Copolymer microstructure determination by the click of a button; reactivity ratios of comonomers from a single MALDI-ToF-MS measurement.

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ABSTRACT: The microstructure (random, gradient, block or alternating) of a copolymer reflects on the physical properties of the polymeric material. In order to classify the topology of the copolymer, knowledge of the reactivity ratios of the monomers is required. Conventional ways to determine these reactivity ratios demand in most cases tedious laboratory work. Here, a novel method is described to derive these ratios from a single MALDI-ToF-MS spectrum by employing either a Monte Carlo approach to numerically simulate a first order Markov chain or the analytical form of the first order Markov chain. A single MALDI-ToF-MS spectrum proved to give very good estimates of the reactivity ratios of comonomers from copolymer's synthesized by free radical polymerization, ring-opening polymerization of lactones and lactides or ring-opening copolymerization of anhydrides plus epoxides.

INTRODUCTION

One of the ultimate challenges in polymer chemistry is the ability to control the physical properties of a copolymer by tailoring its microstructure. Knowing the reactivity ratios of the comonomers allows predicting and tuning of the copolymer's microstructure both with respect to composition and topology. The classical method to ascertain reactivity ratios is by determining the comonomer composition of a range of polymers prepared with different feed compositions. Various statistical methods to determine reactivity ratios have been reported which deal with either the differential or the integral form of the Mayo-Lewis equation.[1] Nevertheless, most methods have the disadvantage that quite some reactions have to be performed with different feed compositions. Moreover, comparison of ratios obtained by different methods often shows a relatively large variety due to differences in the statistical approach, for example as the result of linearization. Often the error structure of the measured data is not taken into account, leading to systematic errors in the obtained parameters. Choosing the right statistical method is therefore crucial for the reliability of the outcome.[1,2] In copolymerization sometimes solvent effects are observed. These solvent effects can even be induced by the change in feed composition (take for example copolymerization in the aqueous phase with acrylic acid as one of the comonomers). A fast and reliable method to determine the reactivity ratios at one feed composition, making it possible to study the effect of changing the feed composition on the reactivity ratios would therefore be highly desired.

Since a copolymer is a statistical mixture of individual molecules, a copolymer sample obtained from a single experiment in principle contains all the information required to retrieve the reactivity ratios. These ratios on their turn allow us to in detail predict the copolymer microstructure. At one feed composition an average copolymer composition is obtained, determined by the reactivity ratios. But this average composition is a resultant of a chemical composition distribution, which in itself is determined by the reactivity ratios too.

MALDI-ToF-MS is a fast and accurate technique to determine copolymer compositions and is very useful to elucidate the copolymers topology as well as to study mechanistic aspects of various copolymerization systems.[3-5] Since MALDI-ToF-MS gives information on individual polymer chains, access to homo-propagation and cross-propagation probabilities becomes available.[6] It is even possible to look at effects of chain length on reactivity ratios because this information is also contained in the spectra. The probabilities provide the reactivity ratios by simulation of a first order Markov chain by using for example the Monte Carlo method. The first to apply MALDI-ToF-MS to determine reactivity ratios of comono-

mers were Suddaby and Willemse but they still required data from different reactions.[4,5]

Here we report on a reliable method to determine reactivity ratios based on a single MALDI-ToF-MS spectrum of the copolymers. The reactivity ratios have been determined for three different types of copolymerizations i.e. free radical polymerization, ring-opening polymerization of cyclic esters as well as ring-opening copolymerization of oxiranes and anhydrides. The reactivity ratios were initially obtained by simulating a first order Markov chain by using both the Monte Carlo approach. During our study we managed to derive an expression in analytical form of a first order Markov chain, which provided an exact analytical mathematic solution for the reactivity ratios.

EXPERIMENTAL SECTION

Reagents. Free radical: Monomers were purified by conventional methods. 2,2'-azobis(isobutyronitrile) (AIBN) was recrystallized from methanol. 1-Dodecanethiol (DDT) was used without further purification and purchased from Aldrich. Ring-opening: 1,5-dioxepan-2-one and 4-methyl-ε-caprolactone were prepared according to literature procedures.[38,39] D-Lactide was a gift from Purac. ε-Caprolactone, δ-valerolactone and tin (II) 2-ethylhexanoate (Sn(Oct)2) were purchased from Aldrich.

Synthesis. Free radical: A mixture of comonomers (6 mmol) in required molar ratio, initiator AIBN and chain transfer agent DDT (in a molar ratio of 500:10:1 respectively) was reacted in a 1.5 mL crimp lid vial placed into an aluminum heating block at 60 or 70 °C. Prior to reaction, the mixture was deoxygenated by flushing with Argon for a few minutes. Crude samples were taken with an interval of 30 s to undergo immediate MALDI-ToF-MS analyses. Ring-opening: A mixture of comonomers (10 mmol) in required molar ratio and a drop of Sn(Oct)2 was reacted in a 1.5 mL crimp lid vial placed into an aluminum heating block at 130 °C. Crude samples were taken with an interval of 5 minutes to undergo immediate MALDI-ToF-MS analyses.

MALDI-ToF-MS Analysis. MALDI-ToF-MS analysis was performed on a Voyager DE-STR from Applied Biosystems equipped with a 337 nm nitrogen laser. An accelerating voltage of 25 kV was applied. Mass spectra of 1000 shots were accumulated. The polymer samples were dissolved in THF at a concentration of 1 mg·mL-1. The cationization agent used was potassium trifluoroacetate (Fluka, >99%) dissolved in THF at a concentration of 5 mg·mL-1. The matrix used was trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenylidene] malononitrile (DCTB) (Fluka) and was dissolved in THF at a concentration of 40 mg·mL-1. Solutions of matrix, salt and polymer were mixed in a volume ratio of 4:1:4, respectively. The mixed solution was hand-spotted on a stainless steel MALDI target and left to dry. The spectra were recorded in the reflectron mode as well as the linear mode.

RESULTS AND DISCUSSION.

Methodology. Recently, we have reported on the use of MALDI-ToF-MS to determine polymer topologies and to study mechanistic aspects of various copolymerization systems.3,5 In-house developed software was used to unravel complete MALDI-ToF-MS spectra to provide full characterization including the copolymer's chemical composition and in most of the cases even the copolymer topology (random, gradient, block, alternating). MALDI-ToF-MS spectra of a copolymer can be deconvoluted by employing equation 1:

$$m_{calc} = n_1 Mw_1 + n_2 Mw_2 + E_1 + E_2 + M^+ \quad (1)$$

where E_1 and E_2 represent the molar masses of the end groups at opposite sides of the chain, $n_1 Mw_1$ and $n_2 Mw_2$ represent the number and molar mass of the repeating units of the two different comonomer, and M^+ the mass of the cation. With this equation, a complete matrix with $n_{1,i}$ rows and $n_{2,j}$ columns can be constructed for a given set of end groups and cation, see Figure 1. The peaks in the spectrum are assigned to a certain position in the matrix employing the inequality:

$$\left| m_{\exp} - m_{calc} \right| \le \frac{\Delta m}{2} \quad (2)$$

in which $m_{\exp}$ represents the experimental mass, m_{calc} the calculated mass and Δm the accuracy (1-2 g·mol^{-1}). By calculating the natural abundance isotope distributions for each position in the matrix and rescaling it to the corresponding highest-intensity mass-peak, a full spectrum can be simulated as well as the corresponding chemical composition matrix in the form of a contour plot (e.g. Figure 3).

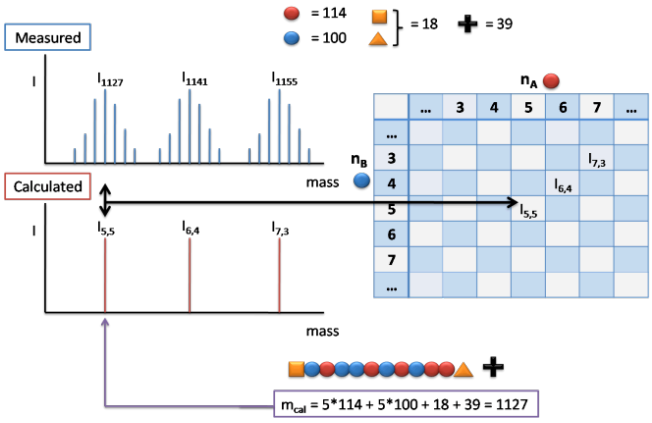

Figure 1. Schematic representation of the matrix of a copolymer with monomers of weight 114 and 100 g·mol^{-1}, -H + -OH end groups and K^+ as the cation.

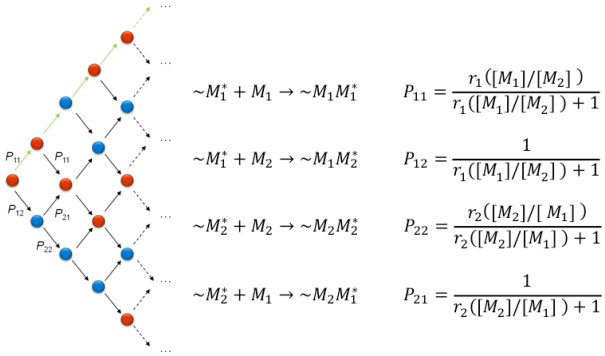

Figure 2. Description of the four possible probabilities in a copolymer.

Usually we can start processing the MALDI-ToF-MS information from chain lengths around 7-10 monomer units because in the low molecular weight region there is overlap with the signals of the matrix. Willemse has shown that chain length dependent propagation (and thus also chain length dependent reactivity ratios) levels of at chain lengths around 10.[5]

Also the effects of the initiator fragment on copolymerization are not expected to extend to larger chain lengths.[7]

The chemical composition distributions for the chain lengths covered by the total chain length distribution can be obtained by diagonally walking through the matrix from (0, i) to (i, 0) after normalization using the sum of intensities within this chain length (2 × i). The distribution of monomer repeating units along an individual chain can be described by a first order Markov chain by means of the Mayo-Lewis (terminal) model.[8] In the terminal model for copolymers we can distinguish four probabilities P_{11}, P_{12}, P_{21} and P_{22} (Figure 2).

In fact, the chemical composition distributions obtained by deconvoluting a MALDI-ToF-MS spectrum, can be fitted to this model if the probability density function of the first order Markov chain based on the propagation probabilities for a given chain length can be determined theoretically.

Initially, the numerical Monte Carlo method was employed in order to calculate the probability density function of a first order Markov chain. The Monte Carlo method can be used to numerically simulate a single, first order Markov chain with as input the propagation probabilities and the chain length.[7,8] The distribution of comonomers along a polymer chain is modeled by a simple stochastic process generating 0's and 1's according to the following transition matrix:

from/to	0	1
0	P_{11}	$1\text{-}P_{11}$ (=P_{12})
1	$1\text{-}P_{22}$ (=P_{21})	P_{22}

The Monte Carlo simulation starts with a binomial distribution (P_{11} + P_{22} = 1) corresponding to a completely random copolymer as initial estimate and is then fitted to the recorded MALDI-ToF-MS distribution making use of the least sum of squares method. Applying this transition matrix '*n*' time results in a distribution of 0's and 1's, resembling the chemical composition distribution as obtained from the MALDI-ToF-MS spectrum. The best fit of the model is found when the sum of squares has its least value; *i.e.* P_{11} and P_{22} are fitted until the sum of squares converges to a minimum.[2j] Although Monte Carlo computations proved to give accurate and reliable outcomes an analytical solution providing exact outcomes is obviously preferred.

The derivation of an expression in analytical form of a first order Markov chain is not straightforward and requires an extensive use of linear algebra. The Fourier theory was used to compute the probability mass function of a first order Markov chain.[9] The main advantage of using Fourier transforms is their ability to compute analytical formulas, which otherwise are difficult to obtain, in a relatively simple way. Tobita performed a similar derivation, but made use of a probability generating function instead, which results in multiple differentiations against a single integral in our method.[10] The derivation of the analytical solution is given in the Supporting Information.

In summary, the analytical formulae for the probability is written explicitly as function of chain length and P11 and P22:

$$P_a\left(N_1(n)=m\right)=\int_{-\pi}^{\pi} e^{-ikm}\sum\left(P_{11}0 \quad (P_{22}0)e^{ik}\right)\begin{pmatrix} P_{11} & (1-P_{11})e^{ik} \\ (1-P_{22}) & (P_{22})e^{ik}\end{pmatrix}^{n-1}\frac{dk}{2\pi}$$

The P_a0 was chosen as the feed composition or otherwise, in the case of free radical polymerization, if pre-knowledge was available about the starting radical affinity for monomer A or B. Note that $P_{11}0 + P_{22}0 = 1$whereas $P_{11} + P_{22}$ only equals 1 in case of a binomial distribution (as mentioned before).

Free radical copolymerizations. Most reactivity ratios of comonomers reported are for copolymers formed via a free radical polymerization. The *Polymer Handbook* reports a vast number of reactivity ratios for many comonomer pairs.[11] Probably the most reported reactivity ratios are for the free radical copolymerization of styrene/methyl methacrylate (STY/MMA) and therefore this copolymer was included in our study. Next, we explored the copolymer of vinyl acetate and (meth)acrylates since the reactivity of these (meth)acrylates is much higher than of vinyl acetate,[12] enabling us to explore our method's limits. Furthermore, copolymers of various (meth)acrylates and copolymers of (meth)acrylates and styrene obtained via free radical polymerization were studied. The low conversion bulk polymerizations were performed at 60 °C or 70 °C using AIBN as initiator and 1-dodecanethiol as chain transfer agent. The chemical composition matrices of the copolymers obtained with MALDI-ToF-MS were plotted in a 2D surface contour plot. The contour plots in Figure 3 are characteristic for free radical copolymerizations at low conversion for which the polydispersity is relatively high.

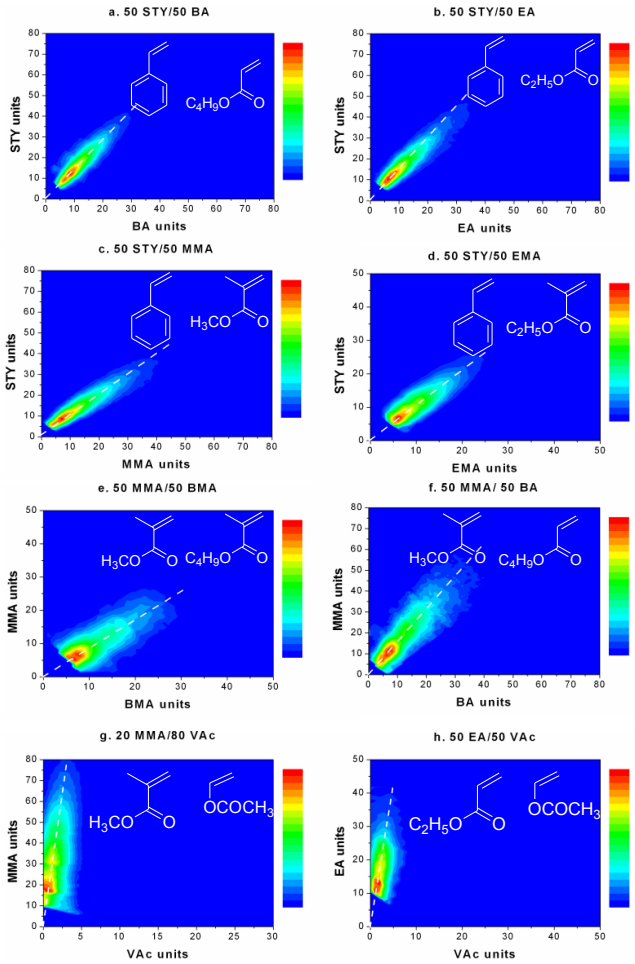

Figure 3. Contour plots of the deconvoluted MALDI-ToF-MS spectra of copolymers prepared via free radical polymerization: a) styrene/butyl acrylate, b) styrene/ethyl acrylate, c) styrene/methyl methacrylate, d) styrene/ethyl methacrylate, e) methyl methacrylate/butyl methacrylate, f) methyl methacrylate/butyl acrylate, g) methyl methacrylate/vinyl acetate, h) ethyl acrylate/vinyl acetate.

The contour plots of the MMA/VAc and EA/VAc comonomer pairs are steep and lie against the ordinate, clearly illustrating the much higher reactivity for MMA and EA compared to VAc. The combination of acrylates, methacrylates and styrene (Figure 3) resulted in more random to alternating copolymers, with a slightly higher reactivity for styrene compared to the acrylates and methacrylates. The fact that the shapes of the contour plots in Figure 3 are symmetric indicates that there is little composition drift between different chain lengths, which was indeed confirmed by analysis of the composition for various chain lengths (Figure 4).

To appoint discrete values for the reactivity ratios, the most abundant chain length has been used, although it was found that in most cases negligible variations in the ratio were observed for less abundant chain lengths. The obtained reactivity ratios for the comonomers in the different copolymers are given in Table 1 together with corresponding literature values reported for classical methods. Comparison of our results with these literature values evidently demonstrates the ability of our method to produce reasonably good point estimates, with the major advantage that our method is simple and relatively fast. The deviations observed can at least partly be explained by variations in the conditions applied during different studies and the different statistical methods applied for evaluating the reactivity ratios.[2]

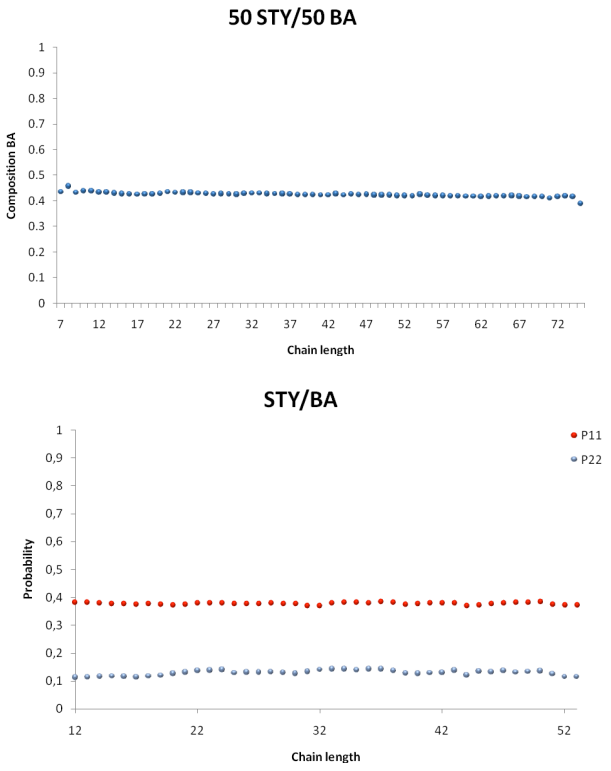

Figure 4. a) Composition versus chain length for the copolymer of styrene and butyl acrylate. b) Homo-probabilities, P_{11} and P_{22} versus chain length for the copolymer of styrene and butyl acrylate.

The copolymers of styrene and (meth)acrylates have a more narrow distribution than the copolymers synthesized from (meth)acrylates only, a correlation also expressed in the Stockmayer equation by the product of reactivity ratios $r_1 \cdot r_2$. The Stockmayer equation gives the relation between chemical composition and chain length.[24]

Table 1. Reactivity ratios of free radical copolymerizations determined by MALDI-ToF-MS using the Monte Carlo method (gray background) compared to literature values.

T (°C)	r_{STY}	r_{BA}	r_{STY}	r_{EA}
50	0.73	0.33[12]	0.79	0.15[13]
70	0.79	0.21	0.85	0.20
80			0.80	0.48[14]
T (°C)	r_{STY}	r_{MMA}	r_{STY}	r_{EMA}
50			0.67	0.26[11]
55			0.62	0.35[15]
60	0.53	0.45[16]		
70			0.65	0.29[11]
70	0.55	0.39	0.68	0.40
T (°C)	r_{MMA}	r_{BMA}	r_{MMA}	r_{BA}
50	0.91	1.09[17]		
60	0.79	1.27[18]	1.77	0.29[20]
70	0.96	1.04[19]		
70	0.81	1.28	1.78	0.66
T (°C)	r_{MMA}	r_{VAc}	r_{EA}	r_{VAc}
30	28.60	0.04[21]		
60	20.0	0.015[22]	4.68	0.03[23]
60	23.0	0.03	6.27	0.07

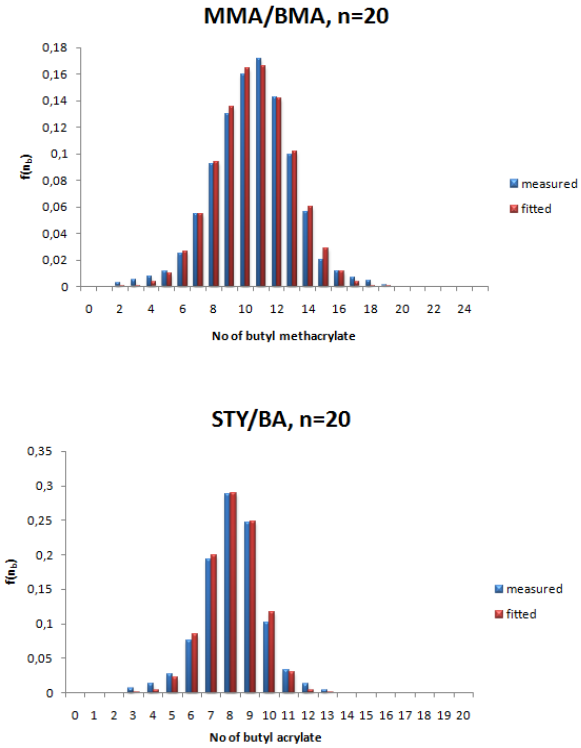

Figure 5. Chemical composition distributions recorded (—) and fitted by using the Monte Carlo method followed by minimizing the LSSQ (—) for the copolymer synthesized with methyl methacrylate/butyl methacrylate and styrene/butyl acrylate.

Several of the recorded chemical composition distributions and the fitted distributions by employing the Monte Carlo

method followed by a LSSQ fit are shown in Figure 5. The chemical composition distributions for other systems are given in the supporting information. As can be seen from Figure 5, the simulated distributions match the measured ones very well.

Ring-opening copolymerizations. Typical examples of copolymers obtained by ring-opening polymerization are copolymers of lactides and lactones[25] or the copolymerization of epoxides and anhydrides.[26] Although aliphatic polyesters have attracted considerable attention as a result of their biocompatibility and (bio-) degradability,[25] the number of reactivity ratios reported in literature for polyesters obtained by ring-opening polymerization is rather limited. A probable reason might be that transesterification, which often occurs as a competing side reaction, dramatically complicates the determination of the reactivity ratios. Hence, to obtain reliable reactivity ratios it is of importance to record MALDI-ToF-MS spectra in the beginning of the reaction at low conversion when transesterification is absent or limited.

The lactide monomer can give insight in the amount of transesterification by formation of isolated -OCH(Me)C(=O)- sequences, which cannot be formed by propagation.[3] The presence of such sequences would obviously reveal the ability of the catalyst to transesterify at the polymerization temperature applied. Another indication of transesterification is the formation of cyclic structures, which are also easily detectable by MALDI-ToF-MS.

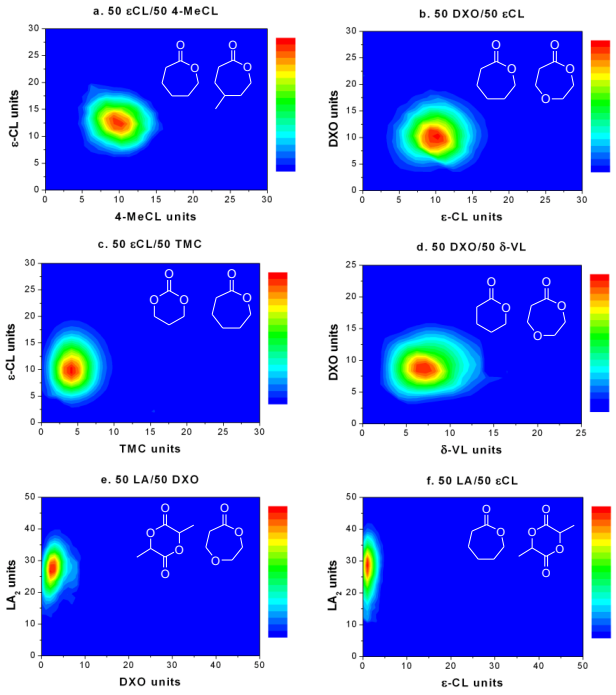

Figure 6. Contour plots of the deconvoluted MALDI-ToF-MS spectra of copolymers prepared via ring-opening polymerization: a) *ε*-caprolactone/4-methyl-*ε*-caprolactone, b) *ε*-caprolactone/1,5-dioxepan-2-one, c) *ε*-caprolactone/trimethylene carbonate, d) *δ*-valerolactone/1,5-dioxepan-2-one, e) lactide/1,5-dioxepan-2-one, f) lactide/*ε*-caprolactone.

For this study we prepared several copolymers. To minimize the influence of the catalyst (*e.g.* steric hindrance) on the reactivity ratios, a single catalyst ($Sn(Oct)_2$) was used for all ring-opening copolymerizations. The comonomer pairs used were *ε*-caprolactone/4-methyl-*ε*-caprolactone, *ε*-caprolactone /1,5-dioxepan-2-one, *ε*-caprolactone/trimethylene carbonate, 1,5-dioxepan-2-one/*δ*-valerolactone, 1,5-dioxepan-2-one /lactide and finally *ε*-caprolactone/lactide. The contour plots obtained from the deconvoluted spectra are given in Figure 6. The point estimates of the reactivity ratios obtained by Monte Carlo simulation method and the values reported in the literature for the comonomer pairs are given in Table 2.

Table 2. Reactivity ratios of ring-opening copolymerizations determined by MALDI-ToF-MS using the Monte Carlo method (gray background) compared to literature values.

T(°C)	r_{CL}	r_{MeCL}	r_{DXO}	r_{CL}	r_{CL}	r_{TMC}
25	1.5	0.6[27]				
60			1.3	0.9[29]		
100					2.41	0.20[32]
100					2.70	0.38[32]
110			1.6	0.6[30]		
110					2.13	0.39
130	1.1	0.8	1.22	0.68		
T(°C)	r_{DXO}	r_{VL}	r_{LA}	r_{DXO}	r_{LA}	r_{CL}
70					17.9	0.58[27]
80					57.1	0.39[33]
90					14.4	0.36[34]
110	2.3	0.5[28]			42.0	0.36[33]
115			10	0.1[31]		
130					34.7	0.24[33]
130	1.6	0.8	7.95	0.10	18.8	0.04
150					44	0.28[35]

As can be seen from Figure 6, the shapes of the plots for the ring-opening copolymerizations are very different compared to the plots of the copolymers synthesized by free radical polymerizations (Figure 3). This is the result of a difference in total chain length distribution originating from the different copolymerization mechanism. In case of free radical polymerization, the total chain length has a Schultz-Flory type of distribution that is analogous to a step growth reaction while the ring-opening polymerization exhibits a Poisson-like distribution in analogy to living polymerizations, *i.e.* a more cigar like plot in case of free radical polymerization and a more oval to circular plot for ring-opening polymerization. A circular shape complicates the determination of the copolymer's microstructure since the distinction between a random and a block copolymer can no longer be made without knowing the synthetic history. The copolyesters synthesized from *ε*-caprolactone/4-methyl-*ε*-caprolactone and *ε*-caprolactone/1,5-dioxepan-2-one are close to a perfectly random system ($r_1 \cdot r_2 = 1$). Vion *et al.*[27] reported r-values of a similar system in which *ε*-caprolactone was reacted with 6-methyl-*ε*-caprolactone and their findings are in good agreement with ours. Trimethylene carbonate has a lower reactivity compared to *ε*-caprolactone resulting in long sequences of subsequent ester functionalities. Albertsson and Eklund found similar values for the reactivity ratios of these comonomers using the same catalyst.[32] The polymerizations of lactide with 1,5-dioxepan-2-one or *ε*-caprolactone show a tendency to make lactide homopolymer. Although, the reactivity ratios for *ε*-caprolactone and lactide reported in the literature are widely scattered, in agreement with our observation most of them show a much higher reactivity for lactide. The fact that within the

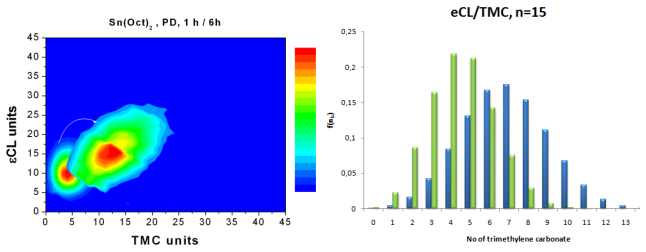

Figure 7. a) Contour plot before (original plot used to calculate r-values) and after transesterification. b) The chemical composition distribution for chain lengths 15 of the copolymer synthesized from ε-caprolactone and trimethylene carbonate before (—) and after transesterification (—).

polymerization time applied in our study no [-OCH(Me)C(=O)-] fragments were formed excludes interference of transesterification reactions.[3] Hiljanen-Vainio *et al.* and Faÿ and coworkers reported a much smaller difference in reactivity ratios between lactide and ε-caprolactone.[36] It is assumed that both deviating values for the reactivity ratios are the result of competing transesterification processes. Figure 7 shows what happens when the reactivity rations are determined at different conversions. During the polymerization transesterification takes place making the contour plots more cigar-shaped due to a broadening of polydispersity. Hence, calculation of reactivity ratios should be determined at low enough conversion when transesterification is not yet significant.

Another interesting ring-opening reaction is the reaction between oxiranes (M_1) and anhydrides (M_2).[26] This system illustrates two special situations that can occur for copolymerizations, *i.e. i)* a perfectly alternating incorporation of both monomers ($P_{11} = 0$, $P_{22} = 0$) affording a polyester or *ii)* a possible subsequent incorporation of one of the two comonomers ($P_{11} > 0$, $P_{22} = 0$) resulting in a poly(ester-*co*-ether). Contour plots of a purely alternating system (cyclohexene oxide – cyclopropane anhydride) and a system in which ether bonds co-exist (cyclohexene oxide – succinic anhydride) are given in Figure 8. The perfectly alternating copolymer corresponds to a $P_{11} = 0$ and $P_{22} = 0$, whilst the poly(ester-*co*-ether) corresponds to a $P_{11} > 0$ for the oxirane and a $P_{22} = 0$ for the anhydride.[26b] As expected, the contour plot of the alternating copolymer is a line at the diagonal. The contour plot for the poly(ester-*co*-ether) is cut off at the diagonal, which is the cross over point from an excess of the first monomer to an excess of the second monomer. From this plot it is clear that a random poly(ester-*co*-ether) is formed.

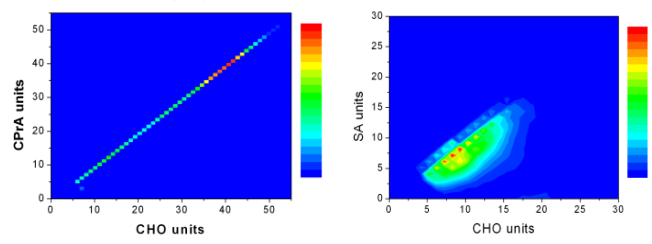

Figure 8. Contour plots, *Left:* Cyclohexene oxide copolymerized with 1,3-cyclopropane dicarboxylic anhydride resulted in a purely alternating polyester. *Right:* Cyclohexene oxide copolymerized with succinic anhydride resulted in a poly(ester-*co*-ether).[26b]

Comparison of recorded, Monte Carlo and analytical chains. Although the outcome of the Monte Carlo calculations were satisfactory, an additional prove of the correctness of the computations performed is in any case advisable and desirable. During the course of this project, we managed to derive the analytical solution for the first-order Markov chain. Hence, a comparison study of the homo-propagation probabilities obtained by Monte Carlo simulations and by fitting the analytical solution has been performed (Table 3). As expected the analytically computed Markov chain gives very similar to identical values for the propagation probabilities as the Monte Carlo method. However, the analytical method is much faster (2-3 orders of magnitude) than the Monte Carlo simulations. With the availability of the analytical solution of the first order Markov chain it is now possible to compute highly accurate and reliable reactivity ratios based on the analysis of a large span of chain lengths in a very short time.

Table 3. Comparison of homo-propagation probabilities determined by Monte Carlo simulations and by the analytical solution by fitting to a first order Markov chain.

Pair		*N*	*Probabilities Monte Carlo*		*Probabilities Analytical*	
ROP			P_{11}	P_{22}	P_{11}	P_{22}
CL	MCL	18	0.51	0.40	0.51	0.40
CL	DXO	20	0.42	0.50	0.41	0.50
CL	TMC	15	0.69	0.28	0.70	0.27
VL	DXO	15	0.47	0.57	0.47	0.57
DXO	LA	20	0.14	0.92	0.07	0.93
CL	LA	30	0.03	0.95	0.1	0.97
Free radical			P_{11}	P_{22}	P_{11}	P_{22}
STY	BA	20	0.41	0.12	0.41	0.12
STY	EA	20	0.45	0.17	0.47	0.15
STY	MMA	19	0.37	0.28	0.37	0.26
STY	EMA	16	0.38	0.32	0.37	0.32
MMA	BMA	15	0.48	0.55	0.48	0.55
MMA	BA	20	0.62	0.42	0.62	0.41
VAc	MMA	18	0.18	0.82	0.19	0.85
VAc	EA	15	0.08	0.86	0.09	0.89

Confidence intervals for r-values. The r-values determined for all the systems have good point estimates as we have shown but without a standard error and confidence intervals, one cannot give a verdict on the accuracy of these values. The error in the reactivity ratios partly depends on the accuracy of the weighted feed ratios, but also on the error in propagation probabilities. The latter is determined by an error in the recording of the actual MALDI-ToF mass spectra but also by an error in fitting of the first order Markov chain. In order to determine confidence intervals, multiple MALDI-ToF mass spectra of the same polymer on the same spot on the sampling target plate were recorded (for the spectrum of 50 mol% ε-caprolactone / 50 mol% 4-methyl-ε-caprolactone) and subjected to the procedure of determining propagation probabilities. In addition, these 15 spectra were used to create an approximating distribution f(x, N(x, n-x)) for each number of monomers within a certain chain length, which was applied as re-sampling source for statistical bootstrapping. The bootstrap method is a re-sampling method capable of determining standard errors of point estimators with an unknown standard error.[37] The individual bootstrap samples for the number of

monomers constituting the chemical composition distribution of chain length 23, were reconstructed to 150 new chemical composition distributions by using the covariance matrix, which is given in the supporting material. In Figure 9, the blue dots represent the probabilities calculated for the 15 recorded chemical composition distributions for chain length 23 and the red dots represent the 150 propagation probabilities determined by bootstrapping. The bootstrap standard errors are given in Table 4 along with the lower and upper confidence intervals. As can be seen, a standard error of less than 5% is obtained.

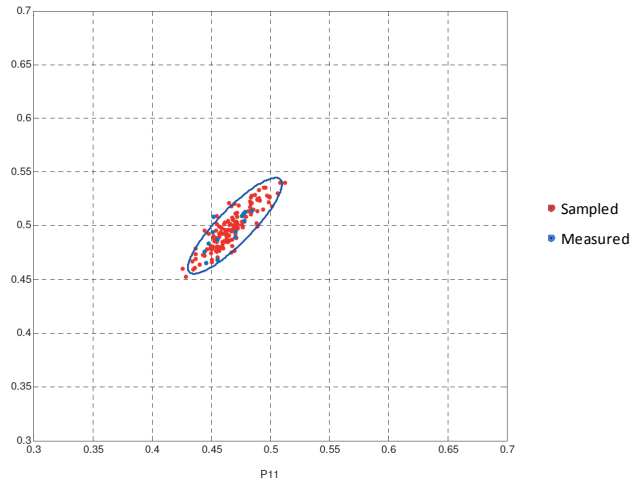

Figure 9. Confidence intervals for the homo propagation probabilities determined from the most abundant chain length of n = 23.

Table 4. Standard error and confidence intervals determined by statistical bootstrapping.

		Standard Error	Confidence Interval	
	Estimate		*Lower*	*Upper*
P_{11}	0.47	0.016	0.434	0.499
P_{22}	0.50	0.018	0.461	0.534

An intrinsic MALDI-ToF-MS problem is differences in ionization efficiency both in mass as in composition. A polymer chain richer in one of the monomers can ionize better or worse than another polymer chain with less of that monomer. The ultimate way to test the applicability of the method is to investigate whether the obtained reactivity ratios can indeed be used to pre-define a copolymer's composition. For this study we used the ε-caprolactone/1,5-dioxepan-2-one system. The reactivity values (r_{DXO} = 1.2, r_{CL} = 0.7) were obtained for a 50 mol%/50 mol% mixture of the two comonomers. Based on these reactivity ratios a feed composition of 30 DXO : 70 eCL should result in a copolymer with a composition of 37 DXO : 63 eCL. The actual composition for the most abundant chain length was indeed found to be 37 mol%, which exactly corresponds with the predicted composition. Based on their similarity, the two monomers used in this example are expected to give a similar ionization efficiency of the corresponding homo- and copolymers. To make sure differences in ionization ability do not affect the outcome, it is advised to test several comonomer ratios.

CONCLUSIONS

The main conclusion that can be drawn from this study is that MALDI-ToF-MS, in combination with the analytical solution of the firs-order Markov chain, proofs to be a fast and accurate tool to determine reactivity ratios. It was expected that chain termination and initiation effects would be profound in these relatively short chains (< 50 monomers) resulting in r-values diverting from literature reported. However, the r-values in any case of both the free radical and ring-opening polymerizations were at least in the same order of magnitude and often even within the joint confidence intervals reported for the r-values. This was not expected as long chains are generally seen as a prerequisite for the Mayo-Lewis equation. However, as mentioned before, the region of chain lengths below 10 monomer units has not been studied and in that region these effects must be visible.

The method as presented in this contribution is certainly not considered as the Holy Grail to determine r-values. It was merely an attempt to investigate the possibility to use a single MALDI-ToF-MS spectrum to retrieve reliable reactivity ratios. Evidently, a more extensive investigation on the method's limitations is required related to different feed compositions and effects of conversion. At the moment we are investigating the applicability of the method for somewhat smaller oligomers produced in the aqueous phase of emulsion copolymerizations. More feed compositions for the same comonomer pair have to be examined as well as multiple systems with similar r-values but different propagation rates to establish a better understanding of the relation between CLD and CCD. Nevertheless, we might conclude that a single MALDI-ToF-MS spectrum can be used to obtain not only a good idea about a polymer's total chain length distribution, microstructure and composition but can also give a surprisingly good estimate of reactivity ratios. In this respect MALDI-ToF-MS is a unique analytical tool. This can result in an enormous time profit and minimization of tedious laboratory work.

ASSOCIATED CONTENT

The derivation of the analytical form of the probability mass function, experimental and simulated MAlDI-ToF-MS, measured and calculated chemical composition distributions, composition versus chain length plots and homo-probability versus chain length plots.

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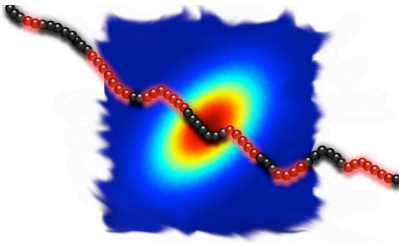

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