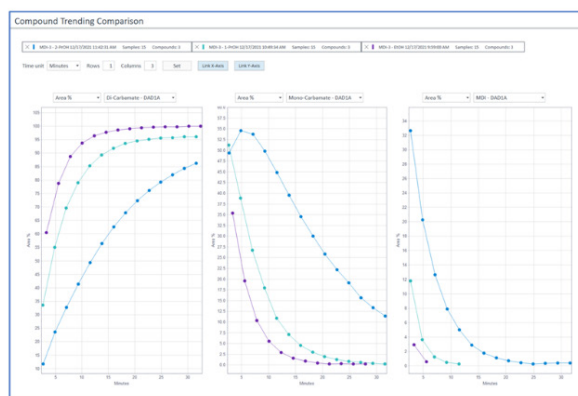


Which Reaction Shows the Best Performance?

Comparison of online LC experiments with Agilent Online LC Monitoring Software



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Abstract

This application note presents a feature of the Agilent Online LC Monitoring Software that enables comparison of different experiments. This functionality can be used to compare the results of replicates, document their reproducibility, and compare multiple experiments with varied reaction conditions affecting factors such as kinetics or yield. The software provides a comparative visualization of results from different experiments at a glance, enabling quick evaluation of individual experiments' success or revealing the influence of different parameters on the reaction.

Introduction

Molecules containing reactive functional groups are difficult to analyze by LC. Normally, derivatization reactions must be carried out before analysis. For isocyanates, alcohols are very common derivatization agents that lead to formation of carbamates. Methanol is the most common reactant to deactivate isocyanates. The present study contains an assessment of reaction time with other short-chain alcohols, such as ethanol, 1-propanol, and 2-propanol.

This application note demonstrates the use of the experiment comparison functionality included in the Online LC Monitoring Software. The comparison of a small-molecule carbamate formation reaction from 4,4'-methylene diphenyl diisocyanate (MDI) with different alcohols (Figure 1) serves as an example. Comparison of the respective trending plots shows the influence of the different molecular sizes of the alcoholic compounds and their impact on reaction speed.

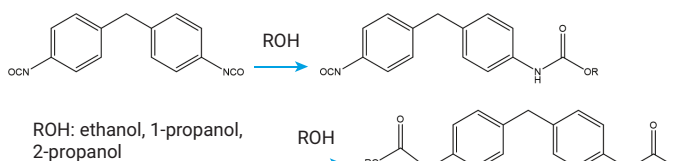


Figure 1. Reaction of MDI with an excess of different C₂- and C₃-alcohols to mono- and dicarbamates.

Experimental

Instrument

- Agilent 1290 Infinity II High-Speed Pump (G7120A)
- Agilent 1260 Infinity II Online Sample Manager Set (G3167AA): Agilent 1260 Infinity II Online Sample Manager (G3167A) clustered with external valve (part number 5067-6680) located at the Agilent 1290 Infinity Valve Drive (G1170A) and Agilent Online LC Monitoring Software
- Agilent 1290 Infinity II Multicolumn Thermostat (G7116B)
- Agilent 1290 Infinity II Diode Array Detector (G7117B) with Agilent InfinityLab Max-Light Cartridge Cell (10 mm, G4212-60008)
- Mettler Toledo EasyMax 102

Column

Agilent ZORBAX Eclipse XDB-C8 column, 2.1 × 30 mm, 1.8 μm (part number 924700-906)

Software

- Agilent OpenLab CDS, version 2.6, or later versions
- Agilent Online LC Monitoring Software, version 1.2

Analytical method

Parameter	Value
Solvents	A) water, B) acetonitrile (ACN)
Analytical Flow Rate	1.0 mL/min
Generic Gradient	ACN:H ₂ O 40:60 to 80:20 in 0.8 min, 95:5 at 1.0 min, 40:60 at 1.01 min Stop time: 1.2 min
Column Temperature	40 °C
Agilent Feed Injection (Automatic)	80% of analytical flow rate
Flush Out Solvent	ACN:H ₂ O 40:60 (S2)
Flush Out Volume	Automatic
Injection Volume	1 μL
Needle Wash	3 s, water:ACN 1:1 (S1)
Diode Array Detector	240 ±4 nm, ref.: off, 40 Hz data rate

Sampling for direct injection

Cycle time: 2 minutes, taking 15 samples per experiment. The actual cycle time was slightly longer due to additional time required for flushing steps.

Sample delivery pump

- **Pump used:** Agilent 1260 Infinity II Isocratic Pump (G7110B)
- **Flow rate:** 5 mL/min
- Solvent stream from reaction vessel to Online Sample Manager reactor interface and back to reaction vessel

Reaction conditions

- **Solvents:** EtOH, 1-PrOH, 2-PrOH (35 mL for each campaign)
- Stirring at 25 and 35 °C
- **Reaction started by adding educt:** 1 mL of a 0.5% MDI solution in toluene

Chemicals

- Methylene diphenyl diisocyanate (MDI)
- Ethanol, 1-propanol, 2-propanol

Solvents and chemicals

- All solvents were purchased from Merck, Germany.
- MDI was provided by DOW.
- Fresh ultrapure water was obtained from a Milli-Q integral system equipped with an LC-Pak polisher and a 0.22 μm membrane point of use cartridge (Millipak).

Results and discussion

The reaction of diisocyanates with alcohols to form carbamates is a two-step reaction where the first isocyanate functionality quickly reacts with the alcohol to form the monocarbamate. The second step is a slower reaction that yields the dicarbamate (Figure 1).

For the monitoring of the reaction, a fast method for the separation of monocarbamate, dicarbamate, and MDI was developed. Figure 2 shows the resulting chromatographic separation for the reaction of MDI with 2-propanol. The dicarbamate elutes at 0.940 minutes, the monocarbamate at 1.051 minutes, and the MDI at 1.152 minutes.

The formation of monocarbamate from MDI is typically very fast and cannot be monitored. The full reaction can be followed by monitoring the decrease of the monocarbamate and the increase of the dicarbamate as final product. This process can be displayed via Online LC Monitoring Software in a trending plot for a single reaction, such as the reaction of 2-propanol and MDI (Figure 3A). The results including area%, peak area, peak height, and retention time for the selected sampling points in Figure 3A (large dots) are shown in Figure 3B. An overlay of the respective chromatograms is shown in Figure 2.

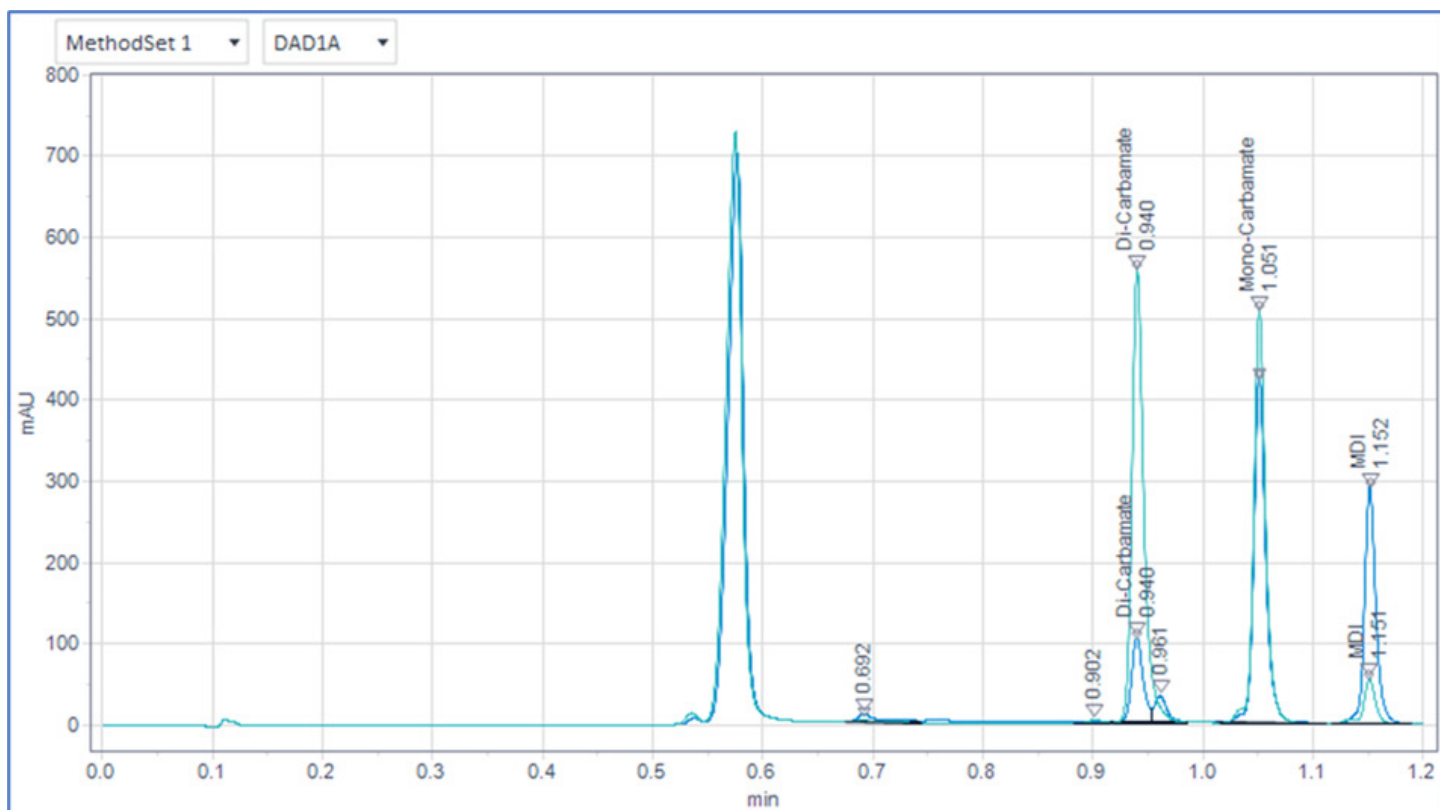


Figure 2. Fast separation of mono- and dicarbamate formed from MDI and 2-propanol. The peak at 0.58 minutes is toluene, which was used as a solvent for MDI. This peak was not integrated and is not included in the calculation of area% results.

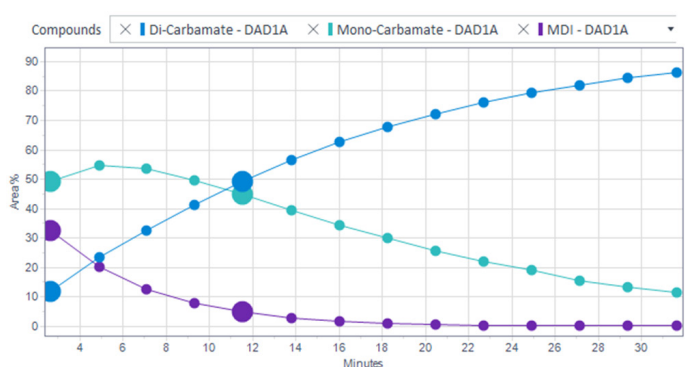


Figure 3. Trending plot of the reaction of MDI with 2-propanol. The green line represents the decreasing area% of the monocarbamate. The blue trace indicates the formation of dicarbamate. The purple trace relates to the decreasing MDI.

Table 1. Results for the highlighted samples (large dots) in Figure 3.

Results						
Sample	Compound	Signal	RT (min)	Area%	Area	Height
	<MULTIPLE>	DAD1A				
Sample-2	Di-Carbamate	DAD1A	0.940	11.780	75.644	103.657
	Mono-Carbamate	DAD1A	1.051	49.339	316.828	420.573
	MDI	DAD1A	1.152	32.668	209.776	288.651
Sample-6	Di-Carbamate	DAD1A	0.940	49.376	421.133	555.427
	Mono-Carbamate	DAD1A	1.051	44.839	382.435	505.001
	MDI	DAD1A	1.151	5.030	42.901	54.726

The described trending plot is typically used to monitor a reaction in near real time, where the results occur as the analytical run of the respective sampling point is finished. Afterwards, the results of only one single experiment with all included sampling points can be examined simultaneously.

The comparative analysis of more than one finished experiment can be performed with the Compound Trending Comparison functionality in the Online LC Monitoring Software. As an example, data were generated from reactions of MDI with different C₂- and C₃-alcohols (ethanol, 1-propanol, and 2-propanol). The resulting data files were selected for comparison and displayed according to the different compounds as shown by the screenshot in Figure 4.

As seen in Figure 4A, the slowest reaction to form the dicarbamate in the comparison occurs with 2-propanol as the alcoholic compound (blue trending plot), starting with 10 area% of dicarbamate in the first sample and 85 area% in the last. The formation of dicarbamate occurs faster with 1-propanol (green trending plot) and fastest with ethanol (purple trending plot). With ethanol, the respective dicarbamate already occurs with 60 area% in the first sample. Figure 4B displays the monocarbamates generated as intermediates and eventually consumed. For the slow consumption of the monocarbamate from the reaction with 2-propanol, there is a slight increase of the area% at the beginning of the experiment (Figure 4B, blue line). Monocarbamate is formed and consumed faster in the reactions of MDI with ethanol and 1-propanol. Figure 4C shows the consumption of MDI, which was slow for the formation of the 2-propanol carbamate: MDI was detected throughout the experiment. For ethanol, the MDI is completely consumed after 5 minutes and not detected in the following samples.

Besides the reactivity of the compounds, other parameters like the reaction temperature can have an influence on the speed of the reaction. To evaluate the effect of temperature, the reaction of MDI and 2-propanol was also performed at 35 °C. The result was compared to the reaction of 1- and 2-propanol with MDI at 25 °C (Figure 5). The elevated reaction temperature increases the speed of the reaction of MDI with 2-propanol, forming the derived dicarbamate, to such an extent that the area% values obtained over time were almost comparable with the reaction with 1-propanol (Figure 5A, blue trending plot). The consumption of the intermediate monocarbamate also occurs faster compared to the reaction at 25 °C (Figure 5B, blue trending plot). Identical behavior was observed for the consumption of MDI (Figure 5C, blue trending plot).

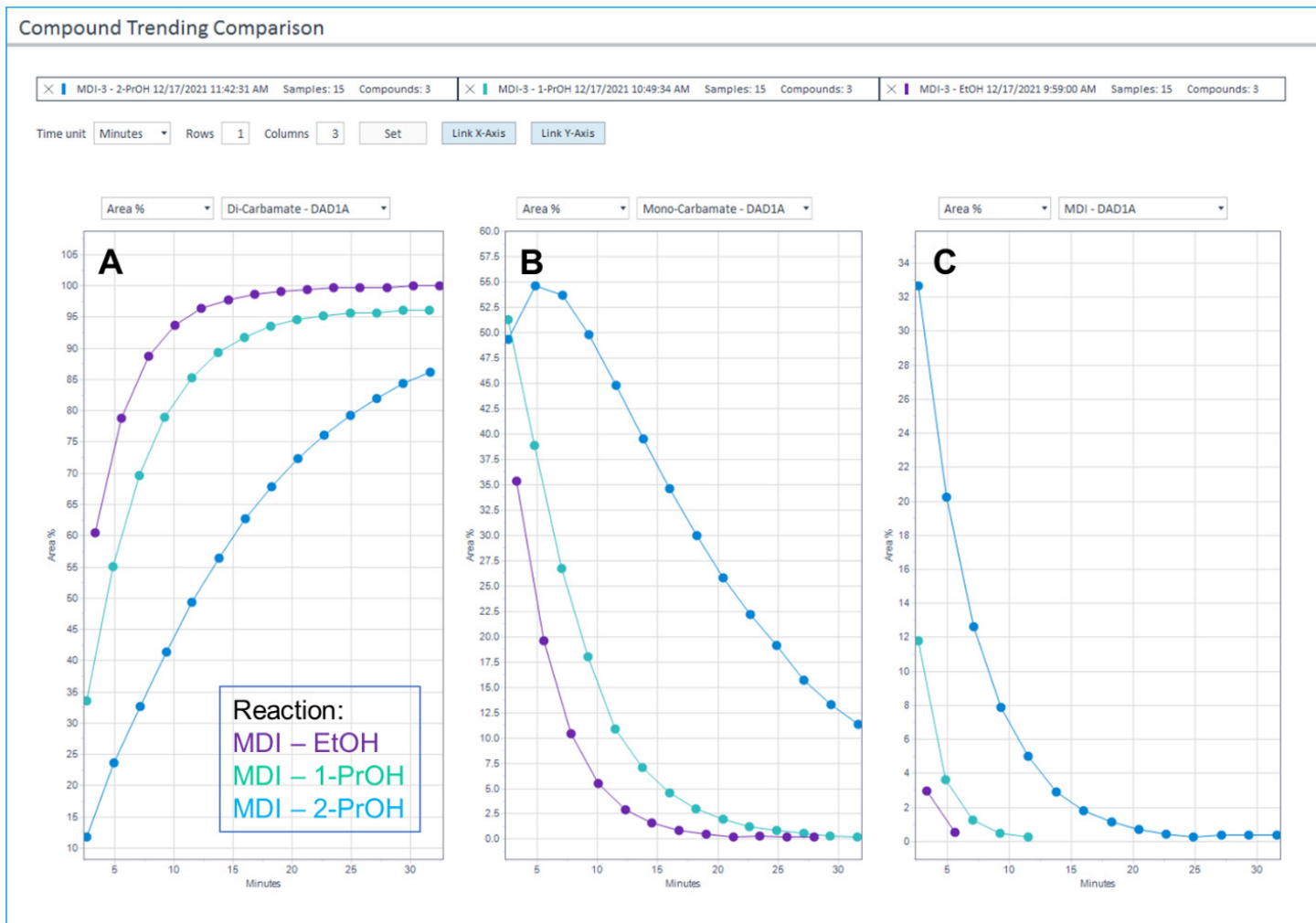


Figure 4. Compound trending comparison of three experiments for the formation of dicarbamates from MDI and ethanol, 1-propanol, and 2-propanol at 25 °C. (A) Comparison of the formation of dicarbamate products. (B) Consumption of the very quickly formed intermediate monocarbamate. (C) Consumption of MDI. The selected experiment names can be found at the top of the window. The row and column matrix can be defined freely. Compounds can be selected using drop-down menus.

Compound Trending Comparison

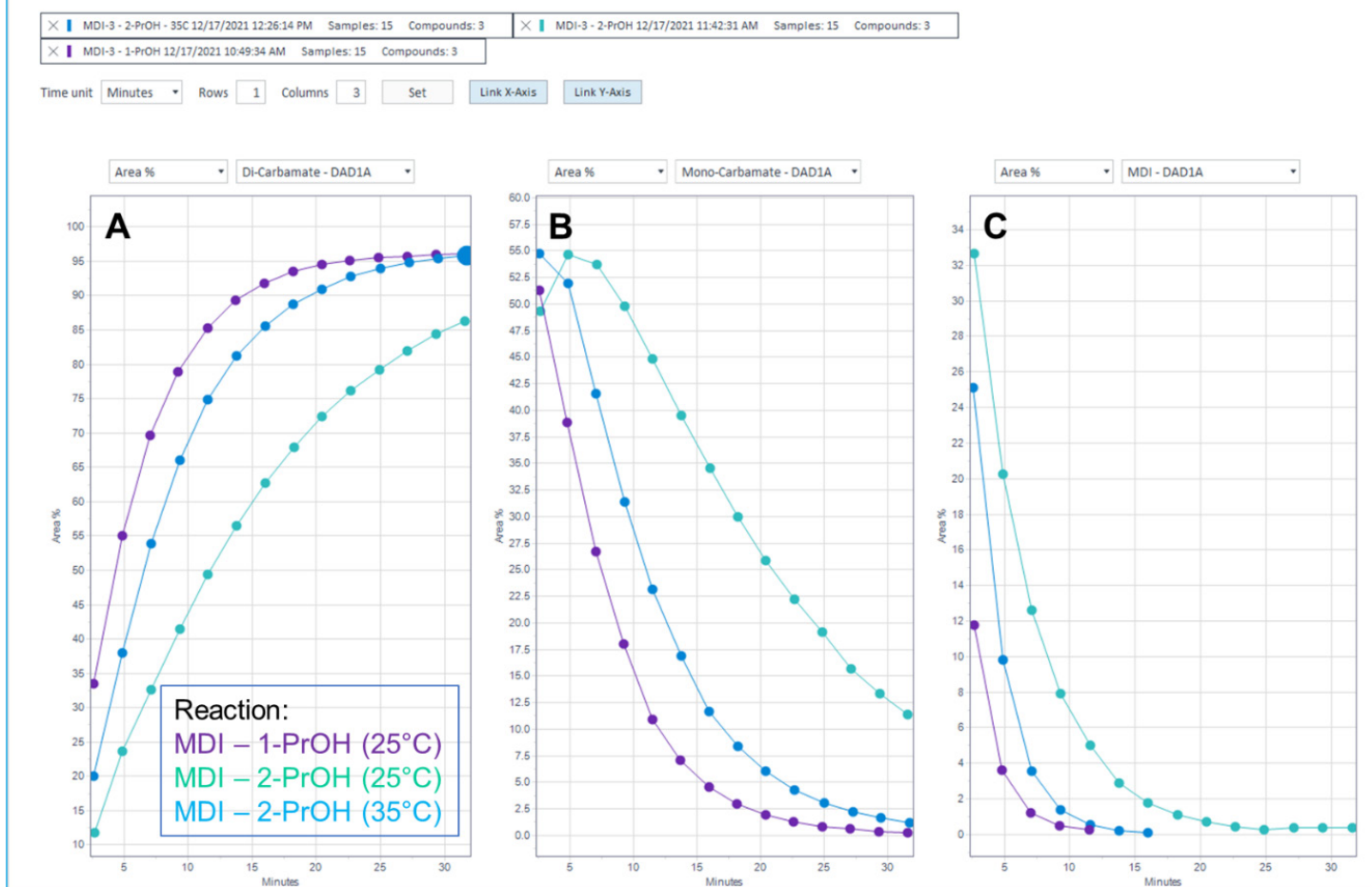


Figure 5. Effect of elevated temperature (35 °C) on the formation of dicarbamate from MDI and 2-propanol in comparison to the carbamate formation of 2- and 1-propanol with MDI at 25 °C. (A) Trending plots of dicarbamate formation. (B) Trending plot of consumption of initially generated monocarbamate. (C) Trending plot of MDI consumption.

Conclusion

This application note demonstrates the use of the Compound Trending Comparison feature in the Agilent Online LC Monitoring Software. With this functionality, it is possible to compare the results of completed experiments in terms of their differences due to varying reaction parameters. This feature enables quick decisions to optimize the reaction, maximizing product yield in less time.

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DE63051937

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Printed in the USA, May 12, 2023
5994-5922EN