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Chromium(III)-Promoted C(2) Isotopic H-Exchange in Coordinated *N*-Methylimidazole: Exceptionally Rapid or Slow and Normal?

Charles R. Clark,* Allan G. Blackman, and
Andrea J. Clarkson

Department of Chemistry, University of Otago
P.O. Box 56, Dunedin, New Zealand

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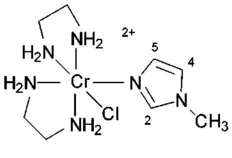
One of the more unusual phenomena associated with chromium(III) chemistry is the enhancement of C(2) (and C(4), C(5)) isotopic H-exchange reported to occur on binding *N*-methylimidazole to the metal. The effect was originally documented in this journal[1] for OH^--catalyzed detritiation of labeled *cis*-$[Cr(en)_2Cl(N\text{-}MeIm)]^{2+}$ (**1**), with the $Cr(en)_2Cl^{2+}$ moiety being described as 20-fold more effective in promoting exchange than H^+, and, equally surprisingly, some (10^5−10^6)-fold more effective than similar Co(III) species. The result was further elaborated,[2] and is now well established in the literature through its recent appearance in an authoritative review.[3] An outstanding Lewis acid capability for Cr(III) species would suggest wider catalytic potential. Metal ion binding to carbonyl-O will activate a carbonyl group toward attack by nucleophiles, and peptide synthesis based on this approach is an area of current interest.[4] Ru(III), Ti(IV), Zr(IV), Ta(V), and Co(III) centers provide useful activation, but Cr(III)-based reagents have not been investigated. If Cr(III) centers are indeed as polarizing as has been suggested[1−3] they should be particularly effective in promoting the reaction. Such considerations led us to test the original findings relating to enhanced C(2) isotopic H-exchange in *N*-methylimidazole, but in so doing we have discovered that these are considerably in error. In this communication we describe the synthesis of authentic **1** as its ClO_4^- salt, report the crystal structure of this compound, and demonstrate that the rate of C(2) isotopic H-exchange for Cr(III)-coordinated *N*-methylimidazole is in no sense unusual.



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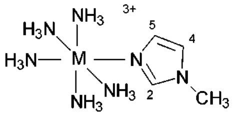

2a M = Cr
2b M = Co

[**1**]$(ClO_4)_2$ is available in moderate yield (30%) via the Ag^+-induced solvolysis of *cis*-$[Cr(en)_2Cl_2](ClO_4)$ in dry acetone and in situ treatment of the resulting solvento product with *N*-methylimidazole. The complex is orange-red in color, consistent with the presence of the CrN_5Cl chromophore,[5] and its composition was established by microanalysis (C, H, N, Cl). Single-crystal X-ray analysis substantiated the cis configuration, Figure 1. Acidic solutions of **1** are stable at room temperature over periods of hours, but in alkali slow OH^--assisted loss of chloride occurs with generation of $[Cr(en)_2(OH)(N\text{-}MeIm)]^{2+}$: $k_{obs} = k_{OH}[OH^-]$, with $k_{OH} = (6.5 \pm 0.5) \times 10^{-3}$ M^{-1} s^{-1}, 25.0 °C, and $I = 1.0$ M ($NaClO_4$). When this reaction is carried out in $NaOD/D_2O$ only small amounts of deuterium are incorporated at C(2) in the N-MeIm ligand (and none at C(4), C(5)) in the time scale of base hydrolysis. Owing to the paramagnetic nature of Cr(III) the degree of H/D exchange was assessed using indirect ^1H NMR measurements. Thus, aliquots (0.90 mL) of [**1**]$(ClO_4)_2$ (25 mg) in 0.10 M $NaOD/D_2O$ (3.0 mL, 25.0 °C) were quenched into DCl after 22.5, 45, and 67.5 min (5, 10, and 15 × $t_{1/2}$ for hydrolysis; $k_{obs} = 2.63 \times 10^{-3}$ s^{-1} for this condition, see Supporting Information), and exchange at C(2) in the N-MeIm moiety evaluated (9.8 ± 0.9%, 15.4 ± 0.8%, and 20.5 ± 1%, respectively; four experiments) following its liberation on reduction (Zn/Hg amalgam) of the $[Cr(en)_2(OD_2)(N\text{-}MeIm)]^{3+}$ hydrolysis product and isolation by IE chromatography. The magnitude and time dependence of deuterium incorporation signifies that some (6 ± 2)% occurs in intact **1**, with $[Cr(en)_2(OD)(N\text{-}MeIm)]^{2+}$ also being reactive. Furthermore, a value of 6% deuterium incorporation into **1** at $[OD^-] = 0.10$ M implies a second-order rate constant for OD^--catalyzed exchange in this species, k_H, of ca. 2×10^{-3} M^{-1} s^{-1}.[6] This is some 10^6 times smaller than the detritiation rate constant originally reported[1] for OH^--catalyzed exchange at C(2) in what was purported to be ^3H-labeled **1** ($k_T = 6.0 \times 10^3$ M^{-1} s^{-1}, 35 °C), and the two sets of results are clearly incompatible.

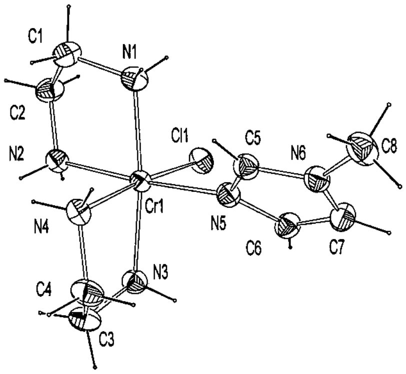

Figure 1. Structure of the *cis*-$[Cr(en)_2Cl(N\text{-}MeIm)]^{2+}$ cation with thermal ellipsoids shown at the 50% probability level; $R1 = 0.0390$.

The synthesis of a hygroscopic material originally reported[1] as [**1**]Cl_2 involved the reaction of *cis*-$[Cr(en)_2Cl_2]Cl{\cdot}H_2O$ with *N*-methylimidazole in aqueous solution. In our hands the published procedure[2] consistently gave mixtures in which [**1**]Cl_2 was absent (<2% of $[Cr]_T$, see Supporting Information), with the main component being an air-stable purple complex that did not contain *N*-methylimidazole. The absence of the latter ligand was shown by reduction of the complex, removal of inorganic products (IE chromatography), and ^1H NMR analysis of the organic fraction. The complex behaved as a 4+ charged ion on IE chromatography, and microanalysis (C, H, N, Cl) suggested its formulation as the dibridged species $[(en)_2Cr(\mu\text{-}OH)_2Cr(en)_2]Cl_4{\cdot}2H_2O$. This was verified by comparisons with an authentic sample.[7] Formation of the dimer under the conditions of synthesis is in accord with the known tendency of aniono- and aqua-Cr(III) species to form hydroxo-bridged polymers under aqueous alkaline conditions.[8] In the absence of X-ray structural data the earlier workers[1,2] used microanalysis (C, H, N), and UV−vis and IR spectroscopies to characterize the material thought to be [**1**]Cl_2, and this resulted in its mis-identification. Their tritiation/detritiation experiments

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[1] Buncel, E.; Clement, O.; Onyido, I. *J. Am. Chem. Soc.* **1994**, *116*, 2679.
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[3] Buncel, E.; Clement, O.; Onyido, I. *Acc. Chem. Res.* **2000**, *33*, 672.
[4] See: Browne, R. J.; Buckingham, D. A.; Clark, C. R.; Sutton, P. A. *Adv. Inorg. Chem.* **1999**, *49*, 307 and references therein.
[5] Cf. Red $[Cr(NH_3)_5Cl]Cl_2$: Schlessinger, G. *Inorg. Synth.* **1960**, *6*, 138.
[6] Since exchange in **1** and hydrolysis are competitive processes each first order in $[OD^-]$ the value of k_H may be obtained from the following relationship: $k_H = k_{OD} \times$ (% exchanged product)/(% hydrolyzed product) = $(2.63 \times 10^{-2}) \times (6/94) \approx 2 \times 10^{-3}$ M^{-1} s^{-1}. See, for example: Espenson, J. H. *Chemical Kinetics and Reaction Mechanisms*, 2nd ed.; McGraw-Hill: New York, 1995; pp 58−61.
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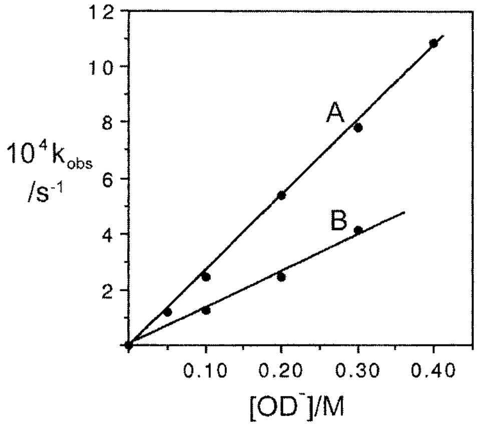

Figure 2. Plots of k_{obs} versus $[OD^-]$ for H/D exchange at C(2) in $[Co(ND_3)_5(N\text{-}MeIm)]^{3+}$ (**A**) and $[Cr(ND_3)_5(N\text{-}MeIm)]^{3+}$ (**B**); D_2O, 25.0 °C and $I = 1.0$ M ($NaClO_4$).

on this substance (aqueous conditions; neutral to slightly acidic pH)[1,2] therefore relate to the dimer and/or to impurities present in it.[9] Since a scintillation counting procedure was used to determine rate constants the results were readily misinterpreted owing to the inability of this technique to distinguish the sites of exchange. Exchange at C(2) (and at C(4), C(5)) in a nonexistent *N*-methylimidazole ligand was thus assumed.

Precise quantitation of the effect of a Cr(III) center on H/D exchange in coordinated *N*-methylimidazole was obtained using the pentaammine complex **2a**. This species retains its integrity in alkaline solution over the time required for complete deuterium substitution at C(2), and individual kinetic runs ($[OD^-]$ = constant, 25.0 °C, $I = 1.0$ M $NaClO_4$) were monitored over at least $2 \times t_{1/2}$.[10] The resulting values of k_{obs} are plotted against $[OD^-]$ in Figure 2, together with corresponding data for the Co(III) analogue **2b**. The rate law $k_{obs} = k_H[OD^-]$ holds for both, with $k_H = (1.3 \pm 0.2) \times 10^{-3}$ M^{-1} s^{-1} for **2a** and $(2.5 \pm 0.3) \times 10^{-3}$ M^{-1} s^{-1} for **2b**. It is clear from these data that the Co(III) and Cr(III) centers are comparably effective in promoting exchange. The $Cr(NH_3)_5^{3+}$ and $Co(NH_3)_5^{3+}$ moieties perturb the pK_a of coordinated water to similar extents (viz. $[Cr(NH_3)_5OH_2]^{3+}$, $pK_a = 5.20$;[11] $[Co(NH_3)_5OH_2]^{3+}$ $pK_a = 6.31$[12] (25.0 °C, $I = 1.0$ M, $NaClO_4$) versus H_2O, $pK_a = 15.7$), and this property provides a good measure of relative polarizing ability; however, each is considerably less electron withdrawing than H^+ (H_3O^+, $pK_a = -1.7$). Exchange in imidazoles appears to proceed via an ylide mechanism and electron-withdrawing substituents will increase C−H acidity and enhance the rate at which the proton is abstracted by OH^-. Wong and Keck[13] report a second-order rate constant for OD^--catalyzed H/D exchange at C(2) in $N\text{-}MeImD^+$ of 1.1×10^2 M^{-1} s^{-1} at 25 °C, which is ca. 10^5 fold greater than the rate constants for the corresponding reactions of **1**, **2a**, and **2b** and entirely accords with the much greater polarizing ability of D^+ (and H^+) compared to Cr(III) and Co(III) centers.

In summary, the original report of extraordinarily rapid C(2) H-isotopic exchange in **1** is in error; the exchange rate at C(2) in *N*-methylimidazole bound to Cr(III) is ca. 10^6 times slower than was earlier communicated, and is unexceptional when compared to the effects of N-protonation and Co(III) binding.

Supporting Information Available: References 14−21. Syntheses of *cis*-$[Cr(en)_2Cl_2]ClO_4$ and $[\mathbf{1}](ClO_4)_2$ and experimental procedures and tables giving rate data for alkaline hydrolysis of **1** (**S1**), and H/D exchange at C(2) in **2a** and **2b** (**S2**), crystal and structure refinement details (**S3**), atomic coordinates and equivalent isotropic displacement parameters (**S4**), bond lengths and angles (**S5**), anisotropic displacement parameters (**S6**), and hydrogen coordinates and isotropic displacement parameters (**S7**) for $[\mathbf{1}](ClO_4)_2$ (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Depending on workup conditions $[Cr(en)_2Cl(OH_2)]Cl_2$ and a red species of charge >4+ (probably a hydroxo-bridged trimer) were also present in the solid first isolated. The pure dimer was obtained following two crystallizations from EtOH/H_2O. The previously reported rate data[1, 2] appear to refer to exchange at various amine centers.

(10) For a particular $[OD^-]$ the degree of H/D exchange in **2a** was monitored following acid quenching at various times, with sample workup and ^1H NMR analysis of recovered *N*-methylimidazole as described for **1**, above.

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