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Dramatically Enhanced Carbon Acidity of the Nitrobenzyl Fragment in a Nickel(II) Scorpionate Complex

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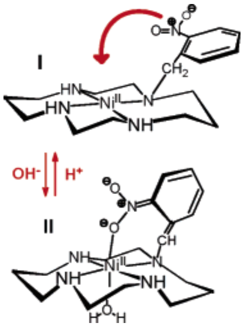
ABSTRACT



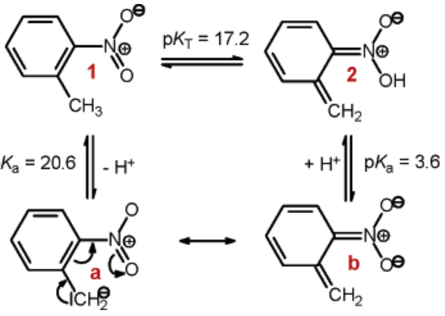
The –CH$_2$– group of the 2-nitrobenzyl pendant arm of the scorpionate complex I deprotonates in basic aqueous solution (pK_a = 10.6), due to the coordination of the nitronate group to the nickel(II) center. Metal coordination enhances 2-nitrobenzene acidity by 10 orders of magnitude.

The 2-nitrobenzyl chromophore, which presents an intense absorption band centered at ~330 nm, is widely utilized as a signaling unit in host−guest recognition processes,[1] as a photosensitive protecting group,[2] and for the photorelease of biologically relevant compounds (e.g., caged ATP).[3] Nitrobenzyl photochemical activity is related to the nitro-to-*aci*-nitro tautomerization process. In the case of 2-nitrotoluene (**1**), a pK_T = 17.0 ± 0.2 for the tautomerization equilibrium was calculated from the thermodynamic cycle illustrated in Scheme 1.[4]

It appears that the scarse tendency of 2-nitrotoluene to convert to the *aci*-nitro tautomer is related to the very low Brønsted acidity of the −CH$_3$ group (pK_a(**1**) = 20.6),[4] a feature probably related to the loss of aromaticity associated with the formation of the nitronate ion (mesomeric form **b** in Scheme 1).

We considered the opportunity of enhancing the acidity of the 2-nitrobenzyl fragment by stabilizing the nitronate ion

Scheme 1



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(1) Boiocchi, M.; Del Boca, L.; Esteban-Gómez, D.; Fabbrizzi, L.; Licchelli, M.; Monzani, E. *J. Am. Chem. Soc.* **2004**, *126*, 16507−16514.

(2) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley-Interscience: New York, 1999.

(3) Il'ichev, Y. V.; Schwörer, M. A.; Wirz, J. *J. Am. Chem. Soc.* **2004**, 126, 4581−4595.

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through coordination to a metal center. In this connection, we prepared molecule **3**, in which a 2-nitrobenzyl pendant arm has been covalently linked to the nitrogen atom of a cyclam ring. The 2-susbstituted positional isomer was chosen in order to favor the coordination of the nitro-nitronate group to the metal, immobilized within the cyclam ring.

Cyclam and its derivatives firmly encircle divalent transition metal ions to give complexes, which are especially stable with respect to demetalation.[5] For instance, the square planar $[Ni^{II}(cyclam)]^{2+}$ complex lasts in 1 M $HClO_4$ with a lifetime $\tau = 30$ years.[6] On reaction of $Ni^{II}(CF_3SO_3)_2$ with **3** (LH), the yellow diamagnetic $[Ni^{II}(LH)](CF_3SO_3)_2$ complex salt was obtained in a crystalline form, whose molecular structure was determined through X-ray diffraction studies. Figure 1 shows an ORTEP view of the metal complex.

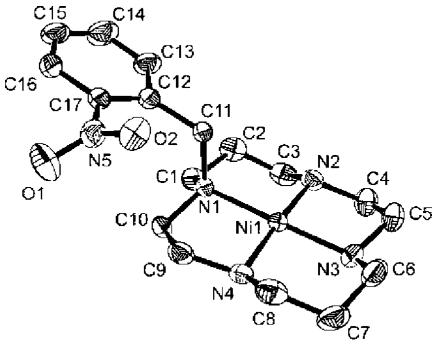
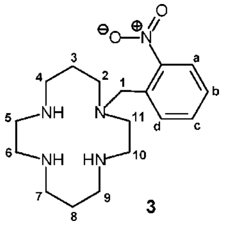


Figure 1. ORTEP diagram of the $[Ni^{II}(\mathbf{3})](CF_3SO_3)_2{\cdot}CH_3OH$ complex. Thermal ellipsoids are drawn at the 30% probability level. Hydrogen atoms, triflate anions, and a methanol solvent molecule have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Ni1−N1 1.985(4), Ni1−N2 1.945(4), Ni1−N3 1.933(5), Ni1−N4 1.930(4); N1−Ni1−N2 93.68(18), N1−Ni1−N3 178.52(19), N1−Ni1−N4 88.03(17), N2−Ni1−N3 86.10(21), N2−Ni1−N4 174.66(19), N3−Ni1−N4 92.32(20).



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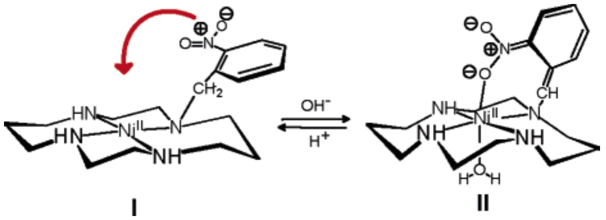
The metal shows a regular square-planar coordination geometry, the mean deviation for nitrogens from the N1−N2−N3−N4 best plane being 0.055(5) Å, while the deviation of Ni1 from such a plane is 0.032(1) Å. The Ni^{II}−N bond distances, ranging from 1.936(5) Å (average of the three Ni^{II}−secondary amine bonds) to 1.985(4) Å (Ni^{II}−tertiary amine), are those expected for a low-spin ion.[7] Most importantly, the nitro group is completely excluded from the coordination sphere, being far away from the metal center, at a quite long distance: 4.83 Å, from Ni^{II} to the nearest oxygen atom (O2). Probably because of steric reasons, the nitro group is not coplanar with the aromatic ring, but the two planes form an angle of 45.6°.

When dissolved in water, the metal complex shows an intense absorption band at 330 nm, due to the nitrobenzyl group, with a shoulder at 450 nm, which is ascribed to the d−d transition of the low-spin square-planar Ni^{II} center, thus confirming the noncoordination of the nitrobenzyl pendant arm in solution. When the pH is increased through addition of standard NaOH, no modification of the spectrum is observed until pH 10, when the shoulder at 450 nm begins to decrease and a new, weaker band develops at 550 nm. Such a spectral pattern is typically noted in the presence of a low-spin to high-spin conversion, which accompanies a change of the coordination geometry from square-planar to octahedral.[7] It is suggested that, in basic solution, the $-CH_2-$ group linking the cyclam ring to the 2-nitrobenzene fragment undergoes deprotonation, which induces the following events: (i) movement of the pendant arm toward the metallocyclam subunit; (ii) electronic rearrangement to give the anion of the nitronic acid; and (iii) formation of a coordinative bond between one oxygen atom of the $-NO_2^-$ group and the Ni^{II} center. At the same time, a water molecule occupies the remaining site of the coordination octahedron. The overall process is pictorially illustrated in Scheme 2.

Scheme 2



The plot of absorbance at 450 nm vs pH (see inset, Figure 2) exhibits a sigmoidal profile, which has been fitted through a nonlinear least-squares procedure,[8] to give a pK_A value of 10.71 ± 0.01 for the acid dissociation equilibrium: $[Ni^{II}(LH)]^{2+} \leftrightarrows [Ni^{II}(L^-)]^+ + H^+$. Solid and dashed lines in the inset indicate the % concentration of the two species present at the equilibrium, **I** and **II** (as illustrated in Scheme 2), respectively, over the investigated pH range. On addition of standard acid, the band at 450 nm is fully restored, demonstrating the reversibility of the process.

This indicates the intramolecular nature of the process and confirms the hypothesis that deprotonation is facilitated by coordination of the nitronate anion to the nickel(II) center.

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(4) Schwörer, M.; Wirz, J. *Helv. Chim. Acta* **2001**, *84*, 1441−1458.

(5) Busch, D. H. *Acc. Chem. Res.* **1978**, *11*, 392−400.

(6) Billo, E. J. *Inorg. Chem.* **1984**, *23*, 236−238.

(7) Boiocchi, M.; Fabbrizzi, L.; Foti, F.; Vázquez, M. *Dalton Trans.* **2004**, 2616−2620.

(8) Gans, P.; Sabatini, A.; Vacca, A. *Talanta* **1996**, *43*, 1739.

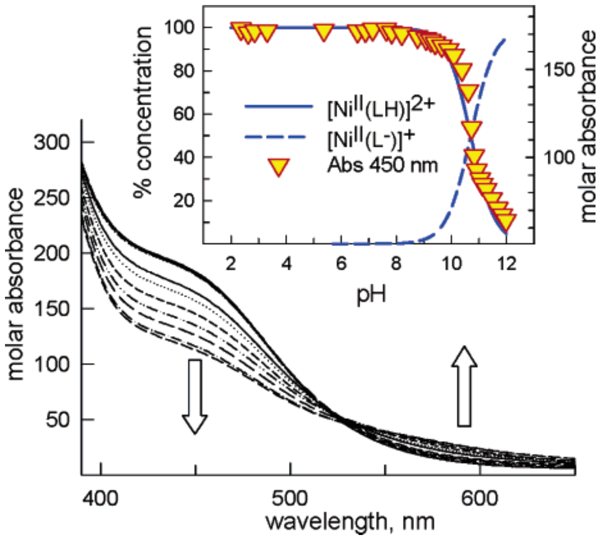

Figure 2. Visible spectra recorded over the course of the titration of an aqueous solution of $[Ni^{II}(\mathbf{3})](CF_3SO_3)_2$ with standard base. Inset: change of the absorbance at 450 nm with pH.

Occurrence of the process sketched in Scheme 2 was substantiated by ^1H NMR titration experiments. In particular, a 7.5×10^{-3} M solution of $[Ni^{II}(LH)](CF_3SO_3)_2$ in CD_3OD was titrated with a standard solution of potassium *tert*-butoxide in the same solvent. Figure 3 shows the ^1H NMR spectra obtained over the course of titration and illustrates well the spin conversion of the diamagnetic $[Ni^{II}(LH)]^{2+}$ complex to the paramagnetic $[Ni^{II}(L^-)]^+$.

First of all, it should be observed that the spectrum of $[Ni^{II}(LH)]^{2+}$ displays somewhat broad signals, which indicate a small, yet detectable, paramagnetic contribution. This may be due to the fact that paramagnetic excited states, close in energy to the diamagnetic ground state, are being populated at room temperature. Such a fraction of paramagnetic complex could not be detected by the less sensitive spectrophotometric technique. Even if the presence of broad signals does not allow the complete assignment of the resonances, the peaks of the protons of the aromatic residues and those in positions 3 and 8 of cyclam can be easily assigned by observing their relative intensity and position in the spectrum. In the following discussion, the other resonances in the molecule are tentatively assigned by considering their chemical shifts, integrals, and isotropic shift changes during titration. On addition of base, all protons of the $-CH_2-$ groups directly linked to the nitrogen atoms of the cyclam ring undergo a downfield shift. This is ascribed to a direct contact effect associated with the presence of σ interactions between the unpaired electrons in d_{x2-y2} and d_{z2} orbitals of the high-spin Ni^{II} center and cyclam nitrogen atoms. Signals pertaining to protons in positions 3 and 8, which are farther away from metal-bound nitrogen atoms, undergo an upfield shift, which indicates that, besides the direct contact contribution, an important contribution of pseudocontact polarization is present. Most significantly, signals of protons in **1**, belonging to the $-CH_2-$ group linking the cyclam ring to the 2-nitrobenzene moiety, undergo, on base addition, an upfield shift and, after addition of 1 equiv of base, disappear. This unequivocally indicates the deprotonation of the benzylic $-CH_2-$ group. Moreover, the addition of base causes a marked broadening of the aromatic protons of the 2-nitrobenzyl moiety to below the signal-to-noise ratio. The large increase in the relaxation rate for these protons cannot be ascribed to dipolar contribution to the relaxation, in view of their distance from the metal center, or to a direct contact effect, as such an effect should vanish along the π skeleton. It is suggested that broadening of the aromatic protons is due to a significant contribution of spin polarization through π orbitals to the ^1H NMR relaxation rates. In particular, following $-CH_2-$ deprotonation and $-NO_2^-$ coordination to Ni^{II}, a significant fraction of unpaired electrons of the paramagnetic metal center can be delocalized onto the π system of the 2-nitrobenzyl moiety.

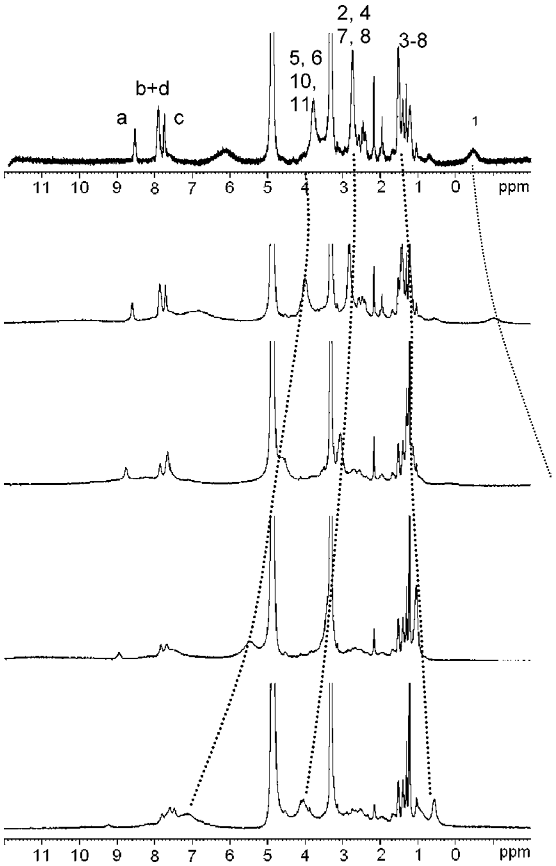

Figure 3. ^1H NMR spectra recorded over the course of the titration of a 7.5×10^{-3} M solution of $[Ni^{II}(\mathbf{1})](CF_3SO_3)_2$ in CD_3OD with potassium *tert*-butoxide, up to 1 equiv of base.

Comparison of pK_a values of 2-nitrotoluene and of the $[Ni^{II}(LH)]^{2+}$ complex (20.6 and 10.6, respectively) highlights the role that metal ions can have in enhancing the acidity of carbon acids. A previous example refers to the Zn^{II} complex of a cyclen ligand, equipped with a 4-bromophenacyl-pendant arm.[9] Coordination to the Zn^{II} center of the negatively charged oxygen atom of the enolate form induced a reduction of pK_a of the $-CH_2-$ group by ~10 log units (from 18.3 of acetophenone to 8.4 of the Zn^{II} cyclen complex), providing an example of metal-driven cheto$\leftrightarrows$enol tautomerization and modeling the activity of the zinc-containing enzyme aldolase. Moreover, it has been shown that the pK_a of 1,3-diketones in MeCN solution can be reduced by as much as 12 log units, due to the interaction of the enolate form with coordinatively unsaturated Cu^{II} ion(s), inside a concave receptor.[10] In the present case, the high endergonicity of the deprotonation of nitrobenzyl $-CH_2-$ fragment is balanced by the favorable contribution associated with the formation of a coordinative bond between Ni^{II} and an oxygen atom of the nitronate fragment (an enthalpy term). The pH-controlled coordination of a side-chain covalently linked to a metallocyclam subunit and bearing a deprotonatable donor group (ammonium,[11] carboxyamide,[12] sulfonamide)[13] has been observed in a variety of metal complexes with cyclam derivatives. These ligands were named *scorpionands*,[14] considering the fact that an aggressive tail can sting from the top a chelated and immobilized individual (the metal). It appears that scorpionate arrangement and facilitated coordination of the covalently linked pendant arm (a favorable entropy term) are essential for the occurrence of metal-induced $-CH_2-$ deprotonation. The use of the cyclam ring provides, as a further advantage, the occurrence of a square-to-octahedral geometry change, which brings in the additional energy contribution of the axial binding of a water molecule.

In conclusion, it has been demonstrated that a proximate metal center can effect a drastic reduction of pK_a of carbon acids and assist otherwise unfavorable tautomeric conversions.

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Supporting Information Available: Details of syntheses of **3** and $[Ni^{II}(\mathbf{3})](CF_3SO_3)_2$ and X-ray crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] Kimura, E.; Gotoh, T.; Koike, T.; Shiro, M. *J. Am. Chem. Soc.* **1999,** *121*, 1267−1274.

[10] Zhong, Z.; Postnikova, B. J.; Hanes, R. E.; Lynch, V. M.; Anslyn, E. V. *Chem. Eur. J.* **2005**, *11*, 2385−2394.

[11] Lotz, T. J.; Kaden, T. A. *J. Chem. Soc., Chem. Commun.* **1977**, 15−16.

[12] Siegfried, L.; Comparone, A.; Neuburger, M.; Kaden, T. A. *Dalton Trans.* **2005**, 30−36.

[13] Fabbrizzi, L.; Foti, F.; Licchelli, M.; Maccarini, P. M.; Sacchi, D.; Zema, M. *Chem.−Eur. J.* **2002**, *8*, 4965−4972.

[14] Fabbrizzi, L.; Licchelli, M.; Pallavicini, P.; Parodi, L. *Angew. Chem., Int. Ed.* **1998**, *37*, 800−802.