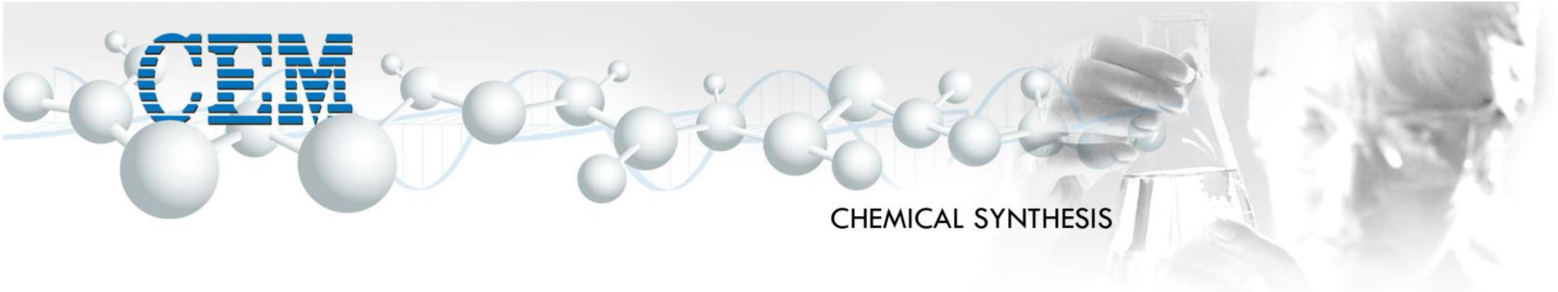


Simple and Efficient Microwave-Assisted Hydrogenation Reactions at Moderate Temperatures and Pressures

Microwave irradiation is a powerful tool in organic synthesis due to its ability to speed up chemical reactions and increase product yields. Indeed, dedicated microwave synthesizers have found their way into mainstream organic synthesis for most types of reactions, with the exception of hydrogenations. Typically, hydrogenation reactions that utilize microwave irradiation proceed by way of a hydrogen transfer reaction or use a reagent that generates hydrogen gas in situ.[1] This was the driving force for Dr. Grace Vanier to explore the ability to add hydrogen gas directly to the reaction mixture (Figure 1). Hydrogenations under microwave irradiation use power instead of high pressure (> 1000 PSI) to drive a chemical reaction to completion. This allows for conditions at moderate temperatures (50 – 80 °C) and low pressures (50 – 200 psi) for a safer reaction without sacrificing high yields.

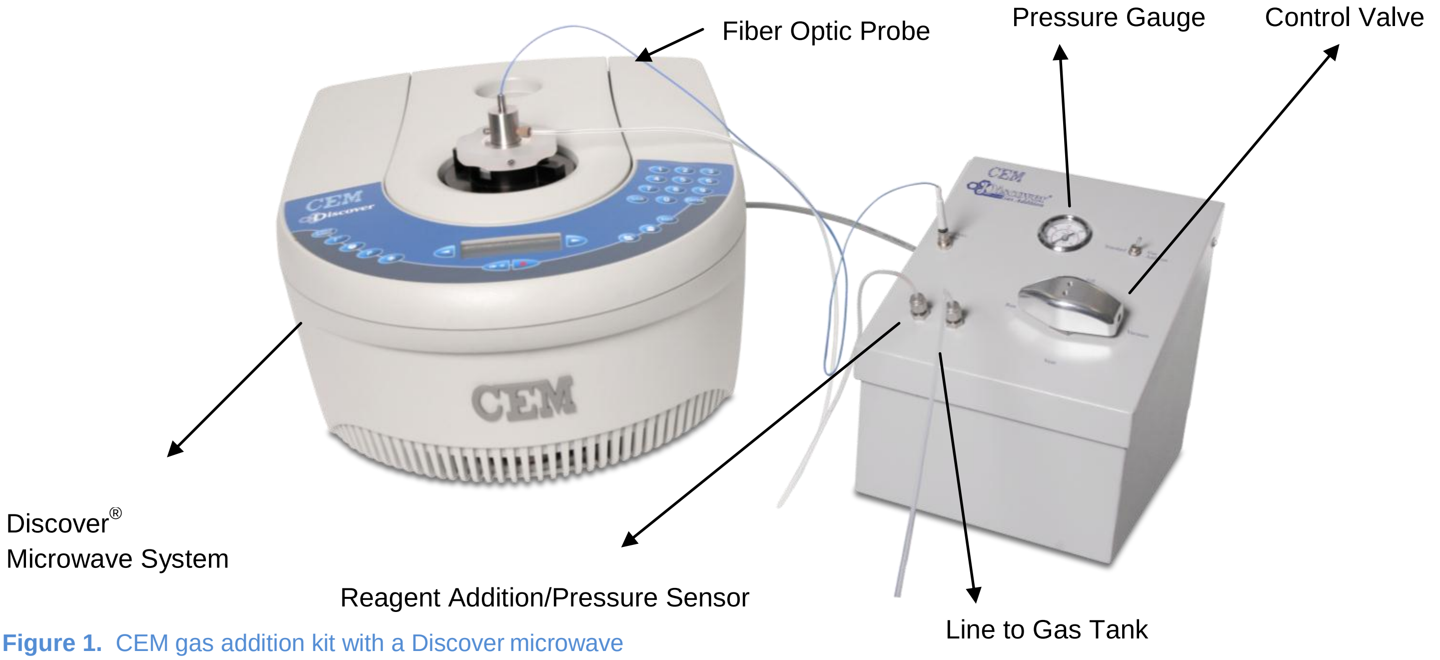
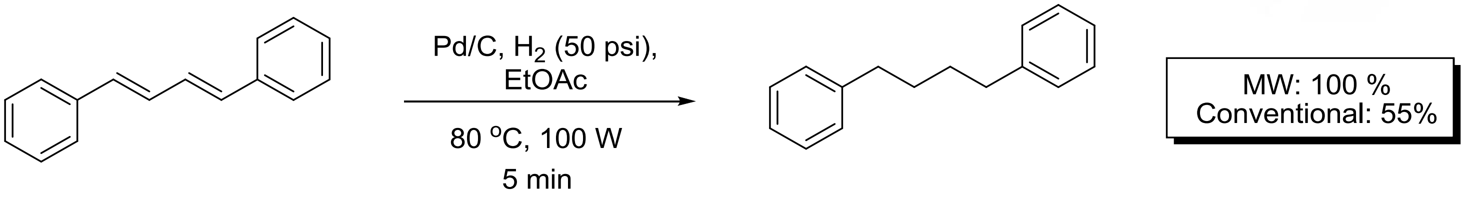


Figure 1. CEM gas addition kit with a Discover microwave

The results of Vanier's study were reported in a 2007 *Synlett* publication. An initial solvent, temperature, and catalyst loading study was conducted to determine the optimal reaction parameters: ethyl acetate, 80 °C, and 1 mol % Pd/C (10 wt%). It should be noted that above 80 °C, the conversion decreased drastically – most likely due to the decrease in solubility of the gas as the solvent temperature increased.

The hydrogenation of *trans*,*trans*-1,4-diphenyl-1,3-butadiene (Scheme 1) was completed in five minutes at 80 °C and 50 psi of H_2. The temperature profiles for the hydrogenation in both the microwave and oil bath were carefully overlapped for comparison. The oil bath experiment was accomplished by placing the reaction vial in an oil bath at a preset temperature. Careful control of the time to temperature and cool-down ensured an accurate comparison between the two systems. The hydrogenation performed in the microwave resulted in complete conversion after 5 minutes, compared to 55 % conversion from the reaction in the oil bath in the same amount of time.

Scheme 1. Reduction of *trans, trans*-1,4-diphenyl-1,3-butadiene using the CEM gas addition kit



MW: 100 %
Conventional: 55%

A sampling of various reduction substrates is shown in Table 1. Methyl cinnamate (Entry 1) was reduced in three minutes in 99 % yield. Tri-substituted olefins (Entry 2) were readily reduced in five minutes in 99% yield. Tri-substituted α,β-unsaturated ketones (Entry 3), which can be tedious to hydrogenate in high yields, required twenty minutes with an 89 % yield. Entry 4 shows the reductive amination between benzaldehyde and aniline in three minutes with a 98 % yield. After five minutes, benzylamine was reduced in the presence of excess hydrogen gas, giving aniline and toluene – as determined by GCMS. This procedure also worked with other functional groups beyond olefins. Carbobenzyloxy-L-proline deprotection was completed (Entry 5) in five minutes in over 99 % yield with complete retention of stereoconfiguration. In Entry 6, 2,6-dimethyl-nitrobenzene was reduced to 2,6-dimethylaniline in fifteen minutes with the assistance of the PowerMAX simultaneous air cooling feature. Figure 2 shows the amazing effect simultaneous air cooling can have on the delivered power.

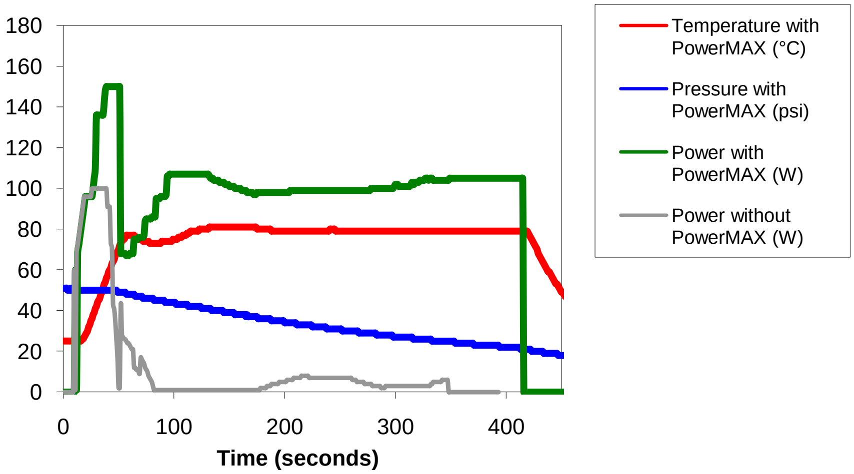
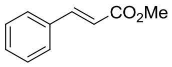
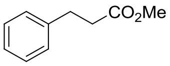
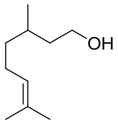
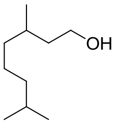
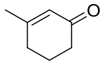
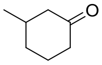
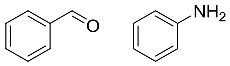
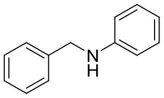
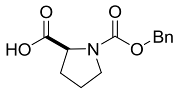
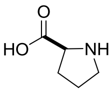
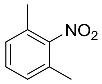
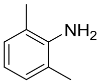
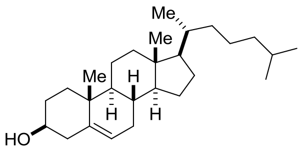
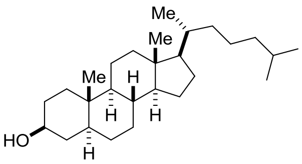


Figure 2. Reaction parameters with and without PowerMAX simultaneous cooling for the reduction of 2,6 – dimethylnitrobenzene

As the reaction proceeds, the pressure (blue line) steadily decreases, indicating that hydrogen is being consumed. The temperature (red line), with and without PowerMAX, is relatively constant throughout the reaction. The power curves, however, are quite different. Without PowerMAX (grey line), the power drops drastically to 5 – 10 W after the reaction reaches temperature because the reaction contents are efficient microwave absorbers; very little power is needed to maintain an 80 °C temperature. With PowerMAX (green line), the power input averages around 100 W, a twenty-fold increase. It should be noted that the temperature of the two comparison reactions did not change, only the power input.

Lastly, cholesterol, a more complex molecule, was reduced in excellent yields. Conventionally, this hydrogenation can be performed in 24 hours to give about 60% yield. Through the use of simultaneous cooling, the hydrogenation of cholesterol was completed in only five minutes to give 100 % isolated yield. This reaction was also performed in the oil bath setup as a comparison to give 3 % isolated yield of the product. The substantial difference in both time and yield demonstrate the power of simultaneous cooling to get more microwave energy into the reaction, thus driving the reaction to completion. The hydrogenation of cholesterol was found to be a selective hydrogenation as well; the addition of the hydrogen takes place selectively opposite to the axially oriented methyl group.

Table 1. Hydrogenations of various substrates[a]

Entry	Reactant	Product	Time (min)	Yield (%)
1			3	99
2			5	99
3			20	89
4			3	98
5			5	99
6			15	99[b]
7			5	99[b] (Oil bath 3)[c]

[a] Reaction conditions: EtOAc, 80 °C, 50 psi, 1 mol% Pd/C (10 wt%)
[b] PowerMAX simultaneous cooling used.
[c] Performed in an oil bath with an internal temperature of 80 °C.

References

1) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*. Wiley- VCH, Weinheim, 2005.
2) Vanier, G. S. *Synlett* 2007, 131 – 135. DOI: 10.1055/s-2006-958428