An NMR Direct Evidence of the Formation of a Ternary NADH/Mg^{2+}/$PhCOCO_2Me$ Entity Using Silyl-tagged β-Lactam Peptide Models

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The enantioselectivity of the NADH-mediated reductions is governed by the formation of a ternary complex substrate / metal / NADH[1]. The complexation between metal ions and several NADH models has been extensively investigated including NMR, UV, IR, and fluorescence studies, and the structural features of some of them have been established in detail. In contrast, very few examples of ternary entities have been reported[2] and none of these reports has provided information on their structure.

Herein we describe some key conformational and structural features of a series of binary and ternary complexes formed from silyl-tagged chiral NADH β-lactam peptides, magnesium perchlorate and methyl benzoylformate in CD_3CN-d_3. Owing to the incorporation of two diastereotopic trimethylsilyl groups in these rigidified NADH peptidomimetics, NMR analysis led us to demonstrate that their binary NADH/Mg^{2+} complexes participate in a conformational equilibrium at room temperature. After the addition of methyl benzoylformate, the formation of a new NADH/Mg^{2+}/$PhCOCO_2Me$ ternary entity was established from ^1H, ^{13}C and DOSY experiments. 2D-ROESY experiments proved to be particularly helpful to unravel the structure of this ternary species, intermolecular cross-peaks between the OMe group of the substrate and the NADH model being detected.

"Ab initio" molecular calculations and enantioselective asymmetric reduction reactions were also performed with the aim to elucidate the structure of the observed ternary entity. We assumed a hexacoordinated magnesium ion with two CD_3CN molecules completing the coordination sphere[3] in order to propose a ternary model in agreement with the observed ROESY cross-peaks.

To the best of our knowledge, these results represent the first direct observation of a ternary α-keto ester/Mg^{2+}/NADH entity in solution by NMR techniques.

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