Mimicking the Role of NADH and FADH2 with Homogenous Hydrogenation Catalysts and Parahydrogen Providing 13C-Hyperpolarized Biochemical Intermediates for 13C-MRI or 13C-MRS

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Introduction

Many biochemical transformations, be it within the metabolism or synthesis of fatty acids, amino acids, or carbohydrates, involve reductions and oxidations, formally equivalent to hydrogenations or dehydrogenations. In biochemistry, these tasks are performed by enzymes, whereby universal key reactants are flavin adenine dinucleotide (FAD), the precursor molecule to 1,5-dihydro-FAD ($FADH_2$) or nicotinamide adenine dinucleotide (NAD+) and its reduced form, NADH, respectively. Figure 1 outlines the functions of these redox couples and the corresponding reaction steps, in which they participate. Dysfunctions or lack of some of the required enzymes can cause serious diseases, and a more detailed understanding of these transformations is very desirable, accordingly.

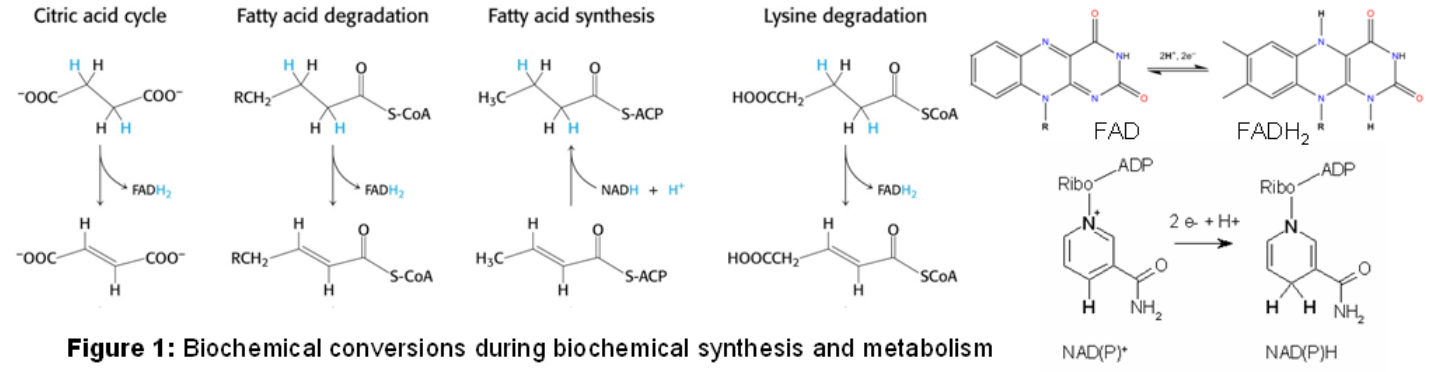

Figure 1: Biochemical conversions during biochemical synthesis and metabolism

Method and Results

In order to use ^{13}C-MRI[1] or ^{13}C-MRS, two powerful but insensitive methods for studying the role of biologically active compounds, some form of signal enhancement is required, such as ^{13}C-hyperpolarization derived from PHIP[2]. Accordingly, *in situ* parahydrogenation of the unsaturated compounds as detailed in Fig. 1 to their corresponding saturated derivative using an appropriate homogeneous hydrogenation catalyst will not only mimic these biochemical transformations, i.e., reductions, in a chemically equivalent way, but it will also introduce the required hyperpolarization into the hydrogenation products. If these reactions are carried out at very low magnetic fields, the initial parahydrogen-derived ^{1}H-hyperpolarization is also transferred to the heteronuclei, notably to ^{13}C, but also to ^{15}N and ^{31}P.

Figure 2 outlines typical homogeneous catalysts for use in aqueous solutions and Figure 3 details the results obtained in the form of ^{1}H- and ^{13}C-PHIP NMR spectra during the hydrogenation of acetylene dicarboxylic acid dimethylester yielding maleic acid dimethylester when using a Rh-containing catalyst and fumaric dimethylester when using a Ru-based catalyst instead. Likewise, parahydrogenation of maleic acid dimethylester at low magnetic fields yields dimethyl succinicnate in ^{13}C-hyperpolarized form.

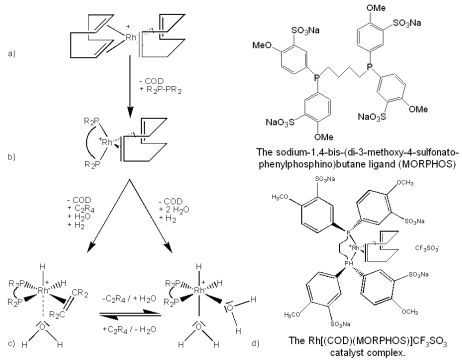

Figure 2: Ligands and catalyst complexes for parahydrogenation of unsaturated compounds.

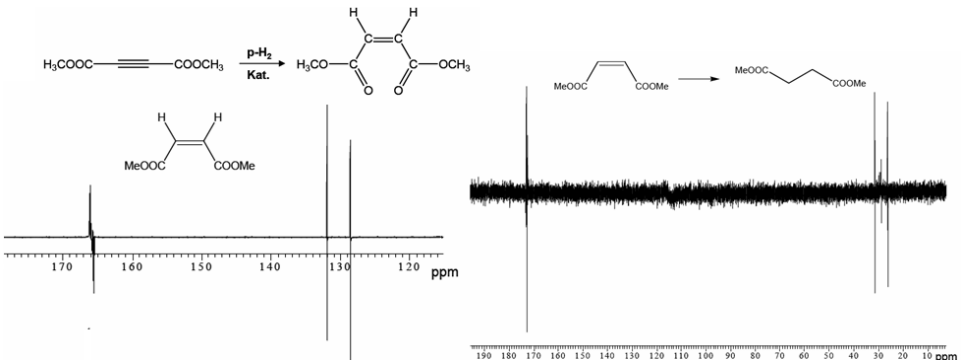

Figure 3: ^{13}C-NMR spectra of hyperpolarized maleic acid dimethyl ester and its hydrogenation product dimethyl succinate.

Discussion and Conclusions

The systems outlined in Fig. 3 simply serve as characteristic examples for reaction steps and compounds as detailed in Figure 1. One of the advantages of these systems is that both the unsaturated precursor and its hydrogenation product both occur naturally in biological metabolic chains and hence are biodegraded and discarded accordingly. The homogeneous catalysts used function well in aqueous systems as required here. Due to the fact that they are positively charged, they don't dimerize, - thereby becoming chemically inactive, - but they may be removed using oppositely charged ion exchange resins as pioneered by others[1] before.

References

1.) Golman K, Axelsson O, Jóhannesson H, et al. Mag. Res. Med. 46, 1-5, **2001.**

2.) Bowers CR, Weitekamp D, Phys. Rev. Lett., **57**, 2645, **1986**; Natterer J, Bargon J, Prog. Nucl. Mag. Res. Sp. **31**, 293-315, **1997.**