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How does overcoordination create ion selectivity?

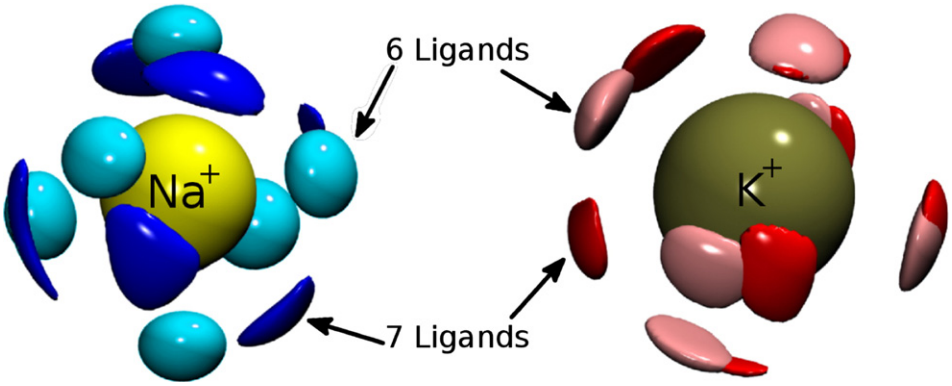
Michael Thomas [a], Dylan Jayatilaka [b], Ben Corry [a,*]

[a] Research School of Biology, The Australian National University, Canberra, Australia
[b] School of Chemistry and Biochemistry, University of Western Australia, Perth, Australia

HIGHLIGHTS

- We describe how ion selectivity can arise by 'overcoordination'.
- There is a point at which the ligands form a 'full' shell around an ion.
- This happens with a lower number of ligands for smaller ions.
- Beyond this, adding ligands significantly changes the positions of all the ligands.
- Selectivity arises when this point has been reached for one ion but not another.

GRAPHICAL ABSTRACT



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ABSTRACT

Some biological molecules can distinguish between ions of similar nature, which may be achieved by enforcing specific coordination numbers on ions in the binding site. It is suggested that when this number is favourable for one ion type, but too large for another, this creates ion selectivity through the proposed mechanism of 'overcoordination'. Much debate has occurred about the role overcoordination plays, and suggestions made as to how molecules can enforce particular coordination numbers, but there has not been an examination of the microscopic underpinning of ion selectivity by overcoordination. Here we use molecular-dynamics to systematically investigate how the number of ligands affects the ion–ligand and ligand–ligand interaction energies, and thus the thermodynamic ion selectivity, of a combination of model systems: three ions ($Li^+/Na^+/K^+$) with three different ligands (water/formaldehyde/formamide). We find that the ligand–ligand repulsion controls the changes in geometry of each system with changing ligand number. Ion selectivity by overcoordination is achieved as smaller ions exhibit anomalous geometrical changes with the addition of extra ligands, whilst larger ions do not.

1. Introduction

The ability of proteins to discriminate between ions is integral to many biological processes, such as enzyme function and the regulation of membrane potentials [1]. One well studied example of ion differentiation arises in the exquisitely selective potassium ion channels.

* Corresponding author at: Research School of Biology, The Australian National University, Canberra, ACT 0200, Australia. Tel.: +61 2 6125 0842.
E-mail address: ben.corry@anu.edu.au (B. Corry).

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These channels display up to a 1000 fold preference for K^+ over Na^+ [2–5], despite the fact that the two ions are both spherical in nature, have the same charge and differ in atomic radii by only 0.38 Å. Whilst a range of mechanisms have been put forward to explain selectivity in potassium channels, including the snug-fit hypothesis [6–10], the chemical nature of the coordinating ligands [11–17] and the more recent kinetic hypothesis based on different binding sites for Na^+ and K^+ [18–20], a number of studies suggest that 'overcoordination' plays a role in ion discrimination in the potassium channel KcsA [16,17,21–31]. Overcoordination arises when the chemical environment enforces a large coordination number on ions in a binding site that is thermodynamically less favourable for one ion than another.

A number of studies have addressed two key questions about ion selectivity by overcoordination:

1. How important is overcoordination in establishing ion selectivity in a particular molecule [17,21,22,25,28–30]? This question has been extensively investigated in regard to selectivity in K^+ channels; if selectivity is achieved via a thermodynamic mechanism (and not a kinetic mechanism as suggested by some recent studies [18–20]), the literature seems to point to overcoordination playing an important role.
2. By what means are these molecules able to enforce a particular coordination number? Here the focus is on mechanisms that can constrain the position of the coordinating ligands. An example of this is the hydrogen bonding networks present in K^+ channels that could act as a radial spring on the coordinating ligands, thus enforcing a large coordination number [10]. Also, it has been suggested that the lack of hydrogen bond donors keeps the carbonyl oxygens that line the selectivity filter in K^+ channels free to coordinate the permeating ions [27].

In contrast to these questions that have been much studied in the literature, a third key issue relating to ion selectivity by overcoordination has received surprisingly little attention:

3. Through what physical means does enforcing a coordination number create ion selectivity? Whilst it is known that a large number of coordinating ligands produce more favourable interactions for larger ions than smaller, what physical phenomena give rise to this? Perhaps the explanation is obvious, but to the best of our knowledge this issue has not been addressed head on and systematically studied.

In this study, we do not attempt to answer the first and second questions, but instead focus on the third question: determining the microscopic basis of the concept of ion selectivity by overcoordination.

Studies conducted by Noskov et al. [13,14] investigated the interplay of ion–ligand and ligand–ligand interactions in search of the cause of selectivity in potassium ion channels. It was concluded that the geometry of the ion binding site is governed by the ion–ligand interaction, whilst the ligand–ligand interaction influences ion selectivity [13] and that these "can be directly modulated by the number and the type of ligands involved in ion coordination" [14]. However, what we wish to study is how these interactions and ion selectivity vary with the number of ligands coordinating to an ion, not how a particular binding site achieves selectivity.

The aim of this study is not to reproduce the properties of any particular binding site, but to use simplistic systems to investigate in principle how coordination numbers can influence ion selectivity. As coordination does influence selectivity in these models, we can examine why this is the case. Some of these factors may play a role in biological systems. We employ three simple ligands to examine the effect of the chemical nature of the binding site, but do not explicitly include structural or environmental factors that are likely to be at play in a real ion binding molecule.

The methods employed in this study are classical molecular dynamics techniques utilising a non-polarisable force field [32], which has been shown to produce ion partitioning between bulk liquids, such as formaldehyde and water [17], and *N*-methylacetamide and water [13]. Ion selectivity by overcoordination is readily apparent from the simulations conducted here, in addition to similar simulations in previous work [17,21]. More detailed investigations (such as those employing polarisable force fields or quantum mechanical calculations) may illuminate additional effects not captured here. However, given that ion selectivity is apparent in our classical model, we can understand the mechanisms that lead to selectivity in this situation.

To investigate why overcoordination creates selectivity, free energy perturbation (FEP) MD simulations were conducted on a series of model systems. These consisted of either n water, formaldehyde or formamide molecules whose oxygen atoms were constrained to a 3.5 Å sphere about either Li^+, Na^+, and K^+ (for $n = 1$–10). This distance represents the first minimum in the radial distribution function of K^+ in bulk water. The constraining sphere acts to hold a number of ligands near the ion whilst allowing the ligands to adjust their relative positions. Inside this sphere, the ligands are completely free to move about, very different from the snug-fit mechanism where ligands are constrained to particular positions. Strictly enforcing the coordination number would require a different radius of constraint for each ion type, to keep each ligand in the inner shell. However, we feel that the use of a single radius best represents binding sites in molecules, as the molecular scaffold that holds the ligands near the ion is the same

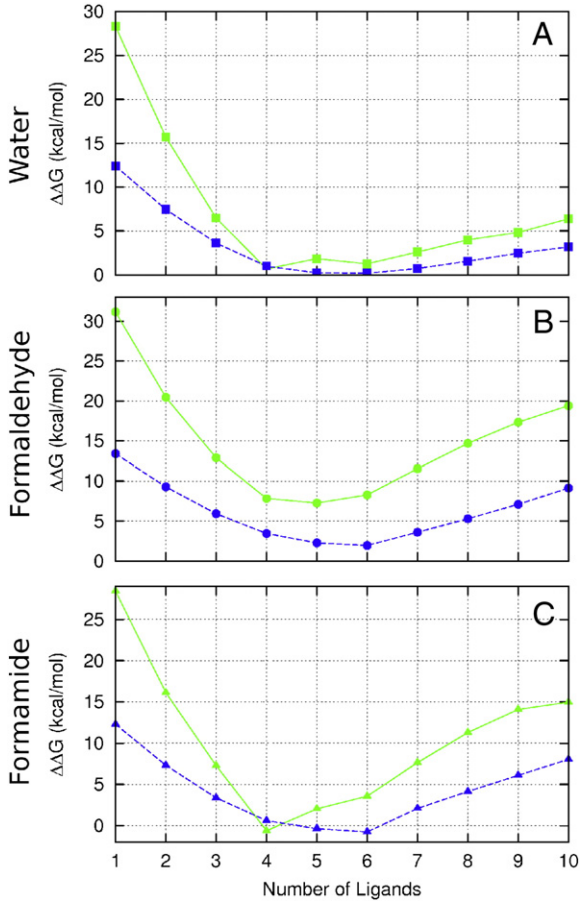

Fig. 1. Relative free energy values, $\Delta\Delta G(Na^+,K^+) = \Delta G_{site}(Na^+ \rightarrow K^+) - \Delta G_{Bulk}(Na^+ \rightarrow K^+)$ of the exchange reaction between Li^+ and K^+ (green), Na^+ and K^+ (blue) and K^+ and itself (which by definition is zero), in model binding sites with varying number of ligands, n, and bulk water. The three types of ligands that are modelled are (A) water, (B) formaldehyde and (C) formamide. A positive value indicates that K^+ is preferred over the other ion in the model site.