Solvents for ring-closing metathesis reactions†

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A study of the influence of eight diverse solvents on a Grubbs II-catalysed ring-closing metathesis (RCM) reaction reveals a complex dependence of the different reaction steps on the solvent and suggests acetic acid as a useful solvent for RCM reactions.

Olefin metathesis reactions catalysed by the 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ruthenium complex **Ru** (Grubbs II catalyst)[1] continue to be of great importance[2] (the 1999 paper describing the preparation of this complex has been cited *ca.* 1300 times). Despite the numerous mechanistic and computational studies of these reactions,[3,4] relatively few publications have focused on solvent effects, even though solvents influence both the rate and *cis*/*trans* stereoselectivity.

Experimentally, studies by several groups have identified solvent influences on both rates and turnover frequencies of metathesis reactions.[4–6] Computational studies[3a] support the observation by Grubbs that more polar solvents lead to higher initiation rates, due to their greater stabilising effect on the complex **Ru***, resulting from phosphine dissociation.

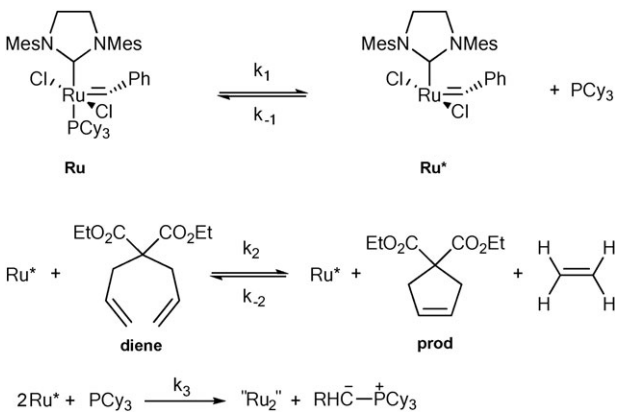
The stereoselectivity of ring-closing metathesis (RCM) using **Ru** can be highly solvent-dependent. For example, Wang and Forsyth, in a ring-closing reaction to form the macrolide-containing domain of phorboxazole A, observed almost complete selectivity for the desired *cis* isomer when the reaction was carried out in hexanes, whereas a slight predominance of the *trans* isomer was found in toluene.[7]

In this study, we aimed first to develop a model of solvent influences on the rates of ring-closing reactions catalysed by Grubbs II catalyst **Ru** that matched kinetic data collected in a set of diverse solvents. We then wished to use our model to explain the chemical basis for the observed effects.

The model reaction we elected to study was the RCM of diethyl diallylmalonate (**diene**) to yield the corresponding cyclopentene (**prod**) and ethylene, since the starting material is readily available and it is known that the reaction can be followed by NMR spectroscopy.[8] Eight solvents, all available to us in perdeuterated form, were selected to include a representative range of polarities and functional groups. The two solvents most widely used for RCM reactions, dichloromethane and toluene, were included amongst them.

Kinetic data were obtained using ^{1}H NMR spectroscopy at 298 K with 0.12 M **diene** and 0.0067 M **Ru** (where solubility permitted), and with 0.12 M 1,3,5-trimethoxybenzene as the internal standard,[9] noting that the ^{1}H NMR signal due to the aromatic H-atoms of the standard in perdeutero acetic acid is almost zero due to rapid deuterium exchange. Since we aimed to develop a model of direct relevance to synthetic chemists, no special precautions were taken to exclude air or moisture. Spectra were recorded at 2 min intervals for 4 h. Spectra were examined carefully to select peaks that would integrate cleanly, with particular care being needed to avoid overlap with the many broad peaks due to the catalyst species.

A number of reaction schemes and corresponding kinetic models were developed, based on extensive reading of the literature.[3,4,10] The best match to the data, based on the application of reaction progress kinetic analysis[11] and maximum likelihood estimation,[12] is given in Scheme 1, and in the kinetic model in eqns (1)–(5). The key features are (i) a first, reversible, dissociative step to form **Ru*** and tricyclohexylphosphine (**PCy_3**), in accordance with the literature,[3,4] (ii) treatment of the entirety of the subsequent metathesis reactions as a single, reversible rate-determining step, (iii) an assumption that the barrier to ethylene coordination is negligible,[3d] and that there is always a sufficient amount of ethylene in solution (confirmed by NMR spectroscopy), so that the concentration of ethylene is not included in the rate expression for the reverse metathesis reaction, and (iv) irreversible deactivation to form a diruthenium species ("Ru_2" in Scheme 1). A mechanism for deactivation from the methylidene analogue of **Ru*** has been proposed.[10] In our model, we have not treated the methylidene and benzylidene species as distinct, and have assumed that the rate of deactivation is independent of phosphine concentration.



Scheme 1 Mes = mesityl (2,4,6-trimethylphenyl).

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Table 1 Rate constants fitted to experimental data[a] for the RCM of **diene**

Solvent	k_1/s^{-1}	k_{-1}/l mol^{-1} s^{-1}	k_2/l mol^{-1} s^{-1}	k_{-2}/l mol^{-1} s^{-1}	k_3/l mol^{-1} s^{-1}
Dichloromethane	0.0617	0.373	0.137	0.00775	0
Cyclohexane	0.241	0.0363	0.523	0.0123	0
Toluene	0.159	0.0159	0.195	0.0128	0.0207
Acetic acid	0.527	0.00808	1.412	0.00872	0.029
Chlorobenzene	0.239	0.405	0.301	0.0197	0.0344
Acetone	0.0146	2.434	1.676	0.231	3.000

[a] All NMR data were recorded on a Bruker DRX500 at 500.13 MHz.

The evolution of the concentration of the five key species in the reaction is given by:

$$\frac{d[Ru]}{dt} = -k_1[Ru] + k_{-1}[Ru^*][PCy_3] \quad (1)$$

$$\frac{d[Ru^*]}{dt} = k_1[Ru] - k_{-1}[Ru^*][PCy_3] - 2k_3[Ru^*]^2 \quad (2)$$

$$\frac{d[PCy_3]}{dt} = k_1[Ru] - k_{-1}[Ru^*][PCy_3] - k_3[Ru^*]^2 \quad (3)$$

$$\frac{d[diene]}{dt} = -k_2[diene][Ru^*] + k_{-2}[prod][Ru^*] \quad (4)$$

$$\frac{d[prod]}{dt} = k_2[diene][Ru^*] - k_{-2}[prod][Ru^*] \quad (5)$$

Experimentally, there is insignificant conversion of **diene** in both isopropanol and propionitrile. For isopropanol, this appears to be due to the very low solubility of the catalyst, whereas propionitrile is expected to coordinate **Ru*** and reduce its catalytic activity.[13] Values for the five rate constants were obtained for each of the six remaining solvents by fitting to concentration data for **prod** (Table 1). The catalyst is sparingly soluble in both cyclohexane and acetic acid, and only 0.0004 M **Ru** was used in these cases in order to maximise dissolution.

To facilitate a comparison of the influences of the six solvents in which turnover occurred, we carried out simulations of the kinetic data based on the observed rate constants from Table 1.[12] The normalised conditions we selected were 0.10 M **diene** and 0.00042 M catalyst. The simulated evolution of the product with time is shown in Fig. 1. Most unexpectedly, acetic acid clearly emerged as the best solvent for the RCM of **diene**. The reaction in dichloromethane, a solvent commonly used for RCM reactions, was significantly slower, though it did proceed to completion. Cyclohexane was the only other solvent of our set in which complete conversion was predicted, but the very poor solubility of the catalyst in cyclohexane meant that this was not achieved in practice. Fig. 2 shows the predicted evolution of the active catalyst **Ru*** during the reaction. In dichloromethane and cyclohexane we recorded no deactivation.‡ Acetic acid, as well as the two aromatic solvents, led to some deactivation, whereas in acetone, catalyst deactivation dominated the reaction's progress, limiting conversion to around 60%.

Dichloromethane and acetic acid appear to represent two strategies in terms of successful solvents for this RCM reaction. First, as described by Grubbs,[4] the strategy represented by dichloromethane is to minimise catalyst deactivation. Fig. 2 shows that, of the solvents we studied, dichloromethane and cyclohexane do not promote deactivation under these reaction conditions. A second strategy is to maximise the rates of the productive reactions, in which case some catalyst deactivation can be tolerated. Table 1 shows that acetic acid has relatively high values for k_1 and k_2, relatively low values for k_{-1} and k_{-2}, and an intermediate value for k_3, the rate constant for deactivation.

We note that the rate constants reported in Table 1 for the two equilibrium processes are highly correlated. We next plan to determine values for the equilibrium constants computationally, and thereby to adjust these data.

We developed a basic model of solvent effects to gain a better understanding of the observed differences in rate and yield. For each rate constant, we used the solvent data to fit solvatochromic eqn (6), which relates the logarithm of the rate

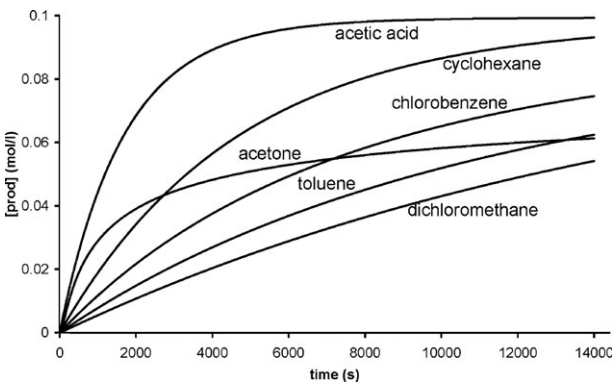

Fig. 1 Simulated concentration of product, based on observed rate constants, in the reaction of 0.1 M **diene** with 0.00042 M catalyst.

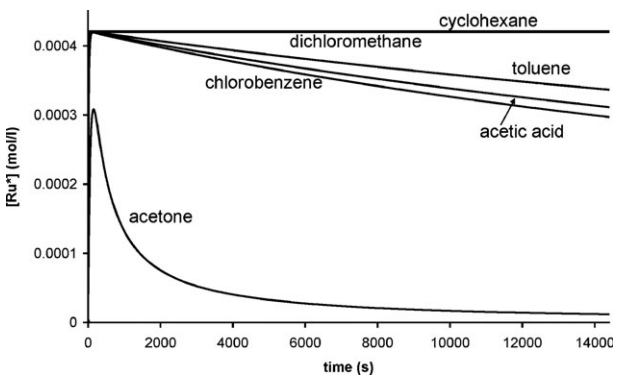

Fig. 2 Simulated concentration of active catalyst **Ru*** in the reaction of 0.1 M **diene** with 0.00042 M catalyst.

Table 2 Solvatochromic coefficients for the five rate constants in the proposed kinetic model

Rate constant	$c_{o,i}$	$c_{A,i}$	$c_{B,i}$	$c_{S,i}$	$c_{\delta,i}$	$c_{\delta_H,i}$/ MPa^{-1}
k_1 (i = 1)	−16.888	3.097	4.039	−15.129	2.225	6.304
k_{-1} (i = −1)	−0.4720	−4.237	−0.3051	4.496	−1.922	−0.5062
k_2 (i = 2)	−17.555	2.239	5.151	−15.634	1.733	6.707
k_{-2} (i = −2)	−17.833	−0.1985	4.876	−15.372	1.188	6.570
k_3 (i = 3)	−95.272	11.196	35.701	−81.849	14.621	34.707

constant to five solvent properties:[14] the solvatochromic parameters[15] A, B and S, a polarisability correction factor, δ, and the cohesive energy density, δ_H^2, in MPa. A is a measure of the solvent's hydrogen bond acidity, B of its hydrogen bond basicity and S of its dipolarity/polarisability. The factor δ is equal to 1 for aromatic solvents, 0.5 for polyhalogenated aliphatic solvents and 0 for other solvents. The rate constant $k_{i,j}$ for reaction i in solvent j is given by:

$$\log k_{i,j} = c_{o,i} + c_{A,i}A_j + c_{B,i}B_j + c_{S,i}S_j + c_{\delta,i}\delta_j + \frac{c_{\delta_H,i}}{100}\delta_{H,j}^2 \quad (6)$$

where the c coefficients are the reaction parameters reported in Table 2. They are considered solvent-independent.

An examination of Table 2 shows that, with the exception of the solvatochromic coefficient for hydrogen bond acidity c_A, the rate constants for the metathesis process k_2 and k_{-2} are affected to the same extent by all coefficients. Therefore, the best way to influence the productive step using the solvent seems to be to increase its hydrogen bond acidity, taking care not to adversely affect the rate of deactivation. Deactivation is best suppressed by solvents that have a high polarisability, S, which is one reason why dichloromethane is a good choice of solvent for RCM reactions. The parameter values reported in Table 2 were obtained using a limited set of solvents, which results in wide confidence intervals. In a more detailed study, we plan to expand the range of solvents used, in order to increase the statistical significance of this model of solvent influence on the reaction.

The beneficial effect of acetic acid on the RCM of **diene** was confirmed in synthetic studies. **Diene** (1.0 g) in acetic acid (50 ml) with just 8.8 mg (0.25 mol%) Grubbs II catalyst underwent complete conversion to the cyclopentene product in 3 h at room temperature, as judged by TLC and NMR spectroscopy, with a yield after aqueous work-up of 82%. Using dichloromethane instead of acetic acid under the same conditions, *i.e.* 0.25 mol% catalyst, led to only 80% conversion after 5 h, as judged by NMR spectroscopy. Pleasingly, acetic acid is rated highly as an environmentally favourable solvent.[16]

We do not yet understand how acetic acid improves the outcome of this RCM reaction, though we note that acid additives, including acetic acid, have been shown to suppress isomerisation processes, probably caused by ruthenium hydride intermediates, which compete with RCM.[17] Nor can we be sure that acetic acid will have the same effect on other metathesis reactions. Hence we plan further computational, solvent design and synthetic studies.

In conclusion, our systematic investigation of solvent influences on a metathesis reaction highlights significant variation in productivity, resulting from a fine balance between initiation, catalytic turnover and catalyst deactivation. One of the traditional solvents for metathesis, dichloromethane, is effective mainly because the rate of catalyst deactivation is negligible. Surprisingly, acetic acid is revealed to be a more productive solvent for the RCM of **diethyl diallylmalonate**, due to notably faster rates of initiation and catalytic turnover; synthetically, the RCM of **diethyl diallylmalonate** is efficient with only 0.25 mol% of Grubbs II catalyst.

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Notes and references

‡ Plotting rate *vs.* substrate concentration at different catalyst concentrations[11] in dichloromethane confirmed that the rate of deactivation is negligible in dichloromethane.

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