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O_2 activation at a trispyrazolylborato nickel(II) malonato complex†

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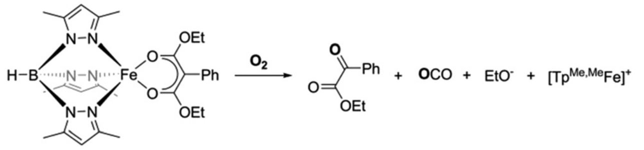
To support mechanistic inferences made for an iron-based dioxygenase model, a nickel analogue, *i.e.* a TpNi-malonate (1) was prepared. 1 proved to represent a rare case of a nickel complex reacting with O_2 in a controlled manner – mechanistically different from the iron case – and leads to hydroxylation of the malonate.

The acetylacetone dioxygenase, Dke1, catalyses the degradation of β-diketones and β-ketoesters to yield the corresponding carboxylic acids and α-ketoaldehydes, and the active site is deceptively simple containing iron(II) coordinated by three histidine residues and water.[1,2]

As the mechanism by which this site operates to accomplish dioxygenation was discussed controversially (initial O_2 binding at the substrate or activation at the iron(II) center in the initial step)[3–7] we set out to test the possibility of an O_2 activation scenario for the acetylacetone dioxygenase with the aid of low molecular weight analogues. For the simulation of the His_3 ligand set within Dke1 we chose the well-known trispyrazolylborato ligand (Tp) and diethyl malonate as a substrate ligand, that is a representative of the family of β-ketoesters which are cleaved by Dke1, too. Hence, the complex $Tp^{Me,Me}Fe$(Phmal), **I** (Scheme 1), was synthesized and a structural investigation showed that a vacant coordination site was available at the Fe(II) center for the complexation and activation of O_2.[6]



I

Scheme 1 Oxidative cleavage of diethyl phenylmalonate at a $Tp^{Me,Me}Fe$ complex.

Treatment of an acetonitrile solution of **I** with dry dioxygen at r.t. was shown to lead to ethyl benzoylformate, which is one of the products expected in case of a dioxygenase activity of **I** analogously to the function of Dke1. The second one – $EtOCO_2^-$ – apparently decomposed already during the reaction to give ethanolate and CO_2. With this functional model in hand we investigated the role of iron(II) in this conversion by performing additional control experiments, where iron(II) was formally replaced by lithium(I), iron(III) and also nickel(II). The results on lithium(I) and iron(III) alone,[6] namely inertness towards O_2, already indicated that iron(II) is essential and the likely reason is, that it has to activate O_2 in the initial step. On the basis of these results gathered for **I** a corresponding primary step was postulated for the Dke1, too,[6] and indeed three years later this idea was supported through the results of extensive DFT calculations performed by Solomon *et al.*[5]

The results obtained after replacement of iron(II) by nickel(II) brought about observations, though, that deserved further attention, which is the topic of this contribution.

Results and discussion

After having established for **I** that the cleavage reaction requires iron(II) as described above,[6] we felt that convincing additional support would be provided by showing that the reaction of Scheme 1 does not occur analogously in case of a corresponding nickel complex, since typically O_2 is not activated at nickel(II) centers.[8] So far, Dke1 relevant reactivity at a nickel(II) center was observed only for the combination of $Ni(acac)_2(H_2O)_2$ and ethylenediamine in water under aerobic conditions, or upon irradiation of Ni^{II} diketonate complexes.[9]

Accordingly, the complex $Tp^{Me,Me}Ni$(Phmal) (**1**) was prepared by reaction of $Tp^{Me,Me}NiOAc$ with PhmalLi in good yields (63%) (Scheme 2). **1** was characterized *via* ^1H NMR, UV/Vis and ESI/MS spectroscopy, and *via* the Evans method a

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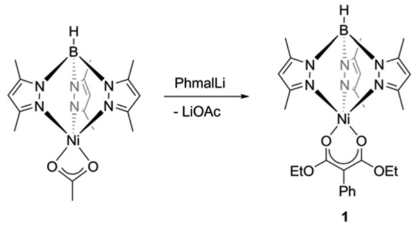


Scheme 2 Synthesis of **1**.

magnetic moment of $\mu_{\mathrm{eff}} = 3.21\mu_{\mathrm{B}}$ was determined, suggesting a high-spin ground state. Attempts to grow single crystals of **1** failed but crystals for the corresponding phenyl derivative $\mathrm{Tp^{Ph,Me}Ni(Phmal)}$ (**2**) could be obtained, which was synthesized similarly (starting from $\mathrm{Tp^{Ph,Me}NiBr}$) and characterized analogously to **1**. Their investigation by X-ray diffraction revealed a structure as expected, very similar to the one of **I**, with nickel in a square pyramidal coordination environment ($\tau = 0.04$) and a vacant coordination site (Fig. 1); the results of DFT calculations predicted an analogous structure for **1** in a high-spin ground state in agreement with the experimental findings (Fig. 1).

1 is a green compound dissolving in non-coordinating solvents with green color, while with nitriles blue solutions are obtained, indicating an interaction of the nitrile molecules with the Ni center and consistently **2** dissolves with green color also in nitriles, probably as the phenyl residues effectively shield the nickel center with respect to nitrile binding. This solution behaviour was already discussed by Akita *et al.* for the starting compound $\mathrm{Tp^{Me,Me}NiOAc}$:[10] solutions in dichloromethane are green color, whereas acetonitrile solutions appear to be blue and it was suggested that this is due to the additional coordination of one acetonitrile molecule to the metal center. We could confirm this hypothesis by X-ray crystal structure analysis of the coordinatively saturated Ni complex $\mathrm{Tp^{Me,Me}NiOAc(MeCN)}$ (for details see ESI†). If a blue solution of **1** in acetonitrile is exposed to dry O_2, it quickly changes color to green within minutes, thus suggesting that a reaction has taken place at the nickel center that alters the donor situation. By contrast, the phenyl derivative **2** behaves inert towards O_2, which was inferred not only from a lack of color change but also chemically (work-up) and spectroscopically. Consequently, it may be concluded that the O_2 reaction requires some space at the Ni center. To gain more information we monitored the O_2 reaction with UV/Vis spectroscopy (Fig. 2). **1** shows a strong band at 272 nm corresponding to a $\pi \rightarrow \pi^*$ transition, which was observed to continuously lose in intensity upon addition of O_2, while a new shoulder at 251 nm emerged. This shows that the reaction with O_2 involves the Phmal ligand and further insight were sought in an ESI/MS investigation. The spectrum of **1** dissolved in acetonitrile shows a peak at $m/z = 613.25$ corresponding to the sodium adduct of the complex as well as a smaller one at $m/z = 629.25$ that belongs to the corresponding potassium adduct (Fig. 3). After two hours of stirring in an O_2 atmosphere, a peak for the sodium adduct of the mono-oxygenated complex was observed at $m/z = 629.21$, assignable to $[\mathbf{1} + \mathrm{O} + \mathrm{Na}]^+$, as well as one at $m/z = 645.20$ that could be assigned either to the corresponding potassium adduct $[\mathbf{1} + \mathrm{O} + \mathrm{K}]^+$ or to the sodium adduct of the dioxygenated complex. $^{18}O_2$ labelling studies then allowed a clear assignment of the peak at $m/z = 649.20$ to $[\mathbf{1} + 2{}^{18}\mathrm{O} + \mathrm{Na}]^+$ (Fig. 3). We note that these are not the only peaks observed in the spectrum but they suggest that the reaction with O_2, which according to the results described above, involves both the Ni and the Phmal ligand, corresponds to an oxygenation. This hypothesis was confirmed by work up of such a reaction mixture after 2 h by addition of 3 M hydrochloric acid and filtration over silica to remove the nickel salts formed. This provided the organic products in an overall yield of 78%, with Phmal hydroxylated in the C_α position as the major product according to GC/MS; using $^{18}O_2$ a labelling of 41.3% was found (probably the aqueous workup procedure leads to a partial loss of label). Only small amounts of ethylbenzoyl formate, the sole product of the reaction of **I** with O_2,

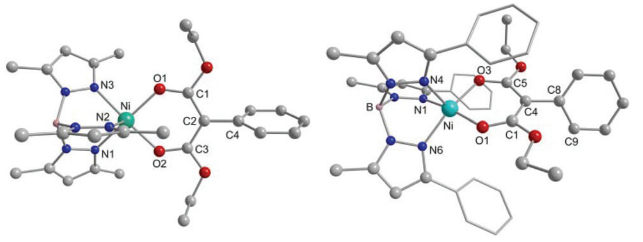


Fig. 1 Left: Molecular structure of **1** as predicted by DFT calculations (B3LYP/Def2-TZVP, triplet state); right: molecular structure of **2** as determined by single crystal X-ray diffraction; selected bond lengths [Å] and angles [°] for **2**: Ni–O1 1.9773(11), Ni–O3 1.9848(11), Ni–N1 2.0232(13), Ni–N4 2.0382(13), Ni–N6 2.0705(13), O1–C1 1.2616(18), O3–C5 1.2561(19), C1–C4 1.409(2), C4–C5 1.408(2); N1–Ni–N4 92.27(5), N1–Ni–N6 92.43(50), N4–Ni–N6 85.84(5), O1–Ni–N1 101.86(5), O1–Ni–N4 165.79(5), O1–Ni–N6 92.06(5), O3–Ni–N1, O3–Ni–N4 90.49(5), O3–Ni–N6 168.09(5), Ni–O1–C1 126.24(10), Ni–O3–C5 126.59(10), C1–C4–C5 118.65(14).

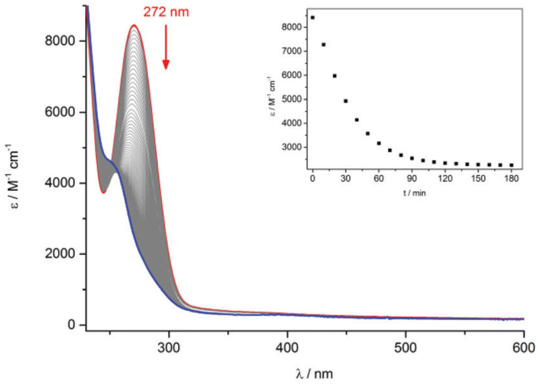


Fig. 2 UV/Vis spectrum of $\mathrm{Tp^{Me,Me}Ni(Phmal)}$ in acetonitrile (0.12 mM) at r.t. showing an intense band at 272 nm ($\varepsilon = 8414\ \mathrm{M^{-1}\ cm^{-1}}$); after O_2 addition measurements every 60 s.

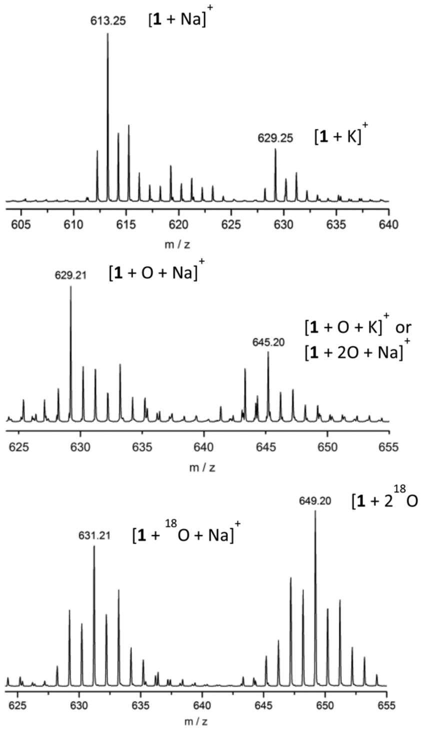


Fig. 3 ESI/MS spectra of **1** in acetonitrile (top) after treatment with $^{16}O_2$ (middle) and $^{18}O_2$ (bottom).

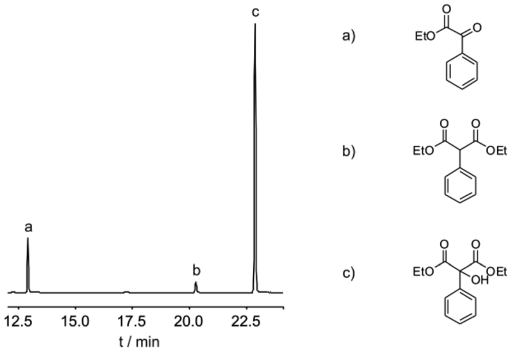
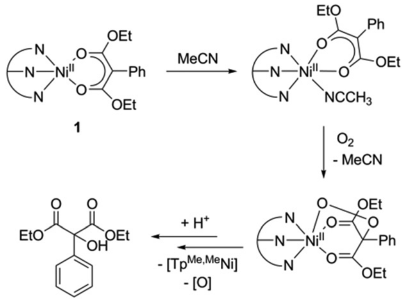


Fig. 4 The products of the reaction of **1** and O_2 after 2 h and work-up; ratio of HPhmal : ethylbenzoyl formate : HOPhmal = 1 : 4 : 24.

were formed (HPhmal : ethylbenzoyl formate : HOPhmal = 1 : 4 : 24) (Fig. 4), which is reasonable assuming that **1** will react *via* a different mechanism that does not involve an O_2 activation step analogous to **I**. Also highvalent intermediates, comparable to the $Fe^{IV}{=}O$ species described in the mechanism proposed for the Dke1 by Solomon and coworkers,[5] or the dinuclear Pd^{III} species proposed by Ritter and coworkers for the α-hydroxylation of β-dicarbonyl moieties are unlikely.[11] Other reactions hydroxylating diethylphenylmalonate using molecular oxygen as the oxidant are suggested to proceed *via* radical intermediates,[12,13] for which there was no evidence in case of **1**.



Scheme 3 Mechanistic proposal for the reaction of **1** and O_2.

A conceivable mechanism is shown in Scheme 3, and it is based on a nickel-organoperoxide. Only few compounds of that type are known and recently, by investigating a β-diketiminato nickel(II) compound, we brought evidence for the first time, that they can be formed through addition of O_2 to a nickel(II) complex.[8] This is of interest also in the context of the recent identification of a nickel/O_2 adduct after treatment of the substrate complex of a Ni-dependent quercetinase with O_2 and the suggestion that this intermediate reacts further to give a nickel organoperoxide.[14] Despite a lot of effort (Raman spectroscopy, EPR) in case of **1** unfortunately, we failed to isolate or identify the green intermediate species of the system after O_2 treatment. DFT calculations suggested the structure shown in Fig. 5 with a triplet ground state for a potential nickel peroxoorgano intermediate. Other structures were tested but were all significantly higher (>22 kJ mol^{-1}) in energy. It becomes obvious that one of the carbonyl donors got detached in favour of the new Ni–O bond. Formation of the peroxide was calculated to be exothermic by 13 kJ mol^{-1}. This finding is in good agreement with a similar peroxo intermediate with an O–O bridge between a Cu(II) and the chloro-substituted C_α atom of a diketone predicted by DFT calculations, suggested to react further *via* an oxidative aliphatic carbon–carbon bond cleavage within the diketonate unit.[15]

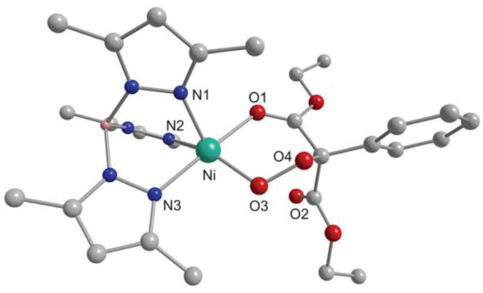


Fig. 5 Optimized structure (B3LYP/Def2-TZVP, triplet state) of a potential organoperoxonickel intermediate. H atoms have been omitted; selected bond lengths [Å] and angles [°]: Ni–O1 2.206, Ni–O3 1.925, Ni–O2 3.997, Ni–N1 2.046, Ni–N2 2.087, Ni–N3 2.100, O3–O4 1.543; N1–Ni–N2 91.8, N1–Ni–N3 90.1, N2–Ni–N3 87.1, O1–Ni–N1 94.6, O1–Ni–N2 90.0, O1–Ni–N3 174.6, O3–Ni–N1 119.1, O3–Ni–N2 149.1, O3–Ni–N3 94.1, Ni–O3–O4 116.5, O1–Ni–O3 86.0.

Conclusions

A TpNi^{II} complex with a diethylmalonate substrate ligand has been found to react readily with O_2. The reaction was shown to require space at the nickel center and to involve the diethylmalonate ligand. In ESI/MS studies a peak for the dioxygenated complex was detected. A mechanism involving a nickel organoperoxide intermediate was thus suggested, which, however, eluded direct identification. Work-up brought evidence for the oxygenation of the diethylmalonate, though, and as one should expect, assuming that the iron complex **I** reacts with O_2 *via* a different mechanism due to the capability of iron(II) to directly activate O_2 and form highvalent oxido species, the product in case of **1** is different from the cleavage product observed in case of **I**. The studies thus bring further evidence that nickel(II) complexes can in fact activate O_2, if conjugated π systems are bound, that upon contact with O_2 can transfer an electron so that a nickel(III) state can be avoided. It remains unclear, though, whether O_2 binds to nickel or the C_α atom first or whether it adds to both simultaneously.

Conflicts of interest

There are no conflicts of interest to declare.

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