Vanadium(V) Oxoanions in Basic Water Solution: a Simple Oxidative System for the One Pot Selective Conversion of L-Proline to Pyrroline-2-Carboxylate

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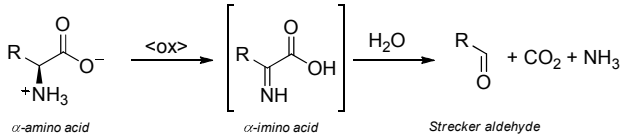
The unprecedented, direct chemical oxidation of L-proline to pyrroline-2-carboxylate was achieved in water (pH ca. 10) by means of NH_4VO_3/NH_3 or V_2O_5/MOH (K = Na, K), and the anion was fully characterized as ammonium or alkaline metal salts. Quantitative yield and higher atom economy performance were supplied with the latter system, the alkaline salts being more stable than the ammonium one. Different mixed valence V(IV)/V(V) compounds precipitated from the reaction mixtures depending on the nature of the employed base. A possible reaction mechanism is proposed according to DFT calculations. The analogous reaction of *trans*-4-hydroxy-L-proline with NH_4VO_3/NH_3 afforded pyrrole-2-carboxylic acid in 81% yield, while sarcosine underwent prevalent decomposition under similar experimental conditions. Instead, no reaction was observed with primary (glycine, L-alanine, L-phenylalanine) and tertiary α-amino acids (*N*,*N*-dimethyl-L-phenylalanine, *N*,*N*-dimethylglycine).

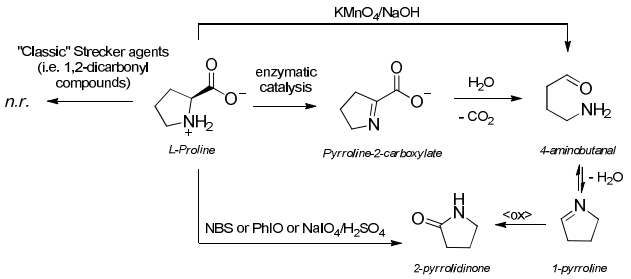
Introduction

α-Imino acids are intermediates in the Strecker degradation of α-amino acids (see Scheme 1).[1] This decarboxylative oxidation process is promoted by a variety of inorganic and organic agents and plays a key role in food chemistry.[2] As a direct consequence, α-imino acids are relatively unstable substrates and only a few of them have been isolated.[3]



Scheme 1. The Strecker degradation of a generic primary α-amino acid.

Among this class of compounds, pyrroline-2-carboxylic acid, HP2C (conjugate base: pyrroline-2-carboxylate, $P2C^-$) has aroused interest for its biochemical role[4] and utility in organic synthesis.[5] This α-imino acid has been obtained in solution by the cyclization of 5-amino-2-oxopentanoic acid in water[6] or its *N*-C(=X)NH_2 derivatives (X = O, NH) in trifluoroacetic acid.[7] However, it is more desirable to obtain $P2C^-$ from a cheap and natural starting material such as L-proline.
To the best of our knowledge, the direct conversion of L-Proline to HP2C has been achieved only via enzymatic routes (Scheme 2).[8] In fact, classic Strecker degradation agents, such as ninhydrin or 1,2-dicarbonyl compounds, do not react with L-proline as well as other secondary amino acids.[1] On the other hand, the oxidation of L-Proline by organic oxidants, such as *N*-bromosuccinimide in water[9] or iodosylbenzene in various solvents,[10] yields 2-pyrrolidinone. The same product has been obtained by treatment of L-proline with $NaIO_4$ in aqueous H_2SO_4 (pH = 2).[11] Alkaline $KMnO_4$ reacts with L-Proline affording 4-aminobutanal, *i.e.* the corresponding Strecker aldehyde.[12]



Scheme 2. Overview of oxidation reactions of L-proline.

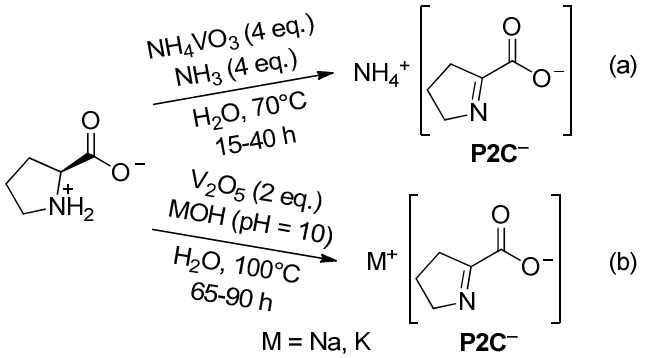
A selective dehydrogenation at the CH−NH position of L-Proline without undesirable side reactions (such as decarboxylation and over-oxidation of the product) was achieved only using protecting strategies on the α-amino acid. For instance, sodium pyrroline-2-carboxylate has been isolated with a five-step synthesis involving the preparation of L-Proline methyl ester, oxidation with ^{t}BuOCl and final basic hydrolysis of the ester.[5] A second multistep synthesis of the sodium salt Na[P2C] has been reported, involving coordination of L-proline to Cu(II), oxidation of the coordinated ligand by MnO_2/H_2O_2 and dissociation of the α-imino acidate ligand performed with an anion-exchange resin.[13]
The possible use of transition metals as "protecting groups" for this synthesis is limited by the fact that pyrroline-2-carboxylate is a good *N*,*O*-chelating ligand[14] and it is therefore difficult to dissociate from the metal centre at the end.
In the light of the possible roles played by vanadium in living organisms,[15] the interaction of vanadium ions with α-amino acids and oligo-peptides in water medium has aroused a considerable attention.[16] However, vanadium(V) is known to exhibit a poor affinity towards α-amino acids in aqueous solution[17] (unless peroxo[18] or hydroxylamido[19] ions are present) and only one (not fully characterized) oxovanadium(V)-amino acid complex has been isolated so far.[20] Moreover, the orthovanadate ion, $[VO_4]^{3-}$, is isoelectronic with other oxo-metallate ions of the first transition series, such as $[MnO_4]^-$ and $[CrO_4]^{2-}$, but the former is featured by a significantly lower electrochemical reduction potential.[21] Therefore, we reckoned that vanadium(V) was an interesting candidate in order to explore its oxidation chemistry towards α-amino acids.

In this paper, we report on the reactions of a series of α-amino acids with V(V) species in alkaline medium, providing a route for the one pot proline to pyrroline-2-carboxylate conversion.

Results and Discussion

Conversion of L-proline to pyrroline-2-carboxylate: reaction optimization and solid state isolation of M[P2C], M = Na, K.

Ammonium vanadate was initially studied as a commercially available, possible oxidative agent respect to L-proline. Thus, when mixtures of NH_4VO_3 and L-proline in water were treated with ammonia and heated at 70°C for 24-48 hours, a redox reaction took place. The resulting dark coloured solutions were investigated by NMR spectroscopy, revealing the selective oxidation (dehydrogenation) of L-proline to the corresponding α-imino acidate ($P2C^-$), Scheme 3a. The black precipitate, separated by filtration, was characterized by XRPD, which indicated the presence of the mixed-valence V(V)-V(IV) salt $(NH_4)_2V_3O_8$ in mixture with unreacted NH_4VO_3 (see Figure S1 given as Supporting Information).



Scheme 3. V(V)-mediated one pot conversion of L-proline to pyrroline-2-carboxylate ($P2C^-$).

The formation of $P2C^-$ in the NH_4VO_3/NH_3/L-proline system was investigated by varying the ratios between the reactants (see Experimental and Table S1 given as Supporting Information).

It should be noted that the initial pH of reaction mixtures was not measured: the pH value decreased over time due to the progressive dissolution of NH_4VO_3 (not completely soluble under the selected conditions). Therefore, representative pH values corresponding to a given NH_3/NH_4VO_3 molar ratio were determined by NH_3 titration of a dilute solution of NH_4VO_3 (Figure S2). The redox process occurred only within a limited window of pH values (modified via the NH_3/NH_4VO_3 ratio); this fact may be related to the pH-dependent speciation of vanadates in solution.[21b,22]

The optimal reaction parameters were established to be NH_3/NH_4VO_3 ratio = 1 (corresponding to pH = 9.8 for a dilute solution), NH_4VO_3/L-proline ratio = 4 and vanadium loading = 1.0 mol L^{-1} (see Table S1 for details). Assuming $(NH_4)_2V_3O_8$ as the only vanadium product, the stoichiometry requires six V(V) ions per L-proline, two of them undergoing reduction to V(IV) and the other four being incorporated within $(NH_4)_2V_3O_8$ (Equation 1). A partial aerobic re-oxidation of V(IV) to V(V) may account for the discrepancy between theoretical (6) and experimental (4) value of the optimal NH_4VO_3/L-proline ratio.

$$6\ NH_4VO_3 + C_5H_9NO_2 \rightarrow (NH_4)[C_5H_6NO_2] + NH_3 + 2\ H_2O + 2\ (NH_4)_2V_3O_8 \qquad (1)$$

Under the optimized conditions, a $P2C^-$ yield of 55% in solution was obtained after 25 h at 70°C (entry #14 in Table S1). However, the thermal and vacuum instability of ammonium pyrroline-2-carboxylate prevented the yield from reaching higher values, and the isolation of the salt in the solid state.

These drawbacks were overcome by cation exchange, from NH_4^+ to Na^+ or K^+. In fact, the quantitative formation of M[P2C] (M = Na, K) was achieved when 2:1 mol/mol mixtures of V_2O_5 and L-proline were treated with MOH up to pH = 10 and then heated at reflux temperature for 67 or 90 hours, respectively (Scheme 3b).

Sodium and potassium pyrroline-2-carboxylate could be isolated as ivory-white crystalline materials in low to moderate yields, allowing the full spectroscopic characterization of the anion (IR, UV-Vis, ^1H and ^{13}C NMR). To the best of our knowledge, the potassium salt is unprecedented, while Na[P2C] was previously obtained only by multi-step synthetic protocols.[5,13]

The black precipitates, filtered off at the end of the reaction, were identified as V(IV)-V(V) species NaV_2O_5 (XRPD (figure 1), spectroscopic and analytical techniques) and $K_2V_3O_8$ (spectroscopic and analytical techniques), respectively. The observed XRPD pattern corresponding to NaV_2O_5 is shown in Figure 1.

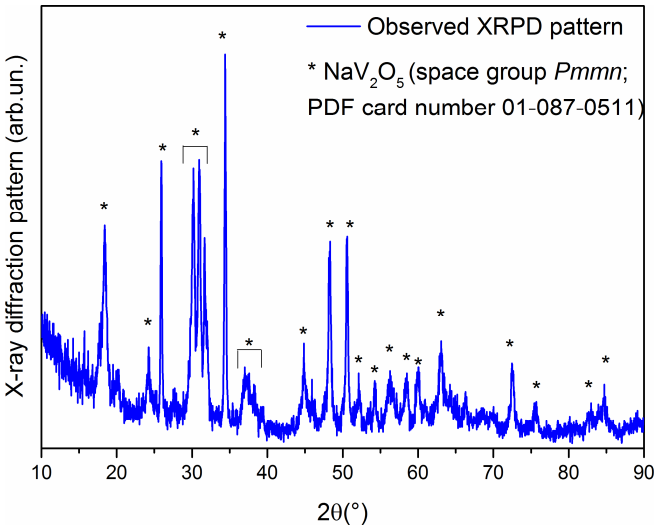
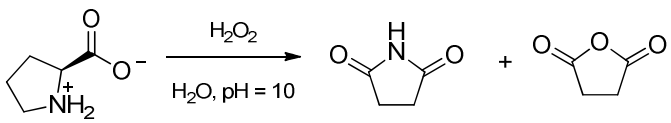


Figure 1. X-ray powder diffraction pattern of the black precipitate from the reaction of V_2O_5 with L-proline in aqueous NaOH solution at pH = 10. Reference PDF card from ref. 23.

To the best of our knowledge, the reactions reported in Scheme 3 represent the first example of direct chemical oxidation of L-proline to pyrroline-2-carboxylate, avoiding the use of group-protecting strategies. It is worthy to note that, in every cases, vanadium complexes with either L-proline or $P2C^-$ were not detected in solution or in the solid state, thus confirming the reluctance of vanadates to bind monoanionic *N,O* ligands (see Introduction).[17]

A series of oxidants have been reported to promote the oxidation of L-proline to products different from $P2C^-$ (see Introduction). In order to expand the knowledge on the oxidation chemistry of L-proline in water, and to see the possibility of performing the transformation to $P2C^-$ by oxidant species alternative to V(V), H_2O_2 and $Ce(SO_4)_2$ were tested under similar experimental conditions. While no reaction occurred in the presence of cerium(IV) sulfate, the reaction of L-proline with hydrogen peroxide gave a 81/19 mixture of succinimide and succinic anhydride (Scheme 4). This outcome reinforces the idea that V(V) holds unique features so to make possible the direct L-proline to $P2C^-$ conversion.



Scheme 4. Oxidation reaction of L-proline with H_2O_2.

L-Proline to $P2C^-$ conversion: DFT study.

Possible intermediates in the selective oxidation of L-proline by V(V) were studied by means of DFT calculations, considering water as continuous medium. One H_2O molecule was explicitly added to the computational models.

According to ^{51}V NMR spectroscopy, polynuclear V(V) oxo-anions may be generated in water under the experimental conditions described above (see Figures S3 and S4),[22] and a model based on four vanadium centres was chosen to balance the computational requests and the reliably of the simulations.

All the attempts to computationally obtain coordination compounds between the conjugate base of L-proline and $[V_4O_{12}]^{4-}$ or $[V_4O_{11}(OH)]^{3-}$ were unsuccessful because of the electrostatic repulsion between L-prolinate and the anions. On the other hand, a complex was obtained using $[V_4O_{10}(OH)_2]^{2-}$ as a reactant. It has to be highlighted that the protonation of $[V_4O_{12}]^{4-}$ up to $[V_4O_{10}(OH)_2]^{2-}$ resulted thermodynamically viable from preliminary DFT calculations, while the formation of $[V_4O_9(OH)_3]^-$ is unlikely in basic solution.[24]

The generation of $[V_4O_{10}(OH)_2(L\text{-prolinate})H_2O]^{3-}$ (**A,** Figure 2) from $[V_4O_{10}(OH)_2{\cdot}H_2O]^{2-}$ and L-prolinate is favourable, being the corresponding Gibbs energy variation about −11.8 kcal mol^{-1} at 343.15 K. The optimized geometry of **A** is shown in Figure 2. The coordination involves the carboxylate moiety, which is κ^1-bonded to a vanadium centre. The $V{-}O_{carboxylate}$ distance is 2.056 Å. The interaction of L-prolinate with the metal anion is enforced by a hydrogen bond between the other oxygen atom of the carboxylate group and a bridging hydroxo ligand ($O_{carboxylate}$---H, 1.565 Å; O–H, 1.007 Å). On the other hand, the NH fragment does not appear involved in any meaningful interaction. The cyclic structure of the polyoxovanadate is maintained after coordination, even though one vanadium centre is five-coordinated.

The most likely subsequent intermediate involves the one-electron transfer from coordinated L-prolinate to the polyoxo anion, to obtain the triplet state geometry **B** depicted in Figure 2. The Gibbs energy variation is only slightly positive, around 5.9 kcal mol^{-1}. The presence of a V(IV) centre, bound to L-prolinate, is confirmed by the spin density surface shown in Figure 2. The amino acidate ligand has radical character, and the unpaired electron is mainly localized on the nitrogen atom. The coordination mode of the amino acidate is comparable to that already described for intermediate **A**, but it has to be remarked that the oxidation of the ligand is accompanied by hydrogen migration from the nitrogen atom to one of the oxo-ligands, converting into a terminal hydroxo.

Another hydrogen migration from L-prolinate to the polyoxovanadate could afford intermediate **C** (Figure 2). The relative orientation of the L-prolinate ligand with respect to the polyoxometalate skeleton makes scarcely probable the direct H-migration from the carbon atom in alpha position. On the other hand, the hydrogen atoms of the N-bonded CH_2 should be quite acidic because of their closeness to the electron-poor nitrogen. The hydrogen migration from the CH_2 group causes the conversion of another oxo-ligand to a terminal hydroxo-. The formation of **C** from **B** is accompanied by a strongly negative Gibbs energy variation, −34.7 kcal mol^{-1}. A detailed investigation of the geometry optimization steps affording **C** suggests that a water molecule takes part to the proton transfer. As highlighted by the spin density surface of **C**, a second electron transfer accompanies the hydrogen migration. The intermediate is a pyrroline-5-carboxylate (P5C$^-$) complex of a polyoxovanadate containing two V(IV) centres, bridged by a OH-ligand. The coordination mode by the carboxylate group is the same as that described for the intermediates **A** and **B**.

The simple dissociation of the ligand from the polyoxo anion is not favourable, but the P5C$^-$ anion may be displaced by water to form **D** (Figure 2). Even if the simple reaction depicted in Figure 2 has positive ΔG, we must consider the concentration of water, the alkaline pH and therefore the presence of OH^- ions as good nucleophiles, and the decomposition of the final mixed-valence compound to unsolvable species as presumable driving forces. The tautomerization of pyrroline-5-carboxylate to the final pyrroline-2-carboxylate is favourable by about 3.5 kcal mol^{-1}.

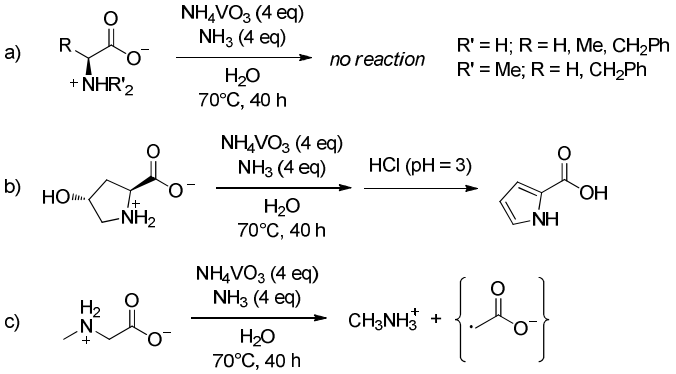
Figure 2 about here

Figure 2. DFT-optimized structures of possible intermediates involved in the oxidation of L-prolinate to pirrolidine-2-carboxylate and relative Gibbs energy values (kcal mol^{-1}, T = 343.15 K). C-PCM/ωB97X calculations, water as continuous medium. Colour map: light grey, hydrogen; dark grey, carbon; red, oxygen; blue, nitrogen; green, vanadium, light blue, spin density surface (isovalue = 0.01 a.u.). Cartesian coordinates of the DFT-optimized structures are collected in a separated. xyz file.

Substrate scope and mechanistic investigation.

Considering the results described in the previous paragraph, we were interested to see whether the observed V(V)-oxidation of proline could be extended to other α-amino acids. Therefore, a series of α-amino acids (Scheme 5) were allowed to react with NH_4VO_3 under the conditions optimized for L-proline (4 eq. NH_3, 4 eq. NH_4VO_3, 70 °C, 40 h). No reaction was observed with α-amino acids having tertiary amino groups (*N*,*N*-Dimethyl-L-phenylalanine, *N*,*N*-dimethylglycine), as expected since C=N bond formation for these substrates would imply the breaking of carbon-nitrogen bonds. On the other hand, reaction mixtures of secondary α-amino acids (*N*-methylglycine (sarcosine), *trans*-4-hydroxy-L-proline) rapidly turned black followed by the precipitation of $(NH_4)_2V_3O_8$ as found for L-proline (Scheme 3a). Pyrrole-2-carboxylic acid was isolated in 81% yield from *trans*-4-hydroxy-L-proline after acidification of the reaction mixture with HCl and subsequent Et_2O extraction (Scheme 5b). This product was previously obtained by the oxidation of *trans*-4-hydroxy-L-proline with $CuSO_4/H_2O_2$.[25] The formation of the aromatic pyrrole ring is probably the driving force for the dehydrogenation-dehydration of the α-amino acid. On the other hand, the oxidation of sarcosine by NH_3/NH_4VO_3 was not selective, yielding methylammonium and several unidentified species deriving from the $[CH_2CO_2^-]$ fragment (Scheme 5c). DFT calculations indicate that the coordination mode of the sarcosinate anion to $[V_4O_{10}(OH)_2{\cdot}H_2O]^{2-}$ should be analogous to that discussed for L-prolinate (see Figure S5).

Surprisingly, reaction attempts involving primary α-amino acids (glycine, L-alanine, L-phenylalanine) led to clean recovery of the starting materials (Scheme 5a).



Scheme 5. V(V)-mediated conversion of b) *trans*-4-hydroxy-L-proline to pyrrole-2-carboxylate and c) sarcosine to methylammonium. No reaction was observed with primary or tertiary α-amino acids (a).

In order to find a possible explanation for the lack of reactivity of primary α-amino acids, a DFT study was carried out by choosing glycine as a representative compound. On theoretical grounds, the coordination of glycinate to $[V_4O_{10}(OH)_2{\cdot}H_2O]^{2-}$ resembles that described for L-prolinate (Figure 3, intermediate **E**). Nevertheless, the formation of the corresponding triplet state (intermediate **F** in Figure 3) requires more energy (ΔG = 12.6 kcal mol^{-1}). More

important, the required, subsequent hydrogen migration may involve only the alpha-carbon and it is, differently from the case of L-prolinate, not thermodynamically favourable (ΔG = 3.5 kcal mol^{-1}). In the resulting species (intermediate **G** in Figure 3), the organic ligand maintains its radical character, and only one metal centre has been reduced to V(IV). In summary, the more difficult V(V)-oxidation of glycinate with respect to prolinate is presumably at the basis of the different reactivities observed with these two α-amino acids.

Figure 3 about here

Figure 3. DFT-optimized structures of possible intermediates in the interaction of glycinate with $[V_4O_{10}(OH)_2{\cdot}H_2O]^{2-}$ and relative Gibbs energy values (kcal mol^{-1}, T = 343.15 K). C-PCM/ωB97X calculations, water as continuous medium. Colour map: light grey, hydrogen; dark grey, carbon; red, oxygen; blue, nitrogen; green, vanadium, light blue, spin density surface (isovalue = 0.01 a.u.). Cartesian coordinates of the DFT-optimized structures are collected in a separated .xyz file.

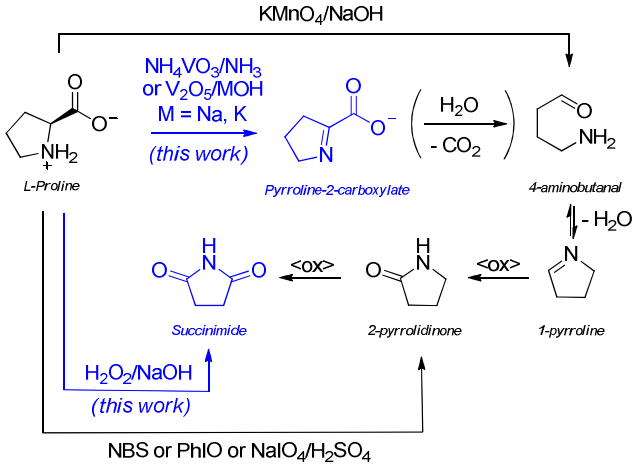
To shed more light on the mechanism of oxidation of secondary α-amino acids by V(V), the reactions with L-proline and *trans*-4-hydroxy-L-proline were then performed in D_2O. In the case of L-proline, 3,3-dideutero-1-pyrroline-2-carboxylate (P2C-d_2^-) was NMR identified in solution at the end of the reaction. The incorporation of deuterium in the C3 position of P2C$^-$ has been previously observed and associated to a fast equilibrium occurring between the cyclic imino and acyclic oxo-amino species in solution.[26] However the yield of P2C-d_2^- (35% after 30 h) was significantly lower than that of P2C$^-$ under the same conditions (55% after 25 h). The replacement of ^{1}H with ^{2}H in the O−H and N−H bonds of the intermediates in Figure 2 caused negligible changes of the relative energy values calculated by DFT (see Figure S6). The slower rate of the reaction can be therefore explained by supposing that, in the rate-determining transition state, E−hydrogen bond breaking occurs, preceded by H/D exchange.

Conversely, the reaction of *trans*-4-hydroxy-L-proline in D_2O afforded pyrrole-2-carboxylic acid, without incorporation of deuterium, in the same yield as in the H_2O experiment. These facts suggest that the mechanism of oxidation of L-proline and its 4-hydroxy analogue are different, and that hydrogen bonding may play a key role in the formation of pyrroline-2-carboxylate.[27] Another indication in this sense was obtained by using Et_3N as a base: no reaction between V_2O_5 and L-proline occurred after 40h at 70°C, while MOH/V_2O_5/L-proline mixtures (M = Na, K) gave a quantitative conversion to P2C$^-$ (Scheme 3B).

Conclusions

The interaction of vanadium ions with α-amino acids has aroused a great interest due to possible biological implications, and vanadium(V) was found to exhibit a poor affinity towards these biologically relevant compounds. This aspect, combined with the peculiar reduction potential of V(V) species, allows to selectively achieve the unusual, one pot conversion of L-Proline to the corresponding α-imino acidate, using NH_4VO_3 or V_2O_5 as oxidants in basic water medium. The best results, in terms of atom economy, yield and product stability, being obtained with V_2O_5. It is remarkable that the straightforward V(V) mediated oxidation of L-Proline is not reproducible with alternative chemical oxidants, including H_2O_2, leading to different outcomes (Scheme 6). Analogous amino acid to imino acid conversion was not observed by allowing a series of α-amino acids to interact with NH_4VO_3/NH_3. The unique properties associated to L-proline, among the family of α-amino acid compounds,[28] are probably responsible for the specific outcome observed. However, vanadium(V) oxyanions in basic aqueous solution were capable of reacting only with secondary α-amino acids, primary and tertiary α-amino acids resulting to be unreactive. It should be noted that most of the oxidizing agents employed in the classical Strecker degradation of α-amino acids, either are effective towards primary amino acids only, or do not show any substrate selectivity.

Our results suggest the possible convenience in the use of simple and cost effective V(V) compounds as stoichiometric oxidative agents for exploring uncommon organic synthetic pathways.



Scheme 6. Overview of oxidation reactions of L-proline.

Experimental

a) General

All manipulations were performed in air with common laboratory glassware. Reactions were carried out using deionised water. Solvents and reagents, including α-amino acids, NH_4VO_3 (≥ 99%) and V_2O_5 (98%) were used as received from Sigma-Aldrich. An Orion pH-meter equipped with a Hamilton glass pH-electrode was used for pH measurements. The instrument was routinely calibrated with standard pH = 2.0, 5.0 and 11.0 buffer solutions (Carlo Erba). Infrared spectra (4000-650 cm^{-1}) were recorded at 298 K on a FT IR-Perkin Elmer Spectrometer, equipped with a UATR sampling accessory. Spectra in the 200-650 cm^{-1} region were recorded in the transmission mode on CsI tablets. UV-Vis measurements were carried out at 298 K on a GE Healthcare Ultrospec 2100 pro spectrophotometer, using 1 mm quartz cuvettes in the 200-800 nm range. NMR spectra were recorded at 293 K on a Bruker Avance II DRX400 instrument equipped with a BBFO broadband probe. The chemical shifts were referenced to the non-deuterated aliquot of the solvent (^{1}H and ^{13}C) or to external standards (^{51}V to $VOCl_3$). The ^{1}H and ^{13}C NMR spectra were assigned with the assistance of DEPT-135 and ^{1}H-^{13}C correlation experiments (*gs*-HSQC and *gs*-HMBC).[29] A sealed capillary tube with C_6D_6 was used when NMR analysis was performed on aliquots of the reaction mixture in a non-deuterated media. In this case, NMR yield was estimated from the relative intensity of ^{13}C signals of analogous carbon atoms in the α-amino acid reactant and the product. Magnetic susceptibilities (reported per V atom) were measured on solid samples at 298 K with a Magway MSB Mk1 magnetic susceptibility balance (Sherwood Scientific Ltd). Diamagnetic corrections were introduced according to König.[30] Melting points and decomposition temperatures were determined on a STMP3 Stuart scientific instrument with a capillary apparatus. Carbon, hydrogen, nitrogen analyses were performed on a Carlo Erba mod. 1106 instrument. The vanadium(IV) and vanadium(V) contents were determined according to the method proposed by Mittal and Mehrotra.[31]

X-Ray powder diffraction analysis (XRPD) were performed by a Thermo ARL X´TRA powder diffractometer, operating in the Bragg-Brentano geometry and equipped with a Cu-anode X-ray source (K_α, λ =1.5418 Å), using a Peltier Si(Li) cooled solid state detector. The patterns were collected with a scan rate of 0.02 °/s in the 5°-90° 2θ range. The phase identifications were performed with the PDF-4+ 2015 database provided by the International Centre for Diffraction Data (ICDD). Polycrystalline samples were ground in

a mortar and then put in a low-background sample holder for the data collection.

b) Reactions between V(V) ions (NH_4VO_3 as precursor) and L-proline in aqueous ammonia solution.

The determination of the optimum conditions for pH (as a function of the NH_3/V molar ratio) and the analysis of vanadium species in solution through ^{51}V NMR spectroscopy are given as Supporting information (Figures S3 and S4).

i) Optimization of the reaction conditions.

NH_3/V molar ratio. A suspension of NH_4VO_3 (8.4 mmol) in H_2O was treated with variable amounts of NH_3 (NH_3/V molar ratio = 0.1, 1.0, 2.1) then with L-Proline (2.1 mmol, V/Pro molar ratio = 4.0) and diluted with H_2O (final volume of the solution: 10 mL). Higher values of pH (12.2, 14.3) were obtained as follows: NH_4VO_3 (8.4 mmol) was suspended in H_2O, treated with NaOH until complete dissolution of the solid (pH = 14.3) and diluted with H_2O (final volume of the solution: 10 mL). The pH was adjusted to 12.2 by adding the appropriate amount of 37% HCl. The mixture was heated at 70°C with a reflux condenser for 40-65 h. When a reaction took place, a black suspension was obtained within 1 h whose ^{13}C NMR spectrum showed the resonances of L-proline (unreacted starting material) and 1-pyrroline-2-carboxylate (P2C$^-$) anion [$^{13}C\{^1H\}$: δ = 175.8 (*C*=O); 171.9 (*C*=N); 60.3 (*C*H_2-N); 35.9 (*C*H_2-C=N); 22.0 (CH_2-*C*H_2-CH_2) ppm]. The highest NMR yield (40% after 45 h) was obtained with NH_3/V molar ratio = 1.0; no reaction was observed with a NH_3/NH_4VO_3 ratio of 0.1 and when the pH was adjusted to ≥ 12 (see table S1, entries #1-5).

Vanadium/L-Proline molar ratio. Reactions were performed with NH_4VO_3 (6.4 mmol), 28% NH_3 (NH_3/V molar ratio = 1.0), variable amounts of L-Proline (V/Pro molar ratio = 1.0, 2.0, 4.0, 8.0) and H_2O (final volume of the solution: 4 mL). The mixtures were heated at 70°C for 18-42 h with a reflux condenser yielding black suspensions. The formation of P2C$^-$ was observed in all cases; the highest NMR yield of P2C$^-$(60% after 31 h) was obtained by using a Vanadium/L-proline molar ratio of 4 (see table S1, entries #6-9).

Vanadium concentration. Reactions were performed with variable amounts of NH_4VO_3 (2.4, 4.0, 6.4, 8.0 mmol), 28% NH_3 (NH_3/V molar ratio = 1.0), L-Proline (V/Pro molar ratio = 4.0) and H_2O (final volume of the solution: 4 mL). The mixtures were heated at 70°C with a reflux condenser for 25-45 h yielding black suspensions. Comparable NMR yields of P2C$^-$ (50-60% after 20-30 h) were obtained when the amount of NH_4VO_3 exceeded 1.0 mol·L^{-1} (see table S1, entries #10-13), as expected for a saturated system. Therefore, we performed further reactions with a vanadium loading of 1.0 mol·L^{-1}.

Temperature and time. Reactions were performed with NH_4VO_3 (4.0 mmol), 28% NH_3 (NH_3/V molar ratio = 1.0), L-Proline (V/Pro molar ratio = 4.0) and H_2O (final volume of the solution: 4 mL). The mixtures were heated at 70°C or 100°C with a reflux condenser yielding black suspensions. NMR analysis was performed at various times. The highest NMR yield (60%) was reached when operating at 70°C for 46 h (see table S1, entries #14-15). Formation of by-products and a lower P2C$^-$ yield (40°C) were observed for a longer reaction time (67 h). No trace of P2C$^-$ was found working at 100°C even for shorter reaction times.

ii) Isolation of products in the optimized conditions.

The reaction was carried out with NH_4VO_3 (749 mg, 6.4 mmol), L-Proline (184 mg, 1.6 mmol), 28% NH_3 (0.45 mL, 6.5 mmol) and H_2O (6.0 mL). The mixture was heated at 70°C with a reflux condenser for 45 h. Therefore, the black suspension was allowed to cool to room temperature and filtered. The black residue was washed with acetone and dried under vacuum. This solid was identified by XRPD analysis as a mixture of NH_4VO_3 and $(NH_4)_2V_3O_8$ (0.41/0.59 molar ratio, respectively).[32] Yield: 626 mg, 90% with respect to the vanadium introduced. Anal. calcd. for $(NH_4VO_3)_{0.41}((NH_4)_2V_3O_8)_{0.59}$: H, 2.73; N, 9.48; V(IV), 8.89; V(V), 38.42. Found: H, 2.68; N, 9.98; V(IV), 9.50; V(V), 38.0. IR (solid state): ν = 3210m-br, 3008m-br, 2814m-br, 1678w, 1652w, 1416s, 1262w, 993m (V^{IV}=O), 932s, 809s (V^{IV}-O-V^{IV}), 733s (V^{V}-O-V^{V}), 524w, 502w, 426m, 365m, 333w, 242w cm^{-1}. Magnetic susceptivity: $\chi_g = 2.027\times10^{-6}$ cm^3·g^{-1}; $\Sigma\chi_m^D = -102.5\times10^{-6}$ cm^3·mol^{-1}; $\chi_m^P = 5.78\times10^{-4}$ cm^3·mol^{-1}; μ = 1.16 μ_B.[33] All attempts to isolate ammonium pyrroline-2-carboxylate from the filtrate solution were unsuccessful.

c) Reactions between V(V) ions (NH_4VO_3 as precursor) and α-amino acids in aqueous ammonia solution.

General procedure. A suspension of NH_4VO_3 (4.0 mmol) in H_2O (3.7 mL) was treated with 28% NH_3 (0.28 mL, NH_3/V molar ratio = 1.0) and with the selected α-amino acid (1.0 mmol, Vanadium/amino acid molar ratio = 4.0). The mixture was heated at 70°C with a reflux condenser for 40 h and analyzed by $^{13}C\{^1H\}$ NMR spectroscopy.

i) α-Amino acid = glycine, L-alanine, L-phenylalanine, *N*,*N*-dimethyl-L-phenylalanine, *N*,*N*-dimethylglycine. No reaction took place (colourless solution + colourless solid). The starting material is the only species identified in solution.

ii) α-Amino acid = sarcosine, *trans*-4-hydroxy-L-proline. The mixture darkened. At the end of the reaction, the black suspension was allowed to cool at room temperature and filtered. The black residue was washed with acetone and dried under vacuum. This solid was identified as a mixture of NH_4VO_3 and $(NH_4)_2V_3O_8$, having identical IR spectrum with the product obtained with L-proline (section b/ii). Organic products were identified or isolated as follows.

Sarcosine. The unreacted α-amino acid and $CH_3NH_3^+$ ($^{13}C\{^1H\}$: δ = 25.3 ppm, 65% NMR yield) were identified in solution. A number of low intensity signals were observed, due to the extensive decomposition of the carboxymethyl fragment of sarcosine. $^{13}C\{^1H\}$: δ = 179.3, 177.0, 173.4, 171.1, 167.9, 166.4, 165.7, 164.0, 137.2, 65.5, 60.1, 58.6, 53.3, 43.4, 37.8, 35.4, 28.0 ppm.

***Trans*-4-hydroxy-L-proline**. The pH of the filtrate solution was adjusted to 3 with 37% HCl. The aqueous phase was extracted with Et_2O. Pyrrole-2-carboxylic acid was isolated as a colourless solid after solvent removal under vacuum. Yield: 90 mg, 81%. IR (solid state): ν = 3351s, 3124w-m, 3007w-m-br, 2918w-m, 2850w-m, 2700w-m, 2753w-m, 2624w-m, 2574w-m, 2514w-m, 2075vw, 1892vw-br, 1654s, 1553m-s, 1436s, 1389m-s, 1323s, 1263m, 1187s, 1120vs, 1080m, 1034s, 947m, 878s, 845m, 749vs, 687m-s cm^{-1}. ^1H NMR (DMSO-d_6): δ = 11.54 (s, 1H, COO*H*); 6.95 (dd, 1H, C*H*-NH); 6.73 (dd, 1H, C*H*-C-C=O); 6.14 (dd, 1H, CH-C*H*-CH) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ = 162.7 (*C*=O); 124.1 (*C*H-NH); 123.1 (*C*-C=O); 115.5 (*C*H-C-C=O); 110.0 (CH-*C*H-CH) ppm.

d) Reactions between V(V) ions (NH_4VO_3 as precursor) and α-amino acids in ammonia D_2O solution.

The general procedure followed is identical to that described in section c except for the solvent (D_2O). The Vanadium-containing solid isolated from these mixtures was identified as a mixture of ND_4VO_3 and $(ND_4)_2V_3O_8$.[34] IR (solid state): ν = 3091v-w-br, 2348m-w-br (ND_4^+), 2222w-br, 2135w-sh, 2091w-sh (ND_4^+), 1401vw, 1115vw, 1073m-w (ND_4^+), 983m, 925w-m, 905w, 799s, 726s cm^{-1}.

i) α-Amino acid = L-proline. The unreacted α-amino acid and 3,3-dideutero-1-pyrroline-2-carboxylate anion[26] (P2C-d_2^-) were identified in solution. NMR yield: 35% after 30 h. $^{13}C\{^1H\}$ NMR (D_2O): δ = 175.7 (C=O), 171.9 (C=N), 60.3 (CH_2-N), 36.6-34.4 (m, CD_2), 21.7 (*C*$H_2$$CD_2$) ppm.

ii) α-Amino acid = sarcosine. The unreacted α-amino acid and $CH_3ND_3^+$ were identified in solution. NMR yield: 35% after 76 h.
^1H NMR (D_2O): δ = 2.5 (s) ppm. $^{13}C\{^1H\}$ NMR (D_2O): δ = 24.3 ppm.

iii) α-Amino acid = *trans*-4-hydroxy-L-proline. Non-deuterated pyrrole-2-carboxylic acid was isolated as a colourless solid. Yield: 91 mg, 82% (reaction time 63 h).

e) Reactions between V(V) ions (V_2O_5 as precursor) and L-Proline in basic aqueous solution.

General procedure. A suspension of V_2O_5 (10 mmol) in H_2O (20 mL) was treated with L-proline (5.0 mmol, V/Pro molar ratio = 4) and the selected base until pH = 10. The brown-green suspension was heated at a specified temperature and analyzed by $^{13}C\{^1H\}$ NMR spectroscopy. Products were identified or isolated as follows.

i) NaOH as base. A dark suspension was obtained after 67 h at 100°C with quantitative formation of P2C$^-$ (^{13}C NMR analysis). The reaction mixture was allowed to cool to room temperature and filtered. The solid was recovered by filtration, washed with water and dried in vacuo affording black NaV_2O_5. The brown filtrate was added of acetone which caused the precipitation of a pale brown solid ($NaVO_3$) which was recovered by filtration and dried in vacuo. The yellow filtrate solution was dried in vacuo and the residue was re-dissolved in few mL of ethanol. Et_2O addition caused the precipitation of sodium pyrroline-2-carboxylate, Na(P2C), as an ivory solid. The product was isolated by filtration, dried under vacuum and stored under N_2.

NaV_2O_5. Identified by XRDP analysis and IR spectroscopy. Yield: 1,36 g, 66% with respect to the vanadium introduced. IR (solid state): ν = 1607w, 1412w, 1301vw, 992m, 963m, 916w-m, 875w-m cm^{-1}.

$NaVO_3$. Identified by XRDP analysis and IR spectroscopy.[35] Yield: 750 mg, 31% with respect to the vanadium introduced. IR (solid state): ν = 1599w, 1416w, 960w-m, 929w-m, 869vs cm^{-1}.

Na(P2C). Yield: 54 mg, 8%. Melting point: 255°C (decomposition). IR (solid state): ν = 2951w, 2926w, 2867w, 1663vw, 1638w, 1606m-s (COO^-), 1448w, 1409m (COO^-), 1300m, 1257w-m, 1208w, 1155vw, 1134w-m, 1043w, 1009w, 988w-m, 915vw, 885vw, 780m, 723w-sh cm^{-1}. ^1H NMR (D_2O) δ = 3.77 (m, 2H, CH_2-N); 2.66 (m, 1.5H, CH_2-C=N)[36]; 1.85 (m, 2H, CH_2-CH_2-CH_2) ppm. $^{13}C\{^1H\}$ NMR (D_2O) δ = 176.8 (*C*=O); 171.9 (*C*=N); 60.3 (CH_2-N); 35.9 (*C*H_2-C=N); 22.0 (CH_2-*C*H_2-CH_2) ppm. UV-Vis (H_2O): λ_{max} (ε/L·cm^{-1}·mol^{-1}) = 205 ($1.8\cdot10^3$), 252 ($3.6\cdot10^2$), 307 ($9.1\cdot10$) nm.

ii) KOH as base. A dark suspension was obtained after 90 h at 100°C with quantitative formation of $P2C^{--}$ (^{13}C NMR analysis; 75% NMR yield after 67 h). From this reaction mixture, $K_2V_3O_8$, KVO_3 and potassium pyrroline-2-carboxylate, K(P2C), were isolated as described in section e-i.

$K_2V_3O_8$. Yield: 1.50 g, 62.5% with respect to the vanadium introduced. IR (solid state): ν = 977m, 936m, 926m, 811s, 734s cm^{-1}.

KVO_3. Identified by XRPD and IR analysis.[37] Yield: 903 mg, 32.7% with respect to the vanadium introduced. IR (solid state): ν = 3247vw-br, 1593w, 1393w, 1320w-sh, 963w-m, 912m, 894w-m, 846w-m, 760w-br, 666vw cm^{-1}.

K(P2C). Yield: 226 mg, 35%. Hygroscopic solid. ^1H and ^{13}C spectra in D_2O are identical to the sodium salt.

iii) NEt_3 as base. A yellow solution was obtained after 40 h at 70°C. Unreacted L-Proline was the only species identified in solution.

f) Reactions between H_2O_2 and L-Proline in aqueous solution.

A solution of L-proline (5 mmol) in H_2O (15 mL) was treated with 30% H_2O_2 (5 mL, 50 mmol) and then with NaOH until pH = 10. The resulting colourless solution was refluxed for 50 h then allowed to cool to room temperature. The aqueous solution was extracted with Et_2O and the organic phase was dried in vacuum. The residue was identified as a mixture of succinimide (81%) and succinic anhydride (19%) by NMR analysis. IR (solid state): ν = 2934w-m, 2533w, 2251w-m, 2087w-m, 1771w, 1682vs, 1555m, 1417m-s, 1379s, 1344s, 1298m-s, 1264m, 1198s, 1177m-s, 1093w-m, 1046m-s, 890m, 802m-s, 677w-m cm^{-1}. ^1H NMR (D_2O): δ = 2.71 (s, 4H, CH_2, succinic anhydride); 2.58 (s, 4H, CH_2, succinimide) ppm. $^{13}C\{^1H\}$ NMR (D_2O): δ = 183.2 (succinimide, *C*=O); 177.5 (succinic anhydride, *C*=O); 29.5 (succinimide, *C*H_2); 29.2 (succinic anhydride, *C*H_2) ppm.

Computational Details

The computational geometry optimizations were carried out without symmetry constrains, using the range-separated DFT functional ωB97X, [38] in combination with the split-valence polarized basis set of Ahlrichs and Weigend.[39] The "unrestricted" formalism was applied for compounds with unpaired electrons, and the lack of spin contamination was verified by comparing the final $<S^2>$ values with the theoretical ones. The stationary points were characterized by IR simulations (harmonic approximation), from which zero-point vibrational energies and thermal corrections (T = 298.15 K and 343.15 K) were obtained.[40] The C-PCM implicit solvation model was added to ωB97X calculations, considering water as continuous medium.[41] The software used was Gaussian '09.[42] Preliminary DFT calculations were carried out *in vacuo* with the EDF2 [43] hybrid-GGA functional and the 6-31G** basis set, [44] using the Spartan '16 software. [45] package.

Supporting Information

Detailed description of the determination of pH as a function of the NH_3/V molar ratio, Figures S1-S6 and Table S1.

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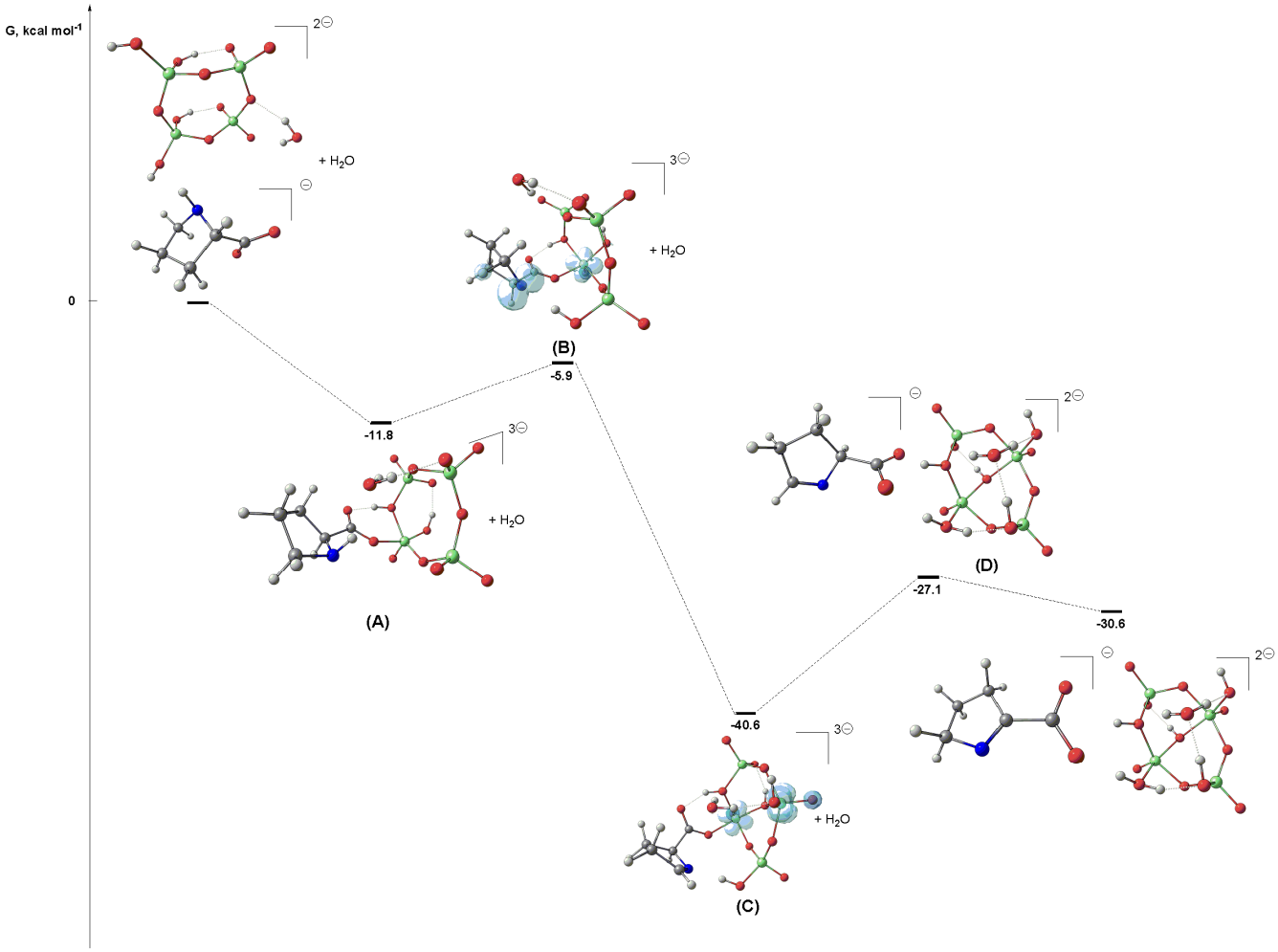

Figure 2. DFT-optimized structures of possible intermediates involved in the oxidation of L-prolinate to pirrolidine-2-carboxylate and relative Gibbs energy values (kcal mol^{-1}, T = 343.15 K). C-PCM/ωB97X calculations, water as continuous medium. Colour map: light grey, hydrogen; dark grey, carbon; red, oxygen; blue, nitrogen; green, vanadium, light blue, spin density surface (isovalue = 0.01 a.u.). Cartesian coordinates of the DFT-optimized structures are collected in a separated. xyz file.

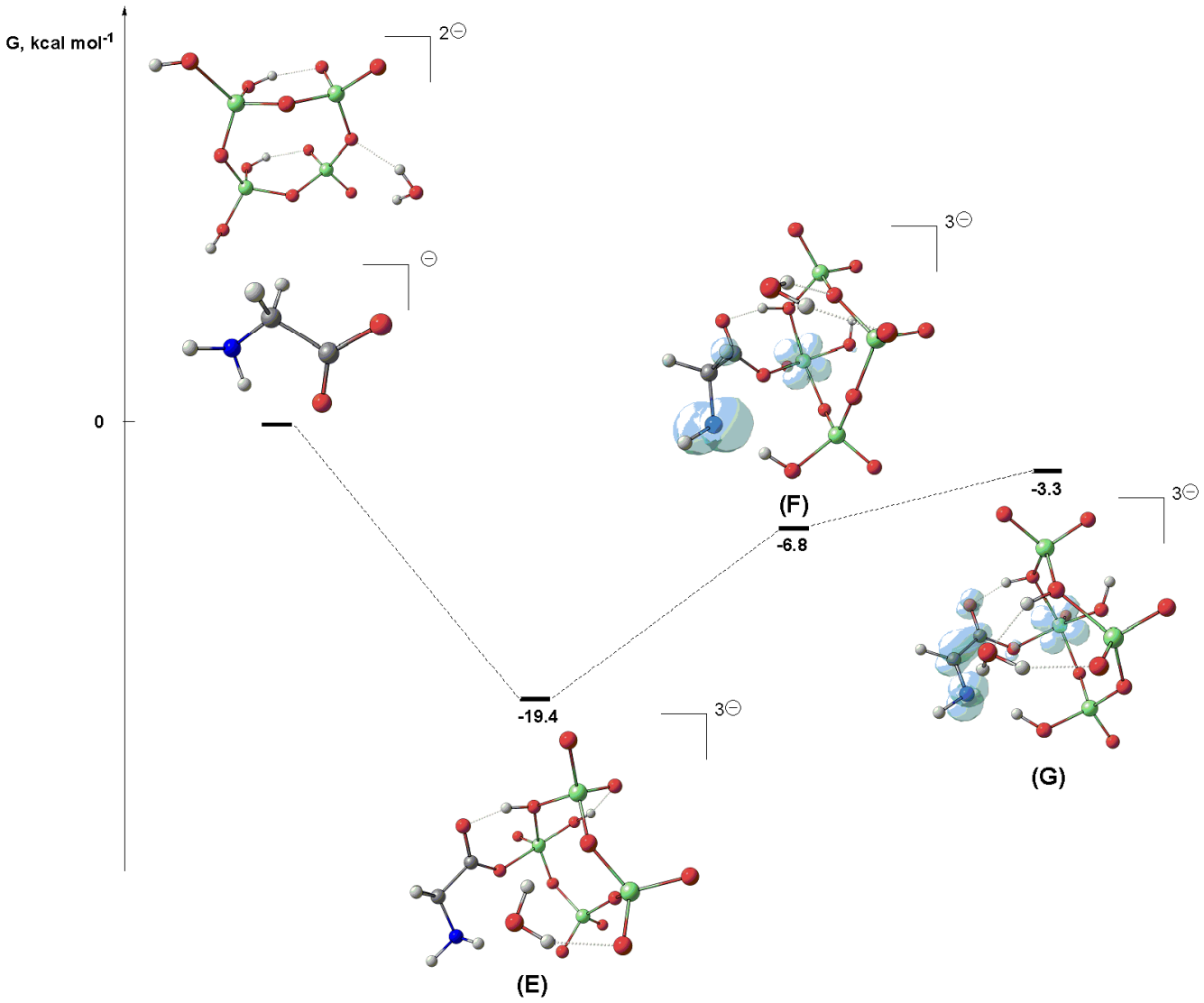

Figure 3. DFT-optimized structures of possible intermediates in the interaction of glycinate with $[V_4O_{10}(OH)_2 \cdot H_2O]^{2-}$ and relative Gibbs energy values (kcal mol^{-1}, T = 343.15 K). C-PCM/ωB97X calculations, water as continuous medium. Colour map: light grey, hydrogen; dark grey, carbon; red, oxygen; blue, nitrogen; green, vanadium, light blue, spin density surface (isovalue = 0.01 a.u.). Cartesian coordinates of the DFT-optimized structures are collected in a separated .xyz file.