

UV-VIS SPECTROSCOPY IN THE DETERMINATION OF DISSOCIATION CONSTANTS OF SOME DRONATES

Z. Ferenčíková,^{1*} M. Meloun,¹ T. Pekárek,²

¹Department of Analytical Chemistry, University of Pardubice, Pardubice, Czech Republic

²Zentiva k.s, Praha, Czech Republic

*zuzka.ferencikova@seznam.cz

The mixed dissociation constants of two nitrogen-containing bisphosphonates acids H₄L, alendronate and risedronate at various ionic strengths *I* and at 25°C and at 37°C have been determined with the use of the nonlinear regression analysis of the multiwavelength spectrophotometric pH-titration data.

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 p*K*_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 H₂L²⁻ species differs from that in HL³⁻ only as a consequence of protonation of the **N** site and not of the **P** site.

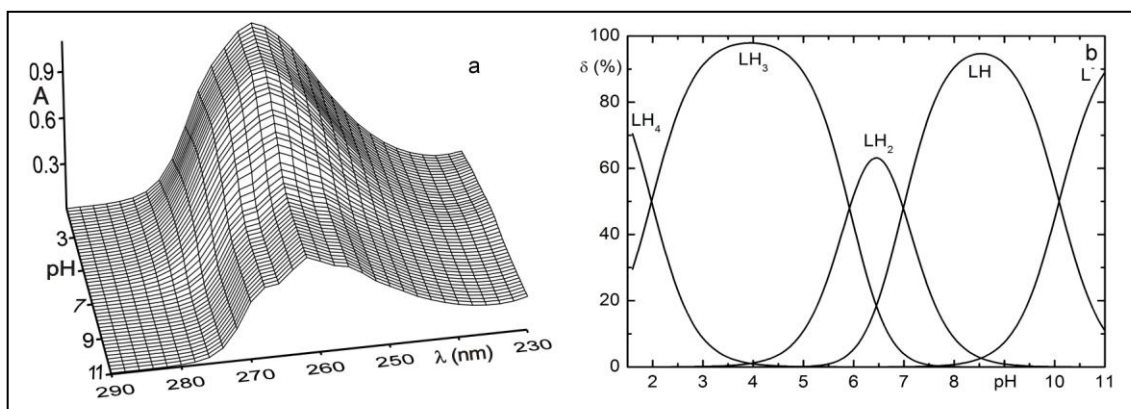


Figure 1. (a) The 3D-absorbance-response-surface representing the measured multiwavelength absorption spectra in dependence on pH at 25°C for risedronate, (b) the distribution diagram of the relative concentration of five variously protonated species in dependence on pH at 25°C

In general, all three N-BPs are pentaprotic acids, but after dissolution, they may be treated as tetraprotic or triprotic acids. pH-titration of tetraprotic weak acid H₄L with a strong base (e.g. NaOH) involves eight solution species H₃O⁺, OH⁻, H₄L, H₃L⁻, H₂L²⁻, HL³⁻, L⁴⁻, and the sodium cation Na⁺.

1. A. M. Hounslow, J. Carran, R. J. Brown, *et al*, *Journal of Medicinal Chemistry*, **51**, 4170, (2008)

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