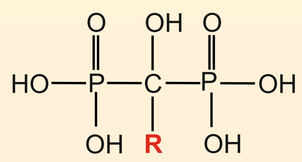
Thermodynamic dissociation constants of some dronates using potentiometric titration data

Z. Ferenčíková[a)], M. Meloun[a)], T. Pekárek[b)]
[a)]University of Pardubice, Department of Analytical chemistry, [b)]ZENTIVA Group k.s., Prague
zuzana.ferencikova@student.upce.cz

Summary

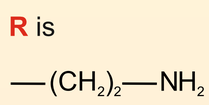
Alendronate sodium, Ibandronate sodium and Risedronate sodium belong to a group of drugs called nitrogen-cointaining bisphosphonates (N-BPs). This drugs are used to treat osteoporosis owing to their high potential at inhibiting osleoclast-mediated bone resorption. The dissociation constants of this three N-BPs were determinated at different ionic strength and of 25°C and 37°C using pH-spectrophotometric and/or pH-potentiometric titration methods.

Theory



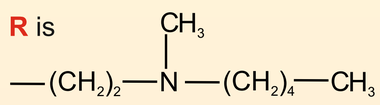
Alendronate

R is



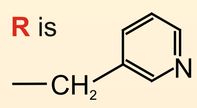
Ibandronate

R is

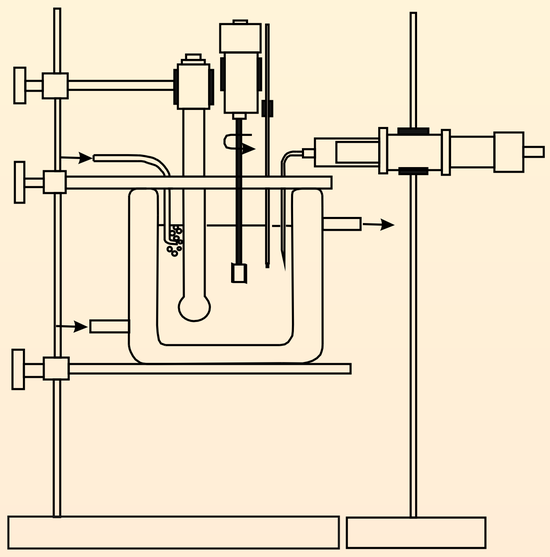


Risedronate

R is



The N-BPs have a six groups which can dissociate: five H^+ donors (four POH groups, one gemine OH^- group) and one amino group as the H^+ acceptor. To determine dissociation constants for polyprotic system in which the dissociation steps ase well separated ($\Delta pK_a = |pK_{a,i+1} - pK_{a,i}| > 3$) is possible; If the dissociation steps are close and overlapping, the $pK_{a,i}$ values describe the stoichiometry but not the site of protonationas there are intermediate species that have the same number of protons but at different protonation sites.The acid-base properties of three N-BPs in aqueous solution have been studied in pH range from 2 to 12 and can be described in terms of four dissociation steps: $pK_{a,2}$, $pK_{a,4}$, $pK_{a,5}$ related with dissociation of POH groups and $pK_{a,3}$ related with dissociation of NH_3^+. The mixed dissociation constants were determined at different ionic strengths and of 25°C and 37°C using ESAB2M and HYPERQUAD2008 for potentiometric data and SQAUD(84) and SPECFIT/32 for spectrophotometric data. The thermodynamic dissocaition constatns were estimated applying Debye-Hückel equation.

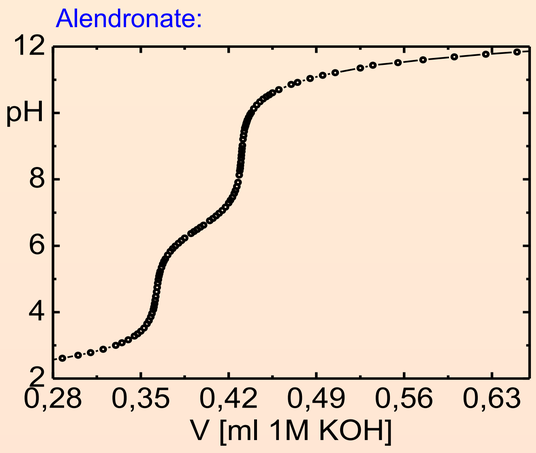


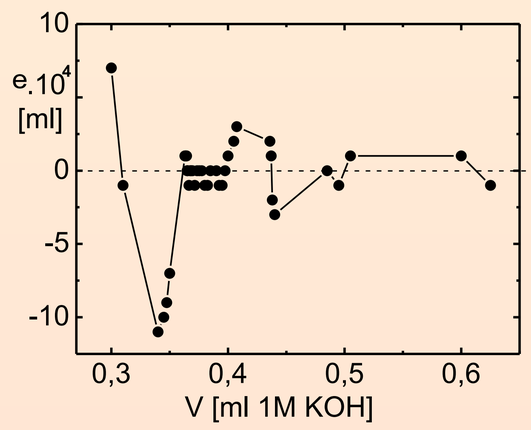
Reaction vessel in which protonation reaction is adjusted

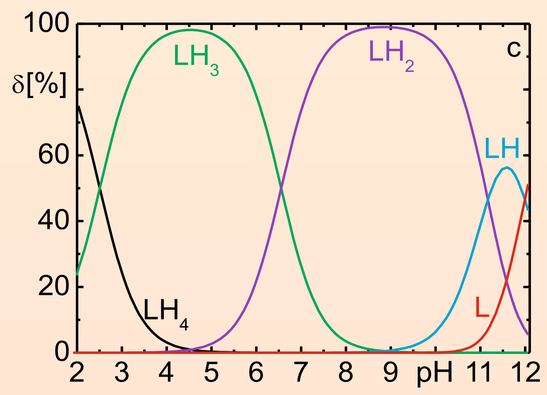
Results and Discussion:

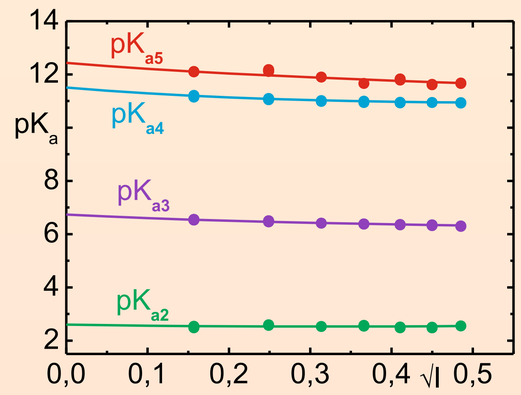
pH potentiometric titration

Alendronate:

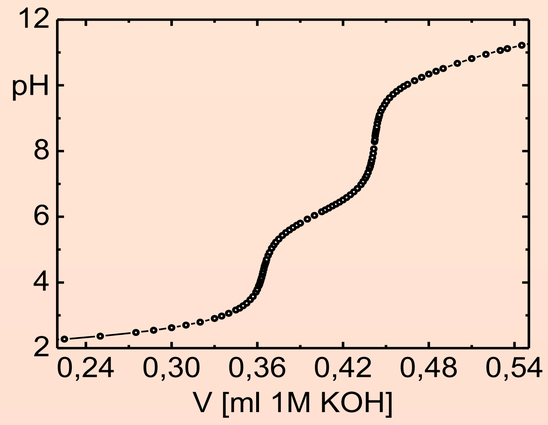


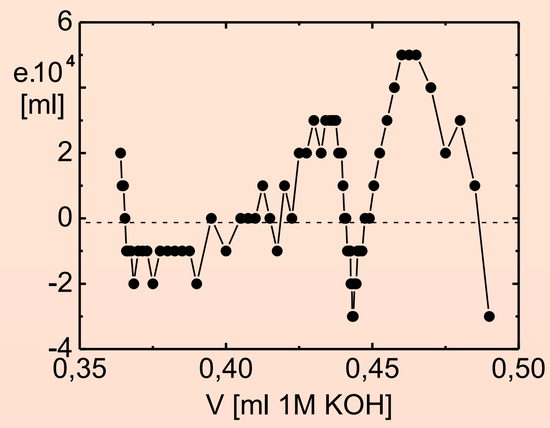


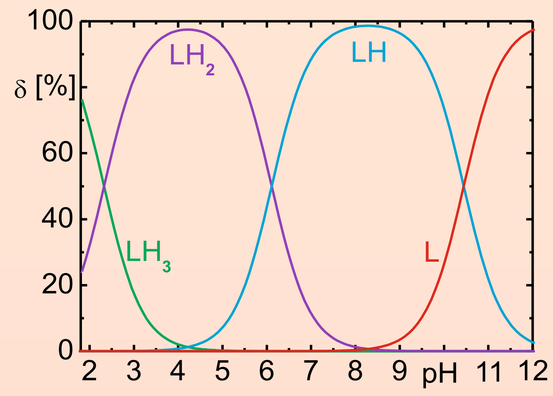


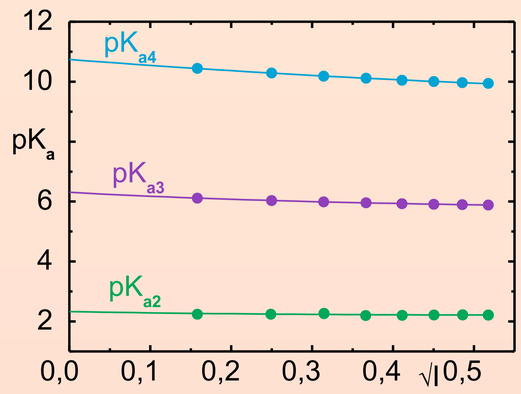


Ibandronate:

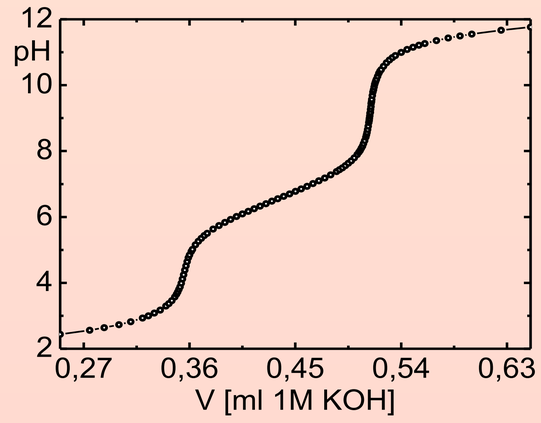


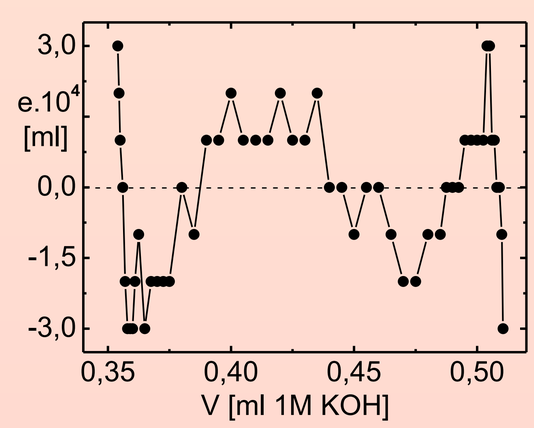


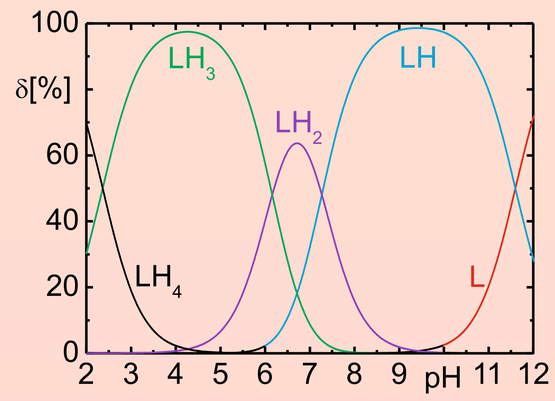


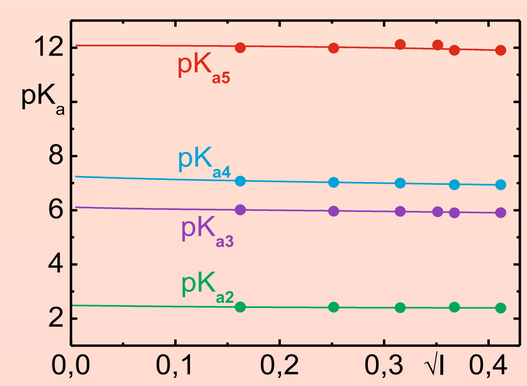


Risendronate:



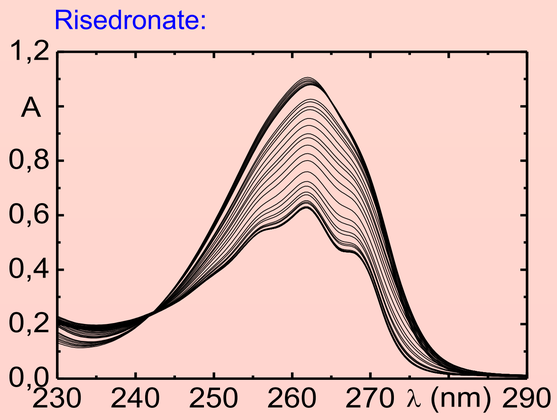


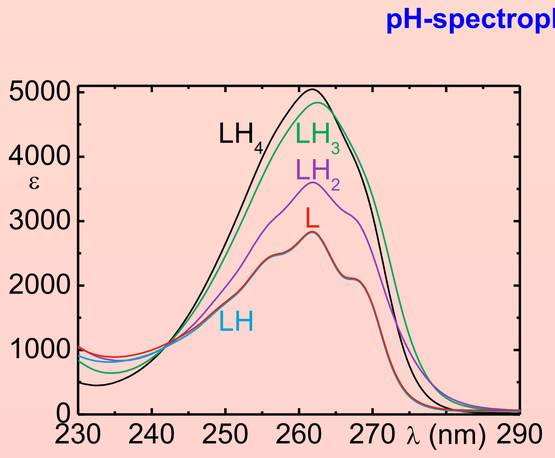


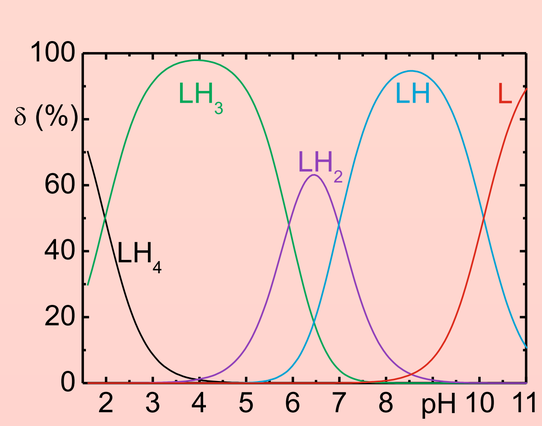


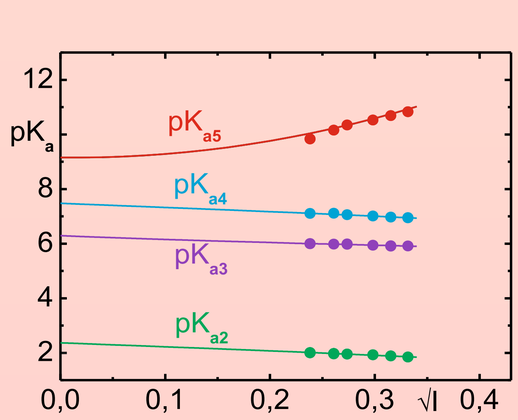
pH-spectrophotometric titration:

Risedronate:









Conclusion:

The thermodynamic dissociation constants were estimated by nonlinear regression of (pK_a,I) data and a Debye-Hückel equation. Goodness-of-fit test based on regression diagnostics is measure of a reliability of parameters and prove that reliable estimates for alendronate pK^T_{a2}=2.60(0) and 2.76(1), pK^T_{a3}=6.73(0) and 6.77(1), pK^T_{a4}=11.51(2) and 11.29(1), pK^T_{a5}=12.44(3) and 11.82(3) at 25°C and 37°C, respectively, for ibandronate pK^T_{a2}=2.33(1) and 2.50(1), pK^T_{a3}=6.31(1) and 6.37(0), pK^T_{a4}=10.74(1) and 10.65(1) at 25°C and 37°C, respectively, and for risedronate pK^T_{a2}=2.48(3) and 2.43(1), pK^T_{a3}=6.12(2) and 6.10(2), pK^T_{a4}=7.25(2) and 7.23(1), pK^T_{a5}=12.04(5) and 11.81(2) at 25°C and 37°C, respectively, were found.

Acknowledgement:

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Literature:

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