

Microwave-Assisted Ring-Closing Metathesis Revisited. On the Question of the Nonthermal Microwave Effect

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Abstract: The ring-closing metathesis reactions (RCM) of six standard diene substrates leading to five-, six-, or seven-membered carbo- or heterocycles were investigated under controlled microwave irradiation. RCM protocols were performed with standard Grubbs type II and a cationic ruthenium allenylidene catalyst in neat and ionic liquid-doped methylene chloride under sealed vessel conditions. Very rapid conversions (15 s) were achieved utilizing 0.5 mol % Grubbs II catalyst under microwave conditions. Careful comparison studies indicate that the observed rate enhancements are not the result of a nonthermal microwave effect.

In recent years, the olefin metathesis reaction has attracted widespread attention as a versatile carbon–carbon bond-forming method.¹ Many new applications have become possible because of major advances in catalyst design. In particular, the advent of well-defined ruthenium-based metathesis precatalysts has triggered an explosive growth of interest in this transformation both from the organic and polymer chemist communities.² Among the numerous different metathesis methods, ring-closing metathesis (RCM) has emerged as very powerful method for the construction of small, medium, and macrocyclic ring systems.¹ Of particular interest in this context are the syntheses of complex natural products using RCM strategies,^{3a} including the preparation of the effective DNA cleaving agents turrianes,^{3b} the piperidine alkaloid (–)-halosaline,^{3c} or the odoriferous (*R*)-(+)-muscopyridine.^{3d}

In general, metathesis reactions are carried out at room temperature or at slightly elevated temperatures (e.g., at 40 °C in refluxing methylene chloride), sometimes requiring several hours of reaction time to achieve full conversion. Very recently, microwave irradiation has been introduced as a tool to enhance the effectiveness of

the RCM method.⁴ With microwaves, otherwise sluggish RCM protocols have been reported to be completed within minutes or even seconds, instead of hours at room temperature.^{5–9} Examples include microwave-enhanced standard olefin metathesis reactions in solution phase,^{5–7} the use of poly(ethylene glycol)-supported olefinic substrates,⁸ polystyrene-bound ruthenium catalysts,⁵ domino RCM reactions involving dienyne,⁹ and alkyne metathesis protocols.^{3b} In all these cases, significant rate enhancements were observed using microwave heating.

Because of the experimental simplicity of RCM transformations and the fact that metathesis chemistry is typically carried out in homogeneous solution in unpolar solvents that are weak absorbers of microwave energy, RCM reactions seem ideally suited to study the existence of so-called nonthermal microwave effects.¹⁰ Several groups have suggested that the direct activation of one or both of the polar reagents in the RCM process (i.e., the catalyst and/or the olefin) is responsible for the observed rate enhancements.^{5,7} Here we report a thorough reinvestigation of microwave-assisted RCM chemistry employing dedicated single-mode microwave applicators, specifically addressing the issue of the involvement of nonthermal microwave effects.

Our starting point in these investigations involved RCM reactions of six standard model substrates **1a–f** producing five-, six-, or seven-membered carbo- or heterocycles **2a–f** (Scheme 1). Apart from the well-investigated Grubbs type II catalyst **3**,² we have also employed the cationic ruthenium allenylidene catalyst **4** in our studies. This family of cationic ruthenium metathesis initiators is readily prepared from commercially available precursors and can be applied to the formation of essentially all rings with five or more members in good to excellent yields.^{11,12} However, RCM reactions with this catalyst generally require prolonged heating at elevated temperatures.^{11,12} We were particularly interested to see if the polar cationic nature of catalyst **4**, allowing for interaction with microwaves by an ionic conduction

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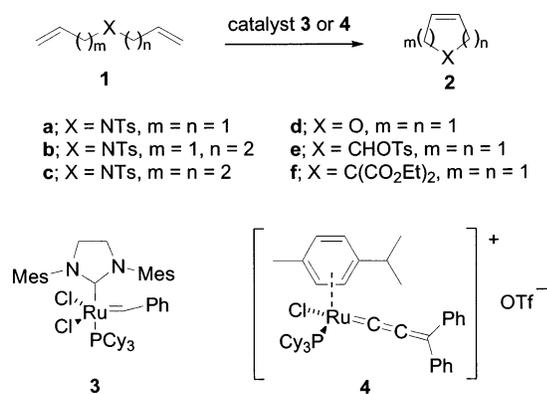
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SCHEME 1



mechanism,¹³ would lead to enhanced activity under microwave irradiation.

Initial optimizations of microwave-assisted RCM reactions with catalyst **4** were conducted with *N,N*-diallyltosyl amide substrate **1a** (Ts = tosyl). A variety of different microwave irradiation conditions (time/temperature) and solvents such as methylene chloride (DCM), carbon tetrachloride (CCl₄), 1,2-dichloroethane (DCE), and toluene were investigated. High conversions (94%) were achieved by exposing substrate **1a** in DCM or CCl₄ to sealed-vessel microwave irradiation at 100 °C for 20 min, employing 2 mol % catalyst **4**. Use of DCE as a solvent required somewhat higher reaction temperatures (140 °C) to achieve similarly rapid conversions. At the same time, the formation of byproducts resulting from the cycloisomerization or double-bond isomerization of diene **1a** was more pronounced at those higher reaction temperatures.¹⁴ The results obtained in DCM at 100 °C compared very favorably with classical protocols where reaction times of 16 h were necessary in order to achieve full conversion in refluxing (40 °C) DCM (at room temperature, the conversion was only 46% after 16 h).¹⁵ Having a set of optimized conditions for RCM reactions with the cationic metathesis initiator **4** in hand, we next explored the usefulness of the microwave-assisted RCM protocol to substrates **1b–e**, which have proved to be more difficult for metathesis reaction under conventional conditions (DCM, 40 °C, data not shown). Using the microwave approach made it possible to convert all dienes to the ring-closed products with good conversion within 20 min at 100–140 °C reaction temperature. However, note that a reaction temperature higher than 100 °C did not always lead to a higher conversion. While for diene **1b** a temperature of 140 °C was tolerated, providing 93% conversion to the six-membered heterocyclic product **2b**, for substrates **1e,f**, an increase in reaction temperature or time did not provide higher conversion rates. For diene

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(14) At 140 °C in DCE (microwave irradiation), up to 40% byproducts were formed via different isomerization processes. Employing DCM as a solvent at 100 °C led to formation of less than 5% of the cycloisomerization product. For structural and mechanistic details on this isomer formation, see ref 11. For substrates **1b–f**, no byproducts were encountered in the RCM process.

(15) Originally reported conditions (ref 11) on the RCM of diene **1a** with catalyst **4** (2.5 mol %) in toluene required 19 h (90% conversion) at room temperature or 5 h at 80 °C (99% conversion).

TABLE 1. Reaction Conditions for Microwave-Assisted Ring-Closing Metathesis of Dienes **1a–f** with Allenylidene Catalyst **4** (Scheme 1)

diene	mol % catalyst	time (min)	temp (°C)	conversion ^a
1a	2	20	100	94 ^b
1b	2	20	140	93
1c	2	20	100	88
1d	2	20	100	>98 ^c
1e	4 ^d	20	100	90
1f	4	20	100	61

^a Conversions were determined by ¹H NMR analysis of the crude reaction mixture. ^b Mixture of product **2a** and the cycloisomerized byproduct (94:6) was obtained. See ref 14 for details. ^c Determined by HPLC. ^d With 2 mol % catalyst, the conversion was 68% (100 °C, 20 min).

1e for example, an increase of the reaction temperature from 100 to 120 °C or a prolonged irradiation time from 20 to 30 min did not lead to better than 67% conversion (Table 1). For both substrates **1e** and **1f**, it was necessary to increase the catalyst concentration to 4 mol % in order to obtain good conversions within 20 min (90 and 61%, respectively). Most likely, prolonged microwave irradiation of the reaction mixture leads to inactivation (thermal degradation) of the catalytic system. This assumption was also supported by visual inspection of the reaction mixture after high-temperature microwave irradiation. Deactivation of the red-colored catalyst **4** was evident by a change in color from dark red to brown. In contrast, for RCM reactions leading to full conversion, the color of the reaction mixture after microwave irradiation was yellow.

We next investigated the reactivity of the Grubbs type II catalyst **3** in the microwave-assisted RCM transformations **1** → **2**. In our hands, the Grubbs system proved to be very active toward all substrates **1a–f**, leading to high conversions even at room temperature (89% conversion for **1a** with 2 mol % Grubbs in 1 h). For the microwave experiments, in contrast to the ruthenium allenylidene metathesis initiator **4**, here full and clean conversions (>98% by ¹H NMR) were achieved within 2–5 min for all six cases using DCM as a solvent at 60 °C. Remarkably, 0.5 mol % catalyst **3** were sufficient to achieve those results.¹⁶ These findings are in agreement with very recent reports on rapid RCM reactions under microwave conditions employing Grubbs type II catalyst **3**, although higher catalyst loadings (1–12%) were utilized in those studies.^{5–7} Further refinement of conditions led to even faster reaction rates by addition of small amounts of an ionic liquid such as 1-butyl-3-methylimidazolium hexafluorophosphate (bmimPF₆) to the reaction mixture. It has been reported earlier that small amounts of an ionic liquid can be employed as additives in order to increase the dielectric constant of an otherwise nonpolar solvent medium in microwave-assisted reactions.¹⁷ We find that here it is not necessary to conduct RCM chemistry in neat

(16) For example, for substrate **1a**, it was demonstrated that the concentration of catalyst **3** could be further reduced to 0.25 mol % and still lead to complete conversion to **2a** (60 °C, 2 min). Further reduction in catalyst concentration to 0.1 mol % showed incomplete conversion.

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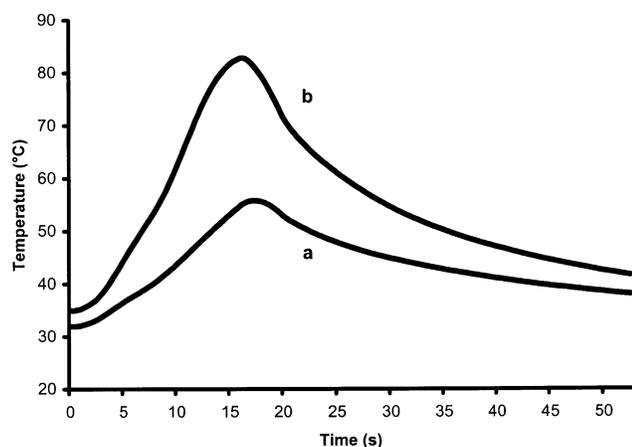


FIGURE 1. Heating profiles for microwave-heated DCM doped with 1-butyl-3-methylimidazolium hexafluorophosphate (bmimPF₆) (300 W power, 15 s total irradiation time). Experiments were carried out in a 5 mL sealed glass vial containing 2 mL of DCM. Profile a: neat DCM. Profile b: 0.04 M bmimPF₆ in DCM. Temperatures were recorded on the outer surface of the glass vial by an IR sensor. The cooling profiles (compressed air cooling) are also shown.

ionic liquids as recently described by Mayo et al.⁵ Using the ionic liquid to dope the weakly absorbing solvent DCM suffices to achieve very rapid conversions. In the case of diene **1a**, for example, we find that 15 s of microwave irradiation afforded full conversion. For very short reaction times under microwave conditions, it is essential to look at the corresponding heating profiles to rationalize the observed results. Figure 1 displays the heating profile of neat DCM and a 0.04 M bmimPF₆-doped DCM solution under single-mode microwave irradiation. It is worth noting that neat DCM is *not* microwave transparent ($\tan \delta = 0.042$)¹³ and will heat up significantly in a single-mode microwave reactor as a result of the high power density applied in a single-mode cavity,^{4b} although this heating effect is in part also due to a heating of the borosilicate glass vessel, which is not completely transparent to microwave irradiation either (see below). Figure 1 demonstrates that the ionic liquid-doped medium is absorbing microwave energy considerably faster than the neat solvent. While the conversion for a RCM run with substrate **1a** (0.5 mol % catalyst **3**) in the ionic liquid-doped medium was >98% after 15 s of irradiation, only 57% conversion was achieved in neat DCM after the same time period. This is not surprising since the reaction temperature during the full irradiation event (0–15 s) is significantly lower for the neat solvent (Figure 1).

Disappointingly, it was not possible to use the cationic catalyst **4** in conjunction with an ionic liquid-doped solvent. With both bmimPF₆ and bmimBF₄ (0.04 M in DCM), conversions were below 30%, presumably due to catalyst deactivation.¹² All further studies on the existence of a nonthermal microwave effect in RCM reactions were conducted with Grubbs type II catalyst and model substrate **1a**.

To truly investigate the influence of selective heating of a polar reagent or catalyst on the rate of the RCM reaction, it was necessary to exchange the standard borosilicate glass reaction vessels for a custom-made

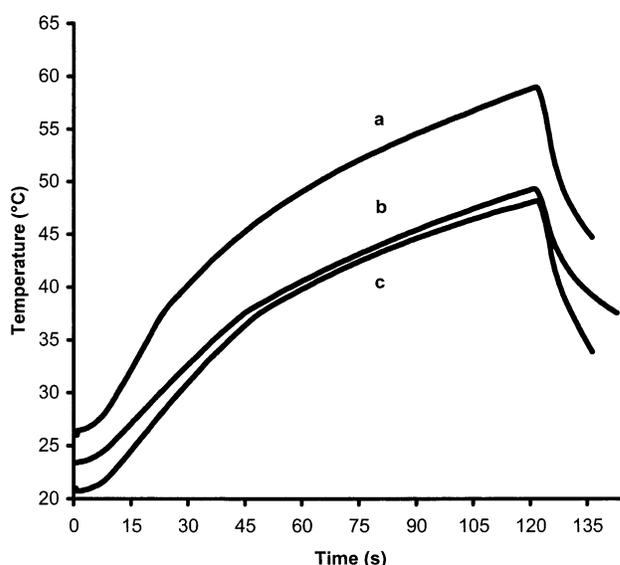


FIGURE 2. Heating profiles for 0.05 M solutions of diene **1a** (a), 0.005 M solution of catalyst **3** (10 mol %) (b), and neat DCM (c) in a quartz vessel at 100 W constant microwave power. Temperatures were recorded on the outer surface of the quartz vial by an IR sensor. The heating profile for the reaction mixture **1a** + **3** in DCM (not shown) is very close to the profile for the diene (irrespective of the catalyst concentration).

quartz vessels. As shown in Figure S1 in Supporting Information, self-heating of the quartz vessel is minimal as compared to that of the standard glass vial, as tested by filling the vial with a microwave-transparent solvent such as CCl₄. For the weakly microwave-absorbing DCM, the effect is not as pronounced as for CCl₄, but still significant (see Figure 2). Disappointingly, CCl₄ was not an effective solvent for metathesis chemistry. Performing experiments under conditions identical to those described above for the transformation **1a** → **2a** using catalyst **3** (100 °C, 2–5 min), switching from DCM to CCl₄, led to a dramatic reduction in efficiency. Even in the presence of an ionic liquid (bmimPF₆ or bmimBF₄) the conversion was not higher than 30% under all tested conditions. Therefore, all further experiments aimed at the investigation of nonthermal microwave effects were conducted in DCM using a quartz microwave reaction vessel.

We next looked at the individual heating profiles of both the catalyst **3** and the olefin **1a** in DCM, and the actual reaction mixture containing the catalyst and the substrate in DCM using the microwave-transparent quartz vessel. In our studies (Figure 2) performed at a constant 100 W power, it became evident that the diene **1a** showed a significant microwave absorption. Even at the comparatively low concentration of 0.05 M, the change in the heating profile compared to the pure solvent was dramatic. In contrast, the absorption of the Grubbs catalyst **3** even at 10 mol % concentration (0.005 M solution) was negligible. It has been argued that polar molecules (here diene **1a**) can act as so-called “molecular radiators” creating microscopic hotspots upon microwave irradiation in unpolar solvents.¹⁸ It has further been argued that this selective heating/activation of the re-

agents (as opposed to the bulk solvent) may lead to rate enhancements through a nonthermal microwave effect.^{5,7,11,18}

To investigate the existence of any nonthermal microwave effects, we next have conducted careful comparison studies between microwave and thermal (oil bath) experiments. Any difference in the results between a metathesis experiment done in an oil bath with an equilibrated reaction temperature of 60 °C and one in a microwave experiment at the same temperature would indicate the presence of a nonthermal/specific microwave effect. We have therefore exposed our model diene substrate **1a** to Grubbs catalyst **3** (0.5 mol %) in DCM to a 60 °C reaction temperature derived from a standard oil bath. To be able to fully compare with the microwave results, the thermal reaction was carried out in the same reaction vessel as the microwave run, using exactly the same reaction parameters. To mimic the rapid, direct heating typically observed in microwave chemistry,⁴ the diene solution in DCM was preheated to 60 °C in an oil bath before a solution of the metathesis catalyst **3** was added via syringe through the Teflon septum (for details, see Experimental Section). Under these thermal conditions, full conversion of diene **1a** to the metathesis product **2a** was observed within 2 min. This result corresponds to the microwave-heated experiment described above. To further compare microwave and thermal heating, we have also carried out another series of experiments at 40 °C reaction temperature, involving reflux conditions in an oil bath and microwave irradiation at the same ca. 40 °C temperature. Again, there was a close correlation between the results obtained by thermal and microwave heating (Table 2).

In contrast to the recent publication by Mayo et al.,⁵ who have investigated the exact same substrate/catalyst/solvent system (albeit in a domestic microwave oven), we do not find any evidence for a significant nonthermal microwave effect.¹⁹ Although our investigations have

(18) For a discussion of the concept of molecular radiators, see for example: (a) Kaiser, N.-F.; Bremberg, U.; Larhed, M.; Moberg, C.; Hallberg, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3595–3598. (b) Steirer, A.; Stadler, A.; Mayer, S. F.; Faber, K.; Kappe, C. O. *Tetrahedron Lett.* **2001**, *42*, 6283–6286. See also ref 10.

TABLE 2. Conversion (%) in Model RCM Reaction (1a → 2a) Using 0.5 Mol % Catalyst 3 in DCM^a

time (min)	25 °C	40 °C		60 °C	
		conversion ^b	MW ^c	conversion ^d	MW ^c
2				>99	>99
5	13	65	70		
10	27	92	>99		
20	46	>99	>99		
30	60				
90	>99				

^a Conversions were determined by HPLC analysis (215 nm) of the crude reaction mixtures. ^b Thermal heating under open vessel reflux conditions. ^c Sealed vessel single-mode microwave irradiation at 40 or 60 °C. ^d Thermal heating under sealed vessel conditions.

confirmed that selective heating of the diene substrate under microwave conditions takes place (Figure 2), this is apparently not instrumental for the progress of the metathesis reaction. For the RCM chemistry studied herein, it does not matter if the energy is directly transferred to one of the reactants (probably the diene) or to the bulk of the solvent by thermal or microwave heating. The comparatively rapid metathesis transformations **1** → **2** observed herein can be rationalized solely by taking thermal effects (Arrhenius equation) into account.

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Supporting Information Available: Experimental procedures and Figure S1. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(19) Very rapid 15 s conversion **1a** → **2a** experienced with ionic liquid-doped DCM (Figure 1) could also be reproduced by thermal heating at 80 °C (see Experimental Section for details).