Silicone-specific identification of trace polydimethylsiloxanes in wines with 2D-diffusion-ordered nuclear magnetic resonance spectroscopy (DOSY-NMR)

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Abstract. Present work stresses a novel analytical approach for increasing the specificity of standard NMR approaches for identifying polydimethylsiloxane (PDMS) and further silicone moieties in wines' organic extracts, by including a second dimension that correlates chemical shifts with diffusion coefficients by means of pulsed-field gradient diffusion ordered spectroscopy (DOSY-NMR). Each silicone source in wines is unambiguously assigned by correlation of both local chemical environments and by a unique diffusion coefficient value, in turn related to a hydrodynamic radius (R_H) that can be obtained with respect proper internal standards. Obtained PDMS diffusion coefficient values and hydrodynamic radii in wines' extracts, in agreement with expected values, present a selectivity and specificity so far not reported, that positions DOSY-NMR spectroscopy as an alternative in oenology for controlling PDMS limits.

1 Introduction

Polydimethylsiloxanes (PDMS) or dimethyl polysiloxane are classified by the Joint FAO /WHO Expert Committee on Food Additives (JEFCA) as a structure-shaping food additive (E900), with an acceptable daily intake (ADI) of 1.5 mg/kg body weight per day, generally used as a foam-suppressor and as anti-foaming agent [1,2]. However, silicone moieties and particularly PDMS may be as well present as a contaminant of diverse food packaging processes and as a silicone trace from greases used in diverse machine components, amongst others [3,5]. Diverse analytical methods have been proposed to identify and quantify PDMS, including: i) Atomic absorption (AAS) and emission (AES) spectroscopies, whereas despite its sensitivity and specificity, it determines solely total silicon content (organic and inorganic) in a destructive way, discarding the possibility to trace uniquely PDMS, even coupled with an Inductively Coupled Plasma (ICP) unit; ii) Fourier Transform Infrared (FTIR) and Raman molecular absorption spectroscopies are non-invasive techniques that despite their performance for speciation analysis in diverse food matrixes, their high detection limits and their spectral resolution will hamper the trace analysis of PDMS and iii) One-dimensional ^{1}H or ^{29}Si nuclear magnetic resonance spectroscopy have recently been proposed as alternatives for chemical speciation of silicone traces in foodstuffs such as wines with low limits of detection (1.5 mg/l), magnetic field-enhanced limits of quantifications (0.06 mg/kg at 80 MHz 1H frequency; 0.00 6 mg/kg at 500 MHz 1H frequency) and high specificity. However, unambiguous assignments of a full set of either ^{29}Si chemical environments or ^{1}H-^{29}Si heteronuclear NMR interactions in liquid-state foodstuffs with a plethora of silicone sources, results cumbersome and unintuitive, mostly at modest magnetic fields (≤14 Teslas or 600 MHz 1H frequency).

Present work stresses a novel analytical approach for increasing the specificity of standard NMR approaches for identifying polydimethylsiloxane (PDMS) and further silicone moieties in wines' organic extracts, by including a second dimension that correlates chemical shifts with diffusion coefficients by means of pulsed-field gradient diffusion ordered spectroscopy (DOSY-NMR), inspired in our previous works for obtaining diffusion-coefficient dependent polydispersity indexes used as Critical Quality Attribute (CQA) of complex pharmaceutical formulations [6,7] and for describing polymerization reactions in dendromeric nanoparticles [8]. Each silicone source in wines is unambiguously assigned by correlation of both local chemical environments and by a unique diffusion coefficient value, in turn related to a hydrodynamic radius (R_H) that can be obtained with respect proper internal standards. Obtained PDMS R_H in wines' extracts, in agreement with expected values, present a selectivity and specificity so far not reported, with a non-invasive method with required limits of detection and

quantification with conventional NMR magnetic fields and probes, as a novel tool in oenology for controlling PDMS limits

2 Materials and methods

2.1 Sample preparation of wine organic extracts

A set of 5 commercial Mexican Malbec monovarietal wines from Coahuila, Mexico (Casa Madero, Parras, México, [25º27'2" N, 102º10'37" W] from 2015, 2016, 2017, 2018 and 2019 vintages, were obtained for the present study. 50 millilitres of each wine sample were versed in spherical flask for a rotary vacuum evaporation procedure for hydroalcoholic solvent elimination. The remanent red viscous liquid (Fig. 1.1., left) is mixed with 20 ml of CCl_4 HPLC grade (≥99.9% purity, CAS No. 56-23-5) as medium of an organic extract whereas PDMS will be solubilized [9]. Organic extracts are favoured within a 42 kHz high-frequency sound waves ultrasonic cleaner (Cole-Parmer, Vernon-Hills, Illinois, United States of America), whereas the mixture is left at the ultrasound during 10 minutes at 37ºC (Fig. 1.1., middle). After high frequency ultrasonication (Fig. 1.1., right), mixture is versed into a separatory funnel for phase separation with no further convection (Fig. 1.2). After phase separations, CCl_4 extract is versed in a 100 ml beaker for further treatments (Fig. 1.3) whilst aqueous extract is mixed with 20 ml of CCl_4 HPLC grade, ultrasonicated and phase separated two more times in order to have a final volume of 60 ml of CCl_4 extract within the beaker. Finally, CCl_4 excess is eliminated with the aid of a rotary vacuum evaporator until having between 10 and14 mg of a yellowish oil (Fig. 1.4.).

2.2.1 NMR spectroscopy. Acquisition details

For each 2015-2019 Coahuila Malbec batches, wine organic extracts were dissolved in 650 µL of deuterated benzene-d6 (CAS No. 1076-43-3, with 99.96% of deuteration) mixed with 25 µL of a 2 mM solution of internal standard tetramethylsilane (CAS No. 75-76-3).

All NMR spectra were recorded at 14.1 Tesla of static magnetic field on a Bruker 600 AVANCE III HD (Bruker BioSpin, Ettlingen, Germany) equipped with a 5-mm 1H/D BBO probe head with z-gradient. The following set of NMR experiments were conducted:

(a) Standard quantitative ^{1}H-one dimensional direct polarization NMR experiments (q-^{1}H-NMR, Fig. 3, left) were carried out by previously calibrating the 90º hard pulse (9.45 µs @ 23.69 kHz). By using 64 transients of 65,536 complex points, having recycling delays of 15 s and with acquisition times of 2 seconds, have produced experimental times of 66 minutes per spectrum.

(b) Diffusion-ordered nuclear magnetic resonance spectroscopy (DOSY-NMR) was adapted from our previous reports [6-8], by applying 128 gradient levels in the indirect F1 dimension, with a linear increase from 2% up to 98%, using a gradient field strength up to 54 Gauss cm^{-1}, merged in 16 transients per gradient increase (Fig. 2B) comprising 23074 complex points in F2 were used. The diffusion delay (***Δ***, Fig. 2A, Eq. (3)) was 100 ms and the length of the square diffusion encoding gradient pulse (δ in Fig. 2A, Eq. (3)) was 2.1 milliseconds to assure accurate gradient encoding - decoding signal attenuation. No apodization function within the direct F2 dimension was needed for semi-Fourier transformation prior to Inverse-Laplace indirect F1 transformation (P(D) term in Eq. (3)). The obtained average diffusion coefficients (Eq. (5)) were internally referenced with respect the benzene-d6 solvent signal at a value of 2.01 x 10^{-9} m^2s^{-1} (Fig. 3, right). The observed average diffusion coefficients ($D_{average}$, Eq. (5)) are strongly dependent on the sample temperature (T in Eq. (1)) and viscosity (η in Eq. (1)) as established in the Stokes-Einstein expression relating diffusion of molecular species in liquid media:

$$R_H = \frac{k_B T}{6\pi\eta D} \qquad (1)$$

In consequence $D_{average}$ (Eq. (5)) can be overestimated if convection occurs in the sample. Thus, to prevent convection effects, sample temperature was maintained at 298 K and a gradient stimulated echo (STE) [6-8] pulse scheme was adapted to the gradient encoding-decoding module (pulse sequence, Fig. 2A).

2.2.2 NMR spectroscopy. Processing details

(a) For standard quantitative ^{1}H-one dimensional direct polarization NMR experiment, no apodization function was applied during Fourier-Transform.

(b) The processing details for 2D-DOSY NMR spectra (Figs. 3 and 4) comprise first a semi-Fourier transform of the F2 dimension with no use of any apodization function. Inverse Laplace transformations for obtaining the diffusion dimension (Eqs. (3)-(5)) were carried out with the Bruker BioSpin Dynamics Center Topspin module (Billerica, MA, United States of America), by using a least-squares fitting routine with a Monte Carlo error estimation analysis [6-8].

(c) NMR postprocessing of the full 2015-2019 Malbec organic extracts' q-^{1}H-NMR (Sect. 2.2.1.a.) input data matrixes for producing the supervised Orthogonal Projections to Latent Structures Discriminant Analysis (OPLS-DA) [10] shown in Fig. 4 top, was carried out as follows: ppm calibration and manual phase corrections were conducted using Bruker TopSpin 4.2.0 software (Billerica, MA, United States of America). Global and intermediate baseline corrections, least-squares or parametric time warping NMR alignments, variable size bucketing for untargeted profiling, and data matrix normalization were carried out with NMRProcFlow software [11].

2.3 Multivariate statistical analysis

Data pre-processing comprising normalization by sum (for adjust differences amongst samples), transformation (Log) and autoscaling (mean centering divided by

standard deviation of each variable), applied to remove any possible variation during experimental phase, in order to make features as comparable between them as possible, as well as statistical analysis workflow for obtaining the OPLS-DA year of vintage fingerprint (Fig. 4), from the constant sum normalized q-^{1}H-NMR (Sect. 2.2.1.a.), input data matrixes were developed with MetaboAnalyst 5.0 software [12]. In all cases, T2 Hotelling's regions depicted by ellipses in score plots of each model define a 95% confidence interval [13]. Supervised OPLS-DA was carried out with a Monte-Carlo cross-validation simulation with 10 test partitions per 100 permutations for testing [14]. Reliability of each classification per supervised model, was evaluated in terms of goodness of the fit (R^2) and goodness of prediction (Q^2) [15,16].

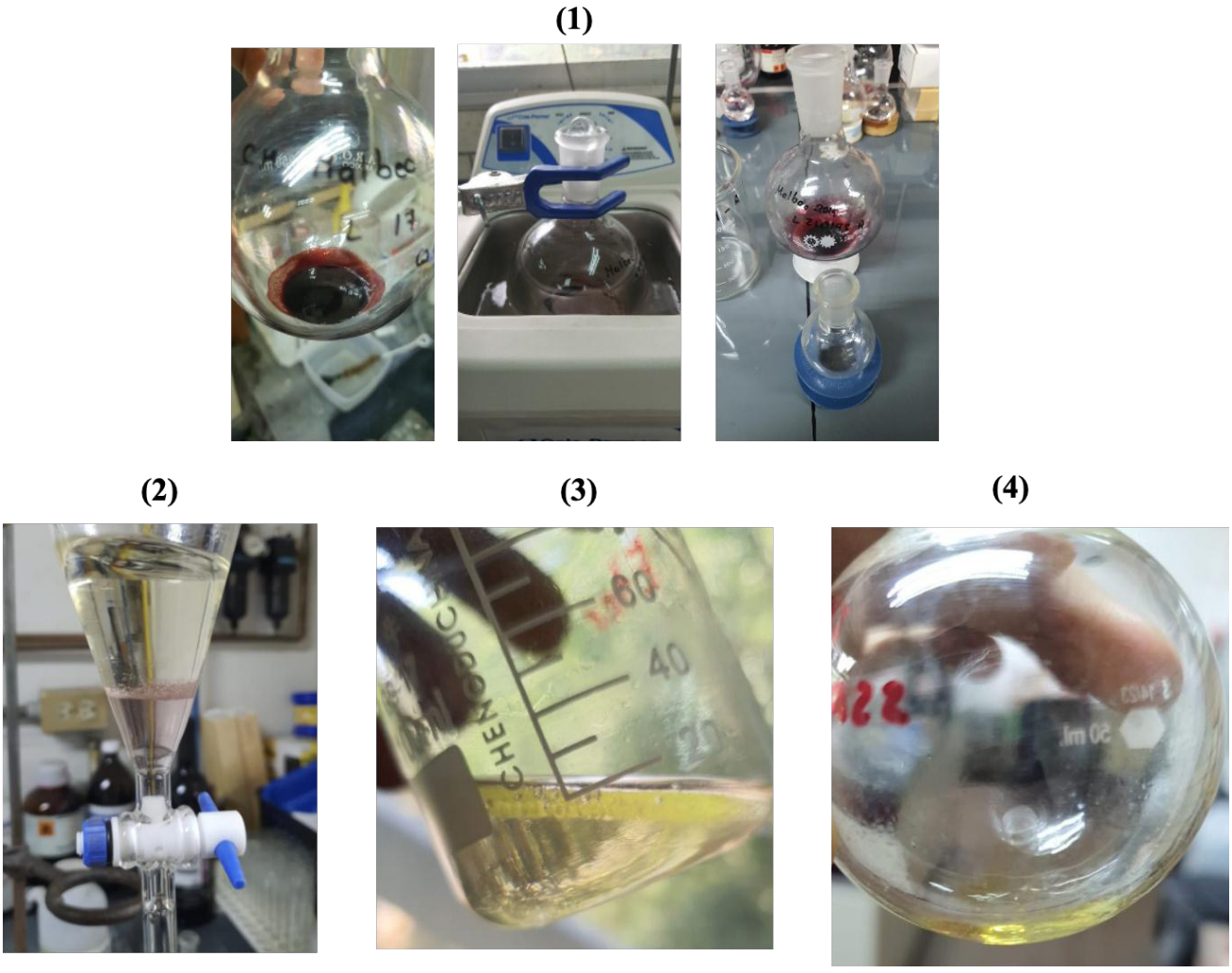


Figure 1. Sample preparation of Coahuila's Malbec organic extracts needed to identify PDMS. (1) Left / right: hydroalcoholic solvent elimination. Middle: wine concentrated extract mixed with 20 ml of CCl_4 HPLC grade for PDMS solubilization [9] and 42 kHz high-frequency sound waves ultrasonication during 10 minutes at 37ºC. (2) Left: after high frequency ultrasonication, mixture is versed into a separatory funnel for phase separation with no further convection. (3) after phase separations, CCl_4 extracts are versed in a 100 ml beaker for further concentration. (4) CCl_4 excess is eliminated with the aid of a rotary vacuum evaporator until having between 10 and 14 mg of a yellowish oil.

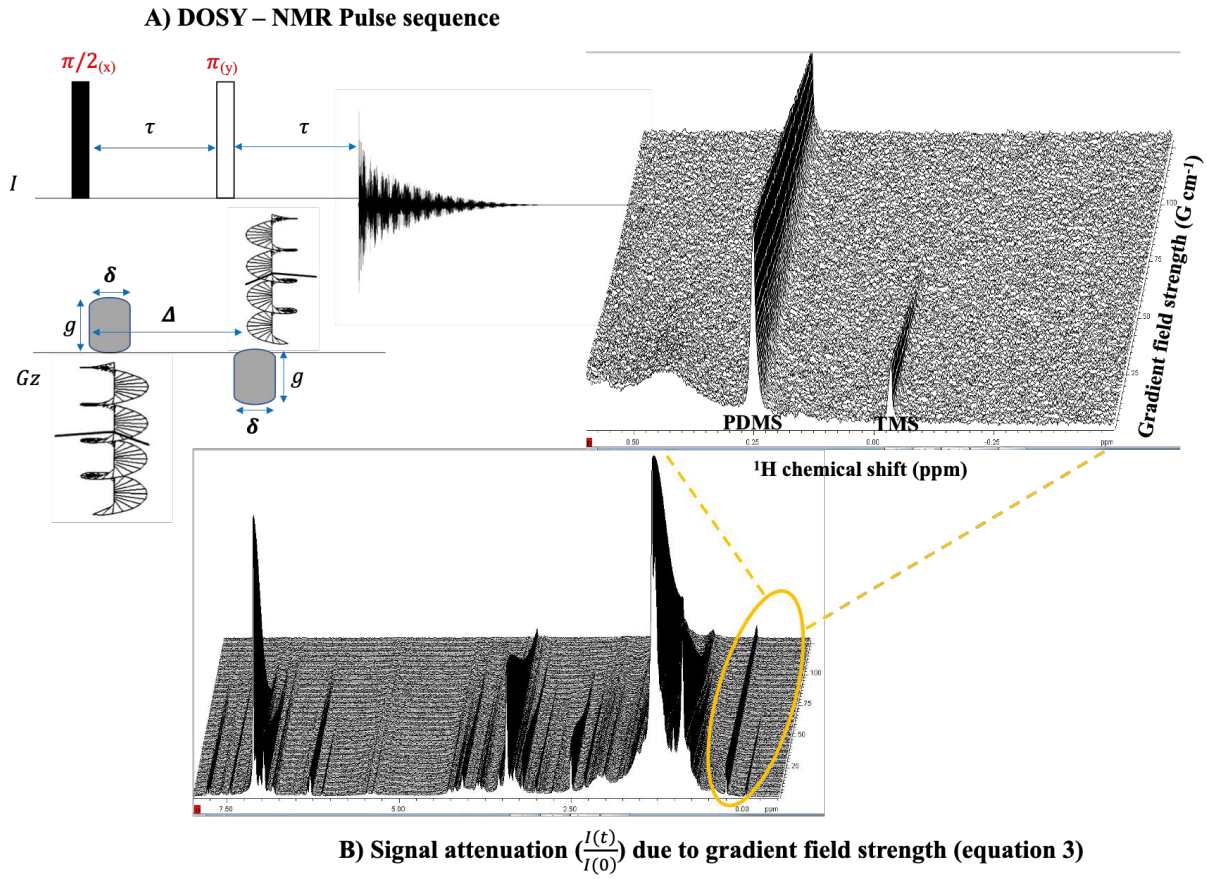


Figure 2. (A) Pulse sequence describing a DOSY – NMR experiment by means of applying a pulse-field gradient stimulated echo with gradient encoding & decoding during the τ -180º-τ echo module. ***Δ***: diffusion delay (duration between gradient encoding and decoding of 100 ms for the present work; δ: length of the square diffusion encoding gradient pulse 2.1 milliseconds in the present work for assuring signal decay of all spin systems except for PDMS; g: gradient amplitude from 0.04 G/cm (2%) up to 54 G/cm (100%) defining the indirect F1 dimension. (B) ^{1}H-NMR signal-attenuated spectra due to the application of gradients. An amplification between 0.5 and -0.5 ppm for illustrating differences between signal decays of TMS (standard with expected short R_H) and PDMS (expected moiety with biggest R_H within the extract).

3 Results

For a monodispersed sample, the diffusion coefficients (D) can be computed from PFG-DOSY monoexponential signal decay with Eq. (2):

$$I(\boldsymbol{g}) = I(0)exp[-(\gamma g\delta)^2 \, \mathrm{D} \, (\Delta - \frac{\delta}{3})] \quad (2)$$

γ: ^{1}H gyromagnetic ratio

g: gradient amplitude (from 2 to 98% of the maximum gradient strength of 54 G/cm)

δ: length of the diffusion encoding gradient pulse (gradient pulse duration of 2.1 ms in the present work)

Δ: diffusion delay (100 ms in the present work)

The non-exponential behavior of polydisperse solutions such as Malbec's organic extracts can be represented with an extension of Eq. (2) as follows:

$$\frac{I(t)}{I(0)} = \int_0^\infty P(D)e^{\left[-D(\gamma g\delta)^2\left(\Delta-\frac{\delta}{3}\right)\right]}dD \quad (3)$$

Numerical inverse Laplace transform (ILT) [17] is used in the present work to fit the distribution *P(D)* defined in non-exponential signal attenuation curves (Eq. (3) and Fig. 2), needed to extract the Diffusion Coefficient Distributions (DCDs) from DOSY NMR signal decay, to obtain in turn the Molecular Weight Distribution (MWD) from DCDs at the low concentration regime [18].

The entire set of computed diffusion coefficients (D) with Eq. (3), define in turn the DCD. The empirical scaling law that relates in turn the diffusion DCD and MWD [19] by means of the scaling parameters (K, α), is only valid within polydisperse systems at low concentrations, whereas K, α are retained as constants:

$$DCD = K(MWD)^{-\alpha} \quad (4)$$

Again, if the system is diluted enough, the empirical scaling law also establishes the relation between the weight-average molecular weights ($\dot{M}_w$) and the average from the diffusion coefficient distributions ($D_{average}$), expressed as [19]:

$$D_{average} = K(\dot{\mathrm{M}}\mathrm{w})^{-\alpha} \quad (5)$$

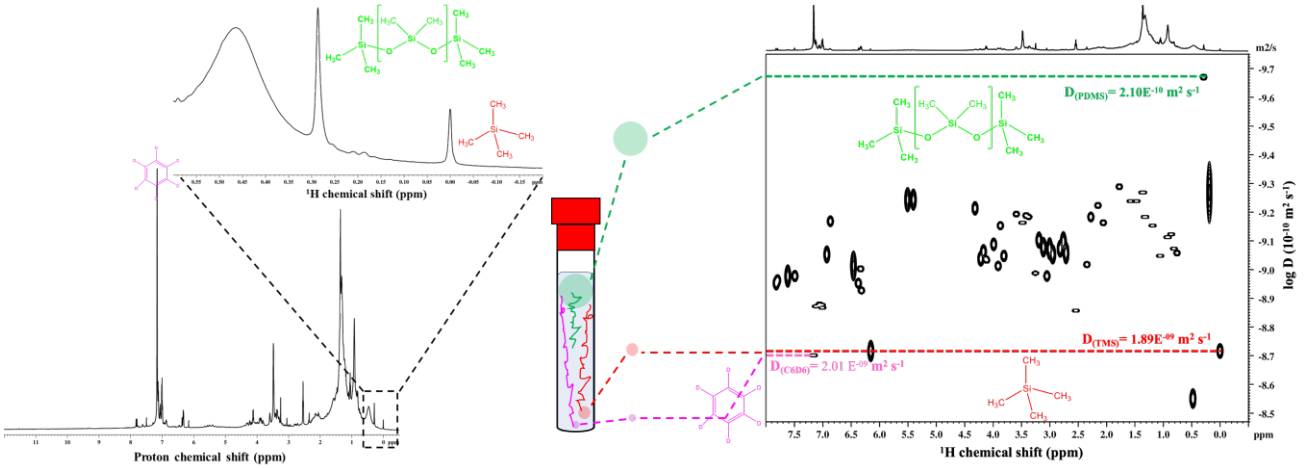
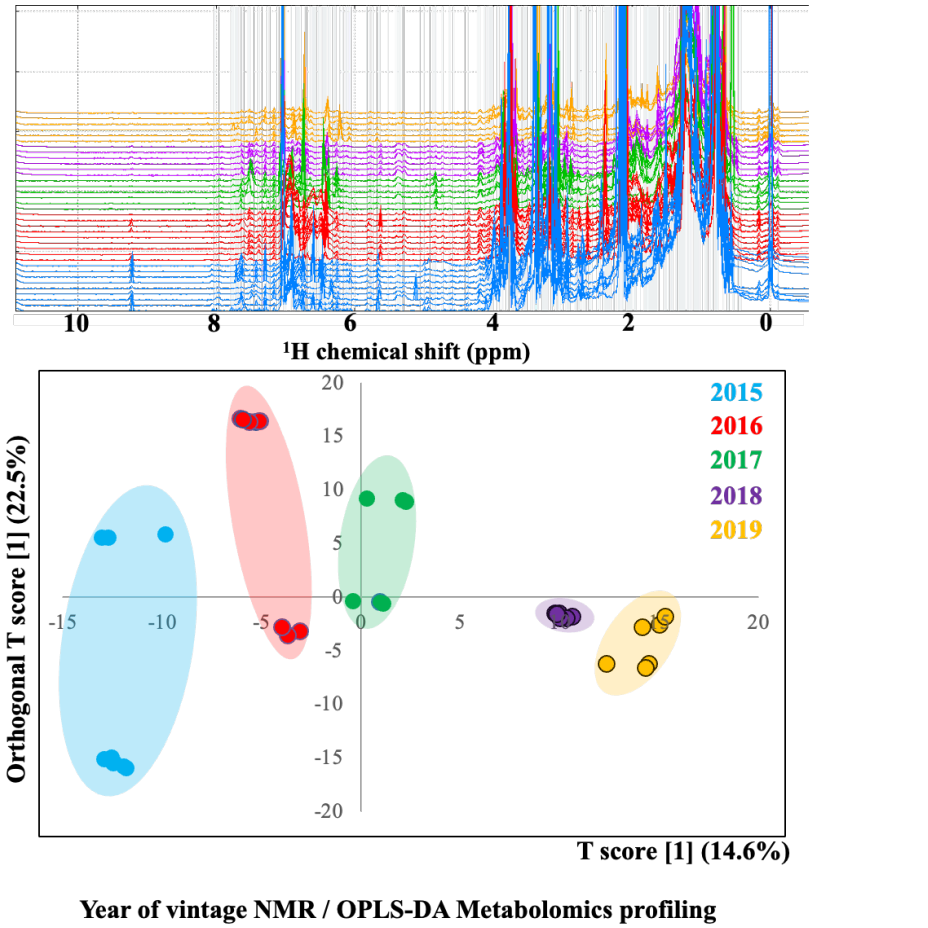


Figure 3. Left: q-^{1}H-NMR spectrum (Sect. 2.2.1.a) of a Mexican Malbec 2019 organic extract showing the relevant assigned signals such as benzene-d6 (magenta), tetramethylsilane (red) and extracted PDMS (green). Right: the 2D DOSY-NMR spectrum of the same Mexican Malbec 2019 organic extract, showing the average diffusion coefficients obtained with pulse sequence shown in Fig. 2A and Eqs. (3)-(5), with values of D= 2.01x10^{-9} m^{2}s^{-1} (benzene-d6), 1.89x10^{-9} m^{2}s^{-1} (TMS) and 2.1x10^{-10} m^{2}s^{-1} (PDMS), correlated with their ^{1}H chemical shifts at respectively 7.25 ppm, 0.0 ppm and 0.285 ppm.

In agreement with OIV resolutions [20] and recent literature [21] PDMS average molecular weight Mw is expected to be in a range between 6800 and 30000 Daltons, with hydrodynamic radii (R_H) between 5 and 30 nanometers. Biggest tackles for PDMS identification in food matrixes mostly comprise limited chemical speciation and possibilities to identify trace silicon moieties. AAS and AES spectroscopies [22,23], as well as ICP [23] and FTIR / Raman [24] analytical methods suffer from either lack of specificity (i.e., lack of chemical speciation, detecting only total organic-inorganic silicon content) and / or sensibility (high limits of detections). Even 1D-^{1}H-NMR spectroscopy by exclusively using a chemical-shift analysis of CH_3-Si moieties might lack of specificity, as within the proton chemical range between 0 and 0.5 ppm, diverse methyl silanes or siloxanes spin systems might limit the identification of PDMS. Once established the hurdles that involve PDMS identification and the theoretical background of DOSY-NMR spectroscopy applied in complex matrices, it is briefly described the full workflow for unambiguously detecting PDMS by 2D-DOSY-NMR from wines' organic extracts. Figure 1 resumes sample preparation within a basis of PDMS extraction with CCl_4 and the use of ultrasonication with phase separation. 50 milliliters of wine samples produce an average of 10-14 milligrams of organic yellowish oil extract (Fig. 1.4.). The concentrated organic extract is dissolved in 0.65 ml of C_6D_6 and 0.025 ml of $(CH_3)_4$ Si at a concentration of 2x10^{-3}M. Malbecs' organic extracts from all 2015-2019 vintages were analyzed first with standard quantitative ^{1}H-NMR experiments (Figs. 3 left and 4), NMR Data Matrix for OPLS-DA). All spectra show two signals between 0.3 and 0.0 ppm proton chemical shift mainly assigned as respectively PDMS (green in Fig. 3 left, with an experimental ^{1}H chemical shift of 0.285 ppm) and TMS (red in Fig. 3 left, with an experimental referenced ^{1}H chemical shift of 0.0 ppm), in full agreement to previous reports (Fig. 1, reference [9]. However, in both present work and state of the art [9], it remains unclear the correct assignment by exclusively using 1D NMR schemes, particularly if in observed overlaid proton chemical range between 0.6 and 0.3 ppm -revealed in both reports as a broad resonance of approximately 180 Hz of frequency width at half heigh (FWHH)- might be some PDMS traces or further CH_3-Si moieties, not or incorrectly assigned. In response to this chemical speciation limitation that q-^{1}H-NMR spectroscopy possess, the implementation of a second dimension with 2D-DOSY-NMR is justified. The DOSY-NMR experiment generates a second dimension by having series of embedded 1D-^{1}H NMR experiments (128 stacked 1D-^{1}H NMR experiments for the present study, see Sect. 2.2.1.b and Fig. 2B), whereas the variable within the second dimension is the gradient strength increase ("g" in Fig. 2A, DOSY-NMR pulse sequence) from 0.04 G/cm (2%) up to 54 G/cm (100%) gradient amplitude. In order to obtain a diffusion coefficient dimension as observed in 2D-DOSY-NMR spectra in Figs. 3 right and 4 bottom, signal attenuation of each resonance observed in stacked 1D-^{1}H-NMR series (Fig. 2B) due to gradient field strength, is mathematically fitted with Eqs. (3-5) [6-8] in order to have an average diffusion coefficient second dimension, either in absolute value or in its -log simplified representation are valid DOSY representations.



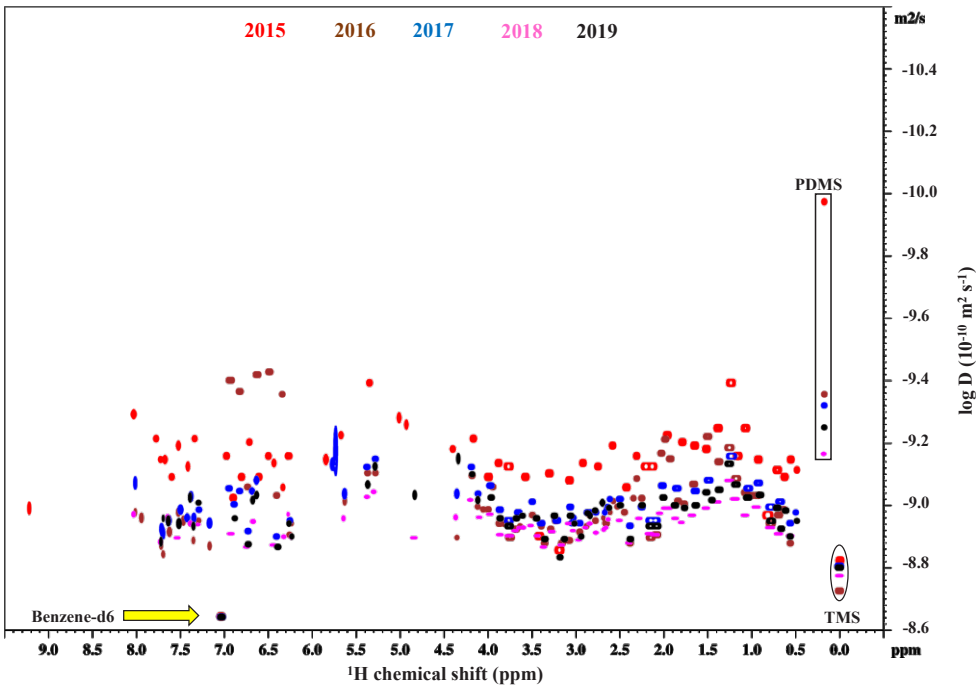


Figure 4. Top: Supervised Orthogonal Projections to Latent Structures Discriminant Analysis (OPLS-DA) score plot obtained from the q-^{1}H-NMR data matrix of the 2015 (blue), 2016 (red), 2017 (green), 2018 (violet) and 2019 (yellow) Coahuila's Malbec organic extracts, as a year of vintage metabolomics fingerprint [10]. Bottom: The 2D-DOSY-NMR spectrum of 2015 (red), 2016 (brown), 2017 (blue), 2018 (magenta) and 2019 (black) Coahuila's Malbec organic extracts acquired for PDMS identification. As in Fig. 3, the obtained average diffusion coefficients were internally referenced with respect the benzene-d6 solvent signal at a value of 2.01 x 10^{-9} m^2s^{-1} (-log *D*= 8.69).

As observed in Figs. 3 right and 4 bottom, multiexponential mathematical fitting of each ^{1}H chemical shift signal attenuation due to gradient field strength increment in DOSY-NMR experiment (Fig. 2B), produce different (-log) diffusion coefficients with a range between $2.01x10^{-9}$ m^2s^{-1} (-log *D*= 8.9) and $2.1x10^{-10}$ m^2s^{-1} (-log *D*= 9.7). The smaller the $D_{average}$ value is (the more negative is the -log *D* value), the slower the translational diffusion will be, typically attributed to species with bigger R_H. In other words, species with higher molecular weight (higher R_H), will have a smaller diffusion value, equivalent to a more negative -log *D* value, and thus will appear at the upper y-axis of the 2D-DOSY-NMR spectra in Figs. 3 right and 4 bottom. Diffusion values are referenced with respect the C_6D_6 solvent moiety, with ^{1}H chemical shift of 7.25 ppm and a $D_{average}$ value of $2.01x10^{-9}$ m^2s^{-1} (-log *D* of 8.69), in full agreement with previous reported data [25]. With respect the benzene-d6 diffusion reference, TMS chemical shift internal standard reference (0.0 ppm) produce a $D_{average}$ value of $1.89x10^{-9}$ m^2s^{-1} (red in Fig. 3 right and -log *D* TMS values within a range of 8.70 - 8.81 in Fig. 4 bottom). Interestingly, PDMS (^{1}H chemical shift of 0.285 ppm) present an order of magnitude slower $D_{average}$ value of $2.1x10^{-10}$ m^2s^{-1} (green in Fig. 3 right, -log *D*= 9.67) with translational diffusion intervals between $6.6x10^{-10}$ m^2s^{-1} (-log *D*= 9.18) and $1.25x10^{-10}$ m^2s^{-1} (-log *D*= 9.9).

Validation of $D_{average}$ values can be done by substituting de diffusion coefficient value in Eq. (1), considering that the Boltzmann constant (K_B) is $1.38x10^{-23}$ J/K temperature (*T*) of DOSY-NMR experiments was 298 K in all cases, dynamic viscosity (η) of the organic extract with C_6D_6 and 2 mM of TMS was 70 centipoise average, in order to obtain R_H of PDMS with respect TMS, by referring each diffusion coefficient with respect the C_6D_6 $D_{average}$ value of 2.01 x 10^{-9} m^2s^{-1} (-log *D*= 8.69), that in turn will provide a R_H average value of 0.15 nm for deuterated benzene. State of the art reports R_H values for TMS and $CDCl_3$ of respectively 2.05 Å (0.25 nm) and 1.65 Å (0.165 nm) [25].

Table 1. Experimental $D_{average}$ values and calculated R_H [in square parenthesis] for PDMS and TMS in 2015-2019 Malbec organic extract batches.

Malbec batch	PDMS (δ= 0.285 ppm) *D* (m^2s^{-1}) [R_H (nm)]	TMS (δ= 0.0 ppm) *D* (m^2s^{-1}) R_H (nm) Ref. value= 0.25 nm [25]
2015	$1.25x10^{-10}$ [24.76]	$1.51x10^{-9}$ [0.21]
2016	$4.47x10^{-10}$ [6.98]	$1.95x10^{-9}$ [0.16]
2017	$4.78x10^{-10}$ [6.51]	$1.55x10^{-9}$ [0.2]
2018	$7.1x10^{-10}$ [4.4]	$1.74x10^{-9}$ [0.18]
2019	$5.75x10^{-10}$ [5.42]	$1.58x10^{-9}$ [0.2]

Table 1 reports the diffusion coefficients of each PDMS / TMS silicone moieties characterized in each 2015-2019 Malbec batches. Said $D_{average}$ values are substituted in Eq. (1) for obtaining hydrodynamic radii of identified PDMS within organic extracts.

Finally, Fig. 4 top shows the NMR based metabolomics supervised OPLS-DA score plot [10] obtained from the q-^{1}H-NMR data matrix (Sect. 2.2.1.a) of the 2015-2019 Coahuila's Malbec organic extracts, as a year of vintage metabolomics fingerprint. It is shown that despite coming from a wine extract, quantitative proton NMR data matrix of Malbec's organic extracts is sufficiently discriminant towards an unambiguous identification of samples' year of vintage. The last opens the venue for a novel wine metabolomics generation for identifying and quantifying relevant discriminant metabolites towards diverse discriminant factors. Furthermore, 2D-DOSY NMR spectra of each 2015-2019 Malbec organic extract present a specific holistic diffusional pattern whereas PDMS and TMS calculated R_H values (Table 1) are in full agreement with expected values [25].

4 Conclusions

Present work attends for the first time a required OIV method for identifying polydimethylsiloxanes in wine samples. The methodology includes an organic extraction of the oenological sample with ultrasonication and phase separation in order to retain PDMS in a CCl_4 matrix. Nuclear magnetic resonance spectroscopy of wine organic extracts for PDMS identification has shown its specificity for identifying $(CH_3)_3$-SiO-$[(CH_3)_2$-SiO-$]_n$-OSi-$(CH_3)_3$ polymers by DOSY-NMR, whereas PDMS will present a range of diffusion coefficient values between 7.1 x 10^{-10} m^2s^{-1} and 1.25 x 10^{-10} m^2s^{-1} that define expected PDMS hydrodynamic radii between 4.4 and 24.76 nm. Finally, for the first time, a NMR based metabolomics supervised approach has been tested for a wine organic extract, showing the capacity of the q-^{1}H-NMR data matrix to discriminate relevant oenological factors such as year of vintage. DOSY-NMR limits of detection, quantification and linearity for PDMS quantitative analysis will be elsewhere published.

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