Published in final edited form as:

Org Lett. 2007 November 8; 9(23): 4885–4888. doi:10.1021/ol7022505.

Olefin Metathesis in Homogeneous Aqueous Media Catalyzed by Conventional Ruthenium Catalysts

Joseph B. Binder[†], Jacqueline J. Blank[‡], and Ronald T. Raines^{*,†,‡}

Department of Chemistry, University of Wisconsin–Madison, 1101 University Avenue, Madison, WI 53706-1322, USA, and Department of Biochemistry, University of Wisconsin–Madison, 433 Babcock Drive, Madison, WI 53706-1544, USA

Abstract

Olefin metathesis in aqueous solvents is sought for applications in green chemistry and with the hydrophilic substrates of chemical biology, such as proteins and polysaccharides. Most demonstrations of metathesis in water, however, utilize exotic complexes. We have examined the performance of conventional catalysts in homogeneous water–organic mixtures, finding that the second-generation Hoveyda–Grubbs catalyst has extraordinary efficiency in aqueous dimethoxyethane and aqueous acetone. High (71–95%) conversions are achieved for ring-closing and cross metathesis of a variety of substrates in these solvent systems.

As a highly effective means for creating carbon–carbon bonds, olefin metathesis is a privileged reaction in the armamentarium of synthetic and polymer chemists.¹ Readily available and highly active ruthenium catalysts **1–4** have popularized metathesis chemistry in organic solvents (Figure 1).^{2,3} On the other hand, metathesis in aqueous solvents largely remains the domain of catalysts designed expressly for use in water (Figure 2).^{4,5,6} Despite the allure of aqueous olefin metathesis for biological applications⁷ and green chemistry,⁸ the synthesis of these water-soluble ligands and complexes imposes barriers to their wider use. Developing aqueous reaction conditions suitable for catalysts such as **1–4** is an alternative approach. In the initial work with well-defined catalysts in aqueous systems, Grubbs and coworkers performed ring-opening metathesis polymerization (ROMP) with **1** in aqueous emulsions,⁹ a method that allowed Kiessling and coworkers to synthesize biologically active glycopolymers.¹⁰ For ring-closing metathesis (RCM) and cross metathesis (CM), Blechert and coworkers employed commercially-available **2** and complex **6c**, a relative of commercially-available **4**, in water–methanol and water–DMF mixtures.⁶ Although they achieved high conversion in the ring-closure of *N*-tosyldiallylamine (**8**) in 3:1 water/methanol and 3:1 water/DMF over an extended reaction time of 12 h, these reactions were not accomplished in homogenous systems: neither the substrate nor the catalyst was dissolved completely in the aqueous phase. In most cases

raines@biochem.wisc.edu.

[†]Department of Chemistry.

[‡]Department of Biochemistry.

detailed in their report, the ruthenium complex was only sparingly soluble in the aqueous reaction mixture.

Metathesis in homogeneous aqueous systems would likely be faster and more versatile than in these heterogeneous systems. An effective system for metathesis with commercially available catalysts in homogeneous aqueous media would not only make this chemistry more accessible, but also highlight the limitations of the standard catalysts in water, informing catalyst-design efforts. Yet, reports of the use of common metathesis catalysts in an aqueous context are limited. For these reasons, we chose to test the capabilities of catalysts **1–4** in homogeneous aqueous media, and we report the results of our exploration herein. First, we screened various organic solvents as co-solvents for RCM of **8** in a homogeneous aqueous solution (Table 1). The solvents typically used for olefin metathesis reactions, such as CH₂Cl₂, 1,2-dichloroethane, and toluene, are immiscible with water, so we resorted to water-miscible solvents. Tetrahydrofuran (THF), used previously as a solvent for ROMP and acyclic diene metathesis with varying success,¹¹ failed as a cosolvent for RCM. On the other hand, the ethylene glycol ether-based solvents dimethoxyethane (DME or glyme) and poly(ethylene glycol) (PEG) were excellent co-solvents. Their improved results with respect to THF and dioxane could relate to their better coordinating ability.¹² Able to coordinate the tetracoordinate ruthenium complexes of the metathesis catalytic cycle, these ethers could more ably protect them from detrimental coordination by water. Grubbs and coworkers suggest that decomposition of metathesis intermediates in water results from water coordination at ruthenium in the methylidene-propagating species.¹³ Interestingly, these results show that the protective environment of the PEG-bearing ligand in **6a** can also be provided by ethylene glycol ethers in the bulk solvent.

Next, we studied the performance of different commercially available catalysts in the DME–water solvent system with substrate **8** (Figure 3). Phosphine-free complex **4** displayed the highest turnover, with both *N*-heterocyclic carbene (NHC) complexes outperforming the 1st-generation catalysts. The more σ -donating NHC ligand could aid olefin coordination over attack by water, favoring metathesis with the 2nd-generation catalysts as opposed to decomposition. The advantage of **4** over **2** is more difficult to rationalize because both complexes produce the same propagating species. The improved performance of **4** could be due to the presence of the chelating isopropoxy moiety, which could potentially protect the catalyst from decomposition in water prior to entry into the catalytic cycle, as suggested by Blechert and coworkers for metathesis in organic solvents.¹⁴ Although the ether ligand binds more loosely than does the phosphine of **2** (**4** initiates >800-fold faster at 25 °C),¹⁵ its rebinding to ruthenium prior to metathesis is unimolecular. As a result, the ether ligand is more likely to rebound the coordinatively unsaturated intermediate, protecting it from water to preserve the complex in solution.¹⁴ In addition to helping select known catalysts for use in water–organic systems, these results can inform the design of water-soluble catalysts. The combination of a chelate and an NHC produces a more effective catalyst for aqueous metathesis, as borne out by complexes **6a**, **6b**, and **7**. Future catalyst designs should incorporate these features.

Following the identification of **4** as the superior catalyst in the water–DME system, the progress of RCM in acetone–water was monitored to evaluate the rate of the reaction and the lifetime of catalytically-active species (Figure 4). The majority of RCM occurred within 90 min of the beginning of the reaction, as is typical for RCM of **8** with this catalyst and temperature.¹⁶ Notably, this reaction is far faster than the 12-h reaction time reported by Blechert and coworkers for their heterogeneous systems.¹⁰ Nevertheless, catalyst decomposition also proceeds quickly in the aqueous solvent, with the results of the trial with 0.5 mol % catalyst indicating that the majority of the catalytically-active species is destroyed within 90 min. In organic solvents, on the other hand, complex **4** can be recovered after RCM reactions requiring several hours.³

With optimized reaction conditions established, we probed the RCM of a variety of dienes using complex **4** in aqueous DME and acetone solutions. Under these homogeneous conditions, substrates with a variety of substituents were metathesized to form five-, six-, and seven-membered cyclic products (Table 2). High conversion was consistently achieved with traditional non-polar substrates, except for diallyldiphenylsilane (**14**). Water-soluble substrates such as **11** and **16**—a putative model for peptide substrates—were more challenging, requiring increased catalyst loading and organic cosolvent concentrations for high conversion. As it has with many other metathesis systems, diallyldimethylammonium chloride (**12**) resisted RCM.^{5,17} Complex **4** is also capable of homodimerization of allyl alcohol (**18**) in acetone–water, achieving good conversion over several hours (Table 3). Nevertheless, CM of other substrates in aqueous solvents has proven elusive for us as well as others.^{5,18}

The effectiveness of **4** for RCM and CM in aqueous–organic solution is comparable to that of complex **6b**, which is among the best catalysts for metathesis in pure water. Two conclusions can be drawn: homogeneous aqueous–organic mixtures could be advantageous for some olefin metathesis reactions, and the principle advantage of current aqueous metathesis catalysts is merely water solubility. Conventional catalysts such as **4** are active in aqueous solvents, and hence can be used for metathesis of polar molecules if the substrate is amenable to aqueous DME, PEG, or acetone. For instance, some enzymes and polysaccharides are compatible with aqueous DME,¹⁹ suggesting that these biomolecules might be suitable for a metathesis strategy that avoids the synthesis of specialized complexes. Moreover, we have found that ribonuclease A is >90% soluble in 3:2 DME/phosphate-buffered saline (PBS). In this solution, complex **4** is not only soluble, but also catalyzes the quantitative RCM of *N*-tosyldiallylamine (**8**), even in the presence of ribonuclease A.²⁰ Thus, apart from its insolubility in pure water, **4** is nearly as effective in the presence of water as are specialized complexes like **6b**. Hence, additional advances in aqueous metathesis will require enhanced ligands that not only provide water solubility but also improve upon the NHC and isopropoxy chelate in protecting the complex from water.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We are grateful to A. Choudary (University of Wisconsin–Madison) for critical review of this manuscript. J.B.B. was supported by an NDSEG Fellowship sponsored by the Air Force Office of Scientific Research. This work was supported by grant GM44783 (NIH). NMRFAM was supported by grant P41RR02301 (NIH).

References

1. Grubbs, R.H. *Handbook of Metathesis*. Wiley-VCH; Weinheim, Germany: 2003. Nicolaou KC, Bulger PG, Sarlah D. *Angew Chem, Int Ed* 2005;44:4490–4527. (b) Grubbs RH. *Angew Chem, Int Ed* 2006;45:3760–3765.
2. (a) Schwab P, Grubbs RH, Ziller JW. *J Am Chem Soc* 1996;118:100–110. (b) Kingsbury JS, Harrity JPA, Bonitatebus PJ Jr, Hoveyda AH. *J Am Chem Soc* 1999;121:791–799. (c) Scholl M, Ding S, Lee CW, Grubbs RH. *Org Lett* 1999;1:953–956. [PubMed: 10823227]
3. Garber SB, Kingsbury JS, Gray BL, Hoveyda AH. *J Am Chem Soc* 2000;122:8168–8179.
4. (a) Mohr B, Lynn DM, Grubbs RH. *Organometallics* 1996;15:4317–4325. (b) Binder JB, Guzei IA, Raines RT. *Adv Synth Catal* 2007;349:395–404.
5. (a) Hong SH, Grubbs RH. *J Am Chem Soc* 2006;128:3508–3509. [PubMed: 16536510] (b) Jordan JP, Grubbs RH. *Angew Chem, Int Ed* 2007;46:5152–5155.
6. Cannon SJ, Rivard M, Zaja M, Blechert S. *Adv Synth Catal* 2003;345:572–575.

7. (a) Banasiak DS. *J Mol Catal A: Chem* 1985;28:107–115. (b) Mortell KH, Gingras M, Kiessling LL. *J Am Chem Soc* 1994;116:12053–12054. (c) Miller SJ, Blackwell HE, Grubbs RH. *J Am Chem Soc* 1996;118:9606–9614. (c) Jenkins CL, Vasbinder MM, Miller SJ, Raines RT. *Org Lett* 2005;7:2619–2622. [PubMed: 15957905] (d) Stymiest JL, Mitchell BF, Wong S, Vederas JC. *J Org Chem* 2005;70:7799–7809. [PubMed: 16277299]
8. (a) Streck R. *J Mol Catal* 1992;76:359–372. (b) Yao Q, Zhang Y. *Angew Chem, Int Ed* 2003;42:3395–3398. Cornils, B.; Herrmann, W. *Aqueous-Phase Organometallic Catalysis*. 2. Wiley-VCH; Weinheim, Germany: 2004. (d) Clavier H, Grela K, Kirschning A, Mauduit M, Nolan SP. *Angew Chem, Int Ed* 2007;46:6786–6801.
9. (a) Fraser C, Grubbs RH. *Macromolecules* 1995;28:7248–7255. (b) Lynn DM, Kanaoka S, Grubbs RH. *J Am Chem Soc* 1996;118:784–790. (c) Mecking S, Held A, Bauers FM. *Angew Chem, Int Ed* 2002;41:544–561.
10. (a) Manning DD, Hu X, Beck P, Kiessling LL. *J Am Chem Soc* 1997;119:3161–3162. (b) Kanai M, Mortell KH, Kiessling LL. *J Am Chem Soc* 1997;119:9931–9932.
11. (a) Jin W, Fukushima T, Kosaka A, Niki M, Ishii N, Aida T. *J Am Chem Soc* 2005;127:8284–8285. [PubMed: 15941252] (b) Tastard CY, Hodge P, Ben-Haida A, Dobinson M. *React Funct Polym* 2006;66:93–107.
12. Smid, J. *Ions and Ion-Pairs in Organic Reactions*. Szwarc, M., editor. 1. Wiley Interscience; New York: 1972. p. 85-151. (b) Seddon WA, Fletcher JW, Catterall R, Sopchysyn FC. *Chem Phys Lett* 1977;48:584–586.
13. Towards a second-generation aqueous Grubbs metathesis catalyst: Understanding ruthenium methylenide decomposition in the presence of water (Jordan, J. P.; Hong, S. H.; Grubbs, R. H. Presented at the 229th National Meeting of the American Chemical Society, San Diego, CA, March 2005; Paper INOR-619).
14. Maechling S, Zaja M, Blechert S. *Adv Synth Catal* 2005;347:1413–1422.
15. Love JA, Morgan JP, Trnka TM, Grubbs RH. *Angew Chem, Int Ed* 2002;41:4035–4037.
16. Zaja M, Connon SJ, Dunne AM, Rivard M, Buschmann N, Jiricek J, Blechert S. *Tetrahedron* 2003;59:6545–6558.
17. Lynn, DM. PhD Thesis. California Institute of Technology; Pasadena, CA: 1999.
18. Connon SJ, Blechert S. *Bioorg Med Chem Lett* 2002;12:1873–1876. [PubMed: 12086837]
19. (a) Miller JF, Graves DJ. *Biochem Biophys Res Commun* 1981;99:1377–1383. [PubMed: 7259781] (b) van Tol JBA, Stevens RMM, Veldhuizen WJ, Jongejan JA, Duine JA. *Biotechnol Bioeng* 1995;47:71–81. [PubMed: 18623368] (c) van Langen LM, Oosthoek NHP, van Rantwijk F, Sheldon RA. *Adv Synth Catal* 2003;345:797–801. (d) Yoon JH, McKenzie D. *Enzyme Microb Technol* 2005;36:439–446.
20. *Reaction conditions*: 4 mol % 4, 0.025 M substrate 8, 0.2 mg/mL ribonuclease A, 3:2 DME/PBS, 24 h, rt, under air. It is noteworthy that water comprises 80% of the molecules in this reaction mixture.

6a R = CH₂OPEG-Me, R' = R'' = H

6b R' = [CH₂N⁺(Me)₂CH₂CH₂N⁺Me₃]₂·2 Cl⁻, R = R'' = H

6c R'' = O*i*Pr, R = R' = H

Figure 2.
Metathesis catalysts adapted for aqueous solvents.

Figure 3.

RCM conversion of 0.05 M substrate **8** catalyzed by complexes **1–4**: 1 mol % [Ru], 2:1 DME/water, 24 h, rt, under air.

Figure 4. Kinetics of RCM of 0.05 M substrate **8** catalyzed by complex **4** in acetone–water monitored by ¹H NMR spectroscopy.

Table 1

RCM catalyzed by **2** in aqueous media

solvent ^a	conversion (%)
4:1 THF/H ₂ O	3
4:1 1,4-dioxane/H ₂ O	5
4:1 DMF/H ₂ O	75
4:1 (CH ₃) ₂ CO/H ₂ O	>95
4:1 DME/H ₂ O	>95
3:1 PEG-500 dimethyl ether/H ₂ O	>95

^a Mass:mass ratio.

Table 2RCM of representative dienes catalyzed by **4** in aqueous media under air

substrate	solvent ([substrate], M)	mol % 4	conversion (%) (time, h)
9	2:1 (CD ₃) ₂ CO/D ₂ O (0.05)	3	>95 (2)
	2:1 DME/H ₂ O (0.05)	3	85 (3)
10	2:1 (CD ₃) ₂ CO/D ₂ O (0.05)	3	90 (2)
	2:1 DME/H ₂ O (0.05)	3	>95 (3)
8	2:1 (CD ₃) ₂ CO/D ₂ O (0.05)	3	>95 (2)
	2:1 DME/H ₂ O (0.05)	1	95 (24)
11	2:1 (CD ₃) ₂ CO/D ₂ O (0.01)	10	>95 (48)
	4:1 DME/H ₂ O (0.05)	10	77 (24)
12	2:1 (CD ₃) ₂ CO/D ₂ O (0.05)	3	0 (2)
13	2:1 (CD ₃) ₂ CO/D ₂ O (0.05)	3	>95 (2)
14	2:1 (CD ₃) ₂ CO/D ₂ O (0.05)	3	0 (2)
	2:1 DME/H ₂ O (0.05)	3	0 (3)
15	2:1 (CD ₃) ₂ CO/D ₂ O (0.05)	3	>95 (2)
16	4:1 DME/H ₂ O (0.02)	40	>95 (24)
17	2:1 (CD ₃) ₂ CO/D ₂ O (0.05)	3	>95 (2)
	2:1 DME/H ₂ O (0.05)	3	75 (4)

CM catalyzed by **4** in an aqueous medium under air

C=CCO **18**
 $\xrightarrow[2:1 \text{ (CD}_3)_2\text{CO/D}_2\text{O, rt, air}]{10 \text{ mol \% } \mathbf{4}, 0.1 \text{ M substrate } \mathbf{18}}$
OCC=CCO