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The Impact of Water on Ru-Catalyzed Olefin Metathesis: Potent Deactivating Effects Even at Low Water Concentrations

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Supporting Information Placeholder

ABSTRACT: Ruthenium catalysts for olefin metathesis are widely viewed as water-tolerant. Evidence is presented, however, that even low concentrations of water cause catalyst decomposition, severely degrading yields. Of 11 catalysts studied, fast-initiating examples (e.g., the Grela catalyst $\text{RuCl}_2(\text{H}_2\text{IMes})(=\text{CHC}_6\text{H}_4\text{-2-O}^i\text{Pr-5-NO}_2)$) were most affected. Highest water-tolerance was exhibited by slowly-initiating iodide and cyclic (alkyl)(amino)carbene derivatives. Computational investigations indicated that hydrogen-bonding of water to substrate can also play a role, by retarding cyclization relative to decomposition. These results have important implications for olefin metathesis in organic media, where water is a ubiquitous contaminant, and for aqueous metathesis, which currently requires superstoichiometric “catalyst” for demanding reactions.

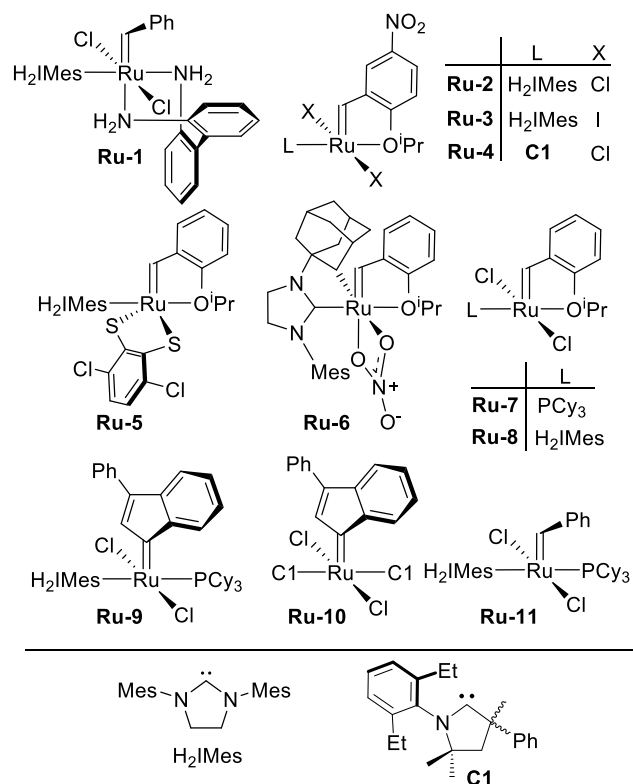
Keywords olefin metathesis, catalyst decomposition, macrocycle, conformation, water, aqueous metathesis, chemical biology, Z-selective

Olefin metathesis has been widely embraced for its versatility in the catalytic assembly of carbon-carbon bonds.^{1,2} The demand for catalysts that integrate high activity with robustness has intensified with a recent explosion in applications in chemical biology,^{3-5a} materials science,⁶ and chemical manufacturing.⁷ Tolerance for water is critical in many contexts, most prominently olefin metathesis in water-rich environments. Successes in aqueous metathesis of model substrates with ruthenium catalysts⁵ (see, e.g., Chart 1) have been leveraged to advance metathetical modification of proteins,³ peptides,⁸ and DNA,^{4b,9} and to develop water-soluble materials for drug delivery and other applications.^{6a-e,10,11}

These applications place extreme demands on the water-tolerance of the catalysts. Decomposition by water is increasingly identified as an obstacle to olefin metathesis in chemical biology^{3,5a} (where Isenegger and Davis describe bioconjugation as a race between metathesis and decomposition)^{3a} and biomaterials applications.^{6a-e,10-12} The catalyst loadings required are routinely orders of magnitude above those in organic media: in highly demanding contexts such as protein modification, the Ru reagent must be used in significant stoichiometric excess.¹³ An anticipated, undesirable consequence is

accelerated bimolecular decomposition of the active species,¹⁴ and associated side-reactions. Decomposed catalyst is believed to trigger both DNA degradation^{9,15} and C=C migration.¹⁶

Chart 1. Olefin Metathesis Catalysts Discussed



Given that the problems of water co-solvent are only beginning to be widely recognized,^{3,5a,17,18} it is unsurprising that challenges arising from low levels of water have not yet been considered. Here we demonstrate that even 0.1–1% v/v water¹⁹ can severely limit the productivity of leading NHC and CAAC ruthenium catalysts. We also identify catalyst features that maximize water-tolerance, a finding that offers new opportunities in organic synthesis, and in broader contexts in which water is an essential co-solvent.

RCM macrocyclization (mRCM) represents a methodology of major current interest for the production of antiviral therapeutics.^{7,20} The first indication that even low concentrations of water might impede mRCM emerged in reactions involving the dianiline catalyst **Ru-1** (Chart 1). In our hands, **Ru-1** was exceptionally efficient,²¹ outperforming even the leading nitro-Grela catalyst **Ru-2** in mRCM of challenging, highly flexible substrates bearing multiple polar sites. Synthetic collaborators, however, observed variable performance. We speculated that the discrepancy might arise from the established²¹ hydrogen-bonding capacity of **Ru-1**. Sensitivity to water would have gone unobserved in our original work because rigorously dry²² solvents were used, a standard protocol in organometallic chemistry. In broader synthetic practice, water is a ubiquitous, little-regarded contaminant. It thus seemed plausible that water-induced decomposition might contribute to the inconsistent performance of **Ru-1**.

To probe this point, we examined the impact of water on mRCM of **1** (Figure 1a, dotted-fill).²³ This reaction affords the olfactory lactone **2** via a concentration-dependent ring-chain equilibrium.²⁴ High dilutions are essential to favour the cyclic product, as with any conformationally flexible diene.^{24,25} For **1**, in which the ester functionality confers the sole conformational bias toward cyclization,²⁶ a diene concentration of ≤ 5 mM is required.²⁴ At catalyst loadings of 0.05 mol%, this translates into 2.5 μ M Ru: even low concentrations of water are thus stoichiometrically significant.

In dry toluene, mRCM of **1** reached 83% yield within 0.5 h at RT (Figure 1a). Addition of 0.01% water – that is, 100 ppm by volume – caused a ca. 60% drop in yield. At higher proportions of water (0.1 or 1% v/v), mRCM failed, signifying near-complete catalyst decomposition.

As shown in Figure 1b, the Grela catalyst **Ru-2** is decomposed to a lesser extent, affording 30% mRCM in the presence of 0.1% v/v water (vs 87% mRCM in dry toluene).²⁷ More robust is the iodide analogue **Ru-3**. Water – somewhat unexpectedly – is emerging as a much more aggressive agent than O₂ in Ru-catalyzed olefin metathesis,²⁸ and this higher water-tolerance is thus presumed to be key to the strong performance of **Ru-3** in aerobic metathesis.²⁹ One probable contributor to improved tolerance is the limited capacity of **Ru-3** to enter into hydrogen-bonding interactions with water. ROH...Cl–Ru interactions have been reported for related metathesis catalysts,^{30,31} and the higher water-sensitivity of **Ru-1** vs **Ru-2** is consistent with stronger H-bonding to a dangling NH₂ functionality.

To assess the potential impact of water on *E/Z* selectivity, two *Z*-selective catalysts (**Ru-6**, **Ru-5**) were also examined. Their lower reactivity necessitated use of elevated temperatures (60 °C) and higher catalyst loadings. For **Ru-5**, only 17% mRCM was observed even with 5 mol% catalyst: added water had no impact, probably because only a small proportion of catalyst had initiated.³² **Ru-6** afforded 64% mRCM in the anhydrous reaction (0.5 mol% Ru), and 25% in the presence of water. Of note, water had negligible impact on *Z*-selectivity (**Ru-6**, 85%; **Ru-5**, 70%). We infer that decomposed catalyst does not promote *E/Z* isomerization, at least for **Ru-6**.

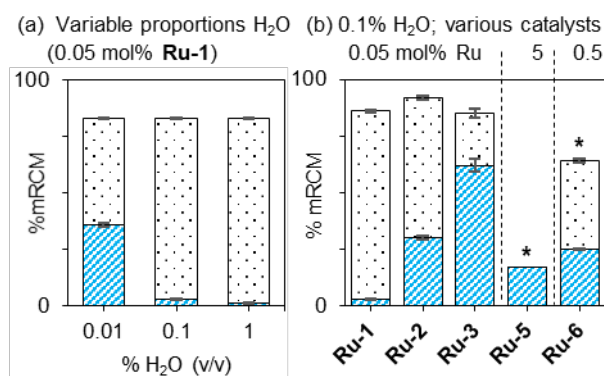
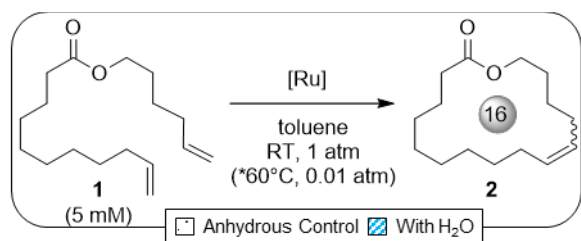
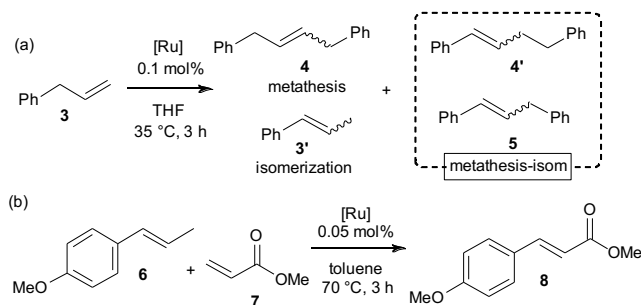


Figure 1. Impact of water on mRCM. (a) For **Ru-1** at 0.5 h. (b) For various catalysts at 2 h (except **Ru-6**: 24 h). ***Ru-5**, **Ru-6**: 60 °C, 0.01 atm.³³ For tabulated data, see Table S1.

Strikingly, however, water significantly accelerated positional isomerization in the self-metathesis of allylbenzene **3** (Figure 2a). Terminal phenylpropenes are notoriously susceptible to isomerization to the conjugated β -methylstyrenes.^{16c} For **Ru-6**, 8% isomerization was observed for the anhydrous reaction, vs 75% with 1% H₂O present. In comparison, **Ru-3** showed more isomerization in the anhydrous reaction, but added water affected primarily conversions.

A second, more demanding intermolecular metathesis reaction was also examined. In the cross-metathesis of anethole **6** with methyl acrylate **7** (Figure 2b), a ca. 30% drop in productivity was observed for **Ru-3** in the presence of 1% water.



rx	cat	% H ₂ O	% conv	% yield ^a (%Z)	% isom
(a)	Ru-6	0	69	61 (>95)	8
	Ru-6	0.1	57	47 (>95)	10
	Ru-6	1	77	2 (>95)	75
	Ru-3	0	80	39 (23)	41
	Ru-3	1	61	27 (22)	34

(b) ^b	Ru-3	0	73	73 (0) ^c	–
	Ru-3	1	51	50 (0) ^c	–

^a Yield of **4** (self-metathesis) or **8** (cross-metathesis). ^b **Ru-6** is omitted, as it showed no reaction. ^c Solely *E*-**8** is formed.

Figure 2. Impact of H₂O on: (a) self-metathesis of allylbenzene. (b) cross-metathesis of estragole and methyl acrylate.

To assess whether the negative impact of water is limited to relatively challenging reactions, we turned to RCM of diethyl diallylmalonate **9** (Figure 3). Diene **9** sets a notoriously low bar for olefin metathesis activity: the extreme facility with which it undergoes RCM makes it a correspondingly aggressive test for the impact of water. Here, in addition to the catalysts examined above, we include benzylidene, indenylidene, NHC and CAAC catalysts.^{29,34–36} Initial experiments were conducted at 0.005 mol% catalyst (50 ppm vs substrate), to enable ‘anhydrous’ TONs in the thousands even for less active catalysts, without masking decomposition.³⁷

Shown in Figure 3a are TONs at 2 h, at which point conversions in the presence of water plateau (Fig. S1) for all but **Ru-10** and **Ru-7**. Notwithstanding the ease of this RCM reaction, yields decreased sharply in the presence of 1% H₂O for all catalyst surveyed. TONs of only 600 or 1 800, respectively, were observed for **Ru-1** and **Ru-2** (vs ca. 18 000 in the anhydrous control reaction). Iodide complex **Ru-3** gave maximum TONs (9 800). For **Ru-4**, a top-performing catalyst under anhydrous conditions, TONs dropped by 60% (from nearly 19 000 to 8 000).

Given the high susceptibility of **Ru-4** to bimolecular decomposition,^{14b} its performance relative to **Ru-3** was reevaluated at a catalyst loading 5-fold lower (Figure 3b). TONs in the anhydrous control reaction *increased* in both cases: by nearly 4x for **Ru-4**, and 2.5x for **Ru-3**. Clearly, bimolecular coupling occurs for both catalysts, even at 10 μ M Ru. Higher water-sensitivity is evident at the lower catalyst loading: that is, decomposition by water competes more strongly with bimolecular decomposition as catalyst concentrations decline. **Ru-3** remains most productive (TON 21 000, vs 14 000 for **Ru-4**).

In Figure 3c, we assess catalyst water-tolerance independent of metathesis activity, by normalizing TONs in the presence of water to those under anhydrous conditions. For added context, water-tolerance is plotted against TONs in the presence of water: best performance is thus high on both axes. Least tolerant are the fast-initiating catalysts **Ru-1** and **Ru-2** (3% and 10%, respectively), suggesting that increased time in the active cycle increases vulnerability. Consistent with this analysis is the improved tolerance (27–44%) of the catalysts highlighted in the blue band in Figure 3b, none of which are fast-initiating.^{38,39} Most robust is iodide catalyst **Ru-3**

(56% tolerance). Slow initiation⁴⁰ is again a plausible contributor, in addition to the bulk and poor H-bonding capacity of the iodide ligands.^{29,34,35}

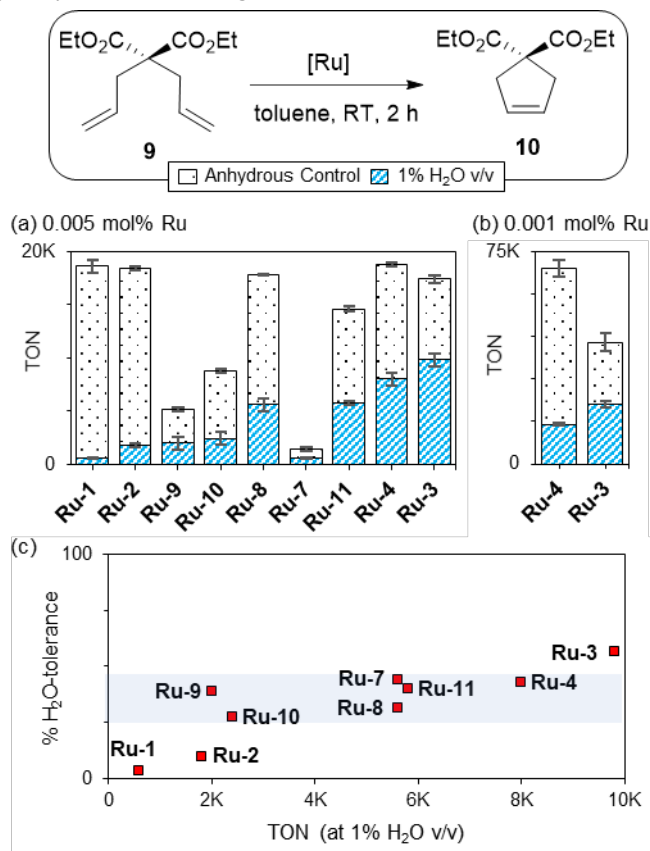


Figure 3. (a) Impact of H₂O on RCM of **9**. (b) Plot of catalyst water-tolerance, $100 - [(\Delta\text{TON}/\text{TON}_{\text{anhyd}}) \times 100]$, vs TON (0.005 mol% Ru). Blue band signifies intermediate tolerance. For rate curves and tabulated data, see SI.

The discussion above focuses on the impact of water on the catalyst. Given evidence for H-bonding of water to macrolactones, however,⁴¹ we queried whether H-bonding to the substrate might alter preferred diene conformations, and hence the thermodynamics and/or kinetics of cyclization. To probe this point, we undertook a computational study of the impact of one H-bonded water molecule on the preferred conformations of **1** and **9**. The 1:1 ratio corresponds to 0.01% v/v H₂O and 0.05 mol% Ru (Figure 1a). The highly precise ANAKIN-ME neural-network force field^{42,43} was used for extensive screening of possible geometries; calculated electronic energies for the most relevant conformers were refined using single-point energy calculations at the DLPNO-CCSD(T)/CBS level of theory.

Reaction free energies for RCM of **1** and **9** (see SI), showed no clear change due to bound water, indicating that the negative effect is not thermodynamic in origin. The impact of water on pre-organization was therefore examined. In the absence of water, the most stable conformer for diene **1** is essentially linear, with an end-to-

end distance of >12 Å. In comparison, a distance of 3.72 Å is calculated for the most stable conformer of **9**. Seen for the latter, but absent for **1**, is a stabilizing π -stacking interaction between the two C=C bonds, a previously overlooked contributor to the facile RCM of **9**. As expected, bringing the two C=C bonds of **9** into proximity incurs no penalty ($\Delta G=0.0$ kcal/mol: Figure 4a). For **1**, the cost is higher (5.8 kcal/mol), consistent with the lower RCM reactivity of **1**.

The impact of H-bonded water on cyclization is shown in Figure 4b. For both **1** and **9**, the diene conformation most favourable to cyclization is predicted to be less accessible in the presence of even one molecule of water, with a negative impact on the cyclization kinetics. Macrocyclization of **1** is impeded by location of the water molecule in the middle of the nascent cycle. For **9**, the water molecule is outside the forming ring, but nevertheless stabilizes the linear conformation. Indeed, water destabilizes the pre-cyclic conformation even more strongly for **9** than for **1** (by 5.6 or 2.7 kcal/mol, respectively: Figure 4b),⁴⁴ in part by disrupting the C=C π -stacking arrangement seen for anhydrous **9**.

The unexpectedly greater negative impact of H₂O on cyclization of **9** is supported by experiment. On repeating the RCM of **9** at the 5 mM diene concentration employed in mRCM, using the most robust catalyst **Ru-3**, we observe lower catalyst water-tolerance for **9** than **1** (30% vs 73%; Figure S3). Water thus has a greater negative impact on **9** than **1**. By retarding the rate of metathesis relative to catalyst decomposition, therefore, H-bonded water can exacerbate catalyst decomposition, further limiting RCM performance in the presence of water.

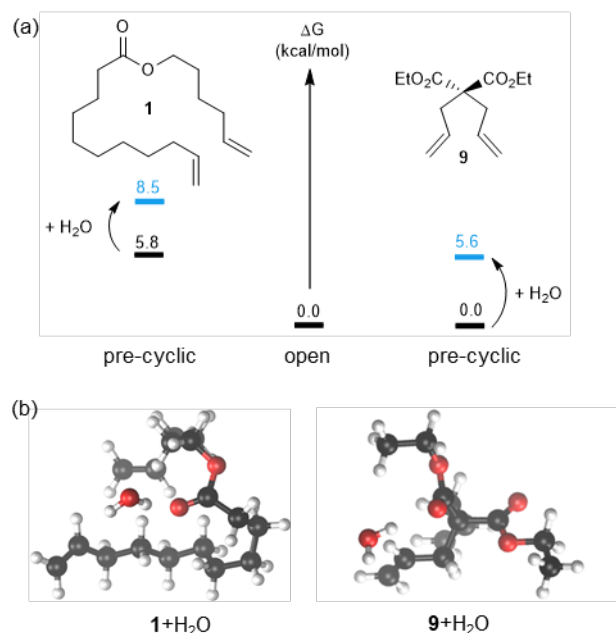


Figure 4. (a) Impact of 1 H₂O on the free energies required to adopt the incipient (“pre-cyclic”) conformation for **1** and **9**. (b) Destabilization of pre-cyclic conformations by H-bonded water. C..C distances: 3.72 Å (**1**); 4.21 Å (**9**).

The foregoing demonstrates that even low levels of water severely degrade the productivity of leading ruthenium catalysts for olefin metathesis. This is an important clue to the pathways by which water triggers decomposition: it points toward direct attack by water on the catalyst, independent of any effects arising from water as a medium. Fast-initiating catalysts prove particularly vulnerable. Maximum productivity is seen for slower-initiating, bulkier iodide and CAAC catalysts, which emerge as the systems of choice where drying is impractical, or water is an essential co-solvent. These findings represent the first insights into structure-decomposition relationships for olefin metathesis in the presence of water. They will aid in deconvoluting the mechanisms by which water causes decomposition, and ultimately, design of truly water-tolerant olefin metathesis catalysts.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.

PDF file: experimental and computational details, numerical data for Figs. 1–4

xyz files: computed xyz coordinates and energies

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example, 100 equiv in ref b). Davis makes cogent arguments for this sacrifice in light of the strategic importance of the modified protein target (ref 3a). Nevertheless, Vinogradova notes that protected peptides and solid-phase synthesis are widely employed in olefin metathesis of peptidic substrates, to circumvent decomposition. See: ref 3b.

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(31) Torker, S.; Khan, R. K. M.; Hoveyda, A. H., The Influence of Anionic Ligands on Stereoisomerism of Ru Carbenes and Their Importance to Efficiency and Selectivity of Catalytic Olefin Metathesis Reactions. *J. Am. Chem. Soc.* **2014**, *136*, 3439–3455.

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(37) Least active is the first-generation Hoveyda catalyst **Ru-7**, for which TON at 2 h = 600 when water is present. The water-tolerance of **Ru-7** was therefore re-assayed at 24 h (TON 13 300). Its water-tolerance was maintained: 44%, vs 42% at 2 h.

(38) Literature evidence for slow initiation is given in Table S3. While direct comparisons are limited, the Grubbs group established that the observed rate constants for initiation of a series of CAAC catalysts was on the order of 10⁻³ s⁻¹ and below, even at 60 °C. See (a) Engle, K. M.; Lu, G.; Luo, S.-X.; Henling, L. M.; Takase, M. K.; Liu, P.; Houk, K. N.; Grubbs, R. H., Origins of Initiation Rate Differences in Ruthenium Olefin Metathesis Catalysts Containing Chelating Benzylidenes. *J. Am. Chem. Soc.* **2015**, *137*, 5782–5792. (b) Marx, V. M.; Sullivan, A. H.; Melaimi, M.; Virgil, S. C.; Keitz, B. K.; Weinberger, D. S.; Bertrand, G.; Grubbs, R. H., Cyclic Alkyl Amino Carbene (CAAC) Ruthenium Complexes as Remarkably Active Catalysts for Ethenolysis. *Angew. Chem., Int. Ed.* **2015**, *54*, 1919–1923. For context, initiation of **Ru-10** and **Ru-9** was slower than **Ru-4** by 225 and 900x (respectively) at RT. See: ref 14c.

(39) For the slow initiation of **Ru-11** even at 80 °C, see: (a) Sanford, M. S.; Love, J. A.; Grubbs, R. H., Mechanism and Activity of Ruthenium Olefin Metathesis Catalysts. *J. Am. Chem. Soc.* **2001**, *123*,

6543–6554. Re-entry into catalysis is much slower for the resting-state methylenide species formed by **Ru-11** and the indenylidene catalyst **Ru-9**, by 275 x in the case of **Ru-11**. See (b) Lummiss, J. A. M.; Higman, C. S.; Fyson, D. L.; McDonald, R.; Fogg, D. E., The Divergent Effects of Strong NHC Donation in Catalysis. *Chem. Sci.* **2015**, *6*, 6739–6746. (c) Lummiss, J. A. M.; Perras, F. A.; Bryce, D. L.; Fogg, D. E., Sterically-Driven Metathesis: The Impact of Alkylidene Substitution on the Reactivity of the Grubbs Catalysts. *Organometallics* **2016**, *35*, 691–698.

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(43) The new neural network force field ANAKIN (ref 42) affords the best accuracy-to-cost ratio for organic molecules, with ab initio-quality energies and geometries, for the reduced computational cost of classic force-field simulations.

(44) In the equilibrium between the extended conformer and its pre-cyclic form, the added water molecule favours the extended conformer by 100-fold for **1**, vs 5 orders of magnitude for diethyl diallylmalonate **9**. For anhydrous **1**: $\Delta G = 5.8$ kcal/mol (i.e. $K = 5.5 \times 10^{-5}$). With 1 H₂O: $\Delta G = 8.5$ kcal/mol (i.e. $K = 5.7 \times 10^{-7}$). For anhydrous **9**: $\Delta G = 0$ kcal/mol ($K = 1$). With 1 H₂O: $\Delta G = 5.6$ kcal/mol ($K = 8 \cdot 10^{-5}$).

Maximum H₂O-tolerance

- slow initiation
- bulky X, L

