

# Optimizing the ZS-9 Potassium Ion Trap: Pore Size and Thermodynamics

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## BACKGROUND

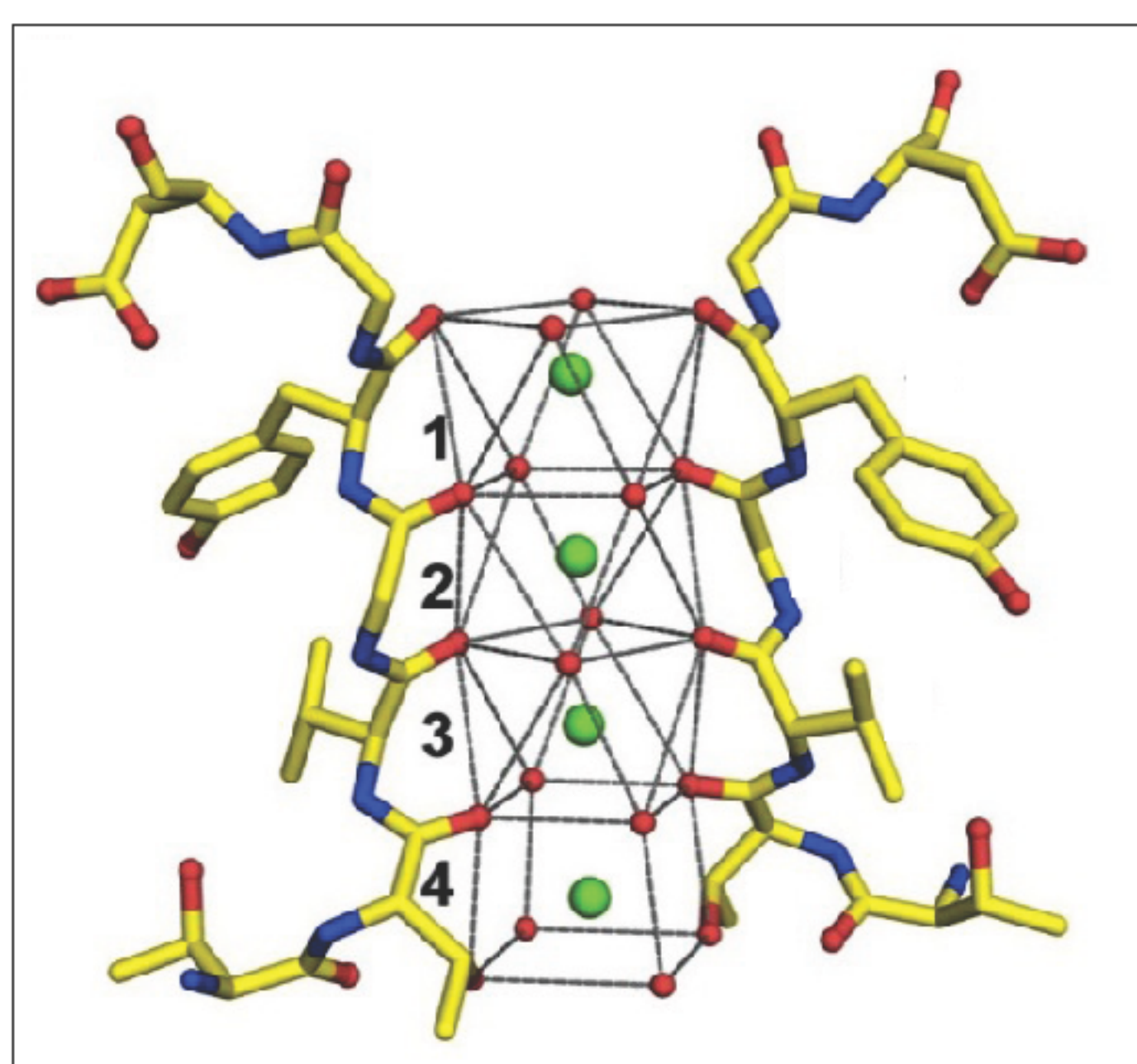
### HYPERKALAEMIA

- Renin-angiotensin-aldosterone system (RAAS) blockers (e.g., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers, spironolactone) increase the risk of hyperkalaemia, thereby limiting their use in patients who would otherwise benefit.<sup>1-4</sup>
- Hyperkalaemia is an independent risk factor for cardiovascular mortality. It impairs cardiac function, potentially leading to life-threatening arrhythmias.<sup>5-6</sup>
- Organic polymer resins represent a non-specific cation-exchange that must wait to traverse the entire gastrointestinal (GI) tract to reach the colon before having any appreciable impact on serum potassium (K<sup>+</sup>). In the colon, a high concentration of K<sup>+</sup>, mediated by aldosterone, outcompetes other cations such as Ca<sup>2+</sup>, Mg<sup>2+</sup>, and Na<sup>+</sup>.
- The only FDA-approved treatment for hyperkalaemia in the US is the organic ion exchange resin sodium polystyrene sulfonate (Kayexalate®), which is associated with serious GI adverse events, such as colonic necrosis.<sup>7</sup> Moreover, because of its questionable efficacy, there exists an unmet need for safe and effective treatments for hyperkalaemia.<sup>8</sup>

### PHYSIOLOGICAL POTASSIUM (K<sup>+</sup>) CHANNELS

- Potassium (K<sup>+</sup>) and sodium (Na<sup>+</sup>) ions are similar in size (3.0 and 2.3 Å, respectively)<sup>9</sup>, yet physiological K<sup>+</sup> channels are able to discriminate between the two by a factor of 10,000, through the use of a selectivity filter (Figure 1).<sup>10</sup>

Figure 1. Selectivity Filter in K<sup>+</sup> Channels<sup>11</sup>

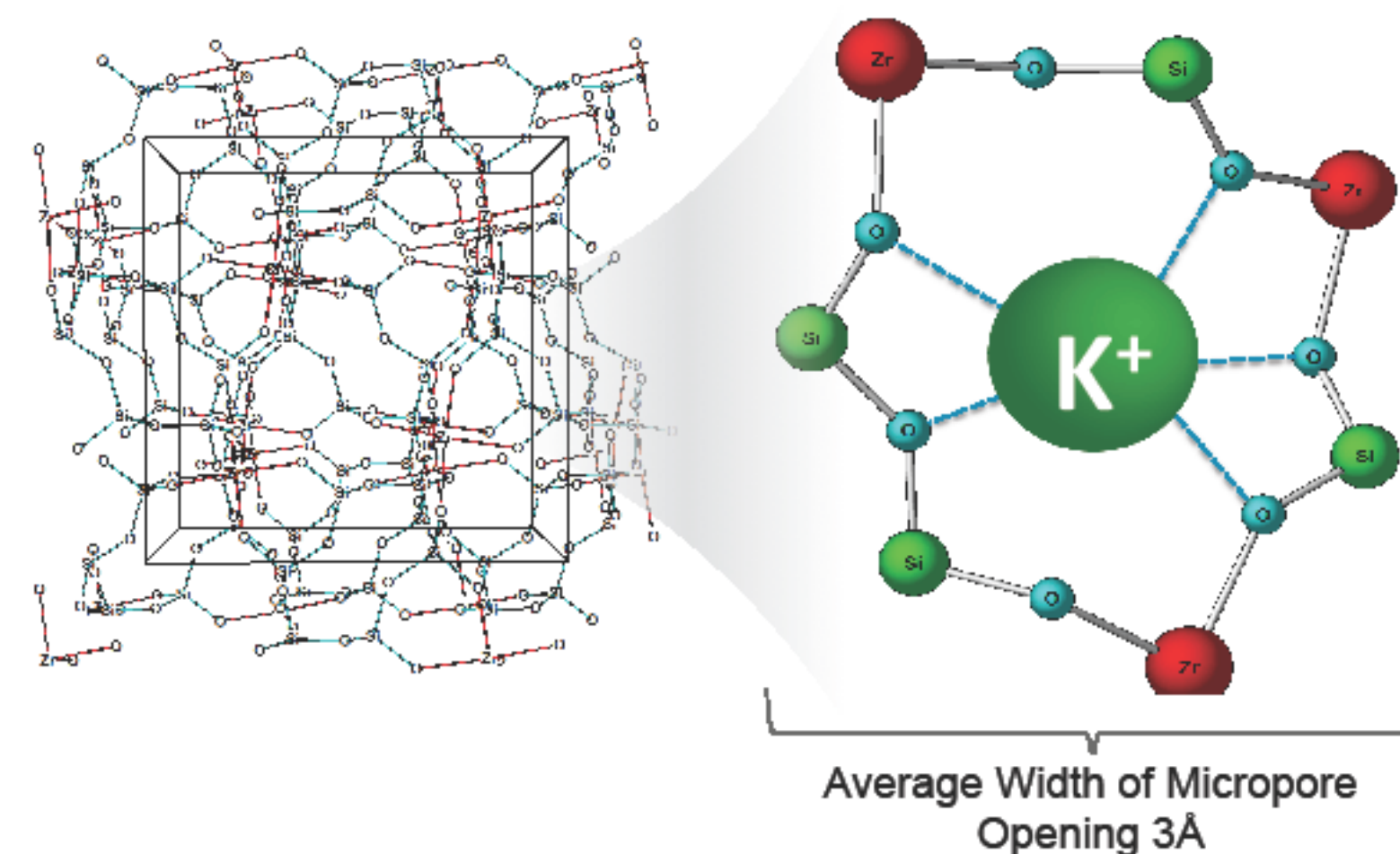


- Each binding site consists of a "cage" of 8 oxygen ligands coordinating 1 K<sup>+</sup> ion (inset).
- The cage favors the interaction with K<sup>+</sup> over Na<sup>+</sup> because Na<sup>+</sup> is too small to have an optimal number of interactions with the carbonyl oxygens. Interactions with Na<sup>+</sup> are therefore thermodynamically less favourable than K<sup>+</sup>.
- An optimal number of interactions with carbonyl oxygens balances the energy lost due to dehydration, making it energetically favourable for K<sup>+</sup> ions to move through the selectivity filter of the K<sup>+</sup> ion channel.

### ZS-9

- ZS-9 is a microporous zirconium silicate compound that selectively removes excess K<sup>+</sup> *in vivo*.
- Unlike organic polymers (e.g., Kayexalate), ZS-9 is an inorganic crystalline cation exchange compound that has a high capacity to selectively entrap monovalent cations, specifically excess K<sup>+</sup> and ammonium ions, as it traverses the GI tract.
- Also distinct from organic polymer resins, ZS-9 does not swell within the GI tract, so is likely to be less prone to GI side effects associated with organic polymer resins.
- Phase 2 and Phase 3 clinical studies of ZS-9 given orally for treatment of hyperkalaemia have demonstrated rapid and sustained reduction in serum K<sup>+</sup>, with a favourable safety profile and low rate of GI adverse events.<sup>12,13</sup>

Figure 2. Structure of ZS-9



- Octahedrally and tetrahedrally oxygen-coordinated zirconium and silicon atoms
- Oxygen atoms act like bridges to form a cubic lattice structure
- Pore opening of ZS-9 framework is an asymmetrical seven-member ring
- Diameter of unhydrated K<sup>+</sup> ion ≈ ZS-9 pore opening, so K<sup>+</sup> cations fit within the ZS-9 lattice structure after dehydration

### HYPOTHESIZED MECHANISM OF ACTION OF ZS-9

- It is hypothesized that ZS-9 uses a selectivity filter akin to those of physiological K<sup>+</sup> channels (Figure 2).
- To pass through the selectivity filter, an ion must first shed its coat of water and interact with the carbonyl oxygens. Although the K<sup>+</sup> channel filter can accommodate both K<sup>+</sup> and Na<sup>+</sup> ions, only K<sup>+</sup> ions are large enough to interact with an optimal number of carbonyl oxygens after dehydration.
- Hydrated cations, such as Mg<sup>2+</sup> and Ca<sup>2+</sup>, have larger ionic diameters (8.5 Å and 8.2 Å, respectively) than K<sup>+</sup> (6.6 Å) and require more energy to shed their hydration shells.<sup>9</sup>
- Energy regained by interaction with oxygen atoms in the ZS-9 structure is hypothesized to be greater than the energy lost in dehydration of the K<sup>+</sup> ion, making it energetically favourable to enter the ZS-9 pore opening.

## OBJECTIVES

- The purpose of this study was to determine the pore size of ZS-9 and to model thermodynamic stability for Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup>, and Mg<sup>2+</sup> within the ZS-9 lattice structure.

## METHODS

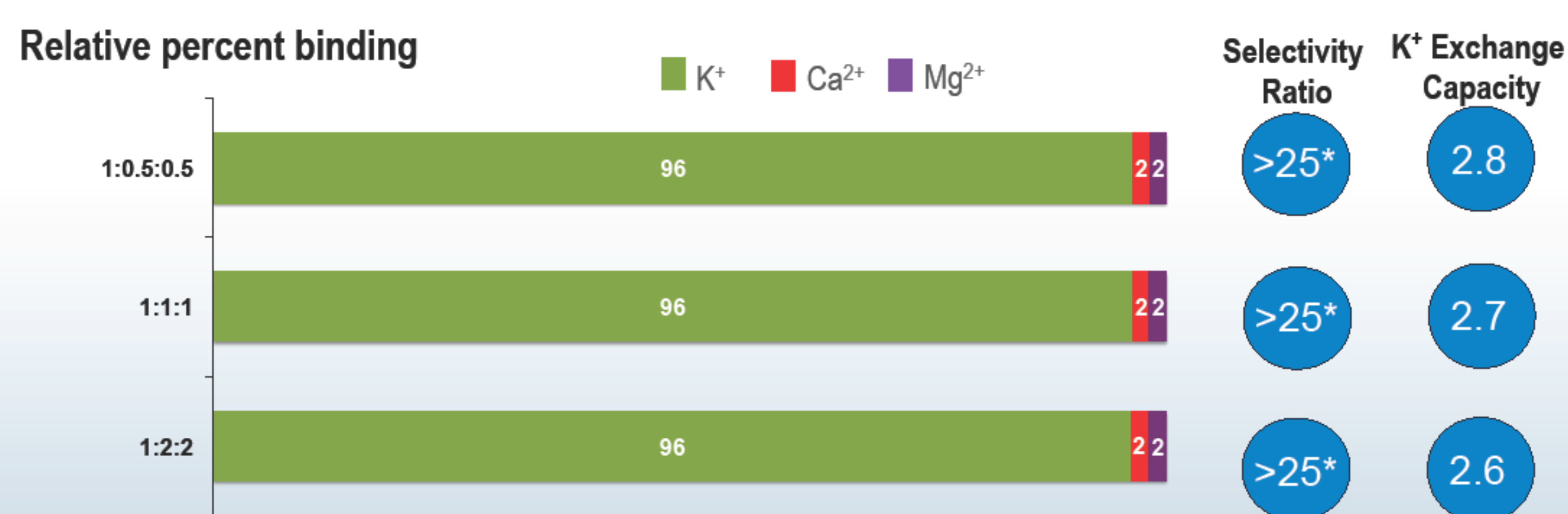
### Selectivity Ratio Calculations

- ZS-9 or Kayexalate was added to solutions containing standard ppm concentrations of K<sup>+</sup>, in addition to Ca<sup>2+</sup> and Mg<sup>2+</sup>, at different ratios (1:0.5:0.5, 1:1:1, 1:2:2). After 2 hours, an aliquot was taken and the cations quantified by ion chromatography (Dionex Model ICS-1100, coupled to an AV-DV autosampler). Selectivity ratios were calculated as [K<sup>+</sup>] / [Ca<sup>2+</sup>] + [Mg<sup>2+</sup>].

### Structural Studies and Thermodynamic Stability Modeling

- ZS-9 was dried and ground in an agate mortar, then placed into a powder diffractometer. Data were collected at room temperature with monochromated Cu α<sub>1</sub> radiation (λ=1.5406 Å). Rietveld least squares structural refinements were performed, and the interatomic distances were calculated from the resulting atom positions. The size of the pore opening was calculated by subtracting twice the atomic radius of oxygen (van der Waals radius, r=1.52 Å) from center-center interatomic distances.
- The predicted energies for different cation forms of ZS-9 (ie, Na-ZS-9, K-ZS-9, Ca-ZS-9 and Mg-ZS-9) and alkali and alkaline earth oxides from models were used to estimate the cation exchange energies in ZS-9. All energies were computed relative to the Na<sup>+</sup> form of ZS-9, defined as the reference state.

Figure 3: ZS-9 had a >25-fold selectivity for K<sup>+</sup> over either Ca<sup>2+</sup> or Mg<sup>2+</sup> at all concentration ratios

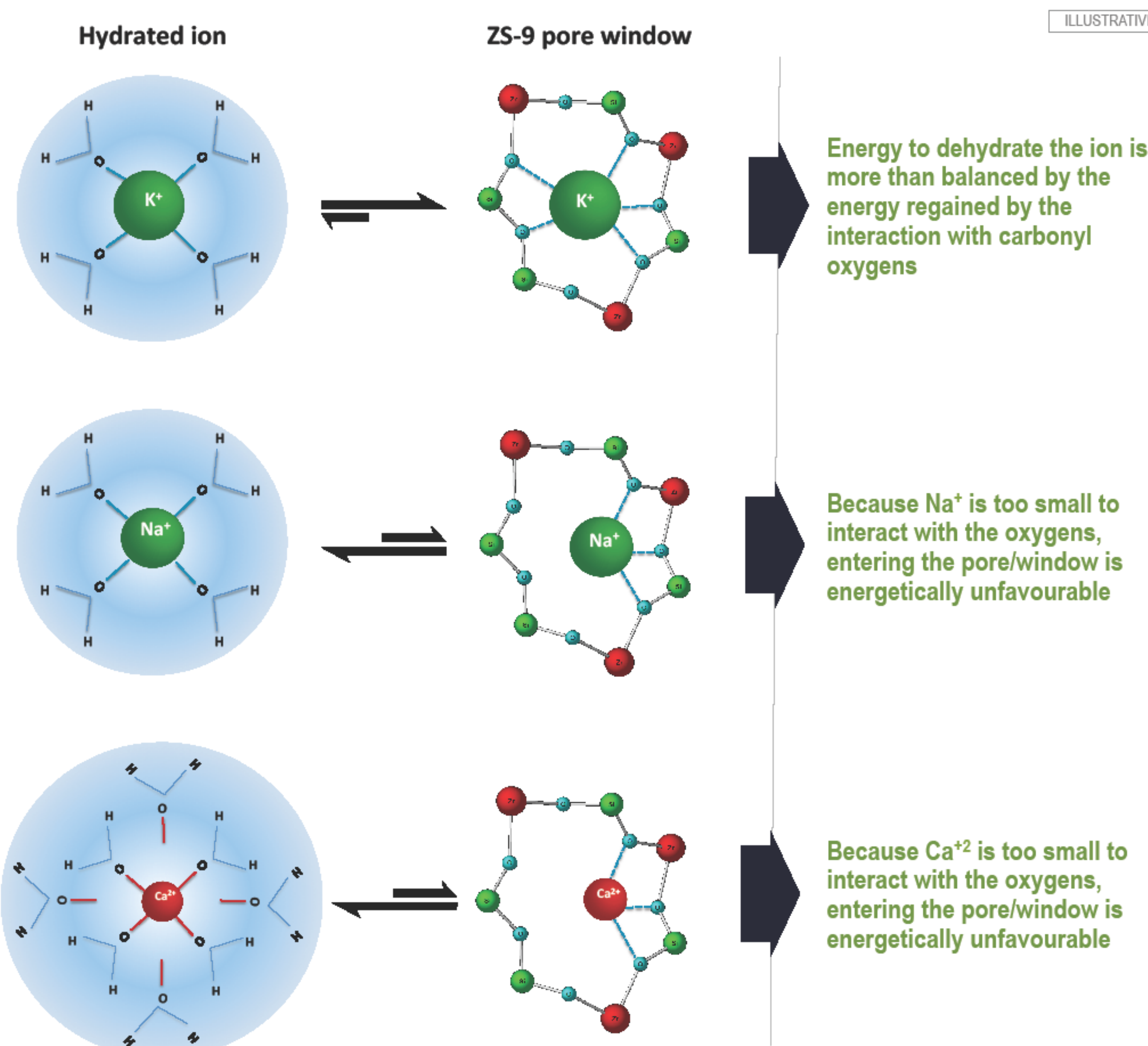


\*Exchange capacity of Ca<sup>2+</sup> and Mg<sup>2+</sup> was below the set detection limit of 0.05 mEq/g; therefore 0.05 mEq/g was assumed for calculation purposes.

Table 1. Energetics for Cation Exchange

	eV	Kcal/mol	Energy per Na cation (kcal/mol)
<b>Energetics for Na-Mg Cation Exchange</b>			
$\text{Na}_{16}\text{Zr}_8\text{Si}_{24}\text{O}_{72} + 8\text{MgO} \rightarrow \text{Mg}_8\text{Zr}_8\text{Si}_{24}\text{O}_{72} + 8\text{Na}_2\text{O}$	29.01	669.0	
$8\text{Na}_2\text{O} + 8\text{H}_2\text{O} \rightarrow 16\text{Na}^+_{(\text{aq})} + 16\text{OH}^-_{(\text{aq})}$		-534.2	
$8\text{Mg}^{2+}_{(\text{aq})} + 16\text{OH}^-_{(\text{aq})} \rightarrow 8\text{MgO} + 8\text{H}_2\text{O}$		149.8	
$\text{Na}_{16}\text{Zr}_8\text{Si}_{24}\text{O}_{72} + 8\text{Mg}^{2+}_{(\text{aq})} \rightarrow \text{Mg}_8\text{Zr}_8\text{Si}_{24}\text{O}_{72} + 16\text{Na}^+_{(\text{aq})}$		284.6	17.8
<b>Energetics for Na-K Cation Exchange</b>			
$\text{Na}_{16}\text{Zr}_8\text{Si}_{24}\text{O}_{72} + 8\text{K}_2\text{O} \rightarrow \text{K}_8\text{Zr}_8\text{Si}_{24}\text{O}_{72} + 8\text{Na}_2\text{O}$	-5.82	-134.1	
$8\text{Na}_2\text{O} + 8\text{H}_2\text{O} \rightarrow 16\text{Na}^+_{(\text{aq})} + 16\text{OH}^-_{(\text{aq})}$		-534.2	
$8\text{K}_2\text{O} + 8\text{H}_2\text{O} \rightarrow 16\text{K}^+_{(\text{aq})} + 16\text{OH}^-_{(\text{aq})}$		341.5	
$\text{Na}_{16}\text{Zr}_8\text{Si}_{24}\text{O}_{72} + 16\text{K}^+_{(\text{aq})} \rightarrow \text{K}_8\text{Zr}_8\text{Si}_{24}\text{O}_{72} + 16\text{Na}^+_{(\text{aq})}$		-326.8	-20.4

Figure 4. ZS-9 Size Selectivity Filter is Energetically More Favourable for K<sup>+</sup> Interaction



## RESULTS/CONCLUSIONS

- The structure of ZS-9 consists of units of octahedrally and tetrahedrally coordinated zirconium and silicon atoms with oxygen atoms acting as bridges between the units, forming an ordered cubic lattice structure. The framework is negatively charged due to the octahedral [ZrO<sub>6</sub>]-2 units. The pore opening of ZS-9 is composed of an asymmetrical seven-member ring with an average size of ~3 Å (Figure 2).
- ZS-9 has a >25-fold selectivity for K<sup>+</sup> over other ions (Figure 3).
- Thermodynamically, ZS-9 with K<sup>+</sup> was calculated to be more stable than ZS-9 with Na<sup>+</sup> (Table 1). The K<sup>+</sup> form of ZS-9 was 20.4 kcal/mol more stable than the Na<sup>+</sup> form.
- In conclusion, ZS-9 has a high specificity for K<sup>+</sup> ions and is thermodynamically more stable in its interactions with K<sup>+</sup>, compared with other ions, lending support to the hypothesized mechanism of action that ZS-9 has a similar selectivity filter as physiologic K<sup>+</sup> channels.
- Unlike organic polymer resins like Kayexalate, the specificity for K<sup>+</sup> demonstrated by ZS-9 may account for its rapid serum K<sup>+</sup> lowering effects within an hour.
- If approved, ZS-9 will be a novel, first-in-class therapy for hyperkalaemia with improved capacity, selectivity, and speed for entrapping K<sup>+</sup> when compared with currently available options.

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