Quantitative collision induced mass spectrometry of substituted piperazines — A correlative analysis between theory and experiment

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Bojidarka Ivanova[*], Michael Spiteller

Lehrstuhl für Analytische Chemie, Institut für Umweltforschung, Fakultät für Chemie und Chemische Biologie, Universität Dortmund, Otto-Hahn-Straße 6, 44221 Dortmund, Nordrhein-Westfalen, Germany

ABSTRACT

The present paper deals with quantitative kinetics and thermodynamics of collision induced dissociation (CID) reactions of piperazines under different experimental conditions together with a systematic description of effect of counter-ions on common MS fragment reactions of piperazines; and intra-molecular effect of quaternary cyclization of substituted piperazines yielding to quaternary salts. There are discussed quantitative model equations of rate constants as well as free Gibbs energies of series of m −independent CID fragment processes in GP, which have been evidenced experimentally. Both kinetic and thermodynamic parameters are also predicted by computational density functional theory (DFT) and *ab initio* both static and dynamic methods. The paper examines validity of Maxwell−Boltzmann distribution to non−Boltzmann CID processes in quantitatively as well. The experiments conducted within the latter framework yield to an excellent correspondence with theoretical quantum chemical modeling. The important property of presented model equations of reaction kinetics is the applicability in predicting unknown and assigning of known mass spectrometric (MS) patterns. The nature of "GP" continuum of CID−MS coupled scheme of measurements with electrospray ionization (ESI) source is discussed, performing parallel computations in gas−phase (GP) and polar continuum at different temperatures and ionic strengths. The effect of pressure is presented. The study contributes significantly to methodological and phenomenological developments of CID−MS and its analytical implementations for quantitative and structural analyses. It also demonstrates great prospective of a complementary application of experimental CID−MS and computational quantum chemistry studying chemical reactivity, among others. To a considerable extend this work underlies the place of computational quantum chemistry to the field of experimental analytical chemistry in particular highlighting the structural analysis.

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1. Introduction

Mass spectrometry has become a major analytical approach over last few decades with irreplaceable *trans*-disciplinary application [1,2]. In order to capture the current trend in applied MS and variations among methods that are used in the analytical practice, it needs to be stressed that more recently major outstanding contributions are instrumental methodological newcomers associated with development of ionization methods, mass analyzers and detection approaches, among others [3,4]. Through combining different MS methods with a relevant software there is a clear trend in developing imaging technique as well [5,6]. The main goal of these innovations is improvement of method performances and instrumental characteristics [4]. The great advantage of MS is associated with capability to elicit high accurate and precise analytical information about single analyte of interest in a complex multicomponent mixture. Mass spectrometry exhibits: *(i)* flexible instrumental schemes, allowing improvement of instrumental design; *(ii)* ultra−high resolving power; *(iii)* high accuracy, precision and selectivity; *(iv)* fast operating and detection times; *(v)* simple and limited number of sample pretreatments, including instrumental capability for direct assay; *(vi)* low concentration limits of detection and quantification of *fmol−attomol* concentrations; *(vii)* low instrumental and linear limits of detection and quantification; *(viii)* analysis of large scale of molecular weights from low molecular weight (LMW) analytes to (bio)macromolecules with weights $\in$ 10−100 kDa; *(ix)* study of homogeneous and

heterogeneous systems, including analysis of aerosols, semi−liquid, liquid and solid−state phases [1–6]. There is important to under-line that ones of central methodologies of analysis are based on soft ionization methods such as ESI and matrix−assisted laser desorption ionization (MALDI) mass spectrometry. Very particularly de-velopments of imaging techniques has resulted to analytical information from living cells, whole organs and bodies [5,6]. This has led to implementation of MS to medicine, clinical diagnostics, clinical microbiology and structural biology [7,8]. Furthermore underlining great applicability of MS to metabolomics, including plant−omics, it is not formal to distinguish LMW analysis of bio-logical samples from quantification of LMW analytes in complex environmental samples. There is already becoming routine appli-cation of MS based methods coupled with chromatographic ap-proaches to environmental analytical chemistry [9–14]. For the sake of brevity, we shall here only mention other *trans*-disciplinary research which also broadly employ MS like forensic chemistry, nuclear forensics, pharmacy, agricultural sciences, food sciences, archeology and more [15,16].

The physical phenomena of MS processes are different to different ionization methods [1–16]. They are among most impor-tant part determining a quantitative treatment of GP fragment re-actions. Despite much greater contribution of MS to the science, developments to GP phenomena are rare. To the largest part of MS methods, phenomenology and molecular/ionic level interactions remain not well understood. It could be perceived that there is a rather lack of fundamental works devoted to theoretical and experimental analyses, depending on ionization methods. In particular, complementary application of computational quantum chemistry and MS is limited to effort mainly devoted to under-standing of fundamental concepts of electron impact (EI) and chemical ionization (CI) MS [17–22]. A computational study has treated qualitatively relations between molecular conformation and relative intensities of MS peaks at ion mobility MS [19]. There are few more recent studies devoted to conformational analysis of fragment ions and non−covalent interactions of MS species under ESI−experimental conditions [20–22]. An essential part of them are relating to qualitative MS in GP employing capability of computational chemistry to predict highly accurate energetics depending on molecular conformations of the species. However, there has not been proposed quantitative equation-models corre-lating reaction kinetics.

Following the latter line of reasons, one of the main goals of this research is development of quantitative relations of kinetics and thermodynamics of CID−MS reactions, studying fragment patterns of substituted piperazines under different conditions (Scheme 1). Despite questions that such as formulation of this, first, goal has generated, we should point out that according to literature data, knowledge of fundamentals of CID−MS processes is less under-stood quantitatively. The second strand of the work is quantitative correlation of experimental kinetics and thermodynamics with computationally predicted parameters on the base on a molecular design and prediction of electronic structure and properties of MS fragment species. As the analysis of references [18–22] shows and was mentioned above, major contributions of implementation of computational quantum chemistry to problematic of MS phe-nomenology are associated with EI and CI mass spectrometry. However, by contrast to CID−MS phenomena, EI and CI ones are relatively well understood. At this point it is necessary to be underlined, that talking about 'mass spectrometry' as analytical method, it is important to note that it encompasses a set of different as theoretical physical backgrounds and phenomenology methods, including instrumental design and schemes; and processes of ion formation from bulk solids, surfaces, liquids and semi−liquids upon various conditions. The ESI−MS is based on assumption about a
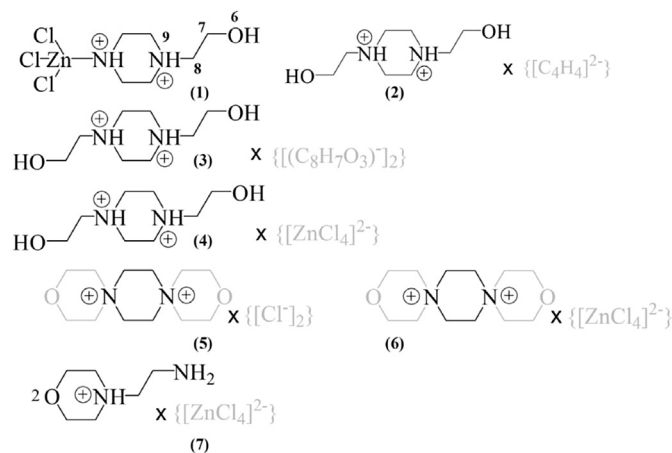
Scheme 1. Chemical diagrams of analytes (**1**)–(**7**); Atom labelling schemes.

formation of quasi equilibrium ions based on unimolecular re-actions [23,24]. On this view next developments have led to the concept about applicability of Iribarne−Thomson model equation of a quasi-equilibrium state giving a relation between rate constant (k) of reactions using Eyring's equation of transitions state theory [25–31]. The theory claims that relation between intensities of MS peaks at ESI−MS conditions and rate constant of these reactions at different times (t) is an exponential function, known as 'survival yield' [25,26]. It has been postulated that ions are produced in ground state, by contrast to EI−MS and internal energy is deter-mined by distribution over vibrational/rotational states [31–34].

However, CID reactions, among most comprehensive theoretical studies along line 'GP phenomenology' are based on theoretical concepts treating non−Boltzmann GP phenomena under collision processes. Presumably, there is expected non−Boltzmann distri-bution of internal energy. In spite of Maxwell−Boltzmann distri-bution has been proposed to CID [25–31]. We will mention our more recent study, devoted to CID thermochemistry of peptides [32], where direct application of the theory stated above to ESI and correlating CID processes has resulted to a quantitative relation that rate constants of reactions obtained under one and the same experimental CID conditions and describing one and same type fragment processes are mutually connected quantitatively, furthermore, with a statistical significant confidence level 96.42%. Or these latter processes are expressed quantitatively by one and the same model equation. In this context, the first ultimate goal of this work, therefore, is to be seen a new theoretical concept treating quantitatively relations between kinetic parameters, but, within m−(independent) CID experiments at different conditions and various analyte objects. We should now stress a certain general-ization about 'quantitative treatment of CID−MS'. We distinguish between 'quantitative mass spectrometry' employing intensity ra-tios of MS peaks *into* linear calibration model (it already has a routine application to the field of analytical chemistry [35]) from quantitative statistical models of kinetic and thermodynamic pa-rameters. Our study should be understood, therefore, as a quanti-tative treatment of latter quantities of CID−MS reactions. We provide a correlative analysis between thermodynamic free Gibbs energetics of systems and molecular conformations stabilized as a result of CID. There are discussed new evidences supporting an assumption about stabilization of conformational states under CID processes, which are far from equilibrium ones. The results shed light on phenomenology of CID−MS beyond classical understand-ing about thermodynamic stability of systems valid to spontaneous