Providing 1H- and 13C-Hyperpolarized Gamma-Aminobutyric Acid (GABA) for Parahydrogen-Enhanced MRI and MRS

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Introduction

In the mammalian central nervous system (CNS), g-amino butyric acid (GABA) is the main inhibitory neurotransmitter. GABA is a highly flexible molecule existing in many low-energy conformations. Three major GABA receptors, $GABA_A$, $GABA_B$, and $GABA_C$ are known, of which $GABA_A$ and $GABA_C$ receptors are members of a superfamily of transmitter-gated ion channels, and $GABA_B$ transmembrane receptors.[1] Pharmacological sensitivity to drugs is determined by the subunit composition of the receptor. Combined biophysical and molecular biological studies have revealed important insights into the structure and function of the GABA receptors, and these insights have helped to define their role in synaptic inhibition and the ion channel mechanisms by which different neuropsychiatric drugs work. The CNS effects of benzodiazepines, barbiturates, and alcohol have been linked to the GABA-chloride channel receptor complex. There is, however, a need for new tools to investigate further the $GABA_C$ receptor function. Among the known ligands that show $GABA_C$ receptor subtype selectivity are derivatives of trans (TACA)- and cis (CACA)-4-aminocrotonic acid, for example 2-methyl-TACA. Both TACA and CACA are naturally occurring. Their *in situ* hydrogenation using parahydrogen provides an access to ^{1}H-, ^{13}C-, and ^{15}N-hyperpolarized GABA thanks to the Parahydrogen Induced Polarization (PHIP) phenomenon.

Method and Results

We have investigated the parahydrogenation of a variety of unsaturated substrates (Figures 1 & 2) to provide ^{1}H-, ^{13}C-, and ^{15}N-hyperpolarized a, ß-, and g-amino acids from suitable unsaturated precursors. Table 1 lists characteristic experimental conditions. For GABA both trans (TACA)- and cis (CACA)-4-aminocrotonic acid qualify for that purpose, Figure 1 outlines their structure.

Table 1

Precursor	Catalyst	Solvent
Ethylamino-4,4,4-trifluorocrotonate	[(dppb)Rh(cod)]BF_4	Acetone-d_6
Ethylamino-4,4,4-trifluorocrotonate	Ir-cat	Acetone-d_6
3-Ethylamino ethylcrotonate	[(dppb)Rh(cod)]BF_4	Acetone-d_6
3-Ethylamino ethylcrotonate	Ir-cat	Acetone-d_6

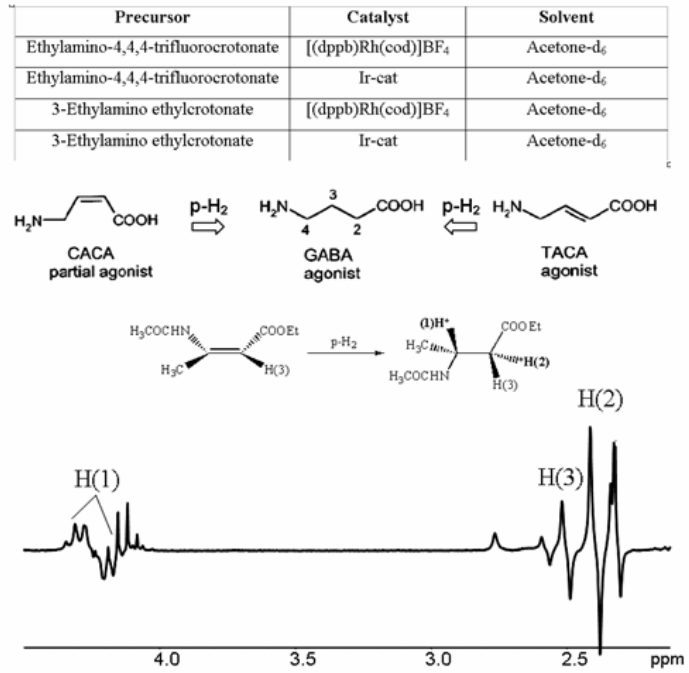

Figure 1

Scheme 1

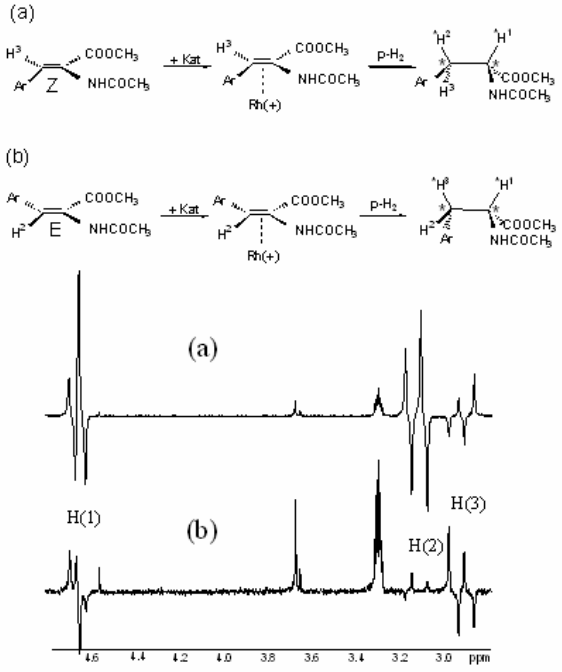

Figure 2

Conclusions

MRS and MRI studies using hyperpolarized GABA have important implications for the understanding of how neurotrans-mitter systems may be involved in illness. Future understanding of disease states, drug effects, and therapeutic successes and failures may be expressed in terms of differences in the structure and function of specific receptors and their associ-ated ion channels.

References

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