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Hydroxide-Induced Degradation of Olefin Metathesis Catalysts: A Challenge for Metathesis in Alkaline Media

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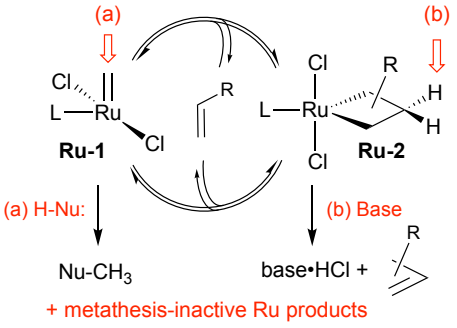
Supporting Information Placeholder

ABSTRACT: Hydroxide ion is shown to be a potent disruptor of Ru-catalyzed olefin metathesis, in a study of the Hoveyda catalyst **HII**. Addition of $[N^nBu_4][OH]$ immediately terminates metathesis via **HII**, an effect traced to formation of bis(hydroxide) complex **HII-OH**. The latter was synthesized for direct study. **HII-OH** initiates very slowly on reaction with olefins, and decomposes in the first cycle of metathesis. Computational analysis reveals rapid bimolecular coupling between **HII-OH** and its four-coordinate methylidene derivative. Importantly, fully decomposed catalyst also accelerates decomposition of **HII-OH**. The H-bonding capacity of the hydroxide ligand is proposed as a powerful driving force for decomposition.

Keywords. *olefin metathesis, catalyst decomposition, N-heterocyclic carbene, water, aqueous metathesis, hydrogen-bonding, chemical biology*

Ruthenium-catalyzed olefin metathesis offers exceptionally powerful methodologies for the assembly of carbon-carbon bonds.[1] In many applications in total synthesis,[2,3] pharmaceutical manufacturing,[4] and chemical biology,[5-7] metathesis is carried out on densely-functionalized substrates bearing polar functional groups, in the presence of variable amounts of water. We speculated that hydroxide ion might pose a common, unrecognized challenge to catalyst function under such conditions. At the extreme is the metathetical modification of proteins in water buffered to pH >7, a forefront application that necessitates use of the Ru complex in high stoichiometric excess.[6] While clever strategies have been designed to accelerate metathesis relative to catalyst degradation,[7] the basis of the problem remains ambiguous. Understanding the unintended, non-metathetical reactivity of the Ru=CHR bond under such conditions is thus of both fundamental and practical importance. The present work was aimed at assessing the impact of hydroxide on the productivity and fate of the second-generation Hoveyda catalyst **HII**, an exemplary, widely used metathesis catalyst.

Prominent among the decomposition pathways now known to disrupt Ru-catalyzed metathesis are those enabled by nucleophiles and Bronsted base (Scheme 1). Nucleophiles have been shown to attack the methylidene carbon of **Ru-1**,[8,9] while Bronsted bases readily deprotonate the metallacyclobutane (MCB) intermediate **Ru-2**.[10,11] The potential engagement of hydroxide ion in either manifold was anticipated.[12-14] Unexpectedly, however, a potent new decomposition pathway was identified, which appears unique to Ru-hydroxide species. Here we describe transformation of **HII** into bis-hydroxide complex **HII-OH**, and bimolecular decomposition of **HII-OH** during the first cycle of metathesis.



Scheme 1. Decomposition of Metathesis-Active Species by (a) Nucleophiles; (b) Bronsted Base. L = H_2IMes; Red Arrows Indicate Sites of Attack.

Our attention was first drawn to the potential of hydroxide ion to hinder metathesis in studies of the impact of Bronsted base on metathesis productivity.[10,15] Yields were negatively affected by the presence of strongly basic enolate anions,[10] but dropped even further when water was added as a sacrificial proton source.[15] (In contrast, sacrifical phenols restored metathesis activity). Likewise suggestive was a preliminary survey of the impact of common contaminants on metathesis

productivity. These experiments examined the impact of additives on turnover numbers (TON) in cyclization of diethyl diallylmalonate (DDM, **A**; Figure 1), with the rationale that any agents capable of disrupting this exceptionally facile ring-closing metathesis (RCM) reaction merit attention. As shown in Figure 1a, either water or morpholine **C** (a basic contaminant present in technical grade toluene)[16] caused TONs to drop by approximately half, but a 50% further decrease occurred when *both* water and morpholine were present.

The premise that hydroxide ion might be responsible was tested via a knockdown experiment, in which [N^{n}Bu$_4$][OH] (a THF-soluble source of hydroxide ion)[17] was added during RCM. Metathesis activity immediately ceased (Figure 1b; red line), even at catalyst loadings 20x higher than those used in the original screen. To assess whether this drop reflects attack on the active species **Ru-1** or **Ru-2**, or on the precatalyst **HII**, a second experiment was carried out, in which hydroxide was added prior to substrate. RCM activity (blue line) was completely suppressed. This suggests that hydroxide ion attacks **HII** to yield a ruthenium product that is either completely inactive, or decomposes in the first cycle of metathesis.

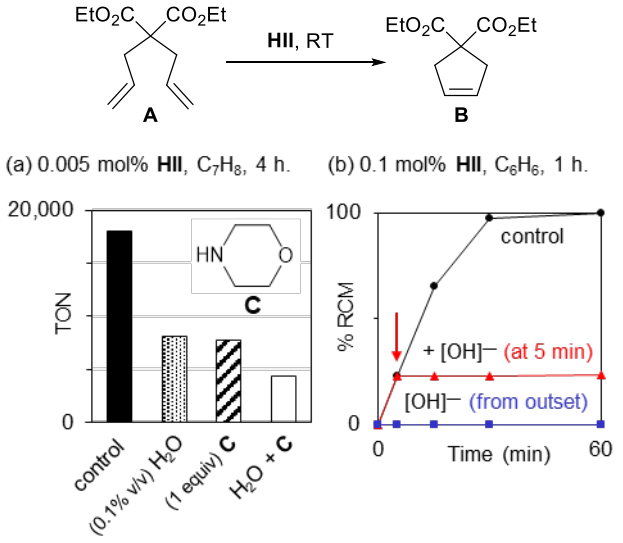
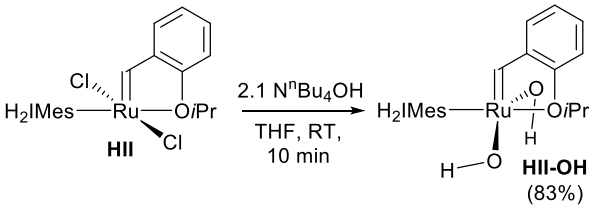


Figure 1. Impact of additives on RCM. (a) Water, morpholine **C**, or both. (b) [N^{n}Bu$_4$][OH] (2 equiv vs Ru).

Synthesis of the putative hydroxide complex was undertaken for closer examination. Accordingly, aqueous [N^{n}Bu$_4$][OH] was added to a solution of **HII** in THF (Scheme 2).[18] As use of 1 equiv hydroxide per Ru resulted in 50% consumption of **HII**, a 2:1 stoichiometry was employed. A colour change from green to red occurred over the time of mixing, and ^{1}H NMR analysis revealed a new singlet for the benzylidene proton at 14.04 ppm (cf. 16.72 ppm for **HII**). Reaction was complete in <10 min even on 200 mg scale, and bis-hydroxide **HII-OH** was isolated in ca. 85% yield. Complete selectivity for salt metathesis was evident, as expected from reactions of related Ru alkylidenes with aryloxide ion,[19] but in contrast with reactions of hydroxide with Ru-CO complexes, which yield Ru formates via attack on the carbonyl ligand.[12a,b]

With the exception of the Ru=C*H*Ar signal, the chemical shifts and multiplicities of all proton signals for **HII-OH** accord closely with those for **HII**. An additional singlet was observed for the Ru-O*H* protons at 1.1 ppm, the assignment of which was confirmed by exchange with degassed D_2O.[20] The structure depicted for **HII-OH** in Scheme 2 is that predicted by density functional theory (DFT) analysis: specifically, a distorted trigonal bipyramidal geometry,[21] with an HO–Ru–OH angle of 139.1° (Table S2). In comparison, the Cl–Ru–Cl angle for **HII** is nearly 20° larger (computed: 155.1°; crystallographic:[22] 156.5°).



Scheme 2. Synthesis of HII-OH.

Consistent with the knockdown behaviour seen in Figure 1b, **HII-OH** proved unreactive toward DDM. Even with 10 mol% of **HII-OH** at 60 °C, <3% RCM was evident after 2 h (cf. 100% within 15 min at RT with 1 mol% **HII** as catalyst). Slow initiation of **HII-OH** is not surprising, given the inductive withdrawal of electron density from the Ru center by the oxygen ligands. The compressed HO–Ru–OH angle may also be relevant, as Ru metathesis catalysts with cis-anionic geometries are known to initiate very slowly.[23]

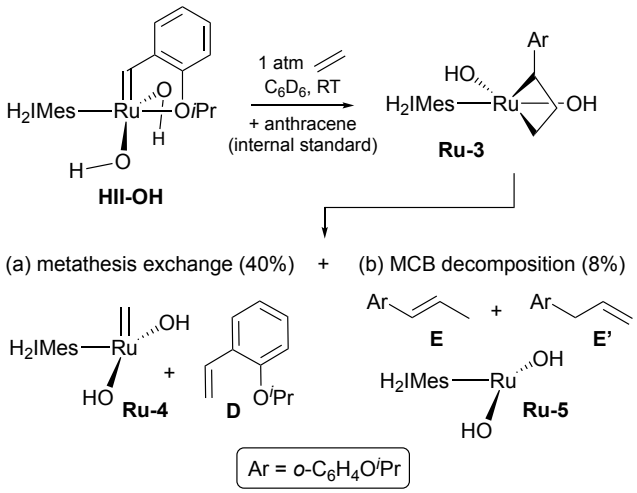
Computational analysis of the initiation step, undertaken using ethylene as a model olefin (Scheme S4a),[24] revealed a higher energy barrier to cycloaddition for **HII-OH**, relative to **HII** (20.9 kcal/mol, vs. 16.7 kcal/mol). The resulting metallacyclobutane is trigonal bipyramidal in both cases, but intramolecular H-bonding of the OH ligands (ca. 2 Å) stabilizes a cis-anionic geometry for **HII-OH**, in contrast with the trans-anionic geometry seen for **HII** (Scheme S4b).

While this energy difference accounts for slower reaction of **HII-OH**, it does not account for the complete loss of metathesis activity. We infer that **HII-OH** is considerably more susceptible to decomposition. In examining the relevant pathways, we first considered those established for **HII** and related catalysts (see Introduction). Nucleophilic attack by hydroxide on the benzylidene carbon (cf. Scheme 1a) is expected to liberate the aldehyde HC(O)Ar (Ar = *o*-C$_6$H$_4$-O^{i}Pr).[25] This aldehyde is indeed detected, but in minor, variable amounts, depending on rates of mixing.[26] The alternative possibility, in which a hydroxide ligand deprotonates the MCB **Ru-3** (cf. Scheme 1b), is unlikely given the ca. 41 kcal/mol barrier calculated by DFT analysis (Scheme S5). A potent new decomposition pathway thus appears to be

operative. Given that the sole difference between **HII** and **HII-OH** lies in the nature of the anionic ligands (and given that related $Ru(OAr)_2$ and $Ru(\kappa^2\text{-}O_2C_6R_4)$ exhibit notably high metathesis productivity),[19] the hydroxide groups appears to play a critical, negative role.

To gain deeper insight, we reacted **HII-OH** with ethylene, using a sealed NMR tube to retain any volatile products (Scheme 3). Loss of the [Ru]=C*H*Ar signal for **HII-OH** was complete within 24 h. Unexpectedly, however, only ca. 50% of the **HII-OH** complex had participated in metathesis, as judged from the combined yields of styrenyl ether **D** (Scheme 3a) and propenes **E**/**E'** (Scheme 3b). These propenes are presumed to form via β-elimination from the MCB **Ru-3**, a well-established decomposition pathway for **HII**[27,28] and other metathesis catalysts.[29] The computed barrier to elimination of **E**/**E'** from **Ru-3** is comparable to that for cycloreversion (15.9 vs. 17.0 kcal/mol, respectively).

The fact that these organic products account for only 50% of the starting **HII-OH** is puzzling. As Ru(OH) complexes are known to form hydroxy-bridged dimers with remarkable facility,[30,31] we queried whether bimolecular coupling might consume **HII-OH** prior to metathesis. We recently reported that **HII** and related metathesis catalysts decompose via dimerization of $RuCl_2(H_2IMes)(=CH_2)$, **Ru-1**.[29] In the case of **HII-OH**, slow initiation limits the concentration of the corresponding hydroxo complex **Ru-4**. This disfavours homo-coupling of two **Ru-4** molecules, but opens the door to *hetero*-coupling with the large excess of **HII-OH** present (Figure 2, bottom). Trapping of **HII-OH** upon formation of **Ru-4** could account for the engagement of only 50% **HII-OH** in metathesis.[32]



Scheme 3. Products Generated in the First Cycle of Metathesis. (a) Via Metathesis Exchange. (b) Via MCB Decomposition.[a]

[a] Path (a) is quantified from the yield of **D**; Path (b) from the yield of **E**+**E'** (4% each).

DFT calculations indicate that hetero-coupling of **HII-OH** is indeed thermodynamically favoured relative to ethylene binding. The latter is endergonic by 13.3 kcal/mol. Because these calculations are based on gas-phase entropies, however, they greatly exaggerate the entropic penalty to dimerization. If we adopt one proposed correction factor, and add 50% of the gas-phase entropy to account for the change from perfect gas to perfect solution,[33] the heterodimer is –12.4 kcal/mol more stable than **HII-OH** + **Ru-4**, whereas the ethylene complex lies at +14.9 kcal/mol. Hetero-dimerization is thus greatly favoured relative to ethylene binding (the requisite first step for formation of **D** and **Ru-4**). Consistent with this picture, kinetics experiments indicate that decomposition is first order in [Ru] (Figure S2). That is, formation of **Ru-4** is rate-limiting.

Two conformers of the anticipated[29,34,35] heterodimer are predicted to be thermodynamically favoured with respect to **HII-OH** + **Ru-4**. These are **transoid-** and **cisoid-Ru-6**, of which the former is the more stable (ΔG –4.0 kcal/mol). Liberation of styrenyl ether **D** from **transoid-Ru-6** is inhibited by the relative disposition of the two ylidene groups on opposite sides of the $Ru_2(\mu\text{-}OH)_2$ plane. Precedents from the chloride system[29] suggest that elimination of **D** from **cisoid-Ru-6** could be feasible, if the methylidene ligand can adopt the conformation shown in **cisoid-Ru-6'** (inset, Figure 2). However, the proportion of **D** liberated via the sum of metathesis and decomposition should then approach 100%. The observed 40% yield of **D** argues against such an elimination pathway. Instead, the cumulative data suggest that while bimolecular coupling is thermodynamically favoured relative to metathesis, C=C coupling and elimination is inhibited.

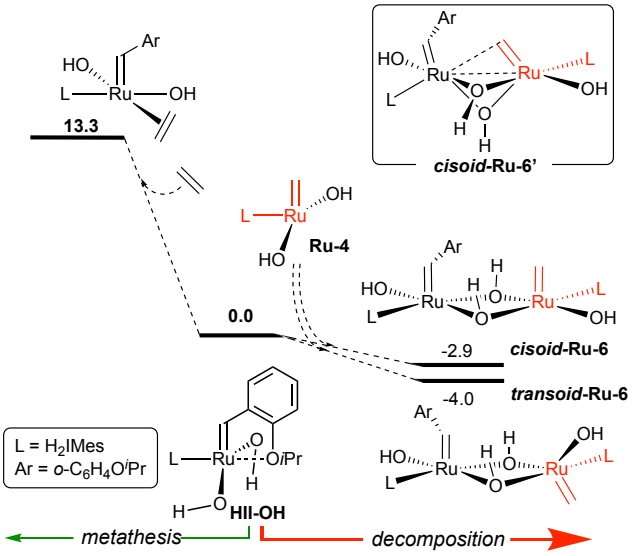


Figure 2. Competing reaction pathways for **HII-OH**: ethylene binding, vs. hetero-coupling with **Ru-4**. Gibbs free energies (kcal/mol) computed at the PBE-D3M(BJ)/cc-pVQZ+ECP28MDF/PCM(Benzene) // M06L/cc-pVDZ+ECP28MDF) level of theory. The free energy for the heterodimer is underestimated, owing to exaggeration of the entropic penalty to dimerization: see text.

To confirm that decomposed Ru-OH species can trap **HII-OH**, we added fresh catalyst to a solution of the decomposed material (Figure 3). Disappearance of the fresh **HII-OH** was indeed much faster than in the control reaction of **HII-OH** under N_2. (As expected, however, it is slower than decomposition of **HII-OH** under ethylene). Importantly, the corresponding experiment with **HII** caused negligible decomposition of fresh **HII** (Figure S3). The H-bonding capacity of the hydroxide ligands thus appears to be critical in promoting attack of decomposed Ru-OH species on fresh catalyst.

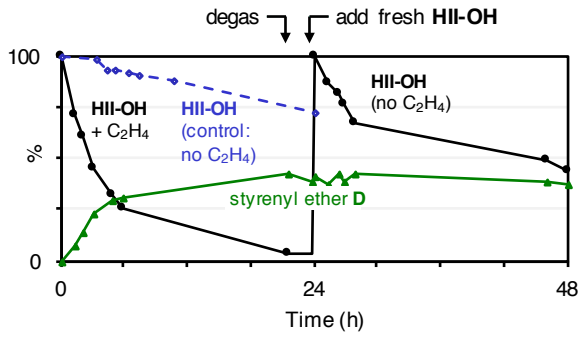


Figure 3. Accelerating effect of decomposed catalyst on the decomposition of **HII-OH**. Black: (left) Decomposition of **HII-OH** under C_2H_4; (right) impact of decomposed **HII-OH** on fresh precatalyst. Green: proportion of **D** formed during experiments indicated with black lines).

While coupling of **HII-OH** with **Ru-4** is thus plausible, we were unable to detect the alkylidene protons of **Ru-6** by NMR analysis, or to observe agglomerated species by DOSY-NMR. This, as well as the steady degradation in NMR signal-to-noise ratios over the 24 h timescale of decomposition (Figure S11) is consistent with rapid transformation of **Ru-6** into paramagnetic products. Paramagnetism may result from the versatile coordination modes and redox properties of the hydroxide ligand,[30,31] although multisite alkylidene binding is also feasible.[36,37]

The foregoing demonstrates that hydroxide ion is an unexpectedly potent disruptor of Ru-catalyzed olefin metathesis. Termination is traced to the slow initiation and rapid decomposition of the bis(hydroxide) complex **HII-OH**. A notable feature is the capacity of the decomposed Ru species to sequester and decompose the precatalyst **HII-OH**, behaviour that arises from the H-bonding capacity of the hydroxide ligand. These results highlight previously unrecognized challenges to metathesis under conditions that can generate hydroxide, and more particularly metathesis in alkaline water.

ASSOCIATED CONTENT

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

PDF file: experimental and computational details, NMR spectra

xyz files: computed xyz coordinates and energies

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(17) The $[N^nBu_4][OH]$ reagent was employed as a solution in degassed water, rather than as its alternative formulation as a solution in methanol, to circumvent formation of methoxide derivatives which rapidly decompose via β-elimination. See: (a) Beach, N. J.; Lummiss, J. A. M.; Bates, J. M.; Fogg, D. E., Reactions of Grubbs Catalysts with Excess Methoxide: Formation of Novel Methoxyhydride Complexes. *Organometallics* **2012**, *31*, 2349–2356. (b) Dinger, M. B.; Mol, J. C., Degradation of the First-Generation Grubbs Metathesis Catalyst with Primary Alcohols, Water, and Oxygen. Formation and Catalytic Activity of Ruthenium(II) Monocarbonyl Species. *Organometallics* **2003**, *22*, 1089–1095.

(18) The ammonium salt was used, as reaction with excess KOH yielded an equilibrium mixture. Similar behaviour was reported in salt metathesis with KBr and KI. See: J. Wappel, C. A. Urbina-Blanco, M. Abbas, J. H. Albering, R. Saf, S. P. Nolan, C. Slugovc, Halide Exchanged Hoveyda-Type Complexes in Olefin Metathesis. *Beilstein J. Org. Chem.* **2010**, *6*, 1091–1098.

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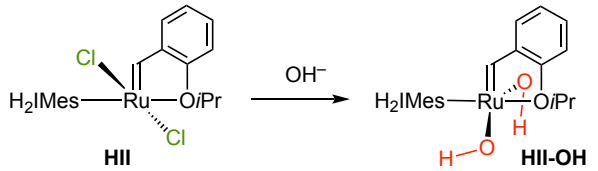

HII metathesis-active

HII-OH metathesis-inactive