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Studies on 8-tertbutyl Caffeine: An in silico approach to mechanistic studies

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ABSTRACT

Amminecobalt (III) promoted aerial oxidation of alkyl hydrazines undergoing homolytic alkylation of xanthines selectively at C-8 position. No modeling studies have been done previously on these compounds. An attempt was made to predict the mechanism involved in this spontaneous reaction using molecular modeling. The predictions revealed that homolytic aromatic substitution of alkyl radical exhibits primary isotopic effect. We try to correlate the importance of in silico approaches towards mechanistic studies in such compounds.

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1. INTRODUCTION

Xanthines, a group of alkaloids are purines consisting of organic heterogeneous aromatic compounds with six membered and five membered rings fused together. Structurally caffeine, methylated xanthine and adenine are similar to act as adenosine receptors but cannot stimulate receptors. Xanthines have been identified in most tissues and fluids of over a hundreds of species of plants, but found generally in cultivated plant seeds of berry of *Coffea arabica* (Coffee beans), leaves and leaf buds of tea bush *Camellia Sinensis* (Tea), nuts of *Cola acuminate*, seeds of fruit cacao *Theobroma cacao* (Cacao) and in other common herbs[1]. Above all, many xanthine derivatives serve as important compounds and potential therapeutic agents for cure and intervention of many diseases including Alzheimer's [2] Of xanthines, methylated xanthines are of continuous interest due to their therapeutic value and therefore used as mild stimulants [3] adenosine receptors [4], calcium release channels in physiological processes [5] and bronchodilators [6] further enhancing potency and selectivity towards specific biological targets.

In the recent past, aqueous organometallic chemistry has attracted much interest due to the reduced requirement for organic solvents. It has been known that many organocobalt (III) complexes are sensitive to oxygen or moisture as hydrolysis of cobalt (III)-carbon bond is dependent on the nature of the ligand and requires mild conditions. As alkylcobalt (III) acts as potential radical source, *e.g.* in organic synthesis related bond homolysis *via* oxidation, reduction, thermolysis, photolysis and sonolysis have been employed. Homolytic aromatic substitution is a well-known method for the preparation of 8-substituted caffeines. For example, 8-methylcaffeine has been prepared by irradiation of a mixture of caffeine and tert-butylperacetate with ultraviolet light [7]. Similarly, 8-(1-adamantyl) caffeine and 8-cyclohexyl caffeine have been obtained by employing photochemically prepared radicals [8]. Other 8-alkylcaffeines have been synthesized by reaction with solvent-

derived alkyl radicals using benzoyl peroxide as a radical initiator [9]. Further studies on nucleosides reaction solvents such as ethers and alcohols in UV light with or without sensitizers known to yield C-8 alkylated products [10]. Earlier, we reported that cobalt (III) in aqueous ammonia solution serves as a catalyst for obtaining new carbon-carbon bonds by homolytic aromatic substitution. The amminecobalt(III) promoted aerial oxidation of alkyl hydrazines affords alkyl radicals, and some primary alkyl radicals have been trapped by the pentaamminecobalt(III) to form alkyl cobalt(III) cations[11].

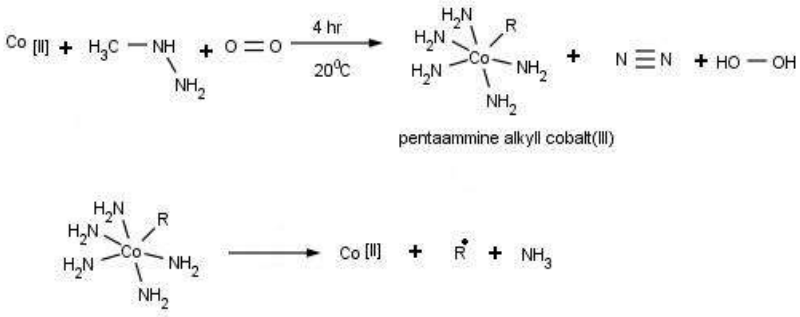

Figure 1. Synthesis of pentaammine alkyl cobalt (III) complex and release of free radicals

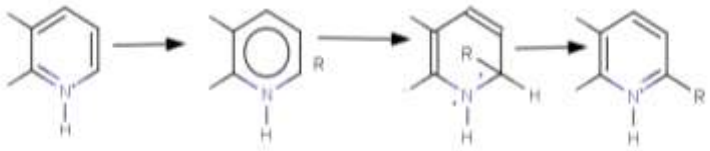

Figure 2. C-Alkylation of purines as postulated by (M Meada et al 1974) with intermediates

However, these compounds are labile and decompose to return alkyl radicals. Therefore we have synthesized and represented a set of alkyl radical substitution selectively at C-8 position of xanthine to circumvent the mechanistic studies predicted using HPLC, NMR and molecular modeling techniques. Alkyl radicals were generated by the homolysis with tert-butyl hydrazine while caffeine was chosen for the mechanistic study (See Figure 1). Correlating this, we have synthesized C8-alkyl xanthines using cobalt as catalyst. C-alkylation has possible scope in radical reaction on nucleosides and purine bases has been studied and the intermediates were postulated [12, 13]. These studies have been done on purines and nucleosides by methyl radical produced in the presence of iron (II) (See Figures 2 and 3).

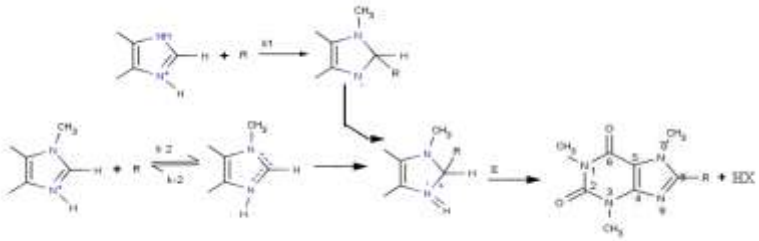

Figure 3. Mechanistic representation of C-8 hydrogen-substituted with alkyl group wherein two unstable intermediates lead to the formation of C-8 alkyl xanthenes.

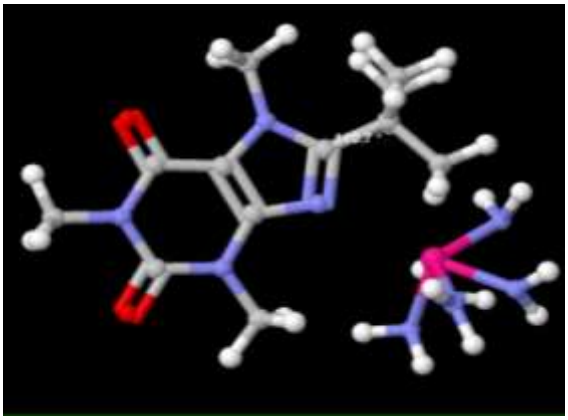

Figure 4. 3D model of 8-tert-butyl xanthine with bond angle 110.70, cleavage of bond between pentaammine cobalt (III) and alkyl moeity is sterically arranged at C-8 position of xanthine

2. CONCLUSION

The aromatic electrophilic substitution in case of xanthines is well known to occur in the π electron rich 5-membered ring. The aminocobalt promoted oxidation of monoalkyl hydrazines forms primary alkyl radicals, which get substituted at C-8 position of xanthines as shown by spectroscopic studies, i.e. 13C, 50 Co NMR and ESR. The molecular modeling studies carried out on 3-D structure of xanthine and aminocobalt complex validate that the alkyl group of latter is sterically favorable for C-8 alkylation of xanthine. We hope in silico strategies can be derived on such compounds which would provide predictive confirmation of intermediates.

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