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Nucleophilic versus Electrophilic Reactivity of Bioinspired Superoxido Nickel(II) Complexes

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Dedicated to Helmut Schwarz on the occasion of his 75th birthday

Abstract: *The formation and detailed spectroscopic characterization of the first biuret-containing monoanionic superoxido-Ni^{II} intermediate [LNiO$_2$]$^-$ as Li salt **2** [L = MeN[C(=O)NAr)$_2$; Ar = 2,6-iPr$_2$C$_6$H$_3$)] is reported. It results from oxidation of the corresponding [Li(thf)$_3$]$_2$[LNi^{II}Br$_2$] complex **M** with excess H$_2$O$_2$ in the presence of Et$_3$N. The [LNiO$_2$]$^-$ core of **2** shows an unprecedented nucleophilic reactivity in oxidative deformylation of aldehydes, in stark contrast to the electrophilic character of the previously reported neutral Nacnac-containing superoxido-Ni^{II} complex **1**, [L'NiO$_2$] (L' = CH(CMeNAr)$_2$). According to Density Functional Theory (DFT) calculations, the remarkably different behaviour of **1** vs **2** can be attributed to their different charges and a two-state reactivity, in which a doublet ground state and a nearby spin-polarized doublet excited-state both contribute in **1** but not in **2**. The unexpected nucleophilicity of the superoxido-Ni^{II} core of **2** suggests that such a reactivity may also play a role in catalytic cycles of Ni-containing oxygenases and oxidases.*

Mononuclear dioxygen-metal species (O$_2$-M) have been implicated as key intermediates in biocatalytic cycles of dioxygen activation with heme and non-heme metalloenzymes.[1] A number of metal complexes binding an O$_2$ unit, such as superoxido- and peroxido-metal species, have been synthesized as chemical models of O$_2$-M intermediates, and their reactivity has been intensively investigated.[2] Whereas, mononuclear peroxido-metal species are generally associated with oxidative nucleophilic reactions (e.g. aldehyde deformylation), superoxido-metal complexes are typically considered as electrophilic oxidants leading to hydrogen-atom abstraction (HAT) from a C-H bond and oxygen-atom transfer (OAT) to alkenes, phosphines or sulfides. However, very recently nucleophilic reactivity of a superoxido-iron[3] complex with aldehydes has also been demonstrated, which supports the ascribed roles of superoxido-iron species as both electrophilic[4] and nucleophilic[5] reactants in biology. A copper-superoxido complex[6] also exhibited both nucleophilic and electrophilic properties in a related study.

Superoxido-nickel complexes (Table S1) are also attractive targets for biomimetic synthetic studies. Evidence has been accumulating that O$_2$-Ni species participate in biological oxidations; for example in quercetin-2,4-dioxygenase.[7] Lessons learned from synthetic models can be useful to uncover structure-reactivity relationships of respective metalloproteins. Indeed, recent synthetic advances have led to the isolation and characterization of a few well-characterized superoxido-nickel model complexes, and all of them are capable of performing electrophilic oxidation reactions.[8] In particular, the isolable side-on superoxido-nickel(II) complex [L'Ni^{II}O$_2$] **1** (Scheme 1), involving a monoanionic β-diketiminate ligand L', exhibited a dioxygenase-like reactivity when exposed to *para*-substituted di-*tert*-butylphenols,[8c][9] affording an unprecedented oxidation product incorporating both oxygen atoms from a single O$_2$-Ni subunit. The mechanism of this transformation is proposed to involve the mediation of a oxido-Ni^{III} species formed via O–O bond homolysis of an arylperoxido-Ni^{II} intermediate; this parallels the generally accepted mechanism for metal-mediated activation of dioxygen to generate high-valent oxido-metal units by O–O bond homolysis or heterolysis of (hydro)peroxido-metal cores in various oxygenase and oxidase enzymes.[10]

Nucleophilic reactivity of superoxido-Ni complexes is, however, unprecedented in the literature. The recently demonstrated ability of superoxido-Cu and -Fe species to undergo a nucleophilic attack of the electrophilic carbonyl carbon atom in aldehydes[3,4] raised the question whether or not such reactivity could be realized with other superoxido-metal complexes as well. In our continuous effort to uncover structure–reactivity relationships of mononuclear dioxygen-metal intermediates, we now report the synthesis and reactivity of the novel superoxido-Ni^{II} complex monoanion [LNi^{II}O$_2$]$^-$ in **2** based on the biuret ligand L (generated from **LH$_2$**, Scheme 1). We show that although the electronic structures of the O$_2$–Ni cores in **1** and **2**

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can both be described in terms of the presence of a low-spin Ni^{II} (d^8; S_{Ni}=0) ion bound to a S=1/2 superoxide ($O_2^{-•}$) anion radical, they exhibit different reactivity patterns. Whereas, the neutral superoxido-Ni complex **1** exhibits electrophilic HAT reactions with substrates containing weak N-H/O-H bonds,[9] monoanionic **2** performs nucleophilic attack to carbonyl carbons leading to deformylation of aldehydes. In addition to the different charges of **1** and **2**, a two-state reactivity (TSR) model, in which a doublet ground state and a nearby doublet excited-state both contribute, provides a useful model for interpreting the reactivity trends of **1** vs **2**.

The 2,6-diisopropylphenyl-substituted biuret **LH$_2$** (Scheme 1 and Scheme S1) was prepared by coupling of the dichloroformyl-methylamine with two molar equivs. of 2,6-diisopropylaniline in the presence of triethylamine (Et$_3$N). Reactions of equimolar amounts of the deprotonated biuret ligand L^{2-} and NiBr$_2$(thf)$_{1.5}$ in tetrahydrofuran (thf) afforded the blue $[LNi^{II}Br_2]^{2-}$ dianion, which is obtained as the dilithium salt $[Li(thf)_3]_2[LNi^{II}Br_2]$ **M** (Scheme 1; CCDC 1832378). Complex **M** is paramagnetic with $S = 1$ (μ_{eff} = 3.1 Bohr magnetons) in the electronic ground state, in accordance with the presence of a tetrahedral (Td) coordinate d^8-Ni^{II} ion (Scheme 1). The starting materials **LH$_2$** and **M** were characterized by a number of spectroscopic techniques, including ^{1}H-NMR spectroscopy, electrospray ionization mass spectrometry (ESI-MS), elemental analyses, UV-Vis and IR spectroscopy (Figs. S1-S3).
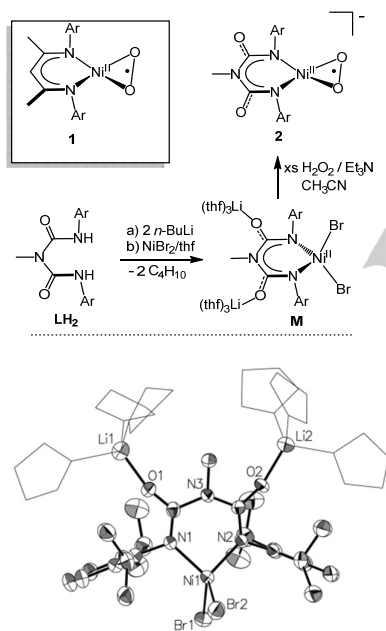
Scheme 1. Synthesis of the nickel(II) precursor complex $[Li(thf)_3]_2[LNi^{II}Br_2]$ (**M**) supported by a dianionic bidentate biuret ligand L^{2-} and its reaction with hydrogen peroxide and Et$_3$N to yield **2**; Ar = 2,6-$^iPr_2C_6H_3$ (top); the inset shows the structure of **1**. The molecular structure of **M** (bottom) determined by X-ray diffraction analysis.

The typical synthesis of superoxido-nickel(II) intermediates involves the activation of dioxygen (O$_2$) at Ni^I centers[8a,c,d] or reaction of Ni^{II} complexes with excess of hydrogen peroxide (H$_2$O$_2$) and Et$_3$N.[8b] Consistent with its Ni^{II} assignment, complex **M** did not react with O$_2$, but was readily oxidized in presence of

excess H$_2$O$_2$ and Et$_3$N in acetonitrile at 25°C to form a metastable yellowish-orange species **2** with a half-life ($t_{1/2}$) of 30 min at 25°C. The yellowish-orange color is associated with an UV-Vis absorption band at 455 nm (ε = 5900 M^{-1} cm^{-1}) with a shoulder near 300 nm (Fig. 1). The nature of the yellow-orange species can be established by a variety of spectroscopic techniques. ESI-MS (Fig. S4) of **2** showed the existence of an intense peak at a mass-to-charge ratio (m/z) value at 539.3 whose mass and isotope distribution patterns correspond to $\{Li_2[LNiO_2]\}^+$. Upon introduction of ^{18}O into **2** using H$_2^{18}$O$_2$, mass shifts from 539.3 to 543.3 (Fig. S5), thereby demonstrating that two oxygen atoms from H$_2^{18}$O$_2$ are incorporated into **2**.

In contrast to $[LNi^{II}Br_2]^{2-}$, which is EPR silent, the X-band EPR spectrum of **2** at 10 K shows a slightly rhombic signal at g_x=2.21, g_y=2.17, and g_z=2.06 (Fig.1, inset). Spin quantification of the EPR signal can account for > 85 % of the total nickel spins present in solution, thereby showing that **2** represents the major product of the reaction of $[LNi^{II}Br_2]^{2-}$ with H$_2$O$_2$ at 25°C. The observed g-anisotropy ($\Delta g = g_z - g_x$) of 0.15 resembles quite closely the Δg value of 0.12 determined for "free" $O_2^{-•}$ in water with g = [2.10, 2.00, 1.98].[11] A larger Δg of 0.23 has, however, been previously noted for a superoxido-Ni(II) complex with the unpaired electron located in the d$_{z^2}$ orbital of the Ni center.[12] We therefore conclude that the electronic structure of **2**, like **1**, is consistent with a predominantly superoxide-centered radical (S = 1/2) coupled to a square planar (SqP) low-spin d^8-Ni^{II} center. Notably, **1** exhibited a lower Δg of 0.06.[8c] This could be correlated to the nature of spin distribution at the ground state, with **1** exhibiting larger $O_2^{-•}$ radical character with polarization of spins at Ni^{II} center (negative spin density), while **2** exhibiting relatively less $O_2^{-•}$ radical character with delocalization of spin density at Ni^{II} as revealed by density functional theoretical (DFT) calculations (see below).
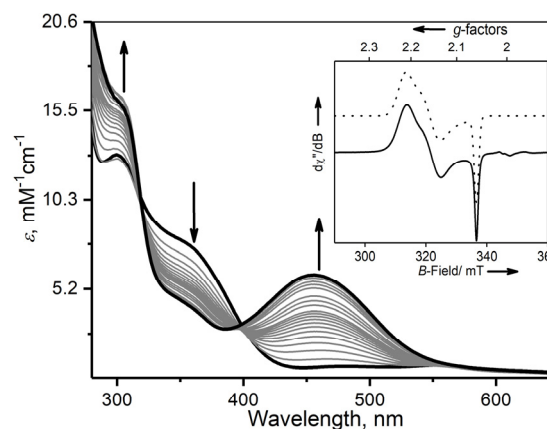

Figure 1. UV-Vis spectral changes associated with the reaction of $[LNi^{II}Br_2]^{2-}$ with excess H$_2$O$_2$ and Et$_3$N to form **2** in CH$_3$CN at 25°C. In the inset is shown the experimental (bold) and simulated (dotted) X-band EPR spectrum of a 2 mM solution of **2** in CH$_3$CN at 10K.

The infrared photodissociation (IRPD) spectrum[13] of the D$_2$-tagged $[LNiO_2]^-$ anion (Fig. 2 left and Fig. S6) contains an oxygen sensitive band at 980 cm^{-1}, which shifts to 932 cm^{-1} upon ^{18}O labelling. The isotope shift of 48 cm^{-1} agrees well with the calculated (57 cm^{-1}) shift for a diatomic O-O bond stretching vibrational mode. Furthermore, the O-O vibration in **2** (980 cm^{-1})

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appears at similar energy to the side-on superoxido nickel complex **1** (971 cm⁻¹). This, together with the similar EPR spectra of **1** and **2**, may also point to a side-on superoxido nature of **2**.

Ni *K*-edge X-ray absorption spectroscopic studies were performed to directly probe the Ni oxidation state and geometry in **2**. Figure 2 (right) shows a comparison of the Ni *K*-edge spectrum of **2** with its precursor **M**, as well as **1**. Notably, both **1** and **2** show an intense 1s-to-4p+ shakedown transition along the edge at ~8338.5 eV that is not seen in **M**. Furthermore, the 1s-to-3d pre-edges in **1** and **2**, found at 8333.2 eV, are significantly weaker than that of **M** ($E_{pre-edge}$ = 8333.25 eV). Both observations can be attributed to a *SqP* coordination geometry of Ni in **1** and **2** vs the *Td* symmetry of **M**.[14] In addition, the absence of any pre-edge shift in **1** and **2** compared with **M** is consistent with a Ni^{II} assignment for both complexes, corroborating our EPR analysis. Extended X-ray absorption fine structure (EXAFS) analysis of **M** reveals retention of the 4-coordinate XRD structure in solution (Fig. S7, Table S2a) with two Ni-N/O scatterers @ 1.93 Å and two Ni-Br scatterers @ 2.40 Å. The Fourier transform of the EXAFS of **2** shows loss of the dominant Ni-Br scattering seen in **M** at r = 2.1 Å along with a shift to lower r for the putative Ni-N/O shell around r = 1.5 Å (Fig. S7). This is consistent with the near-stoichiometric conversion of **M** to **2** upon reaction with H_2O_2. Analysis of the EXAFS data of **2** (Fig. S7; Table S2b) shows a best fit of four N/O scatterers at 1.85 Å, which is comparable to the average Ni-N/O distance of 1.838 (2) Å of **1**.[8c]
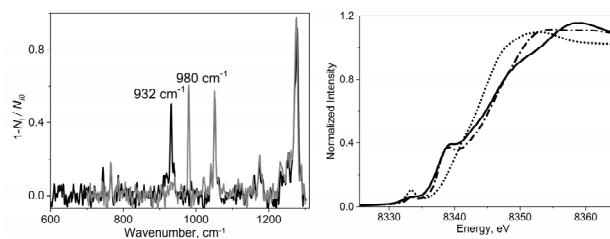

Figure 2. Left: D$_2$-tagging IRPD spectra of [LNi^{II}O$_2$]⁻ complex anion (*m/z* 525, grey trace) and ¹⁸O-labeled [LNi^{II}O$_2$]⁻ complex (*m/z* 529, black trace) recorded with the ISORI instrument; right) Ni *K*-edge XANES spectra of **1** (solid line), **2** (dash-dotted line) and **M** (dotted line) in frozen CH$_3$CN solutions at 4K.
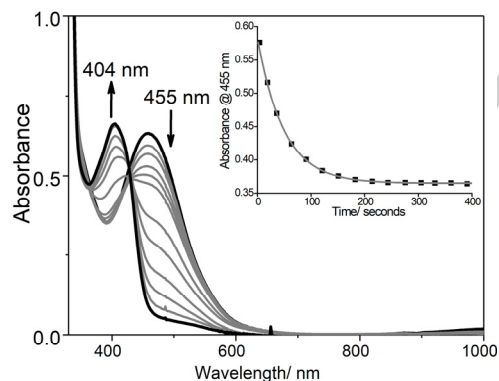

Figure 3. Absorption spectral changes associated with the reaction of a 1 mM solution of **2** in CH$_3$CN with PPA (25 mM) at 25°C. In the inset is shown the time trace of the decay of the 455 nm band (black squares) corresponding to **2** and the pseudo-first order fitting (solid line).

Usually, the superoxido-nickel(II) cores act as strong electrophiles and are typically unreactive towards other electrophiles. Thus, although **1** oxidised O–H and N–H groups from various exogenous organic substrates, addition of benzaldehyde to **1** did not result in any change in its UV-Vis spectra.[9] In contrast, **2** did not demonstrate any electrophilic HAT reactivity towards the weak C-H bonds of dihydroanthracene or O-H bonds of *para*-substituted di-*tert*-butylphenols. However, a pseudo-first order decay of the absorption feature at 455 nm (Fig. 3) and the subsequent formation of acetophenone (75% yield; Fig. S8A) and Ni(II) products (based on EPR (silent) and ESI-Mass spectroscopic methods; Figure S8B) were observed upon addition of 2-phenylpropionaldehyde (2-PPA) to a preformed solution of **2** at 25°C. The rate constant increases proportionally with the substrate concentration (Fig. S9), affording a second-order rate constant, k_2, of 0.00012 M⁻¹ s⁻¹ at 25°C. Additional mechanistic studies with *para*-substituted benzaldehydes (*para*-Y-C$_7$H$_5$O; Y = *t*Bu, Me, H, Cl,) reveal a good linear correlation of the rate to the σ$_{P^+}$ values of the *para* substituents (Fig. S10). A positive Hammett ρ value of +0.44 is obtained, which supports the nucleophilic character of the [Ni^{II}O$_2$·⁻]⁻ core in **2** in the oxidation of benzaldehydes. To our knowledge, **2** is the only example of a superoxido-metal complex that shows any reactivity with *para*-substituted benzaldehydes. The nucleophilicity of **2** is also demonstrated by its ability to undergo reaction with cyclohexane-carboxaldehyde (CCA) to afford cyclohexane-carboxylic acid in 76% yields (Fig. S11).

DFT calculations were performed in order to understand the contrasting reactivity patterns of neutral **1** and monoanionic **2** (see *Supporting Information)* complexes. **1** has two low lying *S* = 1/2 states (Fig. 4). The ground state (GS), ²**1a**$_{ls}$, has low-spin ls-Ni^{II} and the unpaired electron is mostly localized on the O$_2$ ligand. The first excited state (ES), ²**1a**$_{hs}$, arises from an antiferromagnetic coupling between the *S* = 1 high-spin hs-Ni^{II} and the *S* = 1/2 O$_2$·⁻ centers. In addition, a ferromagnetic coupling between the hs-Ni^{II} and the *S* = 1/2 O$_2$·⁻ centers results in an *S* = 3/2 (⁴**1a**$_{hs}$) ES (Fig. 4). The ⁴**1a**$_{hs}$ (²**1a**$_{hs}$) states lie at 25.1 (36.3) kJ mol⁻¹ higher in energy relative to the ²**1a**$_{ls}$ GS. The ²**1a**$_{ls}$ state features short Ni-O (1.89 Å) and Ni-N (1.87 Å) distances, in good agreement with the experiment (Fig. 4, Table S3). In contrast, the presence of unpaired electrons in the d$_{x^2-y^2}$ and d$_z^2$ orbitals of the *S* = 1 Ni^{II} ion makes the O$_2$ binding unfavorable, resulting in relatively longer Ni-O distances in the ²**1a**$_{hs}$ state (Fig. 4, Table S3). As expected, the geometry around the Ni^{II} center is *SqP* in ²**1a**$_{ls}$ but *Td* in the ²**1a**$_{hs}$ state. Thus, although ²**1a**$_{ls}$ is assigned as the ground state, the calculated low energy of the ²,⁴**1a**$_{hs}$ states would suggest that both of these spin-states are accessible for reactivity. Notably, the ²**1a**$_{hs}$ state is associated with a large negative spin-density at the oxygen atoms; furthermore, it involves greater charges both at the oxygen and the Ni^{II} sites compared to the ²**1a**$_{ls}$ state. As demonstrated previously by one of us,[15] such a spin-polarized electronic structure in superoxido-metal species may lead to electrophilic reactivity. Thus, a two-state mechanism is proposed in **1**, with the excited ²**1a**$_{hs}$ state being responsible for the electrophilic reactivity.

For monoanionic **2**, the calculated ground state is also ²**2a**$_{ls}$, with the Ni-O (1.88 Å) and Ni-N (1.86 Å) distances in good agreement with the EXAFS data (Fig. 4, Table S3). However, the stronger electron donation from the dianionic biuret ligand L destabilizes the d$_{x2-y2}$ and d$_{z2}$ orbitals of the *S* = 1 Ni^{II} ion, which makes the spin-polarized ²**2a**$_{hs}$ state extremely high-lying in energy (+63.2 kJ mol⁻¹ relative to ²**2a**$_{ls}$) and hence is unlikely to be relevant for the reactivity of **2**. In addition, the ⁴**2a**$_{hs}$ state is also

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very high in energy (see Fig. 4). Thus in the absence of any low lying excited states, the reactivity of **2** likely occurs solely at the ground ^{2}**2a**$_{ls}$ state. Furthermore, the oxygen atoms in the ^{2}**2a**$_{ls}$ state carry higher negative charge than in the ^{2}**1a**$_{ls}$ state, as evident from the Natural Population Analysis (Fig. S13). This explains the higher nucleophilicity of **2** relative to **1** in presence of added electrophiles.
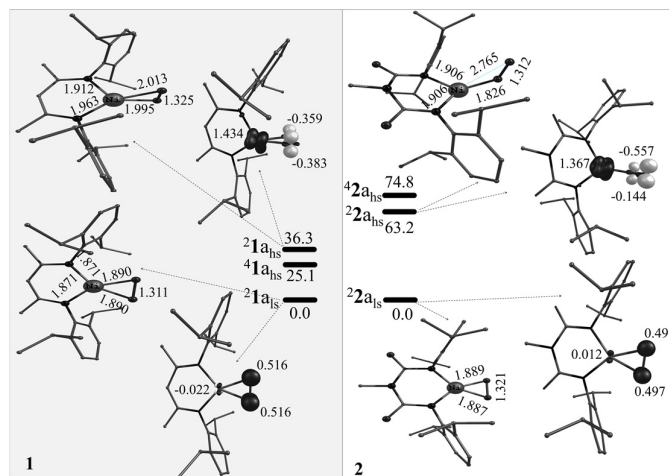

Figure 4. Relative energies (kJ mol^{-1}) of the DFT-derived ground- and excited-states of **1** and **2**, respectively, along with the optimized geometries and spin-density (positive: black, negative: grey) plots of ^{2}**1a**$_{ls}$ (^{2}**1a**$_{hs}$) and ^{2}**2a**$_{ls}$ (^{2}**2a**$_{hs}$) states (see also Fig. S12).

In conclusion, the contrasting reactivity of putative superoxido-nickel(II) intermediates in bio-relevant oxidation reactions is strongly dependent on subtle electronic changes as shown for **1** and **2**. The unexpected nucleophilicity of the superoxido-Ni^{II} core in **2** suggests that such a reactivity may also play a role in catalytic cycles of Ni-containing oxygenases and oxidases. Furthermore, the contrasting reactivity of **1** and **2** can be explained by results of DFT calculations. Notably, an identical GS has been predicted for both **1** and **2** in spite of their different charges; this is also reflected in the experimentally determined comparable O-O vibrational energies, Ni-N/O bond distances, EPR *g*-tensors, and Ni K-edge/pre-edge energies for **1** and **2**. However, the nature of the ES differs in the two cases. The observed electrophilic reactivity of **1** is most probably due to the availability of two closely lying spin states, ^{2}**1a**$_{ls}$ GS and ^{2}**1a**$_{hs}$ ES, wherein the spin-polarized ^{2}**1a**$_{hs}$ state has a much lower reaction barrier than the ^{2}**1a**$_{ls}$ state. In contrast, the ^{2}**2a**$_{hs}$ state is energetically not accessible for **2**, which shuts down the electrophilic reactivity pathway. Strong-electron donation by the dianionic biuret ligand L then results in a single-state nucleophilic reactivity on the ^{2}**2a**$_{ls}$ surface. The higher availability of the T_d Ni^{II}-hs state in **1** compared to **2** is plausibly reflected in the appearance of more intense broad absorptions in the 800-1100 nm region in the electronic spectra of **1** (Fig. S14). These bands are presumably originating from the ligand-field (LF) transitions arising from a d^8-Ni^{II} center, which is expected to be spin and symmetry allowed (and hence more intense) in a *Td* geometry and forbidden (with zero-intensity) in a pure *SqP* geometry.[16] To conclude, this study provides evidence that the TSR theory, well

established for oxido-metal complexes,[17] may also provide a framework for understanding the reactivity of superoxido-metal species.

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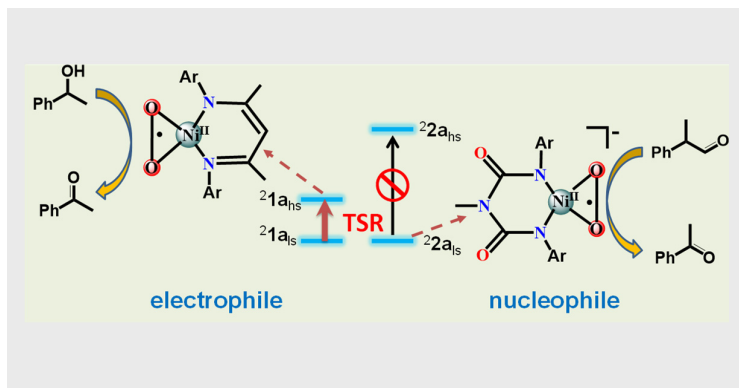
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Nucleophilic vs Electrophilic Reactivity of Bioinspired Super-oxido Nickel(II) Complexes

Switching Reactivity of Superoxo: A two state reactivity (TSR) rationalizes the contrasting reactivity patterns of two superoxido-nickel(II) complexes involving the monoanionic β-diketiminate and dianionic biuret ligands. This study underlines the importance of subtle electronic differences, which change the reactivity of biologically relevant O_2-M intermediates.