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► **To cite this version:**

N. Bosnjakovic - Pavlovic, Josselin Prevost, A. Spasojevic-De-Biré. Crystallographic Statistical Study of Decavanadate Anion Based-Structures: Toward a Prediction of Noncovalent Interactions. *Crystal Growth & Design*, 2011, 11 (9), pp.3778-3789. 10.1021/cg200236d . hal-00633676

HAL Id: hal-00633676

<https://hal.science/hal-00633676v1>

Submitted on 24 Sep 2020

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Journal:	<i>Crystal Growth & Design</i>
Manuscript ID:	cg-2011-00236d.R1
Manuscript Type:	Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Bošnjaković-Pavlović, Nada; Ecole Centrale Paris, Laboratoire Structures, Propriétés et Modélisation des Solides (SPMS), UMR CNRS 8580; University of Belgrade, Faculty of Physical Chemistry Prévost, Josselin; Ecole Centrale Paris, Laboratoire Structures, Propriétés et Modélisation des Solides (SPMS), UMR CNRS 8580; University of Belgrade, Faculty of Physical Chemistry Spasojevic - de Biré, Anne; Ecole Centrale Paris, Laboratoire Structures, Propriétés et Modélisation des Solides (SPMS), UMR CNRS 8580

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Crystallographic statistical study of decavanadate anion based-structures: toward a prediction of noncovalent interactions

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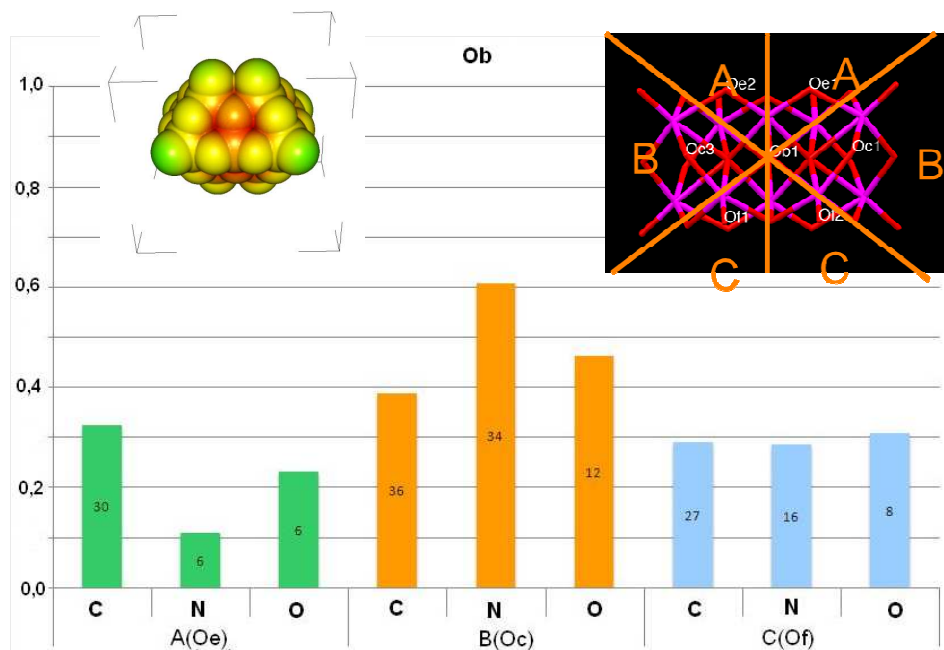
ABSTRACT

We have retrieved from the Cambridge Structural Database (CSD), the Inorganic Crystal Structure Database (ICSD) and the Protein Data Bank (PDB) decavanadate based compounds, in order to find intermolecular interactions between decavanadate oxygen atom and different proton donor type (D = O, N, C). 63 different structures have been found containing decavanadate anion, leading to 2975 intermolecular contacts belonging to the 48 structures for which the hydrogen bonds have been localised. In a previous study, (Bosnjakovic-Pavlovic *et al.*, Inorg. Chem., 2009) we have predicted the preferential noncovalent interactions with the different oxygen atoms of the decavanadate anion. These predictions are confirmed, in the present study. Noncovalent interactions are strongly different as a function of the oxygen atom type. The Ob, triply-linked, and Oc, double-linked oxygen atoms, for which the electrostatic potential in the vicinity have the lowest value, are mainly involved in the strong as O-H...O, N-H...O interactions, while the mono linked Of or Og are mainly involved in weakest noncovalent interactions such as C-H...O or cation interactions. Binding properties of decavanadate anion in biological systems are illustrated using PDB. Anion binding behaviour in small-molecule structures and in macromolecular structures is in good agreement.

These results are important in the context of the various biological applications of the decavanadate such as, for example, inhibition of the Ca²⁺ ATPase, myosin ATPase, and new development in insulin mimetic.

Graphical abstract

We have performed a crystallographic statistical study of decavanadate anion based-structures focalising on O-H...O, N-H...O and C-H...O noncovalent interactions from (Cambridge Structure Database) CSD, Inorganic Crystallographic Structure Databank (ICSD) and Protein Data Bank (PDB) bases. The noncovalent interactions are strongly different depending on the decavanadate oxygen atom type. The Ob and Oc oxygen atoms are mainly involved in the strong O-H...O, N-H...O while Of or Og are mainly involved in weakest hydrogen bonds such as C-H...O or cation interactions.



1. Introduction

Investigations of the interactions of the decavanadate (V_{10}) with peptides or proteins, which play fundamental role in biological systems, have been a subject of growing interest in recent years. It has been documented that these interactions are important since that the biological properties of V_{10} result from interactions with viral enzymes or viral cell envelopes. The understanding of these interactions at a molecular level is essential for the interpretation and the development of potent compounds with selective enzymatic affinity.

V_{10} has been referred of biochemical importance and is considered belonging to the major protein-bound species.¹ For example, recent studies demonstrated that, after one and seven days of *in vivo* administration, V_{10} , when compared to other oligomers, species, induces different effects on anti-oxidant enzymes, lipid peroxidation, subcellular vanadium distribution and tissue damage in liver, kidney and heart.²⁻³ However, its presence in significant amounts can be explained by the existence of special cell compartments where vanadium can be accumulated and preserved from decomposition acting as a protective “cage”. Aureliano *et al.* have formulated the hypothesis that mitochondria might be a target for V_{10} .⁴ Recently, *in vivo* studies demonstrate that in mitochondria, where vanadium was shown to accumulate,^{2,5,6} nM concentration of V_{10} induces membrane depolarization,⁷ inhibition of oxygen consumption,⁸ necrotic cell death,⁹ inhibition of extracellular matrix (ECM) mineralization.¹⁰ Willsky *et al.* propose that V_{10} forms in the acidic compartment analogous to lysozyme in cells treated with

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3 vanadate, and ultimately is extruded into the medium.¹¹ They confirm the possibility that
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5 V_{10} form intracellularly. It has also been reported that V_{10} inhibits or activates proteins.¹²⁻
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²⁹ These studies have shown that V_{10} membranes targets are channels³⁰⁻³² and
metabotropic receptors³³ but are also pumps such as Ca^{2+} ATP-ase.³⁴

While the inhibition of enzymes by POV's has been well documented, the primary
mechanism for biological activity remains elusive. Investigations of POM's in the
presence of enzymes and proteins have provided additional information on their mode of
action. The pioneer studies on the interaction between decavanadate and proteins were
performed with ribonuclease, in 1973.³⁵ Crans³⁶ and co-worker first have structurally
characterized a decavanadate - dipeptide complex. Noncovalent interactions have been
investigated through combined crystallographic, spectroscopic, and enzymatic studies
with mutant as well as wild-type enzymes.³⁷⁻⁴¹ Meicheng *et al.* observe hydrogen bonding
interaction between the 4-ethylpyridinium cation and the decavanadate ion that involves
doubly and triply oxygen atoms.⁴⁰ Very weak hydrogen bonding interactions between
guanidinium ion and singly and doubly coordinated oxygen atoms in decavanadate
anions have also been observed.⁴¹ At a molecular level the mechanism of action is played
via noncovalent interactions between the V_{10} anion and the biological target.

From a geometric point of view, the $[V_{10}O_{28}]^{6-}$ anion is represented in Figure 1.
Due to the complexity of the structure, it is necessary to characterize precisely the
different environment of oxygen and vanadium atoms. If we classified the oxygen atoms
according to their vanadium coordination, four type of oxygen atoms are involved in this
anion: O1x - bonded to only one vanadium atom; O2x - shared between two vanadium
atoms; O3x - shared between three vanadium atoms. O6x - have a six-fold coordination

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3 of vanadium atom. Considering now different vanadium atoms, there are three types: type
4 I, type II and type III, (Figure 1b). Thus, oxygen atoms have to be classified in subtypes
5 according to new labels (type a, b, c, d, e, f, and g). In a previous study,⁴² we have
6 experimentally determined the electron and electrostatic properties of
7 $\text{Na}_3\text{V}_{10}\text{O}_{28}(\text{C}_4\text{N}_3\text{OH}_5)_3(\text{C}_4\text{N}_3\text{OH}_6) \cdot 10\text{H}_2\text{O}$ and we have analyzed carefully the hydrogen
8 bonding network between V_{10} anion and other part in structure. Crystal structure of the
9 title compound is stabilized by an extensive hydrogen bonding network, which involved
10 the V_{10} anions, cytosine and water molecules. V_{10} anion is able to accept all type of
11 proton donor (oxygen, nitrogen and carbon) letting the structure containing several
12 varieties of intermolecular interactions, such as $\text{O-H}\cdots\text{O}$, $\text{N-H}\cdots\text{O}$, $\text{C-H}\cdots\text{O}$. The main
13 result of this study is that the noncovalent interactions are strongly different depending on
14 the oxygen atom type. The O_b and O_c oxygen atoms, are involved mainly in the strong
15 $\text{O-H}\cdots\text{O}$, $\text{N-H}\cdots\text{O}$, while O_f or O_g are mainly involved in weakest hydrogen bonds such
16 as $\text{C-H}\cdots\text{O}$ or cation interactions. We have determined the molecular electrostatic
17 potential in order to visualize nucleophilic molecular regions and we have found that the
18 most negative region of the electrostatic potential takes place in the vicinity of O_b and O_c
19 atoms. Similar results have been previously found from *ab initio* theoretical calculations
20 performed for an isolated $[\text{V}_{10}\text{O}_{28}]^{6-}$ anion.⁴³⁻⁴⁶ Therefore, the most basic accessible sites
21 for protonation are oxygen atoms of type b and c.

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Analysis of interactions between V_{10} and organic part using the Cambridge
Structural Data Base (CSD)⁴⁷ can provide structural evidence for the role of the anion.
Hydrogen bonds and their environment have a well defined geometry in the crystalline
state. CSD provides a large amount of experimental data that allows hydrogen bonds

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3 geometries to be analyzed at a high statistical level,⁴⁸ and therefore CSD is a major
4 source of knowledge on intermolecular interactions of all types. CSD have been used
5 extensively in studies of common strong hydrogen bond having oxygen or nitrogen as
6 donors and acceptors.⁴⁹⁻⁵⁴ Nowadays, the noncovalent interactions studies take two
7 directions: i) the study of weak hydrogen bonding; major contribution of CSD analysis
8 have been to support in identification of short C-H...O contacts as hydrogen bonds⁵⁵⁻⁵⁶ or
9 C-H... π interaction,⁵⁷⁻⁵⁸ ii) an increasing interest in the energy crystal landscape.⁵⁹⁻⁶²

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20 Ferreira da Silva *et al.*,⁶³ published a survey concerning the donor-acceptor
21 intermolecular interactions for the compounds containing the $[H_nV_{10}O_{28}]^{6-n}$ anion, based
22 on a CSD. They systematised the solid-state supramolecular motifs in order to understand
23 the key factors determining the crystal packing of V_{10} . They have concluded that crystal
24 lattice packing in the solid state packing are closely related to the anion interaction with
25 organic molecules, cations and / or water molecules. The three-dimensional
26 supramolecular structure is formed by a network of N-H...O, O-H...O and C-H...O
27 hydrogen bonds, in which the cations, anions and water molecules are involved. When
28 the V_{10} are unprotonated and the cations are small, columbic interaction with inorganic
29 cation and hydrogen bonds with organic cations and water molecules play an important
30 role. Cations act as bridging atoms between the layers, forming the three-dimensional
31 array.
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49 According to our previous paper, we have ranked the oxygen atoms from the most
50 negative to the less negative (Ob, Oe, Oc, Od, Of and Og). The question, which arises, is
51 the following: can we correlate this observation with the preferential noncovalent
52 interactions which occurs in the different compounds for which the crystal structure is
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3 known? That means, is there any preferential interaction depending of the V_{10} different
4 oxygen? Thus, the aim of this statistical study is to correlate the predictions with the
5 observations in different V_{10} based structures and therefore to study if there are some
6 trends in these interactions, according to the donor or the oxygen atom, or on the
7 contrary, if there is no trend.
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18 We have performed a statistical study on the O-H...O, N-H...O and C-H...O
19 noncovalent interactions for structures which contain V_{10} anion, from (Cambridge
20 Structure Database) CSD⁴⁷, Inorganic Crystallographic Structure Databank (ICSD)⁶⁴ and
21 Protein Data Bank (PDB)⁶⁵ bases and from crystallographic structures not included in
22 these three crystallographic databases.^{42,66} We have investigated these interactions
23 depending of the oxygen type of decavanadate: Ob, Oc, Od, Oe, Of and Og. We have
24 founded 2975 contacts: 866 O-H...O interactions, 889 N-H...O and 1220 C-H...O
25 interactions. This paper presents an analysis of the interactions according to the following
26 parts: i) general analysis of the geometry of hydrogen bond; ii) a study of the influence of
27 different binding type according to the different oxygen atoms type, proton type, ..., iii)
28 and finally, a comparative analysis with macromolecular structures. Binding properties of
29 V_{10} anion in biological system are illustrated using PDB.
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49 **2. Methods**

50 **2.1. CSD**

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53 The CSD⁴⁷ was searched for compound containing V_{10} anion and retrieved
54 depending on the oxygen type Ob, Oc, Od, Oe Of and Og (30 structures found).⁶⁷ Con
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3 Quest⁶⁸ software was used to search intermolecular contacts. The searches were restricted
4 to entries with: a) error-free coordinate sets in CSD check procedures; b) no
5 crystallographic disorder; c) no polymeric connections, d) crystallographic R factor lower
6 than 0.10 and e) protons were placed at their normalized position. For each interaction,
7 we have determined the D-H...O distance and angle. The search reveals interactions
8 which are shorter than the sum of the van der Waals radii. The 33 structures found are
9 listed in Table 1. In bold those (30) where the proton was localized.

20 21 **2.2. ICSD**

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23 The ICSD⁶⁴ was searched for compound containing V₁₀ anion. The Mercury
24 software has been used to determine the geometry of the 14 structures found for which
25 the proton was localized.^{66, 69a-k}

30 31 32 **2.3. PDB**

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34 To compare the small molecule results with those from macromolecular
35 structures, the PDB⁶⁵ was searched for V₁₀...H-donor interactions. The enzyme-
36 decavanadate complexes were found through a PDB search using the 'decavanadate'
37 keyword. 3 structures were found. We have investigated the intermolecular interactions
38 between the decavanadate anion and the protein structure. Molekel software⁷⁰ has been
39 used to visualize some results.

50 51 **3. Results and discussion**

52 **3.1 Geometrical description**

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3 From the electrostatic potential (EP) values, we have predicted the preferential
4 non-covalent interactions (Figure 2) with the different oxygen atoms of the V_{10} anion.⁴²
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6 The strongest interactions take place in the most negative electrostatic potential region
7 (the red part), and the weakest interactions in the less negative region (the blue part). This
8 scheme does not mean that there is no interaction of N-H...O type at the Of or Og site, it
9 means, that the strongest interactions take place preferentially at the Ob and Oc site and
10 the weakest at the Of and Og site.
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20 Figure 3 represents the D...O distance and the D-H...O angle distribution where
21 D...O distance is less than 3.5 Å (D is the donor atom). 866 O-H...O interactions has been
22 analyzed. The O...H distances show an accumulation between 1.7 and 2.2 Å (Figure 3a)
23 and another lower peak at about 2.6 Å, while the D-H...O angle exhibits values between
24 150 and 180° (Figure 3b). Preference for linearity in the O-H...O case has been assessed
25 by analyzing the distribution of angle.⁴⁸ The percentage of short O...O interactions (about
26 48%) found for the first peak (at lower distance) could be taken as an indicator of the
27 strength of this interaction type. Statistically, one can observe two peaks of O...O
28 interactions a strong one and a weaker one. 889 N-H...O interactions show wide variation
29 in N...O distances as well as significant variation in the angle (Figure 3c and 3d). The
30 geometry of C-H...O interactions is analyzed using 1220 interactions from 32 crystal
31 structures. All these interactions follow the trend expected for hydrogen bonds, namely
32 for C-H...O angle opens up as the distance between donor and acceptor increases. C-
33 H...O interactions are mainly at long distance (2.4 to 3.0 Å) and angle from 110 to 160°.
34 In term of angularity, all these interactions follow the trend expected for hydrogen
35 bonds.⁵⁶
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4 In order to go deeply in a geometrical parameter description, the relationship
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6 between D...O and D-H...O is drawn in Figure 4 according to the V_{10} different oxygen
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8 types which are represented in different color (from red to blue). These colors correspond
9
10 to the color used for visualization of electrostatic potential values at the V_{10} molecular
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12 surface (Figure 2). O-H...O noncovalent interactions (Figure 4a) for the oxygen Ob, Oc
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14 and Od are mainly at a short length (1.7 to 2.1 Å) and high angles (140 to 180°) whereas
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16 for Of and Og, interactions are at longer distances (2.3 to 3.0 Å) and smaller angles (90 to
17
18 100°). The same observations can be made for the N-H...O interactions (Figure 4b) in a
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20 less pronounced way. Concerning the C-H...O interactions there is no particular trend
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22 according to the type of the oxygen of V_{10} but the interactions are mainly at long distance
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24 (2.3 to 3.0 Å) and angle from 100 to 160° (Figure 4c). It is therefore clear, that the
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26 directionality of the noncovalent interaction depends on the oxygen atom type. Ob and
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28 Oc oxygen atoms induce strong directionality for O-H...O and N-H...O interactions with
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30 short distances and high angle. Of and Og can form O-H...O and N-H...O interactions but
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32 with very long distances (2.3 - 2.7 Å) and with smaller angle (100 to 140°). This explains
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34 the two peaks observed in Figure 3 for O...O and a wider dispersion for N...O interaction.
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45 3.2. V_{10} binding

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47 Figures 3 and 4 have revealed geometrical characteristics in noncovalent
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49 interactions according to the donor or the V_{10} oxygen atom type. The next step consists
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51 on focalising on the binding of each V_{10} oxygen atom type. In Figure 5, 2061 interactions
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53 with O-H...O or N-H...O $< 145^\circ$ have been rejected in order to conserve those which are
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55 significant. This cut-off value has been chosen according to the existence of hydrogen
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3 bonds Bond Critical Point in charge density studies of V_{10} structures.⁴² Figure 5a
4 represents the ratio of each type of O-H...O, N-H...O and C-H...O interactions, after
5 normalization by the number of each type of interactions, for a corresponding O_{dv}
6 oxygen. For example, for Ob and Oc, O-H... O_{dv} and N-H... O_{dv} interactions represents
7 about 80% of the interactions whereas for Oe and Og, they represent only about 50%. It
8 is in agreement with the fact that Ob and Oc induce hydrogen bonds with strong
9 directionality, which is not the case for Of and Og. In order to describe more precisely the
10 interactions, we have to take into account that the different V_{10} oxygen atom types have
11 not the same occurrence in the anion structure. For example, a noncovalent interaction
12 has two times more probability to take place with an Oc atom than an Ob (Figure 1).
13 Within this normalization, Figure 5b indicates that C-H... O_{dv} interactions are more
14 frequent for each type (from 40% to 75%) and N-H... O_{dv} interactions are less frequent
15 (28 to 5%). Ob or Oc are more polyvalent than Of or Od. Finally, one has to take into
16 account the nature of the donor molecules. Therefore, we have counted for each structure,
17 the possibility of each molecule to take part in a D-H... O_{dv} interaction, and normalized by
18 using this value (Figure 5c). This graph is nearly the same as the one with only
19 normalization by the occurrence of each O_{dv} , but predominance of C-H... O_{dv} interactions
20 is less high. It shows that for a same number of possible non covalent bond for a given
21 structure, carbon atom makes more noncovalent interactions than oxygen or nitrogen
22 atom. Oxygen and nitrogen atoms are similar, but nitrogen makes a little more
23 noncovalent interactions than oxygen atom for a same number of bonds. This graph also
24 indicates that Ob and Oc are polyvalent (each type of interactions are represented in
25 similar proportions), but Oe and Og have more contacts from C-H...O type (65-70%)
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3 while Od and Of have about 55% of C-H...O interactions. Once again it is in agreement
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5 with the type of interaction made by carbon (not strong) and by oxygen and nitrogen
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7 (stronger), while the Of behaviour seems to be an exception.
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10 11 12 **3.3. Multifurcated hydrogen bonds and mutiacceptor oxygen** 13

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15 Another interesting point of the description of the noncovalent interactions with a
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17 V_{10} anion is the number of interactions *per* hydrogen (multifurcation). Contacts with an
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19 angle O-H...O or N-H...O $< 145^\circ$ have been rejected. About 60% of the interactions
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21 arised from monofurcated protons, while 25% from bifurcated protons (one proton for
22
23 two interactions) and 15% from trifurcated protons (one proton for three interactions)
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25 (Figure S1 in supplementary material). On the other side, we have studied the number of
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27 interaction according to a given oxygen V_{10} atom type. Contacts after rejection and
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29 normalization by the number of contacts for a considered oxygen atom (48 structures
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31 analysed) are represented in red color (Figure 6) by the occurrence of the oxygen atom
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33 type in V_{10} anion. That means that in average Ob presents a little more than one contact
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35 while Og has a an average of more than 1,5 contacts per oxygen atom. In the green bar
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37 the oxygen atoms which have no contact, have been excluded of the statistic. In blue bar,
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39 only contacts from monofurcated protons are considered. This figure shows that
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41 considering all contacts, each oxygen atom type has at least one contact in average. The
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43 fact that Ob has mainly one noncovalent interaction, could be explained by its position in
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45 the V_{10} anion, (a triply bonded with vanadium) which is i) less accessible than the other
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47 types and ii) generally strongly bonded (a closer geometry). The oxygen types which
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49 have the most contacts are Od, Of and Og. Og presents hydrogen bonds more than two in
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3 average. The number of contacts from monofurcated protons is quite smaller letting all
4 types having less than one contact from monofurcated proton.
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8 9 10 **3.4 Deeply insight into the localisation of the proton near the V₁₀ anion.** 11 12 **Influence of the 2nd neighbours** 13

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15 To go deeply insight into the noncovalent interactions with the V₁₀ anion, we have
16 also studied the proton position in the neighbourhood of the corresponding O_{dv}, by
17 analyzing its proximity to O_{dv} in term of verticality and in term of influence with the
18 neighboured oxygen atoms. To characterize the proximity of the O_{dv} verticality, we have
19 used a γ angle (Figure 1 b). The angle γ indicates the position of the proton compared
20 with the verticality of the corresponding oxygen atom. Analysis of γ angle (Figure 7, and
21 Figures S3, S4, S5 in supplementary material) shows a difference depending on the
22 oxygen atom and donor type. For O-H...O_{dv} and N-H...O_{dv} interactions, Ob and Oc which
23 are involved in strong hydrogen bonds, the γ angle is high (120 to 180°). Dispersion can
24 be observed for Of, but Og has a γ angle smaller than Ob and Oc ranging mainly from 70
25 to 140°. For the C-H...O_{dv} interactions the behaviour is not so clear. Under 120°, mainly
26 interactions with Of and Og are presents but over it's more homogeneous. Therefore, γ
27 seems, to a certain extent, to have a similar behaviour as the D-H...O_{dv} angle. The
28 observation of the dihedral angle X-O_{dv}...H-D versus the O_{dv}...H distance, where X is V
29 when O_{dv} is Of or Og and a dummy atom leading to X-O_{dv} perpendicular to the plane of
30 the neighbours of O_{dv} give no particular behaviour.
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48 In order to check the influence of the neighbours, we have then analysed the
49 proton position in the neighbourhood of the corresponding O_{dv} (Figure 8). For each
50 noncovalent interaction, the distances between the proton and the first neighbours of the
51 corresponding O_{dv} have been determined. We have divided the neighbourhood of the O_{dv}
52 in sectors containing one of the neighbours in order to determine in which sector the
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4 proton lies. Results are presented separately for the oxygen atom type and for each type
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6 frequency is given in each sector according to the donor. The number of identical sectors
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8 is taken into account. Interactions with angles $\text{N-H}\cdots\text{O}_{\text{dv}}$ and $\text{C-H}\cdots\text{O}_{\text{dv}} < 145^\circ$ have been
9
10 rejected. There is generally no particular behaviour for $\text{C-H}\cdots\text{O}_{\text{dv}}$ interactions but some
11
12 differences for $\text{N-H}\cdots\text{O}_{\text{dv}}$ and $\text{O-H}\cdots\text{O}_{\text{dv}}$ interactions. For Ob, the frequency of protons
13
14 which are in the sector B is a little higher for $\text{N-H}\cdots\text{O}_{\text{dv}}$ and $\text{O-H}\cdots\text{O}_{\text{dv}}$ interactions. The
15
16 neighbours are Oc, Oe and Of which are on a side of V_{10} have more or less a similar
17
18 position in the space. As Oc is a more electronegative atom than Oe and Of, therefore
19
20 more attractive, it may explain the higher proportion in the sector B.
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23 For Oc (Figure S6a), we have taken into account the fact that Of and Og are not in
24
25 the same plane as the other neighbours. After that, the graph shows that Of and Og have
26
27 only a few protons above them, which can be explained by the fact that they are not in the
28
29 plane of the other neighbours but are above the plan and therefore unable the proton
30
31 position. Most of the protons of $\text{O-H}\cdots\text{O}_{\text{dv}}$ interactions are in sector F (above Oe), which
32
33 has the most free environment. For $\text{N-H}\cdots\text{O}_{\text{dv}}$ interactions, a little more are in sector D
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35 (above Od which is more electronegative) but the differences are not very significative
36
37 between sectors. Od (Figure S6b) and Og (Figure 8b) are not in the same plane than Oc.
38
39 For the same reasons, as those expressed for Oc almost no proton is in the sector B. They
40
41 are above Oc.
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44 For Oe (Figure S6c), there are two sectors A and B with Oc and Ob respectively.
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46 The graph shows that $\text{O-H}\cdots\text{O}_{\text{dv}}$ and $\text{N-H}\cdots\text{O}_{\text{dv}}$ interactions are mainly in the sector A,
47
48 which may be explained by the fact that Oc has a freer environment although Ob is more
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50 electronegative. For Of, there are no significant differences between the two sectors A
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52 and B (Oc and Ob respectively). Only a little more are above Ob, which is the contrary as
53
54 the case of Oe, but which might be explained by the fact that a lot of protons are
55
56 bifurcated between the two Of, therefore above Ob. For Og (Figure 8b), there are three
57
58 different sectors A, B and C, above Oe, Oc and Od respectively. Mainly, $\text{N-H}\cdots\text{O}_{\text{dv}}$
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4 interactions are in the sector B, whereas O-H...O_{dv} interactions are more in the sectors A
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6 and C with the same quantity.
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8 The observation of the proton in the neighbourhood of the corresponding O_{dv}
9
10 indicates that there is a competition between the steric effect and the EP values. The
11
12 steric effect seems to be predominant and protons of O-H...O_{dv} and N-H...O_{dv} interactions
13
14 are more above O_{dv} with the free environment. Steric effect is particularly important for
15
16 neighbour atoms which are not in the same plane as the others. In case where there is no
17
18 steric effect, EP values are important and protons are above the more electronegative O_{dv}.
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21 **3.5 Decavanadate binding with proteins**

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24 While the inhibition of enzymes by V₁₀'s has been well documented, the primary
25
26 mechanism for biological activity remains elusive. Previously reported studies^{37,41}
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28 illustrate the importance of the noncovalent interactions between V₁₀ and peptides. It is
29
30 clear from these studies that the vanadate interacts very strongly with positively charged
31
32 proteins. Therefore, this is particularly important if we take into account the possible
33
34 interaction mechanism of V₁₀ with proteins, where formation and breaking of hydrogen
35
36 bonds presumably play fundamental role. From the chemical point of view, types of
37
38 interactions realized in small molecule are identically to those observed in protein. As in
39
40 the case in small structure, the V₁₀ can be bonded by varies modes of interactions.
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46 Three structures have been retrieved from PDB,⁶⁵ Acid phosphatase A (**2d1g**),⁷¹
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48 Tyrosine kinase (PDB ID **3gqi**)⁷² and Ca²⁺ ATPase (PDB ID **1kju**) coordinates are only
49
50 available for the two first structures (Figure 9). Acid phosphatase A is a respiratory burst-
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52 inhibiting acid phosphatase from the American Centers for Disease Control and
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54 Prevention (Category A bioterrorism agent) *Francisella tularensis* and prototype of a
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3 super-family of acid phosphatases and phospholipases C. Felts⁷¹ has reported the 1.75-Å
4 resolution crystal structure of Acid phosphatase A complexed with the inhibitor
5 orthovanadate, the first published structure for any member of this super-family.
6
7
8 Nevertheless, the precision of this structure could be taken as 0.01Å on the interatomic
9 distances, and 3° on the angles. Therefore that allows us to study precisely the
10 intermolecular network. A tyrosine kinase is an enzyme that can transfer a phosphate
11 group from ATP to a protein in a cell. The phosphates inhibitor sodium orthovanadate
12 was applied in order to prevent dephosphorilation of tyrosine kinase. Crystal complex of
13 tyrosine kinase – protein were not formed in the absence of 2mM vanadate. Table 2
14 summarizes the intermolecular interactions between V₁₀ and the rest of the structure, in
15 these two protein structures. In **2d1g**, V₁₀ anion is linked to the B chain of the asymmetric
16 unit through three histidine and a lysine, linked to the A chain (obtained with a symmetry
17 operation) through two asparagine, and linked to one water molecule. In **3gqi** structure,
18 V₁₀ is binded with the asparagine (Asn), arginine molecules and aspartic acid. The contact
19 Ob...N_{Asn} with the distance N...O about 2.62 Å is the shortest contact, and can be assumed
20 as hydrogen bond.
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41 In both structures, the stronger interactions take place on the most reactive oxygen
42 atoms (N-H...O interactions with a dN...O < 2.70 Å at Ob, Oc). This is in agreement with
43 the experimental results from Crans *et al.*, where they have found that the protonated
44 amino terminus of the Gly-Gly dipeptide are connected with triply bridging oxygen atom
45 of decavanadate anion (Ob) *via* hydrogen bonds. (d_{N-H...O} = 2.707(4)Å). Therefore, these
46 results show that the V₁₀ noncovalent behavior we have observed, remains the same when
47 the anion is bounded to a protein.
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3.6. Cation interaction

Another interesting result can be deduced from statistical study on a selection of inorganic and organic structures. The structures analyzed ^{69a,d,f,g,i,k; 73a-j} contain mainly Na⁺, K⁺, or Ca²⁺ cations due to the fact that these cations are generally involved in the enzymes activated or inhibited by V₁₀. In table 1, the noncovalent interactions are classified by the oxygen type of the V₁₀. Concerning the cation interactions, one can observe that the cation are mainly linked to the Of oxygen than to the Og atom, while these two atoms present equivalent values of electrostatic potential. Therefore, cation with the highest positive charge forms a coordination polyhedron with the molecule of water. The less positive cation includes V₁₀ anion in its coordination polyhedron. This is generally done with Of.

4. Conclusion

Study of polyoxovanadate containing organic molecules, especially the role of the organic cations placed in the structure of the decavanadate is a key-factor in the understanding of the direct interactions of vanadate with cellular proteins and enzymes. This could be an important key to reveal the physiological functions of vanadium oxoanions.

This work represents a systematic description and interpretation of noncovalent interaction including V₁₀. The noncovalent interactions are strongly different depending on the oxygen atom type. The Ob and Oc oxygen atoms are involved mainly in the strong O-H...O, N-H...O while Of or Og are mainly involved in weakest hydrogen bonds such as

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3 C-H...O or cation interactions. These statistical observations are completely in agreement
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6 with our experimental determination of the electrostatic potential and its transferability
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8 property we have previously established.⁴² Due to the potent different types of interaction
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10 (strong and weak DH...O bonds, cations...O), V₁₀ could definitively try to be used, as a
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12 crystallization agent. That could be done in the case where orthovanadate is an inhibitor.
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14 The pH conditions have to be carefully controlled. Our H-bond or cation interaction
15
16 predictions fit well with two protein structures (2d1g and 3gqi). It could even help for
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18 determining some remaining water molecules in further structures. Our atomic net
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20 charges,⁴² and our H-bond and cation interaction predictions could be suitably used in the
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22 docking computations^{18, 19, 30} and would probably give better results than the common
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24 used charges.
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32 **Acknowledgements**

33
34
35 A part of this paper, have been done during the join PhD thesis of NB-P between
36
37 the University of Belgrade, Faculty of Physical Chemistry and Ecole Centrale Paris. The
38
39 authors would thank the French foreign Minister for a COCOOP support on this project.
40
41 NB-P would thank the Ministry of Science and Technological Development of the
42
43 Republic of Serbia (Project 142043) and Ecole Centrale Paris for assistant professor
44
45 invited position. The second part of this paper was the subject of the Master-1 internship
46
47 exchange at the University of Belgrade, Faculty of Physical Chemistry of JP, JP thanks
48
49 the Faculty of Physical Chemistry for its welcome.
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56 **Supporting Information Available.**
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Figures S-1 to S-6 present additional representation of the noncovalent interactions.

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Figure captions

Figure 1. V_{10} atom labelling.

Figure 2. Schematic representation of the main expected non covalent interactions with V_{10} anion according to ref 39. a) strong interactions such as O-H... O_{dv} or N-H... O_{dv} b) weak interactions such as C-H... O_{dv} or cation interactions. V_{10} 3D isodensity surface ($0.007 \text{ e} \cdot \text{\AA}^{-3}$) colored by the electrostatic potential values ($\text{e} \cdot \text{\AA}^{-1}$)

Figure 3. Distribution of the D...O distances and D-H... O_{dv} angles. a and b) O-H... O_{dv} , c and d) N-H... O_{dv} , e and f) C-H... O_{dv} interactions

Figure 4. Distribution of the D-H... O_{dv} angles versus the H... O_{dv} distances according to the oxygen atom type for each donor type; a) O-H... O_{dv} interactions, b) N-H... O_{dv} interactions and c) C-H... O_{dv} interactions.

Figure 5. Frequency of each type of interaction for each oxygen atom type: a) normalization by the number of interaction type; b) normalized by the occurrence of O_{dv} type; c) normalization by the number of bonds type.

Figure 6. Number of contacts for each oxygen atom type: all contacts (red), all contacts for binded oxygen atom (green), contacts from monofurcated protons (blue).

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4 **Figure 7.** Distribution of γ angle and distance $O_{dv}\cdots H$ according to the oxygen atom type
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6 for each donor type for: a) $O-H\cdots O_{dv}$ interactions, b) $N-H\cdots O_{dv}$ interactions and c)
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8 $C-H\cdots O_{dv}$ interactions.
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13 **Figure 8.** Frequency of the proton position in the O_{dv} neighbourhood for $D-H\cdots O_{dv}$
14 interactions according to the donor type for each oxygen atom type: a) O_b and b) O_g . The
15 number of interactions considered is written on each stick. The number of identical
16 sectors is taken into account.
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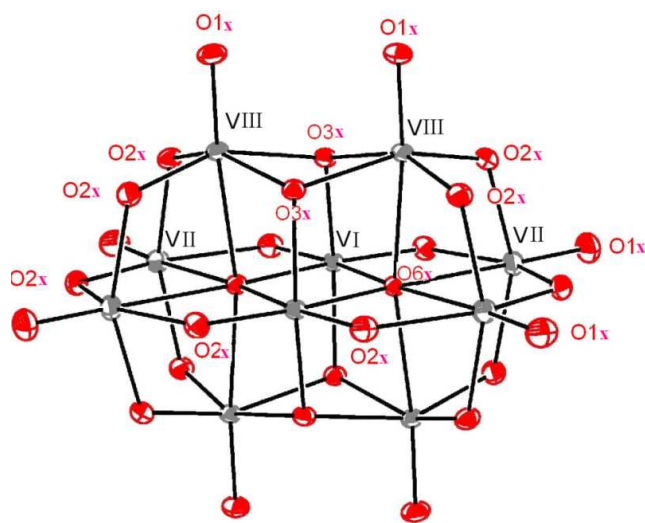
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25 **Figure 9.** a) Interactions between V_{10} anion and protein. a) **PDB Id 2d1g.** $N-H\cdots O$
26 contact in the asymmetric unit. The 3 histidine groups (HIS495, HIS 496, HIS497) and
27 the lysine (LYS394) are indicated. b) **PDB Id 3gqi** $N-H\cdots O$ contact in the asymmetric
28 unit. The asparagine (ASN506), aspartic acid (ASP503) and arginine (ARG507) are
29 indicated.
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3 **Table captions**
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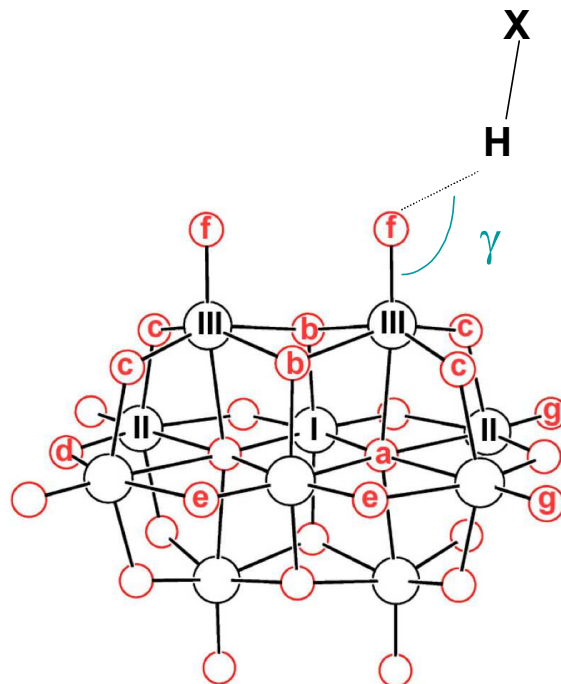
7 **Table 1.** Molecule structures used in this manuscript. In case of decavanadate - cation
8 interaction the oxygen type engaged in the interaction is indicated.
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14 **Table 2.** Hydrogen bonds between V_{10} and protein from **2d1g** and **3gqi** structures.
15 Distances $d(D...O) \leq 3.20 \text{ \AA}$ have been reported.
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Figure 1

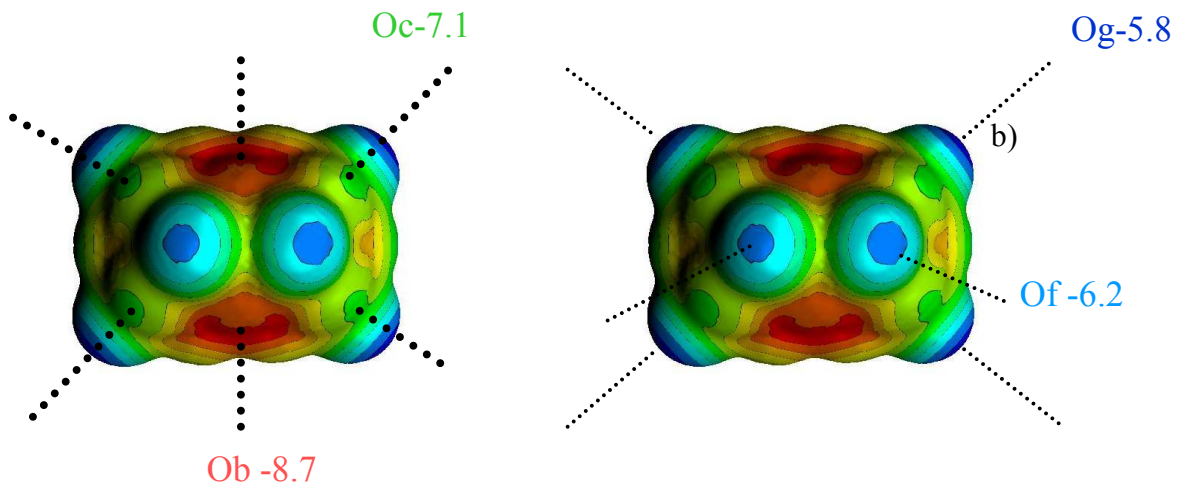


a)



b)

Figure2



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Figure 3

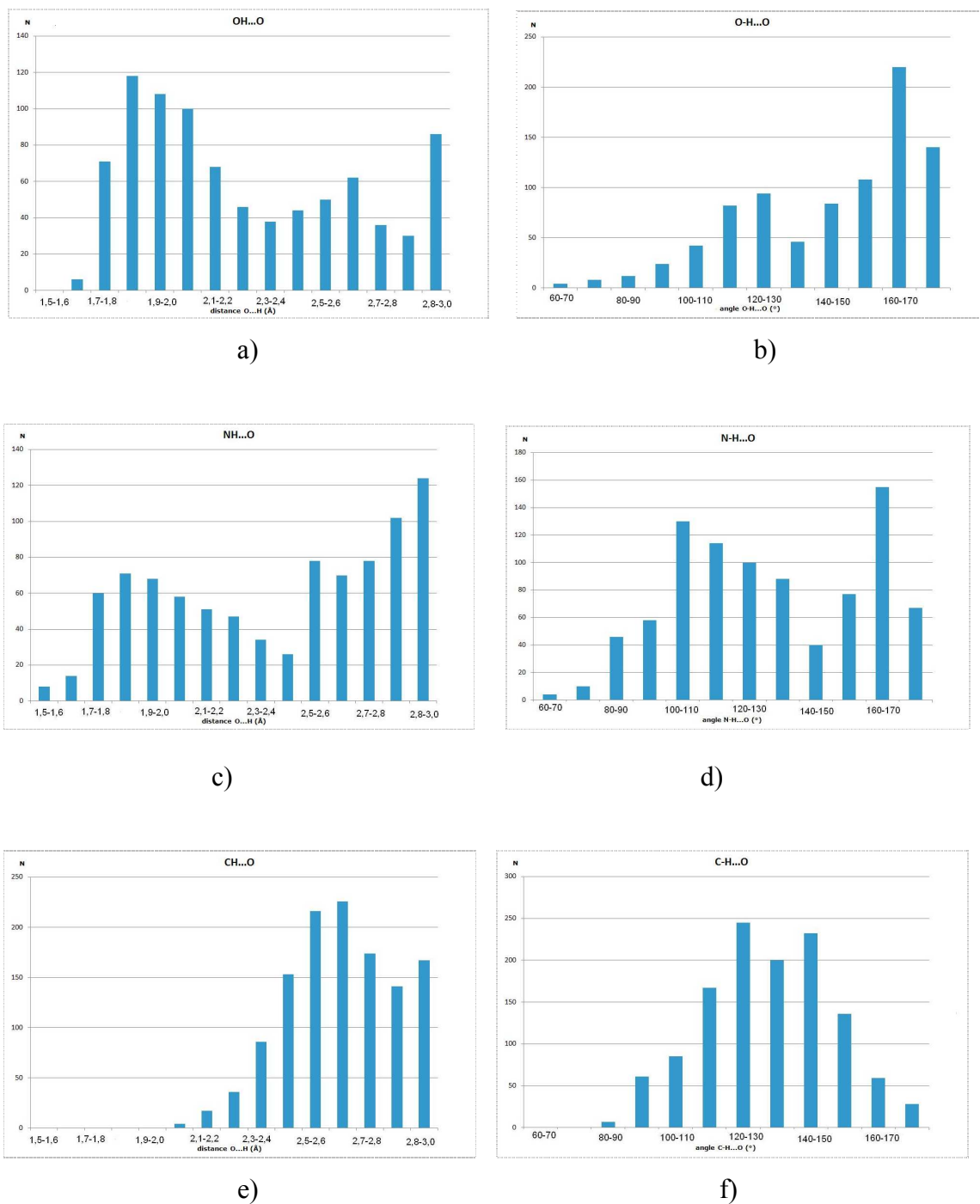
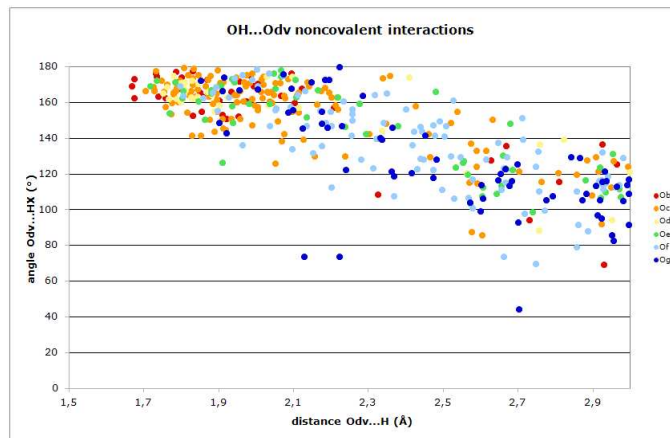
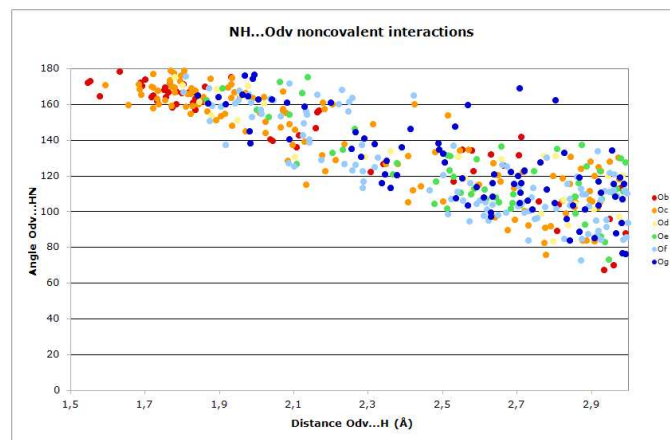


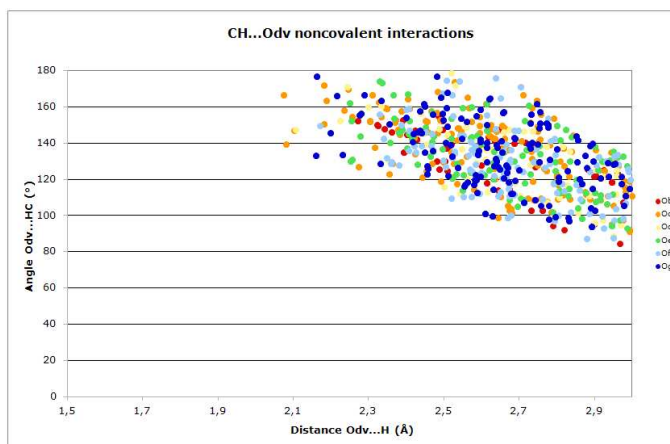
Figure 4



a)

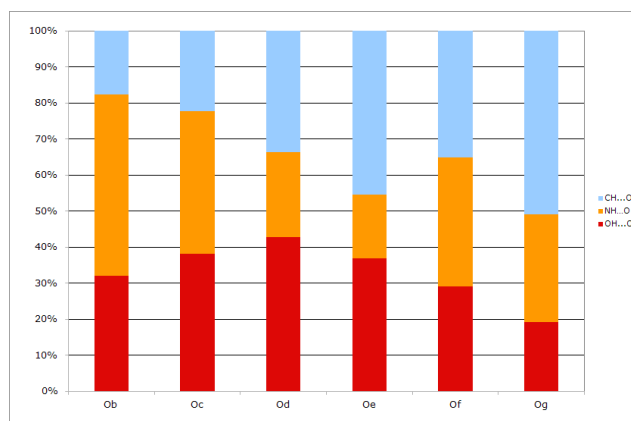


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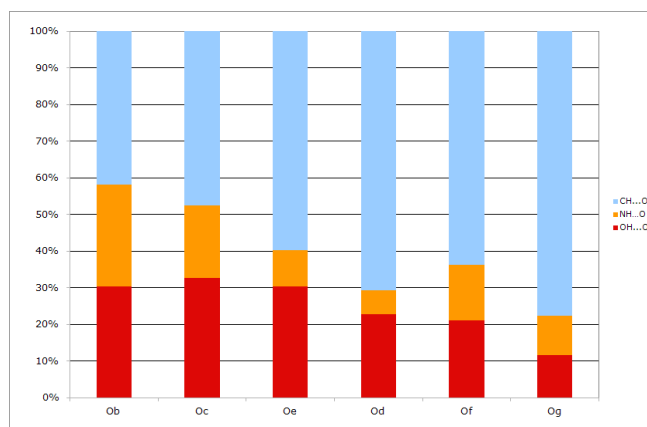


c)

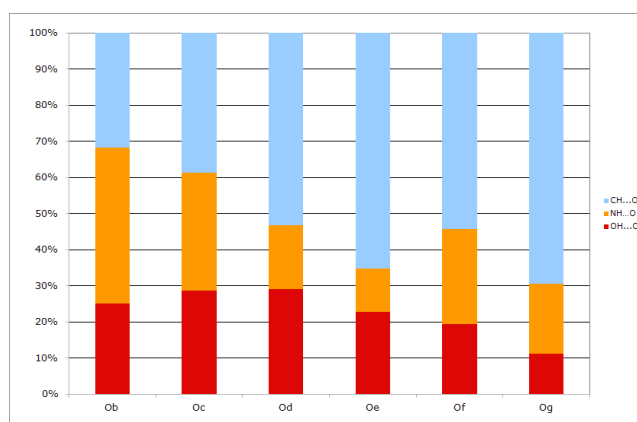
Figure 5



a)



b)



c)

Figure 6

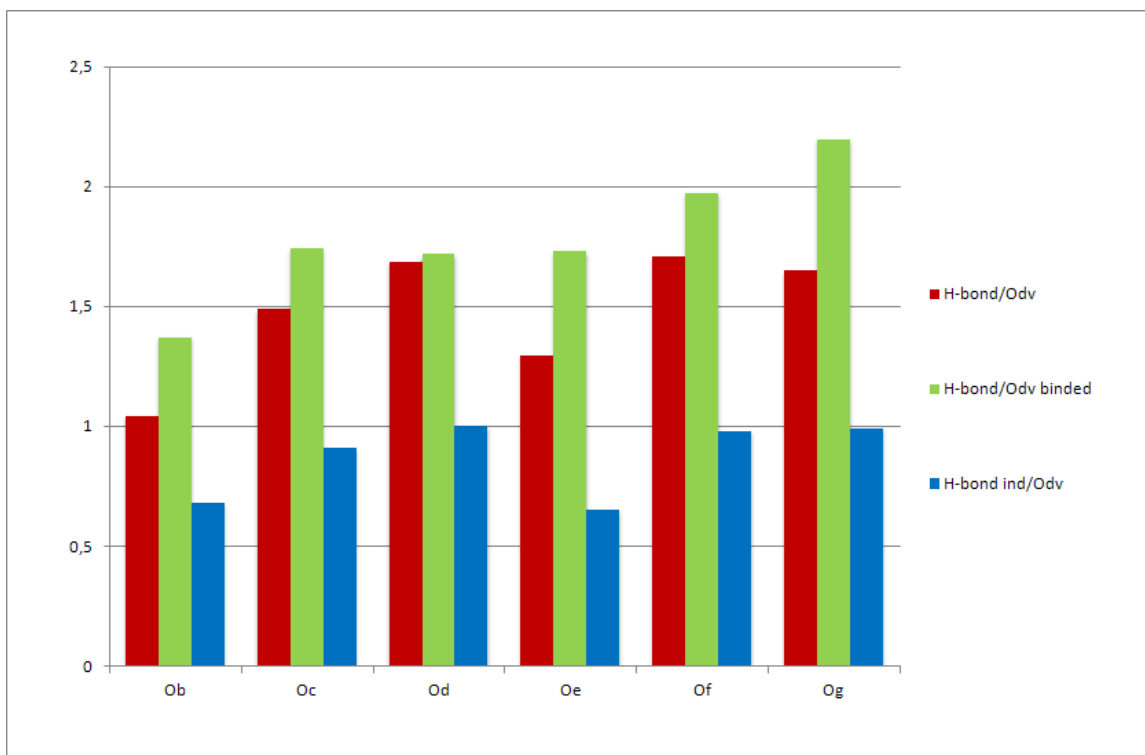
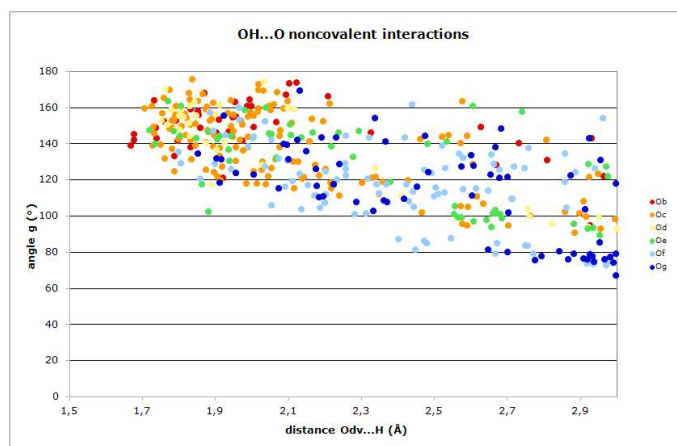
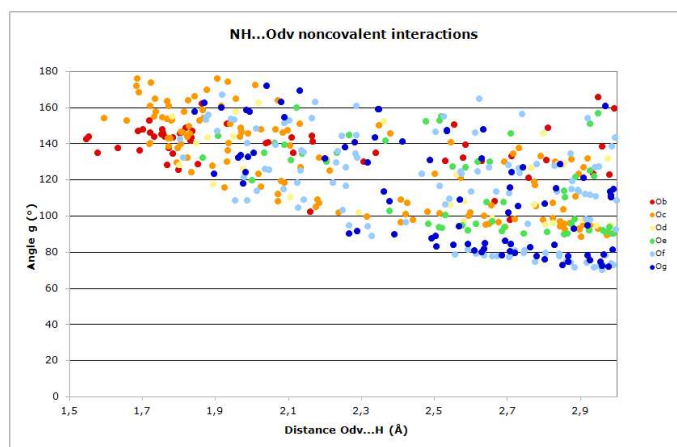


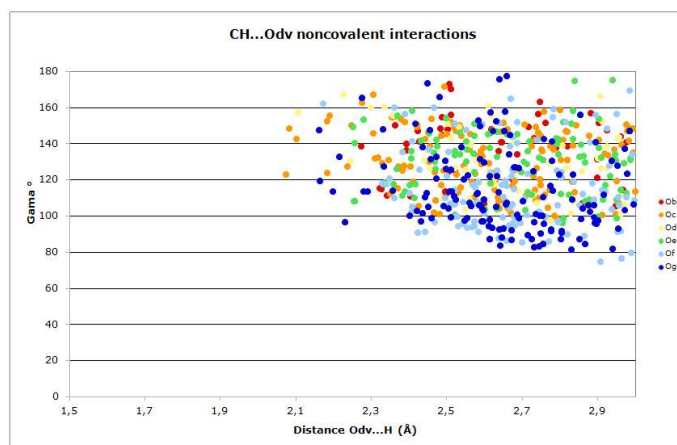
Figure 7



a)

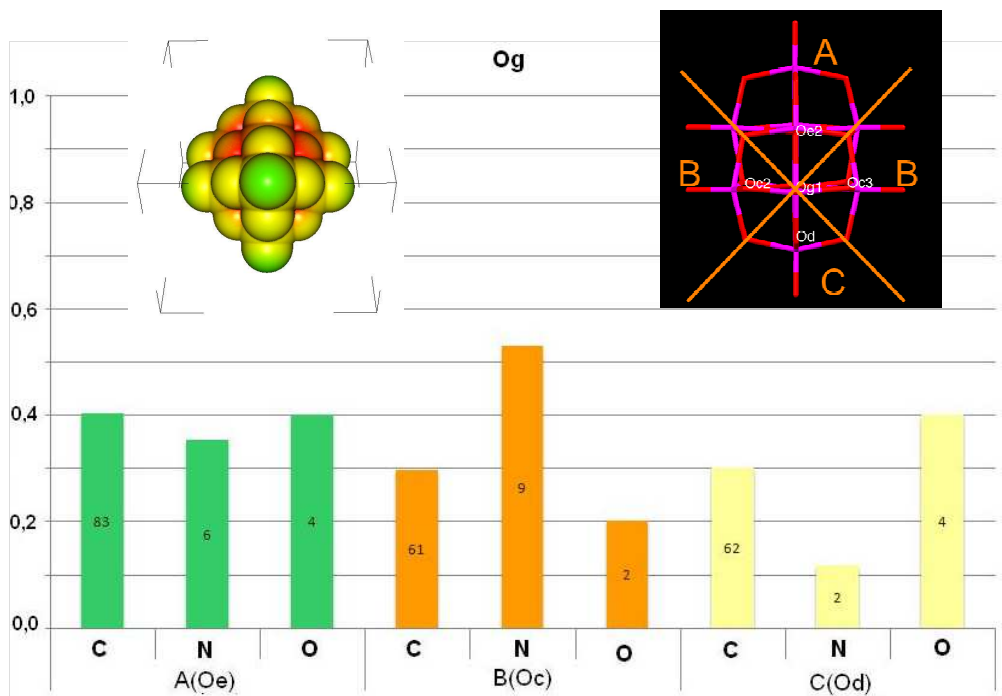
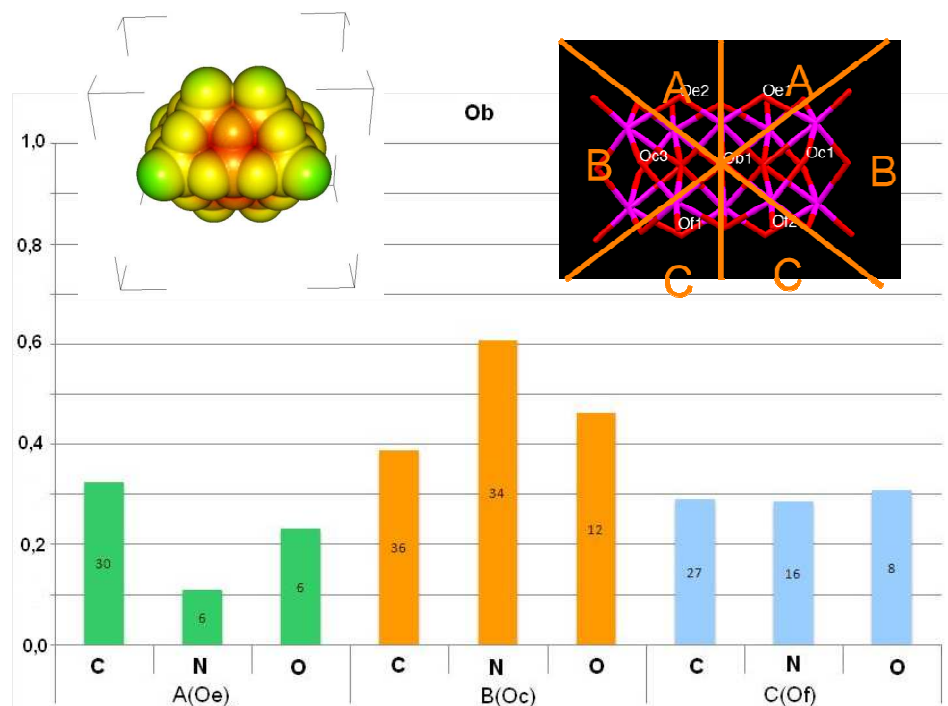


b)



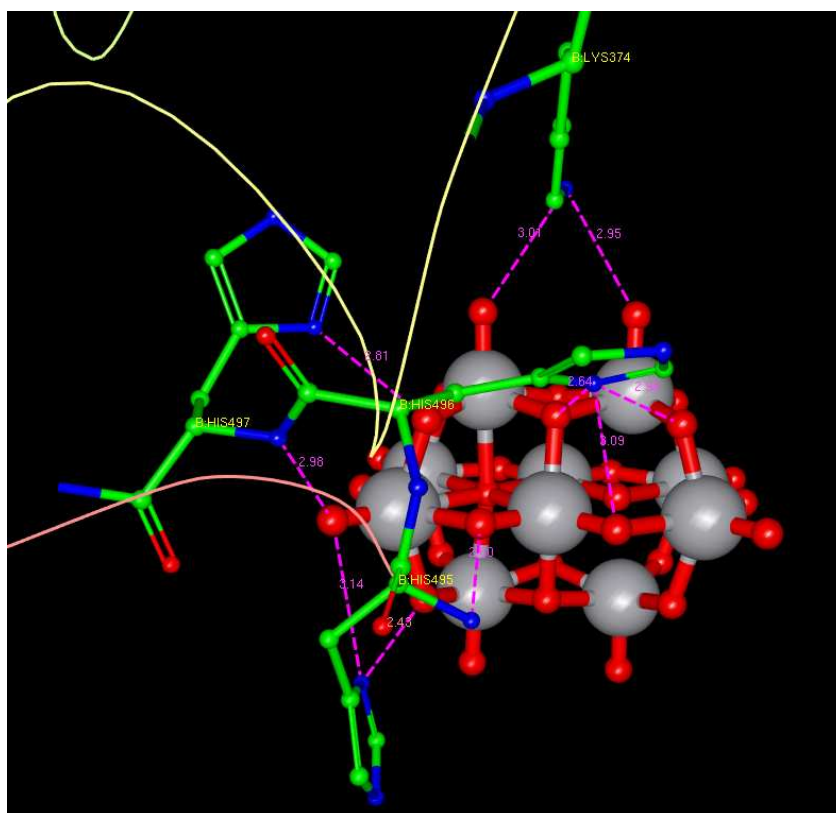
c)

Figure 8

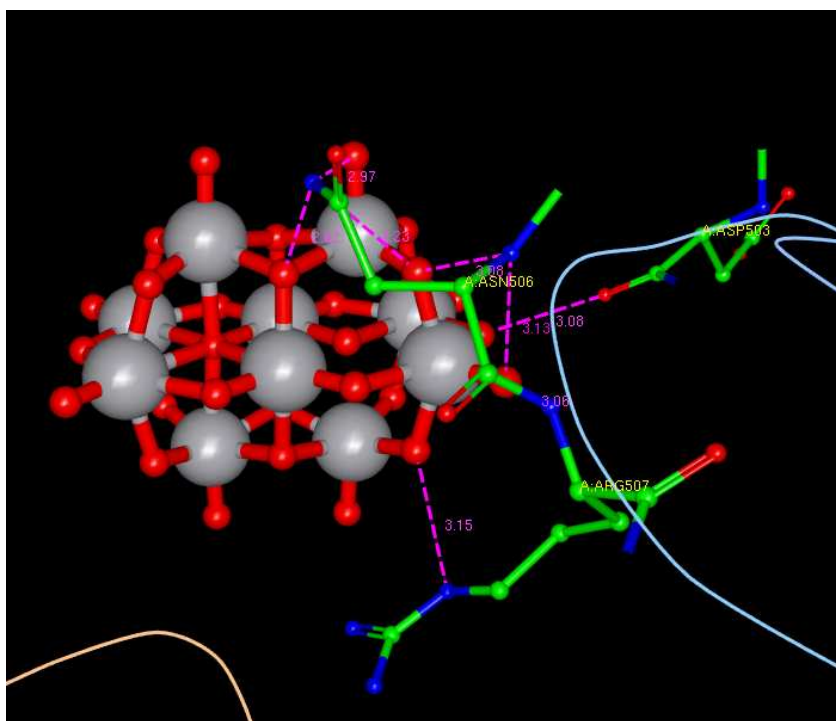


b

Figure 9



a)



b)

Table 1.

Oxygen type	Cation	Formula	CSD REFCODE or ICSD Id or PDB Id	Reference
Organic compounds				
Of	Na	Na ₃ [V ₁₀ O ₂₈] (C ₄ N ₃ OH ₅) ₃ (C ₄ N ₃ OH ₆) ₃ · 10H ₂ O		42
		(C ₈ F N H ₁₁) ₆ [V ₁₀ O ₂₈] 4H ₂ O	DIWYIS	67a
		(C ₆ H ₇ N ₂ O) ₆ [V ₁₀ O ₂₈] 2H ₂ O	DIKREV	67b
		(C ₇ N H ₁₀) ₆ [V ₁₀ O ₂₈] 2H ₂ O	WILWUK	22
		3[C ₅ H ₁₆ N ₂] ²⁺ [V ₁₀ O ₂₈] 6H ₂ O	GIHCAC	67c
		(C ₄ H ₁₄ N ₂) ₃ [V ₁₀ O ₂₈] 5H ₂ O	JEWCOE	67d
		(C ₅ H ₇ N ₂) ₆ [V ₁₀ O ₂₈] 2H ₂ O	DEFPIO	67e
		[C ₄ H ₁₄ N ₂] ₃ [V ₁₀ O ₂₈] 6H ₂ O	MENSAA	67f
		[C ₃ H ₁₂ N ₂] ₂ [Cu (H ₂ O) ₆] [V ₁₀ O ₂₈] · 7H ₂ O	YEDZOX	67g
		(C ₃ N ₂ H ₁₂) ₃ [V ₁₀ O ₂₈] 5.5H ₂ O	QERQEK	67h
		(C ₄ H ₁₂ N O) ₆ 2(C ₃ H ₈ O) [V ₁₀ O ₂₈] 2H ₂ O	VAXJUA	67i
Og	K	[V ₁₀ O ₂₈] (C ₂ H ₁₀ N ₂) ₂ K ₂ 4H ₂ O	JAJOJ	67j
		[C ₂ H ₁₀ N ₂] ₂ [Na ₂ (H ₂ O) ₁₀][V ₁₀ O ₂₈]	MAJKUE	67k
		(C ₆ H ₁₄ N ₅ O) ₆ [V ₁₀ O ₂₈] 6H ₂ O	FESYUY	67l
		[H ₁₂ CoO ₆] ₃ [V ₁₀ O ₂₈] [C ₁₂ H ₂₄ O ₆] ₂ · 10H ₂ O	AJETEO	67m
		(C ₁₄ H ₃₀ N ₂ O ₄) ₂ [V ₁₀ O ₂₈] 6H ₂ O	HABYIT	67n
		C ₂₀ H ₄₈ N ₄ O ₁₆ Zn ₂ 2[NH ₄] [V ₁₀ O ₂₈] · 6H ₂ O	WUNNEY	67o
		C ₂₀ H ₄₈ N ₄ O ₁₆ Mn ₂ 2[NH ₄] [V ₁₀ O ₂₈] · 6H ₂ O	WUNNIC	67o
		(C ₂₄ H ₂₀ As) ₂ (C ₄ H ₁₀ N O) ₄ [V ₁₀ O ₂₈] 4H ₂ O	UHEBOY	67p
		[C ₂ H ₈ N] ₆ [V ₁₀ O ₂₈] · H ₂ O	QETZOE	67q
		Na [H ₃ N] [CH ₂] ₂ NH ₃) _{2.5} [V ₁₀ O ₂₈] · 5H ₂ O	XISGUB	67r
		[C ₄ H ₁₂ N] ₂ [H ₁₂ Mn O ₆] ₂ [V ₁₀ O ₂₈] · 2H ₂ O	LALVUP	67s
		[Hpy ⁺] ₄ [C ₁₄ H ₁₃ N ₂] ₂ [V ₁₀ O ₂₈]	GOPDOE	67t
		[Li(H ₂ O) ₄] ₂ [N(CH ₃) ₄] ₄ [V ₁₀ O ₂₈] · 4H ₂ O	NONKUW	67u
Of,Og	Na	[Na] ₄ [N(CH ₄) ₄] ₄ [V ₁₀ O ₂₈] · 20H ₂ O	TIPWOE	67v
		[C ₂ H ₁₀ N ₂] ₃ [V ₁₀ O ₂₈] · 2H ₂ O	ZOZBIZ	67w
		(C ₂ H ₈ N O) ₆ [V ₁₀ O ₂₈] 6H ₂ O	YUFFUA	67x
		(C ₄ H ₁₂ N O) ₆ [V ₁₀ O ₂₈]	YUFTAU	67y
		(C ₃ H ₁₀ N) ₆ [V ₁₀ O ₂₈] 4H ₂ O	HIDLEL	67z

		$(\text{NH}_4)_6(\text{Gly-Gly})_2[\text{V}_{10}\text{O}_{28}] \cdot 4\text{H}_2\text{O}$	YETYIF	36
		$(\text{C H}_6 \text{ N}_3)_6 [\text{V}_{10}\text{O}_{28}] \cdot 6\text{H}_2\text{O}$	HAKYAT	67aa
Inorganic compounds				
		$(\text{NH}_4)_6[\text{V}_{10}\text{O}_{28}] \cdot 5\text{H}_2\text{O}$		66
Of, Og	Na	$\text{Na}_4 \text{ K}_2 [\text{V}_{10}\text{O}_{28}] \cdot 18\text{H}_2\text{O}$	249156	69a
Of	K	$\text{Na}_4 \text{ K}_2 [\text{V}_{10}\text{O}_{28}] \cdot 18\text{H}_2\text{O}$	249156	69a
		$(\text{NH}_4)_4\text{Li}_2[\text{V}_{10}\text{O}_{28}] \cdot 10\text{H}_2\text{O}$	59853	69b
		$[\text{Li}_6(\text{H}_2\text{O})_{16}\text{V}_{10}\text{O}_{28}]_n$	170991	69c
Oc, Og	Na	$\text{Mg}_2 \text{ Na}_2 [\text{V}_{10}\text{O}_{28}] \cdot 20\text{H}_2 \text{ O}$	59839	69d
		$\text{Na}_{5.22}\text{Li}_{0.78}[\text{V}_{10}\text{O}_{28}] \cdot 20\text{H}_2\text{O}$	170783	69e
Og	Na	$\text{Cu Na}_4 [\text{V}_{10}\text{O}_{28}] \cdot 23\text{H}_2 \text{ O}$	281319	69f
Of, Og	K	$\text{K}_4\text{Na}_2\text{V}_{10}\text{O}_{28} \cdot 10\text{H}_2\text{O}$	281347	69g
		$[\text{NH}_4]_4 \text{ Na}_2 [\text{V}_{10}\text{O}_{28}] \cdot 10\text{H}_2\text{O}$	280357	69h
Oc,Og	K	$\text{K}_4 \text{ Na}_2 [\text{V}_{10}\text{O}_{28}] \cdot 10\text{H}_2 \text{ O}$	170750	69i
		$[\text{NH}_4]_2 [\text{Co} (\text{H}_2\text{O})_6]_2 [\text{V}_{10}\text{O}_{28}] \cdot 4\text{H}_2\text{O}$	84282	69j
		$[\text{NH}_4]_2 \text{ Mg}_2\text{V}_{10}\text{O}_{28} \cdot 16\text{H}_2\text{O}$	39217	69k
Oc,Og	Rb	$\text{Rb}_2 \text{ Mg}_2 [\text{V}_{10}\text{O}_{28}] \cdot 16\text{H}_2 \text{ O}$	39218	69k
Oc,Og,Of	K	$\text{K}_2 \text{ Mg}_2 [\text{V}_{10}\text{O}_{28}] \cdot 16\text{H}_2 \text{ O}$	39216	69k
Oc, Of, Og	K	$\text{K}_2 (\text{Co} (\text{H}_2 \text{O})_6)_2 [\text{V}_{10}\text{O}_{28}] \cdot 4\text{H}_2 \text{ O}$	281298	69g
Of	Na	$\text{Na}_3 (\text{NH}_4)_3 [\text{V}_{10}\text{O}_{28}] \cdot 12\text{H}_2\text{O}$	412811	73a
Of	Na	$[\text{Ni} (\text{H}_2\text{O})_6]_2 [\text{Na} (\text{H}_2\text{O})_3]_2 [\text{V}_{10}\text{O}_{28}] \cdot 4\text{H}_2\text{O}$	280901	73b
Of	Na	$[\text{Na}_4 (\text{H}_2\text{O})_{14}] [\text{Ni} (\text{H}_2\text{O})_6] [\text{V}_{10}\text{O}_{28}] \cdot 3\text{H}_2\text{O}$	280960	73c
Og, Oc	K	$((\text{H}_2 \text{O})_2 \text{ K} (\text{H}_2 \text{O})_3 \text{ Co} (\text{H}_2 \text{O})_3)_2 [\text{V}_{10}\text{O}_{28}]$	410930	73d
Of	K	$\text{K}_2 \text{ Ba}_2 [\text{V}_{10}\text{O}_{28}] \cdot 8\text{H}_2\text{O}$	88871	73e
Of,Og	Na	$\text{Na}_6 [\text{V}_{10}\text{O}_{28}] \cdot 12\text{H}_2\text{O}$	066807	73f
Of,Og	K	$\text{K}_2 \text{ Mg}_2 [\text{V}_{10}\text{O}_{28}] \cdot 16\text{H}_2 \text{ O}$	105264	73g
Of	Na	$\text{Na}_6 [\text{V}_{10}\text{O}_{28}] \cdot 18\text{H}_2\text{O}$	014079	73h
Of	Ca	$\text{Ca}_3 [\text{V}_{10}\text{O}_{28}] \cdot 16\text{H}_2\text{O}$	014309	73i
Of, Og	K	$\text{K}_2 \text{ Zn}_2 [\text{V}_{10}\text{O}_{28}] \cdot 16\text{H}_2 \text{ O}$	27439	73j
Protein structure with decavanadate				
		Acid phosphatase A	2d1g	71
		Tyrosine kinase	3gqi	72

Table 2.

	2d1g			3gqi		
	Oxygen type	Amino acid	d(D...O) (Å)	Oxygen type	Amino acid	d(D...O) (Å)
NH...O	Oc	HIS	2.44	Ob	ASN	2.62
	Oe	HIS	2.61	Of	ASN	2.97
	Ob	HIS	2.65	Og	ARG	3.06
	Oc	ASN	2.70	Oc	ASN	3.08
	Oc	HIS	2.81	Og	ASN	3.13
	Oe	ASN	2.87	Oc	ARG	3.15
	Oc	HIS	2.94	Oc	ASN	3.23
	Of	LYS	2.95			
	Og	HIS	2.98			
	Of	LYS	3.02			
	Oe	HIS	3.10			
	Oc	ASN	3.11			
	Og	HIS	3.14			
OH...O	Of		2.86	Od	ASP	3.08
CH...O	Oe	HIS	2.94			
	Oc	HIS	2.94			
	Oc	LYS	2.94			
	Oc	HIS	3.01			
	Og	HIS	3.10			
	Oc	HIS	3.20			

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