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**Williams R J P.** The biochemistry of sodium, potassium, magnesium, and calcium. *Quart. Rev. Chem. Soc.* 24:331-65, 1970.  
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The use of the four named metal ions in biology is examined in terms of their known physical and analytical chemistry. The combination with organic ligands is made selective through the radius ratio of the cation to the binding molecule. Iso-morphous replacement by probe cations was shown to give a method for their study. [The SCI® indicates that this paper has been cited in over 260 publications since 1970.]

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In this paper I tackled the very general problem of our understanding of the evolved uses of sodium, potassium, magnesium, and calcium cations in biological systems, for example, in nerve transmission and in muscle action. In order that full functional use could be developed, living systems had to be able to distinguish each of the four ions using chemical combinations and to separate them. The principles of the selective binding of the four cations in biology were shown to be related to the known analytical chemistry for estimating one of the metal ions in the presence of the other three by the use of organic reagents. In effect the chemistry is based upon electrostatic forces, but in aqueous solution the subtle nature of radius-ratio effects had to be described.

The paper shows how particular matching of cation and anion sizes can generate selectivity orders. The most refined form of radius-ratio combination between a metal ion and a ligand is the design of a ligand in a constrained ring to fit precisely the size of a particular cation. This was well known in porphyrin and vitamin B<sub>12</sub> (iron and cobalt) chemistry

but was extended here to all the above four metal cations. The original theory was proposed in 1953<sup>1</sup> and its application was just becoming apparent in both chemistry and biology in 1970. Today these ideas are seen to apply very generally to ion channels, ionophores, and ion binding to both small and large molecules such as proteins.<sup>2</sup>

In a biological system it is not just necessary for an individual cation to be bound to a ligand, but the cation must then be transferred across membranes against gradients of charge and concentration. The way in which such pumps work is still unknown, but their value in generating the necessary energized conditions for nerve transmission (Na,K) and muscle activation (Ca) was already fully established. It was not understood how the release of the cations from their energised states caused transformation, especially on binding to new proteins. Today a general explanation is available<sup>3</sup> as an extension of the original paper. The chemistry of each cation is somewhat different on either side of a biological membrane, since the concentration of each element changes across the membrane. On release from the constraint of the membrane, the cation diffuses to the site where it acts as a trigger.

A second part of the paper considered the ways in which the action of the four cations can be studied by replacement by other cations of similar radius and charge, "isomorphous replacement," which carried excellent spectroscopic probe properties. The use of thallium to mimic potassium has proved of great value in understanding the interaction of cations with ion carriers and channels, (e.g., in studies of gramicidins). The use of manganese and lanthanide cations has proved extremely valuable in the analysis of the function of magnesium and calcium and especially in the regulatory description of the properties of calmodulins and troponins C.

The development of this approach to the examination of biomineralisation was foreseen.<sup>4</sup> The work has led to whole new areas of bio-inorganic chemistry separate from my earlier work with Vallee.<sup>5</sup>

In part, this work led to my being awarded the Sir Hans Krebs medal by the European Biochemical Societies. The publication of the medal address is reference 2.

1. Williams R J P. A systematic approach to the choice of analytical reagents for metal ions. *Analyst* 78:586-95, 1953. (Cited 7 times since 1955.)
2. .... The symbiosis of protein and metal functions. *Eur. J. Biochem.* 150:231-48, 1985.
3. Dalgarno D, Klevit R E, Levine B A & Williams R J P. The calcium receptor and trigger. *Trends Pharmacol. Sci.* 5:266-71, 1984.
4. Williams R J P. An introduction to biominerals and the role of organic molecules in their formation. *Phil. Trans. Roy. Soc. London B* 304:411-24, 1984.
5. Vallee B L & Williams R J P. Metallo-enzymes: the entatic state of their active sites. *Proc. Nat. Acad. Sci. US* 59:498-604, 1968. (Cited 260 times.)