

Analytical Capabilities of Surface-Assisted Laser Desorption/Ionization in the Determination of Low-Molecular-Weight Volatile Compounds

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Abstract—Main approaches to the determination of low-molecular-weight chemical compounds by surface-assisted laser desorption/ionization (SALDI) are considered. Analytes are adsorbed from a gas phase on the surface of a specially prepared solid-state substrate. Then, the surface is exposed to pulse laser radiation, which leads to ionization and desorption of ions to be detected with a mass analyzer. The factors responsible for the efficiency of ionization are examined, the instrumental versions of SALDI are presented, and the metrological characteristics of this method are given. The high ionization efficiency of basic compounds, which is higher than the efficiency of traditional ionization methods by orders of magnitude, the mild conditions of ionization, the simplicity of performance, and the possibility of combinations with analyte separation systems characterize SALDI as an exceptionally promising method for the determination of low-molecular-weight volatile compounds.

Keywords: mass spectrometry, surface-assisted laser desorption/ionization, adsorption, determination of low-molecular-weight compounds

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The development of laser technology in the recent decades led to the appearance of new approaches and methods in the mass spectrometry of organic compounds. Laser desorption/ionization (LDI), which was proposed at the turn of the 1970s–1980s for the ionization of nonvolatile organic and bioorganic compounds, can serve as a clear example [1, 2]. Within the framework of this approach, the analyzed test sample is applied to a solid surface, which well absorbs laser radiation. Then, pulsed laser radiation is focused onto the surface, and the supported compounds pass into a gas phase and become ionized under the action of this radiation. In the early works on LDI, in the majority of cases, ionization occurred due to cationization—the addition of a metal cation (usually, Na^+ or K^+), which was present or specially added as a salt to the test sample, to the molecule. Metallic substrates were used as solid bodies, and the test sample was supported as a film from units to thousands of monolayers in thickness. Currently, this version of LDI is frequently referred to as direct laser desorption/ionization (direct LDI).

The above approach was found fruitful, and it was further developed in the middle 1980s when two fundamentally new LDI methods were proposed. Their distinctive feature was that a special matrix that well absorbed laser radiation was also supported onto the

surface of a metallic substrate in addition to the analyte. The first method is based on the application of ultra-fine metal powders plus a liquid as a matrix [3]. With the use of the suspensions of cobalt nanoparticles in glycerol, the mass spectra of peptides and proteins with mass-to-charge ratios m/z to 100000 were detected for the first time [3]. Thus, these most important bioorganic compounds were introduced into the range of problems to be solved with the aid of mass spectrometry. In 2002, the author of this method K. Tanaka became a Nobel Prize winner for the development of soft laser desorption methods for the mass-spectrometric analysis of biological macromolecules.

Karas et al. [4] proposed to use nonvolatile low-molecular-weight organic acids as matrices and, on this basis, developed the principles of the second method referred to as matrix-assisted laser desorption/ionization (MALDI). The matrix fulfills the following two basic functions: the transfer of analyte molecules into a gas phase and their ionization. The action of laser radiation leads to the pulse evaporation (ablation) of the matrix and the cocrystallized analyte. A comparatively high pressure region (a torch), in which ionization reactions occur, is formed over the sample surface. The protonation of analyte molecules is the main (but not only) ionization channel. At present, MALDI is the main mass-spectrometric

method for the determination of high-molecular-weight compounds. However, in spite of great success, MALDI has a number of serious disadvantages, of which the following can be noted:

—an intense background signal due to matrix ions makes the determination of low-molecular-weight compounds (to approximately 600 amu) difficult to perform or, in many cases, impossible;

—there is no universal matrix (a large number of matrices are known, and it is necessary to previously know analytes from which class of chemical compounds are present in the test sample for the correct selection of a matrix);

—quantitative analysis is difficult to perform.

These and some other problems stimulated further studies in the area of LDI, which led to the development of a new method referred to as surface-assisted laser desorption/ionization (SALDI) [5]. The first version of SALDI was closely related to the Tanaka method based on the use of the suspensions of graphite microparticles in glycerol or water as a matrix [5, 6]. The development of the method led to the appearance of matrix-free version of SALDI, in which the suspension of graphite microparticles was replaced by a graphite base layer with a rough surface (emitter of ions) [7, 8]. Wei et al. [9] made a major step in this direction to propose the use of porous silicon as the material of a solid substrate—the emitter of ions. At present, both SALDI versions are dynamically developed, and new methods appear based on the use of various nanoparticles and solid substrates. All the above makes it difficult to unambiguously define the concept expressed by the term SALDI. Thus, for instance, in the early versions of the list of mass-spectrometric terms recommended by International Union of Pure and Applied Chemistry (IUPAC), SALDI was initially defined as a version of MALDI, which uses a liquid plus particles as a matrix, and then, as an independent method of the formation of gas-phase ions from molecules deposited on a particular surface that is irradiated with a pulsed laser. In the most recent version (at the point in time of writing this article) of the list, SALDI is considered as a “class of matrix-free laser desorption/ionization techniques for biological macromolecules” [10]. This definition also cannot be considered good. Of course, the determination and identification of high-molecular-weight bioorganic compounds, which are supported to a surface by precipitation from solution, is an important part of SALDI studies; however, the possibilities of the method are substantially wider.

This article describes the analytical characteristics of SALDI in the determination of compounds with relatively low molecular weights, which can be supported onto the surface by adsorption from a gas phase.

Factors controlling the efficiency of SALDI in the detection of volatile compounds with low molecular

weights. Figure 1 shows a schematic diagram of the SALDI ion source. The analyte compounds are adsorbed from a gas phase on the surface of an emitter of ions, which is mounted in the ion source of a mass spectrometer. Solid substrates are used as the emitters of ions because the application of nanoparticles in SALDI usually implies the liquid-phase supporting of a sample (a suspension of nanoparticles with the test liquid sample). Pulsed laser radiation is focused on the surface of the substrate. The action of radiation initiates the ionization of analytes and the desorption of ions. The resulting ions are accelerated, separated in accordance with the values of m/z , and detected in a mass analyzer. The protonation of molecules is the basic channel of ionization in the positive ionization mode.

In this diagram, the efficiency of SALDI is determined by the following three main factors: the physicochemical composition of the emitter of ions, the parameters of laser radiation, and the chemical properties of the analyte.

Physicochemical composition of the emitter of ions.

In the course of the development of the method, a wide range of different substances were studied as the potential emitters of ions, and only a small number of materials (mainly, semiconductor materials) were found effective for SALDI. Silicon materials found the widest use; among their advantages, the high efficiency of ionization, the extremely high degree of material purity, and the comparative ease of its treatment for the formation of an active surface layer should be noted. The purity of material solves the problem of background signals, and its treatment is necessary because the efficiency of SALDI on the surface of single-crystal substrates is extremely small [8, 11]. The well-known methods of the formation of an active layer are diverse. Chemical and electrochemical etching is most frequently used for silicon materials [9, 12]. Furthermore, chemical and plasma-chemical deposition from a gas phase [13], surface bombardment with atoms or ions [8], radiofrequency sputtering [12, 14], etc., found use. The structure and morphology of the formed active layers are also diverse; for example, these are porous amorphous nanocrystalline layers and nanofibers. However, note that the effective silicon emitters of ions possess the following common property: all of them belong to the class of strongly disordered semiconductor materials with a high density of structural defects and related localized states—effective traps of charge carriers.

The chemical surface composition also plays an important role. The process of porous silicon activation [12, 15], which consists in an increase in the ion signal in the course of the surface treatment of freshly prepared porous silicon by low-intensity laser radiation of in the presence of residual water vapor (at a pressure of 10^{-4} – 10^{-5} Pa), can serve as a good example. The chemical aspect of activation consists in the replacement of silane SiH, SiH₂, and SiH₃ groups by

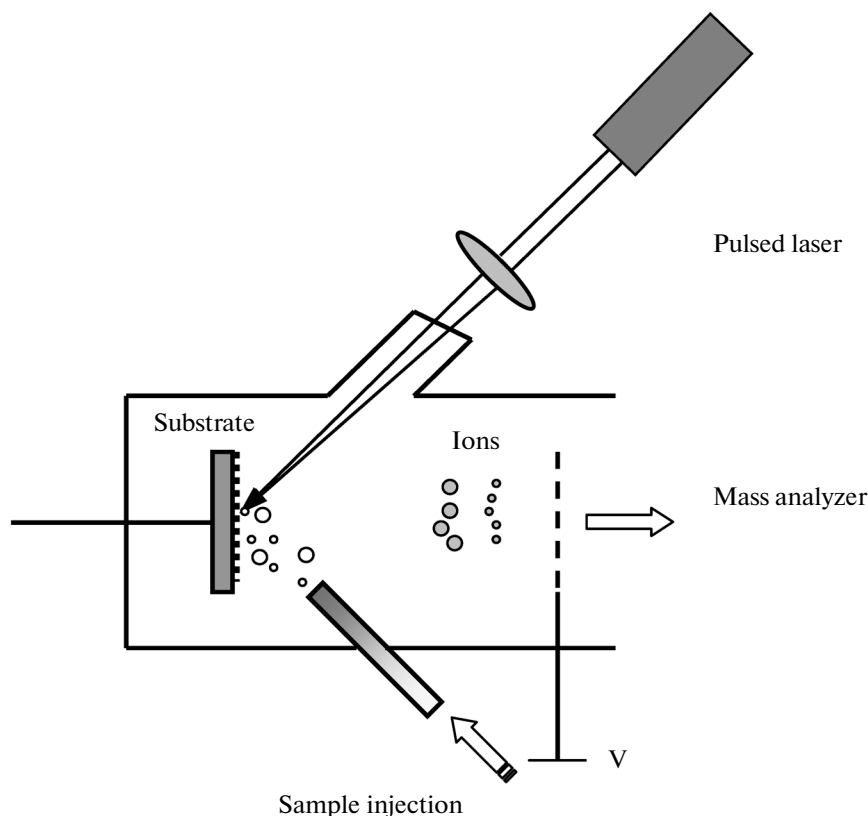


Fig. 1. Schematic diagram of a SALDI ion source for the detection of low-molecular-weight volatile compounds.

the silanol Si–OH groups, which play an important role in the process of ionization on the surface of silicon [11, 12, 16]. In the course of activation, the efficiency of SALDI increases by more than two orders of magnitude.

Laser radiation. At the initial stages of the development of the method, basic approaches to the description of the SALDI mechanism were based on a simple model, according to which the function of laser radiation mainly consisted in the rapid heating of the emitter of ions with the subsequent desorption of molecules supported onto its surface. In the course of the development of the method, a large body of experimental and theoretical data was accumulated to allow one to differently consider the role of laser radiation. The following functions of radiation in the SALDI processes can be recognized [15]:

- the cleaning of the surface to ensure the desorption of organic pollutants from its surface;

- the laser-induced activation of the ion emitter surface—the formation of proton-donor groups on the surface, for example, by the dissociative adsorption of water molecules with the formation of SiOH[−] groups;

- the laser-induced ionization of chemical compounds. Radiation generates nonequilibrium charge carriers in the material of the emitter of ions. Accord-

ing to the mechanism of SALDI on the surface of silicon materials proposed by Alimpiev et al. [12], the separation of photogenerated charges occurs under the conditions of a high density of structural defects, which finally leads to the localization of holes near the surface proton-donor groups. As found by quantum-chemical calculations, positive charge localization decreases the energy of deprotonation of the SiOH group by about 4 eV to convert this group into a strong acid and thus to ensure effective proton transfer to the molecule adsorbed on it.

- the laser-induced desorption of ions. According to the results obtained by Grechnikov et al. [17], the desorption occurs by a thermal mechanism due to the rapid local heating of the surface under the action of laser radiation at temperatures much lower than the melting point or the decomposition temperature of the active layer. Therefore, the repeated irradiation of the surface does not change its ionizing properties (in contrast to MALDI); this is principally important for the quantitative analysis of volatile compounds.

The emission of a nitrogen laser (wavelength, 337 nm) or the third harmonic emission of an Nd:YAG laser (wavelength, 355 nm) is commonly used for laser desorption/ionization on the silicon surfaces.

Chemical properties of an analyte. Protonation is the main process of the formation of positively charged ions in SALDI, which assumes the dependence of the efficiency of ionization on the energy of proton affinity and the basicity of compounds to be determined. In this respect, SALDI is close to another method widely used for determining compounds in a gas phase: chemical ionization. The theoretical and experimental studies carried out by Grechnikov et al. [18] showed that only compounds whose gas-phase basicity (GB) is higher than 820 kJ/mol are effectively ionized on silicon substrates under SALDI conditions. In this case, the efficiency of ionization exponentially increases with the GB of the analyte. The values of GB were determined experimentally for many compounds, and they can be comparatively easily calculated with the use of currently available program packages for quantum-chemical calculations for other compounds. The presence of a reduced nitrogen atom, whose lone electron pair serves as a protonation site of the molecule, in the molecule is an important structural-chemical indicator of the possibility of the efficient detection of the compound by SALDI. The majority of published data on SALDI were obtained in the studies of such compounds.

SALDI instrumentation for the determination of volatile compounds with low molecular weights. Even at the early stages, the development of SALDI was primarily based on the application of commercial laser mass spectrometers equipped with a MALDI ion source. Usually, the SALDI analysis of test samples includes the supporting of a solution, which contains test compounds, onto the active surface of the emitter of ions, the installation of the emitter of ions in the ion source of a mass spectrometer (after solvent evaporation), the action of laser radiation on the surface, and the measurement of mass spectra. Obviously, this method of sample introduction is unsuitable for the determination of volatile compounds. The widespread use of MALDI mass spectrometers, on the one hand, contributed to the development of the SALDI method; however, on the other hand, it was responsible in many respects for the basic trend in this development: the qualitative or semiquantitative analysis of test samples containing slightly volatile and nonvolatile analytes. In turn, this fact was reflected in the above definition of SALDI [10]. The problem of determining volatile compounds was usually not posed, and studies with the use of volatile compounds were limited to the explanation of the mechanisms of laser desorption/ionization on different surfaces [8, 19].

In recent years, several new approaches to the instrumental implementation of the method were developed to perform the quantitative determination of volatile compounds.

Combination of SALDI with gas chromatography (GC). Alimpiev et al. [20] were the first to implement a combination of a time-of-flight mass spectrometer equipped with a SALDI ion source with GC. The

interface between the chromatograph and the mass analyzer was designed in such a way as, on the one hand, to ensure a forward flow of the test compounds to the support surface, which occurred under high-vacuum conditions, but, on the other hand, to exert no effect on the quality of the resulting mass spectra. In contrast to classical ion sources with electron or chemical ionization, in the SALDI method, the ionized molecules are adsorbed and accumulated on the surface of the emitter of ions; therefore, the ion signal is proportional to the irradiated surface area. For increasing this surface area and, therefore, for decreasing the limit of detection, the surface of substrate is scanned with a laser beam in the instrument. The repetition frequency of laser pulses is an important factor: high-frequency lasers have an advantage because they afford the high quality of chromatograms and the high sensitivity of analysis due to an increase in the irradiated area.

In particular, the efficiency of the combination of SALDI and GC was demonstrated using the highly sensitive analysis of solutions containing 12 phenyl alkyl amines with similar chemical properties as an example [21].

Rotating ball interface. Another approach developed for the rapid analysis of liquid and gaseous test samples is based on the use of a technique for sample introduction into a mass spectrometer schematically shown in Fig. 2 [22, 23]. A few (usually, two or four) SALDI-active substrate layers are symmetrically arranged in a vacuum-tight rotation unit made in the form of a rotating ball. One of the substrate layers is located out of the mass spectrometer, and the test sample is applied to it by one or other method. At the same time, the opposite substrate layer is located in the ion source and irradiated by laser emission, and the desorbed ions are detected. Then, the ball is turned to 180° (with the use of two substrate layers), and the process is repeated. The ball interface is compatible with different sample supporting methods. In the analysis of gaseous media (for example, in on-line monitoring of the atmosphere), a forward gas flow to the surface of the substrate layer is generated. In the analysis of solutions, which contain nonvolatile analytes, the test sample is applied by thermal spraying or electrospraying; the interface developed makes it possible to deliver and analyze liquid test samples with volumes to 10 μ L for several seconds [23].

Combination of SALDI with thermal desorption sample injection. Under the conditions of thermal desorption sample injection, the test sample is placed in a heated microcell, from which the sample components are separately evaporated under the action of programmed temperature gradients. The microcell is located near the surface of the emitter of ions, for example, in the vacuum chamber of a mass spectrometer. Another version was proposed by Grechnikov et al. [24] based on a combination of thermal desorption sample injection with the ball interface. In this

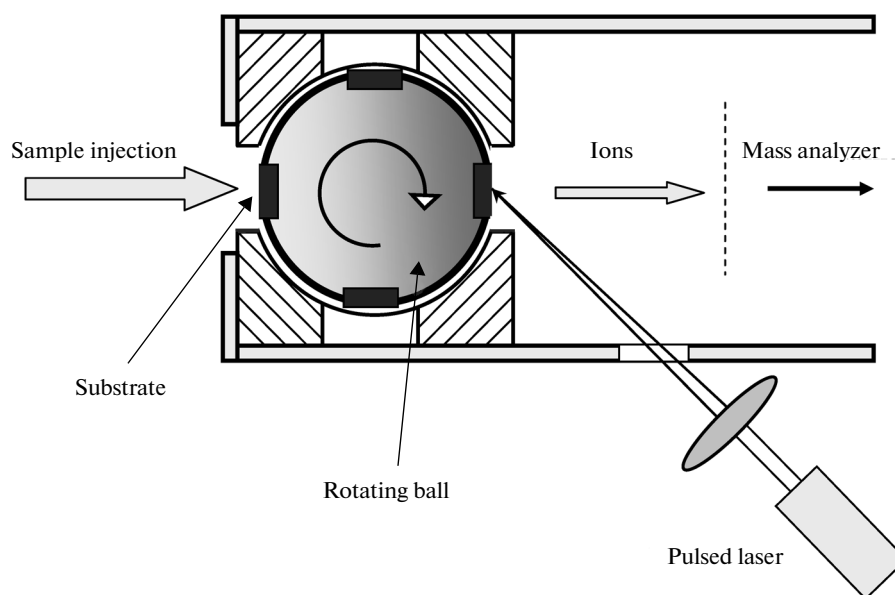


Fig. 2. Schematic diagram of a sample injection unit based on a rotating ball.

version, the microcell evaporator equipped with a resistance heater and a temperature sensor is arranged out of the mass spectrometer at a distance of 1–2 mm from surface of one of the substrate layers fixed on the rotating ball. The sample injection unit ensures the almost complete transfer of compounds to be determined to the surface of the substrate layer, the rapid transfer of the substrate with the analyte supported onto its surface to the vacuum chamber of the mass analyzer, and the positioning of the substrate in the ion source. The programmed thermal desorption makes it possible to support a wide range of test compounds onto the active surface by adsorption from a gas phase and to preliminarily separate them in accordance with volatility.

Membrane sample injection. The use of membrane sample injection, which is based on the diffusion of analytes through a membrane from a high-pressure region (for example, with atmospheric pressure) into a vacuum region in the mass analyzer, is also promising. The distinctive feature of the combination of SALDI with membrane injection is that the membrane is simultaneously the emitter of ions; that is, the membrane material is chosen to ensure the possibility of formation of analyte ions on the membrane surface facing the analyzer under the action of laser radiation on the membrane [25]. In particular, porous silicon can be used as a membrane.

Analytical characteristics of SALDI in the determination of volatile compounds with low molecular weights. *Ionization efficiency.* The efficiency of ionization—a ratio of the number of ions of a compound desorbed from the laser-irradiated surface to the number of molecules of the compound that arrive at this

surface per unit time—is one of the most important parameters responsible for the analytical characteristics of SALDI. Obviously, the efficiency of ionization with gas-phase sample injection is the product of the probabilities of three processes: the probability of the adsorption of a neutral molecule upon collision with the surface, the probability of its ionization, and the probability of its desorption in the form of a protonated molecule. The efficiency of ionization was determined for a number of nitrogen-containing basic compounds, whose GB values lie in a range from 845 to 977 kJ/mol, with the use of chromatographic sample injection and a Knudsen effusion cell [15, 18]. For the test compounds, the efficiency of ionization varied from 7×10^{-6} to 1.4×10^{-2} depending on the GB value. The results obtained show that SALDI can potentially ensure the detection of nitrogen-containing compounds at a level of attomoles (10^{-18} mol) or at a level of tens and units of zeptomoles (10^{-21} mol) for highly basic compounds in terms of substance that arrives at the laser-irradiated surface. This suggests the unique possibilities of SALDI with respect to the sensitivity of analysis. However, such possibilities have not been implemented entirely. Thus, for instance, the flow utilization factor of analyte molecules in a chromatograph–mass spectrometer with a SALDI ion source [20] was 10^{-3} ; that is, only one of a thousand of molecules injected into the instrument arrived at the laser-irradiated surface [18]. Nevertheless, the limits of detection reached on this instrument are substantially lower than those obtained on commercial chromatograph–mass spectrometer instruments with electron ionization. For example, a comparison of the metrological characteristics of SALDI, electron ionization,

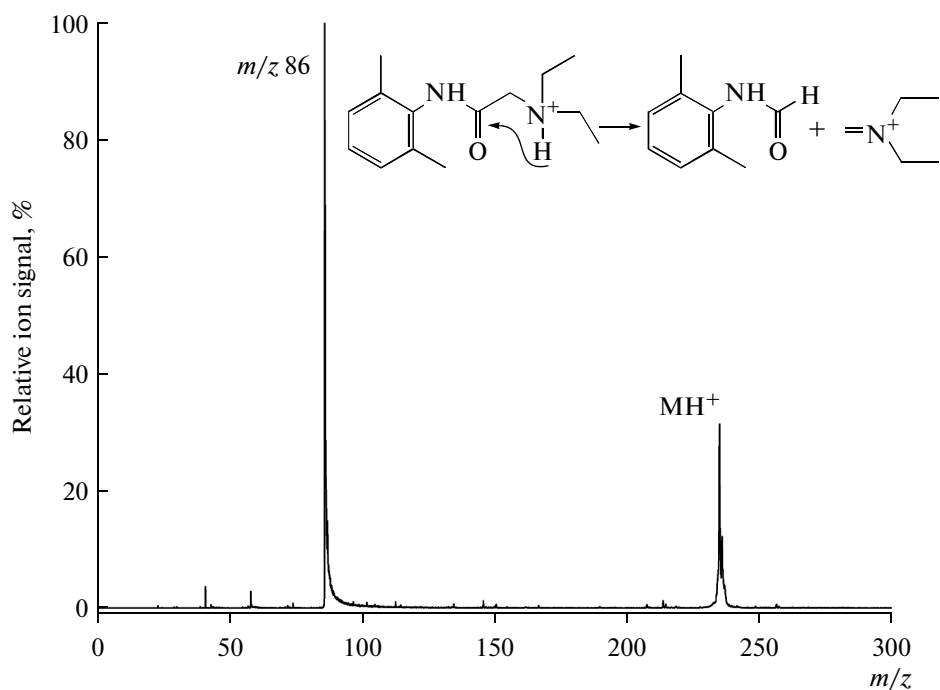


Fig. 3. SALDI mass-spectrum of lidocaine. Insert: schematic diagram of the fragmentation of protonated lidocaine molecules with the formation of a fragment peak with m/z 86.

and chemical ionization in the determination of phenyl alkyl amines showed that the limits of detection of these compounds by the SADLI method were lower by two orders of magnitude than those in the case of traditional ionization methods [26].

Selectivity. The high selectivity of the method is caused by the following factors:

(1) The selectivity of ionization. As noted above, only compounds with relatively high basicity (GB) are effectively ionized in the SALDI process. On the one hand, this fact limits the range of compounds to be determined; however, on the other hand, it makes it possible to reach high selectivity of analysis and a low level of background signal. In particular, for the majority of solvents used in analytical practice, the values of GB are much lower than 820 kJ/mol; therefore, even solvents taken in an excess do not give a contribution to the ion signal. Note that the high selectivity of ionization is especially important for the analysis of complex test samples, for example, biological fluids, and it makes it possible to considerably simplify sample preparation and to increase the accuracy of analysis [24, 26].

(2) The selectivity of a mass analyzer. It is important that the ions formed in the SALDI process start from the same surface, whose spatial position is clearly determined, and the starting time of ions is synchronized with a laser pulse, whose duration is about 1 ns. Therefore, this method is well compatible with time-of-flight mass spectrometry, and the use of even a sim-

ple linear time-of-flight mass spectrometer makes it possible to reach relatively high resolution [20].

(3) SALDI belongs to soft ionization methods. The usually recorded mass spectra contain the peak of protonated analyte molecules and a small number of peaks due to fragment ions. As an example, Fig. 3 shows the SALDI mass spectrum of lidocaine. The presence of a peak that determines the molecular weight of the compound and peaks due to diagnostically significant fragment ions, which characterize the structure of the molecule, considerably simplifies the identification of analytes in the experimental mass spectra.

(4) The compatibility of SALDI with analyte separation systems.

Reproducibility and dynamic range. Because the efficiency of ionization in SALDI critically depends on the physicochemical surface composition of the emitter of ions, the reproducibility of the results of analysis is considered one of the most complex problems in this method. New approaches to the instrumental implementation of SALDI made it possible to advance in the solution of this problem. The best results were obtained with the use of a combination of SALDI with GC because the emitter of ions constantly occurs in a vacuum under the action of desorbing laser radiation (because of this, its physicochemical surface composition remains unchanged) and the gas chromatograph makes it possible to reproducibly inject the samples. In this case, the relative standard

deviation of analytical signals for all of the test analytes was smaller than 0.05 ($n = 5$) [20, 21]. The reproducibility of results was worse with the use of a combination of SALDI with thermal desorption sample injection: the relative standard deviation of signals was approximately 0.10 ($n = 5$) [24].

Figure 4 shows typical calibration graphs for the GC–SALDI MS determination of three aryl alkyl amines as an example [26]. It is evident that the concentration characteristics remain linear over a range of four orders of magnitude and then reach a level of saturation. Note that, even in the section of saturation of the calibration graphs, the surface coverage with analyte molecules does not exceed 0.01 monolayer. This is an important difference of SALDI from direct LDI, in which an analyte is applied as a layer with a thickness of up to thousand of monolayers. The surface effect is absent under the conditions of direct laser desorption/ionization, and ionization is determined by gas-phase processes in a plume formed under exposure to laser radiation. In this case, the efficiency of ionization is much lower (by several orders of magnitude) than the efficiency of SALDI.

Prospects for further development. The above results suggest that SALDI is an effective method for the determination of low-molecular-weight volatile compounds, and it can be used for solving a wide range of problems in the areas of medical diagnostics, pharmacology, ecology, safeguarding, etc. However, its further development is necessary for the complete implementation of the high analytical potential of this method. Here, the following several important lines can be recognized:

—the development of new materials for the emitters of ions and new methods for the formation of active surface layers with a required set of physico-chemical properties;

—the creation of new and the improvement of well-known versions of the instrumentation of this method. For example, the modification of an interface unit between a chromatograph and a SALDI ion source can increase the sensitivity of a GC–SALDI mass spectrometer by three orders of magnitude. The combination of this method with high-resolution mass analyzers, in particular, the orbital ion trap (Orbitrap), is also promising [27]. A broad dynamic range (to 10^6 ions) together with the high mass resolution and the possibility of the precise determination of masses demonstrate the advantages of Orbitrap over time-of-flight analyzers. Makarov et al. [28] were the first to implement the SALDI–Orbitrap combination for the determination of nonvolatile compounds as an example. Further development of this combination will make it possible to substantially improve the analytical parameters of SALDI in the determination of volatile low-molecular-weight analytes.

—the expansion of the range of compounds to be determined by the SALDI method. As noted above,

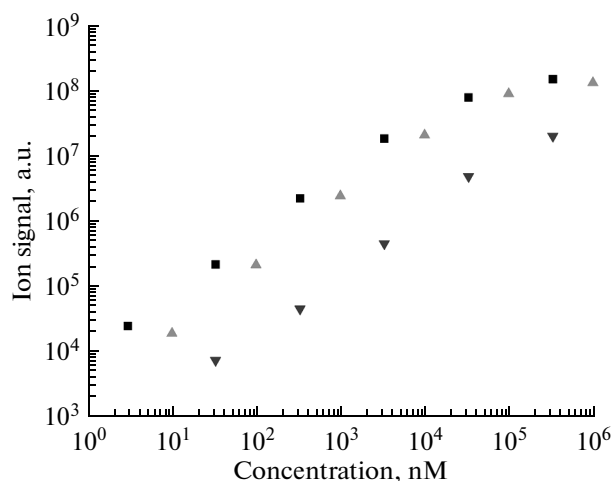


Fig. 4. Calibration graphs for the determination of (■) *N,N*-dipropyl-1-phenylethylamine, (▲) *N,N*-dimethylbenzylamine, and (▼) 1-benzylamine by the GC–SALDI MS method. Emitter of ions, amorphous silicon [26].

the traditional version based on the use of the protonation reaction of molecules on the surface of silicon substrate layers makes it possible to ionize only compounds with relatively high basicity. For expanding the number of determined analytes, derivatization can be used in order to increase the basicity of compounds, although this will noticeably complicate the analysis and increase its duration. Another approach consists in the use of the negative ion detection mode. Thus, for instance, Alimpiev et al. [29] demonstrated that SALDI can be used for the determination of the ultralow concentrations of trinitrotoluene, which undergoes ionization with the formation of deprotonated molecules, in a gas phase. However, the processes of ionization and desorption of negatively charged ions are still not clearly understood and the optimum parameters responsible for the analytical characteristics of this method were not found. A new approach to ionization for the production of the ions of molecules that absorb laser radiation also seems very promising [30]. Unlike traditional versions of SALDI, this new approach uses laser-induced ionization by electron transfer from the molecule adsorbed on the substrate layer to the substrate material (or in the opposite direction); therefore, it was referred to as laser-induced electron transfer desorption–ionization (LETDI) [31]. In this case, the efficiency of ionization does not depend on the basicity of the compounds to be determined. The development of this direction opens prospects for a significant expansion of the range of compounds determined by the SALDI method.

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