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(Article begins on next page)

When the surface matters: prebiotic peptide bond formation on the TiO₂ (101) anatase surface through periodic DFT-D2 simulations

¹Stefano Pantaleone, ²Piero Ugliengo, ¹Mariona Sodupe*, ¹Albert Rimola*

¹*Departament de Química, Universitat Autònoma de Barcelona, Bellaterra 08193, Catalonia, Spain*

²*Dipartimento di Chimica and Nanostructured Interfaces and Surfaces (NIS) Inter-Departmental centre, Università degli Studi di Torino, Via P. Giuria 7, 10125 Torino, Italy.*

E-mail corresponding authors:

albert.rimola@uab.cat

mariona.sodupe@uab.cat

Abstract

The mechanism of the peptide bond formation between two glycine (Gly) molecules has been investigated by means of PBE-D2* and PBE0-D2* periodic simulations on the TiO₂ (101) anatase surface. This is a process of great relevance both in fundamental prebiotic chemistry, as the reaction univocally belongs to one of the different organizational events that ultimately led to the emergence of life on Earth, as well as from an industrial perspective, since formation of amides is a key reaction for pharmaceutical companies. The efficiency of the surface catalytic sites is demonstrated by comparing the reactions in gas phase and on the surface. At variance with the

uncatalyzed gas-phase reaction, which involves a concerted nucleophilic attack and dehydration step, on the surface these two steps occur along a stepwise mechanism. The presence of surface Lewis and Brønsted sites exerts some catalytic effect by lowering the free energy barrier for the peptide bond formation by about 6 kcal mol^{-1} compared to the gas-phase reaction. Moreover, the co-presence of molecules acting as proton transfer assistants (*i.e.*, H_2O and Gly as well) provide a more significant kinetic energy barrier decrease. The reaction on the surface is also favourable from a thermodynamic standpoint, involving very large and negative reaction energies. This is due to the fact that the anatase surface also acts as a dehydration agent during the condensation reaction, since the outermost coordinatively unsaturated Ti atoms strongly anchor the released water molecules. Our theoretical results provide a comprehensive atomistic interpretation of the experimental results of Martra et al. [Angew. Chem. Int. Ed. 2014, 53, 4671], in which polyglycine formation was obtained by successive feedings of Gly vapour on TiO_2 surfaces in dry conditions and are, therefore, relevant in a prebiotic context envisaging dry and wet cycles occurring, at mineral surfaces, in small pool.

Introduction

Since the first experiments on prebiotic chemistry, during the fifties/sixties of the last century, there are still several open questions that have not been unambiguously answered. Miller's experiments demonstrated that by mixing simple molecules such as CH_4 , NH_3 , H_2O and H_2 in a reactor under UV light and electric discharges a complex mixture of organic compounds, including different amino acids, is obtained.^[1-2] In the same line, Oró's experiments showed that the addition of a mixture of HCN and NH_3 in a water solution yielded the formation of adenine (one of the four nitrogenous bases),^[3] while by adding H_2CO in the mixture the synthesis of ribose and deoxyribose (the

sugars that are part of the nucleotide) was observed,^[4] in agreement with the Butlerov formose reaction.^[5-7] These experiments paved the way for the development of a new field of research; *i.e.*, the prebiotic chemistry, and since then, many theories have attempted to explain how the complex machinery of life emerged in a primitive Earth and which energy sources could have helped starting up the implicated processes, such as UV radiation,^[8-13] hydrothermal energies of the deep sea,^[14-15] meteorites as catalysts^[16-17] and their impact as a source of energy,^[18-20] and redox energies.^[21-22] In the last years, this subject has been growing up continuously and, nowadays, is covering not only the prebiotic chemistry on Earth but also in the Universe.^[23-24] Indeed, major efforts are being devoted to study the formation of molecules in astrophysical environments. Considered molecules range from the synthesis of fundamental molecules such as H₂,^[25-26] H₂O,^[27-30] NH₃,^[31-32] CH₄^[19, 33] and CO₂,^[34-36] to the formation of evolved organic compounds,^[37-39] some of them being of biological relevance such as amino acids, nucleobases and sugars, as revealed by their high contents in meteorites.^[40-43]

The next step after the synthesis of the biomolecular building blocks is the formation of the corresponding biopolymers, which are essential macromolecules for life. This is the case, for instance, for the synthesis of peptides by polymerization/condensation of amino acids through the peptide bond formation, or the linkage of ribose/deoxyribose with nitrogenous bases and phosphates, through N-glycosidic and phosphoester bonds, respectively, to form a nucleotide monomer, which in turn polymerize via phosphodiester bonds to form a nucleotide strand.^[44-47]

The present work focuses on the problem of the amino acid polymerization, and in particular deals with the condensation between two glycine molecules, which is accompanied by water elimination, as the simplest test case for the peptide bond

formation reaction. In gas phase, this reaction is kinetically hampered because of the high activation energy barrier, about 45-55 kcal mol⁻¹ according to previous calculations.^[48-52] Moreover, since the reaction releases water, the process is thermodynamically unfavourable when it occurs in water solution, as it would be the case in a primordial ocean.^[53] A possible solution to the dehydration problem arose from the biophysicist J.D. Bernal in 1949, who suggested that the first peptides (and other biopolymers) could have been formed on the surfaces of naturally-occurring minerals.^[54] Indeed, minerals can immobilize amino acids, protect them from adverse conditions, and concentrate them, providing favourable conditions for their polymerization. Moreover, the interaction between the amino acids and the minerals (either on the surfaces, the interlayer regions in clays, or inside cavities of mesoporous minerals) can induce an electronic structure reorganization of the amino acids, thus activating them; *i.e.*, the surface can provide the proper catalytic sites responsible for the lowering of the energy barrier.^[53] More recently, Smith^[55] suggested that minerals might have scavenged organic species for catalytic assembly into specific polymers protected from prompt hydrolysis and photochemical destruction. Along the same line, Orgel^[56] proposed the “polymerization on the rocks” paradigm, stating that oligomers can be elongated by repeated condensation cycles on the mineral surfaces and that the affinity of a surface for an oligomer increases with its length up to an almost irreversible adsorption. Within this context, an interesting hypothesis to overcome the “water problem” (*i.e.*, in water solution the reaction is disfavoured), or more general, the “water paradox”^[57] (*i.e.*, water is essential for life but it inhibits the formation of biopolymers mandatory for life), is that based on fluctuating environments in the prebiotic Earth. That is, daily fluctuations of temperature and seasonal fluctuations of humidity, which readily occurs under natural conditions, could have led to cycles of drying and rewetting

allowing the condensation reactions.. This theory is supported by experimental evidences; for instance, Lahav et al.^[58] showed that systems consisting of clay, water, and amino acids subjected to cyclic variations in temperature and water content produced long oligopeptides in higher yields; Muller and Schulze-Makuch showed that macroscopic cycles, including drying, might drive a chemical reaction that would be endergonic in isolation.^[59]

In addition to this prebiotic interest, the reaction of the peptide (and amide) bond formation is also of interest for industrial purposes. Indeed, formation of amide bonds by condensation of non-activated amines and carboxylic acids catalysed by nanostructured mineral oxide surfaces holds potentialities as a sustainable route for the industrial production of amides.^[60-61] Nowadays, the amide formation reaction is a key process for pharmaceutical companies, in which, in the current synthetic routes, the adoption of powerful activating agents is routinely used. Unfortunately, these routes are expensive and environmentally unfriendly, with toxic/corrosive by-products and large quantities of waste. Thus, developing clean and low cost synthetic strategies with good atom economy is highly pursued.^[62]

Many experimental works have focused on the polymerization of amino acids on different minerals surfaces such as silica,^[63-67] clays,^[58, 68] alumina,^[63-65, 69-72] iron oxides^[73] and hydroxides^[74] and titania.^[75-77] Although different theoretical works on the peptide/amide bond formation on particular models for mineral surfaces such as silica,^[50, 52, 67] aluminosilicates,^[48, 51, 78] zeolites^[79] or iron sulphides^[80] were reported, this process has not been hitherto addressed on TiO₂, despite experimental evidences of its catalytic role.^[76] In this work, we present, for the first time, quantum chemical simulations addressing the mechanism of condensation between two glycine molecules on the TiO₂ (101) anatase surface. This work is inspired on the experimental findings of

Martra and co-workers,^[76] in which in-situ IR and mass spectrometry measurements identified the formation of long glycine oligomers (up to 16-mers) from successive feedings with monomers from the vapour phase on the (101) and (001) facets of anatase nanoparticles.

Titanium dioxide was identified, albeit as a minor mineral, in Eoarchaen (4.0–3.6 Gy) mineral deposits and specifically in metavolcanic rocks and schist in the first stage of mineral evolution (see Table 1 of ref. ^[81]). The potential presence of TiO₂ was not limited to endogenous processes, since it was found in meteorites that played a key role in supplementing the early Earth with extra matter, including carbon. For instance, TiO₂ was found in the Allan Hills meteorite A77307 (type: CO3.0 ordinary chondrite), the Martian meteorite EETA79001 or the Chicxulub impact crater (see ref. ^[82] and references therein). Three recent papers addressed the role of TiO₂ as a key mineral in origin of life.^[82-84] Despite being a minor mineral, TiO₂ is called in action as a catalyst, therefore its abundance does not need to be very high to be effective in prebiotic processes. On industrial and technological applications, TiO₂ nanoparticles have been extensively investigated in several fields due to their exclusive catalytic and physico-chemical properties.^[85-86]

In previous works by some of us, the two-glycine condensation reaction was simulated on a surface model of sanidine feldspar containing both Lewis and Brønsted sites.^[51, 78] Results indicated that the co-presence of these two sites is crucial for the catalytic activity of the surface. The TiO₂ (101) anatase surface also presents Lewis acidic sites and Brønsted basic sites represented by pentacoordinated Ti atoms and bivalent O atoms, respectively, in the outermost positions of the surface. That is, Ti atoms can accept lone pairs of donor atoms (*e.g.*, N or O), while O surface atoms can become Brønsted bases by accepting protons released by acidic compounds. This is

indeed the case for glycine, which on the (101) anatase surface spontaneously transfers the -COOH proton to the surface giving rise to a $\text{glycine}^-/\text{surface}^+$ ion pair.^[87] In this work, kinetic and thermodynamic effects of the TiO_2 (101) anatase surface, caused by the presence of Ti Lewis atoms and O Brønsted sites, for the peptide bond formation between two glycine molecules is demonstrated by periodic DFT-D2 simulations. Moreover, the work also shows that the presence of H_2O or a third glycine molecule acting as proton transfer assistant induces a significantly lowering of the energy barriers. This last subtle aspect is relevant during the drying process, as it shows that the peptide bond formation is more favoured in micro solvation conditions than under a completely dry situation.

Computational Details

Methods

Periodic DFT calculations were carried out with the Vienna *Ab-initio* Simulation Package, (VASP) code,^[88-91] which uses a projector-augmented wave (PAW) pseudopotentials^[92] to describe the ionic cores and a plane wave basis set for the valence electrons.

Geometry optimizations and frequency calculations were performed with the PBE-D2* method; that is, the pure Perdew-Burke-Ernzerhof (PBE) functional^[93] plus the *a posteriori* correction term D2^[94] proposed by Grimme to account for dispersion forces (missed partly in PBE) but whose initial parametrization was modified for extended systems (D2*^[95]) providing accurate results for the calculation of cohesive energies and adsorption processes within a periodic treatment.^[96-98] The reaction energetics were refined by performing single-point energy calculations at PBE0^[99]-D2* theory level on the optimized stationary points.

For the present work the kinetic energy cut-off was set to 500 eV, the self-consistent field (SCF) iterative procedure was converged to a tolerance in total energy of $\Delta E = 10^{-4}$ eV for minima optimization and $\Delta E = 10^{-6}$ eV for transition state optimization, while for all PBE0 single point energy calculations was set to $\Delta E = 10^{-6}$ eV. The tolerance on gradients for geometry optimization was set to 0.01 eV/Å for each atom in each direction. For transition state optimization, the DIMER method^[100-103] was used, and in some difficult cases the climbing image – nudged elastic band (CI-NEB) method^[104-109] was resorted. The k -points mesh was set to (3,3,1) for all the reaction studied. The Monkhorst-Pack sampling of the Brillouin zone was used for the k -points mesh. The above computational parameters ensured a full numerical convergence on all the computed properties described in this work.

Vibrational frequencies of a reduced Hessian matrix (*i.e.*, considering only the displacements of the atoms corresponding to the reactant molecules and to the first layer of the surface) were computed, at the Γ point, by numerical differentiation of the analytical first derivatives, using the central difference formula (*i.e.* two displacements for each atom in each direction). Frequency calculations were useful to characterize reactants, products and intermediates as minima of the potential energy surface (no imaginary frequencies) and that transition state structures are saddle points (one imaginary frequency associated with the reaction coordinate). From the calculated frequencies, moreover, we computed free energy values at $T = 298.15$ K using a home-made script that allows us to calculate quasi-harmonic (QH) thermochemical corrections. The QH approach was proposed by Grimme^[110] in which frequencies lower than the 100 cm^{-1} cut-off are replaced by free rotor modes when building up the entropy. This improves the calculation of vibrational entropy which would be underestimated when considering very low frequency values; to avoid discontinuity close to the cut-off

value, a damping function is used to interpolate the values of entropy computed with the two approaches. Due to the high computational cost of PBE0-D2* method for the frequency part, free energy values at PBE0-D2* were obtained by adopting the PBE-thermal corrections to the PBE0 electronic energies.

For all the reactant structures, both in gas phase and on the surface, we carried out a Bader charge analysis in order to examine whether the surface infers any electronic structure reorganization to the reactants. In particular, we tracked the charge on the C atom where the nucleophilic attack occurs. Calculations were performed with the Bader charge analysis code developed by the Henkelman group.^[111-113]

Visualization and manipulation of the structures have been done with the MOLDRAW package^[114] and figures rendered with the POVRAY program.

Surface models

Starting from the crystal bulk structure of the TiO₂ anatase polymorph, we built a crystalline periodic slab model for the non-polar (101) surface (see Figure 1) with a thickness of 10 Å (3 layers of TiO₂). This was shown to be the compromise between the accuracy and the computational cost.^[87] For the reaction mechanisms only the internal atomic positions were optimized, while the cell parameters remained fix to the experimental values.^[115]

The standard 1×1 unit cell for the TiO₂ (101) anatase surface has as lattice parameters $a = 3.7845$ Å, $b = 5.1197$ Å, and an angle of 90 degrees (see Figure 1). However, to simulate the reaction without steric clashes of the adsorbates while keeping a reasonable computational cost, we used a 2×2 supercell for all the condensation reactions but for the reaction in presence of two H₂O molecules, in which we used a 3×2

super-cell. The distance between artificial slab periodic images, regulated by the c value, was defined ensuring an empty space of 10 Å between the outermost atom of the adsorbed amino acid and the upper layer. This condition is satisfied by setting the c value to 25 Å, large enough to avoid mutual fictitious interactions between the periodically repeated slabs.

Results and Discussion

The gas-phase -NH-C(=O)- peptide bond formation through the condensation of two glycine (Gly) molecules is a concerted reaction.^[48] It involves a nucleophilic attack of the NH_2 group of one Gly to the C atom of the carbonyl CO group of the other Gly. This step is simultaneous to a proton transfer from the attacking NH_2 group to the OH group of the second glycine, thus yielding the elimination of one water molecule (see Scheme 1).

The reaction has already been studied theoretically in gas phase,^[48, 50-52, 78] adopting either the reaction of $\text{NH}_3 + \text{HCOOH} \rightarrow \text{NH}_2\text{CHO} + \text{H}_2\text{O}$ as the simplest model reaction, or the reaction between more complex forms such as $\text{NH}_3 + \text{CH}_3\text{COOH} \rightarrow \text{NH}_2\text{COCH}_3$) or the actual $\text{Gly} + \text{Gly} \rightarrow \text{NH}_2\text{CH}_2\text{CONHCH}_2\text{COOH}$ (this latter species hereafter referred to as GlyGly) condensation reaction. These calculations indicated that the reactions have free energy barriers at $T = 298 \text{ K}$ (ΔG_{298}^\ddagger) ranging from 45 to 55 kcal mol^{-1} , depending on the type of reaction and the method employed. The calculated reaction free energies at $T = 298 \text{ K}$ ($\Delta_r G_{298}^0$) indicated that these processes are either isoergonic or slightly exoergonic. In this work, the uncatalysed gas-phase reaction has an intrinsic free energy reaction barrier $\Delta G_{298}^\ddagger = 41.8 \text{ kcal mol}^{-1}$ and a free reaction energy $\Delta_r G_{298}^0 = -7.3 \text{ kcal mol}^{-1}$ (see Figure S1 of supplementary information,

SI). These values will be our reference to assess the catalytic role of the (101) anatase TiO₂ surface.

Gly + Gly on the TiO₂ (101) anatase surface

A previous work by some of us^[87] showed that the most stable complex of Gly interacting with the (101) anatase surface is that in which Gly is deprotonated due to a proton transfer from the COOH group to the surface. This structure will be referred to as Gly/TiO₂ system along the work. The Gly/TiO₂ system was chosen as the pre-reactant adduct through which the peptide bond formation occurs by the reaction with an incoming Gly molecule from the gas-phase.

Figure 2 shows the free energy profile at T = 298 K of the reaction, taking as the 0th energy reference the asymptote SGG-AS. This asymptote is defined as infinitely separated Gly/TiO₂ and an isolated Gly molecule (considered in gas-phase). The reason to choose this asymptote as a reference, is to mimic, as close as possible, the chemical vapor deposition scenario carried out in the experiments by Martra et al.^[76] This setup account for the entropic cost (disfavouring the reaction) due to the encounter of Gly from gas-phase with that adsorbed at the TiO₂ surface. It is worth mentioning that other reference asymptotes could have also been chosen, such as that in which both Gly molecules are adsorbed on the surface. Nevertheless, the step in which one Gly should desorb from the surface to reach and react with the second target adsorbed Gly provides the same scenario simulated by our reference asymptote.

At variance with the process in gas-phase, the reaction on the surface adopts a stepwise mechanism. The first step involves the simultaneous nucleophilic attack and the proton transfer. In this case, however, since the adsorbed Gly is in its deprotonated

state, H₂O cannot be released. The dehydration takes place in the second step, in which the proton formerly attached to the surface is transferred to the OH group to finally give water as a product. The water molecule, once formed, can be adsorbed at the surface, either through H-bond with surface O atoms or by interaction with a coordinatively unsaturated Lewis Ti atom: the latter process turned out to be the most favourable one. The calculated free energy profile is overall more favourable towards the peptide bond formation than the uncatalysed gas-phase process. The first step shows the highest energy barrier ($\Delta G_{298}^{\ddagger} = 35.6 \text{ kcal mol}^{-1}$), while the energy barrier of the dehydration step (with respect to the SGG-AS asymptote) is $\Delta G_{298}^{\ddagger} = 17.5 \text{ kcal mol}^{-1}$. The first step is about 6 kcal mol^{-1} lower than the analogous process in gas phase, thus showing that the interaction with the surface does indeed exert a catalytic effect. With the aim to have deeper insights onto this aspect, we have performed a Bader charge analysis of the reactant structure, in particular of the C atom of the carboxylic group. The interaction with the surface induces an increase of the positive charge of the C atom of the COO group. Indeed, for gas-phase Gly, Bader charge is $1.51 e$, while on the surface (*i.e.*, the Gly/TiO₂ complex) it is $1.58 e$. This means that the C atom becomes more electrophilic upon adsorption and accordingly more prone to be attacked by the N atom of the incoming Gly molecule. Such charge differences are also reflected on the values of the C-N distance in the reactant and transition state structures of the uncatalyzed reaction and on the surface. On the surface the C-N distances are significantly shorter (2.866 and 1.604 \AA for SGG-R and SGG-TS1, respectively, see Figure 2) than in the gas phase (3.077 and 1.631 \AA , respectively, see Figure S1 of SI). Despite the catalytic effect, the barrier is still significantly high due to the fourth-membered ring present in the transition state structure (see structure SGG-TS1 of Figure 2). The thermodynamics of the reaction is, however, only favourable when the formed water interacts with the

surface through a surface Ti atom ($\Delta_r G_{298}^0 = -23.6 \text{ kcal mol}^{-1}$, see structure SGG-P2 of Figure 2). This fact is very important, showing that the surface can act as a dehydrating agent capturing the formed water, thereby displacing the reaction towards the peptide bond formation. Indeed, although in both structures the interaction is through Ti—O and Ti—N dative bonds plus an H-Bond (see SGG-P2 and SGG-AS, respectively), dispersion forces are more favourable in the first structure by about 6 kcal mol^{-1} .

Gly + Gly on the TiO₂ (101) anatase surface under moderately dry conditions

A catalytic role of the (101) anatase surface was demonstrated in the previous section. However, the energy barrier is still too high to be surmountable at normal thermodynamic conditions. As mentioned above, the high kinetic barrier is due to the fourth-membered ring transition state (SGG-TS1) structure which is geometrically highly strained. Thus, a reasonable way to decrease the energy barrier is by reducing the geometrical strain of the transition state. It has long been recognized that traces of water may act as a catalyst for this purpose, as even few water molecules can act as a proton transfer assistant through the proton relay mechanism. Accordingly, we have studied the peptide bond formation on the (101) anatase surface in the presence of 1 and 2 water molecules assisting the proton transfer of the first step, mimicking moderately dried conditions.

The calculated free energy profile at 298 K for the reaction assisted by one water molecule is shown in Figure 3. The 0th energy reference is the asymptote SGGF-AS, which involves the Gly/TiO₂ system and the isolated gas-phase Gly and H₂O molecules, all of them infinitely separated. The energy barrier of the first step is lowered to $\Delta G_{298}^\ddagger = 20.7 \text{ kcal mol}^{-1}$, which means a reduction of about 15 kcal mol^{-1} compared to the non-

water-assisted mechanism confirming the proton relay as a mechanism to relieve the strain in the ring activated complex (SGGW-TS1) by expanding it to a sixth-membered ring. In relation to the second step, calculated $\Delta G_{298}^{\ddagger}$ is 22.9 kcal mol⁻¹ (see SGGW-TS2), 5.4 kcal mol⁻¹ higher than the corresponding step in the non-water-assisted reaction. This increase is due to the destabilization of the SGGW-TS2 transition state shown by the distance of the newly formed H_{surface}...O_{Gly}. In SGGW-TS2 (non-water-assisted), this distance is 1.153 Å, while it becomes as large as 1.465 Å in SGGW-TS2 (1-water-assisted) showing an almost completely broken surface OH bond with a corresponding higher kinetic barrier. As for the non-water-assisted mechanism, the thermodynamics of the reaction is favourable ($\Delta_r G_{298}^0 = -29.3$ kcal mol⁻¹, see SGGW-P2) only when the two water molecules in the final product (namely, that assisting the proton transfer and the one formed in the process) are interacting with Ti surface atoms through coordinative bonds.

Figure 4 shows the calculated free energy profile at 298 K for the reaction assisted by two water molecule. Herein, the reference asymptote corresponds to Gly/TiO₂ plus a gas-phase Gly molecule and two isolated gas-phase water molecules (SGG2W-AS). Considering only the potential energy surface, we identified a first stationary point (SGG2W-R) in which the N-C bond forms without the simultaneous H transfer. Here, a HOOC-CH₂-NH₂⁺-COO²⁻-CH₂-NH₂ zwitterionic species is formed. This is at variance of the two previous processes, in which the N-C bond formation took place simultaneously to the H transfer. Such a zwitterion species is stabilized (in terms of potential energies) by the interactions with the two water molecules. Interestingly, formation of this stationary point is barrierless, as the energy decreases continuously by decreasing the N-C distance (*i.e.*, by performing a scan calculation using the N-C distance as the distinguished coordinate). However, when considering the free energies,

SGG2W-R is found to be unstable (*i.e.*, it is 5.6 kcal mol⁻¹ more energetic than the asymptote) mainly due to entropic effects, therefore it can be neglected.

This peptide bond step is followed by the proton transfer from the NH₂ to the COO groups. Here, the two water molecules assist the proton transfer. The transition state structure (see SGG2W-TS1 of Figure 4) exhibits an even less strained ring (with eight-members) than the 1-water-assisted analogue. The intrinsic free energy barrier of this step is actually low ($\Delta G_{298}^{\ddagger} = 8.0$ kcal mol⁻¹) due to the geometry relaxation of the transition state. The next and final step, is the formation and release of water, which occurs by proton transfer from the surface to the OH group. This dehydration step is endergonic by $\Delta G_{298}^{\ddagger} = 18.3$ kcal mol⁻¹, which is somehow smaller than the 1-water-assisted analogue step. The final product is the peptide attached on the surface with three water molecules coordinatively interacting with the Ti Lewis sites and the reaction is esoergonic by large amount ($\Delta_r G_{298}^0 = -45.0$ kcal mol⁻¹).

Gly + Gly on the TiO₂ (101) anatase surface in the presence of a third Gly molecule

The two previous sections reported how the energy barriers involved in the peptide bond formation can be significantly reduced by the catalytic activity exerted by: i) the interaction of Gly with the surface Ti Lewis sites, which makes the C atom more electrophilic; ii) a proton relay mechanism through the involved water molecules. The proposed mechanisms showed that condensation between two Gly molecules (and, by extension, between amino acids) is feasible in a prebiotic scenario under the premise of two conditions: i) the reaction has to occur on anatase surfaces; ii) fluctuating wetting/drying cycles have to operate. These results, however, do not actually explain the experimental findings obtained by Martra et al.,^[76] in which Gly-based oligopeptides

were formed on anatase TiO₂ surfaces by condensation of the sublimated monomers. In their experiments, the presence of initial water molecules in the experimental set up were ruled out, since the mineral samples were outgassed at high temperatures to remove adsorbed water while the Gly monomers arrived at the surface from the vapour phase. The aim of this last section is, thus, to provide an atomistic interpretation of these experimental results. We anticipate that the proposed mechanism advocates the role of a third Gly molecule participating in the reaction as a proton transfer assistant through its COOH group.

Figure 5 shows the free energy profile at T = 298 K of the calculated mechanism. The 0th energy reference asymptote (SGGG-AS) is Gly/TiO₂ plus two Gly molecules infinitely separated. We also identified a stationary point in which the N-C bond is formed, in agreement with the same finding for the mechanism involving two water molecules. In this case, charges of the organic moiety are stabilized by its interaction with the third Gly molecule. At variance with the 2-H₂O-assisted mechanism, the stationary point is stable by 5.8 kcal mol⁻¹ in free energy with respect to the asymptote. Accordingly, it can be classified as an intermediate species of the reaction. The next step, involving the proton transfer from the NH₂ group, is assisted by the COOH group of the third Gly. In this proton-assisted mechanism, the C=O group acts as a proton acceptor and the OH as a proton donor (see structure SGGG-TS1 of Figure 5). The transition state structure exhibits a low strained eight-membered ring (as occurred in the 2-H₂O-assisted mechanism). The corresponding intrinsic $\Delta G_{298}^{\ddagger}$ is very low (2.0 kcal mol⁻¹, with respect to SGGG-INT1). It is worth mentioning that the intermediate structure SGGG-INT2 occurring after the proton transfer () is only 0.3 kcal mol⁻¹ higher in energy than the TS. This is due to the thermal corrections needed to calculate the free energies. The final step leads to the water elimination and has an

intrinsic $\Delta G_{298}^{\ddagger}$ value (i.e., with respect to SGGG-INT1) of 17.7 kcal mol⁻¹ (see SGGG-TS2). The transition state is a product-like species, the emerging water molecule being almost formed with a large C-OH distance (2.234 Å, *i.e.* practically broken). The most stable structure for the final product is SGGG-P2 ($\Delta_r G_{298}^0 = -26.7$ kcal mol⁻¹), in which the released water is coordinated to the Ti surface atom, while the third Gly is interacting with the formed peptide. It is worth mentioning that the same process (*i.e.*, the peptide bond formation assisted by a third Gly molecule) has been calculated in absence of the anatase surface. The reaction was found to be concerted with a calculated $\Delta G_{298}^{\ddagger}$ of 23.4 kcal mol⁻¹ (see Figure S4 of SI), which implies a decrease to almost half of the barrier computed for the uncatalyzed gas-phase process. However, the energy barrier on the surface is even lower, indicating that the anatase surface is of paramount importance.

Interestingly, the highest calculated free energy barrier of the proposed mechanism is that involving the H₂O formation (SGGG-TS2 of Figure 5). The reaction taking place in the experiments of Martra et al.^[76] occurred at the IR beam temperature; *i.e.*, about 50 °C (323 K). Accordingly, we have calculated the free energy barrier at this temperature ($\Delta G_{323}^{\ddagger} = 16.5$ kcal mol⁻¹), as well as the rate constant for the rate determining step using the classical Eyring equation (considering a first-order reaction since it starts from SGGG-INT2). The obtained results are $k \approx 46$ s⁻¹ and a $t_{1/2} \approx 1.5 \times 10^{-2}$ s, thus indicating that the reaction is actually fast and, therefore, the occurrence of this mechanism is feasible under the experimental conditions.

Conclusions

In the sequence of organizational events leading to the emergence of life, many competing scenarios have been proposed to explain the appearance of the first biopolymers such as proteins and RNA. Formation of an amide bond between two amino acids to give a peptide (*i.e.*, the peptide bond formation reaction) is a critical and poorly understood step in this organizational ladder. A major concern is the so-called “water problem”, since the reaction in highly diluted water solutions is thermodynamically disfavoured because amino acid condensation is followed by water elimination. The reaction also presents low kinetics with reaction half-times of the order of several centuries. An old, but still fashionable suggestion was proposed by Bernal,^[54] in which mineral surfaces play a key role in the reaction, by concentrating the monomers and catalysing their polymerization by action of surface active sites. This polymerization on the rocks, in combination with fluctuating wetting/drying cycles,^[58] in which the condensation becomes possible during the drying cycle, is one of the hypotheses to explain the occurrence of the peptide bond formation under prebiotic conditions in the primordial Earth. Despite a great deal of successful experimental work using several minerals (see Introduction), few attempts have been provided from the computational viewpoint to give a mechanistic interpretation of the catalytic role of the surfaces. The present article aims to fill in this gap for the particular case of the condensation reaction between two glycine (Gly) molecules in presence of the TiO₂ (101) anatase surface containing both coordinatively unsaturated Ti atoms and O atoms acting as Lewis and Brønsted sites, respectively, by means of periodic PBE0-D2* simulations.

For all the studied reactions, the most stable adduct of Gly on the anatase surface was taken as the pre-reactant complex, in which Gly is in its deprotonated form due to a spontaneous proton transfer to the surface.^[87] The main conclusions can be drawn from

comparing the energetics for the uncatalyzed gas-phase reaction, with those resulting on the TiO₂ surface. The gas-phase process is concerted and envisages a nucleophilic attack of the NH₂ group of one Gly to the C atom of the COOH group of the other Gly, forming a N-C bond, followed by a proton transfer from the NH₂ group to the OH group to release water. In gas phase, the free energy barrier (T = 298 K) was computed to be 41.8 kcal mol⁻¹ and the free reaction energy -7.3 kcal mol⁻¹. All the studied condensations on the (101) anatase surface adopt a stepwise mechanism, in which the nucleophilic attack and the release of water splits in two steps because of the deprotonated state of Gly in the Gly/TiO₂ pre-reactant complex.

The Gly + Gly/TiO₂ reaction presents a free energy barrier decrease for the N-C nucleophilic attack step of about 5 kcal mol⁻¹. This activation energy reduction is caused by the Gly/TiO₂ surface interaction, which renders the C atom more electrophilic than in the gas phase, as indicated a Bader charge analysis. The final dehydration step takes place by proton transfer from the surface to the OH of the organic moiety releasing water, with an intrinsic free energy barrier of 17.5 kcal mol⁻¹. The thermodynamics of the reaction is also more favourable than the gas-phase process because the released water can interact favourably with the (101) anatase surface through covalent dative bonds between the O atom of the water and surface Ti Lewis sites. These largely favourable reaction free energies are kept for the other studied reactions, indicating that the surface clearly helps the global reaction energies.

The reaction has also been studied in the presence of 1 and 2 water molecules acting as proton transfer assistants. Their presence dramatically reduces the free energy barriers for the nucleophilic attack to 20.7 and 8.0 kcal mol⁻¹, respectively. This reduction is due to the low-strained rings present in the corresponding transition state structures in the proton transfer (6th- and 8th-membered rings, respectively) compared to

the highly strained ring in the non-water assisted reactions (4th-membered ring). In both cases, due to this energy barrier decrease, the final dehydration becomes the more energetic step, with energy barriers of 22.9 and 18.3 kcal mol⁻¹, respectively.

Finally, the Gly + Gly/TiO₂ condensation reaction has also been studied in the presence of a third Gly molecule, acting as proton transfer helper. This last process, corresponds to the aggregation of glycine molecules during the drying process on the TiO₂ surface. Here, the mechanism involves three steps. The first is the N-C bond formation, which occurs in a barrier less fashion, forming a stable intermediate, in which a HOOC-CH₂-NH₂⁺-COO²⁻-CH₂-NH₂ organic moiety is attached at the surface. The second step, is the proton transfer from the surface to the organic moiety. This proton transfer is assisted by the COOH group of the third Gly, in which the C=O group acts as proton acceptor and the OH group as proton donor, forming a low strained 8th-membered ring. The calculated free energy barrier is of 2 kcal mol⁻¹. The final step is the dehydration, which is found to be the most energetic one with a free energy barrier of about 11.9 kcal mol⁻¹. This mechanistic proposal is consistent with and provides an atomistic interpretation of the experimental findings obtained by Martra et al.,^[76] in which catalytic polymerization of Gly monomers on TiO₂ surfaces was successfully achieved by successive feedings of the monomers within strict gas-phase conditions.

Supplementary Information

Free energy profiles for the reactions in absence of the TiO₂ surface, absolute and relative potential energies of all the stationary points, and fractionary coordinates of all the optimized structures.

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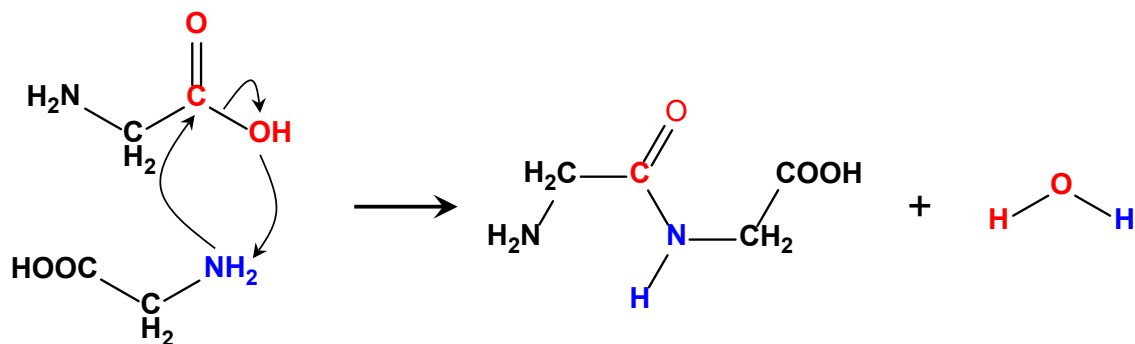
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Scheme 1. Reaction of the peptide bond formation between two glycine molecules adopting a concerted mechanism. Atoms in red and blue are those actually involved in the condensation reaction.

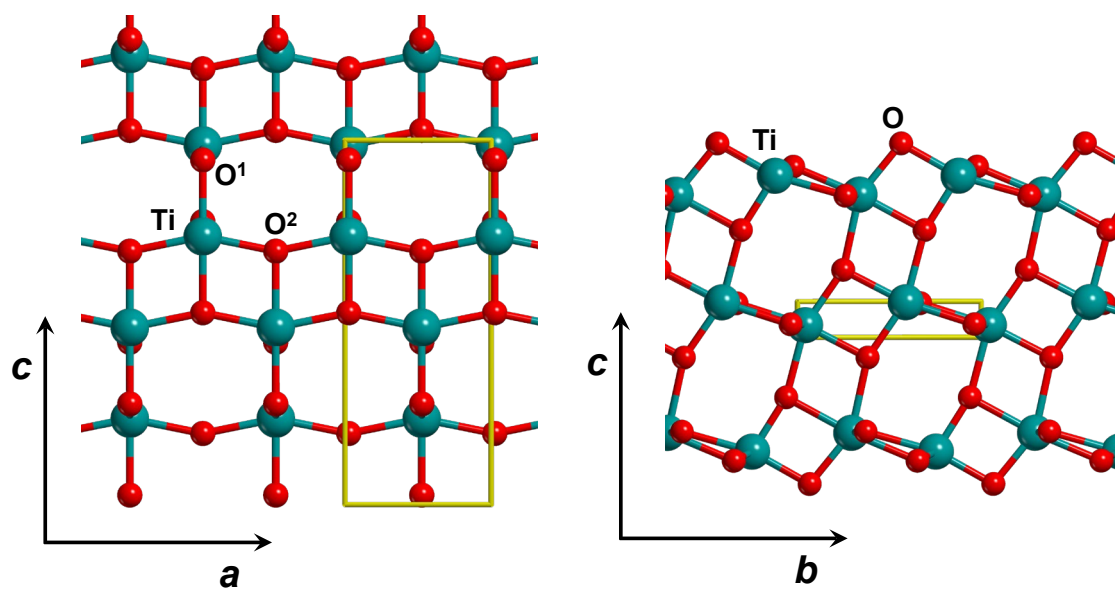


Figure 1. PBE-D2* optimized structure of bulk anatase (left) and lateral view of the (101) anatase surface (right).

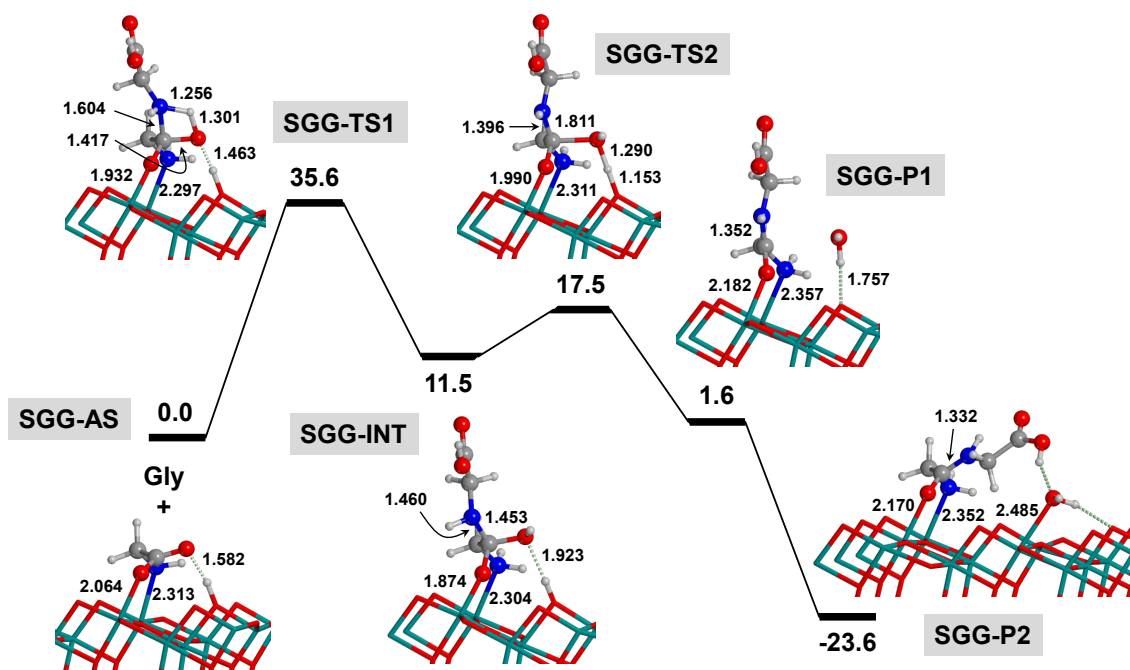


Figure 2. Relative free energy profile ($T = 298 \text{ K}$) in kcal mol^{-1} at PBE0-D2*//PBE-D2* theory level for the peptide bond formation between two Gly molecules on the (101) anatase surface. The asymptote 0th energy reference is Gly/TiO₂ + Gly (SGG-AS structure). Bond distances are in Å.

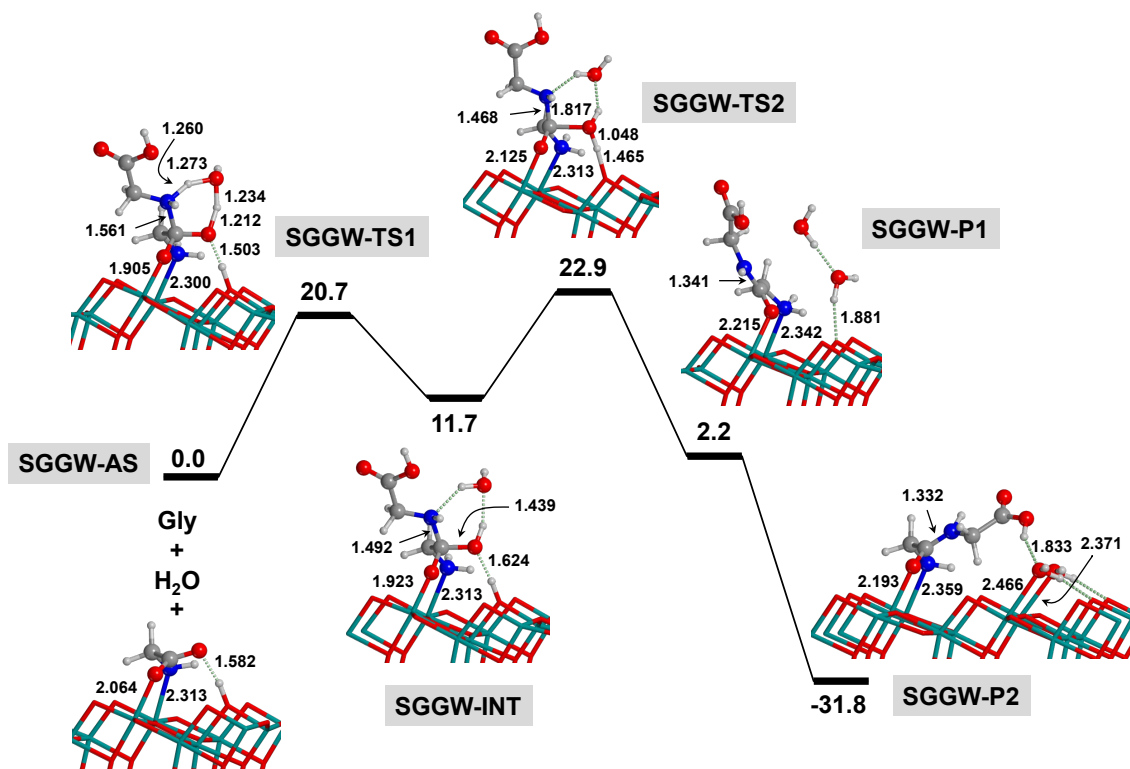


Figure 3. Relative free energy profile ($T = 298$ K) in kcal mol⁻¹ at PBE0-D2*//PBE-D2* theory level for peptide bond formation between two Gly molecules on the (101) anatase surface in the presence of 1 water molecule assisting the proton transfer. The asymptote 0th energy reference is Gly/TiO₂ + Gly + H₂O (SGGW-AS structure). Bond distances are in Å.

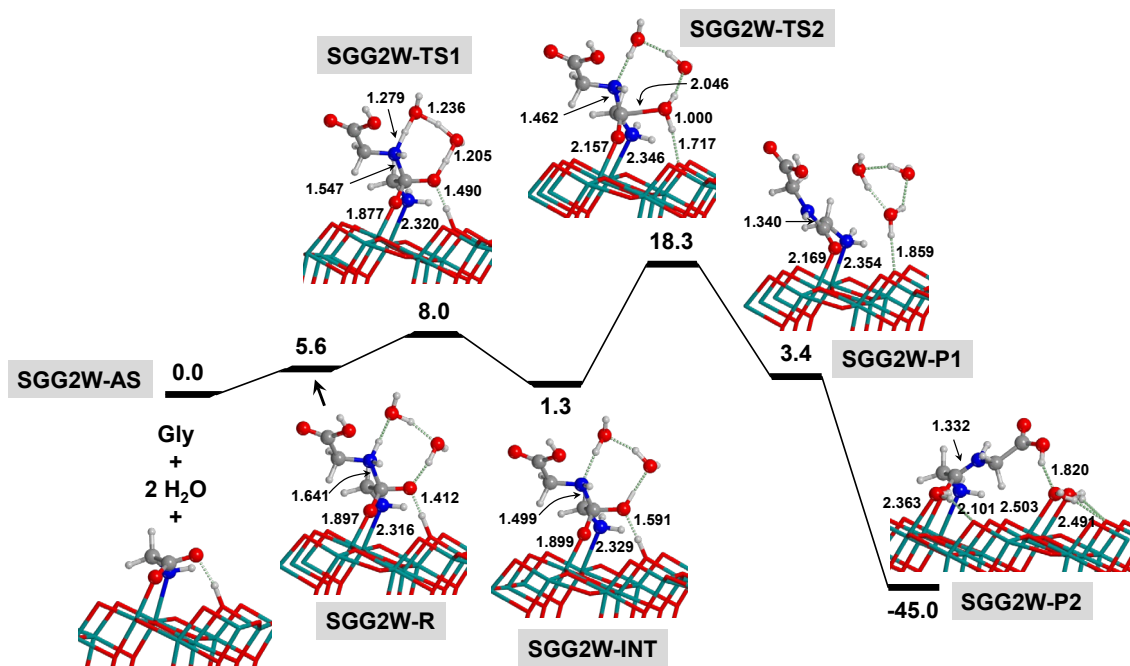


Figure 4. Relative free energy profile ($T = 298$ K) in kcal mol⁻¹ at PBE0-D2*/PBE-D2* theory level for the peptide bond formation between two Gly molecules on the (101) anatase surface in the presence of 2 water molecule assisting the proton transfer. The asymptote 0th energy reference is Gly/TiO₂ + Gly + 2H₂O (SGG2W-AS structure). Bond distances are in Å.

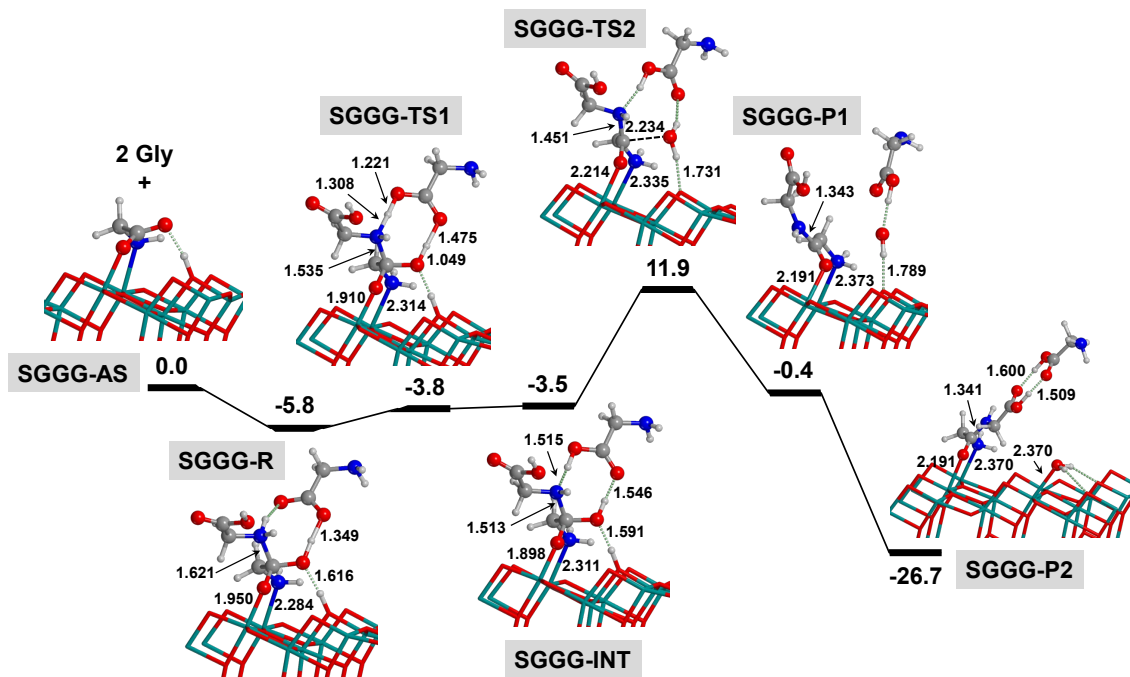
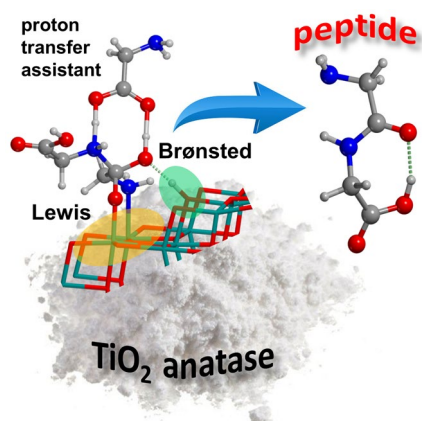


Figure 5. Relative free energy profile ($T = 298$ K) in kcal mol⁻¹ at PBE0-D2*//PBE-D2* theory level for the peptide bond formation between two Gly molecules on the (101) anatase surface in the presence of third Gly molecule assisting the proton transfer. The asymptote 0th energy reference is Gly/TiO₂ + 2Gly (SGGG-AS structure). Bond distances are in Å.

Graphical Abstract



Peptide bond formation from unactivated amino acids is catalysed by a fruitful interplay between TiO_2 surface Lewis/Brønsted sites and proton transfer assistant molecules