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Boc-protection on L-DOPA: an easy way to promote underwater adhesion

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Abstract: Mussels' ability to adhere to underwater surfaces has attracted a lot of attention from the scientific community. As proteins containing L-DOPA (3,4-dihydroxyphenyl-L-alanine) are involved in mussels' adhesion, a common strategy to synthesize adhesives is the incorporation of this amino acid into other compounds. Here we report a study on four compounds of the family of Boc_x-$(L\text{-}DOPA)_n$-OMe (x = 1-3; n = 1,2), that we prepared through simple synthetic steps. Three of them showed the capability of underwater adhesion: while they are not adhesive in the dry phase, the adhesiveness is triggered when the dried sample is immersed in water or any aqueous solutions. The introduction of protecting groups stabilizes L-DOPA, preventing the oxidation of the catechol moiety and enhances the hydrophobicity, helping the removal of water from the surface to bind. These molecules show good adhesiveness, with different properties, so they may be all used as adhesives for different purposes. These outcomes pave the way for new set of applications for these materials as green and biocompatible adhesives.

Introduction

When it comes to underwater adhesion, shellfish are the true experts.[1] Marine organisms' mechanism of adhesion has been largely studied and inspired the production of a huge number of synthetic adhesives for underwater purposes. Over the last few decades, the *Mytilus edulis* (blue mussels) attracted much attention for its ability to secrete the byssus.[2,3] Mussels use the byssus, a protein-based adhesive, for securing themselves to various underwater surfaces, such as sea rocks and ship hulls, and resist detachments even in marine's harsh and wavy conditions.[4,5] The byssus consists of a bundle of threads composed by three parts: the adhesive plaque, the rigid distal thread and the flexible proximal thread. The byssal thread is composed by the mussel foot, which is the flexible part responsible for the adhesion on the target surface. So far, roughly 25-30 different mussel foot proteins (mfps) have been identified in byssus, 5 of them (mfp-2 to mfp-6) being unique to the plaque (Figure 1).[3,4,6] Mfp-3 and mfp-5 are considered the main responsible for the adhesion of the plaque to the surface; they contain a particularly high amount (up to 30 mol%) of the post-translationally modified tyrosine to 3,4-dihydroxyphenyl-L-alanine (L-DOPA).[7] For this reason, it is widely believed that DOPA, and especially its catechol group, has a dominant role in binding to the surface.[2,6,8,9] Moreover, DOPA can efficiently remove the layer of water and ions which generally covers hydrophilic submerged surfaces, while tyrosine, lacking of catechol group, cannot.[3,10]

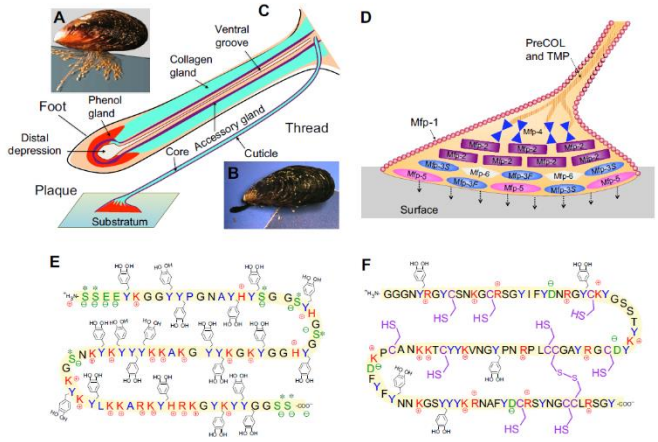


Figure 1. (A) The mussel byssus. (B) To make a new thread, the foot emerges from the living space within the mussel shell and touches a surface. (C) Three gland clusters – phenol, collagen and accessory glands – synthesize and stockpile specific byssal proteins. (D) Schematic representation of the distribution of known proteins in the byssal plaque and distal thread. (E) Sequence of Mfp-5 from Mytilus edulis, showing the prominence of DOPA (Y-methyl catechol), Lys (K), Ser (S) and Gly (G). (F) Sequence of Mfp-6 from M. californianus with abundant Cys (C), Arg (R) and Lys (K), Gly (G) and Tyr (Y). Color key: Tyr/Dopa (blue), cationic side chains (red), anionic side chains including phosphoSer (green) and thiols (purple). Reproduced from ref. [3] with kind permission of The Company of Biologists Ltd.

DOPA is related to a variety of different adhesion mechanism, not fully understood yet, involving hydrogen bonding, metal-oxide coordination, cation-π and hydrophobic interactions, all depending also on the characteristics of the surrounding environment (such as pH, ions concentrations, material of the surfaces to attach).

In the preparation of synthetic adhesives inspired to mussels, the incorporation of DOPA, catechol groups or other hydrophilic moieties is a common strategy, to overcome the interactions of water with the surface and to provide cohesive forces to the adhesive.[8,11–14] The role of hydrophobic groups in the removal of water has not been exploited likewise in designing underwater adhesives. It is worth noticing that in water the adhesive forces

required to separate two hydrophobic surfaces are very high, even higher than the adhesive forces necessary to separate mfps from model mica surfaces,[15] and it is also much easier to remove water from two hydrophobic than hydrophilic surfaces.[16,17] The design of adhesives which include hydrophobic groups is likely to improve adhesion in wet environments, as recently reported.[18–22] In sea water DOPA is susceptible to oxidation to DOPA-quinone, which cannot form hydrogen bonds with surfaces and has lower adhesive properties. In mussels, DOPA oxidation tendency is limited not only by tautomerization of DOPA-quinone to α,β-dehydro-DOPA (restoring the possibility to form hydrogen bonds), but also by the presence of nonpolar amino acids located close to DOPA.[8]

Because of their unique wet adhesive properties, mussels inspired adhesives are interesting for several applications, but have recently attracted lot of attention especially in the biomedical and tissue engineering field, as surgical glue or drug delivery systems.[6,23] For these purposes, a systematic understanding of the behaviour, stability and adhesion mechanisms of these compounds is necessary.

In this work, a family of Boc_x-L-$(DOPA)_n$-OMe (Boc = *t*-butyloxycarbonyl; Me = methyl; x = 1-3; n = 1,2) molecules was synthesised. The number of Boc groups was progressively increased, substituting one or both -OH in the catechol group and compared with the dimer molecule, Boc-$(L\text{-}DOPA)_2$-OMe, having all the catechol groups free. These compounds were used to form films that were tested through tack test, in order to understand how the introduction of nonpolar groups and the increase in the hydrophobicity of the molecules could affect their adhesive properties. The production of these films is of great interest for the production of highly biocompatible adhesives that may find applications as wound closure materials or as carrier of bioactive compounds.[24–26]

Results and Discussion

We prepared Boc-L-DOPA-OMe **1** (methyl (*S*)-2-((*t*-butoxycarbonyl)amino)-3-(3,4-dihydroxyphenyl)propanoate), Boc_2-L-DOPA-OMe **2**, as a 1:1 inseparable mixture of the *meta*-protected ***m*-2** (methyl (*S*)-2-((*t*-butoxycarbonyl)amino)-3-(3-((*t*-butoxycarbonyl)oxy)-4-hydroxyphenyl)propanoate) and the *para*-protected ***p*-2** (methyl (*S*)-2-((*t*-butoxycarbonyl)amino)-3-(4-((*t*-butoxycarbonyl)oxy)-3-hydroxyphenyl)propanoate) isomer and Boc_3-L-DOPA-OMe **3** (methyl (*S*)-3-(3,4-bis((*t*-butoxycarbonyl)oxy)phenyl)-2-((*t*-butoxycarbonyl)amino) propanoate) by modification of commercially available L-DOPA (Figure 2). The first step was the preparation of the molecules containing an increasing number of Boc protecting groups. The protection of the primary amine is selective, yet the hydroxyl groups on the catechol are reactive too towards this reaction and a mixture of compounds **1**, **2** and **3** is obtained in presence of wide amount of Boc_2O. For this reason, we found selective preparations for the three compounds.

Boc-L-DOPA-OMe **1** is obtained by methylation of commercially available L-DOPA, followed by the selective protection of the nucleophilic primary amine group, according to a reported procedure (Scheme S1).[27,28]

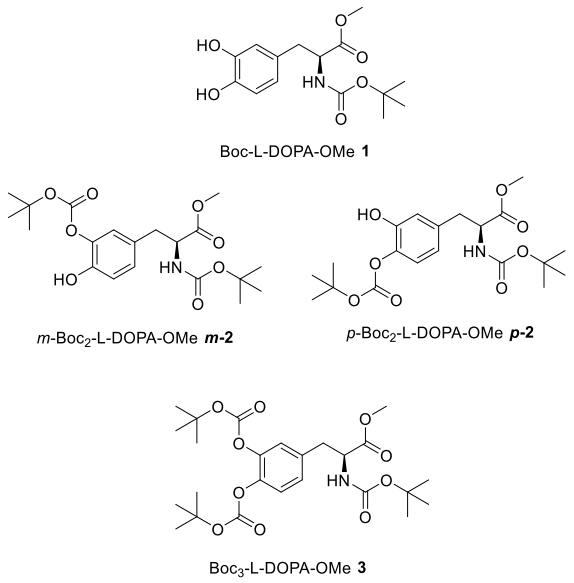


Figure 2. Chemical structure of the derivatives of L-DOPA described in this work.

The preparation of Boc_2-L-DOPA-OMe **2** implied several problems, due to the presence of the two hydroxyl groups of the catechol moiety (Scheme S2). The selective introduction of a single Boc group on the ring was difficult, even though several different procedures were tested. In any case, Boc_2-L-DOPA-OMe was always obtained as an inseparable mixture of *meta* and *para* protected regioisomers ***m*-2** and ***p*-2** (Figure 2) in about a 1:1 ratio, together with little amounts of Boc-L-DOPA-OMe **1** and/or Boc_3-L-DOPA-OMe **3** (Figure S2). The best result was achieved by reaction of Boc-L-DOPA-OMe **1** with a stoichiometric amount of Boc_2O and $NaHCO_3$ in water and THF, with a final yield of about 60% after purification by flash chromatography. Curiously, the direct preparation of Boc_2-L-DOPA-OMe **2** from L-DOPA-OMe·HCl did not afford the same results. The presence of two regioisomers ***m*-2** and ***p*-2** could be checked only by ^{1}H NMR (Figure S2) as they are inseparable by LC-MS analysis.

In contrast, the preparation of the fully protected Boc_3-L-DOPA-OMe **3** was selectively obtained in excellent yield by reaction of Boc-L-DOPA-OMe **1** with two equivalents of Boc_2O, in presence of DMAP (4-(dimethylamino)pyridine) in acetonitrile (Scheme S3).[29]

With the increase of the number of Boc groups, the molecules polarity and hydrophilicity are strongly modified, as Boc-L-DOPA-OMe **1** is far more hydrophilic than the fully protected Boc_3-L-DOPA-OMe **3**. The hydrophilicity variation may be proved with the analysis of the contact angles between thin layers of molecules **1**, **2** or **3** and an aqueous medium.[30]

To carry out the test, a small amount of the sample is deposited as ethyl acetate solution on a glass slide of an optical tensiometer just enough to cover the entire surface. After the solvent evaporation, we measured the contact angles obtained with three media: MilliQ water, 1M $CaCl_2$ aqueous solution and a phosphate-buffered salin (PBS) solution at pH = 7.4, which is commonly used to imitate the property of the body fluids. Several examples of formation of three dimensional networks among peptides and Ca^{2+} ions have been reported,[31–34] and the

presence of DOPA enhances this effect, as it has the ability to chelate Ca^{2+} ions.[28,35–37]
The values of the contact angles under the different conditions are reported in

Table 1 and shown in Figures S3-S5.

Table 1. Contact angles of dried surface of **1**, **2** (**m-2** + **p-2**) and **3** with the aqueous solutions listed below.

	H_2O	$CaCl_2$ 1M	PBS pH 7.4
1	54.7±3.9°	58.0±1.8°	49.9±1.0°
2	78.2±2.0°	63.7±1.0°	76.6±5.4°
3	94.0±0.5°	81.1±1.7°	84.0±1.1°

As we could foresee, there is a continuous increase of the contact angle going from **1** to **3**, although this effect is more evident in MilliQ water. The adhesion efficiency can be linked to the hydrophobicity of the molecule, thus to the contact angle.[18,38]
Materials that are tacky or sticky are easily identified by touch, however, quantify tack is not straightforward. The formation of the adhesive bond is not directly measured but assessed by breaking bonds by means of tack tests.[39] To evaluate the ability of films of **1**, **2** and **3** to adhere to a solid surface when brought into contact by a very light pressure, we performed tack tests using a rheometer.
To prepare the films, 20 mg of each molecule were dissolved in ethyl acetate (1 mL) and poured in a 25 mm glass petri dish (deposition area = 490.6 mm^2) previously fixed on a disposable aluminium plate for rheometer. After solvent evaporation, 1 mL of MilliQ water was added on the top of the dry layer, covering the whole surface (Figure 3).

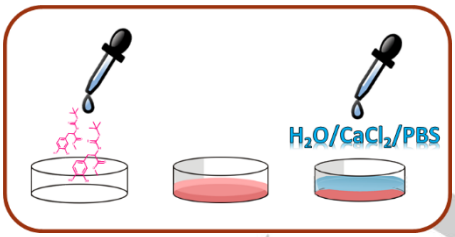


Figure 3. Procedure for the preparation of the films of **1**, **2** and **3** to test their adhesive properties.

Films of **1**, **2** and **3** are not adhesive in the dry phase, the adhesiveness is generally triggered when the dried sample is immersed in water or any aqueous solution. Adhesion in humid conditions is a fundamental challenge to both natural and synthetic adhesives. Yet some glues from different biological systems appear to enhance their performances with increasing humidity.[40]
To perform the tack test, 25 N force is applied from the rheometer shaft for 5 mins. The experiment was conducted at a crosshead speed of 50 µm/s (3 mm/min). All measurements were repeated at least three times (Figure 4). When the shaft applies a compression force on the sample, the instrument registers a positive force on the graph; while going back to its former position (detachment phase) it registers a negative force. In any case, the absolute value should be taken.
Both Boc_2-L-DOPA-OMe **2** and Boc_3-L-DOPA-OMe **3** behave quite differently from Boc-L-DOPA-OMe **1**. In fact, **2** and **3** reach the maximum scale of the rheometer at 50 Newton, while **1** shows no adhesion at all. Moreover, the films of **3** completely detach from the petri dish at the end of the experiment and attach to the shaft (Figure 5). The film on the shaft is brittle in nature and breaks into small pieces by touching. This behavior prevents the film multiple use.

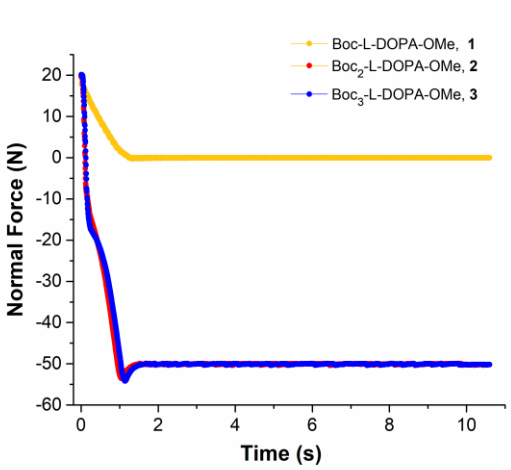


Figure 4. Rheometer tack tests for molecules **1**, **2** and **3** in water.

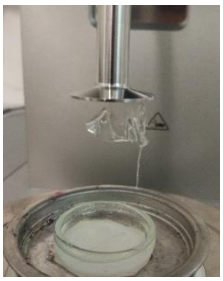


Figure 5. Adhesive film of **3** after the tack test.

The adhesive properties of films of **1**, **2** and **3** were tested also in 1M $CaCl_2$ aqueous solution and in PBS solution at pH = 7.4. To test **1,** we used the rheometer under the same conditions previously reported for the analysis in MilliQ water: **1** behaves in the same way in the three media, in agreement with the analysis of the contact angles which range between 50° and 58° (Figure S6).
As the rheometer tack tests for **2** and **3** reached the upper limit of the instrument sensitivity, we analysed the adhesive properties of films of **2** and **3** with traction tests, using an Instron 4465 testing system, as it has a wider measuring capacity, up to 5 kN load cell, although with a reduced sensitivity. The tests were carried out with a 100 N load cell. In order to have a good comparison, we tested the behavior of **2** and **3** in the three aqueous media.
The mechanical analysis of the films of **2** and **3** are summarised in Figure 6.

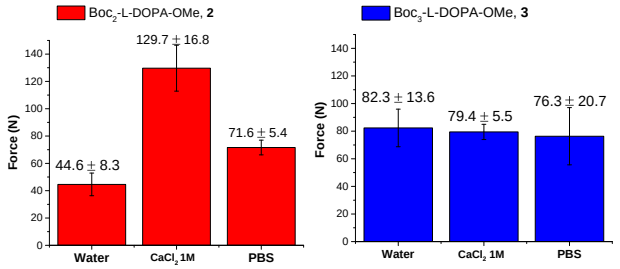
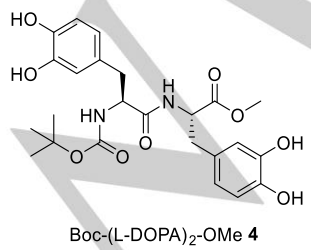


Figure 6. Results for traction tests performed on films of **2** (left) and **3** (right) with an Instron 4465 testing system. Samples were prepared using the same geometry (petri dish with 25 mm of diameter), deposition method and addition of the triggers used for tack tests. All experiments were repeated at least three times.

Among them, the most intriguing material is the film of **2**, that shows good adhesiveness and good resistance to use. In fact, its adhesiveness is remarkable if compared with the tack strengths of already reported polymers containing DOPA.[41,42] When the traction test for **2** was performed in a 1M $CaCl_2$ solution, the instrument could not detach the cell from the sample, meaning that the necessary force was higher than 100 N, the maximum force for that cell. For this reason, this experiment was repeated using a 1 kN load cell and an average value of 129.7 ± 16.8 N was measured. Unfortunately, this material is obtained by deposition of an inseparable mixture of ***m*-2** and ***p*-2**, so the deposition on the glass surface cannot be controlled. It is difficult to control the effective ratio and the behavior of the two components and the exact 1:1 ratio in any sample is not guaranteed.

In contrast, Boc_3-L-DOPA-OMe **3** is a pure compound and has high adhesiveness as it ranges between 76.3 and 82.3 N in all the media, showing the best results in water. These adhesive values are higher compared to what reported in literature for more complex polymeric systems.[41,42]

With the aim of finding another molecule of the same family having good properties and high reproducibility, we synthesized another compound, Boc-(L-DOPA)$_2$-OMe **4** (methyl (*S*)-2-((*S*)-2-((*t*-butoxycarbonyl)amino)-3-(3,4-dihydroxyphenyl) propanamido)-3-(3,4-dihydroxyphenyl)propanoate) (Figure 7). The preparation of this molecule was suggested by the strong adhesive properties of oligomers containing more than one catechol group.[43–45]



Boc-(L-DOPA)$_2$-OMe **4**

Figure 7. Chemical structure of the derivative of Boc-(L-DOPA)$_2$-OMe **4**.

Boc-(L-DOPA)$_2$-OMe **4** was prepared through some easy steps in good yield starting from the already described Boc-L-DOPA(OBn)$_2$-OMe (Scheme S4).

To check the adhesive properties of the films produced by deposition of **4**, we measured the contact angles as we previously reported with the three aqueous media (Table 2 and Figure S7).

Table 2. Contact angles of dried surface of **4** with the aqueous solutions listed below.

Solvent	Boc-(L-DOPA)$_2$-OMe **4**
H_2O	69.3±2.5°
$CaCl_2$ 1M	71.2±2.2°
PBS pH 7.4	67.7±3.9°

The measured contact angles range between 67.7° and 71.2°. This positive outcome encouraged us to record the tack tests of the films in the three media, using the same technique that we previously described (Figure 8 and Table 3).

From the tack test in the three media, it is very clear that the application of $CaCl_2$ solution has a strong impact on the adhesive property of the molecule, compared with both the PBS solution and MilliQ water.

Table 3. Rheometer average values and standard deviations for compound **4** in the different aqueous media.

Solvent	**4**, Normal Force (N)
H_2O	16.4 ± 4.9
$CaCl_2$ 1M	46.7 ± 5.8
PBS pH 7.4	15.4 ± 0.8

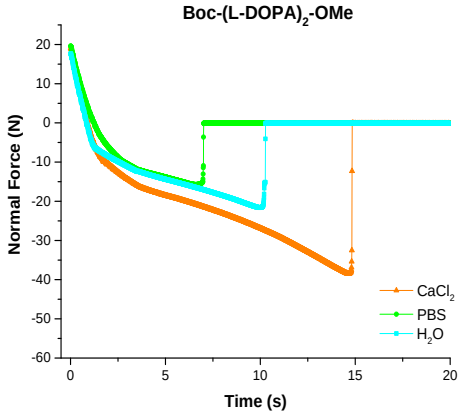


Figure 8. Tack tests for Boc-(L-DOPA)$_2$-OMe **4** in the three aqueous media.

It is interesting to notice how for these molecules the increase in adhesive forces and contact angle values can be nicely correlated to the number of Boc groups substituting the catechol in all the aqueous media tested (Figure S8). The increased adhesion of compound **4** compared to the monomer **1** may be yet ascribed to the additional catechol group.[8]

To verify and to quantify the multiple use properties of films of **4**, we repeated the tack test on the same sample for three times in 1M $CaCl_2$ aqueous solution, that is the medium where the films showed the most promising properties (Table 4). These measures were not executed for films of **2** and **3**, as we could not use the rheometer, which has more reliability than the Instron in terms of sensitivity and reproducibility.

Table 4. Rheometer values of the multiple adhesion trials for compound **4** in 1 M and 0.1 M $CaCl_2$ solutions.

Trial	Normal Force (N) 1M $CaCl_2$	Normal Force (N) 0.1M $CaCl_2$
1	50.0	43.8
2	48.4	32.0
3	41.4	26.1

The repeated tests were done on the same sample with the same parameters, except the enhanced crosshead speed at which the shaft moves up for the test (1000 m/s or 60 mm/min), to check the behavior of the material under these conditions (Figure 9a).

The results reported in Figure 9a clearly show that the film of **4** exhibits repeated adhesiveness even though the adhesive strength is slightly decreased in each trial. This result demonstrates the strong resistance against destructive effect of water, which often adversely influences the strength of adhesiveness.[10,46–48] Moreover, an increase in the crosshead speed results in a faster detachment of the shaft from the adhesive film (from 14 s to 2 s) but does not affect the maximum force required. We repeated the tack test under the same conditions using a 0.1M $CaCl_2$ aqueous solution, to check the effect of the variation of concentration of Ca^{2+} ions (Figure 9b).

Under these conditions, the adhesive strength decreases in each trial more than in 1M $CaCl_2$, and in general the values are intermediate between the results obtained in water and 1M $CaCl_2$ (Figure 8). This outcome is in agreement with the previously reported high affinity of the catechol moiety with Ca^{2+} ions:[31–37] when the Ca^{2+} ions concentration decreases, the film efficiency for repeated measurements decreases accordingly.

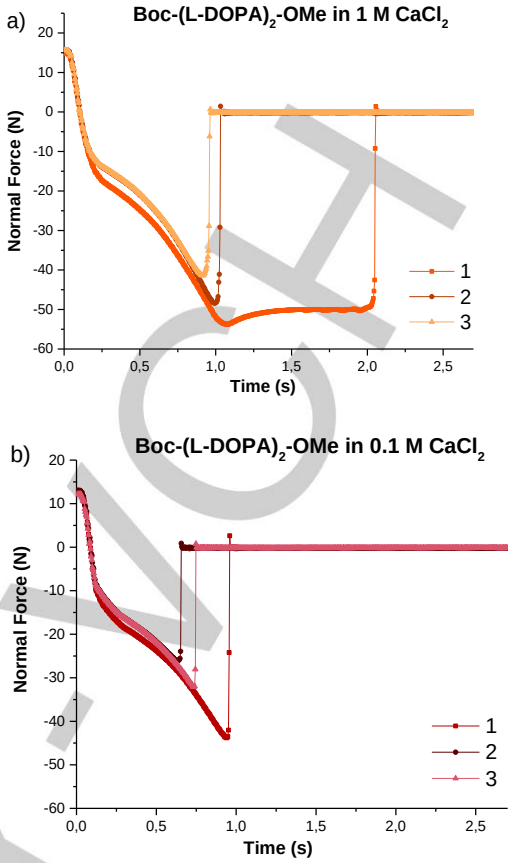


Figure 9. Repeated tack tests for Boc-$(L\text{-DOPA})_2$-OMe 4: (a) in 1M $CaCl_2$ aqueous solution; (b) in 0.1M $CaCl_2$ aqueous solution

Conclusion

In this work, a family of four L-DOPA based compounds were synthesized and their adhesive properties were tested. Three of them showed the capability of underwater adhesion: while they are not adhesive in the dry phase, the adhesiveness is triggered when the dried sample is immersed in water or any aqueous solutions. The introduction of protecting groups on the catechol moiety not only stabilizes the compounds inhibiting the oxidation, but also increases the hydrophobicity of the compounds analysed. Molecules **2**, **3** and **4** have different properties, so they all may be used as adhesives for different purposes:

- Boc_2-L-DOPA-OMe **2** films show satisfactory performances for all the media tested, mainly in $CaCl_2$ aqueous solution, suggesting that the presence of Ca^{2+} is crucial for the formation of a complex with higher adhesion capability;
- Boc-$(L\text{-DOPA})_2$-OMe **4** has a similar behavior, showing the highest adhesion value in $CaCl_2$, yet appearing less efficient than **2**. Additionally, **4** shows the ability of repeated adhesion in $CaCl_2$ aqueous solutions.
- Finally, Boc_3-L-DOPA-OMe **3**, where the catechol group is fully protected, shows the best performance among these molecules in PBS solution, so it may be used for biomedical purposes.

In this work we have investigated how these functionalizations play a pivotal role in the adhesive behavior of L-DOPA, yet the process controlling this phenomenon needs further studies, as we cannot exclude that the changes in the cohesive strength

across compounds may be also due to the introduction of protecting groups and water absorption fenomena.
These outcomes pave the way for new set of applications for these materials as green and biocompatible adhesives.

Experimental Section

Synthesis: General Remarks. Solvents were dried by distillation before use. All reactions were carried out in dried glassware. The melting points of the compounds were determined in open capillaries and are uncorrected. High quality infrared spectra (64 scans) were obtained at 2 cm^{-1} resolution with an ATR-FT-IR Bruker Alpha System spectrometer. All spectra were obtained in 3 mM solutions in CH_2Cl_2. All compounds were dried *in vacuo* and all the sample preparations were performed in a nitrogen atmosphere. NMR spectra were recorded with a Varian Inova 400 spectrometer at 400 MHz (^{1}H NMR) and at 100 MHz (^{13}C NMR). Chemical shifts are reported in δ values relative to the solvent peak. HPLC-MS was used to check the purity of compounds. For the details of the synthesis and characterization of compounds **1-4**, see the Supporting Information.

Contact angle - Each sample is dissolved in ethyl acetate and deposited on a glass slide to cover all the surface. The slide is placed in a vacuum desiccator to allow solvent evaporation and avoid powder contamination. The measurements are performed using a contact angle meter Attension Theta Lite (optical tensiometer), using static contact angle (Young-Laplace) analysis mode. A single drop (5 µL) of solvent (MilliQ water, 1M $CaCl_2$ or PBS at pH = 7.4 solutions) at 25 °C is dropped on the sample, recording the contact angle for 10 s. Each measure was repeated three times for each solvent and molecule. The contact angle value was taken after 3 s, once the droplet reached a stability plateau.

Tack Test - Tack tests were performed using an Anton Paar Rheometer MCR 102. All experiments were performed with a plate-system (Ø=25 mm, plate-geometry), at a temperature of 23 °C controlled by the integrated Peltier system. Already predefined tack test definitions in the RheoCompass (Rheometer software) with minor changes were used to carry out the tests. Samples were prepared pouring a solution of 20 mg of each molecule in 1 mL ethyl acetate in a 25 mm glass petri dish (deposition area = 490.6 mm^2) previously fixed on a disposable aluminium plate for rheometer. After solvent evaporation, 1 mL of the trigger solution (MilliQ water, $CaCl_2$ 1M solution or PBS solution) is poured into the petri dish on the dry layer of the deposited molecule, to cover the whole surface. 25 N force is applied from the shaft for 5 mins for the curing of the adhesive material. The experiment was conducted at a crosshead speed of 50 µm/s (3 mm/min). All measurements were repeated at least three times.

Traction Test - Instron 4465 testing system was used to perform the measurements. Samples were prepared using the same geometry (25 mm petri dish), deposition method and addition of the triggers used for the Tack Test. A load cell of 100 N was used, applying 15 N force for 5 mins for the curing of the adhesive material. The experiment was conducted at a crosshead speed of 50 µm/s (3 mm/min). All measurements were repeated at least three times.

Acknowledgements

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Supporting Information. Synthesis and characterization of compounds **1-4**; ^{1}H NMR and ^{13}C NMR and IR spectra of compounds **1-4**; pictures of the contact angles of dried surface of **1-4** with aqueous solutions.

Keywords: Contact angles • L-DOPA • tack tests • traction tests • underwater adhesion

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Entry for the Table of Contents

Among four compounds of the family Boc_x-$(L\text{-}DOPA)_n$-OMe (x = 1-3; n = 1,2), three of them show good adhesiveness. The introduction of protecting groups stabilizes L-DOPA, preventing the oxidation of the catechol moiety and enhances the hydrophobicity. These materials show good adhesiveness, with different properties, so they may find applications as green and biocompatible adhesives.

Key topic

Molecular biocompatible adhesives