"Condensative Chain Polymerization"—A Way Towards "Living" Polycondensation?

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A significant portion of the commercial polymers is prepared by polycondensation techniques. In particular the synthesis of polyesters and polyamides is based on melt condensation which has been a well established technical process since the 1930s.[1] However, even today the problem of how to reach the high conversions which are required for high molar mass polycondensates is not fully solved. In contrast to chain-growth processes, a significant increase in molar mass can be achieved only at conversions above 90% in the step-growth process of the polycondensation reaction. The theoretical degree of polycondensation at 90% conversion is only 10, at 99% it reaches 100. Growth does not occur specifically at the chain end but instead occurs as a result of reactions between monomers, dimers, and already formed oligomers. In general equilibrium reactions are involved in polycondensation. Thus, the products of polycondensation reactions usually have a molar mass distribution $\bar{M}_w/\bar{M}_n$ of 2. Molar mass and polydispersity is controlled by statistics and the degree of conversion; the end groups of the polymer can be controlled to some extent by the choice of monomers and the reaction stoichiometry. Chain-growth polymerization processes allow the formation of high molar mass products even at low monomer conversion, which means that high molar mass polymer chains and a significant amount of monomer can be present at the same time. The molar mass is controlled by the monomer/initiator ratio, and functional end groups can be introduced through the initiator or by a terminating agent.

There are numerous methods for controlled polymerization—ionic and radical—available which allow the formation of polymers with a molar mass distribution $\bar{M}_w/\bar{M}_n$ of less than 1.1. Attempts are being made in academic circles to synthesize polycondensates in a controlled manner, that is, with control over the structure and molar mass. Examples of this work are the perfectly branched dendrimer species[2] which have been studied intensively over the last 10 years, and also the synthesis of well-defined oligomers. However, the transfer of these repetitive synthetic approaches into an industrial process is problematic because of the high costs and scale-up problems.

In recent years, however, a high level of control over molar mass, polydispersity, end groups, and architecture has also become a high priority for commercial polymers. Thus, it should be possible to generate new polymer property profiles from known monomers and established techniques. This trend can be seen in the field of chain-growth polymerization with the rapid development of the metallocene polymerization of olefins[3] and controlled radical polymerization.[4]

Yokozawa and Suzuki[5] of the Kanagawa University have presented a new technique which should allow a level of control over molar mass and polydispersity in polycondensation reactions that up to now was only possible in controlled chain-growth processes. When analyzed in detail the new technique actually represents a conversion of the polycondensation reaction into a chain-growth reaction; this is done by promoting growth only at the "reactive" end of the polymer chains through the use of suitable monomers, initiators, and special reaction conditions. The authors call this process "condensative chain polymerization" in accord with the more specified classification of polymerization reactions by the IUPAC commission in 1994.[6] This term was given to chain-growth reactions which involve the typical initiating and growth steps but also the elimination of low molar mass species.

The first investigations were reported by Lenz[7] in the 1960s. Later, Robello et al.[8] used the "self condensation" of 4-halobenzenesulfinate for the preparation of poly(p-phenylene sulfone); for this reaction they discussed a chain-growth mechanism which had some of the features of a living process. The important features of the reaction were the formation of high molar mass products even at low monomer conversion and the absence of oligomers in the final product, something which can not be avoided in a classical step-growth process. However, the synthesis of polyesters with acyclic monomers and full control over molar mass, polydispersity, and end groups could not be achieved.

In model studies, Yokozawa and Shimura[9] demonstrated that some monomers suitable for polyester synthesis, for example 4-(trimethylsilyloxy)benzoyl chloride or the combination of 4-bromophenol and carbon monoxide, have the potential to let the condensation reacton run by a chain-

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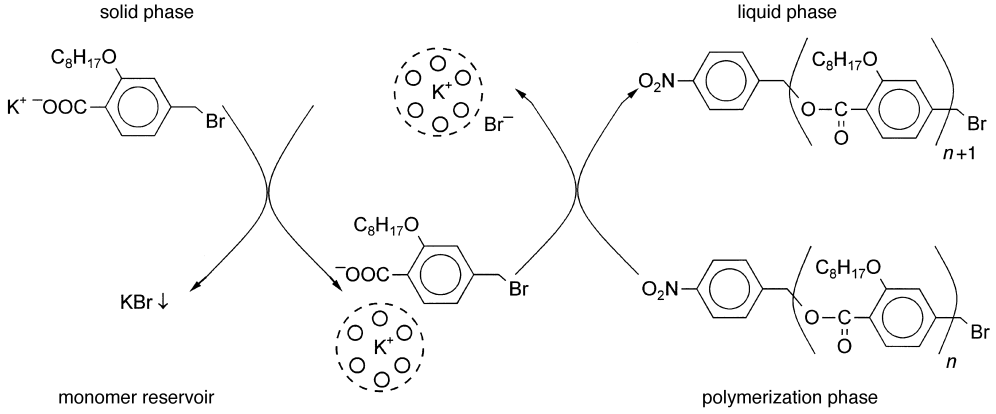
  1433-7851/00/3919-3407 $ 17.50+.50/0

growth mechanism. Here, in a monomer A-B, the reactivity of the functionality B towards A is increased by the reaction of an "initiator" with the functionality A, for example an electron donating substituent is converted in an electron withdrawing group. However, this method must still be converted into a working polymerization process.

It is essential for good control that the reaction occurs exclusively at the end of the growing chain, this means the monomers must not react with each other. To meet this condition Yokozawa and Suzuki took advantage of a heterogeneous reaction, with a phase transfer catalyst as outlined in Scheme 1. In principle, the use of phase-transfer catalysis in polycondensation processes is not new,[10] but up to now it has not been used to control the products in this way.



Scheme 1. Mechanism of the controlled polycondensation according to Yokozawa and Suzuki.[5]

Yokozawa and Suzuki first dispersed the solid monomer, potassium-4-bromomethyl-2-*n*-octyloxybenzoate, in a nonsolvent (acetone). The addition of [18]crown-6 allows a small amount of the monomer to be solubilized. In solution, the monomer can react with the initiator, 4-nitrobenzylbromide, to form a *para*-nitrobenzyl ester. The best results were obtained when initiator and crown ether were used in equimolar amounts, for example, 10 mol% of each, with respect to the monomer. After initiation, the chain growth starts, potassium bromide precipitates, and a small amount of [18]crown-6 is liberated. This leads again to the solubilization of a small amount of monomer which can add to the ends of the oligomers in the reaction solution. By this mechanism, the amount of free monomer in solution is always very small and therefore the self condensation of monomer molecules can be suppressed.

The important criteria in this reaction are the solubility of monomer, initiator, and growing polymer chain. If the solubility of the monomer in the reaction medium is too high, then a parallel step-growth reaction can take place. If the amount of crown ether is too low, too little monomer enters the reaction mixture and so homogeneous growth starting from all initiator molecules can not take place. The growing polymers chains naturally have to be soluble in the reaction media even at higher molar mass. Therefore, transfer of this polymerization process to other monomer systems is not simple and only a selected number of monomers will fulfill all the necessary criteria.

The system described, in which an alkoxy-substituted poly(benzyl ester) is formed, demonstrates that the detailed analysis of the reaction development and of the properties of the reagents is required for the success of the reaction. Polymerization in acetone at 25 °C with 7 mol% of initiator and [18]crown-6 leads to a linear increase of molar mass with conversion, the polydispersity $\bar{M}_w/\bar{M}_n$ for all the samples is below 1.3, and the ratio of end groups (after the reaction of the benzyl bromide end groups with potassium 4-methoxyphenolate) to initiator groups is very close to 1 even at low conversion. Therefore, one can assume a chain-growth mechanism with almost exclusive growth at the chain end.

A further experiment was carried out to investigate whether the molar mass can be controlled by the monomer/initiator ratio. For this, the amount of initiator was varied from 100 to 7 mol%, with respect to the monomer, and the polymerization reaction was driven to complete conversion. A linear relationship between molar mass and the monomer/initiator ratio was found. In addition, the molar masses of the products agreed well with values calculated on the basis of the monomer/initiator ratio, which indicates a high initiator efficiency. The $\bar{M}_w/\bar{M}_n$ was again below 1.3. The reaction exhibits the features comparable to those of a controlled polymerization of vinyl or cyclic monomers. To be able to transfer these results into a commercially viable process it is necessary to reduce the initiator concentration further so that products can be prepared that have molar masses above 5000 g mol^{-1} and thus have interesting materials properties.

Yokozawa and Suzuki demonstrated convincingly that control of molar mass, polydispersity, and end groups can be achieved in polycondensates if the step-growth process is converted into a controlled chain-growth reaction. Logically, the kinetics follow those of a chain-growth mechanism when termination and side reactions are suppressed. Since a heterogeneous, phase transfer catalyzed process is involved, which has already been introduced successfully in industrial polycondensation processes, a transfer to commercial use seems possible. If this method can be applied successfully to other monomers one can imagine that the presented concept might have the same importance for polymer synthesis as the recent developments in controlled radical polymerization. Certainly, the area of classical polycondensation will not be revolutionized tomorrow, but one can expect many new ideas to be initiated by this work from Yokozawa and Suzuki.

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Isopenicillin N Synthase: An Enzyme at Work

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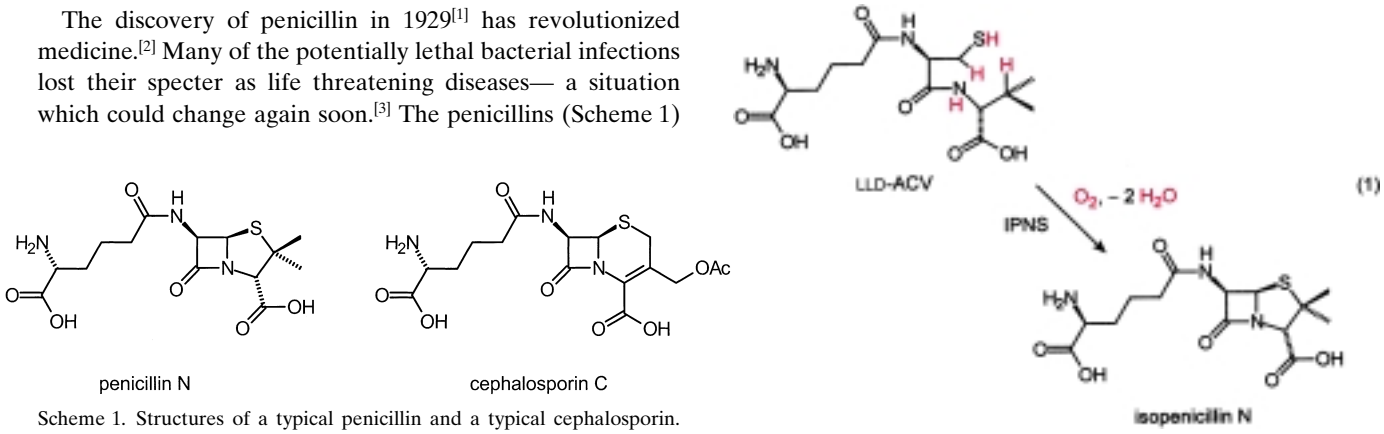
The discovery of penicillin in 1929[1] has revolutionized medicine.[2] Many of the potentially lethal bacterial infections lost their specter as life threatening diseases— a situation which could change again soon.[3] The penicillins (Scheme 1)



Scheme 1. Structures of a typical penicillin and a typical cephalosporin. Ac = acetyl.

were the first antibiotics, and for a long time the term "penicillin" was used by the general public as a synonym for "antibiotic".

Further milestones were set with the determination of the structure of penicillin[4] and the first total synthesis of a naturally occurring penicillin.[5] The laboratory synthesis of penicillin and its derivatives turned out to be quite a challenge because of its bicyclic structure, which makes the β-lactam ring particularly labile.[6] It is not surprising then that the question, "how does nature do it?" attracted the attention of the scientific community.

Most of the early information came from fairly indirect evidence.[7] The immediate precursor, the linear tripeptide L-α-aminoadipoyl-L-cysteinyl-D-valine (LLD-ACV), is first assembled from its component amino acids by the action of ACV synthase, which also mediates the necessary epimerization of valine. The key step, the stoichiometrically simple oxidative cyclization [Eq. (1)], is brought about by a single, non-heme iron-containing enzyme dubbed isopenicillin N synthase (IPNS). Further enzymes are then responsible for the epimerization of isopenicillin N to penicillin N, the derivatization to other penicillins, and the ring expansion that eventually leads to the various cephalosporins.

Despite considerable effort enzyme-free intermediates of this process have never been found. This indicates that both rings are formed within the same enzyme–substrate complex. Studies with modified substrates served to define the properties of the active site. A surprising range of variations of both the aminoadipoyl and the valinyl termini of ACV are tolerated, which helped the gathering of mechanistic information. Thus, if D-valine was replaced by other amino acids containing allyl or cyclopropylmethyl groups as "radical clocks", the appearance of the typical rearrangement products indicated that an (perhaps conformationally restrained) isopropyl radical intermediate is presumably involved in the formation of the thiazolidine ring.[8] The L-aminoadipoyl terminus may be replaced by a range of nonpolar substituents of similar size that are not necessarily terminated by a carboxylic group. This is good evidence that the corresponding part of the binding region of IPNS is nonpolar but contains a hydrogen-bonding site at the end of the pocket.[7] The central cysteine unit, however, is essentially inviolate. This is

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