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Oligomers as Intermediates in Ring-Closing Metathesis

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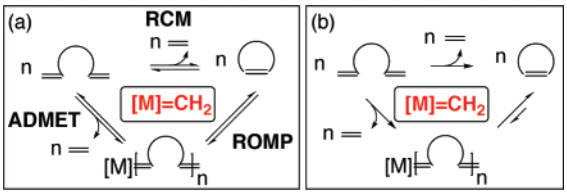
Olefin metathesis is one of the most powerful tools for carbon−carbon bond formation in current use.[1] Ring-closing metathesis (RCM) and cross-metathesis (CM) reactions have had a major impact on organic synthesis, and feature as key steps in an increasing number of natural product syntheses.[1b,e,f] In the classic view of olefin metathesis, RCM and CM reactions are considered competing pathways, the latter leading to ADMET (acyclic diene metathesis) oligomers. Observation of ADMET during attempted RCM is not uncommon,[2] and is viewed as a major synthetic impediment. Dimers or oligomers have sometimes been induced to form RCM products by heating[2a,b,h,i] or treating with a more reactive catalyst,[2c,d] behavior typically ascribed to reversible metathesis (Scheme 1a). We suggest, however, that the conventional concepts of reversibility are of limited relevance in metathesis of unhindered α,ω-dienes (the most typical class of substrates), because efficient volatilization of ethylene renders both RCM and ADMET pathways essentially irreversible; Scheme 1b. Here we show that metathesis of representative α,ω-dienes (ester, ether, catechol, malonate derivatives) by second-generation catalyst **1** affords oligomers, even at millimolar concentrations of diene, except where the conformational bias toward RCM is very high. RCM products are obtained in high yields on longer reaction, via a concentration-dependent backbiting reaction. ADMET pathways can thus be viewed as intrinsic, rather than inimical, to RCM. These findings have important implications for the synthetic protocols used to assemble medium and large cycloolefins by RCM.

Our attention was first drawn to the potential intermediacy of oligomers in RCM in metathesis of diene **4a** under Ziegler conditions (Figure 1).[3] While RuCl(OC$_6$Br$_5$)(IMes)(py)(CHPh) **3** (IMes = *N*,*N*'-bis(mesityl)imidazol-2-ylidene) effected complete formation of 16-membered **5a** by the end of the 15 min addition period, **1** and **2** yield <40% **5a** at this stage, despite near-complete consumption of **4a**.[4] MALDI-MS and GC analysis reveal that involatile ADMET oligomers account for the balance of material (Figure 1). ^{1}H NMR analysis is less useful, the spectrum of the isolated oligomers closely resembling that of a **4a**/**5a** mixture. The rapidity of oligomerization, even at ≪5 mM **4a**, is noteworthy. Importantly, however, ring-closing is near-quantitative on a longer reaction (**1**, 9 h; **2**, 1 h). Dienes **4b** and **4c** likewise form ADMET oligomers as the kinetic products on reaction with **1** or **2**, and yield the 14- or 20-membered macrolactones (**5b**, **5c**) on extended reaction.

Given the millimolar solubility of ethylene in organic solvents at elevated temperatures under 1 atm C$_2$H$_4$,[5] retroreaction of the oligomers under Ar or N$_2$ is improbable, unless the rate constant for back-reaction with C$_2$H$_4$ greatly exceeds that for reaction with diene. Diffusion-controlled volatilization of C$_2$H$_4$ under standard RCM conditions (open vessel, reflux, Ar or N$_2$) limits ethenolysis,

Scheme 1. Metathesis Manifolds Depicting (a) Reversible and (b) Irreversible Loss of Ethylene



rapidly rendering C$_2$H$_4$-evolving steps irreversible. Identification of ADMET oligomers as the major initial products, followed by quantitative conversion to cyclic products *despite* efficient volatilization of ethylene, requires that the oligomers function as intermediates in RCM. This implies that the ADMET-backbiting sequence (Scheme 1b) functions as the dominant route to the RCM products.

In the conceptually related process of relay RCM, intramolecular ring-closing (cf. backbiting) is driven by irreversible loss of cyclopentene.[6] In the present case, the involatile, slightly strained rings generated by backbiting of the metal-terminated oligomers can readily participate in ring-chain (backbiting-ROMP) equilibria, the concentration-dependence of which is predicted by Jacobson−Stockmayer theory.[7] Polymerization−cyclodepolymerization equilibria have been much discussed in the ROMP literature.[8,9] In (e.g.,)

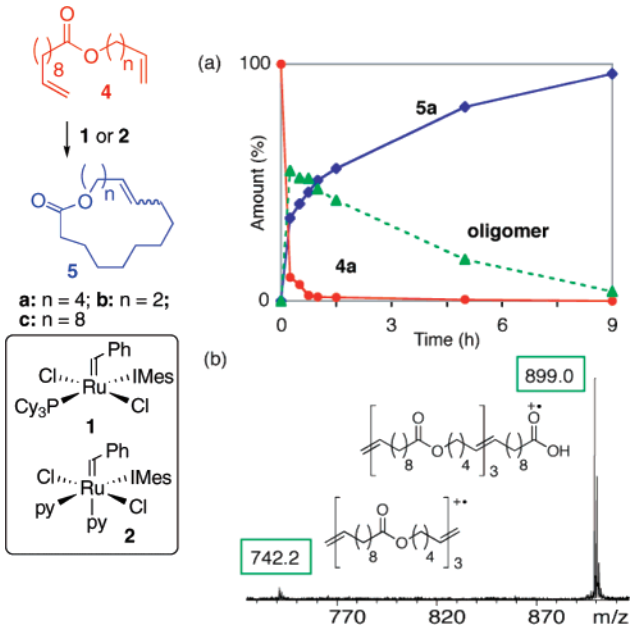


Figure 1. (a) Metathesis of **4a** via **1** (5 mol %; **2** behaves similarly); dropwise addition, refluxing CH$_2$Cl$_2$ ([S] ≪ 5 mM); GC analysis.[4] (b) MALDI-TOF mass spectrum of involatile product isolated after 15 min. The tetramer has undergone a McLafferty rearrangement.

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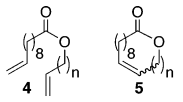
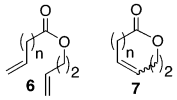
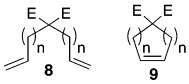
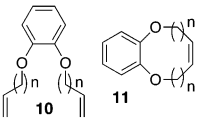
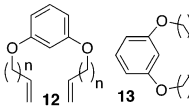
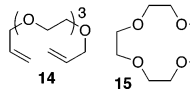
Table 1. Diene Metathesis by **1** (5 mol %)[a]

Diene Substrate	RCM Target	Target: ring size (EM) (EM in mM)	[S] (mM)	T_{Equil} (h)	% oligomers at 15 min[b]	% RCM at equilibrium
 **4**	**5**	**a**: n = 4; **b**: n = 2; **c**: n = 8				
		5a: 16 (29)	100	0.25	85	10
			5	5	51	99
		5b: 14 (24)	5	3	32	94
		5c: 20 (–)	5	3	55	91
 **6**	**7**	**a**: n = 4; **b**: n = 2; **c**: n = 1				
		7a: 10 (1.9)	5	0.5	10	41
			0.5	0.75	6	95
		7b: 8 (0.57)	5	0.75	12	0
			0.05	3	25	0
		7c: 7 (55)	5	0.75	20	29
			0.5	3	7	78
 **8**	**9**	**a** n = 2, **b**: n = 1; E = CO_2Et				
		9a: 7 (23)	0.5	0.75	45	49
		9b: 5 (2.1 x 10^6)	100	0.25	0	100
 **10**	**11**	**a**: n = 2; **b**: n = 1				
		11a: 10 (28)	5	1	44	41
			0.5	0.5	7	85
		11b: 8 (750)	5	0.5	0	99
			100	0.75	18	61
 **12**	**13**	**a**: n = 3; **b**: n = 2				
		13a: 13 (2)	0.5	3	42	0
		13b: 11 (<2)	0.5	3	29	0
 **14**	**15**	**15**: 14 (–)	5	0.5	100	4
			0.5	0.5	24	92

[a] Diene, **1** mixed in CH_2Cl_2 (22 °C); heated to reflux after 15 min. GC-FID quantification;[4] identity of RCM products confirmed by GC-MS. *E*/*Z* ratios in RCM products: **5a**/**c**, 72:28; **5b**, 89:11; **7a**, 41:59; **7c**, **9a**/**b**, **11a**/**b**, 0:100; **15**, 53:47. For EM values, see refs 3b and 11. [b] Calculated by difference.

ROMP of cyclooctadiene, polymer chains dominate at 1.8 M, but C_{12} rings are extruded at 0.13 M.[9b] Likewise, an unsaturated 21-membered macrocycle underwent ROMP at 0.7 M, but at 20 mM, the polymer liberated cyclomonomer and decreasing amounts of cyclodimer, trimer, and tetramer.[10] For oligomers of **4a**−**c**, the smallest rings (**5a**−**c**) form at 5 mM, but oligomers emerge at intermediate concentrations.

The kinetic bias of **4a**−**c** toward ADMET at 5 mM suggests that other macrocyclic or medium-ring compounds, for which effective molarity (EM) values are comparable or lower,[3b,11] should also undergo RCM via the oligomerization−backbiting mechanism. Of the ester, malonate, catechol, and polyether substrates shown in Table 1, all oligomerize at 5 mM except diethyl diallylmalonate **8b** (EM > 10^6)[11a] and catechol **10b** (EM 750).[3b] For **8b**, the gem−dimethyl and Thorpe−Ingold effects exert a powerful bias toward cyclization, and solely RCM is observed even at 100 mM. For **10b**, the small ring size and backbone rigidity favor cyclization, but oligomers emerge at 100 mM.

Equilibrium EM_{eq} values for saturated lactones tend to track the more usual, kinetic, EM values. The latter thus serve as a guide to the relative dilutions required to maximize backbiting. An exception is hexalactone, which has an EM_{eq} value ca. tenfold lower than expected from the kinetic EM value.[11b] Higher dilutions are indeed required for seven-membered **7c**, as well as **9a**. The presence of the metal in the cyclic transition state may increase the strain energies for these substrates. Where ring strain is too high, or the probability of encounter too low, cyclization fails, even at high dilution. Thus, oligomers of **12** do not cyclize at 0.5 mM, and formation of eight-membered **7b** fails even at 0.05 mM. Finally, we note that the oligomerization−backbiting mechanism does not require a conformational predisposition toward backbiting in the substrate. Polyether **14** undergoes preferential ADMET at 2.5−20 mM, consistent with the literature report,[2j] but diluting to 0.5 mM yields >90% **15** in 0.5 h.

While submillimolar substrate concentrations might be used to minimize oligomerization and enforce direct RCM, this would retard the bimolecular reaction between substrate and catalyst. The opposite approach greatly improved RCM efficiency for **4a**. By mixing **4a** and **1** at 100 mM, and diluting to 5 mM to promote backbiting, we obtained **5a** in 1 h (cf. 9 h for the Ziegler method).

Oligomers are overwhelmingly regarded as inimical to formation of RCM products. The foregoing demonstrates that this is a false premise. At dilutions compatible with efficient metathesis, ADMET oligomers provide a key vector for efficient synthesis of medium or large rings. Protocols designed to impede oligomerization prolong reaction times and potentially limit yields. An intriguing inference is the possibility that some "failed" RCM reactions may be more promising than they originally seemed. Failure may be an artifact of an inappropriately high concentration regime, or not permitting sufficient time for the reaction to evolve toward equilibrium. Preliminary results reveal similar behavior for other (Mo, Ru) metathesis catalysts. Detailed studies are under way, and will be reported in due course.

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Supporting Information Available: Synthetic details.This material is available free of charge via the Internet at http://pubs.acs.org.

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