THALESNano


# Deuteration Reactions Using the H-Cube® Continuous Flow Reactor

## INTRODUCTION

Deuterium-labeled compounds are widely used as research tools in chemistry. Their importance lies in a number of applications, such as:

- proving reaction mechanisms
- investigation of a compound's pharmacokinetic properties
- internal standards in mass spectrometry
- compound structure determination in NMR spectroscopy.

Conventional techniques for the synthesis of deuterated compounds utilize $D_2$ gas as a deuterium source. However, there are drawbacks to utilizing deuterium gas on a laboratory scale, such as the handling of the gas itself. Other methods have been employed to overcome this difficulty such as catalytic H–D exchange reactions between $H_2$ and $D_2O$. However, these methods are time consuming and do not produce high purity $D_2$ and they also require high pressure, the use of a special catalyst, or an excess amount of a strong base or acid[1].

The H-Cube® continuous flow system is capable of generating deuterium gas from the electrolysis of $D_2O$, which is readily available in 99.98% purity and is easy to handle.

## TECHNIQUE

High purity deuterated compounds can be generated in high yield as long as a few guidelines are followed. The first step is to remove the $H_2O$ from the water tank. This is easier to perform if your system is made of stainless steel with the "Purge Water" function on the Service screen.

Step1: Drain the water from the reservoir using a syringe.

Step 2: Remove the back of the water reservoir with the supplied Allen wrench. Clean and dry the insides with a paper towel.

Step 3: Go to the Service screen. Press the "Purge Water" function and press Stop after 10 seconds.

Step 4: Replace the back of the water reservoir. Add 30 mL of deuterated water. Press "Purge Water" for 10 seconds.

Step 5: Remove the back of the water reservoir, dry the inside again, and press "Purge Water" for 10 seconds again.

Step 6: Replace water reservoir back and fill with deuterated water. Press "Purge Water" to refill cell with $D_2O$.

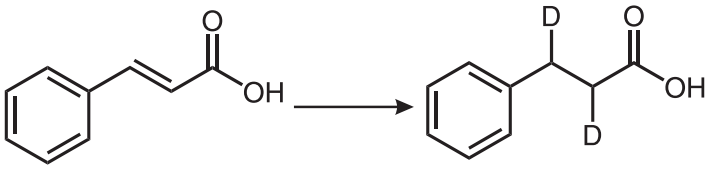
Step 7: Take a blank CatCart® (titanium) and pass the reaction solvent and run the system at Full H2 mode for 20 minutes. Remove blank cartridge.

## RECOMMENDATIONS

- Only use an aprotic solvent to avoid H–D exchange.
- Do not use hydrogen saturated catalysts such as, Raney catalysts for the reaction.

There are two literature examples of where the H-Cube® has been utilized for the deuteration of compounds.

Fülöp *et al.* performed deuterations on a series of unsaturated compounds[1]. Optimum conditions were first explored using cinnamic acid as a standard.



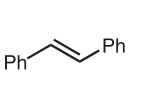
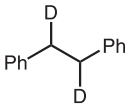
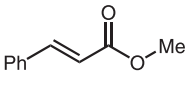
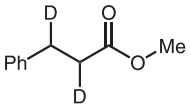
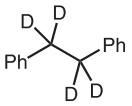
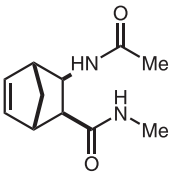
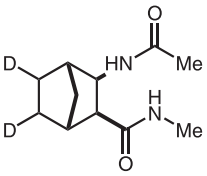
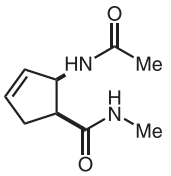
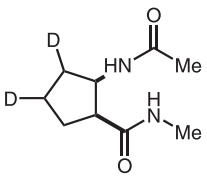
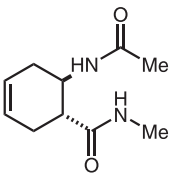
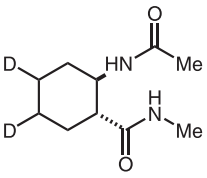
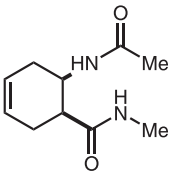
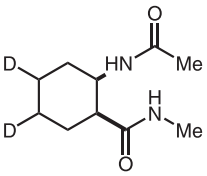
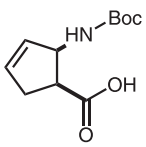
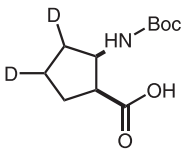
Early reactions using methanol and 10% Pd/C led to only a 30% incorporation of deuterium into the molecule. Changing from methanol to an aprotic solvent, ethyl acetate, increased deuterium incorporation to 70%. The catalyst was then changed to a less active catalyst (5% $Pd/BaSO_4$) to reduce the deuteration of the phenyl ring and selectively deuterate the double bond. This catalyst change increased deuterium content to 95%. The reaction was carried out at room temperature. Pressures in the 40-60 atm range and flow rates between 0.7-2 mL/min did not affect yield or deuterium levels.

Once the optimized conditions had been found, the same conditions were applied to a series of other unsaturated compounds. The results are displayed in Table 1.

As you can see from the results, the products were synthesized in near quantitative yield with a high deuterium incorporation. No purification was necessary. The structures included foldamer building blocks, so there is potential for structure elucidation via deuteration where bacteria labeling is not possible. The $D_2O$ consumption was very low (4.41 µL/min), which is a much higher deuterium efficiency when compared to other methods.

The other paper is from Kappe *et al.* and describes the deuteration of ethyl cinnamate[2]. Using a flow rate of 1 mL/min, 10% Pd/C, room temperature, and Full H2 mode, the product was successfully synthesized in 92% yield with a 95% degree of deuterization.

Table 1: Deuteration of selected unsaturated compounds

| Entry | Substrate | Product | D[a] (%) | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  |  | 99 | 99 |
| 2 |  |  | 97 | 98 |
| 3 |  |  | 93 | 97 |
| 4 |  |  | 96 | 98 |
| 5 |  |  | 96 | 99 |
| 6 |  |  | 95 | 99 |
| 7 |  |  | 97 | 95 |
| 8 |  |  | 98 | 98 |

[a] Deuterium content in %.
[b] Isolated yield.

## CONCLUSION

Utilizing $D_2O$ instead of $H_2O$, the H-Cube® is able to deuterate compounds in high yield and with a deuteration incorporation of >95%. These results offer up the H-Cube® as a reliable alternative to other deuteration methods.

## REFERENCES

[1] Mándity, I.M.; Martinek T.A.; Darvas, F.; Fülöp, F.; *Tet. Lett.*; **2009**; 50; 4372-4374.
[2] Irfan, M.; Petricci, E.; Glasnov, T.; Taddei, M.; Kappe, O.; *Eur. J. Org. Chem.;* **2009**; 1327-1334