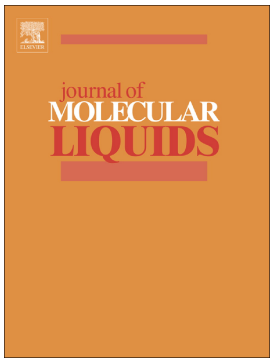

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Multiple Dissociation Constants of the Intepirdine Hydrochloride Using Regression of Multiwavelength Spectrophotometric pH-Titration Data

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Abstract: Spectrophotometric and potentiometric pH-titrations of the Neurotransmitter Intepirdine hydrochloride INN.HCl for three dissociation constants determination were compared. A nonlinear regression of the pH-spectra (REACTLAB, SQUAD84) and of the pH-titration curve (ESAB) determined three multiple dissociation constants. A sparingly soluble neutral molecule LH of INN.HCl was capable of protonation to form the still soluble three cations LH_2^+, LH_3^{2+} and LH_4^{3+} in pure water. Although the change of pH somewhat less affected changes in the chromophore, three consecutive thermodynamic dissociation constants were estimated pK^T_{a1} = 5.64, pK^T_{a2} = 7.31, pK^T_{a3} = 8.85 at 25°C and pK^T_{a1} = 5.51, pK^T_{a2} = 7.15, pK^T_{a3} = 8.77 at 37°C. The graph of molar absorption coefficients of variously protonated species according to wavelength shows that the spectrum of species LH_2^+ and LH vary in colour, while protonation of chromophore LH_2^+ to LH_3^{2+} and LH_4^{3+} has less influence on chromophores in Intepirdine hydrochloride molecule. As the spectral response on the chromophore in the INN.HCl molecule is not large, it was necessary to test a reliability whether it is possible to estimate the dissociation constants even from such small spectrum changes. Three multiple thermodynamic dissociation constants of 3×10^{-4} M INN.HCl were determined by the regression analysis of potentiometric titration curves pK^T_{a1} = 5.14, pK^T_{a2} = 8.38, pK^T_{a3} = 9.33 at 25°C and pK^T_{a1} = 5.17, pK^T_{a2} = 8.31, pK^T_{a3} = 9.07 at 37°C. The macro-dissociation constants of INN.HCl were estimated according to the chemical structure analysed by two pK_a predictors, the MARVIN and ACD/Percepta programs. The resulting protonation scheme of INN.HCl was suggested.

Keywords Dissociation constants; Intepirdine hydrochloride; spectrophotometric titration; REACTLAB; SQUAD84; ESAB;

Highlights:

- Protonation of Intepirdine studied with UV-spectra analysis and pH-metric titration
- Three pK^T_{a1}, pK^T_{a2}, pK^T_{a3} determined at 25ºC and 37ºC in aqueous medium
- The number of protonated species estimated from the rank of UV-absorbance matrix
- The ε_{LH3} and ε_{LH4} show the influence of protonation on chromophore in Intepirdine