Journal of Macromolecular Science, Part A
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597274

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To cite this Article Kricheldorf, Hans R. , Lomadze, Nino and Schwarz, Gert(2009) 'Cyclic Poly(salicylic acid) by Zwitterionic Polymerization of Salicylic Acid O-Carboxyanhydride', Journal of Macromolecular Science, Part A, 46: 4, 346 — 352
To link to this Article: DOI: 10.1080/10601320902724743
URL: http://dx.doi.org/10.1080/10601320902724743

Journal of Macromolecular Science®, Part A: Pure and Applied Chemistry (2009) **46**, 346–352

ISSN: 1060-1325 print / 1520-5738 online
DOI: 10.1080/10601320902724743

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Cyclic Poly(salicylic acid) by Zwitterionic Polymerization of Salicylic Acid O-Carboxyanhydride

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Received and Accepted October 2008

The ring-opening polymerization of salicylic acid O-carboxyanhydride (SOCA) was studied under various reaction conditions and analyzed by means of MALDI-TOF mass spectrometry with regard to the formation of cyclic poly(salicylide)s. First, two thermal polymerizations were performed in the melt at 170°C and cyclic oligosalicylates were found possibly resulting from "back-biting". Second, polymerizations catalyzed by a highly nucleophilic carbene in dioxane at 20, 50 or 80°C. In these cases, the formation of the detected cyclic polysalicylides was most likely formed by end-to-end cyclization of zwitterionic chains. Third, imidazole-initiated polymerizations were performed in bulk at 140°C. In agreement with a nucleophilic initiation linear chains having imidazolide endgroups were detected in addition to the mass peaks of cyclic polysalicylates.

Keywords: salicylic acid; ring-opening polymerization; cyclization

1 Introduction

Three synthetic methods were reported yielding cyclic oligo-salicylides together with low molar mass linear polymers (Scheme 1): first, polycondensations of salicylic acid with phosphorous oxychloride (1–6); second, polycondensations of O-acetyl salicylic acid (Aspirin^R) (7–9); and third, polycondensation of O-trimethylsiloxy-benzoyl chloride (7). Those papers mainly concentrated on purification and characterization of the cyclic oligoesters which were isolated up to cyclic hexamer. Polycondensations of salicylic acid by means of thionyl chloride were reported by Patel et al. (9, 10). Those authors believed that the acid chloride was the true monomer, but this monomer was not characterized. Hence, it is not clear, if the cyclic sulfite was also formed (Sch. 2) or not. Furthermore, those authors did not discuss the formation of cyclic oligo- and polyesters. When the sodium salt of salicylic acid was treated with phosgene under mild conditions, a cyclic O-carboxyanhydride (SOCA in Scheme 2) was obtained as a crystalline monomer (11, 12). Its polymerizations were studied under various reaction conditions by Saegusa et al. (12). However, formation of cyclic oligo- or polyesters was again not studied and discussed.

More recently, it was found that several classes of cyclic monomers such as α-amino acid N-carboxy anhydrides (13) (NCAs, **1** and **2** in Scheme 3), dithiolane-2,4-dione (**3**) (14), α-hydroxyisobutyric anhydrosulfite (**4**) (15) yield cyclic polymers upon heating above 100°C. Cyclic polypeptides (16, 17) or poly(thio ester)s (14, 15) were also obtained, when these monomers were treated with non-protic catalyst such as pyridine DMSO or N-methyl pyrrolidone. A Zwitterionic polymerization mechanism was postulated as the most likely explanation for the formation of cyclic polymers as exemplarily illustrated in Scheme 4 for the thermal polymerization of SOCA (discussed below). A Zwitterionic mechanism was also postulated for the formation of cyclic polylactides, when D,L-lactide was polymerized with a nucleophilic carbene as catalyst (18). However, a Zwitterionic mechanism is not absolutely necessary for syntheses of cyclic polymers as demonstrated by the formation of cyclic polypeptides by imidazole-catalyzed polymerizations of NCAs (19). In this context, it was the purpose of the present work to reinvestigate polymerizations of SOCA under various reaction conditions to find out, if significant fractions of cyclic oligomers and polysalicylides are formed.

2 Experimental

2.1 Materials

Salicylic acid and diphosgene were purchased from Fluka AG (Buchs, Switzerland) and used as received. 1,2,4-Trip

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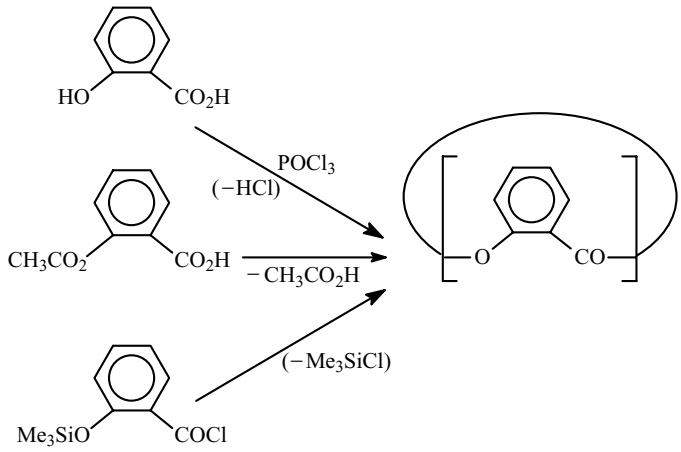
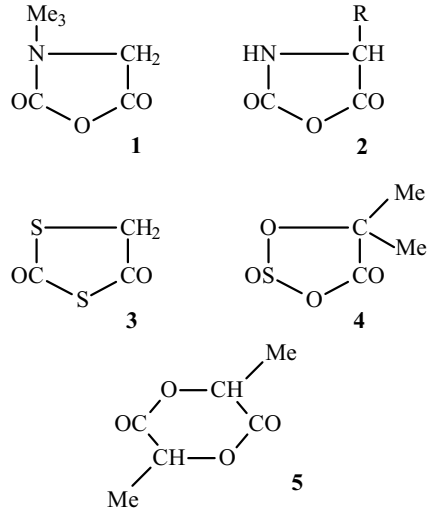
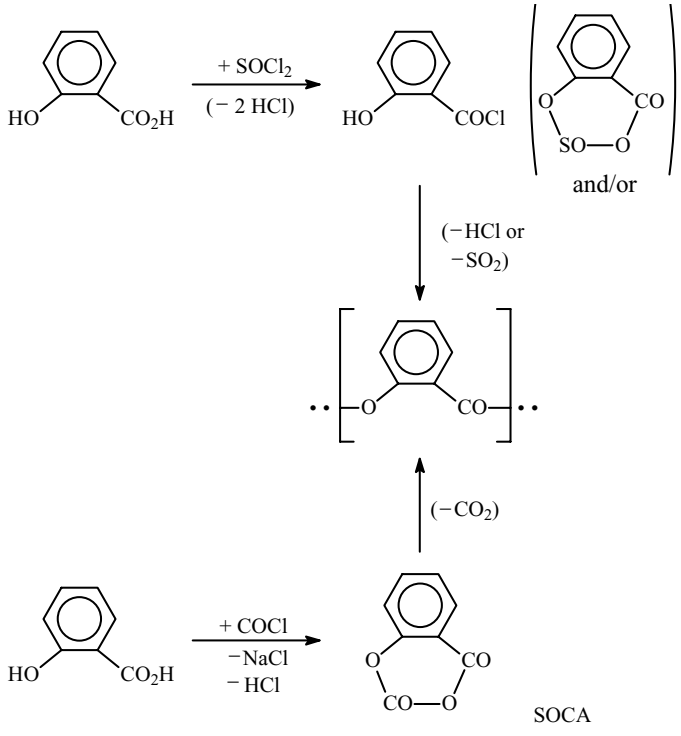


Sch. 1. Syntheses of cyclic oligo salicylides.

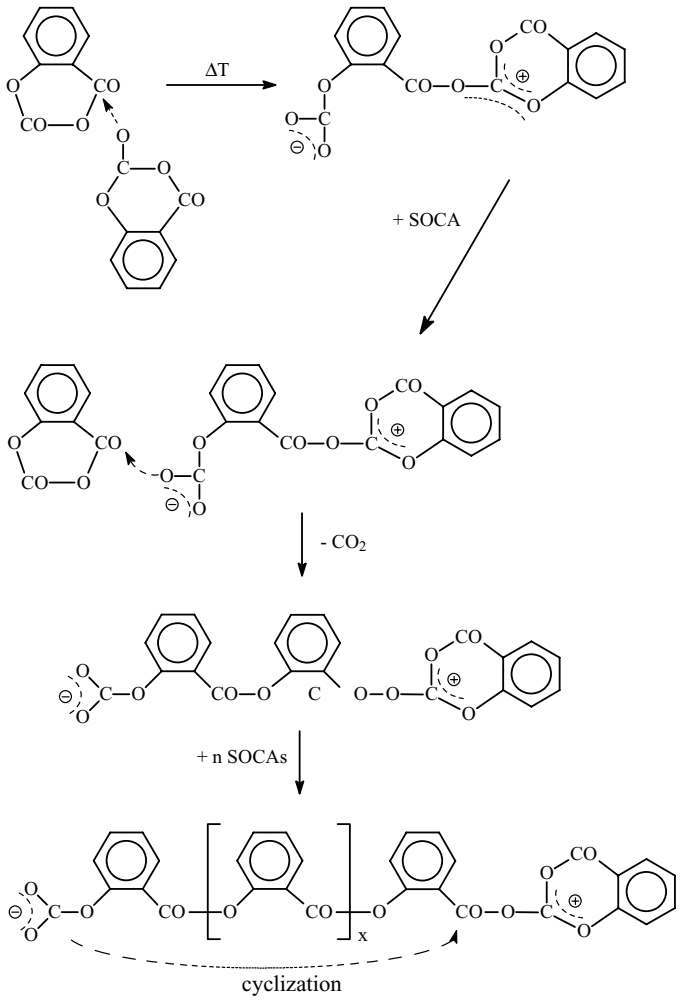


Sch. 3. Monomers yielding cyclic oligomers and polymers in polymerizations catalyzed by aprotic nucleophiles.

henyl-4,5-dihydro-^{1}H-1,2,4-triazol-5-ylidene (TDTC) was purchased from Acros Organics (Geel, Belgium) and used as received. Imidazole (Acros Organics) was azeotropically dried with toluene and stored in a dessicator over P_4O_{10}. SOCA was prepared from the bissodium salt of salicylic acid and diphosgene according to the procedure of Davies (11), but toluene was replaced by dry dioxane as reaction medium.



Sch. 2. Polymerizations of salicylic acid by means of thionyl chloride or phosgene.



Sch. 4. Mechanism of the thermal Zwitterionic polymerization of SOCA.

Table 1. Polymerizations salicylic acid O-carboxyanhydride (SOCA)

Expt. no.	*Catalyst*	*Solvent*	*Temp. (°C)*	*Time (h)*	*Yield (%)*	η^a_{inh} *(dL(g))*
1	—	—	170	30	86	0.05
2	—	—	170	20	90	0.05
3	Imidazole (M/cat = 20:1)	—	140	8	71	0.04
4	Imidazole (M/cat = 40:1)	—	140	8	77	0.06
5	"Triazolyl carbene"	1,4-Dioxane	20	24	96	0.09
6	"Triazolyl carbene"	1,4-Dioxane	50	24	95	0.07
7	"Triazolyl carbene"	1,4-Dioxane	80	8	92	0.06

[a]Measured at 20°C with c = 2 g/L in CH_2Cl_2.

2.2 Polymerizations

2.2.1. *Thermal polymerization (Nos. 1 + 2, Table 1)*

SOCA (10 mmol) was weighed under argon into a 10 mL sample tube equipped with silanized glass walls. The sample tube was closed with a septum allowing for the escape of CO_2, but preventing access of air and placed into an oil bath preheated to 170°C. After 24 h the crude reaction product was characterized by MALDI-TOF mass spectrometry and ^{13}C NMR spectroscopy.

2.2.2. *Initiation with imidazole (Nos. 3 + 4, Table 1)*

SOCA (10 mmol) and imidazole (o.5 or 0.25 mmol) were weighed under argon into a 10 mL glass flask having silanized glass walls. The reaction vessel was closed with a septum and immersed into an oil bath preheated to 140°C. After 8 h, the cold reaction product was dissolved in CH_2Cl_2 and precipitated into dry diethyl ether. The precipitated product was isolated by filtration and dried at 20°C in vacuo.

2.2.3. *Initiation with TDTC (Nos. 5–7, Table 1)*

SOCA (10 mmol), TDTC (0.5 mmol) and dioxane (8 g) were weighed into a 25 mL Erlenmeyer flask having silanized glass walls. After 24 h at 20°C (or 24 h at 50°C or 8 h at 80°C) the reaction mixture was poured into dry diethyl ether and isolated by filtration.

2.3 Measurements

The inherent viscosities were measured in a mixture of CH_2Cl_2 and trifluoroacetic acid (volume ratio 4:1) using an automated Ubbelohde viscometer thermostated at 20°C. The 400 MHz ^1H-NMR spectra were recorded on a Bruker "Avance 400" FT-NMR spectrometer in 5 mm o.d. sample tubes. DMSO-d_6 containing TMS served as solvent. The MALDI-TOF (MT) mass spectra were measured with a Bruker Biflex III mass spectrometer equipped with a nitrogen laser (λ 0 337 nm). The irradiation targets were prepared from $CHCl_3$ solutions containing 10 vol% of TFA with dithranol as matrix and K-trifluoroacetate as dopant. The calculated masses of the potential reaction products were listed in Table 2.

3 Results and Discussion

The first two polymerizations of SOCA were conducted by heating to 170°C in bulk without addition of a catalyst (Nos. 1 + 2, Table 1). These conditions were selected for two reasons. Firstly, both melting temperature and thermostability of SOCA are relatively high compared to the properties of the aliphatic anhydrides 1-4 in Scheme 3. Secondly, these reaction conditions were previously selected by Saegusa et al. (12). The variation of the reaction time had little influence on yield, solution viscosity and MALDI-TOF mass spectrum. These mass spectra showed that cyclic polysalicylides were the prevailing reaction products at masses < 2 000 Da (Figure 1), whereas at higher masses linear chains terminated by water or salicylic acid dominated. This result allows for the following conclusions. Firstly, thermal polymerizations of SOCA may yield cyclic oligomers and polymers quite analogous to thermal polymerizations of other cyclic anhydrides (Nos. 1-4, Scheme 3). Secondly, the detection of cycles up to degrees of polymerizations (DPs) around 30 suggests that a special mechanism such as that formulated in Scheme 4 is responsible

Table 2. Masses calculated for cyclic and linear polysalicylates including $K^{\oplus}$-doping

DP	*Cycles + K*	***La**-chains + K*	***Lb**-chains + K*
5	639.5	657.5	707.5
6	759.7	777.7	827.7
7	879.8	897.8	947.8
8	999.9	1018.0	1068.0
9	1120.1	1138.1	1188.1
10	1240.2	1258.1	1308.2
11	1360.3	1378.3	1428.3
12	1480.4	1498.4	1548.4
13	1600.5	1618.5	1668.5
14	1720.6	1738.6	1788.6
15	1840.7	1856.7	1908.7
16	1960.8	1978.8	2028.8
17	2081.0	2099.0	2149.0
18	2201.0	2019.0	2269.0
19	2321.1	2339.1	2389.1
20	2441.3	2459.3	2509.3

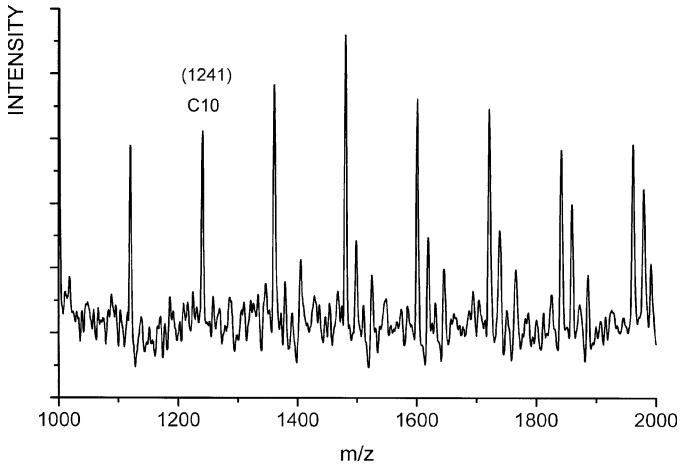
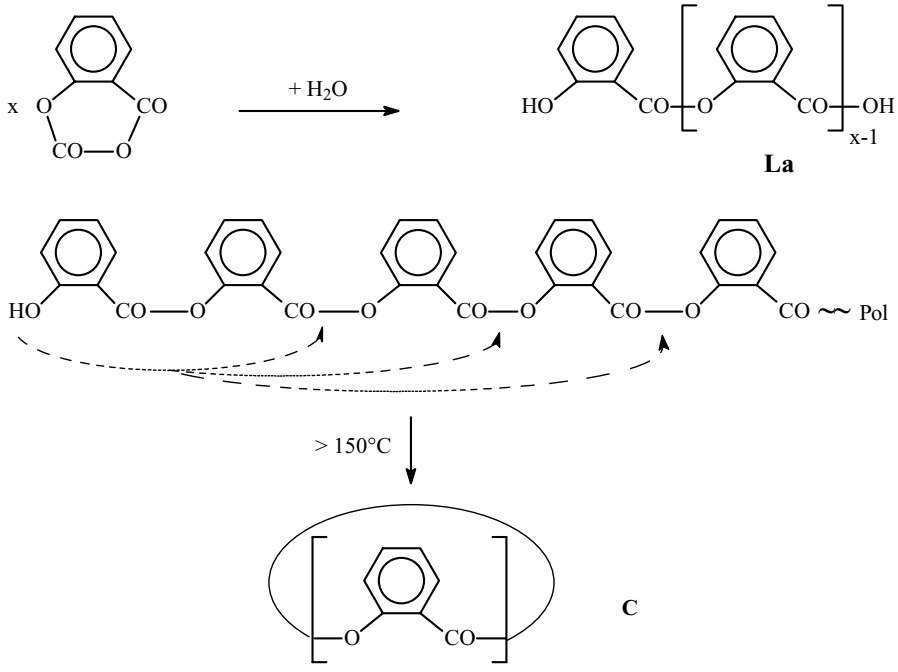


Fig. 1. MALDI-TOF mass spectrum of the virgin reaction product obtained by thermal polymerization of SOCA at 170°C in bulk (No. 1, Table 1).

for their formation. In previous studies, (performed before MT mass spectrometry was available) including high temperatures and equilibration reactions only cyclic oligomers up to DP = 6 were detected. Hence, equilibration via back-biting (Scheme 5) should mainly yield the particularly stable cyclic dimmers, tetramers and hexamers. Thirdly, the linear chains (**La** in Scheme 5) may, in principle, result from initiation by a moisture or by termination of active chain ends by moisture. However, quite analogous to previous investigations of other cyclic anhydrides all necessary precautions were applied to avoid initiation by water. Therefore, the most likely explanation is the contamination of SOCA with a small amount (e.g. $\leq 1\%$) of free salicyclic acid which is difficult to detect and difficult to remove.

For two polymerizations conducted in bulk immediately above the melting point of SOCA imidazole was used as initiator (Nos. 3 + 4, Table 1). Again, low solution viscosities were found regardless of the monomer-initiator ratio and the MT mass spectrum (Figure 2) indicated the formation of cyclic polysalicylides. Particularly interesting was the finding that in addition to the OH-terminated **La** chains (Scheme 5) peaks of imidazole-terminated **Lb** chains were present (Scheme 6). The presence of these chains prove that imidazole indeed initiated the chain-growth by a nucleophilic attack onto the most reactive CO groups of the SOCA ring. The formation of cyclic is then most likely the result of an end-to-end cyclization (Scheme 6). It is well known from several decades that imidazolide groups are far more electrophilic than normal amide groups and react easily with amino groups at 20°C and with alcohols below 100°C. In agreement with this high reactivity imidazole-initiated polymerizatiaons of NCAs (**1**, Scheme 3) yielded cyclic polypeptides and imidazole-initiated polymerizations of L-lactide (**5**, Scheme 3) yielded cyclic polylactides (20). Yet, due to the higher nucleophilicity of NH_2- or HO-CH endgroups (relative to the phenol groups of the **Lb** chains) cyclization was so rapid that imidazole-terminated chains were not detectable.

Finally, three polymerizations of SOCA were performed in dioxane with TDTC at three different temperatures. However, the high yields and the low solution viscosities were independent on the temperature. The MT mass



Sch. 5. Formation of cyclic oligosalicylates by „back-biting" at high temperatures.

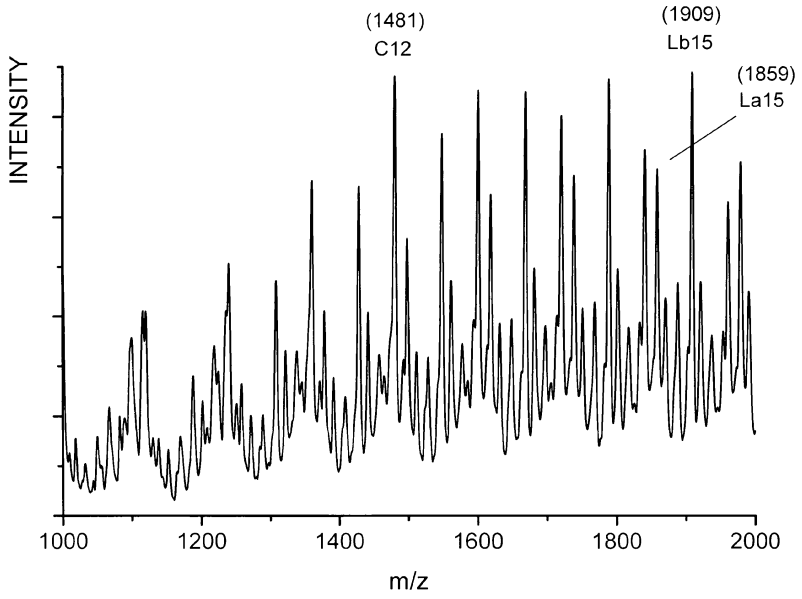
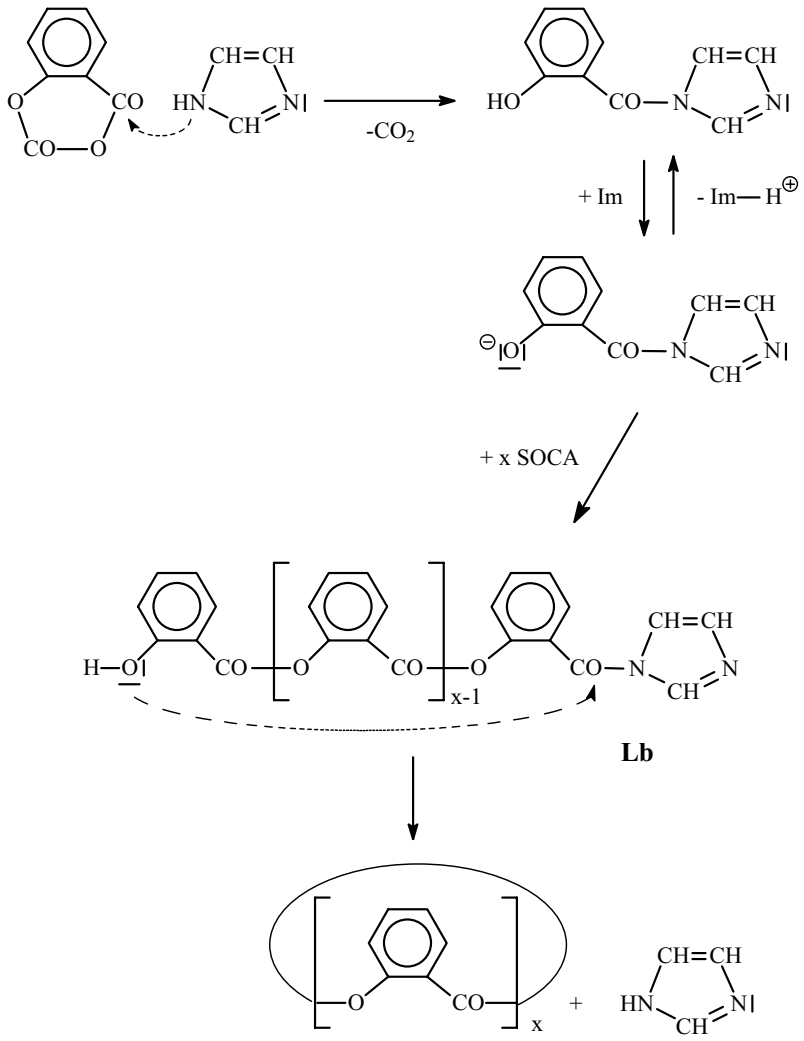


Fig. 2. MALDI-TOF mass spectrum of the virgin reaction product obtained by imidazole-initiated polymerization of SOCA at 140°C (No. 3, Table 1).



Sch. 6. Imidazole-initiated polymerization of SOCA.

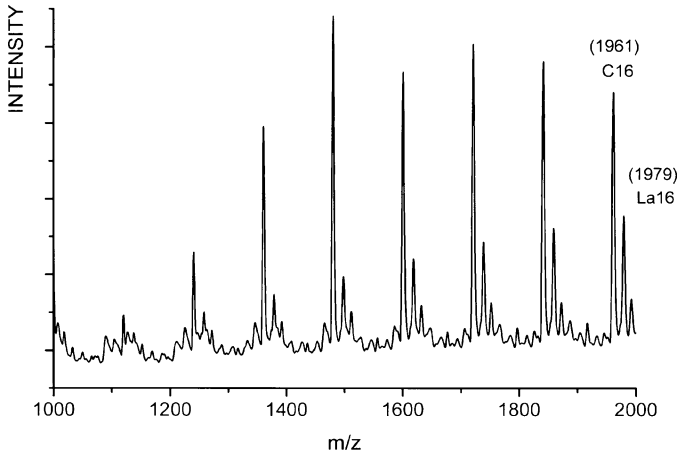
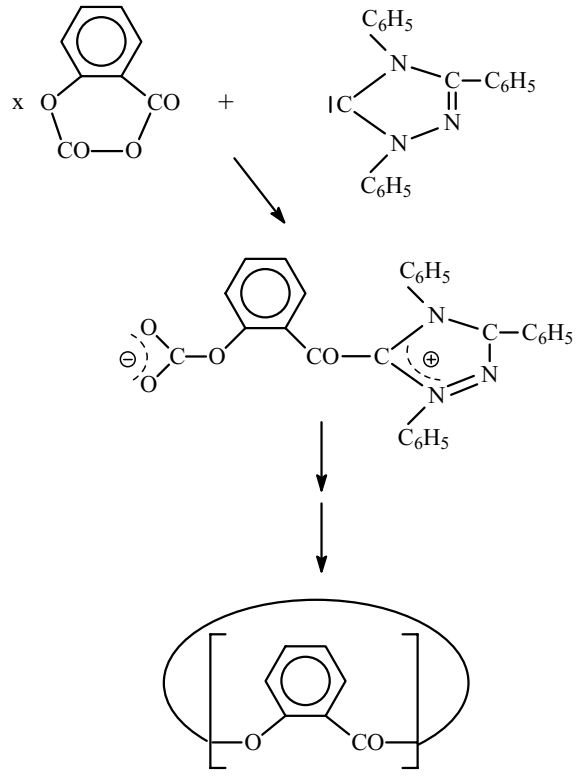


Fig. 3. MALDI-TOF mass spectrum of the reaction product obtained by TDTC-catalyzed polymerization of SOCA in dioxane at 50°C (No. 6, Table 1).

spectra of all three samples were nearly identical and proved the formation of cycles (Figure 3) which were the prevailing products up to masses around 3,000 Da. Yet, weaker peaks were still detectable up to masses around 4,000 Da. The formation of such large cycles at temperatures as low as 20°C is best explained by a zwitterionic polymerization involving end-to-end cyclization (Scheme 7) and certainly not by "back-biting" degradation of linear chains. In the case of



Sch. 7. Formation of cyclic salicylides by carbene-initiated Zwitterionic polymerization of SOCA.

"TDTC"-catalyzed polymerizations of D,L-lactide[18] high yields of cyclic oligomers and polymers were also obtained at room temperature. Furthermore, the MT mass spectra proved the existence of rapid equilibration reactions. Equilibration reactions require a successful attack of the TDTC carbene onto the polylactide chains (forming zwitterionic intermediates), but in this case it does not prove that the cycles were formed by "back-biting" reactions.

Finally, it should be mentioned that low solution viscosities were found for all reaction products indicating low molar masses with number average molecular weights (M_ns) in the range of 1000-2500 Da. Similarly, low M_ns were also reported for almost all reaction products by Saegusa et al. (12) and in our previous publication dealing with the polycondensation of acetyl salicylic acid (7). Such low M_ns are in perfect agreement with a high cyclization tendency of poly(salicylide)s.

4 Conclusions

The results of this work demonstrate that SOCA reacts analogously to the other cyclic anhydrides studied before (formulas 1-4, Scheme 3). Thermal polymerizations and imidazole or TDTC (carbene)-catalyzed polymerizations all yielded significant amounts of cyclic polysalicylides with DPs for above those detected in previous studies (1–12). For the results of thermal and TDTC (carbene)-catalyzed polymerizations a zwitterionic mechanism is the most likely explanation. Particularly interesting is the detection of linear chains having imidazolide endgroups (**Lb**), because they support the mechanism outlined in Scheme 6, and thus, also confirm analogous mechanisms formulated for imidazole-catalyzed polymerizations of NCAs and L-lactide. In summary, the polymerizations of SOCA studied in this work complete the picture of structure-reactivity relationships elaborated for the monomers **1-4** in Scheme 3. An optimization of yields or molecular weights of the cyclic polysalicylides was not intended in this study, because no further characterization or application was intended.

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