaged. The simple eq 1, below, provides a means to determine K_{IP}, where [KV] is the neutral ion-paired species {K[VO_2(salhyph(H)$_2$)]}, [K^+_{free}] is the K^+ cation free from ion-pairing, and [V^-_{free}] is the free anion [VO_2(salhyph(H)$_2$)]$^-$. The values reported in Table 1 are each averages from 26 conductivity measurements, shown with one standard deviation. A value of K_{IP} = 0.041 ($\pm$0.003) mM^{-1} was determined for the R = H parent compound (Table 1).

$$K_{IP} = \frac{[KV]}{[K^+_{free}][V^-_{free}]} \quad (1)$$

Prior studies have shown that alkylation reactions of monoanionic zinc-thiolate complexes occur with rate constants greater than 100 times that of an analogous neutral species.[53,54] Greater anionic charge enhances nucleophilicity and reactivity toward electrophilic alkylating agents. Here, reactivity of the neutral, ion-paired {K[VO_2(salhyph(H)$_2$)]} species can be anticipated to be significantly less than that of the anionic V^-_{free} species [VO_2(salhyph(H)$_2$)]$^-$. Thus one can assume that only anionic V^-_{free} reacts with (CH_3CH_2O)$_2SO_2$ and that the reactivity of the neutral KV species is, relatively speaking, insignificant. Scheme 1 shows [VO_2(salhyph(H)$_2$)]$^-$ reacting to yield products via a multi step process (vide infra) whereas {K[VO_2(salhyph(H)$_2$)]} is unreactive.

Given that ion-pairing decreases nucleophilic reactivity, addition of a K^+ source may enhance ion-pairing of

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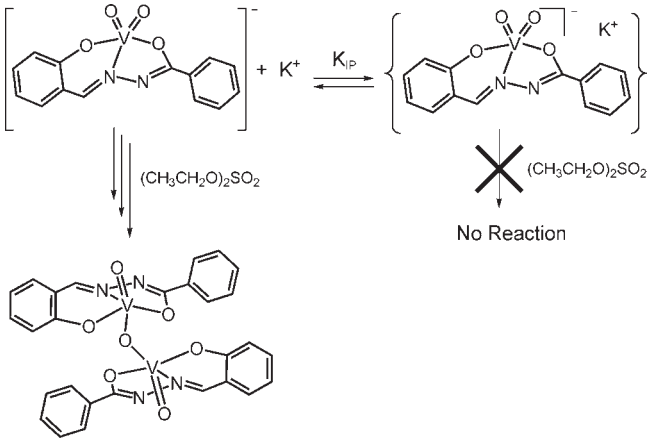
Scheme 1. "Free" $[VO_2(salhyph(H)_2)]^-$ Anion Reacts with $(CH_3CH_2O)_2SO_2$ to Generate Products. The Neutral, Ion-Paired Species $\{K[VO_2(salhyph(H)_2)]\}$ is Relatively Unreactive



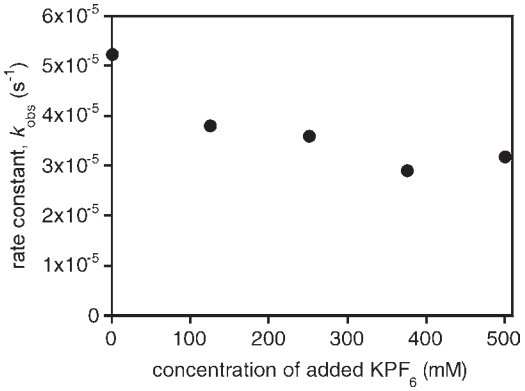


Figure 4. Rate constants as a function of added KPF_6. $K[VO_2(salhyph(H)_2)]\cdot CH_3OH$ was 200 mM and $(CH_3CH_2O)_2SO_2$ was 20 mM.

$[VO_2(salhyph(H)_2)]^-$, deplete V^-_{free}, and further slow down the reaction of these oxidovanadium species with $(CH_3CH_2O)_2SO_2$. To confirm this ion-pairing scheme, experiments were performed in which the concentration of V_{total} was maintained at 200 mM and the $(CH_3CH_2O)_2SO_2$ concentration was also held constant at 20 mM. Then varying amounts of KPF_6 were added, and the reaction kinetics measured. The chosen KPF_6 concentrations were 0, 125, 250, 375, and 500 mM. Kinetic data are shown in Figure 4 and indicate that k_{obs} values decrease with increasing concentrations of added K^+. Suppressed rate constants ranged from 3.8×10^{-5} s^{-1} down to 2.9×10^{-5} s^{-1}, relative to 5.3×10^{-5} s^{-1} without any added KPF_6. There will be an ion pairing equilibrium constant associated with the KPF_6, alone, in solution such that all of the added KPF_6 does not yield K^+_{free} for ion pairing with V^-_{free}. Nonetheless added KPF_6 does decrease the reactivity of the vanadium compounds. These data support Scheme 1 in which ion-pairing of $[VO_2(salhyph(H)_2)]^-$ suppresses reactivity.

The ion-pairing equilibrium constants (K_{IP}'s) indicate that a starting KV concentration of 200 mM yields only ~59 mM of the reactive, anionic $[VO_2(salhyph(H)_2)]^-$ form (Table 1). With a $(CH_3CH_2O)_2SO_2$ concentration of 20 mM, pseudo-first-order conditions may not be preserved. However, during the reaction as the V^-_{free} is consumed, the ion-pairing equilibrium will replenish the depleted V^-_{free} from the large supply of ion-paired KV. Consequently, the concentration of V^-_{free} changes less than a lone reagent in solution. With the V^-_{free} concentration changing relatively little during the reaction, pseudo-first-order conditions are likely to be sufficiently maintained here.

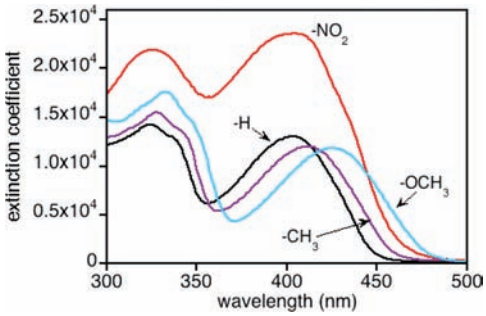


Figure 5. UV−vis spectra in DMSO for the series of $K[VO_2(salhyph(R)_2)]$ complexes with varied substituents (R = $-NO_2$, -H, $-CH_3$, $-OCH_3$).

Table 2. UV-vis Data in DMSO for $K[VO_2(salhyph(R)_2)]$ Compounds

compound	λ_{max} (nm)	extinction coefficient (ε, cm^{-1} M^{-1})
$K[VO_2(salhyph(\mathbf{NO_2})_2)]\cdot H_2O$	402	23,570
$K[VO_2(salhyph(\mathbf{H})_2)]\cdot CH_3OH$	404	13,000
$K[VO_2(salhyph(\mathbf{CH_3})_2)]$	412	11,980
$K[VO_2(salhyph(\mathbf{OCH_3})_2)]$	425	11,790

Absorption Spectroscopy of $K[VO_2(salhyph(R)_2)]$ Compounds. From the conductivity measurements and, perhaps, the kinetic data, substituted $K[VO_2(salhyph(R)_2)]$ compounds may display a relation to Hammett parameters in which the electron donating ability of the -R group on the ligand influences reactivity of the complexes. To further investigate this potential phenomenon, and to provide more direct evidence for electronic differences in this series of compounds, UV−vis spectra were collected, shown in Figure 5 and Table 2. The λ_{max} values appear to correlate with the electron donating abilities of the ligands. The peak at ~400 nm is not present in the spectra of the ligands alone, and the V(V) ions do not possess *d* electrons that may transfer to the ligand. Thus the transition at ~400 nm likely corresponds to a ligand-to-metal charge transfer (LMCT). With increased donation of electron density (e.g., R = $-OCH_3$ or $-CH_3$) the absorbance at ~400 nm may red shift to lower energy. With increased electron density on the ligand, the transfer of an electron from the ligand to the metal center is easier, requires less energy, and hence appears shifted toward the red. Conversely, an electron withdrawing group such as $-NO_2$ hinders the LMCT, requiring increased energy to transfer an electron from the ligand to the metal, thereby exhibiting a potential blue shift.

Taken together, there are now three sources of data indicating that this series of compounds may exhibit a trend in electronics. The UV−vis spectra show greater electron donating substituents yielding red-shifted LMCT spectra. Conductivity data show higher ion-pairing propensity with increased electron donating substituents.

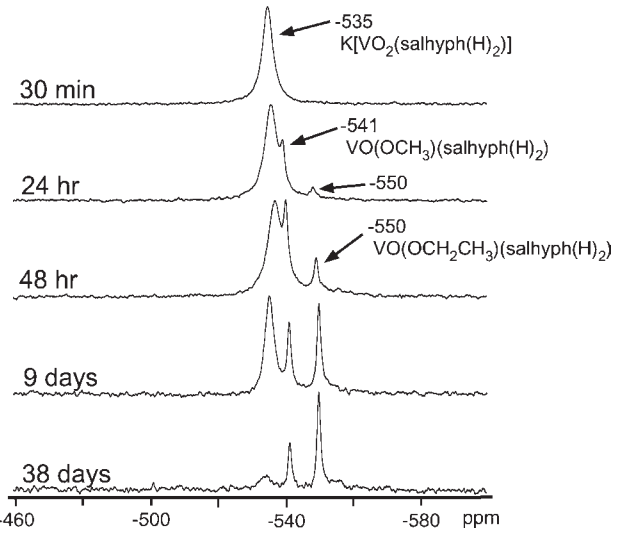


Figure 6. ^{51}V NMR spectra of a 1:1 reaction between K[VO_2(salhyph-$(H)_2$)]·CH_3OH and $(CH_3CH_2O)_2SO_2$ (50 mM each) in acetone-d_6. To aid visualizing resonances, each spectrum is shown adjusted with the tallest peak set to a constant vertical height. Overall spectral intensities decreased as the reaction progressed, and the majority of vanadium crystallized out of solution by 38 days.

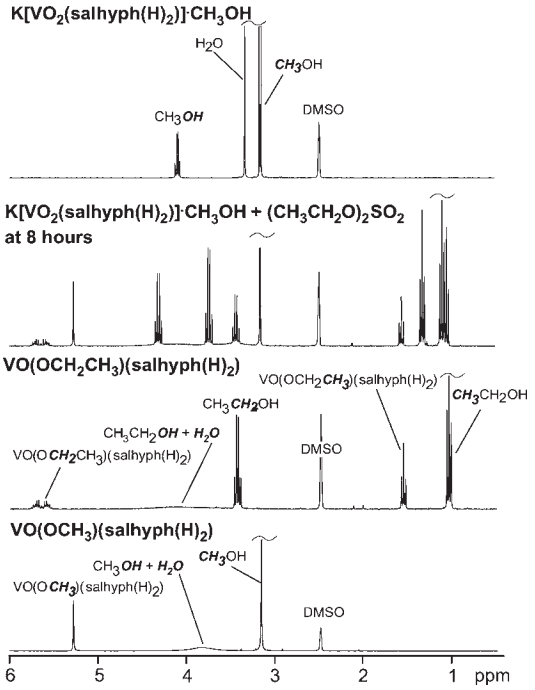


Figure 7. ^{1}H NMR spectra of (from top) the starting K[VO_2(salhyph-$(H)_2$)]·CH_3OH, a 1:1 alkylation reaction between K[VO_2(salhyph-$(H)_2$)]·CH_3OH and $(CH_3CH_2O)_2SO_2$ in progress (8 h), genuine VO-(OCH_2CH_3)(salhyph$(H)_2$), and genuine VO(OCH_3)(salhyph$(H)_2$), all in DMSO-d_6.

Lastly, the observed rate constants may (or may not) provide a range of reactivity that changes depending upon the ligand substituent. These data indicate that a small degree of control can be exerted over alkylation reactions of oxidovanadium compounds by changing the surrounding ligand.

Reaction Mechanism. The reaction between K[VO_2-(salhyph$(H)_2$)]·CH_3OH and $(CH_3CH_2O)_2SO_2$ is known to be first-order with respect to $(CH_3CH_2O)_2SO_2$ from the pseudo-first-order kinetic runs showing monoexponential decay of $(CH_3CH_2O)_2SO_2$ over time (Supporting Information, Figure S1). Kinetic experiments were also carried out to determine the reaction order with respect to vanadium. Unfortunately a clear dependence upon K[VO_2(salhyph$(H)_2$)]·CH_3OH was not obtained. These efforts are described in Section S8 of the Supporting Information. Mechanistic insights were then pursued by direct observation of reaction intermediates. The ^{51}V NMR spectra of the alkylation reactions were collected, while in progress, to determine the presence of reaction intermediates. The ^{51}V NMR spectra were acquired in both DMSO-d_6 and acetone-d_6. Although the same species were found in both solvents, the resonances were more distinct in acetone-d_6 and are discussed here (Figure 6). Analogous spectra in DMSO-d_6 are supplied in the Supporting Information, Figure S2. Recall that alkylation proceeds at a much slower rate in less polar acetone, thereby providing more time to note spectral changes.

The ^{51}V NMR spectra of a 1:1 reaction between K-[VO_2(salhyph$(H)_2$)]·CH_3OH and $(CH_3CH_2O)_2SO_2$ (50 mM each) in acetone-d_6 taken at varied times are shown in Figure 6. At 30 min only the starting K[VO_2(salhyph-$(H)_2$)]·CH_3OH is present at −535 ppm. As the reaction continues two peaks grow in, one at −541 ppm and another at −550 ppm. Further time showed the majority of material to have crystallized from the acetone-d_6 solution, with the ^{51}V NMR spectral intensities decreasing over time. After 38 days there is minimal starting K[VO_2(salhyph$(H)_2$)]·CH_3OH remaining, and two products at −541 and −550 ppm are present. An analogous reaction run in DMSO-d_6 was 100% complete within ~27 h.

These alkylation reactions viewed by ^{51}V NMR spectroscopy allow for intermediate and product determination. The −535 ppm peak is the starting K[VO_2-(salhyph$(H)_2$)]·CH_3OH and is observed to decrease with time. With a [VO_2(salhyph$(H)_2$)]$^-$ nucleophile and an $CH_3CH_2^+$ electrophile from the $(CH_3CH_2O)_2$-SO_2 alkylating agent, direct alkylation of an oxidovanadium may occur. The corresponding intermediate would be an ethoxy VO(OCH_2CH_3)(salhyph$(H)_2$) species. This VO(OCH_2CH_3)(salhyph$(H)_2$) compound was prepared separately[49] and a ^{51}V NMR spectrum in acetone-d_6 shows a peak at −550 ppm (see Supporting Information, Figure S3). Thus the reaction peak at −550 ppm is assigned to VO(OCH_2CH_3)(salhyph$(H)_2$). The analogous methoxy VO(OCH_3)(salhyph$(H)_2$) compound was also prepared, and a ^{51}V NMR resonance was observed at −541 ppm (Supporting Information, Figure S3). The peak at −541 ppm in the alkylation reaction can be assigned to VO(OCH_3)(salhyph$(H)_2$). Lattice crystallization CH_3OH from the starting K-[VO_2(salhyph$(H)_2$)]·CH_3OH is the likely source of this alcohol to generate VO(OCH_3)(salhyph$(H)_2$) (vide infra). Analogous spectra were taken in DMSO-d_6 and are also found in the Supporting Information, Figure S4.

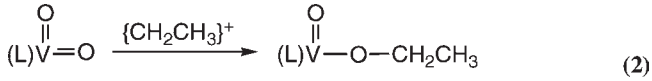
These alkylation reactions were also examined by ^{1}H NMR spectroscopy. The VO(OCH_2CH_3)(salhyph$(H)_2$) compound we synthesized was not soluble enough in acetone-d_6 to obtain very clean spectra; therefore, the

Table 3. ^{1}H and ^{51}V NMR Spectroscopic Data for $K[VO_2(salhyph(H)_2)]\cdot CH_3OH$, an Alkylation Reaction, and Two Proposed Intermediates $VO(OCH_2CH_3)(salhyph(H)_2)$ and $VO(OCH_3)(salhyph(H)_2)$[a]

complex	aliphatic ^{1}H NMR (δ, ppm) DMSO-d_6	^{51}V NMR (δ, ppm) DMSO-d_6	^{51}V NMR (δ, ppm) acetone-d_6
$K[VO_2(salhyph(H)_2)]\cdot CH_3OH$	*none*	−532	−535
$VO(OCH_2CH_3)(salhyph(H)_2)$	1.56 (t, 3H) 5.45−5.7 (m, 2H)	−541	−550
reaction product # 1	1.56 (t, 3H) 5.45−5.7 (m, 2H)	−541	−550
$VO(OCH_3)(salhyph(H)_2)$	5.28 (s, 3H)	−534	−541
reaction product # 2	5.27 (s, 3H)	−534	−541
$\{[VO(salhyph(H)_2)]_2O\}$	*none*	−580	*not soluble*
red-brown crystals	*none*	−580	*not soluble*

[a] For clarity DMSO, methanol, and water resonances are not listed.

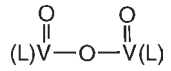
^{1}H NMR spectra are reported in DMSO-d_6. Figure 7 focuses on the aliphatic peaks. Full scale spectra in DMSO-d_6 are provided in Supporting Information, Figure S5. Although not as clear as when in DMSO-d_6, analogous full scale ^{1}H NMR spectra in acetone-d_6 are shown in Supporting Information, Figure S6. In spectra of the alkylation reaction, a multiplet at 5.4−5.7 ppm, a triplet at 1.56 ppm, and a singlet at 5.27 ppm grow in while the reaction progresses (Figure 7). When the compound $VO(OCH_2CH_3)(salhyph(H)_2)$ is synthesized separately and examined by ^{1}H NMR in DMSO-d_6, a multiplet corresponding to the methylene hydrogens on the $VO(O\boldsymbol{CH_2}CH_3)(salhyph(H)_2)$ appears at approximately 5.4−5.7 ppm. The methyl hydrogens show a triplet at 1.56 ppm (Figure 7). These data agree with the ^{51}V NMR data described above in that $VO(OCH_2CH_3)(salhyph(H)_2)$ is a reaction intermediate likely formed as a result of direct alkylation of an oxido moiety. Equation 2 depicts this transformation.



(2)

When the methoxy compound $VO(OCH_3)(salhyph(H)_2)$ is synthesized separately and characterized, the ^{1}H NMR spectrum in DMSO-d_6 shows a singlet at 5.28 ppm, corresponding to the methyl protons (Figure 7). This resonance provides an assignment of the 5.27 ppm singlet found in the alkylation reaction. Here, too, the ^{1}H NMR data agree with the ^{51}V NMR data and indicate that $VO(OCH_3)(salhyph(H)_2)$ is a reaction intermediate. Below a route to $VO(OCH_3)(salhyph(H)_2)$ during this alkylation reaction is proposed. Table 3 summarizes the ^{1}H and ^{51}V NMR spectroscopic data from the reaction and compounds synthesized separately, in both DMSO-d_6 and acetone-d_6.

When carrying out these NMR experiments in acetone-d_6, red-brown crystals deposited upon the walls of the NMR tube. This crystallization appears to provide an end point to the alkylation of $K[VO_2(salhyph(H)_2)]\cdot CH_3OH$. This phenomenon was not observed in DMSO-d_6, owing to the increased solubility of all species. To characterize this solid reaction product in detail, larger scale experiments were carried out in non-deuterated acetone (~0.39 g of $K[VO_2(salhyph(H)_2)]\cdot CH_3OH$). The resulting crystals were examined by ^{1}H and ^{51}V NMR spectroscopy in DMSO-d_6 as well as X-ray crystallography. Previously we reported the X-ray crystal structure of this compound, $\{[VO(salhyph(H)_2)]_2O\}$, a dinuclear vanadium(V) species with a bridging oxygen and a terminal oxygen on each vanadium center.[42] This compound



was reported earlier[44−46] and was prepared here by the literature procedure.[46] This genuine sample was used for comparing the NMR properties to the reaction product crystals, and they were found to be the same compound. Relevant ^{1}H and ^{51}V NMR spectral data are provided in Table 3. Supporting Information, Figure S7 shows the ^{1}H and ^{51}V NMR spectra of $\{[VO(salhyph(H)_2)]_2O\}$.

Now that two reaction intermediates and the final product have been identified, a reaction scheme for the alkylation of $K[VO_2(salhyph(H)_2)]\cdot CH_3OH$ is proposed. The starting $K[VO_2(salhyph(H)_2)]\cdot CH_3OH$ transforms, eventually, into the dinuclear compound $\{[VO(salhyph(H)_2)]_2O\}$. Along the way $VO(OCH_2CH_3)(salhyph(H)_2)$ and $VO(OCH_3)(salhyph(H)_2)$ are both formed and then depleted. Scheme 2 shows a proposed reaction sequence built from the data presented above. The $[VO_2(salhyph(H)_2)]^-$ anion reacts with the alkylating agent $(CH_3CH_2O)_2SO_2$. Direct alkylation of an oxido group generates the ethoxy-containing compound $VO(OCH_2CH_3)(salhyph(H)_2)$. Formation of the observed ethanol can then take place. Although the DMSO solvent was dried and distilled, some residual water persists (cf., Figure 7). This water may be able to protonate $VO(OCH_2CH_3)(salhyph(H)_2)$ and induce release of CH_3CH_2OH. The vanadium-containing product from CH_3CH_2OH loss would be $[VO(salhyph(H)_2)]^+$. This proposed intermediate has not been observed. Perhaps this species is short-lived or too low in concentration to observe. Similar high valent metal-oxido species have been speculated to exist in catalytic cycles, but not observed directly.[55,56] This proposed "one oxido short" $[VO(salhyph(H)_2)]^+$ intermediate is likely cationic and electron deficient, relative to the anionic starting material. Another observed intermediate is the methoxy complex $VO(OCH_3)(salhyph(H)_2)$. Methanol was introduced into the system from the crystalline $K[VO_2(salhyph(H)_2)]\cdot CH_3OH$ starting material. This CH_3OH may coordinate to the electron deficient $[VO(salhyph(H)_2)]^+$ compound. With indications that $VO(OCH_2CH_3)(salhyph(H)_2)$ can release CH_3CH_2OH to generate $[VO(salhyph(H)_2)]^+$ and that this

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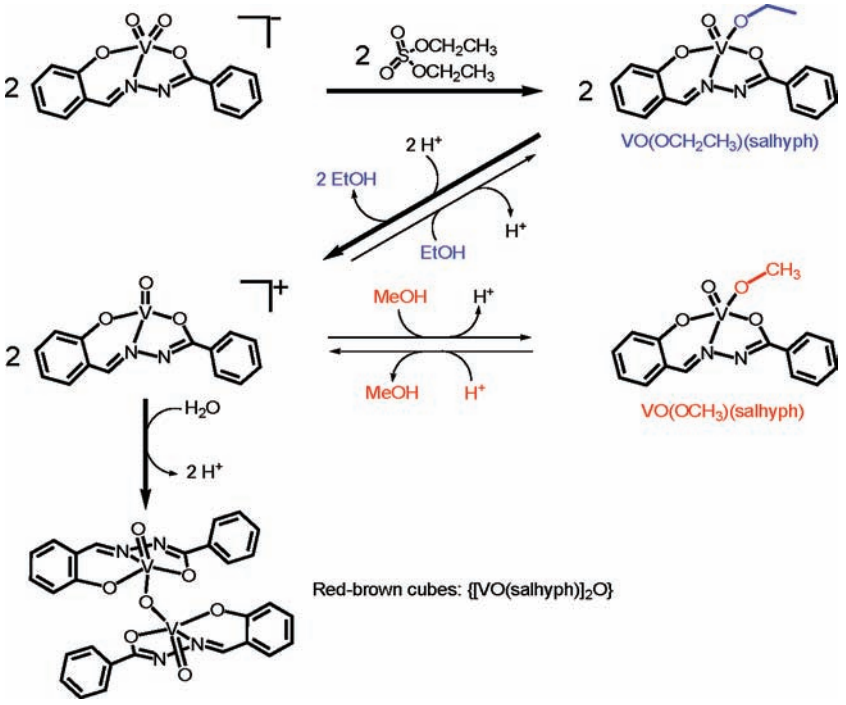
Scheme 2. Proposed Reaction Mechanism for the Alkylation of $[VO_2(salhyph(H)_2)]^-$



$[VO(salhyph(H)_2)]^+$ can bind CH_3OH, alcohol binding and release may be in equilibrium. Thus the interactions between $[VO(salhyph(H)_2)]^+$ and alcohols are denoted with double arrows.

Next formation of the dinuclear end product $\{[VO(salhyph(H)_2)]_2O\}$ is considered. Reaction of 2 equiv of the "one oxido short" $[VO(salhyph(H)_2)]^+$ cationic intermediate with 1 equiv of residual water, followed by loss of protons, provides a plausible route to this dinuclear complex. Also worth considering is protonation (or alkylation) of $VO(OR)(salhyph(H)_2)$ esters to yield $\{[VO(salhyph(H)_2)]_2O\}$.[48] Such a process would require either condensation of two $[VO_2(salhyph(H)_2)]^-$ or $VO(OR)(salhyph(H)_2)$ compounds followed by loss of an oxido (or alkoxide). Given the high coordination number of $[VO_2(salhyph(H)_2)]^-$ and $VO(OR)(salhyph(H)_2)$, adding a bridging ligand from one complex to the other during condensation may be unlikely. Note, however, that higher coordination number vanadium complexes certainly exist. Yet another route to consider in formation of the $\{[VO(salhyph(H)_2)]_2O\}$ anhydride is 1 equiv of the cationic $[VO(salhyph(H)_2)]^+$ reacting with 1 equiv of the anionic starting $[VO_2(salhyph(H)_2)]^-$ to generate the neutral dinuclear $\{[VO(salhyph(H)_2)]_2O\}$.

To provide insight on the most likely route to $\{[VO(salhyph(H)_2)]_2O\}$, a 1:1 reaction between $[VO_2(salhyph(H)_2)]^-$ and $(CH_3CH_2O)_2SO_2$ was carried out. Concentration data (not shown) obtained from ^1H NMR integrals indicated that starting $[VO_2(salhyph(H)_2)]^-$ and $(CH_3CH_2O)_2SO_2$ were initially converted completely to $VO(OCH_2CH_3)(salhyph(H)_2)$ and CH_3CH_2OH. Consequently there remains no $[VO_2(salhyph(H)_2)]^-$ for reaction with $[VO(salhyph(H)_2)]^+$. Furthermore, the kinetic data (Table 1) indicate that $K[VO_2(salhyph(H)_2)]\cdot CH_3OH$ will consume $(CH_3CH_2O)_2SO_2$ significantly more rapidly than the background reaction with DMSO. If the background reaction is relatively insignificant in the presence of $[VO_2(salhyph(H)_2)]^-$, all $(CH_3CH_2O)_2SO_2$ will be consumed by $[VO_2(salhyph(H)_2)]^-$ and none of this vanadium complex will be available to combine with $[VO(salhyph(H)_2)]^+$. Taken together, $[VO(salhyph(H)_2)]^+$ reacting with residual water to yield $\{[VO(salhyph(H)_2)]_2O\}$ is favored. The stoichiometry in Scheme 2 is denoted accordingly. Crystallization of $\{[VO(salhyph(H)_2)]_2O\}$ from acetone solutions provides a thermodynamic end point for this reaction sequence. Similarly, the $\{[VO(salhyph(H)_2)]_2O\}$ complex is observed by ^{51}V NMR spectroscopy in DMSO-d_6 solution at the end of the reaction (c.f., Supporting Information, Figure S2).

Generally speaking, metal-oxidos are known to be nucleophilic toward reagents such as silyls,[57−59] electron poor olefins,[60] and alkylating agents.[61] More specific to oxidovanadium, electrophilic silicon, germanium, and tin reagents have been shown to react with the oxido of vanadyl ($V^{4+}=O$) oxygens.[57−59,62,63] The ability to observe a $VO(OCH_2CH_3)(salhyph(H)_2)$ reaction intermediate here provides support for direct attack of an alkylating agent upon a terminal oxido. There may be some generality to this mechanism given that the reactivity of $(CH_3CH_2O)_2SO_2$ with $[VO_2(salhyph(H)_2)]^-$ was

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found to be mirrored by CH_3CH_2I, $CF_3SO_2OCH_2$-CH_3, $NH_2CON(NO)CH_3$, and $CH_3SO_2OCH_3$.[42] Another interesting feature of this system is the eventual conversion of the starting alkylating agent into the corresponding alcohol. This transformation could be beneficial in the context of attempting to detoxify alkylating carcinogens.

Conclusions

Here we have presented a detailed study on the alkylation reactions of a series of oxidovanadium complexes. Results include kinetic data, spectroscopic insights, observation of reaction intermediates, and characterization of the reaction products. Both conductivity and kinetic data show that $K[VO_2(salhyph(R)_2)]$ ion-pairs to an appreciable extent when in DMSO and acetone. The anionic, free $[VO_2(salhyph(H)_2)]^-$ anion exhibits appreciable nucleophilicity toward an alkylating agent whereas the ion-paired form, $\{K[VO_2(salhyph(H)_2)]\}$, is unreactive, relatively speaking.

Potential trends in the properties of $[VO_2(salhyph(R)_2)]^-$ (R = -NO_2, -H, -CH_3, -OCH_3) were examined by conductivity, UV−vis absorption spectroscopy, and kinetic studies. Electron donating groups (R = -CH_3, -OCH_3) may have resulted in more ion-pairing, red-shifted LMCT transitions, and enhanced reaction kinetics when compared to the parent (R = -H) compound. Conversely, an electron withdrawing substituent indicated opposite features such as a blue-shifted LMCT band and a slower reaction with $(CH_3CH_2O)_2SO_2$.

Taken together, these results indicate that some control may be exerted over interactions between metal-oxido compounds and alkylating agents. Given that we are unable to avoid exposure to all environmental carcinogens, new cancer prevention strategies are needed. Conversion of alkylating toxins into alcohols via a carcinogen interception process could provide an additional strategy to aid ongoing efforts. The ability to tune the electronics and reactivity of metal-oxido compounds may be a useful tool in the design of compounds able to consume alkylating agents and prevent cancer.

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Supporting Information Available: Complete ^1H and ^{51}V NMR spectra for select alkylation reactions, alkylation controls, and synthesized compounds in DMSO-d_6 and acetone-d_6. Discussion of the attempts to determine the rate law and reaction order. This material is available free of charge via the Internet at http://pubs.acs.org.