Electronic Supplementary Information (ESI) of "Nanoscale chemical characterization of biomolecules using tip-enhanced Raman spectroscopy"

1. TERS characterization of biomolecules

Nanoscale lateral spatial optical resolution (SOR) down to 1 nm (and even below) can be obtained using tip-enhanced Raman spectroscopy (TERS). While intensities of TERS marker bands can fluctuate depending on experimental conditions, wavenumbers are most often consistent with those observed in surface-enhanced Raman scattering (SERS) experiments. Nucleic acids, proteins and lipids show characteristic bands in TERS spectra (Table S1).

Table S1 Best achieved spatial resolution (SOR) and TERS marker bands for different biomolecules and biomaterials

Biomolecule/Biomaterial	SOR (nm)	Selected TERS marker bands (spectral regions in cm^{-1})	References
DNA	< 1 nm	Adenine (710-740, 1320-1340, 1460-1500); Guanine (640-680); Cytosine (760-800, 1410-1430); Thymine (740-790); Deoxyribose ring / OPO stretch (790-890).	1-7
RNA	< 1 nm	Adenine (710-740, 1320-1340, 1460-1500); Guanine (640-680); Cytosine (760-800; 1410-1430); Uracil (1250-1300).	1, 5,8
Haemoproteins	< 2 nm	Haem vibrations (Cytochrome c: 748-755, 1372-1378, 1493-1507, 1565-1591, 1607-1636; Haemoglobin: 660-680, 749-754, 1124-1128, 1298-1312, 1355-1378, 1545-1553).	9-14
Amyloid aggregates	~ 1 nm	Cys/Met (650-775); Tyr (817-877); Pro (899-905); Phe (997-1056); Amino acid $=NH_2^+$ and NH_3^+ vibrations (1051-1180); Amide III bands (1218-1345); Amide I bands (1624-1700).	1, 15-25
Lipid membranes	< 20 nm	Ester C=O stretch (1720-1753); CH stretch (2800-3000).	20, 23, 26-29
Viruses	< 10 nm	Guanine (640-680); Cys/Met (655-690); Adenine (710-740); Cytosine (760-800); Tyr (824-854); Phe (1000-1045); Amino acid $=NH_2^+$ and NH_3^+ vibrations (1051-1168); Amide III bands (1235-1332); Amide I bands (1630-1680).	30-35
Cells	< 10 nm	Cholesterol (690-708); Tyr (825-866); Phe (991-1039); Amide III bands (1200-1338); Amide I bands (1618-1695), Ester C=O stretch (1720-1753).	28, 36-41

2. TERS sample preparation

The selection of an appropriate TERS substrate depends on several factors: (i) TERS configuration, where transparent substrates such as glass, are a requirement for bottom illumination; (ii) gap-mode TERS requires the use of a noble metal substrate, commonly Au; (iii) physicochemical properties of the chosen biomolecule. The three most commonly used non-metallic substrate materials for TERS are glass, silica, and mica. Their Raman spectra under laser irradiation at 633 nm are plotted in Figure S1. Borosilicate glass slides contribute as a background without narrow Raman bands. Si wafers mainly show an intense band centred at 520 cm^{-1}. As AFM tips are generally made of Si, this band can be used as a marker to estimate the evolution of the metal coating of TERS tips during an experiment with an AFM-based TERS system. The spectral signature of mica slides present Raman bands centred at 262, 410 and 701 cm^{-1}. As very few Raman bands of biomolecules are positioned below 550 cm^{-1} (and even below 710 cm^{-1}), the substrate contribution does not hinder Raman features of interest to characterize biomolecules. Furthermore, when the substrate is coated with Au or covered by Au nanoplates to work in "gap-mode" configuration, the substrate contribution can be significantly reduced due to the screening effect of gold. If a surface treatment is applied however (silanization, functionalization with thiols, etc), the molecules grafted on the substrate can show a specific TERS signature that is superimposed onto the fingerprint of the biomolecule deposited on top (Table S2). Special care must be taken for spectral interpretations in this case.

The sample preparation method strongly depends on the biomolecule to deposit. Substrate treatments may be necessary and special care during the washing and drying steps is crucial. Table S2 describes different procedures to prepare samples convenient for TERS experiments. For simplicity, this table does not detail the preparation of liquid solutions and suspensions containing biomolecules. The reader can refer to bibliographical references for further information on this point.

Table S2 Sample preparation for different biomolecules and biomaterials

Biomolecule/ Biomaterial	Sample preparation	References
DNA	Mg^{2+} mediated DNA deposition on mica: Drop-casting of a 10 µL aliquot of DNA solution (1–3 µg/mL double-stranded DNA, 10 mM HEPES, 50 mM NaCl, 5 mM $MgCl_2$) on freshly cleaved mica (~ 0.1 mm thickness) → 5 min incubation → Surface washing with deionised water (10 times) → Drying with N_2 flow.	2
	Mg^{2+} mediated DNA deposition on mica: Drop-casting of a 20 µL aliquot of DNA solution (0.5 ng/µL double-stranded DNA, 2 mM $MgCl_2$) on freshly cleaved mica → 10 min incubation → Surface washing with 1 mL of ultrapure water (2 times) → Drying with N_2 flow.	3
	DNA deposition on silanized mica: Deposition of a 15 µL aliquot of APTES solution (0.1 % (v/v) in ultrapure water) on freshly cleaved mica → 1 min incubation → Substrate washing with 1 mL of ultrapure water (once) → Drying with N_2 flow → Drop-casting of a 20 µL aliquot of dilute 0.5 ng/µL double-stranded DNA solution onto the silanized mica substrate → 3 min incubation → Surface washing with 1 mL of ultrapure water (2 times) → Drying with N_2 flow.	3
	DNA combing on glass: Cleaning of glass coverslip by ultrasonication (5 min in acetone, 5 min in isopropanol, 5 min in ultrapure water) → Drying with compressed air flow → UV-ozone treatment (30 min) → Immersion of the glass coverslip in 50 µL OTS diluted in 25 mL hexane (12 h under N_2 atmosphere) → Ultrasonication in hexane and chloroform (3 times, 2 min) → Substrate rinsing with ultrapure water → Drying with N_2 flow → Drop-casting of a 8 µL aliquot of DNA solution (18.2 µg/mL double-stranded DNA in acetate buffer solution) onto the treated glass coverslip → 10 min incubation → Sample tilting for combing.	4

	Mg^{2+} mediated DNA deposition on mica: Drop-casting of 1 µL aliquot of DNA solution (10–100 ng/µL single-stranded DNA, 20 mM HEPES, 20 mM $MgCl_2$) onto mica→ Incubation under Ar atmosphere → Surface rinsing in distilled water (2 times) → Drying with Ar flow.	5
	DNA deposition on Au nanoplates: Coating glass coverslip with 10 mM APTMS → 2 h incubation → Substrate rinsing in ultrapure water → Drying with N_2 flow → Deposition of a few drops of Au nanoplates solution onto the substrate → 30 min incubation → Substrate rinsing with ultrapure water → Deposition of a 10-15 µL aliquot of DNA solution (prepared from 5 µg double-stranded DNA) → Surface washing with ultrapure water (a few times).	6
	DNA deposition on Au substrate: Au substrate cleaning with compressed air → Drop-casting of 0.4 nM – 40 pM single-stranded DNA solution in 1X TAE-Mg^{2+} buffer (40 mM Tris-HCl pH 7.5, 20 mM acetic acid, 2mM EDTA, 12.5 mM magnesium acetate) onto the Au substrate → 30 s incubation → Removal of excess water in N_2 atmosphere → Surface washing with 50 µL of ultrapure water (once) → Drying at room temperature.	7
RNA	RNA deposition on Au nanoplates: Centrifugation of Au nanoplates on a clean glass coverslip (3000 rpm, 10 min) → Substrate washing in 70 °C water → Drying under vacuum → Drop-casting of a 1 µL aliquot of dilute RNA solution → Incubation under Ar atmosphere → Surface rinsing in distilled water (2 times) → Drying with Ar flow.	5
	RNA deposition on Au substrate: Au substrate cleaning with compressed air → Drop-casting of a 50 µL aliquot of heat-shocked 6.88 nM RNA solution in 1X TAE-Mg^{2+} buffer (40 mM Tris-HCl pH 7.5, 20 mM acetic acid, 2 mM EDTA, 12.5 mM magnesium acetate) onto the Au substrate → 30 s incubation → Removal of excess water in N_2 atmosphere → Surface washing with ultrapure water (once) → Drying at room temperature.	8
Haemoproteins	Deposition of cytochrome c on glass: Cleaning of a glass coverslip by ultrasonication (5 min in acetone, 5 min in absolute ethanol, 5 min in ultrapure water) → Drying in N_2 → Sputtering of 10 nm Au on the clean glass coverslip → Incubation in the dark for 18 h in 2 mM ethanolic solution of MUA → Copious substrate rinsing with absolute ethanol → Drop-casting of a 3 µL aliquot of cytochrome c solution (0.1 mM in ultrapure water) → Drying in air at room temperature.	9
	Deposition of cytochrome c on glass: Spin-coating of several µL of a commercial cytochrome c aqueous solution → Drying in air at room temperature	10
	Deposition of haemoglobin on mica: Drop-casting of a 5 µL aliquot of haemoglobin solution (1 pM in ultrapure water) onto ultra clean mica substrate (10 mm diameter, 0.21 mm thickness) → Drying under vacuum.	12
	Deposition of hybrid protein nanofibers on glass: Drop-casting of a 10 µL aliquot of nanofiber solution (produced from 100 µg/mL human serum albumin and human haemoglobin solutions in ultrapure water) onto cleaned glass coverslip.	13
	Deposition of cytochrome c and deoxy-myoglobin on glass: Deposition of 0.3 mM cytochrome c solution and 0.1 mM deoxy-myoglobin solution onto a glass coverslip (~10 µL/cm^2).	14
Amyloid aggregates	Deposition of $A\beta_{1-42}$ fibrils on Au substrate: Cleaning of a Si wafer in acetone, ethanol and deionized water → Drying with Ar flow → 100 nm Au coating at a deposition rate of 0.03-0.04 nm/s onto the cleaned Si wafer → Flame annealing of the resulting Au substrate using a Bunsen burner (4 min) → Gluing of the flame-annealed Au surface to clean Si wafer → Drying of the glue overnight in air → Storage of the resulting Au substrate template under vacuum until use → Mechanical cleavage using a razor blade to expose a contamination-free and flat Au surface → Deposition of a 30-40 µL aliquot of $A\beta_{1-42}$ fibril solution (prepared from 100 µM solution of $A\beta_{1-42}$ in DMSO, 10 mM HCl in ultrapure water pH 2.0, phosphate buffer pH 7.4) → 40-60 min incubation at ambient temperature → Surface rinsing with 0.5 mL of ultrapure water.	15, 17
	Deposition of insulin fibrils on glass: Drop-casting of a 10 µL aliquot of dilute insulin fibril solution (prepared in HCl pH 1.5) on pre-cleaned glass coverslip → 2-3 min incubation → Suction of the excess suspension using a pipette → Surface washing with pH 1.5 HCl (2 times) → Drying with Ar flow.	16, 18, 19

	Deposition of hIAPP fibrils on glass: Deposition of a drop of hIAPP fibril solution (prepared from 1 mg/mL hIAPP solution in ultrapure water dilute in 50mM phosphate buffer pH 2.0 or in 5mM phosphate buffer pH 7.8) onto glass coverslip → 10 min incubation → Surface washing with ultrapure water → Drying with Ar flow.	20
	Deposition of insulin fibrils on Au nanoplates: Immersion of a glass coverslip covered by Au nanoplates in dilute insulin fibril solution (prepared in HCl pH 1.5) → 20 h incubation → Surface washing with ultrapure water → Drying with Ar flow.	21
	Deposition of amyloid aggregates ($A\beta_{1-42}$ and L34T fibrils, oG37C oligomers) on Au substrate: Cleaning of a glass coverslip by ultrasonication (5 min in acetone, 5 min in absolute ethanol, 5 min in ultrapure water) → Drying in N_2 → Sputtering of 10 nm Au onto the clean glass coverslip → Spin-coating of a 3 µL aliquot of concentrated amyloid fibril solution onto the Au substrate.	22, 24
	Deposition of Tau(K18) fibrils on Au substrate: Cleaning of a glass coverslip by ultrasonication (5 min in acetone, 5 min in absolute ethanol, 5 min in ultrapure water) → Drying in N_2 → Sputtering of 10 nm Au on the clean glass coverslip → Drop-casting of a 3 µL aliquot of fibril solution onto the Au substrate → Spreading of the solution and removal of the excess solution with N_2 flow → Drying under high vacuum (2 h).	23
	Deposition of insulin fibrils on Au nanoplates: Deposition of Au nanoplates onto a clean glass coverslip by centrifugation (5000 rpm, 15 min) → Substrate washing in distilled water → Drying under vacuum → Drop-casting of an aliquot (20-100 µL) of dilute insulin fibril solution (prepared in HCl pH 2.4) on the glass coverslip covered by Au nanoplates → 2-3 min incubation → Removal of excess solution → Surface washing with ultrapure water → Drying with Ar flow.	25
Lipid membranes	Deposition of a lipid monolayer on glass: Deposition of the lipid monolayer using a Langmuir-Blodgett trough with ultrapure water as the liquid phase (11 µL of 1 mM chloroform solution of DPPG lipid)	20
	Deposition of a lipid monolayer on Au substrate: Cleaning of a Si wafer in acetone, ethanol and deionized water → Drying in N_2 → 100 nm Au coating at a deposition rate of 0.03-0.04 nm/s onto the cleaned Si wafer → Flame annealing of the resulting Au substrate using a Bunsen burner (4 min) → Gluing of the flame-annealed Au surface to clean Si wafer → Drying of the glue overnight in air → Storage of the resulting Au substrate template under vacuum until use → Mechanical cleavage using a razor blade to expose a contamination-free and flat Au surface → Air-plasma treatment (1 min) → Direct immersion in ultrapure water → Preparation of the lipid monolayer using a Langmuir-Blodgett trough with the ultrapure water as liquid phase (25 µL of 1 mg/mL DOPC and DPPC solution in chloroform, 10 min evaporation, compression rate 2 mm/min) → Monolayer transfer onto the Au substrate via vertical Langmuir-Blodgett technique at 2 mm/min at room temperature.	26
	Deposition of a lipid monolayer on Au substrate: Preparation of Au(111) substrate using the Clavilier method → Annealing in a hydrogen-oxygen flame of the Au(111) substrate → UV-ozone cleaning for 10 min → Transfer of the Au(111) substrate to a clean Langmuir-Blodgett trough, with the Au surface immersed in the water used as subphase → Preparation of the lipid monolayer (30 µL of 1 mg/mL DPPC solution in chloroform, evaporation 30 min, compression rate 5mm/min) → Monolayer transfer onto the Au(111) substrate via vertical Langmuir-Blodgett technique at 2 mm/min transfer speed and 20 mN/m surface pressure at room temperature.	27
	Deposition of a lipid bilayer on mica: Cleavage of the mica substrate with adhesive tape → Immediate immersion of the freshly cleaved mica substrate in the lipid containing buffer solution (4:1 POPC/DOPS mixture) → 10 min incubation → Removal of excess lipid and buffer solution by surface washing with doubly distilled water (4 times) → Drying with Ar flow.	28, 29
Viruses	Deposition of virus particles on glass: Cleaning with a mixture of concentrated nitric acid and hydrogen peroxide of a glass coverslip (storage in Ar if necessary) → Drop-casting of a 10 µL aliquot of virus solutions diluted in sterile filtered, deionized water onto the	30

	cleaned glass coverslip → Drying under ambient conditions → Surface washing with 100 µL sterile filtered, deionized water → Drying under ambient conditions.	
	Deposition of virus particles on mica: Drop-casting of a 2 µL aliquot of dilute virus solutions onto freshly cleaved mica or clean glass coverslip → Drying under ambient conditions.	31
	Deposition of virus particles on Au nanoplates: Drop-casting of a 10 µL aliquot of virus solution onto 70 nm Au-coated mica or onto 70 nm-thick Au microplates → 5 min incubation → Removal of the excess solution using a pipette → Surface rinsing with deionized water (4-5 times) → Drying at room temperature.	34
Cells	Deposition of human cells on glass: Fixation on a clean glass coverslip performed by removing the culturing medium, washing the sample with phosphate-buffered saline (PBS) and treating cells with 2% formaldehyde and PBS.	36, 41
	Deposition of spores on glass: Drop-casting of a 50 µL aliquot of a 10^5 spores/mL water suspension of mature wild-type spores on a clean glass coverslip → Drying under ambient conditions.	37
	Deposition of bacteria on glass: Deposition of a droplet of dilute bacterial water suspension on a clean glass coverslip → Drying under ambient conditions.	38, 39
	Deposition of bacteria on glass: Drop-casting of a 10 µL aliquot of a 1 µM bacterial suspension in buffer solution on a clean glass coverslip → Drying with Ar flow.	40

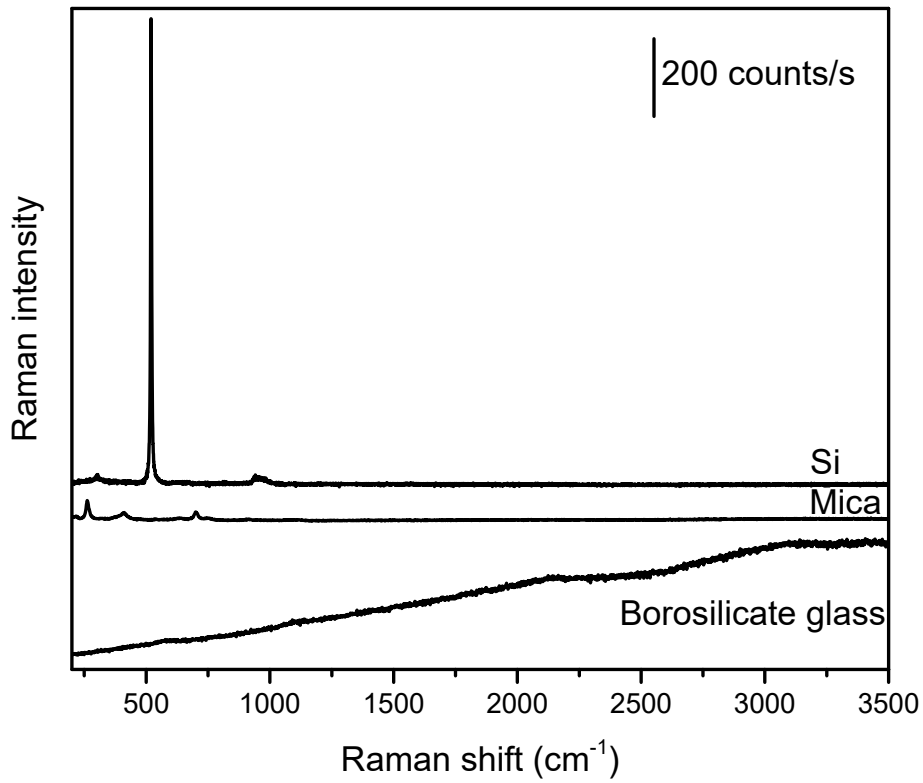

Fig. S1 Raman spectra of a Si wafer, a mica slide, and a borosilicate glass coverslip. *Experimental parameters: excitation wavelength λ = 633 nm, laser power P = 7.5 mW, short-working-distance 50X objective (NA = 0.75), acquisition times 1-10 s.*

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