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# Molecular Modeling of Phenyl-Boronic Acids and Catechol-Borate Esters: A Mechanistic Rationale for Boron Binding to Melanin Catechols, Regarding the $^{10}$Boron Neutron-Capture Therapy of Melanoma

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**Abstract**

The $^{10}$boron neutron-capture therapy (BNCT) is an emerging anti-tumor therapy based on the accumulation of a $^{10}$B isotope within the tumor followed by irradiation with low-energy neutrons. The nuclear fission process produces $^{7}$lithium, $^{4}$helium, and λ rays within the tumor tissue, inducing specific tumor cell damage and death. $^{10}$B can be delivered either as simple B-containing agents or as B clusters. In the first case, boronic acid derivatives such as 4-borono-phenylalanine (BPA) are currently applied for BNCT of melanoma and other tumors. Although it can be assumed that BPA would act as a precursor metabolite for melanin biosynthesis, the precise action mechanism is not yet clear. Direct binding of this boronic acid to a target substrate, namely the catechol groups from already synthesized melanin, could be an alternative mechanism. In keeping with this, high affinity for melanin would explain the action mode of boronic acids as melanoma seekers. DOPA- and dopamine-borate esters are also potential B-carrier candidates for BNCT, and they could be incorporated as melanin precursors or binding reagents. In this work, molecular modeling methods have been applied to analyze the structure of boronic acid and borate ester derivatives, as well as their interaction and binding mode with the recently proposed catechol-porphycene model for the melanin polymer. Interestingly, remarkable structural features drawn from chemical geometry, and also molecular orbital calculations, support the possibility that boronic acids and borate esters could be reactive agents for direct binding to melanin catechols.

**Keywords:** $^{10}$Boron; Borate esters; BNCT; Catechols; Boronic acids; Melanin; Melanoma

**Abbreviations:** BNCT: $^{10}$Boron neutron-capture therapy; BPA: 4-borono-phenylalanine; DA: dopamine; DHI: dihydroxy-indole; DHICA: DHI-carboxylic acid; CBE: Catechol-borate ester; LUMO: Lowest-unoccupied molecular orbital; CPBA: Catechol-phenylboronic acid

## Introduction

The $^{10}$boron neutron-capture therapy (BNCT) of cancer is a novel therapeutic modality that counts with an increasing biomedical potential and many interesting applications [1-8]. BNCT requires a $^{10}$B-containing agent that accumulates selectively in the tumor, which is then subjected to irradiation with low-energy thermal neutrons. When a neutron is captured by the $^{10}$B isotope, a nuclear fission occurs generating extremely energetic $^{4}$He (α particle), $^{7}$Li and γ radiation [4,9], which damages tumor cells because of the very short braking distance (~10 and ~5 μm) of the emitted α particles and recoiling $^{7}$Li nuclei in condensed matter, respectively [2].

Boron content in the tumor must be high enough (around $10^{9}$ $^{10}$B atoms/cell) to allow for enough capture reactions to occur for confined cell lethality [5,9]. So, the chemistry of boron-containing metabolites and boron clusters has been reviewed [9,10,11]. $^{10}$B-containing agents are mainly BPA (4-borono-phenylalanine), and deca- or dodeca-clusters of B atoms such as GB-10 and BSH [1,5,8,12], which are the only ones approved for use in Oncology, especially for BNCT of skin melanomas [13-18]. As an amino acid analogue, non-specific binding of BPA to proteins of cells and tissues are expected to occur. Therefore, BPA would be highly unlikely to be a specific melanin precursor such as catechol amines and oxidation products, namely 3,4-dihydroxy-L-

phenylalanine (L-DOPA), dopamine (DA), dihydroxy-indole (DHI), and DHI-carboxylic acid (DHICA). In any case, BPA will be taken up by cancer cells because of enhanced amino acid transport displayed by proliferating cells. In the case of melanoma, response to BPA after BNCT has been proposed to be due to the formation of complexes with L-DOPA, DHI, or DHICA monomers, and thus the drug would be later incorporated into melanin [7,19]. In an early attempt to carry $^{10}B$ into melanoma cells L-DOPA-borate was synthesized [20], but no further results have been reported by applying this catechol-borate compound.

Vicinal aliphatic and aromatic cis-diols such as catechols, flavonols, β-diketones, anthraquinones, etc., form stable borate complexes [20-25]. Boronic acid (C-B[OH]$_2$) derivatives are applied for detection of glycols and catechols [23]. Interestingly enough, the binding affinity of PBA for catechol is about 6000 times higher than that for ethylene-glycol [26]. Borate complexes formed at alkaline pH (higher than ~8), lose the hydroxyls at acid pH (lower than ~7) and become neutral (non-ionized) trigonal borate ($BO_3$) esters [20]. Boric acid, borates, and boronic acids react easily with catechols [25-27]. Therefore, simple compounds such as BPA and catechol-borate ester (CBE) could form specific complexes directly with catechols from an already formed melanin, and work then as melanin-reactive drugs, and not as melanin precursors. This somewhat intriguing, but expected feature, seems to have been overlooked. Nevertheless, a mechanistic rationale for the possible binding of boronic acids and catechol-borate esters to melanin catechols is here described using a chemical and molecular modeling approach. The chemical structures of model compounds that will be analyzed, namely catechol-borate and phenyl-boronic acid, are shown in Figure 1. Concerning the chemistry of melanin and its precursors, several reviews have been published on melanin structure and its biosynthesis [28-30], being the most representative structure the porphyrin-like graphitic model from Olivieri and Nicolaus [31], and also the recent poly-catechol-porphycene (poly-CPo) model [32,33], based on the Olivieri and Nicolaus structure [31].

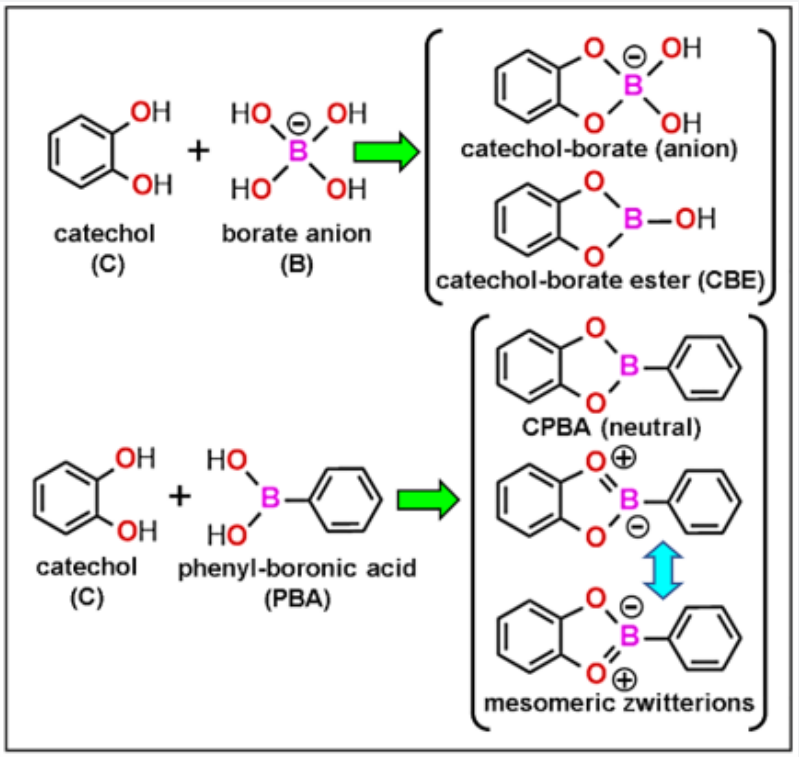


**Figure 1:** Chemical structure of analyzed model substrate, catechol (C), reagents and reaction products. Top: Borate anion (B), and tetrahedral or trigonal catechol-borate esters (CBE). Bottom: phenyl-boronic acid (PBA), and trigonal CPBA product. Observe the resonant zwitterions from CPBA (blue arrow).

## Methodology

Following previous studies on modeled chemical structures [30,34-38], the use of chemical drawn, and molecular modeling software allowed to analyze and illustrate the structure of some boron-containing agents. Chemical structures with formal double bonds were drawn with ChemDraw Ultra v12.0 software. Molecular modeling of melanin precursors, drugs and model compound was carried out with the HyperChem v7 and v7.5 software, using geometry optimization by Molecular Mechanics


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Force Field (MM+), converged at energy E = 0.1, 0.05, or 0.01 kcal/(Å mol). Energy minimization and calculation of molecular orbitals (MOs) were performed using either the semi-empirical PM3 method (Polak-Riviere algorithm, conjugate gradient) converged at E = 0.1 or 0.05 kcal/(Å mol), or the extended-Hückel method. To illustrate molecular structures and processes, MOs were represented as Jorgensen-Salem surface or Gouraud shaded 3D isosurfaces, using adequate orbital contours (1/orbital radius). Electrostatic potentials were recorded by plotting molecular graphics tool (contour value: 0.05, grid mesh size: fine).

It must be noted that the ground singlet (S0) state. and the first photo-excited singlet (S1) state of small aromatic molecules, are also represented by different MOs. The highest-occupied molecular orbital (HOMO), and lowest-unoccupied molecular orbital (LUMO) states represent the energy levels of ground and excited states of the molecule, respectively [39]. In HOMO-d and LUMO+d, d is a value from 0 to the maximum energy level, and the separation between HOMO-0 and LUMO+0 corresponds to the forbidden Fermi's energy gap (Eg). Orbital lobes corresponding to phases of π-electron conjugation are denoted by different colors. Fused lobes with the same color are in-phase, and those with isolated (unfused) lobes are out-of-phase.

## Results and Discussion

In the presence of borate anions or boronic acids, the catechol group forms in vitro a catechol-borate ester (CBE) or the boronic compound, catechol-phenylboronic acid (CPBA). The geometry of PBA and CBE, shown as space-filling (atomic volume) models, offers a more realistic representation of the molecular structure, as is clearly observed in Figure 2. Considering the stereochemistry of boronic acids and the formation of catechol-borate esters [25,26,40,41], molecular modeling methods are very suitable to illustrate their molecular shape and orbitals. The characteristic trigonal or tetrahedral configuration of neutral borate or borate anion in PBA or CBE, respectively, was found in atomic volume models (Figure 2), in agreement with chemical features of boric acid and anionic esters. Borate and boronic compounds are expected to occur as charged tetrahedral anions, neutral trigonal forms, or trigonal zwitterions, depending on the pH and type of solvent [20,26], but the stabilizing π-electron resonance between O and B atoms of the borate ester in the zwitterion mesomers of trigonal esters seems to have been rather overlooked. Interestingly, molecular modeling shows a clear π-conjugation involving the O-B-O atoms of the borate ring, as is revealed in the corresponding HOMO and LUMO patterns of trigonal CBE (Figure 3).

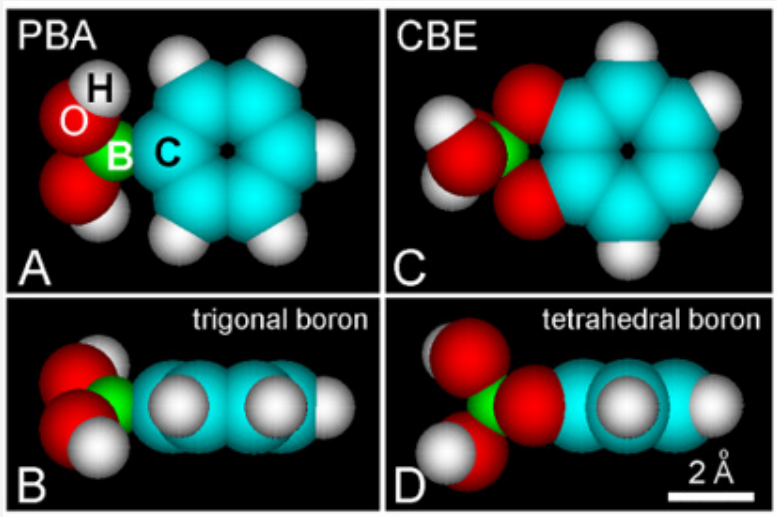


**Figure 2:** Frontal (A, C) and lateral (B, D) views of atomic volume models of phenyl-boronic acid (PBA) and catechol-borate ester (CBE), showing the trigonal and tetrahedral molecular geometry, respectively. PM3 (Polak-Riviere) geometry optimization converged at E = 0.1 kcal/(Å mol), Gouraud shaded isosurface.

Regarding zwitterions, the B-containing pentagonal ring shows high stability due to 6π-electron resonance [40], which also occurs for other heteroaromatic pentagonal rings stabilized by π-electron delocalization [42,43]. In its valence state with three available electrons, the B atom has one 2s-electron and two 2p-electrons, and therefore, trigonal (3q) $sp^2$-hybrid orbitals determine the binding behavior of boron [44, 45]. Likewise, the O atom is characterized by tetrahedral (4q) $sp^3$ hybrid orbitals, and then π-electron conjugation is allowed for O-B-O bonding. In keeping with this, the O-B bond length in tetrahedral borates is 1.49 Å, whereas it is only 1.40 Å in trigonal esters. In the case of phenyl-boronic acid, in addition to the O-B-O conjugation revealed in MOs image (Figure 4, A), a differential distribution of partial charges in B and O atoms is clearly observed. Figure 4, B shows the localization of the highest negative and positive charges in the trigonal CPBA complex (see Figure 1). This reveals that the B


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atom is positive (δ = + 0.26 eV), contrary to the commonly claimed negative charge of B represented in chemical formulations, which instead, appears distributed on each O atom (δ = -0.18 eV). Comparing trigonal and tetrahedral structures, the differential negative charge for $BO_3$ and $BO_4$ groups is -0.18 and -0.75 eV, respectively.

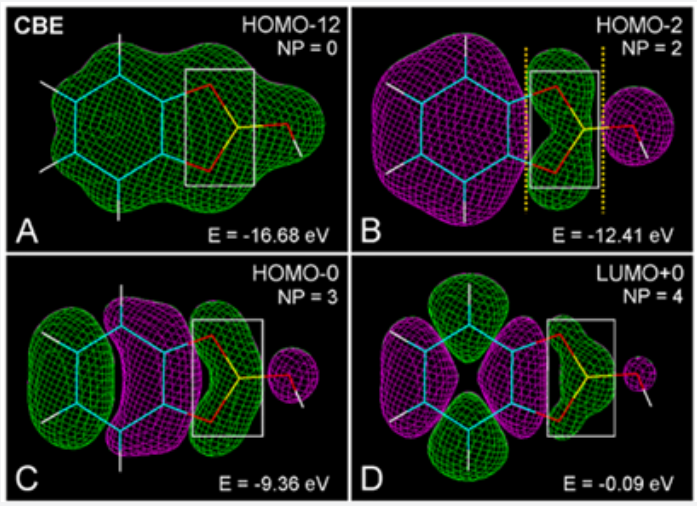


**Figure 3:** (A-D) Gallery of wire models with molecular orbitals of the uncharged trigonal CBE represented in frontal view (C: cyan, O: red, N: blue, H: white, B: yellow). PM3 (Polak-Ribiere) energy minimization converged at energy E = 0.05 kcal/(Å mol), and Jorgensen-Salem surface with orbital contour: 0.003 at different HOMO and LUMO energy levels (values in eV), with positive (green) and negative (violet) molecular lobes. Rectangles indicate the O-B-O bonds from the catechol-borate ester showing π-electron conjugation. Nodal planes (NP, dashed orange lines in HOMO-2) separate green and blue orbital lobes, with high energy levels corresponding to high number of nodal planes [39].

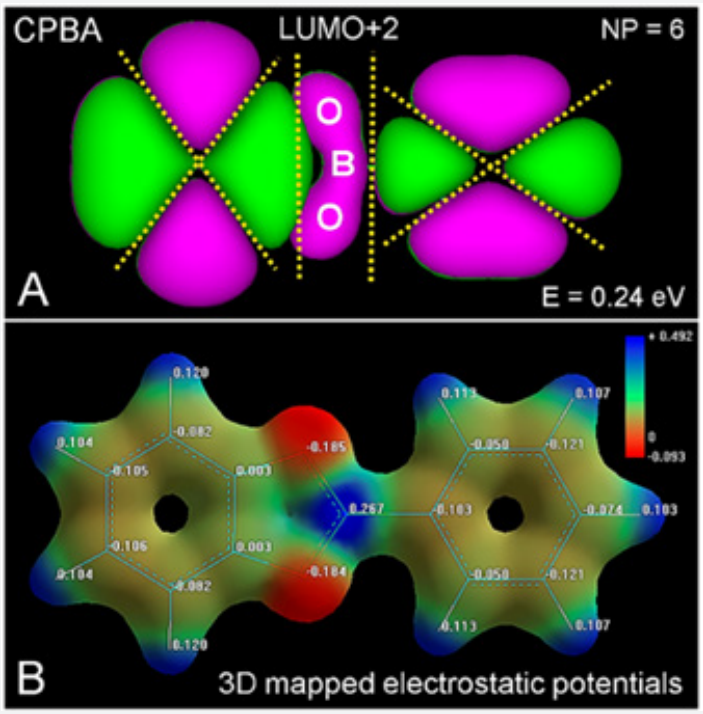


**Figure 4:** Molecular parameters of CPBA after PM3 (Polak-Ribiere) optimization converged at E = 0.05 kcal/(Å mol). (A) LUMO+2 energy level (E = 0.24 eV), Gouraud shaded isosurface, orbital contour: 0.004, showing the O-B-O bonds with π-electron conjugation, and nodal planes (NP, dashed orange lines). (B) 3D mapped isosurface plotting of electrostatic potentials (translucent surface, contour value: 0.05) from negative to positive values (red → green → blue).


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Eumelanin contains a great amount of catechol groups [28,33,46-48], which can react with borate anions and boronic acids (see Figure 1). Borate-ligand 1:1 and 1:2 complexes are the most and less usual, respectively [25,27], which could difficult the occurrence of borate 1:2 complexes using melanin catechols. However, a variety of easily synthesized arylboronic acids [49] would allow a more direct reaction with catechol groups. Boron-containing metabolite precursors could be incorporated into the polymer during biosynthesis. As each catechol group can bind a single borate anion or boronic acid, numerous borate esters are introduced into melanin. Binding of metal ions can account for up to 6 x $10^{20}$ sites per gram of dried melanin [50], and thus, catechol sites would account for a large amount of melanin-bound B atoms. At pH > 4 catechols from synthetic DOPA-melanin are ionized [51] and thus, it is a basophilic polyanion. At pH < 8 most borates esters are uncharged [20,26], and then melanin-borates complexes must be neutral and remain unstained.

Studies on the localization of boron-containing drugs for BNCT have shown rather poor results. BPA was found in the cytoplasm and nuclei of human glioblastoma and murine sarcoma cells [52-54]. In the case of melanocytes, PBA should be accumulated specifically within melanosomes. As they are acidic organelles with a clear lysosome lineage [55] and intramelanosomal pH range of 3-5 [56], the occurrence of negatively charged borate esters of eumelanin is unlikely to occur in living melanocytes. Regarding the recently proposed catechol-porphycene (CPo) model [32,33], it must be noted that this structure fulfills all characteristic features of natural and synthetic eumelanins, appearing as a multilayer graphitic structure. Modeling of a planar tetra-CPo molecule with catechol-attached PBA residues illustrates the possible organization of the polymer (Figure 5). Long continuous LUMO+4 lobes showing trigonal OBO groups, and fused CC and N:HN orbitals are clearly visible, accounting for the massive aromatic conjugation of this graphitic material. It is conceivable that the great amount of catechol groups makes melanin a suitable substrate to form borate esters, but the simple binding mechanism of boronic acids to melanin catechols have been mostly overlooked. Although a role as melanin precursor for BPA cannot be excluded, the main action mechanism could be a direct chemical reaction with suitable substrates such as aromatic diols, as seems to occur in the case of some melanoma seekers [37].

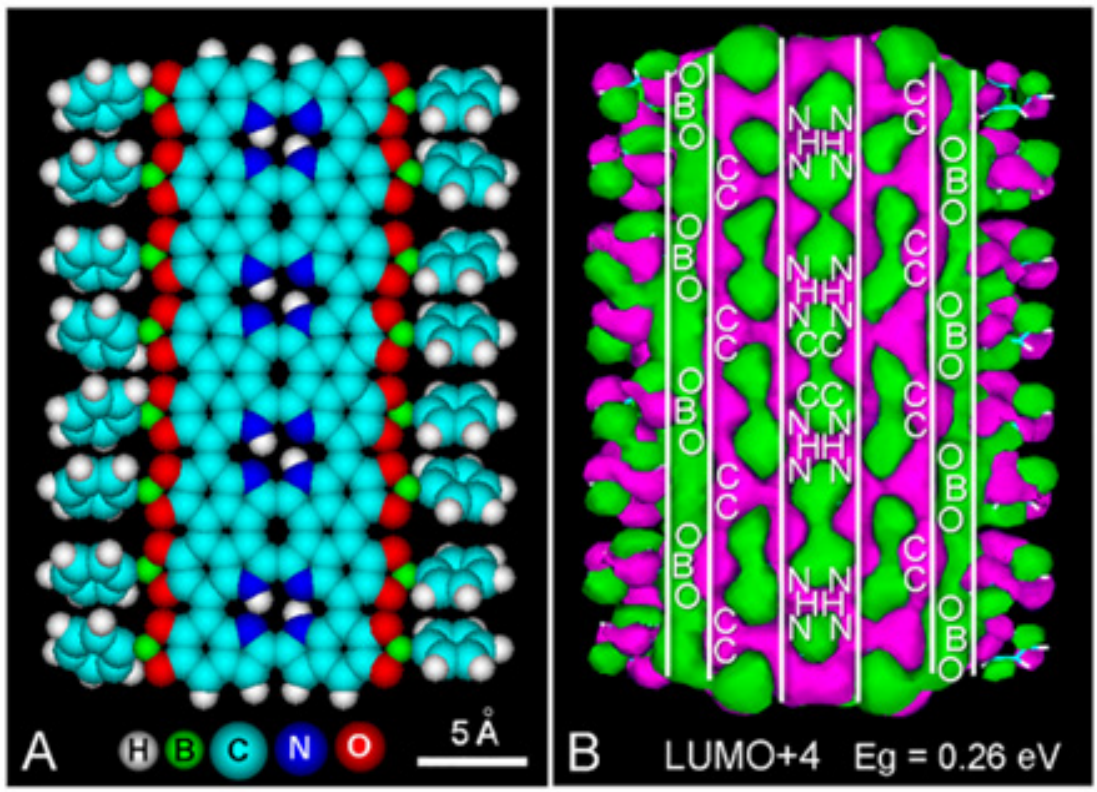


**Figure 5:** (A) Frontal view of an atomic volume model of tetra-CPo, after geometry optimization with MM+ converged at E = 0.1 kcal/(Å mol), with incorporated PBA units along the external edges. (B) Corresponding LUMO+4 energy level (E = -9.97 eV) followed by extended-Hückel energy minimization (calculated 1248 orbitals, Gouraud shaded isosurface, orbital contour = 0.0001, Eg = 0.26 eV). Note the planar structure of the oligomer and the extended longitudinal LUMO+4 lobes (vertical white lines) corresponding to the π*-electron conjugation of borate groups (OBO), CC and N:HN atoms. N:HN bonding distances are 2.7-2.8 Å.


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## Conclusions

In spite of the increasing biomedical interest in using BNCT against melanoma, the reaction mechanism of $^{10}$B-carriers with melanin remains unclear, but nevertheless some new interpretations and predictions are put forward in this work. It may be assumed that catechol-borate precursors could be either incorporated during eumelanin biosynthesis or directly bound to catechol groups of already formed polymers. The application of molecular modeling methods for analyzing the incorporation mechanism of $^{10}$B-carriers into melanin revealed interesting structural features of both reagents and reaction products. In keeping with this, OBO π-conjugation in trigonal boronic and borate groups is clearly demonstrated, as well as its participation in the extended longitudinal LUMO+4 energy level of a melanin model based on a poly-catechol-porphycene structure containing PBA units. Geometric and energetic considerations suggest that this proposal of a direct reaction between a boronic acid and melanin catechols may be right, resulting on a rather simple way to attach $^{10}$B to the melanin content of melanoma cells for BNCT.

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