Thermodynamic dissociation constants of some dronates using potentiometric titration data

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Mixed dissociation constants of three nitrogen-containing bisphosphonates acids H_JL, alendronate, ibandronate and risedronate at various ionic strengths I and at 25°C and at 37°C have been determined with the use of regression analysis of potentiometric titration data. Three nitrogen-containing bisphosphonates *i.e.* risedronate, ibandronate and alendronate denoted as N-BPs are the antiresorptive drugs [1] most widely used to treat osteoporosis owing to their particularly high potency at inhibiting osteoclast-mediated bone resorption [2]. Bisphosphonates N-BPs are now the major drugs used in the treatment of postmenopausal osteoporosis and represent the first-line therapy in the majority of patients. Early studies showed that the P–C–P backbone in bisphosphonates was a major contributor to bone binding affinity. Hounslow et al. [1] showed that the macroscopic pK_as and chemical shifts in NMR for the macrospecies were deconvoluted into microconstants by determining the site-specific protonation mole fraction. This can be achieved by assuming that the chemical shift of a nucleus I in the H_2L^{2-} species differs from that in HL^{3-} only as a consequence of protonation of the **N** site and not of the **P** site (Figure 1).

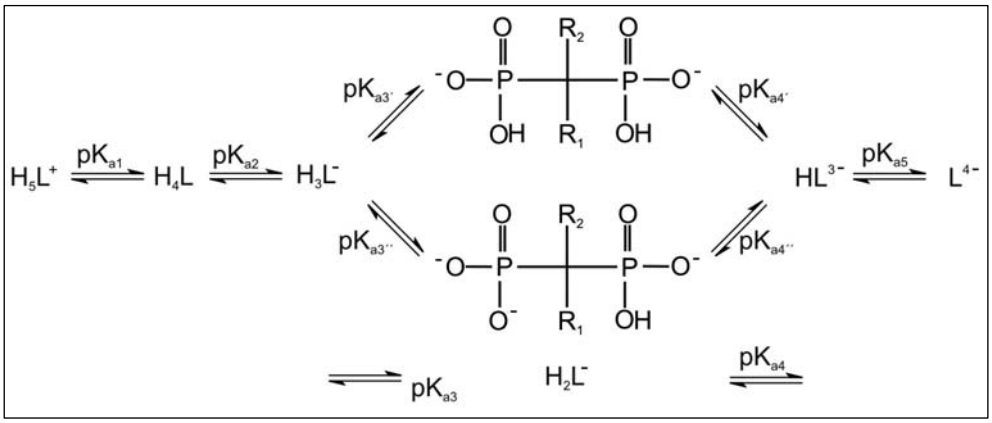

Figure 1: Dissociation of nitrogen-containing bisphosphonates N-BPs according to [1].

In general, all three N-BPs are pentaprotic acids, but after dissolution, they may be treated as tetraprotic or triprotic acids. Titration of tetraprotic weak acid H_4L with a strong base (e.g. NaOH) involves eight solution species H_3O^+, OH^-, H_4L, H_3L^-, H_2L^{2-}, HL^{3-}, L^{4-}, and the sodium cation Na^+. For adjusted value of ionic strength the potentiometric titration of a mixture of HCl and N-BPs drug acid with potassium hydroxide was carried out. The initial tentative value of dissociation constant of the drug studied corresponding to the midpoint value in each plateau of the potentiometric titration curve data (Figure. 2) has been applied by the nonlinear regression ESAB and/or HYPERQUAD programs and gave the values of pK_{a2},

pK_{a3}, pK_{a4} and pK_{a5}. The pK_a values obtained by deconvolution of the potentiometric titration curve indicated that this N-BP dissociates in a manner similar to that elucidated for risedronate (Figure 2).

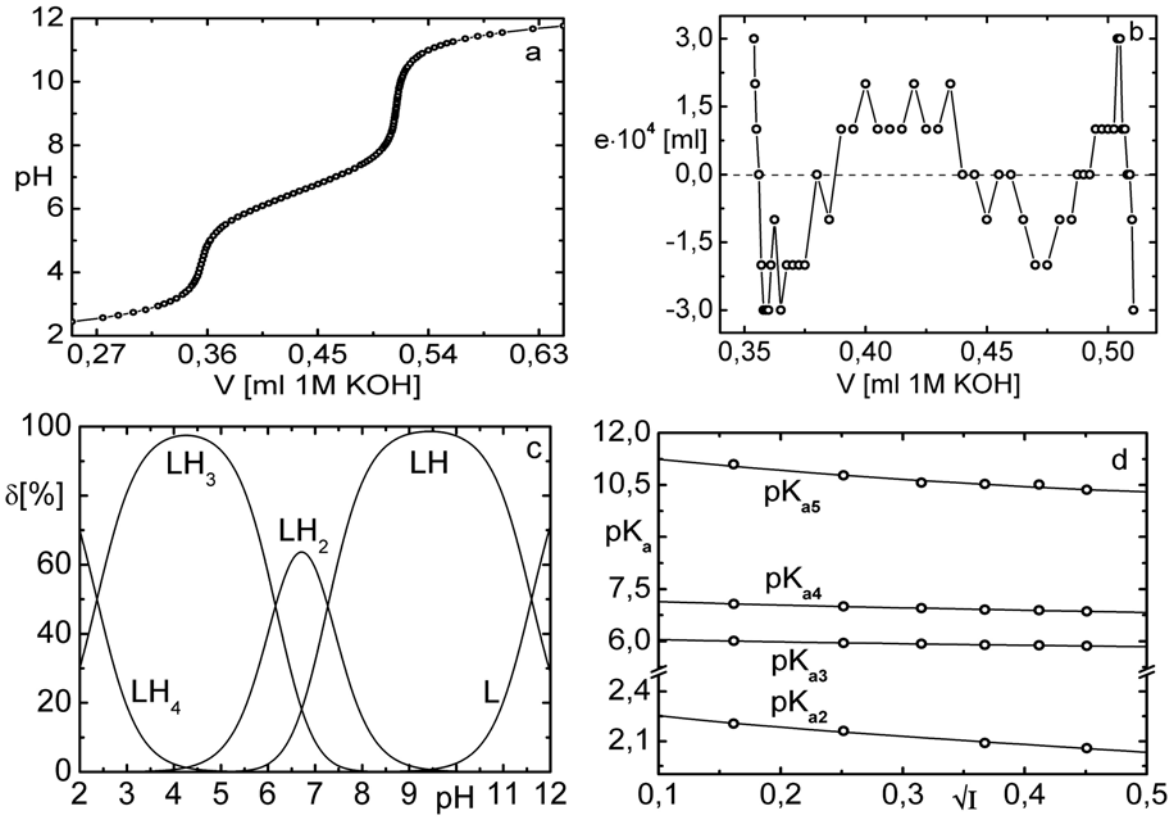

Figure 2: Protonation equilibria of risedronate analyzed with ESAB (a) potentiometric titration curve of risedronate; (b) plot of residuals; (c) distribution diagram of relative presentation of all species of protonation equilibrium, (d) dependence of the mixed dissociation constant pK_a of risedronate on the square root of an ionic strength, which leads to parameter estimates pK_{a2}^{T} = 2.365(20), pK_{a3}^{T} = 6.158(7), pK_{a4}^{T} = 7.270(8) and pK_{a5}^{T} = 11.600(123), in the brackets are the standard deviations in last valid digits.

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References:

[1] Hounslow, A. M.; Carran, J.; Brown, *et al.* Determination of the Microscopic Equilibrium Dissociation Constants for Risedronate and Its Analogues Reveals Two Distinct Roles for the Nitrogen Atom in Nitrogen-Containing Bisphosphonate Drugs, *Journal of Medicinal Chemistry* **2008**, *51*, 4170

[2] Fleisch, H. *Bosphosphonaties in Bone Disease. From laboratory to tha Patient.* The Parthenon Publishing Company: New York and London, **1995**