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Title: Design of New Sensitive Targeted pH Probes for Mitochondrial, Acidic and Cytosolic pHs Determination by ³¹-P NMR and EPR

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Abstract

In the last decades, spectral techniques such as ³¹-P NMR and EPR have become privileged strategies for the non-invasive study of the biological events affecting the energetic metabolism and free radical-related processes, respectively. Using NMR, the variations of the cytosolic pH can be monitored through the pH-dependent chemical shift (δ) behaviour of the endogenous phosphate (Pi) resonance peak. However, due to its neutral pKa and poor sensitivity, the Pi ³¹-P NMR peak cannot precisely probe more acidic vacuoles participating in proton transport mechanisms, or alkaline organelles such as mitochondria. In our search for improved non-invasive pH probing at subcellular level, we recently developed a series of cell permeable α -aminophosphonates with pKa ranging 2-8 and showing a 4-fold improved NMR sensitivity ($\Delta\delta$ up to 11 ppm between the chemical shift of acidic and basic media) as compared to Pi. The same concept was applied to EPR pH measurement by using the ³¹-P coupling constant a_P of persistent nitroxide free radical probes. This led to the design, synthesis and evaluation of a series of non-toxic pH-sensitive (Δa_P up to 3-4 Gauss between acidic and basic media) and stable β -phosphorylated nitroxides. The presentation will cover the design and the biological applications in vitro and in vivo of selected pH probes in normal and pathological situations.