

Chelation-Controlled Radical Chain Reactions Studied by Electrospray Ionization Mass Spectrometry

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Dedicated to Professor Manfred Hesse on the occasion of his 70th birthday

Abstract: Electrospray ionization mass spectrometry (ESI-MS) is a novel tool for the investigation of chemical reactions in solution and for the direct detection and identification of reactive intermediates. The tributyltin hydride mediated addition of *tert*-butyl iodide to dimethyl 2-cyclohexyl-4-methylene-glutarate (**2**) in the presence of Lewis acids was investigated by ESI-MS using a microreactor coupled on-line to an ESI mass spectrometer. For the first time we have been able to show that transient radicals in radical chain reactions can be detected unambiguously

under steady-state conditions in the reaction solution and can be characterized by ESI-MS/MS and accurate mass determination. The detection of different heterodimer radical complexes by ESI-MS/MS has provided new insights into the mechanism of Lewis acid controlled radical chain reactions. Dimeric chelate complexes of glutarates, such

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as **2** and **3**, and Lewis acids, like Sc(OTf)₃, MgBr₂·OEt₂ and LiClO₄, were observed as well as higher aggregates with additional equivalents of Lewis acid. Evidence for a dynamic equilibrium of the complexes in solution was found by NMR spectroscopy. The ESI-MS investigation of the chelation of glutarate **2** with various Lewis acids has led to the conclusion that the tendency for Lewis acids to form dimeric chelate complexes and higher aggregates has an important effect on the stereoselective outcome of the radical reactions.

Introduction

The recent developments in mass spectrometric ionization methods at atmospheric pressure (API),^[1] for example, atmospheric pressure chemical ionization (APCI)^[2,3] and electrospray ionization mass spectrometry (ESI-MS),^[4] have enabled solutions to be investigated by mass spectrometry. ESI-MS is a powerful tool that enables ions present in solution to be transferred into the gas phase and to be analysed by mass spectrometry. High sensitivity and a large dynamic range render mass spectrometry an ideal tool for the direct investigation of chemical reactions in solution^[5] and in particular for the detection of reactive intermediates present in very low concentrations. Previously, we introduced a novel method by which transient radical cations in preparatively important electron-transfer-initiated radical-cation chain reactions in solution can be directly investigated by using a microreactor system coupled on-line to an ESI mass spectrometer. In this system a chemical reaction is initiated by mixing two liquid flows in close proximity to the ionization source. Transient radical cations were unambiguously detected and characterized by ESI-MS/MS.^[6] Furthermore, we re-

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Supporting information for this article is available on the WWW under <http://www.chemeurj.org/> or from the author. Additional MS/MS spectra of complex ions [**3**-Sc(OTf)₂]⁺ (*m/z* 654), [**3**₂-Sc(OTf)₂]⁺ (*m/z* 967), [**3**₂-Sc₂(OTf)₃]⁺ (*m/z* 1459), [**2**-**3**-Sc(OTf)₂]⁺ (*m/z* 909), and [**2**-**3**-Sc₂(OTf)₃]⁺ (*m/z* 1401). The investigations into the effect of different ESI-MS conditions on the ESI mass spectra and additional NMR experiments as well as data from high-resolution mass spectrometric measurements.

ported on the possibility of studying stable radicals in solution by ESI-MS.^[7] In this paper we present our results on the detection of transient radicals in radical chain reactions.^[8]

Many synthetically important radical chain reactions occur in solution.^[9] However, so far no method has been available that has allowed the direct detection and examination of transient radicals in these reactions. Free radicals are neutral species and therefore can normally not be detected by ESI-MS. However, Bayer,^[10] Karst^[11] as well as Porter^[12] and their co-workers have shown that nonpolar organic compounds such as alkenes can be cationized in ESI-MS by adding transition-metal salts like AgNO₃, which form π complexes.

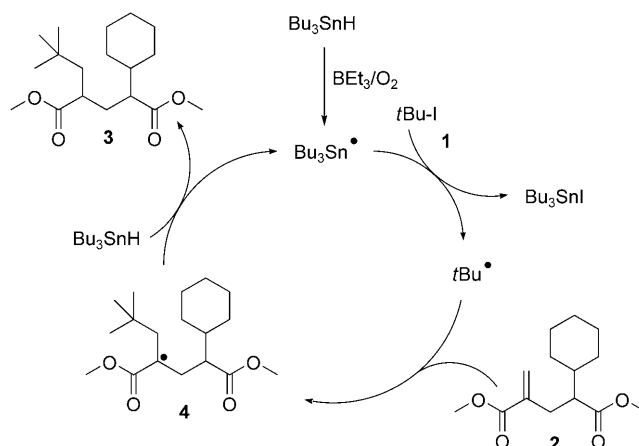
It is well known that the stereoselectivity of radical reactions can be steered by Lewis acids if the substrate acts as a Lewis base by chelating the metal atom of a Lewis acid in solution.^[13] Complexation of chiral Lewis acids allows enantioselective radical reactions to take place.^[14] Unfortunately, little is known about the structure and reactivity of these different complexes.^[13b] Recently, we reported on 1,3-stereoselection in tin hydride mediated radical additions to dialkyl 2-alkyl-4-methyleneglutarates in the presence of Lewis acids.^[15] Lewis acids such as lithium perchlorate (LiClO₄), magnesium bromide–diethyl etherate (MgBr₂·OEt₂), and scandium triflate [Sc(OTf)₃] were found to give high stereoselectivities in appropriate solvents like diethyl ether or dichloromethane, but not in tetrahydrofuran, while others such as indium trichloride (InCl₃) and zinc bromide (ZnBr₂) showed only moderate stereoselectivities. A third group consisting of cerium trichloride (CeCl₃) and magnesium ethoxide [Mg(OEt)₂] rendered the reaction completely unselective. We assumed that dialkyl glutarates are able to chelate the Lewis acids, thus controlling the stereochemical outcome of the reaction. Furthermore, we suggested that dialkyl glutarate–Lewis acid complexes, for example, of Sc(OTf)₃, might dissociate to form a chelate complex cation and a triflate anion, thus allowing the detection of the Lewis acid–ester complex by ESI-MS.

Quite recently, Schwarz et al. reported on the coordination of iron(III) cations to β -ketoesters, as studied by ESI-MS.^[16] However, the ESI mass spectral behavior of complexes of Lewis acids and diesters has not been studied up to now. Therefore, an ESI-MS investigation of the formation of complexes of diesters and Lewis acids became another important aspect of our work so that we might gain an insight into the complexes that exist in solution. Furthermore, NMR spectroscopic studies of the complexes were carried out. The intriguing results thus obtained are presented in this paper.

Results

Formation of complexes of diesters and Lewis acids: To start our investigations we took separate measurements of dimethyl 2-cyclohexyl-4-methyleneglutarate (**2**) and dimeth-

yl 2-cyclohexyl-4-neopentylglutarate (**3**), the substrate and product, respectively, of the tin hydride mediated addition of *tert*-butyl iodide (**1**) to **2** (Scheme 1) in the presence of 1.2 equiv of scandium triflate by ESI-MS using a quadrupole ion trap mass spectrometer.



Scheme 1. Tributyltin hydride mediated addition of *tert*-butyl iodide (**1**) to dimethyl 2-cyclohexyl-4-methyleneglutarate (**2**), stereoselectively giving dimethyl *syn*-2-cyclohexyl-4-neopentylglutarate (**3**) via transient adduct radical **4** in the presence of Sc(OTf)₃.^[15]

The ESI mass spectrum (Figure 1a) of the substrate solution shows the monomeric scandium triflate complex ions [2·Sc(OTf)₂]⁺ at *m/z* 597 and [2·Sc(OTf)₂·Et₂O]⁺ at *m/z* 671 as well as the dimeric complex ions [2₂·Sc(OTf)₂]⁺ at *m/z*

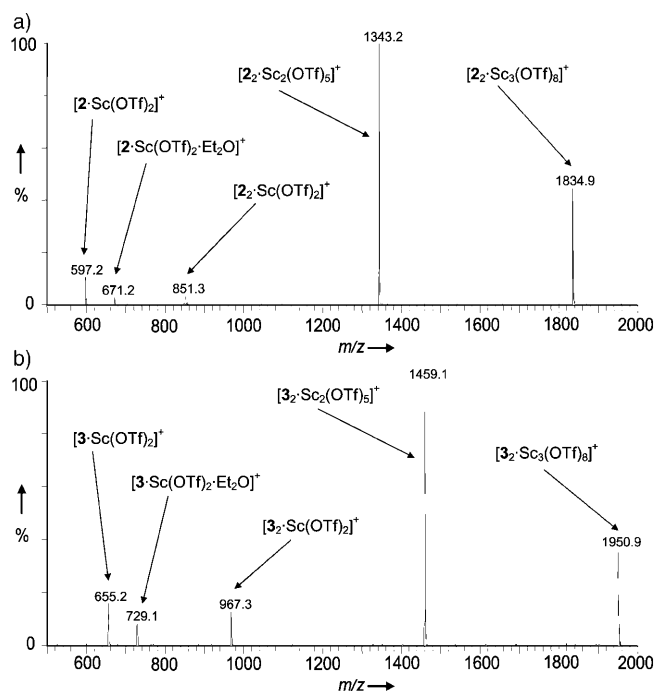


Figure 1. a) Positive ESI mass spectrum of a solution of dimethyl 2-cyclohexyl-4-methyleneglutarate (**2**) in the presence of scandium triflate (1.2 equiv) in diethyl ether. b) Positive ESI mass spectrum of a solution of dimethyl 2-cyclohexyl-4-neopentylglutarate (**3**) in the presence of scandium triflate (1.2 equiv) in diethyl ether.

851, $[2_2 \cdot \text{Sc}_2(\text{OTf})_5]^+$ at m/z 1343, and $[2_2 \cdot \text{Sc}_3(\text{OTf})_8]^+$ at m/z 1835. Also, dimeric cluster ions of the general composition $[2_2 \cdot \text{Sc}(\text{OTf})_2 \cdot \{\text{Sc}(\text{OTf})_3\}_n]^+$ ($n=3-6$) were detected in low abundances up to m/z 4000. Mixing a solution of glutarate **2** and of $\text{Sc}(\text{OTf})_3$ in a micromixer coupled on-line to an ESI mass spectrometer showed the complex formation to be a fast process. After a mixing time of about 1 s the distribution of the monomeric and the different dimeric complexes was fully established. The ESI mass spectrum of a solution of **3** in the presence of $\text{Sc}(\text{OTf})_3$ is depicted in Figure 1b. The monomeric complex ions $[3 \cdot \text{Sc}(\text{OTf})_2]^+$ (m/z 655) and $[3 \cdot \text{Sc}(\text{OTf})_2 \cdot \text{Et}_2\text{O}]^+$ (m/z 729) and the dimeric complex ions $[3_2 \cdot \text{Sc}(\text{OTf})_2]^+$ (m/z 967), $[3_2 \cdot \text{Sc}_2(\text{OTf})_5]^+$ (m/z 1459), and $[3_2 \cdot \text{Sc}_3(\text{OTf})_8]^+$ (m/z 1951) can be observed. Additional dimeric cluster ions of the general composition $[3_2 \cdot \text{Sc}(\text{OTf})_2 \cdot \{\text{Sc}(\text{OTf})_3\}_n]^+$ ($n=3-6$) were detected up to m/z 4000. Ions complexed with diethyl ether such as $[2 \cdot \text{Sc}(\text{OTf})_2 \cdot \text{Et}_2\text{O}]^+$ and $[3 \cdot \text{Sc}(\text{OTf})_2 \cdot \text{Et}_2\text{O}]^+$ were evidently formed by ion-molecule reactions in the ion trap as could be shown by isolation of, for example, $[3 \cdot \text{Sc}(\text{OTf})_2]^+$: The formation of $[3 \cdot \text{Sc}(\text{OTf})_2 \cdot \text{Et}_2\text{O}]^+$ was observed and the abundance of this ion increased with increasing trapping time.

The monomeric and dimeric complex ions were studied by tandem mass spectrometry after collision-induced dissociation (CID).^[17] The MS/MS spectrum of the monomeric substrate complex ion $[2 \cdot \text{Sc}(\text{OTf})_2]^+$ (m/z 597), depicted in Figure 2a, shows the fragmentation of CF_2SO_3 (-130 u) giving the product ion m/z 467 accompanied by adduct ions formed with water (m/z 485) and diethyl ether (m/z 541). By isolating the product complex ion $[2 \cdot \text{Sc}(\text{OTf})_2 - \text{CF}_2\text{SO}_3]^+$ (m/z 467) formed it could be demonstrated that these adduct ions were formed by ion-molecule reactions between the product complex ion and water and diethyl ether, respectively, within the collecting time in the ion trap.^[18]

Figure 2b presents the MS/MS spectrum of complex ion $[2_2 \cdot \text{Sc}(\text{OTf})_2]^+$ (m/z 851). It shows the loss of **2** (-254 u), resulting in the formation of monomeric complex ion $[2 \cdot \text{Sc}(\text{OTf})_2]^+$ (m/z 597) and addition of diethyl ether yields $[2 \cdot \text{Sc}(\text{OTf})_2 \cdot \text{Et}_2\text{O}]^+$ at m/z 670 (compare Figure 1a). The MS/MS spectrum (Figure 2c) of complex ion $[2_2 \cdot \text{Sc}_2(\text{OTf})_5]^+$ (m/z 1343) shows the loss of neutral $\text{Sc}(\text{OTf})_3$ (-492 u) to give complex ion $[2_2 \cdot \text{Sc}(\text{OTf})_2]^+$ at m/z 851 and of $2 \cdot \text{Sc}(\text{OTf})_3$ (-746 u) to give complex ion $[2 \cdot \text{Sc}(\text{OTf})_2]^+$ at m/z 597. The MS/MS spectra of the complex ions $[3 \cdot \text{Sc}(\text{OTf})_2]^+$ (m/z 655), $[3_2 \cdot \text{Sc}(\text{OTf})_2]^+$ (m/z 967), and $[3_2 \cdot \text{Sc}_2(\text{OTf})_5]^+$ (m/z 1459) exhibit characteristic fragmentations corresponding to those of the complex ions of **2**. Remarkably, in a mixture of glutarates **2** and **3** in the presence of scandium triflate heterodimeric complex ions $[2 \cdot 3 \cdot \text{Sc}(\text{OTf})_2]^+$ and $[2 \cdot 3 \cdot \text{Sc}_2(\text{OTf})_5]^+$ were detected in addition to the corresponding homodimeric complex ions.

Dialkyl malonates, succinates,^[19] as well as adipates^[8] exhibited the corresponding monomeric and dimeric complex ions in the presence of scandium triflate.

The formation of monomeric and/or dimeric diester-Lewis acid complexes can be assumed to have an important

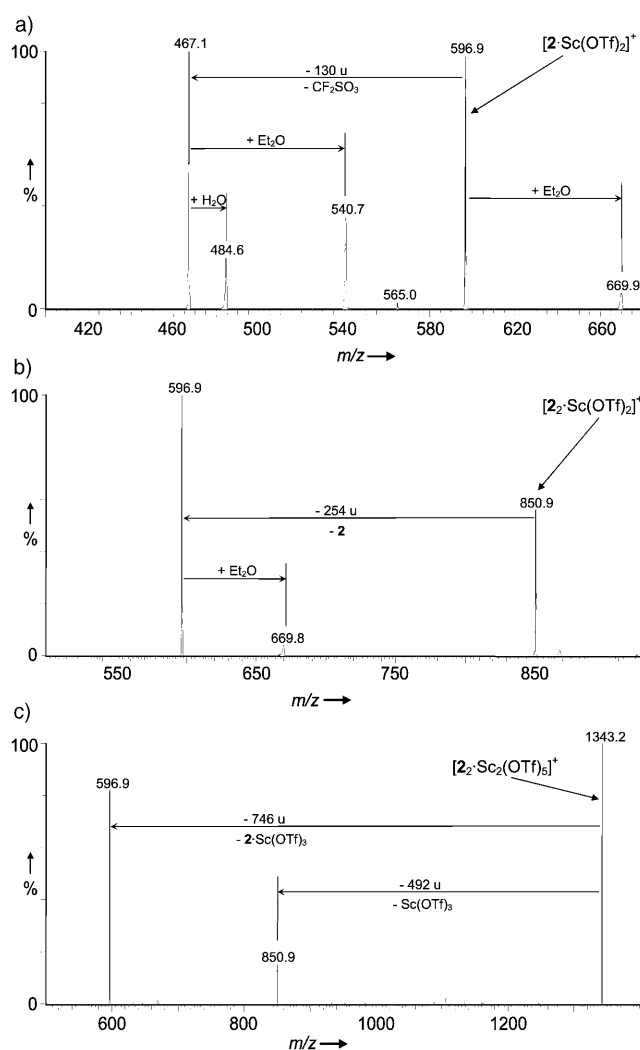


Figure 2. a) ESI-MS/MS spectrum of complex ion $[2 \cdot \text{Sc}(\text{OTf})_2]^+$ (m/z 597) from a solution of dimethyl 2-cyclohexyl-4-methylene-glutarate (**2**) in the presence of scandium triflate in diethyl ether. b) ESI-MS/MS spectrum of complex ion $[2_2 \cdot \text{Sc}(\text{OTf})_2]^+$ (m/z 851) from the same solution. c) ESI-MS/MS spectrum of complex ion $[2_2 \cdot \text{Sc}_2(\text{OTf})_5]^+$ (m/z 1343) from the same solution.

impact on the stereochemical outcome of chelation-controlled radical reactions. However, the detection of such ions in the ESI mass spectra may not be unambiguous evidence for the occurrence of all these species in solution as some of these may be formed during the ESI process. Therefore, we studied the complexes of the diester and various Lewis acids and their ESI mass spectra as well as their NMR spectra in more detail.

Variation of the Lewis acid: Dimethyl 2-cyclohexyl-4-methyleneglutarate (**2**) and the respective Lewis acid (1.2 equiv) were dissolved in diethyl ether and the ESI mass spectra were recorded. In the presence of lithium perchlorate and magnesium bromide-diethyl etherate the mass spectrum exhibited monomeric and dimeric complex ions, as in the presence of scandium triflate. The mass spectrum in the pres-

ence of lithium perchlorate is presented in Figure 3a. It shows the monomeric complex ions $[2 \cdot \text{Li}]^+$ at m/z 261 and $[2 \cdot \text{Li} \cdot \text{Et}_2\text{O}]^+$ at m/z 335, and the dimeric complex ions

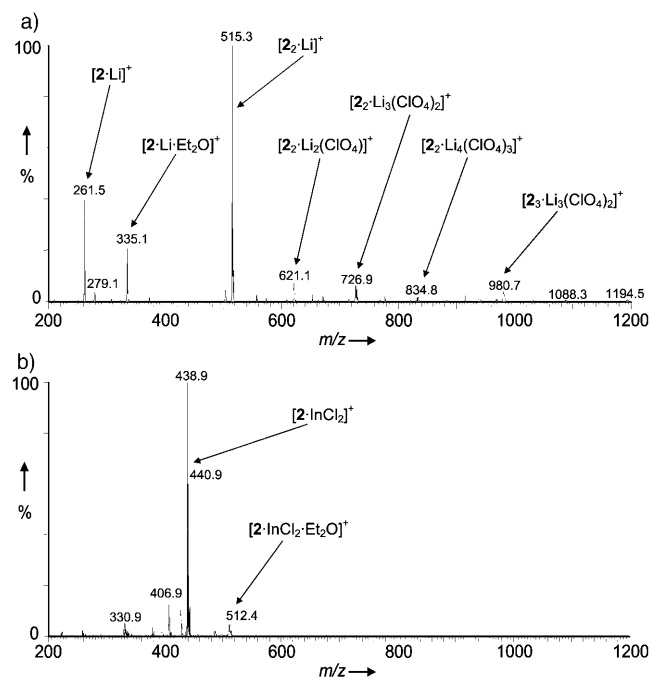


Figure 3. a) Positive ESI mass spectrum of a solution of dimethyl 2-cyclohexyl-4-methyleneglutarate (**2**) in the presence of lithium perchlorate (1.2 equiv) in diethyl ether. b) Positive ESI mass spectrum of a solution of dimethyl 2-cyclohexyl-4-methyleneglutarate (**2**) in the presence of indium trichloride (1.2 equiv) in diethyl ether.

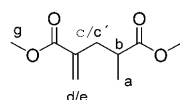
$[2_2 \cdot \text{Li}]^+$ at m/z 515 and $[2_2 \cdot \text{Li}_2 \cdot (\text{ClO}_4)_n]^+$ at m/z 621, and higher dimeric aggregates with compositions of $[2_2 \cdot \text{Li} \cdot (\text{LiClO}_4)_n]^+$ ($n=0-8$). Furthermore, an additional series of low-abundance cluster ions with compositions of $[2_3 \cdot \text{Li} \cdot (\text{LiClO}_4)_n]^+$ was identified (e.g. $[2_3 \cdot \text{Li}_3 \cdot (\text{ClO}_4)_2]^+$ at m/z 981). The ESI mass spectra of ester **2** in the presence of zinc bromide and indium trichloride (see Figure 3b) exhibit only monomeric complex ions like $[2 \cdot \text{InCl}_2]^+$ (m/z 439) and $[2 \cdot \text{InCl}_2 \cdot \text{Et}_2\text{O}]^+$ (m/z 512). Remarkably, in the presence of aluminum triisopropylate, cerium trichloride, and magnesium ethoxide no characteristic complex ions were detected with ester **2**.

Effect of the ESI-MS conditions on the ESI mass spectra: Detailed investigations of the effect of ESI conditions on the ESI mass spectra of the chelate complexes were per-

formed by using scandium triflate because, in contrast to lithium and magnesium, scandium is a monoisotopic element, thus, giving simpler mass spectra. Also, scandium triflate showed the highest stereochemical outcome of all the investigated Lewis acids. Dimethyl 2-cyclohexyl-4-methyleneglutarate (**2**) was used as the diester and the relative abundances of the ions $[2 \cdot \text{Sc}(\text{OTf})_2]^+$ and $[2_2 \cdot \text{Sc}(\text{OTf})_2 \cdot (\text{Sc}(\text{OTf})_3)_n]^+$ were determined. It turned out that the ratio of the relative abundances of these ions was neither dependent on the spray voltage (3.0–5.0 kV) nor on the concentration of **2** and of scandium triflate (10^{-4} – 10^{-3} M). Variation of the molar ratio of **2** and scandium triflate between 1:10.8 and 4.2:1 led to a variation in the ratio of the abundances of $[2 \cdot \text{Sc}(\text{OTf})_2]^+$ and $\Sigma[2_2 \cdot \text{Sc}(\text{OTf})_2 \cdot (\text{Sc}(\text{OTf})_3)_n]^+$ from 1:2 to 2.5:1. The temperature of the “heated capillary” used for the desolvation of the ions also had an important impact on the mass spectra. Remarkably, the ratio of the abundances of $[2 \cdot \text{Sc}(\text{OTf})_2]^+$ and $\Sigma[2_2 \cdot \text{Sc}(\text{OTf})_2 \cdot (\text{Sc}(\text{OTf})_3)_n]^+$ changed from 1:2 at 200 °C, the temperature normally used for the measurements, to 1:8 at 50 °C. Thus, the ion $[2 \cdot \text{Sc}(\text{OTf})_2]^+$ seems to be formed preferentially or exclusively by thermal fragmentation of the dimeric ions in the ion source.

NMR investigations of the chelate complexes: NMR spectroscopic investigations of dimethyl 2-methyl-4-methyleneglutarate (**5**) and dimethyl 2-methyl-4-neopentylglutarate (**6**) in the presence of scandium triflate, magnesium bromide–diethyl etherate, and lithium perchlorate were carried out in order to gain a deeper insight into the Lewis acid–diester complexes. Tables 1 and 2 list the ^1H and ^{13}C NMR chemical shifts, respectively, obtained for compound **5** in the

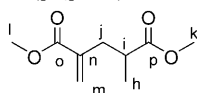
Table 1. ^1H NMR spectroscopic shifts (300 MHz) of dimethyl 2-methyl-4-methyleneglutarate (**5**) in the presence of scandium triflate in deuteriated chloroform (CDCl_3), diethyl ether ($[\text{D}_{10}]\text{Et}_2\text{O}$), and tetrahydrofuran ($[\text{D}_8]\text{THF}$).



Solvent	Ratio 5/Sc(OTf) ₃	a	c	c'/b	δ [ppm] d	e	f	g
CDCl_3	–	1.17	2.41	2.63–2.83	5.59	6.20	3.65	3.76
CDCl_3	1:1.2	1.34	2.45	2.81–3.06	6.07	6.60	4.07	4.11
$[\text{D}_{10}]\text{Et}_2\text{O}$	–	1.11	2.37	2.58–2.78	5.54	6.12	3.57	3.69
$[\text{D}_{10}]\text{Et}_2\text{O}$	1:1.2	1.28	2.43	2.89–3.05	5.96	6.43	3.85–4.15	
$[\text{D}_8]\text{THF}$	–	1.10	2.37	2.64/2.71	5.57	6.12	3.58	3.69
$[\text{D}_8]\text{THF}$	1:1.2	1.10	2.37	2.64/2.70	5.57	6.12	3.58	3.69

presence of 1.2 equiv of scandium triflate in deuteriated chloroform, tetrahydrofuran, and diethyl ether. In CDCl_3 and $[\text{D}_{10}]\text{Et}_2\text{O}$, large shifts in the ^1H and ^{13}C resonances were observed relative to the signals of uncomplexed glutarate **5**, while in $[\text{D}_8]\text{THF}$ no shifts in the characteristic signals were observed. The largest proton shifts ($\Delta\delta$), in the range of $\Delta\delta=0.35$ – 0.48 ppm, were found for the methoxy

Table 2. ^{13}C NMR spectroscopic shifts (75 MHz) of dimethyl 2-methyl-4-methyleneglutarate (**5**) in the presence of scandium triflate in deuteriated chloroform (CDCl_3), diethyl ether ($[\text{D}_{10}]\text{Et}_2\text{O}$), and tetrahydrofuran ($[\text{D}_8]\text{THF}$).



Solvent	Ratio 5/Sc(OTf) ₃	δ [ppm]									
		h	i	j	k	l	m	n	o	p	
CDCl_3	–	16.86	36.00	38.41	51.37	51.73	126.82	137.79	167.06	176.17	
CDCl_3	1:1.2	16.55	33.93	40.76	56.78	57.13	135.28	135.42	174.10	185.56	
$[\text{D}_{10}]\text{Et}_2\text{O}$	–	17.28	37.10	39.20	51.24	51.69	126.42	139.39	166.94	175.72	
$[\text{D}_{10}]\text{Et}_2\text{O}$	1:1.2	16.89	36.14	40.39	54.08	54.73	130.67	138.12	170.49	181.68	
$[\text{D}_8]\text{THF}$	–	17.21	36.91	39.23	51.44	51.87	126.67	139.38	167.23	176.03	
$[\text{D}_8]\text{THF}$	1:1.2	17.22	36.93	39.29	51.52	51.92	126.75	139.40	167.33	176.06	

groups (f/g) and the vinylic protons (d/e) in CDCl_3 , while in $[\text{D}_{10}]\text{Et}_2\text{O}$ slightly smaller shifts, $\Delta\delta = 0.17\text{--}0.26$ ppm, were observed. All other proton resonances were shifted to lower fields by $\Delta\delta = 0.04\text{--}0.23$ ppm.

The corresponding ^{13}C NMR spectra (Table 2) exhibited resonances shifted to lower fields for the methoxy (k/l) and carbonyl (o/p) carbon atoms as well as for the terminal carbon atom of the double bond (m). Upfield shifts were observed for the signals of the methyl carbon (h), the double-bond carbon (n), as well as for the α -carbon atom (i). The largest shifts were registered for the carbonyl carbon atoms (o/p) in CDCl_3 ($\Delta\delta = 7.04, 9.39$ ppm) and $[\text{D}_{10}]\text{Et}_2\text{O}$ ($\Delta\delta = 3.55, 5.96$ ppm). Another large shift to a lower field was detected for the signal of the terminal carbon atom of the double bond (m) with $\Delta\delta = 8.46$ ppm in CDCl_3 and $\Delta\delta = 4.25$ ppm in $[\text{D}_{10}]\text{Et}_2\text{O}$. When deuteriated THF was used as the solvent, no shifts in the signals of glutarate **5** were observed after the addition of the Lewis acid. However, in addition to the typical ^{13}C NMR signals of the pure solvent, further signals, shifted to lower fields, belonging to THF complexed with scandium triflate were detected.

The strongest effects on the chemical shifts were observed with scandium triflate, followed by magnesium bromide–diethyl etherate, and finally by lithium perchlorate. The *syn* and *anti* diastereomer of the saturated glutarate **6** showed similar shifts in the presence of scandium triflate as well as magnesium bromide–diethyl etherate.

The NMR investigations yielded definite line spectra, which suggested the presence of only one species. However, the ESI mass spectrometric investigation of glutarate **2** in the presence of scandium triflate (Figure 1a) showed the presence of monomeric and dimeric complexes. This contradiction led us to assume that a dynamic equilibrium of the different complexes could be present in solution. Therefore, low-temperature NMR experiments were carried out. Surprisingly, the width of the signals increased with decreasing temperature, which prompted us to perform an NMR titration. The behavior of dimethyl 2-methyl-4-methyleneglutarate (**5**) was studied by varying the molar ratios of **5** and scandium triflate (10:1, 5:1, 2:1, 1:1, 1:2, and 1:5). The resulting ^1H NMR spectra are presented in Figure 4.

At molar ratios of 10:1 and 5:1 the Lewis acid had no effect on the resonances of ester **5**, but starting from a ratio

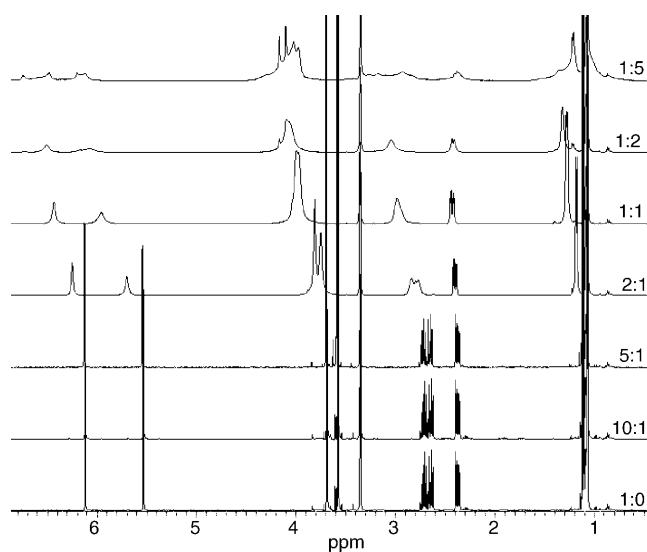


Figure 4. ^1H NMR spectra (500 MHz) of dimethyl 2-methyl-4-methyleneglutarate (**5**) in the presence of different amounts of scandium triflate (5/Sc(OTf)₃ = 1:0, 10:1, 5:1, 2:1, 1:1, 1:2, and 1:5). The signals $\delta = 1.07$ ppm and 3.35 ppm arise from the solvent diethyl ether and were not shifted.

of 2:1 the signals were shifted downfield. As the concentration of scandium triflate was increased (1:1, 1:2, and 1:5) the effect of complexation and thus the shift to lower field as well as the broadening of the signals became more significant. When the glutarate/scandium triflate ratio was 1:2 and 1:5 additional signals from glutarate **5** appeared; this characteristic was most striking at a ratio of 1:5, affecting the signals in the range of $\delta = 2.5\text{--}3.5$ ppm and $\delta = 6\text{--}7$ ppm. In the respective NMR spectra the signals arising from the d and e protons as well as the f and g methyl protons were doubled, indicating that several complexed diester species must be present in solution.

Reaction of *tert*-butyl iodide with dimethyl 2-cyclohexyl-4-methyleneglutarate (2**) mediated by tributyltin hydride—ESI-MS measurements:** We decided to use the tributyltin hydride mediated addition of *tert*-butyl iodide (**1**) to dimethyl 2-cyclohexyl-4-methyleneglutarate (**2**), initiated by triethylborane in the presence of Sc(OTf)₃, which leads stereoselectively and in good yields to the *syn*-addition product di-

methyl 2-cyclohexyl-4-neopentylglutarate (**3**), for our ESI-MS studies (Scheme 1).

The reactions were carried out by mixing a solution of glutarate **2**, **1** and $\text{Sc}(\text{OTf})_3$ in diethyl ether saturated with air and a solution of tributyltin hydride containing triethylborane under argon in a microreactor coupled on-line to the ESI ion source. Thus, the reacting solution was continuously fed into the mass spectrometer. The mass spectrum of this solution after a reaction time of approximately 30 s is depicted in Figure 5.

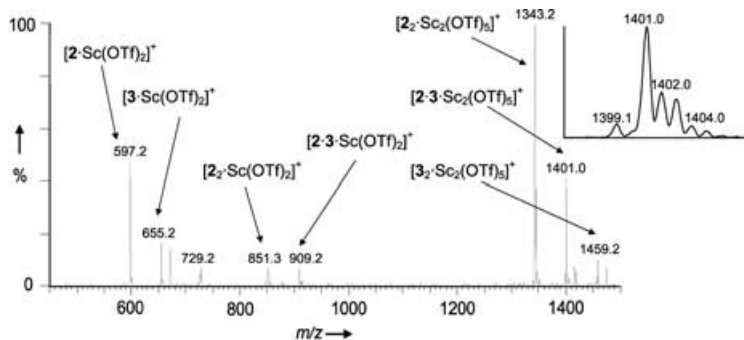


Figure 5. Positive ESI mass spectrum of the reacting solution of the tributyltin hydride-mediated addition of *tert*-butyl iodide (**1**) to dimethyl 2-cyclohexyl-4-methyleneglutarate (**2**) in the presence of scandium triflate in diethyl ether resulting in addition product **3** after a reaction time of approximately 30 s.

All the monomeric and dimeric complex ions of substrate **2** and product **3** described previously (Figure 1a, b) can be observed (m/z 597 $[\mathbf{2}\cdot\text{Sc}(\text{OTf})_2]^+$, m/z 671 $[\mathbf{2}\cdot\text{Sc}(\text{OTf})_2\cdot\text{Et}_2\text{O}]^+$, m/z 851 $[\mathbf{2}_2\cdot\text{Sc}(\text{OTf})_2]^+$, m/z 1343 $[\mathbf{2}_2\cdot\text{Sc}_2(\text{OTf})_5]^+$, m/z 655 $[\mathbf{3}\cdot\text{Sc}(\text{OTf})_2]^+$, m/z 729 $[\mathbf{3}\cdot\text{Sc}(\text{OTf})_2\cdot\text{Et}_2\text{O}]^+$, m/z 967 $[\mathbf{3}_2\cdot\text{Sc}(\text{OTf})_2]^+$, and m/z 1459 $[\mathbf{3}_2\cdot\text{Sc}_2(\text{OTf})_5]^+$). Furthermore, two new signals at m/z 909 and 1401 are present, which appear in neither the substrate nor the product mass spectra. These additional species were identified by MS/MS experiments and high-resolution ESI-MS measurements as heterodimeric complex ions of the substrate and product $[\mathbf{2}\cdot\mathbf{3}\cdot\text{Sc}(\text{OTf})_2]^+$ and $[\mathbf{2}\cdot\mathbf{3}\cdot\text{Sc}_2(\text{OTf})_5]^+$.

The relative abundances of the complex ions of the substrate $[\mathbf{2}\cdot\text{Sc}(\text{OTf})_2]^+$ (m/z 597) and product $[\mathbf{3}\cdot\text{Sc}(\text{OTf})_2]^+$ (m/z 655) were determined at different reaction times and are presented in Figure 6. Two conclusions can be drawn: It is possible to follow the reaction course by ESI-MS and, particularly important, the radical chain reaction had not finished at the moment of ionization. This is highly significant because an ongoing reaction is necessary if transient radicals are to be successfully detected under steady-state conditions by ESI-MS.

An intermediate radical complex ion $[\mathbf{4}\cdot\text{Sc}(\text{OTf})_2]^+$ with an expected mass of m/z 654 could not be observed unambiguously in the mass spectrum (Figure 5). This is due to the fact that the steady-state concentration of radical **4** in the radical chain reaction, which is estimated to be approximately 10^{-7}M , is four orders of magnitude lower than the concentration of substrate **2** and of product **3**. Thus, the signal of the radical complex ion $[\mathbf{4}\cdot\text{Sc}(\text{OTf})_2]^+$ is expected to disappear into the chemical noise. Indeed, by zooming

into the underground a very weak ion at m/z 654 is revealed with an intensity in the range of the chemical noise. By using the MS/MS technique,^[4] which allows the separation of the ions of interest from all other ions, and from their mass spectrometric characterization by CID, we were able to detect and characterize the intermediate radical **4** as a monomeric complex ion $[\mathbf{4}\cdot\text{Sc}(\text{OTf})_2]^+$ (m/z 654, Figure 7a). The MS/MS spectrum of this radical complex ion exhibits the characteristic fragmentation of CF_2SO_3 (-130u) giving the product ion m/z 524 accompanied by adduct ions with water (m/z 542) and diethyl ether (m/z 598), which are formed by ion-molecule reactions in the ion trap.^[18]

Owing to the appearance of heterodimeric complex ions of substrate **2** and product **3** we deduced that radical **4** should also be observed in the reacting solution as a heterodimeric complex ion with substrate **2** and product **3**, respectively. Such an ion, for example, $[\mathbf{2}\cdot\mathbf{4}\cdot\text{Sc}_2(\text{OTf})_5]^+$ (m/z 1400)

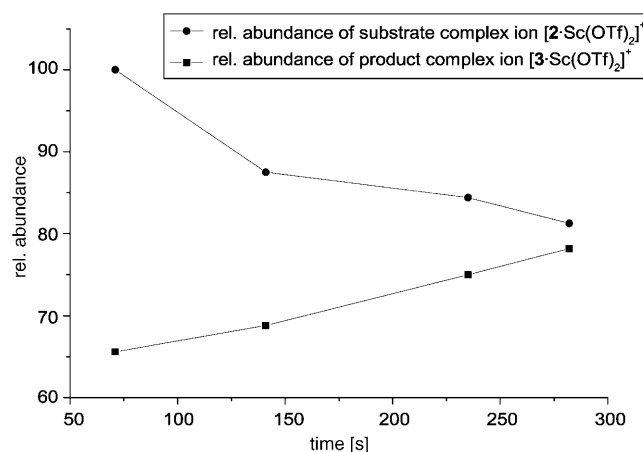


Figure 6. ESI-MS investigation of the tributyltin hydride mediated addition of *tert*-butyl iodide (**1**) to dimethyl 2-cyclohexyl-4-methyleneglutarate (**2**) in the presence of scandium triflate in diethyl ether. Relative abundances of the complex ions of substrate $[\mathbf{2}\cdot\text{Sc}(\text{OTf})_2]^+$ (m/z 597) and product $[\mathbf{3}\cdot\text{Sc}(\text{OTf})_2]^+$ (m/z 655) versus reaction time.

could not be observed unambiguously in the mass spectrum (Figure 5, insert). In contrast, the expected ions should be detectable by MS/MS, thus providing additional, independent and unambiguous evidence of the intermediate radical. The MS/MS spectrum of the heterodimeric complex ion of the substrate and radical $[\mathbf{2}\cdot\mathbf{4}\cdot\text{Sc}_2(\text{OTf})_5]^+$ (m/z 1400) is shown in Figure 7b. Two main and characteristic fragmentations of this ion are evident: dissociation by loss of the neutral radical complex $\mathbf{4}\cdot\text{Sc}(\text{OTf})_3$ (-803u) gives the substrate complex ion $[\mathbf{2}\cdot\text{Sc}(\text{OTf})_2]^+$ (m/z 597) and loss of the neutral substrate complex $\mathbf{2}\cdot\text{Sc}(\text{OTf})_3$ (-746u) results in the radical

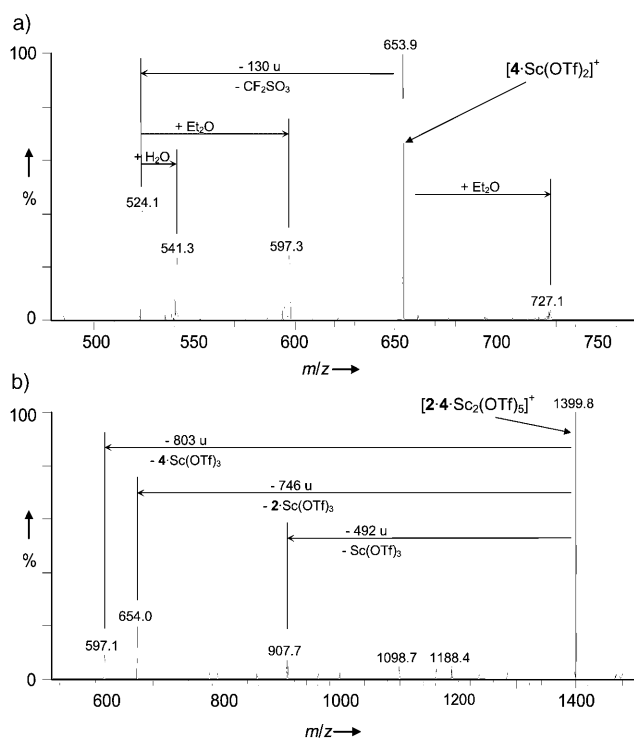


Figure 7. a) ESI-MS/MS spectrum of the radical complex ion $[4\bullet\text{Sc}(\text{OTf})_2]^+$ (m/z 654) formed by the tributyltin hydride mediated addition of *tert*-butyl iodide (**1**) to dimethyl 2-cyclohexyl-4-methyleneglutarate (**2**) in the presence of scandium triflate in diethyl ether. b) ESI-MS/MS spectrum of the substrate-radical complex ion $[2\bullet 4\bullet\text{Sc}_2(\text{OTf})_5]^+$ (m/z 1400) from the same reacting solution.

complex ion $[4\bullet\text{Sc}(\text{OTf})_2]^+$ (m/z 654). Additionally, fragmentation to complex ion $[2\bullet 4\bullet\text{Sc}(\text{OTf})_2]^+$ (m/z 908) by loss of $\text{Sc}(\text{OTf})_3$ (-492 u) was observed. Control measurements of substrate **2** and product **3** in the presence of $\text{Sc}(\text{OTf})_3$ showed no signals that could be attributed to the monomeric and heterodimeric radical complex ions. The elemental composition of the ions $[4\bullet\text{Sc}(\text{OTf})_2]^+$, $[2\bullet 4\bullet\text{Sc}_2(\text{OTf})_5]^+$, and $[3\bullet 4\bullet\text{Sc}_2(\text{OTf})_5]^+$ could be confirmed by accurate Q-ToF measurement of their mass.

Discussion

The detection and characterization of transient adduct radicals by mass spectrometric methods is certainly the most important result arising from this study of the tributyltin hydride mediated radical chain reaction in the presence of a Lewis acid. A solution of glutarate **2** and *tert*-butyl iodide (**1**) and $\text{Sc}(\text{OTf})_3$ in diethyl ether saturated with air and a solution of tributyltin hydride containing triethylborane under argon were mixed using an effective micromixer coupled on-line to an ESI mass spectrometer. The radical chain reaction started spontaneously and steady-state conditions were established by pumping the reacting solution continuously into the ESI source. The reaction course could be followed (Figure 6) indicating that a solution containing an ongoing radical chain reaction was sprayed into the ion source. The

steady-state concentration of the chain-carrying radicals was high enough (estimated to be approximately 10^{-7} M) to allow their detection and characterization by ESI-MS/MS provided that the reacting solution was continuously fed into the mass spectrometer and that many spectra could be accumulated. The transient complexed adduct radical **4** was detected directly and unambiguously and characterized by three independent ESI-MS/MS measurements as monomeric complex ion $[4\bullet\text{Sc}(\text{OTf})_2]^+$ and heterodimeric complex ions $[2\bullet 4\bullet\text{Sc}_2(\text{OTf})_5]^+$ (Figure 7), and $[3\bullet 4\bullet\text{Sc}_2(\text{OTf})_5]^+$. In addition, the accurate masses of these ions were determined.

As an alternative mediator tris(trimethylsilyl)silane was employed which gave the same results.^[8] Comparable results were also obtained for the radical allylation of 2-iodoadipate with allyltributyltin.^[8] This method can generally be applied to radicals containing functional groups that are able to chelate Lewis acids such as $\text{Sc}(\text{OTf})_3$, MgBr_2 , and LiClO_4 . *tert*-Butyl as well as tributylsilyl radicals, which lack Lewis base functionality, could not be detected. However, it may be possible to observe even these radicals by operating the ESI source as an electrolytic cell to ionize neutral species, as has been shown with, for example, the trityl radical.^[7]

It is remarkable that various Lewis acids can form chelate complexes with diesters; the ionization of the complexed species in the electrospray process has enabled their investigation by ESI-MS.^[10] It was surprising that we observed monomeric ions formed from 1:1 chelates and dimeric ions containing two diester molecules with one, two, or more Lewis acid equivalents. So far mostly monomeric 1:1 complexes have been assumed in discussions of Lewis acid controlled diastereoselective radical reactions,^[13,15] and for Lewis acid controlled enantioselective radical reactions, in addition to the bidental radical ligand, a second chiral bidental ligand has been discussed.^[14]

Our results provide unambiguous evidence for the presence of dimeric and possibly heterodimeric chelate complexes of $\text{Sc}(\text{OTf})_3$, MgBr_2 , and LiClO_4 in solution. The most convincing evidence is provided by the correlation between the existence of dimeric complex ions observed by ESI-MS and the diastereoselectivity of the radical addition reaction (Table 3). High diastereoselectivities were obtained when dimeric complex ions containing two diester molecules with one or more Lewis acid equivalents were observed in the ESI mass spectrum, which was the case with $\text{Sc}(\text{OTf})_3$, $\text{MgBr}_2\cdot\text{OEt}_2$, and LiClO_4 . Lewis acids such as InCl_3 and ZnBr_2 , which exclusively give monomeric complex ions containing one diester molecule, showed very low diastereoselectivity, and no selectivity was observed at all with Lewis acids such as $\text{Al}(\text{O}i\text{Pr})_3$, CeCl_3 , and $\text{Mg}(\text{OEt})_2$, which gave no signals from characteristic complex ions in the ESI mass spectra. These results can easily be rationalized. With $\text{Al}(\text{O}i\text{Pr})_3$, CeCl_3 , and $\text{Mg}(\text{OEt})_2$, no chelation occurred, resulting in an unselective reaction, as was observed in the absence of a Lewis acid. Lewis acids that only form monomeric complexes can only modestly modify the transition state of the hydrogen transfer and the diastereoselective outcome of the reaction. In contrast, Lewis acids that form dimeric

Table 3. Complex ions of dimethyl 2-cyclohexyl-4-methyleneglutarate (**2**) with various Lewis acids observed by ESI-MS and the diastereoselectivity of the tributyltin hydride mediated addition of *tert*-butyl iodide.^[15]

Lewis acid	Complex ions observed by ESI-MS	¹³ C Chem. shifts of CO groups [ppm]	Product ratio, <i>anti/syn</i>
–	–	167.14, 176.24	52:48
Al(<i>i</i> PrO) ₃	no characteristic complex ions	[a]	50:50
CeCl ₃	no characteristic complex ions	[a]	52:48
InCl ₃	exclusively monomeric complex ions	[a]	44:56
LiClO ₄	monomeric, dimeric complex ions and higher aggregates	168.46, 178.14	18:82
MgBr ₂ ·(Et ₂ O) ₂	monomeric, dimeric complex ions and higher aggregates	169.36, 179.27	2:98
Mg(OEt) ₂	no characteristic complex ions	[a]	52:48
Sc(OTf) ₃	monomeric, dimeric complex ions and higher aggregates	172.86, 184.30	01:99
ZnBr ₂	exclusively monomeric complex ions	[a]	45:55

[a] Not measured.

chelate complexes are expected to have a much greater effect on the diastereomeric transition states.

The shifts of NMR resonances are considered to be a good indicator of the formation of complexes formed between Lewis acids and substrates.^[20] Childs and Guindon and their co-workers showed through similar NMR studies that carbonyl resonances were shifted to lower fields by the complexing influence of Lewis acids, which was interpreted as monomeric 1:1 complexation.^[21] Our NMR experiments with glutarates **5** and **6** under the complexing influence of lithium perchlorate and magnesium bromide–diethyl etherate in chloroform and of scandium triflate in chloroform and diethyl ether showed large shifts of the resonances relative to those of the uncomplexed ester, thus strongly indicating chelate formation of the Lewis acids through the carbonyl groups. The greatest downfield shift, as well as the highest diastereoselectivity, was observed with Sc(OTf)₃ and the lowest with LiClO₄.

Further NMR experiments comprising the variation of the ratio of glutarate **5** and Sc(OTf)₃ provided evidence for a dynamic equilibrium of several complexes in solution. As the concentration of the Lewis acid increased the equilibrium shifted to higher Lewis acid aggregates, accompanied by signal broadening as well as larger shifts of the resonances to lower fields. With a sufficiently large excess of Lewis acid additional resonances of the glutarate were registered. NMR investigations in tetrahydrofuran did not show any complexing influence of Sc(OTf)₃ on the glutarate, a result that is in very good agreement with our findings in THF that the Lewis acid does not influence the stereochemical outcome^[15] and that no diester–Lewis acid complex ions could be detected by ESI-MS. THF acts as a much better donor towards the Lewis acid than the diester, which was

confirmed by NMR spectroscopy in which the resonances of THF itself were shifted.

In the ESI spectra of solutions of diesters **2** and **3**, respectively, and Sc(OTf)₃ monomeric complex ions like [2·Sc(OTf)₂]⁺ and [3·Sc(OTf)₂]⁺ (Figure 1) were observed and at first it might seem reasonable to assume that these ions are formed by dissociation of the monomeric complexes [2·Sc(OTf)₃] and [3·Sc(OTf)₃], respectively, present in solution. However, our observations that monomeric ions like [2·Sc(OTf)₂·Et₂O]⁺ and [3·Sc(OTf)₂·Et₂O]⁺ are not extracted from the original diethyl ether solution but are obviously formed in the ion trap by the gas-phase reaction of diethyl ether and [2·Sc(OTf)₂]⁺ and [3·Sc(OTf)₂]⁺, respectively, rather indicate that they might indeed not be present in the original solution or if so, then only in minor amounts in equilibrium with dimers, but rather might be formed in the spray desolvation process by fragmentation of dimeric complex ions like [2₂·Sc(OTf)₂]⁺. In agreement with this, decreasing the temperature of the heated capillary used for the desolvation process gave rise to a dramatic change in the ratio of the dimeric and monomeric ions from 2:1 at 250 °C to 8:1 at 50 °C.

Another important consequence of a dynamic, rapidly equilibrating system of different dimeric and possibly monomeric complexes is the formation of heterodimeric complexes. Such complexes, for example, [2·3·Sc(OTf)₂]⁺ and [2·3·Sc₂(OTf)₅]⁺ were observed in solution mixtures of glutarates **2** and **3** with Sc(OTf)₃ as well as in reacting solutions of the radical addition of *tert*-butyl iodide to glutarate **2** (Figure 5) and the radical allylation of dimethyl 2-iodoadipate in the presence of Sc(OTf)₃.^[8]

The unambiguous detection of heterodimeric complexes of radical and substrate or product such as [2·4·Sc₂(OTf)₅]⁺ and [3·4·Sc₂(OTf)₅]⁺ in the reacting solution of the radical chain reaction has to be considered an important finding. Evidently, the fact that radical **4** is involved in different complexes causes there to be decisive energetic differences in the hydrogen transfer to **4**, and thus in the stereoselectivity of the reaction. Moreover, because at the beginning of the reaction the formation of exclusively heterodimeric complexes with the substrate is possible, while with the progress of the reaction increasingly heterodimeric complexes with the product are formed, it can be expected that the diastereoselectivity will change during the reaction. We are not aware of this behavior having been discussed previously in the literature. However, Guindon and co-workers observed that the diastereoselectivity of MgBr₂·OEt₂-controlled allylations of α -iodo- β -alkoxy esters varied significantly depending on the stereochemistry of the substrate. The relatively *anti*-configured iodide precursor showed a higher stereoselectivity than the *syn* iodide. Normally, the configuration of a halide precursor does not have an impact on the outcome of the radical reaction. Guindon and co-workers rationalized the observed effect through different stabilities of the diastereomeric chelate complexes.^[21b] In the light of our results it could be expected that the intermediate radical in a heterodimeric complex with *syn* and *anti*

iodide, respectively, may possibly be allylated with different stereoselectivity. Additionally, Guindon and co-workers reported that a three-fold excess of $\text{MgBr}_2 \cdot \text{OEt}_2$ was needed to obtain the highest diastereoselectivities in the allylation reaction whereas an equimolar amount only produced modest stereoselectivity.^[21b] We also observed ions of higher aggregates of chelate complexes like $[\mathbf{2}_2 \cdot \{\text{Sc}(\text{OTf})_3\}_n]$ ($n=1-6$) by ESI-MS, which suggests that besides the dimer chelate with only one equivalent of $\text{Sc}(\text{OTf})_3$ these may also be present in solution, thus also affecting the stereochemical outcome of the reaction and possibly improving the stereoselectivity. Similar aggregates were observed with LiClO_4 and with $\text{MgBr}_2 \cdot \text{OEt}_2$. Clearly, the next step in the ESI-MS investigation of Lewis acid controlled radical reactions should be studies to answer the question as to whether all of the different radical species react with the same or similar reactivity with the radical trap or whether their reactivities are so different that only the most reactive radical species present in the dynamic equilibrium of the complexes that exist in solution are trapped.

Finally, it is possible that the higher aggregates of chelate complexes like $[\mathbf{2}_2 \cdot \{\text{Sc}(\text{OTf})_3\}_n]$ ($n=1-6$) are not present in solution but may be formed in the ESI spray process. In accordance with this hypothesis, the highly charged drops formed during the spray process should contain smaller amounts of scandium triflate and glutarate as the concentration of the starting solution is decreased. As a consequence, lower concentrations should induce an increase in the formation of monomeric complex ions. Such behavior was observed by Kebarle and Peschke^[22] for NaCl cluster ions, which in principle should also apply to our $\text{Sc}(\text{OTf})_3$ -containing ester solutions. However, we observed approximately constant relative abundances of the complex ions with different concentrations of starting solutions in our investigations, which indicates that the formation of dimeric complex ions like $[\mathbf{2}_2 \cdot \{\text{Sc}(\text{OTf})_3\}_n]$ ($n=2-6$) in the spray process may be excluded.

Conclusions

In conclusion, a preparatively important radical chain reaction controlled by Lewis acids was studied with an ESI mass spectrometer coupled on-line to a microreactor under conditions very similar to the preparative reaction. Dimeric chelate complexes of diesters and Lewis acids were observed and evidence was found for a dynamic equilibrium of the complexes in solution. For the first time we have shown that transient radicals in radical chain reactions can be detected unambiguously under steady-state conditions in the reacting solution and can be characterized by ESI-MS/MS and accurate mass determination. The detection of heterodimeric chelate complexes of the radical and the substrate as well as the product in Lewis acid controlled radical reactions by ESI-MS/MS provides information that cannot be obtained by other techniques. An investigation of various Lewis acids led to the conclusion that the tendency for Lewis acids to

form dimeric complexes and higher aggregates has an important effect on the stereoselective outcome of chelation-controlled radical reactions.

Our method, a microreactor-coupled API mass spectrometer, proved to be a convenient tool for the investigation of reactions and of the reactive intermediates formed in solution. The method can generally be applied to all reactions in solution, presuming that the species of interest are ionic or can be ionized.

Experimental Section

The mass spectrometric experiments were performed on a Finnigan LCO (Thermo Finnigan San José, CA, USA) quadrupole ion trap mass spectrometer equipped with a standard ESI ion source and a stainless steel metal capillary (110 μm inner diameter, 240 μm outer diameter, 120.5 mm length, Metal Needle Kit, Thermo Finnigan). The volume of this metal spray capillary (120.5 mm length, 110 μm inner diameter) is about 1.14 μL . Sample solutions were infused into the capillary using the dual syringe pump of the LCO at flow rates in the range of 2.5–100 $\mu\text{L min}^{-1}$. By connecting a microreactor (ALLTECH, PEEK MIXING TEE) to the ESI spray capillary reaction times from 0.7 to 28 s can be monitored.^[6b] Longer reaction times can easily be realized by using a fused silica transfer capillary of variable length between microreactor and spray capillary. Mass spectra of the reacting solution can be acquired by this method in a reaction time range of approximately 1 s up to several minutes. ESI operation conditions: a spray voltage of +4.5 kV and a heated capillary temperature of 200 °C (unless otherwise noted). CID (collision gas helium) was performed in the ion trap region. The effective isolation width for CID experiments was set at 1.5 u with a collection time of up to 2000 ms. Data acquisition and analysis were carried out using the Xcalibur (version 1.2, Thermoquest Finnigan) software package. Additionally, high-resolution ESI-MS experiments were carried out on the quadrupole-time of flight Micromass Ultima Q-ToF instrument.

NMR spectra were recorded with a Bruker AM 300 (^1H 300 MHz and ^{13}C 76 MHz) or a Bruker AM 500 (^1H 500 MHz and ^{13}C 126 MHz) Fourier-transform NMR spectrometer (Bruker, Fallanden, Switzerland) at 20 °C using TMS or solvent signals as the internal standard, respectively.

Cerium trichloride, indium trichloride, magnesium bromide–diethyl etherate, scandium triflate, triethylborane, and zinc bromide were obtained from Aldrich (Steinheim, Germany), whereas tributyltin hydride was purchased from Lancaster (Frankfurt, Germany). Aluminum triisopropylate, *tert*-butyl iodide (**1**), lithium perchlorate, and magnesium ethoxide were purchased from Fluka (Deisenhofen, Germany). Deuterated chloroform, tetrahydrofuran, and diethyl ether were obtained from Deutero (Kastellaun, Germany). Diethyl ether was freshly distilled after refluxing over sodium/benzophenone. All other chemicals were used without further purification.

Dimethyl 2-cyclohexyl-4-methyleneglutarate (**2**), dimethyl 2-cyclohexyl-4-neopentylglutarate (**3**) as a mixture of diastereomers, [*anti*-**3**]/[*syn*-**3**]=1:1, dimethyl 2-methyl-4-methyleneglutarate (**5**), and dimethyl *anti*-2-methyl-4-neopentyl-glutarate (*anti*-**6**) as well as *syn*-**6** were synthesized according to published procedures.^[15]

Reaction of *tert*-butyl iodide with dimethyl 2-cyclohexyl-4-methyleneglutarate in the presence of scandium triflate mediated by tributyltin hydride: Dimethyl 2-cyclohexyl-4-methyleneglutarate (**2**) (5.1 mg 20 μmol), scandium triflate (1.2 equiv, 11.8 mg, 24 μmol), and *tert*-butyl iodide (**1**) (14.8 mg, 80 μmol) were dissolved in absolute diethyl ether (20 mL) to give a solution being 1×10^{-3} M in **2**. The solution was cooled to 0 °C and saturated with air through a glass syringe. A solution of triethylborane (2.5 equiv, 50 μmol , 50 μL of a 1 M solution in hexane) and tributyltin hydride (2.5 equiv, 14.6 mg, 50 μmol) was prepared in absolute diethyl ether (20 mL) under argon. The solutions were mixed using a dual syringe

pump feeding in the low dead volume microreactor that was coupled directly to the ion source of the mass spectrometer. The reacting solution was fed continuously into the ESI-MS.

Investigation of the complex formation of dimethyl glutarates 2, 3, 5, and 6 with Lewis acids (aluminum triisopropylate, cerium trichloride, indium trichloride, lithium perchlorate, magnesium ethoxide, magnesium bromide–diethyl etherate, scandium triflate, and zinc bromide) by ESI-MS: The respective dimethyl glutarate (20 μmol) and Lewis acid (1.2 equiv, 24 μmol) were dissolved in absolute diethyl ether (20 mL). This 1×10^{-3} M stock solution was directly used in the ESI measurements.

Investigation of the complex formation of dimethyl glutarates 2, 5, and 6 with Lewis acids (scandium triflate, magnesium bromide–diethyl etherate, and lithium perchlorate) by NMR spectroscopy: The respective dimethyl glutarate (0.1–0.2 mmol) and Lewis acid (1.2 equiv) were stirred in deuteriated solvent (CDCl_3 , $[\text{D}_{10}]\text{Et}_2\text{O}$, and $[\text{D}_8]\text{TfHf}$) (1 mL, 0.1–0.2 M) for 45 min and filtered if necessary. The 0.1–0.2 M solutions were finally measured at room temperature. NMR titration: A stock solution of substrate 5 (0.1 M) in deuteriated diethyl ether was prepared. In total, six flasks were then prepared by adding increasing amounts of scandium triflate (0.1, 0.2, 0.5, 1.0, 2.0, and 5.0 equiv) to 1 mL of the stock solution. All solutions were stirred for 1 h, filtered if necessary, and the ^1H NMR spectra were recorded at room temperature.

Acknowledgements

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