Electrospray ionization mass spectrometric solvate cluster and multiply charged ions: a stochastic dynamic approach to 3D structural analysis

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Abstract

The data analyzed in this paper are on quantitative and 3D structural determination of ionic ensembles and multiply charged solvates ions of type $[(\text{Cl})(\text{H}_2\text{O})_x(\text{H}_3\text{O})_y(\text{CH}_3\text{CN})_z]^+$, $[(\text{Cl})(\text{O}_2)_x(\text{CH}_3\text{OH})_y(\text{NH}_4)_z]^+$, $[(\text{O}_2)_x(\text{H}_2\text{O})(\text{H}_3\text{O})(\text{CH}_3\text{CN})]^+_n$ and $[(\text{Cl})(\text{H}_2\text{O})_2(\text{H}_3\text{O})(\text{CH}_3\text{CHNH}_2)]^+$ observable under electrospray ionization conditions in presence of Zn^{II} -ion containing metal-organics, where $x = y = z = 1-3$ are the number of molecules, respectively, ions participating into each of the interacting ensemble, while “n” denotes the number of interacting ensembles forming the more complex ionic clusters. The major theoretical problem we have to deal with is the applicability of our more recently developed stochastic dynamic concept and formulas connecting among the mass spectrometric variable *intensity*, the so-called *stochastic dynamic diffusion parameters* (D_{SD}), the temperature (T) and the analyte concentration in solution to such challenging molecular/ionic systems from the perspective of molecular structure. The D_{SD} parameters of analyte ions correlate linearly with the so-called *quantum chemical diffusion parameters* (D_{QC}) according to the Arrhenius’s theory. The work has demonstrated persuasively that these equations are capable of providing reliable analytical information about so complex ensembles of interacting species. It shows their significant advantages as analytical approaches, amongst other rival concepts, to quantify the mass spectrometric outcome *intensity* highly accurately, selectively, precisely and sensitively. The thermodynamics parameters of common reactions of the following ionic species observable under electrospray ionization experimental conditions of some tetrachlorozinc(II) complex ions of metal-organics are examined. These are the ions $[(\text{Cl})(\text{H}_2\text{O})(\text{H}_3\text{O})_2(\text{CH}_3\text{CN})_3]^+$ (m/z 214/216), $[(\text{Cl})(\text{H}_2\text{O})(\text{H}_3\text{O})_2(\text{CH}_3\text{CN})_2]^+$ (m/z 173/175), $[(\text{Cl})(\text{H}_2\text{O})_2(\text{H}_3\text{O})_2(\text{CH}_3\text{CN})]^+$ (m/z 150/152), $[(\text{Cl})(\text{H}_2\text{O})(\text{H}_3\text{O})_2(\text{CH}_3\text{CHNH}_2)]^+$ (m/z 134/136,) $[(\text{Cl})(\text{H}_2\text{O})_2(\text{H}_3\text{O})(\text{CH}_3\text{CHNH}_2)]^+$, $[(\text{Cl})(\text{H}_2\text{O})(\text{H}_3\text{O})_2(\text{CH}_3\text{CN})]^+$ (m/z 132/134,) $[(\text{Cl})(\text{H}_2\text{O})_2(\text{H}_3\text{O})_2(\text{CH}_3\text{CN})]^+$ (m/z 183/185), $[(\text{CH}_3\text{OH})(\text{H}_2\text{O})_5(\text{NH}_4)(\text{CH}_3\text{CN})_3]^+_{-3}$ (m/z 263,) and $[(\text{CH}_3\text{OH})(\text{H}_2\text{O})(\text{H}_3\text{O})(\text{CH}_3\text{CN})]^+_{-31}$ (m/z 110,) respectively.

Keywords Mass spectrometry · Solvate clusters · Diffusion · Quantum chemistry · Zn^{II} -complexes

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1 Introduction

The current paper addresses the 3D structural analysis of solvate clusters and multiply charged species in presence of Zn^{II} -ion containing metal-organics of small molecules by means of electrospray ionization mass spectrometry (ESI-MS) and our model formulas (1)–(4) developed more recently [1–5] as powerful approaches to treat quantitatively the experimental variable *intensity* (I) of analyte's peaks.

$$D_{SD}^{\text{tot}} = \sum_i^n D_{SD}^i = \sum_i^n \left(1.3194 \cdot 10^{-17} \times A^i \times \frac{\bar{l}_i^2 - (\bar{l}_i^2)}{(\bar{l}_i - \bar{l}_i)^2} \right) \quad (1)$$

$$\ln\left(\frac{(\bar{l}_i - \bar{l}_i)^2}{(\bar{l}_i - \bar{l}_i)^2}\right) = -\ln\left(-\left(\ln\left(\frac{k_B \times T}{m}\right)\right)^3 \times \frac{2 \times \Delta t \times T \times k_B}{m \times D_{SD}}\right) \quad (2)$$

$$\ln\left(\frac{(\bar{l}_i - \bar{l}_i)^2}{(\bar{l}_i - \bar{l}_i)^2}\right) = -\ln\left(-\left(\ln\left(\frac{k_B \times T}{C_M \times (m/z)}\right)\right)^3 \times \frac{2 \times \Delta t \times T \times k_B}{C_M \times (m/z) \times D_{SD}}\right) \quad (3)$$

$$A^i = \frac{m}{-\ln\left(\frac{k_B \times T}{m}\right)^3 \times 2 \times T \times \Delta t \times k_B} \times D_{SD}^i \quad (4)$$

What is obtained as analytical information by these equations is highly accurate, precise, selective and sensitive quantification of the measurable variable depending on the analyte concentration in solution (C_M) [4–6] and the temperature (T) by introducing the D_{SD} -parameter as mentioned above. Equation (4) has been written as a conjunction between the statistical parameter A_i obtained as a result from the SineSqr fitting of the experimental function $(I - \langle I \rangle)^2 = f(t)$ and the D_{SD} -parameter within the framework of the empirical modification of the characteristic function *diffusion* in the forward Fokker–Planck equation, which we have carried out [5]. Equation (4) aims at explaining the physical meaning of the statistical parameter.

For the purposes of this study we would like to emphasise that the D_{SD} -parameter correlates linearly with the D_{QC} -one, thus, establishing a direct connection of MS outcomes and other experimental factors with 3D molecular and electronic structures of the analytes. The chemometrics of a small-scale research, so far, has shown correlation coefficients $|r| = 0.9557_5 - 0.9998_1$ looking at D_{QC} and D_{SD} data of organics and metal-organics [3]. The correlation between theory and experiment according to Eq. (2)

shows $|r| = 0.9900 - 0.9995$ [4, 5], while the chemometrics according to Eq. (3) yields to $|r| > 0.9999_4$ [6].

This contribution offers the reader a study of solvate species and multiply charged solvent containing complexes, which quantitative and structural determination by mass spectrometry represents significant analytical challenge, despite, superior method performances of the instrumentation [1–5]. At first consideration the reader might suppose that the observation of such clusters and multiply charged cations are a typical phenomenon under ESI-MS conditions. Thus, this issue, presumably, can be regarded as a well-studied problem, due to enormous effort devoted to develop MS methodology for analytical purposes over decades [7–16]. However, there is an important part of research contributions to study solvation-desolvation reactions under ESI-MS conditions. We should say much about it. The area has been a topic of great interest, because of the ESI method has been developed primarily as a powerful approach to analyse microscopic molecular structures and properties of analytes in solution [17–19]. The method is capable of transferring the analyte from solution to the mass spectrometric analyser without to change their 3D molecular structure. ESI-MS, therefore, appears a prominent approach to quantify noncovalent interactions [20].

Given that, it is doubtful, that there can be added innovative knowledge on this issue. Despite, enormous effort and newcomers of the ESI-MS method and in spite of its almost routine implementation into the analytical practice as irreplaceable approaches to quantify, up until now, its phenomenology and exact mechanism of ionization of the analyte from the initial solution are a matter of debate [7–22]. It is acknowledged that the method transfers a small fraction of the analyte in solution into the mass analyser [23]. This simplistic picture does not provide in-depth understanding neither of the mechanisms of ionization of analytes, nor of the mechanisms of formation of cluster ions. It does not detail mechanisms of production of multiply charged species, as well. The major reason, why there is a rather lack of consensus about these aspects of the ionization reactions of molecules under ESI experimental conditions is that different MS phenomena could be explained within the framework of more than one theoretical proposals. We would like to consider arguments available to the different important concepts, amongst others, in addition to, known controversy in experimental results in order to highlight the crucial contribution of this work and our model formulas (1)–(4) to detail quantitatively and structurally at a molecular level ESI-MS processes.

To begin with, there is a broad range of interpretations of basic proposals behind the ionization phenomena. The major one is that under ESI experiment to a sample

in polar solution—its concentration is $< 10^{-5}$ M—there is applied electrical potential (~ 35 V) yielding to plume of charged droplets with nearly maximal charge and radius $R \sim 200\text{--}100\text{ }\mu\text{m}$ [7–30]. These droplets produce droplets having smaller size ($R < 39\text{ }\mu\text{m}$.) At a critical size, where the repulsion due to Coulombic forces overcomes the droplets' surface tension, there is obtained the so-called *Coulombic fission* or emission of micro-to-nano-size particles ($R = 0.1\text{--}1\text{ }\mu\text{m}$ [31–35]) and current stream $< 1 \cdot 10^{-6}$ A [7]. The droplet's charge at the critical size is functionally related with the surface tension within the framework of the Reyleigh's equation [30]. The quantitative relation of the dispersion ratio depends on the charge of the droplet, its radius and the surface tension coefficient [36]. However, when the critical radius becomes $< 1\text{ }\mu\text{m}$ [31], then there is unable to observe experimentally the ejected offspring drops from parent drops. The transport of analytes from bulk solution in the droplets to their surfaces at micro-to-nano-scale size particles is determined by turbulent flow [21]. The chemical content of the surface and in the bulk of the droplets should be different. This raises a dynamic concentration gradient. The energetics of such systems is determined by the *Lewis acidic-base* interaction, *Lifschitz-van der Waals*, *Brownian free energy* and *electrostatic interaction* terms, respectively [31–35]. The *Brownian free energy* determines the inter particle interactions at micro-to-nano-size particles. The instability of such systems and their time evolution behaviour are determined by the surface inhomogeneity of the surface tension. The accident *fluctuations* of the latter parameter and the gradient of the surface charge density are balanced [12]. A model of aerosol particles of single ion of analyte and *solvent shell*, in this context, has met a qualitative confirmation. Charged species of type $[\text{Na}(\text{H}_2\text{O})_n]^+$ (n denotes the number of solvent water molecules; $n = 3\text{--}7$) have been mass spectrometrically determined. However, the ions of alkali metals lack of coordination capability of solvents. The so-called *solvent shell* can be described as physically heterogeneous layer. It is between the analyte and the vacuum. It can have or cannot have analyte-solvent microstructure. Therefore, mechanistic insights of solute-solvent, solvent-solvent and solute-solute interactions should be detailed at a molecular level. Many of these ESI-MS phenomena observed, so far, have been explained successfully using the shown above concept of ionization mechanism. It has been developed by Iribarne and Thomson [33, 34]. It is called *ion-evaporation model*. Nevertheless, often ESI-MS outcomes have been tackled successfully by the so-called *charge-residue model* by Dole [37]. It assumes that the final droplet contains only one molecule of the solute. It is detected when the last solvent molecule is evaporated. Other observations have been successfully detailed by an extended *charge-residue model* by Gamero-Castano and

de la Mora, as well [38]. It represents a combination of the aforementioned models stating that within the concept of the *ion-evaporation model* only singly charged ions can be realized. The same is true for the model of Hogan et al. [39], which, again, can be described as a combination from the models, mentioned before.

Despite, successful application of *ion-evaporation* and *charge-residue models*, as well as, their extended concepts, there are controversial experimental data on their application, focusing attention on mechanisms of formation of macromolecular ions under ESI-MS conditions. A maximum charged state of a macromolecule needs to use additives with significantly high surface tension; or, the surface tension does not appear the only factor in maximizing the droplets' charge. Moreover, there are controversial optical spectroscopic data on experiments designed to answer to a question: "Where are produced analyte ions: in plume entering the interface or in the atmospheric interface?" A production of analyte ions in entering the interface has been proposed studying organic reactions of charged micro-droplets over a span of the time of millisecond.

Since, the central goal of this contribution is to quantify and determine structurally ESI-MS multiply charged ions and solvate clusters, the reader has to keep in mind the following facts, determining the research task as a significant challenge. One point that emerges from the description of the ESI-MS methodology, so far in this introductory section is that the exact mechanisms of formation of clusters and multiply charged ions are not fully understood, as well [40]. Clusters can be formed in the final stage of the process of desolation. The phenomenon has been explained with high concentration of the analytes and strong solute-solvent interactions in micro-to-nano-size droplet particles. Besides, there is a lack of knowledge on multiply charged ions under ESI-MS conditions [41–43]. Because of, such species are unstable in *gas-phase* (GP). Conversely, the multiply charged ions are predominantly stable in condense phase, due to, electrostatic solute-solvent interactions and a process of solvation [41]. In the so-called GP the Coulombic repulsion dominates. There is a lack of stabilizing factors typically found in condense phase. Multiply charged ions are fragile to fragment processes or electron loss. Nevertheless, such types of ions have been detected mass spectrometrically by ESI method [44–48]. Further, it is acknowledged that the changed state of the species in solution does not correspond frequently to this observed mass spectrometrically [49]. There has been documented the increasing in this changed state by adding less volatile additives to the initial analyte solution. Therefore, there has been proposed an important role of the droplet's surface tension parameter in determining the charge-state of the measurable analyte. Also, in the ESI plume there is a change of the pH [50–52].

In the light of these assumptions and observations [21, 22, 41, 44–48] there arises a very important question whether the ESI-MS continuum can be regarded as a GP. Because of, if we are going to carry out a comparative analysis between experiment and theoretical quantum chemical treatment of thermodynamics, diffusion, kinetics and structural parameters, from the perspective of computational chemistry—a strategy, which we use to determine structurally MS species according to Eqs. (1) and (2)—there should be detailed experimental and molecular factors in order to ensure a reliable theoretical data. Work [21] assumes, in this context, that the *free Gibbs energy* (hereafter ΔG) values are obtained by summing up energy parameters of the molecular system in bulk and on the surface. Since, the derivation of Eq. (2) sheds light of the latter issue, we will draw conclusions about the accurate prediction of thermodynamics and diffusion parameters of ESI-MS processes in section “Discussion” by adding new experimental and theoretical facts.

So far, in this introductory section we have taken a brief look at concepts of ionization mechanisms. Besides, we have introduced our SD equations which we have developed as approaches to quantify the temporal behavior of the variable *intensity* with respect to short spans of the scan time.

However, little attention has been focused on challenge tasks of theoretical analysis of D_{QC} parameters of solvate cluster and multiply charged ions. Passing over the difficulty in detail understanding of the nature of the MS continuum, we can at this point turn to another problem. The task of determining the D_{QC} data theoretically has its own problems, as well. Their roots are in modeling of solute–solvent and solvent–solvent interactions. Since, the ΔG -parameter, which we employ as quantitative criterion determining the thermodynamics stability of MS ensembles of interacting molecules and ions in clusters and multiply charged species is very sensible toward perturbation or change of the multidimensional molecular structure of the species, respectively, their intramolecular/ionic interaction networks, it should be obvious that the micro-molecular ensembles should produce many MS peaks. This research task tolerates a significant amount of uncertainty in determining D_{QC} parameters of ionic ensembles, requiring pinpointing subtle perturbations of electronic structures and intermolecular/interionic interaction schemes. Reliable conclusions on D_{QC} parameters of such systems have to be judged precisely in the light of a statistically representative set of models of species.

Looking at the interdisciplinary application of our study, this tackled very important problematic is characterized by a direct line between fundamental aspects of the quantitative MS analysis of solvate clusters and multiply charged ions

and the application of formulas (1)–(4) to study atmospheric aerosols [53, 54].

To sum up, throughout this paper we put a very strong emphasis on applicability of our stochastic dynamic (SD) concept [1–6] and Eqs. (1), (2) and (4) to quantify and determine 3D structurally not only molecular ions of analytes, but also very complex and challenging from the perspective of the experimental MS and theoretical quantum chemistry analytes such as clusters of charged solvents and multiply charged species.

2 Experimental

2.1 Materials and methods

Mass spectrometric data were obtained by TSQ 7000 instrument (Thermo Fisher Inc., Rockville, MD, USA). A triple quadrupole mass spectrometer (TSQ 7000 Thermo Electron, Dreieich, Germany) equipped with an ESI 2 source were used to ESI-MS measurements. A LTQ Orbitrap XL (Thermo Fisher Inc.) was utilized. A combination of mass detectors (trap, linear ion trap and orbitrap) accumulating spectra over a span of the time of the measurements $\tau = 17$ min (1020 s) was used. (Consider the experimental conditions in Table A1.) The experimental datasets were processed by QualBrowser 2.7, ProteoWizard 3.0.11565.0 (2017) and AMDIS 2.71 (2012) software. The chromatographic analysis was carried out by Gynkotek (Germering, Germany) HPLC instrument. It is equipped with a preparative Kromasil 100 C18 column (250 × 20 mm, 7 μ m; Eka Chemicals, Bohus, Sweden) and a UV detector set at 250 nm.

2.2 Synthesis and sample pretreatment

2.2.1 Synthesis

The coordination metal-organic complex species of type tetrachlorozinc(II) dianion with *bis*(2-hydroxy-quinolinium) (1) and 2-morpholinium-4-yl-ethylammonium (2) counterions were synthesized according to [55]. The monitoring of the reactions has been carried out by UV–VIS spectroscopy. The 3D molecular structures determined crystallographically of analytes (1) and (2) can be found in [55].

2.2.2 Determination of statistical parameters accuracy and precision

The *accuracy* has been obtained using measurements in multiplication of crystals (1) and (2) at concentration 1 μ g (mL)^{−1} according to [56–61].

2.2.3 Determination of statistical parameters repeatability and reproducibility

The *repeatability* is evaluated, as well. Three independent measurements of two replicated crystalline samples of (1) and (2) are processed by chemometrics. The convention [56–61] is used to calculate the *repeatability* and *reproducibility*. They are determined according to formulas: $2 \cdot (2)^{1/2} \cdot \text{sd}'(\text{yEr} \pm)$ and $2 \cdot (2)^{1/2} \cdot \text{sd}''(\text{yEr} \pm)$. The $\text{sd}'(\text{yEr} \pm)$ and $\text{sd}''(\text{yEr} \pm)$ denote short and long-time standard deviations. The latter parameter is obtained over a span of time $t = 3$ months.

2.3 Theory/computations

2.3.1 Quantum chemical computations

The GAUSSIAN 98, 09; Dalton2011 and Gamess-US [62–64] program packages were used. The output files were visualized by GausView03 [65]. Ab initio and DFT molecular optimization was carried out by means of B3LYP, B3PW91 and ω B97X-D methods, respectively. The Truhlar's functional M06-2X was used, as well [66, 67]. The algorithm by Bernys was taken into determine the ground state (GS.) The stationary points at the potential energy surface (PES) were obtained by harmonic vibrational analysis. The criterion confirming minima of the energy is the absence of imaginary frequencies (negative eigenvalues) of second-derivative matrix. The basis set cc-pVDZ by Dunning, 6–31++G(2d,2p) and quasirelativistic effective core pseudo potentials from Stuttgart-Dresden(-Bonn) (SDD, SDDAll, <https://www.cup.uni-muenchen.de/oc/zipse/los-alamos-national-laboratory-lanl-ecps.html>) were used [68]. The zero point vibrational energy (ZPE) and vibrational contributions have been accounted for up to a magnitude value of 0.3 eV. Species in solution were examined by of explicit super molecule and “mixed” approach of micro hydration. The polarizable continuum method (PCM) is used. The effect of the ionic strengths in solution was accounted for integral-equation-formalism polarizable continuum model (IEF-PCM). Merz-Kollman atomic radii and heavy atoms UFF topological models were used. Large species were treated using own N-layer integrated molecular orbital and molecular mechanics (ONIOM) method. The electrostatic potentials (ESPs) and natural bond orbital (NBO) methods are applied, as well. The molecular dynamics (MD) was performed by ab initio Born Oppenheim (BO) approach. The BOMD was also carried out at M062X functional and SDD or cc-pvDZ basis sets, without to consider periodic boundary condition. The trajectories were integrated using Hessian-based predictor–corrector approach with Hessian updating for each step on BO PES. The step sizes were 0.3 and 0.25 amu^{1/2}Bohr. The trajectory analysis stops when: (a) centres of mass of a dissociating fragment

are different at 15 Bohr, or (b) when the number of steps exceed the given to as input parameter maximal number of points. The total energy was conserved during the computations within at least 0.1 kcalmol^{−1}. The analysis was performed by fixed trajectory time speed ($t = 0.025$ or fs) starting from initial velocities. The velocity Verlet and Bulirsch-Stoer integration approaches were used.

The Allinger's molecular mechanics force field MM2 was also employed [69]. The low order torsion terms is accounted with higher priority rather than van der Waals interactions [69]. The accuracy of the method comparing with experiment is 1.5 kJ.mol^{−1} studying diamante [70] The differences in heats of formation of alcohols and ethers is |0.04|–|6.02| kJ.mol^{−1} [70].

Crystallographic structural data on complexes (1) and (2) were used to input atomic coordinates during quantum chemical computations.

2.3.2 Our stochastic dynamic theory

Consider reference [1–6].

2.3.3 Chemometrics

The software R4Cal Open Office STATISTICS for Windows 7 was used [61]. The statistical significance was checked by *t*-test. The model fit was determined upon by F-test. Analysis of variance (ANOVA) was also used. The nonlinear fitting of experimental MS data was carried out by means of searching method based on Levenberg–Marquardt algorithm [56–60].

3 Results

3.1 Mass spectrometric data

3.1.1 Method performances

The D_{SD} parameters according to Eq. (1) are determined *per* span of scan time, which appears to be the major reason why the statistical parameters are determined *per* span of the scan time, as well. Figure A1 shows standard deviation and standard error of the measurements of (1) the *m/z*-values at about $\text{sd}(\text{yEr} \pm) \approx \text{se}(\text{yEr} \pm) \approx 10^{-5}$. The chemometrics of the *m/z*-value of (1) at *m/z* 111 shows the same order in magnitude of the value of the error contribution. However, the data on the *m/z*-values of the peak of (1) at *m/z* 134 clearly illustrate different magnitude of the value of the error of the measurements over different spans of the scan time. The $\text{sd}(\text{yEr} \pm) \approx 10^{-4}$ and $\text{se}(\text{yEr} \pm) \approx 10^{-5}$ are obtained over the span of the scan time $t = 9$ –13mins; and, $\text{sd}(\text{yEr} \pm) \approx 10^{-5}$ and $\text{se}(\text{yEr} \pm) \approx$

10^{-6} over $t = 13\text{--}16$ min. Thus, over different spans of the scan time we operate with different order in magnitude of the values of the standard deviation and standard error even quantifying MS peaks of the same analyte and dataset of m/z -values from a single measurement. In this context, the great advantages of our quantitative treatment of the MS intensity outcomes according to formulas (1)–(4) per span of the scan time is clearly demonstrated with the results depicted in the latter figure—our method provides significantly more accurate and precise quantitative description of the MS outcomes, comparing with the chemometric analysis of the data over the whole time of the measurements. The ANOVA analysis of the m/z -values of the peak at m/z 111 observed in the two compounds (1) and (2) shows that the datasets are equal. Therefore, from the perspective of chemometrics there is described the same or a common MS ion (Table A2.)

3.1.2 Isotope shapes of solvate cluster and multiply charged ions

Before getting to determine D_{SD} -parameters of complex ions of solvent molecules, there is an important matter that requires to be addressed. It is associated with the adequate assignment of complex ions on the base on the ratios of the isotope sub shapes. We will engage ourselves in an amount of discussion of such assignment including both theoretical and experimental ratios of isotope sub-components of common peaks of ions. Figures 1, 2 and A2 depict experimental ESI(+)–MS spectra of compounds (1) and (2). The isotope MS shapes at m/z 134.07/136.07 and 150.07/152.07 are assigned to solvate species $[(Cl)(H_3O)_2(H_2O)CH_3CHNH]^+$ and $[(Cl)(H_3O)_2(H_2O)_2CH_3CN]^+$. Mixed solvate complexes of H_2O and CH_3OH molecules are known [71]. Despite, the fact that there are mainly mixed ligand solvate complexes of transition metal ions, the chalcogenide ions, due to, electrostatic interactions appears a

Fig. 1 Chromatographic data on (1) (a); ESI-MS spectra of (1) within different range of the spectra (b); chemical diagrams of analyte (1) and ionic species; theoretical and experimental m/z -values and the ratios of the intensity values of the sub-peaks of the isotope shapes in (%)

Fig. 2 ESI-MS spectra of (2) within different range of the spectra; chemical diagrams of ionic species; theoretical and experimental m/z -values and the ratios of the intensity values of the sub-peaks of the isotope shapes in (%)

coordinative center of species of the type shown above. As can be seen, there is good agreement of experimental with theoretical values of intensity ratios of sub-peaks within the framework of the two isotope shapes. We will detail the chemical reactivity of the solvent acetonitrile under ESI-MS experimental conditions. Despite, acetonitrile exhibits a significant chemical stability under ESI-MS conditions, showing a rather great competitive binding capability of transition metal ions, thus producing corresponding metal solvate complexes [5, 71–85], the catalytic hydrogenation of nitriles is among the most preferred synthetic method yielding to secondary and primary amines [86]. In particular, their catalytic hydrogenation of acetonitrile in presence of transition metal ions is documented [86, 87]. The high chemical reactivity of the imine CH_3CHNH intermediate causes for determination of acetonitrile covalent adducts, mass spectrometrically [88–90]. Several mechanisms of the

reaction have been proposed, starting with the first work by von Braun [91] and a latter modification by Greenfield [92], in addition to a mechanism involving intramolecular proton transfer from acetonitrile CH_3 -group [93]. Following the reaction scheme, where the proton becomes attached to the N-atom of the nitrile CN -group of the solvent there has been proposed that the active intermediate could be stabilized only in presence of metal ion [94, 95]. In the light on our MS results we detail mechanistic aspects of the reaction (I) shown in Fig. 1 theoretically below accounting for the known concepts [91–95].

Among the another issues that we will address by this sub-section is the formation of charged water clusters of type $[(\text{O}_2)(\text{H}_2\text{O})(\text{H}_3\text{O})(\text{CH}_3\text{CN})]^+$ (m/z 110) under ESI-MS conditions. The monomeric unit shows theoretical intensity ratio of the sub peaks of the isotope shape m/z 110.0453 (100.0%) and m/z 111.04869 (2.2%). The

experimental data assume that a multiply charged ion $[(O_2)(H_2O)(H_3O)(CH_3CN)]^+_{50}$ having theoretical intensity ratios m/z 5503.2701 (100.00%), m/z 5502.2667 (89.9%) and m/z 5504.2734 (55.1%) occurs. This assumption agrees well with the experiment (Consider Figure A2, Appendix A in ESM.)

The same is true for the ion $[(CH_3OH)(H_2O)(H_3O)(CH_3CN)]^+_{31}$ showing theoretical intensity values of the monomeric unit: m/z 110.0817 (100.0%) and 111.0851 (3.3%).

The multiply charged ion is characterized by m/z 3413.5366 (100.0%), 3412.5333 (96.7%) and 3414.54 (51.2%), respectively.

Since, it is not immediately clear how can be detected multiply charged species by means of mass spectrometry, due to significant complexity of observable ions in the spectra of compounds (1) and (2), at this point we include a simple hypothetical example of ion in order to illustrate the rules allowing us to assign experimental spectra of multiply charged clusters, if any. Preliminary, we should emphasize, however, what there is understood under *multiply charged species* of polycations. There is understood *charged clusters of interacting singly charged ensembles*. Let us describe an ensemble of singly charged solvate ion of type $[(CH_3CN)(H_3O)]^+$. It is characterized by mass-to-charge values m/z 60/61 having intensity ratio of the sub peaks 100:2.2%. If an experimental spectrum contains MS peaks at the same m/z -values, but exhibiting ratios of the intensity-values, which do not correspond to those values determined within the framework of rules of the isotope compositions according to the atomic isotopes of an element, then there is highly probable that the observable MS complex peak to belong to a multiply charged ions. Turning back to the later example let us assume that experimentally we observe MS peaks at m/z 60/61, however, the intensity ratio is 100:4.4% instead of 100:2.2% which should correspond to singly charged ionic ensemble as shown above. *Multiply charged ion* of type $[(CH_3CN)(H_3O)]^+_2$ in this case should have the same m/z -values, because of the peaks positions are determined within the framework of the relation MW/N , where MW denotes the molecular weight of the multiply charged ion, while N means the number of interacting ensembles of singly charged ions within the framework of the multiply charged cluster. In the context of employment of the notion "multiply charged ion" as shown above, we write the charged species as $[(CH_3CN)(H_3O)]^+_2$, instead of as $[(CH_3CN)_2(H_3O)_2]^{2+}$. In this case $N=2$. Thus, highlighting that the dication do not represent an ensemble of interacting two molecules of acetonitrile and two charged water cations, but it is cluster of interacting two singly charged of type $[(CH_3CN)(H_3O)]^+$. In other words, the intermolecular/ionic interactions within the framework of the singly

charged ensembles are kept at a large degree. Such species should exhibit the same m/z -values like the corresponding singly charged cation, but the intensity ratio of the sub components should be different. Thus, depending on the number of N there is obtained different ratios of the intensity-values of the sub peaks. By means of the mass spectrometry only looking at the intensity ratios can be determined the number of interacting charged ensembles within the framework of a multiply charged cluster. For instance, if there is cluster of type $[(CH_3CN)(H_3O)]^+_3$ or $N=3$, the intensity ratio of the peaks at m/z 60/61 should be 100:6.7%; for $N=4$ there is obtained theoretically the intensity ratio 100:8.9%; $N=5$ –100:11.1%; $N=7$ –100:15.6%; $N=21$ –100:46.7%, et cetera. With this simple example we hope that it becomes clear that the intensity ratio of the sub peaks of a complex peak is a very sensible quantitative characteristic allowing determining unambiguously the number of singly charged species within the framework of multiply charged cluster of ion.

A mechanism of ion-formation has been proposed looking at atmospheric pressure chemical ionization (APCI) MS spectra [96]. It involves ionization of N_2 molecule yielding to a cation-radical $[N_2]^+$. The latter species induce a series of ion-molecular processes of type:

and

In presence of CH_3CN molecules, there have been proposed species of type $[(CH_3CN)_m(H_2O)_p + H]^+$ ($m=1-3$; $p=0-1$.) Despite the fact that radical reactions appear atypical ESI-MS phenomenon, there scarce data on this problematic [97]. The latter reference discusses, as well as, reactions of stabilization of anion radical of the oxygen molecule $[O_2]^{-\cdot}$ under negative operation mode. This superoxide is initial species producing anions of solvent molecules and $HOO^\cdot$ radical. Eventually, such mechanism can be adopted in explaining the stabilization of O_2 -containing cluster of ion at m/z 110, in spite of, that we study ESI reactions under positive operation mode. An argument advancing the later statement will be shown in the section "Theoretical data" looking at the thermodynamics of superoxide anion and cation radicals. The same is true for the MS peak at m/z 263 showing experimental intensity ratios of the isotope components of the shape 100:24.04%. It could be assigned to multiply charged ion of type $[(CH_3OH)(H_2O)_5(NH_4)(CH_3CN)_3]^+_{13}$ intensity-values of ensemble: 789.5792 (100.0%), 790.5825 (23.4%) and

790.5762 (4.5%), respectively. The corresponding data on the monomeric complex unit are 263.1931 (100.0%) and 264.1964 (7.8%). Looking at the low abundance of the MS ions at m/z 263/265, which yields to an error contribution of the noise to the intensity values of the sub peaks, the shape can be assigned to the monomeric ensemble of ions $[(CH_3OH)_3(O_2)_3(NH_4)(Cl)_3]^+$. As can be expected the theoretical intensity ratio of the isotope sub peaks should be 100:32 0%, which in general does not agree well with the experiment. Nevertheless, the ensemble reveals a significant thermodynamic stability in polar protic continuum due to the highlighted electrostatic interactions of the solvent molecules with the chalcogenide ion (below.) The elemental composition and the content of the ensemble of solvate species corresponding to the MS peaks at m/z 214/216 and 173/175 are detailed in Fig. 2. The thermodynamics of the reactions of such complex ions is detailed theoretically in the next Sect. 3.2.2. The same is true for the thermodynamics of the reactions (X)–(XV) which has been detailed in order to evaluate precisely the effect of the solvent exchange on the thermodynamics of changed solvate ensembles, which unable to understand the governing forces in solution causing for stabilization of such species under soft-ionization MS conditions. In the light of contribution [95] there are examined as well as ionic species with hydrogenated products of the solvent acetonitrile. For instance, these are ions $[(Cl)(CH_3CH_2)_2NH_2]^+$ (m/z 183/185) and $[(Cl)CH_2CHN(CH_2CH_3)_2]^+$ (m/z 134/136), in spite of, the fact that the mass spectrometric data reported so far have shown that the aliphatic amines do not typically stabilize ionic ensembles with chalcogenide counter ions.

3.1.3 Determination of mass spectrometric stochastic dynamic diffusion data

The temporal behavior of the MS parameter intensity of MS ions of (1) and (2) is treated quantitatively according to Eq. (1). The data are summarized in Tables A3–A6 and A3–A7 (Appendix A in ESM.) The calculations tasks point-by-point has been detailed in [1]. The D_{SD} parameters are listed. The correlative analysis between D_{SD} values of MS peaks at m/z 150/152 and 134/136 of (1) and (2) shows $r=0.9916_1$ looking at the peaks at m/z 136, 150 and 152 and $r=0.7883_4$, including the value of the MS ion at m/z 134 (Figure A8.) If we are beginning to see comparatively between the chemometrics of the m/z -values in Sect. 3.1.1 and the D_{SD} parameters detailed in this part of the work, then it is enough clear that only accounting for the formed data there is unable to distinguish both the compounds (1) and (2). However, as far as, the D_{SD} parameters reflect a unique 3D and electronic structures of the analyte peaks; and, accounting for the fact that the different isotopes

exhibit different chemical reactivity; then, depending on the chemical content of the environment we are able not only to distinguish between both the systems (1) and (2), but, also to monitor the affect of the continuum on the multidimensional geometry parameters and subtle electronic effects of the species. Conversely, the quantification of the m/z -values which have limitations in context unambiguous sensitive determination of common species with respect to different chemical content of the ESI-MS continuum, the analysis of D_{SD} parameters provide not only highly accurate, precise and sensitive determination of common species and their isotopes, but, importantly the analysis if highly selective. The results from this study agree excellent with the quantification of the MS intensity of cyclodextrins within the low m/z -values [1]. They provide further pro-arguments our innovative strategy and model relations and their significant applicability to selective quantitative and 3D structural analyses of complex multicomponent systems.

3.1.4 Functional relationship between the mass spectrometric stochastic dynamic diffusion parameters and the temperature

Our evidence for the validity of Eq. (2) consists of the chemomeric data reflecting the correlation among the experimental observable variable intensity; the experimental factor temperature; and the D_{SD} parameters showing excellent coefficients of correlation $r=0.9985_9$ (1) and 0.9900_8 (2) (Fig. 3.) The deviation from the absolute correlation is a result from the error contribution of the chemometric fitting procedure determining the D_{SD} parameters as shown in Figures A4 and A5. Analogously, the correlative analyses so far, the validity of formula (2) is confirmed experimentally looking at the data in this paper, as well.

3.1.5 Functional relationship between the mass spectrometric stochastic dynamic diffusion parameters and the statistical fitting parameter 'A'

From what has been presented in the preceding sections we might infer that we provide a general SD theory and empirically testable model quantitative equations connecting among mass spectrometric variables, experimental parameters and molecular properties, respectively. Despite the empirical verifiability of model Eqs. (1)–(3), which has been demonstrated not only in this work, but also in few of our previous contributions devoted to the same issue, we shall have more to say about the functional relationship between the D_{SD} -parameter and the statistical fitting parameter 'A', which is obtained as a result from *curve-fitting approach* used to connect the experimental measurable outcome-intensity and diffusion parameters according to our formulas. This is

Fig. 3 Relations between $\ln(I - \bar{I})^2$ and $-\ln\left(-\ln\left(\frac{k_B \times T}{m}\right)^3 \times \frac{2 \times T \times \Delta t \times k_B}{m \times D_{SD}}\right)$ of MS ions of (1) and (2); chemometrics; temperature and scan time (Δt) (s). Tables A4 and A6 show the $\ln(I - \bar{I})^2$ and D_{SD} ($\text{cm}^2 \text{s}^{-1}$) values (Appendix A in ESM.)

a common approach to fit calculated diffusions to corresponding experimental data depending on the theoretical diffusion concept. Within the framework of our theory the fitting of the experimental relationship $(I - \langle I \rangle)^2 = f(t)$ is carried out by nonlinear SineSqr function yielding to excellent-to-exact correlation coefficients between theoretical and the experimental curves [1–6] (See Figures A4, A5 and A7, as well; Appendix A in ESM). Obviously, the nonlinear function is utilized as a flexible strategy that approximates the experimental pattern exactly from the perspective of the chemometrics. However, important in a methodological development of a quantitative method is not only the

statistical significance of the chemometric parameters, but also the physical meaning of the parameters constituting the corresponding functional relationships or equations. Thus, we derive Eq. (4) from Eqs. (2) and (3). Figure 7 depicts the empirical testability of formula (4) showing excellent statistical parameter accounting for the correlation between theory and experiment $|r| = 0.9801$ and 0.9974 . Owing to the fact that Eqs. (1) and (2) are universally applicable to different classes of molecules and ionization MS methods [1–6], the chemometric result in the latter figure assumes that Eq. (4) is also relatively general formula or even universally applicable relationship, as well.

3.2 Theoretical data

3.2.1 Interionic/intermolecular interactions of clusters and multiply charged solvate species — geometry parameters and energetics

The issue of the theoretical analysis of ionic ensembles of solvates raises difficulty not only associated with the complex variation of the intermolecular/interionic interaction networks, but also with interionic proton transfer processes, which itself points to a very strong influence on the energetics of these systems. In order to tackle this problematic maximum reliable, in this subsection we develop statistical treatment of a set of ensembles of interacting solvate complex ions corresponding to the mass spectrometrically observable peaks presented in the preceding sections of the paper. The derivation of the different ensembles is carried out by both static and molecular dynamic computations. Figure 4 depicts the energetic and DFT optimization of ensemble $[(\text{Cl})(\text{H}_2\text{O})(\text{H}_3\text{O})_2(\text{CH}_3\text{CHNH})]^+$, which should correspond to MS ion at m/z 134/136. This complex ion is an example of molecular/ionic ensemble exhibiting interionic proton transfer effect from the H_2O^+ -cation to the imine derived from the catalytic dehydrogenation of the solvent CH_3CN . As can be seen, a proton is associated to the $=\text{NH}$ group from the chemically modified solvent molecule; thus, producing a charged $=\text{NH}_2^+$ imine and a neutral solvent

water molecule. The composition of the complex ion corresponding to its most stable state is; therefore, $[(\text{Cl})(\text{H}_2\text{O})_2(\text{H}_3\text{O})(\text{CH}_3\text{CHNH}_2)]^+$ (Tables B1–B3, Appendix B in ESM.) It is characterized by weak-to-moderate interionic $\text{NH}_2^+\cdots\text{OH}_2$ and $\text{HOH}\cdots\text{Cl}$ interactions with bond lengths $r(\text{N}\cdots\text{O})$ and $r(\text{O}\cdots\text{Cl})$ within a range of values 2.631–3.133 Å. Figure B1 depicts the energetics and selected geometry parameters of the ionic ensemble $[(\text{Cl})(\text{H}_2\text{O})_2(\text{H}_3\text{O})_2(\text{CH}_3\text{CN})]^+$ corresponding to the peak at m/z 150/152. The most stable equilibrium state is characterized with a higher symmetry of the interacting network comparing with the initial classical MD and MM structure of the ensemble. Strong-to-moderate $\text{H}_2\text{O}^+\text{H}\cdots\text{OH}_2$, $\text{H}_2\text{O}^+\text{H}\cdots\text{Cl}$ and $\text{H}_2\text{O}^+\text{H}\cdots\text{NC}(\text{CH}_3)$ bonds are obtained, theoretically. The bond lengths $r(\text{O}\cdots\text{O})$, $r(\text{O}\cdots\text{Cl})$ and $r(\text{O}\cdots\text{N})$ vary within values of 2.476–2.911 Å. The difference in the energy of the equilibrium and the stationary state SS_2 —both exhibiting a lack of negative frequencies—is $\Delta E = |0.010593|$ a.u. The optimized molecular ensemble $[(\text{Cl})(\text{H}_2\text{O})_2(\text{H}_3\text{O})_2(\text{CH}_3\text{CN})]^+$ corresponding to MS peak at m/z 183/185 is depicted in the Figure B2. Again, the ionic complex ion exhibits a higher symmetry and a series of strong-to-moderate interionic/molecular hydrogen bonds of types $\text{H}_2\text{O}^+\text{H}\cdots\text{O}(\text{H})$, $\text{H}_2\text{O}^+\text{H}\cdots\text{Cl}$, $\text{OH}\cdots\text{Cl}$, $(\text{CH}_3)\text{O}(\text{H})\text{H}\cdots\text{Cl}$ and $(\text{CH}_3)\text{O}(\text{H})\text{H}\cdots\text{O}$ showing bond lengths $r(\text{O}\cdots\text{O})$ and $r(\text{O}\cdots\text{Cl})$ within the range of values of 2.444–3.031 Å. These results agree well with MD data on charged proteins [98] showing that the position of the chalcogenide Cl^- -ion affects

Fig. 4 DFT optimization of the molecular ensemble at m/z 134/136: Total energy (a.u.) versus the optimization step number; selected geometry parameters as bond lengths (Å) of the ionic ensemble at the initial (IS) and the final (FS) states; interionic proton transfer effect (PTE) from H_3O^+ ion to the acetonitrile solvent is highlighted

indirectly the conformational change of the molecule. As can be expected and as our results clearly show the effect of the Cl^- -ion on the molecular structure of the interacting ensemble of species in solvate clusters of ions is increased additionally, due to the great variation of the positions of the solvent molecules. It is obvious; therefore, that in cases of solvate ions and multiply charged species the complexity of the MD analysis is increased dramatically comparing with the analysis of clusters of charged proteins.

The participation of Cl^- -ion in adducts under ESI-MS experimental conditions has been observed previously [99].

Figure B3 shows the energetics of clusters of multiply charged ions together with selected optimized geometry parameters.

In what follows in this subsection we would like to turn in brief to whether there is an affect of the type of the solvent on the PT phenomena of self-associates of ions or interionic/intermolecular networks. As can be expected there should be a range of D_{QC} values depending on the different structural units and the position of the proton. We would like to concentrate on the molecular optimization data of the ionic ensembles at m/z 132/134 and m/z 183/185 (Figures B2 and B4) thus, turning to a very germane matter of the reliability of the multidimensional structural interpretations of such complex systems and the capability of the D_{QC} data to account for subtle electronic effects. The description of the latter problematic beefs up the proper understanding of the reliability of the theoretical D_{QC} values. The latter case, when the ionic associate contains only CH_3OH molecules, there is a lack of PTE. Conversely, the acetonitrile tends to participate into PT processes stabilizing not only hydrogenated derivatives, but also $\text{H}-\text{N}^+\equiv\text{C}-\text{CH}_3$ charged species. The latter phenomenon is associated with a decreasing in the total energy of the system at about $\Delta\Delta G=|0.11|$ a.u. The ionic unit at m/z 132/134 shows weak-to-moderate intermolecular/interionic interactions of type $\text{CH}_3-\text{C}\equiv\text{N}^+-\text{H}\cdots\text{Cl}$ (2.88105), $\text{HOH}\cdots\text{Cl}$ (2.95929–3.3836 Å). Besides, all cases of ionic associates with participation of H_3O^+ and H_2O species show a stabilization of $[\text{H}_2\text{O}\cdots\text{H}\cdots\text{OH}_2]^+$ structural subunit, where the proton is almost centered between the two O-centers of the solvent water molecules. A direct evidence of the latter assumption follows from the obtained OH bond lengths of the H_2O molecules at about $r(\text{O}-\text{H}) \approx 0.9$ Å. Conversely, the $\text{O}\cdots\text{H}$ bonds of the proton of the ensemble $[\text{H}_2\text{O}\cdots\text{H}\cdots\text{OH}_2]^+$ are at about $r(\text{O}\cdots\text{H}) \approx 1.19$ Å (Figure B4.) As far as, from the studied solvents only CH_3CN seeks to establish PT associates, its presence in the initial analyte solution under ESI-MS experimental conditions difficult, in addition, the structural characterization of the solvate multiply charged ions and corresponding ionic ensembles. However, its underlined chemical reactivity

makes sense of further development of ESI based studies in solution which able to detail comprehensively both molecular and environmental factors governing the $\text{N}-\text{X}$ ($\text{X}=\text{C}, \text{H}, \text{N}$, and more) covalent bond formation, which contribute crucially to the field of catalysis and the improvement of the catalytic efficiency of the processes of hydrogenation of nitriles. As aforementioned, such studies directly impact on the industrial scale application of the reaction. Thereby, it goes without saying that the data on the next Sects. 3.2.2 and 3.2.3 have not only fundamental scientific impact on the research, but also an applied-oriented one.

3.2.2 Thermodynamics of clusters and multiply charged solvate species

It seems evident from the brief description in the introductory section of the state-of-the art of development of ESI-MS method that the paramagnets affecting on the thermodynamics of fragment reactions depend on many experimental and molecular factors; and, in general, are currently debatable. For this reason, herein, we study comparatively theoretical thermodynamics of the MS fragment path in GP and polar continuum (Tables B3 and B4.) The determination of the *solvation fee Gibbs energy* (ΔG_{Solv}) is carried out within the framework of the assumption that the systems are at chemical equilibrium. In general, the ESI-MS has been proven as methods capable of determining the equilibrium constants of noncovalent interacting systems [100–102]. Figure 5 presents the functional relationships between the absolute total intensity values (I^{TOT}) with respect to the *free Gibbs energy* parameters at gas- and condenses phases. As can be seen in both cases there are obtained excellent statistical parameters showing $|r|=0.93$ and 0.97 . This fact, agree well with the conclusions in work [5], which have been drawn on the base on our theoretical concept behind the derivation of Eqs. (2) and (3) as well as few experimental facts therein, indicating that the ESI-MS continuum cannot be regarded neither as gas-phase nor as a liquid state. Thereby, further research efforts are needed in order to understand in-depth the thermodynamics of the ESI-MS reactions with respect to molecular factors and a broad scale of experimental factors and parameters.

3.2.3 Chemical reactivity of acetonitrile

In this part of the paper, we give an account of mechanistic aspects of chemical reactions of solvate charged species, yielding to abundance MS ions at m/z 134/136. In particular, we concentrate on the process of formation of CH_3CHNH_2 ion in the ensemble $[(\text{Cl})(\text{H}_2\text{O})_3(\text{CH}_3\text{CHNH}_2)]^+$, obtained by a hypothetical catalytic hydrogenation of

Fig. 5 Correlative analysis between the absolute total intensity values (I^{TOT}) [arb. units] of MS ions at m/z 134, 150 and 183 of (2) and the free Gibbs energy (ΔG^{GP}) [a.u.] in the gas-phase, respectively, the solvation free Gibbs energy (ΔG_{sol}) (kcal mol⁻¹) in polar protic con-

tinuum; chemometrics; the experimental I^{TOT} values are: 325,591.4 (m/z 134), 188,892.1 (m/z 150) and 111,441.3 (m/z 183), respectively; the thermodynamic data are according to Tables B2 and B4

the solvent acetonitrile as mentioned in Sect. 3.1.2. As aforementioned, the catalytic hydrogenation of nitriles is among the most studied reactions with an industrial scale application to produce primary, secondary or tertiary amines from nitriles. Enormous effort has dealt with improving of the reaction's efficiency. A common concept is that the first step of the process is associated with attachment of hydrogen to the N-atom of the nitrile group leading to imine, which exhibits significant chemical reactivity. In order to stabilize such imine, there has been proposed as an intermediate step of metal ion-imine bonding, leading to metal-organics or organometallics. However, if we try to detail examples of intermediates, then it must be emphasized that the largest part of these intermediates are unidentified, so far [95]. For this reason, the analysis in this subsection encompasses detail thermodynamic description of the catalytic hydrogenation of CH_3CN as an isolated process and within the framework of the ensemble of charged solvate species of the type shown above. The major reaction steps (II)–(VIII) hypothesized previously [95] and depicted in Figure A9 are examined. The most important outcome in the context of the experimental conditions under ESI-MS measurements is that the latter

processes exhibit different thermodynamic preference. For instance, reactions (IV) and (VII) appear spontaneous processes in solution. Conversely, all other reactions exhibit underlined negative ΔG values in the gas-phase, which means depending on the experimental conditions different associates containing hydrogenation products of interaction of acetonitrile under ESI-MS measurements are expected.

3.2.4 Quantum chemical diffusion parameters—determination and correlation with the experiment

Table 1 summarizes the D_{QC} parameters of MS species with respect to different isotopes determined at the equilibrium state and different stationary states. The data in Tables B1 and B2 are used. The data in the first table are tightly connected with the sensitivity of our 3D structural analysis based on the correlation between D_{SD} and D_{QC} parameters; because of, it is obvious that a great difference is obtained in the ΔD_{QC} values between the corresponding equilibrium and stationary states. It varies within $\Delta D_{\text{QC}} \approx [7] - [2903]$. This fact enable us, to distinguish unambiguously between the 3D molecular and electronic structures

of the analytes; furthermore, in quantitative terms. This is among the most important issues talking about precise, accurate, selective and sensitive multidimensional structural analysis, based on mass spectrometry and employing our stochastic dynamic concept and model Eq. (1)–(3). Moreover, it is the major focus of the current study. As we have saw at the first part of the section “Results” the same is true for the D_{SD} parameter determined experimentally. These facts ensure a high reliability of the structural analysis based on our concept and both experimental and theoretical outcomes, when there is used high resolution mass spectrometric and high accuracy quantum chemical data. The later claim suggests a significant coefficient of correlation between theory and experiment; or, between D_{SD} and D_{QC} parameters. As the chemometric results shown in Fig. 6 evidence, there is excellent parameter $|r|$. It is $|r|=0.9359$. In order to, illustrate the high selectivity of the D_{QC} parameter the latter figure shows the D_{QC} data on the isotope of the ion $[(^{37}\text{Cl})(\text{H}_2\text{O})(\text{H}_3\text{O})(\text{CH}_3\text{CNH})]^+$ (m/z 134). As can be seen the difference in (ΔD_{QC}) parameters of the species belonging to the same m/z values is $\Delta D_{QC}=|61.5797|$.

Accounting for the very high complexity of the analyte objects described in the current study such chemometric parameter clearly indicates that the linear correlation between the D_{SD} and D_{QC} parameters is not abstractly conceivable. Conversely, we present a highly reliable tool for 3D determination of the molecular structures of the analytes even looking molecular ensembles with a significant variation of the intermolecular/interionic interactions. So far, we have obtained excellent coefficient of

linear correlation between the D_{SD} and D_{QC} parameter [1–5] studying relatively structurally restricted molecular objects. This is the first paper, where we demonstrate the applicability of formulas (1)–(3) for molecular objects showing very flexible self-assembly units and intermolecular/ionic networks. With the latter figure we defend our concept arguing its great theoretical virtue comparing with known quantitative concepts for treatment of the MS outcome *intensity*. Equations (1)–(3) not only provide a highly accurate quantification of the MS intensity parameter, but also they are capable to determine the 3D conformation of the analytes, which dramatically extends the capability of the mass spectrometry as robust analytical instrumentation, far beyond its current routine application to quantify analytes in many interdisciplinary research areas.

4 Discussion

There are important aspects that call for comments on. First, a question we have to ask is do our model Eqs. (1), (3) and (4) provide mass spectrometric multidimensional molecular structure of multiply charged ions and solvate clusters? Because of, the paper aims at providing the reader a backdrop not only to aspects of quantitative analysis, but also 3D structural determination of solvate ensembles observed under experimental ESI-MS conditions, pinpointing, in parallel, aspects of the soft-ionization MS phenomena associated with the nature of the so-called ESI-MS *continuum*. Therefore, the issue concerns the

Fig. 6 Correlative analysis between D_{SD} ($\text{cm}^2 \text{s}^{-1}$) and D_{QC} data on MS ions; the later values are obtained at equilibrium and stationary states; chemometrics

problem of the nature of the environment around of the detected analyte ions. To get a proper grip on the term *continuum*, let us detail what is meant when we use it, instead of, a GP talking about experimental MS conditions. Let us return to our SD theory behind the derivation of Eq. (2) [5]. Essentially, it follows the line of truths in the seminal Einstein's work on theoretical modeling of the temporal motion of solid spherical particles in liquid phase [5]. Therefore, the phenomena which we proposed appear at least a kind of reinterpretation of the Einstein's view. (Consider the characteristic function *diffusion* according to Einstein and its empirical modification which we carry out. These are Eqs. (4 and (5)) [5].) The derivation of the Einstein's characteristic function is for homogeneous liquid. The fact that Eq. (2) shows excellent coefficients of correlations between theory and experiment assumes that the behavior of the MS ions can be expressed as movement in heterogeneous liquid, rather than in the GP. Moreover, a recent contribution devoted to thermodynamic of Zn^{II} -ion containing species under the same experimental conditions has shown that there is a sufficient linear correlation between the total intensity of the analyte ions I^{TOT} and the solvation *free Gibbs energy* ΔG_{sol} of the fragment MS reactions ($|r| = 0.6747$.) The latter parameters have been computed in polar protic continuum [103]. Therefore, the relation of our SD theory and empirical modification of the characteristic function diffusion (See Eq. (5) in reference [5]), which relates to aspects of Einstein's though modeling his Eq. (4) meet agreement with the experimental ESI data. Since, we have explored a concept of diffusion in homogeneous liquid, which is only modified according to Eq. (5) [5] and (2) in this work, it is logical to assume that the ESI continuum can be described as a polar environment. The new experimental facts (Sect. 3.2.2) confirm the validity of our statement and agree with those presented in works [5, 108]. The correlative analysis between the absolute total intensity of MS species and the *free Gibbs energy* data on gas-phase, respectively, on solution shows excellent coefficients of correlations ($|r| = 0.93$ and 0.97 .) In order to grasp this problem more adequately we have drawn a conclusion that the ESI-MS continuum cannot be regarded neither as GP, nor as pure homogeneous liquid looking, namely, at the latter chemometric data. It may be objected that such understanding does not allow correlating experimental and theoretical thermodynamics by mass spectrometry and quantum chemistry. However, a more recent contribution [21] not only agree with our assumption about the nature of the ESI-continuum, but also provides a solution of the problem shows that the *free Gibbs energy* for such systems depending on the size of the ESI-MS droplets can be described as a sum of the energetics of the species in bulk liquid and on the surface of the droplets. This approach requires to draw

distinction among the analyte systems toward the size of the ESI-droplets it does not address directly the question how to compute the ΔG - parameters of ESI-MS reactions by quantum chemical methods. However, it may help the reader's understanding toward the adequacy of our model Eqs. (2) and (4) and to explain partially why we have obtained excellent coefficients of linear correlation between theory and experiment, when we used these latter formulas quantifying the experimental variable *intensity*. The objector might argue for an explicit functional relation allowing correlating directly MS and theoretical thermodynamics. It establishing as is self-evident from the results so far needs further research effort. Despite, looking at the quantitative relations between D_{QC} and D_{SD} parameters reported so far, excellent coefficients of correlations are obtained [1–5]. There is an additional reason to argue for, in favor of our understanding about the nature of the ESI-MS continuum. Moreover, model Eq. (2) can be regarded as a vastly preferable approach to quantify the discussed experimental variables, because of Eq. (3), which is derived by Eq. (2) shows excellent correlation between D_{SD} parameters and concentration of the analyte in solution ($r > 0.999$ [6].) Looking at the complexity of the ESI-MS processes [104] the later chemometric parameters clearly show that our innovative model equations appear prominent and indispensable tools for a successful bridging the gap of knowledge among measurable outcomes of mass spectrometric experiments, experimental factors and parameters such as concentration of the analyte in solution and temperature and molecular structure and properties of the analyte, respectively.

Second, in the correlative analysis between the D_{SD} parameters according to Eqs. (1)–(4) and the so-called diffusion coefficients (D_{CMM}), obtained within the framework of the so-called *current monitoring method* (CMM) [105] it has been stressed that, again, there is obtained good-to-excellent coefficients of linear correlation ($r = 0.96012$ – 0.99942) [5, 106]. However, an in-depth analysis of the methods used to write the CMM model equation shows that it uses different routes, which have been exploited by derivation the corresponding mathematical models, again, accounting for the temporal behavior of the experimental MS measurable parameter *intensity*. Its key idea is based on the Fick's second law expressing a functional relationship between the concentration of the analytes in solution and their diffusion coefficients. The CMM has been developed into modelling of diffusion processes in nanochannels, approximating the concentration of the analyte at the boundary of the nanochannels. Therefore, in settling the question about the application of the CMM to correlate its D_{CMM} parameters with the D_{SD} data according to our SD concept we need to emphasize that essentially the CMM method expresses the diffusion of

analyte ions even at high concentrations in bulk solution [105]. Therefore, it describes classical diffusion process in solution accounting for the equilibrium of the nanochannel surface charge due to analyte ions and their concentration in the bulk solution. In this context, the contributions devoted to correlative analysis between D_{SD} and D_{CMM} data [5, 106] constitute a very important step of the further understanding of the nature of the soft ionization MS environment, in particular looking at the ESI- and APCI-MS methods. Drawing the boundary among the methodology use to the Einstein's theory, discussed above, and the concept behind the CMM—both being theories describing

stochastic phenomena in bulk solution—in addition to our SD concept showing good-to-excellent mutual correlations among the corresponding diffusion parameters, we would like to stress that the experimental facts and arguments presented so far support for our hypothesis about the nature of the ESI-MS continuum which has been put forward.

Third, at this point we will only mention, as well as, that there is considerable evidence provided by other authors that under ESI-MS experimental conditions the molecules can be kept intact as in solution [107–109].

Fig. 7 Relations between the statistical parameter A_i and the D_{SD} data ($\text{cm}^2 \text{s}^{-1}$) of (1) and (2) (a); Relations among the statistical parameter A_i and the parameters according to Eq. (4) (b); chemometrics

Table 1 Theoretical D_{QC} data on MS ions obtained at their equilibrium (ES) and stationary (SS) states; Δ difference in values; the Z-matrix, vibrational modes and the energetics of the ions are summarized in Tables B1–B3

Complex ion	m/z	ES	SS	Δ
$\{[(Cl)(H_2O)_2(H_3O)(CH_3CNH)]^+\}$	132/134	3.6313	–	–
$\{[(^{37}Cl)(H_2O)_2(H_3O)(CH_3CNH)]^+\}$	132/ 134	3.61807	–	–
$\{[(Cl)(H_2O)_3(CH_3CHNH_2)]^+\}$	134/136	65.1977 ₉	353.0787 ₇₆	[287.881]
$\{[(^{37}Cl)(H_2O)_3(CH_3CHNH_2)]^+\}$	134/ 136	6.6418 ₂	353.9485	[347.30668]
$\{[(Cl)(H_2O)_2(H_3O)_2(CH_3CN)]^+\}$	150/152	7.4091	0.0967 ₉	[7.3123]
$\{[(^{37}Cl)(H_2O)_2(H_3O)_2(CH_3CN)]^+\}$	150/ 152	7.3618 ₃	0.0954 ₁	[7.2664]
$\{[(Cl)(H_3O)(CH_3OH)_3(CH_3OH_2)]^+\}$	183/185	154.4875	3057.6466	[2903.1591]
$\{[(^{37}Cl)(H_3O)(CH_3OH)_3(CH_3OH_2)]^+\}$	183/ 185	155.34708	–	–
$\{[(O_2)(H_2O)(H_3O)(CH_3CN)]^+\}$	110	25,624.49	–	–

This study, therefore, together with those ones reported previously [1–6, 106] tell us that the development of models of the ESI-MS phenomena based on a description of the processes as single solvent [110] fails to reproduce the real process under ESI-MS experimental conditions, due to reasons mentioned before. Moreover, systematic research on kinetics and thermodynamics of chemical reactions has shown that there is increasing in reaction rates in MS droplets comparing with the corresponding parameters of the same reactions in bulk liquids [111–113].

Finally, it is the task of this section to discuss, as well as, the relationship between the statistical data on D_{SD} and “A” as they are summarized in Tables A4, A6 and Fig. 7 according to Eq. (4). Because of, as Fig. 7 in subsection 3.1.4 shows there is significant statistical correlation. However, if $A_i \equiv D_{SD}^i$, then Eq. (1) becomes $\langle (I - \langle I \rangle)^2 \rangle = 1.3194 \cdot 10^{-17} \cdot (\langle I^2 \rangle - \langle I \rangle^2)$. The latter relationship contradicts to the definition of the variance according to the stochastic theory, which we used to derive Eqs. (1) and which is behind all of the adopted interconnected theoretical concepts which we used, however [1–6]. The definition is: $\langle (I - \langle I \rangle)^2 \rangle = \langle I^2 - 2 \cdot I \cdot \langle I \rangle + \langle I \rangle^2 \rangle = \langle I^2 \rangle - \langle I \rangle^2$ [114]. In fact, the variance or s^2 accounts for the *fluctuation* or the dispersion of the mean value of the MS intensity as a random variable [114]. Therefore, the approximation of the statistical parameter “A” with diffusion lack of physical meaning within the firework of the presented theory and functional relationships. Moreover, as the results in the latter figure show there is obtained deviation from the linearity looking at the data on the MS ions at m/z 150 and 185 of analyte (1). Conversely, Eq. (4) provides a reliable explanation of, and more insights into the physical meaning of the statistical parameter “A”.

Despite, the fact that the tendency of the experimental fact sketched above provokes rather further conjectures about the nature of the ESI-MS continuum, showing a more complex picture of the ionization mechanisms, it contributes crucially to the debate about the ESI-MS phenomena. Because of, the discussed in this section proposals and model equations, rather show that ESI-MS method provides analytical information in condense phases. Thus,

we describe the soft-ionization ESI method as rather analytical approach to condense phase analyses. Accounting for the fact that it has been developed primarily as quantitative method for analysis of liquid, gas, viscous samples and aerosols [115, 116] and, in parallel, looking at the fact that the latter issue has crucial importance for the research tasks of the environmental analysis and the climate, it is self-evident, on the one hand the significant affect of our study on those, and many other, research fields. Because of, under our hypothesis about the nature of the ESI-MS continuum, we have shown by means of chemometrics based on a correlative analysis between theory and experiment that those theoretical concepts describing the temporal behavior of the species in condense phase fix statistically significant the ESI-MS phenomena which sheds additional light on the dispute over the ESI-MS ionization mechanisms presented above.

5 Conclusion

We have constructed an innovative stochastic dynamic theory and model formulas [1–6] connecting the experimental mass spectrometric variable *intensity* with diffusion parameter, the concentration of the analyte in solution, and the experimental factor temperature. There has been provided proof of the fact that the diffusion parameters of MS ions within the framework of this theory correlate with the Arrhenius's quantum chemical diffusions within the framework of his transition state theory. Therefore, the direct connection of measurable outcome of the MS ions with their 3D molecular and electronic structures is established. Since, the formulas have been tested on covalently bonded molecular systems or metal–organic coordination compounds of transition metal ions, there is a rather difficult question: Do the latter model equations applicable to noncovalent bonded species of solvate clusters and multiply charged ions with a significant variation of the positions of the molecules/ions within the framework of the 3D ensemble and the interionic/molecular interaction

networks? This paper is, namely, an attempt to answer the latter question. Herein, we have tried to address this issue maximal persuasively for the reader looking at theoretical quantum chemical and experimental MS data on a set of experimentally observable species. Despite the significant complexity of these analytical objects, we have argued the validity of our theory by a correlative chemometrics between theory and experiment showing coefficient of correlation between D_{SD} and D_{QC} parameter $|r|=0.9359$. Therefore, our formulas should be understood as highly accurate, precise, sensitive and selective models expressing quantitatively relations among measurable mass spectrometric variables and properties of the molecules. Accounting for the fact that we have studied solvation associates, the latter statement implies that our functional relations appear prominent tools for quantitative and 3D structural analysis of aerosols, which impact crucially on research on health and climate.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval This article does not contain any studies with animals performed by any of the authors; This article does not contain any studies with human participants or animals performed by any of the authors, Humans have not be involved in the study.

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