An Investigation of the Condensation Kinetics in Poly(Ester-Amide) and Poly(Ester-Sulphide) Preparation

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Summary: Synthetic processes leading to hydrophilic biodegradable polymers for bio-inspired applications were investigated from a kinetic point of view. In accordance with the reported mechanism of ester aminolysis, polycondensation reactions of α-amino-ω-esters, diesters, and diamines resulted markedly dependent on the basicity of the alkoxide leaving-group, being relatively fast for penthachlorophenate monomers. Furthermore, experimental data concerning the homopolycondensation of penthachlorophenyl α-amino-ω-oligo(ethyleneglycol) succinates of different degree of oligomerization clearly showed the existence of concurrent first and second-order processes, which were attributed to the intramolecular cyclization and intermolecular polycondensation reaction, respectively. In contrast to theoretical predictions based on the collision theory, however, minor incidence of the cyclization reaction was shown by the shortest monomers, thus suggesting a significant kinetic effect due to steric hindrance and solvent-reagent interactions. Analysis of the base-catalyzed Michael-type addition of α,ω-oligo(oxyethylene)dithiols to methyl (meth)acrylate allowed for the optimization of the relevant polymerization process involving hydrophilic diacrylates. Interestingly, very low reaction rates were determined for methacrylic components, supposedly because of steric and electronic factors connected to the presence of the α-methyl group. Minor effects on the reaction rate were also induced by solvent polarity and catalyst nature.

Keywords: biodegradable polymers; intramolecular cyclization; kinetics (polym.); Michael addition; polycondensation

Introduction

In the last few years, much attention was devoted to the use of polymeric materials in medicine and biology. Indeed, the peculiar characteristics of macromolecular compounds often allow for the preparation of polymeric materials able to play both passive and active roles in many healing processes.[1] The increasing quest for bioactive polymers boosted researches aimed at the design

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of multifunctional macromolecules suitable for therapeutic applications. Accordingly, several methods of polymer preparation were reconsidered and adapted to current demands.

Polycondensation is the oldest and simplest methodology for the synthesis of macromolecular compounds. Despite widespread application for the preparation of commodity polymers, its many drawbacks often prevent adequate tuning of the final polymer properties. In fact, the polycondensation addition mechanism implies that the molecular weight of the polymerization products depends on both feed composition and extent of functional group conversion.[2] Therefore, type of reagents, solvent, temperature, and catalysts must be chosen properly in order to get polymeric materials with the characteristics of choice. On the other hand, often polycondensation products are biodegradable materials, thus representing a valuable option for the formulation of polymeric devices able to be bioadsorbed once their therapeutic function is over.

Following our continuing interest in the synthesis, characterization, and utilization of bioerodible and biodegradable polymers for biomedical application,[3-6] we prepared a series of functional poly(amide)s, poly(ester-amide)s, and poly(ester-sulphide)s by either polycondensation or Michael-type polyaddition of synthetic and semisynthetic functional monomers.[7-9] In all cases, the kinetic features of the multistep polymerization process were thoroughly investigated. Indeed, kinetic data provided useful hints on the polymerization mechanism, which may be exploited in the design of improved biodegradable polymeric materials.

Experimental

Kinetic Investigation of Poly(tartaramide) Formation

A 0.5-1.7 M solution of methoxyethylamine in anhydrous methanol was placed in a suitable quartz cell, then 2-4 μl of dimethyl *iso*propylidenetartrate were added under stirring. The time evolution of the solution absorbance was monitored at 235 nm. Absorption spectra were recorded at 25 °C by a Jasco Uvidec 510 spectrophotometer thermostated by a circulating water bath.

Kinetic Investigation of Hydrophilic Poly(ester amide) Formation

Triethylamine was quickly added to dichloromethane solutions or dispersions of α-amino-ω-oligo(ethyleneglycol) succinate hydrochlorides by varying the base to monomer ratio (Table 1). The polycondensation kinetics of the resulting α-amino-ω-oligo(ethyleneglycol)succinates were monitored spectrophotometrically. Fast kinetic runs were followed by a stopped-flow instrument equipped with a diode array or a phototube detector, having 5 and 0.1 ms time resolution, respectively. Slow kinetic runs were performed in quartz cells by using a Jasco Uvidec 510 spectrophotometer. All polycondensation experiments were carried out at 25 °C.

Table 1. Experimental conditions and monoexponential kinetic parameters relevant to the investigated aminolysis reactions

Run	Et_3N	Monomer		Amine/Monomer	$k_{obs}\,10^2$	A_∞	χ^2
	(M^{-1})	Type	(M^{-1})	molar ratio	(s^{-1})		
M1	$5.63\cdot10^{-1}$	DMIPT	$3.63\cdot10^{-3}$	155	0.008	0.42	$6.55\cdot10^{-3}$
M2	$7.97\cdot10^{-1}$		$3.63\cdot10^{-3}$	220	0.013	0.43	$1.19\cdot10^{-3}$
M3	1.13		$7.26\cdot10^{-3}$	155	0.022	0.83	$3.61\cdot10^{-3}$
M4	1.67		$4.54\cdot10^{-3}$	369	0.054	0.49	$7.44\cdot10^{-4}$
M5	2.09		$3.63\cdot10^{-3}$	576	0.072	0.41	$1.73\cdot10^{-4}$
T1	$3.50\cdot10^{-3}$	PSP3NH	$2.8\cdot10^{-5}$	125	4.03	0.26	$5.16\cdot10^{-5}$
T2	$3.50\cdot10^{-2}$		$2.8\cdot10^{-4}$	125	4.03	1.57	$1.03\cdot10^{-3}$
T3	$3.50\cdot10^{-3}$		$2.8\cdot10^{-4}$	12.5	4.04	1.58	$8.74\cdot10^{-3}$
T4	$7.00\cdot10^{-4}$		$2.8\cdot10^{-4}$	2.5	4.36	1.35	$3.21\cdot10^{-2}$
T5	$2.00\cdot10^{-2}$		$4.0\cdot10^{-5}$	500	4.74	0.90	$5.08\cdot10^{-3}$
T6	$2.00\cdot10^{-2}$		$4.0\cdot10^{-5}$	500	4.77	0.95	$6.14\cdot10^{-3}$
T7	$1.25\cdot10^{-4}$		$5.0\cdot10^{-5}$	2.5	4.00	0.15	$5.67\cdot10^{-6}$
T8	$1.25\cdot10^{-3}$		$5.0\cdot10^{-4}$	2.5	4.30	0.41	$3.89\cdot10^{-4}$
T9	$1.25\cdot10^{-2}$		$5.0\cdot10^{-3}$	2.5	4.90	0.61	$2.15\cdot10^{-2}$
D1	$1.4\cdot10^{-3}$	PSP2NH	$5.6\cdot10^{-4}$	2.5	0.46	1.76	$9.6\cdot10^{-3}$
D2	$1.4\cdot10^{-2}$		$5.6\cdot10^{-4}$	25.0	0.48	1.82	$1.14\cdot10^{-2}$
D3	$1.4\cdot10^{-2}$		$5.0\cdot10^{-3}$	2.8	0.48	1.45	$1.95\cdot10^{-2}$
D4	$5.4\cdot10^{-2}$		$2.2\cdot10^{-2}$	2.5	0.59	2.30	$1.04\cdot10^{-1}$
D5	$5.4\cdot10^{-1}$		$2.2\cdot10^{-2}$	24.5	0.63	2.40	$2.08\cdot10^{-1}$

Kinetic Investigation of Hydrophilic Poly(ester-sulphide) Formation

A solution of 4.0 mmol of diethyleneglycol dithiol or triethyleneglycol dithiol, 8.0 mmol of tertiary amine (triethylamine or 1,4[2,2,2]diazabicyclooctane), 10 mg of 2,6-di-*t*-butyl-*p*-cresol, and 2.0 mmol of hexadecane as internal standard in 10 ml of solvent (benzene, 1,4-dioxane, or chloroform) was heated at the selected temperature under nitrogen atmosphere. Then, 8.0 mmol

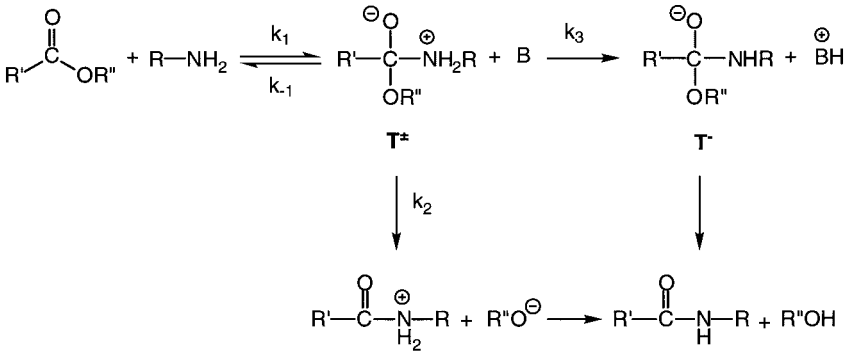
of methyl (meth)acrylate was quickly added to this mixture. At time intervals, 100 ml samples of the reaction solution were withdrawn, diluted with 200 ml of the reaction solvent, and analyzed by gas-liquid chromatography by a Perkin-Elmer Autosystem chromatograph equipped with Alltech DB-1 capillary columns.

Results and Discussion

General Kinetic Characteristics of the Aminolysis Reaction

Poly(amide)s and poly(ester-amide)s were prepared by ester aminolysis polycondensation reactions. Extensive kinetic investigation of ester aminolysis clearly demonstrated the formation of a tetrahedral intermediate zwitterion $T^{\pm}$ upon amine addition to the carboxyl ester group (Scheme 1).[10]

Then, $T^{\pm}$ degrades towards the amide product by either giving rise to a protonated amide and an alkoxide moiety that quickly rearrange to amide and alcohol by proton exchange, or by base catalyzed formation of T^{-}, a very reactive anionic intermediate that eventually decomposes to amide.



Scheme 1. Mechanism of ester aminolysis

Under the assumption of a small and time-constant concentration of $T^{\pm}$ (stationary state hypothesis), the reaction rate is given by:

$$\frac{d[P]}{dt} = \frac{k_1(k_2 + k_3[B])}{k_{-1} + k_2 + k_3[B]}[CO][NH] \quad (1)$$

[P], [NH], [CO] are the concentrations of the amine, amide, and ester, respectively, whereas [B] is the concentration of all basic compounds and k_1, k_{-1}, k_2, and k_3 are the rate constants of the reaction steps. Experimental investigation of ester aminolysis showed the occurrence of two limit kinetic behaviors that correspond to preferential collapse of $T^{\pm}$ into either reactants or products, respectively. In the first case, $k_{-1} \gg k_2 + k_3[B]$, and eq. 1 can be transformed into eq. 2 by splitting the [B] term into the contributions of the reacting amine [NH] and a generic base catalyst [B_{car}], and by grouping the rate constants.

$$\frac{d[P]}{dt} = (k_a + k_b[B_{cat}] + k_{ac}[NH])[CO][NH] \quad (2)$$

In the second case, $k_{-1} \ll k_2 + k_3[B]$, and eq. 1 is transformed into eq. 3, typical of a simple bimolecular process:

$$\frac{d[P]}{dt} = k_1[CO][NH] \quad (3)$$

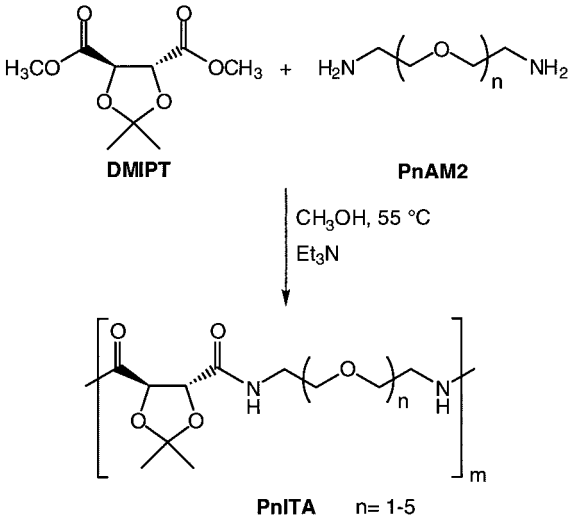
In general, aliphatic esters with poor leaving groups, such as methoxyl and ethoxyl groups follow the rate law shown in eq. 2, whereas eq. 3 kinetics is typical of good leaving groups, such as *p*-nitrophenyl and pentachlorophenyl esters. Indeed, the thermodynamic stability of $T^{\pm}$ is very low in the absence of strong electron withdrawing substituents or aromatic structures and the basic strength of the leaving alkoxide group has a major effect on the kinetic rate.[11] Accordingly, aminolysis of methyl and ethyl esters is usually carried out in strong polar solvents that provide $T^{\pm}$ enthalpic stabilization, in the presence of base catalysts. On the other hand, aminolysis of activated esters is performed out in moderately polar solvents in presence of an equimolar amount of base in order to avoid progressive protonation of the amine reagent.

Synthesis of Poly(tartaramide)s

Recently, aldaric acids have attracted strong interest as monomeric precursors of new poly(amide)s, since these materials could add biocompatibility and biodegradability characteristics to the excellent mechanical and rheological properties of nylons.[12]

Poly(aldaramide)s can be obtained by aminolysis of inexpensive methyl and ethyl aldarates, whose α-hydroxyl functions are thought to increase the reaction rate by providing an anchoring site for the approaching amine as well as favoring $T^{\pm}$ enthalpic stabilization.[13]

We prepared hydrophilic poly(tartaramide)s[7] starting from (R,R)-dimethyl *iso*propylidenetartrate (DMIPT) and a series of oligo(oxyethylene) diamines in methanol at 55 °C (Scheme 2). Triethylamine was used as base catalyst, since its mild characteristics prevented racemization of the tartaric units in the polymer.



Scheme 2. Synthesis of poly(tartaramide)s

It is worth noting that protection of tartrate hydroxyl groups allowed for polymerization reactions in homogeneous phase. Moreover, controlled deprotection may represent a convenient way to modulate the hydrophilic characteristics of the prepared poly(tartaramide)s.[7]

The reaction kinetics of tri(oxyethylene)diamine with DMIPT was monitored by acid-titration of the free amine groups. Fitting the plot of amine concentration *vs* time by the integrated eq. 2 indicated that the polycondensation reaction has a marked autocatalytic character ($k_{ac} \approx 3 \cdot 10^{-4}$). Investigation of the model aminolysis reaction between DMIPT and monofunctional 2-

methoxyethylamine provided further information on the polycondensation kinetics. In all experiments, pseudo-first order conditions were ensured by setting the amine to ester molar ratio in the 150-600 range. Indeed, when [CO] << [NH], in absence of catalysts, eq. 2 becomes:

$$\frac{d[P]}{dt} = k_{app}[CO] \quad (4)$$

where:

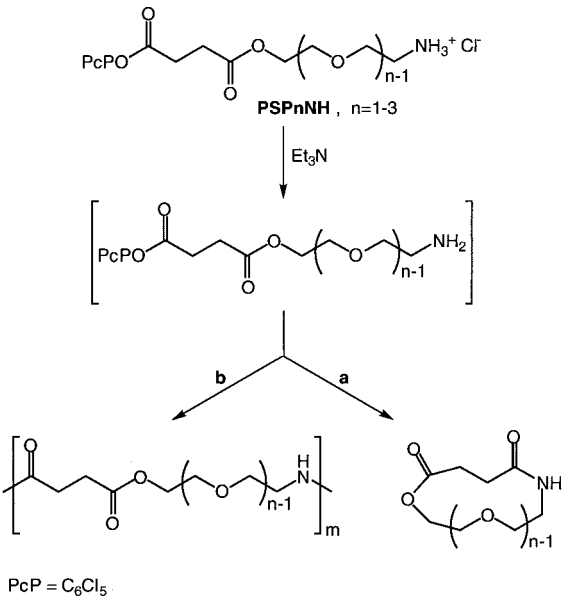
$$\frac{k_{app}}{[NH]} = k_a + k_{ac}[NH] \quad (5)$$

Monoexponential fits of the time variation of the solution absorbance at 235-240 nm, where the tartaric amide group has a significant extinction coefficient, were characterized by very good correlation coefficients. Accordingly, k_{app} values were determined as function of the starting amine concentration (Table 1, runs M1-M5). Following eq.5, a linear fit of $k_{app}/[NH]$ *vs* [NH] gave $k_a = 0.46 \cdot 10^{-4}$ and $k_{ac} = 1.49 \cdot 10^{-4}$, the value for k_{ac} being also in good agreement with the kinetic constant determined for the polymerization process. In accordance with the significant difference between k_a and k_{ac}, DMIPT aminolysis in methanol resulted a rather slow process critically dependent on base catalysis. The kinetic characteristics of the polycondensation reaction may account for the medium-low molecular weights of the recovered poly(tartaramide)s. In fact, side reactions of ester aminolysis such as ketene formation are known to proceed with rate constants comparable with those of the main process in solution, and doubtless they will prevent very large conversions to polymeric material. Significantly, DMIPT-based poly(amides) with improved physical chemical characteristics were recently obtained by carrying out the polycondensation process in bulk at fairly high temperatures.[14]

Synthesis of Hydrophilic Poly(ester-amide)s

Recently, poly(ester-amide)s attracted scientific interest, since they may be designed to couple the excellent mechanical properties of poly(amide)s and the biodegradability of poly(ester)s.[15] Poly(ester-amide)s can be obtained by polycondensation provided that the monomer contains an active ester group.[16-17]

In order to prepare hydrophilic biodegradable poly(ester-amide)s, we synthesized a series of pentachlorophenyl ω-aminooligo(oxyethylene) succinate hydrochlorides containing 1-3 oxyethylene units (PSPnNH), that were then homopolymerized.[8] The polycondensation reactions were carried out either in bulk or in dichloromethane solution, in the presence of excess triethylamine (Scheme 3, path **a**).



Scheme 3. Synthesis of Hydrophilic Poly(esteramide)s

The large extinction coefficient of the pentachlorophenyl group at 250-360 nm allowed for accurate kinetic investigation of the PSPnNH polymerization in solution, which indicated a tendency of the monomers to undergo intramolecular cyclization (Scheme 3, path **b**).

The polymerization of PSP3NH was investigated by a stopped flow UV technique, by monitoring the 270-360 nm absorbance by a diode array instrument. The starting monomer concentration was varied between $2.8 \cdot 10^{-5}$ and $5.0 \cdot 10^{-3}$ M, the upper value being close to maximum solubility of the compound in dichloromethane. Correspondingly, the

triethylamine/monomer molar ratio was changed in the 2.5-500 range (Table 1, runs T1-T8). If the functional group reactivity is independent of the polymerization degree, the polycondensation rate can be described by eq. 3 with [CO] = [NH], and therefore should be second order in monomer concentration. However, in all cases the absorbance time variation showed a first order dependence, as confirmed by the very good correlation coefficients of experimental data monoexponential fits. Accordingly, the first-order kinetic parameter (k_{obs}) resulted almost independent of the concentration of both monomer and triethylamine. The observed minor variations were attributed to slightly different experimental temperatures.

Comparison of polymerization experiments carried out under anhydrous conditions (Run T5) and in air (Run T6) ruled out the occurrence of ester hydrolysis by air moisture. Therefore, monomer cyclization by an intramolecular aminolysis reaction appeared to be the only possible explanation for the observed first order kinetics. In addition, the increase of both χ^2 and k_{obs} with the enhancement of the monomer concentration (Runs T8-T9) indicated a progressive deviation from the first order kinetics, in accordance with the possible occurrence of a secondary polycondensation process. Evaluation of the cyclization and polymerization rate constants were performed by using a kinetic model comprising parallel first order and second order polymerization processes, for which the rate law is represented by:

$$-\frac{d[\mathrm{PSPnNH}]}{dt} = k_{cycl}[\mathrm{PSPnNH}] + k_{pol}[\mathrm{PSPnNH}]^2 \qquad (6)$$

Kinetic data collected in runs P11 and P13 were fitted by the integrated form of eq. 6, providing good estimates of k_{cycl} and k_{pol} (Table 2).

The k_{cycl}/k_{pol} ratio resulted to be 0.095 and 0.112 in runs T8 and T9, respectively. If the monomer molecules have an extended all-trans conformation, simple considerations based on the collision theory[18] afford $k_{cycl}/k_{pol} = 0.1$, in good agreement with experimental values. The same value can be evaluated from the condensation theory of linear system at equilibrium.[19] Under the assumption that the cyclization and condensation reactions have similar ΔH, the theory yields $k_{cycl}/k_{pol} = 0.14$ for a fully extended conformation, whereas 0.2-1.3 values are obtained for more

folded structures. Furthermore, the k_{cycl}/k_{pol} ratio allows for evaluating the monomer concentration at which the polymerization process prevails:

$$\frac{v_{cycl}}{v_{pol}} = \frac{k_{cycl}}{k_{pol}} \cdot \frac{1}{[PSPnNH]} \quad (7)$$

In the case of PSP3NH monomer, both theoretical and experimental k_{cycl}/k_{pol} values indicate that the polymerization process becomes favored (> 90%) at a monomer concentration larger than 1 M. Indeed, only bulk polycondensation allowed for the preparation of high molecular weight poly(ester amide)s from PSP3NH.[8]

Table 2. Kinetic parameters relevant to the condensation of PSPnNH, as evaluated by fitting absorbance data to the integrated form of eq. 6

Run	Monomer		k_{cycl}	k_{pol}	k_{cycl}/k_{pol}	χ^2
	Type	(M)	(s^{-1})	(M^{-1} s^{-1})	(M)	
T8	PSP3NH	$5.0 \cdot 10^{-4}$	$4.1 \cdot 10^{-2}$	0.43	0.095	0.0001
T9		$5.0 \cdot 10^{-3}$	$3.5 \cdot 10^{-2}$	0.31	0.113	0.0030
D1	PSP2NH	$5.6 \cdot 10^{-4}$	$4.5 \cdot 10^{-3}$	0.16	0.028	0.0068
D2		$5.6 \cdot 10^{-4}$	$4.6 \cdot 10^{-3}$	0.47	0.098	0.0028
D3		$5.0 \cdot 10^{-3}$	$4.8 \cdot 10^{-3}$	0.05	0.096	0.0048
D4		$2.2 \cdot 10^{-2}$	$5.2 \cdot 10^{-3}$	0.08	0.065	0.0122
D5		$2.2 \cdot 10^{-2}$	$4.9 \cdot 10^{-3}$	0.12	0.041	0.0247

The low solubility of PSP1NH and PSP2NH hydrochlorides in dichloromethane prevented the use of a stopped-flow apparatus for kinetic investigations. Therefore, suspensions of the hydrochlorides were quickly mixed with suitable amounts of triethylamine, and the resulting clear solutions were transferred in quartz cells for monitoring their absorbance within the time. Monoexponential fits of PSP2NH spectroscopic data afforded rate constants fairly dependent on monomer concentration and one order of magnitude lower than those of PSP3NH (Table 1, runs D1-D5). These results clearly suggested a reduced importance of PSP2NH cyclization. Indeed, fitting of the experimental data by the integrated eq. 8 yielded k_{cycl}/k_{pol} values in the 0.03-0.1 range, indicating that cyclization and polymerization rates should be comparable at a PSP2NH concentration lower than 0.1 M. Significantly, the cyclization process resulted almost completely absent in the polycondensation of PSP1NH, which was found to obey a second order kinetic process with $k_{pol} = 2.7 \cdot 10^{-2}\ M^{-1}s^{-1}$ ($\chi^2 = 0.0031$).

Collision theory considerations indicate a more favorable cyclization process as the molecular length of the monomer decreases, because of the increased local concentration of reacting functional groups. However, experimental results for PSPnNH showed an opposite trend, clearly demonstrating that two functional groups on the same molecule cannot be considered completely independent. In some cases, the number of atoms between the reactive ends and the presence of polar groups may give rise to steric tensions that limit or even inhibit the formation of a ring.[20-22] Indeed, molecular models of the cyclic compounds highlighted the presence of empty space within PSP3NH and PSP2NH rings and steric crowding in PSP1NH ring.

Synthesis of Hydrophilic Poly(ester-sulphide)s

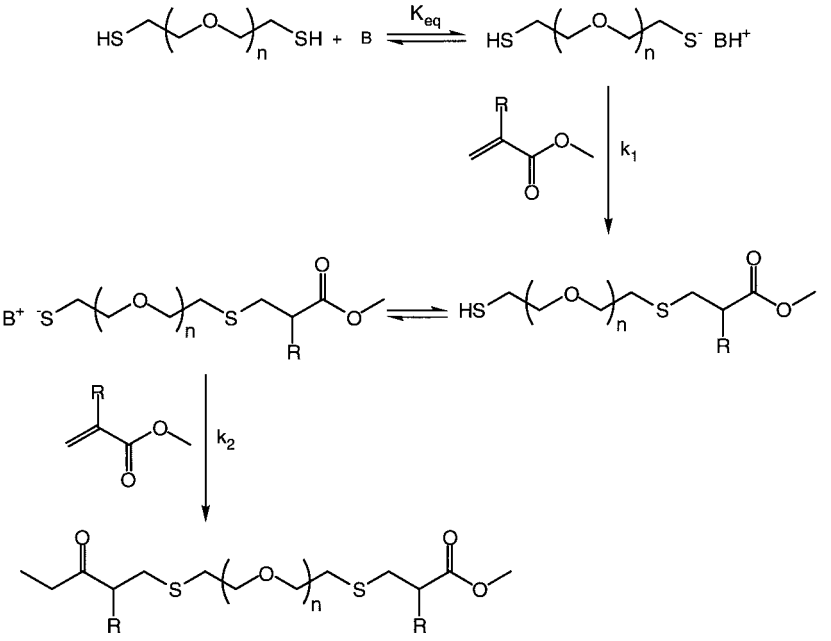
Poly(ester-sulphide)s comprise a class of potentially biodegradable polymers which should display better thermal stability than poly(ester-amide)s of similar structure, due to the presence of sulfur-carbon bonds instead of nitrogen carbon links in the main chain.[23] Therefore, hydrophilic poly(β-thioester)s were prepared by base-catalyzed Michael-type polyaddition of synthetic oligo(oxyethylene) dithiols and diacrylates.[9] Optimal polymerization conditions were assessed by preliminary kinetic investigation of model Michael-type addition reactions. Experiments were performed by reacting the dithiol with 2 equivalents of methyl (meth)acrylate and 2 equivalents of tertiary amine in different solvents; concentrations of reagents and products were monitored within time by GLC analysis. According to a Michael-type addition mechanism (Scheme 4), the thiolate-ammonium ion pair is responsible for the nucleophilic attack at the double bond of the (meth)acrylic ester. In turn, the ion pair is formed by fast proton exchange between a thiol group and the basic catalyst. A rapid proton transfer from the ammonium cation to the anionic adduct affords the addition product while restoring the amine catalyst.[24] By assuming that the low acidity of thiols prevents significant formation of dithiolates, and that the first equilibrium constant is the same for dithiols and monothiols, the kinetics of the model reactions can be described by a system of equations that account for two consecutive addition steps:

$$\frac{d[A]}{dt} = k_1K_{eq}[B][A][DT] + k_2K_{eq}[B][A][MT]$$

$$-\frac{d[DT]}{dt} = k_1K_{eq}[B][A][DT] \qquad (8)$$

$$-\frac{d[MT]}{dt} = k_1K_{eq}[B][A][DT] + k_2K_{eq}[B][A][MT]$$

where [A], [B], [DT], and [MT] are the concentration of (meth)acrylic monoester, tertiary amine, dithiol, and monothiol, respectively. k_1, and k_2 are the kinetic constants of each addition step, whereas K_{eq} is the equilibrium constant of thiol group deprotonation.



Scheme 4. Base-catalyzed Michael-type addition of oligo(ethylene glycol) dithiols to methyl (meth)acrylate

Integration of the differential equation system (8) is possible when the starting concentrations of thiol and (meth)acrylate groups are equal, that is [A] = 2[DT]. Fitting of experimental concentration data allowed for evaluating k_1K_{eq}, k_2K_{eq}, and k_1/k_2 under different conditions of temperature, solvent, catalyst, and reagents (Table 3).

The reactivity of di(ethyleneglycol) dithiol (EG2DT) with methyl acrylate resulted markedly influenced by the nature of solvent and tertiary base catalyst, although the k_1/k_2 ratio showed only a small dependence on these parameters (Table 3, runs MA1-8). When triethylamine (TEA) was used, k_1K_{eq} and k_2K_{eq} resulted slightly lower in benzene than in dioxane. In both solvents, their values were almost one order of magnitude lower than in chloroform, in agreement with the stabilization of ionic species by polar solvents. Both in benzene and in dioxane, the catalytic activity of 1,4[2,2,2]diazabicyclooctane (DABCO) resulted much larger than that of TEA, as expected from the peculiar structure of DABCO that reduces the steric hindrance of nitrogen atoms. However, the activity of DABCO in chloroform was only one-third of that of TEA, possibly because of acid-base interactions between solvent and catalyst that depress the nitrogen basicity. Interestingly, no significant dependence of reaction rate parameters on the temperature was detected, in accordance with previous reports that the total activation energy of the reaction of butanethiol and maleic anhydride is almost zero.[24]

Table 3. Kinetic parameters relevant to Michael-type addition reaction of di(ethyleneglycol) dithiol to methyl (meth)acrylate, as evaluated by fitting experimental data to the integrated form of eq. 8

Run	Catalyst[a)]	Solvent	Temp. (° C)	$k_1 \cdot 10^5$ (M^{-2} s^{-1})	$k_2 \cdot 10^5$ (M^{-2} s^{-1})	k_1/k_2
MA1	TEA	Benzene	30	9 ± 1.0	4.5 ± 0.6	1.99 ± 0.06
MA2	TEA	Chloroform	30	82 ± 3.0	49 ± 2.0	1.68 ± 0.01
MA3	TEA	Dioxane	30	10.0 ± 0.5	5.3 ± 0.4	1.90 ± 0.04
MA4	TEA	Benzene	60	9 ± 3.0	2.1 ± 0.9	4.3 ± 0.4
MA5	TEA	Dioxane	60	12.4 ± 0.7	4.3 ± 0.3	2.88 ± 0.06
MA6	DABCO	Benzene	30	24 ± 3.0	12 ± 1.0	2.04 ± 0.06
MA7	DABCO	Chloroform	30	27 ± 3.0	12 ± 3.0	2.2 ± 0.3
MA8	DABCO	Dioxane	30	45 ± 3.0	18 ± 2.0	2.6 ± 0.2

[a)] TEA = triethylamine, DABCO = 1,4[2,2,2]diazabicyclooctane.

The reaction rate was strongly lowered when methyl acrylate was replaced by methyl methacrylate. This behavior can be attributed to a different stabilization of transition states. Indeed, in the reaction with methyl acrylate, one of the resonant structure has a charged secondary carbon atom, while in methyl methacrylate that atom is tertiary, and therefore less stable. Preliminary results not reported in Table 3, showed a significant decrease of the reaction rate on increasing the length of the oxyethylene segment.

Conclusions

Kinetic investigation of ester aminolysis by two different polycondensation processes provided useful information on the underlying reaction mechanisms. In accordance with the major role played by the nature of the alkoxide leaving group, aminolysis of dimethyl *iso*propylidenetartrate resulted a slow reaction strongly dependent on base catalysis. On the other hand, homocondensation of α-amino-ω-oligo(ethyleneglycol)succinates resulted to be a fast process involving only the ester and amine functions. The latter reaction, however, displayed a complex kinetic behavior due to competition of first-order intramolecular cyclization and second-order intermolecular condensation. Interestingly, only the kinetic data relevant to the monomer having the longest chain resulted in substantial agreement with the behavior predicted by the collision theory. This result clearly demonstrated that other factors, such as steric hindrance and solvent interactions, significantly contribute in determining the pathway of the condensation reaction.
Kinetic investigation of Michael-type base-catalyzed addition of dithiols to methyl acrylate showed a marked dependence of the reaction rate on the nature of both solvent and base catalyst, highlighting the occurrence of polarity as well as complexation effects. On the contrary, the reaction temperature had no effect on the kinetic parameters. It is worth noting that the collected kinetic information allowed for a significant improvement of the reaction yield.

Acknowledgements

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