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REVIEW

The dubious origin of beryllium toxicity

José Elguero[1] **· Ibon Alkorta**[1]

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Abstract
Four mechanisms have been proposed in the literature to explain beryllium toxicity; they can be divided in two groups of two mechanisms: (i) replacement type: models 1 and 2; (ii) addition type: models 3 and 4. At this moment is not possible to select the best model not even to establish if one of these models will be the ultimate mechanism of beryllium toxicity. However, it is important to know the still open discussion about something so important associated with one of the simplest elements of the periodic table.

Keywords Beryllium · Toxicity · Coordination · Proteins

Introduction

Regarding the abundance of beryllium in the environment and the sources for humans, the main conclusions are the following [1–8]:

> Beryllium is found in the earth's crust at a concentration of 2.8 to 5.0 mg/kg. The only significant beryllium ores are beryl, which contains 4% beryllium, and bertrandite, which contains less than 1% beryllium.
> Metallic beryllium, beryllium alloys, and beryllium oxide are derived from beryllium processing and account for 10%, 75%, and 15% of total beryllium hydroxide use, respectively. Annual beryllium air emissions from production and processing are about 8.9 tons/year, which represents 4.4% of total beryllium air emissions from all sources.
> The main source of beryllium in the atmosphere, responsible for emissions of about 200 tons/year and 95% of all atmospheric beryllium, is the combustion of fossil fuels, especially coal. Beryllium enters water in wastewater from iron and steel as well as non-ferrous industries.
> Soluble beryllium compounds are extremely rare in commerce, and only small amounts are occasionally used in research facilities. Other than these minimal amounts, human exposure to soluble species is restricted to extraction and concentration facilities. Approximately 20 tons/year of pure beryllium is used in certain applications, such as X-ray windows, nuclear reactors, and aerospace techniques.
> Beryllium-containing alloys represent the largest percentage (75%) of the beryllium-containing materials market. They are used in electronic, energy, automotive, and aeronautical applications due to their high elasticity, conductivity, electrical and thermal resistance, oxidation resistance, and high melting point.

The toxicity of beryllium is a complex problem because beryllium has both acute and chronic toxicities and also because Be^0 and Be^{2+} are toxic although the toxicity of Be^0 seems to be due to its oxidation to Be^{2+} [9, 10], in the presence of protic acids. This has leaded some authors [11] to use in their papers the word beryllium for both species, a source of confusion. Studies on the toxicity of beryllium and on chronic beryllium disease, CBD, are very numerous and extend over 60 years [1, 5, 8, 12–17]. For many authors, beryllium is the most toxic non-radioactive element in the periodic table [18, 19], but Buchner does not agree having stated that "the acute toxicity of beryllium ions does not exceed that of other toxic cations like Cd^{2+}, Ba^{2+}, Hg^{2+} or As^{3+}" [20, 21].

An aspect of the Be^{2+} properties that is very relevant for its toxicity is its tetracoordination [18, 22–26]. Although hexacoordinated Be^{2+} is a minimum in the potential surface [27, 28], tetracoordinated is much more stable to the point that $[Be(H_2O)_6]^{2+}$ isomerizes into $[Be(H_2O)_4]$

✉ Ibon Alkorta
ibon@iqm.csic.es

[1] Instituto de Química Médica (CSIC), Juan de la Cierva, 3, 28006 Madrid, Spain

$^{2+}$·2 H_2O, i.e., two water molecules prefer to be placed in the second coordination sphere [29–31]. The small size of Be^{2+} is the origin of its tetracoordination [18] and to the name "tetracoordinated proton" [32]. A field of great interest is the search for molecules that can behave as chelating agents of Be^{2+} with the purpose to find detoxifying compounds; these compounds are generally carboxylic acids or carboxylate anions [19, 33, 34].

Finally we must remember the problem encountered when using X-ray crystallography: due to the low number of electrons in Be^{2+} (only two), its localization is not possible via protein X-ray crystallography [21, 35]. This problem is the same with hydrogen atoms (only one electron).

Note that a search in the Brookhaven protein data bank affords 407 structures containing Be [36], but they are all compounds containing $BeF_3^{(-)}$, beryllium trifluoride used as a phosphate analog [37, 38]. In the structures reported in the following discussion, the Be^{2+} atoms are not "seen" but placed in the position that best fit with the ligands.

Discussion

Four mechanisms have been proposed to explain Be^{2+} toxicity:

Model 1: Be^{2+} replaces Mg^{2+} or Ca^{2+} in the protein [16, 39, 40].

Model 2: Be^{2+} replaces H^+ in O···H···O ionic hydrogen bonds (HBs); on the other hand, Mg^{2+} is unable to do this [2, 32, 41]. This mechanism has been questioned [42].

Model 3: In an empty pocket of a protein enters the cluster $[Be_4O]^{6+}$ [43–45].

Model 4: In an empty pocket of a protein enters Be^{2+} and Na^+ without counter anions, that is, in the X-ray structure, there are not anions such Cl^- or $HSO4^-$ [46, 47]. The empty pockets of these proteins before entering Be^{2+} and Na^+ have been found [48, 49].

These models can be classified in two types: (i) replacement type: models 1 and 2; (ii) addition type: models 3 and 4.

Model 1

According to Sukharev [40], the toxicity of Be^{2+} is due to the fact that it can replace Ca^{2+} in phosphatidylserine (Fig. 1):

Comments: (a) in these structures there are no counterions type Cl^-; (b) the charges are not balanced, the missing negative ones should be in other parts of the protein; (c) the phosphate groups play a fundamental role since beryllium has more affinity for phosphates than for carboxylates. Opposed to comment b, and to facilitate possible theoretical studies, in Fig. 2, there are some neutral systems that could be used as simple models of Fig. 1 structures.

Structure A of Fig. 1 is close to that of tetra-aqua beryllium. A search in the Cambridge Structural Database (CCDC) [50] affords seven structures of $[Be(H_2O)_4]^{2+}$ with reference codes CADZIS, CICXOC, INIMAU, KIDREU, KIDREU01, KIQPEH, and MINKUP. In Fig. 3 is represented that of CICXOC [51].

Model 2

Ionic hydrogen bonds, both cationic and anionic, are stronger than neutral HBs. They have a fundamental role on the structure of biomolecules, peptides, and proteins [52, 53]. The replacement of a proton by Be^{2+} ("tetrahedral proton" [32]) produces a profound distortion of the biomolecule, distortion that could explain the beryllium toxicity. This was Scott's "new paradigm" [11, 32] also supported by McDowell [41]. According to Scott, beryllium has the potential to replace

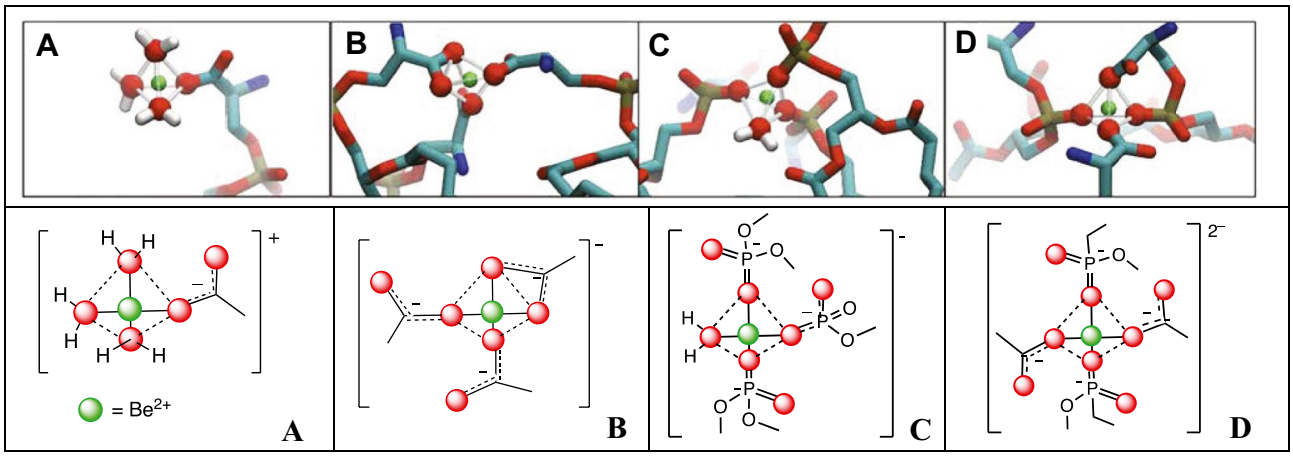


Fig. 1 Top: figures adapted from [40]; bottom the corresponding ChemDraw. Beryllium cations are represented in green

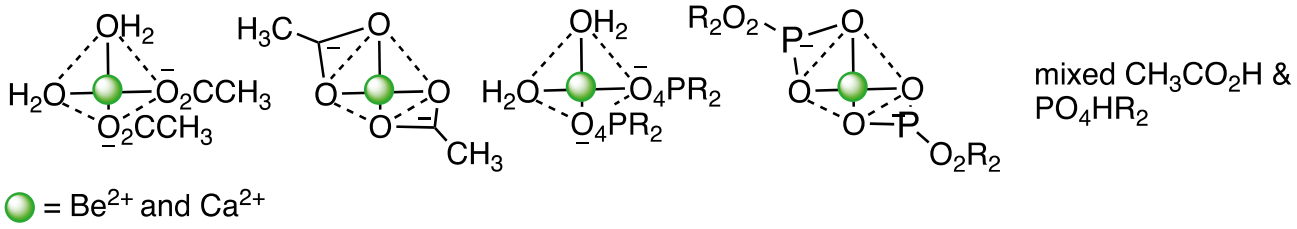


Fig. 2 Models of neutral complexes

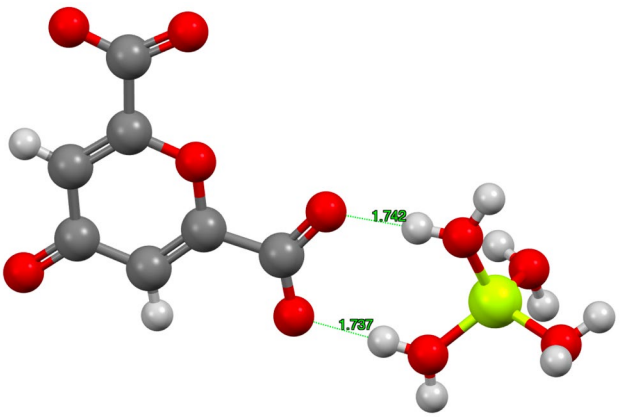


Fig. 3 Structure of CICXOC with the two O···H hydrogen bonds distances (1.737 and 1.742 Å). Beryllium atom in green, oxygen atoms in red

such protons and dramatically alter binding interactions that are known to illicit immune responses. It is known that $[Be(H_2O)_4]^{2+}$ readily deprotonates to afford OH^- centers. Replacing H by Be results in the reaction of Fig. 4 that may go a step further to a tetrahedral Be^{2+} complex.

The concept of "tetrahedral proton" [26] has been frequently cited by our group but independently of the toxicity mechanism [54–59].

Houk [52] based the protic mechanism (Fig. 5) on a series of papers by Gerlt and Gassman [60–62]; these authors propose a mechanism involving an ionic HB. The strong increase in acidity of the protons of the methyl group due to the coordination with $BeCl_2$ has been observed for many other systems [57, 63].

McDowell wrote that: "It was found that the beryllium ion was energetically very effective in displacing the proton from hydrogen bonds, whereas the magnesium ion was unable to

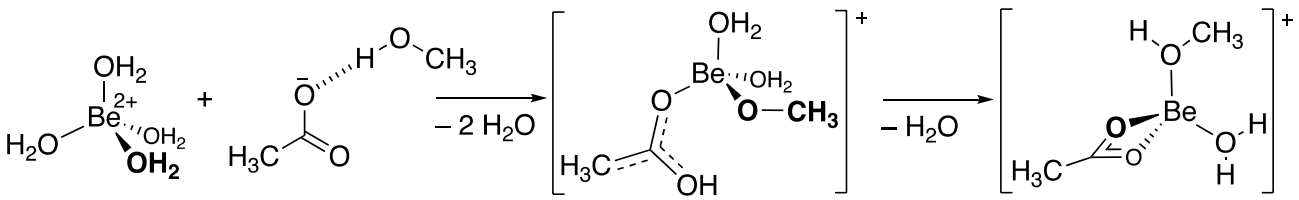
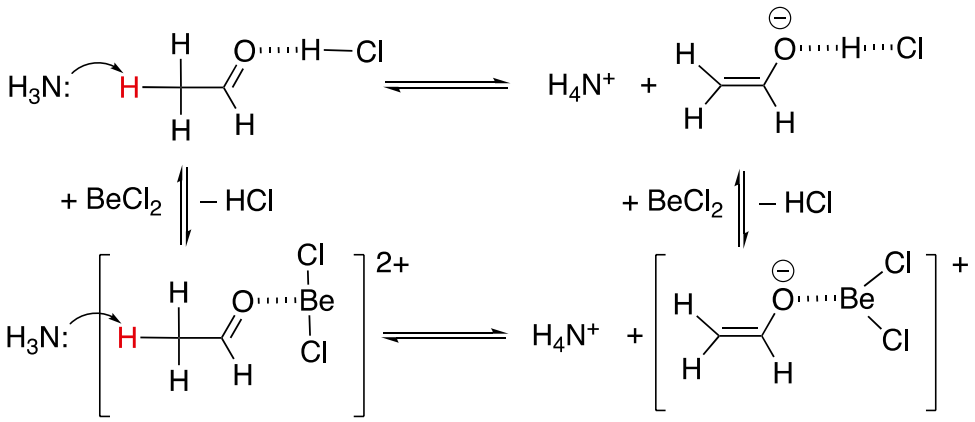


Fig. 4 Scott mechanism [32]

Fig. 5 Example of replacement of H^+ by Be^{2+}



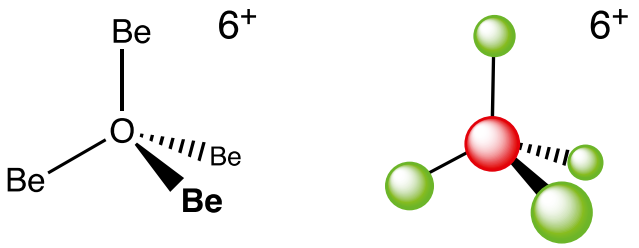


Fig. 6 Two representations of the tetrahedral 6^+ cation

do so." Several models were studied: $Cl^{-}\cdots H–F$, $Cl^{-}\cdots Be–F$, $Cl^{-}\cdots Mg–F$, $H_2O\cdots H–F$, $H_2O\cdots Be–F^{+}$, $H_2O\cdots Mg–F^{+}$ [41].

However, Buchner doubted this mechanism precisely due the high distortion [42]. According to him, "However, the substitution of the two-fold coordinated proton by a tetrahedral coordinated Be^{2+} ion would cause a massive decrease of the bond angle to about 109°. The bond angle in hydrogen bonds tends to be as linear as possible, and almost never below 120°. This would lead to strong changes in the conformation of the protein. It is questionable if a Be^{2+} species would acidify a proton of a hydroxy group enough to liberate it, forming RO^{-}, it and to our knowledge this has not been shown."

Model 3

This model involves "basic beryllium salts," that is $Be_4O^{(6+)}X^{(6-)}$ (Fig. 6). X cannot be a chloride; it must be a bridging ligand such as acetate or nitrate; each oxygen coordinates with a different beryllium atom. Remember that two amino acids have a supplementary CO_2H group, aspartic and glutamic acids (D and E) [44, 45].

This cation is formed by reaction beryllium diacetate with water:

$$4\ BeAc_2 + H_2O \rightarrow Be_4O\ Ac_6 + 2\ AcH\ (CH_3CO_2H) \quad (Be_4O^{6+}\ Ac_6{}^{6-})$$

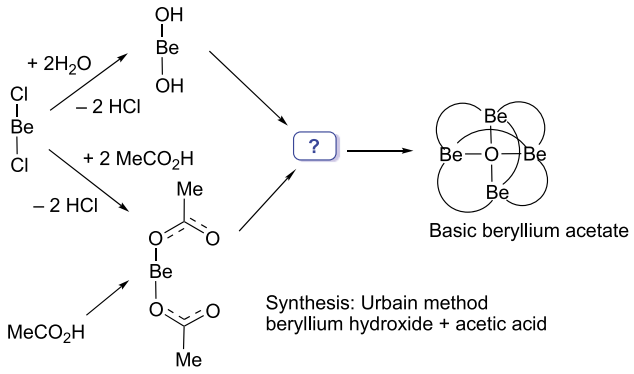


Fig. 8 Urbain method

The main conclusion of the last paper [45] is that the calculated structure (Fig. 7 right) coincides with the protein HLA-DP2β1 that contains Be and Na [48]. In this publication, the location of the Be^{2+} ion was not determined ("how Be-containing complexes might occupy this site"), it was situated from the surrounding O atoms.

The synthesis of Be_4O^{6+} $Ac_6{}^{6-}$ (Urbain method) is represented in Fig. 8. According to the literature basic beryllium acetate (BBA) is obtained from beryllium hydroxide and acetic acid, but in the equation, beryllium acetate is used.

In reference [45], it was written "The composition of a $[Be_4O]^{6+}$/M2/DP2 complex (Fig. 7, right) suggests that its formation under physiological conditions should be a rather slow, rarely occurring process, since four Be^{2+} cations have to accumulate in the small coordination site S and also since an oxide dianion ($O^{=}$) has to be formed. This very general expectation would meet the fact that CBD has long, and partially very long latency times." Actually, the synthesis of the proposed structure in physiological conditions seems highly improbable.

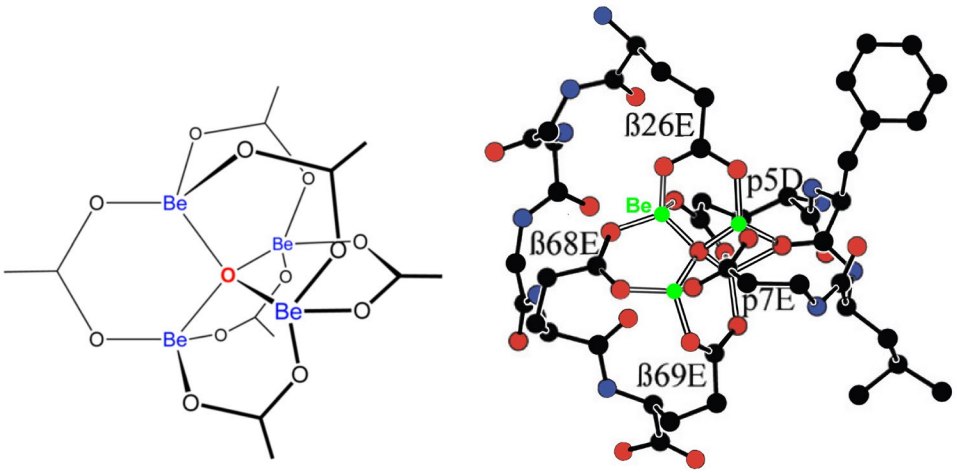


Fig. 7 Left, Be_4O^{6+} $Ac_6{}^{6-}$; right DFT (PBE0 + D3/def2-TZVP) optimized structure adapted from reference [45], $Be_4O.^{6+}$ surrounded by four glutamic (E) and one aspartic (D)

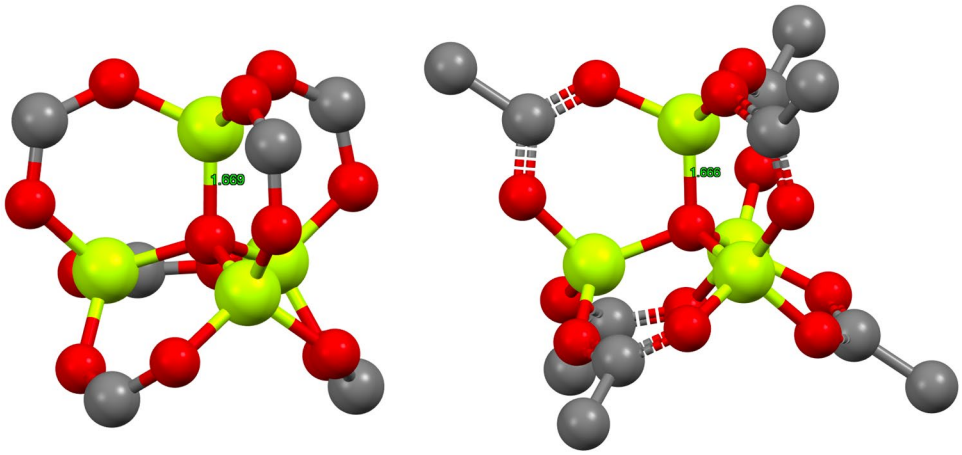


Fig. 9 Left, BAHLIJ (the C-aryl groups have been removed (distance B–O = 1.669 Å); right, BEOACT distance B–O = 1.666 Å). Beryllium atoms in green, oxygen atoms in red

Thirteen X-ray structures like those of Figs. 7 and 8 (right) have been published in the CCDC [50]: BAHLAB, BAHLEF, BAHLIJ, BAHLOR, BAHLUV, BAHQIO, BEOACT, BEOACT01, BEOACT02, BEOACT03, OCOQAY, OCOQEC, and VASFOM. We have represented in Fig. 9 those of BAHLIJ [64] and BEOACT [65].

Model 4

Model 4 is closely related to model 3: instead of a beryllium tetramer, model 4 proposes a Be^{2+} + two Na^{+} [46, 47], but the protein is the same, HLA-DP2, and the anions obviously also the same, **C** and **E**, Fig. 10 [46].

An empty pocket, the same as in model 3, accepts the Be^{2+} cation that rearranges about it (see black arrows). Be^{2+} is tetracoordinated with one aspartic and three glutamic. The structure also includes a Na^{+} cation at 2.74 Å of the Be^{2+}.

A theoretical paper, QM/MM, published in 2020 [47], studied the above proposal and also the M2-peptide in the role of Be^{2+}. They wrote, "A small and electropositive Be^{2+}-ion accompanied by Na^{+}-ions binds to the cavity rather strongly and induces synergistic conformational changes of the amino acid residues at the TCR (T-cell receptor protein) binding surface of the HLA-DP2_M2 complex." Since here is only one beryllium atom, instead of four atoms of the model 3, the carboxylic residues bind using only an O atom.

Buchner wrote in 2020 [67]: "However, due to the inherent low resolution in protein X-ray crystallography a direct localization of the atoms inside the acidic pocket was not possible [46]." Therefore, computational chemistry was used to evaluate the species bound inside. This resulted in two models, which either propose the coordination of a single Be^{2+} ion together with one or two Na^{+} ions [47] or the presence of an oxygen centered $[Be_4O]^{6+}$ tetrahedron [43–45]. Some authors prefer two Na^{+} ions instead of only one [38].

Comparison models 3 and 4

It is possible to find a common stoichiometry for models 3 and 4:

$$\mathbf{Ac_6Be_4O} + 2\ \mathrm{AcNa} \leftrightharpoons \mathbf{Ac_4BeNa_2} + 2\ \mathrm{Ac_2Be} + \mathrm{BeO} \quad \text{both sides correspond to } \mathrm{Ac_8Be_4Na_2O}$$

This reaction should allow comparing the relative stabilities of both models. Note that the highly toxic beryllium oxide is an important technological compound for preparing $KBe_2BO_3F_2$, the sole usable crystal for deep-UV lasers [67].

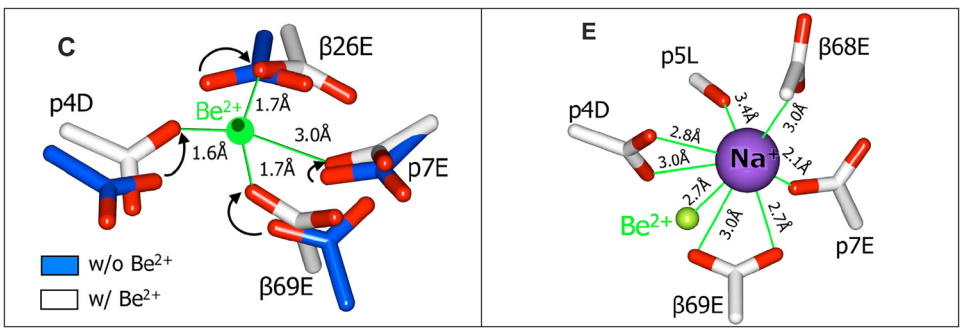


Fig. 10 Structures related to model 4 adapted from reference [46]

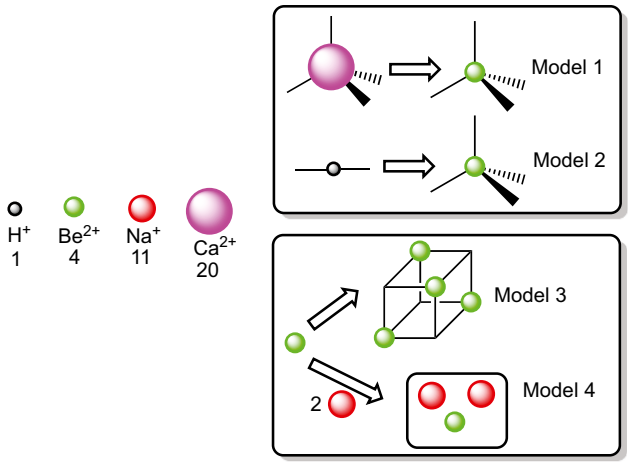


Fig. 11 A schematic representation of the four models with a rough size for the four cations

Conclusions

Currently, it is not possible to select the mechanism amongst the four possibilities; it is even possible that the true mechanism would be a different one.

In Fig. 11, we have tried to summarize the four mechanisms:

The solution to this conundrum may come from a technique that makes it possible to determine the position of beryllium cations in a protein complex. New techniques such single-particle electron cryo-microscopy (cryo-EM) could be a possibility.

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Availability of data and materials The data is available upon request to the authors.

Declarations

Ethical approval Not applicable.

Competing interests The authors declare no competing interests.

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