Manipulating radicals

*Using cobalt to steer radical reactions*

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Mechanistic investigations into the cyclopropanation of electron deficient alkenes with ethyl diazoacetate using [Co(MeTAA)]
Abstract

A detailed mechanistic study of the cyclopropanation of electron deficient alkenes, namely methyl acrylate with ethyl diazoacetate (EDA) was investigated, aiming at understanding both the superior activity and higher sensitivity of the cobalt(II) tetramethylidibenzotetraaza[14]annulene [Co(MeTAA)] catalyst as compared to cobalt(II) tetraphenylporphyrin [Co(TPP)]. Cobalt(III)-carbene radicals were demonstrated to be present as key intermediates in the reaction, using a combination of kinetic studies, experimental (EPR) spin-trapping experiments and supporting DFT studies. Reaction progress was monitored in real time, by observing N₂ formation and measuring its partial pressure under isothermal conditions. Reaction progress kinetic analysis (RPKA) was used to analyse the experimental data. Results showed that the reaction is first order in both [catalyst] and [EDA], and zero order in [methyl acrylate], in agreement with the DFT-calculated mechanism. The DFT calculated activation parameters corresponding to the rate determining step of the reaction (ΔG‡, ΔH‡ and ΔS‡) are in agreement with the experimental values derived from Eyring-analysis of temperature dependent kinetic measurements, thus providing strong support to the proposed metallo-radical mechanism.
1. Introduction

An attractive method to prepare functionalized cyclopropanes is the transition metal complex catalysed reaction of olefins with diazo compounds. Many catalytic systems, such as copper(I) or rhodium(II) complexes, have been applied successfully for the cyclopropanation of electron-rich olefins. However, their catalytic activity towards electron-deficient olefins, such as acrylates, proved to be below par due to the electrophilic character of the Fischer-type metal-carbene complex intermediates typically involved in these reactions. This drawback has been solved by the introduction of cobalt(II) complexes of salen- and porphyrin ligands by the groups of Nakamura, Katsuki and Zhang, capable of both diastereo- and enantioselective cyclopropanation of electron-deficient olefins. This remarkable reactivity suggests a (more) nucleophilic character of the metal-carbene complex intermediate, which is not what one might expect from the reaction of late transition metals with diazo compounds. Formation of Fischer-type carbenes, stabilized by an ester group, would be expected for these systems, but their reactivity towards electron-deficient olefins reveals the contrary.

A few studies aimed at explaining the unexpected behaviour of cyclopropanation of electron-deficient alkenes using [Co\text{II}(salen)] and [Co\text{II}(por)] systems, by performing mechanistic studies and attempting to isolate and detect intermediates. One of them was performed by Gallo, Cenini and coworkers. They investigated the cyclopropanation of styrene with ethyl diazoacetate (EDA) catalysed by cobalt(II) tetraphenylporphyrin [Co(TPP)] by monitoring the reaction in time, using IR spectroscopy. The initial rates method was chosen for performing the kinetic studies, which is a steady state approximation method. Therefore, the reaction was monitored with one of the components always present in large excess. Quite remarkably, the results indicated a first order rate dependence in [styrene], [EDA] and [catalyst]. However, the rate order in [styrene] proved complex and only at low styrene concentrations first order behaviour was observed. In another report from
the same group, kinetic studies were performed in which [Co\textsuperscript{II}(salen)] was used as a catalyst for the cyclopropanation of α-methylstyrene and EDA. This time, a first order rate dependence was found for [EDA] and [catalyst], and zero order for the [alkene].

Based on previous studies of Johnson,\textsuperscript{7} their kinetic studies and using analytical tools such as IR and NMR, Cenini and coworkers proposed that two intermediate metal-carbene complexes [Co(TPP)(CHCOOEt)] can be formed (Figure 2, a and b). The first, called “terminal carbene” a, is the most reactive species and was proposed to isomerise rapidly to form the “bridging carbene” species b, via insertion of the “terminal carbene” into the Co–N bond of the porphyrin. A similar bridging carbene was also observed for [Co(salen)(CHCOOEt)].\textsuperscript{8} Neither one of these metal-carbene complexes were however considered to be the key cyclopropanation intermediates in the study of Cenini and Gallo. Based on the kinetic studies, the authors proposed that the EDA adduct [Co(TPP)(EDA)] reacts directly with styrene in the rate limiting step,\textsuperscript{5} without prior formation of a metal-carbene complex. Any carbene complex formation was proposed to lead to carbene-dimerization side-product formation and catalysts deactivation.\textsuperscript{5}

Studies performed by Yamada and coworkers, on the other hand, showed formation of “terminal carbene” species for both [Co(salen)] and [Co(TPP)].\textsuperscript{9} However, the IR stretch frequency of the carbonyl group indicated a single bond character for the cobalt-carbene bond. Therefore, Yamada proposed that single electron transfer from cobalt to the carbon center occurs, leading formation of a cobalt-carboxyethyl species in which the spin density is delocalized over the α-carbon atom and the carbonyl moiety, which would explain the surprising IR frequency detected experimentally (Figure 2, c).

Remarkably, the deactivated catalyst in the form of [Co\textsuperscript{III}(TPP)(CH\textsubscript{2}COOEt)] has been isolated from the reaction medium and was characterized using X-ray diffraction.\textsuperscript{5} This is also an indication that the intermediate species has radical
character, although the crystallographic evidence is only indirect. As a result of the radical character of the terminal carbene, hydrogen atom abstraction from the reaction medium (or EDA) occurs. To further shine light on the nature of the species involved, Zhang, de Bruin and coworkers\(^\text{10}\) decided to investigate the mechanism of \([\text{Co}^{\text{III}}(\text{por})]\) catalysed cyclopropanation of ethyl diazoacetate with methylacrylate using a combination of EPR, ESI-MS and DFT studies. The reported findings confirmed experimentally the presence of a redox non-innocent carbene ligand, which is formed upon reaction of EDA with the cobalt porphyrin. The EPR spectrum indicates the presence of both a “terminal carbene” showing “carbene radical” character, as well as a “bridging carbene” showing cobalt radical character (Figure 2b). DFT calculations revealed that these species are in dynamic equilibrium, with a low barrier to interconvert them. The DFT calculations further showed that cyclopropanation occurs via a stepwise radical-process, involving formation of the terminal “carbene radical” species (Figure 2c), which is the species reacting with the olefin. The DFT calculated barriers for “carbene radical” formation and its reaction with the olefin were very similar, in agreement with first order kinetics in both [EDA] and the [olefin] suggested by Cenini & Gallo, despite a stepwise reaction mechanism.\(^\text{10}\)

In chapter 2 we described that the catalyst \([\text{Co(MeTAA)}]\), which had never been used before as a carbene-transfer catalyst, is much more active than \([\text{Co(TPP)}]\) in the cyclopropanation of electron deficient alkenes with diazo compounds. The reasons for the improved activity were not obvious, as the [Co(MeTAA)] complex has a very similar structure to that of [Co(TPP)] (Figure 1). Hence, we wondered if the mechanism for olefin cyclopropanation with [Co(MeTAA)] is similar to the one reported for [Co(TPP)] or not, and what could be the reason for the enhanced activity this complex. Therefore, we decided to investigate the reaction mechanism of [CoMeTAA]-catalysed cyclopropanation of methylacrylate, using ethyl diazoacetate as the carbene precursor. The results are described in this chapter. Full system DFT calculations including Grimme’s dispersion corrections have been performed for both [Co(TPP)] and [CoMeTAA] to make direct comparison between the two systems possible. Spin trapping experiments followed by detection by EPR proved a valuable tool in determining if the mechanism follows a radical-type pathway, and Blackmond’s reaction progress kinetic analysis (RPKA) has been used to determine the rate law and to identify catalysts deactivation processes.

RPKA has been chosen over the more common initial rates method in which an overwhelming excess of one or more reactants is used relative to the species of interest. With RPKA the reaction is probed at synthetically relevant conditions, at
concentrations similar to the ones used when not exploring the rate law. In general, the mechanism can vary depending on both the relative and the absolute concentrations of the species involved. Therefore, more representative results of reaction behaviour under commonly utilized conditions are obtained using this approach when compared to traditional kinetic studies using the initial rate approach. By measuring the reactions in its entirety and not just in the initial phases, unexpected behaviour such as catalyst deactivation, product inhibition or even changes in mechanism can be detected. Moreover, reaction progress kinetic analysis requires fewer experiments, is a faster method and arguably is more accurate than traditional kinetic measurements.\textsuperscript{11}

Scheme 1. Proposed mechanism of the [CoMeTAA]-catalysed cyclopropanation of methylacrylate with ethyl diazoacetate.
2. Results and Discussion

The study started with DFT geometry optimizations of the full reaction systems. The investigated reactions are the cobalt(II)-catalysed cyclopropanation reactions of methylacrylate and styrene, using ethyl diazoacetate (EDA) as the carbene precursor. Calculations for both [Co(MeTAA)] and [Co(TPP)] have been performed using no structural simplifications of the molecules involved. This allows for direct comparison of the two catalysts. The [Co(TPP)] optimizations from this work extend the previous reported calculations,\(^{10}\) in which the geometry optimizations were obtained using a lower level basis set, without dispersion corrections and using simplified molecular structures. In the present study, full atom structures, the BP86 functional and the def2-TZVP basis were chosen, and includes Grimme’s version 3 dispersion corrections.

The DFT calculations strongly suggest, as has previously been reported for [Co(TPP)], that the [Co(MeTAA)]-catalysed reaction also proceeds via a stepwise radical addition-substitution pathway (Scheme 1). The key intermediates have “organic radical” character. The first step (I) involves the interaction between [Co(MeTAA)] \(A\) and EDA to form the transient intermediate \(A’\), which loses dinitrogen during step II. This leads to the formation of a carbon-centered radical terminal carbene \(B\) that is in equilibrium with the bridging radical carbene \(E\). The terminal carbene is best described as a one-electron reduced Fischer-type carbene.\(^{12}\) The bridging radical carbene \(E\) is a dormant state of the catalyst and is incapable of forming the cyclopropane. The third step in the cycle (III) is an irreversible radical addition of the carbene radical \(B\) to methyl acrylate, forming \(\gamma\)-radical \(C\) species. The \(\gamma\)-radical \(C\) then easily cyclizes to form the corresponding product during step IV, while the catalyst returns in its original state. This last step is a concerted radical type C–C bond formation with simultaneous homolysis of the Co–C bond. The barrier of this ring-closure reaction is so low that cyclopropane formation is the only favoured reaction pathway, no other pathway, such as addition of another molecule of acrylate being possible. All attempts to react the diazo adduct complex \(A’\) directly with the olefin, as has been proposed by Cenini and Gallo,\(^5\) were unproductive.

An analysis of the initial state of the catalyst is performed in Figure 3. The energy difference between different species reveal that the toluene adduct of [Co(MeTAA)] is the most stable species in solution. Several coordination modes of EDA to the catalyst are possible. However, their energies are 4.3-5.3 kcal mol\(^{-1}\) higher (Figure 3, left). For [Co(TPP)], the energies of these species are even higher, ranging from 5.8 to 9.7 kcal mol\(^{-1}\) above the toluene adduct of the complex (Figure 3, right).
Figure 3. Energy diagram - Substrate Coordination to [Co(MeTAA)] and [Co(TPP)].

Figure 4. Energy diagram of the [Co(MeTAA)] catalysed cyclopropanation of methyl acrylate with ethyl diazoacetate. All energies relative to A (transition state barriers relative to the preceding intermediate).
The calculated free energies for the cyclopropanation steps mediated by [Co(MeTAA)] are shown in Figure 4. The first step is the activation of the ethyl diazoacetate over [Co(MeTAA)] with release of dinitrogen. It appears that this step has a transition state barrier $\text{TS}_1$ of +14.5 kcal mol$^{-1}$, the highest of all reaction steps, suggesting this is the rate determining step. Formation of the carbene radical $\text{B}$, with release of nitrogen, is exergonic. In contrast to the [Co(TPP)] mechanism (Figure 5 and Figure 6), species $\text{B}$ has a much lower energy than the bridging carbene $\text{E}$. Furthermore, to interconvert between the two a $\text{TS}_4$ barrier of +19.6 kcal mol$^{-1}$ needs to be overcome, which is much higher than the barrier for reaction of $\text{B}$ with the acrylate ($\text{TS}_3$). Therefore we anticipate that the bridging carbene is not formed in practice. In contrast, for [Co(TPP)] the bridging carbene $\text{E}$ has a lower free energy (−4.5 kcal mol$^{-1}$) compared to the carbene radical $\text{B}$ (−3.4 kcal mol$^{-1}$). The transition state barrier of interconversions $\text{TS}_4$-CoTPP is also lower than $\text{TS}_4$-CoMeTAA, and that is why species $\text{E}$ was isolated in practice, and proposed as the resting state during catalysis.

Figure 5. Energy diagram of the activation of EDA with [Co(MeTAA)] and [Co(TPP)] and generation of carbene radical or bridging carbene. All energies relative to $\text{A}$ (transition state barriers relative to the preceding intermediate).
The second step, as seen in Figure 4, is the addition of methyl acrylate to the carbene radical B. This addition has a lower barrier ($\text{TS}_2\text{-trans} = +6.7 \text{ kcal mol}^{-1}$) when attacking $\text{trans}$ to the ethyl ester attached to the carbene, compared to $\text{TS}_2\text{-cis} = +11.1 \text{ kcal mol}^{-1}$ for cis attack. This difference (4.4 kcal mol$^{-1}$) is in line with the experimental data showing a high $\text{trans}:\text{cis}$ ratio between the different cyclopropane diastereoisomers of 97:3 (see Chapter 2). Therefore, computations also favour the pathway leading to the formation of the $\text{trans}$-isomer.

The last step is the cyclization of $\gamma$-radical B to form the cyclopropane. The transition state, $\text{TS}_3\text{-CoMeTAA} = +5.8 \text{ kcal mol}^{-1}$ is higher than the corresponding step in the mechanism of the [Co(TPP)]-catalysed cyclopropanation reaction, $\text{TS}_3\text{-CoTPP} = +3.1 \text{ kcal mol}^{-1}$ (Figure 6). However, compared to the other reaction steps, it is still the lowest barrier of the entire energy diagram. Therefore, looking at all free energy barriers, the DFT calculations predict the [Co(MeTAA)]-catalysed reaction to be first order in [EDA] and [catalyst] and zero order in [methyl acrylate]. Nitrogen release and carbene radical formation should be
the rate determining step, with a transition state barrier of \( \Delta G^\ddagger_{298K} = +14.5 \text{ kcal mol}^{-1} \). Comparing this mechanism to the one using [Co(TPP)] as catalyst, it can be observed that all steps are similar, and the main intermediates present similar radical character. However, the relative energies of the involved species, including the transition states, vary significantly. Noteworthy is the high barrier of the nitrogen release step with TS\(_{1-CoTPP}\) = 19.5 kcal mol\(^{-1}\). The difference of +5.0 kcal mol\(^{-1}\) between the transition states of the rate determining step can explain the slower reaction times noticed during experiments when using [Co(TPP)], in contrast to [Co(MeTAA)] (see experimental section, Figure 11). It should further be noted here that the dispersion-corrected DFT calculations of the [Co(TPP)]-catalysed steps reported here differ slightly from previously reported calculations performed in our group\(^{10}\) in the sense that addition of carbene radical B to the acrylate substrate is computed to have a lower barrier than formation of B via TS\(_1\) when using Grimme’s version 3 dispersion corrections, while the computed barriers for these process are very similar in calculations without dispersion corrections.

As such, as shown above for [Co(MeTAA)], DFT therefore predicts first order kinetics in [EDA] and [catalyst], but zero order kinetics in [methyl acrylate] under catalytically relevant reaction conditions for [Co(TPP)]. Only at (very) low acrylate concentrations the reaction should become first order in [methyl acrylate]. This seems to correlate directly with the experimentally determined bell-shaped rate-dependence on the olefin concentration as reported by Cenini and Gallo detected at low olefin concentrations in kinetic studies of styrene cyclopropanation with [Co(TPP)].\(^5\)

Initial experimental efforts to shine more light on the mechanism of the [Co(MeTAA)]-catalysed reactions focused on detecting reaction intermediates using EPR spectroscopy and high-resolution mass spectrometry. Only one previous study has been performed in which “carbene radicals” were directly detected by EPR, and that was the reaction between EDA and [Co(3,5-Di\(^3\)Bu-ChenPhyrin)], a bulky porphyrin ligand with stabilizing hydrogen-bond donor motifs. However, with other, more simple cobalt(II) porphyrin complexes such as [Co(TPP)], similar carbene radical species could not be detected with EPR spectroscopy. Reactions with EDA resulted in EPR silent solutions in the temperature range between 5-70K, implying either EPR silence of the key carbene intermediate (e.g. due to rapid relaxation effects) or rapid decomposition to diamagnetic species (e.g. [Co\(^{III}\)(TPP)-(CH\(_2\)COOEt)], see ref. 5).
The [Co(MeTAA)] complex behaves in a similar manner as [Co(TPP)], and also produces EPR silent solutions (at 20K) upon reaction with EDA (or EDA and methylacrylate). However, high resolution MS obtained via cold spray ionization at −40 °C (Figure 7) revealed the presence of [Co(MeTAA)(CHCOOEt)]⁺, i.e. 1e-oxidized species B or E (m/z=487.1536). Detection of these species is in agreement with the DFT computed mechanism. A species with mass m/z=573.1864, corresponding to [Co(MeTAA)(CHCOOEt)(MeAcrylate)]⁺, was also detected. While this could point to 1e-oxidized species C or F (Figure 7), this could also be the cyclopropane adduct (e.g. bound with its ester-moiety) of 1e-oxidized [Co(MeTAA)] species A.

![Figure 7. Proposed intermediates of the [Co(MeTAA)]-catalyzed cyclopropanation of methylacrylate with ethyldiazoacetate, detected using CSI-HRMS at −40 °C.](image)

Spin trapping can be used as an indirect method to detect radical species by EPR. They usually involve a nitrone as the spin trap, that reacts with a reactive, short lived free radical, thus forming a nitroxide-based persistent radical that can be easily detected by EPR. Most typically, N-tert-butyl-α-phenylnitrone (PBN) or 5,5-dimethyl-pyrroline N-oxide (DMPO) are the spin trapping reagents used in this approach (Figure 8). They easily react with free radicals in the α-position, generating persistent nitroxide radicals that are stable for days and can be detected by EPR at room temperature (Figure 8). Looking at the EPR profile, some information can be inferred about the trapped radical. The most revealing characteristics are the g-value and the hyperfine-couplings.

Upon recording EPR spectra during the [Co(MeTAA)]-catalyzed cyclopropanation reaction, adding PBN or DMPO as the spin traps, we observed an isotropic hyperfine splitting pattern characteristic for a trapped carbon centred radical (Figure 9). The EPR signal of the PBN-trapped species is strong and clean, much more intense than the background signal measured by recording the spectrum under identical conditions, but leaving-out the EDA reagent. The signal obtained from the DMPO...
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adduct is not as clean, but can still be characterized as a carbon trapped radical. Both spin adducts are used as complementary evidence, each characteristic of trapping a carbon center radical. While these experiments do not allow us to distinguish between different carbon radicals, we assume it is the carbene radical complex B (Scheme 1) that is trapped in these experiments (Figure 9). We cannot fully exclude that it is species C that is trapped in these experiments though.

![Diagrams of trapping agents and radicals](image)

Figure 8. Formation of persistent radicals using the most common trapping agents.

![Isotropic EPR spectra](image)

Figure 9. Isotropic X-band EPR spectrum of the PBN- (left) and DMPO- (right) trapped carbon-centered radicals (T = 298 K; microwave frequency: 9.36607 GHz; power: 6.33 mW; modulation amplitude: 1.0 G).

Additionally, we decided to investigate the kinetic profile of the [Co(MeTAA)]-catalyzed cyclopropanation reaction. However, before starting our kinetic studies,
we first examined the influence of some experimental conditions on the outcome of the reaction, such as the order of reagent addition, variations in concentration, or determining the lower limit of catalyst loading. If EDA is added to the reaction mixture after methyl acrylate, the reaction proceeds normally. When this order is reversed, however, the reaction does not take place at all, as is clear from the constant nitrogen pressure, showing no increase. Moreover, the byproducts of the 1,3-dipolar addition products, formed in the uncatalyzed reaction between EDA and methyl acrylate, are observed in the \(^1\)H-NMR spectrum (Scheme 2). This can be explained by catalyst deactivation caused by the reactive carbene intermediate formed from EDA in absence of the acrylate substrate, which will most likely abstract a hydrogen atom from the reaction medium or the EDA substrate to produce the deactivated Co\(^{III}\)-CH\(_2\)COOEt species (in the absence of methyl acrylate). This is in agreement with formation of EPR-silent solutions upon reaction of [Co(MeTAA)] with EDA (\textit{vide supra}). If only ethyl diazoacetate is added to the reaction mixture to see if diethyl fumarate is formed, carbene dimerization (as observed for many other catalysts) is not observed for [Co(MeTAA)], again indicating rapid deactivation to Co\(^{III}\)-CH\(_2\)COOEt species under these conditions.

\begin{scheme}
\textbf{A. 1,3-dipolar cycloaddition}

\begin{center}
\begin{align*}
&\begin{array}{c}
\text{R} \quad \text{N}_2 \\
\Rightarrow
\end{array} \\
&\begin{array}{c}
\text{EWG} \\
\Rightarrow
\end{array} \\
&\begin{array}{c}
\text{1-pyrazoline} \\
\Rightarrow
\end{array} \\
&\begin{array}{c}
\text{EWG} \\
\Rightarrow
\end{array} \\
&\begin{array}{c}
\text{2-pyrazolines} \\
\Rightarrow
\end{array}
\end{align*}
\end{center}

\textbf{B. Carbene dimerization}

\begin{center}
\begin{align*}
\begin{array}{c}
\text{R} \quad \text{N}_2 \\
\Rightarrow
\end{array} \\
&\begin{array}{c}
\text{H} \\
\Rightarrow
\end{array} \\
&\text{[M]} \\
&\Rightarrow \\
&\text{alkenes}
\end{align*}
\end{center}

\textit{Scheme 2. A: 1,3-dipolar cycloaddition between a diazo compound and an electron deficient alkene, observed upon addition of EDA before methyl acrylate. B: Diazo compound dimerization towards alkenes via metal carbenoids\textsuperscript{14} is not observed using [Co(MeTAA)].}

The design of the actual kinetic experiments follows Blackmond’s RPKA method\textsuperscript{11} to measure the reaction progress in time (release of dinitrogen vs time). Release of dinitrogen is directly proportional with EDA consumption over time. It should be noted here that the [Co(MeTAA)]-catalysed reactions are much faster than the
[Co(TPP)]-catalysed ones (see experimental section). We focused mainly on the kinetics of the [Co(MeTAA)]-catalysed reactions in this chapter.

A proper theoretical model of the system is needed for interpreting the results. Here we used the following kinetic model:

The general form of the rate equation for our reaction is:

$$rate = k_r \cdot [EDA]^x[MeAcryl]^y[cat]^z$$

However, looking at the DFT mechanism, we assume $x = 1$, $y = 0$, and $z = 1$, which should be confirmed experimentally. Therefore,

$$rate = k_r \cdot [EDA] \cdot [cat]$$

In a reaction where there is no catalyst deactivation, $[cat] = [cat]_0$

However preliminary results of the kinetic experiments indicate catalyst deactivation. Therefore we assume a 1st order catalyst deactivation process, which should also be confirmed experimentally.

$$\frac{d[cat]}{dt} = -k_d \cdot [cat]$$

$$\frac{[cat]}{[cat]} = -k_d \cdot dt$$

$$\int_{[cat]_0}^{[cat]} \frac{1}{[cat]} d[cat] = \int_0^t -k_d dt$$

$$\ln[cat] - \ln[cat]_0 = -k_d \cdot t$$

$$[cat] = [cat]_0 \cdot e^{-k_d \cdot t} \quad (3.1)$$

Combining the above-mentioned reaction steps in the kinetic rate equation, the integrated form of the rate equation becomes:

$$rate = k_r \cdot [EDA] \cdot [cat]$$

$$\frac{d[EDA]}{dt} = -k_r \cdot [EDA] \cdot [cat]_0 \cdot e^{-k_d \cdot t}$$

$$\frac{d[EDA]}{[EDA]} = -k_r \cdot [cat]_0 \cdot e^{-k_d \cdot t} dt$$
\[
\int_{[EDA]_0}^{[EDA]} \frac{1}{[EDA]} d[EDA] = \int_0^t -k_r \cdot [cat]_0 \cdot e^{-k_d t} dt \\
ln[EDA] - ln[EDA]_0 = -k_r \cdot [cat]_0 \cdot \left(\frac{-e^{(-k_d t)}}{k_d} + \frac{1}{k_d}\right)
\]

\[
[EDA] = [EDA]_0 \cdot e^{\left(-\frac{k_r \cdot [cat]_0 \cdot (1-e^{-k_d t})}{k_d}\right)} \quad (3.2)
\]

where,

\[
k_r = \frac{k_B T}{h} e^{-\frac{\Delta G^+}{R T}} \quad \text{L} \cdot \text{mol}^{-1} \cdot \text{min}^{-1}
\]

\[
k_d = \frac{k_B T}{h} e^{-\frac{\Delta G^\text{cat}}{R T}} \quad \text{min}^{-1}
\]

\[
\Delta G^\text{cat} = \Delta H^\text{cat} - T\Delta S^\text{cat}
\]

\[k_r = \text{reaction rate constant (L} \cdot \text{mol}^{-1} \cdot \text{min}^{-1)}\]

\[k_d = \text{catalyst deactivation rate constant (min}^{-1)}\]

\[k_B = \text{Boltzmann constant (4.970334} \cdot 10^{-20} \text{ m}^2 \cdot \text{kg} \cdot \text{min}^{-2} \cdot \text{K}^{-1})\]

\[t = \text{reaction time (min)}\]

\[T = \text{absolute temperature (K)}\]

\[h = \text{Planck’s constant (3.975642} \cdot 10^{-32} \text{ m}^2 \cdot \text{kg} \cdot \text{min}^{-1})\]

\[\Delta G^\text{cat} = \text{Gibbs energy of activation (kcal} \cdot \text{mol}^{-1)}\]

\[\Delta H^\text{cat} = \text{enthalpy of activation (kcal} \cdot \text{mol}^{-1)}\]

\[\Delta S^\text{cat} = \text{entropy of activation (kcal} \cdot \text{mol}^{-1)}\]

\[R = \text{gas constant (1.987} \cdot 10^{-3} \text{ kcal} \cdot \text{mol}^{-1} \cdot \text{K}^{-1})\]

We fitted all experimental kinetics to the above rate equations, leading in general to excellent fits of the experimental data. We started the experimental kinetic studies by measuring the reaction progress, [EDA] consumption versus time (Graph 1), at three different catalyst loadings, considering equal substrate concentrations. Using the integrated form of the proposed rate equation 3.2, excellent fits of the experimental data were achieved. All experiments having different initial catalyst loadings, but all performed at the same temperature (283 K) afforded \( k_r = 85.0 \) L mol\(^{-1}\) min\(^{-1}\) and \( k_d = 0.18 \) min\(^{-1}\). Obtaining the same rate constants for different experiments performed at the same temperature, is a strong indication that the proposed rate equation 3.2 is correct. However, we nonetheless decided to apply Blackmond’s methodology, by plotting several types of graphs such as [substrate] vs time or Rate vs [substrate], in which the kinetic experiments are discussed in detail.
This method uses a more graphical approach, which is perhaps more intuitive to experimental chemists.

Graph 1. [EDA] vs. time and Conversion vs. time for experiments at different catalyst loadings.

Graph 2. Rate versus [EDA] for experiments at different catalyst loadings.
Conducting experiments at different initial catalyst concentrations, it is possible to determine the order of the reaction in [catalyst]. If the reaction is first order in catalyst, which it is quite often the case for homogeneous catalysts, the rate dependence on the catalyst concentration is linear, and therefore the reaction rate is doubled when the catalyst concentration is doubled. An essential factor that needs to be taken into account in these experiments is that the active [Co(MeTAA)] catalyst concentration does not remain constant throughout the reaction, but decays following a 1st order deactivation process. Catalyst decay is however substantially slower than the catalytic reaction. Importantly, if this deactivation process is not taken into consideration the kinetic data cannot be fitted properly.

From Graph 1 and Graph 2 can be easily observed that the reaction rate increases with the increase in catalyst concentration. However, to determine the reaction order in [Co(MeTAA)] the turn-over frequency (TOF) has to be plotted versus [EDA] (Graph 3). If the curves of different experiments overlap, the reaction is first order in catalyst. An explanation for this can be found in the TOF definition, where TOF = rate/[catalyst]. Doubling both the rate and [catalyst] leads to the same TOF for different experiments at the same [EDA], therefore implying curve overlap. If the reaction has a different order than one, then the curves will not overlap. In Graph 3, the plot of the TOF versus [EDA] at 2.7 mol%, 2.0 mol% and 1.5 mol% [Co(MeTAA)] do overlap, therefore showing first order kinetics in [catalyst].

Graph 3. TOF versus [EDA] for experiments at different catalyst loadings.
To confirm that indeed catalyst deactivation occurs during the catalytic experiments at lower catalyst concentrations, catalytic reactions were explored using different substrate concentrations but keeping the difference between the concentration of methyl acrylate and EDA constant. This are so-called ‘same excess’ experiments ([excess] = [MeAcrylate] – [EDA]). The kinetic data extracted from these experiments can be used to distinguish between catalyst deactivation and product inhibition during catalysis.

Graph 4. [EDA] vs. time and Conversion vs. time for ‘same excess’ experiments.

Three of such ‘same excess’ experiments are shown in Graph 4. Two of them are designed to have lower initial substrate concentrations, chosen such that the initial substrate concentrations of these experiments are equal to the substrate concentrations at 25% and 50% conversion of the standard reaction, respectively (see experimental section). These reactions thus simulate the standard reaction at 25% and 50% conversion, but starting with a fresh batch of catalyst and in absence of product, which provides information about both catalyst deactivation and product inhibition. In absence of catalyst deactivation or product inhibition, the rates should be the same at all conditions and substrate concentrations screened, and hence the Conversion vs Time plots should overlap. This is not the case as seen in Graph 4. The same excess experiments simulating 25% and 50% conversion of the standard reaction but starting with fresh catalyst and in absence of product are clearly faster.
Graph 5. Rate versus [EDA] plots of the ‘same excess’ experiments.

The occurrence of catalyst deactivation and/or product inhibition processes is most clearly visualized by the non-overlapping plots of the reaction rate versus [EDA] (Graph 5). To distinguish between catalyst deactivation and product inhibition, an additional kinetic experiment was performed adding the cyclopropane product to the reaction mixture (Graph 5). Using a lower initial substrate concentration, i.e. 50% of the standard reaction, fresh catalyst and adding the cyclopropane product in the same concentration as formed under the standard reaction condition at 50% conversion, the rate plots overlap nicely, indicating no product inhibition. However, it is clear that the reactions starting with fresh catalyst (magenta and purple curves in Graph 5) are always significantly faster than those after 50% conversion under otherwise identical conditions at the same concentrations of EDA. This clearly points to gradual catalyst deactivation under the applied reaction conditions, in line with the proposed 1st order deactivation rate shown in equation 3.1.
Mechanistic investigations using [Co(MeTAA)]

Graph 6. [EDA] vs. time and Conversion vs. time for ‘different excess’ experiments.

Graph 7. Rate vs [EDA] and TOF vs [EDA] plots for same excess experiments.
The [substrate] reaction orders were determined by conducting experiments at ‘different excess’ concentrations of methyl acrylate. If the reaction is zero order in [methyl acrylate], the concentration of methyl acrylate will have no effect on the reaction rate. Graph 6 shows a plot of the reaction conversion over time as well as the consumption of [EDA] over time, for different excess of methyl acrylate. There is a clear overlap of the curves, with a slight misalignment when both reactions reach a conversion >70%. To see the overlap better, the reaction rate versus [EDA] is plotted in Graph 7, and it indeed shows that the two curves overlay. The reaction is therefore zero order in [methyl acrylate] under the actually applied reaction conditions (i.e. the same reaction conditions as used in the catalytic reactions described in Chapter 2). To determine the reaction order in [EDA] the plot of the TOF (Rate/[catalyst]) versus the EDA concentration should be analyzed. When looking at the graph, it can be seen that the plot is a straight line, which implies first order kinetics in [EDA].

After in depth analysis of all the kinetic data and fitting of the experimental data with the proposed model, we arrive at the following rate equations for the [Co(MeTAA)]-catalyzed cyclopropanation of methyl acrylate with EDA:

\[
\text{rate} = k_r \cdot [\text{EDA}] \cdot [\text{cat}] \tag{3.3}
\]

where, 

\[
[\text{cat}] = [\text{cat}]_0 \cdot e^{-k_d t}
\]

and \( k_r = 85.0 \) L mol\(^{-1}\) min\(^{-1}\) and \( k_d = 0.18 \) min\(^{-1}\) (both averaged over many experiments) measured at 283 K.

These rate constants are temperature dependent, thus we decided to perform the kinetic experiments at three different temperatures (273K, 278K and 283K) in order to derive both the enthalpy and entropy of activation for direct comparison with the DFT calculations. Graph 8 shows, as expected, that the reaction is slower when the reaction is performed at lower temperatures.

After fitting the experimental data using equation 3.2, the reaction rate constants could be obtained at the three different temperatures. Therefore, at 273K a \( k_{273} = 46 \) L mol\(^{-1}\) min\(^{-1}\) was obtained, at 278K \( k_{278} = 64 \) L mol\(^{-1}\) min\(^{-1}\) and at 283K, \( k_{283} = 85 \) L mol\(^{-1}\) min\(^{-1}\).

Eyring equation (3.4) can be used to understand the influence of temperature over the reaction rate as it shows the relation between \( k \) and \( T \), from which Gibbs free energy of activation can be derived.
Mechanistic investigations using \([\text{Co(MeTAA)}]\)

\[
k_r = \frac{k_B T}{h} e^{-\frac{\Delta G^\ddagger}{RT}} \tag{3.4}
\]

The linear form of the Eyring-Polanyi equation (3.5) is most useful for plotting linear graphs, and can be expressed as,

\[
\ln \frac{k_r}{T} = -\frac{\Delta H^\ddagger}{R} \cdot \frac{1}{T} + \ln \frac{k_B h}{h} + \frac{\Delta S^\ddagger}{R} \tag{3.5}
\]

Graph 8. [EDA] vs. time and Conversion vs. time at different temperatures

Performing the reaction at different temperatures, and plotting \(\ln \frac{k_r}{T}\) vs \(\frac{1}{T}\), a straight line is expected from which both \(\Delta H^\ddagger\) and \(\Delta S^\ddagger\) can be derived. The thus obtained experimental values for enthalpy and entropy can then be compared with the DFT calculated values of the rate determining step. Graph 9 presents a good fitting of the reaction rates at three different temperatures. From the fitting equations, we obtained \(\Delta H^\ddagger = 8.89\) kcal mol\(^{-1}\) and \(\Delta S^\ddagger = -26.4\) cal mol\(^{-1}\) K\(^{-1}\), which translates (\(\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger\)) to a free energy activation barrier of \(\Delta G_{298}^\ddagger = +16.8\) kcal mol\(^{-1}\) at 298 K. The substantial negative activation entropy term points to an ordered transition state, as expected for the proposed associative process (from A to the rate limiting transition state TS1; see Scheme 1, Figure 4).
The experimental free energy activation barrier $\Delta G_{298}^{\ddagger}(\text{exp}) = +16.8$ kcal mol$^{-1}$ is in good qualitative agreement with the calculated one $\Delta G_{298}^{\ddagger}(\text{calc}) = +14.5$. The small difference of 2.3 kcal mol$^{-1}$ is likely, at least in part, due to some (experimental and computational) errors in the activation entropy term (Table 1).

**Table 1. Comparison of experimental and DFT calculated activation parameters of the [Co(MeTAA)]-catalysed cyclopropanation reaction of methylacrylate with EDA.**

<table>
<thead>
<tr>
<th></th>
<th>$\Delta G_{298}^{\ddagger}$ a)</th>
<th>$\Delta H_{298}^{\ddagger}$ a)</th>
<th>$\Delta S_{298}^{\ddagger}$ b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+16.8 ($\pm$ 0.3)</td>
<td>+8.9 ($\pm$ 0.3)</td>
<td>-26 ($\pm$ 1.1)</td>
</tr>
<tr>
<td>DFT</td>
<td>+14.5</td>
<td>+7.8</td>
<td>-22</td>
</tr>
</tbody>
</table>

a) Activation energies in kcal mol$^{-1}$; b) Activation entropies in e.u. (cal mol$^{-1}$ K$^{-1}$)

Overall, the experimental and DFT calculated activation parameters are in good agreement. The most reliable parameters (both experimentally and computationally) are the activation enthalpies. The DFT calculated activation enthalpy ($\Delta H_{\text{calc}}^{\ddagger} = +7.8$ kcal mol$^{-1}$) is in excellent agreement with the experimental one ($\Delta H_{\text{exp}}^{\ddagger} = +8.9$ kcal mol$^{-1}$), thus giving strong support to the proposed mechanism shown in Scheme 1.
3. **Summary and Conclusions**

In summary, a detailed mechanistic study of the cobalt(II) tetramethyl-dibenzotetraaza[14]annulene [Co(MeTAA)] catalyzed cyclopropanation of methyl acrylate with ethyl diazoacetate (EDA) has been performed. The DFT study revealed that the overall free energy barriers of the [Co(MeTAA)]-catalysed reaction are significantly lower than for the [Co(TPP)]-catalysed process. In good agreement, experimental kinetic studies revealed substantially faster reactions for the [Co(MeTAA)]-catalysed reactions. Cobalt(III)-carbene radicals were demonstrated to be present as key intermediates in the reaction and were detected using HR-MS and EPR spin trapping experiments. Real-time reaction monitoring allowed us to use reaction progress kinetic analysis (RPKA) to analyze the experimental data. These studies revealed that the reaction is first order in both [catalyst] and [EDA], and zero order in [methyl acrylate], in excellent agreement with the DFT-calculated mechanism. Furthermore, a 1st order catalyst deactivation process was detected, which is much slower than the catalytic reaction steps, but does lead to detectable catalyst degradation during catalysis. The exact nature of this process needs to be further investigated in future studies. The DFT calculated activation parameters of the reaction (ΔG‡, ΔH‡ and ΔS‡) are in agreement with the experimental values, thus providing strong support to the proposed metallo-radical mechanism.

4. **Experimental Section**

**General Details:** Chemicals used during this research were purchased from Sigma Aldrich. Ethyl diazoacetate and methyl acrylate were degassed prior to use, via the freeze-thaw-pump-method. Methyl acrylate was passed through basic alumina before use, to remove stabilizers (radical scavengers). Both substrates are stored refrigerated (4°C). The [Co(MeTAA)] catalyst is not commercially available and was synthesized according to a known procedure. All reactions were performed under an inert atmosphere. Neslab ULT-80 is used as cryostat for isothermal reactions conditions. The kinetic kit used for real-time pressure measurements is the X102 kit from the company Man on the Moon (Figure 10).

**General Procedure for Kinetic Measurements:** To the reaction flask was added a 1.0 cm cylindrical stirring bar, while checking all connections for a leak-free system. Then, the whole system was flushed with nitrogen. The order of addition of the reactants was as following: First the catalyst solution, second the solvent, thirdly the alkene and finally the diazo compound. After addition of the first three reactants, the septum of the reaction flask was replaced and the whole reaction setup was introduced in the thermostatic ethanol bath. The reaction mixture was stirred at 500 rpm and cooled to the desired temperature for 30 minutes. A pressure/temperature measurement was started, then the diazo compound was added at once and the reaction started. Once nitrogen evolution had ended, and the pressure was constant, data recording was stopped. Then, the resulting mixture was
concentrated and the residue purified by flash chromatography (silica gel) or extracted in pentane for analysis of the reaction products.

Figure 10. Kinetic Kit used for gas-release experiments.

Table 2. Reaction conditions for RPKA.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>CoMeTAA</th>
<th>EDA</th>
<th>Methyl acrylate</th>
<th>Toluene</th>
<th>Cyclopropane</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard conditions (1.5%)</strong></td>
<td>750 µL</td>
<td>53 µL</td>
<td>90 µL</td>
<td>1100 µL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.0075 mmol</td>
<td>0.5 mmol</td>
<td>1 mmol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.015 eq</td>
<td>1 eq</td>
<td>2 eq</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Higher catalyst concentration (2%)</strong></td>
<td>1000 µL mmol</td>
<td>53 µL</td>
<td>90 µL</td>
<td>857 µL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.03 mmol</td>
<td>0.5 mmol</td>
<td>1 mmol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.002 eq</td>
<td>1 eq</td>
<td>2 eq</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lower catalyst concentration (1%)</strong></td>
<td>500 µL 0.005 mmol</td>
<td>53 µL</td>
<td>90 µL</td>
<td>1357 µL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.01 eq</td>
<td>0.5 mmol</td>
<td>1 mmol</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Same excess at 25% conversion</strong></td>
<td>750 µL 0.0075 mmol</td>
<td>40 µL 0.375 mmol</td>
<td>79 µL 0.875 mmol</td>
<td>1132 µL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.015 eq</td>
<td>1 eq</td>
<td>2.33 eq</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Same excess at 50% conversion</strong></td>
<td>750 µL 0.0075 mmol</td>
<td>29 µL 0.25 mmol</td>
<td>68 µL 0.75 mmol</td>
<td>1156 µL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.015 eq</td>
<td>1 eq</td>
<td>3 eq</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Same excess at 50% conversion with product addition</strong></td>
<td>750 µL 0.0075 mmol</td>
<td>29 µL 0.25 mmol</td>
<td>68 µL 0.75 mmol</td>
<td>629 µL 530 µL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.015 eq</td>
<td>1 eq</td>
<td>3 eq</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Different excess</strong></td>
<td>750 µL</td>
<td>53 µL</td>
<td>135 µL</td>
<td>1062 µL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.0075 mmol</td>
<td>0.5 mmol</td>
<td>1.5 mmol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.015 eq</td>
<td>1 eq</td>
<td>3 eq</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Reaction Details:** The reaction took place in a flame-dried Schlenk flask (with a total gas volume of 20.1 mL) that was attached to a pressure/temperature sensor and placed in a thermostatic ethanol bath at 283 K. The reaction mixture volume of liquid was kept constant at 2 mL. The different conditions can be found in Table 2. A 0.01 M stock solution of [Co(MeTAA)] in toluene was used for all experiments. A 0.474 M cyclopropane stock solution in toluene was used. All reactions were performed in duplo or triplo, to assure that the data were reproducible.

**Characterization:** Ethyl methyl -1,2-cyclopropanedicarboxylate

\[
\text{Trans-isomer: } ^1H \text{ NMR (400 MHz, CDCl}_3) \delta 4.06 (q, J = 7.1 Hz, 2H), 3.61 (s, 3H), 2.14 - 2.01 (m, 2H), 1.38 - 1.30 (m, 2H), 1.18 (t, J = 7.2 Hz, 3H). ^13C \text{ NMR (101 MHz, CDCl}_3) \delta 172.20, 171.65, 61.04, 52.09, 22.37, 22.08, 15.28, 14.13.
\]

**HRMS (EI):** Calcd. for C_{8}H_{12}O_{4} m/z 172.0736, Found m/z 172.0737.

**GC analysis:** Supelco SPB-1 (Temp program: initial temp = 70° C, 7.00° C/min, final temp = 250° C, final time = 5.00 min) trans-isomer: t = 14.66 min, cis-isomer: t = 14.93 min.

**Comparison of the kinetics between [Co(MeTAA)] and [Co(TPP)].** A preliminary study has been performed to compare the reaction rate between [Co(MeTAA)] and [Co(TPP)]. There is a visible difference between the time needed to reach full conversion (0.65 bar). For [Co(MeTAA)] this is achieved in less than 3 minutes, while for [Co(TPP)] only 50% conversion is reached after 45 minutes. However, full kinetic studies are needed for the [Co(TPP)] system in order to fully compare reaction rates and establish additional mechanistic conclusions about the [Co(TPP)]-catalysed reactions.

![Figure 11. Preliminary reaction rate comparison between the cyclopropanation of EDA and methyl acrylate, catalysed by [Co(MeTAA)] and [Co(TPP)]](image)

**Computational Details:** Geometry optimizations were carried out with the Turbomole program package coupled to the PQS Baker optimizer via the BOpt package. We used unrestricted ri-DFT-D3 calculations at the BP86 level, in combination with the def2-TZVP basis set and a small (m4) grid size. All minima (no imaginary frequencies) and transition states (one imaginary frequency) were characterized by calculating the Hessian matrix. ZPE and gas-phase thermal corrections (entropy and enthalpy, 298 K, 1 bar) from these analyses were calculated. The nature of the transition states was confirmed by following the intrinsic reaction coordinate.
DFT calculations without dispersion corrections strongly underestimate the metal-ligand interactions, as was clear from a series of test calculations. We therefore employed Grimme's version 3 (disp3) dispersion corrections. Used as such, the computed dispersion corrected metal-ligand association/dissociation energies to/from the non-solvated [Co(TPP)] catalyst are overestimated though. This is due to neglected dispersion interactions between the metal binding site of the catalyst and a solvent molecule in solution. We therefore used the Van der Waals complex between [Co(TPP)] and a discrete toluene solvent molecule (interacting with catalyst at the metal binding site) as the energetic reference point in our calculations to prevent overestimation of the metal-ligand interactions as a result of such uncompensated dispersion forces. However, this approach also leads to an erroneous cancelation of translational entropy contributions to the computed free energies. This is because the translational entropy contributions to substrate/product association/dissociation are fully counterbalanced by the translational entropy contributions resulting from dissociation/association of the involved solvent molecule in the DFT calculated thermodynamics ([Co(TPP)(toluene)] + L ↔ [Co(TPP)(L)] + toluene). This is not realistic in comparison to actual solution phase chemistry, for which the translational entropy contributions associated with substrate/product association/dissociation steps can of course not be neglected. Therefore we applied a translational entropy contribution of −26 cal mol⁻¹ K⁻¹ to the computed free energies of all substrate/product binding/dissociation steps in the catalytic cycle. A similar approach was used in a recently published paper from our group.

5. Acknowledgements

We thank Ed Zuidinga for MS measurements, Jan Meine Ernsting for NMR advice, and Marie Brands for help with kinetic experiments (design and labwork).

6. References


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[21] In solution the catalyst is completely surrounded by solvent molecules, leading to small translational entropy contributions to the toluene molecule association/dissociation steps. These are of little influence on the translational entropy contributions associated with substrate/product association/dissociation. Hence, the latter are not canceled by the former in toluene solution.