

RESEARCH NOTE

**Non-stoichiometric Green Organic
Complexes of Caffeine**

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Non-stoichiometric Green Organic Complexes of Caffeine

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Caffeine is known to form complexes by self-association [1] and with other organic compounds [2]. Its biological activity in changing the effects of neurotoxins has been attributed to its formation of stacked complexes [3]. Charge-transfer complexes of caffeine have also been reported [4, 5]. However, complexes reported are stoichiometric and exhibit color only in solution. A search of the literature reveals no reports of non-stoichiometric complexes and especially none showing color in the solid phase. Co-crystallization studies of caffeine with maleic acid have been reported but with no mention of color [6].

Initial studies focused on the reaction between caffeine and maleic anhydride. Weighed amounts of both reactants were placed in a dried test tube in no particular order and heated together on a sand bath. The white solid mixture was heated for a few minutes until the mixture turned into a green liquid. The green liquid mixture was allowed to cool to a green solid. Heating either compound in the absence of the other did not result in the green compound. Two different sources of caffeine from two different manufacturers were used with both forming the colored product.

To test the stability of the green mixture, tests were run under inert atmospheres or under vacuum. Under inert atmospheres, the green liquid on further heating turned black. This observation was also made in the absence of inert conditions. Under vacuum, the green liquid did not change color even on extensive heating. On cooling, the green solid formed and remained green as long as it was kept under vacuum. However, when cooled in air, the solid turns white in a few hours. Sublimation under vacuum resulted in some separation of maleic anhydride from the green mixture leaving the green solid behind.

A $^1\text{H-NMR}$ spectrum of the green solid showed no new peaks. A closer examination of the peaks did show a slight shift in peak values. $^1\text{H-NMR}$ studies have been used in the literature to examine the nature of weak association of caffeine complexes in solution [7]. For our purposes, green mixtures resulting from various molar ratios of caffeine and maleic anhydride were dissolved in CDCl_3 . A $^1\text{H-NMR}$ study of these mixtures shown in Figure 1 showed well defined though small shifts in peak values as the ratio of caffeine to maleic anhydride was changed. The shift in peak value indicates presence of weak intermolecular interactions between caffeine and maleic anhydride molecules in solution. IR spectra of the green solid looked similar to the reactants though there were minor shifts in some peak values. These minor shifts could be indicative of weak intermolecular interactions in the solid state.

Job's method was followed to indicate if complex formation had occurred between these compounds. The plot from Job's method for the reaction between maleic anhydride and caffeine is shown in Figure 2. Clearly, the plot is not a typical Job's plot of a stoichiometric complex. There seems to be an indication of the presence of more than one non-stoichiometric complex.

Similar observations were made from a Job's study of the green mixtures when run at lower concentrations. Repeating these experiments verified the Job's plots recorded earlier. These trials combined with $^1\text{H-NMR}$ results are indicative of an association between these compounds. The association constant was calculated for the two large peaks from Job's plot with $K_a = 18 \times 10^3$ for mole fraction 0.4 and $K_a = 25$ for mole fraction 0.8.

The compounds that do form green liquids with caffeine are maleic acid, fumaric acid and phthalic anhydride. Among these, Job's plots of the green mixtures resulting from maleic acid and phthalic anhydride also indicate the formation of two major non-stoichiometric complexes at different molar ratios. Many other compounds did not form green mixtures with caffeine. Both solids and liquids were tested with different functional groups. These include 2,6,10,14-tetramethylpentadecane, methyl cyclohexane, bicyclo[2.2.1]hepta-2,5-diene,

diphenylacetylene, thioacetamide, benzoic acid, 4-nitrobenzoic acid, p-aminobenzoic acid, benzamide and benzophenone. The formation of the green complex with maleic acid but not with benzoic acid suggests that functional group alone is not the deciding factor to form the green complex. At present, we are uncertain of the reasons for this selectivity. Pursuing molecular modeling studies to understand this better is a future goal.

Figure 1: Dependence of proton chemical shifts for the N=CH proton in caffeine with change in mole fraction of caffeine.

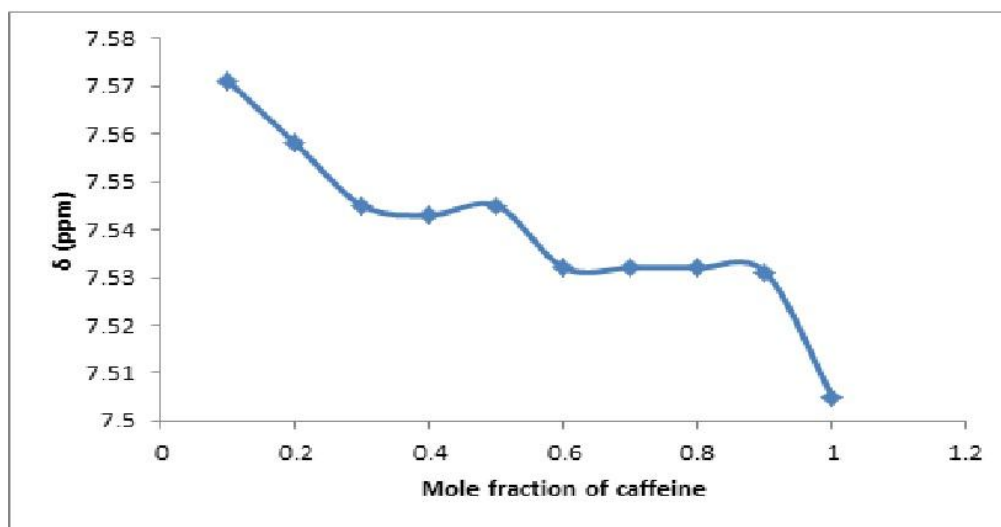
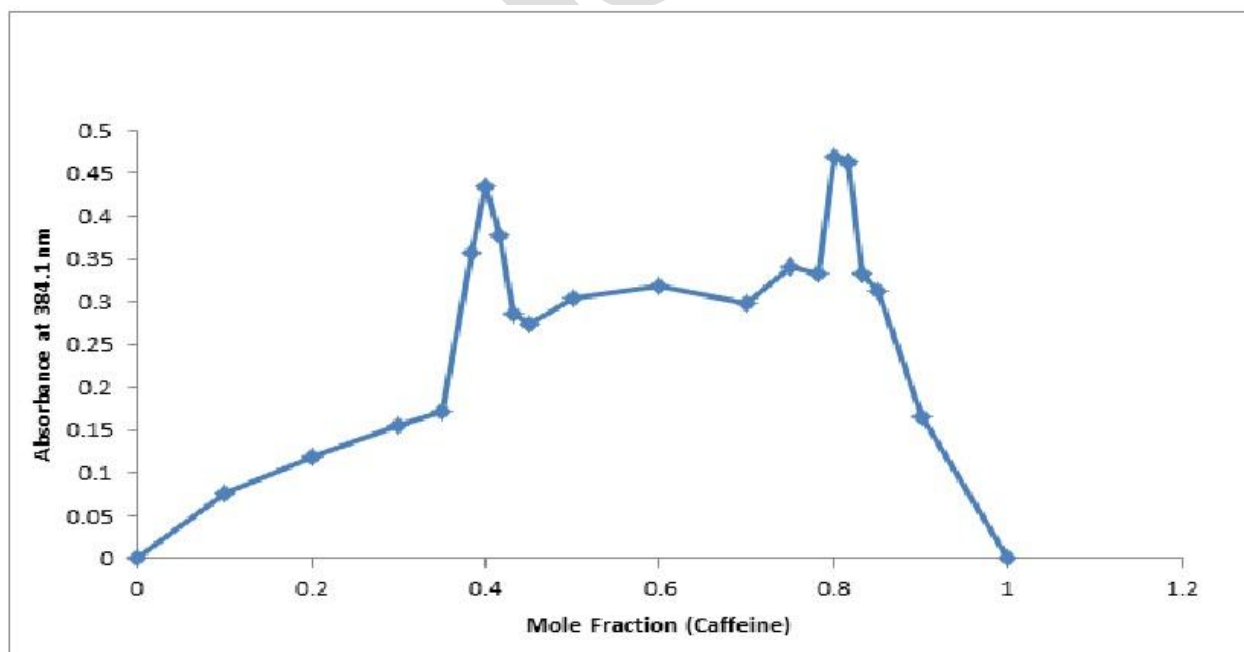


Figure 2: Job's plot of reaction between caffeine and maleic anhydride.



Competing Interests

None declared.

Authors' Contributions

SSY did the work on Job's method; MB did the initial work on reacting caffeine with maleic anhydride; SSY and MB both worked on NMR and IR studies; RR tested caffeine with other organic compounds and JEW provided research guidance for the project and drafted the manuscript.

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