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Mechanistic study of the aquation of nutritional supplement chromium chloride and other chromium(III) dihalides

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ABSTRACT

The mechanism for aquation of dihalotetraaquachromium(III) complexes (*trans*-$[Cr(H_2O)_4TX]^+$, where X or T = Cl, Br, or I), including a common component of many nutritional supplements (X, T = Cl) has been investigated using density functional theory. A number of mechanistic pathways were explored including associative interchange (I_a), and dissociative (D) mechanisms. The overall activation enthalpy for the D pathway of the dichloro (*trans*-$[Cr(H_2O)_4Cl_2]$) system calculated at the PBE0/cc-pVDZ level, with inclusion of an explicit outer sphere water molecule and in aqueous solution (PCM), is in excellent agreement with the experimental result. The results provide a detailed understanding of the mechanism for the hydrolysis of *trans*-Cr(III) complexes, which could be useful in understanding the speciation of Cr(III) complexes in physiological environments.

1. Introduction

Chromium(III) complexes are regularly incorporated into nutritional supplements. However, there is conflicting evidence supporting their nutritional value and in fact questions have been raised about their potential toxicity [1–3]. Consequently there has been some interest in determining the fate of Cr(III) in physiological environments [2,3]. One of the common chromium containing components of nutritional supplements is chromium(III) chloride ($CrCl_3{\cdot}6H_2O$), which actually exists as the dichlorotetraaquachromium complex, *trans*-$[Cr(H_2O)_4Cl_2]Cl{\cdot}2H_2O$ [4]. Although chromium(III) may be of little nutritional benefit to most people, there is evidence to suggest Cr(III) supplements may be beneficial in improving glucose metabolism, maintaining blood sugar and cholesterol levels, weight loss and building muscles in subjects with type II diabetes [1,5,6]. Glinsmann and Mertz reported [7] that oral supplementation with amounts of chromium(III) chloride ranging from 150 to 1000 μg per day for periods of 15–120 days led to improved glucose tolerance in type II diabetics. Chromium chloride has been claimed to pharmacologically influence blood sugar levels in type II diabetics when used at dosages less than the commonly accepted minimum nutritional level of 200 μg/day [7–9]. This claim is largely based on the results of clinical trials and animal studies [10–15]. Anderson et al. [5,16] found that a three month course of supplemental chromium(III) chloride at a dose of 50–200 μg/day significantly improved glucose tolerance and blood sugar levels in diabetics. Similar results were found with a dose of 125 μg/day of yeast-based chromium(III) [17]. There are also reports suggesting that chromium chloride has potential as an anti-depressant and alternatively to reduce lipid deposits [10,11]. The aquation of $[Cr(H_2O)_4Cl_2]^+$, is likely to play an important role in determining the speciation of Cr(III) complexes, prior to binding to biomolecules.

Chromium(III) complexes are generally considered to be kinetically inert which might explain the relatively low absorption (~2–5%) of orally administered chromium(III) supplements. Nevertheless, a deep green solution of $[Cr(H_2O)_4Cl_2]^+$ ion will gradually turn to pale green $[Cr(H_2O)_5Cl]^{2+}$ and then subsequently to violet $[Cr(H_2O)_6]^{3+}$ due to the step-wise replacement of chloride by water [4,18–24]. Therefore there may be significant speciation of chromium(III) in a physiological environment and it is not clear which of these species may have an impact on physiological processes in the body. For example, it has been suggested that chromium may form polymeric species with biomolecules such as lipids, nucleic acids and proteins [2,3,25,26]. Understanding the stability and reactivity of dichlorotetraaqua chromium(III) and other dihalotetraaquachromium(III) complexes will provide a basis for exploring the biochemical pathways of chromium supplements.

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Substitution and aquation reaction mechanisms of metal complexes can be classified according to whether they are associative (A), interchange (I or I_a or I_d) or dissociative (D) [27,28]. The substitution reactions at an octahedral metal center could be expected to show S_N1 (unimolecular) kinetics if the mechanism is dissociative or S_N2 (bimolecular) kinetics if the mechanism is associative or interchange [29,30]. Measurement of the volume of activation ($\Delta V^{\ddagger}$) is often used experimentally to assign a mechanism, with negative values associated with A, I, I_a or I_d pathways and positive values linked to D pathways. Although this approach works well for substitution of neutral ligands, the interpretation of $\Delta V^{\ddagger}$ values for charged leaving groups is less straightforward.

Ardon proposed [31] that ligand substitution reactions of $[Cr(H_2O)_5I]^{2+}$ proceeds *via* a dissociative mechanism with formation of $[Cr(H_2O)_5]^{3+}$ as an intermediate. However, tracer studies by Moore et al. [32] demonstrated that iodide exerts a strong *trans*-effect leading to considerable exchange of H_2O *trans* to the iodide prior to hydrolysis. This is also important for chlorination, which is found to proceed with formation of the *trans*-$[Cr(H_2O)_4ICl]^{+}$ intermediate.

A number of experimental studies have investigated the *trans*-effects in chromium(III) species including dihaloaqua-, [33–35] dihaloammine-, [36–38] and dihalo-bis-(ethylenediammine) -chromium(III) complexes [35,38–42]. Mønsted and co-workers [34] measured the pseudo-first-order rate coefficients for aquation of *cis*- and *trans*-$[Cr(H_2O)_4Cl_2]^{+}$ and reported $\Delta H^{\ddagger}$ values of 101 ± 5 kJ mol^{-1} for *cis* and 96 ± 1 kJ mol^{-1} for *trans* systems. This indicates increased reactivity of the *trans*-isomer. Similarly, Williams and Garner [33] investigated the aquation of the *cis*- and *trans*-$[Cr(NH_3)(H_2O)_3Cl_2]^{2+}$ ion and found activation energies (E_a) of 97 ± 2 and 85 ± 1 kJ mol^{-1}, respectively. Hoppenjans et al. investigated [36] the aquation reactions of the *trans*-dichloro-, *trans*-chloroaqua-, *trans*-bromochloro- and *trans*-chloroiodo-tetraammine chromium(III) [43] complexes and determined that the dihalo complexes aquate much more rapidly than the haloaqua complexes. They also found [36] that Br^- leaves at least 8.7 times faster than Cl^- from *trans*-$[Cr(NH_3)_4BrCl]^{+}$ and the loss of Br^- from bromochloro complex is about 10 times faster than Cl^- from *trans*-$[Cr(NH_3)_4Cl_2]^{+}$. The situation is more complicated for the chloroiodo complex. Analysis of the product ratios suggests the rate of loss of iodide is 30–40 times greater than the loss of chloride from this complex. This reflects the better leaving group ability of I^- versus Cl^-. However, if the ratio is solely due to leaving group ability, the ratio should in fact be much higher. The experimentally observed ratio of products can be explained if the *trans*-directing influence of the iodide is taken into account, which increases the rate of chloride loss.

The mechanistic details of these reactions have also been investigated in several studies. Bushey and Esperson proposed [44] a large *trans* labilizing effect of alkyl groups (–CH_2Cl or –$CHCl_2$) for the 1:1 substitution of H_2O with NCS^- in $[Cr(H_2O)_5CH_2Cl]^{2+}$ and $[Cr(H_2O)_5CHCl_2]^{2+}$. The kinetic data indicate that this reaction proceeds *via* either an S_N1 (dissociative) or an ion-pairing mechanism. Analysis of experimental data for the *trans*-$[Cr(AA)Cl_2]^{+}$, (AA = en, pn, tmd) species, combined with the observed stereochemical changes, indicate formation of a square-pyramidal intermediate, which is indicative of a dissociative mechanism [45]. Similarly, Macdonald and Garner [35] investigated aquation for both *cis*- and *trans*-isomers of $[Cr(en)_2Cl_2]^{+}$. Aquation of *trans*-$[Cr(en)_2Cl_2]^{+}$ led to the formation of *trans*-$[Cr(en)_2Cl(H_2O)]^{2+}$, *cis*-$[Cr(en)_2Cl(H_2O)]^{2+}$ and *trans*-$[Cr(en)Cl_2(H_2O)_2]^{2+}$, whereas aquation of *cis*-$[Cr(en)_2Cl_2]^{+}$ led to only *cis*-$[Cr(en)_2Cl(H_2O)]^{2+}$. The reactions were proposed to proceed *via* a dissociative mechanism (S_N1) that may include *trans*-to-*cis* isomerisation but this could not be confirmed. These results highlight the significant speciation that can occur in these reactions and the need for further investigation.

There have been only a limited number of theoretical studies of the *trans* effect in chromium(III) species under aqueous conditions. Rotzinger [46] carried out an extensive study of the water-water exchange mechanism for a number of complexes including *trans*-$[Cr(NH_3)_4(H_2O)_2]^{3+}$ and *trans*-$[Cr(NH_2CH_3)_5H_2O]^{3+}$. He identified an I_a pathway for the former and an I_d mechanism for the latter due to steric effects.

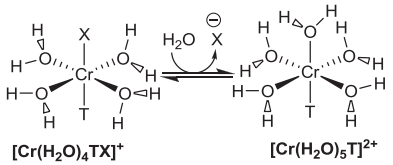
Recently we investigated [47] the aquation of halopentaaquachromium(III) complexes in the series, $[Cr(H_2O)_5X]^{+}$, (X = F, Cl, Br, or I) using density functional theory. On the basis of excellent agreement with experimental activation enthalpies, we proposed that aquation of the fluoropentaaquachromium(III) complex proceeds *via* an I_a pathway, followed by immediate formation of the conjugate base through proton transfer. In comparison, the most likely mechanism for aquation of the X = Cl, Br or I complexes is a variation of the dissociative mechanism. In our earlier study we found that coordination of a water molecule to the outer sphere of the complex had a significant effect on lowering $\Delta H^{\ddagger}$ for the dissociation step. Consequently, we referred to dissociative aquation from these $[Cr(H_2O)_4TX]^{+}\cdots H_2O$ precursor complexes as an associatively activated dissociation process (D_a). Unfortunately this leads to a mixing of the labeling convention of Langford and Gray (D) [28] with the labeling convention of Shriver and Atkins (D_a) [48]. Additionally, the inclusion of the outer sphere water molecule in these systems might best be considered an improvement in the model rather than initiating an alternate reaction pathway. Therefore, to eliminate confusion in this study we use only the D label of Langford and Gray to refer to reaction mechanisms in which the first step involves dissociation of the Cr–X bond.

This current work represents an extension of our previous study to include the aquation reactions of *trans*-$[Cr(H_2O)_4TX]^{+}$ complexes, where T and X are chloride, bromide or iodide ions (See Scheme 1). To the best of our knowledge no computational studies have been reported for the potential energy surfaces for the aquation mechanism of these systems.

The major objective of this work is to provide new insights of the intimate mechanisms of the aquation of the chromium chloride nutritional supplement and related *trans*-$[Cr(H_2O)_4TX]^{+}$ (X or T = Br or I) complexes. This will lead to the development of a better understanding of the stability and speciation of these species in aqueous and physiological environments.

2. Computational methods

Standard density functional and hybrid density functional theory calculations were carried out with Gaussian09 [49]. The geometries of all reactants, transition states, intermediates, and products in this study were fully optimized in the gas phase and solvent (water) at the PBE0/cc-pVDZ level of theory, which we have previously shown to give excellent agreement with experiment for the activation enthalpies of related species [47]. The small-core relativistic pseudopotential and correlation consistent basis set (cc-pVDZ-PP) of Peterson and co-workers was used for iodine throughout these calculations [50].



Scheme 1. Hydrolysis reaction of *trans*-$[Cr(H_2O)_4TX]^{+}$ (X or T = Cl, Br, or I).