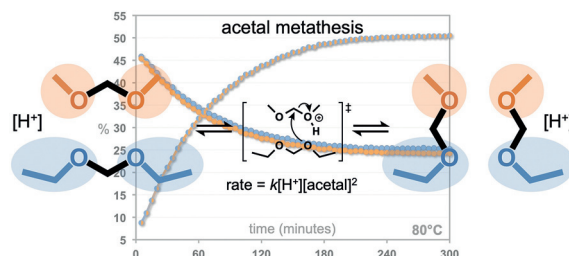# Acetal Metathesis: Mechanistic Insight

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Abstract The origins and recent applications of acetal metathesis are discussed in the context of synthesizing polyacetals via acetal metathesis polymerization (AMP). A kinetic study of the acid-catalyzed acetal metathesis reaction suggests the rate = $k[H^+][acetal]^2$, with $MeOCH_2OMe$ and $EtOCH_2OEt$ interchanging to yield $MeOCH_2OEt$, achieving the statistical 1:2:1 equilibrium distribution in 4 hours at 80 °C and in 1 hour at 90 °C. Upon heating 1,10-decanediol and diethoxymethane, polydecylene acetal is formed with sequential distillation of ethanol, followed by diethoxymethane. A full mechanism for this polymerization is proposed, which begins with a transacetalization sequence to convert the diol into a bisacetal, followed by acetal metathesis to yield a high-molecular-weight polymer.

Key words acetal, metathesis, transacetalization, polyacetal, acid catalysis, kinetic study, nucleophilicity

To many organic chemists, the term 'metathesis' means primarily or exclusively 'olefin metathesis.'[2] The Google search engine largely agrees since the first 80+ image results for 'metathesis' depict some kind of alkene interchange chemistry.[3] However, the IUPAC Goldbook definition is far broader and involves 'the exchange of a bond (or bonds) between similar interacting chemical species so that the bonding affiliations in the products are identical (or closely similar) to those in the reactants.'[4] Our research group has recently explored a variety of metathesis reactions for polymerization, including acetal metathesis polymerization (AMP),[5–7] silicon acetal metathesis polymerization (SAMP),[8] carbonate metathesis polymerization (CAMP),[9] and oxalate metathesis polymerization (OMP).[10] In each case, we have refined the definition of metathesis to

apply to the exchange of a bond between *functional groups of the same name*; thus, the general term *functional group metathesis* (FGM) was introduced.[11,12]

Herein, we focus on the acetal metathesis reaction, describing its origins, our adaptations for polymerization, and mechanistic analysis. In the 1930s, Carothers investigated the relationship between lactones and linear polyesters[13] and logically extended this concept to acetals. He reasoned that 'acetal interchanges are smoothly reversible reactions' and first prepared polyacetals by combining linear α,ω-diols $HO(CH_2)_nOH$ and dibutoxymethane ($BuOCH_2OBu$) along with an acid catalyst.[14] With diols of n = 3 or 4, cyclic products (1,3-dioxane or 1,3-dioxepane) predominated. However, longer diols yielded linear polyacetal polymers as shown in Scheme 1. Note the resemblance of the interchange triangle to that popularized by the pioneers of olefin metathesis, which features key elements of ring-closing metathesis (RCM), ring-opening metathesis polymerization (ROMP), and acyclic diene metathesis (ADMET) polymerization.[2,15,16]
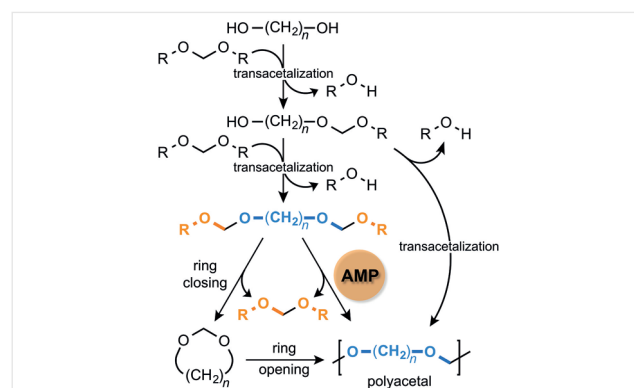
Scheme 1 Acetal metathesis allows the interconversion of bisacetals, cyclic acetals, and linear polyacetal polymers. Acetal metathesis polymerization (AMP) is conceptually related to acyclic diene metathesis polymerization (ADMET).[16]

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As described in Scheme 1, the polyacetal linkage could arise via *transacetalization* with an alcohol chain end, eliminating the alcohol ROH—or via *acetal metathesis polymerization* (AMP), eliminating the acetal ROCH$_2$OR. The former process involves two different functional groups and technically does not constitute metathesis as defined herein. When Carothers employed glycols as starting materials, the mechanistic pathway to polyacetals was not clarified. However, when Carothers heated low-molecular-weight polyacetals (near 1,000 to 5,000 Da) under vacuum, the production of cyclic monomers or dimers seemed to require a metathesis mechanism.[14] Definitive, small-molecule acetal metathesis was demonstrated in 1981 when acid catalysts facilitated the partial conversion of symmetrical acetals MeOCH$_2$OMe and EtOCH$_2$OEt to the mixed acetal, MeOCH$_2$OEt.[17]

Curious about this interchange reaction, we designed experiments to measure its rate, knowing this data would be important for its application to polymerization.[6] In the presence of 0.5 mol% of the Brønsted acid *p*-toluenesulfonic acid (*p*-TSA) in toluene-d_8, the reaction is very slow at room temperature. But at 80 °C, equilibrium between equimolar amounts of MeOCH$_2$OMe and EtOCH$_2$OEt is achieved in 4 hours and at 90°C, equilibrium is achieved in 1 h, yielding 50% of the mixed acetal, MeOCH$_2$OEt, as depicted in Figure 1a.[18] Figure 1b shows the same reaction with the symmetrical acetals plotted separately and yielding the statistical 1:2:1 abundance of MeOCH$_2$OMe:MeOCH$_2$OEt:EtOCH$_2$OEt. This investigation confirmed that the timescale of the reaction is acceptable, especially since most polymerizations are conducted at even higher temperatures.[6]

For this same reaction, analysis of the initial rates is revealing. Figure 2a plots ln[% acetal] vs. time and is a test for the first-order disappearance of each symmetrical acetal at 80 °C (over 100 min) and 90 °C (over 30 min). Figure 2b is a test for a second-order reaction with 1/[% acetal] vs. time and Figure 2c is a test for a third-order reaction with 1/[% acetal]^2 vs. time. Regression analysis indicates the best linear fit is for the third-order consumption of MeOCH$_2$OMe or EtOCH$_2$OEt at either 80 °C or 90 °C, with R^2 = 0.997 to 0.999 (Figure 2c). For the first-order (R^2 = 0.982 to 0.988, Figure 2a) and second-order rate analyses (R^2 = 0.992 to 0.997, Figure 2, b), the corresponding linear fits are somewhat worse. Figure 2d plots log[rate] vs. log[% acetal], where the rate is computed as the slope of the decay curve at each [% acetal] concentration. For the 80 °C reaction, regression analysis from 15 to 105 minutes provides slopes of 3.26 (R^2 = 0.957) and 3.07 (R^2 = 0.969), confirming the preceding determination of a third-order reaction. For the faster 90 °C reaction, regression analysis is valid over a more limited time domain (10–25 min) but provides slopes of 2.70 (R^2 = 0.935) and 3.66 (R^2 = 0.977) that also suggest a third-order reaction. The best interpretation of this kinetic analysis is that the reaction is third-order with rate = k[H$^+$][acetal]^2.
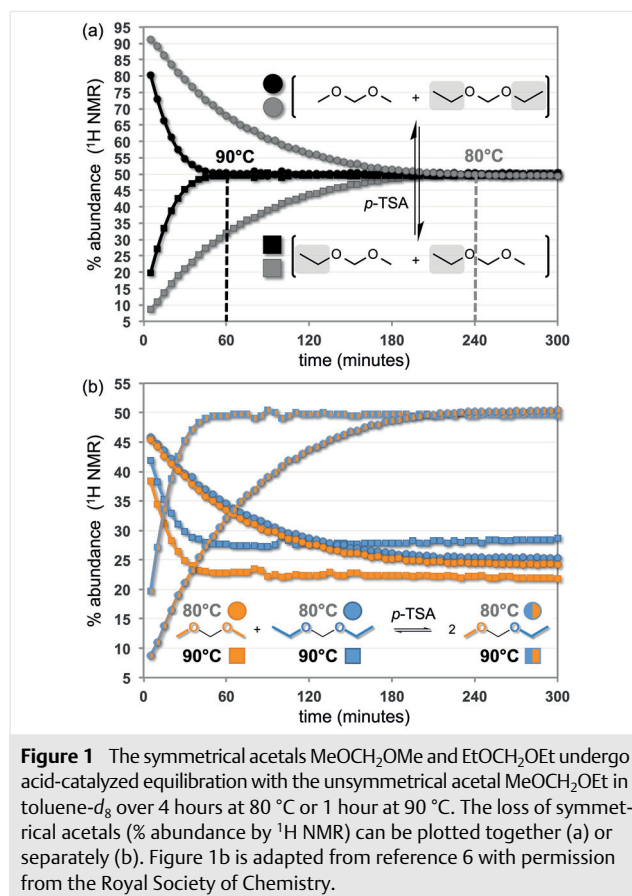

Figure 1 The symmetrical acetals MeOCH$_2$OMe and EtOCH$_2$OEt undergo acid-catalyzed equilibration with the unsymmetrical acetal MeOCH$_2$OEt in toluene-d_8 over 4 hours at 80 °C or 1 hour at 90 °C. The loss of symmetrical acetals (% abundance by ^{1}H NMR) can be plotted together (a) or separately (b). Figure 1b is adapted from reference 6 with permission from the Royal Society of Chemistry.

Our general strategy for acetal metathesis polymerization is to combine a diol (*e.g.*, 1,10-decanediol), excess (30 equiv) diethoxymethane, 2 mol% *para*-toluenesulfonic acid (*p*-TSA, an acid catalyst), and a high boiling solvent (*e.g.*, xylenes) in order to keep down the viscosity of the final polymerization mixture. A specific protocol is as follows: A 100 mL round-bottom flask was charged with 1.74 g (10 mmol) of 1,10-decanediol, 38 mg (2 mol%) of *p*-TSA, 15.0 mL of xylenes, and 37.55 mL (300 mmol) of diethoxymethane. Three sequential distillate fractions were collected over 5 hours during a temperature ramp from T_p = 80–200 °C, followed by a fourth fraction collected with dynamic vacuum at 200 °C for 12 hours. Analysis of these time-resolved polymerization distillates is informative.[19] Figure 3 shows the ^{1}H NMR spectra of the four fractions collected at T = 1, 3, 5 and 17 hours. The first fraction (T_p = 115 °C) was rich in ethanol, the lowest boiling byproduct (bp 78 °C), along with comparable amounts of diethoxymethane; some acetal was expected since it is the most abundant component of the reaction and its boiling point (88 °C) is not much higher than that of ethanol. The second fraction (T_p = 150 °C) was mostly diethoxymethane and was devoid of ethanol, suggesting that the transacetalization of all alcohol groups was complete. The third fraction (T_p = 200 °C) was mainly diethoxymethane but did contain appreciable amounts of
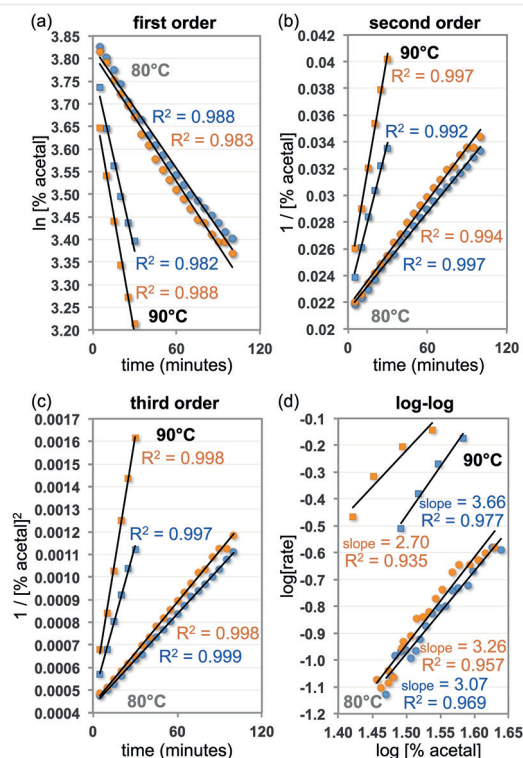
Figure 2 The kinetic analysis of initial rates shows the best fit for third order conversion of acetal (c) versus first order (a) or second order (b) conversion of acetal. Plots of log[rate] vs. log[% acetal] give slopes of 3.26, 3.07, 2.70, and 3.66, also suggesting a third-order reaction.

the high-boiling solvent, xylenes (bp ca. 139 °C). The fourth fraction, also at T_p = 200 °C but under dynamic vacuum, was predominantly xylenes, but did contain noticeable amounts of diethoxymethane. It is reasonable to assume that the small amount of acetal collected in this final fraction did not survive from the initial charge but was evolved as the small molecule of condensation as two chain ends underwent acetal metathesis. After workup, 1.39 g of polydecylene acetal was collected in 75% isolated yield. The number average molecular weight (M_n) was 21,700 Da; the weight average molecular weight (M_w) was 51,700 Da; and the dispersity ($Đ$) was, therefore, 2.38. The average degree of polymerization is 21,700/186 = 117; hence the average polymer can be considered as EtO–[CH$_2$O(CH$_2$)$_{10}$O]$_{117}$–CH$_2$OEt.

Based on the aforementioned behaviors of this system, a composite mechanism can be assembled. The left side of Scheme 2 describes an acid-catalyzed transacetalization mechanism[20] which, in this case, involves the conversion of a diol to a monoacetal, followed by a bisacetal. Note the key oxygen–carbon bond-formation steps occur when an alcohol attacks an oxonium ion, formation of which is commonly invoked as the rate-determining step (RDS).[21] Evolution of the lowest boiling component, ethanol (bp 78 °C), is accomplished, and the reaction can be driven to bisacetal formation by removal of this alcohol. The right-hand side of Scheme 2 describes the acetal metathesis steps and begins with the bisacetal. Either oxygen of the acetal can be protonated,[22] but only protonation of the distal oxygen can result in productive metathesis; proximal oxygen protonation compels the diol end of the acetal to be the leaving group.
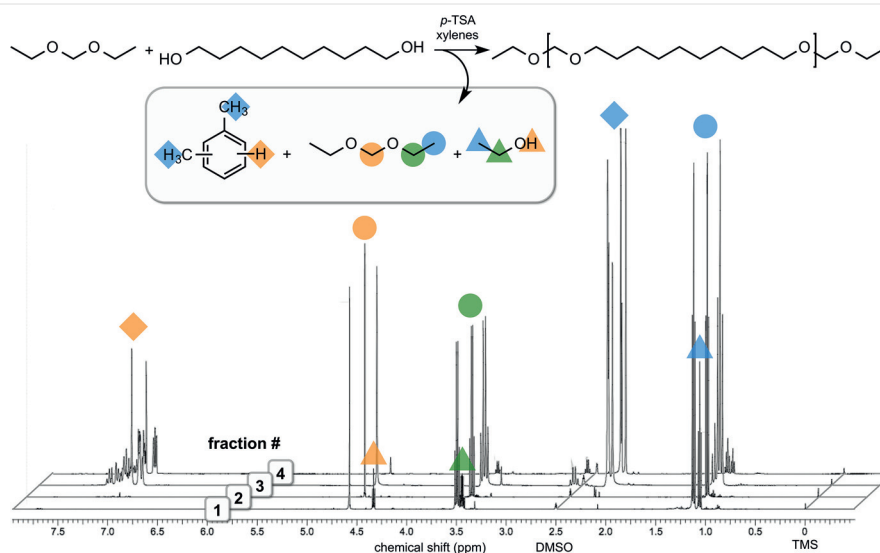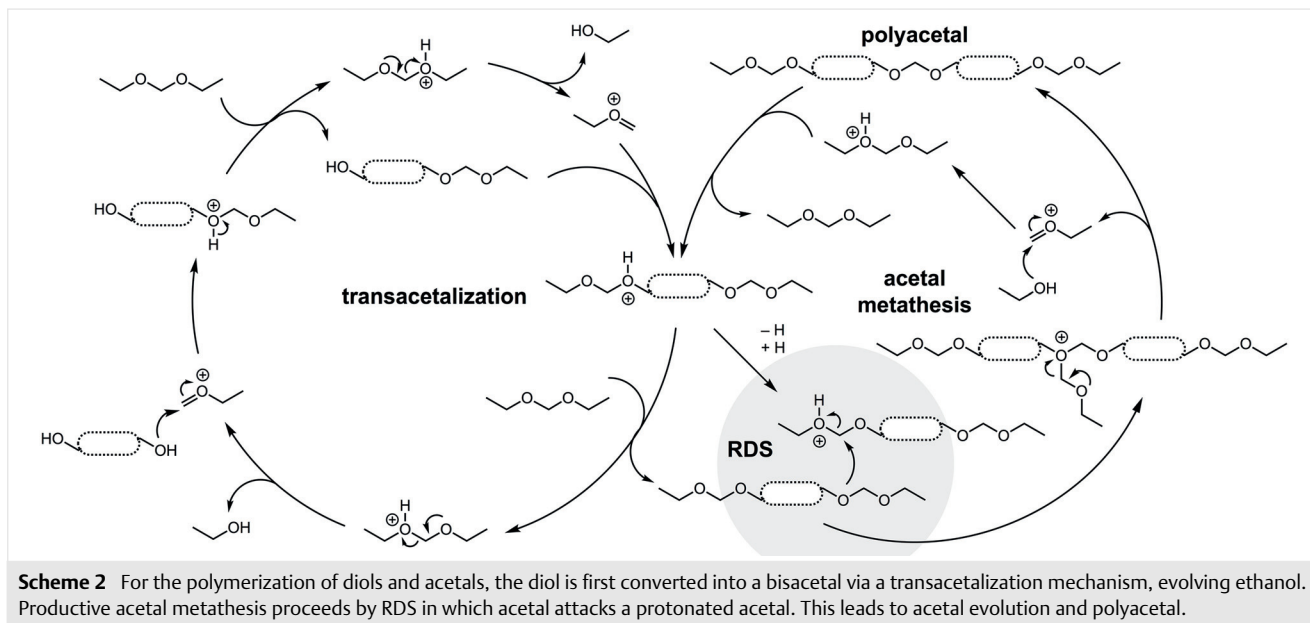

Figure 3 The distillates from the high temperature (80–200 °C) polymerization of diethoxymethane (excess) and 1,10-decanediol are analyzed by ^{1}H NMR spectroscopy. Ethanol (triangles), the product of transacetalization, is found only in the first fraction. Diethoxymethane (circles) is found in the first three fractions and is depleted as acetal metathesis progresses. The fourth fraction is almost exclusively the high boiling solvent, xylenes (diamonds), but contains the diethoxymethane evolved as chain ends react to make high-molecular-weight polymer. These NMR spectra were first published in the Supporting Information of reference 6 and have been adapted here with permission from the Royal Society of Chemistry.

Scheme 2 For the polymerization of diols and acetals, the diol is first converted into a bisacetal via a transacetalization mechanism, evolving ethanol. Productive acetal metathesis proceeds by RDS in which acetal attacks a protonated acetal. This leads to acetal evolution and polyacetal.

Productive metathesis results when the proximal oxygen of a neutral bisacetal attacks a distally protonated bisacetal. This step involves a proton and two acetals, which comports with the third-order rate law suggested by the plots of Figure 2: rate = $k[H^+][acetal]^2$, conducted in toluene. But, this pathway is contrary to several kinetic studies that show the acid-catalyzed hydrolysis of acetals is second order, with rate = $k[H^+][acetal]$, involving oxonium ion formation and its attack.[21,23] In those cases, however, water is the solvent and likely facilitates oxonium ion formation, which reacts rapidly with water as a weak nucleophile. In the present case, the nucleophile is an acetal, but our search uncovered no specific examples from the literature that measured or ranked the nucleophilicity of an acetal.[24] But, if acetals are better nucleophiles than water, then the unusual third order reaction of Scheme 2 could be rationalized.

To quickly address this question, we turned to a computational answer via the nucleophilicity index proposed by Jaramillo et al.[25] parameterized by $\omega^- = [(1/2)\eta_{nuc}(\mu_{nuc} - \mu_{elec})^2]/(\eta_{nuc} + \eta_{elec})^2$. Note that this is a relative (not absolute) scale and depends on both the nucleophile and electrophile. The values μ_{nuc} and μ_{elec} correspond to the chemical potential $((E_{HOMO} + E_{LUMO})/2)$, and the values η_{nuc} and η_{elec} correspond to the hardness $(E_{LUMO} - E_{HOMO})$. The values E_{HOMO} and E_{LUMO} can be computed with various levels of theory. The index ω^- correlates roughly with the extent of charge transfer between the nucleophile and electrophile, as dictated by the frontier molecular orbitals of each.

Table 1 compiles the computed ω^- values (in eV) for water, ethanol, *gauche-gauche* $EtOCH_2OEt$ (the preferred conformation), *gauche-anti* $EtOCH_2OEt$, and *anti-anti* $EtOCH_2OEt$ as nucleophiles attacking the electrophiles MeCl, MeBr, the protonated acetal $EtOCH_2O(H^+)Et$, or the

oxonium ion $EtOCH_2^+$. Acetal appears to be a weak nucleophile with the alkyl halide electrophiles. However, acetal is a numerically superior nucleophile (greater ω^- value) compared to water when the electrophile is strong—here, positively charged.

Table 1 Nucleophilicity Index (ω^-, in eV) Calculated for Various Nucleophile/Electrophile Combinations, Showing Acetals to be more Nucleophilic than Water or Ethanol when Attacking Strong Electrophiles[a]

Electrophile nucleophile	MeCl	MeBr	$EtOCH_2O(H^+)Et$	$EtOCH_2^+$
H_2O	0.009	0.020	0.100	0.241
trioxane	0.000	0.004	0.150	0.315
EtOH	0.000	0.003	0.157	0.325
$MeOCH_2OMe$ (*gauche* ×2)	0.000	0.003	0.160	0.329
$EtOCH_2OH$ (*gauche* ×2)	0.000	0.002	0.162	0.332
$EtOCH_2OEt$ (*gauche* ×2)	0.000	0.002	0.168	0.341
$EtOCH_2OEt$ (*gauche-anti*)	0.000	0.001	0.175	0.351
$EtOCH_2OEt$ (*anti-anti*)	0.001	0.000	0.184	0.363
$EtNH_2$	0.005	0.001	0.217	0.409
EtSH	0.012	0.005	0.252	0.455

[a] Calculated as $\omega^- = [(1/2)\eta_{nuc}(\mu_{nuc} - \mu_{elec})^2]/(\eta_{nuc} + \eta_{elec})^2$ with chemical potential $\mu = (E_{HOMO} + E_{LUMO})/2$ and hardness $\eta = (E_{LUMO} - E_{HOMO})$. In turn, E_{LUMO} and E_{HOMO} are calculated with Spartan 10 according to MP2/6-311++G**.

The essential difference is that acetals have a higher E_{HOMO} versus water and thus have a considerably larger contribution from the chemical potential term: $(\mu_{nuc} - \mu_{elec})^2$. Thus, acetal electrons are more available than those of single oxygen nucleophiles; the computed *electronegativity* (= $-\mu$) of

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water (6.355 eV) is greater than that of the acetal (5.125–5.335 eV). This acetal electron availability/polarizability probably arises from electronic communication between the two acetal oxygen atoms via, in part, anomeric interactions. Computationally, water has $\omega^- = 0.100$ while the *anti-anti* acetal has $\omega^- = 0.184$ for the attack of protonated acetal, the RDS proposed in the mechanism of Scheme 2. To be sure, a value of $\omega^- = 0.184$ does not indicate a strong nucleophile. By this analysis, acetal nucleophilicity (attacking $EtOCH_2O(H^+)Et$) is between that of ethanol ($\omega^- = 0.157$) and ethylamine ($\omega^- = 0.217$). Nonetheless, the comparatively good nucleophilicity of acetals helps to rationalize the unusual third-order kinetics described in Scheme 2, depicting an acetal attacking a protonated acetal.

Note that the RDS of Scheme 2 is analogous to that proposed for the hydrolysis of sucrose (an acetal), which has a rate = $k[H^+][sucrose][H_2O]$ when not conducted under pseudo-first-order conditions.[26] In 1920, Jones and Lewis concluded that the sucrose hydrolysis reaction (also known as inversion) 'is a true bimolecular one, between a molecule of water and a complex ion, formed by the addition of hydrogen ion to the sucrose molecule.'[27] The RDS of Scheme 2 similarly proposes the nucleophilic attack of a protonated acetal. Importantly, the pre-equilibrium constant for [*p*-TsOH] + [acetal] ↔ [acetalH$^+$] + [*p*-TsO$^-$] is small because the pK_a of *p*-TsOH (–2.8) is greater than that of protonated acetal (–4.4).[22] With a much stronger acid, the acetal metathesis reaction would exhibit pseudo-second-order kinetics with rate = [acetalH$^+$][acetal].

The attack of protonated acetal by an acetal yields the trivalent oxonium ion shown in Scheme 2, along with ethanol as the leaving group. Productive acetal metathesis requires the trivalent oxonium ion to lose $EtOCH_2^+$, yielding also the fully metathesized acetal (a polyacetal) at the top of Scheme 2. The complementary metathesis product, $EtOCH_2OEt$, is formed when ethanol adds to $EtOCH_2^+$ and subsequently loses a proton.

In order to confirm the independent operation of the acetal metathesis half of Scheme 2, we synthesized and isolated the bisacetal from 1,10-decanediol: $EtOCH_2O(CH_2)_{10}OCH_2OEt$.[6,28] The pure bisacetal was combined with 1 mol% of *p*-TSA catalyst. Polymerization ensued during a 1 hour temperature ramp up to 125 °C, followed by vacuum at 200 °C for 2 hours. Volatile $EtOCH_2OEt$ was exhaustively removed before the normal polymer workup yielded polydecylene acetal in 95% yield as a white powder. Gel-permeation chromatography (GPC) analysis showed obvious conversion into polymer with M_w = 40,200 Da, M_n = 22,000 Da, and Đ = 1.83 (see the Supporting Information).

Carothers' statement that 'acetal interchanges are smoothly reversible reactions'[14] has been addressed herein with a detailed kinetic analysis. The acid-catalyzed acetal metathesis of $MeOCH_2OMe$ and $EtOCH_2OEt$ to yield $MeOCH_2OEt$ is reasonably fast, with equilibrium reached in 4 hours at 80 °C and in 1 hour at 90 °C. The disappearance of acetal is a third-order reaction, with a proposed rate = $k[H^+][acetal]^2$ and a proposed RDS involving attack of a protonated acetal by an acetal. This is at odds with the consensus mechanism of acetal hydrolysis, for which the rate is second order with rate = $k[H^+][acetal]$; the RDS is formation of the oxonium ion electrophile, which is attacked by water, a weak nucleophile. The higher-order reaction of acetal metathesis is rationalized by the greater nucleophilicity of acetal compared to water, which has been computed (ω^- = 0.184 eV) to be between that of water (ω^- = 0.100 eV) and ethylamine (ω^- = 0.217 eV). We have previously reported that heating linear diols with acetals $ROCH_2OR$ in the presence of acid catalysts yields polyacetals, RO–$[CH_2O(CH_2)_nO]_x$–CH_2OR.[6] Based on the sequence of distillates from this polymerization and the aforementioned kinetic study, a composite mechanism has been proposed. Transacetalization with the diol occurs first, yielding bisacetals and this is followed by a step-growth acetal metathesis mechanism, conceptually similar to that of acyclic diene metathesis (ADMET).[16]

While olefin metathesis reactions seem to dominate the metathesis literature, other functional group metatheses have proven chemically facile and useful. In particular, we have reported polymerization variants of acetal metathesis,[6] silicon acetal metathesis,[8] carbonate metathesis,[9] and oxalate metathesis.[10] Additional functional group metathesis reactions are likely to be identified and exploited—especially for polymerization.

Funding Information

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611833.

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(18) **Protocol for ¹H NMR Analysis of Acetal Metathesis between MeOCH₂OMe and EtOCH₂OEt**
An equimolar stock solution was prepared containing 0.5000 mol (38.05 g) of MeOCH₂OMe and 0.5000 mol (52.08 g) of EtOCH₂OEt. Then, 0.20 mL of this stock solution was added to a *J. Young* NMR tube, followed by 0.8 mL of toluene-*d*₈, and 1.9 mg (0.011 mmol) of *p*-TSA (0.5 mol%). The sample was equilibrated at 80 °C (or 90 °C) for 10 minutes before acquiring ¹H NMR

spectra every 5 minutes for 345 (or 360) minutes. The acetal proton peaks at 4.49 ppm (EtOCH₂OEt), 4.56 ppm (MeOCH₂OEt), and 4.63 ppm (MeOCH₂OMe) were automatically integrated for each spectrum.

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(28) **Protocol for the Bisacetal Synthesis**
A 1 liter round-bottom flask was charged with 17.43 g (0.100 mol, 1 equiv) of 1,10-decanediol, 208.30 g (2.00 mol, 20 equiv) of diethoxymethane, 0.190 g (1 mol%) of *para*-toluenesulfonic acid, and 100 mL of toluene. Ethanol was exhaustively removed via distillation over 24 h, followed by refluxing for 48 h. Workup, as described in the Supporting Information, afforded the bisacetal as a colorless oil in 72% yield (21.03 g).