Vanadium(V) Complexes of Polydentate Amino Alcohols: Fine-Tuning Complex Properties

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Abstract: In aqueous solution, the stability, the structure, and the lability of 12 vanadium(V) complexes were determined and related to the amino alcohol ligand properties. The amino alcohols were chosen to maintain a five-coordinate vanadium geometry in the vanadium complex and were based on diethanolamine as the parent ligand. Apparent and composite stability constants were determined for all 12 complexes. Selected complexes were further examined to determine solution structure, lability, and thermodynamic properties. We empirically show that the formation constants for the series of 12 complexes, when plotted as a function of the pK_a value for the protonated amino alcohol, generate a curve that initially increases as the pK_a value increases and then decreases as the pK_a value continues to increase. The observed associations suggest that the electron-donating capacity of the amino alcohol plays a major role in complex stability; however, metal coordination number, sterics in the amino alcohol, and solvation also are found to affect the stability. Determination of the thermodynamic parameters of selected complexes showed that the enthalpic component was the major contributor to the stability of the complex, but that the entropic component opposed this term. A series of studies was conducted to examine whether the lability of these complexes varied from the parent complexes. Unfortunately, the variation in the lability of these complexes was much less than the variation in complex stability. In summary, these studies describe quantitatively the variation in complex stability and lability as the structure of amino alcohol is modified and explain why some complexes show less stability than predicted on the basis of the pK_a value. In short, this study provides valuable information for the design of additional vanadium complexes with specific properties.

Introduction

The mechanism of the insulin mimetic properties of vanadate, and other vanadium complexes, remains elusive, in part because of the rich aqueous chemistry of vanadium under physiological conditions as well as the complexity of the cell-signaling cascade in which vanadate[1] and other vanadium compounds induce their observed insulin-like action.[2−4] We are investigating the fundamental properties of selected vanadium compounds in order to be able to design compounds with a given desired structure, stability, and lability. These types of studies are important because it has recently been recognized that most of the compounds currently being investigated for their insulin action properties have limited lifetimes under physiological conditions.[1] In view of the complex redox and hydrolytic chemistry these compounds can undergo, it is very difficult to determine what vanadium species are actually responsible for the insulin-like action. Furthermore, the situation is complicated by the fact that many vanadium compounds induce biological responses.[5,6] We, and others, have therefore recently been exploring the development of vanadium compounds that are more stable and less labile under physiological conditions.[1,7]

Modifying ligand structure to generate a complex with more favorable properties with respect to complex stability is well-known.[8−13] In the case of the stability of metal complexes with amine ligands, the inductive effects of the amine have been correlated with the pK_a value of the protonated amine.[8−11] In contrast, the reaction of bis(2,4-pentanediono)copper(II) with pyridine bases showed no correlation between the stability constant and the substituent on the pyridine ring consistent with the greater contribution of solvation and steric effects than that of the electron-donating effects of the amine.[12] Sterics were also found to influence the stability of Ni(II) complexes with primary aliphatic amines[11] and trialkylamines,[13] and Mo(V) complex formation with triphenyl-substituted diethanolamine

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([$HOCH_2$−PhCH]NH[PhCH−PhCHOH]).[14] Sterics also affected the heat of the reaction between vanadyl acetylacetonate and a number of nitrogen and oxygen donors.[8]

Modification of ligand structure has also been used to change the rate and kinetic parameters of metal complexes.[15−19] In general, one expects the ligand pK_a to affect the rate of complex formation if the reaction occurs by an associative mechanism or by a dissociative mechanism where the lability is determined by the leaving group. A variety of vanadium(V) complexes and their complex formation rates have been examined in detail.[20−25] All show similar rates of complex formation. Thus, on the basis of these studies, one would not expect lability changes but, on the basis of other complexes, one might expect sterics to influence the lability. Increasing the steric bulk in aliphatic amines has been found to decrease the rate of Cr−amine complex formation.[16] The increase in the enthalpy of activation term has been determined to be the major contributor to this rate decrease since in the nonpolar solvents studied, no evidence for solvation effects were observed. On the other hand, the electrostatic attraction between V(III) complexes and aminopolycarboxylic acids was found to be important in determining the rate of ligand substitution.[18]

A series of vanadium(V) complexes with diethanolamine derivatives has been found to form 1:1 complexes with a charge of −1.[26] In this study we are systematically examining the effects on complex formation by small ligand perturbations. We have previously shown that the vanadium(V) complex of triethanolamine is labile since the complex undergoes exchange with free ligand in aqueous solution.[23,27] In addition, the aqueous solution structure of this complex is different from the crystal structure of the compound.[28] In the current study, we have selected a series of amino alcohol−vanadium(V) complexes which previous studies have suggested would favor formation of five-coordinate vanadium species in aqueous solution.[29,30] We have modified the parent amino alcohol ligand, diethanolamine, to determine the effect of each modification on the corresponding stability and lability of the corresponding vanadium(V) complexes. To interpret the observed stability pattern, we have determined thermodynamic parameters for several complexes. As described in this paper these studies required that we determine the temperature dependence of the chemical shift for the external reference $VOCl_3$. Collectively, these studies provide information to assist the ongoing quest to design desired properties within this and other families of compounds.

Experimental Section

A. Materials. The reagents used in this work were all of reagent grade. The water was distilled and deionized (DDI) on an ion-exchange column. Chemicals were purchased from Aldrich or Sigma and checked for purity by ^{1}H NMR spectroscopy. Several ligands, including *meso*-2,2′-diphenyliminodiethanol and C_2-2,2′-diphenyliminodiethanol,[31] 2-[2-(hydroxyethyl)amino-2-hydroxymethyl]-1,3-propanediol[32] and 2-[2-(hydroxyethyl)amino]-2-methyl-1-propanol, were prepared following the procedure previously described.[32a]

B. Synthesis. 2-Hydroxy-5-nitrobenzyl Chloride. *p*-Nitrophenol (5.00 g, 35.9 mmol) was dissolved in a mixture of 65 cm^3 of concentrated HCl, 0.5 cm^3 of concentrated H_2SO_4, and 6.6 cm^3 of dimethoxymethane. The stirred solution was heated at 343 K for 5 h under the continuous addition of HCl gas (20 cm^3 of concentrated HCl was added dropwise into 30 cm^3 of concentrated H_2SO_4, generating HCl gas which was slowly bubbled into the reaction mixture). Once the reaction was complete, the mixture was kept at 253 K for 3 h, filtered, and dried under vacuum to give the crude product. After recrystallization from benzene (4.80 g, 25.6 mmol, 72%), a white solid resulted. ^{1}H NMR 300 MHz (D_2O): 4.60 (s, 2H, CH_2Cl), 7.00 (d, 1H, Ar*H*), 8.20 (dd, 1H, Ar*H*), 8.30 (d, 1H, Ar*H*) ppm. ^{13}C{^{1}H} 75 MHz (D_2O): 61.5, 118.0, 118.3, 128.3, 129.1, 130.3, 163.4 ppm.

***N*-(2-Hydroxy-5-nitrobenzyl)iminodiethanol (HNBIDE).** First, 2,5-hydroxynitrobenzyl chloride was prepared from *p*-nitrophenol and then the addition of diethanolamine completed the synthesis. Diethanolamine (1.45 g, 13.8 mmol) was dissolved in 20 cm^3 of 2-propanol, and after the addition of 2-hydroxy-5-nitrobenzyl chloride (1.20 g, 6.40 mmol), the colorless solution immediately turned yellow. This reaction mixture was refluxed overnight. The solution was cooled to room temperature and filtered to remove decomposition products, and a yellow solid was obtained after evaporation of the solvent. Water (10 cm^3) was then added, and the solution was poured into 150 cm^3 of boiling acetone and 5 cm^3 of ethyl acetate. The solution was concentrated to 70 cm^3 and then kept at 253 K overnight to give a yellow solid which was recrystallized from water. The crystals (1.32 g, 5.15 mmol, 80%) were isolated by filtration. (Anal. Found: C, 51.20; H, 6.3; N, 10.77. Calcd for $C_{11}H_{16}N_2O_5$: C, 51.55; H, 6.3; N, 10.93%). ^{1}H NMR 300 MHz (D_2O): 3.20 (t, 4H, CH_2CH_2OH), 3.90 (t, 4H, CH_2CH_2OH), 4.15 (s, 2H, ArCH_2N), 6.55 (d, 1H, Ar*H*), 8.10 (dd, 1H, Ar*H*), 8.20 (d, 1H, Ar*H*) ppm. ^{13}C{^{1}H} 75 MHz (D_2O): 57.3, 58.2, 59.9, 121.2, 121.6, 131.1, 136.2, 178.6 ppm.

2-[2-(Hydroxyethyl)amino-2-hydroxymethyl]-1,3-propanediol (TDEA). Tris(hydroxy methyl)aminomethane (2.00 g, 16.5 mmol) was dissolved in 50 cm^3 of water. To the stirred solution, at 277 K, liquid ethylene oxide (2.47 cm^3, 49.5 mmol) was added, and stirring was continued for 5 h while warming to ambient temperature. The solvent was then removed to give a white solid which was recrystallized twice from 2-propanol and three times from ethanol to give white crystals (2.10 g, 12.7 mmol, 80%). (Anal. Found: C, 43.20; H, 9.13; N, 8.61. Calcd for $C_6H_{15}NO_4$: C, 43.62; H, 9.15; N, 8.47%). ^{1}H NMR 300 MHz (D_2O): 2.75 (t, 2H, CH_2CH_2OH), 3.60 (s, 2H, C(CH_2OH)$_3$), 3.70 (t, 2H, CH_2CH_2OH) ppm. ^{13}C{^{1}H} 75 MHz (D_2O): 45.1, 63.3, 63.9, 65.8 ppm.

2-[2-(Hydroxyethyl)amino]-2-methyl-1-propanol (DMeDEA). 2-Amino-2-methyl-1-propanol (1.00 g, 11.2 mmol) and ethylene oxide (0.839 cm^3, 16.8 mmol) were dissolved in 50 cm^3 of absolute ethanol at 277 K. After the reaction was stirred for 2 h at 277 K, the solution was allowed to warm to ambient temperature. After stirring the solution overnight, the solvent was evaporated, 50 cm^3 of water was then added, and the solution was extracted with chloroform (5 × 30 cm^3). After drying the solution over anhydrous Na_2SO_4, the solvent was removed in vacuo to yield the desired compound (1.04 g, 7.80 mmol, 70%) as

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a colorless oil which crystallizes upon standing at room temperature. (Anal. Found: C, 54.06; H, 10.99; N, 10.35. Calcd for $C_6H_{15}NO_4$: C, 54.10; H, 11.35; N, 10.51%). ^{1}H NMR 300 MHz (D_2O): 1.00 (s, 6H, C(CH_3)$_2$), 2.60 (t, 2H, CH_2CH$_2$OH), 3.35 (t, 2H, CH$_2$$CH_2$OH), 3.60 (s, 2H, C(CH$_3$)$_2$$CH_2$OH) ppm. ^{13}C{^{1}H} 75 MHz (D_2O): 25.2, 45.4, 55.8, 63.7, 70.2 ppm.

***N*-(2,5-Dimethylbenzyl)iminodiethanol (DMeBIDE).** Diethanolamine (14.0 g, 133 mmol) and 2,5-dimethylbenzyl chloride (9.12 cm^3, 62.0 mmol) were dissolved in 100 cm^3 of 2-propanol, and the solution was refluxed for 48 h. After cooling to ambient temperature, 20 cm^3 of water was added and the solution was extracted with ethyl acetate (3 × 50 cm^3). The combined ethyl acetate solutions were dried over Na_2SO_4. The solvent was removed in vacuo to yield *N*-(2,5-dimethylbenzyl)iminodiethanol (12.4 g, 55.6 mmol, 90%) as a colorless oil. (Anal. Found: C, 69.22; H, 9.58; N, 6.20. Calcd for $C_{13}H_{21}NO_2$ C, 69.92; H, 9.47; N, 6.27%. ^{1}H NMR 300 MHz (D_2O): 2.50 (2s, 6H, CH_3ArCH_3), 2.65 (t, 4H, CH_2CH$_2$OH), 3.50 (t, 4H, CH$_2$$CH_2$OH), 3.60 (s, 2H, Ar$CH_2$N), 7.05 (2d, 2H, Ar*H*), 7.10 (s, 1H, Ar*H*) ppm. ^{13}C-{^{1}H} 75 MHz (D_2O): 20.7, 22.6, 57.5, 57.8, 58.6, 130.3, 133.8, 134.1, 135.0, 138.1,139.7 ppm.

C. Potentiometric Measurements of pK_a Values. Using standardized stock solutions of HCl and NaOH, the pK_a values of the new amines, as well as several known amines, were measured by titration at ambient temperature. Amine concentrations ranged from 10 to 70 mM. The titrant volumes (at 0.20 cm^3) were added, and the pH change was measured. The number of experimental points used to define the titrations ranged from 100 to 150 points. The pK_a values were thus calculated from the titration curves generated using the spreadsheet program Wingz. If appropriate an iterative process was used to minimize the deviation in the pK_a value. In addition, the pK_a values for selected amino alcohols were measured by the ^{1}H NMR chemical shift as described under thermodynamic parameters.

D. NMR Spectroscopy. Formation Constant Measurements and Calculations. ^{51}V NMR spectra were recorded on a ACP-300 Bruker NMR spectrometer (7.0 T) at 78.9 MHz. A spectral window of 150 ppm, a 90° pulse angle, and an acquisition time of 0.25 s with no relaxation delay were used. A 15 Hz exponential line broadening was applied before Fourier transformation. ^{51}V NMR chemical shifts are reported with respect to the external reference standard $VOCl_3$ at 0 ppm. Complex and oligomeric vanadate mole fractions were measured using the Bruker integration software. We found no changes in mole fractions of species by integrating spectra obtained with different parameters. Assuming that all vanadium present in solution is in the form of vanadium(V), the total added vanadium concentration combined with the mole fractions of each vanadium complex, concentrations of complex and oligomeric vanadates can be calculated. The reactions describing the system and its pH dependence are shown below in eqs 1−7. The K_{com} and the K_{eq} values (eqs 4 and 7) were derived by linear least squares from plots of formation constants as a function of the multiple of concentrations of amino alcohol and vanadate in the appropriate protonated forms (see text), respectively.

Both $H_2VO_4^-$ and H_2L undergo protonation and deprotonation reactions, and those described in eqs 1 and 2 are important to the complex formation examined here. Complex formation is shown in eq 3 and the equilibrium constant in eq 4.

$$H_2VO_4^- \rightleftharpoons HVO_4^{2-} + H^+ \quad (1)$$

$$H_3L^+ + H_2O \rightleftharpoons H_2L + H_3O^+ \quad (2)$$

$$H_2L + H_2VO_4^- \rightleftharpoons [VO_2L^-] + 2H_2O \quad (3)$$

$$K_{eq} = \frac{[VO_2L^-]}{[H_2L][H_2VO_4^-]} \quad (4)$$

In general, the K_{com} for each complex was measured near the pH (pH$_{exp}$) where optimum amount of complex was observed (pH$_{opt}$) defined as shown in eq 5.

$$pH_{opt} = {}^1/_2(pK_a(H_2VO_4^-) + pK_a(HL^+)) \quad (5)$$

Because it is not possible to distinguish different protonated forms by NMR spectroscopy, only composite formation constants are directly determined. Let the total concentration of free V(V) monomer be V_1, where $[V_1] = [VO_4^{3-}] + [HVO_4^{2-}] + [H_2VO_4^-] + [H_3VO_4]$. Thus, the reaction as defined in eq 6 leads to the definition of K_{com} in eq 7.

$$V_1 + L_{free} \rightleftarrows \text{complex} + H_2O \quad (6)$$

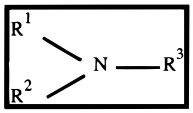
$$K_{com} = \frac{[\text{complex}]}{[V_1][L_{free}]} \quad (7)$$

Structural and Lability Studies. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACP spectrometer (7.0 T) operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C. A 2 Hz exponential line broadening was typically applied to the ^{13}C FIDs prior Fourier transformation. The ^{13}C NMR spectra were acquired with 200 ppm spectral window, a 90° pulse width, and a relaxation delay of 700 ms.

NMR Experiments Leading To Determination of Thermodynamic Parameters. The thermodynamic parameters were measured for vanadium complex (^{51}V and ^{1}H), amino alcohol (^{1}H), and vanadate (^{51}V) using variable-temperature NMR spectroscopy. The temperature range examined was from 298 to 338 K for most experiments, although all vanadium complexes were also studied down to 278 K in one series of experiments. The temperature for the variable-temperature experiments was calibrated using an 80% ethylene glycol sample in DMSO-d_6 to an accuracy of ±1°.[32a] It is well-known that the chemical shift of H_2O is strongly dependent on temperature[32b,c] and potentially will cause erroneous results if measuring the chemical shift against the H_2O signal. For convenience, some of the repeat experiments were carried out in this manner. As a result, we have measured the temperature dependence of the H_2O signal under our conditions using the internal standards tetramethylammonium chloride (TMAC)[32b] and DSS, as well as the instrumental frequency for calibration. The chemical shifts were also checked against external DSS at ambient temperature. We find that the change in chemical shift of H_2O signal (0.016 ppm/deg) under our conditions is within the range of values reported in the literature.[32a] The concentration of vanadium complexes were measured in samples containing a ratio of 1:2 vanadium to ligand at the optimum pH (the formation constant was determined using ^{51}V NMR spectroscopy at the optimum pH). The concentrations of vanadium complex and V_1 were used to determine the K_{eq} from which the $\Delta H°$ was calculated. Four experiments using a minimum of five different temperatures were performed for each complex, and two experiments using five different temperatures were performed for the vanadate parent solution. The thermodynamic parameters for the amino alcohol protonation reaction were determined by measuring the ^{1}H NMR chemical shift at the appropriate series of pH values at various temperatures. These experiments were performed once for the five different temperatures, and additional studies were carried out to ensure no changes were observed when increasing the temperature range studied. The typical experiment was initiated at ambient temperature, and the temperature was then raised. The temperature dependence of the chemical shift for H_2O is well documented,[32b,c] but similar information is not available in the literature for vanadium compounds. It is therefore first necessary to determine the effect of temperature on the chemical shift of the reference compound $VOCl_3$ (0 ppm, 298 K) by recording ^{51}V NMR spectra in the unlocked mode at various temperatures. The chemical shift of $VOCl_3$ changes 0.054/deg, and the data is shown in Figure 4. Furthermore, such information is complicated by the known exchange processes that vanadium(V) complexes undergo.[5,21] Equipped with this information we were able to measure accurately the chemical shift of the species under study in this work at various temperatures.

Sample Preparation for NMR Studies. Vanadate stock solutions were prepared by dissolving sodium metavanadate ($NaVO_3$) in doubly distilled and deionized water. All NMR samples were prepared at room temperature immediately before NMR spectroscopic determinations. The samples all contained 20% (v/v) D_2O. Vanadate and ligand concentrations were varied as needed. The ionic strength was maintained at 0.40 with 4.00 M KCl. The pH measurements were carried out at room temperature using a Corning pH-meter-140 before

Table 1. List of 12 Amino Alcohol Ligands, Their Trivial Names, Abbreviations, and pK_a Values of the Protonated Amines[a]



ligand	abbreviation	R^1	R^2	R^3	pK_a
diethanolamine	DEA	CH_2CH_2OH	CH_2CH_2OH	H	8.88
N-methyldiethanolamine	MeDEA	CH_2CH_2OH	CH_2CH_2OH	CH_3	8.52
triethanolamine	TEA	CH_2CH_2OH	CH_2CH_2OH	CH_2CH_2OH	7.76
triisopropanolamine (tri-2-propanolamine)	TPA	$CH_2CH(CH_3)OH$	$CH_2CH(CH_3)OH$	$CH_2CH(CH_3)OH$	7.86
N-ethyldiethanolamine	EtDEA	CH_2CH_2OH	CH_2CH_2OH	CH_2CH_3	8.66
N-butyldiethanolamine	BuDEA	CH_2CH_2OH	CH_2CH_2OH	$CH_2CH_2CH_2CH_3$	8.99
N-(2-hydroxy-5-nitrobenzyl)iminodiethanol	HNBIDE	CH_2CH_2OH	CH_2CH_2OH	CH_2(*p*-$OHPhNO_2$)	5.60
N-2,5-(dimethylbenzyl)iminodiethanol	DMeBIDE	CH_2CH_2OH	CH_2CH_2OH	CH_2(*p*-CH_3PhCH_3)	7.58
C_2-2,2′-diphenyliminodiethanol	cDPDEA	$CH(Ph)CH_2OH$	$CH(Ph)CH_2OH$	H	5.90
meso-2,2′-diphenyliminodiethanol	tDPDEA	$CH(Ph)CH_2OH$	$CH(Ph)CH_2OH$	H	6.30
2-[2-(hydroxyethyl)amino-2-hydroxymethyl]-1,3-propandiol	TDEA	CH_2CH_2OH	$C(CH_2OH)_3$	H	8.00
2-[2-(hydroxyethyl)amino]-2-methyl-1-propanol	DMeDEA	CH_2CH_2OH	$C(CH_3)_2CH_2OH$	H	9.63

[a] *N*-Phenyldiethanolamine (pK_a = 4.13) was also examined in this work, but since no stable five-coordinate complex formed it is not included in this table.

and after each spectroscopic measurement to ensure that no significant changes (±0.05) occurred during that time. The majority of the samples used in the NMR measurements were prepared and analyzed in duplicate. Selected samples were analyzed in triplicate.

Results and Discussion

Synthesis of Ligands. The new ligands were prepared by conventional procedures involving the nucleophilic attack of amines on ethylene oxide or benzyl chloride derivatives. 2-[2-(Hydroxyethyl)amino-2-hydroxymethyl]-1,3-propanediol was prepared in good yield by the reaction of tris(hydroxymethyl)-aminomethane and ethylene oxide. The hydrochloride salt of this ligand was previously prepared from 1-bromo-2-trityloxy-ethane and tris(hydroxymethyl)aminomethane in the presence of acetyl chloride.[33] We used an excess of ethylene oxide due to its high volatility and isolated pure compound after recrystallizations from ethanol and 2-propanol. The preparation of DMeDEA from 1 equiv of 2-amino-2-methyl-1-propanol with 1 equiv of ethylene oxide lead to a yield of 35% in a mixture of products.[32] We increased the amount of ethylene oxide to 1.5 equiv and thus increased the yield by 35%. We prepared *N*-(2-hydroxy-5-nitrobenzyl)iminodiethanol (HNBIDE) by the condensation of 2-hydroxy-5-nitrobenzyl chloride with diethanolamine in 2-propanol. The synthesis of 2-hydroxy-5-nitrobenzyl chloride was carried out in the presence of excess hydrochloric acid to reduce the formation of 2-hydroxymethyl-4-nitrophenol. The preparation of an isomer (*N*-(4-hydroxy-3-nitrobenzyl)iminodiethanol) was previously reported;[34] however, our isolated yield of 80% is a significant improvement of the reported 64%.

Characterization of Vanadium(V) Complexes in Aqueous Solution. In aqueous solution vanadate and diethanolamine derivatives form complexes with a 1:1 stoichiometry. Table 1 lists names, abbreviations, and structures of the 12 amino alcohols used in this work. The vanadium(V) complexes were characterized using ^{51}V, ^{1}H, and ^{13}C NMR as described previously.[26] Here we describe the pH dependence of the complexes, complex stoichiometry, the apparent composite formation constants (pH dependent K_{com} and pH independent K_{eq}), the solution structure of the complexes, and the complex lability and thermodynamic properties of selected complexes, vanadate, and amino alcohols.

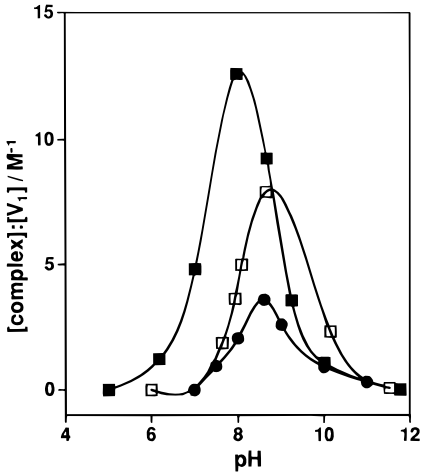


Figure 1. The ratio of the concentration of vanadium complex to the concentration of monomeric vanadate plotted as a function of pH. These reactions were examined in solutions of 10 mM vanadate and 20 mM ligand (TDEA (■), BuDEA (□), and EtDEA (●)). The ionic strength was adjusted to 0.40 using 4.00 M KCl. The solid line connects data points and does not represent a fit.

Complex Stoichiometry and pH Dependence. To determine the experimental conditions appropriate for measuring the formation constants for the series of vanadium(V) complexes generated from the amino alcohols listed in Table 1, the pH dependence (see for example Figure 1) and complex stoichiometry were first determined. Complex stoichiometry was determined by measuring the amount of complex in a series of solutions containing varying vanadate and ligand concentrations. The preliminary data were analyzed, and it was found that one molecule each of $H_2VO_4^-$ and H_2L was needed to form complex. Since these studies also involve measurements at different pH values, the number of protons involved in the reaction is also determined. On the basis of the previously reported vanadium(V) complexes of this type (V−DEA and V−TEA), we expected that the stoichiometries each of $H_2VO_4^-$ and H_2L were 1:1. Furthermore, if the complex is analogous to the V−TEA complex, no protons will form (or be used) in this reaction and accordingly these complexes will have a charge of −1 (and a composition of VO_2L^- as the V−TEA complex).[26]

(33) Fowler, P. A.; Haines, A. H.; Taylor, J. K.; Chrystal, E. J. T.; Gravestock, M. B. *J. Chem. Soc., Perkin Trans.* **1994**, 2229.

(34) Stephanyan, G. M.; Margaryan, S. S.; Iradyan; M. A.; Garibdzhanyan, B. T. *Khim.-Farm. Zh.* **1981**, *15*, 24.

We confirmed these stoichiometries by observing the relationships implied in eq 4.

Although the stability of these complexes is due to the protonation states of each vanadate and amino alcohol, the fact that many of these amino alcohols are used as biological buffers makes it relevant for the life scientist to consider the concentration of total complex in solution as a function of pH. The pH at which the greatest concentration of complex is present can be calculated from the pK_a of the protonated amino alcohol and the pK_a of $H_2VO_4^-$ (eq 5).[26] We measured the pK_a values for new and known amino alcohols by titration at ambient temperature and for selected amino alcohols using the chemical shift dependence as a function of pH at various temperatures. The pK_a of $H_2VO_4^-$ was measured by ^{51}V NMR spectroscopy for a series of solutions at different pH, at ambient temperature and 0.40 M KCl. By plotting the chemical shift as a function of pH, the pK_a of $H_2VO_4^-$ could be calculated to 8.2 which agreed closely with that reported previously.[26] Plots of $[VO_2L^-]$:$[V_1]$ against pH display distinct maxima at pH 8.4 for EtDEA, at pH 8.6 for BuDEA and at pH 8.0 for TDEA.

Formation Constants. It is the intention in this work to document the effects of alkyl substitution on the amino alcohol ligands on the stability of the resulting vanadium(V)-amino alcohol complex. The formation constants were determined by ^{51}V NMR spectroscopy using the studies described above to guide pH range and concentration ranges. As defined in eq 3 this equilibrium constant takes into account the protonation state of both vanadate and amino alcohol which are defined in eqs 1 and 2 for the pH range 6 to 10.[36] (Although it is known that both HVO_4^{2-} and $H_2VO_4^-$ react with L and/or HL^+ when L is alizarin and EDTA,[22] eq 3 describes the fundamental reaction relevant for derivation of thermodynamic properties for this reaction.) Each K_{eq} value was initially calculated from data obtained from solutions containing varying vanadate and ligand concentrations at an appropriate pH value and confirmed by measurement at several other pH values. The K_{eq} values are given in Table 2 for the 12 different amino alcohols.

One series of representative data obtained for the V−EtDEA and V−BuDEA complexes is shown in a plot of the complex concentration as a function of $[H_2VO_4^-]$ $[H_2L]$ in Figure 2. Each set of data was determined in two or three different experiments. These data were used to calculate both the pH-dependent and the pH-independent (see below) equilibrium constants listed in Table 2. All equilibrium constants calculated in this work were determined at an ionic strength at which activity coefficients deviate significantly from 1.[36c] Thus, in Table 2 we report the apparent formation constants with the units M^{-1} to indicate clearly that these constants have not been corrected by their respective activity coefficient. The K_{com} values for the 12 amino alcohols were calculated at pH_{opt} from the measurements described above for determination of the K_{eq} values listed in Table 2. The resulting K_{com} values are given in Table 2.

Effects of Ligand Perturbation on the Formation Constants of $H_2VO_4^-$−H_2L Complexes. First, we consider substitution on the central nitrogen atom of DEA by simple alkyl groups and in this and other comparisons below we focus on the comparison of the K_{eq} values unless otherwise noted. It has previously been shown that the amine nitrogen atom is essential for formation of these V−DEA-type complexes,[26] and indeed we confirm that *N*-phenyldiethanolamine does not form a strong complex with vanadate (see footnote Table 1). On the other hand, MeDEA forms a more stable complex with vanadate than does DEA. Presumably, the MeDEA complex is more stable due to greater electron donation by the amine nitrogen. However, if electron donation were the major factor determining complex stability, the EtDEA and BuDEA complexes should be less stable than the complex MeDEA, but more stable than the DEA complex. As seen in Table 2 the V−MeDEA complex is 4-fold more stable than the V−EtDEA and V−BuDEA complexes and the V−DEA complex is slightly more stable than either of these complexes suggesting that other factors are contributing to the stabilities of the vanadium(V) complexes. The stability pattern was confirmed by examining the complex formed between vanadate and DMeBIDE; its complex is 14- to 20-fold less stable than the V−EtDEA and V−BuDEA complexes.

Second, we consider alkyl substitution on the carbons adjacent to the central nitrogen atom of DEA. Substituents on the carbon atoms adjacent to the nitrogen should increase the electron

Table 2. Summary of the Apparent Equilibrium Constants of Vanadium(V) Complexes Studied in This Work[a]

DEA derivatives	complex ^{51}V δ(ppm)	K_{com} (M^{-1})[b]	pH_{exp}[c]	K_{eq} (M^{-1})	ligand pK_a
DEA	−485	58	8.54	510 (pH 7−11)	8.88[d]
MeDEA	−477	240	8.40	1100 (pH 7−11)	8.52[d]
EtDEA	−476	44	8.47	300 (pH 7−10)	8.66
BuDEA	−474	40	8.60	440 (pH 7−10)	8.99
DMeBIDE	−478	15	7.90	22 (pH 7.5−9.5)	7.58
DMeDEA	−478	28	8.90	2 (pH 7−9)	9.63
tDPDEA	−487	130	7.25	150 (pH 6−10)	6.30
cDPDEA	−487	55	7.00	61 (pH 6.5−10)	5.90
TEA	−479	210	8.00	520 (pH 7−11)	7.76[d]
TPA	−480	430	8.00	950 (pH 7−11)	7.86[d]
TDEA	−484	770	8.16	1600 (pH 7−10)	8.00
HNBIDE	−520	392	6.90	360 (pH 6−10)	5.60

[a] The reactions were studied at 5−50 mM concentrations of amino alcohols and 5−20 mM concentrations of vanadate. The ionic strength was adjusted to a value of 0.40 using a 4.00 M KCl solution. The indicated formation constants have been calculated on the basis of concentrations and have not been corrected for activity coefficients since the assumption that the activity coefficients are 1.0 is not appropriate at this ionic strength. All samples were prepared at ambient temperature in duplicate. [b] K_{com} (M^{-1}) is a pH-dependent measurable quantity (eq 3), and K_{eq} is a pH-independent value (eq 6) obtained from experimental studies. [c] The value pH_{exp} was chosen near pH_{opt} and based on the preliminary plot generated from [complex]:$[V_1]$ versus pH. [d] These pK_a values were reported in ref 34. The other pK_a values were determined as described in the Experimental Section.

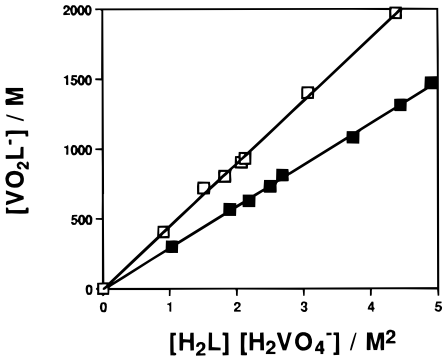


Figure 2. Representative example of the data for determination of the equilibrium constant K_{eq} of the complexes V−EtDEA (■) and V−BuDEA (□) formed in aqueous solution at pH of 8.40 and 8.60, respectively.

(35) (a) Gresser, M. J.; Tracey, A. S. *J. Am. Chem. Soc.* **1986**, *108*, 1934. (b) Tracey, A. S.; Jaswal, J. S. *Inorg. Chem.* **1993**, *32*, 4235.

(36) (a) Perrin, D. D.; Dempsey, B. In *Buffers for pH and Metal Ion Control*. Perrin, D. D., Dempsey, B., Eds.; Chapman and Hall: New York, 1974. (b) Perrin, D. D.; Dempsey, B.; Serjeant, E. P. In *pK_a Prediction for Organic Acids and Bases*; Perrin, D. D., Dempsey, B., Serjeant, E. P. Eds.; Chapman and Hall: New York, 1981. (c) Timmermans, J. *The Physico-chemical Constants of Binary Systems in Concentrated Solutions*; Interscience: New York, 1959.

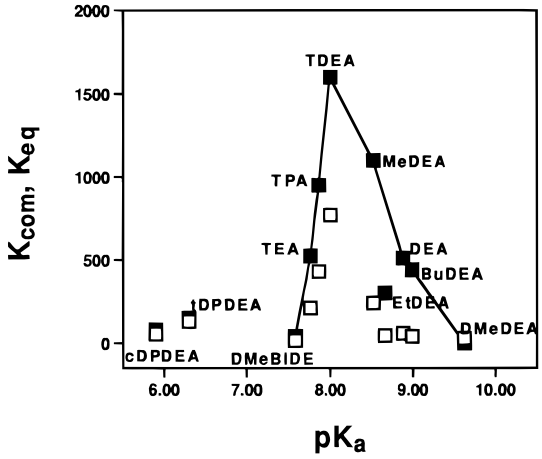


Figure 3. The composite pH-dependent and -independent formation constants K_{com} (□) and K_{eq} (■) plotted as a function of the pK_a of the protonated amine.

donation of the nitrogen atom, but to a much smaller extent. Accordingly, we may anticipate small changes in the formation constant. As seen from Table 2 the V−DMeDEA complex is 300-fold less stable than the V−DEA complex. On the other hand, the complexes V−cDPDEA and V−tDPDEA are 3- to 8-fold less stable than the V−DEA. This series of alkyl substitutions clearly demonstrates that the electron donation of the nitrogen atom is not the only important contributor to the vanadium(V) complex stability. As we show the match between the pK_a of the protonated amine and pK_a($H_2VO_4^-$) is also important, as well as the alkyl substitution on the ligand.

Third, we consider substitution on the central nitrogen atom of DEA by alkyl groups containing functionalities capable of coordinating to the vanadium atom. As described previously, the V−TEA complex is as stable as the V−DEA complex (4-fold more stable if considering K_{com}).[26] It is interesting that the V−TPA complex is 2-fold more stable than the V−DEA complex and the V−TEA complex. These results suggest that the extra chelating functionality, even though it is pendant in aqueous solution,[29] may (the V−TPA and V−TDEA complexes) or may not (the V−TEA complex) contribute to stabilizing the vanadium(V) complex.

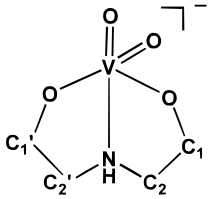
The ability to provide estimates for complex stabilities would be useful for future complex design. Thus it would be useful to identify complexes that fit the empirical bell-curve relationship between K_{com} and pK_a of the protonated amino alcohol and compare their properties to selected complexes that fall off the bell-curve. Such considerations should provide insight into the other factors determining the stability and other properties of aqueous vanadium(V) complexes. Given the fact that 12 complexes have been examined in this work and the importance of amino alcohol pK_a value for complex stability, we examined the possibility that pK_a value for ligand could be a first level predictor for complex stability. Since this kind of crude analysis would be most useful for the life-scientist, we carried out this analysis focusing on the comparisons of K_{com} values. The pK_a values for the protonated forms of DEA, TEA, TPA, TDEA, and DMeDEA follow the generally anticipated trend for aliphatic amines in aqueous solution; the tertiary amine is a poorer base than the secondary amines. On the basis of this information, we examined the relationship between the K_{com} values for the vanadium(V) complexes versus the pK_a values of the protonated form of the amino alcohol. As seen from Figure 3 a bell-curve results with a maximum in the vicinity of pK_a($H_2VO_4^-$). Similarly, we find that the K_{eq} values also follow a bell-curve when plotted against the pK_a of the protonated amino alcohol. The bell-curve dependence demonstrates that the stability of the vanadium(V) complex is not solely dictated by the basicity of the amine nitrogen; the better the base does not imply the more stable complex. The presence of the appropriate protonated form of vanadate is clearly also crucial to the stability of the complex, and it seems reasonable that amino alcohols forming the most stable five-coordinate vanadium(V)−amino alcohol complexes would have a pK_a value of the protonated amino alcohol in the neighborhood of 8−8.2.

Given the above considerations, how far could one modify the structure of the amino alcohol before the resulting complex no longer will follow the empirically observed bell-shaped correlation of K_{com} (or K_{eq}) values shown in Figure 3? It is well-known that alkylating a secondary amine to generate a tertiary amine lowers its basicity in solution even though one would have expected the basicity to increase.[36] In addition, modification of the amine on the carbon framework will significantly affect the pK_a of its protonated form. Thus, alkyl group substitution on the carbon framework increases the pK_a value for the protonated amine as evidenced by the pK_a value for protonated DMeDEA compared to DEA, whereas aryl group substitution decreases the pK_a value for the protonated amine as observed for cDPDEA and tDPDEA.

The amines cDPDEA and tDPDEA are particularly interesting since they have identical formulas, functionalities, and substituents; the only difference between these amines is the stereochemistry of the two phenyl groups. Despite the structural similarities, the difference in the pK_a values for the protonated amines is only 0.4 pH units. The observation that the vanadium(V) complexes formed from these ligands do not adhere to the trend in K_{com} values shown in Figure 3 is perhaps not surprising and suggestive that other factors are also important to the stability of these complexes. Since the pK_a value for the protonated DMeDEA is larger than the pK_a value for DEA one would expect that the K_{com} for the former would be smaller than that observed for DEA. As seen from Table 2 this is indeed observed. However, the K_{com} (or the K_{eq}) value for the two secondary amines, tDPDEA and cDPDEA do not follow the trend shown in Figure 3; both complexes are significantly more stable than anticipated given the low pK_a value of their respective protonated amino alcohols. The complex formed from tDPDEA has a K_{eq} value significantly larger than that for the cDPDEA complex so that even a comparison of these complexes with each other underlines the importance of other factors. Alternative effects that may be important involve phenyl groups stacking which may affect solvent organization around the complex. The effects of differences in water organization should be observable by comparing the thermodynamic parameters of selected complexes and will be examined below.

Solution Structure. The five-coordinate geometry of the V−TEA and V−TPA complexes with a −1 charge in aqueous solution has been well-documented.[28,29] All 1:1 complexes formed from vanadate with DEA, EtDEA, BuDEA, HNBIDE, and tDPDEA are likely to have the five-coordinate geometry of the V−TEA and V−TPA complexes with a −1 charge observed for complexes formed from vanadate and TEA or TPA.[28] Detailed multinuclear NMR studies of the V−TEA and V−TPA systems in aqueous and organic solution compared with the solid-state characterization of these complexes showed the aqueous solution complex to contain a VO_2 unit chelated to a tridentate TEA or TPA ligand.[28] The suggestion of structural similarity between the new complexes described here and the

Table 3. ^{13}C CIS Values[a] for Vanadium(V) Complexes Formed in Aqueous Solution[b] from EtDEA, BuDEA, and tDPDEA and Compared to Carbon Atoms in DEA[c]



complex	C_1	C_2	$C_{1'}$	$C_{2'}$	pH
V−DEA[d]	14.3	5.4	14.3	5.4	9.01
V−EtDEA	14.5	4.5	14.5	4.5	8.53
V−BuDEA	14.5	4.6	14.5	4.6	8.53
V−tDPDEA	12.6	2.2	12.9	2.6	7.20

[a] CIS = δ(complex) − δ(free ligand). [b] The ^{13}C NMR spectra were obtained at ambient temperature in solutions added 600−1000 mM ligand and 400 mM vanadate. [c] Key to ligand carbon atoms is illustrated, and the chemical shifts of part of free ligands are indicated in footnote e. [d] Previously described in refs 23, 26, 28, and 29. [e] DEA/EtDEA/BuDEA/tDPDEA: C_1 (61.0/58.6/58.6/67.6); C_2 (52.4/57.1/57.7/64.8).

other well-known complexes was investigated using ^{1}H NMR and ^{13}C NMR spectroscopy and coordination-induced shift (CIS) values. These results are listed in Table 3 for complexes formed from DEA, EtDEA, BuDEA, and tDPDEA. In the V−TEA/V−TPA complexes a CIS value of ∼15 ppm was observed for coordinated C_1, −1.2 ppm for pendant C_1, and 4.6 ppm for C_2 adjacent to the coordinated amine in a pendant hydroxyethyl arm. The close similarity of for example, the C_1 value of 14.5 ppm for V−EtDEA and V−BuDEA to the CIS values for the V−DEA complex,[29] is indicative that the complexes have very similar solution structures. In contrast, HNBIDE does not have a pendant hydroxyethyl arm: all four functionalities in this ligand are coordinated to the metal ion. Thus, the data suggest that all but the V−HNBIDE complex contain five-coordinate vanadium(V) with a tridentate coordinated ligand with an overall charge of −1.

Recent studies with pyridyl and benzimidazole DEA derivatives show that these ligands form extremely stable complexes with vanadate in aqueous solution.[30] However, structural characterization of these materials shows that they contain six-coordinate vanadium in contrast to most complexes examined in this work.[30] Thus, it is possible that a ligand forming a six-coordinate complex will no longer form complexes that adhered to the relationship shown in Figure 3. Indeed, K_{com} for the HNBIDE complex is 6-fold larger (although K_{eq} is slightly less) than that for the DEA complex. However, in the study with a limited series of six-coordinate vanadium complexes of pyridyl and benzimidazole containing DEA derivatives, we point out that a bell-curve dependence is followed when comparing these six-coordinate complexes among themselves.

Lability Studies. The V−TEA complex is known to undergo both intra- and intermolecular exchange processes in aqueous solution.[27] Multinuclear NMR studies of the V−DEA, V−TEA, and V−Tricine systems[23,27,28] have previously shown that the complex undergoes dynamic processes of several types. Vanadate oligomers undergo intermolecular exchange in solution in the neutral pH range containing above 1 mM uncomplexed vanadate. These processes can be characterized using ^{51}V EXSY spectroscopy and/or ^{51}V NMR line width analysis.[21] Free ligand amine exchanges with chelated amine (intermolecular exchange). The pendent hydroxyethyl arm undergoes intramolecular exchange with the chelated hydroxyethyl arms. These two types of dynamic processes can be characterized in detail using ^{1}H and ^{13}C NMR spectroscopy.[23,27,28] Presumably, all complexes examined here also undergo these dynamic processes in aqueous solution similar to those characterized in detail previously. We will briefly summarize the dynamics of these complexes inferred from previous detailed studies and the experiments carried out to examine these expectations using ^{51}V NMR line width and T_1 measurements as well as variable-temperature ^{1}H NMR spectroscopic experiments on the series of complexes presented in this manuscript.

The line widths of the eight complexes (V−DEA, V−MeDEA, V−TPA, V−BuDEA, V−EtDEA, V−TDEA, V−DMeDEA, V−DMeBIDE) fall within a range of 90−180 Hz, which is close to that of V−TEA (110 Hz). The V−HNBIDE complex (D. C. Crans and A. D. Keramidas, unpublished results), as well as related derivatives[30,37,38] form complexes with vanadium(V) which contain a six-coordinate vanadium atom. Within this structurally limited group of vanadium complexes (i.e., complexes derived from DEA- or EDTA-based ligands), six-coordinate complexes have line widths that fall outside the range of those previously observed for five-coordinate complexes ($\Delta\nu$ > 180 Hz).[29,30,37,38] The vanadium(V) complexes of cDPDEA and tDPDEA also have $\Delta\nu$ values outside this range (290 and 310 Hz). The possibility that the line broadening in the ^{51}V NMR signals caused by increased lability of these complexes, was therefore of interest and addressed by two methods: by measuring the T_1 values for the ^{51}V NMR signals and by variable-temperature ^{1}H NMR studies. Assuming that these vanadium compounds are within the motional limit and that $T_1 \cong T_2$, the relationship $\Delta\nu = (\pi T_1)^{-1}$ should hold (where $\Delta\nu$ is the line width of the signal) and can be used as an indication of contributions of dynamic processes in this series of complexes. Since the measured T_1 values in the ^{51}V NMR spectra were all within 30% of that predicted from the measured $\Delta\nu$, we conclude that all of these complexes, including those from tDPDEA and cDPDEA, show the same lability as the V−DEA and V−TEA complexes on the ^{51}V NMR time scale. The increased line widths of V−cDPDEA and V−tDPDEA are thus not likely to be attributable to a higher degree of chemical exchange on the ^{51}V NMR time scale. This result was confirmed by the variable-temperature ^{1}H NMR experiments for the V−DEA, V−MeDEA, V−TEA, V−cDPDEA, and V−tDPDEA complexes which showed similar levels of dynamic processes in the temperature range of 278−338 K. The spectra for the V−cDPDEA and V−tDPDEA complexes deviated only slightly from the general pattern observed above with respect to the sharpness of the signals attributed to the methylene protons and the methine proton adjacent to the phenyl groups. We conclude that higher lability of the DPDEA complexes cannot account for the observed differences in the ^{51}V line width between the V−TEA, V−cDPDEA, and V−tDPDEA complexes.

Thus, the vanadium complexes of cDPDEA and tDPDEA are exceptions to the empirical correlation between the line width and the ^{51}V NMR chemical shift previously observed for five- and six-coordinate vanadium complexes.[29] Since factors other than dynamic exchange processes can affect the ^{51}V NMR line widths, we determined the thermodynamic parameters ($\Delta H°$, $\Delta S°$, and $\Delta G°$) to obtain further information on the inherent stability of these complexes.

Thermodynamic Parameters for the Formation of Selected Vanadium(V) Complexes, Amino Alcohols, and Vanadate in Aqueous Solution. Before using the K_{eq} for vanadium

(37) Plass, W. *Inorg. Chim. Acta* **1996**, *244*, 221.
(38) Mahroof-Tahir, M.; Keramidas, A. D.; Goldfarb, R. B.; Anderson, O. P.; Miller, S. M.; Crans, D. C. *Inorg. Chem.* **1997**, *36*, 1657.

complex formation to extract the thermodynamic parameters, a few comments are in order. First, the concentration of H_2O has an activity of 1 given the fact that H_2O is solvent. Second, activity coefficients of charged species deviate significantly from 1 under high ionic strength conditions. However, the fact that the complex and $H_2VO_4^-$ both have a charge of -1, combined with the fact that L is neutral, the overall ratio of the activity coefficients is likely to approach 1. Thus, we will not further consider adjustments of the measured formation constants at 0.40 M KCl for calculation of the thermodynamic parameters. Third, for interpretation of the thermodynamic parameters for the complexes it is important that the corresponding parameters for $H_2VO_4^-$ be available under the conditions of the study. In the case of $H_2VO_4^-$, we expect that the $T\Delta S°$ term will dominate over the enthalpic component on the basis of the study reported at lower ionic strength.[39a] However, since some differences are likely based on the differences in conditions of the studies, it is necessary to redetermine these parameters in about 0.40 M KCl. Fourth, as described previously in studies of molybdenum and tungsten complexes of citrate and malate,[40−42] the protonation equilibria of respective ligands and their dependence on temperature must be considered.

For the vanadate salt system, the situation is furthermore complicated by the exchange processes that occur between the monomeric and oligomeric ions which also affect chemical shifts of these species.[26] The protonation reaction of vanadate was measured using ^{51}V NMR chemical shift, as a function of pH and temperature and the $pK_{a,temp}$ value could be derived for each temperature (eq 8). Using eq 8 the concentrations of $H_2VO_4^-$ and HVO_4^{2-} (and $K_{a,temp}$) could be calculated for each temperature and the thermodynamic properties for the protonation reaction of HVO_4^{2-} can be calculated using eq 9.[39a] We

$$\mathrm{pH} = \mathrm{p}K_{a,temp} + (\log \delta(\text{low pH}) - \delta_{temp})/(\delta_{temp} - \delta(\text{high pH})) \quad (8)$$

$$\mathrm{p}K_a = -\Delta H/2.303RT + \Delta S/2.303R \quad (9)[43]$$

measured the temperature dependence of the chemical shift for the reference $VOCl_3$ in order to make appropriate adjustment of chemical shift at various temperatures (Figure 4). Although vanadate and vanadium complexes are labile, under the conditions of this study, such effect contributes little to the observed chemical shift changes. The parameters $\Delta H°$, $\Delta G°$, and $\Delta S°$ obtained in 0.40 M KCl (no buffer) were -5.6 ($\pm$ 1.0) kJ mol^{-1}, -47.8 ($\pm$ 2.1) kJ mol^{-1} and 141.0 ($\pm$ 3.9) J mol^{-1} K^{-1}. These values are all in reasonable agreement if compared to those reported previously[39a−c] although these studies were all carried out under different conditions (ranging from differences in buffers and ionic strength).

Equation 8 was used to calculate the concentrations of $H_2VO_4^-$ at each temperature. Furthermore, the effect of temperature on the amino alcohol protonation reaction under the conditions of the present study needed to be determined

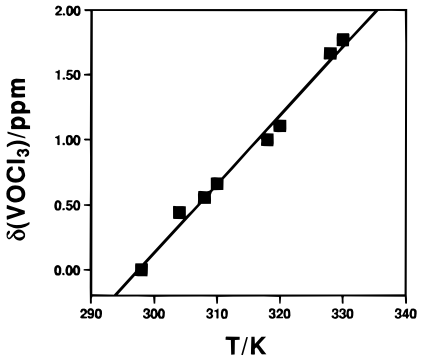


Figure 4. The chemical shift for the reference compound $VOCl_3$ (0.00 ppm, 298 K) is shown at variable temperatures.

before eq 4 could be used to calculate the K_{eq}. Deprotonation of the amino alcohol affects the chemical shift for the adjacent methylene groups in the amino alcohol ligand, and measuring the chemical shift dependence as a function of pH is a sensitive indicator of the pK_a value for the amino alcohol. Although, the ^1H NMR chemical shifts changed as a function of pH for DEA, MeDEA, EtDEA, TEA, tDPDEA, and cDPDEA, we found no observable difference in their respective inflection points (pK_a values). The data for these studies are provided in the Supporting Information. The inflection points were measured from the plots as well as calculated by an iteration using Excel. Plotting the pK_a as a function of $1/T$ (eq 9) led to the determination of the enthalpic and entropic contributions. For all of the ligands, the enthalpic contribution was experimentally indistinguishable from 0 (a very small positive slope ranging from 0.01 to 0.005), since no changes in pK_a values were measured in the temperature range examined (from 298 to 338 K). The entropic contributions were calculated from the intercept of the plots of pK_a against $1/T$ and the resulting parameters are given in Table 4. As expected for a deprotonation reaction, the entropic component of the reaction is responsible for the changes in free energy of the system. The parameters for protonation of the amino alcohol ligands showed in general that an enthalpic contribution to the protonation reaction was experimentally indistinguishable from 0. Correlation of the entropic component with observed $\Delta G°$ values has been observed for other, structurally distinct ligands.[39d]

Using the changes in the deprotonation constant for $H_2VO_4^-$ the $K_{a,temp}$ was calculated for each of the ^{51}V NMR experiments at each temperature. Using these temperature-dependent $K_{a,temp}$ values, the temperature-dependent $K_{eq,temp}$ values for each complex were calculated and used to determine the thermodynamic parameters for complexes. The $K_{eq,temp}$ of different complexes were plotted as a function of the reciprocal temperature, and the thermodynamic parameters, given in Table 4, were obtained. An example of the plots used for deriving the parameters given in Table 4 is provided in Figure 5 for three complexes: V−DEA, V−EtDEA, and V−tDPDEA. All vanadium(V) complexes have negative entropy terms and negative enthalpy terms reflecting the opposing effects of these terms in determination of the overall stability of the complexes. The negative entropic contributions presumably reflect a combination of the chelate formation with loss in the degree of freedom and charges with associated solvation of products and reactants.

The enthalpic component is the major contributor to the stability of V−DEA and V−MeDEA complexes at ambient temperatures, and thus the overall free energy is favorable for complex formation. The small increase in the pK_a of the protonated amine changed slightly the enthalpic term when comparing the parameters for V−DEA and V−MeDEA. The

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(43) Although deprotonation reactions are often considered, we, as well as previous workers, on the simple vanadate anion (see ref 39), examined the protonation reaction. This changes the sign change in eq 9.

Table 4. Thermodynamic Parameters[a,b] for V−DEA, V−MeDEA, V−EtDEA, V−TEA, V−tDPDEA, V−cDPDEA, and Corresponding Free Ligands in Aqueous Solution at 298 K[b,c]

V complexes[a]/ ligands[b]	$\Delta H°$/kJ mol^{-1} [d]	$\Delta S°$/J mol^{-1} K^{-1} [d]	$\Delta G°$/kJ mol^{-1} [d]	pH
V−DEA	−21.2 ± 3.7	−13.5 ± 1.7	−17.2 ± 3.2	8.7
V−MeDEA	−22.2 ± 2.1	−13.9 ± 1.3	−18.1 ± 1.7	8.5
V−EtDEA	−27.5 ± 4.7	−42.0 ± 2.2	−15.0 ± 4.0	8.7
V−TEA	−22.2 ± 1.3	−22.1 ± 2.3	−15.6 ± 2.0	8.1
V−tDPDEA	−26.8 ± 2.9	−50.4 ± 1.7	−11.8 ± 2.4	7.3
V−cDPDEA	−30.6 ± 3.1	−83.6 ± 2.0	−6.0 ± 2.6	7.6
DEA[b]	*e*	180.7± 0.8	−53.8 ± 0.2	8.7
MeDEA[b]	*e*	173.2 ± 0.5	−51.6 ± 0.2	8.5
EtDEA[b]	*e*	175.3± 1.2	−52.2 ± 0.4	8.7
TEA[b]	*e*	158.5± 0.7	−47.2 ± 0.2	8.1
tDPDEA[b]	*e*	132.6 ± 1.1	−39.5 ± 0.3	7.3
cDPDEA[b]	*e*	123.2 ± 0.2	−36.7 ± 0.1	7.6

[a] For the vanadium complexes the enthalpy ($\Delta H°$) and the entropy ($\Delta S°$) were determined from the graph ln(K_{eq}) versus 1/T containing 6−7 experimental points determined in triplicate using a concentration of 10 mM vanadate and 20 mM ligand. The temperature range studied was from 278 to 338 K. In all measurements, the ionic strength was adjusted to 0.40 M using a solution of 4.00 M KCl at a pH near the optimum pH (±0.05). $\Delta G°$ was obtained from the relationship $\Delta G° = \Delta H° - T\Delta S°$. [b] The thermodynamic parameters associated to the protonation equilibrium of the ligands were determined from separate experiments using the appropriate concentration of the amino alcohol and otherwise the same condition as in the determinatiom of those parameters for the complexes (pH and ionic strength). [c] The parameters determined for deprotonation of dissolved 10 mM $NaVO_3$ at 0.40 (adjusted with 4.00 M KCl) were for the enthalpy −5.6 (±1.0) kJ mol^{-1}, the entropy 141 (±4) J mol^{-1} K^{-1}, and free energy −47.8 (±2.1) kJ mol^{-1}. [d] The indicated errors in the thermodynamic parameters are obtained as standard deviation on the resulting data and rounded up from a 95% confidence limit (2σ). [e] The enthalpic contribution was experimentally indistinguishable from 0 ranging from 0.01 to 0.005 kJ mol^{-1} for all amino alcohol ligands.

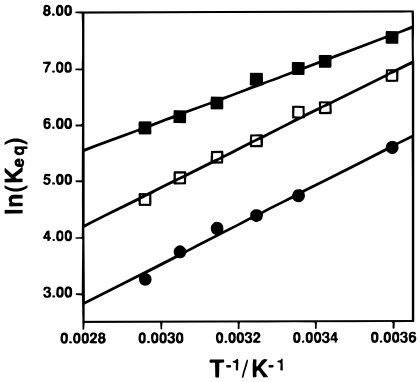

Figure 5. Plots of ln(K_{eq}) as a function of 1/T: (■) V−DEA, (□) V−EtDEA, and (●) V−tDPDEA. The $K_{aH_2VO_4^-}$ of the deprotonation reaction for $H_2VO_4^-$ used in the calculation of K_{eq} of different V complexes at 278 K was extrapolated from the experimental data determined in the temperature range from 298 to 338 K.

change in the enthalpic term in these complexes is directly reflected in the changes in complex stabilities. In a comparison of the parameters for V−DEA with the parameters for V−TEA, a similar trend is observed for the enthalpic component; however, the stability of the V−TEA complex is lower since the pK_a value for this amino alcohol is significantly lower (we note that a comparison of K_{com} shows that more complex is generated in such solutions). It is interesting that the enthalpic (and entropic) component for V−EtDEA is significantly larger than those of the other complexes (with the exception of V−cDPDEA). Comparing the parameters for the V−MeDEA, V−EtDEA, and V−TEA gives the opportunity to examine the effect of the additional functionality in TEA on complex stability. Although the enthalpic contribution for the V−EtDEA is greater than that for V−TEA, the entropic contribution for V−EtDEA is significantly larger resulting in complexes of similar stability. In comparing the parameters for the V−cDPDEA and V−tDPDEA complexes, a difference of 4 kJ is observed in the enthalpic component, whereas a much larger difference is found in the entropic component. The fact that V−cDPDEA is less stable than the V−tDPDEA complex can mainly be attributed to the large unfavorable entropic component.

The large entropic component found for the vanadium(V) complex V−cDPDEA (−83.6 J mol^{-1} K^{-1}) may reflect solvent organization around the complex. The two cis phenyl groups on the α-carbons adjacent to the chelating nitrogen center are too far apart for $\pi-\pi$ stacking. The water molecules must therefore interact with both phenyl groups in the V−cDPDEA complex, whereas the trans phenyl groups in the corresponding V−tDPDEA complex are close enough for some $\pi-\pi$ stacking interactions. We suggest that ligands with large hydrophobic groups such as cDPDEA and tDPDEA are particularly sensitive probes and that the entropic contribution to complex stability can be modified by ligand design. The entropic term clearly is crucial for the stability of this type of complex since the protonated amine pK_a value would have incorrectly predicted both the quantitative and the relative stabilities of these two complexes.

Previously, several observations made for related systems documented the importance of both sterics and the pK_a values of the protonated amines on complex stability. For example, in nitrobenzene solution, thermodynamic quantities for the association reactions between vanadyl acetylacetonate and substituted pyridines or substituted aliphatic amines are sensitive to both steric effects and inductive effects.[8] Similar corresponding observations have been made with other metal systems.[13] In this work we show that thermodynamic properties for the vanadium(V)−amino alcohol complexes are also being governed by both the pK_a of protonated ligand and sterics in the ligand. Corresponding changes were not observed in the lability of these complexes upon ligand changes.

To summarize, changes in the pK_a values of the protonated ligand are accompanied by corresponding changes in complex stability. In addition increased hydrophobicity (i.e., steric bulk) of the amine increases the entropic component which leads to an overall decrease in complex stability and deviation from the empirically found bell-curve-like dependence of the formation constant of this type of complex.

Conclusions

The apparent formation constants for 12 vanadium(V)−amino alcohol complexes were determined. The pH-dependent composite formation constants as well as the pH-independent equilibrium constants of the different vanadium(V) complexes, when plotted against the pK_a values of various protonated amino alcohols display distinct maxima. This bell-curve is not to be mistaken for the bell-curve that describes the stability of each of these complexes individually and has previously been characterized. The electron-donating ability as described by the pK_a values of the amine is not the only factor that influences the stability of the vanadium(V) complexes; complex coordination number, sterics in the amine, and solvation were also found to affect the vanadium complex stability. Determination of the thermodynamic parameters of selected complexes showed that the enthalpic component was the dominant term defining the stability of these complexes and that the entropic component

opposed this term. Modification of the amino alcohol increased the entropic contribution and generally resulted in a decrease in the overall stability of the complex from that observed for the parent systems. Modification of the amino alcohol to generate a ligand that forms a six-coordinate complex in general generates vanadium(V) complexes that are more stable than the corresponding five-coordinate complexes. On the basis of our observations, we suggest that complex stability increases by addition of alkyl substituents, if water soluble functionalities are added in conjunction with the alkyl substituent and the pK_a value for the protonated amino alcohol remains high and above 8.

Variable-temperature ^{1}H and ^{13}C NMR spectroscopy provided little evidence for significant changes in complex lability despite the range of differences in pK_a values of protonated amine, in sterics, and in solvation. The lack of sensitivity of the kinetics of aqueous vanadium(V) complexes has previously been attributed to a dissociative mechanism for complex formation. We conclude that structural modifications of amino alcohol ligands do not significantly affect the lability of vanadium(V) complexes as they change the vanadium(V) complex stability.

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Supporting Information Available: Plots of ligand chemical shift versus pH and *T* (5 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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