Parahydrogen Induced Polarization of Barbituric Acid Derivatives. ^{13}C Hyperpolarization Studies

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Introduction

The application of ^{13}C NMR spectroscopy and imaging for clinical diagnostics has been constrained by the extremely long acquisition times that are required to obtain high SNR under physiological conditions. However, this obstacle could be overcome by in vitro hyperpolarisation of a molecule with long ^{13}C spin lattice relaxation time via Parahydrogen Induced Polarization (PHIP) and subsequent injection into the animal or patient of investigation. Hence, the role of certain target compounds such as anesthetics could be investigated by using MRI techniques. Among the drugs used to treat epilepsy or for injection narcotics, barbiturates like 5-methyl-5-propargylbarbituric acid are attractive from the MRI and chemical point of view because of their long spin lattice relaxation time of the carbons and the straightforward synthesis of model structures.

Method

5-Methyl-5-propargylbarbituric acid was synthesized from urea and the malonic acid derivative methyl-propargylmalonic acid shown in Fig. 1. The unsaturated group is used to introduce polarization into the molecule according to standard PHIP procedures [1]. Parahydrogen was generated by cooling thermal hydrogen with a closed-cycle cryostat setup in the presence of active charcoal to achieve an enrichment of up to 98%. In order to enhance the conversion rate of the hydrogenation reaction of 5-methyl-5-propargylbarbituric acid, the PASADENA experiment (chemical reaction inside the spectrometer) is carried out at elevated temperature and pressure [2]. The high proton polarization is transferred to ^{13}C using a PH-INEPT+ sequence with a delay of 15 ms [3].

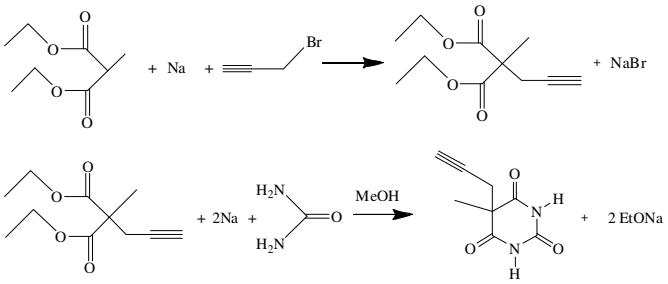

Fig. 1 Two step synthesis of 5-methyl-5-propargylbarbituric acid

Results

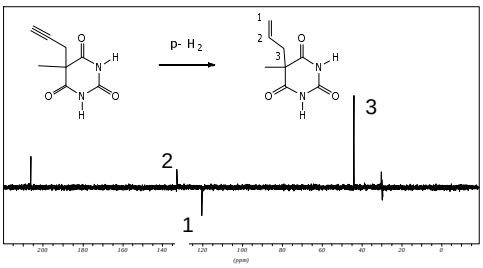

Fig. 2 ^{13}C PH-INEPT+ NMR spectra upon para-hydrogenation of 5-methyl-5-propargylbarbituric acid.

Figure 2 shows the obtained ^{13}C PHIP-NMR spectra of 5-methyl-5-propargylbarbituric acid in acetone-d_6 at ~50°C. The spectrum was obtained 35 s after shaking the NMR tube with the reaction mixture charged with 3 bar of 98% enriched parahydrogen and subsequent insertion into the spectrometer. The conversion of the hydrogenation was almost complete after shaking the reaction mixture twice. By using the PH-INEPT+ sequence with a delay of 15 ms a transfer of polarization to the resulting double bond and the vicinal carbons of the product was observed leading to a signal enhancement of up to 1000 for C_3.

Conclusion

It was shown before by our group that homogeneous hydrogenation of unsaturated barbituric acid derivatives with 50% parahydrogen yielded a substantial increase of the ^{1}H-NMR signals of the reaction products. However, signal enhancement by randomly triggered polarization transfer to ^{13}C in the weak magnetic field could not be observed. Application of a closed-cycle cryostat setup for parahydrogen enrichment up to 98% together with effective INEPT-derived pulse sequences allowed for ^{13}C NMR signal enhancements up to 1000.

References

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