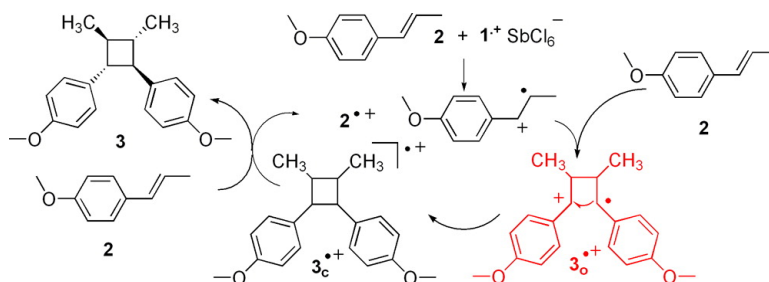


Electron-Transfer-Catalyzed Dimerization of *trans*-Anethole: Detection of the Distonic Tetramethylene Radical Cation Intermediate by Extractive Electrospray Ionization Mass Spectrometry

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Electron-Transfer-Catalyzed Dimerization of *trans*-Anethole: Detection of the Distonic Tetramethylene Radical Cation Intermediate by Extractive Electro spray Ionization Mass Spectrometry

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Electrospray ionization mass spectrometry (ESI-MS) has been introduced as a tool for the detection and characterization of reactive intermediates of reactions in solution.¹ Transients in radical cation chain reactions were detected and characterized unambiguously.^{2–4} The use of a continuous-flow microreactor directly coupled to the ion source of the mass spectrometer allowing reaction times of > 1 s proved convenient to study the transient radical cations because of their steady-state concentration of about 10⁻⁶ M.^{2,3}

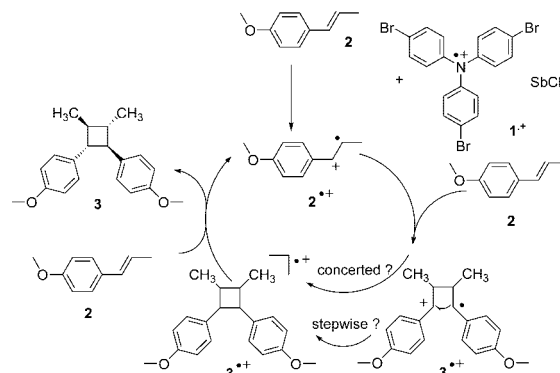
The electron-transfer-catalyzed (ETC) dimerization of electron-rich styrenes, **2**, has been the most thoroughly investigated ETC [2+2]-cycloaddition⁵ as recently discussed in detail.⁶ It could proceed stepwise via the formation of a distonic tetramethylene radical cation **3_o^{•+}** followed by cyclization to give a cyclobutane radical cation **3_c^{•+}** or via a concerted cycloaddition to give in one single reaction step **3_c^{•+}** (Scheme 1).^{5,6} In our recent study of the dimerization of *trans*-anethole **2** initiated by tris(4-bromophenyl)-aminium radical cation **1^{•+}** using continuous flow and a reaction time of 7 s we could detect only radical cation **3_c^{•+}**.² On the basis of ab initio calculations of the dimerization of 4-methoxystyrene, the two-step mechanism was suggested.⁶ However, an unambiguous prediction is not possible on the basis of these results.

EESI-MS is a two-spray setup of an electrospray of a polar solvent and a neutral spray of the analyte, which depends on liquid–liquid extraction between the colliding microdroplets and has been successfully applied for continuous analysis of trace amounts of compounds directly in complex matrices⁷ and in neutral desorption sampling of living objects.⁸ Reaction of methoxide anion with 2,4,6-trinitrotoluene giving the Meisenheimer complex demonstrated the possibility of studying reactions in solution.⁷ Interestingly, proton-catalyzed reactions have been studied recently by ESSI (electrospray ionization).⁹ However, the suitability of using the desolvating droplets of ESI as microreactor for the study of short-lived transients of reactions in condensed phase remained unexplored.

We restudied the ETC dimerization of anethole **2** using EESI-MS and thought that **2** in the neutral spray would be extracted into the charged electrospray droplets containing **1^{•+}**SbCl₆⁻, thus allowing the reaction to take place within the droplets in condensed phase solution. Most importantly, the reaction time is limited by the time of the ions desolvation process, being estimated,¹⁰ and experimentally determined to be in the order of milliseconds.¹¹ Interestingly, no influence of the shrink droplets on the studied equilibrium was found within the spray.¹¹ Using this short time window, we thought to be able to isolate and to characterize by MS–MS transients not observable with currently used techniques. First, some simple reactions have helped us to demonstrate that it works.

For instance, when a solution of diethyl glutarate (DEG) in ethanol was sprayed as neutral and a solution of LiClO₄ in ethanol

Scheme 1. ETC Dimerization of *trans*-Anethol **2** To Give **3**^a



^a Dimerization is promoted by **1^{•+}**SbCl₆⁻ via formation of radical cation **2^{•+}** followed by addition to **2** to give either concerted or, alternatively, stepwise via distonic radical cation **3_o^{•+}**, cyclobutane radical cation **3_c^{•+}** and finally product **3**.^{5,6}

was electrosprayed simultaneously, the EESI mass spectrum showed various chelate complexes of DEG and LiClO₄ such as (DEG)Li⁺ at *m/z* 195, (DEG)₂Li⁺ at *m/z* 383, (DEG)₂(LiClO₄)Li⁺ at *m/z* 489, and (DEG)₂(LiClO₄)₂Li⁺ at *m/z* 595 as was observed in the ESI mass spectrum of an equilibrated 1:1 mixture of both compounds in ethanol.¹² This gives evidence that both substrates have been mixed, and the same species have been formed as were detected from an equilibrated solution. We adapted the liquid–liquid⁷ as well as the gas–liquid EESI setup⁸ for our investigations and obtained for all reactions studied the same results with both setups.¹²

EESI experiments carried out for the reaction of 9,10-dimethylanthracene with **1^{•+}**SbCl₆⁻ and comparison with the respective reaction using a microreactor^{2b} clearly showed the formation of 9,10-dimethylanthracene radical cation at *m/z* 206, characterized by tandem mass spectrometry (MS–MS).¹² The relative signal intensity of this ion compared to the signal belonging to radical cation **1^{•+}** at *m/z* 483 was used to estimate the reaction time in the EESI experiment to be < 4 ms,¹² in good agreement with the desolvation time of the droplets.^{10,11}

Having demonstrated that bimolecular reactions can be studied by EESI-MS, we turned our attention to the open question of the ETC dimerization of **2** (Scheme 1). Substrate **2** was sprayed as a neutral, while **1^{•+}** SbCl₆⁻ was electrosprayed, both dissolved in CH₂Cl₂. The EESI mass spectrum allowed easily detecting anethol radical cation **2^{•+}** at *m/z* 148 which was characterized by MS–MS¹² being fully comparable to the ESI-MS–MS of *m/z* 148 using continuous flow¹² and to the published spectrum.²

Most interestingly, a dimer radical cation at *m/z* 296 could be detected as well. Comparing the EESI-MS–MS (Figure 1a) with the ESI-MS–MS (Figure 1b) of the ion at *m/z* 296 the base peak at *m/z* 148 in the former is most remarkable. This ion is expected

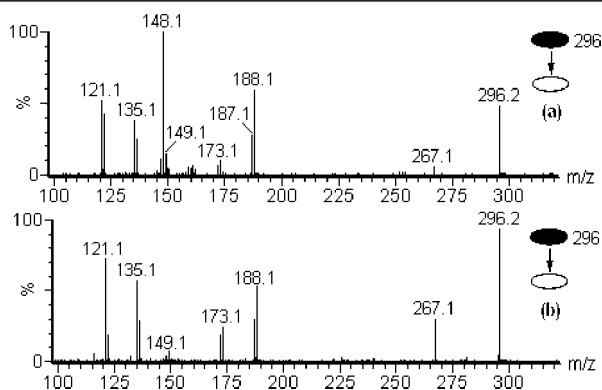


Figure 1. ETC dimerization of *trans*-anethole **2** in CH_2Cl_2 initiated by $\text{I}^{+\bullet}\text{SbCl}_6^-$ (a) EESI-MS-MS of the ion at m/z 296. (b) ESI-MS-MS of the ion at m/z 296 using a continuous-flow microreactor directly attached to the ion source (reaction time 16 s) showing almost exclusively cyclobutane radical cation $\mathbf{3}_c^{+\bullet}$.²

to be the main fragment ion of the distonic radical cation $\mathbf{3}_o^{+\bullet}$ formed by a typical radical-initiated fragmentation.^{12–14} In contrast, with longer reaction times of, for instance, 16 s the intensity of this fragment ion was reduced to <5%. The spectrum (Figure 1b) shows almost exclusively ion $\mathbf{3}_c^{+\bullet}$ which could be unambiguously identified by comparison with the published MS-MS of authentic $\mathbf{3}_c^{+\bullet}$ showing some characteristic fragment ions at m/z 267, 188, 187, 173, 135, 121, but not at m/z 148.² All the fragment ions of $\mathbf{3}_c^{+\bullet}$ can also be found in Figure 1a. Thus, it can be concluded that this EESI-MS-MS shows a superposition of the MS-MS spectra of the distonic radical cation $\mathbf{3}_o^{+\bullet}$ giving preferentially the fragment at m/z 148, and of the cyclobutane radical cation $\mathbf{3}_c^{+\bullet}$ giving the other fragment ions. Interestingly, the low intensity fragment peak at m/z 148 observed in Figure 1b may give evidence of very low amounts of $\mathbf{3}_o^{+\bullet}$ being present in the reaction solution using continuous flow. $\mathbf{3}_c^{+\bullet}$ is by 12 kcal·M⁻¹ more stable than $\mathbf{3}_o^{+\bullet}$,^{2a} in contrast to the respective styrene¹³ and 4-methoxystyrene⁶ intermediates. Thus, a fast ring closing reaction of $\mathbf{3}_o^{+\bullet}$ will be expected and has been observed. Direct useful information about the lifetime of this species may be possible to obtain using an ion trap mass analyzer.

There may be the question on whether the multistep [2+2]-cycloaddition of anethol occurs in solution or whether it can just occur between colliding free (or partly solvated) gas phase reagents. We have recently shown by ESI-MS using a continuous-flow microreactor that the complete ET catalytic cycle (Scheme 1) occurs unambiguously in liquid phase.² We observed the same reaction outcome in EESI-MS (Figure 1), and since two consecutive bimolecular reactions in the gas phase are unlikely, it provides clear evidence of a liquid phase reaction.

Thus, we have been able for the first time to observe and characterize by MS-MS the acyclic distonic tetramethylene radical cation $\mathbf{3}_o^{+\bullet}$ being ring closing to give the cyclobutane radical cation $\mathbf{3}_c^{+\bullet}$ and being detected directly from the ongoing reaction in solution. This result gives strong experimental evidence that the ETC dimerization of anethole **2** takes place stepwise and challenges us to study similar reactions such as ETC catalyzed Diels-Alder reactions.^{3,5}

The initial examples presented in this work demonstrate the great capacity EESI-MS possesses to use ESI droplets as a microvessel for the study of fast reactions in solution in a time window of milliseconds, which may be suited particularly for the observation and identification of reactive intermediates directly in solution¹⁵ undergoing fast intramolecular reactions.¹⁶ It will be important to evaluate the method as a general tool for mechanism study.

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

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