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Direct observation of Ru-alkylidene forming into ethylene in ring-closing metathesis from hyperpolarized ^{1}H NMR

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Ring-closing metathesis was monitored using real-time NMR of ^{1}H hyperpolarized olefins at room temperature. By applying a selective saturation to an observable intermediate, we observed its protons transferring to ethylene. It allowed us to identify the intermediate as a Ru-alkylidene species which appears in the ethylene formation pathway.

Olefin metathesis is a class of carbon redistribution reactions widely applied in organic synthesis.[1,2] The mechanism of transition metal catalysts for olefin metathesis involves an alkene double bond undergoing [2+2] cycloaddition with a metal alkylidene to form a metallocyclobutane intermediate. Subsequent bond cleavage produces a new olefin and a new metal alkylidene, which propagates the reaction.[3,4] Metathesis can increase efficiency by shortening routes to products and requiring fewer resources than traditional synthetic schemes.[5] It is applied in the petrochemical industry for propylene production from C4 olefin feedstock and ethylene.[6] In the polymer field, polynorbornene and polycyclopentadiene are commercially produced by a ring-opening metathesis polymerization.[6] The adoption of metathesis in pharmaceuticals has emerged in recent years as various types of metathesis catalysts have been developed for improving functional group tolerances and increasing catalyst stability.[7,8]

Among metathesis catalysts, a family of N-heterocyclic carbene-coordinated ruthenium complexes originally described by Grubbs is well known for their high activity and stability.[9] Studies to understand the mechanisms for the catalyzed reaction and deactivation of catalysts have aimed at determining structures and identities of the ruthenium-bound intermediate species. Species such as Ru-alkylidene (Ru=CH(R), R = H or alkyl) can be stabilized by introducing a large excess of inhibitors or catalyst precursors. Using these methods, compounds similar to those produced during the catalytic reaction can be observed.[10–13] However, the actual intermediates arising in the reaction may be unstable, which prevents their isolation. Using *in situ* reactions, it is possible to observe such compounds by NMR spectroscopy, albeit often without the possibility to determine their identity or structure.

Here, we apply stopped-flow NMR of hyperpolarized reagents to characterize an intermediate in the ring-closing metathesis (RCM) reaction of diethyl diallylmalonate (DEDAM) catalyzed by Grubbs' third generation (G3) catalyst. Hyperpolarization by dissolution dynamic nuclear polarization (D-DNP) enhances NMR signals by more than three orders of magnitude in the liquid state.[14] It is achieved by first freezing the sample at a temperature of ~1 K, and irradiating with microwaves in the presence of a magnetic field. The sample incorporates target molecules and free radicals in a matrix that forms a glass at a low temperature. Under these conditions, a high electron spin polarization from the radicals transfers to nuclear spins of interest. By rapidly dissolving the thus hyperpolarized sample in a preheated solvent, the nuclear spin polarization can be preserved for immediate use in liquid state NMR at ambient temperature. With this hyperpolarized liquid, the direct observation of transient or low-populated species in ongoing reactions can be achieved with high sensitivity.[15] Reactions that occur within a time period on the order of seconds are best suited for study using D-DNP. Within this time window determined by the longitudinal relaxation time (T_1), a high signal can be obtained by this method. The applicability of real-time D-DNP enhanced NMR to various reactions has been demonstrated, including chemical polymerization reactions or enzyme-catalyzed conversions of biological substrates.[16–19]

Unlike most conventional NMR experiments, hyperpolarization by D-DNP creates the spin population difference that results in NMR signals only at the beginning of

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Electronic Supplementary Information (ESI) available: Experimental details are given in the ESI and include: Dynamic nuclear polarization, NMR spectroscopy, Characterization of selective saturation pulses, Initial buildup of signals from reaction products, Dependence of Ru-alkylidene chemical shifts on 3-bromopyridine concentration. See DOI: 10.1039/x0xx00000x

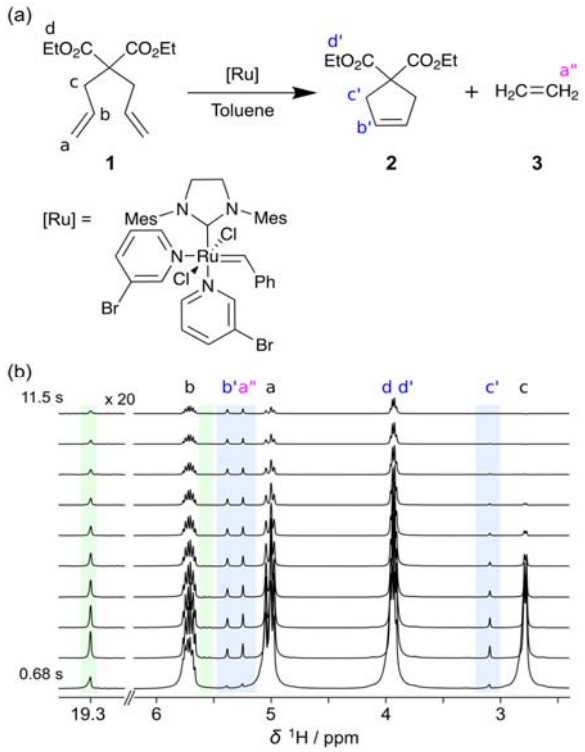

Figure 1 (a) Reaction scheme of DEDAM metathesis. Mes = 2,4,6-tri-methylphenyl (b) Time-resolved ^{1}H NMR spectra of hyperpolarized DEDAM **1** in a reaction with G3 catalyst ([Ru]). Every third acquired spectrum is shown from a dataset with an acquisition delay of 400 ms. The first spectrum shows a larger line width due to sample settling immediately following injection.

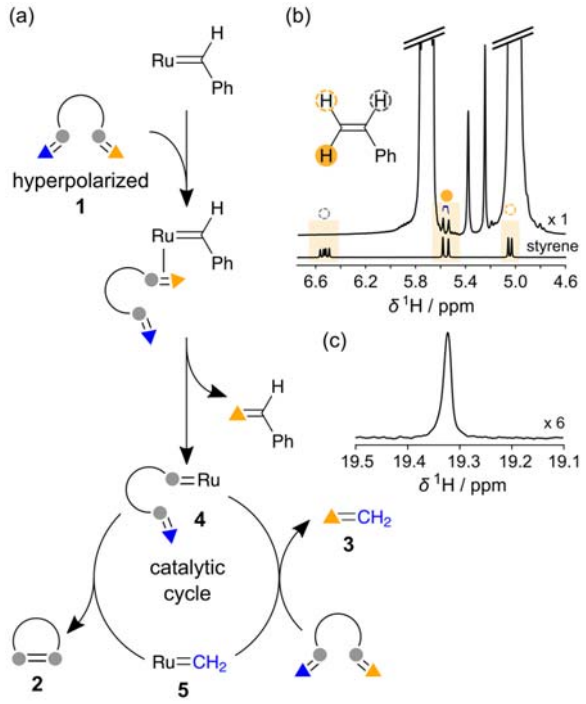

Figure 2 (a) Mechanism of RCM reaction.[21,22] Terminal and internal olefin protons of hyperpolarized DEDAM are indicated by triangles and circles, respectively, to show the movement of these protons throughout the RCM reaction. (**4**: $(H_2IMes)(Cl)_2Ru{=}CH(CH_2C(CO_2Et)_2CH_2CH{=}CH_2)$, **5**: $(H_2IMes)(Cl)_2Ru{=}CH_2$) (b) Part of the ^{1}H hyperpolarized NMR spectrum (Figure 1b) containing styrene peaks. The spectrum of non-hyperpolarized styrene in toluene is displayed below for reference. Open and closed circles indicate the peak assignments. (c) Hyperpolarized ^{1}H NMR signal of Ru-alkylidene complex is from the second bottom-most spectrum in Figure 1b.

the experiment. This spin polarization can be used to correlate chemical shifts between reactant and reaction product, as atoms transfer from one species to another. We have previously shown that these correlations can be obtained by applying selective spin inversion pulses to one of the reactants.[18–20] The population inversion of the selectively addressed spin then transfers to the reaction product, thereby establishing the correlation. However, the fate of lowly populated intermediates, such as those arising in this metathesis reaction, cannot be followed using single inversion pulses. We now introduce a method allowing the continuous selective saturation of such an intermediate signal, while at the same time acquiring real-time NMR spectra during the entire progress of the reaction. The observation of NMR signal changes in a species formed from an irradiated precursor species is reminiscent of the technique of Chemical Exchange Saturation Transfer (CEST).[21] In CEST, however, the irradiated and observed species are in chemical equilibrium, whereas the presently described method is suitable for non-equilibrium systems. Using this method, we show that an observed signal from a metal bound intermediate transfers to a specific reaction product, ethylene. Based on this observation, we identify a Ru-alkylidene complex as the observable intermediate.

Figure 1 shows the spectra acquired after rapidly mixing ^{1}H hyperpolarized DEDAM with G3 catalyst. The reaction occurring *in situ* in the NMR spectrometer was thereby monitored in real-time by acquiring spectra every 400 ms using a small flip angle pulse (16.5° flip angle). The observed signal evolution in the series of hyperpolarized NMR spectra is the result of the combined effects of consumption or production of a species, and loss of hyperpolarization through T_1 spin relaxation. The strong signals observed at 5.00 (a), 5.72 (b), 2.78 (c) and 3.93 (d) ppm stem from the hyperpolarized reactant protons. The signals of products were detected at 5.38 (b') and 3.09 ppm (c') for diethyl 3-cyclopentene-1,1-dicarboxylate (**2**, cyclopentene) and 5.25 ppm (a'') for ethylene **3**. Additional signals, visible in the spectra, which pertain neither to the reactant nor the products **2** and **3**, include a doublet at 5.56 ppm and a singlet at 19.32 ppm. Both of these signals initially grow and decay at a later time (Figure S3a). Considering the signal enhancements provided by hyperpolarization, all of these observable resonances are expected to stem from the originally hyperpolarized DEDAM rather than from other, non-hyperpolarized reaction components. The possible structures corresponding to these additional peaks can be found from the established reaction mechanism of the RCM.[22,23] The movement of hyperpolarized protons originating from DEDAM throughout the reaction is shown in Figure 2a. In the figure, the first ruthenium containing species shown is Ru=CH(Ph), which stands for the activated catalyst [$(H_2IMes)(Cl)_2Ru{=}CH(Ph)$]. The

G3 catalyst is one of the fastest-initiating ruthenium catalysts,[24,25] It can be assumed that the activation, which starts as soon as the hyperpolarized DEDAM is admixed, is completed before the first NMR spectrum is acquired. As displayed in the figure, the first reaction product of the hyperpolarized $=CH_2$ protons is styrene. The observed signal at 5.56 ppm, by comparing chemical shift and *J*-coupling constant to a reference, is the proton *cis* to the phenyl ring of styrene (Figure 2b). The *trans* protons overlap with the intense reactant peaks nearby. The *geminal* proton near 6.5 ppm is not visible in the hyperpolarized experiments. This proton originates from the non-hyperpolarized catalyst. The absence of its signal further confirms that the observed signals are from the originally hyperpolarized reactant.

The signal at 19.32 ppm, based on chemical shift, stems with a high likelihood from a Ru-alkylidene (such as **4** or **5** in Figure 2a). In the following, we aim to establish the identity of this compound by determining the fate of the observed protons transferring to the final product molecules. A selective saturation was applied to this signal, using radio-frequency pulses interleaved with the acquisition of each successive data point of the free induction decay. Pulsing interleaved with acquisition enables a continuous and selective spin saturation of reaction intermediates. Saturation extends over the entire duration of the measurement time, which consists of multiple scans after the injection of the DNP hyperpolarized compound. This pulse scheme was implemented on the NMR spectrometer using the programmatic syntax for homonuclear decoupling (HD), although the goal of the application is different from decoupling. We tested the capability of this scheme to saturate the target spin, and thereby remove its signal from the NMR spectrum, using a stationary sample as described in the supporting information. With saturation for 400 ms at a duty cycle of 10 % and a pulse strength of $\gamma B_1/(2\pi) = 26.5$ Hz (0.12 % of the hard pulse strength), less than 5 % of the signal remained after saturation. The selective saturation showed a narrow saturation width at half height of approximately 0.25 ppm. It further partially excited the spins within ± 2 ppm, which is necessary to take account of when interpreting the data from the selective decoupling experiments.

The selective saturation provides an effect in the spectrum similar to blocking the pathway of the saturated spins. The reaction itself is not affected; rather, the spin polarization is altered to visualize the reaction progress. One spectrum from a series of scans acquired under continuous application of saturation to the species observed at 19.32 ppm is shown in Figure 3a (for the pulse sequence, see Figure S1a). This spectrum can be compared to a reference with off-resonance saturation applied at the opposite end of the spectrum. A spike observed at the frequency of selective saturation is due to the remaining electrical signal from pulsing. In the superposition of the two normalized spectra (Figure 3b), the observed differences are shaded. It can be seen that a single product signal, that of ethylene, is noticeably affected by the saturation. In contrast, the intensities of cyclopentene or DEDAM protons are almost identical in both datasets. The effect of the saturation can be seen even more clearly in the time

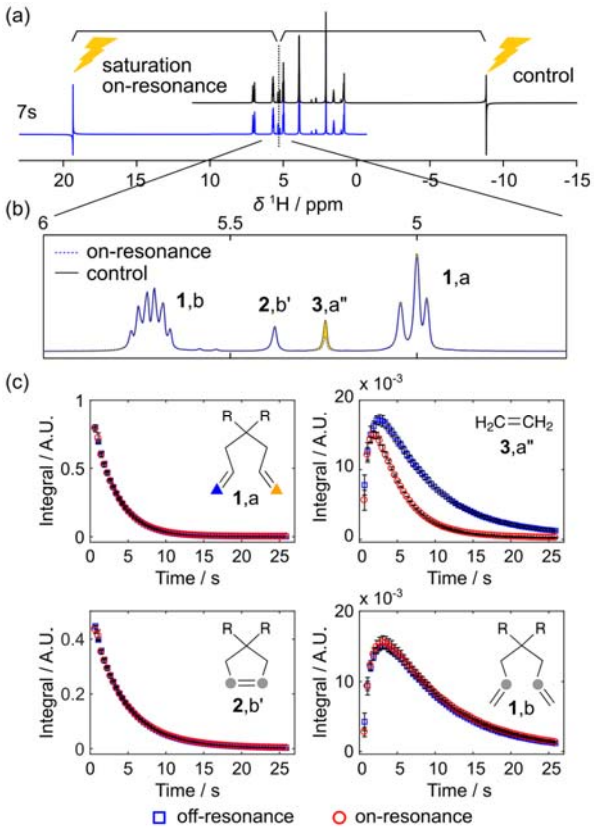

Figure 1 (a) Selective saturation experiment, with on-resonance irradiation of the ^{1}H signal at 19.32 ppm. A second data set includes off-resonance saturation at an identical frequency difference to product peaks, but at the opposite end of the spectrum. The two spectra were obtained in the 17th scan, 7 seconds after injection of the hyperpolarized reactant and start of the reaction. (b) Overlay of the spectra with on- and off-resonance saturation plotted between 4.6 and 6 ppm. The shading indicates the difference between the two spectra. The peaks are assigned as labeled in Figure 1a. (c) Signal integrals of reactant and product protons from the selective saturation experiments, obtained by fitting peaks with Lorentzian shapes. The data points represent averages and error bars indicate the standard deviations from three repetitions. For data normalization, the signal decay of terminal olefin protons of the DEDAM was fit to a single exponential, and the extrapolated intensity at t = 0 was scaled to unit intensity. In all datasets, the scaling factors were determined with a 2 % error or less, and they varied with a standard deviation of 19 %. (R=-CO_2Et)

dependence of signal intensities from all scans of the experiments, in Figure 3c.

The signal decays of the reactant protons, and the signal buildup curves of cyclopentene in the on- and off-resonance saturation experiments are nearly identical. In the same experiments, only the signal buildup of ethylene was affected by the on-resonance saturation. The signal of ethylene in the series of spectra with on-resonance irradiation follows the off-resonance series, but shows a smaller initial increase and more rapid reduction. This indicates that the protons observed at 19.32 ppm transfer to the reaction product ethylene. This species can therefore be identified as a reaction intermediate related to Ru-alkylidene (**5**). The protons of **4** would also be in the hyperpolarized spin state, but were not observed in the spectra with or without saturation. The absence of these signals

is likely due to a short lifetime of the corresponding complex **4**, which undergoes ring closure by intramolecular [2+2] cycloaddition to give **2** and regenerates **5**.

The initial increase of signals contains information on initial formation rates of products. These signal buildup rates can be used to obtain kinetic information about the reaction if relaxation rates are known.[26] In the RCM reaction performed, the signal for the product **2** or **3** showed a slower buildup than that for styrene (Figure S3b). Also, the signal for Ru-alkylidene increased slowly compared to that for styrene, which would be consistent with a faster initial rate of formation of styrene predicted from the scheme in Figure 2a. A quantitative kinetic analysis of this multi-step reaction would, however, require knowledge of additional rates and is not attempted here.

The signal at 19.32 ppm is the only Ru-alkylidene signal observed, likely stemming from the species with the longest lifetime. Since saturation is transferred from this species to the ethylene product, it is implied that its conversion is the rate-limiting step in this branch of the reaction. The actual structure of this species cannot be determined from the single NMR signal. However, since the propagating species $(H_2IMes)(Cl)_2Ru{=}CH_2$ (**5**) is highly reactive,[12,27,28] it appears more likely that the observable Ru-alkylidene species is a coordination complex with an olefin or with a 3-bromopyridine ligand dissociated from the precatalyst. Based on this reasoning, the effect of the addition of excess bromopyridine to the experiment was tested (Figure S4). This addition caused a downfield shift of the Ru-alkylidene signal, which would be consistent with a coordination/decoordination equilibrium of bromopyridine with the $Ru{=}CH_2$ complex (**5**). An influence of pyridine coordination to the propagating ruthenium complex has previously been reported for the related ring-opening metathesis polymerization reaction.[29,30]

In summary, we have demonstrated that continuous saturation interleaved with the acquisition of real-time D-DNP NMR spectra can be used to follow the conversion of a transient intermediate to the reaction product. Thereby, the destination of the saturated proton can unequivocally be identified. Applied to the ring-closing metathesis of DEDAM by G3 Grubbs catalyst, this saturation method allowed to observe a Ru-alkylidene intermediate that appears in the ethylene production pathway. Here, the intermediate signals are well separated from those of the reaction products, but the method can still be applied in other cases by accounting for pulse effects using on- and off-resonance saturation at symmetric positions with respect to the observed product. Continuous saturation can also be applied more generally to complex reactions that produce multiple intermediates, to directly observe the transfer of atoms between species. Saturation can be applied when the intermediate signal is undetectable in a spectrum due to low signal-to-noise ratio. It may therefore further be used to find resonance frequencies of unobservable intermediates to provide structural and mechanistic information pertaining to a reaction.

Conflicts of interest

There are no conflicts to declare.

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<u>Graphical Abstract</u> for the manuscript titled "Direct observation of Ru-alkylidene forming into ethylene in ring-closing metathesis from hyperpolarized ^{1}H NMR" by Y. Kim *et al.*

With hyperpolarization and selective saturation, we identified an observable intermediate as Ru-alkylidene transferring its protons to ethylene in ring-closing metathesis.