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Measurement and optimization of organic chemical reaction yields by GC–MS with supersonic molecular beams

Aviv Amirav *, Alexander Gordin, Youlia Hagooly, Shlomo Rozen, Bogdan Belgorodsky, Boaz Seemann, Hanit Marom, Michael Gozin, Alexander B. Fialkov

School of Chemistry, Tel Aviv University, Tel Aviv 69978, Israel

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ABSTRACT

A new type of gas chromatograph mass spectrometer (GC–MS) was used for semi-online monitoring of organic chemical reactions for their yield optimization, mechanism elucidation, and for obtaining information on the reaction products identity and purity. It was used with reaction mixtures without prior separation and purification as needed for NMR, thereby saving time and effort. Our unique GC–MS named 5975-SMB Supersonic GC–MS is based on GC interface with the MS with supersonic molecular beams (SMB) and on ionization of the sample molecules during their axial flight through an open electron ionization ion source as vibrationally cold molecules. GC–MS with SMB is demonstrated to significantly extend the range of compounds amenable for analysis, practically always giving molecular ions, enabling effective fast GC–MS analysis, and providing elemental formulas via isotope abundance analysis with unit mass resolution quadrupole MS. In addition, it uniquely provides uniform response to all compounds, a feature, which is vital for the measurement of chemical reaction yields. In this manuscript, four different organic synthetic reactions were studied and are described. Based on the collected data, we were able to better understand how the reaction conditions should be optimized in order to maximize the yields and purity of target products. Consequently, we propose that GC–MS with SMB can serve as a novel tool for the fast optimization of chemical reactions.

1. Introduction

Chemical reactions, and particularly organic ones, are typically performed in one of several well-established methods, usually on a small scale. A typical approach involves mixing the reactants together in an appropriate solvent, often with addition of a catalyst, and allowing them to undergo a reaction, which may take from several minutes to few days. The progress of the reaction is either assumed or monitored most-commonly by thin layer chromatography and by NMR, but little or no information is obtained online on the reaction yield or its actual progress. At the perceived end of the reaction, the products are separated and purified by preparative chromatography, distillation, sublimation, selective precipitation or crystallization, processes, which may take several hours or even several days. Subsequently, the purified products are analyzed by ^{1}H and ^{13}C NMR and by high resolution mass spectrometry (often Quadrupole Time of Flight (QTOF) mass spectrometer), typically via flow injection electrospray ionization (FI-ESI). However, while FI-ESI-QTOF provides elemental formulas information, it does not provide information about the synthesis yield, products purity, availability of isomers and on the reaction mechanism, since the already-purified compounds are analyzed and since ESI has non-uniform, highly compound dependent ionization yields. In contrast, GC–MS with its standard electron ionization (EI), unlike ESI, has for volatile compounds approximately uniform, semi-quantitative ionization yield. However, it provides molecular ions only for about 50% of the compounds having molecular weights above 300 amu (our statistical analysis of NIST library) and standard GC–MS is limited to volatile and thermally stable compounds only, which severely restricts its applicability. Furthermore, ion source degradation and peak-tailing reduce the standard EI response uniformity for semi-volatile compounds.

Thus, in order to measure and better optimize chemical reaction yields, new methods and technologies are needed that will enable online, or almost online, monitoring of the reacting compounds and products. Such technology should be applicable to broad range of compounds, enable sample quantitative determination via uniform compound independent response, enable positive sample identification and be compatible with sample separation devices.

In the last two decades our group research has been focused on the development of GC–MS with supersonic molecular beams

* Corresponding author. E-mail address: amirav@tau.ac.il (A. Amirav).

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(SMB) (also named Supersonic GC–MS).[1–6] Supersonic GC–MS is based on a GC and MS interface with SMB and on the electron ionization of vibrationally cold analytes in the SMB (cold EI) in a fly-through ion source. This ion source is inherently inert and further characterized by an ultra fast response time and vacuum background filtration capability.[1,7] The same ion source also offers a mode of classical EI.[8] Cold EI, as a main mode, provides trustworthy enhanced molecular ions combined with effective library sample identification, that is, supplemented and complemented by a powerful isotope abundance analysis method and software,[9] which provides elemental formulas with unit resolution quadrupole MS data. In addition, the range of low volatility and thermally labile compounds amenable for analysis is significantly increased (about doubled) with Supersonic GC–MS due to the use of contact-free fly-through ion source and the ability to lower sample elution temperatures through the use of short GC columns with high carrier gas flow rates.[5] This compatibility with high column flow rates further facilitates effective fast and ultra fast GC–MS analysis,[1–3,10] which was also explored in its use in GC–MS of reaction products.[6]

The basic requirement from a system that should measure reaction yields is that its response will be uniform and compound independent or the response should represent in a *known and systematic manner* the compounds molecular weights and amounts.

Electron ionization, unlike any other ionization method, uniquely provides ionization yields that depend predominantly on the sum of the numbers of each different atom in the ionized analyte[11–13] due to the localized nature of electron–electron interaction in the ionization process. In simple terms, the electron ionization cross section approximately depends on the number of electrons in the molecule, which relates to its molecular weight. Thus, the electron ionization probability for organic compounds approximately linearly increases with the ionized compound's molecular weight hence it is approximately proportional to the sample weight. Consequently, it is well known that standard GC–MS exhibits uniform response to all volatile compounds found in analyzed samples.

For GC–MS analysis, that is, based on a quadrupole mass spectrometry, the ionization yield is further reduced by the mass analyzer and ion detector transmission, hence its response slightly declines with mass. However, for semi-volatile and low volatility compounds, peak-tailing and ion source degradation can significantly reduce the observed signal, sometimes in a difficult to predict way, thus the feature of uniform response of standard GC–MS is eroded and often does not exist anymore. In contrast, in GC–MS with SMB analysis, ion source-related peak-tailing and degradation are completely eliminated, due to the use of a fly-through ion source, thus providing practically uniform compound independent response for all analytes that enter the SMB. The implication of such uniform response is that in a given chromatogram, the peak area relates to the amount (weight) of the analyte.

In Fig. 1, the uniform response of our 5975-SMB Supersonic GC–MS is demonstrated via the comparison of two chromatograms of the same test mixture that included *n*-$C_{16}H_{34}$, methyl stearate, cholesterol and *n*-$C_{32}H_{66}$, each at 0.25 ng on-column amount (*n*-$C_{32}H_{66}$ amount is somewhat lower). As clearly observed, the response of standard EI is declining with the sample volatility and mass, and already for cholesterol its relative response has declined by more than an order of magnitude in the total ion count scale (TIC) (factor of 10.2 in relative peak area). In contrast, the response of 5975-SMB remained unaffected by the sample volatility due to the use of contact-free fly-through ion source and it is very similar to that of GC-FID. In addition, all the four sample compounds had dominant molecular ion in their cold EI mass spectra while for standard EI it was either weak or absent in the case of *n*-$C_{32}H_{66}$.

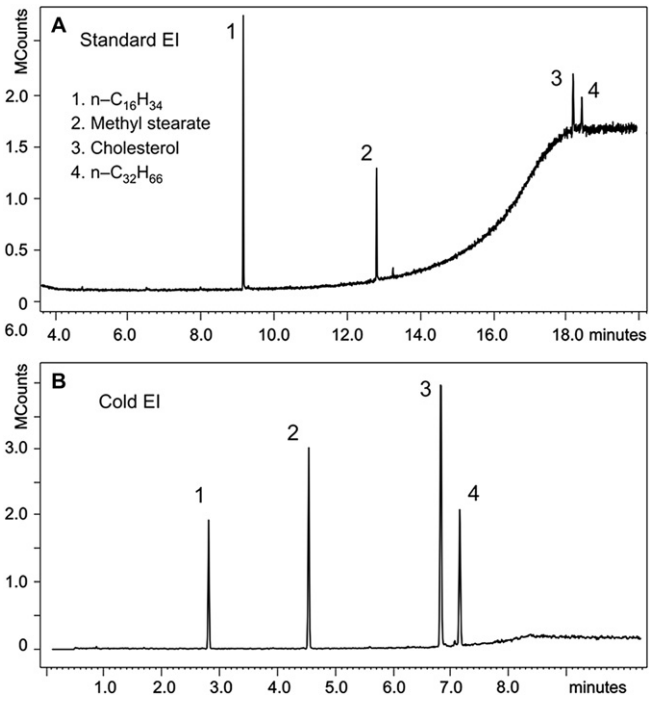


Fig. 1. The analysis of a mixture of *n*-$C_{16}H_{34}$, methyl stearate, cholesterol and *n*-$C_{32}H_{66}$ at about 0.25 ng on-column amount with standard GC–MS (upper trace) and 5975-SMB Supersonic GC–MS (bottom trace). 30 m, 0.25 mm ID capillary column with 0.25 μ DB-5ms UI column was used with the standard GC–MS with 1.2 mL/min column flow rate while only 5 m of that column was used with 5 mL/min column flow rate with the Supersonic GC–MS. The GC oven program was 80 °C followed by 10 °C/min to 320 °C for the standard 5975 GC–MS and 50 °C followed by 30 °C/min to 300 °C for the 5975-SMB.

Thus, the uniform response of GC–MS with SMB can be assumed and routinely used for semi-quantitative analysis. Furthermore, a simple chromatogram with few compounds at various molecular weights could be utilized for obtaining more accurate calibration of the cold EI system response for closer accounting of small experimental mass dependent effects on the response factors dependence on mass.

In this work we describe the use of GC–MS with SMB for the semi-online monitoring of organic reactions (fractions are taken during the reaction time and progress), while optimizing these reactions yields, obtaining information on their mechanisms and determining products purity and identity, including in some cases information regarding existence and possible structures of formed isomers.

2. Experimental: the Supersonic GC–MS systems

2.1. General

Two types of GC–MS with Supersonic Molecular Beams (SMB) (Supersonic GC–MS) were used. The first system was based on the conversion of a Varian 3800 GC plus 1200 triple quadrupole MS (Varian Walnut Creek CA USA) into a Supersonic GC–MS as described in details in Ref. 4. The second system was a recently developed Supersonic GC–MS based on the conversion of an Agilent 7890 GC+5975 MSD (Agilent Technologies, Santa Clara CA USA) into a 5975-SMB Supersonic GC–MS (Aviv Analytical, Hod Hasharon Israel).

GC–MS with SMB is based on the use of an SMB for interfacing the GC to the MS and as a medium for electron ionization of sample compounds.[1] SMBs are characterized by intra-molecular vibrational super-cooling, unidirectional molecular motion with controlled hyperthermal kinetic energy (1–20 eV), mass focusing similar to that in a jet separator, and capability of handling very broad range of column flow rates from standard 1 mL/min (or lower) up to 100 mL/min, without affecting the sensitivity. In these systems the column output is mixed with helium make-up gas (~70 mL/min typical total flow rate), and flows to the supersonic nozzle through a heated and temperature-controlled transfer line. The helium flow can be mixed (via the opening of one valve) with perfluorotributylamine (PFTBA) for periodic system tuning and calibration. The sample compounds seeded in the helium gas expand from a 110 μm diameter supersonic nozzle into a nozzle vacuum chamber, that is, differentially pumped by a Varian Navigator 301 turbomolecular pump (Varian Inc., Torino Italy) with 250 L/s pumping speed. The helium pressure at this vacuum chamber is about 6×10^{-3} mbar. The supersonic expansion vibrationally cools the sample compounds and the expanded supersonic free-jet is skimmed by a 0.8 mm skimmer and collimated in a second differentially pumped vacuum chamber, where an SMB is formed. This second vacuum chamber is pumped by the original GC–MS turbomolecular pump. The SMB, seeded with vibrationally cold sample compounds, flies through a dual cage EI ion source[7] where these beam species are ionized by 70 eV electrons with typically 8 mA emission current. The ions are focused by an ion lens system, deflected 90° by an ion-mirror and enter the original mass analyzer. The 90° ion-mirror is separately heated and serves to keep the mass analyzers clean from sample induced contaminations and for the suppression of helium *meta*-stable induced mass independent noise. Data analysis is performed with the original GC–MS data analysis software (Chemstation for the 5975-SMB) plus the Tal-Aviv Isotope Abundance Analysis (IAA) software (Aviv Analytical, Hod Hasharon, Israel). For ultra fast GC separation, a newly developed low thermal mass fast GC was employed, as described in details in Ref. 10. It is based on the use of a capillary GC column, that is, inserted into resistively heated thin stainless steel tubing, which is mounted on the top of a Varian 3800 GC.

Several columns and variable experimental conditions were used as described in the figure captions. In all cases short columns were used from 1.7 to 15 m with helium column flow rates in the 5–32 mL/min range.

3. Results

In Fig. 2 typical analysis of a chemical reaction mixture is shown, as obtained with the 5975-SMB Supersonic GC–MS. The investigated reaction was a simple A+B→C+D type, aimed at obtaining an intermediate product. As shown, four main GC–MS peaks are observed and the last one that eluted at 3.7 min (Fast GC–MS) was the synthesis target compound as initially perceived by its molecular ion m/z=326.2. (While the 5975 quadruple mass spectrometer had unit resolution its mass accuracy was ± 0.1 amu, which further helped in identification). The reaction of this target molecule (ethyl butyl(4-nitrophenylcarbonyl)carbamodithioate)

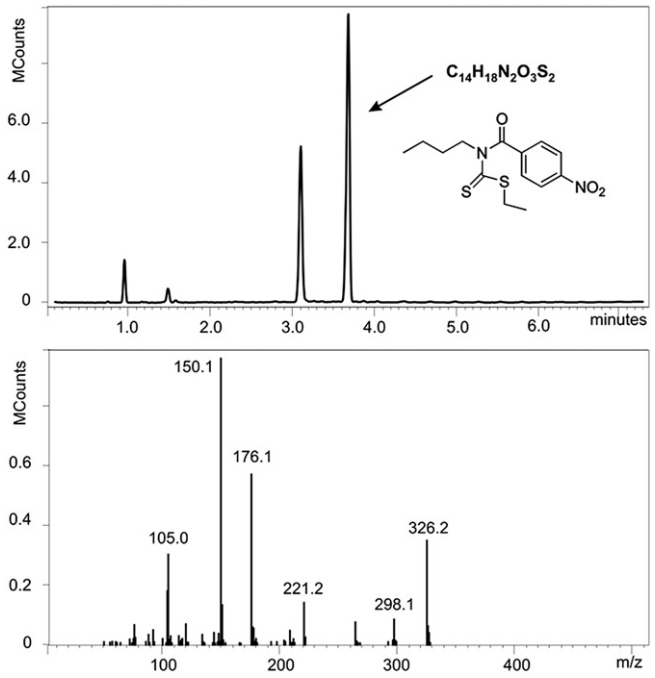


Fig. 2. The analysis of synthetic organic chemical reaction products (reaction mixture) with 5975-SMB Supersonic GC–MS. $C_{14}H_{18}N_2O_3S_2$ was the target product and it is the main total ion chromatogram peak (upper trace) whose cold EI mass spectrum is shown at the bottom trace. A 5 m column with 0.25 mm ID and 0.25 μ RTx-5MSI film was used with 16 mL/min helium column flow rate and 40 °C/min GC temperature programming rate.

with the fluorinating agent, bromine trifluoride, led to the formation of fluorinated product *N*-butyl-4-nitro-*N*-(trifluoromethyl) benzamide, a rare compound with a potential of antifungal properties and as useful electrolyte additives for storage batteries. The synthesis of this ethyl butyl(4-nitrophenylcarbonyl)carbamodithioate was unknown but the use of ethanethiol and coupling reaction with 4-nitrobenzoic acid led to the desired product (shown below in Fig. 3) that was identified by the Supersonic GC–MS.

The ethyl butyl(4-nitrophenylcarbonyl)carbamodithioate (target compound) has a molecular ion m/z=326.2, and isotope abundance analysis using the Tal-Aviv IAA software showed $C_{14}H_{18}N_2O_3S_2$ to be number one in the list of possible elemental formulas with a matching factor of 999 (out of 1000). The IAA software provided further information that all first 20 hits had two sulfur atoms, at least one oxygen atom and 14±2 carbon atoms. This elemental formula was later further confirmed with accurate mass ESI-QTOF and by NMR. However, unique to our approach was the fact that the 5975-SMB Supersonic GC–MS provided valuable information on the reaction yield, prior to sample purification, which related to the target compound peak area ratio to all other peaks. We measured this reaction yield as 59±4%. In addition, an undesirable product with molecular ion m/z=332.2 was identified and information on the reactants stability and their residual amounts was revealed, thereby enabling reaction conditions optimization prior to target compound purification.[14]

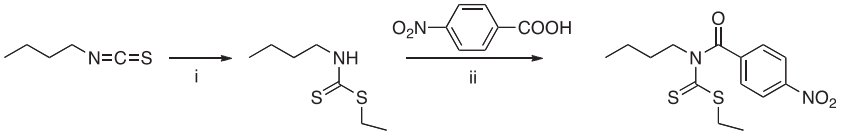
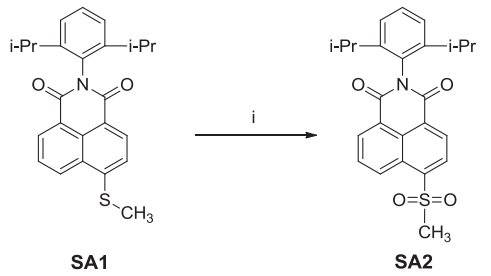


Fig. 3. Reagents and conditions: (i) EtSH, THF, rt, 20 h; (ii) DCC, DMAP, CH_2Cl_2, rt, 18 h.

Figs. 4 and 5 show the monitoring and optimization of another organic reaction, based on analysis by the 5975-SMB Supersonic GC–MS. In this reaction, thioether **SA1** was catalytically oxidized to a corresponding sulfone **SA2**. The fluorescent thioether **SA1** was developed as a potential chemosensor for the detection of peroxides, since the fluorescence spectrum of the resulting oxidation product sulfone **SA2**, is significantly different than the spectrum of the starting thioether **SA1**.[15] For oxidation of **SA1** to the corresponding sulfone **SA2**, $MoO_2Cl_2(OPPh_3)_2$ complex was used as a catalyst and H_2O_2, as the re-oxidant.



SA1 SA2

Fig. 4. Synthesis of compound **SA2**. Reagents and conditions: (i) $MoO_2Cl_2(OPPh_3)_2$ catalyst, H_2O_2, CH_3CN, 60 °C, 24 h.

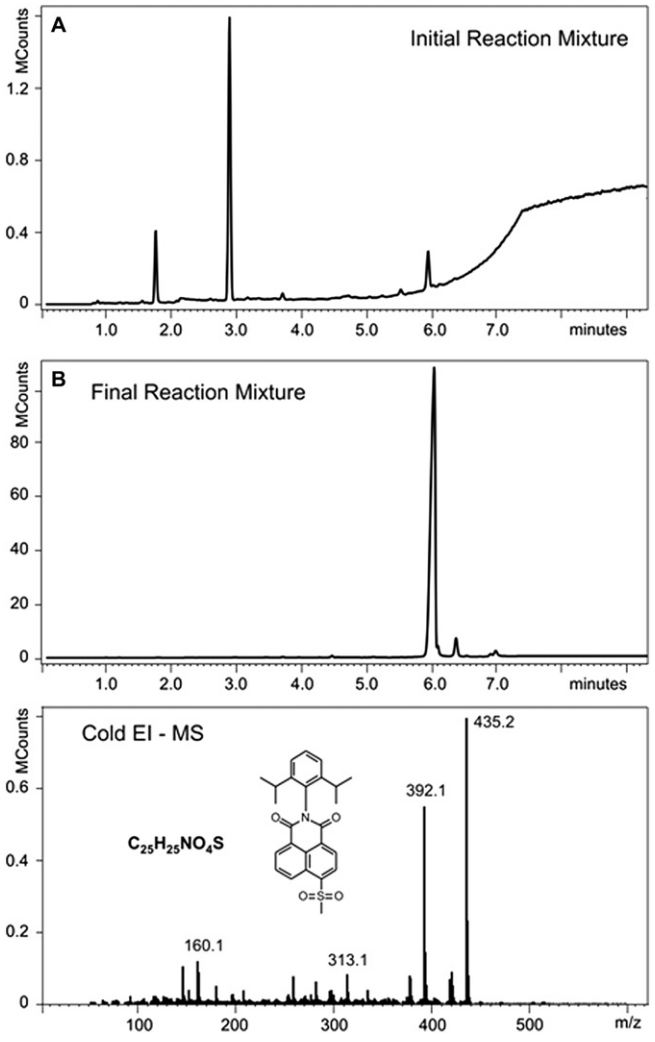


Fig. 5. The analysis of synthetic organic chemical reaction products with 5975-SMB Supersonic GC–MS. **SA2** ($C_{25}H_{25}NO_4S$) was the target product and it is the minor last to elute peak in the upper mass chromatogram and main peak in the middle trace of the finally purified product. The cold EI mass spectrum of this compound is shown at the bottom trace. The small peak after the main peak in the middle mass chromatogram is of its isomer, while the last to elute peaks are of impurities. A 15 m column with 0.32 mm ID and 0.1 μ DB-1HT film was used with 32 mL/min helium column flow rate and 30 °C/min GC oven temperature programming rate.

The transformation from **SA1** to **SA2** was found to be problematic and we had difficulties determining the correct yield for this reaction. A complex mass spectrum, with little information content, was obtained by the FI-ESI-QTOF technique for the isolated **SA2** product. Moreover, based on one of the many peaks in this mass spectrum, oxidation of thioether **SA1** to a corresponding sulfoxide could be easily assumed with a mass spectral peak presumably assigned via its exact mass to an ion containing adduct potassium ion in its composition. This assumption was found to be erroneous by the 5975-SMB Supersonic GC–MS analysis. As shown in the upper chromatogram of Fig. 5, the target sulfone **SA2** emerged as a relatively small peak at near 6 min elution time, whose area related to its yield while other non target compounds were the majority.

The reaction conditions were optimized based on Supersonic GC–MS data, and as shown in the middle chromatogram of the Fig. 5, compound **SA2** was purified, and its cold EI mass spectrum (bottom spectrum, Fig. 5) was dominated by its molecular ion (*m*/*z* 435.2), while isotope abundance analysis of this molecular ion resulted in $C_{25}H_{25}NO_4S$ composition at the top of the list of all possible elemental formulas. The identity of compound **SA2** was later further confirmed by FI-ESI-QTOF and ^{13}C NMR, using chromatographically pure material. However, the ESI-QTOF mass spectrum still contained several peaks and was void of any quantitative information. The 5975-SMB Supersonic GC–MS on the other hand, as shown in Fig. 5, provided quantitative information on the compound **SA2** purity and uniquely indicated that the two small peaks, eluted just after the main peak (one on the main peak shoulder and second at ~6.3 min), were assigned as isomers of this material since they exhibited similar mass spectra with small variations of the relative mass spectral fragment intensities. The additional compound that eluted at around 7 min contained a bromine atom in its structure that most probably originated from an impurity in the starting **SA1**. Fig. 5 clearly shows how the 5975-SMB Supersonic GC–MS analysis of a reaction mixture enabled its optimization and resulted in quantitative information on the product purity and prevailing isomers.

Another example of a chemical reaction yield optimization by using the 5975-SMB Supersonic GC–MS is shown in Figs. 6 and 7. In this case, the synthetic target compound was a biodegradable and potentially reusable derivative of the *S*,*S*-ethylenediaminedisuccinic tetraacid (*N*,*N*′-bis-*n*-dodecyl-S,S-EDDS **X5**; Fig. 6). This chelating agent was specifically designed for improvement of a Sediments Remediation Phase Transition Extraction (SR-PTE) process developed by Brauner and Ullmann for extraction of heavy metals from contaminated soils.[16] The structure of the chelator **X5** was based on *S*,*S*-ethylenediaminedisuccinic tetraacid (**S**,**S-EDDS**, Fig. 6) and contained two dodecyl-alkyl chains to promote an extraction of heavy metal complexes of this ligand into recyclable organic media.

Despite all our efforts, the direct alkylation of **S**,**S-EDDS** was found to be unattainable. Thus, the alternative synthetic strategy for preparation of the desired chelator **X5** included conversion of **S**,**S-EDDS** into a corresponding tetra-butylester **X1** ($C_{26}H_{48}N_2O_8$; *m*/*z* 516.3), which was subsequently subjected to bis-*N*,*N*′-alkylation, giving the key intermediate **X2** ($C_{50}H_{96}N_2O_8$; *m*/*z* 852.7) that was finally hydrolyzed into the target tetraacid. Among all of the evaluated alcohols, used for conversion of the **S**,**S-EDDS** into the corresponding tetraester derivatives, utilizing n-butanol, as a reagent and as a reaction solvent, allowed us to achieve the best esterification yields. Moreover, we found that alkaline hydrolysis of the

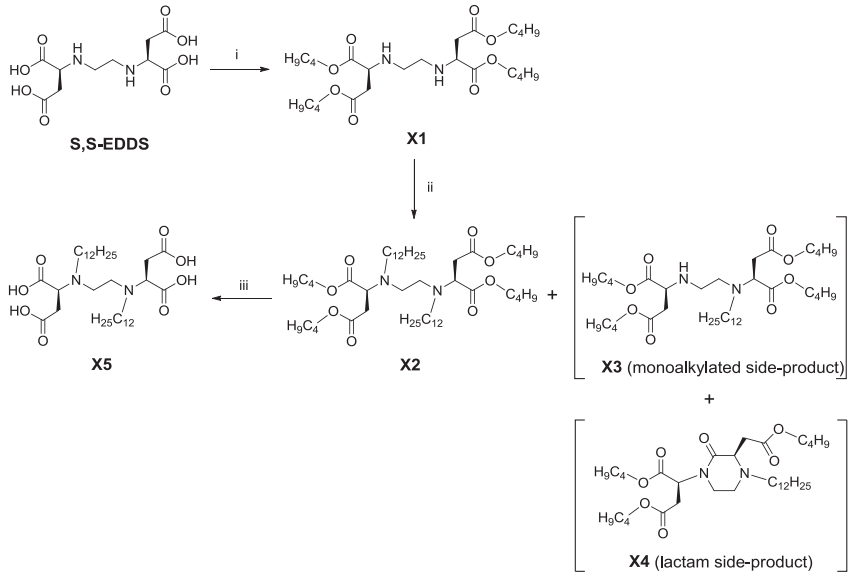


Fig. 6. Synthesis of **X5**. Reagents and conditions: (i) $SOCl_2$, *n*-BuOH, 0→60 °C, 24 h; (ii) dodecylbromide, K_2CO_3, CH_3CN, 80 °C, 48 h; (iii) KOH (aq), THF, RT, 24 h.

N,*N*′-bis-alkylated tetra-butylester **X2** provided almost quantitative yields of the target chelator **X5**.

However, significant challenges in the synthesis, purification, and analysis of the key intermediate **X2** were encountered during development of the second step of the process. Under many reaction conditions, formation of substantial amounts of mono-*N*-alkylated tetraester **X3** ($C_{36}H_{72}N_2O_8$; *m*/*z* 648.5) and lactam **X4** ($C_{34}H_{62}N_2O_7$; *m*/*z* 610.5) side-products were observed as measured with the 5975-SMB (Fig. 7 below). The latter compound is most probably formed in reaction mixtures by an intra-molecular amidation. Only traces of quaternary ammonium derivatives were formed, mostly due to the steric hindrance around the tertiary amines of compounds **X2** and **X3**. These traces were easily removed by a preparative liquid chromatography.

In attempt to find, which conditions, including various solvents, alkylating agents, bases, reagent concentrations and temperature regimes, would lead to a minimum amount of side-products, all evaluated reaction mixtures were monitored by the 5975-SMB Supersonic GC–MS, since standard GC–MS was incapable of analyzing our relatively large and polar starting materials and products while FI-ESI-QTOF is incapable of providing any quantitative information on the reaction progress.

For example, under many non-optimized conditions, the target intermediate **X2** was assumed to be absent by all other techniques but could be observed at about 0.4% yield (retention time of 7.7 min in Fig. 7), even after prolonged heating (5 days) of the reaction mixture (upper chromatogram, Fig. 7). It should be noted that despite concerns regarding our compounds stability under prolonged heating, we still found significant amounts of unreacted starting materials, as well as formed side-products, while no products of decomposition could be detected.

By screening a large number of possible parameters, we were able to optimize our reaction conditions to the lowest amount of side-products, especially of the lactam **X4** (which is a 'dead-end' side-product), and obtain the highest yield of the desired compound **X2**. We found that the best reaction conditions for *N*,*N*′-bis-alkylation of the tetraester **X1** included use of *n*-dodecylbromide as an alkylating agent, CH_3CN as a solvent and K_2CO_3 as a base. A temperature of 80 °C as well as specific concentrations of the starting materials were also very important for the *N*,*N*′-bis-alkylation reaction outcome.

5975-SMB Supersonic GC–MS analysis showed that at optimal conditions the yield of the **X2** is 18% (middle chromatogram, Fig. 7). After compound **X2** separation and purification by liquid chromatography, the reaction yield was determined gravimetrically and was found to be 18.6%, which is in agreement with the 5975-SMB Supersonic GC–MS results (18±3%). Thus, Fig. 7 demonstrates an exceptional ability of the 5975-SMB Supersonic GC–MS to analyze an extended range of compounds that are well beyond the limits of standard GC–MS. In the 5975-SMB Supersonic GC–MS, compounds in the *N*,*N*′-bis-alkylation reaction mixture not only eluted, but also had no ion source peak-tailing and/or ion suppression effects, enabling correct determination of this reaction yield. Moreover, cold EI mass spectrum (bottom mass spectrum, Fig. 7) of compound **X2** provided a good molecular ion peak, despite the presence of two dodecyl chains, which normally preclude the observation of any molecular ion in standard EI, such as with large phthalate esters. The optimization of the above presented process could not be performed without the 5975-SMB Supersonic GC–MS analysis, thereby clearly demonstrating that this technique can serve as a powerful tool for reaction yield optimization.

Sometimes synthetic organic reactions can be fast, hence the obvious next step was to explore the use of ultra fast 5975-SMB Supersonic GC–MS for semi-online monitoring of the progress of fast synthetic organic chemical reactions. We were involved in exploring new ways for selective oxidation of organic compounds at their thioester function. The progress monitoring of sulfur oxidation reaction is demonstrated in Fig. 8, as probed by our low thermal mass fast GC–MS with SMB (1200-SMB Supersonic GC–MS). The organic chemical reaction of the thioester with *meta*-chloroperbenzoic acid (m-CPBA) is shown vs the added amount of oxidizing agent. The upper trace demonstrates the TIC of the mixture from the reactor with two times initial excess of the oxidizing agent and the MS of the last peak in the insert, which is identified as a singly oxidized product. It shows the remaining organic reactant plus the appearance of two isomers of the singly oxidized product. Correspondently, the middle trace was obtained at 3.5 times initial excess of the oxidizing agent. The mass spectrum proves that at least two doubly oxidized product isomers are formed. Finally, the lower trace was obtained with five times excess of the oxidizing agent that yielded triply oxidized product, which was the target of this synthesis. The insert shows the mass spectrum of that desirable triply oxidized product. As shown, each analysis took only 1.5 min.

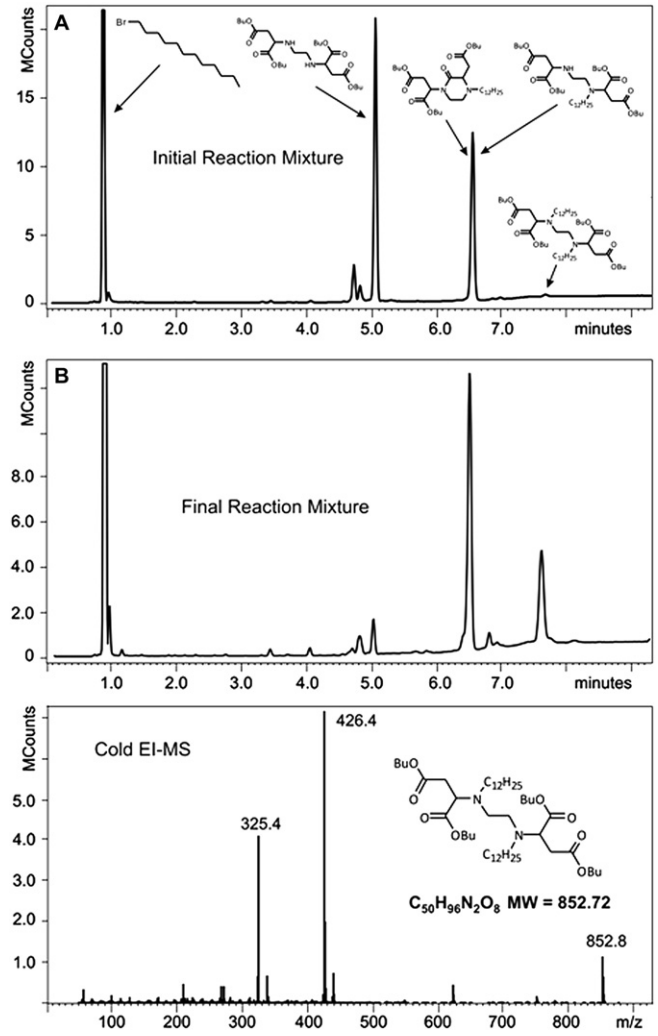


Fig. 7. The analysis of chemical mixture by the 5975-SMB Supersonic GC–MS. **X5** ($C_{50}H_{96}N_2O_8$ (m/z=852.8)) is the target reaction product and it is the last to elute total ion chromatogram peak (upper and middle mass chromatograms) whose cold EI mass spectrum is shown in the bottom trace. The three main peaks before it are of a reaction 'dead-end' lactam plus co-eluting partial substitution product and the two reactants as indicated in the figure. A 15 m column with 0.32 mm ID and 0.1 μ DB-1HT film was used with 32 mL/min helium column flow rate and 30 °C/min GC temperature programming rate.

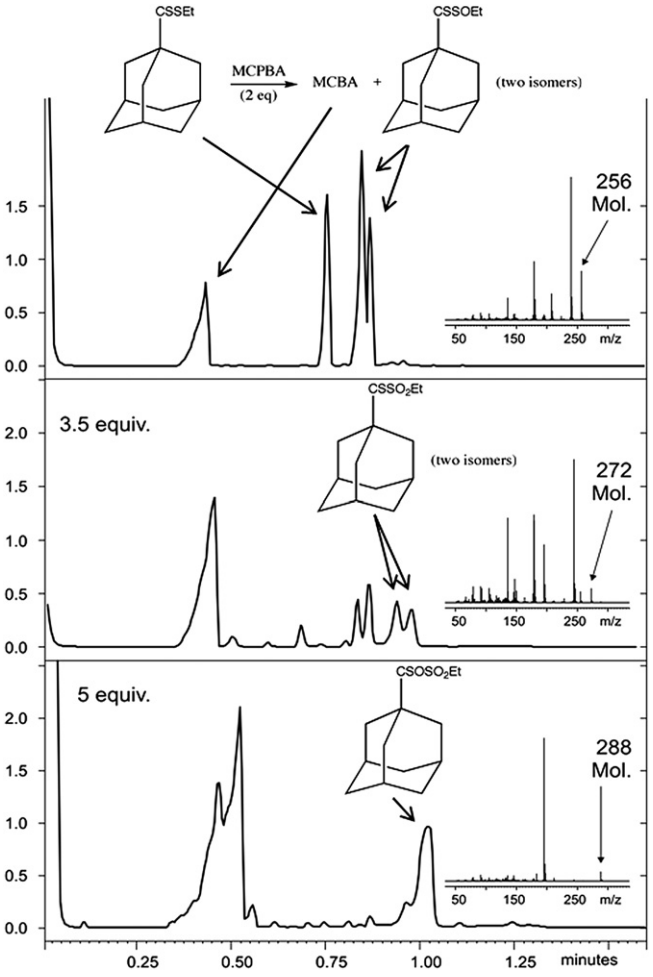


Fig. 8. Fast GC–MS with SMB monitoring of the progress and yield of synthetic organic chemical reaction with the 1200-SMB Supersonic GC–MS. The sample was injected into a Varian 1177 injector with split 20 at 200 °C; and 3800 standard GC oven temperature at 220 °C. The short (1.5 m) fast GC column flow rate was 8 mL min.

The performance of such fast semi-online analysis provided two surprising results for the synthetic chemists: (A) it was found that the reaction took about 5 min to be completed as opposed to 3–5 h perceived rate, which led only to product degradation; (B) it was found that the oxidizing reactant was partially decomposed during the reaction, hence 5 equiv were needed for attaining almost full yield of three oxygen atoms transfer. Thus, semi-online fast GC–MS with SMB monitoring enabled careful 'titration' of the amount of oxidizing reagent needed and the fine tuning of optimal yield in a small fraction of the time and effort, that is, usually needed. We note that these labile compounds are not amenable for either standard GC–MS (degradation) or ESI-MS (poor ionization yield) but are compatible as shown for analysis by the 1200-SMB Supersonic GC–MS.

4. Discussion and conclusions

Organic chemistry and other types of synthetic chemistry, such as the synthesis of drugs, industrial chemicals and fine chemicals can benefit from online or semi-online reaction monitoring for its improved optimization. Among the currently used tools, standard GC–MS is very limited in its applicability (range of compounds), often does not provide molecular ions and due to ion source peak-tailing does not provide fully uniform compound independent peak areas. In addition, standard GC–MS analysis can take up to 40 min. LC–MS requires lengthy LC method development time hence is not often used and electrospray has highly compound dependent ionization yield (plus sometimes ion suppression effects) hence cannot be used for the monitoring of reaction progress or for the provision of reaction yields. NMR is incompatible with the analysis of most mixtures and requires deuterated solvents, hence usually requires compound purification at the mg amount. Thus, currently TLC is often being used with its limited information content for the monitoring of reaction progress.

In this paper we demonstrated the use of the Supersonic GC–MS for the monitoring and optimization of synthetic organic chemical reactions. Our main goal was to advance a new approach for the performance of organic synthesis that will by-pass the lengthy steps of synthetic target compound separation and purification for NMR analysis. According to our approach, the synthetic mixture is analyzed semi-online for the provision of quantitative content information for the purpose of reaction optimization, while leaving the steps of separation and purification to the end after reaction optimization.

The Supersonic GC–MS was demonstrated as uniquely characterized by: (A) having significantly extended range of compounds amenable for analysis due to its use of high column flow rates, short columns and fully inert ion source; (B) having uniform response with cold EI without any ion source peak-tailing; (C) provision of trustworthy enhanced molecular ions to the vast majority of all compounds; (D) being compatible with isotope abundance analysis for the provision of elemental formulas; (E) compatibility with fast and ultra fast GC–MS analysis.

Another important side benefit of semi-online reaction monitoring is the ability to work in micro scale due to the elimination of the need to purify mg amounts as needed for NMR. As a result, micro chemical reaction reactors can be used for the optimization of the reaction yield with significant time, chemicals and solvent saving (also safer), and only at the end larger amount can be used as needed for the final product.

We feel that when combined these benefits can provide a new approach for improved synthetic chemistry.

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