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Stiftung für Stipendien auf dem Gebiete der Chemie
Der Präsident

Prof. Paul Müller*

Chimia 51 (1997) 234–236

ISSN 0009–4293

Frontiers of Laser Chemical Analysis

Renato Zenobi*

Introduction

I have always been fascinated by how the laser, one of the most powerful tools of modern science, can benefit chemists for initiation of chemical reactions, reaction control, probing of the reaction dynamics, spectroscopic investigation of complex molecules, and for ultratrace detection in chemical analysis. During my Ph.D. thesis at Stanford University, I had the opportunity to work on a laser mass spectrometry project, in a research group whose activities reach from state-to-state reaction dynamics all the way to laser detection in capillary electrophoresis. The time I spent at Stanford influenced me profoundly. I was involved in collaborations with scientists from many different fields, I became interested in pursuing research projects on my own, and I also saw that an academic carreer was not as far fetched as it often seems in Europe. Many of my colleages went on to faculty positions at universities in the United States and elsewhere, and I was encouraged to consider this carreer path, too. When I was awarded the *Alfred Werner Fellowship* in 1991, I accepted it because it promised to give me the kind of academic freedom I was hoping for, and I defined it for myself as an 'externally funded junior faculty position' in the Swiss system. The *Werner Fellowship* really gave my carrer a boost: I started to build up my own research group and to publish independently, I successfully attracted research money from several foundations and agencies, and I launched many projects. Some of them still form a basis for my current research at the ETH-Zürich. Below, I briefly explain the areas of research we are currently involved with.

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Renato Zenobi, born in 1961, went through school and college in Zürich and graduated from ETH (Abt. X) in 1986. His diploma thesis, with Prof. *Martin Quack*, was on high-resolution infrared overtone spectroscopy. He then entered the chemistry Ph.D. program at Stanford University, working with Prof. *Richard N. Zare*. His dissertation in 1990 was entitled 'Two-Step Laser Mass Spectrometry'. He completed his scientific education with two postdoctoral appointments, at the Surface Science Center of the University of Pittsburgh (with Prof. *John T. Yates*) and at the University of Michigan (with Prof. *Raoul Kopelman*). In 1991, he won the first *Alfred Werner Fellowship* which allowed him to return to Switzerland and to start building up his own research group at the Ecole Polytechnique Fédérale in Lausanne. In 1994, he was appointed assistant professor of analytical chemistry at the ETH-Zürich.
Renato Zenobi has won several awards and fellowships, among them the *Thomas Hirschfeld Award* in 1989, an *Andrew Mellon Postdoctoral Fellowship* in 1990, and the *Ruzicka Prize* in 1993.

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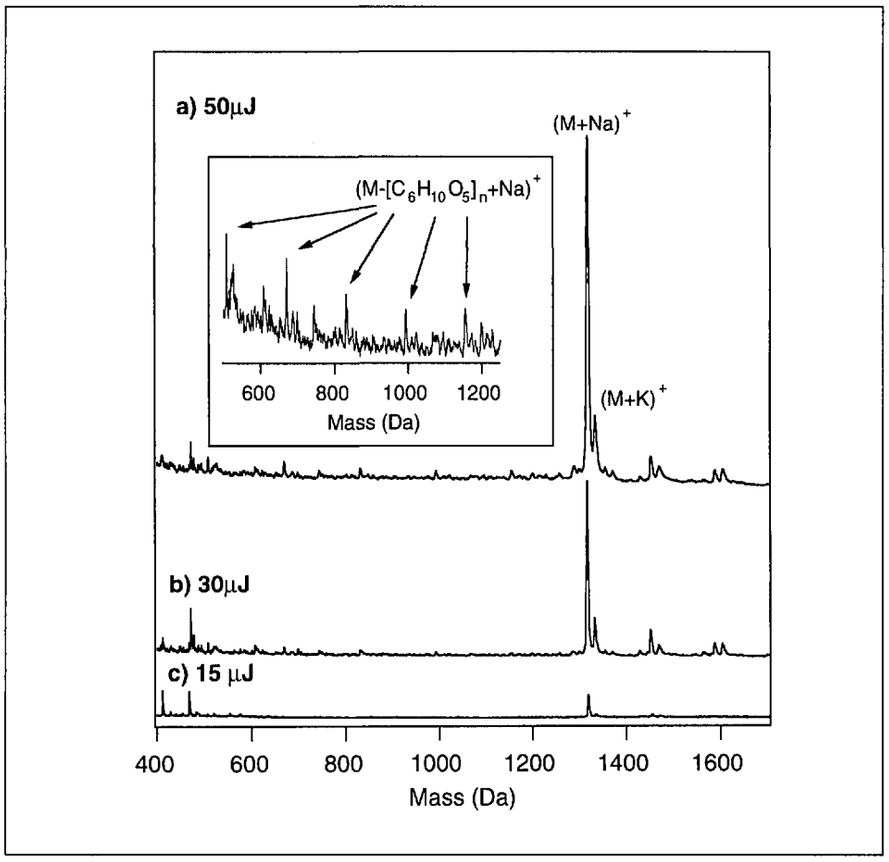

Figure. *UV laser desorption/ionization mass spectra of γ-cyclodextrin obtained using a glycerol/graphite two-phase matrix and average laser pulse energies of* a) *50,* b) *30, and* c) *15 μJ.* Inset shows a magnification of the spectrum in *a*). The higher laser fluence results in enhanced signal intensities as well as some fragmentation that can be used for structural elucidation.

Scanning Near-Field Optical Microscopy (SNOM)

Optical analysis of surfaces with a spatial resolution below the diffraction limit is possible by scanning a subwavelength (< 100 nm) light source in close proximity (< 10 nm, *i.e.*, in the optical near field) to an object. Commercial SNOM tips, produced by pipette pulling techniques applied to optical fibers, suffer from poor transmission (≈ 10^{-6}). We are using chemically etched tips characterized by a much wider opening angle, a short taper region, and an optical transmission approaching 1%. These tips have allowed fluorescence imaging with < 100 nm resolution and excellent signal-to-noise ratios. Very recently, we demonstrated that vibrational spectoscopy with < 200 nm spatial resolution is also possible (using surface-enhanced *Raman* spectroscopy, SERS) [1]. This opens the way to true *chemical* identification in the submicron range. We apply this to the chemical analysis of molecular surface layers and to materials such as diamond. Pulsed laser radiation can also be transmitted through our SNOM tips. This permits surface modification of polymers and laser-induced desorption of molecular films with *ca.* 70 nm resolution [2].

Two-Step Laser Mass Spectrometry (L2MS)

Two-Step Laser Mass Spectrometry (L2MS) uses laser-induced thermal desorption from a surface by an infrared laser pulse, followed by gas-phase photoionization by an ultraviolet laser pulse and time-of-flight mass analysis. It is a powerful method for the ultrasensitive and selective mass spectroscopic analysis of high molecular weight, nonvolatile, and thermally labile substances. It allows rapid and direct analyses of trace constituents in complex mixtures, and can reach a spatial resolution in the μm range. We are applying L2MS to a wide range of difficult analytical problems: The analysis of polycyclic aromatic hydrocarbons in kerogens [3] and on environmental aerosol particle surfaces [4], the detection of porphyrin-based photosensitizers for laser cancer therapy in commercial drug formulations [5], and the spatially resolved *in-situ* analysis of polymer additives [6][7].

Laser-Induced Thermal Desorption (LITD)

The mechanism of intact desorption of thermally labile molecules by Laser-Induced Thermal Desorption (LITD) is still a matter of debate. Using laser spectroscopic methods, we are studying the kinetic and internal energy distributions of test molecules after laser desorption from a variety of substrates. In one study, silylation of silica reduced the internal temperature of laser-desorbed tryptophan by a factor of three, due to the elimination of hydrogen bonding between silanol groups on silica and the adsorbed tryptophan [8]. Results of another study indicate that aniline desorbs from silica with kinetic and internal energies characterized by temperatures below the surface temperature at the time of desorption [9]. However, the latter was extrapolated, not measured simultaneously. We therefore developed a method based on blackbody radiation for noncontact temperature measurement of laser-heated surfaces with < 10 ns time resolution [10].

Matrix-Assisted Laser Desorption/ Ionization (MALDI)

Matrix-Assisted Laser Desorption/Ionization (MALDI) is one of the powerful recently developed mass spectrometric methods for the analysis of nonvolatile compounds of high and very high molecular weight (up to several 100000 Da). The ion formation in MALDI is still a poorly understood process. For instance, samples with high electrolyte concentrations such as blood plasma, milk, and other naturally occurring fluids are difficult to analyze by MALDI [11]. The lack of knowledge on ion formation also hinders the rational design of new MALDI matrices. One major thrust of our research is to unravel the MALDI ion formation mechanism. When studying the matrix supression effect in MALDI-MS, we found a new and general mechanism for MALDI ion generation based on recombination of excited matrix species (excitons) [12]. The new model is consistent with available experimental data and also made predictions that were later confirmed experimentally.

Secondly, the problem of efficiently detecting very high-molecular-weight ions is part of our research efforts. Third, we are working on the design of a particle-based two-phase matrices that are reusable and may be employed as a terminating element of a capillary column for direct

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interfacing of liquid chromatography with MALDI-MS. We have shown that a new matrix consisting of a graphite/glycerol or silicon/glycerol slurry can be used very generally for sensitive MALDI-MS on peptides, proteins, oligosaccharides (*Fig.*), polar and apolar polymers up to molecular weights of 15 kDa [13][14].

Fourier-Transform Mass Spectrometry (FTMS)

Some MALDI ion formation processes take place after desorption, by gas-phase protonation (cationization) reactions in the MALDI plume. If this is the dominant process, fragmentation will be controlled by relative proton (cation) affinities of matrix and analyte. Very limited proton affinity (PA) data on nonvolatile MALDI matrices is available. We are measuring them by bracketing reactions in the FTMS instrument using gaseous reference bases of known PA. We have determined the proton affinity values of the MALDI matrices 2,5-DHB, 4-HCCA, and sinapic acid [15]. The PA values of some common matrix fragments were also measured and found to differ siginificantly from that of the parent molecule. In some cases, this difference amounts to 60 kJ/mol (15 kcal/mol). Furthermore, no correlation between fragmentation of analytes and the PA of the matrices were found.

Received: March 3, 1997

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Chimia 51 (1997) 236–238

ISSN 0009-4293

Stereoselectivity Control of Free-Radical Reactions Using *Lewis* Acids

Philippe Renaud*

The development of new methods for the formation of C,C bonds has attracted the interest of synthetic chemists for a long time. An impressive number of stereocontrolled procedures based on ionic and concerted reactions have been developed. During the last 15 years, radical reactions became a useful tool in organic synthesis. For a long period of time, they were considered as essentially non-stereoselective. However, recent developments have completely altered this belief, and subsequently rules were developed to rationalize and predict the stereochemical outcome of cyclization reactions, reactions in rigid systems, and even reactions in acyclic systems [1]. A few years ago, strongly encouraged by the attribution of the *Alfred Werner* Fellowship, we decided to investigate the use of *Lewis* acids in order to control the stereoselectivity of radical reactions. Some of our recent results are depicted below.

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Michèle Gerster (left) *and* Anna-Reine Fhal (right) *are two graduate students strongly involved in the use of* Lewis *acids in radical reactions*