Supramolecular Control of Stepwise and Selective Carboxylate Ligand Substitution in Aqua-Carboxylato-Bridged Dimetal(II) Complexes

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Molecular organization and selectivity are key components in the design of small molecule synthetic analogs that mimic the subtleties and complexities of metal binding sites within metalloproteins. In one member of the class of dinuclear non-heme iron proteins, ribonucleotide reductase (RR), the catalytically important tyrosine-122 lies within hydrogen-bonding distance of the iron-bound aspartate-84.[1] Thus, the initital synthetic challenge is the incorporation of a single proximate phenol, which is hydrogen-bonded to a carboxylate; the carboxylate, in turn, must be part of the ligand system of a labile, high-spin dimetal(II) complex.[2]

We have recently shown that the rigid convergent dicarboxylic acids **$1H_2$** and **$2H_2$** (Scheme I), developed by Rebek and coworkers,[3] are good hosts for (μ-carboxylato)dimetal(II) model complexes whose structures are dictated by second coordination sphere interactions. Reactions of the dicarboxylates **1^{2-}** and **2^{2-}** with $M_2(H_2O)(CF_3CO_2)_4(tmen)_2$ (M = Fe(II), **3**-Fe, or Co(II), **3**-Co, tmen = *N,N,N′,N′*-tetramethyl-1,2-diaminoethane) give complexes of type **4** (Scheme I).[4] We report here thermodynamic and/or kinetic control of selective exchange reactions of the terminal over bridging carboxylate ligands of **3** using a new set of rigid, multifunctional phenol-containing ligands, **$5H_3$**, **$6H_3$**, and **$7H_2$**, and the bulky monocarboxylic acids **8H**, **9H**, and **10H** (Scheme I). In **$5H^{2-}$** and **$6H^{2-}$**, an intramolecular hydrogen bond between the phenol and one of the carboxylates induces a selective preference for binding the second, otherwise identical, carboxylate. The new ligands were prepared from the appropriate amines and the acid chloride anhydride of Kemp's triacid by the same procedure used for the preparation of **$1H_2$** and **8H**.[3a]

Indiscriminate carboxylate exchange occurs when aromatic or aliphatic carboxylates are added to solutions of **3**-Co.[5] An equilibrium mixture of the 10 possible structures having the formula $Co_2(H_2O)(CF_3CO_2)_n(Me_3CCO_2)_{4-n}(tmen)_2$ (n = 0, 1, 2, 3, 4) is obtained on mixing solutions of **3**-Co with $(Et_3NH^+)(Me_3CCO_2^-)$. All 16 possible resonances of the nine fluorine-containing complexes are observed by ^{19}F NMR spectroscopy (Figure 1a). However, selective replacement of only the terminal carboxylates of **3**-Co or **3**-Fe occurs with **8^-**, **9^-**, and **10^-**, the steric constraints of which rival even the bulkiest 2,4,6-triarylbenzoates.[6] With **9^-**, the only new ^{19}F resonances observed are those of the diamagnetic, uncoordinated carboxylates $CF_3CO_2^-$ and **9^-**, of monosubstituted $Co_2(H_2O)(CF_3CO_2)_3(\mathbf{9})(tmen)_2$ (**11**), where four resonances are expected for C_1 symmetry, and of disubstituted $Co_2(H_2O)(CF_3CO_2)_2(\mathbf{9})_2(tmen)_2$ (**12**), for which the two resonances for C_2 symmetry are seen (Figure 1b, Scheme I). Crystals of $Co_2(H_2O)(CF_3CO_2)_2(\mathbf{10})_2(tmen)_2$ (**13**) were grown from acetonitrile to confirm terminal ligand substitution and to determine the preferred orientation of these bulky carboxylates (Scheme I).[7] The carboxylate in **$7H^-$** is rendered less basic by the intramolecular hydrogen bond to the phenol. In mixtures of **3**-Co and 5 equiv of **$7H^-$**, the monosubstituted complex $Co_2(H_2O)(CF_3CO_2)_3(\mathbf{7H})(tmen)_2$ (**14**) and **3**-Co are the predominant species present (Figure 1c). The first and second substitution equilibrium constants (K_1 = 0.6, K_2 = 0.01) are considerably smaller than the corresponding values for **9^-** (K_1 > 100, K_2 = 3.5).[8a]

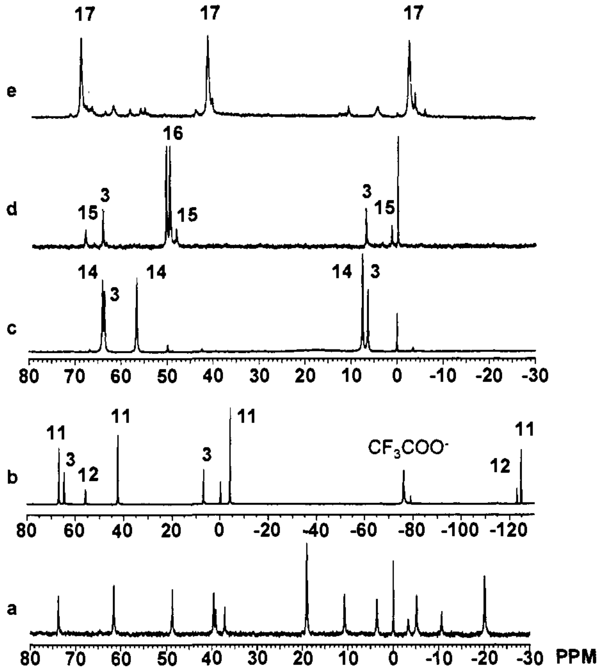

Figure 1. 470-MHz ^{19}F NMR spectra (vs $CFCl_3$ in $CDCl_3$ at 21 °C) of (a) **3**-Co + 2 equiv $(Et_3NH)(Me_3CCO_2)$ (no **3**-Co is present, the 19 ppm resonance corresponds to two species); (b) **3**-Co + 1 equiv of $(Et_3NH)(\mathbf{9})$; (c) **3**-Co + 5 equiv of $(Et_3NH)(\mathbf{7H})$; (d) **3**-Co + 1 equiv of $(Et_3NH)_2(\mathbf{5H})$; (e) **3**-Co + 1 equiv of $(Et_3NH)_2(\mathbf{6H})$ in CD_3CN. Numbers above resonances label complexes defined in the text and Scheme I.

In **$2H_2$**, **$5H_3$**, and **$6H_3$**, one or both of the *o*-methyl substituents, which prevent rotation about the imide bonds of **$1H_2$**, are omitted, thereby allowing facile rotation of the Kemp's moiety. Replacing one of the methyls with a phenol group not only provides some steric hindrance to this rotation but also provides the possibility of an intramolecular hydrogen bond between the phenol and the carboxylate. In **$5H_2^-$**/**$5H^{2-}$** and **$6H_2^-$**/**$6H^{2-}$**, one of the carboxylates resembles **$7H^-$** because it is tied to the phenol by the same

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[1] (a) Sjöberg, B.-M.; Gräslund, A. *Adv. Inorg. Biochem.* **1983**, *5*, 87–110. (b) Nordlund, P.; Sjöberg, B.-M.; Eklund, H. *Nature* **1990**, *345*, 593–598. (c) Mn(II)-substituted R2: Atta, M.; Nordlund, P.; Aberg, A.; Eklund, H.; Fontecave, M. *J. Biol. Chem.* **1992**, *267*, 20682–20688. (d) Apo-R2 structure: Aberg, A.; Nordlund, P.; Eklund, H. *Nature* **1990**, *361*, 276–278.

[2] For a μ-$OFe(III)_2$ phenoxyl radical model complex, see: Goldberg, D. P.; Watton, S. P.; Masschelein, A.; Wimmer, L.; Lippard, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 5346–5347.

[3] (a) Rebek, J., Jr.; Marshall, L.; Wolak, R.; Parris, K.; Killoran, M.; Askew, B.; Nemeth, D.; Islam, N. *J. Am. Chem. Soc.* **1985**, *107*, 7476–7481. (b) Rebek, J., Jr.; Askew, B.; Killoran, M.; Nemeth, D.; Lin, F.-T. *J. Am. Chem. Soc.* **1987**, *109*, 2426–2431. (c) Rebek, J., Jr. *Science* **1987**, *235*, 1478–1484. (d) Rebek, J., Jr. *Angew. Chem.* **1990**, *102*, 261; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245–255.

[4] Hagen, K. S.; Lachicotte, R.; Kitaygorodskiy, A.; Elbouadili, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1321–1324; *Angew. Chem.* **1993**, *105*, 1404–1407.

[5] Analogous reactivity is observed with both **3**-Fe and **3**-Co. Reaction of **3**-Fe with **8** affords peaks at −13.5, 54.6, and 57.6 (monosubstituted complex) and 58.0 ppm vs $CFCl_3$ (disubstituted complex). Resonances for **17**-Fe occur at −14.5, 55.3, and 58.7 ppm. The ^{19}F NMR of the Co systems are presented because of the enhanced spectral resolution resulting from greater dipolar contribution of Co(II) to the isotropic shifts: ref 4 and Lachicotte, R.; Kitaygorodskiy, A.; Hagen, K. S. *J. Am. Chem. Soc.* **1993**, *115*, 8883–8884.

[6] The aryl groups fold back to be level with the CO_2^-, whereas in **8**, **9**, and **10**, the *p*-carbon protrudes 4.0 Å back past the CO_2^-. Callot, H. J.; Albrecht-Gary, A.-M.; Al Joubbeh, M.; Metz, B. *Inorg. Chem.* **1989**, *28*, 3633–3640.

[7] X-ray analysis: **13**·3MeCN crystallizes in the triclinic space group $P\bar{1}$ with a = 13.797(3) Å, b = 14.682(3) Å, c = 17.941(4) Å, α = 80.70(3)°, β = 70.10(3)°, γ = 77.81(3)°, V = 3324(1) Å³, ρ(calcd) = 1.372 g cm⁻³, Z = 2. With 5972 reflections, the structure refined to $R(wR)$ values 7.02 (8.32)%. Reflections for **13** and **16**-Fe were collected at 173 K with Cu Kα (λ = 1.541 78 Å) radiation, $2\theta_{max}$ = 113.5°, on a Siemens P4/RA single crystal X-ray diffractometer. The structures were solved by direct methods (SHELXS-86) and refined by full-matrix least-squares methods (SHELXTL IRIS).

[8] (a) The equilibrium constants were determined from the integrated intensities of the NMR resonances. (b) The strength of the hydrogen bond is reflected by the high pK_a values of the phenolic protons in **$6H^{2-}$** and **$7H^-$** (14 compared to 10 for phenol and **$5H^{2-}$**): Hagen, K. S.; Lachicotte, R.; Kitaygorodskiy, A., manuscript in preparation.

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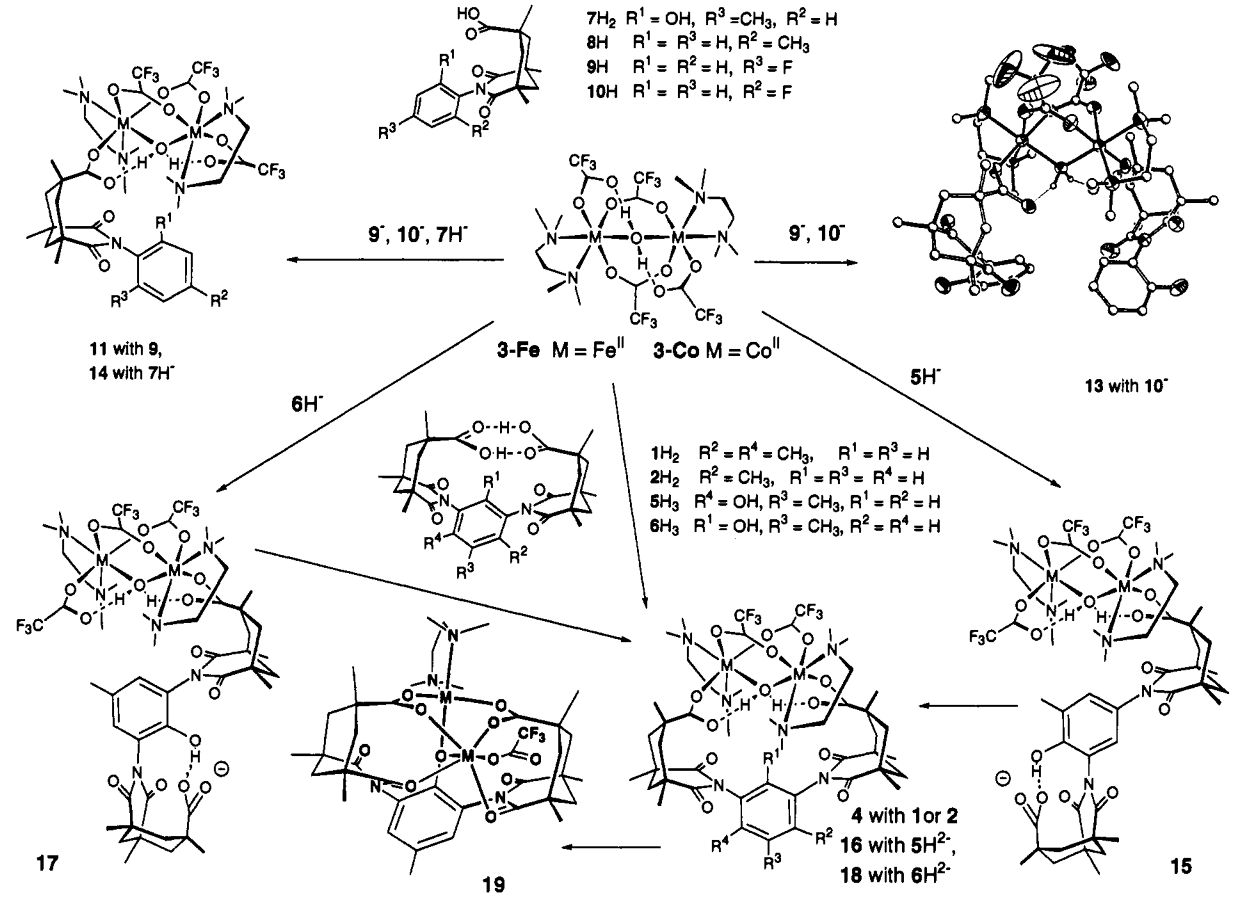
Scheme I



hydrogen bond (in CDCl$_3$ in the presence of triethylamine), while the other resembles **9**$^-$. The hydrogen-bonded conformation undergoes slow exchange on the NMR time scale with all other conformations because the hydrogen bond must be broken to release the carboxylate moiety for rotation about the imide bond.[8b]

Using the values of K_1 and K_2 for the reactions with **7**H$^-$ and **9**$^-$, one would expect a selectivity in substitution reactions such that the carboxylate that resembles **9**$^-$, rather than **7**H$^-$, would exchange more readily with **3**. Indeed, a *stepwise* substitution of the terminal carboxylates of **3**, which is too facile to observe by NMR[4,5] with the dicarboxylates **1**$^{2-}$ and **2**$^{2-}$, is seen with **5**H^{2-} and **6**H^{2-}. Reactions of **5**H^{2-} with **3**-Co show a set of three ^{19}F NMR resonances of the monosubstituted, anionic complex **15** and two peaks for [Co$_2$(H$_2$O)(CF$_3$CO$_2$)$_2$(**5**H)(tmen)$_2$] (**16**) (Figure 1d).[9] The resonances of the former are lost within a few minutes at room temperature because once the hydrogen bond is broken, the second Kemp's moiety now resembles **9**$^-$ and readily substitutes the remaining terminal CF$_3$CO$_2$$^-$ of **15**. However, at 0 °C, the hydrogen bond to the phenol is more stable and the three resonances of **15** and two other sets of three weaker resonances corresponding to other less populated conformations of **15** persist for at least 1 h. Crystals of **16**-Fe and **16**-Co are readily obtained, and the **16**-Fe structure[10] is superimposable on that of **4**, the analogous complex with host ligand **1**.[4]

With **6**H^{2-}, the first ligand substitution takes place readily in acetonitrile, forming the monosubstituted anionic complex **17**, which is stable even at room temperature (Figure 1e). The second substitution step resembles the unfavorable substitution of **7**H$^-$ on **3**-Co, because breaking the hydrogen bond is not productive as the released carboxylate is not in position for an intramolecular substitution. It proceeds more readily in CDCl$_3$ to form the symmetric, neutral complex **18** (only one ^{19}F resonance at 43 ppm). Simulation of the structure of **18** on a computer (by substituting a phenol for R^1 of the crystal structure of **16**) places the phenol 4.8 Å from the irons and within hydrogen-bonding distance (2.5 Å) of the bridging water. Heating a solution of **3**-Co with **6**H^{2-} affords a phenoxy-bridged dimer, Co$_2$(CF$_3$CO$_2$)(**6**)tmen (**19**), as a crystalline solid.[11] The coplanar carboxylates of the diacid and the phenoxide oxygen bridge two metal ions, one of which is five-coordinate (trigonal bipyramidal with tmen ligation), and the other is six-coordinate with the CF$_3$CO$_2$$^-$ *trans* to the phenoxide.

In summary, the number of species in equilibrium in exchange reactions of **3** is reduced from 10 with Me$_3$CCO$_2$$^-$ to three with bulky carboxylates and to only two or one with phenol-containing ligands. The phenol remains in the vicinity of the dimetal complex as found in RR.

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Supplementary Material Available: Experimental details for **5**H$_3$, **6**H$_3$, **9**H, **10**H, **16**, and **19**; ORTEP drawings, crystallographic data, tables of atomic positional and thermal parameters and bond lengths and angles of **13**, **16**-Fe, and **19** (44 pages); calculated and observed structure factors for **13**, **16**-Fe, and **19** (25 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(9) Two closely spaced resonances are seen because the phenol substituent breaks the 2-fold symmetry axis, resulting in distinct bridging CF$_3$CO$_2$$^-$ ligands.

(10) X-ray analysis: **16**·3MeCN crystallizes in the monoclinic space group $P2_1/c$, with a = 22.467(4) Å, b = 15.000(2) Å, c = 21.294(4) Å, β = 116.39(2)°, V = 6428(2) Å^3, ρ(calcd) = 1.334 g cm^{-3}, Z = 4. The structure refined to R(wR) values of 6.70 (8.63)% (5233 reflections).

(11) X-ray analysis (full details will be published elsewhere): **19**·3MeCN crystallizes in the monoclinic space group $Pna2_1$, with a = 19.353(4) Å, b = 14.503(3) Å, c = 17.663(4) Å, V = 4958(2) Å^3, ρ(calcd) = 1.408 g cm^{-3}, Z = 4. With 4004 reflections (collected at 173 K with Mo Kα (λ = 0.710 73 Å) radiation, $2\theta_{max}$ = 45° on a Siemens P4 single crystal X-ray diffractometer), the structure refined to R(wR) values of 6.04 (8.00)%.