Notes

Determination of the Stereoselectivity Factor for an Asymmetric Enantiomer-Differentiating Polymerization: A Revisit

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A stereoselective polymerization has been defined as a polymerization in which a macromolecule is formed from a mixture of stereoisomeric monomer molecules by the incorporation of only one stereoisomeric species. An asymmetric enantiomer-differentiating polymerization (also referred to as stereoelective polymerization, enantiomer-selective polymerization, enantioselective polymerization, or enantioasymmetric polymerization) is a "stereoselective polymerization" in which all the macromolecules are formed by the incorporation of only one type of stereoisomeric species.[1] On the other hand, a polymerization in which, starting from a racemic mixture of a chiral monomer, two types of macromolecules, each containing monomeric units derived from one of the enantiomers, form in equal amounts is termed "racemate-forming enantiomer-differentiating polymerization" (formerly referred to as "stereoselective" polymerization).[1] Therefore, starting from a racemic mixture of a chiral monomer, an asymmetric enantiomer-differentiating polymerization gives an optically active polymer, whereas the polymer resulting from racemate-forming enantiomer-differentiating polymerization is invariably optically inactive.

The above definitions can be illustrated by the ring-opening polymerization of lactides (Scheme 1).[2] Lactide consists of three stereoisomers: a pair of enantiomers (*R,R*-lactide and *S,S*-lactide) and a meso compound (*R,S*-lactide). The enantiopure initiator, salenAlO^{i}Pr complex based on (*R,R*)-Jacobsen ligand ((*R,R*)-salenAlO^{i}Pr), effects a preferential ring-opening polymerization of *S,S*-lactide from a racemic mixture of *R,R*- and *S,S*-lactide (*rac*-lactide).[2] The (*R,R*)-salenAlO^{i}Pr-initiated *rac*-lactide polymerization is an asymmetric enantiomer-differentiating polymerization (Scheme 1a). By contrast, when a racemic initiator, salenAlO^{i}Pr complex based on (*rac*)-Jacobsen ligand ((*rac*)-salenAlO^{i}Pr), is employed to initiate the polymerization of *rac*-lactide, both *R,R*- and *S,S*-lactide are polymerized at the same rate to give invariably an optically inactive polymer. The polymerization proceeds in such a way that (*R,R*)-salenAlO^{i}Pr preferentially polymerizes *S,S*-lactide and (*S,S*)-salenAlO^{i}Pr preferentially polymerizes *R,R*-lactide. The polymerization of *rac*-lactide with (*rac*)-salenAlO^{i}Pr according to the above definitions is a racemate-forming enantiomer-differentiating polymerization (Scheme 1b).

The stereoselectivity factor (*s* or *r*), which is the ratio of the polymerization rate constants of the two enantiomers ($r = k_{fast}/k_{slow}$), is often used to examine the efficiency of a catalyst in a stereoselective polymerization. The *s* value can be experimentally evaluated by measuring the specific rotation of the unreacted monomer. For asymmetric enantiomer-differentiating polymerization of a racemic monomer mixture the following two equations have been presented in the literature:

$$(1 - c)^{r-1} = \frac{1 + (\alpha/\alpha_0)}{1 - (\alpha/\alpha_0)^r} \quad \text{(ref 3)} \tag{1}$$

$$(1 - c)^{r-1} = \frac{1 + (\alpha/\alpha_0)}{[1 - (\alpha/\alpha_0)]^r} \quad \text{(refs 4−8)} \tag{2}$$

where $r = k_{fast}/k_{slow}$, c is the monomer conversion, and α/α_0 is the optical purity of the unreacted monomer at a given conversion.

Comparing eqs 1 and 2 already reveals that one of these equations is not correct. Moreover, in attempts to assess the stereoselectivity of (*R,R*)-salenAlO^{i}Pr in *rac*-lactide polymerization, we observed that neither eq 1 nor eq 2 afforded realistic values. For example, the polymer obtained at 36.3% monomer conversion has an optical purity of 59.8%. The optical purity of the unreacted monomer can thus be calculated to be 34.1%. On the basis of these data, no value of *r* could satisfy eq 1, whereas eq 2 gave an *r* value of 0.18. By definition, the stereoselectivity factor (*r*) should be larger than 1. This led us to reexamine the derivation of the equation.

On the basis of the following assumptions, the (general) equation for asymmetric enantiomer-differentiating polymerization may be established. First, the polymer chain end imposes no or little effect on the stereochemistry of the monomer addition, i.e., the absence of chain-end control. Second, the polymerization is first-order in both enantiomers. With these assumptions, the polymerization rates of *R*- and *S*-enantiomers in an asymmetric enantiomer-differentiating polymerization can be expressed by the kinetic equations

$$-\frac{d[R]}{dt} = k_R[C^*]^x[R]$$

$$-\frac{d[S]}{dt} = k_S[C^*]^x[S] \tag{3}$$

where [C*] denotes the concentration of the active

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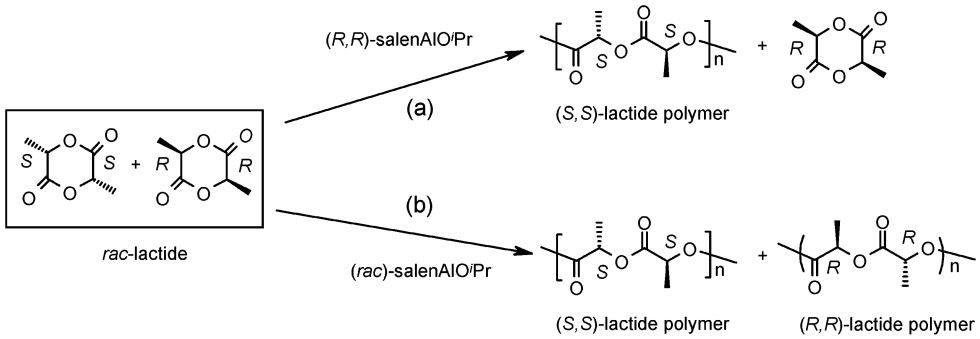
Scheme 1



species and x is the order of the reaction with respect to the catalyst.

Assuming that the *R*-enantiomer polymerizes faster than the *S*-enantiomer, i.e., $k_R > k_S$, dividing the equations above followed by integration gives rise to

$$\frac{[\mathrm{R}]}{[\mathrm{R}]_0} = \left(\frac{[\mathrm{S}]}{[\mathrm{S}]_0}\right)^r \tag{4}$$

where r is the ratio of the polymerization rate constants of the enantiomers ($r = k_R/k_S$).

At a given $[\mathrm{R}]_0$ and $[\mathrm{S}]_0$, the concentration of the respective enantiomers, [R] and [S], can be determined from the monomer conversion (c) and the specific rotation (α) of the unreacted monomer. The enantiomeric excess of the unreacted monomer ($\mathrm{ee_m}$) has a value of α/α_0. In an asymmetric enantiomer-differentiating polymerization where $k_R > k_S$ (this implies that the *S*-enantiomer will be enriched in the monomer pool), $\mathrm{ee_m}$ and c with respect to the concentrations of *R* and *S* can be expressed by

$$\mathrm{ee_m} = \frac{[\mathrm{S}] - [\mathrm{R}]}{[\mathrm{S}] + [\mathrm{R}]} \tag{5}$$

$$c = 1 - \frac{[\mathrm{S}] + [\mathrm{R}]}{[\mathrm{S}]_0 + [\mathrm{R}]_0} \tag{6}$$

The combination of eqs 5 and 6 yields

$$\frac{[\mathrm{R}]}{[\mathrm{R}]_0} = (1 - \mathrm{ee_m})(1 - c)\left(\frac{[\mathrm{S}]_0 + [\mathrm{R}]_0}{2[\mathrm{R}]_0}\right)$$

$$\frac{[\mathrm{S}]}{[\mathrm{S}]_0} = (1 + \mathrm{ee_m})(1 - c)\left(\frac{[\mathrm{S}]_0 + [\mathrm{R}]_0}{2[\mathrm{S}]_0}\right) \tag{7}$$

Equations 4 and 7 afford

$$(1 - c)^{r-1} = \frac{1 - \mathrm{ee_m}}{(1 + \mathrm{ee_m})^r} \frac{2^{r-1}[\mathrm{S}]_0{}^r}{[\mathrm{R}]_0([\mathrm{S}]_0 + [\mathrm{R}]_0)^{r-1}} \tag{8}$$

In case the starting monomer mixture is racemic, i.e., $[\mathrm{R}]_0 = [\mathrm{S}]_0$, eq 8 is simplified to

$$(1 - c)^{r-1} = \frac{1 - \mathrm{ee_m}}{(1 + \mathrm{ee_m})^r} \tag{9}$$

The above equation can be used to determine the stereoselectivity factor ($r = k_{\mathrm{fast}}/k_{\mathrm{slow}}$) by fitting the experimental data of $\mathrm{ee_m}$ at different conversions c with hypothetical curves plotted according to eq 9. Equation 9 can be converted into eq 10.

$$r = \frac{\ln[(1 - c)(1 - \mathrm{ee_m})]}{\ln[(1 - c)(1 + \mathrm{ee_m})]} \tag{10}$$

The stereoselectivity factor (s) can easily be calculated from eq 10 for each set of c and $\mathrm{ee_m}$. For instance, (*R*,*R*)-salenAlO^{i}Pr for *rac*-lactide polymerization (c = 36.3%, $\mathrm{ee_m}$ = 34.1%) calculated according to eq 9 or eq 10 has an s value of 5.5, which is in line with the polymerization kinetics.[10] In an ideal situation, the s values should be constant and not vary with monomer conversion.

The asymmetric enantiomer-differentiating polymerization of a racemic mixture of a chiral monomer will furnish an optically active polymer. The specific rotation of the polymer depends on both the conversion and the stereoselectivity factor exerted by the catalyst. Therefore, the value of stereoselectivity factor in principle can also be calculated by measuring the specific rotation of the polymer and the conversion.

Assuming that (1) the specific rotation (α_0) of an enantiomerically pure polymer does not vary with molecular weight, which has to be evaluated for each type of polymer, and (2) the specific rotation (α) of the polymer follows a linear relationship with the enantiomeric excess of the monomer units in the polymer ($\mathrm{ee_p}$), the value of $\mathrm{ee_p}$ can be experimentally determined from the specific rotation of the polymer, i.e., $\mathrm{ee_p} = (\alpha/\alpha_0)_p$. α_0 can be established by measuring optically pure polymers resulted from the polymerization of enantiopure monomer using a polarimeter. The $\mathrm{ee_p}$ and $\mathrm{ee_m}$ are necessarily related and independent of the stereoselectivity factor, as shown by

$$\frac{\mathrm{ee_m}}{\mathrm{ee_p}} = \frac{c}{1 - c} \quad (0 < c < 1) \tag{11}$$

The combination of eqs 10 and 11 gives

$$r = \frac{\ln[1 - c(1 + \mathrm{ee_p})]}{\ln[1 - c(1 - \mathrm{ee_p})]} \tag{12}$$

Hence, the stereoselectivity of a chiral catalyst in an asymmetric enantiomer-differentiating polymerization of a racemic monomer can also be determined from monomer conversion and the enantiomeric excess of the monomer units in the polymer. This has been verified in the case of (*R*,*R*)-salenAlO^{i}Pr for *rac*-lactide polymerization, in which a constant s value of 5.5 up to 50% conversion has been determined.[10]

It should be noted that eqs 10 and 12 are essentially the same as those used to determine the stereoselec-

tivity factor in kinetic resolution reactions.[7,9] This may imply that the principles advanced for kinetic resolution reactions hold also for asymmetric enantiomer-differentiating polymerizations, which will largely facilitate the mechanistic understanding for stereoselective polymerization.

References and Notes

(1) Hatada, K.; Kahovec, J.; Baron, M.; Horie, K.; Kitayama, T.; Kubisa, P.; Moss, G. P.; Stepto, R. F. T.; Wilks, E. S. *Pure Appl. Chem*. **2002**, *74*, 915−922.

(2) Zhong, Z. Y.; Dijkstra, P. J.; Feijen, J. *Angew. Chem., Int. Ed*. **2002**, *41*, 4510−4513; *Angew. Chem*. **2002**, *114*, 4692−4695.

(3) Odian, G. *Principles of Polymerization*, 3rd ed.; Wiley: New York, 1991.

(4) Sepulchre, M.; Spassky, N.; Sigwalt, P. *Macromolecules* **1972**, *5*, 92−94.

(5) Sigwalt, P. *Pure Appl. Chem*. **1976**, *48*, 257−266.

(6) Spassky, N.; Leborgne, A.; Sepulchre, M. *Pure Appl. Chem*. **1981**, *53*, 1735−1744.

(7) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem*. **1988**, *18*, 249−330.

(8) Spassky, N.; Wisniewski, M.; Pluta, C.; LeBorgne, A. *Macromol. Chem. Phys*. **1996**, *197*, 2627−2637.

(9) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal*. **2001**, *343*, 5−26.

(10) Zhong, Z. Y.; Dijkstra, P. J.; Feijen, J. *J. Am. Chem. Soc*. **2003**, *125*, 11291−11298.

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