Direct gravimetric sensing of GBL by Molecular Recognition Process in Organic Cage Compounds

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1. General remarks

All analytes were used in highest available quality (analytical grade) and without further purification. All reagents were used as purchased in highest available grades. Solvents were desiccated if necessary by standard methods. Nitrogen which was used in the screening experiments was used in a purity of 99.998%.

Melting points (not corrected) were measured with a Büchi Melting Point B-545. IR Spectra were recorded as KBr-pellets on a Perkin Elmer Spectrum 2000 FT-IR spectrometer. NMR spectra were recorded on a Bruker DRX 400 at 278 K at 400 MHz (^{1}H) and 100 MHz (^{13}C) or on a Bruker DRX 500 at 295 K or 340 K at 500 MHz (^{1}H) and 125 MHz (^{13}C). MALDI-TOF. Elemental analyses were determined with a Elementar Vario *EL*. THF was dried over aluminium oxide with the solvent purification station MB SPS-800.Compounds **1**, **M1**, **2** and **M2** were synthesized as published before.[S1]

The experimental primary data were processed with Matlab 7.11.0 (R2010b) (The MathWorks Inc., Natick, Massachusetts, USA).

For the preparation of the diagrams OriginPro 8 SR0 (OriginLab Corporation, Northampton, Massachusetts, USA) were used.

HFF-QCMs with a fundamental frequency of 195 MHz were used (KVG Quartz Crystal Technology GmbH, Neckarbischofsheim, Germany. Type: XA 1600).

The QCM is excited using an aperiodic oscillator circuit and oscillates with its specific load resonance frequency.[S2]Frequency counting is performed using a FPGA (field programmable gate array) which allows asynchronous 28-bit counting with an accuracy of ±0.5 Hz.

2. Synthesis and Characterization of Cage Compounds

Synthesis of cage 3: Cage compound **2** (99 mg, 0.04 mmol), paraformaldehyde (191 mg, 6.3 mmol) and sodium borohydride (110 mg, 2.9 mmol) were suspended under argon in dry THF (17 mL). TFA (5 mL, 64.9 mmol) was slowly added in a period of one hour at room temperature. The mixture was stirred 24 h at room temperature, cooled to 0 °C and a 25% aqueous sodium hydroxide solution (30 mL), brine (20 mL) and dichloromethane (30 mL) were added. The layers were separated and the aqueous phase was extracted twice with dichloromethane (30 mL). The combined organic extract was dried with sodium sulphate and solvent was removed by rotary evaporation. The residue was dissolved in ethyl acetate (3 mL), and methanol (3 mL) was added. The precipitate was collected by filtration and after drying in vacuum 65 mg (61%) of **3** was obtained as a white solid. M.p. 400 °C; ^{1}H NMR (400 MHz, THF-d_8): δ = 9.32 ppm (s, 6H, -O*H*), 7.20 (d, ^{3}J = 8.1 Hz, 12H, triptycenyl-4,5,16-*H*), 7.07 (d, ^{3}J = 2.2 Hz, 12H, triptycenyl-1,8,13-*H*), 6.93 (s, 12H, salicyl-*H*), 6.59 (dd, ^{3}J = 8.1 Hz, ^{4}J = 2.3 Hz, 12H, triptycenyl-3,6,15-*H*), 5.20 (s, 4H, triptycenyl-10-*H*), 5.17 (s, 4H, triptycenyl-9-*H*), 4.37 (s, 24H, -Ar-CH_2-NMe-Ar), 2.77 (s, 36H, -NCH_3), 1.04 (s, 54H, -C(CH_3)$_3$) ppm; ^{13}C NMR (100 MHz, THF-d_8) δ = 3419 (m), 2953 (s), 2903 (w), 2866 (w), 2806 (w), 1609 (s), 1583 (m), 1482 (s), 1392 (w), 1363 (m), 1307 (w), 1244 (w), 1210 (m), 1115 (w), 1079 (m), 1006 (w), 950 (m), 876 (m), 822 (m), 788 (m), 729 (w), 660 (w), 587 (m), 512 (w), 484 (w) cm^{-1}; Elemental analysis calcd. (%) for $C_{164}H_{176}N_{12}O_6 \cdot 2\ H_2O$: C 80.49, H 7.41, N 6.87; found: C 80.27, H 7.17, N 6.82.

Synthesis of cage compound 4: To a suspension of Methoxy imine cage compound (120 mg, 0.05 mmol) in a mixture of 8 mL methanol and 6 mL dichloromethane, sodium borohydride (500 mg, 13.2 mmol) was added under argon and the mixture was stirred for one day at room temperature. 10 mL water was added, the layers were separated and the aqueous phase was extracted three times with 10 mL dichloromethane. The combined organic extract was dried with sodium sulphate and solvent was removed in vacuum to give after drying in high vacuum 120 mg (98%) of **4** as an off-white solid. M.p. 400°C; ^{1}H NMR (500 MHz, THF-d_8): δ = 7.29 (s, 12H, salicyl-*H*), 7.00 (d, ^{3}J = 7.9 Hz, 12H, triptycenyl-4,5,16-*H*), 6.60 (d, ^{4}J = 2.0 Hz, 12H, triptycenyl-1,8,13-*H*), 6.26 (dd, ^{3}J = 7.9 Hz, ^{4}J = 2.1 Hz, 12H, triptycenyl-3,6,15-*H*), 4.99 (s, 4H, triptycenyl-10-*H*), 4.89 (s, 4H, triptycenyl-9-*H*), 4.76 (t, ^{3}J = 5.4 Hz, 12H, Ar-CH$_2$N*H*-Ar), 4.25 (d, ^{3}J = 5.1 Hz, 24H, Ar-CH_2NH-Ar), 3.78 (s, 18H, -OCH_3), 1.15 (s, 54H, -C(CH_3)$_3$) ppm; ^{13}C NMR (125 MHz, THF-d_8): δ = 155.4, 147.9, 147.4, 147.3, 137.2, 133.2, 126.6, 123.5, 109.3, 109.2, 62.1, 56.7, 52.7, 44.7, 35.1, 32.0 ppm; IR (KBr): $\tilde{\nu}$ = 2951 (s),

2867 (w), 1611 (s), 1482 (s), 1362 (w), 1323 (w), 1243 (w), 1201 (w), 1152 (w), 1118 (w), 1009 (m), 933 (w), 880 (w), 835 (w), 796 (w), 776 (w), 579 (m), 512 (w) cm^{-1}; Elemental analysis calcd. (%) for $C_{158}H_{164}N_{12}O_6 \cdot 0.5\ CH_2Cl_2$: C 80.34, H 7.02, N 7.09; found: C 80.68, H 7.03, N 6.70.

Synthesis of cage 5: Cage compound **4** (120 mg, 0.05 mmol), paraformaldehyde (236 mg, 7.8 mmol) and sodium borohydride (130 mg, 3.4 mmol) were suspended under argon in dry THF (21 mL). TFA (5.7 mL, 74.0 mmol) was slowly added in a period of one hour at room temperature. The mixture was stirred 24 h at room temperature, cooled to 0 °C and a 25% aqueous sodium hydroxide solution (45 mL), brine (30 mL) and dichloromethane (45 mL) were added. The layers were separated and the aqueous phase was extracted twice with dichloromethane (45 mL). The combined organic extract was dried with sodium sulphate and solvent was removed by rotary evaporation. The residue was suspended in ethyl acetate (8 mL), collected by filtration and gave after drying in vacuum 70 mg (57%) of **5** as a white solid was obtained. M.p. 251 °C; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.21 ppm (d, ^3J = 8.1 Hz, 12H, triptycenyl-4,5,16-*H*), 7.18 (s, 12H, salicyl-*H*), 6.88 (s, 12H, triptycenyl-1,8,13-*H*), 6.44 (dd, ^3J = 7.9 Hz, ^3J = 1.7 Hz, 12H, triptycenyl-3,6,15-*H*), 5.17 (s, 4H, triptycenyl-10-*H*), 5.02 (s, 4H, triptycenyl-9-*H*), 4.43 (s, 24H, -Ar-CH_2-NMe-Ar), 3.71 (s, 18H, -OCH_3), 2.77 (s, 36H, -NCH_3), 1.11 (s, 54H, -C(CH_3)$_3$) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 154.6 ppm, 149.0, 147.5, 146.9, 136.2, 132.0, 124.7, 123.4, 110.4, 108.9, 61.4, 56.0, 53.1, 51.3, 38.5, 34.7, 31.7 ppm; IR (KBr): $\tilde{\nu}$ = 3436 (m), 2951 (s), 2903 (w), 2866 (w), 2825 (w), 1611 (s), 1580 (m), 1482 (s), 1431 (w), 1393 (w), 1362 (m), 1300 (w), 1201 (m), 1112 (w), 1094 (w), 1081 (w), 1011 (m), 953 (m), 882 (w), 825 (w), 809 (w), 785 (w), 655 (w), 586 (w), 514 (w), 484 (w) cm^{-1}; Elemental analysis calcd. (%) for $C_{170}H_{188}N_{12}O_6 \cdot 5\ H_2O$: C 78.97, H 7.72, N 6.50; found: C 78.97, H 7.42, N 6.53.

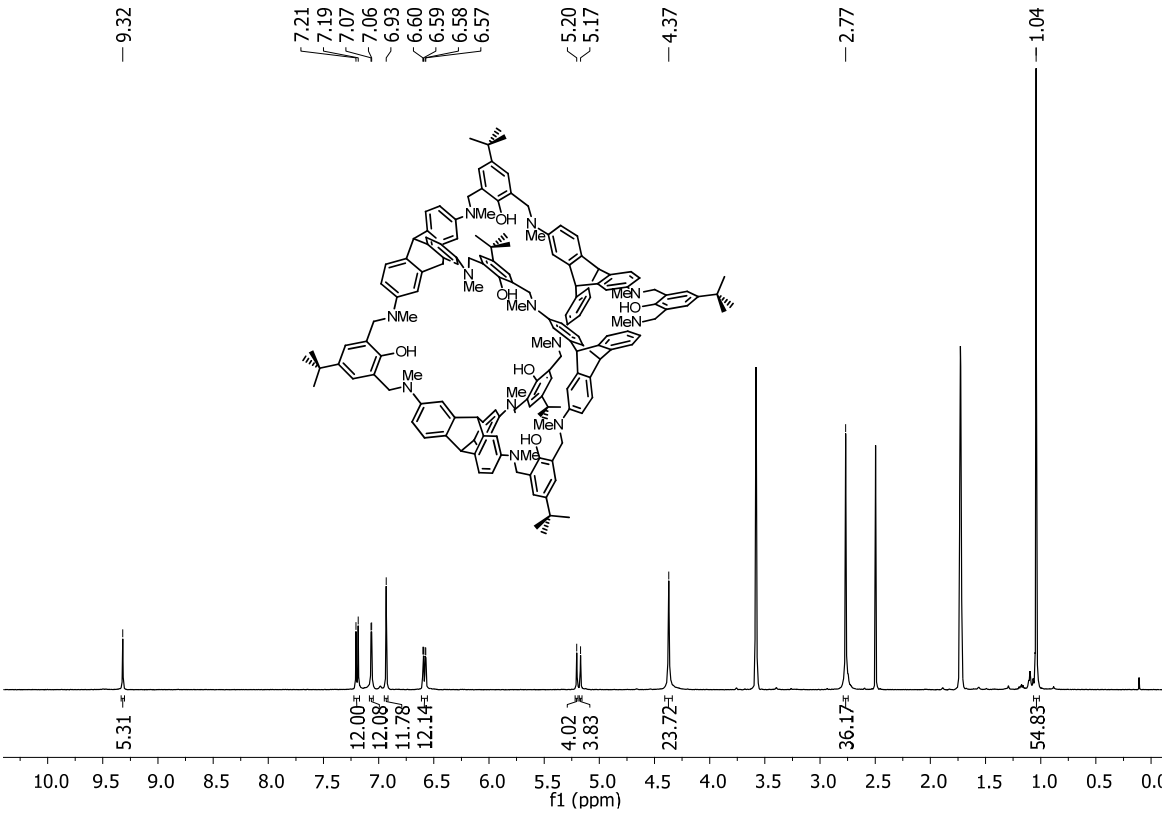


Figure S1: ^{1}H NMR spectrum (400 MHz, THF-d_8) of compound **3**.

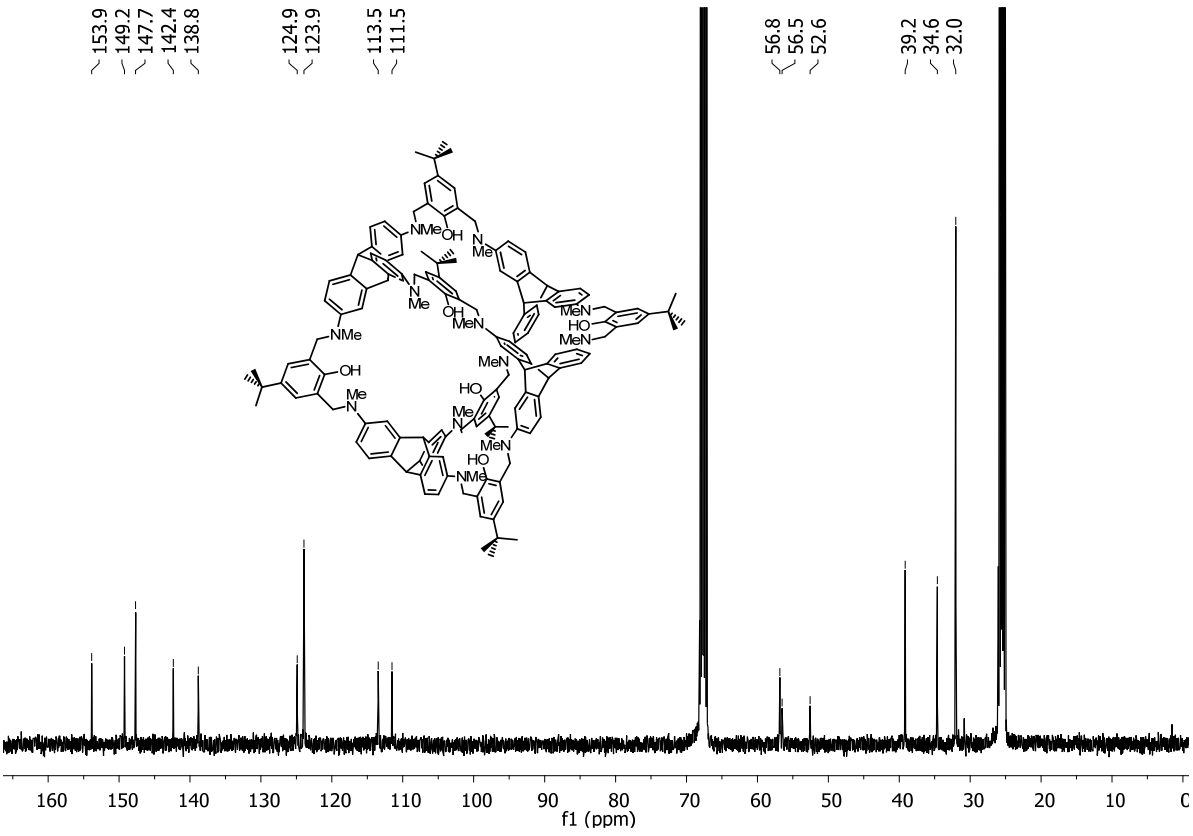


Figure S2: ^{13}C NMR spectrum (100 MHz, THF-d_8) of compound **3**.

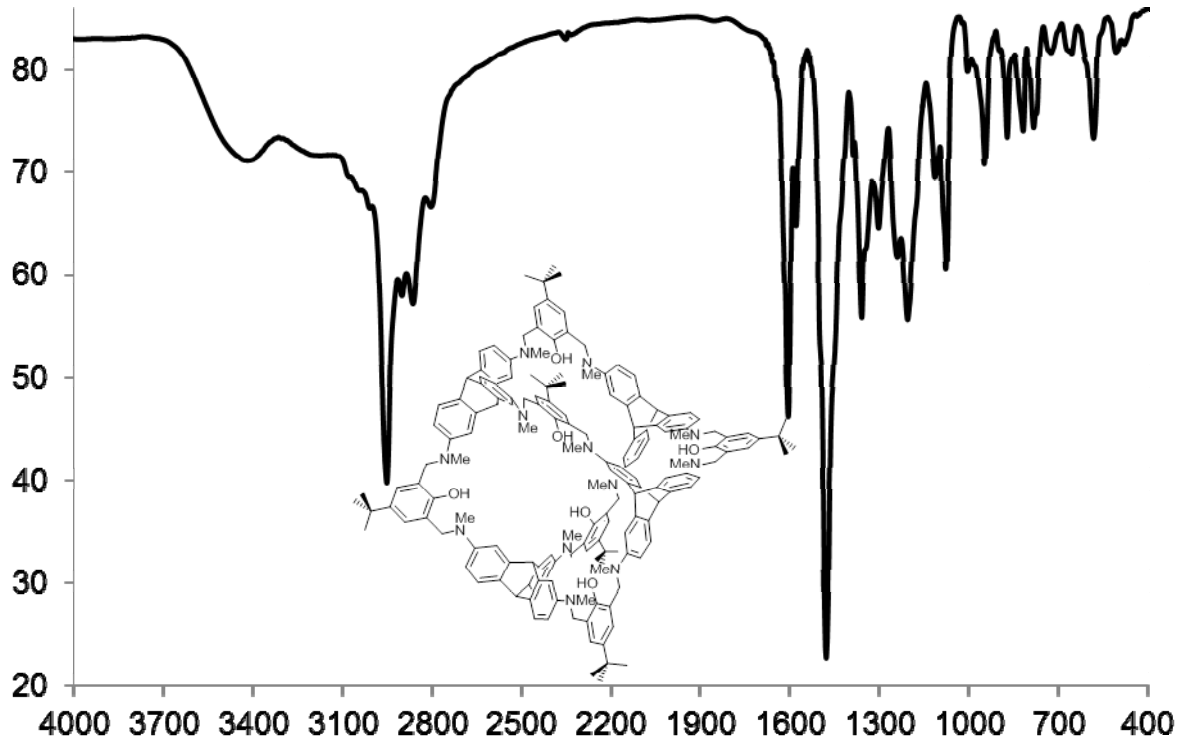


Figure S3: IR spectrum of compound **3**.

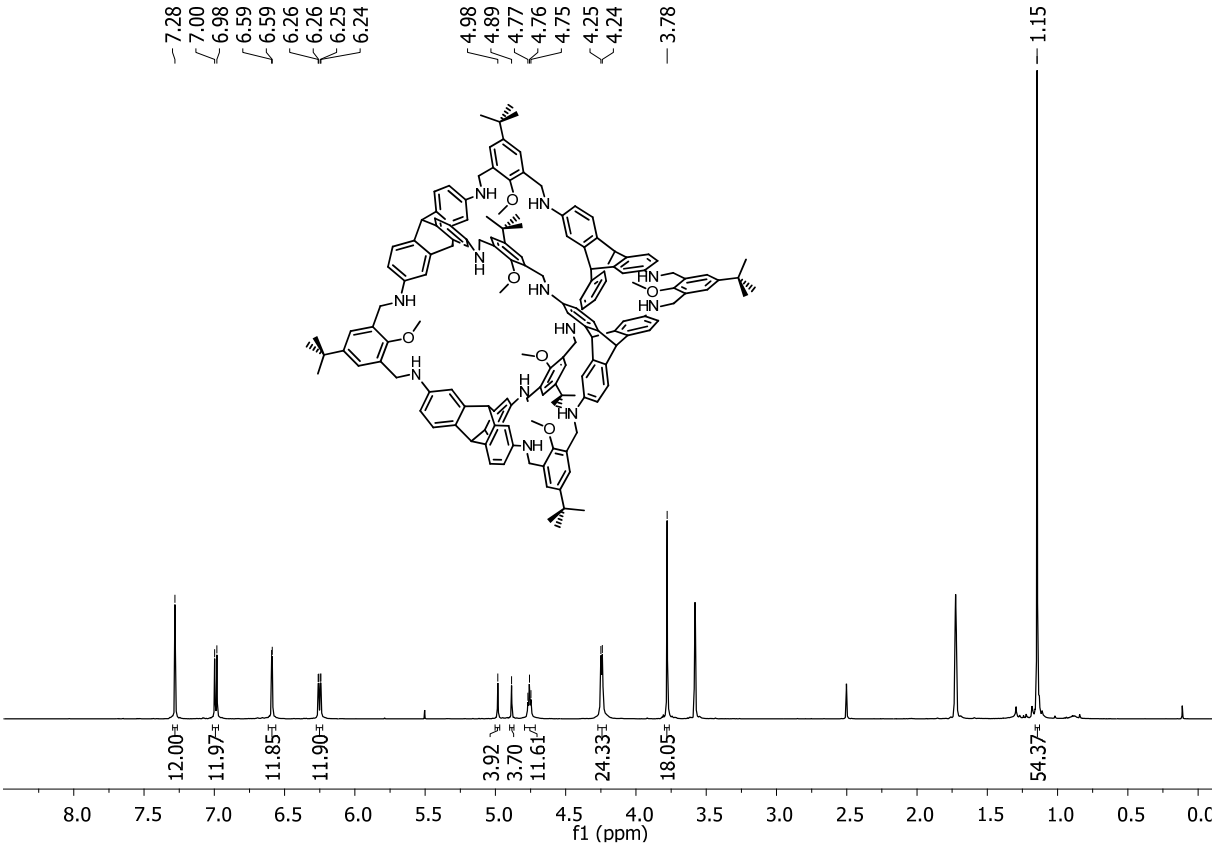


Figure S4: ^{1}H NMR spectrum (500 MHz, THF-d_8) of compound **4**.

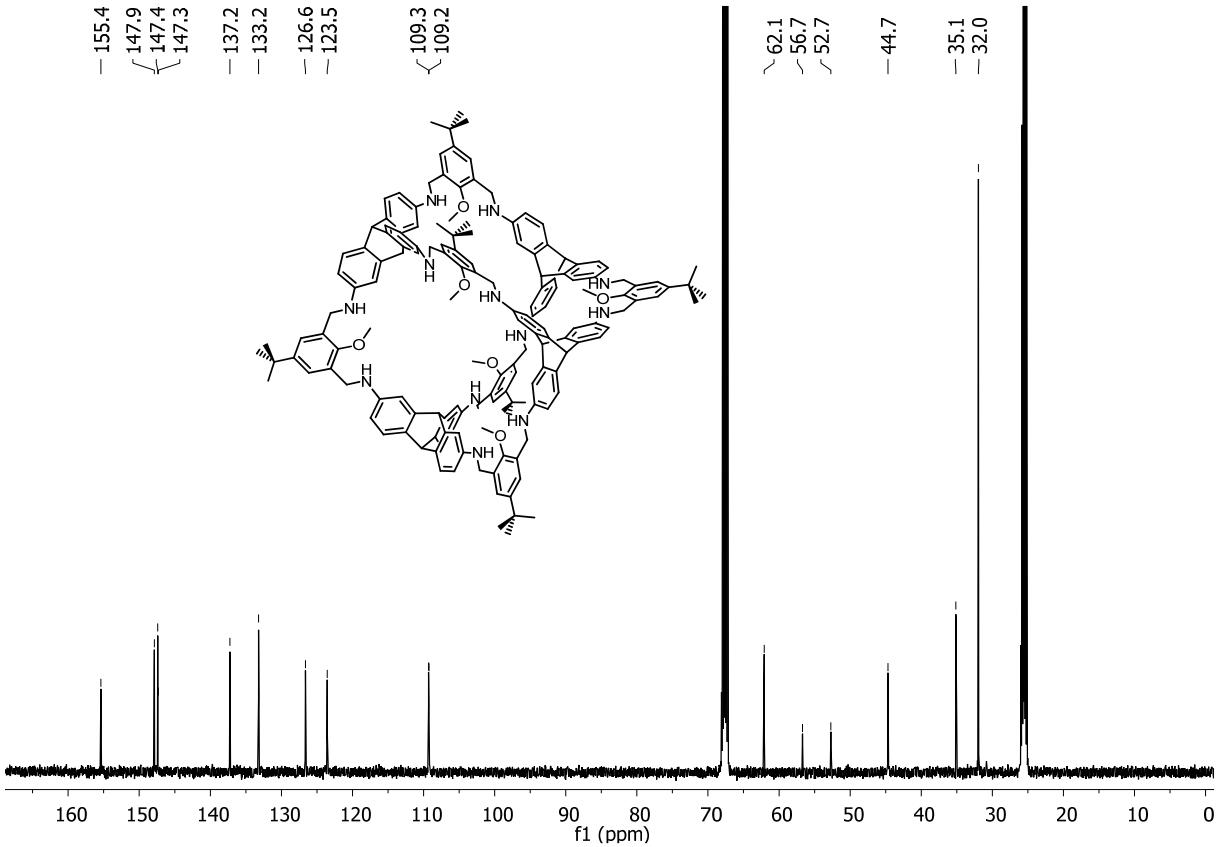


Figure S5: ^{13}C NMR spectrum (125 MHz, THF-d_8) of compound **4**.

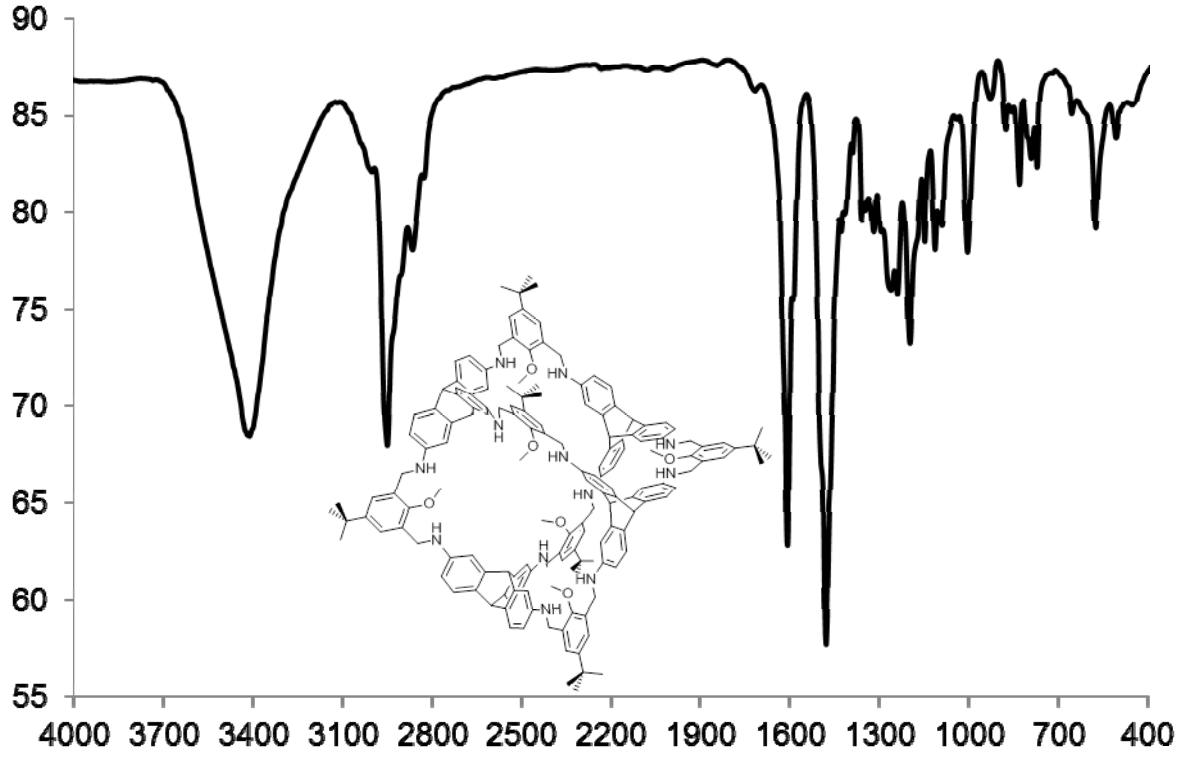


Figure S6: IR spectrum of compound **4**.

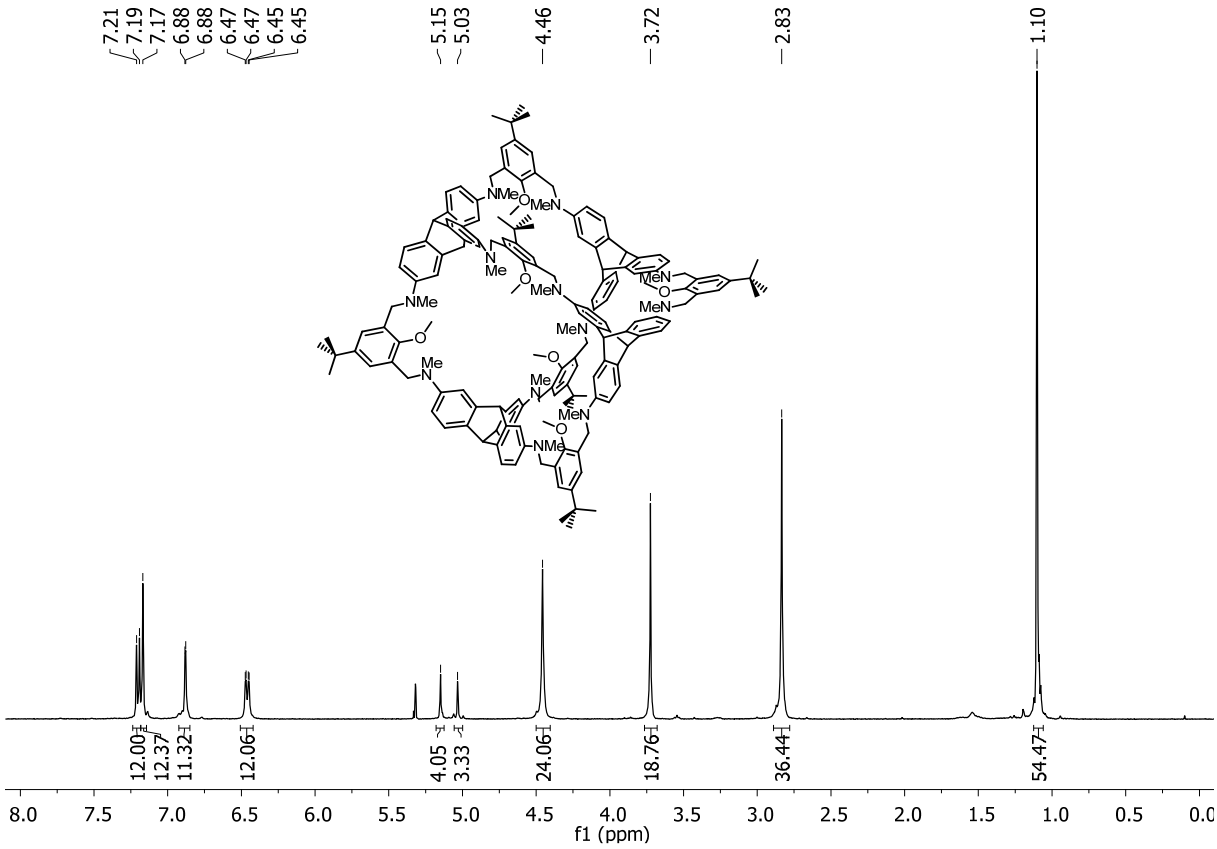


Figure S7: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of compound **5**.

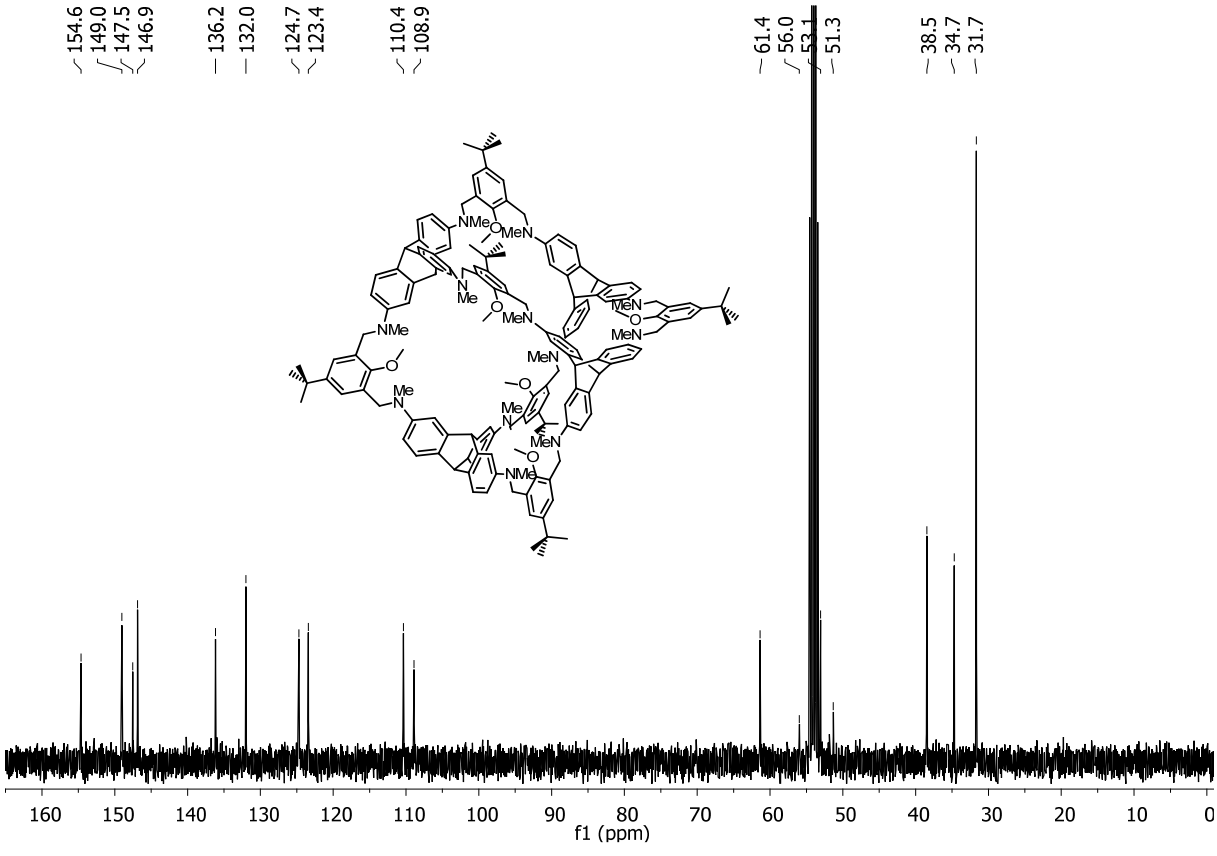


Figure S8: ^{13}C NMR spectrum (100 MHz, CD_2Cl_2) of compound **5**.

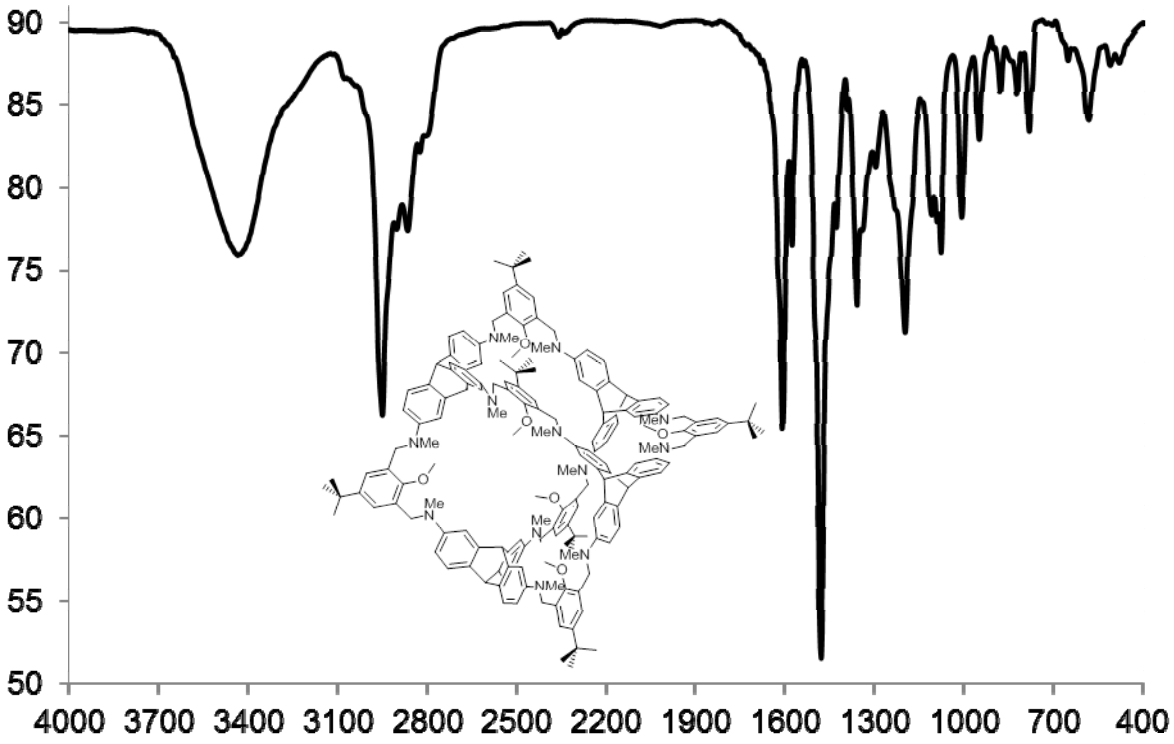
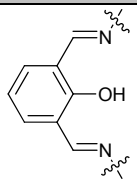
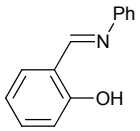
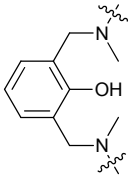
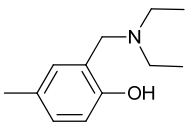
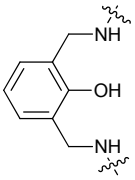
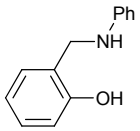


Figure S9: IR spectrum of compound **5**.

3. pKa values of chemically related substances

Table S1 depict the structural elements of the cage compounds **1-3** and chemically comparable substances with their pKa as reported in literature.[S3,S4]

Table S1: Functional groups of the cages **1-3** and the pKa values related substances found in literature

Structural element in the cage	Related substance	pKa (solvent) of the related substance
 **1**	 **S1**	10.25 ($MeOH/H_2O$)[S3]
 **3**	 **S3**	7.15 (EtOH)[S4]
 **2**	 **S2**	2.95 (EtOH)[S4]

The pKa values were measured with the neutral substances (no salts). In all cases the given pKa value represents the deprotonation of the phenol group in the molecule.

In accordance with the considerations in the main manuscript, the proton of the material **3** exhibit the highest acidity while the proton of compound **1** is trapped between the imine and the phenol group (for a graphical representation, see Figure 4, main manuscript). Therefore, the decreasing affinity of the affinity materials **1-3** to GBL in the order of **2** > **3** > **1** is in good agreement with the pKa values reported in literature.

4. Evaluation of affinity

4.1 QCM setup

The resonance frequency of thickness-shear resonators, like the employed quartz crystal microbalances, is largely influenced by the oscillating mass. The sensitivity of the quartz resonator is influenced by several environmental factors and is described by the *Sauerbrey* equation (formula 1),[S5] wherein A is the oscillating area, N the frequency constant and ρ the density of the quartz material. A variation in the oscillating mass Δm directly results in a linear shift Δf_0 of the fundamental resonance frequency f_0.

$$\Delta f_0 = -\frac{f_0^2}{N \cdot \rho \cdot A} \cdot \Delta m \qquad 1$$

The *Sauerbrey* equation applies to homogeneous films with nearly the same viscoelastic properties as the quartz crystal so that no damping of the oscillator appears. Also, the maximum frequency shift has to be lower than 2% of the fundamental frequency, in this case 2000 kHz. This correlation is an easy way to determine affinities from various analytes towards selected affinity materials.[S6]

4.2 Coating protocol

The coating of the quartz crystal microbalances is performed using an electrospray protocol.[S7] This particular method is well established and allows the continuously monitoring of mass deposition onto the quartz upon spraying process. The electrospray solutions are prepared at concentrations of approx. 0.1 mg/mL in a 9:1 mixture of tetrahydrofuran/methanol.

The experimental setup for the coating unit is schematically displayed in Figure S10. The solution for coating is placed in a glass syringe equipped with metal cannula. The metallic part of the needle is contacted with an applied voltage of 5 kV relative to a counter electrode which is represented by the electrode of the QCM to be coated (distance 0.15 m needle tip/electrode). The cannula represents the anode. A constant delivery of the solution during the coating process is achieved by using a syringe pump (5 µL/min, Figure S10/11). The coating process is monitored by measuring the frequency shift of the QCM. Since it is not possible to determine the thickness of the deposited film directly, the amount of affinity material on the quartz device is given by the frequency shift. For screening purposes, all compounds are deposited on 195 MHz QCMs until a frequency shift of 50 kHz is reached.

This shift corresponds to a mass of approx. 10.4 ng of the deposited material on the electrodes.

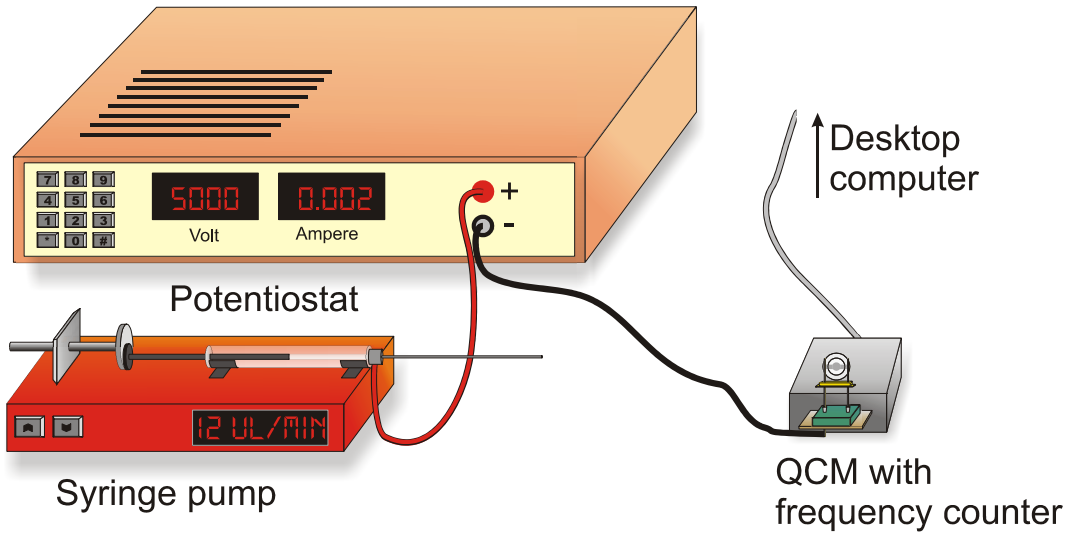


Figure S10: Setup of the coating unit for electrospray

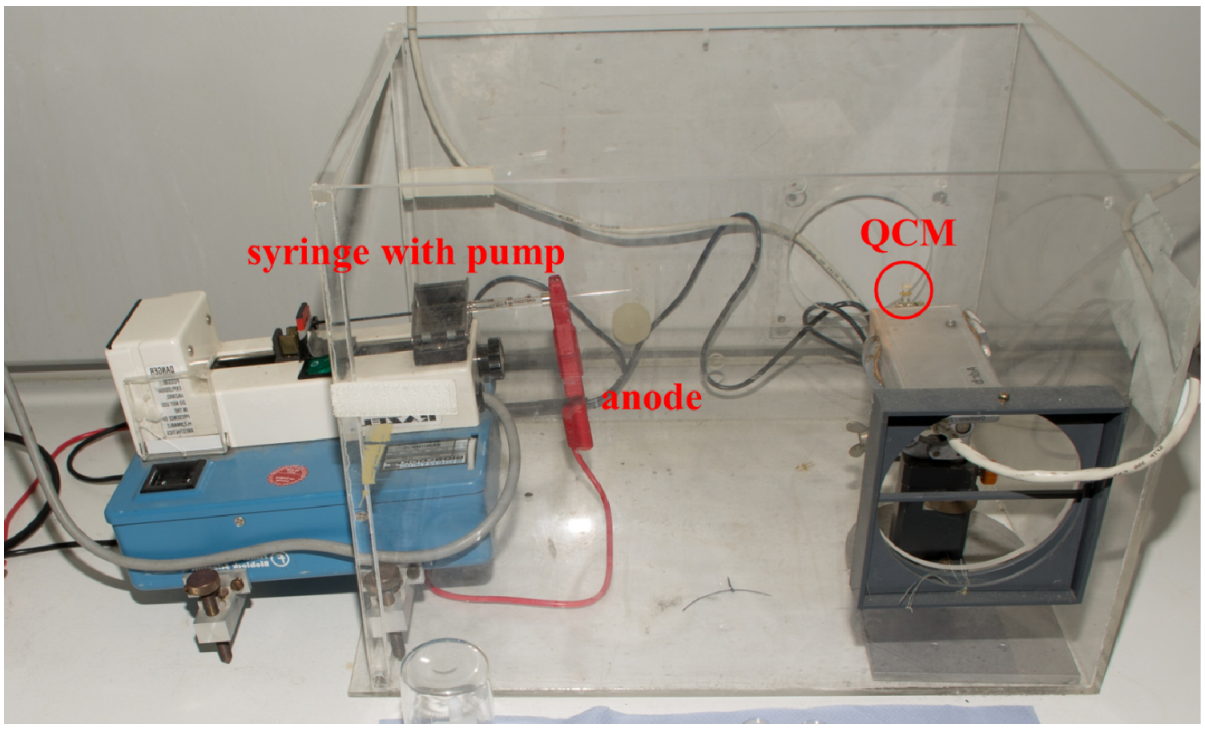


Figure S11: The electrospray setup in the lab

4.3 Setup for measurement of affinity

For determination of affinities precise conditions and concentration of analytes are required. Therefore, a "closed" system connected to a gas mixing unit is used (Figure S12). In this gas mixing unit, the inert nitrogen flow is divided into two streams, both controlled by an individual mass flow controller (MFC) from the Brooks Instrument company (Model 5050S).

Flow 1 remains unchanged in temperature and composition and is used as gas source for dilution purposes, whereas, flow 2 is led through an interchangeable analyte-reservoir which is adjusted to 293.1±0.2 K. The analyte-saturated gas flow 2 is recombined with the pure inert gas flow 1 and led to the measuring chamber. The overall gas flow is set to 200 mL/min. By carefully controlling the flow of the both streams by the MFCs, it is possible to produce gas mixtures with a concentration of 1 to 100% of the vapor pressure of the pure analyte at 293.1±0.2 K.

The central part of the screening setup is the measuring cell which is connected to the gas mixing unit and placed in a temperature controlled environment. We employed a slightly modified GC oven (Hewlett Packard, Palo Alto, CA, USA. Type: HP 5890; Figure S13). The cell is kept constantly at 308 K±0.5 K to exclude temperature influences and to prevent condensation effects within the cell. The cell is designed to operate up to 12 QCM in a parallel fashion.

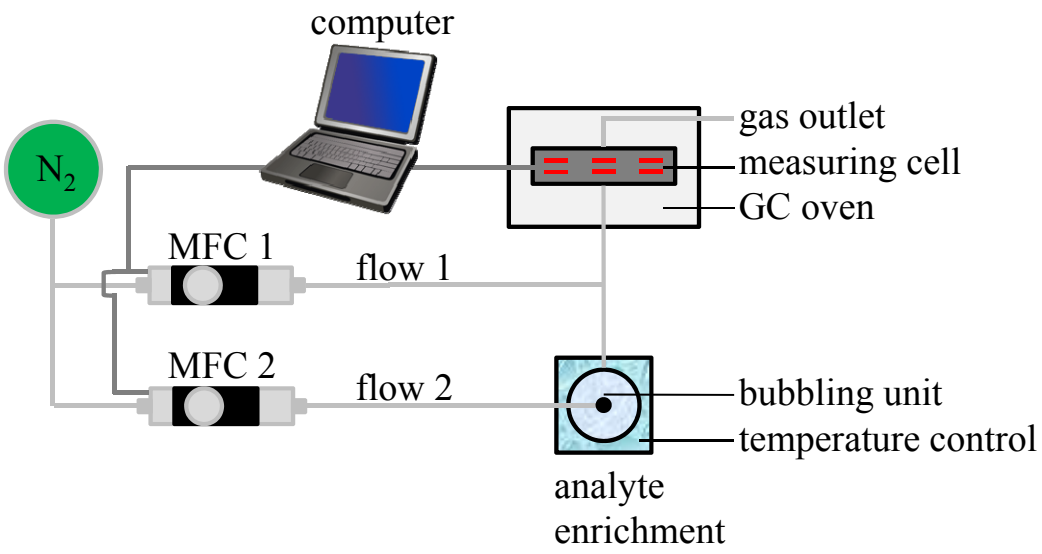


Figure S12: Setup for measurement

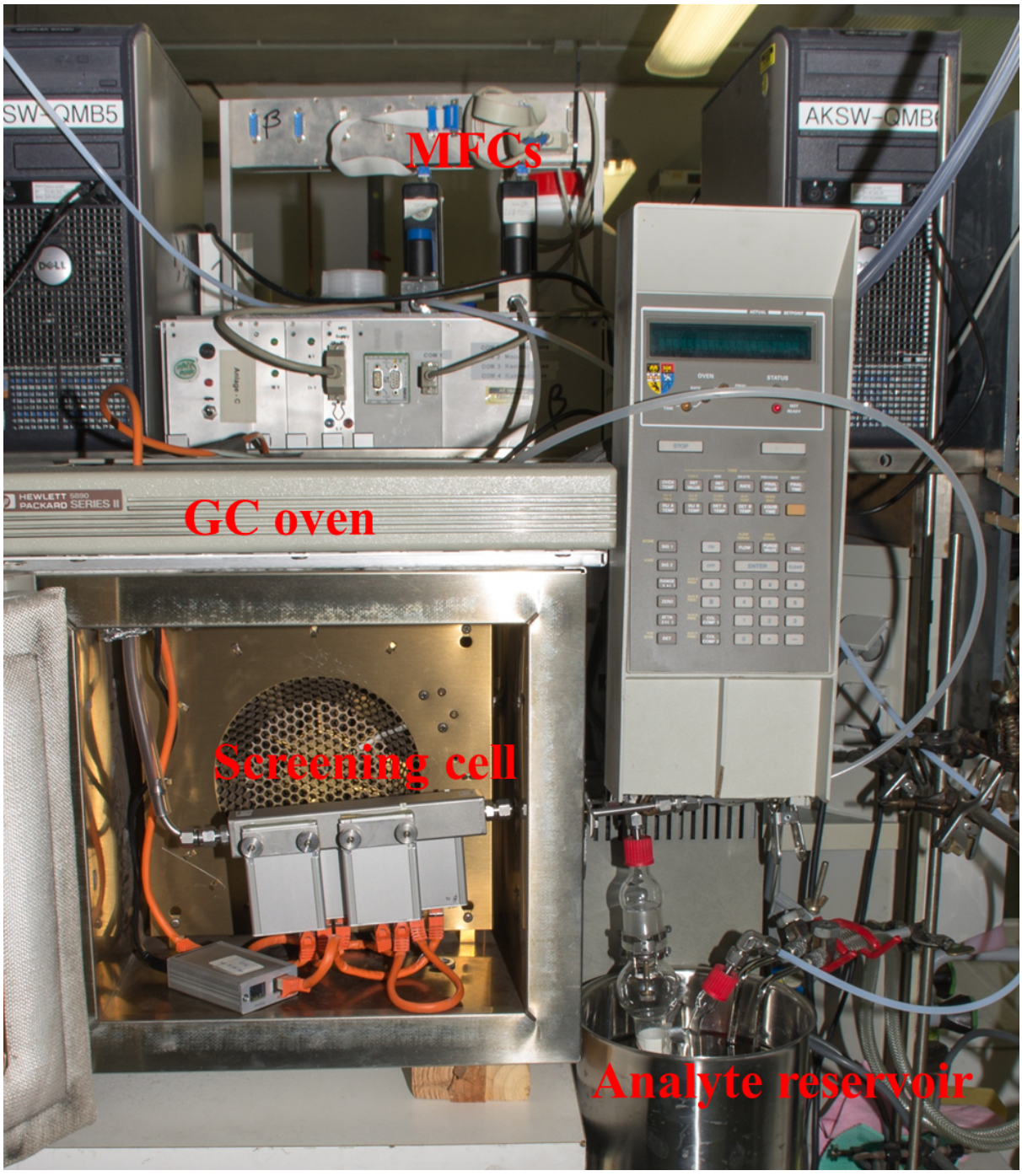


Figure S13: The experimental measurement setup

4.4 Evaluation of the Affinity materials

The following example will show the procedure for determination of affinity. The applied affinity material in this example is the cage compound **3** and employed analyte is water. This procedure is carried out for every affinity material with the individual analyte. In Figure S14 the primary data of a typical measurement for an analyte are depicted. The sensor responses (Figure S14, ΔF_c) were determined by referencing the frequency of the QCM (Figure S14, a) just prior to the admittance of analyte into the chamber to the frequency in equilibrium

(Figure S14, b). The given recovery time between two concentration steps was 1500 seconds in each experiment. The given adsorption time was 1000 seconds for the first five concentration steps and 2000 seconds for the last three.

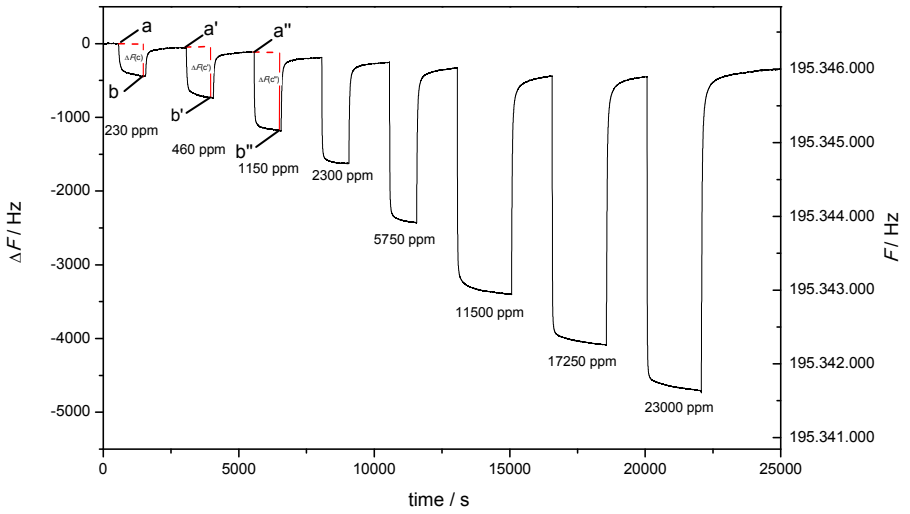


Figure S14: Frequency shifts for different water concentrations (primary data, affinity material **3**)

By plotting the frequency shift vs. the ethanol concentration the constants of the *Langmuir* adsorption isotherm was determined (Figure S15). The graph is obtained by fitting to equation 2.

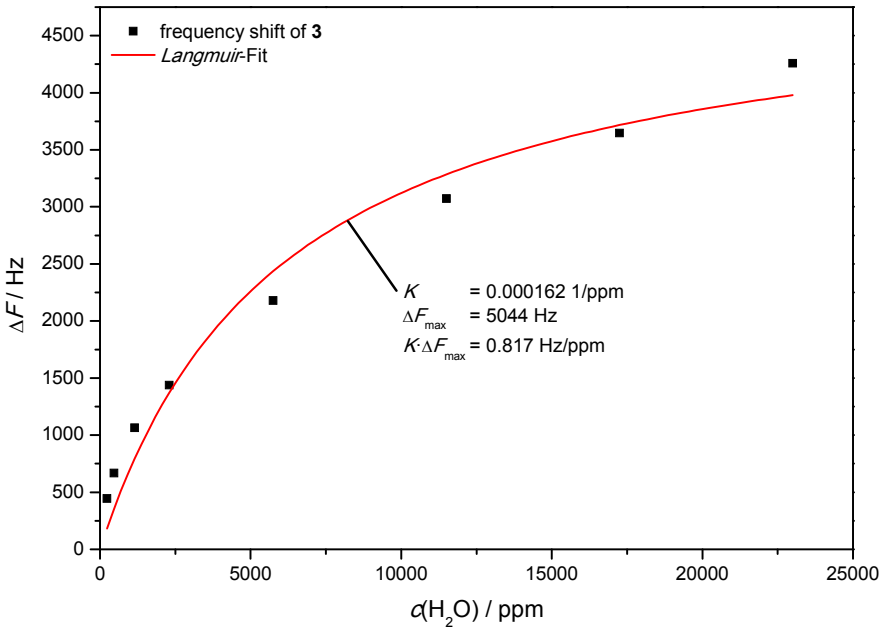


Figure S15: Determination of the affinity from the frequency shifts for different water concentrations (affinity material **3**)

The slope of the linear part of the *Langmuir* equation is the product of the *Langmuir* constants in equation 2

$$\Delta F = \frac{\Delta F_{max} \cdot K \cdot c_{anayte}}{1 + K \cdot c_{anayte}} \qquad 2$$

Since the resulting number is a general information about the affinity of a film or porous material to a respective analyte, $\Delta F_{max} \cdot K$ will be used as the affinity within this study.

Table S2: Overview of screened analytes

analyte	vapor pressure at 20 °C [ppm]	applied concentration range [ppm][a]
$(CH_3)_2CO$	245310[S8]	2453 - 245310
CH_3CH_2OH	59000[S9]	590 - 59000
H_2O	23000[S9]	230 - 23000
GBL	1500[S10]	15 - 1500

[a] For all analytes eight concentrations between 1 % and 100 % of the saturation concentration in the gas phase at 20 °C were chosen.

4.5 Screening results

In order to obtain comparable results, the coating of the QCM was always made with the same mass of affinity material (50 kHz which corresponds to 10.4 ng). By that, a comparable film thickness is achieved. In the following tables, the affinity is presented for the analytes mentioned in chapter 3.4. The affinities were obtained by the procedure described in chapter 3.4.

Table S3: Affinities of the affinity materials 1-5, M1 and M2

analyte	1 [Hz/ppm]	2 [Hz/ppm]	3 [Hz/ppm]	4 [Hz/ppm]	5 [Hz/ppm]	M1 [Hz/ppm]	M2 [Hz/ppm]
$(CH_3)_2CO$	0,0412	0,0692	0,0622	0,0512	0,0422	0,0350	0,0381
CH_3CH_2OH	0,0752	0,064	0,182	0,114	0,0852	0,0672	0,0722
H_2O	0,418	0,524	0,817	0,767	0,5894	0,783	0,740
GBL	2,42	7,41	4,67	3,45	2,29	2,08	2,93

5. References

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