

Supplementary Information

Best practice for sampling in automated parallel synthesizers

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Evaporation tests – setup

The evaporation tests were conducted in a setup with a sampling rack next to the reactor block utilizing a Chemspeed Accelerator SLT 100 platform. The setup is presented in **Figure S1**.

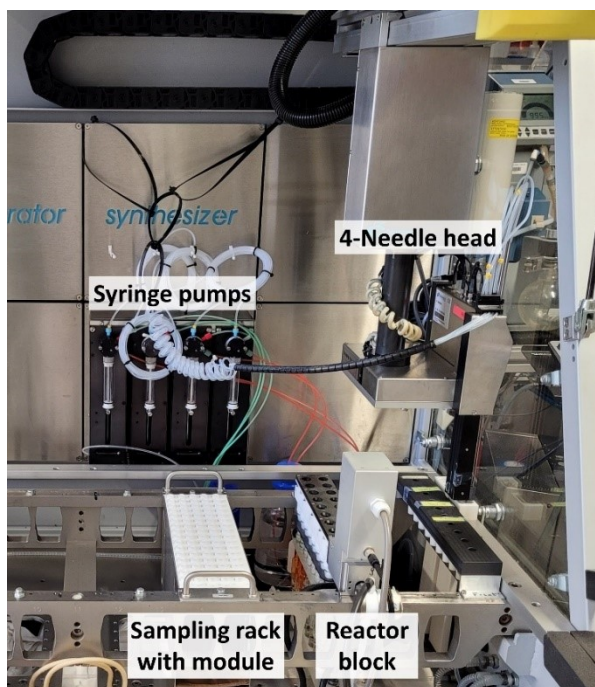


Figure S1: Setup of the evaporation experiment with one reactor block and a sampling rack with a 3D-printed white downholding module installed on top.

As the distance between the heated reactor block and the sampling rack could play a crucial role in the kinetics of the evaporation for the conducted evaporation tests, the distance between the two components was measured (**Figure S2**, distance is 11 cm).

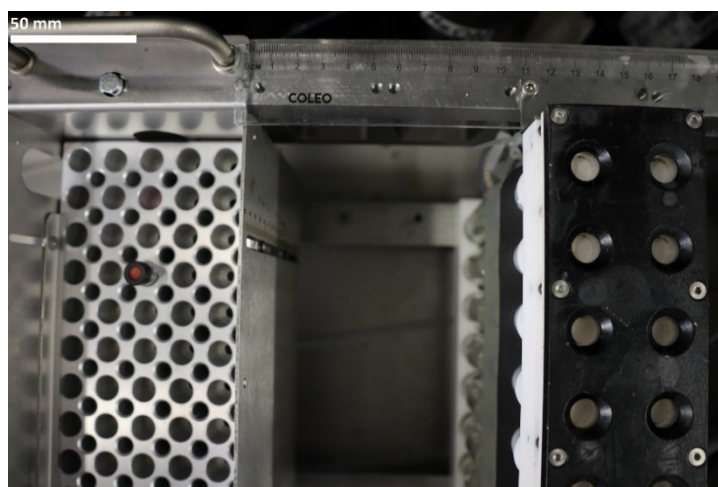


Figure S2: Measurement of the distance between the reactor and the sampling rack.

Evaporation dependence on vapor pressure

The evaporation experiments were conducted with different solvents (for details see main text). The overview of the filling heights of the vials after 24 h with or without used lid are presented in **Figure S3** to **Figure S8**. If evaporation occurred, the determined evaporation rate for the solvent is presented below the respective figure.

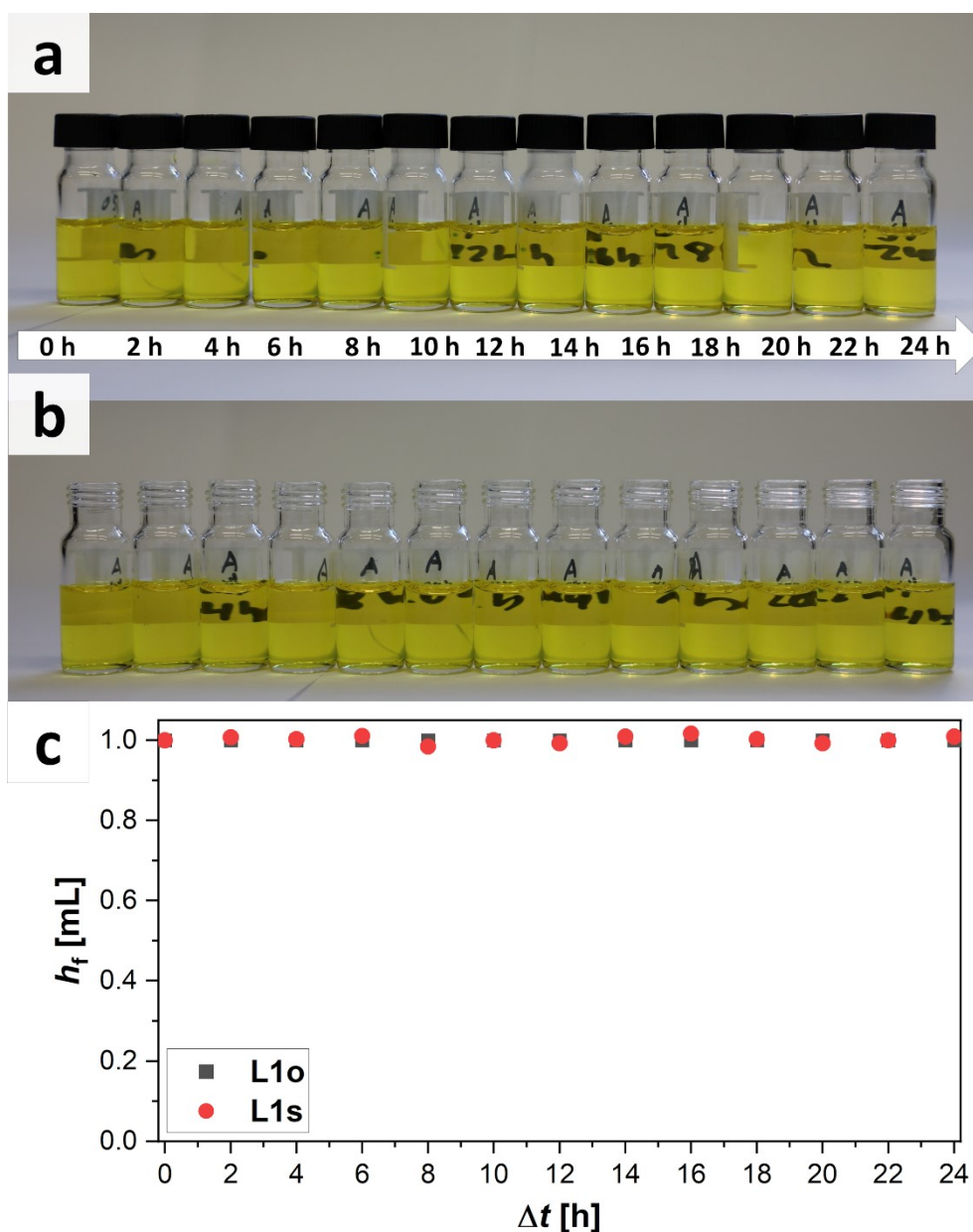


Figure S3: Overview of the results of the evaporation experiment for dimethyl formamide. a: Picture of sealed vials for different elapsed times since filling (L1s). b: Picture of unsealed vials filled at the same time as the sealed ones (L1o). c: Plot of filling height h_f of sealed (red) and unsealed vials (black), against the elapsed time between evaluation and filling Δt .

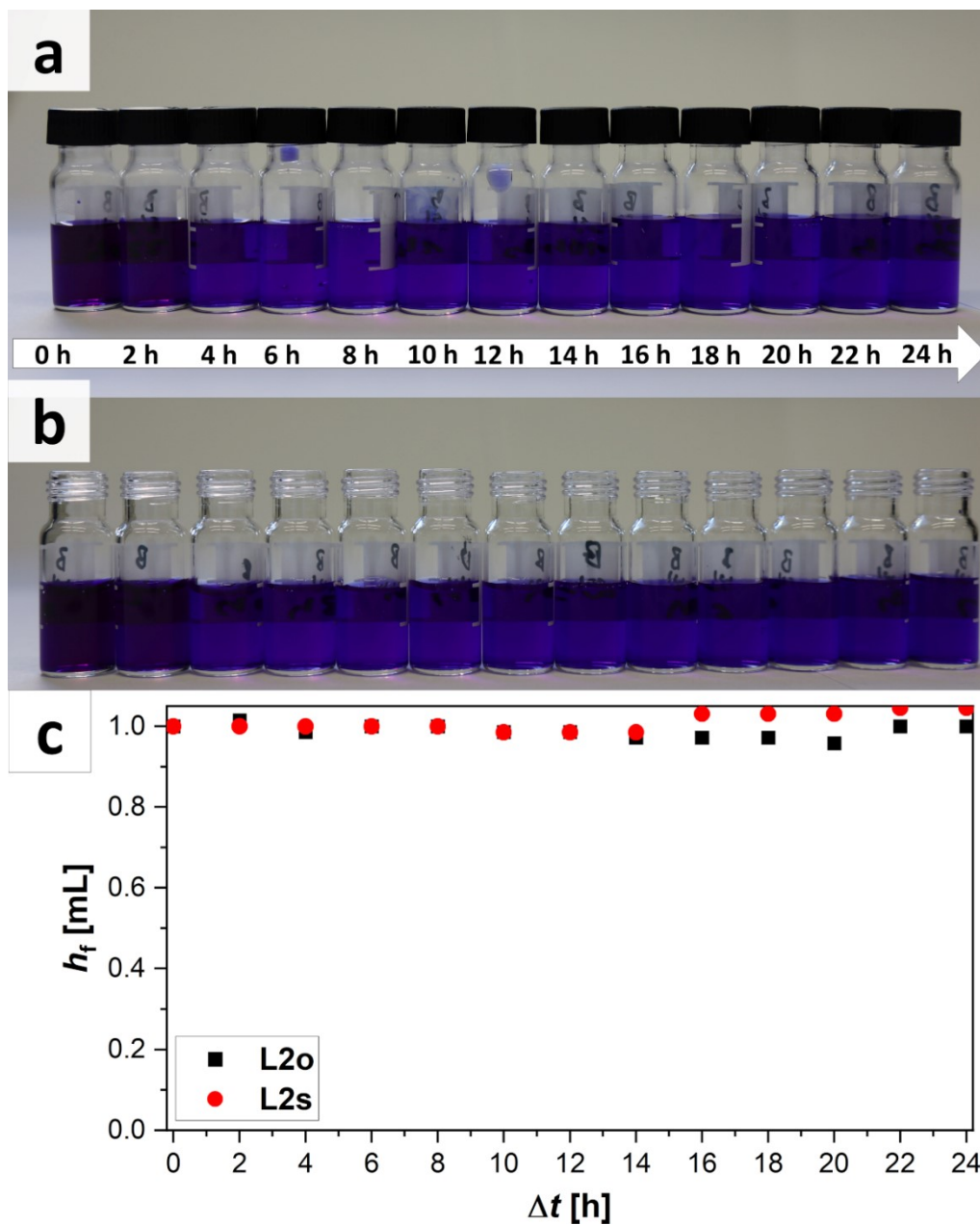


Figure S4: Overview of the results of the evaporation experiment for water. a: Picture of sealed vials for different elapsed times since filling (L2s). b: Picture of unsealed vials filled at the same time as the sealed ones (L2o). c: Plot of filling height h_f of sealed (red) and unsealed vials (black), against the elapsed time between evaluation and filling Δt .

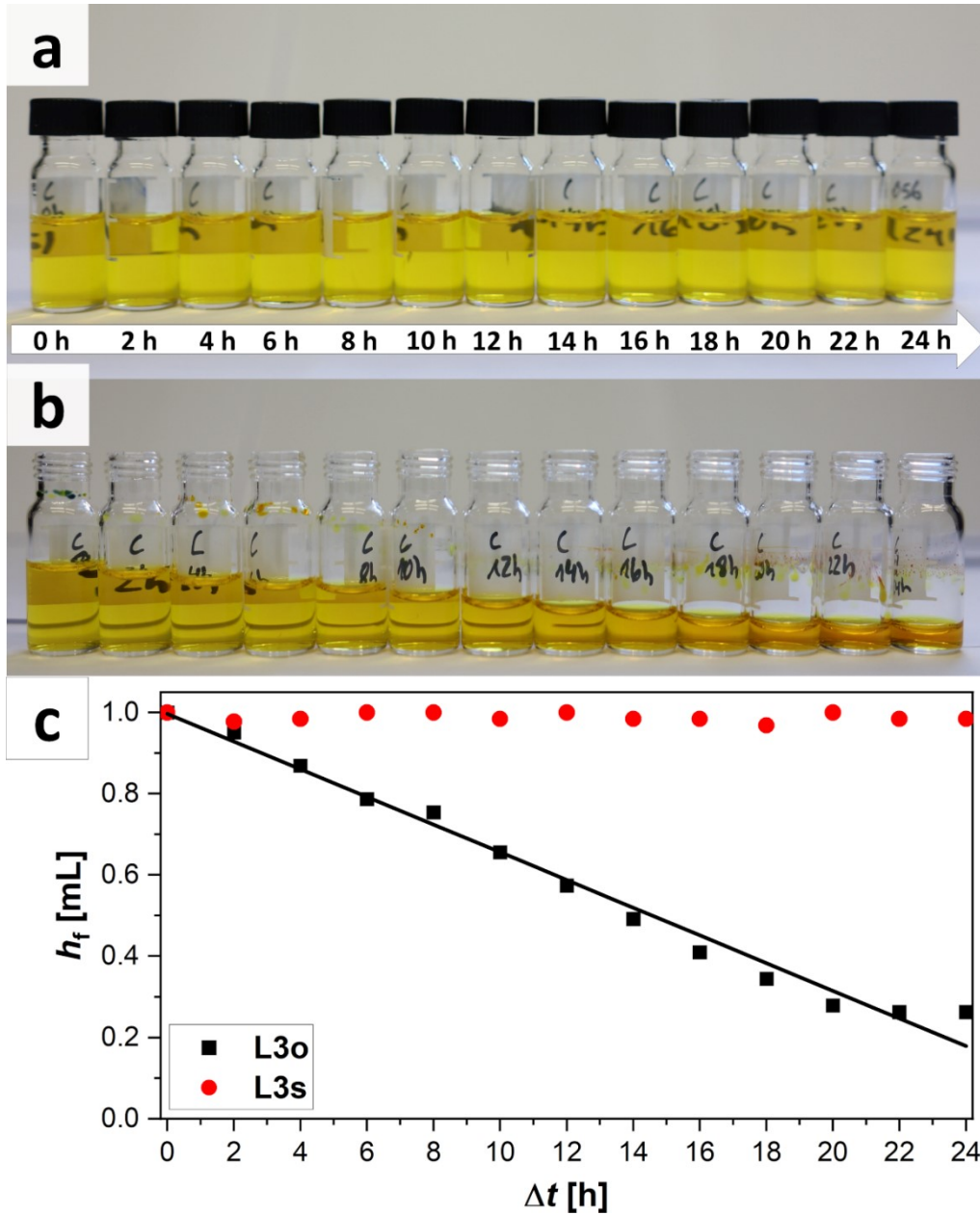


Figure S5: Overview of the results of the evaporation experiment for methanol. a: Picture of sealed vials for different elapsed times since filling (L3s). b: Picture of unsealed vials filled at the same time as the sealed ones (L3o). c: Plot of filling height h_f of sealed (red) and unsealed vials (black), against the elapsed time between evaluation and filling Δt .

The equation for the rate of evaporation of methanol from the unsealed vials **L3o/0h** to **L3o/24h** could be empirically determined from the plot as the equation of a linear fit through the data points:

$$h_f = 0.997 \text{ mL} - 0.034 \frac{\text{mL}}{\text{h}} \cdot \Delta t$$

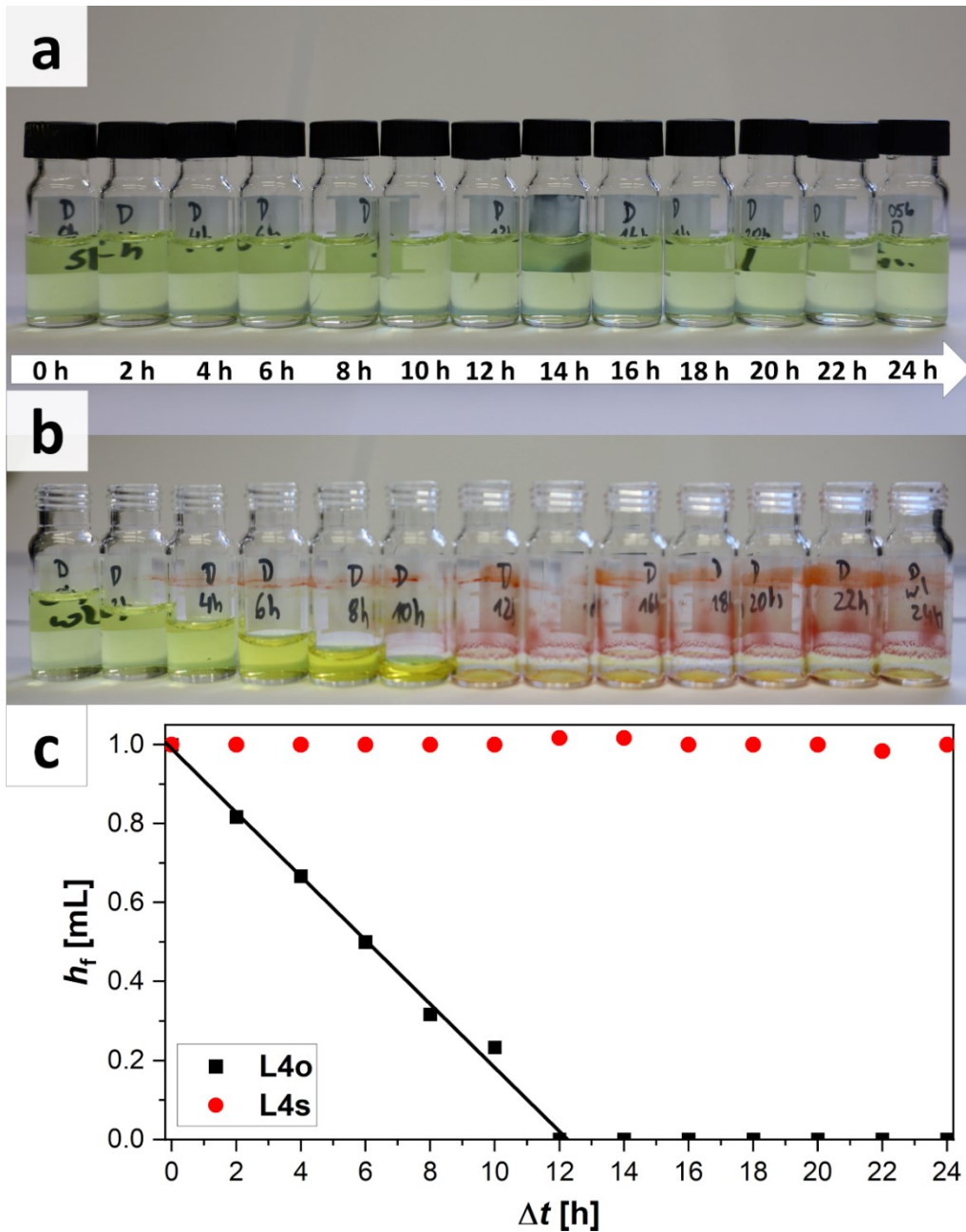


Figure S6: Overview of the results of the evaporation experiment for acetone. a: Picture of sealed vials for different elapsed times since filling (L4s). b: Picture of unsealed vials filled at the same time as the sealed ones (L4o). c: Plot of filling height h_f of sealed (red) and unsealed vials (black), against the elapsed time between evaluation and filling Δt .

The equation for the rate of evaporation of acetone from the unsealed vials **L4o/0h** to **L4o/24h** could be empirically determined from the plot as the equation of a linear fit through the data points:

$$h_f = 0.989 \text{ mL} - 0.081 \frac{\text{mL}}{\text{h}} \cdot \Delta t$$

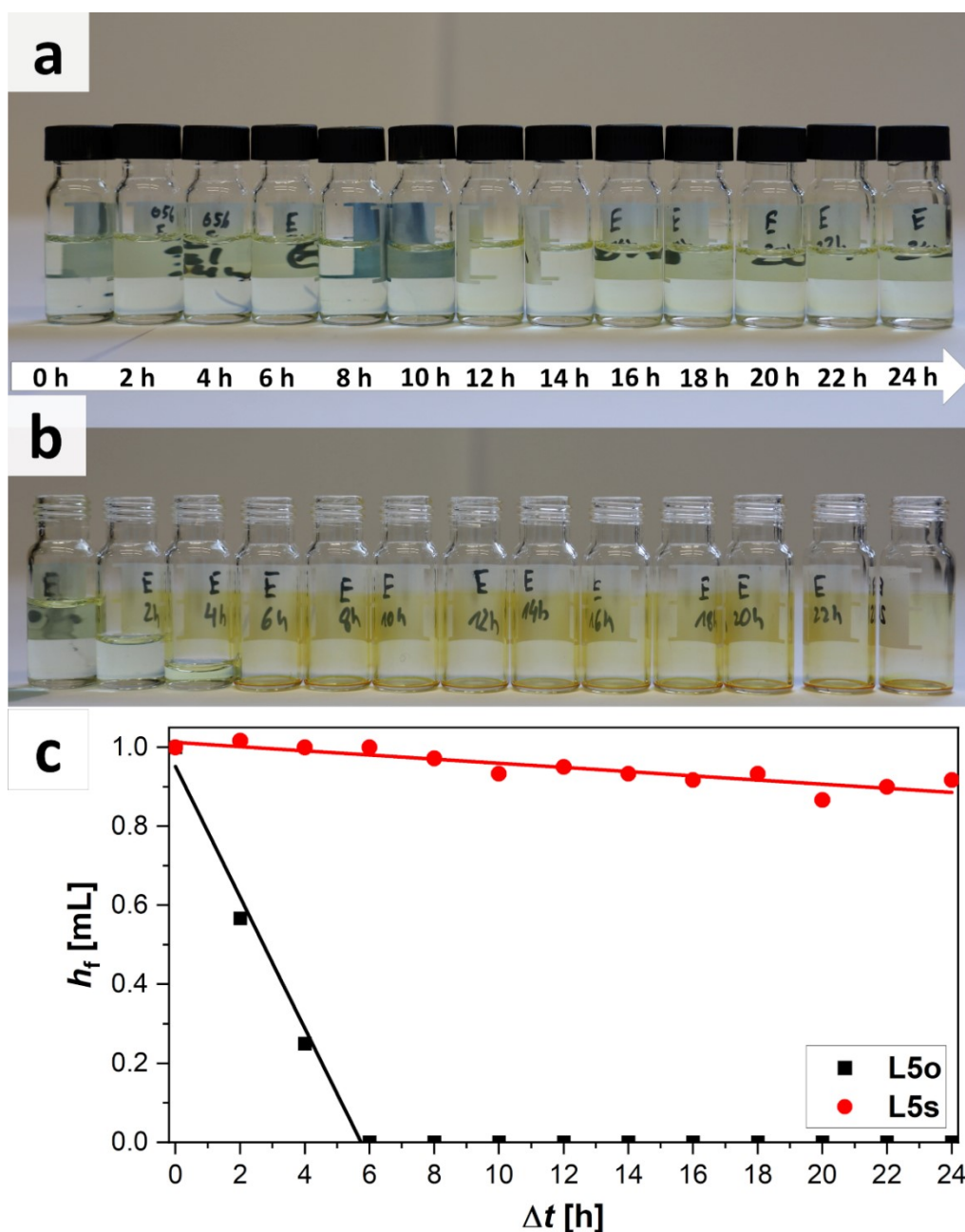


Figure S7: Overview of the results of the evaporation experiment for dichloromethane. a: Picture of sealed vials for different elapsed times since filling (L5s). b: Picture of unsealed vials filled at the same time as the sealed ones (L5o). c: Plot of filling height h_f of sealed (red) and unsealed vials (black), against the elapsed time between evaluation and filling Δt .

The equation for the rate of evaporation of dichloromethane from the unsealed vials **L5o/0h** to **L5o/24h** could be empirically determined from the plot as the equation of a linear fit through the data points:

$$h_f = 0.952 \text{ mL} - 0.166 \frac{\text{mL}}{\text{h}} \cdot \Delta t$$

For the sealed vials **L5o/0h** to **L5o/24h** this equation is:

$$h_f = 1.013 \text{ mL} - 0.005 \frac{\text{mL}}{\text{h}} \cdot \Delta t$$

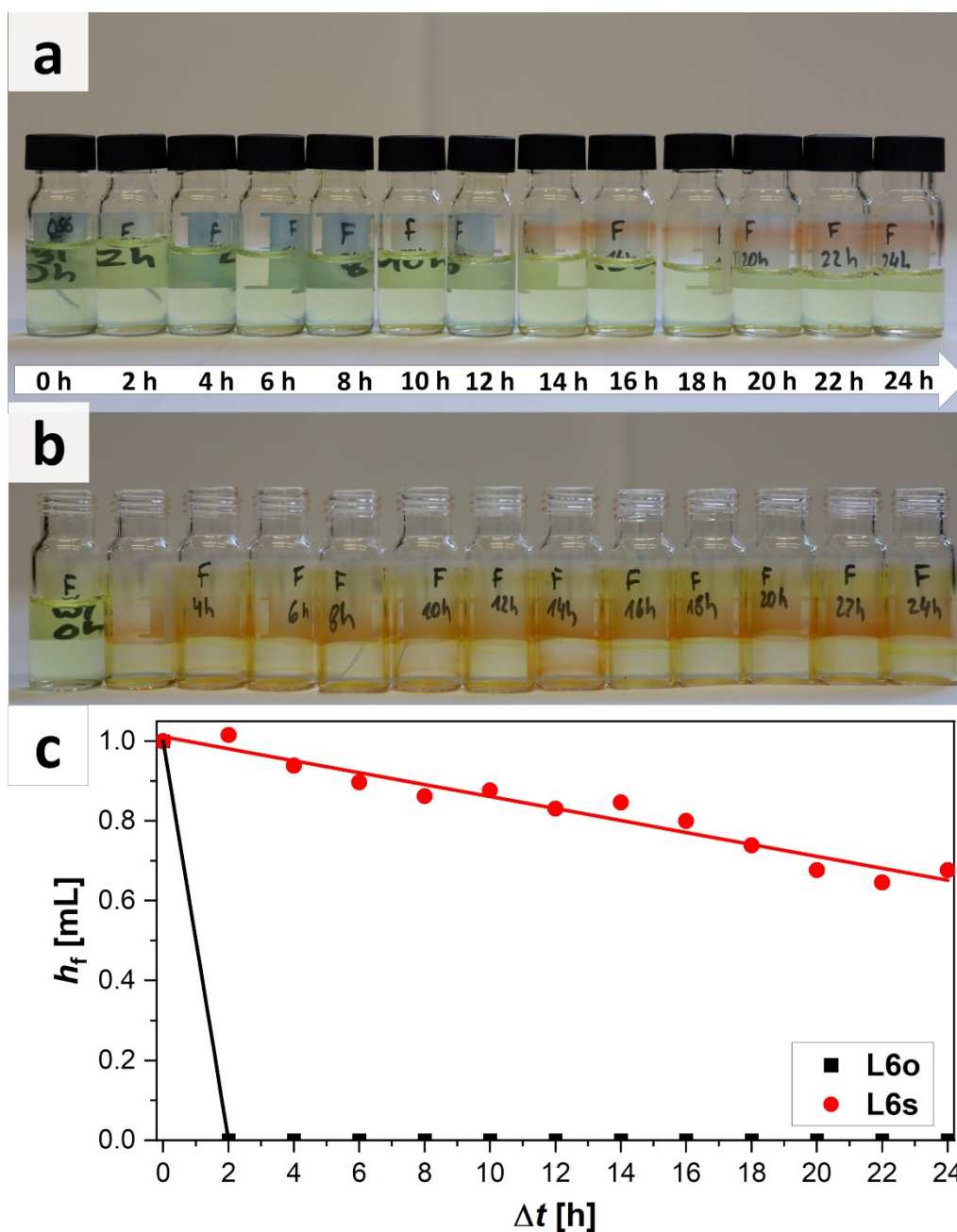


Figure S8: Overview of the results of the evaporation experiment for diethyl ether. a: Picture of sealed vials for different elapsed times since filling (L6s). b: Picture of unsealed vials filled at the same time as the sealed ones (L6o). c: Plot of filling height h_f of sealed (red) and unsealed vials (black), against the elapsed time between evaluation and filling Δt .

The equation for the rate of evaporation of dichloromethane from the unsealed vials **L6o/0h** to **L6o/24h** could be empirically determined from the plot as the equation of a linear fit through the data points:

$$h_f = 1 \text{ mL} - 0.5 \frac{\text{mL}}{\text{h}} \cdot \Delta t$$

For the sealed vials **L6s/0h** to **L6s/24h** this equation is:

$$h_f = 1.011 \text{ mL} - 0.015 \frac{\text{mL}}{\text{h}} \cdot \Delta t$$

NMR measurements for the evaluation of retention

The reaction mixture evaporation tests were conducted (for details see main text). To evaluate the NMR spectra for the change of composition of the samples, the integral of one methylene proton (3') of MMA was compared to the integral of the signal for the *ortho* and *para* protons of anisole (2, 4, 6) which was calibrated to 3. An example for the process is displayed in **Figure S9**.

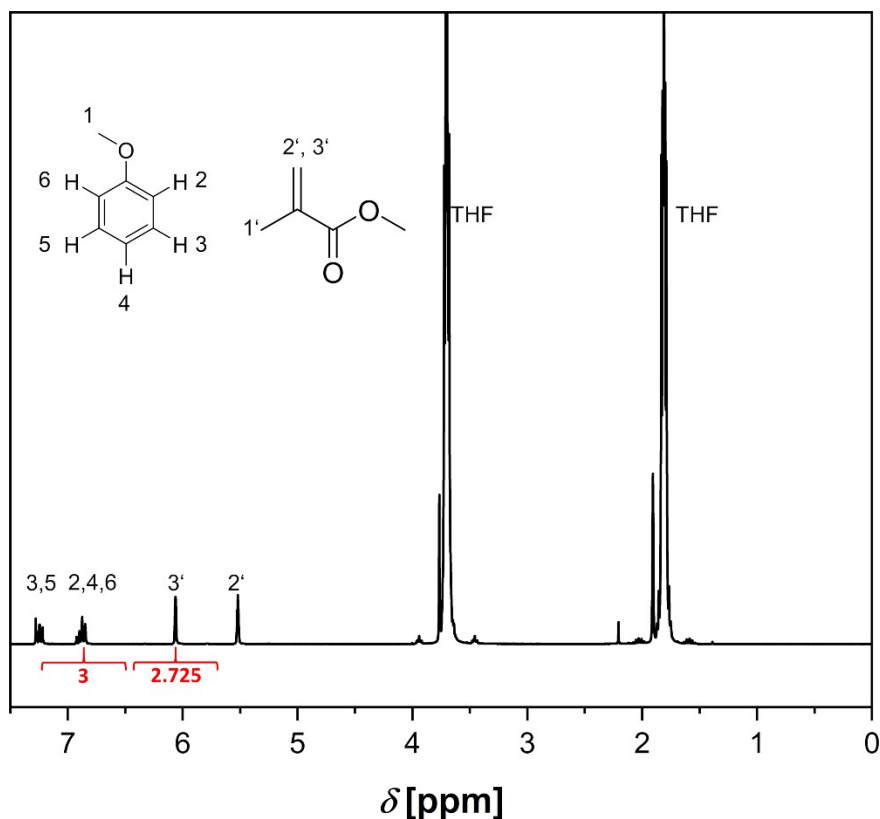


Figure S9: ¹H-NMR spectrum of V1 with peak assignment (300 MHz, CDCl₃).

Furthermore, the other available NMR spectra are represented with the values of the integrals, where applicable, in **Figure S10** to **Figure S14**.

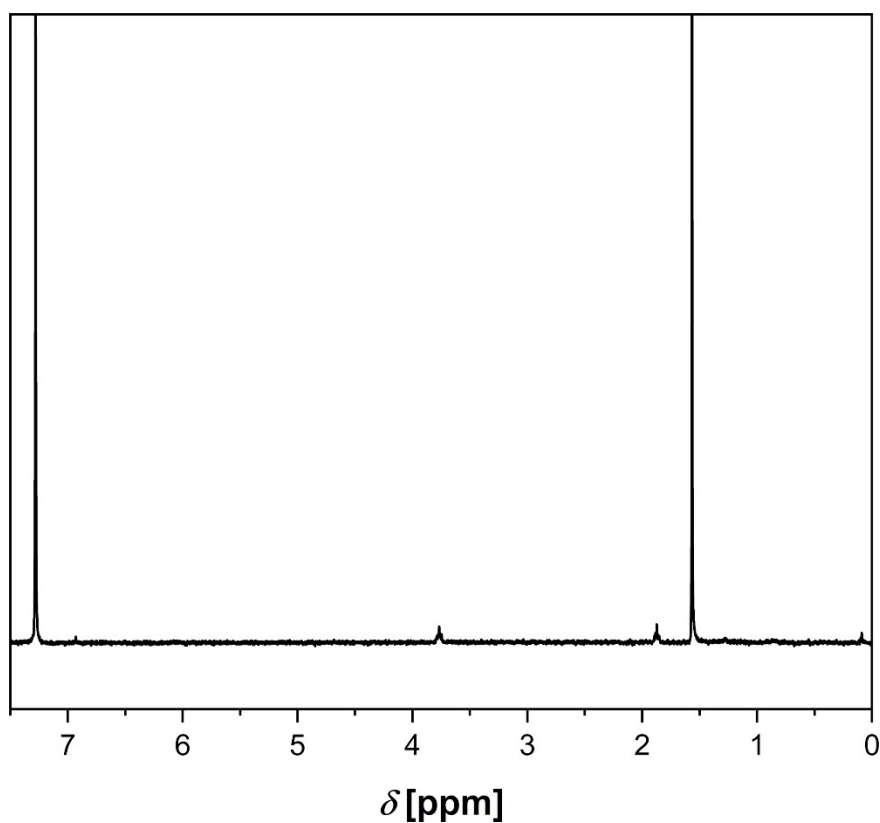


Figure S10: ¹H-NMR spectrum of V3o (300 MHz, CDCl₃).

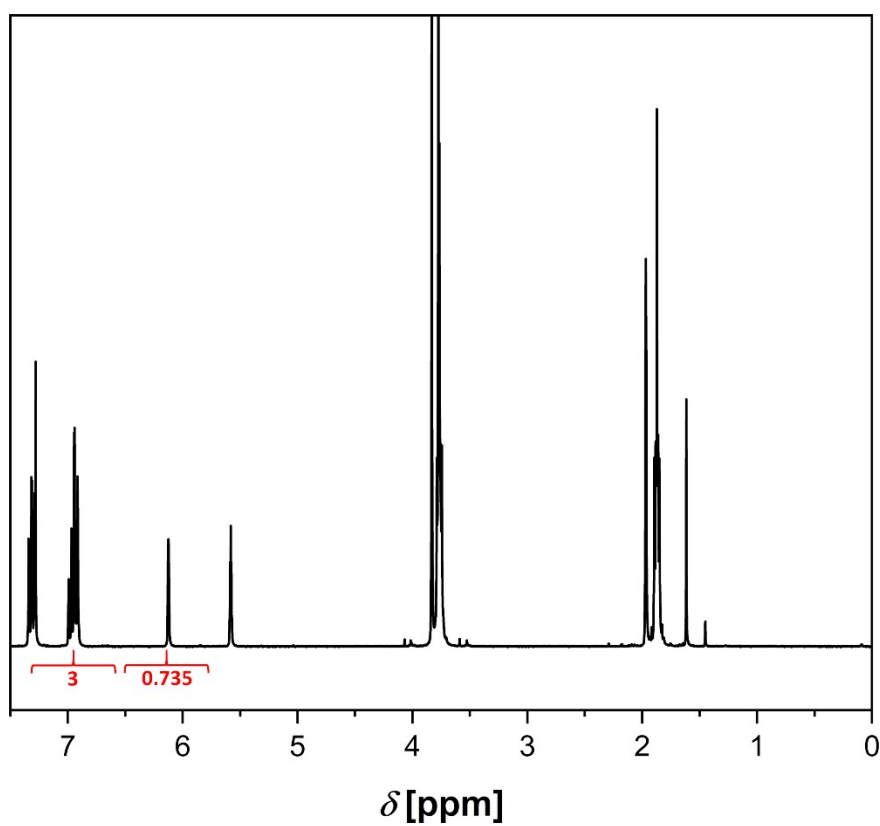


Figure S11: ¹H-NMR spectrum of V2c with integrals for MMA and anisole peak (300 MHz, CDCl₃).

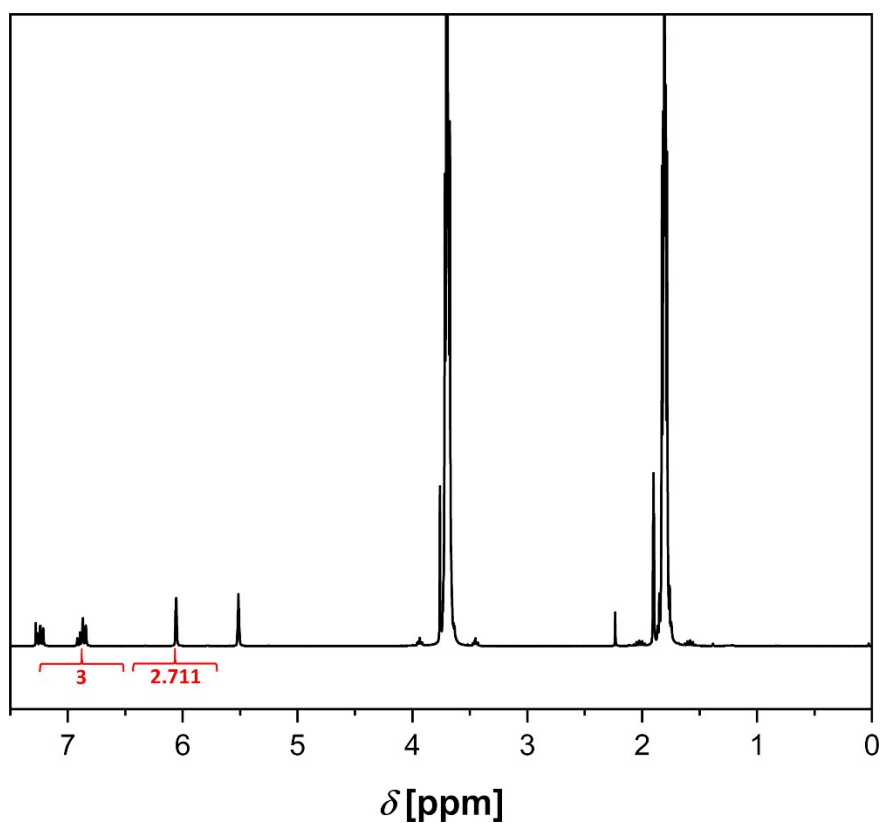


Figure S12: ¹H-NMR spectrum of V3c with integrals for MMA and anisole peak (300 MHz, CDCl₃).

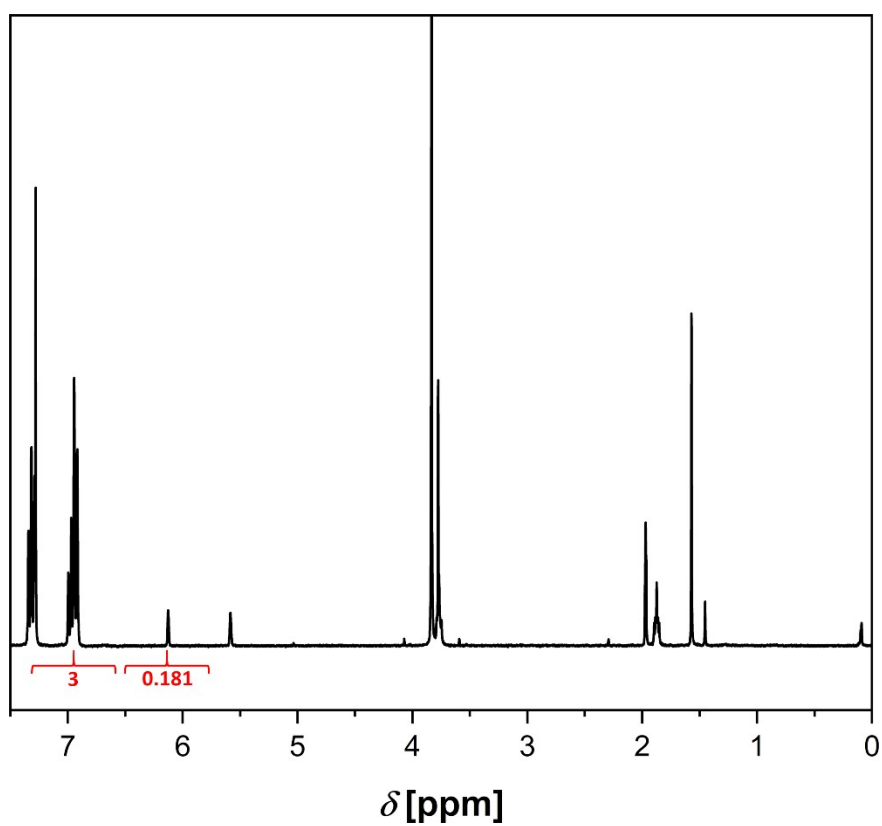


Figure S13: ¹H-NMR spectrum of V2s with integrals for MMA and anisole peak (300 MHz, CDCl₃).

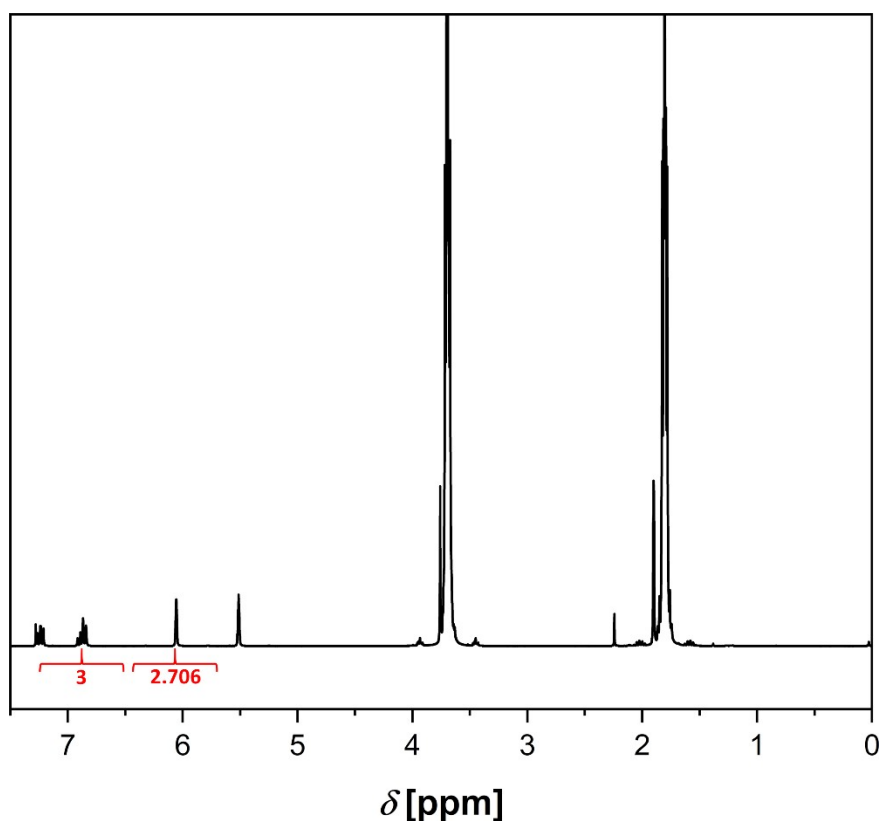


Figure S14: ¹H-NMR spectrum of V3s with integrals for MMA and anisole peak (300 MHz, CDCl₃).

GC measurement for the evaluation of retention

Besides the NMR measurements to evaluate the effect of evaporation on a mixture of methyl methacrylate (MMA) and anisole in tetrahydrofuran (THF), GC experiments were performed as well. The setup of the experiment was the same as for the experiment utilizing NMR spectroscopic measurements and is represented in **Figure S1**. The utilized reaction mixture contained 8.54 mL tetrahydrofuran, 0.4 mL (3.68 mmol) anisole and 1.06 mL (9.95 mmol) of methyl methacrylate. The mixtures were prepared in three different vial options, either unsealed, sealed with a regular septum cap or sealed with a slitted septum cap. A mixture of 75 μL of the reaction solution and 1.3 mL of HPLC grade chloroform was prepared in a 2 mL screw-on vial, capped with a regular rubber septum cap and stored at 5 °C as a reference sample (**V4**). For the evaporation experiment itself, three pairs of samples were built. Each of them included a sample only containing 75 μL of the reaction mixture (**V5**) and one with addition of 1.3 mL of HPLC-grade chloroform (**V6**). The first pair consisted of samples which were stored in unsealed vials (**V5o** and **V6o**). The second pair of samples was kept inside vials capped with a regular rubber septum lid (**V5c** and **V6c**). The last option was to seal the vials with a slitted septum cap (**V5s** and **V6s**). The sample vials were stored in a sample rack next to the reactor block which was heated to 70 °C for 20 h and 15 min. Subsequently, the vials

without prior addition of solvent were topped-up with 1.3 mL of chloroform and three individual GC measurements of each sample were performed. An example spectrum is shown for V4 after normalization of the intensity data in **Figure S15**.

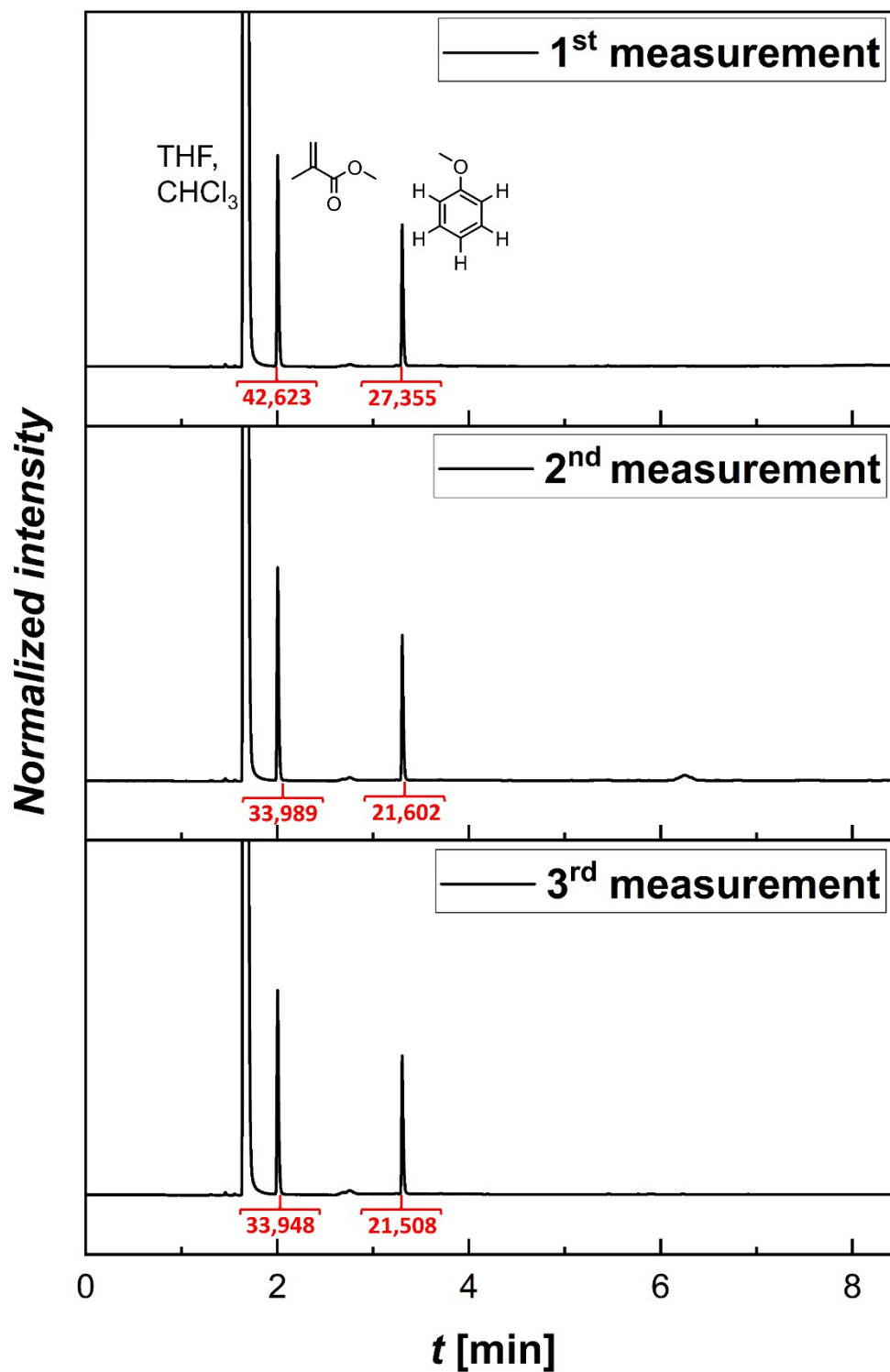


Figure S15: GC spectra of the measurements of V4 with coordinated molecules for the peaks.

There are three visible signals. The first signal at an elution time of 1.9 min is the joined signal of the solvents chloroform and THF. Subsequently, the MMA signal follows at ca. 2 min and the one of anisole at ca. 3.3 min. The ratio of the signal of MMA to anisole was calculated and the average of the ratio of three measurements was used to calculate the ratio retention in comparison to the reference sample. The averages of the areas of MMA A_{MMA}^- and anisole A_{An}^- as well as the ratio of $\frac{A_{MMA}^-}{A_{An}^-}$ and, where applicable the ratio retention RR in comparison to **V4**, are represented in **Table S1**.

Table S1: Overview of the outcome of the GC measurements after the evaporation experiment.

Sample condition	Experiment	A_{MMA}^-	A_{An}^-	$\frac{A_{MMA}^-}{A_{An}^-}$	RR [%]
Reference sample	V4	40,770	26,150	1.560	100
Open vial, no chloroform addition	V5o	0	0	0	0
Open vial, chloroform addition	V6o	241,949	181,512	1.339	85
Regular septum lid, no chloroform addition	V5c	4,689	2,925	0.298	19
Regular septum lid, chloroform addition	V6c	35,360	22,860	1.551	99
Slit septum lid, no chloroform addition	V5s	4,774	15,565	0.306	20
Slit septum lid, chloroform addition	V6s	34,751	22,296	1.548	99

It is obvious that the RR is worst for the non-sealed vial without added solvent **V5o** as total evaporation occurred, which is also visible in **Figure S16**. In general, the options with pre-added solvent performed better compared to the respective options without added solvent, as expected. For the prefilled solvents, the worst RR was achieved for **V6o** (**Figure S17**). Again, occurring evaporation is the reason for this as most of the solution evaporated in the 20 h 15 min and the remaining solution required to be transferred to a 300 μL vial insert to measure it. Hence, the areas of MMA and anisole are larger as most of the solvents (THF and chloroform) evaporated and the solution concentration changed. For both lidded options with pre-added

chloroform (V6c and V6s), the *RR* was the same and very close to 100%. Hence, both options are equally useful for the desired context. The trends of the results of this test are in accordance with the tests conducted under NMR-sampling conditions. The zoomed in, normalized GC spectra of all measurements are presented in the following **Figure S16** to **Figure S21**.

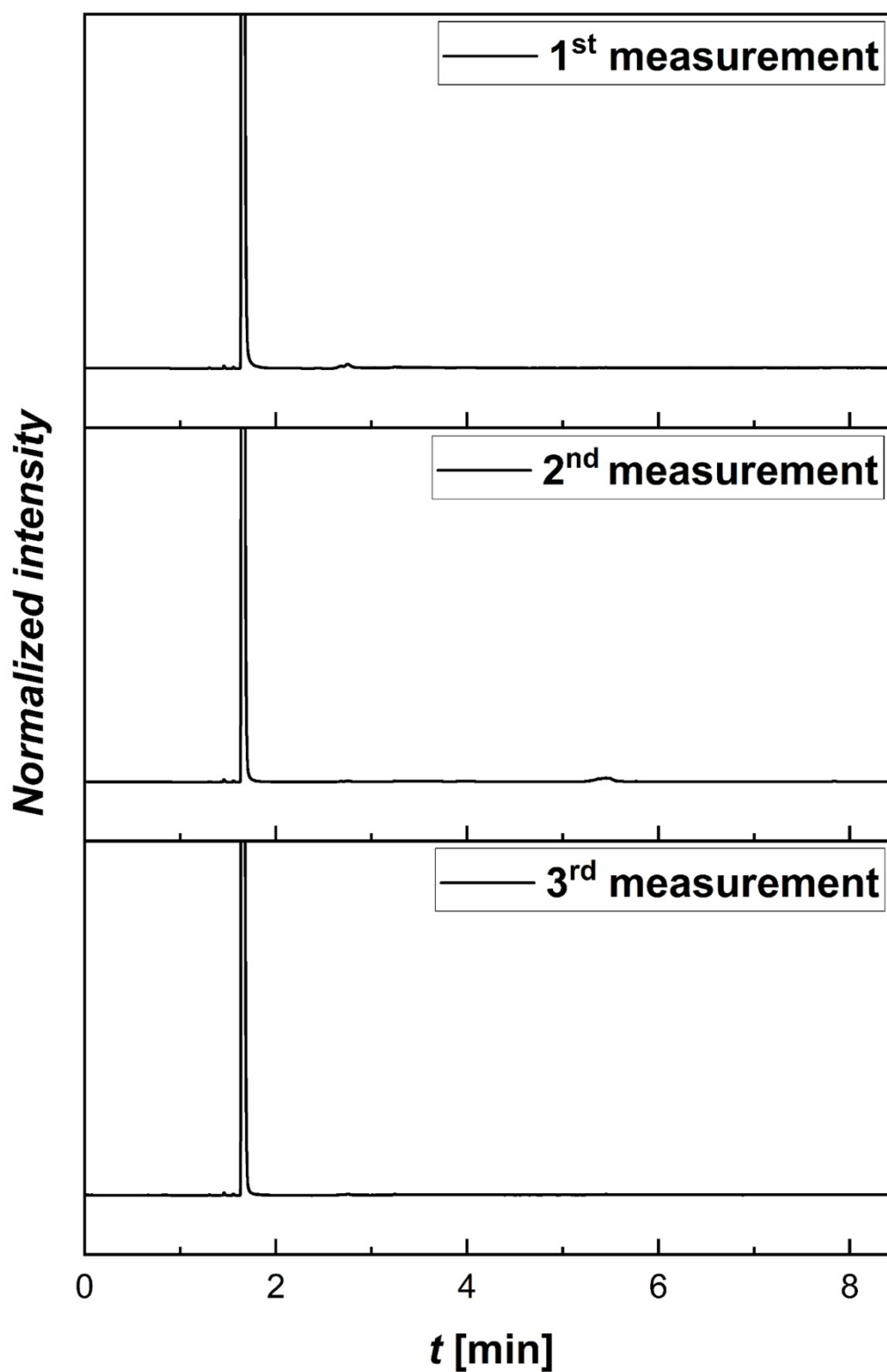


Figure S16: Normalized spectra of the GC measurements of V5o.

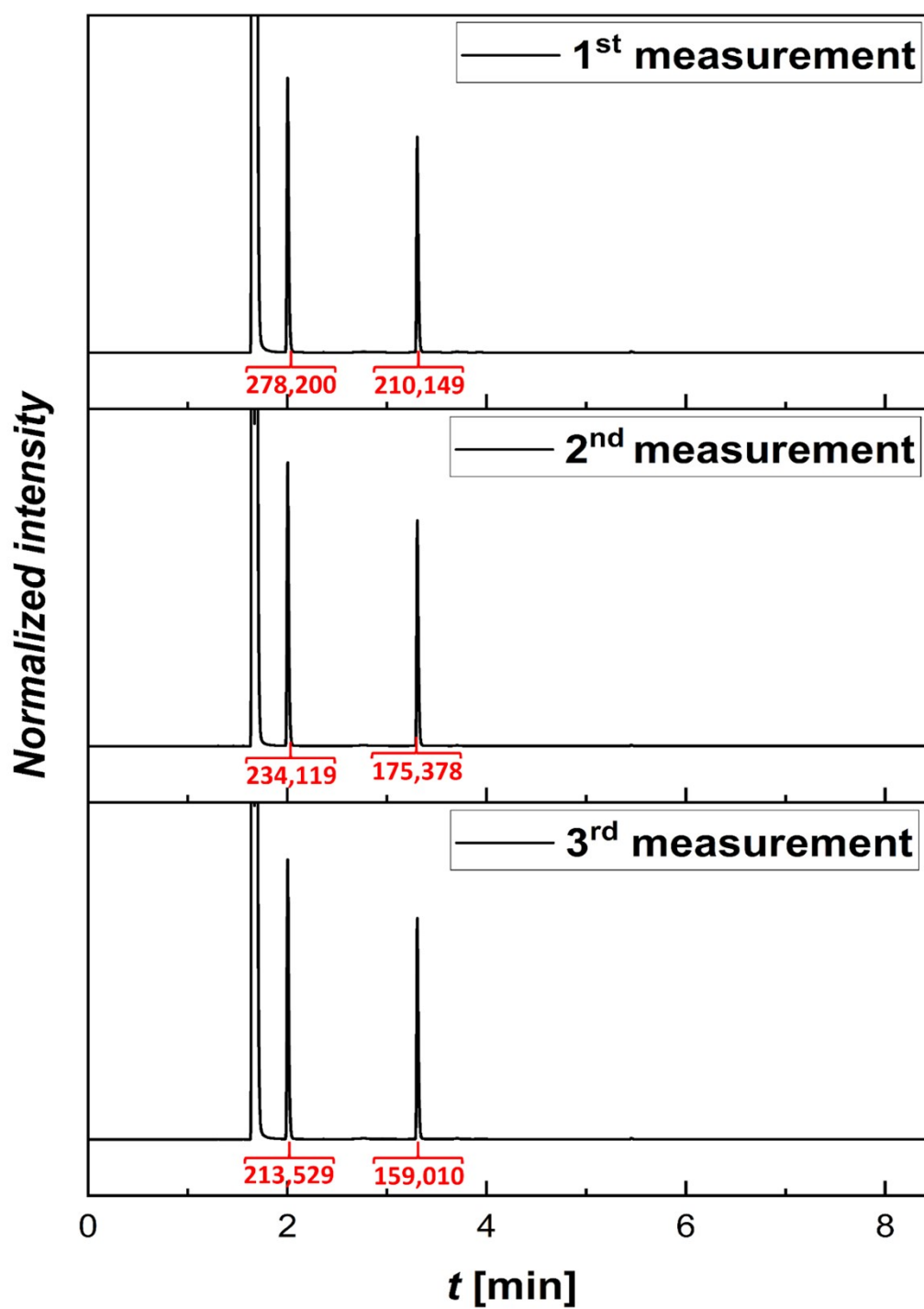


Figure S17: Normalized spectra of the GC measurements of V60.

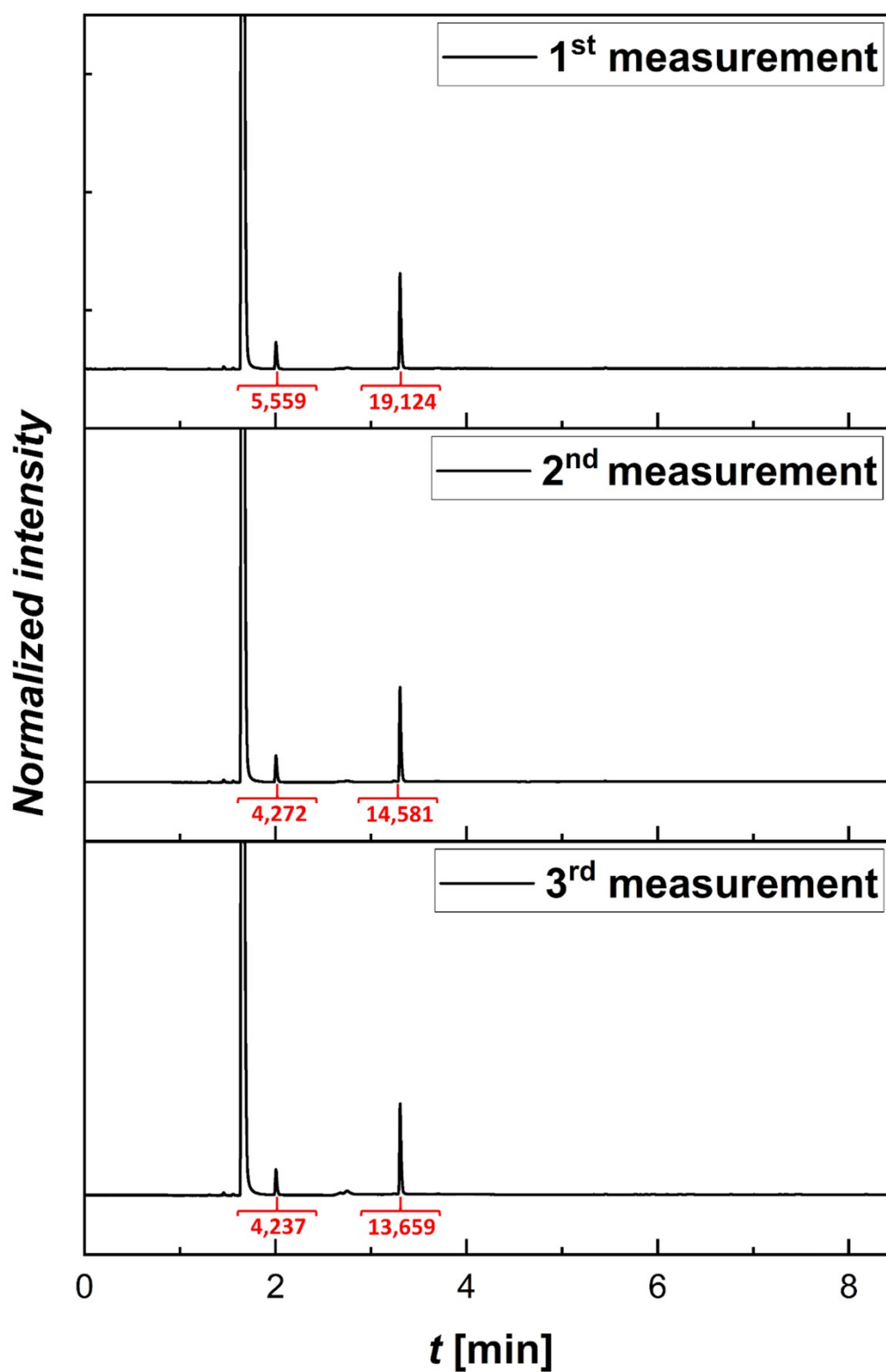


Figure S18: Normalized spectra of the GC measurements of V5c.

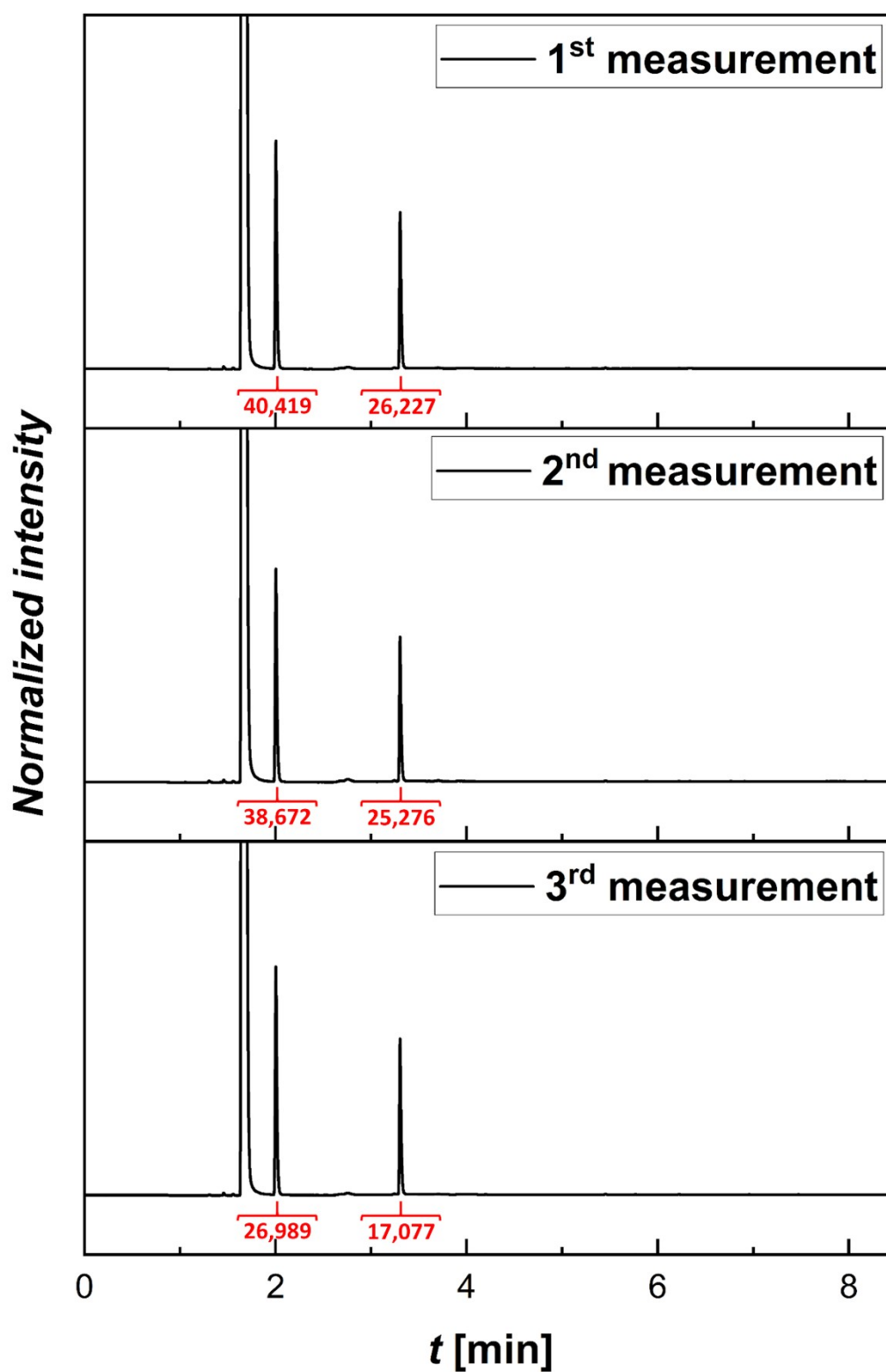


Figure S19: Normalized spectra of the GC measurements of V6c.

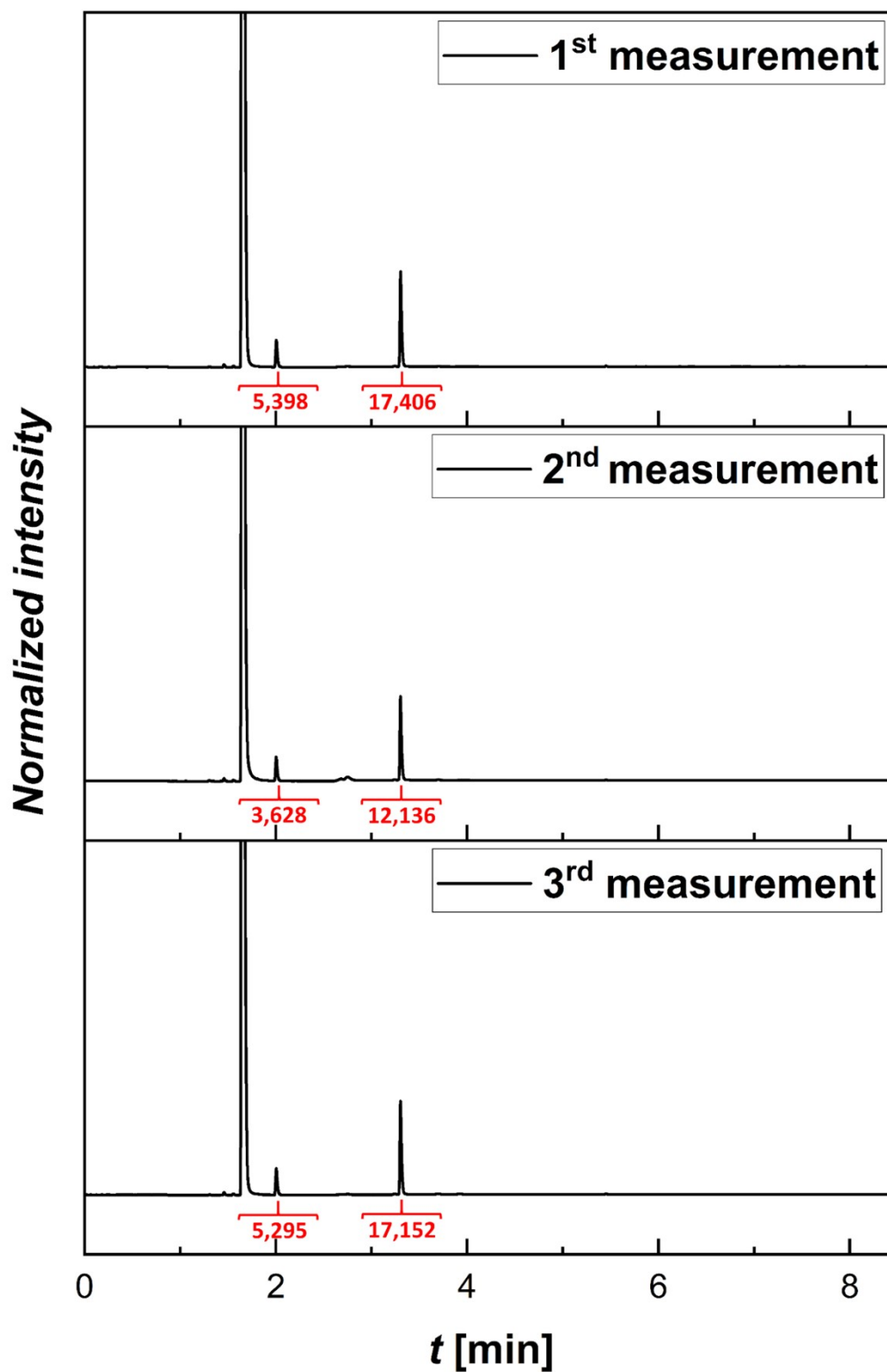


Figure S20: Normalized spectra of the GC measurements of V5s.

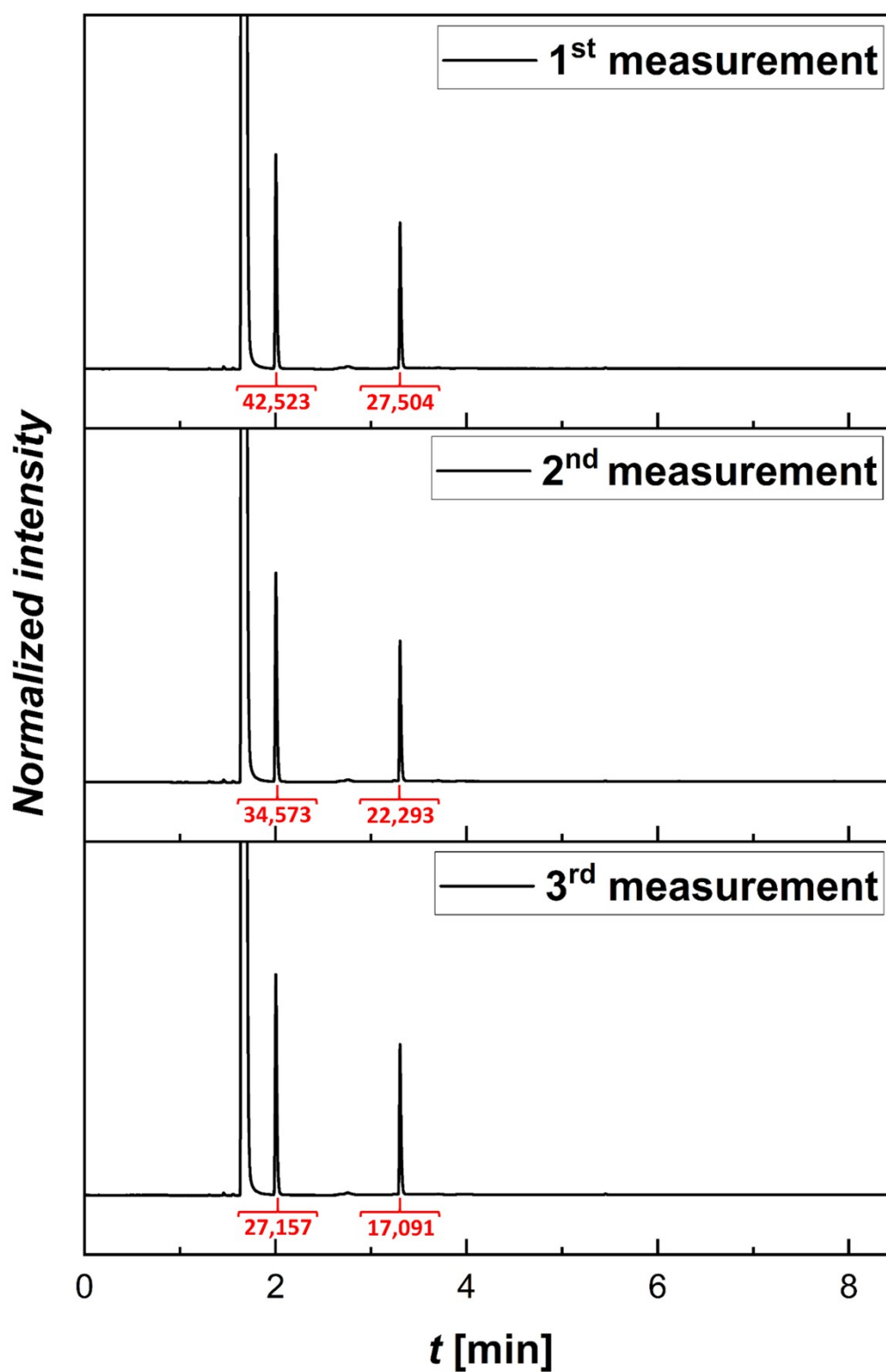


Figure S21: Normalized spectra of the GC measurements of V6s.

Dependence of evaporation on number of septum punctures

The evaporation experiments were conducted with two different solvents (methanol = **P1** and dichloromethane = **P2**) and different numbers of septum punctures (for details see main text). The overview of the filling heights as well as the lids of the vials after 24 h for both lid types (regular rubber septum lid = rl, slit septum lid = sl) are presented in **Figure S22** and **Figure S23**.

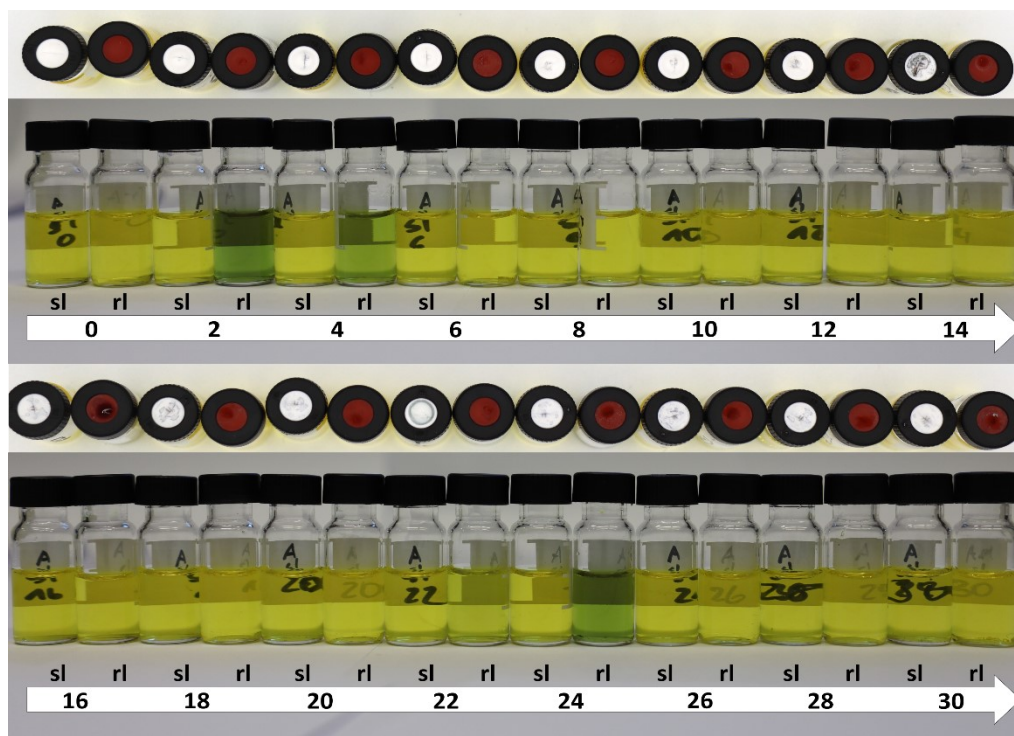


Figure S22: Overview of the lids and filling levels for all vials either with regular rubber septum lid (rl) or slit septum lid (sl) and different numbers of punctures through the septum (0 to 30) utilized for experiment **P1** (evaporation of methanol) after 24 h.

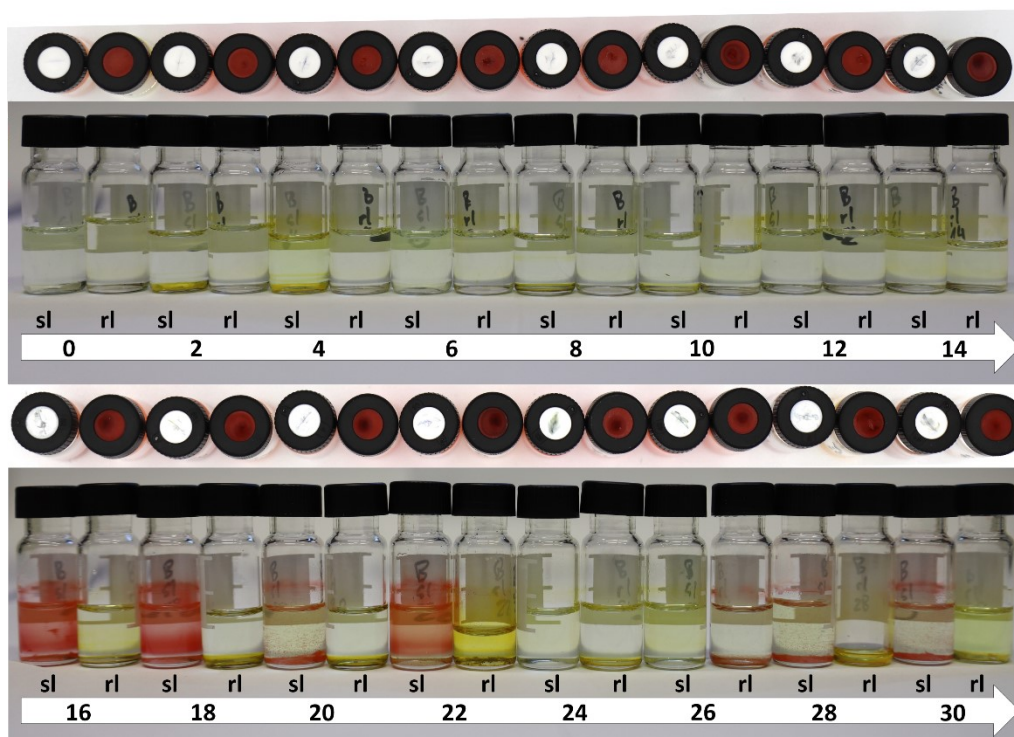


Figure S23: Overview of the lids and filling levels for all vials either with regular rubber septum lid (rl) or slit septum lid (sl) and different numbers of punctures through the septum (0 to 30) utilized for experiment **P2** (evaporation of dichloromethane) after 24 h.

Downholding module design

The downholding module was designed to fulfil the task of keeping the vials in place during the retraction of the needle. However, there is one more feature which helps with sampling inside machines with less precision in the placing of the injection needles. As obvious from the following Figures, the module has chimneys on the top side. For the larger chimneys they consist of a 11.5 mm hole with 1.5 mm edge and an 82-degree slope, ending in a hole of 6 mm diameter, which is the diameter of the septum part in the lids of the sampling vials. In this way, the needle, which can be bend at times, gets directed to the septum part of the vial and impingement of the needle at the side parts of the vial lids is avoided. Additional to the design files which are also part of the ESI (DSI1 to DSI3), some perspectives of the module are represented in the following **Figure S24** to **Figure S28**.

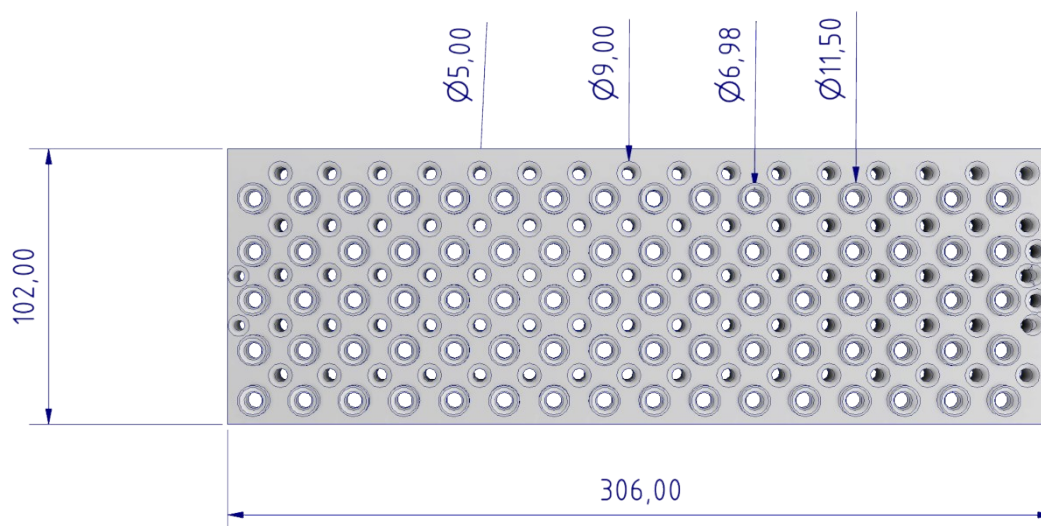


Figure S24: Top view of the module with dimensions for the length, width and diameters of the chimneys in the top (all dimensions are provided in mm).

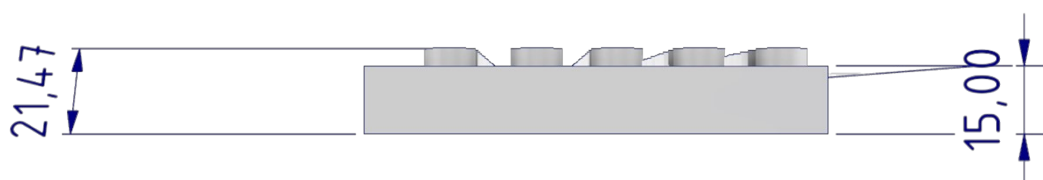


Figure S25: Side view of the module with dimension for the height of the module body as well as the body with chimneys (all dimensions are provided in mm).

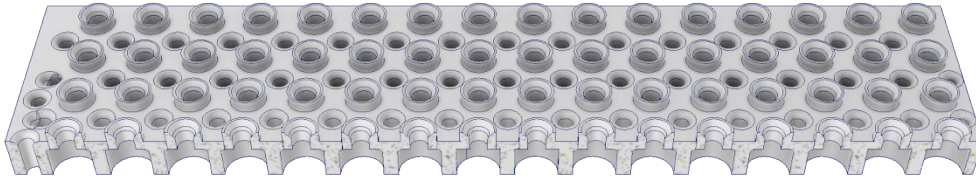


Figure S26: Orthogonal cut view of the module.

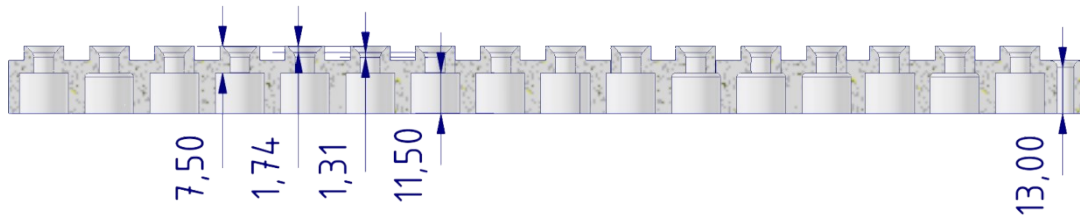


Figure S27: Side cut view of the module with dimensions for the chimneys (all dimensions are provided in mm).

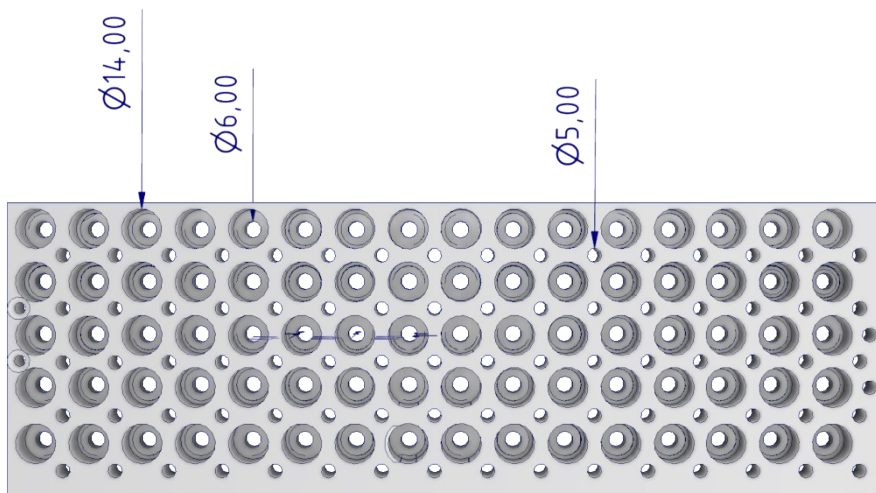


Figure S28: Bottom view of the module with dimensions for the diameters of the chimneys (all dimensions are provided in mm).