SCALABLE DEUTERATION REACTIONS IN CONTINUOUS FLOW AND BATCH – GENERATING D_2 GAS USING THALESNANO'S H-GENIE®

INTRODUCTION

Deuteration reactions have become a crucial part in the life of organic chemists in the fields of drug discovery, molecular labelling and the synthesis of NMR solvents[1,2]. Broadening the scope of deuteration approaches, using deuterium gas in heterogeneous and homogeneous catalytic reactions allows for the design of highly tunable and selective synthetic techniques. Obtaining D_2 gas, however, has posed a bottleneck for researchers working in the field.

ThalesNano's H-Cube® flow chemistry systems provided convenient solution to generating D_2 gas on demand to be used in a wide range of chemical transformations just by switching from H_2O to D_2O in the instruments' water tank.

In this application note we feature the H-Genie® as an option for generating deuterium gas with up to 1000 NmL/min flow rate and 100 bar pressure, allowing for scaling deuteration reactions to the kg/day of production range.

Acetophenone deuteration reactions have been carried out on a ThalesNano flow reactor system consisting of the H-Genie® 2.0 filled with D_2O to generate D_2 gas, a HPLC pump, Mixer Module, Phoenix II Flow Reactor and a Pressure Module.

INSTRUMENTATION AND SAFETY CONSIDERATIONS

The H-Genie® uses patented technology to generate 99.99% hydrogen gas up to 1000 NmL/min at 100 bar via water electrolysis. Switching from regular Type I quality water to D_2O in the instruments internal water tank allows for quick and convenient D_2 gas generation.

With the aim of replacing hazardous H_2 cylinders in laboratories, the H-Genie® was designed with safety as its utmost priority. The instrument boasts a multitude of automated safety features such as a leak test during every initialization, built-in hydrogen sensor, water leak detection and overpressure detection. The internal gas circuit of the instrument is designed to be as small in volume as possible and there is no storage of H_2. This minimizes the amount of H_2 being released during an emergency shutdown.

Water quality is a crucial point for the electrolytic cell's lifetime in the H-Genie®. The water conductivity is constantly monitored by the instrument and if there is a rise in conductivity, first a message appears, warning the user to replace the water. Following this, the instrument shuts down automatically to prevent damage to the electrolytic cell. To avoid this, the H-Genie® features a built-in ion-exchange resin containing water purifier cartridge.

The instrument circulates the water through this cartridge, improving the conductivity over time. The H-Genie® is also equipped with an external emergency button which lets users shut down the system with a quick press.

Used for the deuteration reactions, the Phoenix II Flow Reactor allows users to carry out heterogeneous and homogeneous catalytic reactions up to 100 bar pressure and 450 °C. Coupled with the THS System Controller, a multitude of reactors, gas generators and pumps can be monitored and controlled across a whole fleet, with the availability of automatic sequence programming and user-defined safety triggers.

DISCUSSION AND RESULTS

Using the H-Genie® for generating D_2 gas

Before starting the experiments to switch to D_2O, first the H_2O was drained from the water tank and the water purifier cartridge was replaced with a new one only to be used with D_2O. The new water purifier cartridge did not receive any further preparation treatment, however, a good option to pre-treat the cartridge is to submerge it under D_2O before placing it inside the instrument.

The internal water tank of the instrument was then filled with D_2O and the water circulation pump was started and ran for 5 minutes, following this the tank was drained again. This water tank flushing sequence was repeated a total of 4 times, using 2 kg of heavy water altogether.

While circulating the water without electrolysis the, D-grade (deuterium enrichment of D_2O) decreased with a rate of 0.1% D/hour. When the instrument was turned off, the D-grade decrease was much slower, reaching a final measured value of 97.5%.

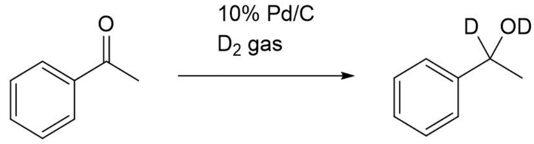
During the acetophenone deuteration experiments the D_2O D-grade even stayed constant over 5 hours. The D-grade was monitored via ^{1}H NMR over a period of 59 days with one refill after 45 days.

During this 45-day period the D-grade degradation was less than 1% with a value of 97.00% compared to the starting 97.92% value.

The refill had increased the D-grade to 97.76%, which continued to slowly decrease over the period of the remaining 14 days to a final value of 97.56%.

Acetophenone reduction with D_2 gas

A reduction reaction of acetophenone was carried out to yield 1-phenylethanol in methanol as a solvent (Scheme 1).



Scheme 1: Reduction of acetophenone to 1-phenylethanol with D_2 gas

100% conversion was achieved at 95°C, 95 bar reaction pressure using 0.25 M substrate concentration and 0.5 mL/min liquid flow rate, 100 NmL/min D_2 flow rate. In an attempt to increase daily throughput, a 1 M concentration was also tried, with the conversion being 69% (Table 1). During the reactions the D-grade of the water was 97.75%.

c [mol/dm³]	Liquid flow rate [mL/min]	D_2 flow rate [NmL/min]	*T* [°C]	*p* [bar]	Conversion [%]	D-grade C-D [%D]
1	0.5	100	95	95	69	89
0.25	0.5	100	95	95	100	85

Table 1: Reaction parameters of the acetophenone deuteration experiments

To determine the deuteration grade, 25 ml of the reaction solution were collected and the solvent was evaporated. The ^1H NMR spectrum (Fig. 1) of the crude material shows 85% deuteration degree at the benzylic position. Even though this is lower than the expected value based on the D-grade of the water used (~97-98%), it can still be considered a great result since protic solvents are known to be detrimental to deuteration[3]. For this reason, the experiment was repeated with hexane as solvent, however, there was no conversion in this case.

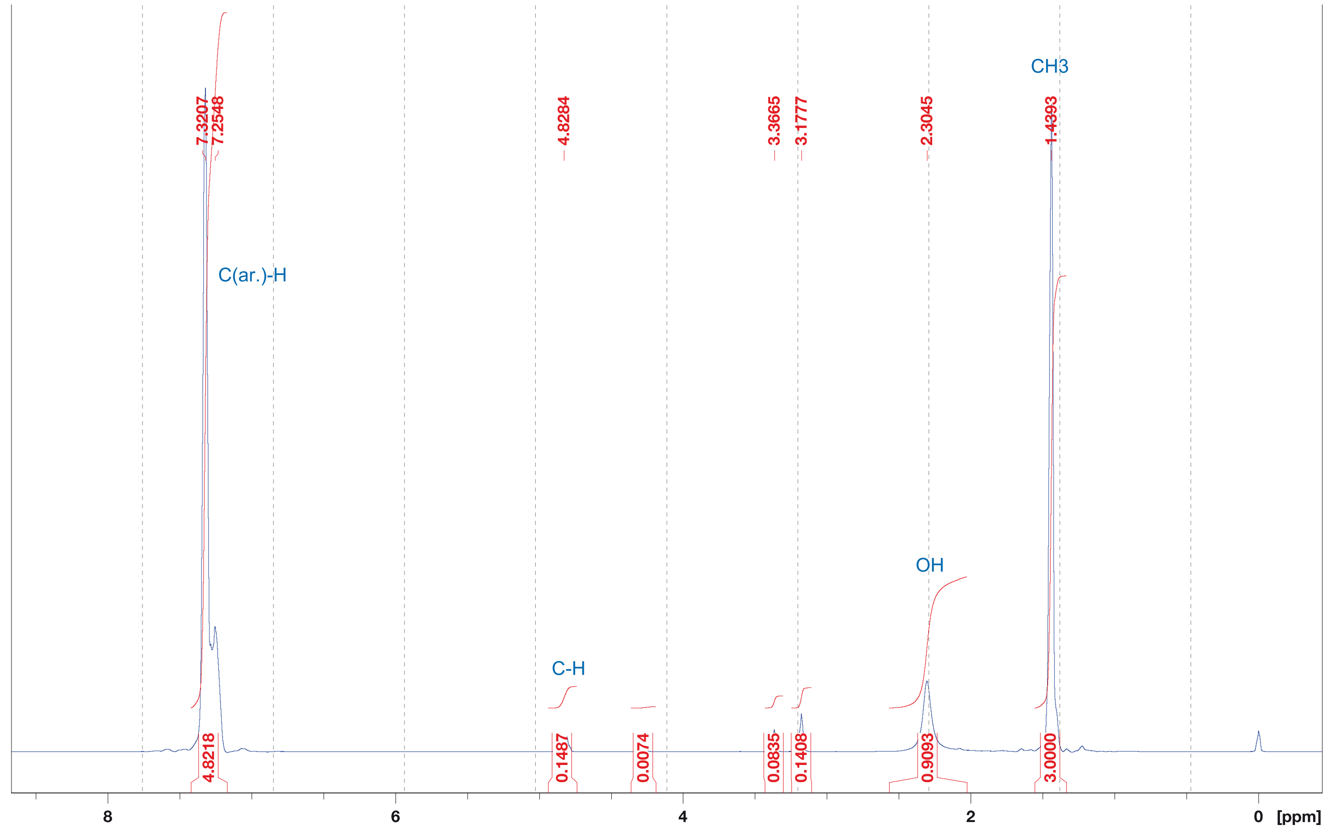


Figure 1: ^1H NMR spectrum of the crude product of the acetophenone deuteration

SUMMARY AND CONCLUSIONS

The importance of deuteration reactions in today's day and age is hard to deny. Our experimental results show that the H-Genie® is capable of generating D_2 gas to be used in key deuterations while the built-in safety features and ease of use provide peace of mind for all users. Coupled with other ThalesNano modules such as the Phoenix Flow Reactor, Pressure Module and THS System Controller the H-Genie® opens new horizons for reaction scaling and flow process automation.

REFERENCES

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