Notes

X-ray Structure of $(NH_4)_6(Gly\text{-}Gly)_2V_{10}O_{28}\cdot 4H_2O$: Model Studies for Polyoxometalate−Protein Interactions†

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Introduction

Applications of polyoxometalates as drugs against herpes and AIDS have increased the interest in the association between polyoxometalate species and proteins.[1,2] Various oxometalates and polyoxometales are potent inhibitors for reverse transcriptase and other related enzymes (see review in ref 3). The anti-AIDS activity of this group of compounds has recently been associated with the ability to bind to the viral cell envelope and not to the inhibition of viral reverse transcriptase.[1,2] Whether the potent biological properties are a result of interactions with viral enzymes or with proteins in the viral cell envelope, understanding these interactions on a molecular level is important to the interpretation and the development of future compounds with selective affinity for particular proteins.

Recent studies with simple oxovanadates have shown significant differences with respect to the affinity of simple oxovanadates for a series of enzymes (see review in ref 3). Simple oxovanadates present in aqueous solution include the monomer ($H_2VO_4^-$, HVO_4^{2-}, VO_4^{3-}), dimer ($H_2V_2O_7^{2-}$, $HV_2O_7^{3-}$, $V_2O_7^{4-}$), tetramer ($V_4O_{12}^{4-}$), pentamer ($V_5O_{15}^{5-}$), and decamer ($H_2V_{10}O_{28}^{4-}$, $HV_{10}O_{28}^{5-}$, $V_{10}O_{28}^{6-}$).[4] Although not all of these vanadate oxoanions have been characterized by X-ray crystallography, these species must represent very different geometric arrangements.[5] Vanadate dimer has been found to be both an inhibitor and an activator for dehydrogenases, isomerases, aldolases, and phosphatases.[6] Vanadate tetramer inhibits dehydrogenases and aldolases.[6,7] Vanadate tetramer also appears to be the active species in photolytically induced cleavage of myosin at the phosphate binding sites, despite the fact that the tetramer only has a modest affinity for this protein.[8] Vanadate decamer shows high affinity for selected kinases, phosphorylase, and reverse transcriptase, as illustrated by its potent inhibition of phosphofructokinase.[9] Vanadate decamer has previously been used to facilitate crystallization of proteins, including the Ca^{2+}-transport ATPase and adenylate kinase.[10]

In spite of the importance of these interactions, no information is presently available regarding the interaction between peptides or proteins with any of these polyoxovanadates or other polyoxometalates at the molecular level. Weak hydrogen bond intermolecular interactions between simple organic substrates and the polyoxometalate species $H_3PMo_{12}O_{40}$ were previously described by Hill.[11] The present study provides new information regarding the structure of the compound $(NH_4)_6(Gly\text{-}Gly)_2V_{10}O_{28}\cdot 4H_2O$ (hereafter abbreviated as **1**), which is formed by the interaction between vanadate decamer and the simple dipeptide glycylglycine (Gly-Gly). It appears that modification of the dipeptide affects the polyoxoanion−dipeptide interaction, since a related complex between the decavanadate anion and glycylhistidine (Gly-His) has a different stoichiometry. The unambiguous structural characterization of the hydrogen bonding observed between Gly-Gly and the decavanadate anion based on unequivocal location of the hydrogen-bonding protons involved clearly illustrates that noncovalent interactions may be important in the interaction between polyoxometalates and proteins. The structure of **1** represents a model of how

† This paper is dedicated to the late Professor Margaret C. Etter.

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Table 1. Structural Details for **1**

$C_8H_{48}N_{10}O_{38}V_{10}$	fw = 1401.9
a = 10.094 (6) Å	space group: $P\bar{1}$ (No. 2)
b = 10.163 (6) Å	T = −100 °C
c = 11.399 (9) Å	λ = 0.7107 Å (Mo Kα)
α = 85.33 (6)°	ϱ_{calcd} = 2.26 g cm^{-3}
β = 79.48 (5)°	μ = 22.8 cm^{-1}
γ = 63.72 (5)°	R_1 = 0.0256 (on F, $I > 2\sigma(I)$)[a]
V = 1030.9 (12) Å^3	wR_2 = 0.085 (on F^2, all data)[b]
Z = 1	

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR_2 = [\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2}$.

polyoxometalates might interact with proteins and demonstrates that the most basic sites on the anion will, if possible, be involved in hydrogen bonding.

Experimental Section

Materials and Methods. The dipeptide salt Gly-Gly·HCl was purchased from Sigma and recrystallized from saturated aqueous solution at 45 °C by cooling to room temperature in air. Other reagent grade starting materials were purchased from Sigma or Aldrich and used without further purification. Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR. NMR spectra were recorded on a Bruker ACP-300 spectrometer operating at 300 MHz for ^{1}H and 79 MHz for ^{51}V. Microanalyses were performed by Desert Analytics (Tucson, AZ).

Preparation of $(NH_4)_6(Gly\text{-}Gly)_2V_{10}O_{28}\cdot 4H_2O$, 1. Decavanadate anion was prepared by adding hydrochloric acid (3 M) to a rapidly stirred solution of NH_4VO_3 (1.00 g, 8.55 mmol) in water (50 mL) to a final pH of 5.80. A solution (~15 mL) of recrystallized Gly-Gly·HCl (1.46 g, 8.69 mmol) was added to the rapidly stirred orange solution of decavanadate over a period of 5 min. The resulting mixture was stirred for 12 h at room temperature, after which a layer of ethanol (100 mL) was added. After 2 days at 4 °C, crystals suitable for study by means of X-ray diffraction were obtained. Supernatant liquid was removed by filtration and the crystals were washed twice with ethanol. Drying in air gave 0.98 g (82%) of **1**. IR (Nujol, cm^{-1}): 3511 (br), 3369 (br), 3175 (br), 1648 (m), 1566 (m), 1505 (m), 1312 (w), 1282 (w), 1252 (w), 1155 (w), 1089 (w), 1038 (w), 1012 (w), 977 (sh), 956 (sh), 941 (s), 895 (w), 880 (v. w), 814 (s, br). ^{51}V NMR (78.94 MHz, D_2O, 297 K): δ −423.0 (2V), −497.4 (4V), −513.7 (4V). ^{1}H NMR (300.1 MHz, D_2O, 297 K): δ 3.72 (s, 2H), 3.66 (s, 2H). Anal. Calcd for $C_8H_{48}N_{10}O_{38}V_{10}$: C, 6.85; H, 3.42; N, 9.98. Found: C, 7.05; H, 3.49; N, 9.97.

Preparation of $(NH_4)_2(Gly\text{-}His)_4V_{10}O_{28}\cdot 16H_2O$, 2. NH_4VO_3 (0.200 g, 1.71 mmol) was dissolved in 15 mL of water and the pH of the solution was adjusted to 5.75 with hydrochloric acid (3 M). Gly-His·HCl (0.440 g, 1.77 mmol) was dissolved in 8 mL of water at pH 5.80; the resulting solution was slowly added to the decavanadate solution. This solution was stirred for 2 days, after which a layer of ethanol (100 mL) was added. Yellow semicrystalline material was obtained after 3 days at 4 °C. Supernatant liquid was removed by filtration, and the product (0.23 g, 64%) was washed with ethanol and dried in air. IR (Nujol, cm^{-1}): 3540 (br), 3390 (br), 3220 (br), 3150 (br), 1679 (s) 1618 (m), 1579 (br), 1542 (sh), 1400 (sh), 1322 (s), 1264 (br), 1190 (sh), 1169 (s), 1109 (sh), 1090 (m), 941 (s), 980 (sh), 958 (s), 840 (m), 808 (m). ^{51}V NMR (78.94 MHz, D_2O, 297 K): δ −421.8 (2V), −498.6 (4V), −514.3 (4V). ^{1}H NMR (300.1 MHz, D_2O, 297 K): δ 3.16 (m, 2H), 3.91 (s, 2H), 4.60 (s, 1H), 7.32 (s, 1H), 7.89 (s, 1H). Anal. Calcd for $C_{32}H_{88}N_{18}O_{56}V_{10}$: V, 23.94; C, 18.03; H, 4.13; N, 11.83. Found: V, 24.40; C, 18.12; H, 3.53; N, 11.59.

X-ray Study of $(NH_4)_6(Gly\text{-}Gly)_2V_{10}O_{28}\cdot 4H_2O$, 1. Unit cell parameters were obtained from a least-squares fit to the automatically centered settings (graphite-monochromated Mo Kα radiation) for 25 reflections obtained from a yellow prism (0.24 × 0.36 × 0.20 mm^3) mounted on a Siemens P4 diffractometer. Those cell parameters, together with selected information related to the crystallographic experiment, are given in Table 1. During data collection ($\theta/2\theta$ scans, bisecting geometry) the intensities of three standard reflections were measured every 97 reflections; no significant changes in those intensities were seen. Semiempirical absorption corrections based on the variations of the intensities of selected reflections on rotation of the diffraction vector were applied to the data by using the program XEMP[12] (T_{min} = 0.72; T_{max} = 0.88).

Table 2. Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2 × 10^3) for **1**[a]

	x	y	z	U_{eq}
V1	1278(1)	4004(1)	3907(1)	8(1)
V2	−1104(1)	5282(1)	2286(1)	11(1)
V3	−3467(1)	7205(1)	4297(1)	10(1)
V4	−434(1)	7402(1)	3632(1)	9(1)
V5	−1839(1)	3828(1)	4666(1)	9(1)
O1	−3050(2)	7208(2)	5990(2)	11(1)
O2	−989(2)	5540(2)	4261(2)	8(1)
O3	1016(2)	3888(2)	2507(2)	11(1)
O4	−416(2)	6729(2)	2174(2)	12(1)
O5	−2452(2)	8392(2)	3961(2)	12(1)
O6	−1090(2)	4961(2)	939(2)	15(1)
O7	−3043(2)	6638(2)	2758(2)	11(1)
O8	−5190(2)	8394(2)	4446(2)	16(1)
O9	−1595(2)	3793(2)	3053(2)	12(1)
O10	−3615(2)	5469(2)	4831(2)	11(1)
O11	355(2)	2715(2)	4621(2)	9(1)
O12	1546(2)	5745(2)	3741(2)	9(1)
O13	−2360(2)	2543(2)	5043(2)	15(1)
O14	44(2)	8719(2)	3270(2)	15(1)
O21	3418(2)	−2060(2)	1893(2)	18(1)
O22	5377(2)	−3753(2)	−1034(2)	21(1)
O23	4339(2)	−1324(2)	−1191(2)	19(1)
N21	1982(3)	77(3)	3532(2)	15(1)
N22	5032(3)	−1151(2)	1030(2)	12(1)
C21	2945(3)	326(3)	2487(2)	16(1)
C22	3844(3)	−1076(3)	1778(2)	12(1)
C23	5918(3)	−2439(3)	274(2)	15(1)
C23	5139(3)	−2512(3)	−728(2)	14(1)
O31	11531(3)	1112(3)	−319(2)	31(1)
O32	8979(3)	1774(3)	1375(2)	30(1)
N41	6933(3)	1177(3)	3163(2)	19(1)
N42	7759(3)	3537(3)	9311(2)	18(1)
N43	5021(3)	4950(3)	7071(2)	16(1)

[a] U_{eq} is defined as one-third of the trace of the orthogonalized U_{ij} tensor.

The structure was solved by direct methods (TREF).[12] All atoms other than hydrogen were refined by using anisotropic thermal parameters. Neutral atom scattering factors with anomalous scattering contributions[13] were employed for all atoms. All structural calculations were performed by using the SHELXTL program library,[12] with the exception of the final refinement calculations, which were carried out by using SHELXL-93.[14]

Since hydrogen bonding was expected to be the controlling factor for interactions between the decavanadate anion, the Gly-Gly zwitterion, ammonium counterions, and occluded water molecules, particular attention was paid to the placement of hydrogen atoms in the structural model. Hydrogen atoms on the carbon atoms (C21, C23) and on the amide nitrogen atom (N22) of the Gly-Gly unit were placed in idealized positions with U_{iso} set at 1.2 U_{eq} for the non-hydrogen atom. The three hydrogen atoms of the protonated amino terminus of the Gly-Gly unit were located in an electron density map and refined as independent atoms with isotropic thermal parameters; since the result was roughly as expected for an alkylammonium group, the $-NH_3^+$ group was treated as an idealized rigid rotor in the final stages of least-squares refinement. All other hydrogen atoms were located in electron density maps and refined as independent atoms with isotropic thermal parameters.

Final atomic coordinates for **1** are given in Table 2, bond lengths and bond angles in Table 3, and interatomic distances and angles involving hydrogen bonded atoms in Table 4. Tables containing other results for **1** may be found in the supplementary material (Table S-I, crystal data and structure refinement; Table S-II, calculated and refined

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Table 3. Selected Bond Lengths (Å) and Bond Angles (°) for **1**[a]

Bond Lengths			
V1–O1*	1.684(2)	V4–O5	1.808(2)
V1–O3	1.687(2)	V4–O4	1.842(2)
V1–O12	1.894(2)	V4–O12	1.980(2)
V1–O11	1.969(2)	V4–O11*	1.999(2)
V1–O2	2.106(2)	V4–O2	2.231(2)
V1–O2*	2.115(2)	V5–O13	1.613(2)
V2–O6	1.591(2)	V5–O9	1.811(2)
V2–O7	1.835(2)	V5–O10	1.820(2)
V2–O4	1.872(2)	V5–O11	1.984(2)
V2–O9	1.895(2)	V5–O12*	2.003(2)
V2–O3	2.026(2)	V5–O2	2.242(2)
V2–O2	2.318(3)	O21–C22	1.242(3)
V3–O8	1.605(2)	O22–C24	1.243(4)
V3–O7	1.807(2)	O23–C24	1.256(4)
V3–O5	1.878(2)	N21–C21	1.475(4)
V3–O10	1.878(2)	N22–C22	1.315(4)
V3–O1	2.049(2)	N22–C23	1.456(4)
V3–O2	2.313(3)	C21–C22	1.510(4)
V4–O14	1.614(2)	C23–C24	1.523(4)

Interatomic Angles			
O1*–V1–O3	107.04(11)	O7–V2–O2	81.04(10)
O1*–V1–O12	98.73(10)	O4–V2–O2	78.20(9)
O3–V1–O12	98.95(10)	O9–V2–O2	77.71(9)
O1*–V1–O11	95.79(10)	O3–V2–O2	74.55(10)
O3–V1–O11	95.22(10)	O8–V3–O7	103.47(12)
O12–V1–O11	155.74(8)	O8–V3–O5	102.21(11)
O1*–V1–O2	165.14(8)	O7–V3–O5	92.18(10)
O3–V1–O2	87.53(11)	O8–V3–O10	102.50(11)
O12–V1–O2	81.44(9)	O7–V3–O10	91.57(10)
O11–V1–O2	79.60(9)	O5–V3–O10	153.38(9)
O1*–V1–O2*	87.59(11)	O8–V3–O1	100.30(11)
O3–V1–O2*	164.98(8)	O7–V3–O1	156.22(9)
O12–V1–O2*	81.71(9)	O5–V3–O1	83.38(9)
O11–V1–O2*	79.59(9)	O10–V3–O1	82.63(10)
O2–V1–O2*	77.71(10)	O8–V3–O2	174.74(9)
O6–V2–O7	102.86(11)	O7–V3–O2	81.77(10)
O6–V2–O4	104.37(11)	O5–V3–O2	77.04(9)
O7–V2–O4	91.43(10)	O10–V3–O2	77.44(9)
O6–V2–O9	99.33(11)	O1–V3–O2	74.46(10)
O7–V2–O9	89.46(10)	O14–V4–O5	101.65(11)
O4–V2–O9	155.45(9)	O14–V4–O4	102.90(11)
O6–V2–O3	101.48(11)	O5–V4–O4	94.50(11)
O7–V2–O3	155.57(8)	O14–V4–O12	100.57(11)
O4–V2–O3	84.61(10)	O5–V4–O12	155.54(9)
O9–V2–O3	84.50(10)	O4–V4–O12	90.37(11)
O6–V2–O2	175.16(9)	O14–V4–O11*	99.43(10)
O5–V4–O11*	89.46(10)	V1–O2–V5	94.23(9)
O4–V4–O11*	156.01(9)	V1*–O2–V5	92.10(8)
O12–V4–O11*	76.91(10)	V4–O2–V5	169.77(9)
O14–V4–O2	175.14(9)	V1–O2–V3	170.00(9)
O5–V4–O2	80.58(9)	V1*–O2–V3	87.67(9)
O4–V4–O2	81.12(9)	V4–O2–V3	86.30(8)
O12–V4–O2	76.51(9)	V5–O2–V3	86.16(8)
O11*–V4–O2	76.19(9)	V1–O2–V2	87.29(9)
O13–V5–O9	102.23(11)	V1*–O2–V2	170.35(9)
O13–V5–O10	102.33(11)	V4–O2–V2	86.18(8)
O9–V5–O10	94.83(11)	V5–O2–V2	86.01(8)
O13–V5–O11	100.47(10)	V3–O2–V2	82.77(9)
O9–V5–O11	90.87(10)	V1–O3–V2	110.58(11)
O10–V5–O11	154.72(9)	V4–O4–V2	113.66(11)
O13–V5–O12*	99.65(10)	V4–O5–V3	114.93(11)
O9–V5–O12*	156.49(9)	V3–O7–V2	114.41(12)
O10–V5–O12*	88.78(11)	V5–O9–V2	114.16(11)
O11–V5–O12*	76.72(10)	V5–O10–V3	114.52(11)
O13–V5–O2	175.09(9)	V1–O11–V5	107.44(10)
O9–V5–O2	81.42(9)	V1–O11–V4*	107.10(10)
O10–V5–O2	80.48(9)	V5–O11–V4*	99.80(10)
O11–V5–O2	76.05(9)	V1–O12–V4	107.33(10)
O12*–V5–O2	76.27(9)	V1–O12–V5*	107.19(10)
V1*–O1–V3	110.26(11)	V4–O12–V5*	99.80(11)
V1–O2–V1*	102.29(10)	C22–N22–C23	119.7(2)
V1–O2–V4	92.00(9)	N21–C21–C22	109.8(2)
V1*–O2–V4	94.50(9)	O21–C22–N22	123.6(3)
O21–C22–C21	119.9(2)	O22–C24–O23	125.4(3)
N22–C22–C21	116.5(2)	O22–C24–C23	116.8(2)
N22–C23–C24	113.1(2)	O23–C24–C23	117.7(2)

[a] An asterisk denotes the following symmetry transformation used to generate equivalent atoms: $-x, -y + 1, -z + 1$.

hydrogen atom coordinates; Table S-III, anisotropic displacement parameters; Table S-IV, hydrogen atom distances).

Table 4. Interatomic Distances (Å) and Angles (deg) Involving Hydrogen-Bonded Atoms in Crystals of **1**[a]

Distances			
H21B···O11	1.799(3)	N42···O4*	2.812(4)
N21···O11	2.707(4)	H42D···O32*	2.14(4)
H21C···O13*	2.24(1)	N42···O32*	2.945(5)
N21···O13*	2.914(4)	H42C···O21*	1.97(4)
H21C···O8*	2.166(5)	N42···O21*	2.839(4)
N21···O8*	2.938(4)	H43A···O22*	1.85(4)
N21···O14*	2.914(3)	N43···O22*	2.775(4)
H41C···O5*	1.94(4)	H43C···O10*	1.91(4)
N41···O5*	2.731(4)	N43···O10*	2.799(4)
H41A···O13*	2.26(4)	H43B···O21*	2.08(4)
N41···O13*	2.992(4)	N43···O21*	2.919(4)
H41B···O23*	1.92(4)	H31A···O4*	2.12(5)
N41···O23*	2.748(4)	O31···O4*	2.912(4)
H41D···O32	2.03(4)	H31B···O23*	2.15(5)
N41···O32	2.857(4)	O31···O23*	2.882(4)
H42B···O22*	1.99(4)	H32A···O31	1.93(5)
N42···O22*	2.798(4)	O31···O32	2.770(4)
H42A···O4*	1.91(4)	H32B···O9*	1.88(5)
		O32···O9*	2.718(4)

Angles			
N21···H21B···O11	174.4(3)	N42···H42D···O32*	153(4)
N21···H21C···O13*	131(1)	N42···H42C···O21*	168(4)
N21···H21C···O8*	142.1(6)	N43···H43A···O22*	167(3)
N21···H21A···O14*	161.4(8)	N43···H43C···O10*	174(4)
N41···H41C···O5*	178(4)	N43···H43B···O21*	162(3)
N41···H41A···O13*	145(4)	O31···H31A···O4*	162(4)
N41···H41B···O23*	152(3)	O31···H31B···O23*	152(5)
N41···H41D···O32	154(4)	O31···H32A···O32	160(4)
N42···H42B···O22*	164(4)	O32···H32B···O9*	161(4)
N42···H42D···O4*	167(4)		

[a] The positions of atoms marked with asterisks were symmetry transformed from the position indicated in Table 2 to give the interaction shown.

Results and Discussion

Synthesis, Formulation, and Solution Properties of 1. The vanadate decamer forms readily in acidic solution and has been well characterized both in solution and in the solid state.[5,15] Mixing a solution of vanadate decamer and a solution of Gly-Gly·HCl yielded crystalline material characterized as **1** (see above). With respect to the formulation of this product, the C–O distances observed (see Table 3) for the Gly-Gly carboxylate group are in the range for deprotonated carboxylates, suggesting that the dipeptide is present as a zwitterion in **1**. If the overall charge of Gly-Gly is thus taken to be zero, the best formulation of **1** consistent with the elemental analysis and mass and charge balance would be $(NH_4)_6$(Gly-Gly)$_2V_{10}O_{28}\cdot 4H_2O$. This formulation is also consistent with the results of the X-ray structure determination (see below). The IR spectrum is similar to that reported for other hexaanionic decavanadate compounds.[5q,5r]

^{51}V NMR spectroscopy of an aqueous solution of **1** showed three resonances at −422, −498, and −514 ppm. These signals are in the range reported previously for vanadium atoms in the decavanadate unit.[5q,r] Attempts were made to observe an interaction between the dipeptide and decavanadate in solution. No changes in the ^{51}V and ^{1}H NMR spectra were observed as a function of complex and dipeptide concentration in aqueous solution. The insolubility of **1** in CH_3CN, CH_2Cl_2, $CHCl_3$, acetone, DMF, DMSO, and THF precluded studies of **1** in these solvents. Preparation of an aqueous solution of **1** followed by addition of up to 40% DMF, CH_3CN, and acetone further showed no evidence for interaction. We conclude that anion interactions with the dipeptide are broken upon dissolution.

Structure of 1. Figure 1 shows the structure and labeling scheme of the decavanadate anion, while Figure 2 shows the hydrogen-bonding interactions involving the decavanadate anion,

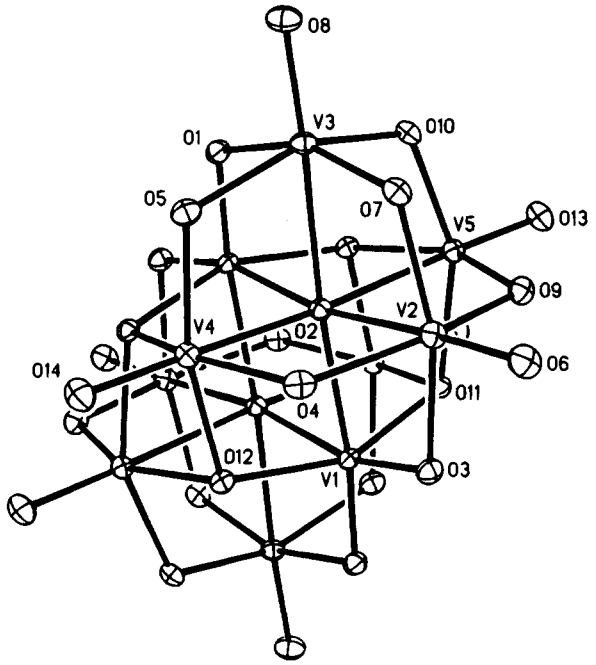

Figure 1. Structure and labeling scheme for the polyoxovanadate anion in **1**.

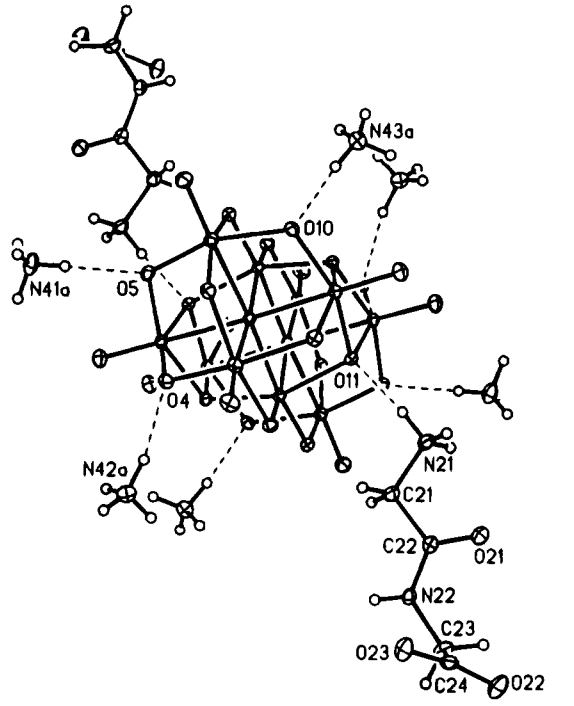

Figure 2. Drawing of a portion of the structure of **1**. Hydrogen bonds between the polyoxovanadate anion, the cations, and the Gly-Gly zwitterion are indicated by dashed lines.

the Gly-Gly unit, and the ammonium counterions. Selected bond lengths and bond angles involving these species are listed in Table 3. As a result of crystallization in space group $P\bar{1}$ with only one formula unit in the asymmetric unit of the unit cell, crystallographic $\bar{1}$ (C_i) symmetry is imposed on the entire complex unit. The bond angles and distances observed for the $V_{10}O_{28}^{6-}$ unit indicate that the geometry is quite similar to that found in previously reported structures of decavanadate salts.[5q,r] The observation of the interactions between the decavanadate anion and the associated NH_4^+ ions and zwitterionic Gly-Gly unit are the most interesting aspects of this structure.

In addition to the NH_4^+ cations and the associated Gly-Gly units, the unit cell also contains four water molecules. No difficulty was encountered in assigning hydrogen atoms to the water molecules and the ammonium ions during the structure solution process; as a result, no disorder involving the water molecules and the ammonium ions occurs in this structure.

The structure of the associated Gly-Gly dipeptide is similar to those of other zwitterionic amino acids and oligopeptides, which typically exhibit C−O(carboxylate) distances of ~1.25 Å[15] (cf. C24−O22 = 1.243(4) Å and C24−O23 = 1.256(4) Å in **1**). The magnitude and equality (within experimental error) of these two C−O distances thus clearly indicate that the carboxylate group is not protonated.

The bond angles in the Gly-Gly unit also compare favorably with corresponding parameters for free zwitterionic oligopeptides.[16] The angle C22−N22−C23 (119.7(2)°) is slightly (~2.5°) larger than normal in **1**, while the angle N22−C23−C24 (113.1(2)°) is slightly (~2°) smaller than normal. These changes may be the result of the interaction between the Gly-Gly unit and the decavanadate anion (see below). The dihedral angle (91.1°) between the plane of the peptide group (N22−C22−O21) and the plane of the carboxylate group (O22−C24−O23) is normal.[16]

In the prototypical structure described by Hill et al.,[11] hydrogen bonding was inferred from heavy atom distances. In the present study, all hydrogen-bonding protons were located and refined to fully reveal hydrogen bonding patterns. The water molecules and ammonium ions interact with the decavanadate anion via hydrogen bonding, as expected (see Table 4).[17] Each of the ammonium ions forms a hydrogen bond with a doubly bridging oxygen atom of the decavanadate anion (N41···O5 = 2.731(4) Å, H41C···O5 = 1.94(4) Å; N42···O4 = 2.812(4) Å, H42A···O4 = 1.91(4) Å; N43···O10 = 2.799(4) Å, H43C···O10 = 1.91(4) Å). Simultaneously, the protonated amino terminus of the Gly-Gly dipeptide forms a hydrogen bond to a triply bridging oxygen atom (N21···O11 = 2.707(4) Å, H21B···O11 = 1.799(3) Å. The Gly-Gly dipeptide actually links adjacent decavanadate units, as a result of hydrogen bonding involving the oxygen atoms of the carboxylate terminus and ammonium ions (not shown in Figure 2; see Table S-IV for details).

The hydrogen bonding interaction between N21 and O11 indicates the presence of higher electron density on the triply bridging oxygen atom. By using ^{17}O NMR and ^{51}V NMR spectroscopy.[5r,18] Day and Klemperer found that triply (Ob) and doubly (Od) bridging oxygen atoms are more basic than terminal oxygen atoms, and that in turn Ob sites are more basic than Od sites. Kempf et al.[19] confirmed that the triply bridging oxygen atoms are more basic than the doubly bridging oxygen atoms by means of *ab initio* and electrostatic potential calculations. Our unambiguous location of hydrogen bonds in the present structure is thus in accord with both experimental and theoretical predictions regarding the basicity of oxygen sites on the vanadate decamer.

Other studies have reported interactions between cations and the oxygen atoms of the decavanadate anion. Micheng et al. observed hydrogen bonding interaction between the 4-ethylpyridinium cation and decavanadate ion that involved doubly and

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triply bridging oxygen atoms.[5n] Very weak hydrogen bonding interactions between guanidinium ion and singly and doubly coordinated oxygen atoms in decavanadate anion have also been observed (O···N = 2.984 Å (terminal O) and 2.970 Å (doubly bridging O).[5v] Selected metal ions such as Na^+ and Ca^{2+} have been found to interact with singly coordinated oxygen atoms, without interacting with triple coordinated oxygen atoms.[5f,j] The H bonds observed in the current structure presumably reflect the flexibility in the Gly-Gly dipeptide in generating those H bonds that are most favorable.

Characterization of 2. Compound **2** was obtained in microcrystalline form and characterized by spectroscopic and elemental analysis. If we assume that the overall charge of the dipeptide in **2** is +1, the formulation most consistent with elemental analysis and mass/charge balance is $(NH_4)_2$(Gly-His)$_4V_{10}O_{28}$·$16H_2O$. Of course, compound **2** varies from **1** in that the second amino acid residue, His, of the dipeptide contains an imidazole functionality where the dipeptide in **1** had a hydrogen atom. Recent structural characterization of a mononuclear vanadium complex of a histidine derivative, shows the protonated imidazole in the histidine and a complex intermolecular H bonding between vanadium complexes.[20] Protonation of the imidazole moiety in vanadium complexes has thus been documented[20] in addition to N-coordination of imidazole derivatives.[21] The overall charge of the dipeptide and its hydrogen-bonding possibilities is dependent on the protonation of the imidazole functionality, and thus, a different stoichiometry of **2** is reasonable. The higher number of water molecules in **2** presumably goes hand in hand with these changes in structure, stoichiometry, and hydrogen-bonding possibilities.

Biological Implications. Vanadate species, including monomer, dimer, tetramer, and pentamer, are labile under physiological conditions, as are the derivatives that have been obtained from these species.[22] Vanadate decamer is significantly less labile at neutral pH, as are derivatives of this polyoxoanion.[23] Vanadate–peptide complexes have been previously characterized in aqueous solutions by using spectroscopic methods, but very little structural information is available for these types of materials.[24] Furthermore, it is not clear whether oxometalates interact with proteins by forming covalent or noncovalent derivatives. This study has shown that vanadate decamers can form complexes with peptides through the most basic functionalities. Furthermore, the very different stoichiometry observed when Gly-His is substituted for Gly-Gly suggests that these types of interactions will vary significantly with the amino acid sequence and the charge on the protein.

The promotion of crystallization that takes place when vanadate interacts with the adenylate kinase and Ca^{2+}-transport ATPase[10] presumably reflects a slight change in folding pattern that allows crystallization of this protein. Vanadate decamer strongly inhibits adenylate kinase, and it has been suggested that this interaction is due to the highly charged active site of this enzyme.[10a] The cAMP-dependent protein kinase is also inhibited by vanadate decamer,[25] but in this case the inhibition appears to be caused by complex formation between vanadate decamer and the kemptide substrate. The interaction that has been illustrated in the solid state for compound **1** was found to be sensitive to amino acid composition of the dipeptide. It now appears likely that variations in peptide sequence will change the interactions between oxoanions and peptides or proteins.

Conclusion

A decavanadate–dipeptide complex has been structurally characterized. The dipeptide was found to bridge between decavanadate molecules by means of hydrogen bonding. Modifying the dipeptide from Gly-Gly to Gly-His altered the interactions between the decavanadate and the peptide significantly. This study illustrates the importance of the noncovalent interactions between a dipeptide and decavanadate and provides the first structural characterizations between oxometalates and peptidic compounds.

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Supplementary Material Available: Table S-I, crystal data and structure refinement; Table S-II, calculated and refined hydrogen atom coordinates; Table S-III, anisotropic displacement parameters; and Table S-IV, hydrogen atom distances (5 pages). Ordering information may be found on any current masthead page.

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