Detection of Transient Radical Cations in Electron Transfer-Initiated Diels−Alder Reactions by Electrospray Ionization Mass Spectrometry

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Abstract: The coupling of a simple microreactor to an atmospheric pressure ion source, such as electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI), allows the investigation of reactions in solution by mass spectrometry. The tris(*p*-bromophenyl)aminium hexachloroantimonate ($1^{\bullet+}SbCl_6^-$)-initiated reactions of phenylvinylsulfide (**2**) and cyclopentadiene (**3**) and of *trans*-anethole (**5**) and isoprene (**6**) and the dimerization of 1,3-cyclohexadiene (**8**) to give the respective Diels−Alder products were studied. These preparatively interesting reactions proceed as radical cation chain reactions via the transient radical cations of the respective dienophiles and of the respective Diels−Alder addition products. These radical cations could be detected directly and characterized unambiguously in the reacting solution by ESI-MS−MS. The identity was confirmed by comparison with MS−MS spectra of the authentic radical cations obtained by APCI-MS and by CID experiments of the corresponding molecular ions generated by EI-MS. In addition, substrates and products could be monitored easily in the reacting solution by APCI-MS.

Introduction

The recent developments of mass spectrometric ionization methods at atmospheric pressure (API), such as the atmospheric pressure chemical ionization (APCI)[1,2] and the electrospray ionization mass spectrometry (ESI-MS),[3] enable the investigation of liquid solutions by mass spectrometry. These ionization methods opened up the access to the direct investigation of chemical reactions in solution via mass spectrometry. In 1986, the first real-time mass spectrometric investigation in electrochemical reactions[4] was reported. The API methods were used to detect and examine intermediates of reactions in solution. The investigations were mostly performed off-line, for example, with the oxidation of tetrahydropterins to radical cations,[5] the homogeneously catalyzed reactions, such as the Suzuki reaction,[6] and the palladium-catalyzed oxidative self-coupling of areneboronic acids,[7] as well as the Mitsunobu[8] and Wittig reactions.[9] Recently, Eberlin et al.[10] detected a cyclic oxatitanium intermediate of the Petasis olefination by APCI-MS. Roglans et al.[11]

and Eberlin et al.[12] examined the Heck olefination of aryl diazonium tetrafluoroborates with a palladium catalyst by ESI-MS and detected aryl palladium intermediates. In the palladium dichloride-catalyzed coupling of vinylic tellurides with alkynes, cationic Pd−Te intermediates were, for the first time, intercepted and characterized by ESI-MS−MS.[13]

The group of Arakawa used an on-line ESI-MS system in which a flowthrough photoreaction cell was attached to an electrospray interface to detect intermediates of photochemical reactions of some transition-metal complexes, with a lifetime of a few minutes.[14] Via direct irradiation of samples in an optically transparent tip of an ESI source, Amster et al. succeeded the direct detection of short-lived iron−cyclopentadiene complexes as key intermediates of cationic photoinduced polymerization of epoxides.[15]

Chen et al. used ESI-MS to generate and isolate the active species of homogeneously catalyzed reactions, such as Ziegler−Natta polymerization[16] or Olefin metathesis,[17] and studied the

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reaction with the substrate in the gas phase. C−H activation of cationic iridium(III) complexes[18] and platinum(II) complexes,[19] as well as the high-valent oxorhenium complex-catalyzed aldehyde olefination,[20] was investigated. Feichtinger and Plattner used the same technique to investigate the formation and reactions of the active species of epoxidation catalysts (i.e., oxomanganese−salen complexes).[21]

The reaction mechanism is the detailed, step-by-step description of a chemical reaction. Most chemical reactions take place through a complex sequence of steps via reactive intermediates. Simple methods for their direct detection, if possible under the conditions of the preparative reaction, are essential for elucidating and understanding the mechanisms of synthetically important reactions in solution. We introduced a novel method to investigate, directly, transient C radicals in preparatively important radical chain reactions in solution by ESI-MS, coupled to a microreactor system. The respective radicals were detected unambiguously and characterized by ESI-MS−MS.[22]

Recently, we reported the first investigation of an electron transfer-initiated radical cation chain reaction in solution using the microreactor coupled ESI-MS system. The transient radical cations of the tris(*p*-bromophenyl)aminium hexachloroantimonate ($1^{\bullet+}SbCl_6^-$)-mediated [2 + 2] cycloaddition of *trans*-anethole were detected and characterized directly and unambiguously in the reacting solution by ESI-MS−MS.[23]

Tris(*p*-bromophenyl)aminium hexachloroantimonate ($1^{\bullet+}SbCl_6^-$) is a well-known, commercially available compound. It is a deep-blue salt consisting of a tris(*p*-bromophenyl)aminium radical cation ($1^{\bullet+}$) and a hexachloroantimonate anion ($SbCl_6^-$). The redox behavior of bromo-substituted triarylamines, in general, was studied systematically by Schmidt and Steckhan by cyclic voltammetry,[24] thus the positive oxidation potential was shown to be 1.30 V against NHE (normal hydrogen electrode), indicating that $1^{\bullet+}SbCl_6^-$ is a one-electron oxidant. For this reason, it was often used as an electron-transfer initiator in organic synthesis, for example, in electron-transfer-initiated Diels−Alder reactions and other cycloadditions pioneered by Bauld and co-workers, which have been recently summarized.[25]

The reaction of phenylvinylsulfide (**2**) and cyclopentadiene (**3**) to give 5-(phenylthio)norbornene (**4**), mediated by aminium salt $1^{\bullet+}SbCl_6^-$, is a very interesting example of an electron-transfer-initiated Diels−Alder reaction which proceeds via a radical cation chain mechanism, as was shown by kinetic investigations.[25,26] The following reaction mechanism has gener-

Scheme 1. Tris(*p*-bromophenyl)aminium Hexachloroantimonate ($1^{\bullet+}SbCl_6^-$)-Initiated Radical Cation Chain Reaction of Phenylvinylsulfide (**2**) and Cyclopentadiene (**3**) To Give the Diels−Alder Product 5-(Phenylthio)norbornene (**4**) via the Reactive Intermediates, $2^{\bullet+}$ and $4^{\bullet+}$
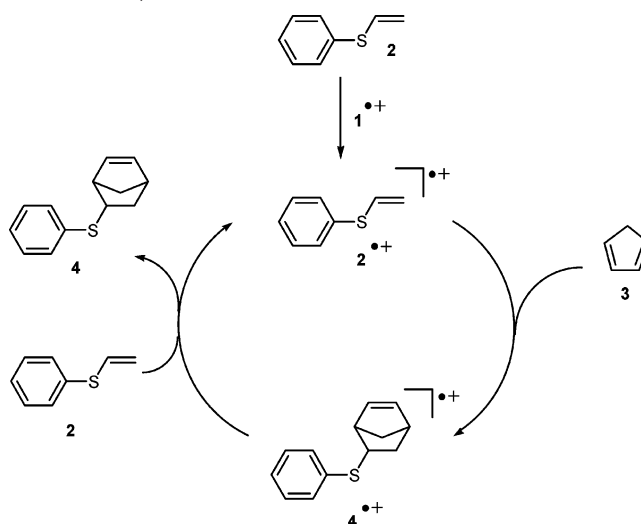

ally been accepted (Scheme 1). The stable radical cation $1^{\bullet+}$ oxidizes dienophile **2** to radical cation $2^{\bullet+}$ which adds to diene **3**, resulting in radical cation $4^{\bullet+}$, which is reduced by substrate **2** to give the Diels−Alder cycloaddition product **4**. The occurring reactive intermediates were indirectly established by kinetic investigations. However, both transient radical cations $2^{\bullet+}$ and $4^{\bullet+}$ have not been directly detected in the reacting solution (e.g., by ESR or UV spectroscopy). Preparatively, this reaction experiment was carried out by the addition of a 30 mol % solution of $1^{\bullet+}SbCl_6^-$ in dichloromethane to a solution of **2** with 14 equiv of **3** at 0 °C; the Diels−Alder cycloaddition product, 5-(phenylthio)norbornene (**4**), was obtained in 30% yield with an *endo*/*exo* ratio of 3:1 after a few minutes.[27]

In chemical textbooks, electron-transfer (ET) processes are classified as outer sphere ETs, involving no significant covalent interactions between donor and acceptor, or inner sphere ETs, involving significant weak to strong covalent interactions between donor and acceptor.[28] Some years ago, Bauld postulated a further mechanism for the electron transfer of the tris(*p*-bromophenyl)aminium radical cation to phenylvinylsulfide. Evidence for such a mechanism was found by kinetic investigations combined with substituent effect studies, which support an electron-transfer process involving an electrophilic attack by the aminium salt to the neutral phenylvinylsulfide, thus forming a distonic radical cation intermediate followed by homolysis of the newly formed covalent bond to give the amine and the phenylvinylsulfide radical cation.[27,29] Furthermore, Bauld discussed the position of the electrophilic attack and differentiated between the attack at the unsubstituted vinyl carbon and the nucleophilic sulfur atom (Scheme 2). Stereochemical studies

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Scheme 2. Possible Structures of the Distonic Radical Cation Intermediate in the Two-Stage Polar Electron Transfer from Tris(*p*-bromophenyl)aminium Radical Cation (**1**•+) to Phenylvinylsulfide (**2**) (refs 27 and 29)
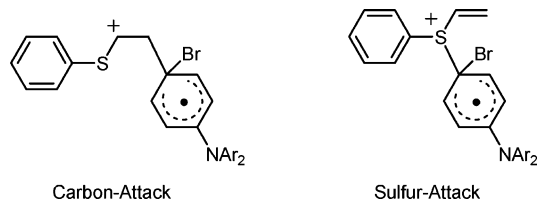
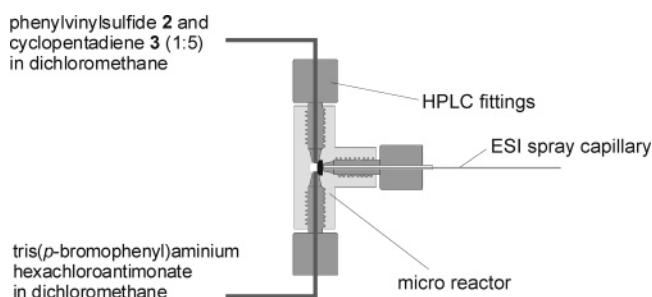of deuterated compounds suggested the attack was at the sulfur atom.

Many more Diels−Alder reactions of electron-rich alkenes, such as dienophile, with electron-rich 1,3-dienes initiated by the aminium salt **1**•+SbCl$_6^-$ have been studied, namely, the reaction of anethole (**5**) and isoprene (**6**) (22% yield),[30] as well as the dimerization of 1,3-cyclohexadiene (**8**) (70% yield).[31] Mechanistic diagnosis methods for the operation of radical cation mechanisms have been developed.[25] However, up to now, it has not been possible to detect directly in the reacting solution the transient radical cations of this important type of reaction.

We decided to study some important examples of this reaction by microreactor-coupled API-MS, focusing on the direct detection and mass spectrometric characterization of the transient radical cations involved. Because the ESI method, in contrast to APCI, normally releases ions preformed in solution, it can be expected that the transient radical cations should be detectable by ESI-MS−MS in the reacting solution under quasi-stationary conditions, despite the presence of other species as was shown in the example of the [2 + 2] cycloaddition of anethole.[23] First, we decided to study the APCI-MS spectra of substrates and products to obtain MS−MS spectra of the authentic radical cations we wanted to detect and to investigate the respective reactions by APCI-MS to measure a reacting solution. For comparison, the MS−MS spectra of the radical cations formed by electron ionization (EI) should be studied, as well. The intriguing results obtained are presented in this paper.

Experimental Section

Tris(*p*-bromophenyl)aminium hexachloroantimonate (**1**•+SbCl$_6^-$), *trans*-anethole (**5**), isoprene (**6**), and 1,3-cyclohexadiene (**8**) were obtained from Aldrich (Steinheim, Germany). Phenylvinylsulfide (**2**), dicyclopentadiene, and dichloromethane were purchased from Fluka (Deisenhofen, Germany). Cyclopentadiene (**3**) was freshly distilled from dicyclopentadiene. Dichloromethane was distilled after refluxing over calcium hydride, and cyclohexadiene was distilled over sodium. The other chemicals were used without further purification. *endo/exo*-5-(Phenylthio)norbornene (**4**) and *trans*-1,5-dimethyl-4-(4′-methoxyphenyl)cyclohexene (**7**) were synthesized according to published procedures[27,30] and characterized by ^{1}H and ^{13}C NMR.

API-MS experiments were performed using a Finnigan LCQ (Thermo Finnigan, San José, CA) quadrupole ion trap mass spectrometer equipped with a standard ESI and APCI ion source. The standard ESI source of the LCQ was used with a stainless steel metal capillary (110 μm i.d., 240 μm o.d., 120.5 mm of length, Metal Needle Kit, Thermo Finnigan), with a volume of 1.14 μL. Sample solutions were infused using the dual syringe pump of the LCQ by varying the flow rate in a range of 2.5−100 μL/min. By connecting a microreactor (ALLTECH, PEEK mixing tee; see Figure 1) to the ESI spray capillary,

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Figure 1. The microreactor allows for the effective mixing of the reactants in solution (e.g., of **2** and **3** with **1**•+SbCl$_6^-$) and the transfer to the mass spectrometer.

we can cover reaction times from 0.7 to 28 s. Longer reaction times can easily be realized using a fused silica transfer capillary of variable length between the microreactor and the spray capillary. Via a fused silica transfer capillary, the microreactor was connected to the LCQ-APCI source. APCI mass spectra of the reacting solution can be acquired by this method in a reaction time range of approximately 1 s to a few minutes.

ESI operation conditions of a spray voltage of +3 kV and a heated capillary temperature of 150 °C were utilized, whereas in the APCI mode, a vaporizer temperature set to 300 °C, a corona discharge of 3 μA, and a capillary temperature of 150 °C were employed. Collision-induced dissociation (CID, collision gas helium) was performed in the ion trap region. The effective isolation width for CID experiments was set at 1.0 u, with a collection time up to 500 ms. Data acquisition and analysis were done with the Xcalibur (version 1.2, Thermoquest Finnigan) software package. Additionally, ESI-MS experiments have been carried out on the quadrupole time-of-flight instruments (Ultima Q-ToF, Micromass) and Q-Star (Applied Biosystems).

The electron ionization experiments were performed using Finnigan MAT 95 (Thermo Finnigan MAT) with an ion source temperature of 220 °C, an emission of 0.1 mA, and an electron energy of 70 eV. The CID spectra in the first free-field region were taken using a B/E-linked scan.

Reaction of Phenylvinylsulfide and Cyclopentadiene. A solution of tris(*p*-bromophenyl)aminium hexachloroantimonate (**1**•+SbCl$_6^-$), 1 × 10^{-4} mol L^{-1}, and a solution of phenylvinylsulfide (**2**), 1 × 10^{-3} mol L^{-1}, with cyclopentadiene (**3**), 5 × 10^{-3} mol L^{-1}, both in dichloromethane, were mixed using a dual syringe pump feeding the microreactor that was coupled directly to the ion source of the mass spectrometer (Figure 1). The reacting solution was fed continuously into the MS and investigated by APCI-MS and ESI-MS, as described above.

Reaction of *trans*-Anethole and Isoprene. The solution of **1**•+SbCl$_6^-$, 1 × 10^{-4} mol L^{-1}, and a solution of anethole (**5**), 1 × 10^{-3} mol L^{-1}, with isoprene (**6**), 5 × 10^{-3} mol L^{-1}, in dichloromethane, were mixed in the microreactor and fed continuously into the MS system.

Reaction of 1,3-Cyclohexadiene. Analogously, the solution of **1**•+SbCl$_6^-$, 1 × 10^{-4} mol L^{-1}, was mixed in the microreactor with a solution of 1,3-cyclohexadiene (**8**), 5 × 10^{-3} mol L^{-1} in dichloromethane, and the reacting solutions were examined by MS.

Control Experiments. Solutions of substrates **2**, **2** with **3**, **5**, **5** with **6**, and **8**, as well as products **4** and **7**, each in dichloromethane, however without **1**•+SbCl$_6^-$, were investigated in the same way by ESI-MS−MS. Radical cations **2**•+, **4**•+, **5**•+, **7**•+, **8**•+, and **9**•+ could not be observed in these experiments. Solutions of products **4**, **6**, and **9**, in the presence of **1**•+SbCl$_6^-$, were studied in the same way. Radical cations **4**•+, **7**•+, and **9**•+ could not be detected. A solution of substrate **2** and product **4** was mixed in the microreactor with a solution of **1**•+SbCl$_6^-$ and was investigated by ESI-MS−MS. Cation **2**•+ was detected unambiguously; **4**•+could not be detected.
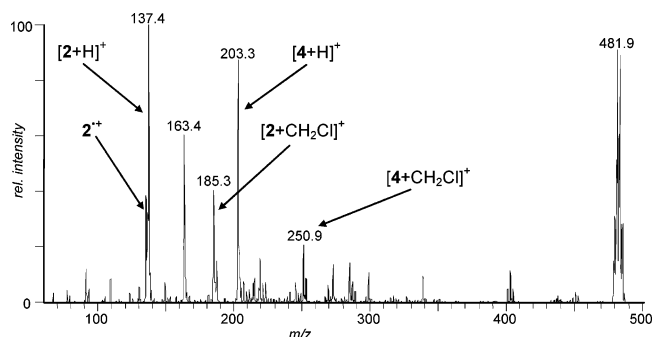
Figure 2. Positive APCI mass spectrum of the reacting solution of phenylvinylsulfide (**2**), cyclopentadiene (**3**), and tris(*p*-bromophenyl)-aminium hexachloroantimonate (**1**•⁺SbCl₆⁻) in dichloromethane after a reaction time of approximately 20 s.

Results

1. Reaction of Phenylvinylsulfide (2) and Cyclopentadiene (3): APCI-MS Measurement. The separate measurements of substrates **2** and **3** and product **4** by APCI-MS were the starting point of the investigations. In the APCI mass spectrum of a solution of **2** in dichloromethane, an intensive ion at *m/z* 137, due to the protonated molecule [**2** + H]⁺, an ion at *m/z* 136, due to the radical cation **2**•⁺, and an ion at *m/z* 185, which can be identified via the characteristic isotopic pattern to become a cationized molecule [**2** + CH₂Cl]⁺, are detected. This chloromethylen adduct ion was found as a typical ion formed in the APCI spray process using dichloromethane as the solvent. Product **4** was measured analogously. The spectrum shows the protonated molecule [**4** + H]⁺ (*m/z* 203), the 5-(phenylthio)-norbornene radical cation (**4**•⁺) at *m/z* 202, and, in addition, the chloromethylen adduct ion [**4** + CH₂Cl]⁺ at *m/z* 251. In both cases, the protonated molecules and the radical cations are generated in the APCI process. Cylopentadiene **3** was examined analoguously. Remarkably, there were no characteristic signals of **3** to observe directly in the APCI-MS experiment. Thus, **3** was not ionized in the APCI process using dichloromethane as the solvent.

To investigate the Diels−Alder reaction, a solution of **1**•⁺SbCl₆⁻ and a solution of **2** with **3**, both in dichloromethane, were efficiently mixed in the microreaction system and fed continuously into the APCI-MS. In Figure 2, the mass spectrum of the reacting solution after a reaction time of approximately 20 s is presented. At *m/z* 479−486, signals derived from **1**•⁺SbCl₆⁻ are observed. The signals of substrate **2** and of product **4** can be recognized, as well, thus pointing out that a solution with an ongoing reaction is being investigated. Some additional ions were observed in the APCI mass spectrum of the reacting solution, giving evidence for the formation of minor byproducts.

APCI-MS−MS of Radical Cations 2•⁺ and 4•⁺. Radical cations **2**•⁺ and **4**•⁺ are formed in the APCI process, allowing the characterization of authentic **2**•⁺ and **4**•⁺ by MS−MS (Figure 3a,b).

EI-MS−MS of the Molecular Ions of Phenylvinylsulfide (2) and 5-(Phenylthio)norbornene (4). Radical cations **2**•⁺ and **4**•⁺ can also be generated by the EI ionization of substrate **2** and product **4**, respectively. The high-energy CID mass spectrum of the parent ion of phenylvinylsulfide **2** (Figure 4a) shows the same fragmentations as the APCI-MS-MS spectrum (Figure 3a). The CID mass spectrum of the 5-(phenylthio)norbornene
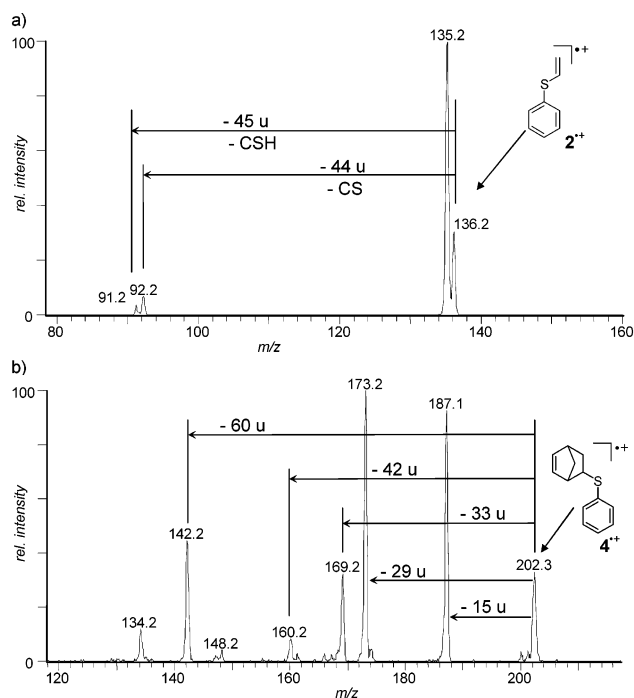
Figure 3. (a) APCI-MS−MS spectrum of the molecular ion of phenylvinylsulfide **2**•⁺ (*m/z* 136). (b) APCI-MS−MS spectrum of the molecular ion of 5-(phenylthio)norbornene **4**•⁺ (*m/z* 202).
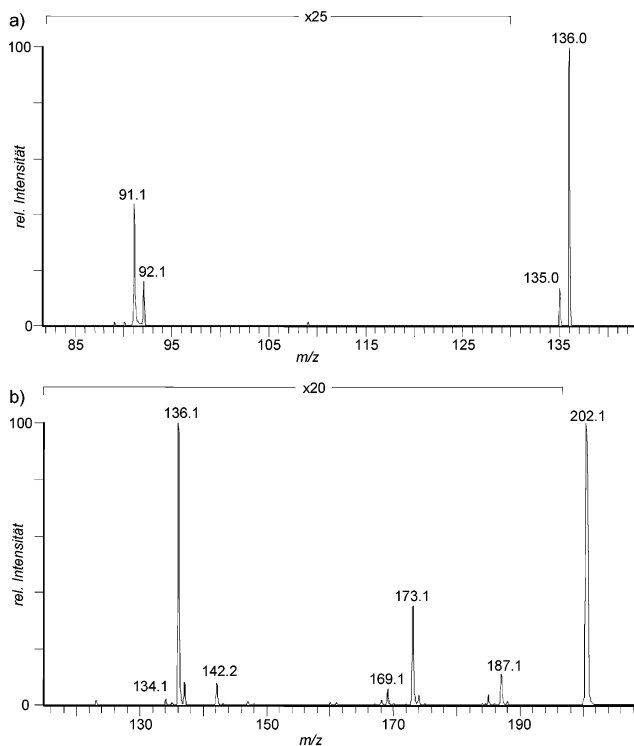
Figure 4. (a) CID mass spectrum of EI-generated parent ion of phenylvinylsulfide **2**•⁺ (*m/z* 136). Zoomed into (25-fold) the mass range of *m/z* 80−130. (b) CID mass spectrum of EI-generated parent ion of 5-(phenylthio)-norbornene **4**•⁺ (*m/z* 202). Zoomed into (20-fold) the mass range of *m/z* 115−195.

molecular ion **4**•⁺ (Figure 4b) shows, in comparison to that of APCI-MS−MS (Figure 3b), an intensive retro-Diels−Alder fragmentation to give the product ion *m/z* 136. It seems to be remarkable that the latter fragmentation cannot be observed in the low-energy CID in the ion trap.
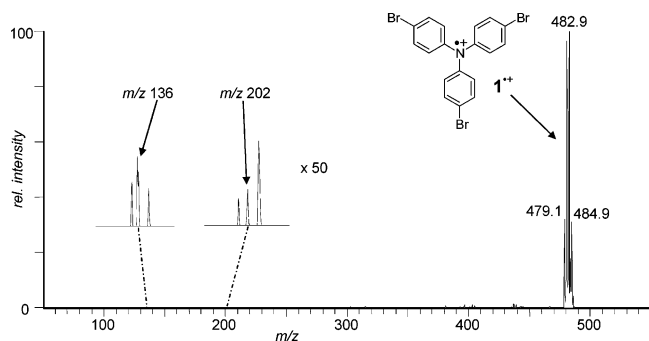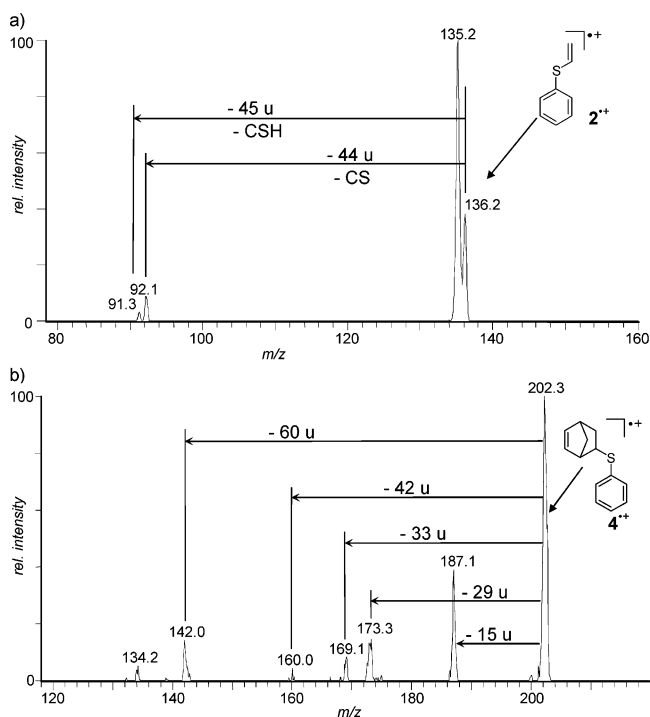
Figure 5. Positive ESI mass spectrum of the reacting solution of phenylvinylsulfide (**2**), cyclopentadiene (**3**), and tris(*p*-bromophenyl)-aminium hexachloroantimonate (**1**$^{•+}$SbCl$_6^-$) in dichloromethane after a reaction time of approximately 14 s.

ESI-MS Investigation of the Diels−Alder Reaction of Phenylvinylsulfide (2) and Cyclopentadiene (3). The reacting solution of the **1**$^{•+}$SbCl$_6^-$-initiated Diels−Alder reaction of **2** and **3** was examined by ESI-MS. The mass spectrum, after a reaction time of 14 s, is depicted in Figure 5, showing the intensive signal of radical cation **1**$^{•+}$ at *m/z* 479−485, with the characteristic isotopic cluster of three bromine atoms. Substrate **2** and product **4** are not ionized in the ESI process. The transient radical cations **2**$^{•+}$ (*m/z* 136) and **4**$^{•+}$ (*m/z* 202) cannot be unambiguously detected in the spectrum directly. Zooming into the chemical underground, we observe recognizable very weak signals at the expected values of the radical cations *m/z* 136 and 202, respectively. Remarkably, signals of similar intensity were observed at *m/z* 135 and 137, as well as at *m/z* 201 and 203.

Using the MS−MS technique,[3] which allows the separation of the ions of interest from all other ions and, by CID, their mass spectrometric characterization, we could detect and identify both radical cations **2**$^{•+}$ (Figure 6a) and **4**$^{•+}$ (Figure 6b) unambiguously in the reacting solution, using the ion trap as well as the Q-Tof instrument. This is confirmed by comparison with the APCI-MS−MS spectra of the authentic ions of **2**$^{•+}$ (Figure 3a) and **4**$^{•+}$ (Figure 3b). The obtained spectra are nearly identical. A cyclopentadiene radical cation could not be observed. The ions at *m/z* 135, 137, 201, and 203 were investigated by ESI-MS−MS and identified by comparison of the those of the spectra obtained by APCI-MS−MS as [**2** − H]$^+$, [**2** + H]$^+$, [**4** − H]$^+$, and [**4** + H]$^+$, respectively.

To rule out that **2**$^{•+}$ and **4**$^{•+}$ are generated in small amounts by the ESI process itself, control experiments in the absence of **1**$^{•+}$SbCl$_6^-$ were performed. Solutions of **2**, **3**, and **4** in dichloromethane were examined by ESI-MS−MS. In the appropriate MS−MS experiments, **2**$^{•+}$ and **4**$^{•+}$ could not be observed, giving clear evidence that the ESI process neither oxidizes substrate **2** to **2**$^{•+}$ nor product **4** to **4**$^{•+}$. Thus, radical cations **2**$^{•+}$ and **4**$^{•+}$ are not formed during the mass spectrometric ionization process in the ESI source, pointing out that transient radical cations **2**$^{•+}$ and **4**$^{•+}$ (Figure 6b,c) were detected directly in the reacting solution. Finally, to rule out that **4**$^{•+}$ is formed by oxidation of product **4** under reaction conditions, or in the ion source, solutions of product **4** and **1**$^{•+}$SbCl$_6^-$ were mixed in the microreactor and investigated as described above for the reacting solution. Cation **4**$^{•+}$ could not be detected.

The postulated distonic radical cation of the two-stage polar mechanism of electron transfer (Scheme 2) is to be expected at

Figure 6. (a) ESI-MS−MS spectrum of ion *m/z* 136 of the reacting solution of phenylvinylsulfide (**2**), cyclopentadiene (**3**), and tris(*p*-bromophenyl)-aminium hexachloroantimonate (**1**$^{•+}$SbCl$_6^-$) in dichloromethane, showing identical fragmentations compared to those in the APCI-MS−MS spectrum of the authentic radical cation **2**$^{•+}$ (Figure 3a). (b) ESI-MS−MS spectrum of ion *m/z* 202 of the same reacting solution, showing identical fragmentations compared to those in the APCI-MS−MS spectrum of the authentic radical cation **4**$^{•+}$ (Figure 3b).
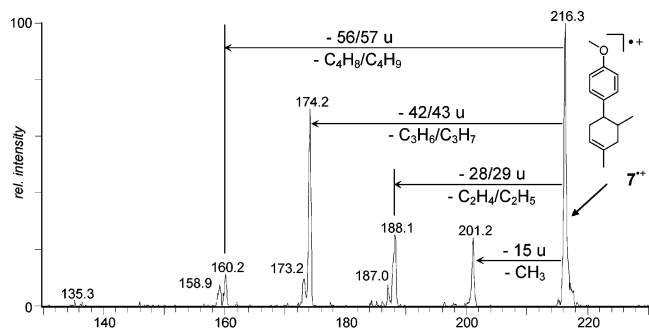
Scheme 3. Tris(*p*-bromophenyl)aminium Hexachloroantimonate (**1**$^{•+}$SbCl$_6^-$)-Initiated Diels−Alder Reaction of *trans*-Anethole (**5**) and Isoprene (**6**) To Give *trans*-1,5-Dimethyl-4-(4′-methoxyphenyl)cyclohexene (**7**) via the Reactive Intermediates, **5**$^{•+}$ and **7**$^{•+}$ (ref 30)
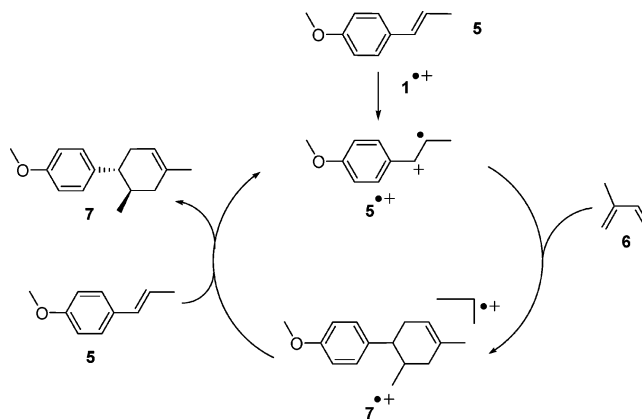
m/z 615−624. Experiments to detect this intermediate directly by MS−MS, as described for radical cations **2**$^{•+}$ and **4**$^{•+}$, were not successful using the ion trap as well as the Q-ToF instruments.

2. Reaction of *trans*-Anethole (5) and Isoprene (6). The Diels−Alder reaction of *trans*-anethole (**5**) and isoprene (**6**) to give *trans*-1,5-dimethyl-4-(4′-methoxyphenyl)cyclohexene (**7**) initiated by aminium salt **1**$^{•+}$SbCl$_6^-$ (Scheme 3) was investigated analogously.[30]

Substrate **5**, product **7**, and the respective reacting solution of the Diels−Alder reaction were studied by APCI-MS. The protonated molecule and the radical cation of substrate **5**[23] and

Figure 7. ESI-MS−MS spectrum of ion *m/z* 216: radical cation **7**•+ of the reacting solution of *trans*-anethole (**5**), isoprene (**6**), and tris(*p*-bromophenyl)aminium hexachloroantimonate (**1**•+SbCl6−) in dichloromethane.

Scheme 4. Tris(*p*-bromophenyl)aminium Hexachloroantimonate (**1**•+SbCl6−)-Initiated Dimerization of Cyclohexadiene (**8**) via Radical Cations **8**•+ and **9**•+ (ref 31)
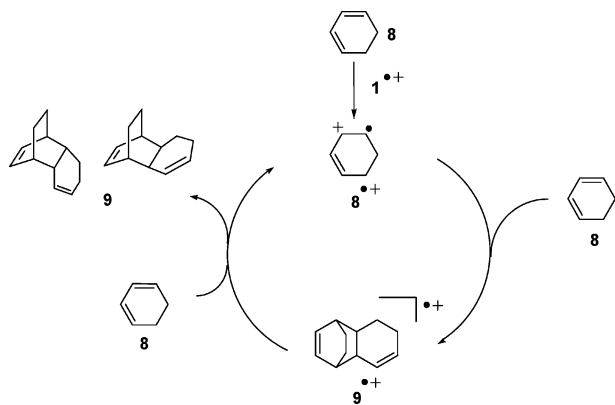
1,5-dimethyl-4-(4′-methoxyphenyl)cyclohexene (**7**), respectively, could be observed in the APCI mass spectra, allowing the characterization of authentic radical cation **7**•+ by APCI-MS−MS. Isoprene (**6**) was not ionized and thus not observed in the mass spectrum of the reacting solution. Remarkably, the minor formation of 1,2-bis(4-methoxyphenyl)-3,4-dimethylcyclobutane, the product of the [2 + 2] cycloaddition of anethole (**5**), was observed in the reacting solution as a protonated molecule at *m/z* 297 and a radical cation at *m/z* 296.[23] The high-energy CID mass spectrum of the molecular ion of Diels−Alder product **7** shows the RDA fragmentation (*m/z* 148) in addition to the fragmentations observed in the APCI-MS−MS spectrum.

The ESI mass spectrum of the reacting solution shows the intensive ion of **1**•+ and the very low intensity signals near the chemical noise at *m/z* 148 and 216 analogously to those shown in Figure 5. Transient radical cation **5**•+ (*m/z* 148) could be detected by MS−MS in the reacting solution. The MS−MS spectrum is in perfect agreement with that of ref 23. The second reactive intermediate, **7**•+, of the radical cation chain reaction could also be detected by MS−MS (Figure 7). Both transient radical cations were detected using the ion trap as well as the Q-Tof instrument. The obtained ESI-MS−MS spectrum of **7**•+ is nearly identical to the APCI-MS−MS spectrum of the authentic radical cation **7**•+. A radical cation of isoprene (**6**•+) could not be detected by MS−MS in the reacting solution.

3. Dimerization of 1,3-Cyclohexadiene (8). The **1**•+SbCl6−-initiated dimerization of cyclohexadiene (**8**) via radical cations **8**•+ and **9**•+ to give the Diels−Alder dimerization product **9** (*endo/exo*, 5:1)[31] was studied analogously (Scheme 4). First, a
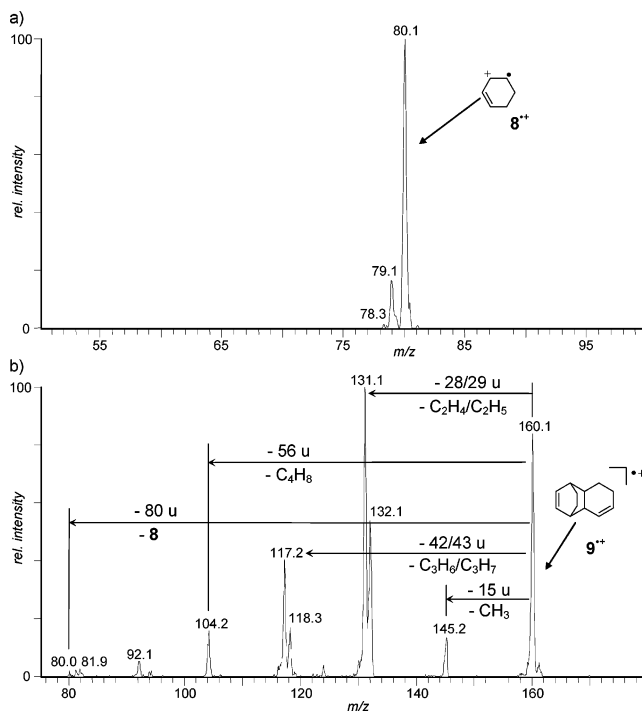
Figure 8. (a) ESI-MS−MS spectrum of ion *m/z* 80: radical cation **8**•+ of the reacting solution of cyclohexadiene (**8**) and **1**•+SbCl6− in dichloromethane. (b) ESI-MS−MS spectrum of ion *m/z* 160: radical cation **9**•+ in the same reacting solution.

solution of **8** in dichloromethane was examined by APCI-MS. Remarkably, **8** could be ionized; however, it did show a relatively low signal-to-noise ratio, giving evidence that the ionization is not very efficient. The APCI mass spectrum shows the protonated molecule [**8** + H]+ at *m/z* 81, the radical cation **8**•+ at *m/z* 80, the protonated molecule [**9** + H]+ at *m/z* 161, and the **9**•+ at *m/z* 160. The APCI investigation of the chemical reaction by mixing the substrate solution with a solution of aminium salt **1**•+SbCl6− shows the protonated product [**9** + H]+ with a higher intensity and substrate [**8** + H]+ with a lower intensity compared to the measurement of the solution of **8**. Authentic radical cations **8**•+ and **9**•+ could be characterized in the reacting solution as well as in the solution of **8** by APCI-MS−MS.

The ESI mass spectrum of the same reacting solution showed the intensive ion of radical cation **1**•+ at *m/z* 479−485. Zooming into the chemical underground, we observed and investigated ions of *m/z* 80 and 160 by MS−MS. The obtained ESI-MS−MS spectra of *m/z* 80 and 160 (Figure 8) are nearly identical to those in the APCI-MS−MS of the authentic radical cations of **8**•+ and **9**•+, respectively, giving unambiguous evidence that transients **8**•+ and **9**•+ are present in the reacting solution.

Discussion

Steady-state conditions are necessary for the detection of the transient radical cations in the radical cation chain reactions (Schemes 1, 3, and 4) by ESI-MS. Therefore, when the solution containing the substrates and the solution with the initiator **1**•+SbCl6− are mixed in the efficient micromixer, the chain reaction is started and steady-state conditions are established. Thus, pumping the reacting solution continuously in the ESI source, a quasi-stationary concentration of the radical cations, the reactive intermediates of the chain reactions, will be

transferred in the mass spectrometer. Because the ESI method normally releases ions preformed in solution, it can be expected that these radical cations should be detectable by ESI-MS−MS in the reacting solution, despite the presence of other species. The quasi-stationary concentration is estimated to be approximately 1×10^{-7} mol L^{-1}, assuming a diffusion-controlled termination reaction. This concentration is 3 orders of magnitude lower than the concentration of radical cation $\mathbf{1}^{\bullet+}$. Thus, the ions of the transient radical cations are expected to disappear in the chemical noise and will not be unambiguously detected in the normal ESI mass spectrum. However, their concentration is high enough to allow the detection and characterization by ESI-MS−MS, considering the fact that the reacting solution is continuously fed in the mass spectrometer and many spectra may be accumulated. Therefore, it is of essential importance that the reaction is not completed at the moment of the electrospray ionization to enable the detection of the intermediates. To verify that a solution with an ongoing chain reaction is being studied, it is also important to be able to follow the reaction by measuring the decrease of the substrate and the corresponding increase of the product. Unfortunately, the neutral substrates are normally not present as preformed ions and will not be ionized by the ESI process. However, this was shown to be possible by using APCI-MS. In the APCI mode, neutral molecules are transferred from the liquid phase into the gas phase and are ionized at atmospheric pressure via either protonation, deprotonation, or charge exchange.[1,2] Thus, the APCI spectrum of the reacting solution (Figure 2) showed signals of substrate **2** and product **4**, and the ESI spectrum showed the intensive signal of the initiator $\mathbf{1}^{\bullet+}$, giving clear evidence that the radical cation chain reaction was not yet finished at the moment of ionization. At the moment of ionization by ESI, as well as by APCI, the reaction in solution is being stopped and the mass spectrum will give a picture of the state of the reaction in solution because, in the gas phase, bimolecular reactions can be excluded. However, low-energy monomolecular reactions of the formed ions, such as rearrangements, are possible and can be expected. Thus, we will observe the thermodynamically most-stable isomer.

Our experimental results give clear evidence that aminium salt-initiated Diels−Alder reactions can be studied successfully by microreactor-coupled API-MS. It may be mentioned that up to now we did not observe any special effects in the microreactor. We used it as efficient micromixing system of two solutions having a very low flow. This system allowed us to detect and to characterize the transient radical cations of dienophiles **3**, **5**, and **8** and adduct radical cations **4**, **5**, and **9** of the radical cation chain reactions investigated (Schemes 1, 3, and 4) directly and unambiguously by ESI-MS−MS. On the other side, it could be demonstrated that radical cations of dienes **3** and **5** are not formed. This was to be expected because the oxidation potential of cyclopentadiene (**3**) is approximately 0.4 V higher than the respective oxidation potential of phenylvinylsulfide (**2**), which is oxidized by radical cation $\mathbf{1}^{\bullet+}$.[27,32] In the case of the Diels−Alder reaction of *trans*-anethole (**5**) and isoprene (**6**), **5** has an oxidation potential ∼0.55 V lower than that of **6**, and therefore **5** was oxidized by radical cation $\mathbf{1}^{\bullet+}$.[33]

Radical cations $\mathbf{2}^{\bullet+}$, $\mathbf{4}^{\bullet+}$, $\mathbf{5}^{\bullet+}$, $\mathbf{7}^{\bullet+}$, $\mathbf{8}^{\bullet+}$, and $\mathbf{9}^{\bullet+}$ could not be observed in the performed control experiments in the absence of $\mathbf{1}^{\bullet+}\mathrm{SbCl_6^-}$. These findings led to the conclusion that the ESI process oxidizes neither substrates nor products to the respective radical cations and pointed out that the transient radical cations were detected directly in the reacting solution. Furthermore, oxidation experiments by mixing products **4**, **7**, and **9** with $\mathbf{1}^{\bullet+}\mathrm{SbCl_6^-}$ showed no respective radical cations, thus excluding the possibility of their formation in the in the gas phase during ESI by the in-source reaction of products with $\mathbf{1}^{\bullet+}$. Additionally, when substrate **2** and product **4** were mixed with a solution of $\mathbf{1}^{\bullet+}\mathrm{SbCl_6^-}$, we detected radical cation $\mathbf{2}^{\bullet+}$ but not $\mathbf{4}^{\bullet+}$, giving clear evidence that radical cation $\mathbf{4}^{\bullet+}$ was not formed by the in-source reaction of $\mathbf{2}^{\bullet+}$ and product **4**.

It may be mentioned that we observed the formation of the [2 + 2] cycloaddition product of **5**, in the reacting solution by APCI, as a minor byproduct. This was also reported to be formed in preparative reactions using a 5-fold excess of diene.[30] Thus, the [2 + 2] cycloaddition of **5** seems to be faster than the Diels−Alder addition to isoprene.

Bauld[27,29] presented convincing evidence of a two-stage polar mechanism of the oxidation of sulfide **2** by the aminium radical cation $\mathbf{1}^{\bullet+}$, giving a distonic radical cation (Scheme 2). We could not detect this ion directly in the reacting solution. This may have different reasons. An explanation could be that the dissociation step is very fast, and thus the lifetime will be too short for the detection by the long collecting ion trap. However, investigations using a Q-ToF−MS with a much shorter collection time failed, as well, to detect this intermediate. Thus, this distonic radical cation may have a very short lifetime, possibly being, more likely, a transition state.

The termination reaction is an important part of a chain reaction. Bauld found a bimolecular chain-termination step by kinetic investigations for the Diels−Alder dimerization of cyclohexadiene (Scheme 4) and assumed a bimolecular coupling of radical cation $\mathbf{8}^{\bullet+}$ to produce a dication.[26b] An alternative bimolecular termination reaction could be a disproportion of two radical cations to give two alkyl cations. The respective ions were observed in the ESI mass spectrum and characterized by MS−MS, which may possibly be an indication for such a termination step (eq 1).

$$\mathbf{8}^{\bullet+} + \mathbf{8}^{\bullet+} \rightarrow [\mathbf{8} \text{ - } \mathrm{H}]^+ + [\mathbf{8} + \mathrm{H}]^+ \qquad (1)$$
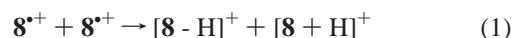
On the basis of ab initio calculations, the Diels−Alder reaction of the 1,3-butadiene radical cation with ethene to give the cyclohexene radical cation $\mathrm{C_6H_{10}}^{\bullet+}$ was described as a concerted, nonsynchronous, activationless cycloaddition.[34] Recent DFT and high-correlated MO calculations of the Diels−Alder reaction of the 1,3-butadiene radical cation with ethene found a stepwise addition involving open-chain intermediates and leading to the cyclohexene radical cation.[35] Similar intermediates were found in comparable quantum-mechanical calculations of the radical cation Diels−Alder reactions of 1,3-cyclohexadiene (**8**) and indole.[36]

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Thus, in the radical cation chain reactions studied, radical cations $4^{\bullet+}$, $7^{\bullet+}$, and $9^{\bullet+}$ could be formed by a stepwise mechanism, which proceeds via a distonic open-chain radical cation followed by ring closure to give the Diels−Alder radical cation. The MS−MS spectra of $4^{\bullet+}$ (Figures 3b and 6b), $7^{\bullet+}$ (Figure 7), and $9^{\bullet+}$ (Figure 8b) give clear evidence that the closed Diels−Alder radical cations were observed exclusively under our experimental conditions. The distonic open-chain radical cations can be excluded due to the missing strong fragmentation of $4^{\bullet+}$, $7^{\bullet+}$, and $9^{\bullet+}$ to m/z 136 ($2^{\bullet+}$), 148 ($5^{\bullet+}$), and 80 ($8^{\bullet+}$), respectively. Obviously, the ring closure of the possible initially formed distonic ion to give the cyclohexene radical cations has to be much faster than our long collecting ion trap as well as the Q-ToF.

Conclusion

In conclusion, three electron transfer-initiated Diels−Alder reactions were studied by APCI and ESI-MS, coupled with a microreactor under conditions very similar to the preparative reaction. The reaction process could be followed easily by APCI. For the first time, the transients of these radical cation chain reactions were detected and characterized unambiguously under steady-state conditions in the reacting solution by ESI-MS−MS. The detection was confirmed by comparison with APCI-MS−MS and EI−CID MS spectra of the respective authentic radical cations. The microreactor-coupled API mass spectrometry is of importance since it can be generally applied to all chemical reactions in solution. Transient intermediates can be detected, presuming that the species of interest are ionic or can be ionized.

Supporting Information Available: Additional MS and MS−MS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JA046157Z

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