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Rates of Formation and Exchange for Oxovanadium(IV)–Glycine Complexes

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Received August 5, 1971

The kinetics of various reactions between VO^{2+} and glycine including the rates of formation of $VOHGly^{2+}$, glycine exchange on $VOHGly^{2+}$, and glycine exchange on $VO(Gly)_2$ in H_2O and D_2O have been studied. The activation parameters determined for the $VOHGly^{2+}$ formation reaction are $\Delta H^{\ddagger} = 12.0 \pm 0.9$ kcal/mol and $\Delta S^{\ddagger} = -4.0 \pm 2.1$ eu; for $VOHGly^{2+}$–HGly exchange, $\Delta H^{\ddagger} = 12 \pm 1$ kcal/mol and $\Delta S^{\ddagger} = -2.7 \pm 2$ eu; and for $VO(Gly)_2$–glycine exchange, $\Delta H^{\ddagger} = 8.0 \pm 0.2$ kcal/mol and $\Delta S^{\ddagger} = -20.0 \pm 0.5$ eu. The rate of exchange for the $VOHGly^{2+}$ species was determined by the nmr line-broadening technique and found to be zero order in glycine. The line-width data in all cases were corrected for outer-sphere line-broadening effects. The nmr data for the $VO(Gly)_2$ exchange reaction were assumed to be first order in glycine. A comparison of rates and activation parameters for similar vanadium(IV) substitution reactions is given.

Introduction

Interest in the chemistry of oxotetraaquovanadium(IV) complexes[1] is exemplified by a number of recent articles which involve the chemical investigations of various oxovanadium(IV) complexes.[2–6] Results of a recent study of the equilibria involved in the VO^{2+}–glycine–H_2O system suggested that the kinetics of these reactions would also be of interest.

The system is characterized by the following equilibria[7,8] at 25°

$$VO^{2+} + HGly \rightleftharpoons VOHGly^{2+} \qquad K_1 = 2.88 \pm 0.08 \qquad (1)$$

$$VO^{2+} + Gly^- \rightleftharpoons VO(Gly)^+ \qquad K_2 = 1.1 \times 10^6 \qquad (2)$$

$$VOHGly^{2+} + \rightleftharpoons VOGly^+ + H^+ \qquad K_3 = 5.30 \times 10^{-5} \qquad (3)$$

$$VOGly^+ \rightleftharpoons VO(Gly)^+ \qquad K_4 = 1.81 \qquad (4)$$

$$VO(Gly)^+ + Gly^- \rightleftharpoons VO(Gly)_2 \qquad K_5 = 5.41 \times 10^4 \qquad (5)$$

$$VO^{2+} + Gly^- \rightleftharpoons VOGly^+ \qquad K_6 = 6 \times 10^5 \qquad (6)$$

$$VOHGly^{2+} \rightleftharpoons VO(Gly)^+ + H^+ \qquad K_7 = 9.6 \times 10^{-5} \qquad (7)$$

$$H^+ + HGly \rightleftharpoons H_2Gly^+ \qquad K_8 = 2.18 \times 10^2 \qquad (8)$$

$$H^+ + Gly^- \rightleftharpoons HGly \qquad K_9 = 3.98 \times 10^9 \qquad (9)$$

$$VO^{2+} + H_2O \rightleftharpoons VOOH^+ + H^+ \qquad K_{m_1} = 1.0 \times 10^{-6} \qquad (10)$$

$$2VO^{2+} + H_2O \rightleftharpoons [(VO)_2(OH)_2^{3+}] + 2H^+ \qquad K_{m_2} = 2.5 \times 10^{-10} \qquad (11)$$

This study reports the kinetics of formation of $VOHGly^{2+}$ as determined by the stopped-flow method and the exchange reactions of HGly with $VOHGly^{2+}$ and $VO(Gly)_2$ as studied by nmr line-broadening techniques. The solvent in all cases was H_2O, except for several additional experiments with $VO(Gly)_2$ in D_2O.

Experimental Section

Preparation of Reagents.—The VO^{2+} stock solution was prepared by the electrolytic reduction of V_2O_5 in excess 3 M $HClO_4$ at a platinum electrode. Reduction was continued until a small amount of V(III) was detected in the solution. This was removed by the addition of small amounts of V_2O_5 and/or the passing of oxygen through the solution until tests for V(III) with iodate ion and V(V) with iodide ion were both negative. These oxidation–reduction reaction tests in which the liberated iodine was absorbed into a CCl_4 layer for detection were sensitive to 10^{-5} M V(III) and 10^{-4} M V(V) in 0.2 M VO^{2+} solutions.

The VO^{2+} stock solution was analyzed by titration with standard $KMnO_4$ and compared with the optical spectrum which was determined with a Cary Model 14 recording spectrophotometer. The total acid concentration was determined by titration of the eluent from a Dowex 50-8X cation-exchange resin with standard NaOH by using phenolphthalein as the indicator.

Commercially available glycine was recrystallized three times from 1:1 methanol–water solvent and oven dried at 110° prior to use. Sodium perchlorate was prepared from stoichiometric amounts of Na_2CO_3 and $HClO_4$ and purified by recrystallization[9] from H_2O.

Glycine-N,N,O-d_3 (D_2NCH_2COOD) was prepared by dissolving 1.0 g of normal glycine in 5 ml of 99.5% D_2O and allowing it to reach equilibrium, followed by removal of the D_2O by distillation under reduced pressure. This procedure was repeated three times with fresh 99.5% D_2O. The glycine-N,N,O-d_3 recovered from this procedure gave only a small HOD peak in the nmr spectrum.

Kinetic Measurements.—Stopped-flow measurements were made at 10° on a Durrum–Gibson stopped-flow apparatus at a wavelength of 760 nm. The concentrations of reactants were such that glycine was always in excess: $9.19 \times 10^{-3} \leq [VO^{2+}] \leq 2.15 \times 10^{-2}$ M; $9.39 \times 10^{-2} \leq [Gly] \leq 2.84 \times 10^{-1}$ M; $1.99 \leq pH \leq 2.99$. All solutions were adjusted with $NaClO_4$ to an ionic strength of 0.2 M before the runs to minimize schlieren problems associated with mixing. Measurements were taken by following the photomultiplier output with a Tektronix Type 564 storage oscilloscope and photographing the traces with a Polaroid camera.

Temperature-jump measurements were made at 25° and a wavelength of 580 nm which corresponds to a maximum for the species $VOGly^+$ and $VO(Gly)^+$ by means of an apparatus similar to that described by Hurwitz and Kustin.[10] Only one relaxation of about 40 msec is observed under the range of conditions used: $3.37 \leq pH \leq 3.88$; $0.4 \leq [Gly] \leq 1.0$ M; $[VO^{2+}] = 0.02$ M. The details of these measurements and the results for a series of related ligands will be published elsewhere.

A Varian A-60 spectrometer equipped with a Varian Model 4343 variable-temperature controller and a standard variable-temperature probe was used to record the nmr spectra. The

(1) For purposes of convenience, the oxotetraaquovanadium(IV) ion will be written as VO^{2+} or oxovanadium(IV) and glycine will be abbreviated as HGly. When glycine is coordinated as a monodentate ligand, the complex is written as $VOHGly^{2+}$. The formula $VOGly^+$ represents the deprotonated form of $VOHGly^{2+}$. For glycine functioning as a bidentate ligand, the complex is specified as $VO(Gly)^+$.

(2) K. Wuthrick and R. E. Connick, *Inorg. Chem.*, **7**, 1377 (1968).

(3) (a) R. P. Dodge, D. N. Templeton, and A. Zalkin, *J. Chem. Phys.*, **35**, 55 (1961); (b) J. G. Forest and C. K. Prout, *J. Chem. Soc. A*, 1312 (1967); (c) J. Selbin, *Chem. Rev.*, **65**, 153 (1965), and references therein.

(4) J. Reuben and D. Fiat, *Inorg. Chem.*, **6**, 579 (1967); **8**, 1821 (1969).

(5) K. Wuthrick and R. E. Connick, *ibid.*, **6**, 583 (1967).

(6) (a) N. S. Angerman and R. E. Jordan, *ibid.*, **8**, 65 (1969); (b) R. E. Tapscott and R. L. Belford, *ibid.*, **6**, 735 (1967).

(7) All equilibrium constants[8] are reported at 25°. In this paper, the rate constants have corresponding subscripts, *i.e.*, $K_i = k_i/k_{-i}$.

(8) (a) H. Tomiyasu and G. Gordon, to be submitted for publication; (b) L. G. Sillén and A. E. Martell, *Chem. Soc., Spec. Publ.*, **No. 25**, Supplement No. 1 (1970); (c) M. Matsukawa, M. Ohta, S. Takata, and R. Tsuchiya, *Bull. Chem. Soc. Jap.*, **38**, 1235 (1965); (d) H. Sigel and R. Griesser, *Helv. Chim. Acta*, **50**, 1842 (1967); (e) H. Kroll, *J. Amer. Chem. Soc.*, **74**, 2034 (1952); (f) F. J. C. Rossotti and H. S. Rossotti, *Acta Chem. Scand.*, **9**, 1177 (1955).

(9) G. Gordon and P. H. Tewari, *J. Phys. Chem.*, **70**, 200 (1966).

(10) P. Hurwitz and K. Kustin, *Inorg. Chem.*, **3**, 823 (1964).

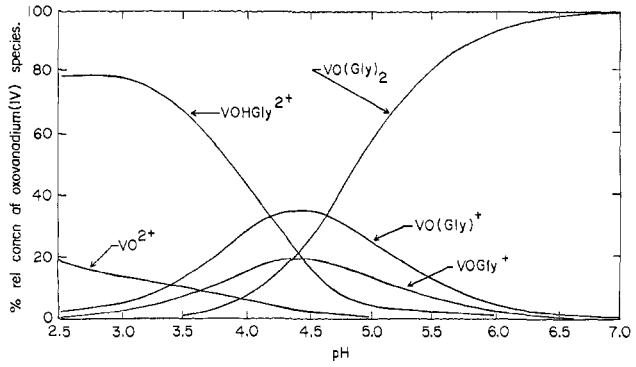

Figure 1.—Plot of relative concentrations of oxovanadium(IV) species as a function of pH. Curves are for 0.03 *M* VO^{2+}, 2.5 *M* glycine, and an ionic strength of 0.2 *M*.

radiofrequency field intensity was held constant at 0.10 G, a value well below that at which saturation begins to broaden the absorption peaks. The scanning rate was either 0.5 or 1.0 G/sec in order to avoid distortion of the peaks. The peak observed was that of the methylene protons of the glycine in the bulk phase. The solutions for the nmr studies varied in the total concentration of vanadyl species from 0.001 to 0.02 *M* and the glycine concentration ranged from 0.5 to 2.5 *M*. The pH was held constant for the determination of each exchange rate and was adjusted by adding 70% $HClO_4$ or 50% NaOH and was measured on a Radiometer Model 26 pH meter equipped with a combination glass–calomel electrode.

For the measurement of exchange of glycine with the $VOHGly^{2+}$ species, the pH was varied between 2.4 and 3.7. For the experiments with the $VO(Gly)_2$ species, the pH was 6.80 ± 0.05. In each case a variation of the pH by 0.25 pH unit from the stated values made no marked difference in the visible spectra of the solutions. A total of 12 independently prepared solutions was used in the study of each exchange rate. The concentrations of the complexes were calculated from spectrophotometric and equilibrium data.[8] The line widths were generally in the range 2–20 Hz and were reproducible to ±0.2 Hz. Each spectrum was recorded at least twice and the average line width was used in all subsequent calculations. Temperatures were monitored by inserting a calibrated copper–constantan thermocouple directly into the probe and by measuring the output with a null-balance voltmeter. The temperatures were maintained to ±0.4° in all nmr runs. No systematic cycling of the temperature could be detected over an extended period of time.

The nmr spectra of several solutions which contained primarily $VO(Gly)_2$ and excess glycine-*N*,*N*,*O*-d_3 were run in 99.5% D_2O and the resulting exchange rate was calculated. In these runs it was possible to significantly increase the total vanadyl concentration since the only absorption due to solvent was a small HOD peak which did not interfere with the methylene proton linewidth measurements. The concentration of $VO(Gly)_2$ varied from 0.02 to 0.1 *M* and resulted in line widths ranging up to 52 Hz.

Results

At pH ≤3.0, the major oxovanadium(IV) species in H_2O is either VO^{2+} or $VOHGly^{2+}$, depending upon the concentration of glycine, as can be seen in Figure 1, and no other species, including the hydrolyzed vanadium species, is present in any appreciable quantity. Thus, it is possible to determine the rate of formation of $VOHGly^{2+}$ independent of the reactions of the other complexes. The visible spectra of various VO^{2+}–glycine complexes have been reported previously.[8a] The reaction was followed at 760 nm and 10–20° by utilizing the stopped-flow technique.

When the VO^{2+} and glycine solutions are mixed in the stopped-flow spectrometer, the protonation reaction for HGly rapidly comes to equilibrium prior to the VO^{2+} and HGly reaction. The rate equation for reaction 1 is given by (12).

$$\frac{d(VOHGly^{2+})}{dt} = k_1[VO^{2+}][HGly] - k_{-1}[VOHGly^{2+}] \quad (12)$$

During the reaction, the glycine is in excess and within experimental error the pH remains constant. The $[VOHGly^{2+}]$ may be determined from the absorbance (A) of the solution, since

$$A = d(\epsilon_m[VO^{2+}] + \epsilon_1[VOHGly^{2+}]) \quad (13)$$

The quantities ϵ_m and ϵ_1 are known[8a] and

$$[VOHGly^{2+}] = \frac{A - (d\epsilon_m[VO^{2+}]_{total})}{d(\epsilon_1 - \epsilon_m)} \quad (14)$$

where d = path length, ϵ_m = extinction coefficient of VO^{2+}, and ϵ_1 = extinction coefficient of $VOHGly^{2+}$.

The appropriate second-order plots were linear for all conditions studied. Values for k_1 were determined by means of a least-squares technique from the slopes of these plots and are listed in Table I. From the data

TABLE I
RATE OF FORMATION OF THE MONODENTATE $VOHGly^{2+}$ SPECIES AT 10° IN 0.20 *M* $NaClO_4$

$[VO^{2+}]_{total}$, *M*	$[Gly]_{total}$, *M*	pH	k_1, M^{-1} sec^{-1}	k_{-1}, sec^{-1}
0.00919	0.0939	2.923	452	143
0.00919	0.1349	2.932	434	137
0.00919	0.2838	2.960	440	139
0.01225	0.1349	2.955	435	137
0.01225	0.1349	2.912	439	139
0.01225	0.2838	2.952	414	131
0.01530	0.0771	2.845	423	134
0.01530	0.0939	2.908	419	132
0.01530	0.1349	2.938	420	133
0.01838	0.0939	2.890	407	129
0.02145	0.0939	2.880	448	142
0.02145	0.1349	2.895	483	153
0.01020	0.1349	2.998	428	136
0.01020	0.1349	2.989	387	122
0.01020	0.1349	2.805	411	130
0.01020	0.1349	2.800	436	138
0.01020	0.1349	2.641	374	118
0.01020	0.1349	2.340	384	121
0.01020	0.1349	2.280	374	118
0.01020	0.1349	2.030	421	133
0.01020	0.1349	1.985	408	129
		Av	421 ± 26[a] Av	133 ± 15[b]

[a] The uncertainty represents one standard deviation. [b] The uncertainty is based on the error reported for K_1 which is about ±6%. This error has been propagated for the average value of k_{-1}.

in Table I it can be seen that k_1 is independent of $[VO^{2+}]$, [HGly], and pH. The values of k_{-1} are calculated based on the value[8a] of K_1 = 3.165 at 10° and 2.88 at 25°. Activation parameters were obtained[11] for formation of $VOHGly^{2+}$ from the rates of reaction as a function of temperatures in the range of 10–20° as shown in Table II. Values of $\Delta H^{\ddagger}$ = 12.0 ± 0.9 kcal/mol and $\Delta H^{\ddagger}$ = −4.0 ± 2.1 eu were calculated for the rate of formation of $VOHGly^{2+}$.

(11) The values for the enthalpy and entropy of activation were calculated by means of a computer program in which the square of the differences between the observed and calculated rate constants is minimized. The data points were weighted according to the square of the reciprocal of the dependent variable such that the per cent deviation was minimized. For a description of the computer program, see the Los Alamos publication LA-2367 + addenda. The present modification of the original program is written in Fortran IV and has been adopted to the IBM 360 Model 65 computer. A complete listing of the program and the associated subroutines is available upon request.

TABLE II
EXPERIMENTAL RATES OF FORMATION OF $VOHGly^{2+}$ AS A FUNCTION OF TEMPERATURE

Temp, °C	k_1, M^{-1} sec^{-1} [a]	k_1^{calcd}, M^{-1} sec^{-1} [b]	$10^{-2}k_{-1}$, sec^{-1} [c]
10	421	411	1.3
12.2	490	492	1.6
13.3	546	535	1.8
15.5	632	641	2.1
17.6	733	756	2.5
18.8	797	830	2.7
20.0	935	911	3.2
25.0		1327[d]	4.6

[a] Average of all experiments at the temperature reported. [b] Calculated[11] from the experimentally determined activation parameters, $\Delta H^{\ddagger} = 12.0 \pm 0.9$ kcal/mol and $\Delta S^{\ddagger} = -4.0 \pm 2.1$ eu. [c] Calculated in terms of the equilibrium constant[8a] (K_1) of 3.165 at 10° and 2.88 at 25° where $k_{-1} = k_1/K_1$, and k_1 is the observed second-order rate constant. [d] Extrapolated from the calculated activation parameters.

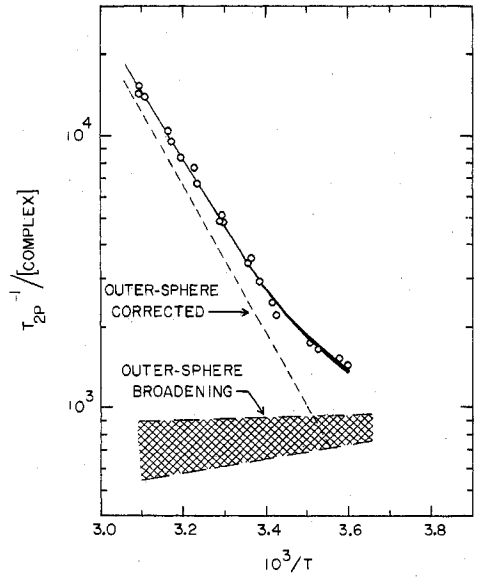

Figure 2.—Plot of glycine line width normalized to unit complex concentration as a function of reciprocal temperature for $VOHGly^{2+}$–HGly exchange: O, average of normalized experimental data points for a minimum of four concentrations at each temperature; ——, least-squares fit of experimental data with weights of $1/k^2$; - - - - -, least-squares fit of experimental data corrected for outer-sphere broadening. The cross-hatched area represents the magnitude of outer-sphere broadening correction and the associated uncertainty.

The rates of exchange for glycine with $VOHGly^{2+}$ and $VO(Gly)_2$ in H_2O and $VO(Gly)_2$ in D_2O were investigated by nmr line-broadening methods[12] where the absorption spectra for the methylene protons on glycine in the bulk phase were observed. It is unfortunate that as exchange becomes more rapid or the $[VO^{2+}]_{tot}$ is increased, the methylene proton peak broadens as does the much more intense H_2O peak and thus limits the total concentration of oxovanadium(IV) species and the temperature range accessible.

The relaxation time is related to the observed line broadening (in hertz) by

$$T_{2p}^{-1} = \pi(lw_p - lw_o) \qquad (15)$$

where lw_p = full line width at half-height in the presence of the paramagnetic species and lw_o = full line width at half-height in the absence of the paramagnetic species.

(12) E. F. Caldin, "Fast Reactions in Solution," Blackwell, London, 1964, p 214.

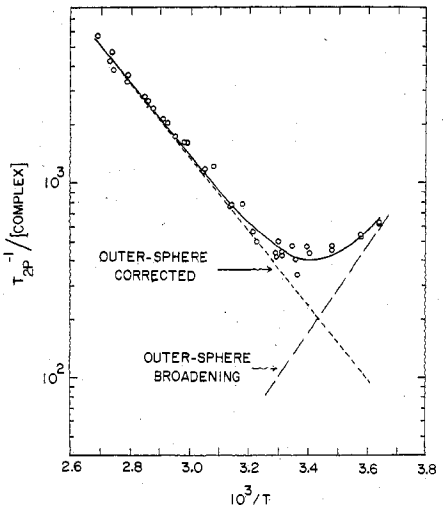

Figure 3.—Plot of glycine line width normalized to unit complex concentration as a function of reciprocal temperature for the $VO(Gly)_2$–glycine exchange in H_2O: O, average of normalized experimental data points for a minimum of three concentrations at each temperature; ——, least-squares fit to the experimental data with weights of $1/k^2$; - - - - -, least-squares fit of experimental data corrected for outer-sphere broadening; — —, outer-sphere broadening correction with a least-squares slope of 5.7 ± 0.9 kcal/mol.

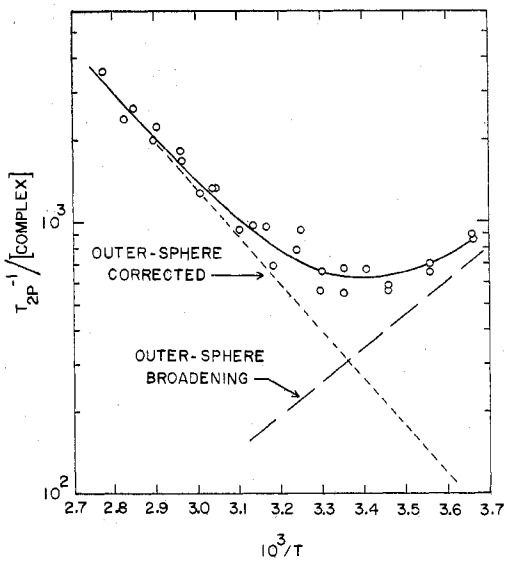

Figure 4.—Plot of glycine line width normalized to unit complex concentration as a function of reciprocal temperature for the $VO(Gly)_2$–glycine exchange in D_2O: O, average of normalized experimental data points for a minimum of three concentrations at each temperature; ——, least-squares fit to experimental data with weights of $1/k^2$; - - - - -, least-squares fit to experimental data corrected for outer-sphere broadening; — —, outer-sphere broadening correction with a least-squares slope of 5.7 ± 1.3 kcal/mol.

Since graphs of ln $(T_{2p})^{-1}$ as a function of reciprocal temperature are linear with negative slopes, it is evident that chemical exchange is controlling the relaxation process[13] over the majority of the temperature range studied. A typical set of normalized line-width data is shown in Figure 2 for the $VOHGly^{2+}$–glycine ex-

(13) T. J. Swift and R. E. Connick, *J. Chem. Phys.*, **37**, 307 (1962).

change reaction. Each data point is the average value of at least three different concentrations at that temperature. The data were normalized to the concentration of $VOHGly^{2+}$ after it was shown that this was the only vanadium complex which resulted in consistent rate constants. The solid line in Figure 2 represents a nonlinear least-squares fit to the experimental data points with weights of $1/k^2$ which minimizes the per cent error. The first-order rate constants are calculated directly from the line-width data by means of the equation

$$T_{2p}^{-1} = P_m \tau_m^{-1} \quad (16)$$

where $P_m = \tau_m/\tau_a$ and τ_a is the lifetime of an uncomplexed glycine ligand. Under the conditions of n[complex] $\ll$ total glycine, P_m can be approximated as

$$P_m = n[\text{complex}]/[\text{glycine}] \quad (17)$$

where n represents the number of coordinated glycine molecules. Thus, the rate constant is given by

$$k_{ex} = \tau_m^{-1} \quad (18)$$

Data for the exchange reaction between $VO(Gly)_2$ and glycine are presented in Figures 3 and 4. The conditions under which these data were collected were pH 6.80, $[Gly]_{tot} = 2.50\ M$, $\mu = 0.50$, and a total oxovanadium(IV) concentration ranging from 2.80×10^{-3} to $2.00 \times 10^{-2}\ M$ in the H_2O solutions and 2.02×10^{-2} to $1.02 \times 10^{-1}\ M$ in the D_2O solutions.

The two dashed straight lines for the chemical-exchange-controlled region[14] in Figures 3 and 4 represent a nonlinear least-squares fit of the data which were corrected for broadening caused by second-sphere interactions.[15] Each individual data point was weighted by $1/k^2$ in order to minimize the per cent error. The resulting dashed line corresponds to the appropriate activation parameters for that exchange process. The rate constants, enthalpy of activation, and entropy of activation for the exchange reactions are tabulated in Table III together with other data on various oxovanadium(IV) systems for comparison. The failure to observe deviations from linearity in the corrected data in Figures 3 and 4 is consistent with our assumption that contributions from other processes can be neglected under the experimental conditions reported.

The effect of ionic strength on both exchange reactions was investigated in the range $0.5 \leq \mu \leq 2.0\ M$. In all cases studied the variation of line width over this range of ionic strength was no larger than was the deviation of line widths of samples of the same ionic strength (± 0.3 Hz).

The concentrations of glycine, oxovanadium(IV), sodium perchlorate, and acid or base were constant enough that variation of medium effects would not be appreciable in comparison with the scatter in the experimental data. Since the viscosity in the H_2O and D_2O solutions varies only slightly and in such a manner as to maintain the ratio nearly constant over the limited temperature range 5–20°, it may be approximated that the effect of this change[16] is the same in both solvents. Thus, we have assumed that the relative line widths are unaffected.

Dependence of the exchange rate on the concentration of glycine should be correlated with the order of the reaction with respect to glycine.[17] A plot of $(lw_p - lw_o)$ *vs.* [HGly] for the $VOHGly^{2+}$–glycine exchange reaction is observed to have a slope of zero order over the range of $0.5 \leq [HGly] \leq 2.5\ M$ with other conditions of $\mu = 0.5\ M$, $[VO^{2+}]_{tot} = 7.04 \times 10^{-3}\ M$, and pH 2.50. Thus, the rate of exchange for the $VOHGly^{2+}$ complex was assumed to be zero order in glycine. The rate of exchange for the $VO(Gly)_2$ species with glycine exhibited a complicated dependence on the glycine concentration which was not readily interpreted over the total range $0.5 \leq [HGly] \leq 2.5\ M$, pH 6.80, $\mu = 0.5\ M$, and $[VO^{2+}]_{tot} = 9.82 \times 10^{-3}\ M$. The activation enthalpy and activation entropy for the $VO(Gly)_2$–Gly reaction are consistent with other second-order processes. The rate constant for this process shown in Table III was calculated assuming that the exchange reaction was first order in glycine[6a,14a] in the $2.5\ M$ solutions. A plot of the line-width dependence for the $VO(Gly)_2$ system is shown in Figure 5. The failure of the data to be linear[18] with a zero intercept, which would be expected if the only process were the second-order process, is probably associated with dimer formation and related complications which will be reported separately.

Discussion and Conclusions

For the reaction between nickel(II) and a variety of amino acids, Cassatt and Wilkins[19] reported a remarkable unreactivity of the protonated form of aliphatic amino carboxylates in which the amino acid is protonated. It is important to note that several reports[19,20] give the rate of formation of the chelated complexes whereas we are reporting the rate of formation of the monodentate complex.

As a matter of fact, the results reported here are not in disagreement with the model proposed by Cassatt and Wilkins[19] if we assume that the rate of monodentate formation proceeds by coordination of the carboxyl group of the amino acid. Thus, the important difference in formation of the bidentate, chelated complex must be the ease of formation of the chelated complex from either the protonated or the unprotonated form of the monodentate complex. As Cassatt and Wilkins[19] pointed out, the overall difference is noted owing to the ease of dissociation as compared to the combined process of loss of H^+ from the NH_3^+ residue and ring closure. In the case of the protonated amino acid,

(14) (a) R. B. Jordan and N. S. Angerman, *J. Chem. Phys.*, **48**, 3983 (1968); (b) N. A. Matwioff, *Inorg. Chem.*, **5**, 788 (1966); (c) T. J. Swift, Ph.D. Thesis, University of California, Berkley, Calif., 1962.

(15) The second-sphere broadening contribution to the total line width in the H_2O samples is 31% at 25° and 3% at 55°. For the D_2O solutions at these temperatures, the contributions are 50 and 11%, respectively. Based on these observations, we conclude that outer-sphere corrections are mandatory. The slope of the temperature dependence of the outer-sphere term seems large when compared to previous results in aqueous solution. For example, interpretation of the data of N. S. Angerman and R. B. Jordan, *J. Chem. Phys.*, **54**, 837 (1971), results in a value of $\sim 4 \pm 1$ kcal/mol. If these lower values are used, the resulting rate constants differ from those reported here by less than 10%.

(16) At 15° the ratio (viscosity of D_2O)/(viscosity of H_2O) = 1.2679 but over a small temperature range (5–20°) this ratio changes by less than 4% and hence the effect of changing viscosity over this temperature range will be negligible.

(17) R. G. Pearson and D. Lanier, *J. Amer. Chem. Soc.*, **86**, 765 (1964).

(18) In that the relative concentration of $VO(Gly)_2$ is at least 10^2 times greater than the concentration of $VO(Gly)^+$, the deviations from linearity at low HGly concentrations are probably not associated with interference from the corresponding $VO(Gly)^+$– or $VOHGly^{2+}$–glycine exchange reactions.

(19) J. C. Cassatt and R. Wilkins, *J. Amer. Chem. Soc.*, **90**, 6045 (1968).

(20) A. F. Pearlmutter and J. Stuehr, *ibid.*, **90**, 858 (1968).

TABLE III
RATES OF REACTION AND ACTIVATION PARAMETERS FOR OXOVANADIUM(IV) SUBSTITUTION REACTIONS

Reaction[a]	Method	k(25°), sec^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	Ref
H_2O exchange on VO^{2+} [b]	^{17}O nmr	5.2×10^2	13.3 ± 0.3	-1.5 ± 1.0	4, 5
CH_3CN exchange on VO^{2+}	Nmr[c]	2.8×10^3	7.05	−20	6a
DMF exchange on VO^{2+}	Nmr[c]	5.7×10^2	7.25	−21.6[c]	14a
MeOH exchange on VO^{2+}	Nmr	5.7×10^2	9.46	−14.2	*h*
H_2O exchange on VO(IDA)[b]	^{17}O nmr	1.2×10^5	11.7	+3.9	2
H_2O exchange on VO(SSA)[b]	^{17}O nmr	1.5×10^5	10.8	+1.2	2
H_2O exchange on VO(TIR)[b]	^{17}O nmr	4.7×10^5	11.8	+7.0	2
$VOHGly^{2+}$ formn	Stopped flow	1.3×10^3 [d]	12.0 ± 0.9	-4.0 ± 2.1	This work
$VOHGly^{2+}$ dissocn	Calcd[e]	4.6×10^2	13.1 ± 1.5	-2.4 ± 2.0	This work
HGly exchange on $VOHGly^{2+}$	Nmr[f]	$<2.5 \times 10^3$	12 ± 1	-2.7 ± 2	This work
HGly exchange on $VO(Gly)_2$	Nmr[g]	3.6×10^2	8.0 ± 0.2	-20.0 ± 0.5	This work
HGly exchange on $VO(Gly)_2$ in D_2O	Nmr[g]	4.0×10^2	7.4 ± 0.7	-21.8 ± 2.0	This work
VOTar formn	Stopped flow	1.8×10^2 [d]			*i*
$VO(Tar)_2^{2-}$ formn	T jump	2.8×10^2 [d]			*i*

[a] IDA = iminodiacetic acid, SSA = sulfosalicylic acid, TIR = tiron, DMF = dimethylformamide, Tar = tartrate. [b] These water-exchange mechanisms are generally regarded as dissociative in nature. [c] It should be noted that the entropy of activation reported by Jordan and Angerman[6a] is most probably in error. Their assumption of four solvent molecules results in a value of $\Delta S^{\ddagger}$ of −15.4 eu which is inconsistent with their reported rate constant. Owing to a lack of availability of tabulated original data, it is difficult to recalculate the appropriate activation parameters. However, if the reported $\Delta S^{\ddagger}$ was determined from a plot of $(T'_{2p}T)$ *vs.* $1/T$, an error of 1.9872 [(ln π) + ln (solvent concn)] could result. With this assumption, we recalculate a value for $\Delta S^{\ddagger}$ of −21.6 eu which is consistent with the reported[6a] rate constant of 5.7×10^2 sec^{-1}. [d] Second-order rate constant, M^{-1} sec^{-1}. [e] $k_{diss} = k_{form}/K_1$ (see data in Table II). [f] Process shown to be zero order in glycine. [g] Process assumed to be first order in glycine in the 2.5 M glycine solutions (see Figure 5). [h] N. S. Angerman and R. B. Jordan, *Inorg. Chem.*, **8**, 1825 (1969). [i] K. Kustin and R. Pizer, *ibid.*, **9**, 1536 (1970).

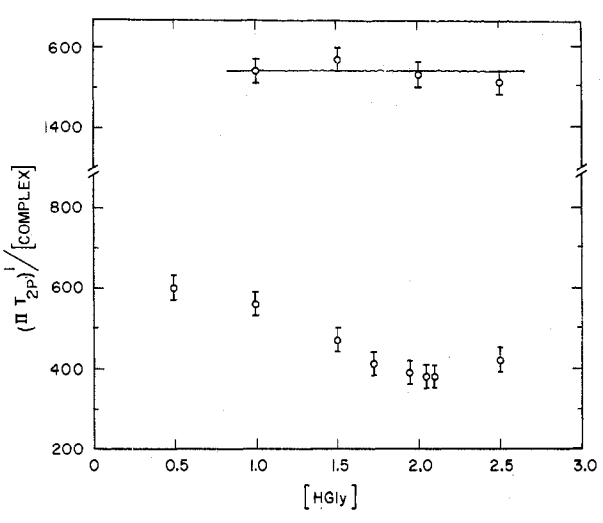

Figure 5.—Line broadening as a function of glycine concentration at 53.9°. The error bars represent the experimental uncertainty. The data are normalized to 1.0 M complex ion concentration: $VOHGly^{+}$–Gly reaction, upper data set; $VO(Gly)_2$–Gly reaction, lower data set.

dissociation wins out. This proposal is also supported by a comparison of the corresponding equilibrium constants for reactions 1 and 6 (2.88 and 6×10^5, respectively). Clearly, the protonated form of the monodentate glycine–vanadium(IV) complex is unstable with respect to dissociation.

The microscopic details of the mechanism of formation of $VOHGly^{2+}$ can be examined from several different points of view. Eigen and Tamm[21] have proposed the following scheme for the formation of a complex between a metal ion and a monodentate ligand

$$M(aq)^{n+} + L(aq)^{-} \underset{}{\overset{K_{os}}{\rightleftharpoons}} [M(aq)\cdots L]^{(n-1)+} \quad (19)$$

$$[M(aq)\cdots L]^{(n-1)+} \underset{}{\overset{k_1}{\rightleftharpoons}} ML(aq)^{(n-1)+} + H_2O \quad (20)$$

where $[M(aq)\cdots L]^{(n-1)+}$ represents an ion pair or outer-sphere association complex with an equilibrium constant K_{os}, and the equilibrium step is rapid compared with the interchange reaction (k_1). If the known rate of water exchange for the aquovanadium(IV) ion is used, approximate values of K_{os} can be calculated from our experimental values of k_1. This calculation results in a value of 2.6 M^{-1} which is much larger than might be calculated based on the Bjerrum equation with activity coefficients included.[19,22,23] This value also results in an unrealistically large value for the distance of closest approach.[19] With such a large value for K_{os}, some deviations from first-order behavior should also be noted in the formation data owing to incipient saturation of the ion-pair equilibrium. No such deviations are noted. On this basis, this proposal of an outer-sphere association in which the rate of water exchange of the aquovanadium(IV) ion is unaffected by complex formation can be discarded. On the other hand, if the outer-sphere process corresponds to the complexation of a protonated glycine in the axial position, then the rate of formation would correspond to the product of the axial complexation equilibrium constant and the water-exchange rate in the equatorial position.[24] If the axial formation constant were about 0.5, complexation would be far from complete under the conditions of the experiments reported in Table I and the corresponding water-exchange rate would have to be increased by a factor of about 6 over that reported for $OV(OH_2)_4^{2+}$ in order to explain the observed rate. This factor of about 6 is not surprising in view of the results of Wuthrick and Connick.[2,5]

One other proposal which requires additional consideration is the possibility of structural effects suggested by Bennetto and Caldin.[25] This alternate explanation for linking the difference between ligand-substitution rates and solvent-exchange rates involves a large effect of solvent structure on the transition state. Bennetto and Caldin[25] suggested that any satisfactory model must take into account reorganization processes

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in the immediate vicinity of the ion. This proposal merits further consideration and it will be particularly interesting to make direct comparisons between VO^{2+} and Ni^{2+} in a variety of solvents as soon as more data are available. Unfortunately, the solvent-exchange data for the VO^{2+}–ligand systems are insufficient to allow meaningful comparisons to be made.

From the rate of formation of $VOHGly^{2+}$ and the equilibrium constant for the reaction it is possible to calculate the rate of dissociation of $VOHGly^{2+}$. Calculated values of k_{-1} at various temperatures are given in Table II. Angerman and Jordan[6a,14a,16] suggested that the activation parameters for the k_{-1} process are indicative of an SN1 type dissociative mechanism. The agreement between the activation parameters for this dissociative process (k_{-1}) and that for the water-exchange reaction strongly suggests similar processes.

Line-broadening techniques allow for calculation of exchange rates at various temperatures and for calculation of the corresponding activation parameters. It has been shown that the exchange rate of glycine on $VOHGly^{2+}$ is independent of the concentration of glycine. This suggests that the rate-determining step in the exchange process must be the loss of the monodentate glycine from the complex. We conclude that the activation parameters for the dissociation of $VOHGly^{2+}$ as calculated from the stopped-flow experiments and the nmr results on the exchange of glycine with $VOHGly^{2+}$ are not distinguishable experimentally [*i.e.*, $\Delta H^{\ddagger}$(stopped flow) = 13.1 ± 1.5 kcal/mol, $\Delta H^{\ddagger}$(nmr) = 12 ± 1 kcal/mol, $\Delta S^{\ddagger}$(stopped flow) = −2.4 ± 2.0 eu, $\Delta S^{\ddagger}$(nmr) = −3 ± 1 eu]. If this is true, the rate of exchange and the rate of dissociation should be identical and the activation parameters of these two processes would necessarily be the same.

The rate of glycine exchange on $VO(Gly)_2$ in aqueous solution at pH 6.8 was found to be 360 sec^{-1} with substantially different activation parameters from that observed with the $VOHGly^{2+}$ exchange reaction. The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are comparable with those for the exchange of CH_3CN and DMF on VO^{2+} in the respective anhydrous solvents.[6a,14a] Angerman and Jordan[14a,16] suggested that these two latter exchange processes could be associated with an SN2 type mechanism in which the formation of a bond with a solvent molecule outside the first coordination sphere is important. If this is the case and if, on the basis of similar activation parameters, similar mechanisms can be inferred, we suggest that the rate of exchange of glycine with $VO(Gly)_2$ is limited by an associative step.

Acknowledgments.—The authors wish to express their appreciation to Mark Miller and David Rablen for their peliminary measurements on this system and to the Atomic Energy Commission for financial support under Contract No. AT-(11-1)-1780.

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Thermodynamics of Ion Association. XXIV. The Formation of Mixed Complexes of Copper with Glycine, Alanine, Serine, and Valine

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Received April 4, 1972

The formation of mixed complexes of copper(II) with pairs of ligands chosen from the series of similar amino acids glycine, α-alanine, serine, and valine has been studied by potentiometric and calorimetric methods at 25° and at an ionic strength of 0.10 ± 0.01 *M* maintained with potassium nitrate. In addition to determining the thermodynamic data for the simple complexes of copper with these amino acids, the following mixed complexes have been characterized: Cu(gly)(ala), Cu(gly)(val), Cu(gly)(ser), Cu(ala)(val), Cu(ala)(ser), and Cu(val)(ser). The data show that the mixed complexes are more stable than the parent binary complexes and that this stabilization is almost entirely due to the statistical effects. Temperature-dependent and temperature-independent components of the thermodynamic properties are calculated and these are discussed in terms of the important factors involved in mixed-complex formation.

Introduction

In mixed-ligand complexes, two or more different ligands, other than the solvent molecule, bond simultaneously to the central metal ion. They are frequently formed in solutions containing metal ions and more than one kind of suitable ligand and are thus of considerable importance as components in natural waters and various biological fluids.

Sarkar and Kruck have reported the isolation of a mixed complex Cu^{II}(histidine)(threonine) from normal human serum[1] and the detection of mixed complexes Cu(histidine)(glutamine) and Cu(histidine)(serine) in solutions prepared at physiological pH.[2] In many instances enzymes are known to be activated by certain metal ions with the formation of a mixed complex among an enzyme, metal ion, and the substrate.[3] The first unequivocal demonstrations of the mediating action of metal ions in the binding of small molecules to proteins were provided by Klotz and Ming[4] and by Gurd.[5] Recently Mildvan and Cohn[6] in their kinetic studies of the pyruvate kinase reaction have made further important contributions to our understanding of the mode

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